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Regenerative nanotechnology in oral and maxillofacial surgery- A literature review

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Abstract

Aim: To comprehensively review the various nano technological advancements in oral and maxillofacial surgery till date.

Background: Regenerative Nanotechnology is at the forefront of medical research and nanotechnological development has changed the perception of the world to the disease and it has thereby revolutionized the field of diagnostic imaging, medicine and surgery. The advent of this technology offers greater patient comfort with minimal patient anxiety, precise selectivity and controllability of the analgesic effect along with complete reversibility of the analgesic. In implants, hydroxyapatite implant coatings manufactured using nanostructured processing has been found to increase the osteoblastic activity in terms of properties like its adhesion, proliferation and mineralization.

Methodology: The study used keywords nanoparticle, nanotechnology, oral and maxillofacial surgery, regenerative medicine and toxicity and the articles generated were analysed to extract data regarding the focus of research area in nanotechnology, its application in the field of maxillofacial surgery and the secondary effects or toxicities due to its application in maxillofacial region.

Conclusion: Although the effect of nanotechnology in the field of oral surgery is limited to the use of currently available materials, rapidly progressing investigations

will ensure developments that seem impossible today are possible in the future.

Clinical Significance

Although several studies have focused on application of nano technology in oral and maxillofacial surgery this review observed that there is lack of well-designed studies focusing on its the application in this region as well as lack of studies focusing on the secondary/ un toward effects of nano particles on oral and maxillofacial region.

Background

The concept of nano technology 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 macro molecular levels; in the scale of approximately 1 to 100 nano meter 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 "nano technology" was coined by Taniguchi in 1974 to describe the ability of engineering materials at the nanoscale[3]

Nano technology offers us the ability to arrange atoms for achieving desired effectiveness and complete control on the structure of matter.[4] The advancement of this technology came from the electronics industry and 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[5]

A well-known example is carbon fibre, which is composed of epoxy (matrix) and carbon (filler), and its minimal weight and improved tensile strength and rigidity make it an highly acceptable and (albeit expensive) material for top performance supercars. Lesser- known examples can be found in nature like an aggressive crustacean called Odontodactylus scyllarus (peacock mantis shrimp) has dactyl clubs are made of nano composite materials that are strong enough to fracture the exoskeleton of crabs and molluscs.[6]

In Oral and Maxillofacial Surgery, nano technology has influenced development of tissue engineering, imaging, delivery of drugs and has improved implants acceptance. Empty nanoscale vesicles like Liposomes have been studied extensively for drug delivery and have shown success. Proteolytic nanoparticles are on the brink of replacing a surgical blade as they have shown to remodel the oral connective tissue in a controlled manner and also has the potential to perform surgeries at cellular level as well as integrated with various materials to impart antibacterial properties. Nanorobotic local anesthetics are composed of a colloidal solution of activated nanosized LA molecules can inhibit neurosensory sensations to a particular tooth or teeth as desired by the surgeon. This review aims to comprehensively review the various nano technological advancements in oral and maxillofacial surgery till date.

Review Results

The study used keywords nanoparticle, nanotechnology, oral and maxillofacial surgery, regenerative medicine and toxicity and the articles generated were analysed to extract data regarding the focus of research area in nano technology, its application in the field of maxillofacial surgery and the secondary effects or toxicities due to its application in maxillofacial region.

The following section focuses on key findings of the data extracted from the reviewed articles

Within nanotechnology, two broad areas of research can be identified: the use of multi-functional therapeutic nanoparticles for head and neck cancer, and the use of nano inspired bio materials for improving bony regeneration specifically for oral and maxillofacial surgery. [9]

- **Nanoparticles are considered in 3 categories[1]**

1. Fullerenes are carbon allotropes that can take up different shapes, such as Carbon nanotubes. Their molecular arrangement confers considerable stiffness and tensile strength (50 times stronger than steel) and are suitable for use as vascular microcatheters, stents, and implants.

2. Nanoparticles, for example quanta dots (QD), can act as carriers of drugs and are particularly suitable for imaging as they emit fluorescence at different wavelengths according to the size of the particle.

3. Nanocomposites are multiphase solid materials that comprises of phases that has one, 2, or 3 dimensions of less than 100 nm. In tissue engineering, scaffolds are improved by nanoparticulate fillers that include silicones, carbon nanotubes, nano clays, and new synthetic nano composites such as polyhedral oligomeric silsesquioxane (POSS), to improve the surface area available for interaction with another component.

There are two main approaches in Synthesis of Nano particles[8]

1. Top-down technique: According to this technique, smaller scale details are incorporated in a microscopic material and are rearranged for the desired property to be achieved.

2. Bottom- Up technique: It begins by synthesizing and designing custom made molecule that has the potential to self-replicate which are then organized into higher macro-scale structures.

Nanomaterials

These are the nano composite materials made up of matrices and fillers[7]

On the basis of phase composition nano materials can be classified[4] as-

1. Single phase solids- Crystalline and amorphous layers.
2. Matrix composites- coated particles.
3. multi-phase systems- colloids aero gels and ferro-fluids

On the basis of dimension nanomaterials can be classified as[4]-

1. Nano rods, nano wires
2. Tubes, fibers, platelets
3. Particles, quantum dots, hollow spheres.

Nanotechnology for tissue engineering

Natural bone is composed of nanocomposite architecture of collagen fibrils, hydroxyapatite, and proteoglycans. New biocompatible nano materials, that have the capability to mimic the natural structure of bone and nanofabrication techniques are now being considered in clinical practice. Among the nano materials used to reconstruct bone are: derivatives of polyhydroxy acids, such as polylactide (PLA), polyglycolide (PGA), poly(-caprolactone) (PCL), and their copolymers poly (lactide-co-glycol ide) (PLGA), poly (lactide-co-caprolactone) (PLC), poly (glycol lid Eco caprolactone) (PGC), and poly (L-lactic acid) (PLLA), and these have been studied extensively.[10]

Studies with have shown that PLLA facilitate colonisation of bony defects and also increase bone generation in combination with BMP-2 and FDA has improved its use in the reconstructive surgery of bone[11,12] Nanocomposite (DB Sint®) made up of biomimetic nanostructured magnesium-hydroxyapatite (HA) and human demineralised bone matrix has also been approved for clinical use[13] As Nano HA is proved to closely simulate the nano structure of natural bone, it can be used to improve the rate of implant acceptance as it gives the prospect of better osteointegration, more natural mechanical properties, less immune reaction, and greater control of cellular responses.[14] The histological analysis presented no evidence of any active marked foreign body reaction and thus acts as a strong osteoconductive bone substitute[15]

Carbon nano tubes (CNT) have shown to support the proliferation of osteoblasts as they possess excellent mechanical properties and have proven to reinforce bone growth when combined with other biomaterials.[16]

Studies have been conducted that have supported the role of nano hydroxyapatite for improved bony regeneration and concluded that polylysine- activated nano hydro xyapatite could function as an osteoinductive material for the growth of bone at sites of alveolar regeneration as well as resulted in the increase in the rate of bony repair when bone morphogenic protein-7 (BMP-7) was seeded on to n-HA/PA and implanted into rabbit mandibles [17,18]

Nano Bone® 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, could be a viable biomaterial in oral and maxillofacial surgery as studies have proven it to be a promising bone substitute as well as in reconstruction of defects in mandibular continuity with histological analysis showing the formation of new trabecular bone [19,20,21,22]

TMJ cartilage regeneration

Autogenous grafting materials are considered gold standard for the treatment of patients with end-stage TMDs but these materials encounter disadvantages such as difficulty in anchoring graft materials, scar tissue formation, and lack of long-term stability[23]. To overcome these limitations, nanomaterials incorporated with cells to amplify the cartilage tissue regeneration. Currently reported functional nanofibers include PCL fibrous scaffolds, PCL-PEG-PCL scaffold, and a novel biomimetic and bioactive electro spun cartilage, loaded with sustained GF delivery microspheres have been applied widely to reconstruct cartilage defect and have showed significant effects in vivo[24,25,26]

Other nanomaterials such as human neutrophil-derived microparticles constructed novel nanoparticles, which including aspirin-triggered resolvin D1 or a lipoxin A4 analog has been found to relieve the inflammation in the TMJ[27]. Additionally, 15d-PGJ2 in PLGA nano capsules has been found to be a promising material to deliver antinociceptive and anti-inflammatory agent to treat TMDs.[28]

TMJ regeneration research remains limited by the difficulties of determining the pathogenesis mechanism, mimicking accurate anatomical structure, and finding suitable animal model, but studies of nanomaterials on TMJ is definitely been taken up.[44]

Nanotechnology in the delivery of drugs

Because of their very small size, nanoparticles possess the ability to penetrate some barriers that cannot normally be crossed by larger microparticles thereby reducing systemic toxicity. Among nano scaled drug delivery systems, liposomes and drug-conjugated nanoparticles for the treatment of cancer are of particular interest.[11] Liposomes have the capacity to encapsulate drugs and when coated with PEG (Polyethylene glycol), the anthracycline doxorubicin pose lower cardiotoxicity and offer greater efficacy than the drug. This formulation is currently being used in a clinical trial for breast cancer[29]

Since cancerous tissues have “leaky” blood vessels, the use of nanoparticles for delivery can enable the drug to reach its target site more effectively. According to this, Doxil® (around 100 nm in diameter) can extravasate through diseased tissue by exploiting the increased permeability and retention effect and thereby act productively at the site[30]

Studies have reported that carbon nanotubes (CNT) can be used to deliver chemotherapeutic agents into head and neck squamous cell carcinoma cells (HNSCC) that overexpress EGFR and found that Cisplatin conjugated to oxidised single-walled CNT with specific receptor ligand EGF showed increased selectivity and therapeutic efficacy in destroying SCC.[31]

Transfection of basic fibroblast growth factor (bFGF) into the stem cells of bone marrow for upregulating vascular tissue regeneration and increase in the osseous formation was studied in mice with cranial defects[32]

Studies have been undertaken where simvastatin was loaded into poly lactide - coglycolide (PLGA) nanoparticles and incorporated them into synthetic bone cement as well as used as a nano fibre scaffold (drug delivery platform) for bony regeneration in rabbits with cranial defects[33,34]

Various drugs with a narrow therapeutic index can be guided to the targeted area by conjugating them with nanomaterials. This allows optimum concentration of the drug at the desired site and prevents dose related side effects and toxicity[35]

Trans-dermal patches and Trans-dermal drug delivery system that bypass the first pass metabolism are being used that goes into systemic circulation with more targeted effect as well as result in least toxicity. Vaccines that contain viral fragments cause immune reactions and thus when these viral fragments are replaced with nanoparticles attached macrophages and human dendritic cells, this selectively activate the T-cell to provide passive immunity without any allergic reactions.

Liposomes with nanoparticles containing anti-proliferative gene p53 DNA have shown potential in prevention of head and neck cancer.[35]

Implantable materials

The natural nanostructure of the bone - composed of organic compound primarily collagen and reinforced with inorganic ones has to be matched by Nanaotechnology for its orthopaedic and dental applications. E.g., Otim (hydroxyl apatite), VITOSSO (hydroxyl apatite and tricalcium phosphate) and Nan OSS are nanoparticles used in cleft patients and osseous defects in the field of oral surgery.[35]

Nano-crystalline hydroxyapatite bone substitute in the form of silica gel has been used for maxillary sinus floor augmentation and the material showed good histological outcomes also 3 months after surgery[36]

Alteration of the immune response can be achieved by introducing certain surface features to the nanocomposite implant materials or the ability of bacteria to colonise it and that reduction of the immune response may be less dependent on surface chemistry than on the surface features of materials at the nano meter scale.[37,45]

Nanomaterials exhibit the property of inhibiting the formation of bacterial bio films. Through reforming a material's architecture, it's resistance to infection can be enhanced as well as resistance to inflammatory process and by doing so, purely "passive" implants, therefore, could become "active" and functional and this is known to have a tremendous impact in plastic surgery where implanted materials are routinely used in cosmetic, reconstructive, and restorative procedures.[9]

In the field of Cancer

The key feature of nanoparticles such as Size (10-100nm) enables it to bypass kidney, leak out of vessels to accumulate inside Tumors, 50-100nm slightly charged nano structure can penetrate into the large Tumors. For superficial Tumors, Cadmium selenide nano particles in the form of quantum dots are used in the detection of Tumors cells which upon exposure to ultraviolet light glow and when injected the cancer cells can be seen as glowing tumor. High energy oxygen molecules are produced due to light which chemically react with Tumors cell and destroy it, without reacting with the other body cells this can be used to assess the tumor margins easily after removal as well as gained importance as a new modality of non-invasive technique for dealing with tumors.[35]

Sentinel node biopsy

QD (Quantum dots -fluorescent semiconductor nano crystals) can be used in the biopsy of sentinel lymph nodes. 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. Trafficking to distinct lymph nodes is 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.[4]

Imaging

Fluorescent semiconductor nanocrystals (QD) have narrow and size-tuneable emission spectra that span from ultra violet to near-infrared. This, together with their prolonged photostability, good photo luminescence, 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.

Combination of QD and with magnetic resonance imaging (MRI) 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 and may have a role in treatment.[38]

Dental Implants

Besides surface chemistry and topography, particle size is another important factor modulating the bone-implant interface [39,40]. For instance, calcium phosphate nanocrystals (20–100 nm range), alumina nano-fibers (2 nm in diameter, 50 nm long) and smaller particles of nano-diamonds have been demonstrated to intensify the Osseo-integrative behaviour in vivo and have caused better osteoblastic proliferation as compared to materials with larger particle size. They have also demonstrated better bone formation capability in these dental implants [41,42]

Despite numerous studies suggesting that dental implants with nanocoating are more biocompatible, it remains unclear if the improved bone formation is due to the chemistry of the coatings, or if it is from the improved nano topography, such as surface roughness that are introduced by the coatings. Future studies on the mechanism of nanocoating associated bone formation should be further investigated[43]

Facial Nerve Regeneration

The inbuilt property of Nano-scaffold to allow external control over the healing tissue can be helpful in nerve regeneration and implant osteo-integration. SF (Silk Fibroin) is known for its excellent bio compatibility, water permeability, and minimal inflammatory reactions, and has been proven with to be productive in the applications of biomedicine, such as wound dressings [44]

Bi-layered SF nanofibers were fabricated to bridge a 5-mm facial nerve defect in a study in rats. Besides SF, Peptide amphiphiles (PAs) is another group of promising candidates in nerve engineering as they are bio compatible, bio degradable protein based and self-assemble capability as well as injectable and able to spontaneously self-assemble into nanofibers [45]

Application of nano scaffolds in clinical treatment remains a distant possibility as very minimal studies are performed owing to the difficulty in creating facial nerve defect model in vivo. In the long run, the combination of nanomaterials with stem cells and/or medication might be explored to adjusting peripheral nerve repair and providing effective basis for clinical therapies[46]

Recent advances

Nano tweezers are under development, which will make cell surgery possible in near future. Nano needles which incorporate nano sized stainless-steel crystals are being developed by Sandvik Bio line, Sweden. Newer anti-bacterial cotton integrated with inorganic nano-structured materials having good anti-bacterial activity is under development 35[,47]

Discussion

Regenerative nanotechnological uses in oral and maxillofacial surgery are increasing rapidly, and there have been recent exciting break throughs. Although the realm of bio materials for bone regeneration is well-established, the use of nanoscience and nano technology specifically for oral and maxillofacial surgery is still new. As we delve into the nano-world, several issues and challenges must be taken into consideration and addressed keenly before nano technology can become common in day-to-day practice.

For instance, nano toxicology is an intense area of research that seeks to elucidate the possible side effects of using nano particles, and their biological interactions with the human body. Although there have been several human studies involving the use of nanoscale bio materials 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.[9]

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 nano particle may mean that the blood–brain barrier can be crossed. Large surface area: volume ratios render nano particles biologically active, which may lead to inflammation and oxidative stress.[9]

Compared with unstable nanoparticles, chemically stable nanoparticles are less toxic and silver nanoparticles having impurities may be easily aggregated, which increases their toxicity due to excessive production of reactive oxygen species and pro-inflammatory mediators [48]

The nanometric size of the materials may allow penetration of the bio logical barrier, production of cytotoxicity, and initiation of immune response to host cells while the surface topography may affect nano particle cellular uptake. [49]

However, literatures are mainly concerned with events in other part in the body (i.e., lung). The overall roles and potential toxic effects of nanomaterials when they are utilized in oral and maxillofacial area are barely summarized [50]

Conclusion

Although the application of nanomaterials has driven the development of cranio-maxillofacial treatment, the side effects of these materials should always be taken into consideration. Only when the issues of technical and regulatory complexities of bringing a nano-product from academia to industry is addressed aptly, we envisage that the shift towards a fully nanotechnological future for oral and maxillofacial surgery will be evolutionary rather than revolutionary.

Clinical significance

Although several studies have focused on application of nano technology in oral and maxillofacial surgery this review observed that there is lack of well-designed studies focusing on the application as well as lack of studies focusing on the secondary/untoward effects of nano particles on oral and maxillofacial region.

References

1. Loizidou M, Seifalian AM. Nanotechnology and its applications in surgery. Br J Surg 2010; 97:463–5.
2. National Science Foundation. Nano technology definition (NSET, February 2000).
3. Taniguchi N. On the basic concept of nano technology. In: Proc Intl Conf Prod Eng. Tokyo, Part II. Japan Society of Precision Engineering 1974; 1974: 18-23.
4. Ma X, Zhao Y, Liang XJ. Theragnostic nanoparticles engineered for clinic and pharmaceutics. Acc Chem Res 2011; 44:1114–22.
5. Pease RF. Electron beam lithography. Contemporary Physics 1981; 22:265–90.
6. Weaver JC, Mill iron GW, Miserez A, et al. The stomatopod dactyl club: a formidable damage-tolerant bio logical hammer. Science 2012; 336:1275–80.
7. Kannan RY, Salacinski HJ, Butler PE, Seifalian AM. Polyhedral oligomeric silsesquioxane nanocomposites: the next generation material for bio medical applications. Acc Chem Res 2005; 38:879–84.
8. Ashley S. Nanobot construction crews. Scientific American. 2001 Sep 1;285(3):76.
9. Shakib K, et al. Regenerative nano technology in oral and maxillofacial surgery. Br J Oral Maxillofac Surg (2014).
10. He L, Liu B, Xipeng G, et al. Microstructure and properties of nano fibrous PCL-b-PLLA scaffolds for cartilage tissue engineering. Eur Cell Mater 2009; 18:63–74.
11. Schofer MD, Roessler PP, Schaefer J, et al. Electro spun PLLA nanofiber scaffolds and their use in combination with BMP-2 for reconstruction of bone defects. PLoS One 2011;6: e25462.
12. Schofer MD, Tünnermann L, Kaiser H, et al. Functionalisation of PLLA nanofiber scaffolds using a possible cooperative effect between collagen type I and BMP-2: impact on colonization and bone formation in vivo. J Mater Sci Mater Med 2012; 23:2227–33.
13. Dallari D, Savarino L, Albisinni U, et al. A prospective, randomised, controlled trial using a Mg-hydroxyapatite- demineralized bone matrix nano composite in tibial osteotomy. Bio materials 2012; 33:72–9.
14. Adamo Poulos O, Papadopoulos T. Nanostructured bio ceramics for maxillofacial applications. J Mater Sci Mater Med 2007; 18:1587–97.
15. Stübinger S, Ghanaati S, Orth C, et al. Maxillary sinus grafting with nano structured biomaterial: preliminary clinical and histological results. Eur Surg Res 2009; 42:143–9
16. Li X, Liu H, Niu X, et al. The use of carbon nano tubes to induce osteogenic differentiation of human adipose-derived MSCs in vitro and ectopic bone formation in vivo. Bio materials 2012; 33:4818–27.
17. Pilloni A, Pompa G, Saccucci M, et al. Analysis of human alveolar osteoblast behaviour on a nano-hydroxyapatite substrate: an in vitro study. BMC Oral Health 2014; 14:22.
18. Behnia H, Khojasteh A, Kiani MT, et al. Bone regeneration with a combination of nanocrystalline hydroxyapatite silica gel, platelet-rich growth factor,

and mesenchymal stem cells: a histologic study in rabbit calvaria. Oral Surg Oral Med Oral Pathol Oral Radiol 2013;115: e7–15.

19. Moller B, Acil Y, Birken feld F, Behrens E, Terheyden H, Wilt fang J. Highly porous hydroxyapatite with and without local harvested bone in sinus floor augmentation: a histo metric study in pigs. Clin Oral Implants Res 2014; 25:871–8.

20. Stübinger S, Ghanaati S, Orth C, et al. Maxillary sinus grafting with a nano-structured bio material: preliminary clinical and histological results. Eur Surg Res 2009; 42:143–9

21. Zamiri B, Shahidi S, Eslaminejad MB, et al. Reconstruction of human mandibular continuity defects with allogenic scaffold and autologous marrow mesenchymal stem cells. J Craniofac Surg 2013; 24:1292–7.

22. Liu Y, Lim J, Teoh SH. Review: development of clinically relevant scaffolds for vascularised bone tissue engineering. Biotechnol Adv 2013; 31:688–705.

23. Helge land, E., Shan bhag, S., Pedersen, T. O., Mustafa, K., & Rosen, A. (2018). Scaffold-based temporo mandibular joint tissue regeneration in experimental animal models: A systematic review. The Bergen stem cell consortium (BSCC), annual meeting, Bergen, Norway, September 3–4, 2017. Tissue Engineering Part B: Reviews, 24 (4), 300–316.

24. Fu, N., Liao, J., Lin, S., Sun, K., Tian, T., Zhu, B., & Lin, Y. (2016). PCL-PEG-PCL film promotes cartilage regeneration in vivo. Cell Proliferation, 49(6), 729–739.

25. Li, G., Fu, N., Xie, J., Fu, Y., Deng, S., Cun, X., … Lin, Y. (2015). Poly (3-hydroxy butyrate-co-4-hydroxy butyrate) based electro spun 3D scaffolds for delivery of autogenetic chondrocytes and adipose-derived stem cells: Evaluation of cartilage defects in rabbit. Journal of Biomedical Nano technology, 11(1), 105–116 (112).

26. Zhu, W., Castro, N. J., Cheng, X., Keidar, M., & Zhang, L. G. (2015). Cold atmospheric plasma modified electro spun scaffolds with embedded microspheres for improved cartilage regeneration. PLoS One, 10(7), e0134729.

27. Norling, L. V., Spite, M., Yang, R., Flower, R. J., Perretti, M., & Serhan, C. N. (2011). Cutting edge: Humanized nano-PR resolving medicines mimic inflammation-resolution and enhance wound healing. Journal of Immunology, 186(10), 5543–5547.

28. Clemente-Napimoga, J. T., Moreira, J. A., Grillo, R., de Melo, N. F. S., Fraceto, L. F., & Napimoga, M. H. (2012). 15d-PGJ2-loaded in nano capsules enhance the anti-nociceptive properties into rat temporo mandibular hyper nociception. Life Sciences, 90(23–24), 944–949

29. Malam Y, Loizidou M, Seifalian AM. Liposomes and nanoparticles: nanosized vehicles for drug delivery in cancer. Trends Pharmacol Sci 2009; 30:592–9.

30. Duncan R. The dawning era of polymer therapeutics. Nat Rev Drug Discov 2003; 2:347–60.

31. Bhirde AA, Patel V, Gavard J, et al. Targeted killing of cancer cells in vivo and in vitro with EGF-directed carbon nanotube-based drug delivery. ACS Nano 2009; 3:307–16.

32. Qu D, Li J, Li Y, et al. Angiogenesis and osteogenesis enhanced by bFGF ex vivo gene therapy for bone tissue engineering in reconstruction of calvarial defects. J Biomed Mater Res A 2011; 96:543–51.

33. Naito Y, Terukina T, Galli S, et al. The effect of simvastatin-loaded polymeric microspheres in a critical size bone defect in the rabbit calvaria. Int J Pharma 2014; 461:157–62.

34. Wadagaki R, Mizuno D, Yamawaki-Ogata A, et al. Osteogenic induction of bone marrow-derived stromal cells on simvastatin-releasing, biodegradable, nano-to microscale fiber scaffolds. Ann Biomed Eng 2011; 39:1872–81.

35. Harsh Verma, et. al. “Application of Nano technology in Oral and Maxillofacial Surgery.” IOSR Journal of Dental and Medical Sciences (IOSR-JDMS), 19(6), 2020, pp. 56-61.

36. Canullo L, Della via C, Heinemann F. Maxillary sinus floor augmentation using a nano-crystalline hydroxyapatite silica gel: case series and 3-month preliminary histological results. Ann Anat 2012; 194:174–8.

37. Mannoor MS, Jiang Z, James T, et al. 3D printed bionic ears. Nano Lett 2013; 13:2634–9.

38. Kobayashi H, Hama Y, Koyama Y, et al. Simultaneous multi colour imaging of five different lymphatic basins using quantum dots. Nano Lett 2007; 7:1711–6.

39. Wang, H., Lin, C., Zhang, X., Lin, K., Wang, X., & Shen, S. G. (2019). Mussel-inspired polydopamine coating: A general strategy to enhance osteogenic differentiation and osseointegration for diverse implants. ACS Applied Materials and Interfaces, 11(7), 7615 –7625.

40. Zhang, J., Liu, J., Wang, C., Chen, F., Wang, X., & Lin, K. (2020). A comparative study of the osteogenic performance between the hierarchical micro/sub micro-textured 3D-printed Ti6Al4V surface and the SLA surface. Bioactive Materials, 5(1), 9–16.

41. Hu, Z., Wang, X., Xia, W., Wang, Z., Zhang, P., Xia, L., Zhu, M. (2019). Nano-structure designing promotion osseointegration of hydroxyapatite coated Ti-6Al-4V alloy implants in diabetic model. Journal of Biomedical Nano technology, 15(8), 1701–1713.

42. Padovani, G. C., Feitosa, V. P., Sauro, S., Tay, F. R., Duran, G., Paula, A. J., & Durán, N. (2015). Advances in dental materials through nano technology-facts, perspectives and toxicological aspects. Trends in Biotechnology, 33(11), 621–636.

43. Wang, H., Liu, J., Wang, C., Shen, S., Wang, X., & Lin, K. (2020). The synergistic effect of 3D-printed microscale roughness surface and nano scale feature on enhancing osteogenic differentiation and rapid osseointegration. Journal of Materials Science and Technology.

44. Liu, J., Yan, L., Yang, W., Lan, Y., Zhu, Q., Xu, H., Guo, R. (2019). Controlled-release neurotensin-loaded silk fibroin dressings improve wound healing in diabetic rat model. Bio active Materials, 4, 151 –159.

45. Tan, A., Rajadas, J., & Seifalian, A. M. (2012). Bio chemical engineering nerve conduits using peptide amphiphiles. Journal of Controlled Release, 163(3), 342 –352.

46. Greene, J. J., McClendon, M. T., Stephanopoulos, N., Alvarez, Z., Stupp, S. I., & Richter, C. P. (2018). Electro physiological assessment of a peptide amphiphile nanofiber nerve graft for facial nerve repair. Journal of Tissue Engineering and Regenerative Medicine, 12(6), 1389 –1401.

47. Nikalje AP. Nanotechnology and its applications in medicine. Med chem. 2015;5(2):081-9

48. Saifi, M. A., Khan, W., & Godugu, C. (2018). Cytotoxicity of nanomaterials: Using nanotoxicology to address the safety concerns of nanoparticles. Pharma ceutical Nano technology, 6(1), 3–16.

49. Hoshyar, N., Gray, S., Han, H., & Bao, G. (2016). The effect of nanoparticle size on in vivo pharmacokinetics and cellular interaction. Nano medicine, 11, 673–692.