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# NOVEL TREATMENTS AND FUTURE PROSPECTS FOR BRAIN TUMOR BY USING NANOTECHNOLOGY: A REVIEW

**Anchal Verma* and Argha Bhowmick***

Master of Pharmacy, Department of Pharmaceutics, University Institute of Pharma Sciences, Chandigarh University.

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***Corresponding Author**
**Anchal Verma**
Master of Pharmacy, Department of Pharmaceutics, University Institute of Pharma Sciences, Chandigarh University.

## ABSTRACT

The central nervous system (CNS), consisting of the brain, medulla spinals, and retina, superintends to the acquisition, integration and process of peripheral data to properly coordinate the activities of the full body. Neurodegenerative and neurodevelopmental disorders, trauma, stroke, and brain tumors will dramatically have an effect on central nervous system functions leading to serious and life-long disabilities. Globally, the social group and economic burden related to central nervous system disorders continues to grow with the ageing of the population so exacting for simpler and definitive treatments. Glioblastoma Multiform (GBM) is one the foremost common intracranial tumors discovered by Burns (1800) and Abernethy (1804) supported gross morphology of the autopsied material and said as "medullary sarcoma" and later "fungus medullary". This review summarizes new developments on pathophysiological aspects of GBM and novel therapeutic methods by victimization engineering to boost quality of lifetime of patients. These novel therapeutic approaches suppose increased penetration of drug medical care into the growth tissues by use of nanomedicine for each the diagnostic and therapeutic functions, observed as "theranostic nanomedicine". Although, the barrier (BBB) is fenestrated round the outer boundary of the growth tissues, the BBB continues to be tight inside the deeper tissues of the growth. Thus, drug delivery could be a challenge for gliomas and needs new therapeutic advances.

**KEYWORDS:** central nervous system; brain tumor; glioblastoma multiform; eurodevelopmental disorders; nanotechnology.

**OUTLINES**



## INTRODUCTION

Brain tumors (BT) was a very serious diseases of the central nervous system that donot have appropriate therapeutic ways these days. The Brain Tumor has a heterogeneous cluster of process like primary and pathologic process tumor of the central nervous system inflicting global death in patients throughout the world having short survival amount once identified. Glioblastoma Multiform (GBM) stage IV is that the most aggressor and rapidly increasing tumor was fatal at intervals 6–12 months during the starting designation in human cases .The instant remedial approaches to GBM is proscribed to clinical procedure given by radiation therapy. These treatments ends up in cell injury of normal cells or tissues and in depth deoxyribonucleic acid injury inflicting serious aspect effects. Moreover, continual radiation and therapy is required to forestall repetition of BT throughout semi-permanent GBM therapy

inflicting quality of lifetime of patients causing extreme discomfort. The incidence of GBM is essentially in case of male patients with age higher than forty five with genetic disorders.

The majority of current offered treatments square measure symptomatic and unable to revive quality of life and halt or ameliorate injury. up to now the explore for new therapies remains while not vital enhancements, and drug delivery – promising new molecules or maybe rehabilitating recent ones – is that the major challenge to be overcome.

Nanotechnology has progressed rapidly by leaps and bounds throughout the past years throughout a broad vary of product domains and over many fields whereby its manifold applications have obtained larger association. It provides ample opportunities, challenges and varied ways that for the biological process work of novel materials, whereby antecedently tried and tested techniques could have reached their full potential and might not be used. Nanoparticles has distinctive multi-dimensional relevancy. These distinctive capabilities of nanoparticles area unit assimilated into giant bulk materials. Nanotechnology is associate elemental science that represents the synthesis and application of materials at molecular levels, and this technology is controlled to recruit the properties of those bulk materials to synthesize novel materials at a nanoscale. Nanoparticles square measure entities that square measure sometimes but diameter (or in some case, 100–500 nm) that square measure diagrammatic within the sort of perishable or non-biodegradable drug carriers, however in most cases, perishable materials square measure for the most part most well-liked because of their wider pertinence and practicability. Nanoparticles will cover each Nano spheres and Nano capsules. The drug is pretty uniformly spread in a very matrix system just in case of Nano spheres, whereas in Nano capsules, the drug is encircled by extremely uniform compound membrane [Rajesh R. Wakaskar et al. 2017].

Nanoparticles have gained interest as drug delivery systems that would come through localized and sustained unleash still as a good risk-to-benefit magnitude relation, vital for clinical applications [Lipka J et al. 2010].

Nanoparticles square measure thought of one among the foremost auspicious and versatile drug delivery systems into inaccessible regions just like the brain, having the ability to supply protection to therapeutic agents whereas with efficiency delivering them into the broken areas. Several nanoparticles formulations are administered intravenously in healthy animals proving their effectualness in crossing the BBB, principally once they are changed with

surfactants or ligands. With this in mind, it's necessary to know BBB modifications in pathology so as to require advantage of those traits to develop new and innovative nanoparticles formulations capable of with success targeting broken areas of the brain.

Thus, there's associate degree pressing have to be compelled to expand our information concerning the GBM pathophysiology and drug development to explore novel therapeutic strategic for a good medical care for BTs.

## HISTORY OF GLIOBLASTOMA

Glioblastoma was 1st delineated by Burns (1800) and Abernethy (1804) in United Kingdom of Great Britain and Northern Ireland as Medullary cancer supported gross morphology on autopsy materials. This is often as a result of the diffuse tumor formation within the central nervous system lacking a transparent border with the healthy tissues. French pathologists termed them as Encephaloide whereas German scientists known as it flora Medullary. These language of gliomas prevailed before the appearance of sunshine research. These malignant tumors area unit originating from interstitial tissue cells of the central nervous system with clear demarcation between healthy tissues. He was the primary to use the term "Glioma" for this brain tumor. Gliomas differentiated into 2 distinct identity as Low Grade Gliomas (now Grades I and II) and High Grade Gliomas (now Grades III and IV) by WHO Classification 2016 [Wesseling & Capper, 2018].

In 1926 neuropathologist Bailey and brain surgeon Harvey Cushing provides 1st elaborate trendy classification of Gliomas that shaped the bottom of WHO recent classification (2016) of various grades of Gliomas [Wesseling & Capper, 2018]. Bailey and Harvey Cushing supported histopathological evidences referred to as gliomas as growth brain tumor Multiform owing to multiform appearances of various cells among a similar kind of tumor samples. They conjointly mention astrocytoma for those tumors that originates from astrocytes. Afterward the term glioblastoma and therefore the astrocytoma was replaced with GBM. (Stoyanov & Dzhenkov, 2018).

## BRAIN TUMORS AND THE BLOOD-BRAIN BARRIER

The blood brain barrier (BBB) strictly regulates that equilibrium of the central nervous system beneath traditional conditions. The BBB is slightly a lot of leaky around growth micro vessels. However, this doesn't enable enough medicine or therapeutic agents to enter into the core of the growth tissues. Thus, therapeutic ways in BT failed to yield desired results up to

now. The BBB is a complex structure comprising the continuous endothelial cells that are joined by tight junctions that consists the main anatomical site. The endothelial cells are more than 85% covered by astrocytic end feet and associated with pericytes. Recent evidences suggests that cerebral endothelial cells together with pericytes and astrocytic end feet constitute the greater BBB function that regulates the passage of materials from blood to brain and vice versa.

The BBB is noncontiguous throughout the BT development method and customarily called blood-tumor barrier (BTB). The BTB is heterogeneously semipermeable to tiny and a few massive molecules however isn't enough receptive enable high drug concentrations from outer boundary in accumulating at intervals the BT. Thus, the BBB continues to be the key limiting think about treating BT effectively.

**ROLE OF THE BLOOD BRAIN BARRIER AND MECHANISM OF TRANSPORT**

The BBB could be a most critical hindrence that isolates brain tissue from the systemic circulation. The BBB could be an advanced structure comprising vessel epithelial tissue cells, intersection progressed (tight intersections and adherence intersection), and astrocytes.. The epithelial tissue cell tight junction progressed restricts the Para cellular movement of polar molecules across the BBB, whereas small nonionic atoms disperse across plasma cell membranes. This barrier acts as a selective gate for the passage of atoms into the cerebrum, and it limits the dispersion of unsafe harmful substances into the brain. It furthermore include a fundamental part within the transportation of fundamental suppliments like aldohexose, amino acids and bigger atoms like hormone, chemical leptin, and iron globulin into the brain and evacuation of metabolites and unsafe substances from the brain by a means of specific receptors and carriers. The tight intersections and adherence junctions (AJ) area unit the structure block of the BBB. The Tight intersections contains basic layer proteins like Claudine, occludin, intersection attached particles, and numerous living substance proteins, whereas AJ contains of a cadherin, catenin, alpha-actinin, and vinculin. Occludin and Claudine type an extravagant of proteins transversings living things and separated with several other living substance staging and restrictive proteins. These area unit critical for the integrity of tight intersections, and disturbance of Adherence intersections ends up in interruption of the BBB. Astrocytes play a significant part within the induction and maintenance of TJ and for polarized expression of carriers inside the barbiturate and albumin epithelial tissue layer. Chemotherapeutic agents have restricted effectiveness within the

treatment of brain tumors thanks to the impdediment to conveyance across the intact BBB and cerebrum-to-blood flow of drug. World Health Organization grade III and IV tumor patients have a noncontiguous BBB. Early examination have incontestable a relationship between the decrease of Tight adherence and growth differentiation and experimental evidences has arised to put TJ inside the forefront on the grounds that design malignant cells ought to survive for spreading. Glioma-derived factors like remodeling protein beta-2, caveolin-1, more active atomic number 8 species, lattice metal proteinases, aquaporin, and unhealthy cytokines square measure to blame for the disruption of tight adherence. The degraded tight adherence and defective BBB don't end in best Materia media and dynamics of chemotherapeutical substances. Because of in tumor cells amplified expression and movement of carriers, drug utilizing compounds and cerebral blood flow dynamics outcomes in inefficient medication present within the brain. The BBB carefully manages the brain molecules concentration and keep up it best for intersection correspondence activity. The concentration is kept up in spite of changes which will happen in plasma following activity or unwellness conditions. The BBB additionally regulates the excitant aminoalkanoic acid salt levels within the cerebrum by keeping the peripheral plasma salt pools from the central salt pool. Also the BBB prevents the section of plasma proteins like albumen, factor II, and plasmin into the cerebrum. The endogenous metabolites or proteins or xenobiotics that most part act as neurotoxins are expelled from the cerebrum through some energy subordinates outflow carriers. Then very polar particles and high-sub-atomic weight atoms that have a bent to make more than six nuclear number 1 bonds can't pass the BBB. However, super particle dissolvability and in this manner the overall sub-atomic mass of particles aren't supreme components for passive transportation ; there square measure many medication atoms that don't adhere to the on top of rule of passive transportation across the BBB .Oxygen and dioxide openly get across the BBB, related to their fixation inclinations, though carbonate particles that have a charge region unit inadequately pervious to the BBB .This can be because of atoms that convey a charge have a reward of communication with charged plasma film components that guides inside the section of those particles across the BBB. Matter transporters zone unit another crucial system for transportation across the BBB. Polar atoms can't diffuse across the BBB, and accordingly there are a unit enormous quantities of tissue transporters inside the BBB. These substance transporters inside the BBB encourage a few fundamental polar supplements, similar to aldohexose and amino acids, into the cerebrum. ATP-restricting holder carriers (ABC carriers) inside the BBB are perceived as a major question for the appropriation and disposal of medication from the cerebrum. These carriers

are at risk for a ton of lower BBB section of very lipotropic drug. These stream carriers are worried inside the evacuation of likely poison endogenous or xenobiotic particles from the cerebrum and assume a significant part in detoxification of the mind. The most widely recognized and broadly considered bedrock discharge carrier is P-glycoprotein (Pgp). Past investigations have incontestable a vital part of Pgp inside the discharge of a scope of lipid-solvent medication out of the brain because of many medication territory unit substrates for these discharge carriers. Elective bedrock discharge carriers blessing inside the BBB zone unit the multidrug obstruction supermolecule (MRP) family and carcinoma opposition supermolecule (BCRP) (Mukesh Kumar et al. 2018).

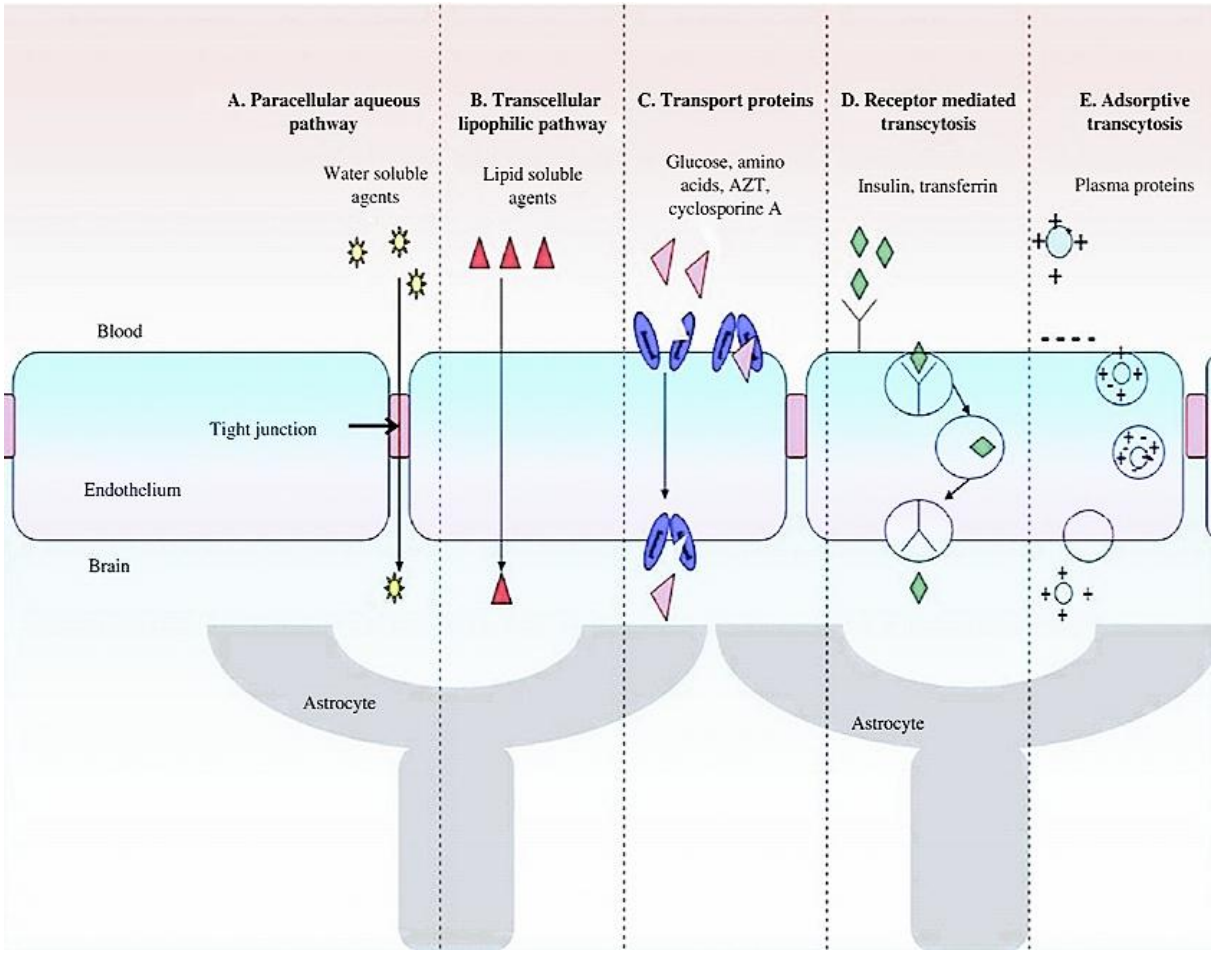


**Figure. 1. Schematic representation of the various transport process of molecules across the BBB [Mukesh Kumar et al. 2018].**

## OPPORTUNITIES FOR NANOTECHNOLOGY TO MEDIATE CNS DRUG DELIVERY

The development of recent methods to treat brain diseases is one amongst the foremost difficult and dear market niches for pharmaceutical corporations. Throughout the method of

development and discovery of recent compounds for the CNS, the prices for reaching clinical test clinical trials will go up to US$100 million and around US$1 billion before reaching the patron [K. Tsaioun, et al. 2009]. Taking into thought these numbers it's of utmost importance to be effective within the development part. However, in recent years, solely a minor variety of brain-directed prescribed drugs have reached the market (3–5%) since most of them were incapable of crossing the BBB in vivo [W.M. Pardridge et al. 2007]. Currently, advances within the field of nanomedicine have generated many platforms that improve drug transport across the BBB, specifically Nanoparticles [D. Peer, et al. 2014– J. Kreuter, et al. 2014]. During this critique, we'll cowl Nanoparticles accustomed transport medicine through the BBB once administered intravenously also because the factors that influence its transportation. Nanoparticles square measure mixture carriers which will have a natural or artificial origin and may vary from one to a thousand nm in size. There are a unit alternative styles of mixture carriers, as an example liposomes and micelles that are extensively studied for drug delivery to the brain. Since they possess distinctive options that distinguish them from compound and inorganic Nanoparticles, this issue won't be coated during this review. Synthetic Nanoparticles could also be ready from compound materials like poly (ethylenimine) (PEI), poly (alkyl cyanoacrylates), poly (amid amine) dendrimers (PAMAM), poly (ε-caprolactone) (PCL), poly (lactic-co-glycolic acid) (PLGA), polyesters poly (lactic acid) (PLA), or from inorganic materials like gold, silica (silica), among others. These carriers will transport medicine by sorb, entrapping or bounding covalently to them [L. Zecca, et al. 2014]. Inorganic Nanoparticles supply benefits over chemical compound Nanoparticles in terms of management over size and form and ease of preparation and functionalization. Most significantly, inorganic Nanoparticles area unit easier to trace by research techniques (e.g. resonance imaging (MRI), TEM) or analytic techniques (e.g. ICP-MS). However, inorganic Nanoparticles even have disadvantages as a result of they could not be degraded (or eliminated through the kidneys) or gift unwanted toxicity (e.g. carbon nanotubes and fullerenes might cause macromolecule peroxidation and O radical formation). On the opposite hand, natural Nanoparticles square measure created from natural polymers, like polysaccharides (chitosan and alginate), amino acids (poly (lysine), poly(aspartic acid) (PASA)), or proteins (gelatin and albumin). Natural Nanoparticles have the advantage of providing biological signals to move with specific receptors/transporters expressed by epithelial tissue cells however they need the disadvantage of batch-to-batch variability, restricted ability for controlled modification and poor pursuit capability by imaging

platforms. The physicochemical properties of Nanoparticles confirm that is that the passage mechanism across the BBB. The subsequent transport mechanisms are represented.

(i) Nanoparticles open TJs between epithelial tissue cells or induce native harmful effects that ends up in a localized permeabilization of the BBB permitting the penetration of the drug in a very morpheme or conjugated with the Nanoparticles;

(ii) Nanoparticles experience epithelium cell by transcytosis;

(iii) Nanoparticles area unit transported through epithelium cells by endocytosis, their content is discharged into the cell living substance so exocytose within the epithelial tissue albumin aspect;

(iv) A mix of many of the mechanisms delineated antecedently. Consistent with some studies, mechanisms ii, iii and iv are the most transport mechanisms of Nanoparticles. Just in case of mechanism ii, many receptors are targeted by Nanoparticles together with siderophilin and lipoprotein receptors. The targeting has been achieved by peptides, proteins or antibodies physically or with chemicals immobilized on high of the Nanoparticles. Nanoparticles area unit exciting systems for brain drug delivery thanks to the likelihood to modulate them in terms of form, size, property, coating, chemistry and surface charge. Control over these options will enhance the flexibility of Nanoparticles to boost the therapeutic agent stability in circulation, to manage the shipment unharness into the required target web site, to reinforce BBB penetration potency and to flee the system.

## NANODELIVERY OF DRUGS AND ENHANCED PERMEABILITY AND RETENTION

In gliomas and different BT loss of epithelial tissue cells tight junctions with alterations in pericytes and coverage of neuroglial cell finish feet enable increase within the peritumoral BTB to tiny molecules [Laredo et al., 2019]. Maturation in conjunction with inflated VEGF production enhances the BTB breakdown leading to infiltration of cancer cells within the brain parenchyma [Di Tacchio et al., 2019]. Proliferation of GBM into the brain cells additional disrupts the vascular system [Song et al., 2020]. These 2 factors play key roles in enhancing the drug permeableness and retention among the neoplasm tissues [Adhikaree et al., 2020]. Nanodelivery of medication in GBM use these benefits of porous BTB and reduced outflow of system lymphatic leading to increased drug concentration and retention into the neoplasm tissue for very long time [Rezaei et al., 2020]. Many Nano formulation is presently being employed for the treatment of gliomas mentioned below.

## ACTIVE TUMOR TARGETING BY NANOPARTICLES

Active or direct targeting of tumors by nanoparticles related to medicine or chemotherapeutical agents is one among the foremost vital therapeutic advances for BT treatment [Rizwanullah, Alam, Harshita, Rizvi, & Amin, 2020; Vanderburgh et al., 2020]. Many varieties of nanoparticles square measure used for this purpose.

## LIPOSOME NANOPARTICLES

Using vesicle nanoparticles for drug or chemotherapeutical agents ends up in a magnified delivery of those molecules at intervals the neoplasm tissue with high retentions capabilities [Formicola et al., 2019]. Combination of liposomes with polythene glycol (PEG) is employed to connect functionalization of medicine and ligands for specific targeting the neoplasm tissues and preventing in accumulating in alternative tissues. Using these principles IL-13 was conjugates with cyst containing antibiotic (DOX) as a result of finest astrocytoma contains IL-13Rα2 in most of neoplasm tissues. Thus, during this case liposomal nanoparticles actively targets GBM cancer cells bypassing the outflow pump (ABC transporter) evoked chemotherapeutical resistance [Gomez-Zepeda et al., 2019]. Similarly, once cyst nanoparticles conjugated with DOX and coronary-artery disease plaque-specific peptide-1 (AP-1) then it binds to IL-4 receptor that's overexpressed in BT cells and transported among the neoplasm cell by endocytosis. Likewise conjugation of endotoxins to the surface of cyst nanoparticles will increase nanoparticles delivery and enhances death in GBM tissues [Duhrsen et al., 2019].

Direct targeting tumor tissues by convection-enhanced delivery (CED) wherever medicine square measure delivered employing a Micro infusion pump into the BT with Nano formulations ends up in superior therapeutic result. Using this CED technique delivery of CPT11/irinotecan liposomal nanoparticles in to the brain parenchyma resulted in a lot of lower general toxicity as compared to constant delivered while not CED [Souweidane et al., 2018]. This means that each nanoparticles delivery into the neoplasm and CED can be utilized in future for higher therapeutic effects.

## POLYMERIC NANOPARTICLES

Further evidences showed that chemical compound nanoparticles, i.e., poly (lactideco-glycolide) PLGA conjugated with chemotherapeutical agent paclitaxel (PTX) and delivered directly into tumor tissues mistreatment CED technique resulted in abundant less general toxicity with high EPR of the drug [Di Mauro et al., 2018]. When PLGA nanoparticles is

delivered mistreatment CED technique with PTX through intracranial root in an exceedingly rat brain tumor model this resulted in longer survival amount as compared to free PTX treatment underneath identical conditions [Di Mauro et al., 2018]. Interestingly, PLGA-nanoparticles with PTX once given while not CED technique the survival amount is shorter than mistreatment CED methodology.

## POLYMERIC MICELLES

In rat and mice brain tumor model once DOX is delivered with compound micelles nanoparticles that have each deliquescent and hydrophobic Novel therapeutic methods for brain tumor exploitation nanomedicine 27characters resulted in longer survival amount if administered exploitation CED technique [Arvanitis et al., 2020]. Thus, conjugation of DOX to amino acid residue of PEG polymer and so used CED to deliver compound micelles into the brain parenchyma during a rat or mice neoplasm models resulted in long survival amount as compared to free DOX [Arvanitis et al., 2020]. This means future potentials of nanoparticles conjugated medicine for higher therapeutic approaches in GBM.

## MAGNETIC NANOPARTICLES

Magnetic nanoparticles might be with progress utilized as medication conveyance vehicles for effective targeting of therapeutic agents. During this methodology, therapeutic agents might be hooked up to the surface or embeded inside an extravagant of synthetic compound and magnetic nanoparticles [Mody et al., 2014b]. This helpful medication conveyance technique depends on the apparatus of an attractive transition to restrict the specific objective inside the body. The fundamental system behind this procedure relies on created heat from the moving magnetic nanomaterials utilizing a strong attractive motion .This therapeutic strategy is noninvasive and safer to focus on the magnetic nanoparticles to the brain tumor tissues [Silva et al., 2011]. Developed antibiotic (DOX) magnetic nanoparticles, during which DOX area unit with chemicals secured to oxide nanoparticles and embedded in PEG functionalized with porous oxide [Chen et al. 2010]. Magnetic nanoparticles can also use in conjunction with focused ultrasound (FUS) to spice up drug targeting synergistically. This synergistic combination can increase the native magnetic nanoparticle concentration inside the targeted tissue. A few investigations have conjointly been checked to make progress inside the low-frequency field of power [Golovin et al. 2017a]. In such an examination, Kim et al. created magnetic vortex micro discs for focusing on neoplasm. The outcomes showed that mechanical data produced by micro discs motions may by determination of target

neoplasm cells and kill those [Kim et al., 2010]. In a new analysis, biogenic Nano estimated cell-determined macrovesicles are focused on adequately by attractive and nutrient M functionalization. During this investigation, micro discs were formed with streptavidin-modified iron compound nanoparticles and adequately redesigned as targeted drug delivery. Nano vectors for conveyance of malignant neoplasm specialists inside the treatment of cerebrum tumor [Zhang et al., 2017b]. The Tfr receptor-restricting amide T7 intercede drug focusing on was furthermore utilized along the edge of the applying by associate degree applied field of power. This dual targeted focused on magnetic PLGA nanoparticle was used for conveyance of paclitaxel and curcumin. Twin focusing on prompts a 10-overlap expansion in cell take-up partner degreed over quintuple expansion in brain focusing in an orthotropic cerebrum tumor model [Cui et al., 2016].

## DENDRIMERIC NANO CARRIERS

Dendrimeric structures have distinctive characteristic properties like monodispersed [Mody et al. 2014a], modifiable surface practicality, membrane transport potency, high drug payload, biocompatibility, and well-defined molecular structure and composition. These distinctive properties of dendrimers build them extremely appropriate Nano carriers for drug targeting. Typically dendrimer design consists of 3 topological domains.

(1) A central core comprising of Associate in Nursing atom or a molecule with a minimum of 2 identical purposeful groups.
(2) Branches, with many interior repetition units structured geometrically during a sequence of radically aligned layers called “generations” and.
(3) Terminal teams that verify the surface properties of the nerve fiber structure [Kesharwani et al. 2015a].

Dendrimeric architectures are ready mistreatment divergent and convergent approaches. In each approaches, dendrimers are synthesized by bit-by-bit growth and branching generations. Dendrimers are represented and classified by their generation numbers. The central nucleus pictured G0 (generation 0), though following additions of branching units were termed as higher generations of dendrimers (G1, G2, G3, etc.). This exponential increase with the addition of every cluster ends up in sterically thronged dendrimers, these results in geometrical changes within the Dendrimeric structures. With the expansion in generations, dendrimers take a round structure because of increasing steric hindrance (Kesharwani et al. 2014a; Kesharwani et al. 2015a). Several ways were developed to move the therapeutic

agents across the brain in an exceedingly site-specific manner. Amongst all the approaches, dendrimers have emerged as promising vectors with nice potential for delivering medicine into the central nervous system. Varied forms of dendrimers, like polyamidoamine (PAMAM), poly-L-lysine (PLL), and poly (propylimine) (PPI) are explored with success within the treatment and diagnosing of brain tumors. Sarin and coworkers have developed a G5 PAMAM dendrimer conjugated with DOX and in chelation with Gd-DTPA. The results incontestable important improvement in targeting as compared to free DOX in an exceedingly gnawer malignant brain tumor model. A PEGylating strategy is additionally used to with success deliver metastatic tumor agents to the targeted web site. He et al. have developed PEGylated PAMAM dendrimers as twin targeting Nano carriers in brain tumor. They ready PEGylated G4 PAMAM dendrimers with Tfr and WGA loaded with DOX. The results incontestable reduced toxicity and inflated accumulation of DOX within the neoplasm website because of targeting effects of Tfr and WGA. Li et al. explored the targeting potential of G4 PAMAM dendrimers anchored with Tfr and encapsulated with estrogen antagonist in brain gliomas. The results indicated quicker drug unleash in infirm acidic conditions (Li et al., 2012). Recently, the PEGylated PAMAM dendrimers were conjointly anchored with varied peptides like angiopep-2 (Xu et al., 2016) and orienting peptides (Pep-1) (Jiang et al., 2016) as an efficient targeting strategy within the treatment of brain tumors. Similarly, PEGylated PLL-based dendrimers loaded with DOX are effectively used for tumor targeting. Nano carriers were coupled to associate degree acid-labile 4-(hydrazinosulfonyl) carboxylic acid (HSBA) linker that causes the discharge of DOX in acidic conditions. The in vivo leads to rats bearing Walker 256 tumors incontestable higher uptake in tumor tissue as compared to regulate tissue of muscle and heart (pH 5) (Kaminskas et al., 2011). Ligand-anchored poly (propyleneimine) dendrimers were conjointly evaluated for his or her brain-targeting potential by Jain and coworkers. They anchored varied substance molecules, like sialic acid (S), glucosamine (G), and concanavalin A (C) to the surface of poly (propyleneimine) (PPI) dendrimers encapsulated with paclitaxel. The results of in vivo pharmacological medicine and bio distribution studies in rats showed a considerably higher accumulation of paclitaxel within the brain as compared to free paclitaxel. The order of targeting potential of assorted ligands below investigation was found as sialic acid, glucosamine, concanavalin A (Patel et al. 2016). Researchers have recently developed a spatially controlled time period Nano carrier by encapsulating tiny polyamidoamine (PAMAM) dendrimers among giant gelatin Nanoparticles (B200 nm). This strategy showed the upper stability of Nano devices within the circulation and increased permeation through the growth vasculature. The PAMAM

dendrimer was free in response to MMP-2 enzymes within the tumor microenvironment and resulted in higher animate thing uptake and deeper tissue penetration during a tumor model. The results have additionally incontestable effective and targeting delivery of immunosuppressant with this technique (Fan et al., 2017).

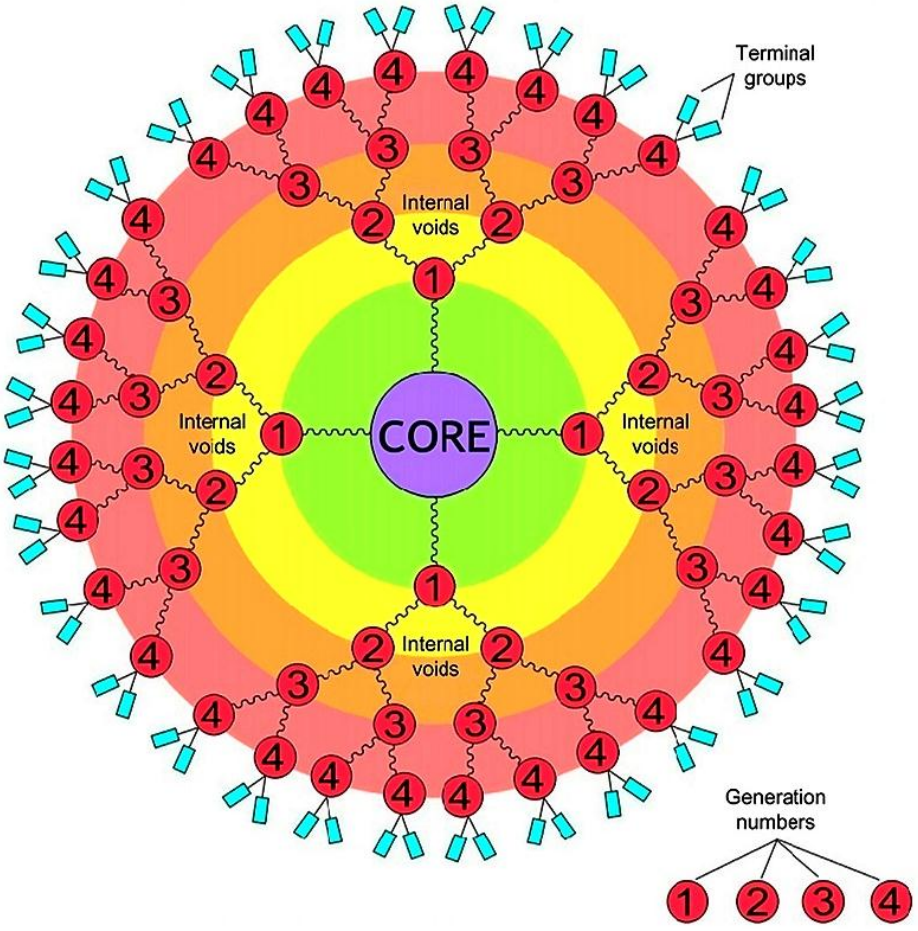


**Figure. 2. Structured diagram of dendrimers presenting its major domains: 1) core, 2) generations, 3) terminal groups, 4) internal voids [Mukesh Kumar et al. 2018]**

## CARBON NANOTUBES

In recent years, CNTs have arisen as a potential conveyance framework for biologically active atoms to help the remedial edges. Presently, functionalized CNT intervene particular and explicit conveyance of biomolecules has acquired tremendous consideration as a potential, promising Nano-engineering due to its distinctive chemical science properties inside the therapy of assorted deadly diseases along with malignancy. Ren et al. used angiopep-2 surface-altered oxidized-multi-walled carbon nanotubes (MWCNTs) for a twin targetting on drug conveyance framework for the treatment of brain tumor.Another example of victimization angiopep-2, has conjointly displayed important outcomes as a targeting

substance for brain delivery victimization MWCNTs.. Expanded entire brain uptake, extended uptake in cerebrum tumor synapses, and expanded cerebrum gathering were found with angiopep-2-functionalized MWCNTs. It was moreover announced that functionalization doesn't significantly affect the element of MWCNTs, showing the significance of functionalized MWCNT breadth towards their gathering at desired sites. Incontestable the pharmacokinetic and pharmacodynamics examinations of the tumor targeting on capability of the DOX-stacked D-α-tocopherol polythene glycol 1,000 succinate-enlivened surface-functionalized MWCNT Nano-detailing and perfect MWCNTs and free anti-infection answer. The creators ended that the explored MWCNTs' Nano-designer had bigger disease focusing on potential on tumor-bearing Blab/c mice. In an extremely very surprising examination, it was found that MWCNTs and attractive Nanoparticles as a twin methodology for treating brain malignancy. During this case, the functionalization was through with poly (acrylic corrosive) by means of atom chemical activity got together with nutrient B and DOX was utilized in light of the fact that the chemotherapeutical specialist. Results exploitation progressed tiny stratigies that DOX-stacked folic corrosive formed MWCNTs speedily aggregated among U-87 cells following the predetermined release of DOX intracellularly thus viably moved into the core with the MWCNTs left inside the living substance. Beside MWCNTs, single-walled carbon nanotubes (SWCNTs) changed with rituximab and to demonstrate the aptitude to by selection target cancerous cells. In light of pharmacodynamics studies, the creators asserted higher bio distribution in an incredibly murine heterograft model of malignant neoplastic diseases, recommending more SWCNTs as a possible delivery platform for selective delivery conveyance (Mukesh Kumar et al. 2018).

## GOLD NANOPARTICLES

Biologically active inflammation additionally can be adorned onto the outside of Au Nanoparticles. The huge outside zone/volume quantitative connection of Au Nanoparticles grants their surface to be covering like a spread of atoms like restorative specialists, site-explicit matter, and protective polymers. A interesting pilot study was directed employing a cell culture method utilizing a assosiate animal model of brain tumor diverse during which PEG-based gold Nanoparticles upheld treatment. The twin activity gold Nanoparticles expanded endurance of mice with orthotropic GBM tumors. The writers conjointly incontestable expanded extravasation and bigger gathering of gold Nanoparticles, showing that this twin methodology significantly disturbs the BBB and will be utilized to build up neoplastic cell focusing on. There discoveries show that PEGylated gold Nanoparticles will

be extensively joined with treatment for the therapy of carcinogenic cells. The gold Nanoparticles were preoccupied by tumor cells nineteen three time quite the conventional brain cells. Also, mice injected with gold Nanoparticles were capable of causation tumor-free survival for quite a year compared to mice receiving radiation solely. Accumulation of medication and Nanoparticles among brain cells, planned a liegeman base approach to reinforce the retention of chemotherapeutics in brain tumors. They devised a Nano-platform, gold NanoparticlesA&C, These was comprised of Ala-Ala-Asn-Cys-Lys-modified gold Nanoparticles, and 2-cyano-6- aminobenzothiazole-modified gold Nanoparticles. This approach exaggerated the buildup of the gold Nanoparticles in brain tumor cells each in vitro and in vivo thanks to the block of Nanoparticle exocytosis and minimizing Nanoparticle back flowing to the blood. The authors extensively utilized DOX as a chemotherapeutical agent to more improve the potency against brain tumor. The median survival time for the DOX-linked Au Nanoparticles-A&C augmented to over 285% compared to the saline cluster. They all over that this approach has potential to elevate Nanoparticle tumor accumulation and so might have a higher clinical outcome. Flexibility of Nano sized (4 nm) glucose-modified gold Nanoparticles to penetrate human brain epithelial tissue by selection and later on to enter astrocytes. The transfer rate of those Nanoparticles across primary human brain epithelial tissue wasn't but thrice quicker than across no brain endothelia. The authors more detailed that development of those Nanoparticles happened across the top and basal plasma films through the cytoplasm with similarly almost no sac or Para cell relocation; anti-infection agents that meddle with sac transport neglected to hinder the movement. The exchange rate also depended on surface alteration of the Nanoparticles. They asserted that the glucose-adjusted Nanoparticles navigate the epithelium, travel through the living thing grid, and confine in astrocytes, and it had been at last total that these Nanoparticles have the ability to cross the blood cerebrum barrier and convey the therapeutic products (Mukesh Kumar et al. 2018).

## VIRAL NANOPARTICLES

Viral vectors are the preeminent unmistakable framework for conveying exogenous hereditary materials to explicit cells, following crossing them to the organelle and in this manner enacting the genomic. Liu et al. shown RVG29 (rabies infection glycoprotein) as a promising substance for practiced cerebrum focusing on cistron delivery. For the point, RVG29 was treated on polyamidoamine (PAMAM) dendrimer exploitation bifunctional PEG, at that point complexed with deoxyribonucleic corrosive, yielding multi-developed

nanoparticles. The outcomes showed that a high capability of BBB interruption capacity assosiate in vitro BBB model was accomplished mistreatment RVG29 substance containing formulation, while in vivo results incontestable higher gathering and cell consolidation inside the brain. This double practical procedure gives a more secure and noninvasive mode for cistron conveyance through the BBB. In another illustration of cistron clinical guide, Zhang et al. used partner antisense strategy with a man-made infection that utilizes a receptor-explicit counter acting agent cistron conveyance framework to treat a tumor. Mice imbued with intracranial U-87 human interstitial tissue cerebrum tumors were treated with a nonviral articulation inclusion body secret writing antisense ribonucleic acid against the human dermal protein receptor cistron. The inclusion body deoxyribonucleic acid is prepacked inside the inside of PEG functionalized immunoliposomes and regulated to the malignant cells with monoclonal immunizer that focus on the mouse globulin receptor and along with the human hormone receptor. The mouse transferrin receptor (TRFR) monoclonal immune response permits transport across the development vasculature, that is of mouse brain inception and along these lines the insulin receptor (INSR) monoclonal neutralizer causes transport across the semipermeable layer and in this manner the atomic film of the human cerebrum neoplastic cell. As a result, the existence of the mice treated week by week with partner endovenous administration of the epidermal development factor receptor (EGFR) antisense cistron clinical guide prepacked at intervals the engineered infection was raised 100% contrasted and mice treated either with a luciferase cistron or with saline. Lee et al. attempted to accomplish higher cell procurement and upgrade the bioavailability utilizing franticness infection based silica-adjusted gold Nano bars upheld a photograph warm standard to treat cerebrum malignant growth. The prepared functionalized Nano pole was infused and will actuate a physiological condition bring about reaction to approach infrared optical maser (808 nm) light, upheld limited surface Plasmon resonance, to successfully suppress brain tumors of mice. Together, these outcomes support the statement that the hydrophobia infection mimetic gold Nano poles are a potential possible epitome delivery platform for treating brain tumors. (Mukesh Kumar et al. 2018).

## NUCLEIC ACIDS-BASED NANOTECHNOLOGY

Oligonucleotides solidified with focused format RNA arrangements will be utilized with progress as a delivery vector to the desired on site. Galectin-1 could be a present at cerebrum sugar binding macromolecules, these are upregulated inside the case of GBM. Galectin-1 is concerned in cancer movement or progression and could be and could be a potent immune

suppressor within the neoplasm microvasculature. As of late, siRNA-customized chitosan Nanoparticles to zero in on Galectin-1 for the treatment of GBM by means of intranasal delivery. This investigation was the first of its sort and on edge focused on chitosan nanoparticle suspensions for the delivery of siRNA into development a couple of hour's once intranasal organization. These Nanoparticles may convoluted siRNA focusing on Galectin-1 to a high share and avoid transferase disruption. The outcomes demonstrated that siRNA Nano definition impressively discouraged the statement of Galectin-1 in every murine and human GBM cell lines. Grouping explicit RNA-obstruction showed a very five hundredth Galectin-1 decrease in tumor-bearing mice. This examination shows that the intranasal pathway is partner in nursing underexplored transport course for delivering siRNA-based treatments focusing on Galectin-1 inside the treatment of GBM. In another use of the siRNA delivery framework. The authors completed that globulin receptor-mediated center shell Nanoparticles are promising siRNA delivery frameworks for specific brain focusing applications. Distinctive to siRNA, Lee et al., incontestable downregulation of oncogenic miRNA-21 for the treatment of brain tumor by protecting tumor suppressors, phosphatase and tensin homolog (PTEN) and customized cell death protein 4 (PDCD4). The author made three-sided intersection (3WJ)- based polymer Nanoparticles by artificial methods gathered from pRNA of infection phi29 DNA bundling engine and formed with folacin. The designed Nano-develop was demonstrated to be promising in silencing miR-21 expression in cerebrum tumor cells each in vitro and in vivo, with good bio dispersion. systemically infused FA-3WJ-LNA-miR21 nanoparticle with productivity recovered PTEN and PDCD4, prompting brain tumor cell caspase-interceded cell death and tumor development regression. Generally, the endurance rate was conjointly impressively improved by FA-3WJ-LNA-miR21 nanoparticle. These outcomes territory unit characteristic of the clinical benefit of FA-3WJ nanoparticle-based cistron clinical guide for the gainful focused on clinical guide of creating and surpressing revenant brain tumor (Mukesh Kumar et al. 2018).

## NANOPARTICLES FOR TREATING BRAIN TUMOR STEM CELLS

Cancer stem cells initiate phenotypically human GBM that originates from GSCs (Shevchenko et al., 2019). Thus, this is often imperative that therapies directed against these stem cells might alleviate GBM development or operation (Bahmad et al., 2020). However, the most drawback is to precisely find the involvement of GSCs in GBM (Ma et al., 2018). This makes treatment methods terribly tough. It's still not bound whether or not GSCs reside within the perivascular space or the hypoxic surroundings of the growth cells (Arvanitis et al.,

2020). There are a unit evidences that nestin cells area unit placed among the perivascular area unit as of the neoplasm wherever growth factors are secreted by the epithelial tissue cells to take care of the population of the GSCs. On the opposite hand, hypoxic microenvironments of the neoplasm cells cause upregulation of hypoxia-inducible issue 1-alpha (HIF-1α) and hypoxia-inducible issue 2-alpha (HIF-2α). It's possible that each these factors induce growth (Tamura et al., 2019).

## FUTURE PROSPECTS AND CONCLUSION

Over the most recent twenty years, huge problems are resolved to create novel conveyance ways against brain disease, beginning from intrusive to noninvasive ways. Nonetheless, as so much on the grounds that the guess cares, next to no or few upgrades are noticed, that doesn't modify the improving of the middle endurance of patients. In any case, some inventive reports are empowering and will be way breaking. For instance, temozolomide, alone or along with various alkylating specialists, seems to be a more hearty stage inside the treatment of cerebrum tumors, because of its BBB porosity properties and low poisonousness. BBB porosity is significant, that grants bigger collection inside the focal sensory system for in anticancer clinical guide. In this manner, the hindrance of developing pathways establishes a delightful system for focused clinical consideration, that is has been examined by single or consolidated specialists. Any improvements can result from an obviously better comprehension of development science and furthermore the pathways worried. Change of the Nano transporter surface properties improves take-up by epithelial tissue cells. Additionally, to by determination convey chemo medication in cerebrum tumors, attractive Nanoparticles square proportion of decent interest, with the probability of recognition and measuring the technique by mister imaging. Moreover, SLNs are discovered to be worthwhile in delivering chemo medication as a result of their reasonable BBB penetrability, low inherent poisonousness, and furthermore the biodegradability of lipids utilized in their preparations. In another measurement to the delivery ways, the intrusive ways, local conveyance of treatment specialists to brain tumors by convection upgraded conveyance (CED) improves drug circulation contrasted with elective ways exclusively determined by dissemination. this technique is furthermore overwhelmed by striking aspects impacts. In general, notwithstanding numerous issues that need to act naturally tended to, directed clinical guide and particulate frameworks square measure promising ways that square measure value turn out any for conservative focal sensory system delivery of chemo medication.

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