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Review

The legacy of nanotechnology: Revolution and prospects in neurosurgery

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ABSTRACT

Nanotechnology has been an ever-growing field since the discovery of carbon fullerenes, and is being assimilated progressively into a variety of other disciplines including medical science. The association with neurosurgery had initially been less well characterized compared to other organ systems, but has recently offered promising future potential for a wide range of utilities including new therapeutic options for Glioblastoma Multiforme, neurprotection against oxidative stress, nerve nanorepair, nanodiagnosis of Alzheimer's disease, nanoimaging with nanoparticles and quantum dots, nanomanipulation of CNS with surgical nanobots, and nanoneuromodulation with nanofibres & nanowires. This article examines such potentials as well as others, of the utility of nanotechnology in Neurosurgery.

1. Introduction to nanotechnology

Nanotechnology involves scales that can be characterized to an order of 10^{-7}–10^{-9} m. In biological terms, this would reflect the range of sizes of viral particles, to the size of the smallest bacterium belonging to the *Mycoplasma* genus. This term should not, however, be limited to mere particles of that order, or their visualization, because it refers to a conglomerate of various disciplines and subspecialties amongst physics, chemistry and biology that is involved in design, synthesis, characterization and applications of devices that can be measured at nanometer scale.[1]

This term was initially coined by Norio Taniguchi in 1974, a professor at Tokyo Science University,[2] and later was popularized by Dr. Kim Eric Drexler, both of whom agreed, although unknowingly, upon nanotechnology as processing, separation, consolidation and deformation of materials by one atom or by one molecule. The idea is however unique to Richard Feynman's famous talk in 1959: "There's plenty of room at the bottom", in which he envisioned the development of nanomachines able to build other nanomachines with atom-by-atom control.[3]

This is currently being managed by two peculiar techniques designated as "top–down" and "bottom–up". The former begins with using a macroscopic material as a prototype and introducing small-scale details in it, such as utilized in creating integrated circuits within silicon wafers in the semiconductor industry.[1] The latter begins by customizing molecules that later assemble and organize themselves into higher order structures.[4] As an example, nanoscale electrode junctions have been created by using specific oligonucleotide sequences that direct the assembly of electrical circuits containing 20 and 30 nm diameter DNA-modified nanoparticles.[5]

This article would explore the various avenues being exploited by researchers in integrating Nanotechnology specifically with applications in Neurosurgery. These include, but are not limited to:

1. Background of nanoparticles and blood brain barrier
2. Therapeutic modalities in Glioblastoma Multiforme, the results of which have been extensively published across the journals

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3. Nanomanipulation involving use of femtosecond laser surgery
4. Neuroprotection against oxidative stress with fullerenols
5. Nanoimaging and Nanodiagnostic modalities with iron oxide nanoparticles and quantum dots
6. Nanoneuromodulation with nanofibres and nanowires for monitoring neuronal electrical activity and stimulation
7. Nanorepair of central and peripheral nerves

2. Blood brain barrier and nanoparticles

The blood-brain-barrier is a highly impermeable barrier formed by the endothelial cells in the central nervous system through tight junctions that are primarily induced by astrocytes.[6] Although circumventricular organs such as pineal gland and area postrema are alienated to this barrier allowing secretion of melatonin into blood and detection of emetic substances respectively, the relatively strict protection afforded by the rest of the brain serves to exclude transmembrane transport of a majority of molecules, especially drugs. Both lipophilic properties and a molecular size of $<$400–600 Da threshold are important properties in determining the relative ease by which transfer occurs across the blood brain barrier.[7] For molecules not satisfying either category, various transporters unique for amino acids, peptides, hexoses etc, exist for their influx.[8] Despite these allowances, the blood brain barrier continues to hinder development of drugs for the central nervous system and in an estimate, the global. CNS pharmaceutical market must grow by $>$500% to be comparable to the global market for cardiovascular drugs.[9] Another analysis has shown that CNS drugs constitute only 12% of the library of drugs that exists, and a meagre 1% drugs have indications for non-affective CNS disorders.[10] This problem is further compounded by the presence of active efflux transporters that includes P-glycoprotein and other members of the ATP-binding cassettes. This is illustrated by the non-nucleoside reverse transcriptase inhibitor Azidothymidine whose active efflux transporter, although hasn't yet been characterized at the molecular level, also exhibits properties of efflux for Didanosine.[11]

While other methods have been attempted to circumvent the BBB such as by direct intraventricular infusions of nerve growth factor in patients with Alzheimer's disease,[12] nanoparticles offer a bigger yet better promise of more efficient drug delivery and alleviated toxicities. These are polymers of alkylcyanoacrylates that can disperse efficiently in an acidified aqueous medium with the addition of surfactant. They can range in size from 1 to 3000 nm that can incorporate drugs either during the polymerization process, or adsorption to preformed nanoparticles.[13] These nanoparticles mask the limitations imposed by the BBB on drug delivery and possibly slow drug release from CNS resulting in decreased peripheral drug toxicities.[14] The manufacturing process offers versatility in achieving different sizes of the nanoparticle through controlling the temperature, pH of the solution, stirring rate, acidifying agent and type of electrolyte.[15] The size of the nanoparticle is likely to affect the transport of nanoparticles, often in conjunction with other parameters such as temperature. In an experiment, it has been demonstrated that transport of smaller particle sizes of the order of 100 nm in comparison to 400 nm size, is especially augmented by a temperature of 42 °C compared to a temperature of 34 °C.[16]

Nanoparticles can be loaded with many different substances such as contrast materials, drugs, dyes, and photosensitizers through adsorption, encapsulation or covalent linkage depending upon the properties established during the manufacturing process. Efficient delivery can be achieved through attachment of specific targeting modalities such as monoclonal antibodies, and the stability can be enhanced through attachment of Poly-ethylene glycol to reduce the half-life and clearance. These nanoparticles behave as macromolecules and are retained within the tumour through Enhanced permeability and retention effect (EPR)[17] even after their serum levels fall. These particles effectively isolate the materials in their core from the surrounding environment in order to reduce systemic effects and removal of material, such as decreasing systemic toxicities of chemotherapeutic drugs through encapsulation into nanoparticles.

3. Nanotherapeutic modalities in glioblastoma multiforme

3.1. Chemotherapy

Glioblastoma Multiforme is the most prevalent and malignant of all adult brain tumours. This tumour is invariably lethal with a median survival rate of an estimated 11.6 months.[18] Long term survival is also associated with this tumour, estimated at 5% (22 patients) for beyond 5 years for patients diagnosed with primary supratentorial glioblastoma multiforme, with 20 patients having a subtotal resection, and 2 with a gross total resection.[19] The current treatment is with maximal surgical resection and adjuvant radiation therapy and chemotherapy with temozolomide.[20] Resection however is not associated with strong survival significance, with a median age of survival being 13 months for resection greater than 98% and survival less than 8.8 months for resection less than 98%.[21] Interstitial chemotherapy with carmustine also only improves the median survival of 11.6 months by 2 months only.[19] These observations reflect the difficulties experienced in adequately treating this tumour. The potential therapeutic options utilizing the principles of nanotechnology have been explored.

Glioblastoma Multiforme has been shown upregulate Low Density Lipoprotein receptors. This has given way for the construction of nano-LDL particles by using a synthetic peptide with the lipid binding domain and the LDL-receptor binding domain of Apo-B100 and combining them with lecithin and cholesteryl oleate. After tagging them with a fluorescent marker, it was demonstrated that these synthetic particles are taken up by the tumour.[22] It has further been demonstrated that these particles can be tagged with lipophilic drugs and are made capable of tumour cytotoxicity. Pacletaxel Oleate has been used in this manner and when used together with suramin (an inhibitor of LDL receptor), tumour cell survival improves.[23] Similarly HDL particles have been constructed with incorporated Paclitaxel and shown to have superior cytotoxicity and 5–20 times lower half maximal inhibitory concentrations than free drugs against cell lines other than Glioblastoma Multiforme.[24] LDL receptors have also been shown to be upregulated on Tenon Capsule's fibroblast after exposure to Transforming Growth Factor-fÒ. This is hoped to become a focus for targetted drug therapy in an attempt to control excessive scarring during conjunctival healing.[25]

Apart from the LDL receptor, Interleukin-13 receptor has also been demonstrated to be upregulated on Glioblastoma Multiforme cells and this fact has been exploited by using a mutated Pseudomonas IL-13 cytotoxin that has been shown to be potent at killing the tumour cells.[26] Modified fullerenes have been conjugated with an IL-13 peptide and demonstrated to show specificity for the tumour cells, and are purported to be utilized as a drug delivery system in near future.[27] Further selective targeting is also demonstrated by boron nitride nanotubes that have been demonstrated to be specifically taken up by the tumour cells.[28] From these results, it can only be hoped that these modalities can offer improve survival rates and durations for patients suffering from this tumour.

Fujita et al[29] have investigated the use of two different monoclonal antibodies, an antimouse transferring receptor antibody and a mouse autoimmune anti-nucleosome antibody 2C5, by tagging

these onto poly(ß-L-Malic acid). The anti-tumour component was antisense oligonucleotides to vascular protein laminin-8. This configuration was intravenously administered into rat models bearing glioma. Fluorescence imaging after 24 h demonstrated a significantly higher tumour accumulation using a platform with two monoclonal antibodies instead of a single one. The authors argue that this tandem configuration enhances tumour targeting potential and efficacy. From these results, it can only be hoped that these modalities can offer improve survival rates and durations for patients suffering from this tumour.

3.2. Gene therapy

Gene therapy involves incorporation of genes into the tumour genome to produce the desired apoptotic effect. Both viral vectors and liposomes have been utilized to deliver the exogenous genes to tumour cells. Lu et al[30] have investigated the use of non-viral vector cationic albumin-conjugated pegylated nanoparticles (CBSA-NP) integrated with the plasmid pORF-hTRAIL (pDNA). The authors intravenously administered the resulting CBSA-NP-hTRAIL to BALB/c mice bearing i.c. C6 gliomas and the released pDNA was present in the nucleus after 6 h and induced apoptosis 48 h after transfection. They inhibited tumour growth and prolonged survival when compared with the blank nanoparticle NP-hTRAIL in mice. This shows the promising utility of CBSA-NP-hTRAIL for noninvasive gene therapy of gliomas.

3.3. Thermotherapy

The effect of hyperthermia on solid glioma tissues implanted subcutaneously in rat models has been investigated. Magnetic cationic liposomes were injected into the solid tumours and subjected to an alternating magnetic field. Rats were divided into four groups with the first receiving no irradiation, second receiving irradiation for 30 min, third for 60 min and the fourth with 90 min. Within the last group, tumour regression was observed in 87.5% of the rats and within the third group, it regressed in 60% of rats. Histological examination showed least MCL dispersion in the first group and the most within the last group, and this factor was found to be significant for tumour regression. Importantly no severe side effects were observed.[31]

Data from animal studies have prompted the investigation of thermotherapy in clinical trials. Maier-Hauff et al[32] injected aminosilane coated iron oxide nanoparticles in 14 patients with recurrent glioblastoma multiforme. The patients were subsequently exposed to alternating magnetic field to cause particle heating. Patients were given 4–10 thermotherapy treatments after instillation of magnetic fluid and single fractions of a radiotherapy series. Although effects were not remarkable, the patients experienced negligible side effects with the therapy leading to the conclusion that thermotherapy can be safely applied on patients with GBM.

3.4. Photodynamic therapy

The idea behind photodynamic therapy (PDT) revolves around the use of a photosensitizer which, after activation with light, would enable cellular oxygen to generate reactive species causing cell toxicity.[33] This was investigated by Reddy et al[34] where the researchers developed multifunctional polymeric nanoparticle with a tumour vasculature targeting F3 peptide and encapsulated PDT and imaging agents. These were administered intravenously to rat models bearing 9L gliomas and significant MRI contrast enhancement was achieved. This was compared with rat models receiving systemic photofrin or nontargeted nanoparticles. The survival was greater than 6 months in two out of five rats receiving targeted nanoparticles with a mean of 33 days whereas survival was only 8.5 days in rats receiving control treatment.

Gold nanoshells have also been investigated in the photothermal treatment of glioma through macrophage-mediated delivery.[35] Nanoshells have a dielectric core that is coated with a gold layer which can absorb Near-infrared light (NIR) and convert it into heat. Macrophages have a natural ability of traversing the Blood Brain Barrier and when loaded with antitumour agents, can serve as vectors for delivery to tumours and surrounding tissues. The authors used empty or nanoshell loaded macrophages and investigated the effects of exposure to NIR laser. Their results demonstrate the avid uptake of nanoshells by macrophages and infiltration into the glioma spheroids. The NIR laser exposure resulted in complete growth inhibition compared to controls.

4. Nanomanipulation and surgical nanorobots

Nanomanipulation is purported to represent what might be termed as “surgery at the nano level”.[36] It involves the use of nanodevices such as nanorobots to be introduced into the vascular system or body cavities, programmed and controlled remotely by the surgeon, and perform various diagnostic and therapeutic functions in a very precise and minimally invasive manner leading to faster recovery, while communicating with the on-site surgeon through signals. Various applications have already been investigated. A rapidly vibrating (100 Hz) micropipette with <1 micron tip has been used to dissect the apical dendrites of rat hippocampal CA1 pyramidal cells which result in complete disconnection of dendrites and maintained cell viability.[37] Axotomy performed in roundword neurons using femtosecond laser surgery resulted in complete regeneration.[38] Laser axotomy was also performed on D-type axons of C. Elegans with femtosecond laser. The researchers also employed confocal fluorescence imaging and laser scanning brightfield for real-time imaging which was used to study the development of incision, presence of any possible collateral damage and improve the technique. The authors argue that the potential of this imaging to be used in nanosurgery and axon regeneration is vast.[39] Other surgical nanorobots outfitted with operating instruments and capable of precise mobility for microvascular surgery, organ transplants, molecular repairs on cells, and eliminating cancerous cells have also been envisioned.[40]

5. Neuroprotection with nanotechnology

5.1. Fullerenols

The brain tissue is especially sensitive to ischaemia which can be precipitated by a variety of systemic conditions such as haemorrhage, cardiovascular compromise or stroke. Fullerenes are molecules composed of large 3-dimensional arrays of evenly spaced carbon atoms. Spherical fullerenes are called buckyballs and cylindrical ones are designated cabon nanotubes. The first fullerene to be discovered was buckministerfullerene, in 1985 by the three eventual Nobel Laureates Robert Curl, Harold Kroto and Richard Smalley. These molecules have been shown to possess antioxidant and free-radical scavenger properties that can reduce NMDA-, AMPA-, and glutamate induced excitotoxic and apoptotic cell death.[41,42] The mechanism is a selective inhibition of glutamate channels resulting in decreased Calcium influx and thereby avoidance of excitotoxic and apoptotic effects on the neurons.[42]

5.2. HIV encephalopathy

HIV Encephalopathy and AIDS–Dementia complex are some of the neurological complications associated with the primary HIV infection alongside vacuolar myopathy, peripheral neuropathies and polymyositis. The usual corresponding CD4+ lymphocyte count is below 200/ƒÝl although with the advent of highly active anti-retroviral therapy (HAART), the delay towards a gradual reduction in lymphocyte count manifests a mild symptom spectrum of encephalopathy.[43] Even though the encephalopathy complex is still continually being reported, evidence suggests that aggressive early HAART treatment to prevent severe immunosuppression may prevent these disorders.[44] Other studies suggest improvement in neuropsychological testing and reversal of neurological symptoms especially motor performance, with HAART initiation compared to patients without HAART who steadily worsen.[45] Therefore aggressive early HAART forms the current standard of care, however most of these drugs have poor CNS penetrance but whether this has any clinical significant remains unknown.[46]

One of the proposed mechanisms for HIV induced neurotoxicity is neuronal apoptosis, through activation of glial cells and macrophages that may not necessarily be directly related to HIV infection, causing oxidative stress. This is especially strongly predominant in basal ganglia and correlates well with HIV Encephalitis.[47] Macrophages are the direct seat of HIV infection and productivity.[48] Therefore in-vitro studies into direct macrophage targeting using colloid nanoparticles and human serum albumin with size <200 nm labelled with Azidothymidine have shown high intake of these nanoparticles and promising results (29).[49] Furthermore the HIV-infected macrophages have demonstrated a higher intake of azidothymidine coated nanoparticles than do non-infected macrophages.[49] The reverse-protease inhibitor, Saquinavir, has demonstrated a 10 times increase in its efficacy in its antiviral effect when compared to an aqueous solution of the drug.[50] Systemic infection by HIV has also been targeted with modified nanoparticles that display ligands for the HIV-specific receptors CD4 and CCR5 on macrophages, especially in lymph nodes.[51]

6. Nanoimaging and nanodiagnostic modalities

6.1. Alzheimer's disease

Alzheimer's disease is the most common cause of dementia in the elderly resulting in significant debility. The accumulation of Beta-Amyloid plaques has been linked to triggering neuronal degeneration by altering the Calcium balance of the neurons.[52] Another theory focuses on deficiency of acetylcholine in the brain and is linked to destruction especially of acetylcholine containing neurons in the basal nucleus of Meynert. This is the subject of pharmacological management of the disease using acetylcholinesterase inhibitors such as galantamine and rivastigmine. Memantine, a non-competitive NMDA receptor antagonist is also used to inhibit over-excitation resulting from glutamate and consequent cell death. These medications form the current symptomatic treatment regimen for Alzheimer's. The NINCDS-ADRDA criteria is used to diagnose Alzheimer's but considerable confusion can exist with other entities such as Frontotemporal dementia.[53] This criteria is now being revised in lieu of availability of several distinctive and reliable criteria of biomarkers available in CSF.[54]

These biomarkers include the presence of tau proteins and beta-amyloid proteins in the cerebrospinal fluids. Detection for phosphorylated tau181P in the CSF resulted in a sensitivity of 94–100% when compared to histopathological confirmation on autopsy.[55] Recently Amyloid-Beta-derived diffusible ligands (ADDLs) have been proposed as the neurotoxins whose presence correlates directly with memory loss associated with Alzheimer's disease.[56] This circumvents the reliance on correlation between presence of Amyloid plaques in the brain which have not been adequately correlated with symptomatology of Alzheimer's disease.[56] The scope of nanotechnology has allowed development of ultra-sensitive bio-barcode assay to measure the concentration of these ADDLs in CSF making it a potential diagnostic tool.[57] This example of a nanodiagnostic promises increased sensitivity, multiplexing capabilities, and reduced cost for many diagnostic applications.[58]

6.2. Imaging by iron oxide nanoparticles

Ferumoxtran-10 is a dextran coated iron oxide nanoparticle that has been used as a contrast adjunct to Magnetic Resonance Imaging of brain for malignant tumours, as compared to the more traditional gadolinium-enhanced MRI scan.[59] It has shown several advantages over gadolinium, allowing for enhancement of those regions of the tumour not visualized with gadolinium, and the ferumoxtran-10 enhancing lesions have persistent increased T1 signal intensity for 2–5 days postoperatively. These findings have the potential in assisting image-guided neurosurgery and improve the diagnosis of lesions caused by multiple sclerosis, stroke etc. Additionally ferumoxtran-10 is taken up by reactive cells in brain allowing for histological examination of the tissue with simple iron staining.

These iron-oxide nanoparticles have other potential applications. They have been shown to assist in determining the density of the Tyrosine kinase Her-2/neu receptor by attaching to the cell surface and being imaged by MR molecular imaging.[60] Determination of this receptor positivity status of breast cancer has significant impact on the staging and treatment of the cancer. Additionally they have been shown to document degree of inflammation in the nephritic rat kidneys, on MR imaging.[61]

6.3. Intraoperative imaging through iron oxide nanoparticles

Achieving adequate resection of margins in brain tumour surgery is a critical step that ultimately determines the outcome and progression free survival.[62] However this can be challenging due to inability to accurately delineate the tumour margins and is based on the subjective impression of the concerned neurosurgeon. Residual tumour may still remain even after total resection of the tumour.[63] While intraoperative MRI is utilized to aid in resection of the tumour margins, abnormalities around the resection area have been observed postoperatively creating potential confusion residual tumour and interpreted as treatment failure.[64] Similarly use of fluorescent dyes to visualize tumour margins can result in inability to concentrate an adequate amount specifically within the tumour area. This has led to the development of Iron oxide nanoparticles that harbour the near-infrared fluorescing molecule (NIRF) Cy5.5 which was detected in a model of gliosarcoma with green-fluorescing protein-expressing 9L glioma cells. Sequestration by microglia and optical and magnetic properties of the probe enabled tumour margin detection by preoperative MRI imaging and intra-operative optical imaging.[65] Another group covalently bound the iron oxide nanoparticles with polyethylene glycol, subsequently functionalizing it with chlorotoxin and Cy5.5. Both MRI and fluorescence microscopy displayed significant uptake of the nanoparticles by the glioma cells.[66]

6.4. Quantum dots

These are alternatives to the Cy5.5 laden iron oxide nanoparticles that are made of semiconductor materials, ranging in size

from 2 to 10 nm and exhibit very unique optical and electrical properties due to their tiny size, which is different from the bulk material. The most significant effect is emission of photons under excitation that is perceived as light by eye. The emitted wavelength depends on the size of the quantum dot rather than the material used. This enables creating different size quantum dots that can emit various wavelengths, including those within the range of visible light, and beyond.[67] Jackson et. al[68] have investigated the use of 705 nm emission Qdot ITK Amino(PEG) Quantum dots by injecting into the tail veins of rats after intracranially implanting C6 gliosarcoma cell lines and sacrificing the animals after 24 h. It was noted that at low doses, the quantum dots were phagocytized by the reticuloendothelial system and at higher doses, it was localized by the microglia present within the gliosarcoma implantation and optically outlining the tumour. The tumour was subsequently excited with UV wavelengths and emitting a deep red fluorescence. While it requires the use of fluorescence imaging and darkening the operative field, it may be possible to fine-tune the quantum dots to emit visible light.[67]

7. Nanoneuromodulation

7.1. Nanofibre brain implants

Implants are commonly utilized in neurosurgery in electrically stimulating of blocking neurons.[69] They form a part of what is known as "biomedical prosthesis" and have indications encompassing use in research in animal models to study behaviour[70] or use clinically as deep brain stimulation for treatment of clinical depression, intractable pain and Parkinson's disease.[71]

These brain implants are designated as foreign by the body and consequently these probes become encapsulated due to a fibrotic response from the glial and immune cells resulting in device failure.[72] The use of carbon nanofibres as neural prosthesis has been demonstrated to achieve better results. Preparation of four substrates, two with conventional diameters of greater than 100 nm and the other two with nanoscale diameters, and implantation showed preferential adherence of astrocytes to substrates of greater diameter. This evidenced decreased adhesion of astrocytes to carbon nanofibres and thereby limited glial tissue expression on the fibres.[73] These Carbon nanofibres have also been doubled as microelectrodes for a retinal prosthesis with results showing good biocompatibility.[74]

7.2. Nanowires

These are structures with diameters of only a few nanometres and extended lengths. Typically the length to width ration is extremely large making them effectively one-dimensional structures. These are futuristic compounds that would be used to link together tiny components into extremely small circuits. These nanowires are purported to have functions in monitoring brain electrical activity without having to use a brain probe and violating the brain parenchyma. Using platinum nanowires, researchers have used blood vessels as the guiding pathway to determining the electrical activity of neurons that are adjacent to the blood vessels.[75] These nanowires can both deliver electrical impulses as well as receive. Because of the potential for targeting specific areas of the brain, they can enable new treatment modalities for various neurological diseases. Electrode stimulation has already been shown to be of clinical benefit to patients of Parkinson's disease[71] and this method of stimulation avoids the use of penetrating brain implants which may result in scarring of the brain parenchyma. Another form of nanowires, polymer nanowires,[75] has the advantage of changing shape in response to electrical fields allowing precise steering through the circulatory system of brain towards the exact spot of interest. These also have the benefit of being 20–30 times smaller than the platinum ones and are biodegradable, allowing for short-term use of brain implants.[75]

8. Nanorepair of nerves

Damage to nerves is a fairly common outcome of traumatic, iatrogenic or infectious processes. There are various examples that can illustrate nerve injuries encountered in clinical practice. Brachial plexus injuries can occur in newborn infants during the process of delivery with a frequency that varies between 0.01 and 0.15%.[76] Cancer chemotherapy such as Cisplatin can damage the 8th Cranial Nerve. Surgical procedures such as dacryocystorhinostomy can also damage the peripherally placed fibres of facial nerve in the vicinity of medial canthal area causing abnormal eyelid closure postoperatively.[77] The success of natural reparative process depends on whether the connective tissue layers around the nerve are intact (which predicts best prognosis according to Seddon's classification of nerve injury) or not.

Currently two modalities are being further developed to aid in nerve recovery: microtechnology and nanotechnology.[78] Both are currently being explored in tandem to address two novel methodologies of treating severe nerve injuries that typically cause incomplete or non-existent functional recovery: microstructured scaffolds to promote regeneration and direct repair by reconnecting the severed axons. The former involves creating a tissue scaffold using microtechnology with precisely altered surface chemistry by nanotechnology, in order to provide a microenvironment favourable for the regeneration of the axon. The latter involves directly attempting to acutely reconnect the severed axons using ultramicrosurgical tools that would permit safe manipulation of the individual axons without incurring damage.[79] Recently in an experiment on mammals with attempt to sever optic tracts and using a self-assembling peptide nanofibre scaffold to create a permissible environment for axonal regeneration, adequate functional return of vision has been reported using visual stimuli to elicit specific behaviour patterns.[80] In another experiment on dogs with induced injury to thoracic sympathetic trunk and phrenic nerves in order to elicit Horner's syndrome and diaphragmatic paralysis, the usefulness of chitosan nano/microfibre mesh tubes (C-tubes) was well evidenced by improvement in Horner's syndrome and response of diaphragm to phrenic nerve stimulation.[81]

9. Conclusion

Nanotechnology provides a futuristic portrayal of the destiny of medicine and surgery. Although incorporation into neurosurgery and neuroscience has been slow compared to other fields of medicine, the experimental work has gained an explosive momentum of late and has provided the realization of potential benefits in addressing various notorious conditions of the nervous system encompassing malignant tumours, nerve injuries, drug delivery mechanisms, novel diagnostic and imaging methods, neuroprotection and unique brain implants and use of exotic compounds such as nanowires in treatment of various neurological conditions such as Parkinson's disease. With the advent and popularity of minimally invasive surgeries and interventional techniques, nanotechnology provides a future platform for further development of neuroscience and neurosurgery along these lines and warrants careful understanding and appreciation by every physician of how medicine could be entirely transformed in near future.

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Author contribution

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