

CURRENT STATUS IN 2003 OF CHONDROCYTE CULTURE TECHNOLOGY AS APPLIED TO HUMAN AUTOLOGOUS CHONDROCYTE IMPLANTATION

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Chondrocyte biology and knowledge has expanded in recent years because of the impetus of human tissue engineering applications associated with the use of autologous chondrocyte implantation (ACI) and articular cartilage repair. It is important to emphasize some new and old data in relation to the 'chondrocyte phenotype' and their use in ACI.

Some important questions will be addressed :

1. What are the consequences of plating cells intentionally at low densities in monolayer culture to obtain maximal cell proliferation rates per unit time to maximize cell numbers for use in human ACI?

The chondrocyte phenotype is 'fragile' and cells will de-differentiate to the fibroblast phenotype and will initially synthesise type 1 collagen and low MW proteoglycans¹ and hence encourage fibrocartilage (FC) formation initially *in vivo* rather than normal HAC and this may explain in part the various biopsy reports from long term ACI studies which demonstrate zonal variation of FC and HAC within the same biopsy at 12 months post ACI^{3,4}.

2. How long do 'de-differentiated chondrocytes' take to revert back to the chondrocyte phenotype once implanted for ACI? Probably about 4-6 weeks⁵ – so FC will initially be deposited rather than HAC if cell number per unit defect volume is too low.

3. Is the number of cells placed into a known sized AC defect important? Yes. We know that chondrocytes plated at high density *in vitro* maintain their differentiated state whilst still proliferating². Hence cells inoculated into known sized AC defects at high densities *in vivo* are more likely to form HAC rather than FC (if inoculated *in vivo* at low densities). Hence this is the reason the size of the defect(s) must be known by the laboratory so that approximate correct normal cell numbers per unit volume of matrix can be implanted per AC defect for optimal repair results and formation of HAC during the early *in vivo* repair process rather than FC. Recent studies by MTE (Henderson, Heirweg & Tuy⁶) have attempted correlation of 12 month MRI repair parameters and second-look histology with marked patient subjective improvement at 12 month follow up (p<0.001) using this quantitative approach with optimal cell numbers per AC defect.

4. Is it possible to utilize cells from the debrided sides and base of AC defects and hence minimize use of normal AC to obtain autologous chondrocytes for ACI? Yes. Chaipinyo et al., 2002⁷ have demonstrated that chondrocytes from debrided human AC are viable and proliferate very well.

5. Is there an age limit to the retrieval and growth *in vitro* of human articular chondrocytes. Yes. Barbero et al., 02⁸. Cell yield decreases after age 40 and cell proliferation decreases after age 20. The use of specific growth factors such as TGF- β , FGF-2 and PDGF β and IGF-1 enhance cell proliferation at any age range and extends chondrogenic potential of proliferated cells until age 55 years.

6. Is the mass growth of pre-formed autologous AC constructs in bioreactors an advantage in human AC repair? Will such constructs attach and bond to the adjacent debrided defect and the subchondral bone plate and allow more rapid mobilization of patients after implantation? Such studies are just commencing and early animal results are promising.

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