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Novel theranostic nanocarriers for brain tumor targeting.

Patel Vimal D*, Shah Jigar N.
Department of Pharmaceutics, Institute of Pharmacy,
Nirma University, Ahmedabad-382481. Gujarat.
email id: *16ftphdp44@nirmauni.ac.in*

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ABSTRACT:

Fast progression and poor diagnosis of brain tumors are still an encounter major health problem, in spite of the use of invasive resection surgery, radiotherapy and chemotherapy in clinics. Growing of tumor in surrounding peripheral tissues creates continuous changing of vasculogenesis and tumor microenvironment could be effective target in brain tumor drug delivery. Targeted drug delivery system increases the drug accumulation in brain tumor and decreases the toxicity in surrounding normal brain tissues. In this review we highlight the latest research, opportunities and challenges for developing theranostic nanocarriers targeted strategies for brain tumor imaging using polymeric nanoparticles, liposomes, micelles, dendrimers, metallic quantum dots, carbon dots, graphene conjugated nano-vectors along with neuronal therapy and neurotoxicity studies and also review molecular trojan for brain delivery.

Brain tumor: Current status

- The brain cancer i.e., both malignant and non-malignant are reported with an average incidence of 28.57 per 100,000 population.
- They are the most common cancers among those ages from 0 to 19 years, with a mean annual age-average morbidity rate of 5.57 per 100,000 population.
- 5-year survival rate of patients suffering from CNS cancers is only 33.3% and this rate is still diminishing, though, for most of other types of malignancies, it is increasing.
- The average duration of survival is even less and fall between 15 to 22 months.
- Gliomas represent 78% of all malignant brain tumors and in males between the age of 20–39 years, are the most common cause of cancer-related death.

Ideal properties of nanoparticles for brain drug delivery:

- Non-toxic, biodegradable & biocompatible
- Particle diameter between 10-100 nm
- Physical stability *in vivo & in vitro*
- Avoidance of RES leads to prolonged blood circulation time
- CNS targeted delivery via receptor-mediated transcytosis across brain capillary endothelial cells
- Scalable & cost-effective manufacturing process
- Amenable to small molecules, peptides, proteinsor nucleic acid
- Formulation stability, minimal chemical degradation/alteration, protein denaturation

Recent Advances In Nano-theranostic Nanocarrier For Brain Tumor Targeting:

Polymeric micelles:

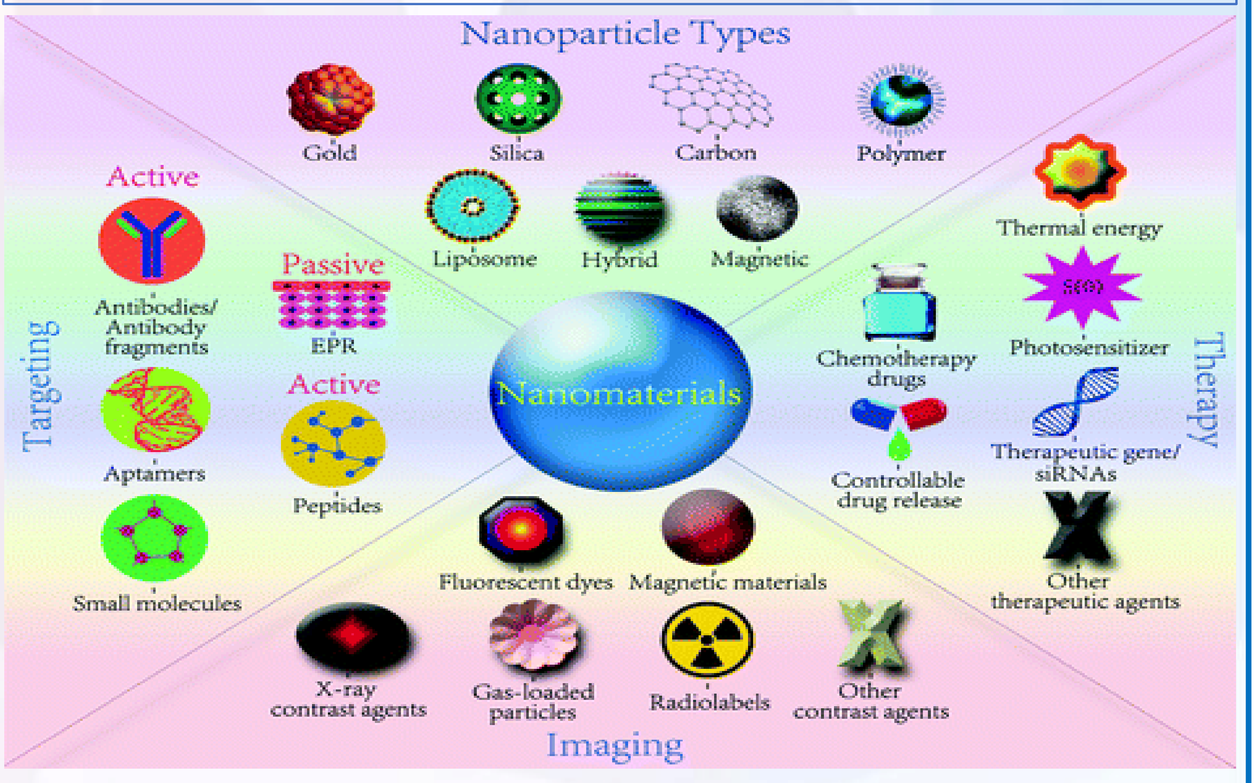
Polymeric material	Drug delivery	Major Findings
c(RGDyK)-PEG-PLA micelles	Paclitaxel	Enhancing anti-glioblastoma effect of paclitaxel. In vitro studies, increases cytotoxicity effect by 2.5 times.
TPGS micelle	Docetaxel	Increases cytotoxicity by 3 fold.
cRGD-(1,2-diamine cyclohexane)-platinum-II	Oxaliplatin	Increases tumor targeting capability of cRGD.
p-HA-PEG-DSPE micelles	Docetaxel	In-vitro cytotoxicity against U87MG increases by 1.2 times Enhance anti-glioblastoma activity of docetaxel.
Angiopep-2 modified PE-PEG tander nano-micelles	Amphotericin-B	Better inhibit of orthopic U87MG human glioma. Uniquely combine brain tumor-targeting & cell-penetrating functions

Metallic quantum dots (QDs):

Metal sourses (Core/Shell)	Surface functionalization	Major Findings
[64Cu]Culns/Zns	PEG-GSH	Active targeting to glioblastoma U87MG cell beared tumor mice
ZnAgInS/ZnS	cRGD-sulfobetaine-PIMA-Histamine	Active targeting to U87MG glioblastoma through cRGD conjugation, High ERP & Low RES
CulnSz/ZnS	CGKRK peptide	Highlight tumor boundaries called “Guerilla”.
CdSe/ZnS	Transferrin	High labelling efficacy of QDs655-transferrin in U87MG human glioma cells.

Graphene quantum dots (GQDs):

Organic precursor	Drug/Gene delivery	Major Findings
D-glucose GQDs	Doxorubicin	The conjugation enhanced DNA cleavage activity of DOX. Boost anti-cancer activity of Doxorubicin,
CD-Asp (D-glucose, L-Aspartic acid)	Transferrin	High selectivity & targeting ability toward orthotopic C6 glioma bearing mice
Folic acid PEGylated GQDs	Angiopep-2	Observed glioma imaging over high sensitivity over normal brain tissues



Polymeric nanoparticles:

Polymeric material	Drug/Gene delivery	Major Findings
PLGA + Poloxamer 188	Doxoribicin	Reduces brain tumor in rat model, increases transcytosis without affecting BBB.
RGD-grafted PLGA with PCL-b-PEG ligand chain	Palcitaxel	Enhances tumor targeting efficiency to $\alpha_v\beta_3$ integrin, increases survival time Reduction in growth of transplantable lymphoid tumor
mPEG-PLA/PLGA	Anti-transcytosis peptidomimetic Abs	Enhancing drug permeability through transcytosis by altering BBB.
cRGDyK-PEG-PEI	Intracranial gene	Targeting specific gene delivery to U87MG cells.

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