tissue and chondrocytes implanted in a damaged knee for production of hyaline-like cartilage. An extracorporeal (outside of the body) artificial liver employing pig liver cells in a hollow fiber reactor is being clinically tested.

Artificial tissues/organs for transplantation that are under active development include liver, pancreas, kidney, fat (for reconstructive surgery), blood vessel, bone marrow, bone, and neurotransmitter-secreting cell constructs. An alternative form of tissue engineering is *in vivo* alteration of cell growth and function. An example would be the use of implanted polymeric tubes with a controlled surface chemistry to encourage and guide reconnection of damaged nerves. Another use of artificial tissue constructs is for toxicological and pharmacological testing of potential new drugs. In this case the artificial tissue or combination of tissues acts as a surrogate, reducing the need to use animals for such testing.

The primary difference between tissue engineering and protein production from mammalian cells lies in the constraints on cell selection. For protein production we prefer continuous, transformed cell lines. A single cell type is desirable. For tissue engineering the goal is to replicate the response of a living tissue. Cells removed from a tissue and cultured as a homogeneous cell type in two dimensions (e.g., on a solid surface) often lose their authentic *in vivo* response. Since cell transformation and cancer are closely related, transformed cells cannot be used for a product for transplantation. Reconstruction of artificial tissues requires a deep understanding of the interactions of one cell with another, control of cellular differentiation processes, and knowledge of how cells interact with surfaces to which they attach. Most often a polymer scaffold is used to guide and organize tissue growth. Maintaining the correct ratio of cell types can be difficult, since some cell types, such as fibroblasts, can "outgrow" others. The appropriate cell types must organize themselves into the appropriate three-dimensional configuration. With such tissues, function requires appropriate structure. Ideally the cells can be multiplied from donor tissue for at least 10 passages and then assume the fully differentiated phenotype when the correct stimulus is applied. A major challenge is the routine, reproducible culture of such cells, and bioprocess engineers are in an excellent position to contribute to this technology.

Of particular importance to many tissue-engineered constructs is the formation of extracellular matrix, the interaction of cells with one another, and the interaction with an artificial surface. Anchorage-dependent cells must attach and spread on a substrate surface to proliferate and function. Cell adhesion is mediated by extracellular matrix proteins such as fibronectin and collagen. Synthetic substrates can be modified by adding synthetic peptide sequences (3 to 6 amino acids) to a surface at the end of a synthetic polymer. The difference in strength of cell–substrate and cell–cell adhesion can greatly alter the three-dimensional organization of the cells.

The use of simulated microgravity reactors coupled with polymer scaffolds has been useful in some cases in the development of certain tissue constructs. The use of microfabrication techniques, where the investigator has control over placement of individual cells, is an intriguing technology for more authentic tissue constructs. An increasingly large array of tools are being developed for controlling the formation of tissue constructs with improved performance.

Development of effective tissue constructs that are biologically complex, such as the liver, is a very difficult problem, and commercial production of transplantable organs