

## Gene therapy in regeneration of the intervertebral disc

Tony Freemont, Stephen Richardson, Christine LeMaitre, Judith Hoyland

*Spine Research Group, Division of Regenerative Medicine, The School of Medicine, The University of Manchester, United Kingdom.*

### Background to regeneration of the intervertebral disc:

Our research is directed towards exploring the importance of the extracellular environment on the function of cells from the central nucleus pulposus (NP) of the intervertebral disc (IVD) and utilizing that information to facilitate strategies for regenerating the degenerate IVD.

The NP is a key component of the IVD. The matrix produced by NP cells is highly hydrophilic, generating sufficient swelling pressure to force the vertebrae apart even under the loads induced by gravity and muscle action that operate on the erect human spine. The NP is also the site of the earliest and ultimately most severe matrix changes in the IVD in degeneration.

Degeneration of the IVD (DIVD) leads to loss of disc matrix, approximation of the vertebrae ("*loss of disc height*"), and mechanical back pain; indeed it is held to be the most common cause of significant chronic back pain and sciatica and as such is one of the most important causes of morbidity and loss of work in the Western world.

Restoring IVD height is a major goal in the management of DIVD and chronic back pain.

Tissue engineering +/- IVD regeneration (IVDR) are obvious approaches to restoring disc height. Before adopting either it is important to understand what roles might be required of the components of putative regenerates and how the local conditions within the degenerate disc might influence their behaviour.

### Our work:

Our approach has been to study the basic biology of IVD degeneration and to formulate a regeneration strategy with our front-line clinical colleagues.

Briefly, we have established:

- An understanding of the pathobiology of IVD degeneration and particularly matrix loss. In particular we have shown that the IL-1 family is key to initiating production of the matrix degrading enzyme cascades that lead to matrix loss and reduction in disc height. And that the best source of cells to populate a regenerate is mesenchymal stem cells (MSC).
- Clinical colleagues would ideally want a regenerative medicine based therapy that could be simply delivered and would result in restoration of the normal anatomy of the motion segment around the degenerate IVD.

Our vision is therefore to produce an injectable proto-regenerate, with: the basic building blocks (cells, biomatrix) from which to regenerate the IVD; and built in regulatory processes to both promote regeneration (programmed extracellular signaling messages) and to inhibit the underlying disease processes within the target IVD.

Part of this strategy is to test the use of gene therapy approaches to regulating cell function.

### This presentation:

In this presentation we will describe two gene therapy experiments made possible through funding from the AO Foundation.

The first is to inhibit IL-1 mediated events in the IVD by using a gene delivery system for the IL-1 inhibitor IL-1Ra.

The second is to promote cell survival, differentiation towards a chondrogenic phenotype and matrix synthesis by MSC using PLLA scaffolds as a paradigm.

Briefly in the first we have been able to totally inhibit MMP and ADAMTs protein expression by native human nucleus pulposus cells in IVD explants by injecting into the explant MSC transfected with IL-1Ra gene in an adenoviral vector.

In the second we have rescued MSC from cell death, and caused them to differentiate into chondrogenic cells synthesizing an NP matrix by transfecting the MSC with the gene for the master chondrogenic regulator gene Sox-9, again in an adenoviral vector and matrix synthesis of stem cells

### REFERENCES:

Richardson SM, Curran JM, Chen R, Vaughan - Thomas A, Hunt J, Freemont A, Hoyland JA. Differentiation of bone marrow stem cells into chondrocyte-like cells on PLLA scaffolds. *Biomaterials*. 2006;27(22):4069-78.

Le Maitre CL, Freemont AJ, Hoyland JA. Preliminary in vitro study of IL-1Ra gene therapy for the inhibition of intervertebral disc degeneration. *Int J Exp Pathol*. 2006;87(1):17-28.

**ACKNOWLEDGEMENTS:** This research work is supported by a grant from the AO Foundation (Davos, Switzerland) through the Biotechnology Advisory Board.