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Applications of Nanotechnology in Reconstructive Surgery

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Abstract

The objective of this review was to critically present and evaluate recent investigations into nanotechnology and it's applications in reconstructive surgery. In addition, this review aims to looks at a plethora of applications with nanotechnology in the subject area of reconstructive surgery. The Medline and PubMed databases were searched for clinical trial and case report publications dealing with reconstructive surgeries involving nanotechnology. Reports that were identified addressed different areas of reconstructive surgery and outlined a clear methodology for their studies. Eight publications show that the use of nanotechnology in reconstructive surgery is promising yet still in its early stages and that extensive research needs to be carried out if the expectation of this advancing technology is to overtake current surgical procedures. However, it is clear that there will be a continued interest and progression in this subject field as nanotechnology science is unveiled.

Keywords

Poly(L-Lactide-Co-Glycolide) (PLGA), Poly(*ε*-Carpolactone) (PCL), Hydroxyapatite/Polyamide (n-HA/PA), Silicon Nanoribbon (SiNR)

Subject Areas: **Bioengineering, Biological Engineering, Biological Materials, Biotechnology, Cell Biology, Composite Material, Molecular Biology, Surgery & Surgical Specialties, Synthetic Biology**

1. Introduction

The notion of nanotechnology is discovered by the Nobel Laureate Richard Feynman and can be defined as the usage of materials that are at a Nano scale size [1]. Conventionally this scale is taken as a range of 1 nm to 100 nm. This technology however is not just a scaled down version of current treatment options but is a novel design that can interact and target anatomical, physiological and biochemical systems in a different way. As everything

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mentioned occurs at a molecular level; nanotechnology reveals itself to have specificity higher than current technologies. Research into the uses of nanotechnology around the subject area of medicine has appeared to increase over the past decade, as it is clear with the number of publications in the field. Reconstructive surgery in particular is an emerging field of biotechnology, combining disciplines in bioengineering, material science and cell biology with an intention of repairing or replacing tissue in an effective manner. In its broadest sense, reconstructive surgery involves intervention that restores a body part to normal anatomy and or function. This review looks at the broad aspects of reconstructive surgery and looks at the various applications of nanotechnology in this field. The review also intends to look at areas where nanotechnology has been used in a research environment with a prospect of ameliorating the results in order to use the technique at a clinical setting.

2. Nerve Repair and Regeneration

Nerve injuries are usually complicated to successfully restore, as mature neurones do not replicate. In the case of small nerve injuries, treatments rely on the microsuture of the severed nerve ends and in the treatment of substantial nervous tissue loss; an autologous nerve graft can be performed. This latter treatment for serious nerve injury can lead to a loss of function at donor sites and painful neuromas. Therefore this treatment option can be contested as being the gold standard [2] [3]. In a recent study, composite scaffolds for nerve regeneration in rats with lesions were presented. The scaffold is a guide tube made of electrospun microfibers of Poly (L-lactide-co-glycolide) (PLGA) and Poly (ε-carpolactone) (PCL). The elctrospinning technique makes it possible to spin flexible scaffolds made of these biodegradable polymers. This scaffold was used to regenerate a 10 mm sciatic nerve gap *in vivo*. An experimental group comprised of rats subjected to the tubular scaffolds implanted at the severed nerve endings and the control simply consisted of the rats with a sciatic nerve lesion. At four months after the surgery, the sciatic nerve failed to reconnect the two stumps in the control group (**Figure 1**). In most of

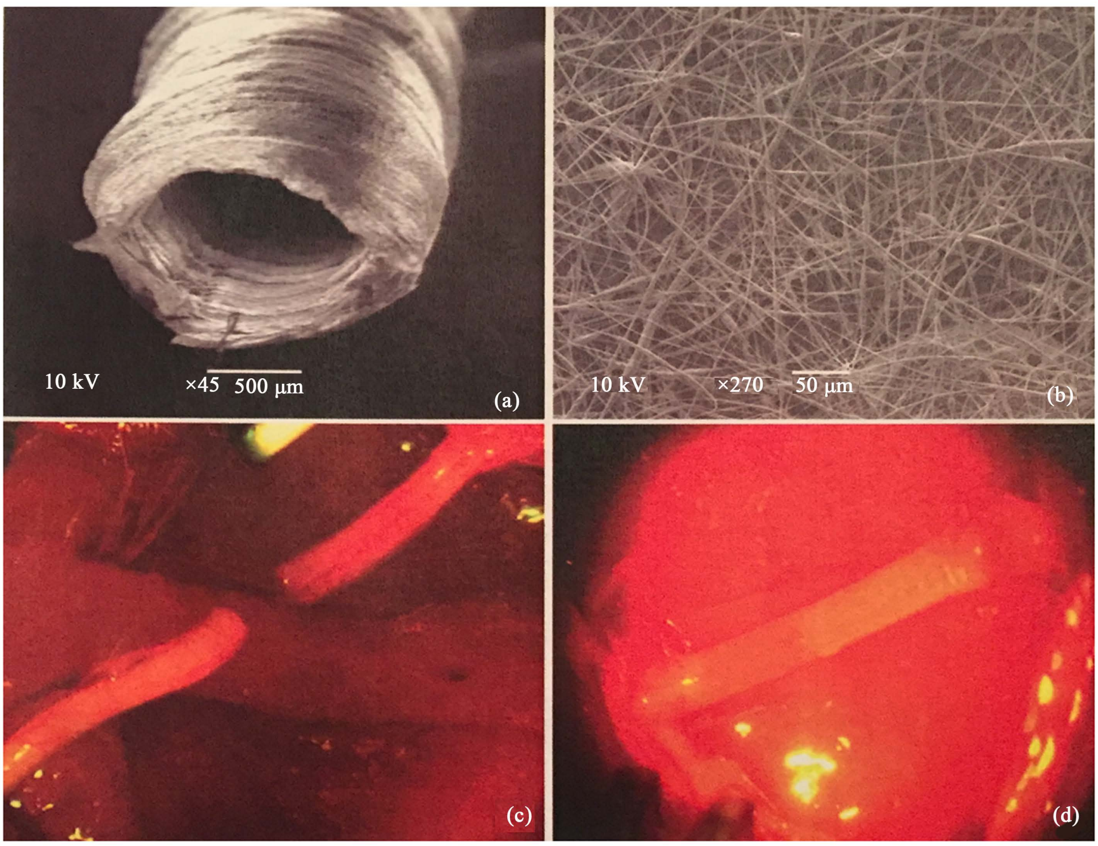

Figure 1. Scanning electron micrograph images of the electrospun PLGA/PCL nerve guide conduit (a) and details of the scaffold wall (b); (c) micrograph of transected rat sciatic nerve; (d) micrograph of prosthesis implanted, filled with saline solution and sutured to the transected nerve [4].

the treated rats, the tubular scaffolds had induced nervous tissue regeneration and reconnection of the sciatic nerve endings. Furthermore, myelination, collagen IV deposits along with neural indicators of re-establishment and re-innervation of target muscles was seen. There was no significant inflammatory response detected in the majority of rats treated. This functional recovery was not satisfactory due to latency in nerve conduction. However the results shown from this study are promising for stimulating and guiding peripheral nerve functional regeneration [4]. Ways to improve the efficacy of the nerve guides by the controlled release of nerve growth factors or Schwann cells along the graft was also discussed [5].

Another study looked at the effect of FK506 nanospheres on the regeneration of anallogeneic nerve after transplant. FK506 has the function of inhibiting the immune rejection in rats [6]. It also has the function of promoting neural regeneration by enhancing the phosphorylation of growth associate protein-43, which promotes neuronal growth [7]. The experiments put FK506 nanospheres around the transplanted tibialis nerve and were used continually at different periods after the operation in different experimental groups. The results showed similar effects of neural regeneration in groups that were given the FK506 immediately and 24 hours after the operation but the group that was given the medication 3 days after the operation had worse neural regeneration. However, the effect in the group with the FK506 3 days after the operation was better than that in the group without medication altogether. This study showed that FK506 has a promoting effect on the restoration of the axon in the early stages after transplantation and that these effects became weaker when the administration of FK506 was delayed [8].

3. Oral and Maxillofacial Surgery

During an angle-reduction ostectomy, fracturing or causing a defect in the mandibular condyle proves to be one of the most serious complications. During reconstruction of the condylar defect, it is necessary to maintain the function of the temporomandibular joint and uniformity anatomically. Autologous bone grafting is the standard method of treatment of mandibular reconstruction currently but in order to do this a large amount of bone must be acquired and shaped into the correct size to then be inserted into the defective area [9]. The use of the nanoscale hydroxyapatite/polyamide (n-HA/PA) in a recent study was shown to be a probable alternative for mandibular reconstruction. This is because the n-HA/PA composite has a close relationship to that of collagen and bone in a normal human bone matrix [10]. Hydroxyapatite on its own is not compatible due to the brittle nature of the mineral. The addition of the polyamide allows for mechanical properties that resemble bone. The study customized and designed an implant based on the patients computed tomography data. This was made by computer-aided design and manufacturing using a three-dimensional printer producing a perfect fitting condylar implant (**Figure 2**). Because of the computer design, there is a restoration of the facial contour and symmetry thus simplifying surgical planning, the manufacturing and significantly reducing the operating time itself. Operational

(a) (b) (c)

Figure 2. (a) Display showing orientation of the implant; (b) inserted implant into defective area and fixed using miniplates; (c) computed tomography scan showing the condylar defect reconstructed 28 days after operation [11].

errors as a result of this implant can be minimised resulting in better precision and stability after screw fixation. The use of this also allows the implant to be tested before the operating procedure. Furthermore the second surgical site and its associated morbidities are effectively avoided, including donor-site infections and unexpected growths. In this study, a 27-year-old woman with a square-shaped face underwent mandibular angle reduction and received the novel implant. The implant does not incorporate into the bone unlike an autogenous graft and so holes and grooves are required to be made for increased mechanical interlocking. The resorption and remodelling rate differs for alloplastic materials so it is unknown what will happen to the implant after a few years. In this patient the lateral pterygoid muscle was not attached to the conduular implant so there was no help from the muscle in side-to-side movements. Therefore the temporomandibular joint in this instance can be stated as not achieving truly normal function. This apparent hinge movement was only apparent after the reconstruction phase. The study here shows a real promise of being the new gold standard approach to solve grafting issues for maxillofacial deferomities but further studies need to be investigated with longer follow-up periods [11].

4. Soft-Tissue Reconstruction

One publication looked at the development of a novel cell-seeding method that allows a controlled number of cells to distribute through a nanofiber scaffold. The study involved rats that received 4 types of implant including primary fibroblast-seeded polycaprolactone (PCL)/collagen nanofiber scaffold, PCL/collagen cell-free nanofiber scaffold, acellular human cadaveric dermis (AlloDerm) and acellular porcine dermis (ENDURAGen). The rats were monitored postoperatively and received enroflaxin in the drinking water for 4 days prophylactically and buprenorphine. This cell seeding method reduces inflammation and increases acceptance despite the fact that the host cells replace the seeded cells. This supports the hypothesis that cell presence is more important fro integration with host tissue than the gathering of cells on constructs long enough for proliferation and producing extra cellular matrix protieins [12]. The multilayer constructs can be folded before it is implanted thus allowing a clinician to time the implant to coincide with the time of surgery. From this study it was observed that cell seeding can occur on a multilayer PCL/collagen nanofiber construct and that this improves vascularization. Cells expressing enhanced green fluorescent protein were used to differentiate between the donor and host cells and the study found that many donor-derived cells were found near the nanofiber surface of individual layers. Cell-seeded implants produced a significantly greater amount of neovascularisation. This may prove to be valuable for dermal augmentation or replacement. The cell seeded constructs may act a study model into further research of engineered constructs [13].

Many amputees use prosthetic limbs as a means to aid in movement or as a cosmetic tool rather than as a functional replacement of the limb. There have been advances in technology that design prosthetics with tactile sensors to provide sensory reception however there continues to be incoordination between the electronics and biological tissue thus impeding the performance of prosthetics in amputee populations. One study proposed the use of a stretchable prosthetic skin that has an ultrathin single crystalline silicon nanoribbon (SiNR) strain, pressure and temperature receptors. The SiNR sensors are tuned to the stretch and mechanical properties of the skin segment. The design in question intends to enhance the perception capabilities of artificial skin in response to the dynamic external environment. The skin prosthesis also has the ability to sense skin moisture and temperature regulation through the integration of stretchable humidity sensors and heaters. The study looks to produce site-specifically designed SiNR mechanical and temperature sensor arrays for prosthetic systems. Interfacing platinum nanowires in the stretchable electrodes allow for the unique capabilities of the prosthesis to merge abiotic functions of the artificial skin with the human body. Ultimately this is the main aim for high performance smart prosthetics [14]. It isn't entirely clear as to whether this technology is ready for use in amputees, as the publication didn't mention the use of the prosthetics in humans or even in an animal model. Therefore the idea of integrating the limb to the body can be still seen as hypothetical until studies start to use clinical trials to determine the efficacy of such prosthetics. It is clear that this technology could prove to be beneficial for the patient with further development of this product by providing a more natural appearance of structure and function, thus enabling clinicians to treat tissue amputations and soft tissue injuries in a safe and reproducible manner.

Another study looked at the use of platelet-rich plasma containing fragmin-protamine micro-nanopartices in split-thickness skin graft donor sites and its effect on promoting epithelialisation and angiogenesis. The study was carried out on rats with different groups receiving different interventions. The results showed that intradermal injections of the platelet-rich plasma containing fragmin-protamine micro-nanoparticles promoted epithelialisation and angiogenesis in split-thickness skin graft donor site wounds (**Figure 3**). The nanoparticles used are

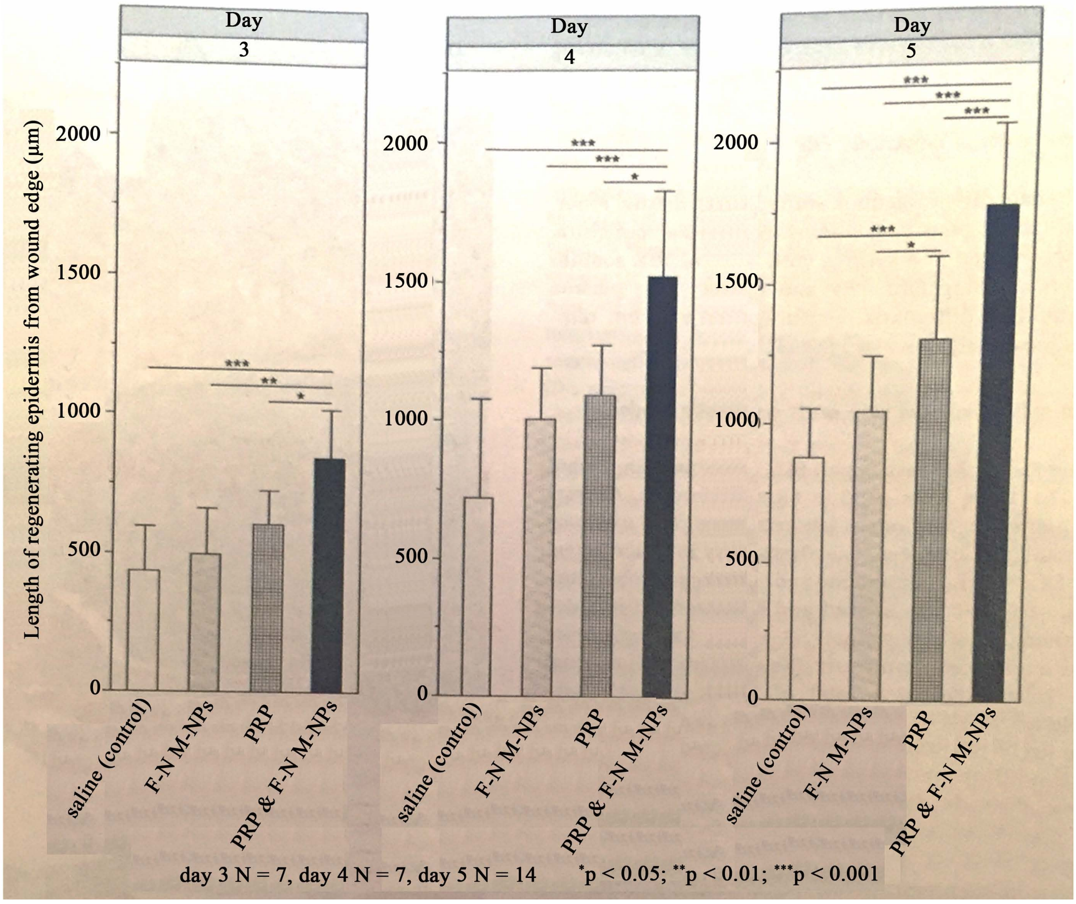

Figure 3. Length of regenerating epidermis from the wound edge. Re-epithelialisation in the platelet-rich plasma-containing fragmin-protamine micro-nanoparticles (PRP & F-N M-NPs) treated group was significantly increased compared with other groups [15].

excellent carriers for growth factors allowing for the induction of local neovascularisation. This was seen through histological slides taken from the rats. The application of this treatment may promise a new treatment for split-thickness skin graft donor site wounds [15].

Orthopaedic surgeons also have to perform reconstructive surgeries and in particular there was a study on humans that used a biomimetic osteochondral scaffold in the treatment of tibial plateau lesions. These articular defects often occur as a result of complications in tibial plateau fractures. There are often deformities after the trauma and poor outcomes, even after internal fixation with screws and acute surgical reduction. The osteochondral scaffold was a biomimetic nanostructured implant composed of a porous 3 dimensional tri-layered structure. The short-term results at 24 months of follow-up support the benefits of the scaffold as it provided symptom relief and a return to satisfactory activity level in most cases. Moreover of the 11 patients that underwent the treatment 3 experienced minor adverse effects but no patient required further surgery for treatment failure during the follow-up period. The remaining 8 patients reported an improvement after the treatment. There is promise of using the osteochondral scaffold as a treatment for tibial plateau lesions in the clinical setting, however the findings presented in this study were only preliminary, therefore further studies need to be taken in order to support the positive results found in this study [16].

5. Collagen

The use of collagen nanofiber scaffolds has been shown to accelerate wound healing through effects on fibroblast and capillary proliferation in rat models [17]. One study showed that by combining eletrospun collagen nanofibers with polymerized microfibers the cell cytocompatibility, morphology and other cell factors are improved *in vitro*. As a result, the same study also used a hybrid scaffold with the aforementioned combinations of nanofibers to reconstruct large tendon defects in a rabbit model. The results showed that there were greater healing responses after the collagen scaffold had been implanted in the tendon defective area and that the host did not reject the implant. Inflammation was induced by the surgical procedure and was enhanced by the collagen scaffold however the scaffold was not rejected. It was seen in this study that the collagen implant was biocompatible in the rabbit models, reducing peritendinous adhesion, muscle fibrosis and atrophy. 60 days post injury saw that the injured tendons of the rabbits fitted with the collagen scaffold was replaced by new tendon. Although this tendon was not mechanically a strong as normal tendons, it was superior to the control tendons [18].

6. Conclusion

Demonstrated by this review, it is clear that there are many applications of nanotechnology in reconstructive surgery and with increasing research into this field of medicine, there will undoubtedly be more. Particularly, nanotechnology has been used in areas of nerve repair and regeneration, oral and maxillofacial surgery, soft tissue reconstructions and collagen implants. Currently, it is difficult to find follow-up studies around novel research and therefore difficult to know whether the results seen in previous studies are reproducible. There is current research into nanotechnology around bone prosthetics and with the further understanding of nanoparticles; there will be a continuation to find applications that will advance capabilities in reconstructive surgery. Although this review is not in entirely inclusive of all the applications in this growing field, I believe that there is some significance to be taken from what has been discussed.

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