

Exemplars materials in development

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Synthetic and engineered polymers Synthetic polymers are those made from chemical processing of natural components or from complex synthesis from precursors such as fossil fuels. There are a great many synthetic polymers that are used in the body, including polymethyl methacrylate (PMMA), which is used to make intraocular lenses and as a cement in joint replacement; Dacron™ (Terylene™), used in vascular grafts; and a range of resorbable materials, including poly(caprolactone) (PCL), poly(lactic acid) (PLA), poly(glycolic acid) (PGA) and copolymers thereof (PLGA). These resorbable polymers have been used in the body for some time as sutures and in other degradable structures. Moreover, they have become widely used in regenerative medicine for the production of scaffolds, on which cells can be seeded and grown prior to, during or after implantation into the body. Synthetic materials can be processed in a range of different ways in order to provide a structure optimised to the intended purpose. Porous monoliths can be produced by foaming processes, which can include but are not limited to infiltration and then expansion of supercritical carbon dioxide in order to create a foamed structure. The pore sizes of such structures may be tailored by modifying process conditions or material compositions (Figure 4.6). Such polymers can also be formed as spheres by using emulsion processing or they can be processed into a mat of fibres using a process known as electrospinning, whereby charged threads of polymer are drawn using an electric field and subsequently deposited onto a surface (Figure 4.7). Manufactured in this way, the materials tend to have a very high surface area and can exhibit structural features across the same length scales as the fibrous components of the extracellular matrix. As a consequence, electrospun patches have been designed for the repair of anatomical structures such as the rotator cuff and have even been used to explore how modifications in matrix geometry may result in pathology. Bioceramics A range of ceramics have been used for the delivery of compounds that can trigger the regeneration of mineralised tissues.

(b) Figure 4.6 Electron micrograph of a poly(lactic acid) scaffold foamed using supercritical carbon dioxide (a) with pore structure assessed using micro-computed tomography (b). (Adapted with permission from Collins NJ, Leeke GA, Bridson RH et al. The influence of silica on pore diameter and distribution in PLA scaffolds produced using supercritical CO₂. J Mater Sci: Mater Med 2008; 19: 1497–502.) 2

® The most widely used such material is Bioglass, a glassy material (a ceramic with no crystal structure) containing calcium, silicate and phosphate ions (Na₂O-CaO-P₂O₅). When placed into an aqueous environment, such as within body fluids, the surface of the ceramic material can break down, releasing the component ions into the surrounding liquid. This can result in the deposition of a bone-like mineral across the surface of the material itself, which can encourage the material to

bond to surrounding hard and soft tissues. In addition, the eluted ions can trigger specific biological responses that include the recruitment and differentiation of mesenchymal cell populations. Bioglass has been used in a range of medical products and has recently been widely applied in remineralising toothpaste formulations (as Novamin). The incorporation of other ions, such as strontium and lithium, into the glassy matrix can drive specific biological processes, enhancing the process of bone formation. Bioglass can be manufactured as a foamed structure and as a monolith. It is most frequently used in porous matrices to drive the process of bone integration. Hydrogels are an emerging and increasingly researched class of materials in regenerative medicine. They consist of hydrophilic polymers that are typically dispersed in an aqueous component to form a hydrocolloid. Interactions between the individual polymer chains can then be formed by modifying the temperature, adding ions or adding a chemical cross-linking agent. The resulting network retains water and forms a solid but highly hydrated structure (typically c. 99wt% water). The high water content of these materials means that nutrients, oxygen and metabolic by-products can diffuse through them. As a consequence, they have been widely used for the encapsulation of cells, typically allowing the maintenance of high levels of viability. Alginate, a seaweed-derived polysaccharide blend, for example, has been used to protect pancreatic islets from immunological attack. In recent years, this approach has been refined to allow for pancreatic islets to be shipped between medical centres (Figure 4.8). Other materials that form gels include chitosan, gellan, collagen and hyaluronic acid. In addition to these biologically derived materials, hydrogels may also be formed from synthetic polymers, including poly(ethylene glycol), and these can be chemically modified to provide specific biological stimuli to entrapped cells. Additive layer manufacturing and hydrogels As described above, hydrogels have been used for cell encapsulation. The potential to modify both the chemical and mechanical properties exhibited by these materials makes them perfect candidates for the growth of tissues outside the body, prior to eventual implantation into a defect site inside the body. As a consequence, hydrogel-based structures have provided scaffolding for many different engineered tissues, ranging from bone through to brain. However, a major issue

Figure 4.7 Electrospun poly(caprolactone) fibres intended for use in tendon reconstruction (courtesy of Dr Anita Ghag). (a) Pump Vibrating technology 100 m Figure 4.8 Schematic of (a) pancreatic β -cell encapsulation and Ellis MJ, Grover LM. Encapsulation and fluidization maintains the viability and glucose sensitivity of beta-cells. *3(8): 1750-7.* (b) Bioreactor column Feeding vessel Peristaltic pump (b) bioreactor cultivation. (Adapted with permission from Nikravesh N, Cox SC, ACS Biomater Sci Eng 2017;

with hydrogels is that they are normally extremely weak during the gelation process, meaning that they will slump and lose their shape when cast. In order to get around this major issue, printed structures may be suspended in a secondary (often shear thinning) medium that provides both a level of support during the printing process and time for the hydrogel to develop sufficient mechanical integrity to support its own weight. Once this point has been reached, the structure can be removed from the supporting medium and washed prior to onward culturing. A wide range of substances have been used to provide support, including Pluronic and agarose; however, the most widely used method currently is known as free-form reversible embedding of suspended hydrogels (FRESH), which uses gelatin. The FRESH method utilises a macerated gelatin-based support matrix. The particulate nature of the gelatin means that the printed hydrogel (which may or may not contain cells) can be deposited within the bed and will be supported while the

mechanical properties exhibited by the as-deposited hydrogel become fully developed. The supporting matrix can then be melted (at 37°C) to leave the complex hydrogel structure. Other suspended printing methods have been developed that do not require the use of an animal-derived support medium (and that are therefore compatible with translation to the clinic) or the elevation of temperature to remove the supporting phase. One such method, suspended layer additive manufacturing (SLAM), uses a supportive matrix formed from hydrogel particulate systems that shear thin but exhibit rapid elastic recovery; this allows for the production of high-resolution prints that can be removed from the supporting bed by the application of a simple wash with water. This method enables the production of structures exhibiting complex morphology, such as the carotid artery (Figure 4.9), and can even be used to produce structures formed or modified from multiple material types, meaning that structures can be tailored with high resolution. With clinical relevance, SLAM has been used to manufacture osteochondral plugs containing both bony and cartilaginous regions. At present, these technologies are most likely to have an impact on disease modelling and drug candidate evaluation, but in the longer term they may emerge as key technologies facilitating tissue regeneration.

Fluid gel print bed Cell containing hydrogel Cross-linker (causes the construct to solidify) Figure 4.9 Schematic showing the formation of complex hydrogel structures using a suspended manufacturing process where a cell containing hydrogel is deposited into a supportive bed. This process allows for the production of hydrogels in complex geometries such as the carotid arteries shown here. (Adapted with permission from Senior JJ, Cooke ME, Grover LM, Smith AM. Fabrication of complex hydrogel structures using suspended layer additive manufacturing (SLAM). *Adv Funct Mater* 2019; 29 : 1904845.)

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