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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-$f$Ò. 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