Review

Regenerative nanotechnology in oral and maxillofacial surgery

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Abstract

Regenerative nanotechnology is at the forefront of medical research, and translational medicine is a challenge to both scientists and clinicians. Although there has been an exponential rise in the volume of research generated about it for both medical and surgical uses, key questions remain about its actual benefits. Nevertheless, some people think that therapeutics based on its principles may form the core of applied research for the future. Here we give an account of its current use in oral and maxillofacial surgery, and implications and challenges for the future. © 2014 The British Association of Oral and Maxillofacial Surgeons. Published by Elsevier Ltd. All rights reserved.

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Brief history of nanoscience and nanotechnology

The concept of nanotechnology was first introduced by the quantum theorist and Nobel laureate Richard Feynman in 1959.\textsuperscript{1} An accepted definition of it is “research and technology development at the atomic, molecular, or macromolecular levels; in the scale of approximately 1 to 100 nanometer range; to provide a fundamental understanding of phenomena and materials at the nanoscale; and to create and use structures, devices, and systems, which have novel properties and functions because of their small and/or intermediate size.”\textsuperscript{2}

The term “nanotechnology” did not make much impact on scientific publishing until Taniguchi coined it in 1974 to describe the ability of engineering materials at the nanoscale.\textsuperscript{3} Because they are extremely small, nanoparticles have a high surface area:volume ratio that confers mechanical, magnetic, optical, and chemical properties that are superior to those of the original materials.

The fundamental concepts behind, and the main driving force in, the advancement of nanotechnology, stemmed from the electronics industry. By the early 1970s the IBM Corporation had created a method called “electron beam lithography” that could be used to manipulate structures as small as 40-70 nm.\textsuperscript{4}

Nanotechnology has continued to increase its economic impact. It has been estimated that by 2015 it will account

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for 11% of manufacturing jobs worldwide, and will be incorporated into £1.9 trillion of manufactured goods annually.\textsuperscript{5} Research and development on the use of nanotechnology in medicine and surgery have kept pace, and nanotherapeutic publications feature prominently in journals such as \textit{Nature Nanotechnology}.

The liposomal formulation of doxorubicin (Doxil\textsuperscript{®}, Janssen Products LP), was the first nanodrug to be approved by the USA Food and Drug Administration (FDA) in 1995.\textsuperscript{6} Polyethylene glycol (PEG) was conjugated on to the surface of the liposome, so it achieved steric stabilisation and was therefore able to prolong its circulation time by avoiding the mononuclear phagocyte system. The small size of Doxil\textsuperscript{®} (around 100 nm in diameter) also enabled it to extravasate through diseased tissue by exploiting the increased permeability and retention effect, which is a phenomenon that relies on the fact that cancerous tissues have "leaky" blood vessels so the use of nanoparticles for delivery can enable the drug to reach its target site more effectively.\textsuperscript{7}

Nanomaterials, or (more specifically) nanocomposite polymers, have been used as biomedical implants. They comprise of two (or more) units that have a synergistic effect, which results in an overall improvement in the performance of the material. Generally, nanocomposite materials are made up of matrices and fillers.\textsuperscript{8} A well-known example is carbon fibre, which is made up of epoxy (matrix) and carbon (filler), and its light weight and high tensile strength and rigidity make it an attractive (albeit expensive) material for high performance superscars (Fig. 1). Lesser-known examples can be found in nature. For instance, an aggressive crustacean called \textit{Odontodactylus scyllarus} (peacock mantis shrimp) has dactyl clubs that are made of nanocomposite materials (Fig. 1).\textsuperscript{9} Its dactyl clubs are strong enough to fracture the exoskeleton of crabs and molluscs, and they can even break aquarium glass tanks with a repeated series of punches.

### Types of nanomaterials

Nanoparticles are considered in 3 categories:

1. Fullerenes are carbon allotropes that can adopt different shapes, such as carbon nanotubes. The cylindrical shape is derived from the hexagonal lattice of carbon atoms, which forms a sheet that can be rolled up. This molecular arrangement confers considerable stiffness and tensile strength (50 times stronger than steel). When an antithrombogenic surface has been added, carbon nanotubes are suitable for use as vascular microcatheters, stents, and implants.\textsuperscript{1,8}

2. Nanoparticles, for example quantum dots (QD), can act as carriers of drugs or as labels for tracking cells. QD are particularly suitable for imaging, because they emit fluorescence at different wavelengths depending on the size of the particle.\textsuperscript{1,8}

3. Nanocomposites are multiphase solid materials in which one of the phases has one, 2, or 3 dimensions of less than 100 nm. In tissue engineering, scaffolds are improved by nanoparticulate fillers that intercalate between layers or are distributed evenly throughout to maximise the surface area available for interaction with another component. Fillers include silicones, carbon nanotubes, nanoclays, and new synthetic nanocomposites such as polyhedral oligomeric silsesquioxane (POSS). The latter confers superior physical properties such as mechanical strength and oxidative resistance to the composite. The amphiphilic nature of POSS increases its ability to support the adherence and growth of cells, which makes it ideal for tissue engineering.\textsuperscript{1,8}

In oral and maxillofacial surgical practice nanotechnology has influenced the development of tissue engineering, imaging, delivery of drugs, and has improved implants.

### Nanoscaffolds for tissue engineering

Natural bone is made up of a nanocomposite architecture of collagen fibrils, hydroxyapatite, and proteoglycans. New bio-compatible nanomaterials, which mimic the natural structure of bone, and nanofabrication techniques are now being used in clinical practice.

Among the nanomaterials used to reconstruct bone are: derivatives of polyhydroxyacids, such as polylactide (PLA), polyglycolide (PGA), poly(e-caprolactone) (PCL), and their copolymers poly(lactide-co-glycolide) (PLGA), poly(lactide-co-caprolactone) (PLC), poly(glycolide-cocaprolactone) (PGC), and poly(L-lactic acid) (PLLA), and these have been studied extensively.\textsuperscript{10}

PLLA has been approved by the FDA for use in the reconstructive surgery of bone.\textsuperscript{11,12} To improve their biological properties, PLLA nanofibres are often combined with hydroxyapatite, or activated with arginylglycylaspartic acid (RGD) peptide, or with proteins such as bone morphogenic protein 2 (BMP-2). It has been shown that PLLA nanofibres facilitate the colonisation of bony defects and, in combination with BMP-2, increase the generation of bone.\textsuperscript{11,12} More recently, nanocomposite (DBSint\textsuperscript{®}), made up of biomimetic nanostructured magnesium-hydroxyapatite (HA) and human demineralised bone matrix, was approved for clinical use.\textsuperscript{13}

Nanophase HA has been shown to have improved osteointegrative properties, and 3-dimensional porous nanoHA scaffolds seeded with bone marrow showed adherence, proliferation, and differentiation of cells, which is promising for the reconstruction of bony defects. NanoHA can be used to make better implants because it more closely simulates the nanostructure of natural bones, and gives the prospect of better osteointegration, more natural mechanical properties, less immune reaction, and greater control of cellular responses.\textsuperscript{14}

Stübinger et al used nanostructured HA-based biomaterial to raise the sinus floor in 20 patients, and found that
the material had excellent biocompatibility with tissue. They noted that within 6 months new trabecular bone had formed with no need for autogenous bone. The histological analysis showed that the nanoimproved biomaterial acted “as a strong osteoconductive bone substitute with no evidence of an ongoing marked foreign body reaction.”15

Nanotube structures have also been shown to have great potential for bony regeneration. Rosette nanotubes (RNT) are new, biomimetic, self-assembled nanomaterials, and materials coated with RNT have significantly increased the growth of cells because of the favourable cellular environment that they create.16,17 Carbon nanotubes (CNT) are other suitable scaffold materials that have been proved to support the proliferation of osteoblasts. They possess excellent mechanical properties, which facilitate their use as reinforcements and, combined with other biomaterials, can support the growth of bone.18,19 Mannoor et al developed a technique to create 3-dimensionally interwoven biological tissues using added manufacturing cells with electronic components derived from structural nanoparticles (Fig. 2).20 They made a bionic ear using 3-dimensional printing of a hydrogel matrix that was seeded with cells, together with an intertwined conductive polymer that consisted of silver nanoparticles. Results showed that chondrocytes were able to proliferate on the bionic ear as well as around the inductive antenna coil, which enabled readouts of inductively-coupled signals from the cochlear electrodes, and also enhanced auditory sensing of radio frequencies.

A study by Hwang et al showed that tissue-engineered alloplastic implants could form the basis of auricular reconstruction (Fig. 2).21 They shaped a commercially available scaffold, MedPor (Porex Surgical Products Group, USA) into an ear. The surface was modified by oxidation to render the scaffold more hydrophilic. Fibrin hydrogel and chondrocytes that had been derived from a rabbit’s ear cartilage were then mixed and spray-coated on to the scaffold. The resulting construct was then implanted into a mouse, and the results showed good biocompatibility.

Using a blending method, Wang et al developed a polyetheretherketone/nano-fluorohydroxyapatite (PEEK/nano-FHA) composite that had antimicrobial properties together with the ability to increase osseointegration.22

Fig. 1. Nanotechnology in the real world. The Lamborghini Aventador (A) is made of carbon fibre (C), a man-made nanocomposite material. The peacock mantis shrimp (B), which has dactyl clubs that are made of calcium-based nanocomposite materials (D), can achieve the acceleration of a .22 calibre rifle. Panels A and C reproduced with permission from Automobili Lamborghini S.p.A. (Copyright 2014, Automobili Lamborghini S.p.A.). Panels B and D reproduced with permission from Weaver et al12 2012 (Copyright© 2012, American Association for the Advancement of Science).
In vitro results showed increased adhesion and proliferation of osteoblasts on the PEEK/nano-FHA. Alkaline phosphatase activity was also upregulated, together with an increase in the mineralisation of cells. The PEEK/nano-FHA nanocomposite also showed its antimicrobial properties by inhibiting the bacterial biofilm on the surface. The in vivo study involved the implantation of PEEK/nano-FHA into the mandible of a dog, and following its osseointegration over 4 weeks. Micro-computed tomography (CT) showed increased bony regeneration, and histological and histomorphometric examination also showed increased bony regeneration on PEEK/nano-FHA.

Another study by Wang et al also illustrated the biocompatibility of a nano-hydroxyapatite/polyamide (n-HA/PA) nanocomposite scaffold, which upregulated osteogenesis. In vitro studies showed that n-HA/PA was able to support the growth and proliferation of osteoblasts, and in vivo studies showed increased bony regeneration when implanted in the mandibles of rabbits. The same group followed up with another study, which showed that bone morphogenic protein-7 (BMP-7) that was transfected into rabbit mesenchymal stem cells resulted in the acceleration of bony repair when seeded on to n-HA/PA and implanted into rabbit mandibles.

Fricain et al reported a method of developing scaffold made of natural polysaccharides (pullulan and dextran), which were then incorporated into a nano-hydroxyapatite to yield a macroporous nanocomposite material. In vitro results showed that when human bone marrow stromal cells were cultured on to the nanocomposite material, they showed an early osteoblastic marker (alkaline phosphatase), as well as a late one (osteocalcin). This indicated that the scaffold promoted osteoblastic differentiation of human bone marrow stromal cells. The in vivo part of the study involved implantation of the scaffold into a goat with a transversal mandibular defect. Micro-CT showed increased mineralisation of bone, and it had completely filled the critical-size bony defect 6 months after implantation. Histological analysis using Masson trichrome staining showed new osteoid tissue in direct contact with the scaffold. Overall, this study confirmed the
feasibility of using pullulan/dextran nanohydroxyapatite as a biomaterial for bony regeneration in oral and maxillofacial applications (Fig. 3).

Deng et al advocated the use of nanohydroxyapatite materials by activating them with heparin. Preosteoblast cells exposed to these apatites showed increased alkaline phosphatase activity as well as increased growth and proliferation. This indicated the potential of heparin-activated nanohydroxyapatites as bioactive material for bony regeneration.

Pilloni et al also supported the role of nanohydroxyapatite as a biomaterial for bony regeneration. They cultured human osteoblasts derived from alveolar bone on polylactin-activated nanohydroxyapatite, and found an increase in the expression of markers of osteoblast differentiation, such as BMP-2,5,7, alkaline phosphatase, and pro-collagen type I chain (COLL-1A2), as well as an increase in cellular adhesion and spreading. They concluded that polylactin-activated nanohydroxyapatite could function as an osteoinductive material for the growth of bone at sites of alveolar regeneration.

Sun et al developed a new method of fabricating a peptide-decorated nanohydroxyapatite. They coated nanohydroxyapatite using a one-step pH-induced polymerisation of dopamine, and a peptide; 3,4-dihydroxyphenylamine was subsequently grafted on to nanoHA coated with polydopamine (pDA) (HA-pDA) through catechol chemistry. Human osteoblast-like MG-63 cells were then cultured on the material, and results showed that the peptide-activated nanohydroxyapatite could induce the adhesion and proliferation of cells. The grafted peptide was also able to maintain high alkaline phosphatase activity that stimulated osteogenic differentiation, which indicated that this scaffold could function as a material for bony regeneration.

Kinoshita et al reported that using an absorbable poly(L-lactide-co-ε-caprolactone)/β-tricalcium phosphate membrane and gelatin sponge activated with basic fibroblast
growth factor could increase alveolar bony regeneration in dogs. Fennis et al also reported that a poly(D,L-lactide) scaffold could be used as a biomaterial for mandibular reconstruction in goats.

Behnia et al investigated the in vitro and in vivo effects of a nanoscaffold, NanoBone® (Artoss, Germany), which is a granular composite of synthetic nanocrystalline hydroxyapatite and silica gel matrix with interconnected pores, the sizes of which range from 10-20 nm. In vitro cell culture showed that mesenchymal stem cells were able to differentiate into an osteogenic lineage. The in vivo part of the study involved rabbits with defects in the parietal bone. Histological and histomorphometric evaluation showed an increase in trabecular bone density, which indicated its osteoinductive potential. Möller et al also studied NanoBone® as a new bone substitute in pigs that had had bilateral sinus augmentation. Microradiography, fluorescence microscopy, and histological examination showed that a considerable amount of bone had regenerated in the test subjects. NanoBone® was also evaluated in humans, as reported by Canullo et al., and Stübinger et al., Canullo et al reported that NanoBone® implanted into 10 patients having sinus lifts showed good bony regeneration histologically 3 months after implantation. Stübinger et al implanted NanoBone® into 20 patients who also had the sinus floor raised. Biopsy specimens of bone using trephine burs were taken after 6 months, and histological analysis showed the formation of new trabecular bone. These studies indicate, therefore, that NanoBone® could be a viable biomaterial in oral and maxillofacial surgery.

Zamiri et al used an allogenic scaffold derived from a human cadaver, which was seeded with mesenchymal stem cells from autologous bone marrow. It was reported that this scaffold could be used for the reconstruction of defects in mandibular continuity (Fig. 3). Indeed, a group led by Teoh et al at the Nanyang Technological University in Singapore has developed a polycaprolactone (PCL)-based scaffold for craniofacial repair (Fig. 3). Its “spinoff” company, Osteopore, manufactures clinically-approved scaffolds under Good Manufacturing Practice (GMP) procedures, and has been approved by the FDA, its products having been used in more than 1000 patients globally for craniofacial reconstruction.

**Imaging**

Current imaging techniques for the diagnosis and staging of cancer have their limitations. Fluorescent semiconductor nanocrystals (QD) have narrow and size-tuneable emission spectra that span from ultraviolet to near-infrared. This, together with their prolonged photostability, good photoluminescence, and high signal:noise ratio, make QD particularly suitable for non-invasive imaging, and they can be used for identification and long-term in vivo monitoring of disease in vivo (Fig. 4).

QD can be attached to paramagnetic ions and used with magnetic resonance imaging (MRI). This combination exploits the high sensitivity of QD fluorescence and the high spatial resolution of MRI, and acts synergistically to enhance the reliability of the pictures obtained. They can also be conjugated to specific peptides to image specific tumour cells selectively in vivo. This concept may have a role in treatment.

**Sentinel node biopsy**

QD can be used in the biopsy of sentinel lymph nodes. Current methods of detection based on lymphoscintigraphy and vital dyes can be confounded by the autofluorescence of background tissue. QD that emit at the near-infrared region are associated with a reduction in the autofluorescence of tissue and can be used in deep tissue imaging, making localisation accurate and sensitive, and subsequent excision of foci of cancer possible.

Kobayashi et al showed that quantum dots could be used as agents for multicolour molecular imaging in lymph nodes (Fig. 4). They injected cadmium-selenium (CdSe) and cadmium tellurium (CdTe) quantum dots into mice, and simultaneously imaged 5 different lymphatic flows. Traffic to distinct lymph nodes was possible using an in vivo spectral imaging system. This illustrates the potential for quantum dots to be used as new imaging agents for cancers of the head and neck.

**Nanotechnology in the delivery of drugs**

Because of their very small size, nanoparticles can penetrate some barriers that cannot normally be crossed by larger microparticles, and thereby reduce systemic toxicity (Fig. 4). Among nanoscaled drug delivery systems, liposomes and drug-conjugated nanoparticles for the treatment of cancer are of particular interest. Liposomes are lipid bilayers that are spherically arranged and have the capacity to encapsulate drugs within their inner aqueous phase. Liposomes coated with PEG and incorporating the anthracycline doxorubicin have lower cardiotoxicity and greater efficacy than the free drug. This formulation is currently being used in a clinical trial for breast cancer.

Kimura et al evaluated the feasibility of using a gelatin hydrogel as a drug delivery system to increase bony regeneration in mice with mandibular distraction. Recombinant human fibroblast growth factor-2 (rhFGF-2) was incorporated into gelatin hydrogel and inserted into the distracted area. Radiographic and micro-CT imaging after 29 days showed that bony formation in the distracted area had increased. Histological examination also showed a larger calcine-labelled area, indicating increased bony regeneration.

Qu et al investigated whether transfection of basic fibroblast growth factor (bFGF) into the stem cells of bone marrow
could upregulate vascular tissue regeneration and increase osseous formation and remodelling in mice with defects in the cranium 8 mm in diameter.\textsuperscript{42} They incorporated bFGF into a nano-hydroxyapatite composite scaffold that had been seeded with bone marrow stem cells, and implanted it into the area of the defect. Histological examination, immunohistochemical analysis, and polymerase chain reaction showed that angiogenic activity had increased by 4 weeks after implantation. Radiographs also confirmed the increase.

Wang et al used human nerve growth factor beta (hNGF\textsubscript{β}) to improve recovery of the inferior alveolar nerve in rabbits with mandibular distraction osteogenesis.\textsuperscript{43} Histomorphometric results showed increased density of myelinated fibres, indicating that hNGF\textsubscript{β} could have a role in the regeneration of nerves in mandibular distraction osteogenesis. This was followed up with another study by the same group, who this time used a collagen/nano-hydroxyapatite composite as a delivery system for hNGF\textsubscript{β}.\textsuperscript{44} They found that the maximal load and bone volume had increased in rabbits with mandibular distraction osteogenesis. They then modified their delivery system with hydrogel,\textsuperscript{45} and found increased bone mineral density and bone volume in the same animals. This observation was confirmed by Byun et al, who showed that greater expression of p75NGFR (a low affinity receptor for NGF) was seen in Schwann cells in dogs with mandibular distraction osteogenesis, indicating its role in remyelination of damaged nerves.\textsuperscript{46}

Gahawar et al encapsulated dexamethasone in a beaded fibrillar scaffold made of poly(ethylene oxide terephthalate)-poly(butylene terephthalate) (PEOT/PBT) as a sustained drug release depot.\textsuperscript{47} The fibrillar scaffolds were manufactured by electrospinning, and the amphiphilic beads acted as a depot for controlled release of the drug integrated into the polyether-ester multiblock copolymer scaffold. Human mesenchymal stem cells cultured on this scaffold showed an increase in the potential for osteogenic differentiation through the upregulation of alkaline phosphatase activity. Mineralisation of the matrix also increased. This study therefore highlights the potential of a new drug delivery platform, and for bone regeneration.

Naito et al loaded simvastatin into polylactide-coglycolide (PLGA) nanoparticles and incorporated them into synthetic bone cement to function as a slow release platform for bone regeneration in rabbits with cranial defects.\textsuperscript{48} After 6 weeks’ implantation, simvastatin-loaded PLGA nanoparticles induced bony formation, as evidenced by histomorphometric results and CT. This indicates that PLGA nanoparticles could serve as a drug delivery platform for
calvarial bony regeneration, as well as acting synergistically with bone cement to improve the healing process.

Wadagaki et al investigated the feasibility of incorporating simvastatin into a biodegradable electrospun PLGA nanofibre scaffold as a drug delivery platform for bony regeneration. Alkaline phosphatase activity in bone marrow stem cells increased, with a simultaneous reduction in osteoclastogenesis. New bone also formed, and there was mineralisation and upregulation of osteoblastic differentiation.

Melancon et al conjugated epidermal growth factor receptors (EGFR) to aptamer-coated and antibody-coated hollow gold nanospheres (HAuNS) using a thiol-terminated single-stranded DNA, and subsequently added the complementary RNA targeted to EGFR. They used nude mice with oral squamous cell carcinoma (SCC), and results indicated that these multifunctional nanoparticles would act simultaneously as both a drug delivery module, and a molecular imaging agent for use in cancer of the head and neck.

Bhirde et al reported that carbon nanotubes (CNT) can be used to deliver chemotherapeutic agents into head and neck squamous cell carcinoma cells (HNSCC) that overexpress EGFR. They found that cisplatin conjugated to oxidised single-walled CNT with specific receptor ligand EGF showed increased selectivity and therapeutic efficacy in destroying SCC.

Implantable materials

Surface features can be introduced to nanocomposite implant materials that alter the immune response to the material or the ability of bacteria to colonise it. The hypothesis is that reduction of the immune response may be less dependent on surface chemistry than on the surface features of materials at the nanometer scale.

Nanomaterials can inhibit the formation of bacterial biofilms. Materials with inherent antibacterial properties like zinc oxide and nitric oxide possess these properties, but so do nanomaterials that have no known chemical antibacterial properties like titanium dioxide. Even more importantly, these properties do not necessarily occur in isolation. A material can be made to resist infection through its nanoarchitecture, to decrease the body’s inflammatory response, to become more highly integrated, to degrade over time, and to deliver drugs. What have until now been purely “passive” implants, therefore, could become “active” and functional. This will have a tremendous impact in plastic surgery where implanted materials are routinely used in cosmetic, reconstructive, and restorative procedures.

Potential side effects and limitations

To exploit nanotechnology fully, and minimise potential toxic effects, the long-term health implications of nanoparticles must be investigated thoroughly. For example, the size of a nanoparticle may mean that the blood–brain barrier can be crossed. Large surface area:volume ratios render nanoparticles biologically active, which may lead to inflammation and oxidative stress. For successful tissue engineering, scaffolds must be developed that are capable of providing the necessary oxygen and nutrients to densely packed cells in whole organs.

Conclusions and future directions

Regenerative nanotechnological uses in oral and maxillofacial surgery are increasing rapidly, and there have been recent exciting breakthroughs. Although the realm of biomaterials for bone regeneration is well-established, the use of nanoscience and nanotechnology specifically for oral and maxillofacial surgery is still new. Within nanotechnology, two broad areas of research can be identified: the use of multifunctional theranostic nanoparticles for head and neck cancer, and the use of nanoinspired biomaterials for improving bony regeneration specifically for oral and maxillofacial surgery.

As we delve into the nano-world, several issues and challenges must be addressed before nanotechnology can become commonplace. For instance, nanotoxicology is an intense area of research that seeks to elucidate the possible side effects of using nanoparticles, and their biological interactions with the human body. Although there have been several human studies involving the use of nanoscale biomaterials for oral and maxillofacial surgery, well-designed double-blind randomised controlled trials (RCT) that compare a “nano product” with a “non-nano product” are few and far between. With the ever-increasing emphasis on evidence-based medicine, more RCT will be crucial in ascertaining the true advantages of using materials based on nanotechnology for oral and maxillofacial surgery.

When we consider the technical and regulatory complexities of bringing a nano-product from academia to industry, we envisage that the shift towards a fully nanotechnological future for oral and maxillofacial surgery will be evolutionary rather than revolutionary. Nevertheless, the advances in nanoscience and nanotechnology for biomedical regenerative use could have far-reaching effects, and would undoubtedly have a considerable impact on, and probably shape, the future of oral and maxillofacial surgery.

Conflict of Interest

We have no conflicts of interest

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