Implants, Surgery and Coatings

Keywords: active implant, passive implant, surgical blade, tweezers, needle, catheter, coating, stent, bone, dental, nanostructure.

4.1 Definition

For the purpose of this report, implants, surgery and coatings describes nanomaterials that can be used in both active and passive implants and in surgical procedures.

4.2 Short Description

The major issues with placing implants in living tissue are rejection by the body and the need for replacement after a few years. This is not only costly but also puts the patient through another set of complicated procedures and their associated problems. In order to be successful, implants should be biocompatible and control the growth of tissues.

Nanotechnology has the capability to improve implant biocompatibility, either by coating implants with nanomaterials or by using nanomaterials as implant materials. Different types of coatings can be applied to improve the sustainability of the implants and protect them against bacterial and fungal infection. Coatings have also been applied in synthetic vascular grafts to avoid the deposition of biological material, thereby reducing the chances of occlusion[1]. Nanoscale materials can be used to make lighter and stronger implants that last longer. Some nanoscale materials can also accelerate cell growth after implantation.

In addition to supporting the basic requirements of implants, nanotechnology can also help to improve the monitoring and control of factors that help the growth of tissues *in vivo* with the use of sensors. This also allows the localised application of stimuli to encourage cell adhesion and growth. Nanotechnology can also be used to create smaller, rechargeable batteries for use in active implants. The technology has also been applied to create corrosion free suture needles with improved strength and ductility. Nanoparticles have also been incorporated into fibres to be used for wound dressings.

The ultimate aim of using these novel technologies in implants, surgery or wound care is to heal the body quickly and efficiently without creating excessive pain or irritation. It may also allow development of biomimetic cures for some of the chronic and degenerative diseases.

This report is aimed at highlighting some of the important developments in the area of passive and active implants, surgery and the use of textiles in wound care. Tissue engineering applications are covered in the regenerative medicine subsector report in this series.

4.3 State of R&D

4.3.1 Bone and Dental Implants

The use of nanomaterials and nanocomposites has made significant advances in the area of bone and dental implants. Nanophase materials have been successfully used on their own and alongside several other polymers to create biocompatible extracellular matrices (ECM) that can enhance osteointegration. These novel materials can provide a porous surface with large surface area and good mechanical integrity and are found to improve cell adhesion, cell spread and migration. In addition, nanofibres of several polymers have been highly useful in creating matrices that can grow living cells and incorporate growth factors to provide stimulation at the appropriate times.

The main reasons for implant failure are poor osseointegration, issues with the bonding of an orthopaedic implant to juxtaposed bone, and the inability of implants to match the physical properties of surrounding bone[2]. In fact, osseointegration is the single most important factor that determines the success of a bone implant. Several studies have shown that when an implant is placed to replace the natural bone, the level of integration and the fastness of healing will depend on the bone-to-implant contact area. If the contact area is higher, it will result in enhanced implant integration into the host bone. The advantage of nanotechnology is that it offers a higher surface area and thereby higher osseointegration potential.

Coating dental implants with nano TiO_2/HA (hydroxyapatite) encouraged nerve regeneration in cultured Schwann cells[3]. No changes in cell morphology or function were observed, indicating the biocompatibility of the material. However, coating materials with nanoscale TiO_2 alone has shown no significant difference to microscale TiO_2[4].

Nanostructured Ti can be used for bone re-engineering, giving increased surface area and osseointegration[5]. Studies using nanophase Ti, Ti_6Al_4V, and CoCrMo alloys saw high deposition of calcium and phosphorus compared with conventional phase metals, indicating that nanophase promotes osteoblast metabolic functions and can be used as materials for orthopaedic applications[6]. Human mesenchymal stem cells (MSCs) have been grown on Ti surfaces with nanoscale TiO_2 patterning[7]. Recently this technique has been used to induce MSC differentiation into bone matrix on titanium surfaces with 15 nm TiO_2 nanopillars[8].

Growth factors and biomolecules can also be immobilised onto implants to enhance growth and integration. TiO_2 nanotubes produced by anodisation have been proposed as drug eluting coatings for implantable devices[9]. The surface of the tubes can be functionalised to attach biomolecules, such as bovine serum albumin. Bone morphogenic protein (BMP) has been immobilised on the surface of Ti based implants to enhance bioactivity and bone formation[10]. The advantage of immobilising BMP is that it allows controlled administration and avoids the common issues associated with overdosing. Implants have been coated with nanocrystalline diamonds to increase the surface area and facilitate immobilisation of BMP[11]. The differentiation and proliferation of cells[12] without changing the overall texture of the specimen can be achieved using these diamonds.

Nanocomposites and nanomaterial coatings have been developed commercially for bone and dental implants. Biomet (http://www.biomet.com/) has recently introduced a new dental implant called NanoTite which deposits nanoscale calcium phosphate crystals to approximately 50% of the implant surface. Angstrom Medica (www.angstrommedica.com) has a product called NanOss™ Bone Void Filler, made of HA nanocrystals for high osteoconductivity and strength in bone replacement. Although nanocomposites and other coatings offer great potential, the cost and difficulty of scale up hinders its fast commercialisation.

Biocompatible oxide ceramic based nanostructured composites have been developed by the EC funded Bioker project, in an attempt to develop new hip and knee replacements as well as for dental implants[13]. The nanocomposites developed offer similar crack resistance to the covalent materials used in implants while avoiding the associated drawbacks due to processing and machining. Some of the composites (containing zirconia nanoparticles) show superior mechanical resistance to commercially available products, better biocompatibility than alumina and the wear test demonstrated that the material can be used for biomedical applications.

The process used to create these nanocomposites used a single step without nanoparticle handling and the particle size could be controlled by changing the processing parameters. This makes the method highly desirable. Currently the continuation of the Bioker project, now called IP-Nanoker (http://www.nanoker-society.org/index.aspx?id_page=121), aims to provide nanoceramics (<100 nm) and nanocomposites (second phases <10 nm) for industrial applications.

High dispersion hydroxyapatite (HA) and zirconia nanocrystal nanocomposites which can mimic the mechanical strength and bioactivity of natural bones have been developed by IBN (http://www.ibn.a-star.edu.sg/)[14]. Enhanced attachment and proliferation of MC3T3 osteoblast cells was seen when a nanocomposite foam of collagen fibres and apatite nanocrystals was used[15]. *In vivo* bone, tissue and blood vessel formation using this scaffold has been demonstrated. The tuneable pore size, high osteoinductivity and high mechanical strength make it ideal for use in load bearing tissue implants.

HA nanoparticles have been widely used for re-engineering due to their enhanced mechanical properties and ability to improve cell growth and proliferation. Needle-like HA nanoparticles with PLLA [poly (L-lactide acid)] have been used to develop composite scaffolds to create bone structures with mechanical strength of natural bones, high porosity, high cell affinity and biocompatibility [16]. Tantalum coated with nanophase HA has shown increased bone growth[17].

4.3.2 Cartilage Implants

One of the biggest problems with cartilage tissue is its' inability to repair itself. Several approaches have been proposed to overcome this. One of the most widely used methods is the regeneration of cartilage tissues *in vitro* on a 3D scaffold and transplanting it to the damaged location. Several nanomaterials and polymers have been proposed as suitable materials to create cartilage tissues.

A PLGA/HA nanocomposite for cartilage regeneration enhanced chondrocyte (cartilage cell) attachment, proliferation and response and doubled the tensile strength[18]. A self-assembled peptide hydrogel was used as a scaffold to encapsulate chondrocytes for cartilage tissue repair and regeneration[19]. Anodised Ti with nanosized pores has been found to increase chondrocyte adhesion and migration[20].

Recently, implants made from carbon nanotube composites were used to grow cartilage cells[21]. Electrical pulses were applied to the composites and accelerated cell growth and production, while the presence of the CNTs gave increased mechanical strength. The biocompatibility of CNTs must be addressed before this application can be realised.

Adult mesenchymal stem cells (MSCs) grown on a nanofibrous scaffold have shown differentiation into chondrocytes[22]. Electrospun nanofibres of a synthetic biodegradable polymer, poly(e-caprolactone) (PCL), were used to construct the scaffold and MSCs were cultured on this scaffold in the presence of TGF-b1. The cells differentiated to a chondrocytic phenotype at a level comparable to that of MSCs maintained as cell aggregates or pellets. The nanofibre scaffolds can be constructed to any size and offer better physical support for cells. These properties make them good candidates for stem cell-based cartilage repair. (For more information on nanotechnology and stem cells please see the Regenerative Medicine subsector report).

4.3.3 Oesophageal, Tracheal and Bladder Implants

Advances in tissue engineering are creating opportunities to do more complex transplants. In the case of tracheal and oesophageal prosthesis, one of the biggest problems is the post-operation side effects like scarring, inflammation and oesophageal constriction. Also, the removal of damaged epithelial cells results in the loss of normal epithelial barrier function.

In the case of tracheal replacement, most existing methods are surgical and the mortality rates are high. It normally requires replacing the tissues with tracheal allografts or autologous portions of gastrointestinal segments. Cell sheet engineering has been used to grow epithelial cells *in vitro* and replace damaged cells using non-invasive methods. Tracheal replacement studies conducted on rabbits have shown successful migration of implanted cells onto the host trachea while the epithelial cell sheets formed a fully functional lumen[23].

For oesophageal transplantation, autologous oral mucosal epithelial cells have been seeded to create cell sheets. Wound healing improved remarkably causing very little inflammation[24].

Bladder cancer can result in removal of a large part of the bladder wall and in some cases the entire wall. Nanotopography, nanoscale features on a surface, plays an important part in improving cell adhesion, proliferation etc. Recent *in vitro* developments using this technique appear promising for future bladder repair.

Nanostructured polymers PLGA, PLA and poly-ether-urethane (PU) were chemically treated to increase surface roughness and used to grow bladder smooth muscle cells[25]. Enhanced cell adhesion was seen and is thought to be due to the roughness and nanotopography of the surface.

Electrospun polystyrene scaffolds have been used to support the growth of smooth bladder cells[26]. Fibrinogen[27] and cellulose acetate[28] have also been used to create nanofibre scaffolds that promote cell adhesion and proliferation of bladder cells. Harrington *et al.*[29] reported coating self assembling peptide-amphiphile (PA) molecules onto PGA and electrospinning to produce nanofibres. The advantage of incorporating PA is that it ends up in creating positively charged lysine moieties on the surface of scaffolds which enhances cell adhesion and matrix deposition. The PAs can also be used to encapsulate cells and other growth factors which can trigger the cell growth.

For a detailed review of nanotechnology in bladder replacement see Cheng *et al.*[30].

4.3.4 Vascular Implants and Stents

One of the biggest challenges in vessel fabrication is the complex multilayer architecture of the tubules. Different approaches based on tissue engineering have been proposed to overcome this. These include seeding cells in scaffolds to produce a 3D structure, cell sheet engineering and the use of hydrogels for cell growth. Electrospinning polymers to produce nanofibre scaffolds has been widely demonstrated as a method to create this complex vascular structure.

A collagen and elastin mix was used to produce fibres that can create three layered vascular tubes[31]. Human smooth muscle cells labelled with magnetic nanoparticles have been seeded onto the luminal surface of a tubular shaped collagen membrane to create vascular grafts[32]. Magnetic force was used to improve the seeding efficiency to 90%. Polydioxanone (PDO or PDS) a colourless, crystalline, biodegradable polymer used mainly in the preparation of sutures has been proposed as a suitable material for engineering vascular grafts[33]. Studies on the mechanical properties of PDO nanofibres show that they resemble that of natural soft tissues like collagen and elastin[34]. Fibres made using PCL/PLA mxtures have shown increased flexibility and elasticity while maintaining the tensile strength of PLA fibres, making them ideal for create vascular graft scaffolds which need to withstand pressures created by blood flow[35].

One of the most widely used implantable devices in vascular intervention is a stent. Stents are thin tubular devices implanted into arteries to support the blood vessels following angioplasty. They are commonly made of stainless steel, cobalt chromium alloys, or more recently Nitinol, an alloy of nickel and titanium with shape memory properties, which means they can be inserted in a collapsed form and expand once in place. While stents are extremely useful in restoring blood flow, their long term use is associated with several compatibility issues often requiring further surgery. Narrowing of arteries at the stent implant location can occur, leading to stent restenosis. One of the reasons for this problem is venous neointimal hyperplasia, aggressive growth of smooth muscle cells, in the vessel wall[36]. Often restenosis leads to the blood clots in the blood vessels, or thrombosis.

Stents are also used for urinary tract blockages and to extract bile from the gall bladder to diagnose diseases like gall stones. One of the issues associated with the use of plastic stents is the formation of sludge, followed by a blockage. This occurs because proteins, glycoproteins and bacteria adhere easily on the surface of the stents and the bile flow is not sufficient to clean the surface[37]. The use of nanotechnology has been suggested as the best possible solution to some of these problems.

The formation of endothelium on stent surfaces is considered as a suitable solution to restenosis. The creation of nanostructured features on the surface of widely used stent materials can promote endothelial cell growth and proliferation[38]. Nanostructured Ti and CoCrMo showed increased endothelial and vascular smooth muscle cell adhesion compared to conventional Ti and CoCrMo. Higher endothelial cell growth compared to muscle cell growth was also seen[39]. Endothelial cells loaded with polymeric magnetic nanoparticles have been targeted to the surface of stents, both *in vitro* and *in vivo* (rats), using a magnetic field[40]. Coating stents with nanoporous ceramic coatings has also been found useful against thrombogenesis. Hydroxyapatite and alumina are being experimented as stent coatings.

Nanoscale sol-gel coatings have been used successfully to reduce sludge accumulation in biliary Teflon stents[41].

Layer by layer deposition of nanocoatings on the surface of arteries have also been reported as a way of treating damaged blood vessels. Self-assembled polysaccharide-based nanocoatings were deposited onto damaged arteries, preventing platelet adhesion and thrombogenesis[42].

Drugs may also be incorporated into stent coatings for controlled delivery when implanted and could be used to treat conditions such as hyperplasia. Deposition of self-assembled monolayers (SAMs) on stent surfaces has been used to create drug eluting stents with excellent stability[43]. PLGA nanoparticle-paclitaxel conjugates were loaded onto vascular grafts and delivered the drug while reducing the initial burst release[44].

4.3.5 Neural Implants

The process of neuron regeneration is extremely difficult, as is developing neural implants Nerve cells require the correct environment and growth factors at the right time to grow and proliferate. They also need inductive scaffolds.

Carbon nanotubes (CNTs) or nanofibres have been proposed as ideal materials to replace or annex axons due to their electrical properties. Carbon nanotube fibres have been used to promote mammalian and neuron cell growth, migration and proliferation[45]. Carbon nanofibres have also been used to reduce scar tissue formation[46]. Astrocytes (glial cells that form scar tissue) adhered less on carbon nanofibres in the lower nanometre range.

Biodegradable polymer scaffolds for nerve tissue generation have been reported[47].

Scaffolds that can overcome the difficulties of axonal regeneration after injury to the central nervous system (CNS) have also been reported[48]. Scaffolds from self-assembling peptide nanofibres were developed in order to avoid the common problems in neural implants like scar tissue formation, gaps in the nervous tissues formed during phagocytosis of dying cells, and the difficulties in axonal extension by adult neurons. Studies on adult hamsters with their eyes disconnected from their brain showed that the use of peptide scaffolds allowed axon growth while inhibiting/discouraging the scar formation. They were also able to conform to the injury site. As the environment changes, the material will remodel to fit the new environment, allowing for regeneration. 75 % of animals treated with nanofibre scaffolds for injury in the optic tract had restored functional vision compared to none without the scaffolds, showing that regenerated axons can support visual behaviour. The fibres mimic the natural ECM and can be can be broken down safely into natural amino acids, thereby reducing the chances of rejection.

Biocompatible self-assembled monolayers, containing 16-mercaptohexadecanoic acid (MHA) and end-thiolated poly(3-(2-ethylhexyl)thiophene) (EHPT) in varying proportions, were formed on gold. When coated on neuron electrodes, the presence of EHPT in the SAM increased biocompatibility and reduced impedance[49]. This method is significant over other types of coatings as it does not increase the separation between electrodes and neurons, so does not reduce the signal strength. It also offers the flexibility to add dopants to improve the conductivity. Nanofibrils fabricated on neural prosthetic devices with a poly(3,4-dioxyethylenethiophene) (PEDOT) coating to improve conductivity and reduce impedance[50]. These conducting polymer coatings offer huge opportunities in neural implants and biosensors.

Layer by layer assembly has also been used to create coatings on the surface of electrodes. Nanoscale coatings were formed on Si/SiO_2 substrates by alternating polycations [polyethyleneimine (PEI) or chitosan (CH)], with polyanions (gelatin or laminin). The coatings didn't alter the impedance, were stable for nearly 7 days and promoted neuron growth[51].

Electrical stimulation is considered as a promising way to restore the functionalities of damaged brain cells. Many techniques have been tried in the past to provide electrical impulses to stimulate the cells. Insertion of micro-machined devices or electrodes of nanotubes and nanowires have been proposed for brain stimulation.

Nanowire arrays have been used as contact sites for neural stimulation and for analysing isolated single unit activities[52]. An array offers higher surface area and is an ideal alternative to the existing neural implants. Also, nanotubes and nanowires have high conductivity making them ideal for electrical stimulation of brain.

Micro-machined devices made from single crystal silicon wafers and silicon on insulator wafers were inserted into the brain and their effects on brain stimulation were studied[53]. Two types of response were seen in animal models. One proportional to the size of the device which was due to insertion of the devices, and a second , a sustained response due to the tissue-device interaction. All animals survived the experimentation period and recovered well from the surgery without any side effects. Micro-machined devices have been used for deep-brain stimulation of the subthalamic nucleus without damaging the neighbouring tissues[54]. This type of stimulation using small devices has significant possibilities in the treatment of degenerative diseases such as Parkinson's and Alzheimer's, and for blindness, spinal injuries etc.

4.3.6 Pacemakers, Retinal and Cochlear Implants

Nanotechnology also has applications in pacemakers. One of the main problems with existing pacemakers is that they are not energy efficient. In most of the cases, the battery needs replaced every two years and even the newest Li batteries only have a lifetime of 7-10 years. Another problem is the pacemakers' intolerance to high electromagnetic fields such as those used in MRI. This may lead to damaged or destruction of the pacemaker and/or the adjacent tissues. Optical fibres have been used instead of electrical leads to solve this problem. However, the need for a constant power source is still necessary. The NASA Ames Research Centre for Nanotechnology (http://www.nasa.gov/centers/ames/) and Biophan (http://www.biophan.com/) have developed a battery suitable for implantable devices such as pacemakers which can convert body heat into electricity[55].

Spintronic technology, which is based on the spins of electrons rather than charge, has applications in medical devices like pacemakers, neurostimulators and cochlear implants. The most common spintronic device is a spintronic sensor which uses the principle of giant magneto resistance (GMR). GMR is a phenomenon of high signal production in relation to small changes in magnetic field when a nonmagnetic conduction layer is sandwiched between two ferromagnetic layers. The optimum thickness of the middle layer for maximum signal production is typically around 3 nm. Copper is often used as the middle layer due to its high resistance at this thickness. Spintronic sensors have been hailed as the next generation sensor devices due to their high sensitivity and precision over other sensors. They can withstand large magnetic fields, making it ideal to use with MRI. However, the key advantage is that it integrates well with the existing devices and conventional semiconductor processing can be used to develop them[56]. Spintronic devices can be mainly used for the replacement of ampoule and MEMS reed switches for the magnetic activation of programming and special modes in implantable devices. The sensors fitted on the implants allow high speed data communication between a remote computer and the implant, allowing real time data monitoring. In the case of cochlear implants, GMR-based sensors can switch signal processing modes without user intervention[57]. NVE Corporation (www.nve.com) makes spintronic devices for the pacemaker and hearing aid market.

Tissue engineering has been used to restore damaged endothelial and epithelial cells in the human cornea. Cell sheet engineering can create corneal epithelial and endothelial cell sheets which can be transplanted to restore vision[58]. Genetically modified corneal epithelial stem cell sheets have been used to treat hereditary corneal diseases[59]. Modified versions of corneal endothelium, which exists as a monolayer under the stroma to maintain its hydration and thickness, have been constructed *in vitro*.

One of the problems with endothelium is that it will not regenerate easily *in vivo*. Using the cell sheet engineering method, endothelial cells have been cultivated and grown on collagen-coated sheets, obtaining a density similar to that of normal tissue[60]. Increased collagen and fibronectin deposition was also observed in ECMs. When tested in rabbit models, the endothelium maintained the stromal hydration and thickness similar to natural cells and reduced the amount of swelling.

A recent clinical study implanted a 4 mm square of retinal tissue containing retinal progenitor cells and the retinal pigment epithelium in the sub-retinal space under the fovea. A large improvement in vision of patients was seen, however this deteriorated over 6 years post-implantation[61]. This demonstrates that tissues can be implanted in sensitive locations without any adverse reactions.

One of the challenges in the field of active implants is how to stimulate nerves without damaging the surrounding tissues. Nerves can also take at least three months to recover after implanting a device. One possible way to avoid this damage is to integrate the nerves with the electrodes and allow them to grow on these. Such a high level of integration would allow packing of a large number of electrodes into a small space, providing a higher level of stimulation. MEMS have been already utilised to create device platforms for integrating a large number of electrodes. However, integrating nerves has proved difficult. Electrodes with polymer coatings have been synthesised to help the nerves to grow and connect faster[62]. These coatings can be designed to release drugs and biomolecules for a prolonged period of time. When tested on retinal implants from rabbits, the neurons grew and extended into the electrodes. The coatings released neutrophins for a period of three months. By using these coatings, a much more efficient electrode-tissue interface can be achieved, which could be used to reduce the high stimulation thresholds required to enhance neuron growth.

60 electrodes have been integrated on a chip and implanted for retinal stimulation. In this system, the patient wears a pair of glasses fitted with a camera which sends wireless signals to the chip implanted on the retina. The electrodes receive these signals, convert them to electrical pulses and send them to the neural cells in the eye, mimicking the role of light sensitive cells. These signals are then relayed to the brain. It offers a significant improvement to those who lost vision due to retinitis pigmentosa or macular degeneration[63]. However, in the future the key will be the ability to manipulate the electrodes to stimulate the cells in such a way that it is recognised by the brain as natural stimulation. Artificial synapse chips and their ability to be used as neurotransmitters in retinal implants have been studied earlier. A prototype device containing 150nm gold electrodes for neuron stimulation has been developed for chemical neurotransmission[64].

Silicon nanowires have been proposed as alternatives to conventional electrodes as they have the ability to detect multiple signals from neurons. Conventional electrodes can only detect 1 or 2 electrical signals but nanowires can detect signals from 50 different points in a neuron[65]. This ability to form multiple junctions offers the capability of simultaneous measurement of the rate, amplitude, and shape of signals propagating along individual axons and dendrites. Another advantage of nanowires is their similar size to axons and so the signal transfer between neurons using them as an interface will be similar to axon-axon transfer. Nanowires can act as field effect transistors and amplify very small signals from neuron-nanowire junctions. They have potential applications in cochlear implants and can also be used to replace damaged nerves or in the treatment of other CNS diseases. Up to 50 nanowires have been incorporated into a small chip, offering another opportunity to use it as a device for diagnostic and drug discovery applications.

4.3.7 Other Developments

Sensors are getting smaller and smaller, but with high sensitivity, due to the unique properties at the nanoscale. These properties have been combined with other technologies, such as artificial intelligence, to create artificial knees which can learn from experiences to reduce the chance of fall in the future. Microprocessors which control smart implant systems have been developed by Ossur (http://www.ossur.com/). The proprietary Bionic Technology allows their RheoKnee™ to learn the users walking patterns and to go beyond the defined parameters to adapt to constant changes in the surroundings to reduce failures.

In therapies which require sustained release of drugs, immunoisolation of implants is very important. Desai *et al.*[66] report the development of a biocapsule which allow the movement of molecules of less than 7 nm while preventing those larger than 15 nm between the capsule and the external environment. Using BioMEMS fabrication methods, they created uniform pore sizes on the surface of membranes with sizes as low as 7 nm. The system was successfully tested for cell delivery in diabetic rats[67]. Diabetes was reverted in rats from day 1 after insulinoma cells encapsulated in the capsule were implanted.

Implantable nanoscale thin films that can be precisely controlled to release chemical agents have been proposed for drug delivery, gene delivery, tissue engineering, diagnostics and chemical detection.

4.3.8 Nanotechnology in Surgery

4.3.8.1 Surgical blades

Advances in novel manufacturing methods have enabled the production of surgical blades with a cutting edge diameter in the region of 5nm -1 µm. Ophthalmic surgical blades which offer a blade edge radii of 5-500 nm have been manufactured from either a crystalline or polycrystalline material[68]. The blades are prepared from crystalline or polycrystalline silicon wafers by mounting them and machining trenches into the wafers. With this method, any required angle can be obtained and the resulting blade has a cutting edge of that of a diamond edge blade. Such blades can be used for various complex surgical operations such as cataract surgery.

However, these blades can bend on contact with tissues and this forces the surgeons to use more cutting force, increasing the chances of tissue damage. Lingenfelder *et al.*[69] report the development of trephines with nanostructured carbon coatings to obtain cutting edges of higher stability and properties like diamonds. Studies conducted on pig cornea using the carbon coated blade revealed smooth surfaces compared to unmodified cutting edges. Force measurements observed a reduction in cutting forces for the modified blades and the cornea treated with the modified trephines showed a smoother surface. This is mainly due to the diamond-like properties of the carbon coated trephines that lowered the frictional coefficient. Additionally, these properties create biological inertness on the surfaces of blades which reduce the physical adhesion to tissues[70].

Diamond-coated surgical blades with an approximate surface roughness of 20 - 40 nm have been developed by GFD Gmbh (http://en.blades.diamaze-gfd.com/).

4.3.8.2 Nanoneedle

Nanoneedles have a typical diameter of 200-300 nm and can penetrate into the cells without causing cell damage or death. Typically they are made from silicon using existing fabrication methods and are used as AFM tips to carry out cell surgery or molecule delivery. The advantage of the needles over existing capillaries is that they can manipulate cell activity and monitor reactions simultaneously without damaging the cells.

Nanoneedles with a length of 6-8µm have been used to penetrate human epidermal melanocytes and HEK293 (human embryonic kidney) cells[71]. There was no shape change in plasma membrane and the nucleus remained intact. In this system the displacement of the needle is accurate and it is possible to monitor and control the force on the needle, potentially enabling single cell manipulation. The position of the needle can be estimated by monitoring the force on the needle. The surface of the needle can also be modified to load and deliver various biomolecules like proteins and nucleic acids.

Pyramid-type AFM tips with an estimated radius of curvature of 50 nm have been used to remove large patches of the outer cell wall of the bacterium *Lactobacillus helveticus*[72]. Recently, CNTs were functionalised to behave as nanoneedles to penetrate plasma membranes and translocate directly into the cytoplasm for drug delivery applications[73].

4.3.8.3 Nanotweezers

Nanotweezers are surgical tools which can be used to grab and move single biological molecules within cells. These tweezers, typically with a thickness in the nanometer range and controlled by electrostatic forces, are developed by attaching carbon nanotubes to the end of electrodes. These nanotubes are then manipulated by electric forces which bends the nanotubes inwards to grab the molecule. The first nanotweezers had a diameter of 50 nm and began functioning at 8.5 V[74]. The physics behind the technique is that the nanotweezer tries to balance the elastic energy cost with the electrostatic energy gain allowing it to close beyond a certain voltage.

Since carbon nanotubes are used as nanotweezers, it is also possible to measure the electrical properties of the materials grabbed. The technique can be applied to manipulate and move biological molecules like DNA. One of the potential applications of nanotweezers is conducting surgery on single cells. Silicon nanotweezers with an initial tip gap of 20 μm were used to perform static and dynamic mechanical manipulations on DNA molecules. The technique was used to study the viscoelastic behaviour of DNA bundles and obtained a resolution better than 0.2 nm in static mode[75].

Nanotweezers have shown that the drug topotecan kills cancer cells by preventing the enzyme DNA topoisomerase I from uncoiling double-stranded DNA in cells. Nanotweezers were used to monitor changes in the length of an individual DNA molecule caused by the action of a single topoisomerase I enzyme. The technique was also used to study how the binding of the drug to this enzyme-DNA complex changed DNA uncoiling[76].

Optical tweezers which use lasers to manipulate biological cells have also been suggested as a method of non-invasive surgery. The intensity of the light and momentum created by the continuous application of laser beam can be used to move and manipulate biomolecules.

4.3.8.4 Femtosecond Lasers

A femtosecond laser is a laser which emits ultrashort optical pulses with durations in the range of femtoseconds (1 fs = 10^{-15} s). These lasers belong to the category of ultrafast lasers or ultrashort pulse lasers capable of creating intensities in the range of 10^{13} W/cm^2. Their ease of use, precision, and ability to localise light make them excellent tools for the manipulation of structures and biological molecules.

Femtosecond lasers have been used to cut and reshape the cornea to correct vision in humans. Using a femtosecond laser, the damage caused to the endothelial tissues on the surface of the cornea has been eliminiated[77]. These lasers have also been used to cut single actin stress fibres in living cells and study the changes in cell shape[78], and to cut chromosomes[79]. They have also been used to remove mitochondria from living cells while retaining cell division[80]. This demonstrates the use of lasers for nanosurgery to remove specific organelles without affecting long term viability.

Due to their precision, femtosecond laser ablation has found several applications in the medicine area. Irradiating targets with repetitive pulses to create cumulative effects has been tailored for specific applications. Femtosecond laser ablation has been used to study the factors that affect nerve cell regeneration and growth[81]. The advantage of this technique is the ability to cut individual axons. The laser system was also used to find out which specific neuron responded to changes in temperature[82]. They have also been used to create artificial occlusion and haemorrhages in rodents to study the effects of strokes on the health of older people[83]. A good review of femtosecond lasers by Nishimura *et al.* is available[84].

4.3.8.5 Catheters

Catheters are small tubes which are inserted into the body cavity to inject or drain fluids or to keep a passageway clear. One of the issues associated with catheters is thrombus formation on the surface of these devices. CNTs have been studied as a suitable material for developing catheters. A polyamide (nylon) catheter reinforced with CNTs was developed for insertion into blood vessels in the brain or heart. The flexibility was increased, the damage upon bending was decreased and thrombus formation was reduced[85].

Catheters can also be coated with silver nanoparticles to give them antibacterial properties and prevent surface biofilm formation[86]. Other antibacterial coatings have been reported in attempts to reduce bacterial colonisation on catheter surfaces[87].

Verimetra Inc. (www.verimetra.com) is developing a 'smart catheter' that incorporates nano biosensors to provide surgeons with real time data on tissue density, temperature and other environmental factors at the site. This will allow them to develop faster methods for preparing, cutting and extracting tissues and fluids. It will also be useful in a variety of surgical areas like cardiovascular surgery, stent insertion, percutaneous transluminal coronary angioplasty, cerebrovascular surgery etc[88].

4.3.9 Wound care and Smart Textiles

4.3.9.1 Silver

Silver, known for its antibacterial properties, has been used for centuries for antimicrobial applications. However, silver nanoparticles smaller than 100 nm are now widely used in consumer products, biomedical equipments, textiles and wound care[89]. The increased surface area offers a larger contact area and hence increased antimicrobial properties. It can also allow silver coatings to be incorporated into new areas e.g. textile incorporation or coating on medical devices. The silver particles' ability to kill microbes rapidly by blocking the respiratory pathway or by breaking the outer walls have made it useful for dressing scars, wounds, acne etc.

The antibacterial properties of silver are utilised in wound dressings. Several methods for incorporating AgNPs into dressings are used. These include padding or spraying, surface treatments on hydrogels, adding it onto material compounds and methods like chemical vapour deposition or ionic plasma deposition[90]. In a multilayer wound care structure, AgNPs are added onto the wound contact layer, normally made of polymers. Actisorb[i], by Johnson & Johnson, is an activated charcoal cloth which incorporates AgNPs for wound dressing. Smith and Nephew's nanosilver dressing, Acticoat[ii], has a broad antimicrobial spectrum effective against most common wound pathogens[91]. Nanosilver dressings are also effective against MRSA[92]. These dressings protect and cover the wound and provide a moist environment for faster healing. They can also reduce the number of dressing changes required. Nanosilver has been shown to increase the speed of wound healing[93].

An eco-friendly and cost effective method for the mass production of nanosilver coated fabrics have been reported[94] and socks containing 0.3 % w/w nanosilver are produced by JR Nanotech (http://www.jrnanotech.com/) to protect against foot infections.

A powder of TiO_2 nanoparticles coated with silver, developed by the German company ItN Nanovation GmbH (www.itn-nanovation.com), is effective against the SARS virus[95]. The powder, marketed as Nanozid, can be added to paints and lacquers to coat operating tables, door knobs or door handles in hospitals to deactivate pathogens like bacteria, virus or fungi.

There are concerns surrounding AgNPs. Currently little is know about their fate within the body or the environment. Nanoparticles may react and interact very differently within the body and in the environment. However, ionic silver is known to be toxic to aquatic organisms, raising concerns for the washing of textiles. More toxicity studies are needed, especially due to the number of products currently available using this technology.

A good report on the issues surrounding nanosilver has been published by the Project on Emerging Nanotechnologies[96]. However, nanosilver adds value to many products and is likely to continue being used extensively in the future.

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[i] http://www.jnjgateway.com/home.jhtml?loc=USENG&page=viewContent&contentId=09008b9880ec8c74

[ii] http://wound.smith-nephew.com/UK/Standard.asp?NodeId=2792

4.3.9.2 Wound care fabrics

Self-assembling peptides have been used to create a nanofibre mesh extracellular matrix to stop bleeding[97]. Hemostasis was achieved in different types of wounds and multiple tissues in less than 15 seconds. The matrix is made of biodegradable, synthetic materials which do not contain any blood products, collagens, or biological contaminants and can be applied directly onto the wound. The material can then break down and be used as building blocks for repair, or excreted. It does not expand once applied, thereby reducing the risk of secondary tissue damage as well as problems caused by constricted blood flow.

Electrospun nanofibrous polyurethane membranes have been used in wound care[98]. The porous nature of the nanofibres allows oxygen permeability, promotes fluid drainage and controls evaporative loss. The use of the fibres increased epithelialisation and the dermis became well organised. Similarly, electrospun silk fibroin nanofibres were reported as suitable materials for use in wound dressings[99].

The concept of smart textiles which can respond to the changes in the environment has been explored to provide new functionalities like self cleaning, sensing and communication. Textiles that incorporate sensors which can measure and monitor changes in the body mechanism have been explored for healthcare applications. In normal cases, sensors are considered separate components which are attached to the textiles to do the monitoring functions. However, the shift is towards functionalised fabrics.

Electrospun CNT fibres have also been proposed for creating smart textiles utilising its strain sensing ability. Piezopolymers electrospun into smart fabrics showed a 35 times increase in strain sensing capability[100]. CNTs have also been incorporated into the fabrics by immersing textiles in aqueous sulfonated polyaniline-carbon nanotube dispersion. The formed textiles doubled the capacitance and increased the conductivity by four times compared to the sulfonated polyaniline dyed textiles. Stretching experiments have shown that the textiles retained their textile behaviour even after repeated stretching indicating that it can be used as wearable strain gauges[101]. The EU Biotex project is exploring the possibility of incorporating biosensors into wound dressings to monitor wound healing. A biosensor is programmed to monitor pH and C-reactive protein expression to measure the degree of inflammation. This monitoring and the capability to signal warnings at an early stage will enable clinicians to detect inflammations and take appropriate action. The technology could also be used in other areas such as skin grafts and ulcer treatments.

More information on nanotechnologies in textiles is available in the observatoryNANO Textiles sector report.

4.4 Additional Demand for Research

- Development of novel biocompatible composites for bone replacements
- Developing biocompatible instruments by better functionalisation.
- Developing ‘smart stents’ which can respond to changes in the environment.
- Surface modification techniques to enhance implant integration.
- Development of novel coatings to immobilise functional molecules on implant surfaces.
- Methods for large scale production of ceramic nanocomposites suitable for bone and dental implants.
- Studies on the potential of nanotubes in implants.
- Development of animal models to test the efficiency and toxicity of various biomaterials.

- Development of novel polymers, polymer mixes and self assembled compounds to improve the stability, biocompatibility and integration of implants.
- Methods to prevent implant related infections.
- Coatings to improve the stability and surface smoothness of surgical blades.
- Development of novel power generating devices which can be implanted to support active implants like pacemakers and cochlear devices.
- Methods for the selective stimulation of nerve cells.
- Methods for further miniaturisation of implantable active devices.
- Techniques to improve the sensitivity of nanosensors and methods for their incorporation in devices.
- Development of functionalised fabrics which can sense environmental changes and respond accordingly.
- Active vs. Passive biomaterials
- Degradation measures
- Active indicators of functionality of implant
- A reachable standard for purity or impurity of an implant
- Shedding standards for various implanted devices
- Molecular medical devices

4.5 Applications & Perspectives

Novel materials, techniques and coatings for implants and stents have enabled the creation of implants with much higher biocompatibility and integration. The ability to control and encourage effective cell growth and differentiation using novel nanostructured materials or nanotopography significantly improves the function and lifetime of implants. More recently there has been interest in 'smart' implants that are dual purpose. For example, implants that can also deliver anti-infection medication or bone implants seeded with magnetic nanoparticles to treat bone cancer. These will allow improved treatment of diseases and significantly reduce patient discomfort. Reproducible, accurate and scaleable methods of patterning surfaces with nanoscale features are required for the production of new implants.

The anti-bacterial properties of silver are well known; however the safety of using silver nanoparticles, particularly on open wounds, should be addressed.

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