Tissue Engineering Approaches to Treat Defects in the Intervertebral Disc and Vertebrae

The intervertebral discs (IVD) of the spine are sandwiched between the bone vertebrae (Fig. 1a). The IVD is made up of an outer “annulus fibrosus” comprised of fibroblasts and type I collagen with a lamellar structure in which the collagen fibers in each lamella are oriented in a particular angle (Fig. 1b). The core of the disc, is the “nucleus pulposus,” which is hyaline cartilage (similar to articular cartilage) with chondrocytes fully contained within (surrounded by) their extracellular matrix composed primarily of type II collagen and aggrecan. The bone and annulus fibrosus are vascularized but the nucleus pulposus has no blood vessels. You have been hired by an orthopaedic company interested in developing novel tissue engineering treatments for spine problems. Explain all of your answers.

1. (30%) In a certain disease condition it is necessary to remove a portion of degenerated annulus fibrosus and nucleus pulposus (procedure called discectomy; Fig. 1c).
   a. What fabrication method would you use to produce a 1-piece scaffold if it were to induce the architecture of the tissues in the defect in Fig. 1c?
   b. Note the principal limitation of this fabrication method?
   c. What would you expect as the outcome of implanting a sponge-like scaffold (alone) into the defect, regardless of how it is fabricated?
   d. What benefits might there be in drilling small holes into the bone above and below the defect, prior to implanting the scaffold alone?

2. (30%) One of the main projects in your company is the production of tissue-engineered nucleus pulposus in vitro. There are questions regarding the most favorable cells and culture conditions to use for the formation of the nucleus pulposus construct in culture. One proposition is that chondrocytes be isolated from the patient’s degenerative nucleus pulposus removed during discectomy. Another approach is that marrow be aspirated from the patient for the isolation of mesenchymal stem cells, and that these stem cells be differentiated to chondrocytes in vitro.
   a. Which of the 2 cell types would you select for the tissue-engineered cartilage?
   b. It has been suggested by the CEO that the application of any type of mechanical loading to the cartilaginous construct as it forms in vitro will be of some benefit, and she has proposed the cheapest approach of applying a constant load to the cartilage as it forms. Do you agree?
   c. At what stage of maturation would you propose that the tissue-engineered nucleus pulposus construct be implanted?

3. (30%) Due to trauma, fissures/defects can form in the nucleus pulposus, annulus fibrosus, and/or in the bone (Fig. 1d). The company is considering the development of an injectable treatment for each of these 3 defects.
   a. For each of the 3 defects select one of the following, and explain the basis of your choice: 1) no treatment required; 2) an injectable self-assembly peptide; 3) cells of the same type as
the tissue; 4) cells of the same type as the tissue incorporated in the self-assemblying peptide. Choose the simplest solution.
b. One of the consultants to your company has proposed that the three defects can simply be treated by giving the patient a systemic injection of drug known to stimulate the proliferation of mesenchymal stem cells in marrow and their release to the general circulation. Do you agree for each of the defects?
c. For the treatment of the defect in the nucleus pulposus, another consultant has suggested the use of embryonic stem cells derived from somatic cell nuclear transfer which have been differentiated to chondrocytes in vitro. Ethical issues aside, do you agree?

4. (10%) Your company has technology to produce sponge-like scaffolds of the same pore structure, but with different mechanical rigidity (hardness). If you were asked to use mesenchymal stem cell-seeded scaffolds for implantation into defects in the nucleus pulposus, annulus fibrosus, and bone, would this technology be of any value? [These would be non-injectable applications for larger defects than that shown in Fig. 1d.]
Fig. 1

Defect in the NP

Defect in the AF

Defect resulting from the removal of degenerated annulus fibrosus and nucleus pulposus

Intervertebral Disc
Annulus Fibrosus
Nucleus Pulposus

10mm