Available online at www.sciencedirect.com
SciVerse ScienceDirect
British Journal of Oral and Maxillofacial Surgery 52 (2014) 884–893
BRITISH Journal of Oral and Maxillofacial Surgery
www.bjoms.com

Review

Regenerative nanotechnology in oral and maxillofacial surgery

Kaveh Shakib[a,b,*], Aaron Tan[b,c], Vukic Soskic[d], Alexander M. Seifalian[b,e,**]

[a] Department of Oral and Maxillofacial Surgery, Royal Free London NHS Foundation Trust, London, UK
[b] UCL Centre for Nanotechnology & Regenerative Medicine, Division of Surgery & Interventional Science, University College London (UCL), London, UK
[c] UCL Medical School, University College London (UCL), London, UK
[d] ORGENTEC Diagnostika GmbH, Mainz, Germany
[e] Royal Free London NHS Foundation Trust, London, UK

Accepted 14 August 2014
Available online 15 September 2014

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.

Keywords: Oral and maxillofacial surgery; Regenerative nanotechnology; Theranostics; Cyborg tissues; Nanomedicine; Nanoimaging

Brief history of nanoscience and nanotechnology

The concept of nanotechnology was first introduced by the quantum theorist and Nobel laureate Richard Feynman in 1959.[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."[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.[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.[4]

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

* Corresponding author. Maxillofacial Consultant Surgeon, Department of Oral and Maxillofacial Surgery, Royal Free London NHS Foundation Trust, London, UK.
** Corresponding author. Professor of Nanotechnology & Regenerative Medicine, UCL Centre for Nanotechnology & Regenerative Medicine, University College London, Royal Free London NHS Foundation Trust Hospital London NW3 2QG.
E-mail addresses: k.shakib@nhs.net (K. Shakib), a.seifalian@ucl.ac.uk (A.M. Seifalian).

http://dx.doi.org/10.1016/j.bjoms.2014.08.006
0266-4356/

for 11% of manufacturing jobs worldwide, and will be incorporated into £1.9 trillion of manufactured goods annually.[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 *Nature Nanotechnology*.

The liposomal formulation of doxorubicin (Doxil®, Janssen Products LP), was the first nanodrug to be approved by the USA Food and Drug Administration (FDA) in 1995.[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® (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.[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.[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 supercars (Fig. 1). Lesser- known examples can be found in nature. For instance, an aggressive crustacean called *Odontodactylus scyllarus* (peacock mantis shrimp) has dactyl clubs that are made of nanocomposite materials (Fig. 1).[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.[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.[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.[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 biocompatible 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(ε-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.[10]

PLLA has been approved by the FDA for use in the reconstructive surgery of bone.[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.[11,12] More recently, nanocomposite (DBSint®), made up of biomimetic nanostructured magnesium-hydroxyapatite (HA) and human demineralised bone matrix, was approved for clinical use.[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.[14]

Stübinger et al used nanostructured HA-based biomaterial to raise the sinus floor in 20 patients, and found that