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as The delivery of cells into damaged tissues has long been used to facilitate enhanced regeneration. The first modern example of successful cell therapy was bone marrow transplantation for the treatment of leukaemia, which was successfully performed in 1956. Since then, cells have been used for the regeneration of a range of different tissues. The following section details exemplars of the use of cells as therapeutic agents, for the regeneration of skin and cartilage (articular and auricular). Skin The tissue that was one of the first regenerated using human cells was skin. The pioneering work of Rheinwald and Green in this area led to the identification of optimal conditions for the growth and maintenance of keratinocytes harvested from skin in culture. The first tissue engineered skin consisted of a layer of keratinocytes grown on a collagenous membrane, which could be directly applied to a healing wound. In the original skin tissue engineering process, the keratinocytes were grown onto a membrane and were cultured in the same system as a layer of confluent but (unable to divide) fibroblasts. The fibroblasts are required in this culture because they provide a series of paracrine factors that allow for the keratinocytes to maintain their phenotype and also mature when lifted to the air-liquid interface. The fibroblasts had to be mitotically inhibited because they tend to proliferate at a greater rate than the keratinocytes and can consequently overtake the complex culture. As a consequence of the need for multiple steps and cell types, in addition to the air-lift required for stratification James George Rheinwald, b. 1948, American research scientist. Howard Green, 1925–2015, George Higginson Professor of Cell Biology, Harvard Medical School, Boston, MA, USA, pioneer in the science of skin regeneration. of the epidermal keratinocyte layer to occur, the process is relatively slow (requiring up to a month). This means that the burn wound to be resurfaced using this process needs to be closed and protected prior to application. This process has been refined over the years and has resulted in the development of a range of technologies, some of which are still on the market. Despite a reasonable level of integration, the skin itself lacks many of the features of normal human skin, for example coloration, and is not in widespread use in the clinic. Articular cartilage regeneration Microfracture or microdrilling (Figure 4.5) into subchondral bone at the base of a chondral defect creates a communication between the intra-articular and subchondral spaces, allowing blood, containing bone marrow stromal cells, to arrive at the defect. Used clinically for more than 30 years, the formation of the clot creates an environment that allows for the reformation of cartilage within the defect, which subsequently provides a level of mechanical function. Although widely used in the clinic with success, the cartilage formed is typically fibrocartilage, which is mechanically inferior to the native articular cartilage and lacks longer term durability.

Skin biopsy – keratinocytes Figure 4.4 Schematic diagram showing the principles of induced pluripotent stem cell (iPSC) therapy. Mononuclear cells from peripheral blood or keratinocytes from a skin biopsy are cultured in vitro and then reprogrammed to become iPSCs by addition of reprogramming factors. The iPSCs are then expanded and selected differentiation factors added to

promote differentiation of iPSCs into the desired specialised cell type for use as therapy.
Reprogramming factors Induced pluripotent stem cells Differentiation factors Cell therapy
Differentiated cells Examples include: chondrocytes Disease neurones modelling myocytes
pancreatic islet cells

To overcome these limitations, research has focused on ways to create an environment in the chondral defect that is more conducive to the formation of articular or hyaline cartilage. Autologous chondrocyte implantation (ACI) is one such method (Figure 4.5). In the first step a small number of are harvested from healthy cartilage within a patient's joint, for example the knee. The cells are then expanded, to increase the cell number, in a laboratory (with good manufacturing practice [GMP] quality standards). In a second procedural step, cells are reintroduced into the defect, classically with a surgically positioned 'roof ' or patch over the defect, prior to injection of the cells below . In 2017, following the evaluation of evidence, the UK's National Institute for Health and Care Excellence (NICE) recommended ACI for use in the National Health Service (NHS). The recommendation was for defined patients who have symptomatic articular cartilage defects of the knee, with a cost-effectiveness estimate thought likely to be less than £20 000 per quality-adjusted life year (QALY) gained.

Autologous chondrocyte Figure 4.5 Examples of (a) endogenous cell targeting (microfracture) and (b) cells being used as a therapy (autologous chondrocyte implantation). (Adapted with permission from Makris E, Gomoll A, Malizos K et al . Repair and tissue engineering techniques for articular cartilage. Nat Rev Rheumatol 2015; 11 , 21-34.)

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