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SURGICAL TECHNIQUES AND INNOVATIONS

Nanotechnology for Surgeons

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Abstract Surgeons are constantly looking for minimally invasive ways to treat their patients, as recovery is faster when a lesser trauma is inflicted upon a patient, scarring is lessened and there are usually fewer complications in the aftermath of the operation. Through nanotechnology, tiny biosensors could be constructed which could take these factors into account, thus shortening a patients recovery period and saving hospitals money, reducing infection rates within the hospital, reducing the waiting lists for operation and allowing doctors to treat more patients in the same period of time. One of the greatest achievements of nanotechnology in surgery will be what we call the “ideal graft”; that is, biocompatible and durable “repairs” of parts of the body like arteries, joints or even organs. At first, these repairs will be used for healing, but soon afterwards, they will be used for transcendence: to enhance current human abilities.

Keywords Nanotechnology · Surgery · Implants coatings · Nanobots · Nanosurgery · Nanosurgical tools

The application of nanotechnology to medicine referred to as ‘nanomedicine’ or ‘nanobiomedicine’ impacts diagnosis, monitoring and treatment of diseases as well as control and understanding of biological systems. Nanotechnologies dedicated to biology are called ‘nanobiotechnologies’. [1–7] Surgery is defined as ‘dealing with the treatment of injury, deformity and disease, by both manual and instrumental means’. Surgery has evolved from ‘no more science than butchery’ to a highly respected science, and even an art. However, we still do not treat diseases and we do not heal. We only open the way for the body to heal itself, as gently as possible. But even the gentlest microsurgeon is very crude in terms of the nanotechnological scale of tissue. After all, a scalpel is millions of times bigger than a cell. In traditional (‘open’) surgery, surgeons have to cut through healthy tissue in order to expose the internal organs to be operated on. Within the last two decades, however, there has been a move towards minimally invasive procedures. The benefits of minimally invasive surgery are: a decreased injury to tissue and so less scarring; fewer complications; less postoperative pain and faster rehabilitation. The driving force nowadays is to make surgery progressively less invasive. By producing a new set of tools on the nanoscale, one can perhaps imagine a surgeon being able to make changes to and track individual cells. Today, the tools have been refined, and the environment, both in and around the patient, is carefully controlled. Surgical tools are now predominately made of stainless steel or tungsten. Titanium instruments have also been introduced, and some advances have been made in diamond-coated blades. Synthetic materials such as polyglactin and polypropylene have now largely replaced natural materials such as hair and animal gut (which tended to produce adverse tissue reactions) as sutures used to close wounds [1, 3].

The potential for the use of nanotechnology in surgery is huge. Surgeons are constantly looking for minimally invasive ways to treat their patients, as recovery is faster when a lesser trauma is inflicted upon a patient, scarring is lessened and there are usually fewer complications in the aftermath of the operation. More radically, the potential of the applications of nanoscience within surgery is nanobots [5, 6, 8–12], which are robots which would be miniaturized for entry into the body through cavities. A nanobot controlled by a surgeon using a computer could perform precise surgery within cells, which humans aren’t capable of as scalpels are

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thousands of times larger than a single cell. Femtosecond laser systems can be used to target and destroy individual organelles without disrupting the rest of the cell. These nanoscale lasers are already being used in corneal surgery and have been used to investigate nerve regeneration in worms to provide insight into possible treatments for human neurological disease. [1, 3]

One of the greatest achievements of nanotechnology in surgery will be what we call the 'ideal graft', that is, biocompatible and durable 'repairs' of parts of the body like arteries, joints or even organs. At first, these repairs will be used for healing, but soon afterwards, they will be used for transcendence: to enhance current human abilities. This trend is already apparent in plastic surgery that aims at appearance enhancement. Expect this trend to appear in other surgical specialties, like orthopaedics for enhanced athletes, transplantation of organs from bioprinting or stem cells, new coronary arteries delivered with angioplasty balloons, enhancement drugs with DNA modifications and many others.

The surgery as such involves diagnosis based on clinical and imaging studies followed by surgery and postoperative period. The better the diagnostic modalities, the better will be the treatment planning and execution of surgery. Diagnostic modalities such as MRI, ultrasound and nuclear imaging modalities are most affected by nanotechnology. They improve quality of diagnosis, planning and execution of surgery. Surgical instruments mostly affected by nanotechnology are scalpel and needles. Targeted drug delivery to site of infection increases efficacy of drug, reducing morbidity and mortality of normal adjacent tissues. This technology helps in reducing trauma during surgery, leading to decreasing postoperative complications

Nanocoated Surgical Blades [1, 13]

By producing a new set of tools on the nanoscale, one can perhaps imagine a surgeon being able to make changes to and track individual cells. This could be very beneficial for neurosurgical aspects, for example and, in addition, the patient will benefit from the reduced trauma of even smaller wounds. The performance of surgical blades can be enhanced significantly when microstructured hard metal is coated with diamond and processed. Major advantages of the diamond nanolayers in this application are low physical adhesion to materials or tissues and chemical/biological inertness. In addition, diamond has a low friction coefficient, decreasing the penetration force necessary. Advances in novel manufacturing methods have enabled the production of surgical blades with a cutting edge diameter in the region of 5 nm–1 μm. The diamond scalpels with a cutting edge of only a few atoms (approximately 3 nm) have been made for applications in eye, neurosurgery and minimal invasive surgery. The width of the scalpel blade is approximately one thousandth of a metal blade.

Ophthalmic surgical blades which offer a blade edge radii of 5–500 nm have been manufactured from either a crystalline or polycrystalline material [14]. 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 equivalent 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 [15].

Trephines with nanostructured carbon coatings to obtain cutting edges of higher stability and properties like diamonds have been developed [16].

Nanoneedles [1, 13, 16]

New suture needles for ophthalmic and plastic surgery are made of stainless steel incorporating nanosize particles (1–10 nm quasicrystals) by using thermal ageing techniques. Such needles have good ductility, exceptional strength and corrosion resistance. Nanoneedles prepared from silicon and attached to an atomic force microscope can be used to penetrate the nucleus of living cells to deliver molecules and may be even used to carry out cell surgery. The sizes of these nanoneedles are 200–300 nm in diameter, and 6–8 μm in length. It was demonstrated that nanoneedles do not indent the plasma membrane and nucleus, but penetrate through the membrane. Minimal deformation of cells is essential for cell manipulation because undesired mechanical responses may interfere with the result of manipulation. By modifying the surface of a nanoneedle, various molecules such as DNA, proteins or chemicals can be loaded by standard immobilization techniques.

Atomic Force Microscopy with a Nanoneedle [1, 13, 16]

Atomic force microscopy is a type of microscopy in which a probe is scanned across the sample to obtain information about its surface, investigating specific properties by contact and indentation of the cell with an ultrathin nanoneedle. This cell surgery technique could be used to induce differentiation from stem cells to prepare healthy cells for donation of functional cells to a patient.

Optical Tweezers [16]

Single-gradient optical trap, often referred to as optical tweezers, is a powerful technique for non-invasive manipulation of micron-sized objects, including single living cells, organelles within cells and viruses, for nanomanipulation of biological molecules. When a continuous wave laser beam strikes an object, forces arising from the momentum of the light itself can precisely reposition objects by steering the laser beam. Nanotweezers are surgical tools, which can be used to grab and move single biological molecules within cells. These tweezers 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 [17]. 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 [18].

Femtosecond Laser Neurosurgery [1, 13, 16]

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}/cm^2. Their ease of use, precision and ability to localize 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 [19]. These lasers have also been used to cut single actin stress fibres in living cells and study the changes in cell shape, and to cut chromosomes. They have also been used to remove mitochondria from living cells while retaining cell division. This demonstrates the use of lasers for nanosurgery to remove specific organelles without affecting long-term viability [16].

Ultrashort pulse laser can perform extremely precise surgery and cut nanosized cell structures, as shown in nerve cells [20]. Usually, conventional lasers first heat the target area, and then cut it, but this increases the risk for tissue damage. The advantage of ‘nanoscissors’ is its ability to cut cell organelles without harming the surrounding tissue. The technique uses a series of low-energy femtosecond (femto= 10–15) near-infrared laser pulses. The low energy and short laser pulse should significantly reduce mechanical effects, i.e. plasma extension and shock waves, heat accumulation and extended thermal damage to the surrounding tissue with respect to other laser-surgery techniques [21]. The femtosecond laser axotomy technique could be used to investigate mechanisms affecting nerve cell regeneration and development. Other applications of femtosecond laser systems are in ophthalmology for corneal refractive surgery [22] and dermatology [23].

Catheters for Minimally Invasive Surgery [1, 13, 16]

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. Nanomaterials, e.g. carbon nanotubes, have been successfully added to catheters used in minimally invasive surgery to increase their strength and flexibility and reduce their thrombogenic effect. Improved electrostatic properties and dense surface topology caused by the nucleation function of the carbon nanotubes have probably contributed to the antithrombotic property. Catheters can also be coated with silver nanoparticles to give them antibacterial properties and prevent surface biofilm formation [24].

Nanocoated or Nanocontoured Implant Surfaces [1, 13]

An implant is an artificial structure whose purpose is to replace or stabilize damaged body functions and include many different types such as hip , knee joints or temperomandibular joint and treatment of bone fractures. Materials such as titanium, cement and polymers were introduced to address biocompatibility problems.

Conventional orthopaedic/dental implants suffer from a restricted lifetime caused by implant failure. There are many reasons for failure of implants such as poor initial growth on surface of implants, which is to integrate bone, generation of wear debris in articulating components of implant, stress and strain imbalance between implant and surround structures [25]. Failure rate can be decreased if implant material stimulates rapid formation of new bone or if an implant is firmly fixed within adjacent bone (osseointegration). Initially, metallic implants preferred for joint replacement were stainless steel and cobalt chrome alloys, primarily used for their good mechanical properties. However, the high Young’s modulus of these materials resulted in stress-shielding and bone resorption. Stress-shielding should be avoided, since living bone must be under some tensile load to remain healthy. Osseointegration minimizes stress and strain imbalances at the tissue-implant interface. Therefore, the implantable material properties should match the mechanical characteristics of the surrounding bone tissue. To correct these failures, various approaches have been tried such as manipulate surface of implant, which will lead to manipulation of osteoblast function. This is done by supersaturation of calcium and phosphate on surface of implant. Another method is by increasing surface roughness of implant material [25–27].

Recent studies have demonstrated that adsorption and confirmation of proteins that mediate specific osteoblast adhesion are enhanced on nanophase material mainly due to their altered surface energetics. The bioactivity of proteins is altered on nanophase materials because both wettability and surface characteristics are close to size of proteins. [25] It is evident from the literature that the hydrophobicity or hydrophilicity of a surface can significantly alter cell behaviour. Moreover, the wettability of a material can allow for characterizing materials with regards to the hydrophobic/hydrophilic categories. Implant or biomaterial surface composition, surface treatment, surface roughness, immobilization of various chemical agents to the surface and presence of nanofeatures on the surface alter the surface wettability and affect cell behaviour. Improved wettability enhances adsorption of vitronectin and fibronectin on nanofeatures that stimulate the osteoblast adhesion.

New coatings are being developed at a nanolevel, which will greatly improve the wear characteristics, fixation and biocompatibility of surgical implants. Similarly, in combination with cells and tissues in the area of regenerative medicine, nanocontoured implant or scaffold surfaces can greatly influence the growth and proliferation of cells in beneficial ways.

Several investigations have been performed, exploring the properties of different coating materials such as nanostructured diamond, hydroxyapatite and metalloceramic coatings.

Chemical vapour deposition has been the most successful method of producing nanostructured diamond coatings, achieving a surface roughness of ~15 nm [28].

Although structure and hardness are strongly affected by processing parameters, it has been shown that nanostructured diamond coatings have good adhesion to titanium alloys and poor adhesion to cobalt-chrome and steel substrates [29]. Ultrahigh hardness, improved toughness, low friction, good adhesion to titanium alloys and biocompatibility characteristics are promising. Life time of orthopaedic implants could increase to upwards of 40 years [30].

For the optimization of bone growth, surface treatments have been applied, such as surface roughening by sandblasting, hydroxyapatite coating [31], formation of titanium dioxide or titania [32]and recently novel nanomaterials such as helical rosette nanotubes [33] and titania nanotubes [34].

In general, hydroxyapatite coatings are more accepted in dentistry than in orthopaedics, but the potential in both fields is high. Hydroxyapatite promotes bone formation around the implant, increases osteoblast (bone-forming cell) functions such as adhesion, proliferation and mineralization. Although hydroxyapatite coatings are now widely used to encourage device fixation and stability, they can lead to undesirable soft tissue, as well as growth of desirable hard tissue. Spire's nanophase hydroxyapatite coatings are modified to selectively encourage hard tissue growth on implants while discouraging the formation of soft tissue growth, which can result in non-optimal performance. Nanostructured metalloceramic coatings are still in the early stage of development and in vitro testing. Advantages are high hardness, very low surface roughness, good adhesion and corrosion resistance [13].

The aspect ratio and physical shape of carbon nanofibres mimic the crystalline dimensions of hydroxyapatite found in bone. Additionally, the dimensions of carbon nanofibres are similar to type I collagen fibres. It is hypothesized that another key parameter to emulate in nanostructures for bone implants is the constituent fibrous nature of bone [35]. Nanofibre rather than nanospherical material simulates more closely the nanometre dimensions of hydroxyapatite crystals and collagen fibres in bone that osteoblasts are accustomed to interacting with [36]. Fibrous encapsulation at the tissue-implant interface decreases the effectiveness of the necessary osseointegration of the implant and often results in clinical failures [36].

Another way to improve the performance of orthopaedic/dental implants can be achieved by modification of the surface roughness, specifically by creating nanometre-scale roughness.

Cell responses might be triggered by changes in surface roughness, i.e. in horizontal as well as vertical directions, in the nanometre domain (<100 nm) rather than on submicron scale (>100 nm). Increase in vitro osteoblast function and osteoclastic (bone-resorbing cells) response was correlated with nanometre surface roughness (ranging from ~20 to 300 nm) for nanophase alumina and poly-lactic-co-glycolic acid cast of carbon nanofibres [13].

Bone Replacement Materials [1, 13]

Hydroxyapatite nanoparticles used as bone replacement material, i.e. bone cement with improved mechanical properties, are commercially available. Indications for bone replacement materials are bone fractures, periprosthetic fractures during hip prosthesis revision surgery, acetabulum reconstruction, osteotomies, filling cages in spinal column surgery and filling in defects in children. Ostim® is an injectable bone matrix in paste form manufactured by Osartis GmbH & Co. KG (Obernburg, Germany). Ostim® is 100 %

synthetic nanoparticular hydroxyapatite and is fully absorbed after a few months.

Synthetic bone product NanOss™. The material is composed of hydroxyapatite nanocrystals, sized and shaped like native bone crystals with the strength of stainless steel. Another synthetic replacement material for cancellous bone grafts is VITOSS. VITOSS® contains β-tricalcium phosphate nanoparticles with a diameter of ~100 nm. It is engineered to resemble human cancellous bone in porosity and structure. Higher porosity and larger surface area, compared to conventional tricalcium phosphate, facilitates faster and increased bioresorption and vascular invasion.

Other Applications of Nanotechnology

Non-composite nanomaterials and nanotechnological approaches cover a wide range of surgical topics, including self-assembling nanofibres for haemostasis [37], nanofabricated drains [38], conduits for nerve repair [39] and means of studying and affecting in vivo processes such as neuroprotection and neuromodulation in real time [40].

'Smart' instruments have sensors embedded in them, which provide the surgeons with data on internal conditions, as they are performing procedures. These are sensors that have embedded technology within the medical device instrument, which allows the surgeon to get an internal perspective of the surgery or procedure they are performing. Smart sensors are currently used by surgeons when performing complicated procedures, but more complex applications for such devices are presently being developed for the market [1–5, 13].

Wound Dressing [13, 41, 42]

Metallic silver is known for its anti-infective properties, which are effective against a wide range of bacteria and microorganisms. A nanoporous silver powder, which can be applied to a range of products, has been developed. Smaller particles give a greater surface area, and, therefore, a better anti-infective surface. Also, less silver is required overall, so there is less risk of any toxic side effects. Applications for nanosilver coatings on medical devices include implants, indwelling catheters and wound dressings, and for burns and other chronic wounds. The nanosilver enters the wound through body fluids and can reportedly kill bacteria in 30 min. Each dressing can last for several days, depending on the thickness of the layer of nanosilver [13]. The effect of organoclay quantity on the structural, swelling, physical and mechanical properties of nanocomposite hydrogel wound dressing was investigated. The results showed that the nanocomposite hydrogels could meet the essential requirements for the reasonable wound dressing with some desirable characteristics such as relatively good swelling, appreciated vapour transmission rate, excellent barrierity against microbe penetration and mechanical properties. The results also indicated that the quantity of the clay added to the nanocomposite hydrogel is the key factor in obtaining such suitable properties required for wound dressing [43].

Tissue Engineering [1, 5, 6, 13, 16]

Tissue engineering has been defined as 'the application of principles and methods of engineering and life sciences towards fundamental understanding of structure-function relationships in normal and pathological mammalian tissues and the development of biological substitutes to restore, maintain or improve tissue function' [44]. Tissue-engineered products typically are a combination of three components, i.e. isolated cells, an extracellular matrix and signal molecules, such as growth factors. Nanotechnology provides new possibilities for the extracellular matrix, often referred to as the scaffold. The extracellular matrix serves three primary roles. First, it facilitates the localization and delivery of cells in the body. Second, it defines and maintains a three-dimensional space for the formation of new tissues with an appropriate structure. Third, it guides the development of new tissues with appropriate function. The interaction of the cells and extracellular matrix is of great importance for the intended function of the final product.

Thus, several of the principles described above for implantable materials in orthopaedics and dentistry, providing greater biocompatibility and/or stimulating the ingrowth of cells into the material in situ, are at least equally valid for tissue engineering scaffolds. Micro- and nanostructured surfaces of scaffold materials have important beneficial effects on cell adhesion and proliferation. Control of (nano)porosity is essential to obtain three-dimensional constructs with the appropriate desired properties. Also, the possibility to tailor mechanical characteristics, matching the target tissue as closely as possible, leads to increased possibilities for successfully functioning tissue-engineered products.

Nanorobots [1, 5–12]

Robots have recently been introduced to undertake basic surgical procedures, and with the help of nanobiotechnology, another dimension of robotics has been developed. This is commonly known as nanorobots or nanobots. These miniature robots are so small that they can be introduced into the body either through the vascular system or through catheters, and with external guidance and monitoring by the surgeon they can perform precise intracellular surgery, which would not be possible with the human hand. The exterior of a nanorobot will likely be constructed of carbon atoms in a diamondoid structure because of its inert properties and strength. Super-smooth surfaces will lessen the likelihood of triggering the body's immune system, allowing the nanorobots to go about their business unimpeded. Glucose or natural body sugars and oxygen might be a source for propulsion and the nanorobot will have other biochemical or molecular parts depending on its task [12].

The preliminary goal is to use various biological elements—whose function at the cellular level creates a motion, force or a signal—as nanorobotic components that perform the same function in response to the same biological stimuli but in an artificial setting. Nanorobots would constitute any passive or active structure (nanoscale) capable of actuation, sensing, signalling, information processing, intelligence and swarm behaviour at nanoscale. These functionalities could be illustrated individually or in combinations by a nanorobot [10]. Some of the characteristic abilities that are desirable for a nanorobot to function are:

i. *Swarm intelligence*—decentralization and distributive intelligence
ii. *Cooperative behaviour*—emergent and evolutionary behaviour
iii. *Self-assembly and replication*—assemblage at nanoscale and 'nanomaintenance'
iv. *Nanoinformation processing and programmability*—for programming and controlling nanorobots (autonomous nanorobots)
v. *Nano- to macroworld interface architecture*—an architecture enabling instant access to nanorobots and their control and maintenance [10]

A surgical nanobot, programmed by a human surgeon, could act as an autonomous on-site surgeon inside the human body. Various functions such as searching for pathology, diagnosis and removal or correction of the lesion by nanomanipulation can be performed and coordinated by an on-board computer while maintaining contact with the supervising surgeon via coded ultrasound signals. Nanorobots will have the capability to perform precise and refined intracellular surgery, which is beyond the capability of manipulations by the human hand.

Nanorobots will be scavengers for atherosclerotic plaque. Minimally invasive microrobots will be used instead of stents inside arteries, for repairs that are currently being performed laparoscopically. Nanoparticle-assisted surgery already illuminates cancers, so that surgeons can completely remove them, or even visually scan the body for metastasis. Nanoparticle-based local drug delivery will also soon help diagnose and treat cancer in a more cell-to-cell fashion, that is, detect and treat cancer in the very first stage of the disease. Individualized therapies, with cancer-specific nanoparticle vehicles, will be available and enhanced by personalized genomics for every patient. Investigations are being performed on creating artificial flagella designed to mimic natural bacteria in both size and swimming technique and on nanobots for retinal surgery.

One goal nanobot is to overturn the basic paradigm of today's medicine, and to shift from a treatment model to a prevention model through the use of in-body sensors, which check for and kill pathogens before the patient has any symptoms [9]. A rapidly vibrating (100 Hz) micropipette with a <1 μm tip diameter has been used to completely cut dendrites from single neurons without damaging cell viability. Axotomy of roundworm neurons was performed by femtosecond laser surgery, after which the axons functionally regenerated [12].

Ethics [45, 46]

However promising nanotechnology might be, the enthusiasm for them must be placed against the backdrop of the proper considerations of safety for the patients and the health-care workers, and in the context of stringent regulatory approval perspectives. The relevant issues go well beyond considerations of biocompatibility of the carriers, their biodistribution and reliability of their production protocols, which of course remain central concerns. By their very tripartite nature, nanoparticles arguably fall under the purview of the three branches of regulatory agencies: drugs, medical devices and biological agents. Therefore, they might have to be examined from these three perspectives accordingly. The main advantage of nanoparticle resides in their multifunctionality—they can incorporate multiple therapeutic, diagnostic and barrier avoiding agents.

Conclusion

Advancements in nanobiotechnology are revolutionizing our capability to understand biological intricacies and resolve biological and medical problems by developing subtle biomimetic techniques. Preliminary investigations support the potential of nanobiomaterials in orthopaedic applications; however, significant advancements are necessary to achieve clinical use. The research areas of implanted interfaces, tissue engineering and therapeutics have been focus over many years. Nanotechnology has enhanced capability in these various areas. Nanotechnology will help the surgeons' life easier by use of surgical tools such as nanoneedles, nanosurgical blades, better diagnostic imaging and better postoperative period by using precisely targeted delivery system for the medicine. This will help in reducing complications by being able to plan treatment with more precision and leading to better execution of the treatment plan.

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