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BIOMATERIALS IN DENTISTRY AND MEDICINE

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ABSTRACT

The widespread use of biomaterials in medicine and dentistry is a relatively new phenomenon dating back to the 1950's yet, today, an estimated 20 million individuals have an implanted medical device.

Despite the huge impact that biomaterials have had on patients' quality of life, improvements in device performance and the development of alternatives to augment available therapies are continuously being sought. Clinical demand, advances in molecular and cell biology and the increased understanding of the role of the tissue-material interface on clinical performance has led to a metamorphosis of the biomaterials' field over the past 25 years. This has resulted in a change in the nature of biomedical devices from being biologically passive to actively integrated.

This chapter explores the development and application of biomaterials over the past 25 years, examining the current clinical demand, the scientific rationale, and the technical challenges to be overcome. As biomaterials are applied in reconstructive surgery and tissue regenerative therapies, these areas are explored with specific examples of recent developments and current research activity used to illustrate the changing perspectives.

INTRODUCTION

Surgical intervention is not always required when tissue is damaged because of the human body's ability to activate the wound response following tissue trauma. The site and magnitude of the tissue injury, however, does dictate the extent to which the original tissue architecture and functionality is restored. For example, minor injuries to bone and epithelial skin do not require intervention as these tissues retain the ability to spontaneously regenerate in a near like-for-like manner, whereas injury to other tissues (*e.g.,* articular cartilage, the pancreas, the spinal cord, the dermis of the skin, brain tissue, neural retina, cardiac muscle, lung or the kidney glomerulus) results in the formation of scar tissue which replaces the lost tissue mass but does not restore tissue architecture or biological functionality [1].

When there is gross, acute or chronic tissue-dysfunction because of extensive traumatic injury or disease (*e.g.* spinal-cord injury or heart disease) surgical intervention to repair or replace the affected tissue is required. The options available to the surgeon include replacement (transplantation), reconstructive or, in a few cases, regenerative surgery [2] but are largely determined by the extent of tissue damage, the anatomical location and function of the tissue and the age and general health of the patient. Millions of patients have benefited from these approaches but many of these treatments fall short of their clinical requirements and may also be associated with the onset of secondary diseases. For example:

1. Replacement or transplant surgery relies on the excision of the dysfunctional tissue or organ and its replacement with viable tissue or organ. The transplanted tissue is generally an autograft (within one individual from one site to another) or homograft/allograft (between different individuals of the same species). Autogenous tissue transplants are used for bone grafts, full-thickness skin grafts, microvascular grafts and arterial-by-pass grafting and remain the 'gold standard' as they typically produce superior clinical results [3-7] *e.g.,* 60 % of bone grafts required in spinal fusion surgery are autografts [8]. However, the harvesting of bone cells, skin or blood vessels requires the patient to undergo additional operations with their associated risks and for some patients they do not have suitable tissue for harvesting.

Allografting or transplantation from a donor is the most effective or only available treatment for many patients. Although allografts are primarily associated with organ transplants they also include bone marrow transplants for patients suffering from various forms of haematopoietic malignancy and corneal transplants for the restoration of vision. For patients with life-threatening end-stage organ failure of the lungs, kidney, heart and liver their only option is organ transplantation. However, allograft organ transplantation is associated with numerous risks including rejection, infection and the patient's requirement of life-long immunosuppressant therapy. In 2005, 27,527 organ transplants were performed in the U.S. [9] compared with 2,880 in the UK and Republic of Ireland in 2000 (Table 1) [10] but these figures do not come close to meeting the demand [11-13] (Table 2). In the U.S. suitable liver donors were found for 1 in 4 patients requiring a transplant in 2005 [9] while only 1 in 12 patients in need of a heart transplant in the UK and Ireland received a donor organ [14]. This situation has been exacerbated by the increase in the number of patients requiring transplants which increased by 5% in the U.S. between 2004 – 2005 while over the same time period the number of organ and tissue donations has increased by 3.5% [9] resulting in less than one third of all patients requiring a transplant being found suitable donor organs [15].

An increase in the availability of donor organs for transplantation would therefore have a major impact on health and this has driven a resurgence of interest in the potential of xenograft application. Xenografting is the transplantation of tissue from one species to another. Chemically-treated xenografts, such as the porcine heart valve, have been used clinically with wide acceptance for many years. More recently acellular porcine, bovine and horse tissue harvested from a variety of sources including the subintestinal submucosa [16-18] and bladder [19] have been clinically applied for a variety of applications [20, 21]. However, the transplantation of viable xenografts runs the risk of xenozoonose and porcine endogenous retrovirus transmission to humans. Additionally, viable porcine tissue transplants are rejected in animal models thus preventing their clinical application [14, 22].

Insert Table 1 here

Insert Table 2 here

2. The increase in life expectancy has led to a greater demand for reconstructive surgery and an extended durability of implants. In 1988 over 8 million surgical procedures were performed in the US alone to treat patients suffering from organ or tissue failure [26] at an estimated cost of 400 billion $US [27, 28] (Table 3). These figures are increasing partly due to an increase in life expectancy [29, 30] (Figure 1) but also because of a change in population dynamics *e.g.* the number of people >50 years in the U.S. was 25.7% in 1990, 27% in 1998 and is predicted to reach 32% by 2010 [31]. These changes have led to an increase in surgical interventions required to treat age-related degenerative diseases such as osteoporosis, atherosclerosis, degenerative disc disease and macular degeneration [32] (Table 4) and have also resulted in the need for implants to possess greater than 30-year survivability rates. Currently the mean lifespan of many cardiovascular prostheses is 15 years [33] (*e.g.* heart valves, bypass grafts), conventional hip replacements performed in patients less than 50 years of age have a 80% survivability rate 10 years postoperatively [34], while in the treatment of macular degeneration retinal pigment epithelial cell (RPE) transplantation has recently be explored [35].

Insert Table 3 here

Figure 1 here

Insert Table 4 here

3. Treatments for organ failure, such as kidney dialysis for acute renal failure and haemofiltration for acute liver failure (Septet^{TM}, Arbios Systems Ltd [40]), are only short-term solutions in the management of the deleterious effects of the dysfunctional organ on the patient's general health [13]. Acute renal failure affects about 200, 000 individuals in the U.S. and has a mortality rate of 55 - 70% even with haemodialysis support [41,42]. Although advances in the development of non-allograft whole organ kidney transplants are being made, they are not

expected to become clinical therapies in the foreseeable future. An extracorporeal kidney-assist device combines immobilised organ cells on a permeable membrane in a bioreactor and offers the advantage over conventional haemodialysis in that it aims to restore the readsorption and endocrine functionality of the kidney [43, 44]. A temporary Renal Bio-Replacement Therapy™ developed by Dr Humes (marketed by RenaMed as RBI-01 but acquired from RenaMed Biologics, Inc. by Nephrion Inc., in a purchase of its assets in 2007) successfully completed Phase II clinical trials with a 72% improvement in the 28-day survival rate of patients receiving renal bioreplacement therapy compared with conventional therapy [45,46].

4. Diabetes is one of the most serious challenges in healthcare world-wide as the number of diabetic patients is predicted to increase to 220 million by 2010, a doubling of its 1994 prevalence [47]. Recently developed pharmacological therapies show improved control of blood glucose levels in the treatment of Type II diabetics (*e.g.* Liraglutide (NN2211) [48, 49]) but Type I diabetics are dependent on insulin injection which results in fluctuations in their physiological blood glucose levels. Elevated blood glucose levels triggers the onset of secondary microvascular and neurologic complications such as cardiovascular disease, glomerularnephritis and proliferative diabetic retinopathy (PDR) [50]. PDR is a major cause of blindness globally affecting 4 % of the world's population (with a projected increase to 5.4% by 2025) [51, 52]. It affects 4.1 million adults over 40 years in the United State (predicted to increase to 6.1 million persons by 2020) with 300 000 of these adults expected to become legally blind as a consequence of PDR within 3 years [53]. Recent approaches to PDR management include oral administration of protein kinase C (PKC) inhibitors (PKC β [54, 55], candesartan, cilexetil and octreotide) [56], which are under Phase III clinical trials [57], anti-VEGF [58-61] and sustained-release steroid implants (Retisert [62]). Although the latter approach reduces retinopathy its clinical applicability is questionable as it is associated with cataract formation and a 33% incidence of glaucoma [63]. The intense clinical management of glycaemia levels however reduces the risk of microvascular and neurologic complications of Type 1 diabetes. Normoglycaemic levels can be achieved by either increasing the number of daily insulin injections or by treatment with an external insulin pump with dosages being adjusted by self-monitoring glucose

measurements [64]. There is, therefore, a demand for approaches to Type I management that control glycaemic levels without relying on patient monitoring.

5. The presence of long-term, indwelling implants predisposes the patient to the lifelong risk of infection and an acquired hypersensitivity [65, 66] to the implanted material necessitating removal of the implant.
6. In paediatric cases the inability of prosthetic substitutes to grow has also limited their widespread clinical application. Additionally, growth of the individual is usually impaired following organ transplantation as a side-effect of steroids used as immunosuppressants [67].

There is, therefore, a need for restorative device designs that improve implant durability and alternatives to augment the currently available clinical therapies. The two main approaches being taken to address these needs are: the development of reconstructive materials with enhanced biological integration and the development of materials designed to aid tissue regeneration.

CLINICAL APPROACHES

REPARATIVE RECONSTRUCTIVE SURGERY

a. Biomaterials in reparative reconstructive surgery

The use of biomaterials (or medical devices or prostheses) in reparative and reconstructive surgery in medicine and dentistry to treat, augment or replace dysfunctional tissue is not a new approach and in fact can be dated back to before 800 BC (Table 5). However, with improvements in aseptic surgical techniques and technological advances in biomaterials science there are now more than 2,700 different kinds of medical devices available [68] with an annual global market value exceeding 36 billion $US [69] with a predicted growth rate of 12% per year [70] (Table 6). Prominent applications of biomaterials include (Figure 2): orthopaedics [39] (*e.g.* hip and knee joint replacements [66, 71-75], bone cements [76, 77], bone fillers [78-80], fracture fixation plates [81-83], and artificial tendons and ligaments [84-87]), cardiovascular [38] (*e.g.* vascular grafts [6, 88-91], heart valves [91], pacemakers [92], stents [93]), ophthalmics [94,95] (*e.g.* corneal implants and artificial corneas [96, 97] and intraocular lenses [98, 99]), dental implants [100] and cements [101-104], cochlear implants [105], tissue adhesives and sealants [106], drug-delivery systems [107] and sutures [88, 108].

Insert Table 5 here

Figure 2 here

Insert Table 6 here

b. Factors governing the clinical performance of implantable biomaterials

Reconstructive surgery relies on the excision of damaged tissue and its replacement by a non-viable, biocompatible biomaterial substitute or prosthesis. An implanted material's biocompatibility, defined as '*the ability of a biomaterial to perform with an appropriate host response in a specific application*' [148], is pivotal to its clinical success. Numerous factors influence a material's biocompatibility as illustrated in Figure 3. The relative importance of each of these factors is dependent upon the application but is primarily influenced by the material-tissue response, contact duration, anatomical site and functional requirements.

Figure 3 here

For a material to be biocompatible, it must:

1. Meet the functional demands of its application *e.g.* be capable of maintaining a load over a few months if it is to be used as a bone plate to immobilise a fracture [149]; reduce water evaporation if it is to be applied as a wound dressing [150,151]; have an optimal refractive index if it is to be used as a vitreous replacement in the eye [152].
2. Elicit an appropriate host response. This allows for complete inertness, should that be desirable or attainable, but it equally allows for specific biological activity that produces a beneficial effect for the recipient. The host response is the reaction of the tissue to the implant, which controls the physiological performance of the patient following placement of the implant and is itself controlled by the characteristics of the material especially by the material's chemical stability at the anatomical site.
3. There is also the need to consider the site of application (*i.e.* specific applications). The biocompatibility characteristics required of a material are related not only to the functional requirements but are also governed by the local physiological environment. The latter varies anatomically and there is therefore no such thing as a

biocompatible material *per se* (*e.g.* the properties of an intraocular lens are quite different from those required of a vascular prostheses).

In investigating the clinical applicability of a material the assessment of its mechanical properties, its wear and degradation (originating from both mechanical and biochemical sources) and the material-tissue interfacial response, at the intended site of implantation, provide indications of deficiencies in biocompatibility. Inappropriate materials' selection has resulted in gross patient disfigurement and fatalities. For example, in the mid-80's 25,000 patients had a temporomandibular joint (TMJ) device, composed of a carbon-alumina porous composite (Proplast®) and a PTFE film, implanted. Following implantation, all of these devices failed due to the build-up of PTFE fragments because of frictional wear debris. The wear debris triggered a giant cell foreign body response causing severe inflammation and extensive bone erosion [153]. For all of these patients re-operation to remove the implant was necessary. Nearly all of the patients were subsequently left unable to chew and were in constant pain whilst other patients also suffered severe facial deformities. The use of zirconia had been advocated for femoral head replacement [154] however the quality of zirconia is highly dependent on the precise manufacturing process used. A change in the manufacturing process in 1988 led to 1 in 3 devices failing [155] as a result of post-implantation grain pull-out increasing the surface roughness 20-fold and by the accelerated transformation of the zirconia from the tetragonal to monoclinic phase in the central area of the head resulting in fracture [156, 157]. Another example of the inappropriate use of a material, due to leachate release, was the application of glass ionomer cement (GIC) in the repair of a skull-base defect following cranial surgery. GICs are used as bone cements in other non-loading applications but the proximal placement of the aluminium-based cement with brain tissue resulted in two fatal cases of post-otoneurosurgery aluminium encephalopathy due the blockage of nerve conduction by released aluminium [158]. These examples show the need for careful consideration of the tissue-material interactions in their entirety for each application.

From the perspective of mechanical compatibility polymeric materials have historically been favoured for soft-tissue replacement and metals or ceramics for load-bearing hard-tissue replacement because these classes of materials have

physical properties similar to that of the tissues they are replacing as demonstrated in Table 7. However, the indicated functional properties of tissues are based on static measurements, which although a useful guideline in material development, do not indicate the influence of cyclic loading and shear. Functional material assessment must therefore also reflect long-term biomechanical performance.

Insert Table 7 here

From a cellular perspective implanted materials from non-biological sources are not attacked by the immune system and have therefore been classified according to the histology at the biomaterial-tissue interface following implantation as inert, resorbable or bioactive [168] (Table 8). Up until the late 1970's it was considered essential for a material to be inert (or pseudoinert) in order to achieve long-term clinical patency. The implantation of an inert biomaterial perturbs the normal wound healing response (Figure 4) and initiates a sequence of events equivalent to a foreign-body reaction (with the exception of titanium which becomes closely approximated to 'nearly normal' host tissue with no intervening fibrous capsule). The sequence of events starts with an acute inflammatory response (Figure 5) and leads, in some cases, to a chronic inflammatory response and/or granulation tissue development, a foreign-body reaction (a special form of non-specific inflammation) and fibrous encapsulation [169]. Fibrous encapsulation walls off the implant from the surrounding tissue by the formation of a fibrous capsule that is formed in the same manner as scar tissue in the normal wound healing response *e.g.*, PMMA bone cement [170-172] and silicone breast implants [173]. The duration and intensity of each of these phases is strongly influenced by numerous factors [174, 175]: the primary chemical structure and composition [176], the surface free energy [174, 177-179] and charge, the implant size, shape [180], porosity and roughness [174, 176] and by the invasiveness of the implantation procedure. The capsule is maintained due to the continued presence of the implant and the capsule thickness is influenced by factors including [174]: motion between tissue and implant with thickness increasing with relative motion [170], chemical activity of material (*e.g.* corroding metals or leaching of polymers where the thickness of the capsule is proportional to the rate of released chemical irritant [181]), the presence of electrical current (*e.g.* the ends of the stimulating electrodes in a pacemaker with the thickness of the capsule being

proportional to the current density), and the shape of the implant (*e.g.* edges and sharp surface features) also increase capsule thickness [180]. In all cases if the implant is removed the capsule may collapse into a residual scar or be completely remodelled.

Insert Table 8 here

Figure 4 here

Figure 5 here

Wound repair following the implantation of a resorbable material (Table 8) is influenced by the rate and mode of resorbtion and by the tolerance of the local tissue to the degradation products. The host tissue may therefore treat the material as a component of the 'normal' tissue and passively resorb the material or it may be walled-off in a manner analogous to the inert materials. In the latter case following resorbtion of the material a collapsed scar forms at the implant site that subsequently remodels.

During the 1980's numerous studies evaluating the material-tissue interface revealed that increased implant survivability was achieved when there was co-operative interaction between the device and the local tissue [226, 227]. The recognition of the benefits of biological interaction has transformed the biomaterials' field over the last 20 years. Bioactive materials are designed to elicit specific, beneficial responses that may be brought about by encouraging tissue ingrowth or adhesion. Tissue ingrowth is a desired response for many implants and has been seen to occur with a wide variety of materials, including metals, ceramics, and polymers. Cellular elements must adhere to the graft surface for ingrowth to occur which is affected not only by the mechanical stability of the implant-tissue interface but also by the surface chemistry, topography and bulk morphology of the implant. For example, tissue in-growth occurs in interconnected porous materials but the nature of the in-growing tissue is dependent on the minimum size of the interconnections between pores. For example, soft tissue will be found in pores with interconnections as small as 1 - 5 μm, mineralized tissue begins to form between pores of 50 and 150 μm while

osteonal bone grows into pores of ≥ 250 μm [228]. An alternative approach, tissue adhesion, is encouraged when there is a close approximation of the tissue and implant. Tissue adhesion occurs by two mechanisms: tissue integration and through surface active responses. In tissue integration cells are encouraged to bind onto proteins adsorbed to the implant surface (Figure 6) [229] while adhesion, induced by surface active responses, is accompanied by a chemical alteration of the implant surface with true tissue bonding resulting in a continuous gradation of properties (both structural and compositional) across the implant-tissue interface.

Figure 6 here

c. Approaches to improving device performance in reconstructive surgery

Many of the developed 2nd generation biomaterials are bioactive materials, or pseudo-inert materials with a bioactive coating, in which improvements in their long-term patency have been attained by encouraging integration between the material and local tissue. For instance:

1. A total hip replacement (THR) is comprised of a femoral stem, femoral head and an acetabular cup [75]. Survival rates for conventional total hip replacements in patients over 65 years at the time of implantation show 80% patency 20 years postoperatively [230]. However, the 15-year patency rates for patients < 50 and < 40 years at the time of implantation are 60 and 54 %, respectively [231]. The significant reduction in the survivability rates in younger more active patients is primarily associated with bone resorption at the implant interface. Other factors influencing patency include prior history of hip fracture and revision with prosthetic femoral stem replacement procedures only being able to be performed twice on the same patient [232] as the femoral bone is weakened by the implantation procedure itself and there are significant problems encountered in removing prosthetic acetabular cups without damaging the pelvic girdle.

   In all patients implant survivability is affected by stress-shielding [233], the stability of the fixation of the femoral stem and the abrasive wear resistance of the femoral head and acetabular cup. Mechanical stimulation is necessary for healthy bone maintenance but because of the modulus mismatch, between the

prosthetic stem and femoral bone, tissue proximal to the prosthetic stem is stress-shielded and resorbed. This leads to aseptic stem loosening which further aggravates bone tissue destruction and accounts for 79 – 82 % of THR failures [234]. Recent attempts to resolve this modulus mismatch have addressed the processing of titanium alloys [235]. The renewed interest in titanium alloys has also been driven by the significant number of patients becoming hypersensitive to stainless steel and cobalt-base orthopaedic joint replacement components [236], and due to concerns regarding systemic toxicology and metal implant debris-induced tumourgenesis (*i.e.,* Cr, Co, Ni are carcinogenic in rodents [237]).

Avenues taken to improve the long-term performance of THRs include:

- Micro-patterning of the femoral stem to promote cell adhesion [238, 239] and the development of bioactive coatings [240] and cements [241, 242]. These latter approaches have significantly contributed to improvements in patency rates (Table 9) due to improvements in tissue integration and adhesion of the implant with the bone tissue.
- Abrasive wear of UHMWPE acetabular cups is an additional significant cause of implant failure as it results in UHMWPE particulate-induced osteolysis necessitating removal of the prosthetic acetabulum. It is hoped that the implementation of changes in the manufacturing of UHMWPE acetabular cups, aimed at reducing free radical formation, will extend clinical survivability [243, 244]].
- Alternative prosthetic acetabular cup designs [245] have received FDA approval *e.g.,* a highly crosslinked polyethylene-on-metal (approved 1997) and an alumina-on-alumina (approved 2000). Concerns raised over the 0.026% failure rates due to liner fractures with 1st generation alumina cup designs have now been reduced to 0.004% with the 3rd generation designs [246], while the coupling of an alumina cup with an alumina liner shows 50 – 200 times less wear, compared with UHMWPE on cobalt chrome or UHMWPE on alumina ceramic [246] and show 5-year patency rates of 97.4%.

Insert Table 9 here

2. Improvements in the interfacial bonding, aesthetics, fracture toughness and flexural strength of posterior dental fillings are also being sought. Currently materials such as composites and resin-modified glass ionomer cements (RMGICs) [248-251] have been advocated in place of amalgams but shrinkage of resin-modified GICs away from the tooth-material interface results in secondary caries [252]. Although conventional GICs show good interfacial bonding [253, 254] their fracture toughness and flexural strength are insufficient for use in posterior Class I and II restorations [255]. New approaches to improving the mechanical properties of conventional GICs include ultrasonic setting [256] and the use of ceramic fillers [257, 258].
3. In other areas of biomaterial application, the exploitation of the ever-increasing understanding of the cell biology and biochemistry of the biomaterial-tissue interface is facilitating the production of advanced bioactive materials. This is reflected by the increase in the worldwide global market for bioactive materials *i.e.* $377.7 million in 2004, $431.4 million in 2005 and an estimated $473.9 million in 2006 [259]. Bioactive ceramics and glass-ceramics designed for orthopaedic application (*e.g.*, hydroxyapatite and Bioglass®, apatite/wollastonite (A-W)) have to date had limited clinical application due to their poor mechanical properties [260, 261] resulting in the focus of orthopaedic development being aimed at improving the chemical bonding of bioactive cements with the bone tissue, the production of aluminium-free bone cements for spinal and cranial surgical applications and glass ceramics.
4. Many diseases of the cardiovascular system require the use of prosthetic materials to replace valves [263] and vascular prostheses [263]. Atherosclerosis is the largest cause of mortality in the U.S. [264] and results in the formation of plaque-like lesions which progressively block the blood vessels as a result of the thickening and hardening of arterial walls. Synthetic blood vessel substitutes such as Dacron®* and ePTFE♦ grafts are clinically successful when used in high-flow, low-resistance vessels [88, 119, 265] (>10 mm) but show poor patency rates when used to graft small diameter vessels [88, 89, 266, 267] (< 6mm) (Table 10). Small-diameter grafts are prone to early thrombosis because of their lower flow rates and the higher resistance in their outflow vessels with

* Dacron®: polyethyleneterephthalate (PET)
♦ ePTFE : expanded PTFE (polytetrafluoroethylene); Trade names: Teflon®, Gore-Tex® or Impra®

thrombogenicity and stenosis due to intimal hyperplasia being major causes of graft failure [267]. A variety of clinical applications including lower-extremity bypass procedures and coronary artery bypass grafting (CABG require small-diameter grafts (<6 mm)) therefore continue to rely on the use of the autogenous saphenous vein or internal mammary artery (IMA) [119] (Table 10). Bypass grafts are however prone to restenosis proximal to the graft-bypass junction [268] and frequently require secondary surgical procedures *e.g.* stenting and secondary graft procedures which themselves are associated with restenosis, significantly increased mortality rates due to the extended operative times, limited supply of suitable autogenous vessels.

In the search for an ideal synthetic blood-vessel substitute numerous approaches aimed at improving their long-term patency have been attempted *i.e.,* the modification of the luminal surface of the graft through the use of heparin bonding[219, 269], pre-implantation endothelial cell seeding [6, 270-272] and surface modification to encourage endothelial ingrowth [146, 273]. Advances in haemostasis, thrombosis and vascular biology have also provided a basis for the development of molecular-designed anticoagulant interfaces and the production of synthetic inhibitors of coagulation and thrombocyte function aimed at improving the haemocompatibility of cardiovascular implants. Additionally the development of hybrid constructs using synthetic materials to form the adventitia and media with a pre-seeded layer of endothelial cells on the inner-luminal surface in contact with the blood show good results with respect to patency [269, 270].

Insert Table 10 here

Although these developments in the design of reconstructive biomaterials are extending the longevity of devices, evidence suggests that if dysfunctional tissue can be induced to regenerate or be replaced by newly synthesised tissue that this would offer a significantly superior clinical therapy, would reduce the incidence of secondary complications, negate hypersensitivity issues and hugely impact on paediatric medicine.

REGENERATIVE MEDICINE

From a biochemical and physiological perspective, tissues metabolise, synthesise and secrete various substances in response to local stimuli. Therefore, the use of non-viable materials to replace tissue results in the loss of biological functionality and/or responsiveness. This loss of biological functionality, the shortfall in donor organ and tissue availability for auto- and allografting and the risk of transgenic transfer from viable xenografts [14] has led to renewed interest in the application of resorbable materials and the development of an entirely new approach to regenerative medicine: tissue engineering. Potential strategies of regenerative medicine include stem cell transplantation, implantation of bioartificial tissues synthesised in the laboratory and the persuasion of the body's own cells to regenerate by rendering the injury environment and/or responding cells regeneration-competent [28]. Tissue regenerative applications include tissues such as skin, cartilage and tendons, ligaments, bone, blood vessels, heart valves, myocardial patches and organs such as heart, pancreas, kidney and liver. To date regenerative therapies for skin and cartilage replacement have been the most successful.

The market for regenerative medicine, although still in its infancy, is rapidly growing and remains an intense area of research that is being driven by the maturation of patents, estimated revenues (*e.g.,* from the cell therapy market alone revenues are expected to exceed 30 billion $US by 2010 [277]) and clinical demand (*e.g.,* the increasing number of patients worldwide presenting with ulcers (*i.e.,* diabetic ulcers 1,745,000; venous ulcers 2,342,000; pressure ulcers 4,440,000) and hospitalised with burns (1,785,000)). In the past 10 years more than 3.5 billion $US have been invested worldwide in research and development, mainly by the private sector, in the US [278, 279]. In 2001 annual investment in R&D was 580 million $US which by 2007 increased to 850 million $US [280]. The slow uptake of research interest in the tissue engineering field outside of the U.S. pre-2000 resulted in over 70% of the global tissue engineering patents filed between 1980 – 2001 being owned by US-based researchers, followed by 18% in Europe (led by Germany and the UK) and 6% in Japan. This lack of investment has also resulted in the disparity of 55 of the 66 registered tissue engineering companies being US owned (*e.g.,* Advanced Tissue Sciences, Genzyme*)* compared with 11 European (*e.g.,* Fidia Advanced Biopolymers (Italy), Smith and Nephew (UK), Amaxa (Germany) BioNova (UK)). To date,

however, only a few tissue-engineered devices are available in the marketplace, primarily in the areas of skin and cartilage regenerative therapies (Table 11) although other therapies are currently at the clinical trials stage [281] (Table 12).

Insert Table 11 here

Insert Table 12 here

Although the term regenerative medicine is often used synonymously with tissue engineering there are application and approach differences that warrant discrimination. This is further confused by the numerous definitions of tissue engineering cited in literature. Tissue engineering has been defined as:

- '*an interdisciplinary field that applies the principles of engineering and life sciences toward the development of biological substitutes that restore, maintain, or improve tissue function or a whole organ'* [26]
- '*the understanding of the principles of tissue growth, and applying this to produce functional replacement tissue for clinical use'* [308]
- '*the application of the principles and methods of engineering and the life sciences toward the fundamental understanding of structure/function relationships in normal and pathological mammalian tissues and the development of biological substitutes to restore, maintain, or improve function'* [27]
- '*the persuasion of the body to heal itself through the delivery, to the appropriate site, of cells, biomolecules and/or supporting structures'* [309]

If regenerative medicine is considered as being subdivided into: stem cell transplantation, immunoencapsulated cell transplantation, *in vitro* tissue engineering and *in vivo* tissue regeneration (Figure 7) then the underlying principle of the first two approaches is the restoration of biochemical function whilst that of the latter two approaches, which are discussed, is the restoration of architectural, mechanical and biochemical function. Distinction of these approaches in this manner enables a clearer perspective of each areas device design requirements.

In vivo Tissue Regeneration

In this context, various device applications that are designed to induce *in vivo* regeneration by the body's own cells have been identified:

1. Biomaterial barriers to block molecular signals that stimulate scar formation or immune rejection. For example, adhesions (fibrous scar tissue) can form following abdominal and thoracic surgery between the skin and internal organs as a consequence of the normal wound healing response. The presence of a resorbable, non-cellular adhesive polymer film prevents the deposition of a fibrin-rich clot between these layers of tissue preventing the development of adhesions [310-312].

Figure 7 here

2. Surface modification of a material may be topographic or chemical. Topographic modification of surfaces includes the modification of the surface texture [313] or roughness [314, 315] which influences cell adhesion, proliferation, orientation and biochemical activity. Chemical modification of surfaces includes the immobilisation of bioactive ligands that may be micro-patterned to modulate cell behaviour [316-320] (biomimetic materials):
   - receptor-mediated control of single and multiple cellular morphologies and functions *e.g.*, by RGD [321, 322] and YIGSR [323] sequences [273]
   - controlled growth factor/cytokine release from devices or transplanted cells to control tissue regeneration:
     - coating or incorporation of bone morphogenic protein on or into bone void fillers [324-327]
     - covalent immobilisation of growth factors *e.g.,* epidermal growth factor (EGF) [328, 329] and VEGF [330, 331]
     - a combination of growth factors such as VEGF and BMP-2 improves bone formation and bone healing [332]
2. Scaffolds or matrices to control and guide wound healing and tissue regeneration. Scaffold material options are diverse and may include:
   a. Autograft, allograft, demineralised bone matrix
   b. Acellular xenografts: *e.g.,* SIS [16-18, 21]
   c. Biopolymers: *e.g.,* collagen [333], fibrin, hyaluronic acid, alginate [334, 335], chitin/chitosan [336-339]

d. Ceramics: *e.g.,* Coral, hydroxyapatite [340], Tricalcium phosphate
e. Synthetic polymers: Poly(lactide) PLA [341], Poly(lactide-co-glycolide) (PLG) [342], caprolactones, methylcellulose, polyesterurethanes [146]
f. Glasses and glass ceramics *e.g.,* resorbable Bioglass® [121, 343]
g. Composites: *e.g.,* Poly(lactide-co-glycolide)/hydroxyapatite [344], collagen-hydroxyapatite [345], collagen-calcium phosphate [346], polyurethane /poly(lactic-co-glycolic) acid [347]
h. Smart matrices: scaffolds combined with immobilised bioactive ligands that induce tissue ingrowth *in vivo* as indicated in c. above.

The following discussion is primarily limited to the use of scaffolds fabricated from ECM polymers, *i.e.* collagen, and its derivative gelatin, hyaluronic acid, fibrin, elastin and composites of these materials, for *in vivo* tissue regenerative applications. The primary advantages of this approach are the reduced number of operations required (*i.e.* no donor tissue is required to be harvested) and therefore reduced recovery time for the patient, there are no issues with regard to cell sourcing, and the degradation products of naturally-derived ECM polymer are readily cleared by the host and are non-immunogenic.

In vivo tissue regeneration relies on the implantation of a biomaterial scaffold into which local or circulating regeneration-competent cells migrate and proliferate. The success of such an approach relies on the inter-relationship between the cell type(s) required to colonise the scaffold, the scaffold-tissue interface and the scaffold.

Insert Table 13 here

The regenerative capacity of tissue cell populations is varied and classified, as indicated in Table 13, as continuously regenerating (renewing) (*e.g.,* the lining cells of the gastrointestinal tract (every 3 days) or the dermis (every 14 days) [349]), inducibly regenerative (expand rapidly in response to tissue trauma *e.g.,* osteoblasts) or static (these cells appear to be non-regenerative *i.e.*, they have become terminally differentiated). The success of *in vivo* tissue regenerative strategies may be predicated by the presence of cell populations with inducible regenerative capacity within the tissue of interest *i.e.,* adult stem cell and progenitor cell populations (*e.g.,* epithelium of the respiratory and digestive tracts, liver, skin keratinocytes) or tissues

that can regenerate by compensatory hyperplasia (such as the liver and the β-cells of pancreatic islets) [28]. However, recent evidence suggests that some regeneration of reputedly static cell populations, *i.e.,* neural [350, 351] and heart [352], can occur under specific conditions and a degree of nerve regeneration [353], although imperfect, has been achieved using an *in vivo* tissue regenerative template [354]. Therefore, the potential clinical applicability of this approach is still speculative.

The scaffold for *in vivo* tissue regeneration must in general fulfil the following criteria [355, 356]:

1. Biocompatible, resorbable materials that resorb in a controlled manner
2. Structure should be open with high porosity and capable of inducing rapid angiogenesis and cellular invasion
3. Manufacturing must be easy, reliable and reproducible
4. Possess appropriate functional properties including appropriate mechanical properties, adherence to the surrounding host tissue, provide a mechanically stable architecture on which cells can proliferate and transfer appropriate physiological mechanical stimuli to the invading cells.

a. Biocompatible, resorbable materials for *in vivo* tissue regenerative scaffolds

The natural scaffold in the body is the extracellular matrix (ECM) the composition and structure of which varies from one tissue to the next *e.g.,* the basal lamina (basement membrane) directly underlying epithelial cells contains laminin, collagen, fibronectin, vitronectin whilst stromal tissue (interstitial matrix) contains matrix-secreting cells (fibroblasts, osteoblasts), collagen, elastin, fibrillin, fibronectin, vitronectin, GAGs[*], glycoproteins and regulatory proteins. Typically these matrices are highly hydrated macromolecular networks that may be envisaged as fibre-reinforced composites composed of various amounts of fibrillar proteins (*e.g.*, collagen (Types I, II and III) and elastin), glycosaminoglycans (*e.g.*, hyaluronic acid, chondroitin-4-sulphate, chondroitin-6-sulphate, dermatan sulphate, heparin and heparin sulphate) and adhesion proteins (*e.g.,* fibronectin and laminin) [348]. The physico-mechanical properties of the ECMs are largely determined by these matrix-forming polymers as they control the tissue integrity, physiology and mechanical

[*] GAGs = glycosaminoglycans

properties, *e.g.,* collagen is primarily responsible for the tensile strength of tissue [348], but the ECM polymers also play a crucial role in cell behaviour. The ECM influences cell adhesion, proliferation, migration, differentiation and apoptosis via an array of transmembranal cell surface receptors including integrins [357] (such as the $\alpha 5\beta 1$ integrin that binds to RGD sequences that are found on several ECM molecules including fibronectin), proteoglycans receptors (*e.g.,* CD36 and CD44) and non-integrin laminin receptors [323] (that bind to sequences such as YIGSR in laminin) that transmit signals intracellularly via the cytoskeleton modulating gene expression [358]. For example, integrins on the surface of cells are low affinity receptors that are present in high copy numbers so that, in general, they can bind weakly to a range of different but related matrix molecules promoting cell-cell interactions and cell-ECM matrix binding [348, 359]. Cell proliferation and differentiation are also modulated by various soluble growth factors and interleukins [360]. Scaffolds for *in vivo* tissue regeneration are not only required to replicate the multifaceted physicomechanical functions of the ECM but are also required to modulate the cell-material interfacial response in a manner analogous to bioactive materials such that specific cell phenotypes adhere to and proliferate on the scaffold synthesising *de novo* tissue-specific ECM which then acts as the tissue regenerative template.

As materials intended to be used as matrices in tissue engineering have to imitate the properties of the tissues that they are replacing it is reasonable to explore the use of these polymers in the development and design of ECM analogues. Physically or chemically modified naturally-derived hydrogel-forming materials, *e.g.,* hyaluronic acid, collagen and gelatin, have frequently been used in tissue engineering applications (Table 14) because they are either components of, or have macromolecular properties similar to, the natural ECM. Three key characteristics of the degradation and resorption process of these materials influence performance:

i. The rate at which the scaffold loses its mechanical properties
ii. The rate at which the scaffold is removed from the implantation site
iii. The nature and concentration of the soluble products that are released into the site as the material is broken down.

The controlled degradation of the mechanical properties alone is a major challenge but in general, most design strategies tend to extend the degradation time over months in order to minimise the risk of early failure [349].

b. Scaffold morphology

One of the primary functional roles of an *in vivo* tissue regenerative scaffold is the definition of the area on or in which new tissue can be laid down by providing structural support and voids. The bulk morphology of the scaffold guides the structure of newly synthesised tissue by controlling its size, shape and vascularisation [361] while the microporosity of the scaffold (pore size, pore shape and volume fraction) affects the rate of the fibrovascular ingrowth [362, 363], a key determining factor in governing the inflammatory response [364].

Insert Table 14 here

Microporosity has long been known to influence cell behaviour at the material-tissue interface *e.g.* high porosity in large diameter vascular prostheses such as ePTFE (IND > 45 μm) encourages neoinitima formation promoting clinical performance [407, 408]. Cellular adhesion and growth on scaffolds and phenotypic expression have also been found to be influenced by pore size and distribution in a cell-type dependent manner [409] (Table 15). Heterogeneity in the pore size and distribution leads to patchy cell adhesion which results in the production of a biomechanically inferior ECM compared with cell growth and ECM production on scaffolds with a uniform pore structure [410]. Additionally, while the shape of the pores affects cell coverage of the scaffold surface *i.e.*, cells aggregate into spherical structures on scaffolds with equiaxed pores while on scaffolds with elongated pores the cells align with the pore axis resulting in reduced biosynthetic activity. Scaffold chemistry and compliance also influence cell behaviour *e.g.,* the *in vitro* seeding of chondrocytes on Type I and Type II collagen scaffolds of equivalent bulk porosity and pore sizes results in differing cell morphologies and biosynthetic activity [386] while the *in vitro* seeding of human mesenchymal stem cells (hMSC) on a collagen-coated polyacrylamide gel with varied degrees of crosslinking, and hence elasticity, results in the hMSCs being induced to differentiate into different tissue lineages [411].

Insert Table 15 here

The scaffold provides the initial surface and mechanical support onto which cells can grow and provide pathways for mass transport. In all settings the mass transport of metabolic substrates (oxygen, glucose and amino acids) into the bulk material and the clearance of products of cell metabolism (carbon dioxide, lactate and urea) are critical for cell survival. This flux of metabolites in and out of most metabolically active tissues is primarily influenced by passive diffusion along concentration gradients. Because the diffusion of oxygen is relatively slow and its consumption high its local tissue concentration becomes the primary limiting factor in cell survival. In metabolically active tissue, the local oxygen concentration is approximately 0.07 mM and oxygen diffusion distances between a capillary lumen and a cell membrane is 40 – 200 μm [349]. Therefore, the thickness of a non-vascularised graft to support cell viability in its central region will be limited by the local oxygen tension. Mathematical modelling of this suggests that a 1 cm thick graft will support 4 times as many viable cells as a 2 cm thick graft but that this number is still 100 – 1000 fold less than the number of cells found in bone or bone marrow aspirates [349]. Potential strategies for overcoming this diffusion barrier are the incorporation of nanostructural features to aid mass transport and the promotion of angiogenesis by the release of angiogenic factors from the scaffold in a spacio-temporally controlled manner at a rate commensurate with progenitor cell infiltration so that the new vasculature can support the mass transport requirements of the invading connective cells [415].

c. Approaches to scaffold manufacture

A major goal in fabricating scaffolds for tissue regeneration is the accurate control of pore size and porosity (>90%) within optimal limits. Various fabrication routes have been applied to address these design requirements including salt leaching [416, solvent evaporation by freeze drying [417-420], solvent-casting and particulate leaching [421, 422], solvent-casting and critical point drying [423], supercritical fluids [424], woven/non-woven fibres [199], membrane lamination [425], fibre bonding [416, 426], phase inversion processes such as liquid-liquid phase separation and liquid-solid phase separation [427], electrospinning [428, 429], *in situ* polymerisation [430], melt molding [431], sintering of compacted powders, 3-D

printing techniques [432, 433], fused deposition modelling and sublimation [434]. Particulate leaching, freeze drying, gas infusion and phase separation fabrication methods lead to the creation of isotropically distributed voids and connected pores while solid free-form fabrication methods including 3-D printing processes and stereolithography create strategically orientated channels and pores with defined macroscopic shapes.

A combinatorial approach of phase separation and freeze-drying is frequently applied in the production of porous hydrogels. In the case of hydrogels, where water is the solvent, ice crystals formed during the freezing process are removed by sublimination during freeze-drying producing pores. The size and number of ice crystals formed during the freezing process govern the diameter, shape and distribution of pores formed in the scaffold [390]. The number, size, homogeneity and rate of growth of ice crystals, and consequently the 3-D porous network, is in turn influenced by the polymer volume fraction, sample volume, rate of freezing and solvent [419]. As each of these 'recipes' possesses a unique heat-transfer rate the scaffolds produced will display diverse morphological and bulk properties.

d. Scaffold functional requirements

Initially a scaffold needs to function in a manner analogous to the tissue that it is replacing and therefore it must possess the appropriate mechanical properties as with conventional replacement materials. This results in two conflicting design parameters in that the strength of a bulk material is reduced by the presence of voids whilst a scaffold's porosity is necessarily high for cell infiltration. Additionally, as cells infiltrate the scaffold they must also be exposed to a combination of biochemical and biomechanical cues reminiscent of that found during embryonic development for tissue-like architectures to be formed. Biomechanical interactions, or mechanotransduction, between the ECM and cells stimulation of cells influences tissue formation, cell adhesion, shape, intracellular biochemistry and gene expression [435-439] which, when in conjunction with exogenous growth factors such as TGF-β, have been shown to stimulate increased ECM synthesis by smooth muscle cells in Type I collagen gels *in vitro* [435]. Stress-induced cell behavioural changes, including cytoskeletal traction, have also been induced by scaffold microtopography

[440], which results in enhanced responsiveness to surface-tethered adhesive proteins such as fibronectin.

IN VITRO TISSUE REGENERATION

Recent advances in the development of small-diameter artificial arteries are discussed here to illustrate the impact of *in vitro* biomechanical and exogenous biochemical conditioning on the mechanical properties of *in vitro* tissue engineering scaffolds [441-443] (Table 16). Other studies have also shown the impact of biomechanical conditioning on cell proliferation, biosynthetic activity and phenotype in cartilaginous and mucoskeletal tissue and on cardiomyocytes and cardiac fibroblasts [444].

The autologous saphenous vein or left internal mammary artery are generally harvested for coronary artery bypass surgery with clinical patency rates of 74 and 88 % at 5 years, respectively. Differences in the patency rates have been attributed to compliance mismatch of the vessels which leads to turbulent flow at the anastomoses and anastomotic intimal hyperplasia. However, 10 – 40% of patients do not have a suitable vessel for harvesting due to size mismatch, previous procedures or venous disease and, as the patency rates of current synthetic grafts are poor in small calibre blood vessels, there is a need for an alternative. The mechanical requirements of completely biological tissue-engineered grafts are required to not only demonstrate physiological burst pressure and compliance but they must also be resistant to rapid degradation and fatigue-induced aneurysm formation *in vivo* [445] if graft longevity is to be achieved. The impact of fabrication on both the mechanical properties and *in vivo* performance of tissue engineered small diameter vascular grafts are presented in Table 16 and their mechanical properties compared with those of native tissues. Comparison of the burst strength of native versus decellularised porcine carotid arteries indicates the impact cells, primarily the smooth muscle cells, have on the mechanical properties of the tissue. *In vitro* the stimulation of cell growth under pulsatile conditions is seen to result in a 6.5 fold increase in the burst pressure of PGA-PHA grafts [441], while in a further study [446] the wall thickness of a PGA-based graft was reported to be significantly lower in static versus pulsatile cultures, 230 versus 380 μm respectively. This latter study also examined the impact of supplementation of the media with exogenous factors and reported a 7-fold increase

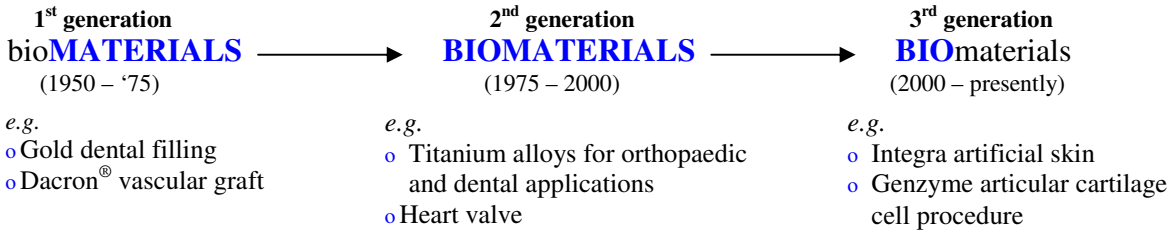
in the burst strength of grafts grown in supplemented media. In a more recent study [445] a graft grown under pulsatile conditions *in vitro*, entirely through the manipulation of the cell biology of autologous cells, has resulted in the production of grafts whose burst pressures are comparable to that of the porcine carotid artery with a compliance intermediary of that of the saphenous vein and internal mammary artery. This latter approach is a significant breakthrough in *in vitro* tissue engineering but the graft's lengthy production time and how remodelling of the implanted graft will influence its rate of biodegradation and resistance to fatigue will ultimately determine its clinical applicability.

Insert Table 16 here

Table 16: Summary of recent advances in vascular engineering (adapted from reference 447)

CHALLENGES AND OPPORTUNITIES

The metamorphosis of the biomaterials' field over the last 50 years to meet the changing and increasingly sophisticated clinical demands was succinctly conveyed by Anderson [452] when he described the development of applied biomaterials as having gone through the transitional changes of:



This perspective clearly identifies the change in the primary character of applied biomaterials.

The speed of change in the biomaterials' field over the past 10 years has primarily been driven by advances in molecular and cell biology with the result that many 1st generation biomaterials have been modified and new materials developed which possess improved interfacial interaction with the host tissue for many traditional applications. Future research and development of biomaterials for surgical replacement is likely to focus on the molecular, cellular and tissue interactions with materials and minimally invasive surgical approaches.

In regenerative medicine, biomaterials continue to play a pivotal role in the development of new clinical therapies. With the continued changes in awareness of the complexities faced in attempting to regenerate human tissue, tissue-engineering may be considered as being 'the application of viable or non-viable bioactive biomaterials to correct degenerative or pathological conditions so that the native tissue functionality and architecture is restored'. One of the major obstacles to overcome in achieving this goal is the spacio-temporal control of tissue-specific cell phenotypes. It is however hoped that, by applying engineering design principles in conjunction with advances in cell and molecular biology, approaches towards reconstructive or regenerative repair will be found for many tissue defects but these technical advances must be considered in the context of the risk/benefit and cost for

the patient. Furthermore, with increased understanding of the cell biology of pathological states it is conceivable that in some instances surgical repair may be obviated by pharmacological intervention *e.g.*, the use of anti-VEGF in the treatment of PDR [58]

Finally, in the research and development of new and improved materials there is also the ongoing issue/dilemma regarding predictive *in vitro* evaluation of clinical performance. This is illustrated by the recent termination of clinical trials with polyurethane small diameter grafts due to increased biodegradation *in vivo*. As current biological test results are test-method and biological model selection-specific, results of such tests may be instructive but may lack correlative power to the clinical safety and efficacy of an implant. Therefore, with the development of biomaterials with increased interfacial tissue interaction and combinatorial biologic-biomaterial tissue engineered implants comes the need for the development of new perspectives and approaches towards the biocompatibility or safety assessment. For example, the behaviour of cells in 2-D cultures is significantly different from that in 3-D cultures (which more closely reflect tissue architecture); the clearance of injected hyaluronan in an arthritic joint occurs at a significantly increased rate due to the increased activity of neutrophils in this inflammatory disease. Equally, without clinical trials, the 'true' long-term physiological performance of biomaterials cannot be monitored and therefore the take-up of new approaches to repair may have a minimum of a 10 year lead-time post clinical trials. Nonetheless, despite the numerous technical difficulties that remain to be solved the potential for future developments in this field remain both challenging and exciting.

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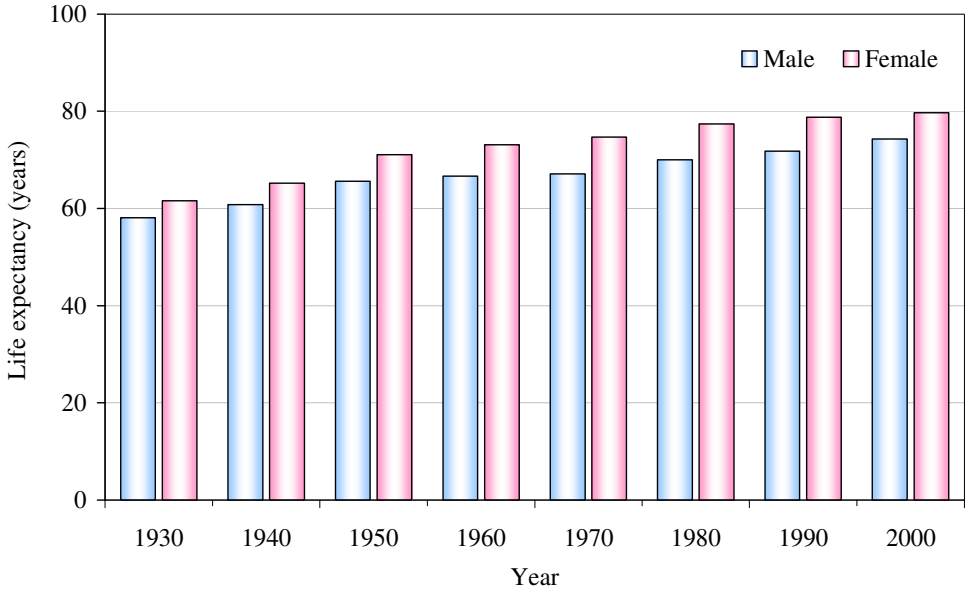


Figure 1: Changes in life expectancy for men and women in the U.S. during the 20th century [30]

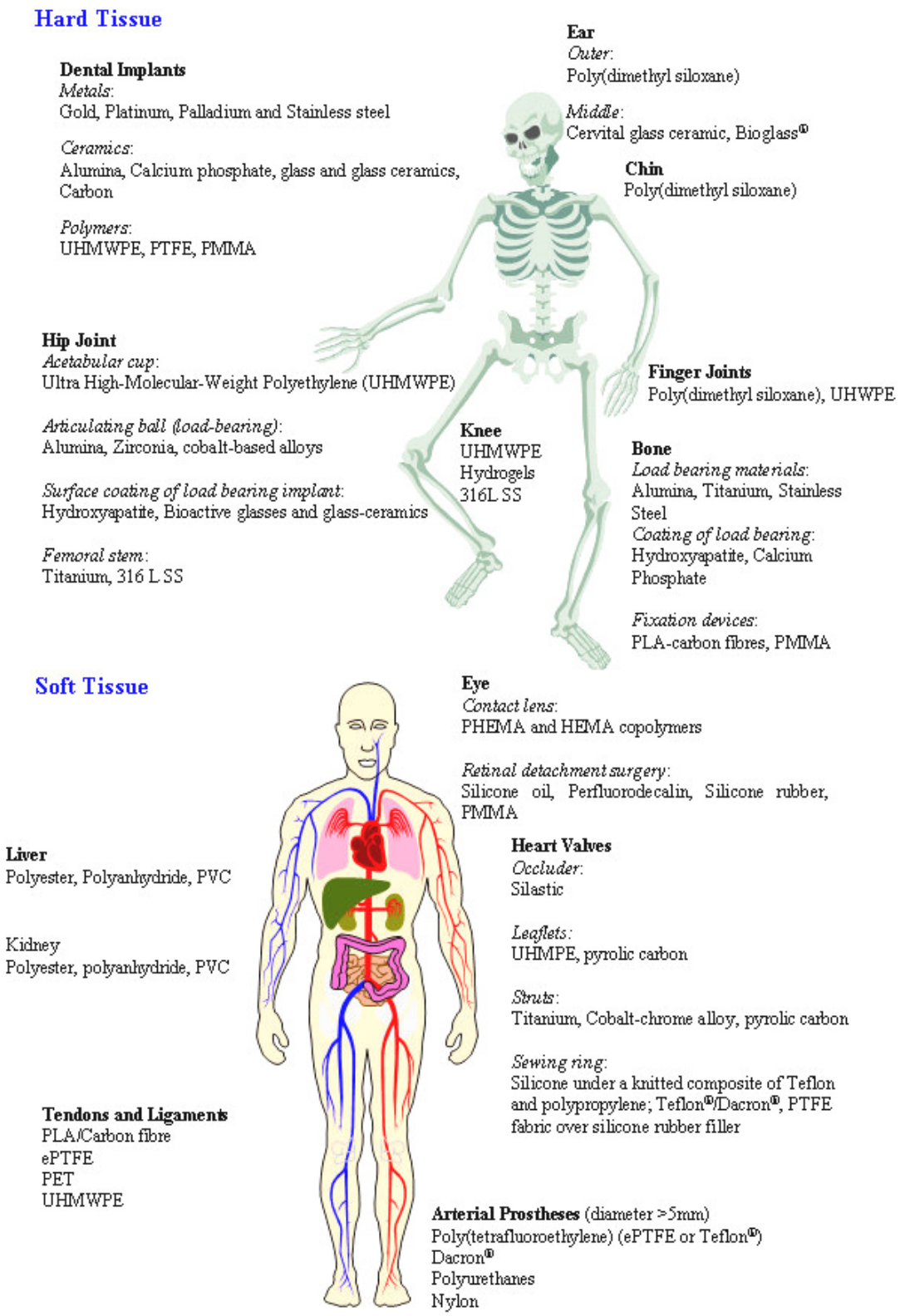


Figure 2: Some examples of the use of implantable biomaterials in medicine and dentistry [88, 94, 141-147]

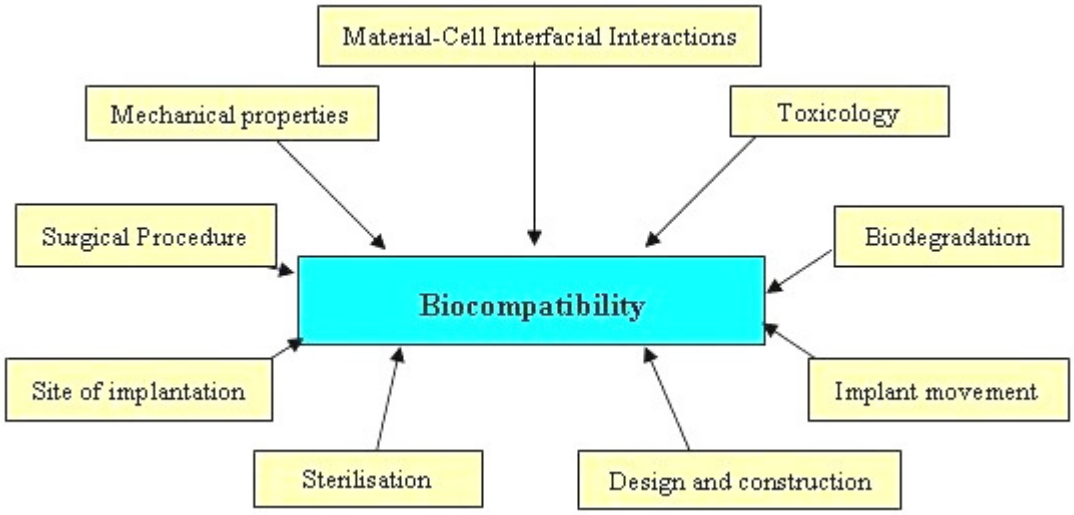


Figure 3: Diagrammatic representation of factors that influence the functional biocompatibility of an implantable device

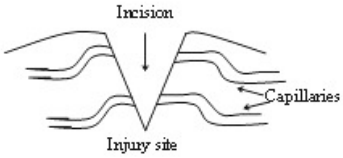
A. Inflammatory Phase

Cellular/Humoral response

1. Damage to tissue and surrounding capillaries results in the release of blood into the wound cavity

o Activation of the clotting system and/or thrombosis

o Coagulation factor XII contacts collagen, foreign proteins, or a foreign material



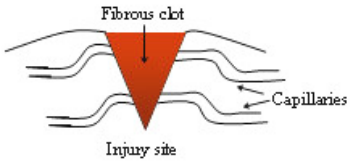
2. Fibrous clot formed by platelets and fibrinogen at the site of injury.

o Local capillaries dilate and the permeability of the vessel endothelium increases

o Increased blood flow to region

o Redness due to increased concentration of red blood cells

o Outflow of plasma to surrounding tissues leads to swelling and pain



Cellular Invasion

o Starts within minutes to hours of injury and results in the migration of inflammatory cells to the wound site

o Neutrophils move into surrounding tissue and phagocytose small particles (0.1 - 1 µm average size) or fragments of tissue or foreign material. Phagocytosis of larger particles begins later by macrophages and foreign body giant cells (FBGC's), while particles greater that 50 µm do not initiate a reaction greater than the bulk material. This process clears particles (dead tissue and foreign material) away from the site

o Inflammation is accompanied by four classical symptoms: redness, swelling, pain and heat. The magnitude of these symptoms is indicative of the degree of inflammatory response

o If tissue injury is extensive or the wound contains irritants or bacteria, substantial tissue damage may occur due to the extracellular release of collagenase

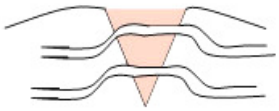
B. The Proliferative or Regeneration Phase

3. Capillaries at site begin to form buds within the fibrous clot

o Granulation tissue formed: characterised by new capillary formation and an increase in fibroblast proliferation

o Formation of new connective tissue: collagen and GAGs are synthesised by fibroblasts

4. Capillaries grow through clot and anastamose re-establishing blood supply



C. Repair and Remodelling

5. Scar tissue forms and begins to remodel

o Forms scar tissue at site which acts as scaffold for cellular reconstruction

o Myofibroblasts activity leads to wound contraction

o As granulation tissue is remodelled there is a decrease in the number of fibroblasts and vessels in the wound.

o Collagen is remodelled into large-diameter fibres and the concentration of proteoglycans changes.

o In skin Type I collagen fibres align to form a scar that is approximately parallel to the surface of the skin.

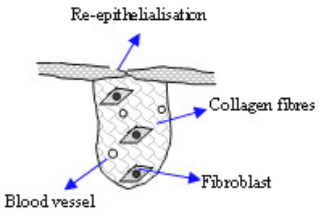


Figure 4: Overview of events following injury through the full thickness of skin

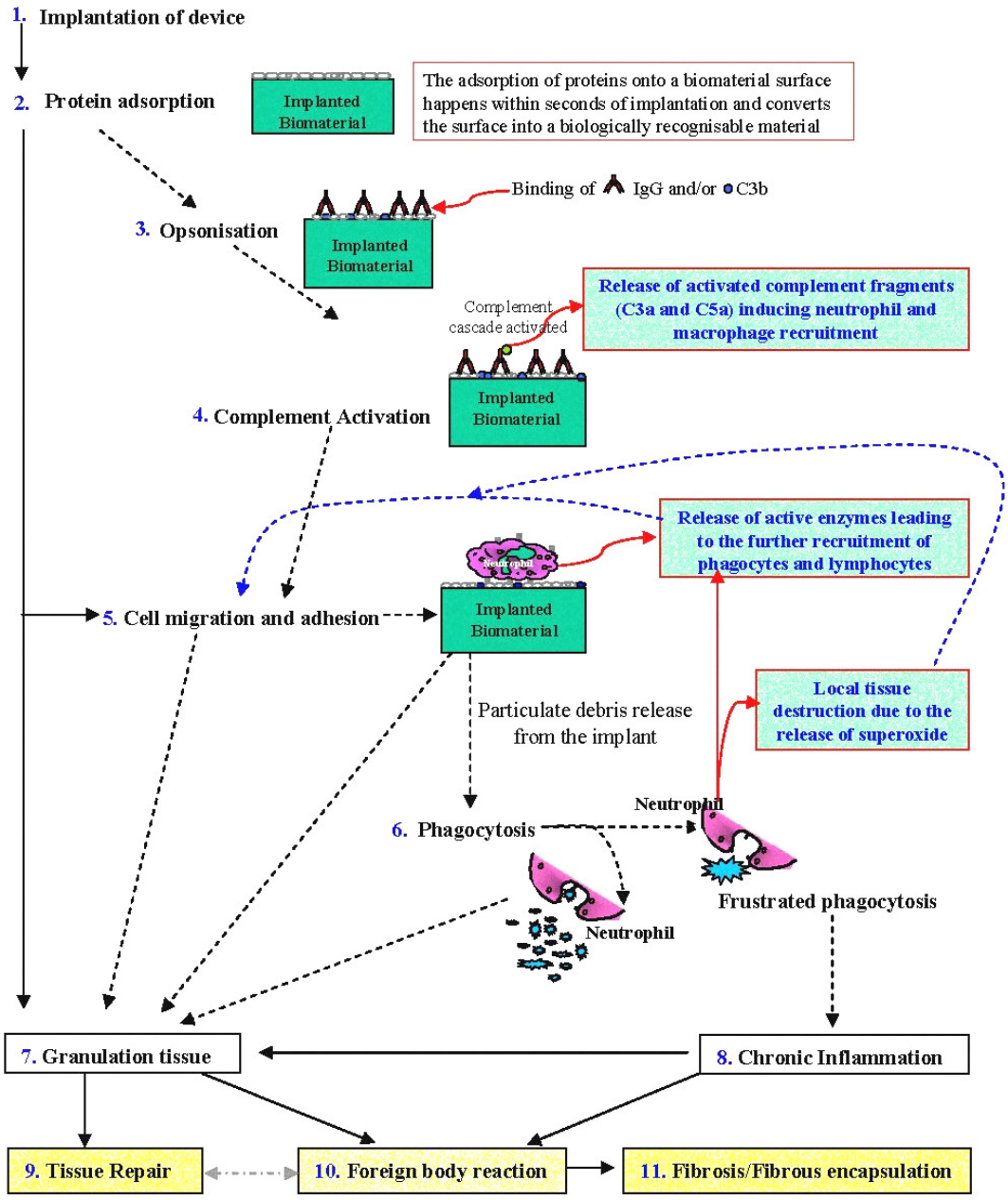


Figure 5: Schematic representation of events leading to fibrous capsule formation following the implantation of a biomaterial [1, 173, 174, 220-225]

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1. The implantation of a medical device results in the release or activation of inflammatory mediators by the injured tissues (histamine, kinins, prostaglandins, leukotrienes, IL-1, IL-6 *etc*) and platelet adherence and aggregation on the endothelial surface of damaged vascular tissue releasing serotonin and fibrinogen. The adjacent blood vessels dilate and the permeability of the capillary walls increases enabling proteins and cells to move to the injury site. This exudation of proteins produces a differential osmotic pressure between the blood and the interstitial space in the injured tissue resulting in water entering the tissue.

   The clotting proteins from the blood diffuse into the interstitial spaces and form clots in the injured tissues and blood vessels. The clot effectively walls off the injured site from the body by laying down a fibrillar matrix, containing fibrin (on which fibrinogen, thrombospondin and platelet granules are bound), complement proteins, activated platelets (which release platelet derived growth factor (PDGF), transforming growth factor-β (TGF-β) (which increases ECM synthesis), platelet-derived endothelial growth factor (pdEGF) and platelet factor 4), neutrophils and endothelial cells. The clot is stabilised by the crosslinking of fibrin by Factor XIIIa providing a scaffold for tissue repair.

2. Implants become exposed to this complex mixture of tissue and plasma proteins which selectively adsorb onto the material's surface within seconds - minutes following implantation. The composition of the adsorbed protein layer is influenced by the material's surface chemistry and topography. It is this layer of adsorbed proteins, and lipids, which modulates cell adhesion at the material-tissue interface and triggers the biological cascades. In general, vitronectin adsorption promotes endothelial cell adhesion and a relatively quiescent wound healing response while fibrinogen absorption promotes platelet (CD41), neutrophil and macrophage adhesion and therefore a far more aggressive local environment.

3. Opsonisation: Opsonins, such as Ig G and complement C3b, may adsorb onto the material surface which bind to receptor ligands on neutrophils and macrophages.

4. Complement activation, in the presence of an implanted device, generally occurs by the alternative pathway although there is evidence that the classical pathway can also contribute presumably subsequent to IgG binding. The binding of C3b to a material's surface triggers the complement cascade with the production of the soluble chemoattractants C3a and C5a which induce phagocyte activation and recruitment to the injury site.

5. Phagocytic cell migration across the endothelium to the site of tissue injury is initiated by their binding to cell adhesion molecules expressed on activated endothelial cells (*e.g.* ICAM-1, VCAM-1 and MAdCAM-1 and E- and P-selectin), whilst activation is triggered by chemotactic molecules (*e.g.* C5a, leukotriene-B_4, fibrin peptide B and thrombin) and by chemokines (IL-8 and MCP-1). The interaction of E-selectin on the endothelial cells with CD15 on leucocytes in the presence of additional chemoactive molecules results in the up-regulation of leukocyte adhesion receptors, (*e.g.* LFA-1$\alpha_L\beta_2$ and VLA-$\alpha_6\beta$ and L- selectin), enabling the leucocytes to bind to ICAM-1 expressed by endothelial cells. Once the leucocytes have crossed the endothelium they interact with the ECM via β_1-integrins or VLA receptors and are 'guided' to the site of injury by chemoattractants such as C5a. The leukocyte cell membrane receptors interact with proteins and other ligands that have adsorbed onto the material surface from the surrounding biofluids and it is this interaction that modulates the cell behaviour at the implant site.

6. Phagocytosis is induced when there is tissue debris and/or particulate debris from the material at the inflammatory site. Neutrophils phagocytose small particles (0.1 - 1 µm average size), fragments of tissue or foreign material while macrophages and foreign body giant cells (FBGCs) phagocytose larger particles (< 20 µm). Particles greater that 50 µm do not initiate a reaction greater than the bulk material *i.e.* PMMA particles are generally encircled by a layer of FBGCs or encapsulated in a fibrous coat in the same manner as the bulk material. The phagocytic cells accordingly 'clean up' the implantation site, which is facilitated when the material is coated with opsonins. An exception to this is frustrated phagocytosis which results in the extracellular release of enzymes from activated neutrophils and macrophages that may cause additional tissue injury as seen with particulate-induced osteolysis in the presence of UHMWPE particulate debris in a THR.

7. Secretion of fibronectin by macrophages and fibroblasts promotes the cytokine-directed migration of endothelial cells, myofibroblasts and lymphocytes into the wound site. The ECM of granulation tissue is primarily composed of fibronectin, hyaluronic acid and Type III collagen and is characterised by new capillary formation accompanied by an increase in fibroblast proliferation.

8. The chronic inflammatory response delays healing in response to a prolonged chemical or physical irritation at the material-tissue interface. In general, chronic inflammation is characterised by the presence of macrophages, monocytes, lymphocytes, the proliferation of new blood vessels and the synthesis of collagen and glycosaminoglycans by fibroblasts and is influenced by the concentration of cytokines such as IFN-γ and TNF which activate macrophages and IL-10, IL-4 and IL-13 that inhibit macrophage activation.

9. Tissue repair occurs by regeneration or replacement (with the formation of scar tissue) which of these processes dominates depends on the tissues involved and the nature and extent of the wound.

10. The foreign body reaction is composed of foreign body giant cells (FBGCs) (formed by the fusion of monocytes/macrophages) and components of the granulation tissue. FBGCs are formed in the presence of particulate debris at the surface of materials with a high surface area to volume ratio, such as fabrics, and when the adsorbed protein coat contains phagocyte adhesion proteins (*e.g.* IgG, C3b, vitronectin *etc*).

11. Some continued inflammatory activity occurs at the implant-tissue interface as the fibrous layer formation progresses to encapsulate the material predominantly composed of collagen Type III. The thickness of this layer is influenced by the chemical activity of the implant and mechanical factors such as implant micromotion.

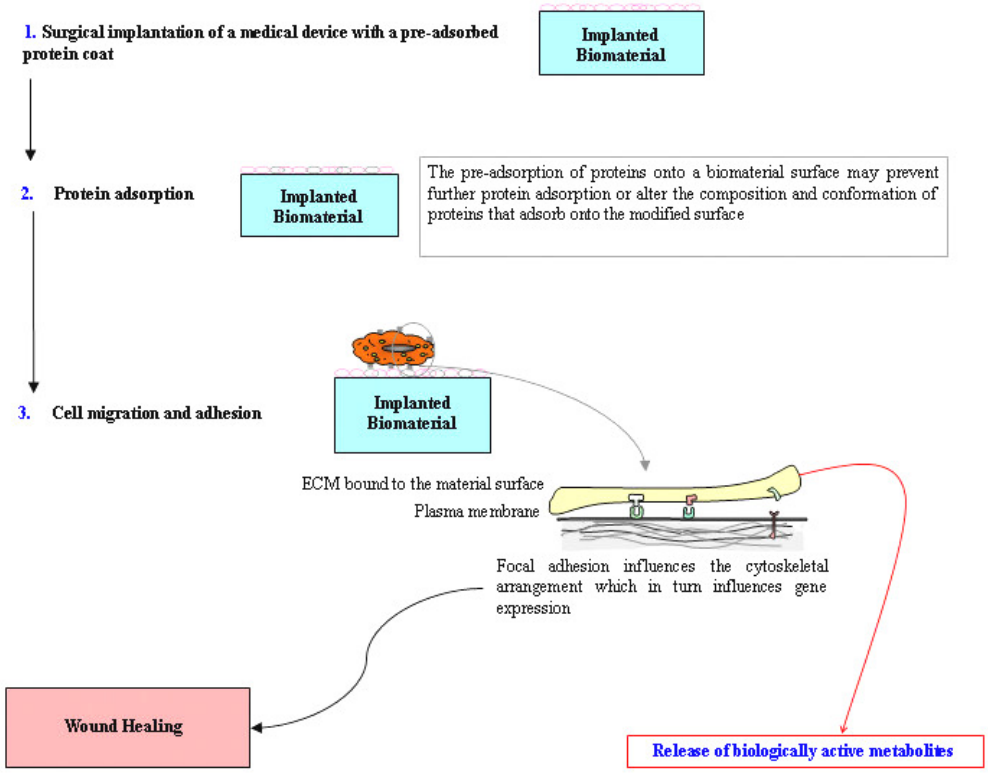

Figure 6: Schematic representation of the events leading to integration following the implantation of a medical device*

* Cell adhesion to biomaterials is mediated by cytoskeletally associated receptors in the cell membrane which interact with the cell adhesion proteins adsorbed to the material surface from the surrounding biofluids triggering multiple functional biochemical signalling pathways within the cell, *e.g.* cell-growth, cell shape and cytoskeletal tension, in a manner analogous to cell-cell communication and patterning during embryological development. The potential of this strategy is exemplified by tissue engineering approaches that employ biomaterials with surfaces designed to stimulate highly precise reactions with proteins and cells at the molecular level. Such materials provide the scientific foundation for molecular design of scaffolds that could be seeded with cells *in vitro* for subsequent implantation or specifically attract endogenous functional cells *in vivo*.

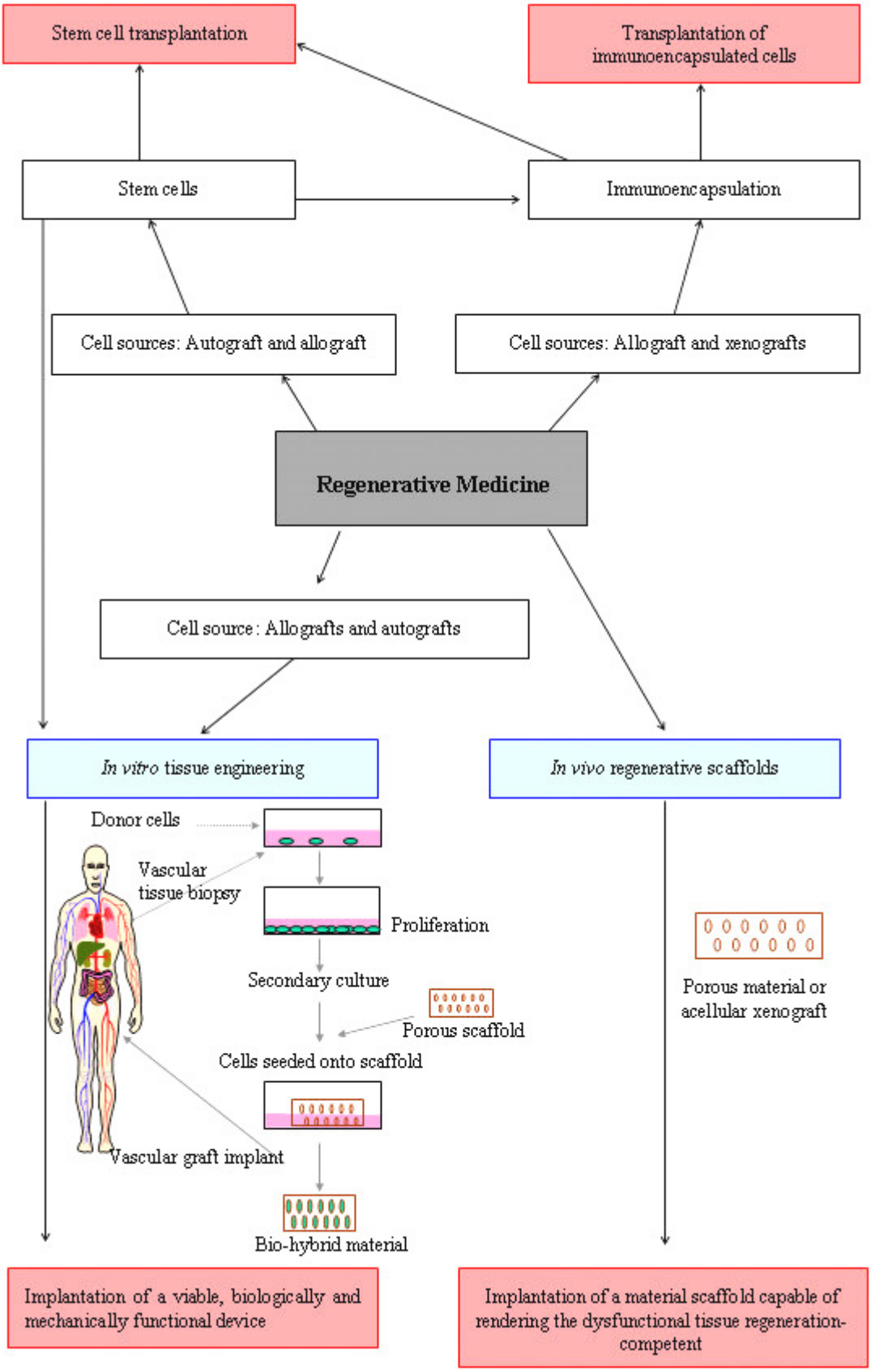

Figure 7: Schematic representation of the interplay of the various fields of regenerative medicine

List of Tables

Table 1: Transplants performed in the United States in 2002 [23] and the UK and Republic of Ireland (RoI) in 2000 [24]

Organ(s) Transplanted	Number of Transplants Performed	
	U.S.	UK and RoI
Cornea	-	2,320
Kidney	14,400	1,823
Liver	5,300	709
Heart	2,200	217
Lung	1,000	98
Kidney and Pancreas	900	-
Pancreas	550	-
Intestine	104	-
Heart and Lung	31	33

Table 2: Number of patients requiring organ transplants in the U.S. in 2000 – 2001 compared with the number of transplants performed in 2002

Transplant Organ(s) Required	**No. on waiting list** (30-06-01) [25]	**No. of transplants performed in 2002** [23] (est. of % required)	**No. of patients who died while on waiting list** (01-07-00 – 30-06-01) [25]
Kidney	49,860	14,400 (29)	2,837
Liver	18,089	5,300 (29)	1,799
Pancreas	979	550 (56)	23
Kidney-Pancreas	2,587	900 (35)	220
Heart	4,200	2,200 (52)	608
Lung	3,798	1,000 (26)	497
Heart-Lung	222	31 (14)	35
Intestine	170	104 (61)	24
All	79,902	24,485 (31)	6,043

Table 3: The number of operations estimated to have been performed in the U.S. in 1989 [26]

Anatomical Site	Operations per year
Skin	4,750,000
Bone	1,340,000
Cartilage	1,150,000
Tendon/Ligament	123,000
Urological	82, 000
Blood vessels	1,360,000
Pancreas	738,000

Table 4: Comparison of the number of devices estimated to have been used in the U.S. (No date given*, 2000♣, 2002♠ or 2003♦)

Clinical Discipline	Application	Number of devices used per Year		
		U.S.		Globally
		Ratner *et al* (1993) [36]	Ratner *et al* (2004) [37]	
Ophthalmology	Intraocular lenses	1 400 000	2 500 000♦	
	Contact lenses	2 500 000		
	Retinal surgery implants	50 000		
	Prosthesis after enucleation	5 000		
Cardiovascular	Vascular grafts	350 000	300 000*	
	Coronary stents		1 500 000*	
	Heart valves	75 000	82 000♣	274 900[38]
	Pacemakers	130 000	400 000*	
	Cardiac assist devices			
	Artificial hearts			
Reconstructive	Breast prosthesis	100 000	250 000*	
	Nose, chin	10 000		
	Penile	40 000		
Dentistry	Dental	20 000	910 000♣	
Orthopaedic	Hips	90 000	250 000♠	700 000[39]
	Knees	60 000	250 000♠	700 000[39]
	Shoulders, finger joints	50 000		55 000[39]
	Bone fixation plates			

Table 5: A brief historical overview of some of the major achievements in the application of materials in medicine and dentistry

Year	Development	Reference
800 BC	Egyptians used linen sutures and strips soaked in natural adhesives to draw wound edges together	[109]
600 BC	Etruscan gold bridge work	[110]
1400's	American Indians used horsehair, cotton and thin strips of leather in the treatment of wounds	[109]
1775	Use of wires of brass, silver and gold in the treatment of bone fractures	[111]
1849	Introduction of the use of percutaneous metal hooks to stabilise fractures	[112]
1895	Bone plates were developed	[113]
1937	Poly(methylmethacrylate) (PMMA) was first used in dentistry	[114]
1950's	Alloys such as stainless steel, cobalt-based alloys and titanium were used in orthopaedics	[39]
1950's	First PMMA cemented hip replacement using a stainless steel femoral stem and UHMWPE acetabulum	[73, 74]
1952	Dacron® arterial prostheses became commercially available	[115]
1960's	Development of first bioresorbable sutures Dexon®	[116]
1961	Contact lenses developed by Wichterle	[117]
1968	Development of a tanned porcine aortic heart valve mounted on Dacron® fabric coated stents	[118]
1970's	Microporous expanded polytetrafluoroethylene (ePTFE) vascular grafts introduced	[119]
1970	Use of collagen in full thickness wound healing in animal models	[120]
1970	Alumina was used in hip replacement	[39]
1972	Bioactive glasses with bone-bonding ability were developed	[121]
1973	Suturing of lacerated tendons	[122]
1974	Development of composite degradable sutures of Poly(glycolic acid) and Poly(lactic acid)	[123]
1975	First glass ionomer cement, ASPA, used in dentistry	[124]
1981	Polydioxanone was developed as a suturing material	[125, 126]
1983	Porous calcium phosphate was used in medical and dental applications	[127]
1985	Bioglass® Ossicular Reconstruction Prosthesis (MEP®) for ossicle replacement	121]
	Resin-modified glass ionomer cements	[128]
1994	Particulate Bioglass®: NovaBone® approved as a bone void filler, Perioglas™ for periodontal disease	[121, 129]
1994	FDA approval of coronary artery stenting	[130]
1994	First soft biomaterial for IOLs introduced by Alcon Laboratories Inc (Acrysof IOL)	[131]
1995	Daily disposable lenses available on the market	[132]
1995	Haptex™ licensed in the UK as a middle ear bone ossicle replacement	[133]
2000	Orthovita receives FDA Clearance for VITOSS Scaffold the First Engineered 90% Porous Beta-Tricalcium Phosphate	[134]
2001	Newer generation of soft silicone foldable IOLs *e.g.* Collamer® IOL, Crytalens® AT-45	[135, 136]
2003	FDA approval of first drug-eluting coronary artery stent	[137, 138]
	Approval of Crytalens® AT-45 Accommodating Posterior Chamber Intraocular Lens (IOL) used to correct the visual impairment of aphakia (absence of the natural eye lens) after cataract surgery	[139]
2004	Bioglass® particulate approved for treatment of tooth hypersensitivity	[121]
2007	Angiotech Pharmaceuticals Inc received clearance from the FDA to market Rex Medical LP's chronic dialysis catheter	[140]

Table 6: Major clinical speciality markets for biomaterials

Application	Market (Billion U.S.$)			Projected Increase (%)
	Europe	U.S.	Global	
Orthopaedic (2000) [69]	3.2	9.16	15.8	
Orthopaedic (2002) [39]	-	-	14	7 – 9 [39]
o Fracture management devices (2000) [39]	-	-	1.5	
o Hip replacement (2002) [39]	-	-	2.5	
o Knee replacement (2002) [39]	-	-	2.5	
Cardiovascular (2000) [69]	1.8	5.4	8.1	
Vascular Graft (2000) [119]	-	-	0.2	
Drug Delivery (2000) [69]	1.7	2.1	6.3	
Wound Care (2000) [69]	1.9	1.8	4.7	

Table 7: Comparison of the mechanical properties of some selected tissues and materials used in specific clinical applications (L = Longitudinal, Trans = Transverse, Circ = Circumferential, C = compression, T = tension)

Tissue Type/ Material	UTS* (MPa)	Elongation to break (%)	Young's Modulus (GPa)	Clinical Application
Aortic Heart Valve (Radial) [159]	0.045	15.3		
Aortic Heart Valve (Circ) [159, 160]	2 - 4.5	10 - 18	41 – 64	
Human Aorta (L) [159]	0.07	77		
Human Aorta (Trans) [159]	1.1	81		
Artery [160]	1 - 1.6	0.8 - 1.1	0.03 - 3	
Dacron®	<40[161], 59 – 72[162]	50 – 300[162]	2.8 – 4[162]	Arterial graft; Tendon and ligament
Teflon (PTFE)	14 – 34[161]	200 – 400[162]	0.4[161]	Arterial graft; Tendon and ligament; Catheter
Elastic Cartilage	3	30	15	
Articular Cartilage [159]	3.4		10 - 21	
Skin [159, 160]	6.2 – 14	78 – 140	23 - 44	
Tendon [160]	59 – 69	8 - 9	966	
Achilles Ankle Tendon [159]	24 – 61	24 – 50		
Human Enamel (Molars)	10[159]		50[163]	
Human Dentin (Molars)	34.5 – 52[159]		18[163]	
Glass Ionomer Cement [163]	170 – 260(C)			Dental
Tibia Fascia [159]	10 – 18			
Femoral Bone (L) [75]	130	3	17(T)	
Femoral Bone (Tangential) [75]	60	1	12	
Femoral Bone [160]	120	1.4	17	
Cortical Bone (L)	133(T)[163, 164] 130 – 180(C)[165]	3.1	10.9 – 29.2[164] 7 – 30	
Cortical Bone (Tangential) [159, 164]	52	0.7		
Spongy bone [75]	2	2.5	0.1	
PMMA♠ (Solid)	35-50, 65(T)[75]	0.5, 5[75] 2 – 10[162]	3[75]	Orthopaedic; Intraocular lens
PMMA Bone Cement [75]	30(T)	3	2	Bone cement
Glass Ceramic [75]	200	<0.1[b]	200	Bone cement
Bioglass [165]	1000(C)		~75	Spinal fusion
Alumina	260(T)[75] 4000(C)[165]	<0.1[b][75]	400[75] 380[165]	Femoral head
Dense Hydroxyapatite [75]	200	<0.1[b]	120	Coating on femoral stem, Bony defect repair
Zirconia	2000(C)[165]		150 – 200[165]	Femoral Head
Titanium Grade 4 [166]	760		110	Dental implant for tooth fixation
Ti6Al4V	860 – 990(T)[75, 163, 166]	10- 14[75, 167]	110[75]	Femoral stem; knee; Dental implant for tooth fixation
Stainless Steel 316L	1000(T)[75, 163]	9[75]	200[75]	Femoral stem, Bone plate for fracture fixation
UHMWPE♣	7.6, 30(T)[163]	150, 200[75]	1[75]	Cemented acetabular cup
Polysulphone [75]	70	50	2.5	Orthopaedic bone plates, screws, intramedullary nails
Silicone Rubber [75]	6	350	<0.01	Orthopaedic; Catheter; Intraocular lens
PEEK	90[161]		3.6[161]	
Polyurethane	1 – 69[161]	600 – 720[166]	0.07 – 6.9[161]	Arterial graft; Artificial heart
D,L-PLA (107 – 550 x 10^3) [162]	29 – 35	5 - 6	1.9 – 2.4	Bone Plate

* UTS = Ultimate Tensile Strength
♠ PMMA = poly(methylmethacrylate)
[b] estimated values
♣ UHMWPE = Ultra high molecular weight polyethylene (> 2 x 10^6 g/mole)

Table 8: Examples of the application of pseudo-inert, bioresorbable and bioactive materials (adapted from Williams [182])

Material Classification	Material		Application
Inert	**Metals**	Titanium alloys	Femoral stem and head[39, 167]
		Stainless steel	Orthopaedics[39, 75, 167], heart valves[37]
	Ceramics	Alumina	Femoral head, articulating joints[183]
		Zirconia	Femoral head[154, 167, 184]
	Polymers	Silicone rubber	Scleral buckles[142], Catheter[185]
		ePTFE	Bypass grafts[6]
		PMMA	Bone cement[186]
		UHMWPE	Articulating joints[73, 74]
Resorbable	**Ceramics**	Calcium Sulphate	Bone graft*[79, 80]
		Tricalcium Phosphate (TCP)	Bone graft*[187, 188]
	Polymers	Poly(L-lactic acid) (PLA)	Suture*[189], Bone fixation[190-192]
		Poly(glycolic) acid (PGA)	Sutures*[189, 193], Bone fixation*, Drug delivery
		Poly(D,L-lactic acid)	Intramedullary plug[194]
		PGA/PLA composite	Sutures[195], Bone fixation
		Poly(α-cyanoacrylate)	Bioadhesives, drug delivery matrices
		Poly(ε-caprolactone)	Drug delivery*, orthopaedic applications
		Poly(orthoesters)	Drug delivery[186, 197]
		Polydioxanone	Sutures, Suture clip, bone pin*
		PHB, PHV and their copolymers*	Drug delivery, sutures, vascular grafts[198]
		Hyaluronic acid esters	Wound healing[199]
		Collagen	Soft-tissue augmentation[200] *e.g.* urinary incontinence*
		Fibrin	Bioadhesive*[201-207] Drug delivery[208-212]
Bioactive	**Inorganic**	Bioglass®	Middle ear*[121], synthetic bone graft[121]
		Hydroxyapatite	Coating of bone implanted devices*[186]
		Glass Ceramics	Dentistry[213]
	Polymers	Galactosylated PVDF† membrane	Promotes adhesion of hepatocytes[214]
		ePTFE + immobilised VEGF	Promotes adhesion of endothelial cells[215]
		Hydrogels + coupled RGD peptides	Promotes healing of diabetic ulcers[216, 217]
		ePTFE + arg-gly-asp(RGD)	Stimulation of endothelial adhesion[218]
		ePTFE + immobilised heparin	Improved haemocompatibility of bypass graft[219]

* PHB = Poly(hydroxybutyrate) and PHV = Poly(hydroxyvalerate)
† PVDF = poly(vinylidene difluoride)

Table 9: 10-year patency rates of femoral stems and acetabular cups of total hip prostheses [247]

Mode of Fixation	10-year Patency Rates (%)	
	Femoral stem	Acetabular cup
Cemented	89	93
Apatite-coated	98	90
Porous-coated	92	82
Smooth	68	69

Table 10: Comparison of the patency rates of vascular grafts used at various anatomical locations

Anatomical location	Graft	% Patency (Years)
Aortiobifemoral	Dacron®	90 (5)[119]
	ePTFE	90 (5) [119]
Femorofemoral	Dacron®	80 (5) [119]
	ePTFE	80 (5) [119]
Femoropopliteal	Saphenous Vein	70 (5) [119]
	Dacron®	43 (3) [274] 40 (5) [119]
	Heparin-bonded Dacron®	55 (3)[274]
	ePTFE	50 (5) [119]
Coronary Artery	Left Internal mammary artery	88 (5)[275]
	Saphenous vein	86 (1)[276] 74 (5)[275]
	ePTFE	59 (1)[276]

Table 11: An overview of some of the tissue engineering therapies currently applied in regenerative medicine following FDA approval

Year of FDA Approval	Development	Company	Indicated Use
1987	Epicel[282, 283]	Genzyme	Only autologous skin graft available; indicated for burn wound closure
1989	Biobrane II[284]	Sterling Drug Inc.	Wound dressing
1994	Alloderm[285]	LifeCell Corp.	Burn surgery
1996	INTEGRA® Dermal Regeneration Template[286, 287]	Integra LifeSciences Corp	Acellular dermal regeneration template for burn and reconstructive surgery
1997	TransCyte* [284, 288]	Advanced Biohealing	Temporary wound cover for burns
1997	Carticel[289-291]	Genzyme	For the repair of clinically significant, symptomatic cartilaginous defects of the femoral condyle caused by acute or repetitive trauma
1998	Apligraf[292, 293]	Organogenesis	Non-infected partial and full-thickness skin ulcers; diabetic foot ulcers
2001	OP-1 Implant[294, 295]	Stryker	Alternative to autograft for recalcitrant bone non-unions
2001	Laserskin®	Fidia Advanced Biopolymers	Biodegradable keratinocyte delivery system
2003	Dermagraft™ [296, 297]	Smith and Nephew Wound Management	For the treatment of wounds related to dystrophic epidermolysis bullosa†
2006	Oasis Wound Matrix[298, 299]	Cook Biotech Inc	Partial and full-thickness wounds, ulcers, surgical wounds
2007	INFUSE™ [300]	Medtronic	Bone Graft

* Formerly Dermagraft-TC Advanced Tissue Sciences Inc.
† Epidermolysis bullosa is a group of inherited disorders in which skin blisters develop in response to minor injury

Table 12: An overview of some of the tissue engineering therapies currently at the clinical trials stage

Company	Product	Application	Reference
Arbios Systems Ltd (formerly Circe Biomedical)	SEPET™	Liver Assist Device	[301]
	HepatAssist	Bioartificial liver	[302]
VitaGen Inc.	ELAD™	Bioartificial liver	[302-304]
Alimera Sciences	Iluvien™	Diabetic macular oedema (DME)	[305]
pSivida Limited	BrachySil™	Pancreatic cancer	[306]
Tengion	Neo-Bladder Augment™	Neurogenic bladder	[307]

Table 13: Regenerative capacity of cells following trauma [348]

Category	Normal rate of replication	Responses to stimulus/injury	Examples
Renewing	High	Modest increase	Epithelium Intestinal mucosa Bone marrow
Expanding	Low	Marked increase	Endothelium Glandular epithelial Vascular smooth muscle Osteoblasts Fibroblasts Liver cells
Static	None/Rare	No replication; replacement by scar	Heart muscle cells Nerves of the CNS

Table 14: Potential applications of biopolymers in tissue engineering applications

Biomaterial	Format	Application	Reference
Hyaluronic acid	Gel	Nerve Regeneration	[365]
	Microspheres	Drug/growth factor delivery	[366, 367]
	Film	Controlled peptide release and protein delivery	[368]
		Adhesion Prevention	[369-375]
	Sponge	Cartilage	[368, 376, 377]
		Wound Healing	[199]
Collagen	Microsphere	Drug/growth factor delivery	[378, 379]
	Film	Heart valves	[337, 380, 381
	Sponge	Cartilage	[382-384]
		Wound Healing	[385-390
		Nerve regeneration	[391]
		Bone regeneration	[392, 393]
		Uretheral repair	[394]
		Small calibre vascular graft	[395]
Gelatin	Gel	Wound Dressing	[396]
	Microsphere	Drug/growth factor delivery	[397-400]
	Sponge	Articular Cartilage	[401]
		Nerve Regeneration	[402]
Collagen-glycosaminoglycan	Sponge	Nerve Regeneration	[403, 404]
		Tendon Regeneration	[405]
		Skin	[406]

Table 15: Optimum pore size for cell specific ingrowth into porous matrices

Cell Type	Pore Diameter (µm)	Reference
Fibroblast	5 - 20	[412-414]
Hepatocytes	20	[412]
Adult mammalian skin	20 - 125	[406]
Endothelial	60 - 80	[407]
Bone Matrix regeneration	80 - 250	[349, 410]

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Table 16: Summary of recent advances in vascular engineering (adapted from reference 447)

Tissue/Scaffold Type	Wall thickness (μm)	Scaffold Material*	Cells†	Cell Growth conditions	Burst Strength (mm Hg)	Compliance (%)	Implantation site	Outcome	Ref
Saphenous Vein	250	Native tissue			1680 ± 307	0.7 – 1.5			[445]
Human Artery	350 - 710	Native tissue			2031 - 4225	4.5 – 6.2			
Porcine carotid artery (Proximal)	810	Native tissue			3124 ± 158				[448]
	519	Decellularised native tissue			2338 ± 245				
No Scaffold			HUVEC, HUVSMC and HSF		2594 ± 501		Canine femoral artery	50% at 7 days	[449]
	407 ± 49	None	Human fibroblasts and EC	Pulsatile	3468 ± 500[a]	1.5 ± 0.3[a]	Abdominal interpositional graft in rats	85% at 225 days	[445]
Synthetic Scaffold		PGA	Bovine aortic SMC and EC	Pulsatile – supplanted media	< 300[b]		Swine saphenous artery	Non-pulsed: thrombosis	[446]
	380			Pulsatile + supplemented media	2150 ± 705[b]			Pulsed patent at 4 weeks	
		PGA-CL/LA	Canine femoral vein SMC and fibroblasts				Canine inferior vena cava	100% at 13 months	[450]
		PGA-PHA	Ovine carotid SMC, EC and fibroblasts				Ovine infrarenal aorta	100% at 5 months	[198]
		PGA-PHA	Ovine carotid EC and myofibroblasts	Static	50 ± 5[c]				[441]
				Pulsatile	326 ± 5[c]				
Biologically-derived Scaffold	750	Uncrosslinked collagen	HDFs	Static	90 ± 10[d]				[451]
	750	GTA Crosslinked collagen			650 ± 170[d]				

* PGA = polyglycolic acid, CL = caprolactone, LA = lactic acid, PHA = poly-4-hydroxybutyrate
† HUV = Human umbilical vein; EC = endothelial cells; SMC = smooth muscle cells; HSF = human skin fibroblasts, HDFs = human dermal fibroblasts
a = 28 weeks; b = 8 weeks; c = 4 weeks; d = 8 days