Emerging Nano-Carrier Strategies for Brain Tumor Drug Delivery and Considerations for Clinical Translation

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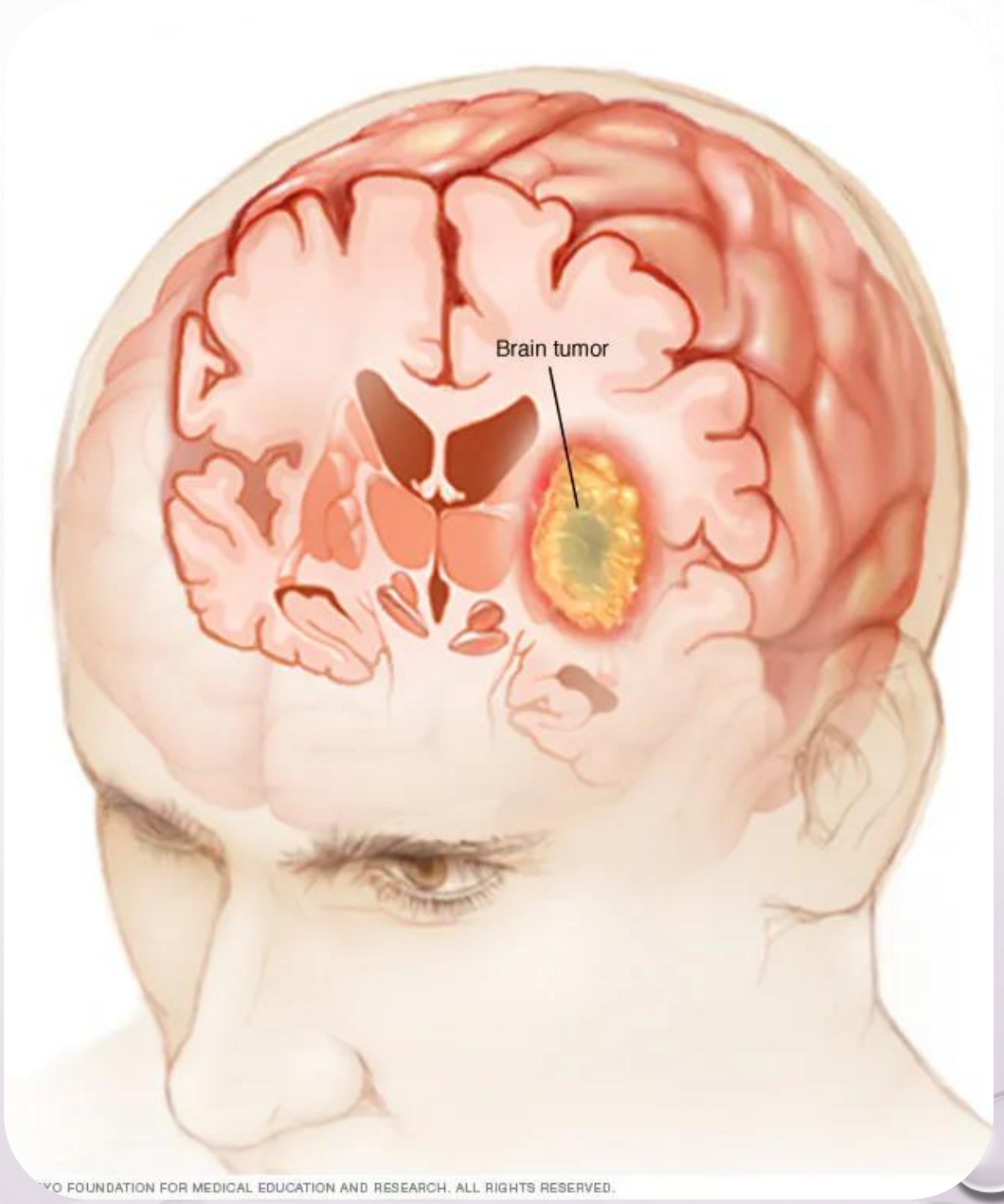
Brain Tumor

A **Brain tumor** is a growth of cells in the brain or near it. Brain tumors can happen in the **brain tissue**. Brain tumors also can happen near the brain tissue. Nearby locations include **nerves**, the **pituitary gland**, the **pineal gland**, and the **membranes** that cover the surface of the brain.

Many different types of primary brain tumors exist.

Some brain **tumors aren't cancerous**.

These are called **noncancerous brain tumors** or benign brain tumors.



Survival rates for Brain tumor remain stubbornly low despite great improvements for most other cancers.

Table 1 The survival rate of different types of cancer

From: Overcoming the blood–brain barrier for the therapy of malignant brain tumor: current status and prospects of drug delivery approaches

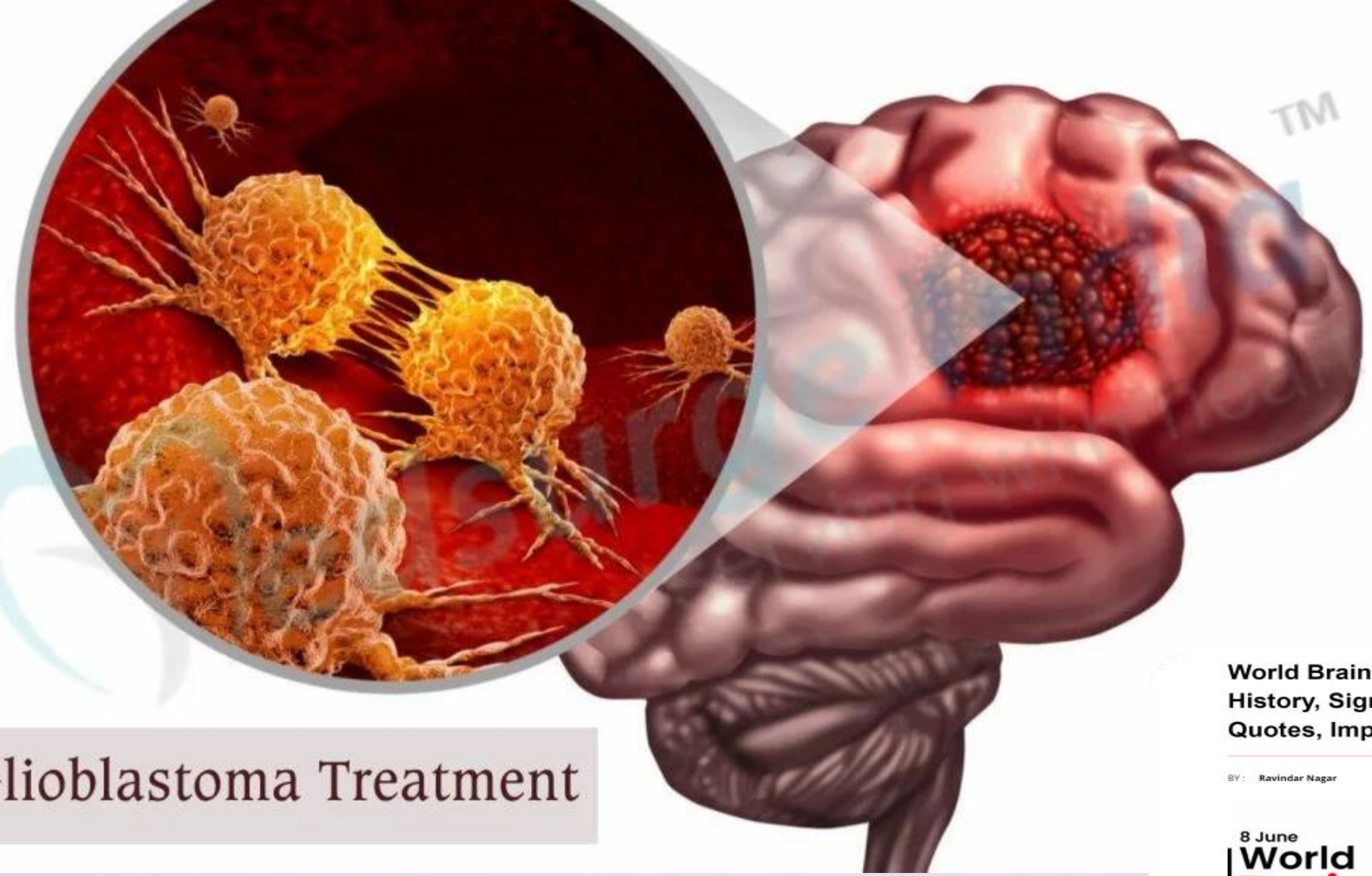
Type of cancer	Brain tumors(%)	Breast(%)	Melanoma(%)	Colon(%)	Multiple myeloma(%)
5-year survival rate	36	77–92	94	54	54
10-year survival rate	31	85	90	51	35
Ref	[2]	[3, 4]	[5, 6]	[7]	[8, 9]

It is also a leading cause of cancer-related death in **children and young adults**.

Table 2 Survival rating among primary brain tumors for patients of different ages

From: Overcoming the blood–brain barrier for the therapy of malignant brain tumor: current status and prospects of drug delivery approaches

Type of cancer		Glioblastoma(%)	Low-grade (diffuse) astrocytoma(%)	Anaplastic astrocytoma(%)	Oligodendroglioma(%)	Anaplastic oligodendroglioma(%)	Ependymoma/anaplastic ependymoma(%)	M
Age	20–44	22	73	58	90	76	92	84
	45–54	9	46	29	82	67	90	79
	55–64	6	26	15	69	45	87	74

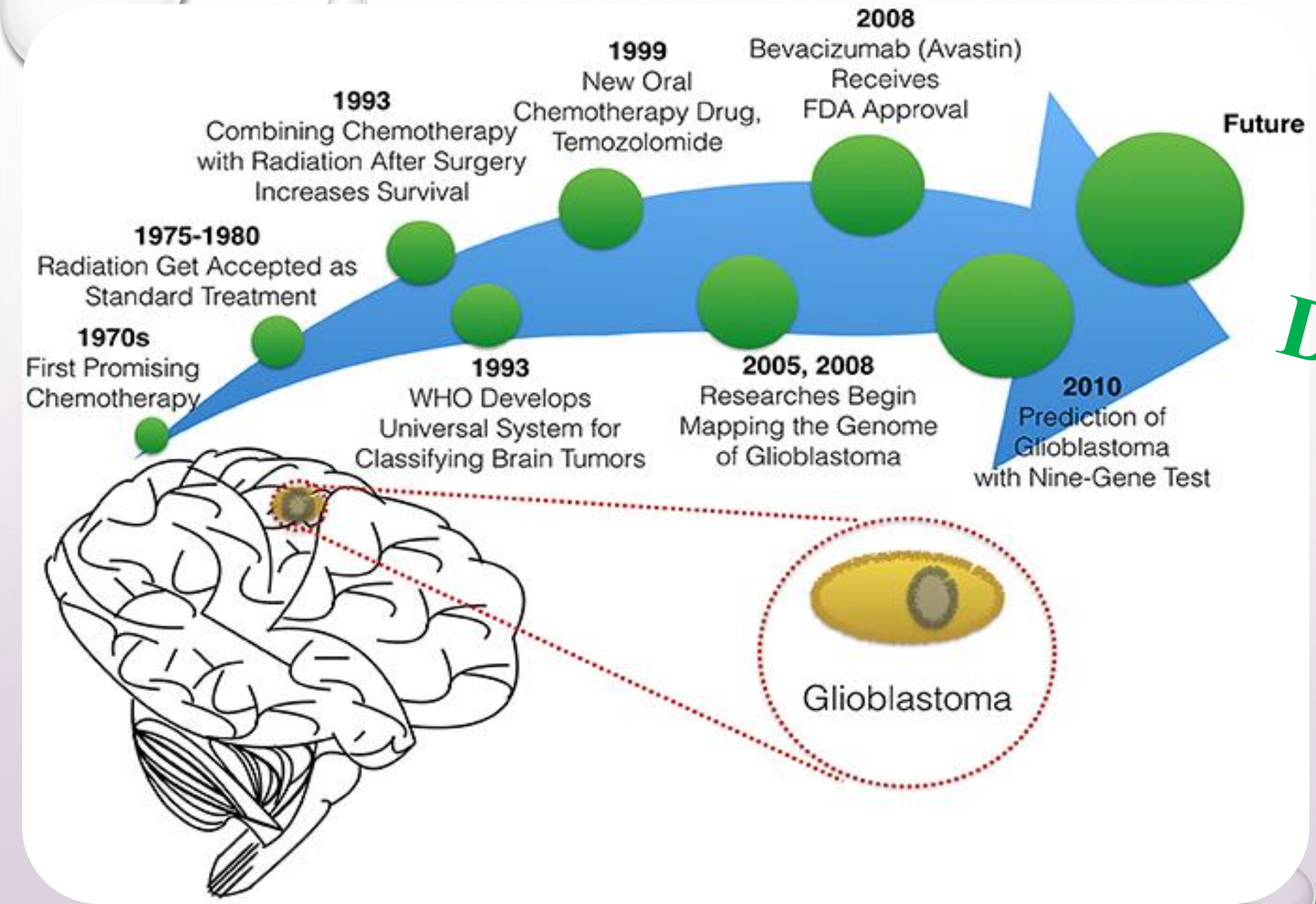


Glioblastoma Treatment

World Brain Tumour Day 2021 Theme, History, Significance, Poster Images, Quotes, Importance and More

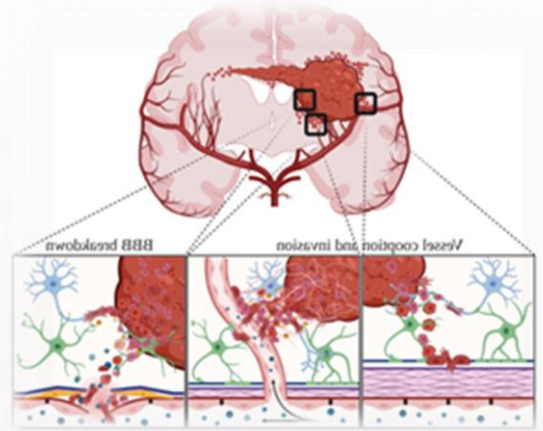
BY : **Ravindar Nagar**

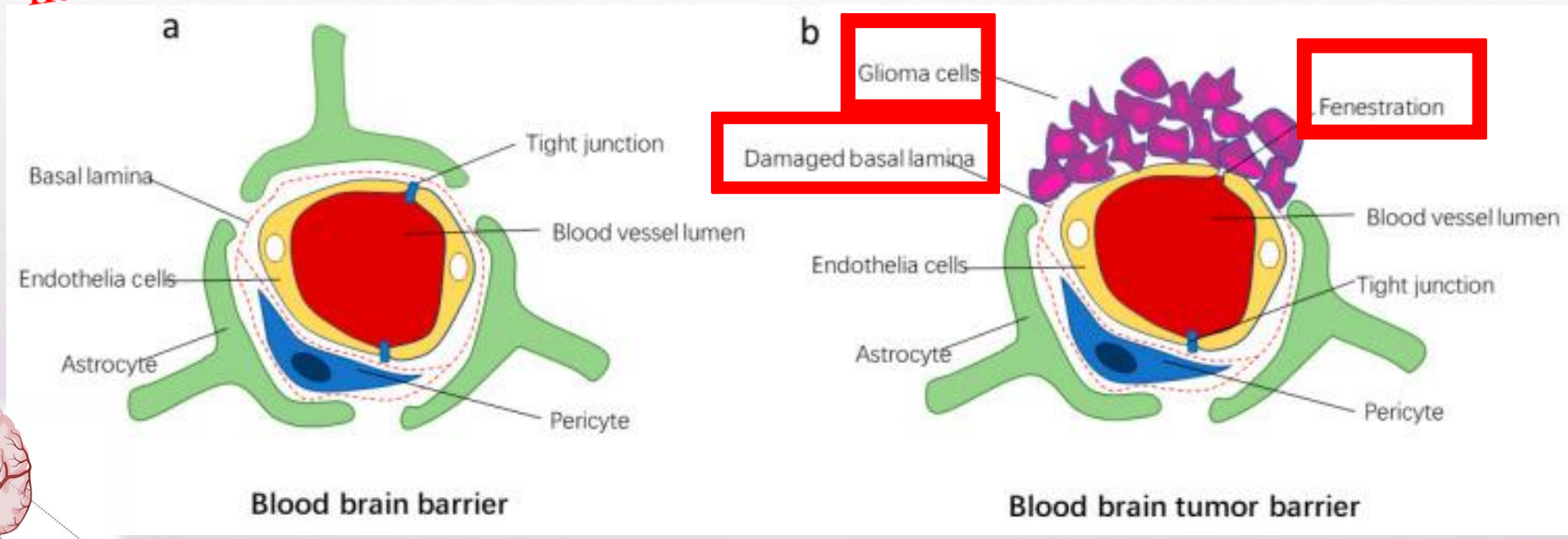
Updated at : June 8, 2021, 3:58 PM

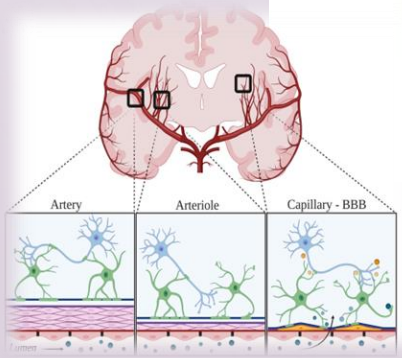

1970s
First Promising Chemotherapy
1975-1980
Radiation Get Accepted as Standard Treatment
1993
Combining Chemotherapy with Radiation After Surgery Increases Survival
1993
WHO Develops Universal System for Classifying Brain Tumors
1999
New Oral Chemotherapy Drug, Temozolomide
2005, 2008
Researches Begin Mapping the Genome of Glioblastoma
2008
Bevacizumab (Avastin) Receives FDA Approval
2010
Prediction of Glioblastoma with Nine-Gene Test
Future
Glioblastoma

DNAzyme

Brain drug delivery is a serious challenge, illustrated by decades of scientific research which has borne little fruit.







Mechanisms of transport through the BBB:

- ✓ **Diffusion (transcellular lipophilic pathway: TLP)**
- ✓ **Carrier-mediated transport (CMT)**
- ✓ **Receptor-mediated endocytosis (RME)**
- ✓ **Absorption-mediated endocytosis (AME)**
- ✓ **Proton pump, cell-mediated transport**
- ✓ **Paracellular waterway**

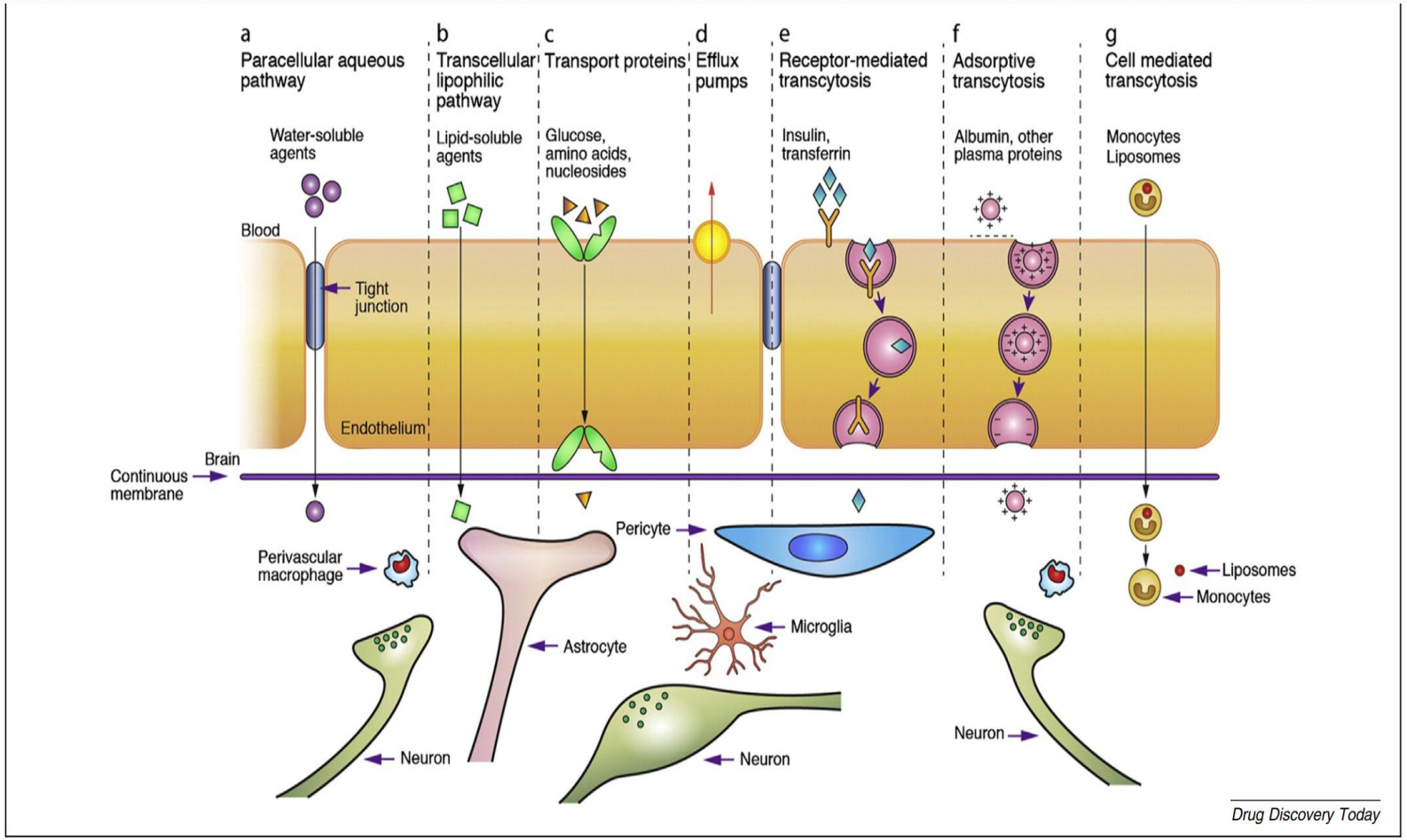


FIGURE 2

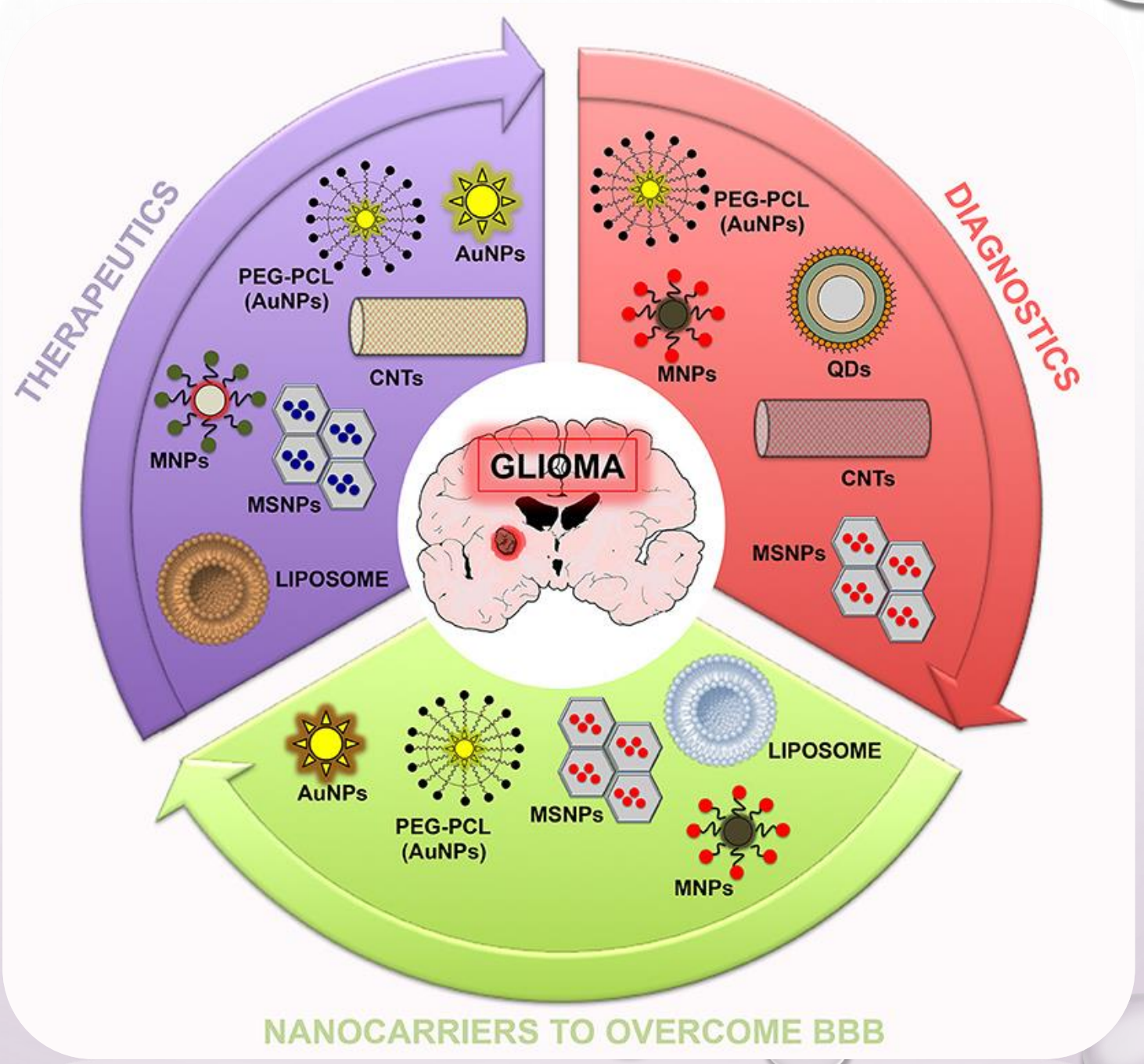
Examples of the application of mechanisms of transport across the blood–brain barrier (BBB) for effective drug delivery. Adapted with permission from [5].

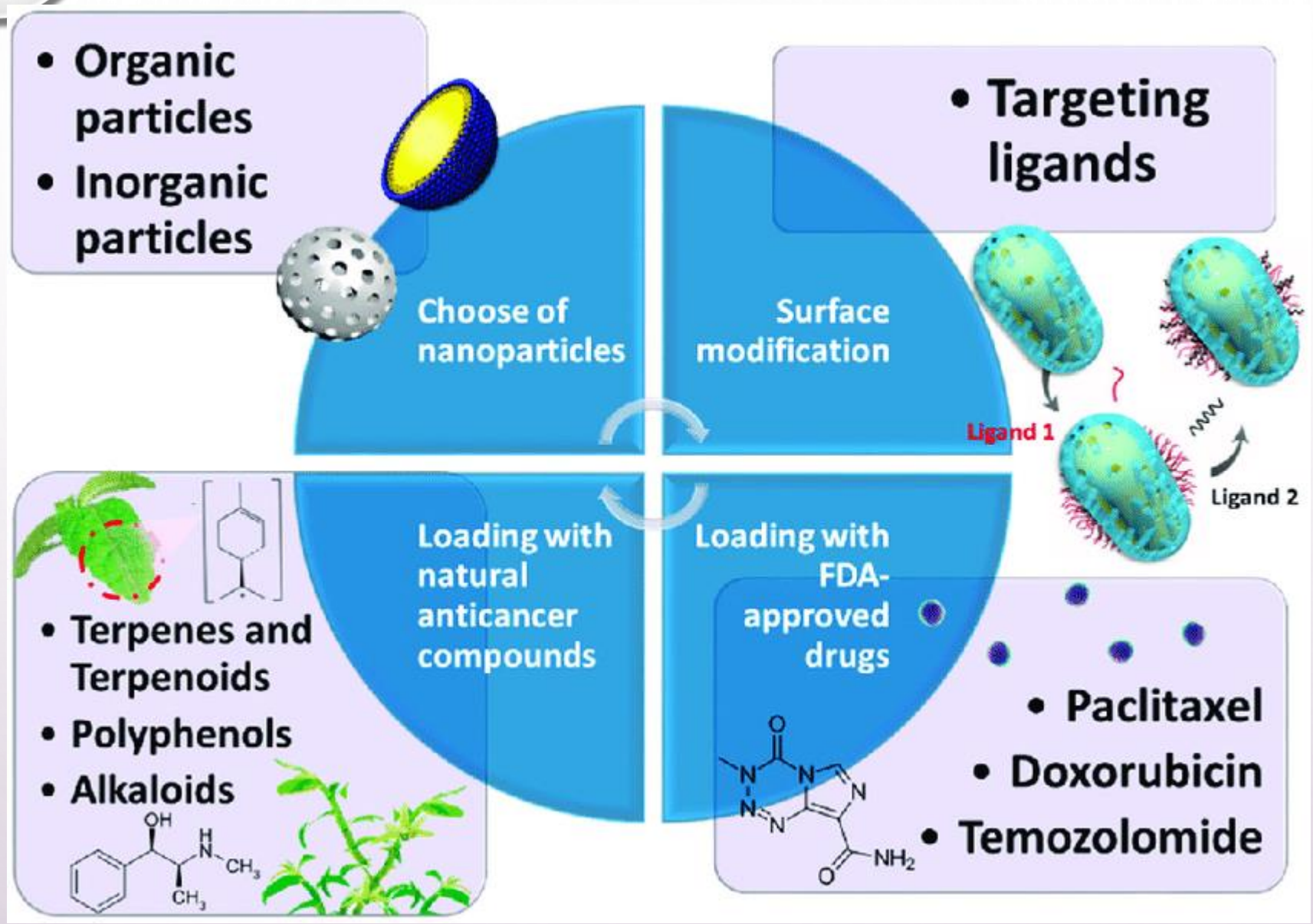
POST-SCREEN (GREY)

Nanomedicines

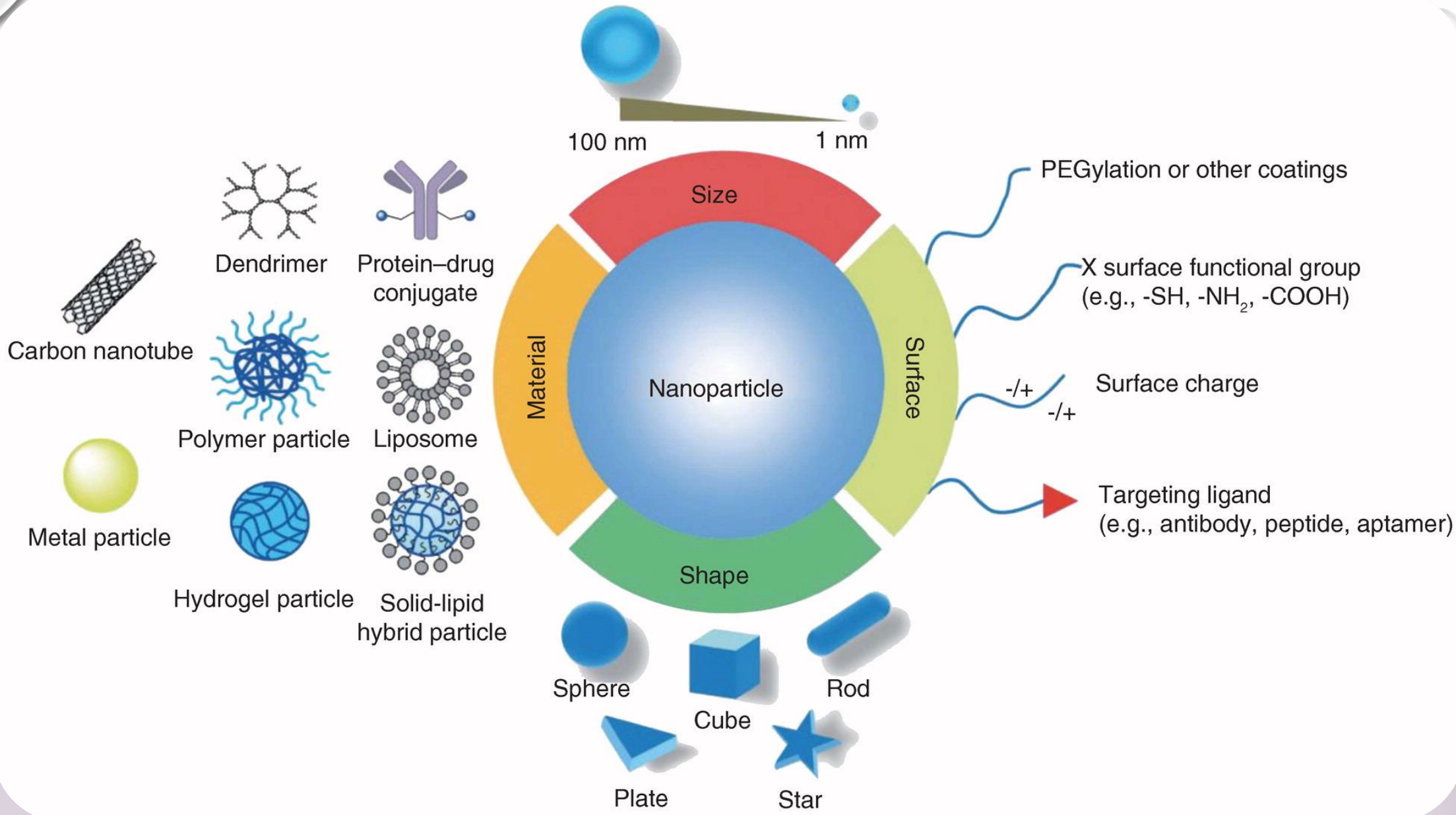
Nanomedicines have great potential to improve therapeutic outcomes for brain tumor patients.

The field is exciting and developing quickly, with research groups around the world creating and discovering new **liposomes**, nanoparticles, extracellular vesicles and **medical devices** for improving brain drug delivery.



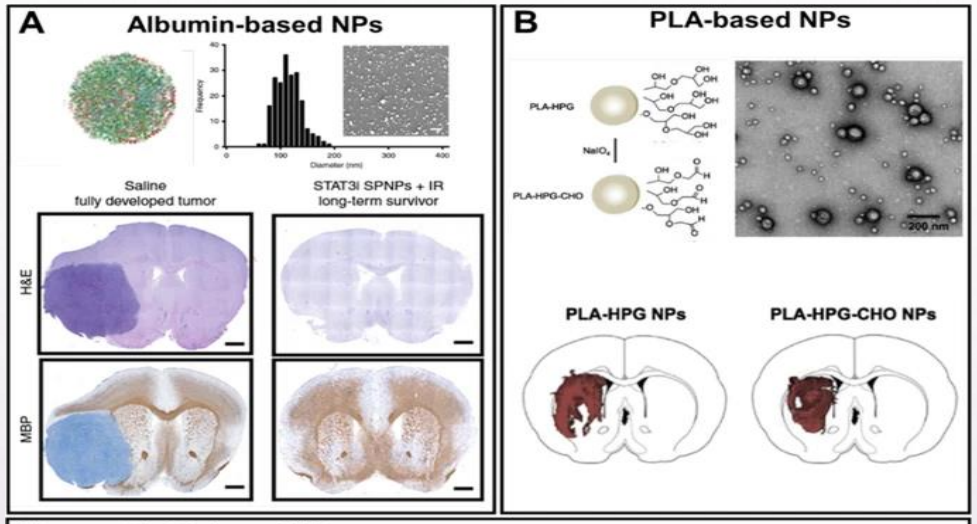


Schematic illustration of the nanocomposites combined with chemotherapy. The drug delivery system for **GBM chemotherapy** can be optimized by the composition of nanoparticles, ligands, and medicine.


100 nm
1 nm
Size
Material
Surface
Shape
Nanoparticle
PEGylation or other coatings
X surface functional group
(e.g., -SH, -NH2, -COOH)
-/+
-/+
Surface charge
Targeting ligand
(e.g., antibody, peptide, aptamer)
Dendrimer
Protein–drug conjugate
Carbon nanotube
Polymer particle
Liposome
Metal particle
Hydrogel particle
Solid-lipid hybrid particle
Sphere
Cube
Rod
Plate
Star

Application of **organic nanocarriers** for brain tumor therapy: 2021

A Characterization of albumin-based NPs with the following histological analysis, **demonstrating tumor inhibition effect** (scale bar = 1 μm).



B Characterization of **PLA-based NPs** and their **biodistribution** in the brain (scale bar = 200 nm).

C SEM images of **PLGA-based NPs** and MR images **before and after** the therapy (scale bar = 1 μm).

D AFM image of **liposomes**, in vivo fluorescent distribution, and histological analysis, **demonstrating the tumor inhibition effect**.

REVIEW

ADVANCED SCIENCE Open Access

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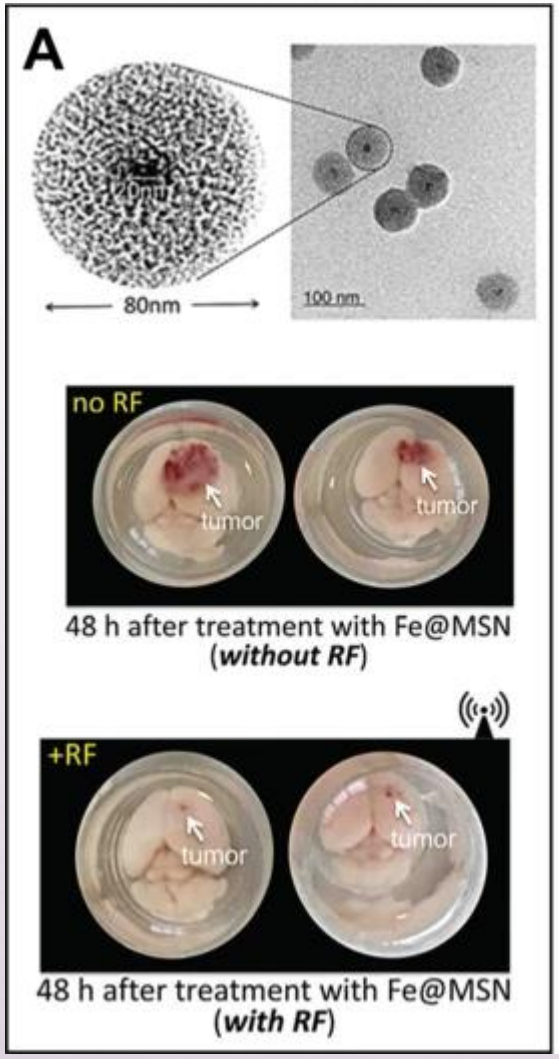
Development of Polymeric Nanoparticles for Blood–Brain Barrier Transfer—Strategies and Challenges

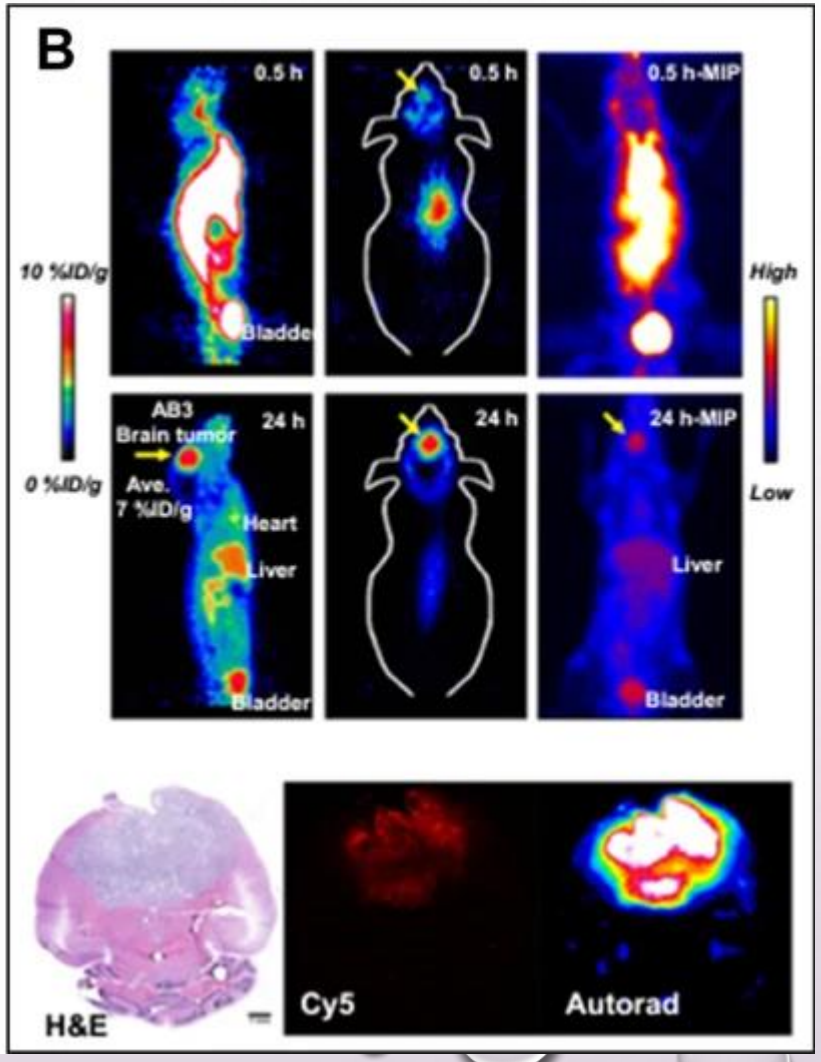
Weisen Zhang, Ami Mehta, Ziqiu Tong, Lars Esser, and Nicolas H. Voelcker**

Adv. Sci. **2021**, *8*, 2003937

Application of SiO2-based NPs for targeting brain tumor: 2022

A TEM images of **IONPs@SiO2** NPs with corresponding macroscopic ex vivo evaluation of their therapeutic efficiency against **GBM tumors** (scale bar = 100 nm).



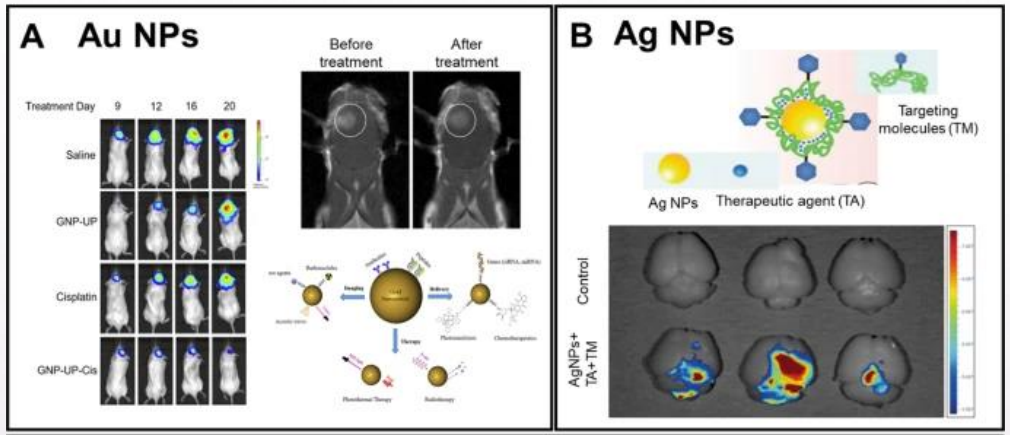


B PET-CT imaging of **radiolabeled core–shell SiO2 NPs** showing clear accumulation of radionuclide signal in the brain tumors with corresponding histological and fluorescent analysis of NPs accumulation in the brain.

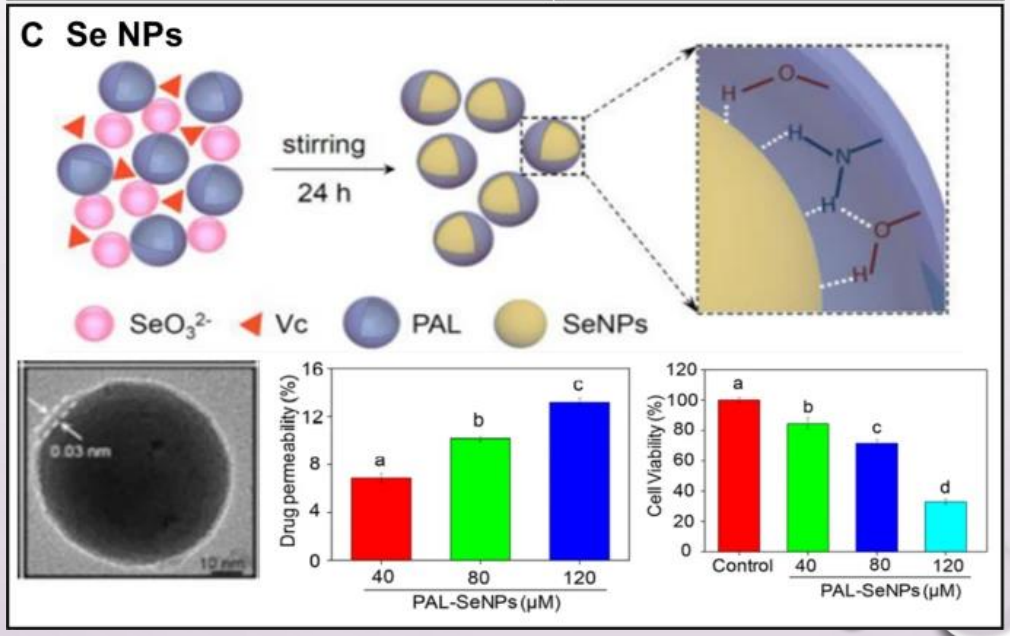
Application of **inorganic nanocarriers** based on **Au**, **Ag**, and **Se** NPs for targeting of brain tumor:

2023

Bioluminescent images of the tumor showing the **specific accumulation of Au NPs** in the glioma and the anti-tumor effect after therapy.

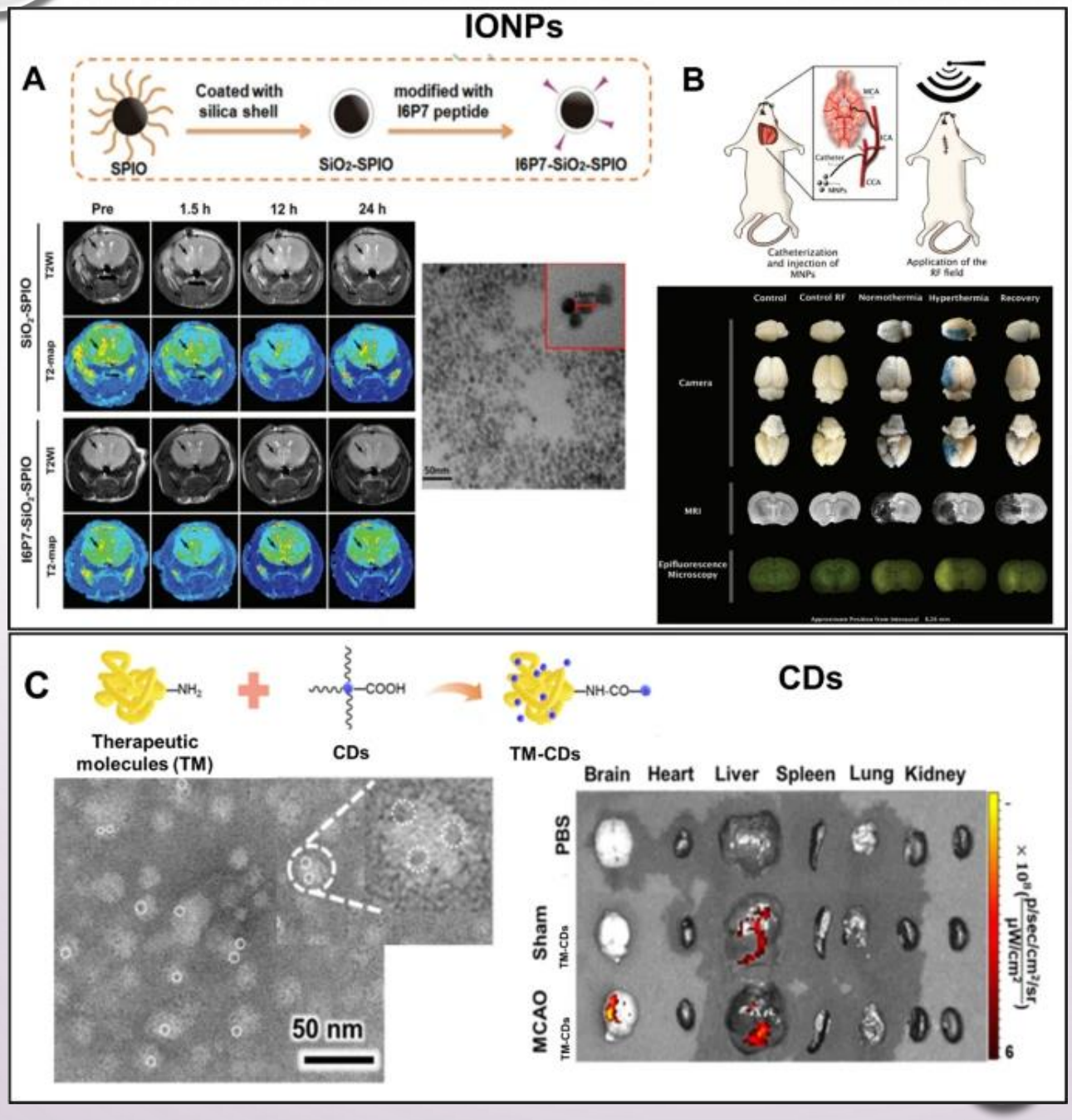


Schematic illustration of the design of **Ag NPs** and ex vivo imaging of the accumulation of Ag NPs in the brain tumor.



Schematic illustration of the synthesis of glioma cell **targeting complexes based on Se NPs**, TEM image of Se NPs and histograms of drug permeability and cytotoxicity (scale bar = 10 nm).

2023



C Scheme of synthesis and TEM image of hybrids based on CDs.

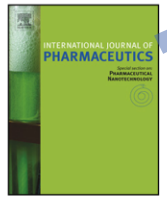
Ex vivo analysis of the main organs (the brain, heart, liver, spleen, lungs, and kidneys) of **mice after a 30-min intravenous injection**, **demonstrating the accumulation of nanohybrids in the brain** (scale bar = 50 nm).

International Journal of Pharmaceutics 509 (2016) 431–438

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm



Pharmaceutical Nanotechnology

How do the physicochemical properties of nanoliposomes affect their interactions with the hCMEC/D3 cellular model of the BBB?

Konstantina Papadia[a], Eleni Markoutsa[a], Sophia G. Antimisiaris[a,b,*]

[a] Laboratory of Pharmaceutical Technology, Department of Pharmacy, University of Patras, Rio 26504, Greece
[b] Institute of Chemical Engineering, FORTH/ICE-HT, Rio 26504, Greece

Nanosized liposomes composed of 1,2-distearoyl-sn-glycerol-3-phosphatidylcholine (DSPC), cholesterol and polyethylene glycol-conjugated phospholipid (PEG), incorporating FITC-dextran (FITC) and in some cases also Rhodamine-conjugated phospholipid (RHO) (as labels) were constructed by the thin film hydration method, followed by extrusion; membranes with pore diameters from 50 to 400 nm were used, while charged vesicles were produced by partially replacing DSPC with 1,2-distearoyl-sn-*glycero*-3-phospho-(1′-rac-glycerol) (DSPG). The uptake of liposomes by hCMED/D3 cells was evaluated by measuring FITC in cells, and their permeability across cell monolayers was evaluated, by measuring the FI of liposome associated-FITC and RHO in the receiving side of a monolayer-transwell system. Results prove that liposome size has a significant effect on their uptake and permeability (for both charged and non-charged vesicles). The effect of liposome charge on cell uptake was slight (but significant), however charge (in the range from −2 to −16 mV) did not significantly affect vesicle permeability; a significant decrease was only demonstrated for the liposome with the highest charge.

Journal of Controlled Release 322 (2020) 390–400

Contents lists available at ScienceDirect

Journal of Controlled Release

journal homepage: www.elsevier.com/locate/jconrel

Review article

Lipid nanocapsules to enhance drug bioavailability to the central nervous system

Rui Pedro Moura[a,b,c,d], Catarina Pacheco[a,b,d], Ana Paula Pêgo[a,b,c,e], Anne des Rieux[f], Bruno Sarmento[a,b,d,*]

[a] *I3S – Instituto de Investigação e Inovação em Saúde, Universidade do Porto, Rua Alfredo Allen 208, 4200-135 Porto, Portugal*

[b] *INEB – Instituto de Engenharia Biomédica, Universidade do Porto, Rua Alfredo Allen 208, 4200-135 Porto, Portugal*

Journal of Molecular Liquids 346 (2022) 118278

Contents lists available at ScienceDirect

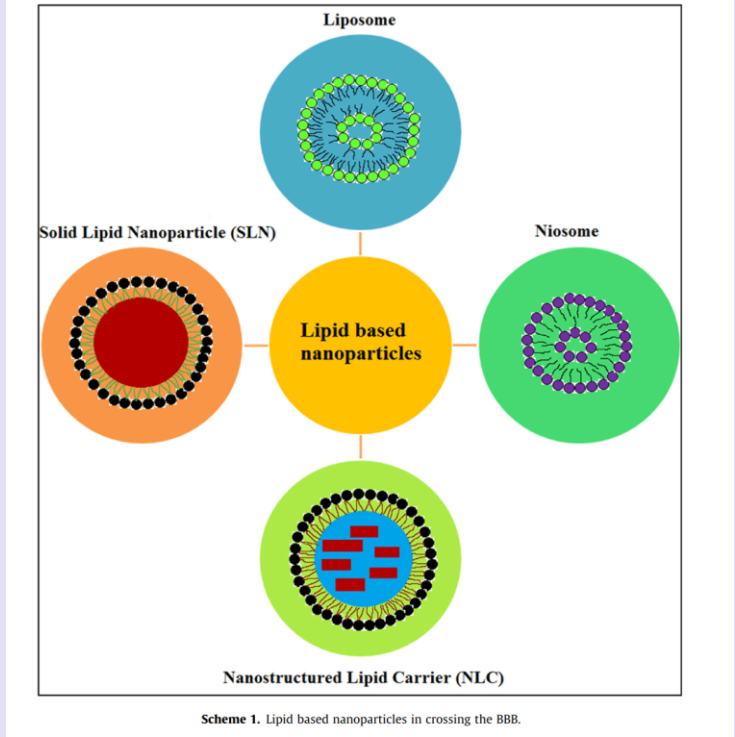
Journal of Molecular Liquids

journal homepage: www.elsevier.com/locate/molliq

Efficiency of lipid-based nano drug delivery systems in crossing the blood–brain barrier: A review

Salar Khaledian [a,b], Maliheh Dayani [c,1], Arad Fatahian [d], Reza Fatahian [a,e,*], Fleming Martinez [f]

[a] Clinical Research Development Center, Taleghani and Imam Ali Hospitals, Kermanshah University of Medical Sciences, Kermanshah, Iran



Scheme 1. Lipid based nanoparticles in crossing the BBB.

Table 3

Advantage and disadvantages of nano lipid based drug delivery system.

NPs	Advantages	Disadvantages
Liposome	Good drug protection, improvement the solubility of hydrophobic drugs, Possibility of simultaneous loading of hydrophilic and hydrophobic drugs, high bioavailability and biodistribution	Low efficiency in loading hydrophilic drugs and low storage stability
SLNs	High efficiency in encapsulation of hydrophobic drugs relative to liposomes, unneeded for organic solvents in production, Biocompatible and biodegradable components, high durability	Possibility of drug leakage in storage time, less drug encapsulation than NLC
NLCs	High efficiency in encapsulation of drugs relative to SLNs, Possibility of more stable drug release, Less drug leakage at storage time	Needing to optimize the solid/liquid lipids ratio
Niosome	Targeting to specific sites, increased stability and high durability relative to liposomes	Drug leakage and particle aggregation

Table 2 (continued)

Nanoplatform	Cargos	Size (nm)	Zeta potential (mV)	Drug loading (DL)/ entrapment efficiency (EE) (%)	Establish PD model	Crossing BBB mechanism	Administration route	References
Mesoporous silica-encapsulated gold nanorod	Quercetin	15.7 × 91.3	N/A	13.5 (DL)	MPTP	Photothermal	Intravenous injection	[121]
Zeolitic imidazolate framework-8	Prussian blue and quercetin	143	N/A	61.3 (EE)	MPTP	Photothermal	Intravenous injection	[122]
Liposome	Recombinant human fibroblast growth factor-20	68.1 ± 2.1	N/A	N/A	6-DOPA	Focus ultrasound-mediated	Intravenous injection	[123]
Nanoparticle	Glial cell-derived neurotrophic factor	50 ± 3	1.5 ± 0.2	N/A	6-DOPA	Focus ultrasound-mediated	Intravenous injection	[124]
Polysorbate 80-modified cerasome	Curcumin	110.43 ± 6.59	−25.0 ± 0.9	86 ± 1.25 (EE)	MPTP	Focus ultrasound-mediated	Intravenous injection	[125]
Lipid nanomicrobubble	Glial cell -derived neurotrophic factor	100 ~ 4200	2.3 ± 1.9	N/A	MPTP	Focus ultrasound-mediated	Intravenous injection	[126]
Lipid nanomicrobubble	Nuclear factor E2-related factor 2	313.5 ± 47.68	14.8 ± 3.99	N/A	6-OHDA	Focus ultrasound-mediated	Intramuscular injection	[127]
Cell membrane-coated nanoparticles	Quercetin	78.8	−35.2	17.6 (DL)	MPTP	Focus ultrasound-mediated	Intravenous injection	[128]

Materials Today Bio 13 (2022) 100212

Contents lists available at ScienceDirect

Materials Today Bio

journal homepage: www.journals.elsevier.com/materials-today-bio

The involvement of extracellular vesicles in the transcytosis of nanoliposomes through brain endothelial cells, and the impact of liposomal pH-sensitivity

Joy N. Reginald-Opara [a], Darren Svirskis [a], Song Yee Paek [b], Mingtan Tang [a], Simon J. O'Carroll [c], Justin M. Dean [d], Lawrence W. Chamley [b], Zimei Wu [a,*]

[a] School of Pharmacy, Faculty of Medical and Health Sciences, The University of Auckland, Auckland, 1142, New Zealand

Review

Liposomal-Based Formulations: A Path from Basic Research to Temozolomide Delivery Inside Glioblastoma Tissue

Roxana-Maria Amarandi [1], Alina Ibanescu [1], Eugen Carasevici [1], Luminita Marin [2] and Brindusa Dragoi [1,*]

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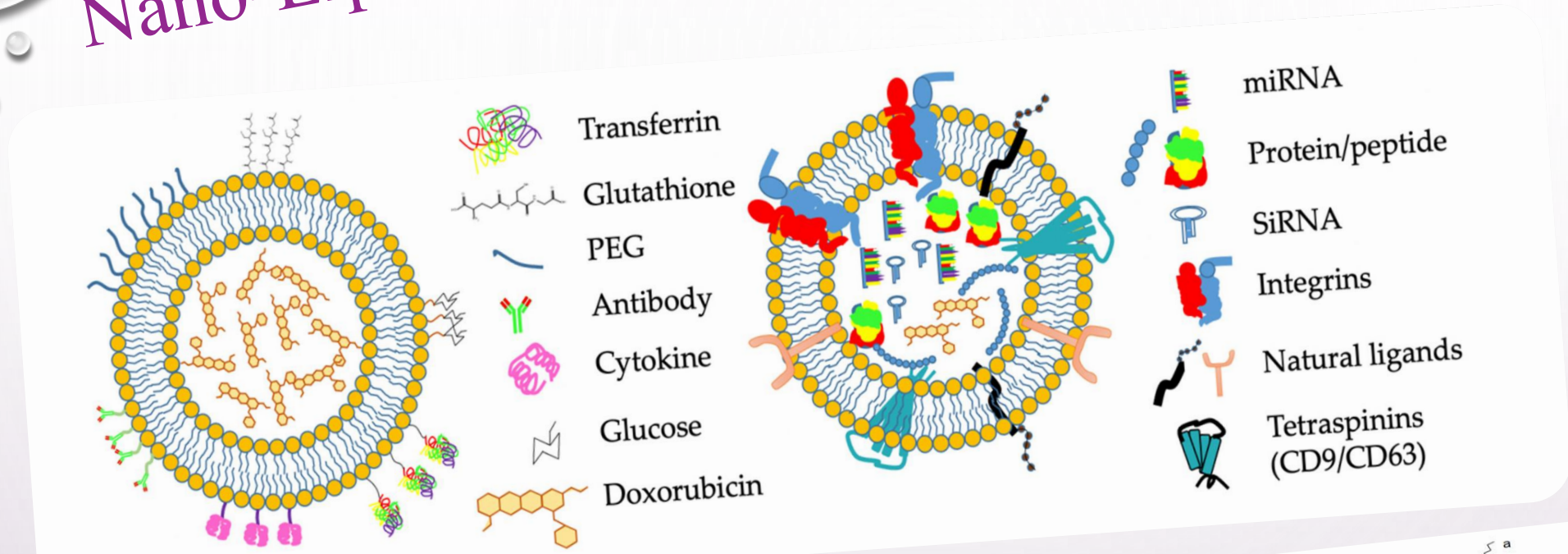
[2] "Petru Poni" Institute of Macromolecular Chemistry of Romanian Academy, Aleea Grigore Ghica Voda, nr. 41A, 700487 Iasi, Romania; lmarin@icmpp.ro

* Correspondence: transcendbd@iroiasi.ro

Nano-Liposomal



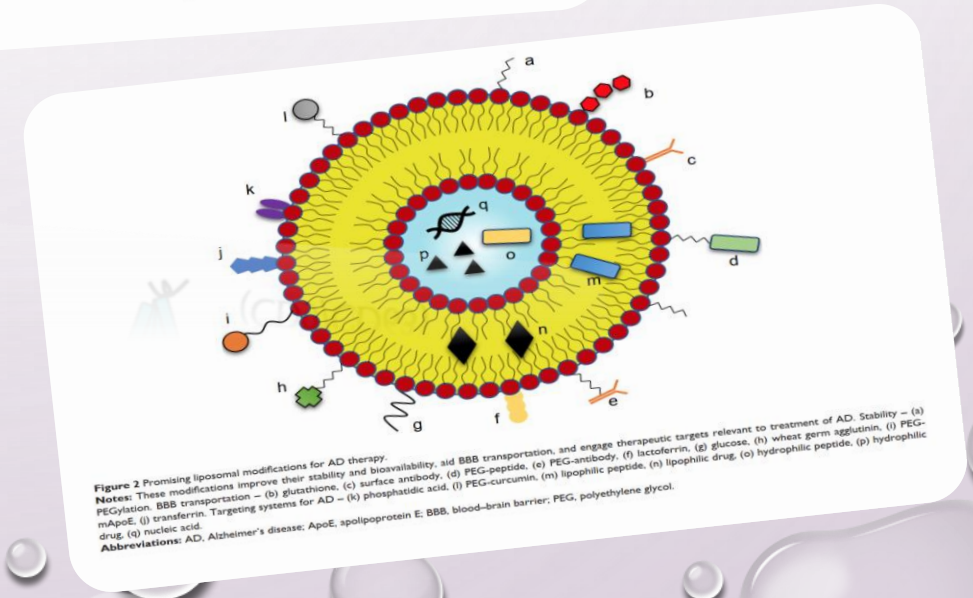


Figure 2 Promising liposomal modifications for AD therapy.
Notes: These modifications improve their stability and biosavailability, aid BBB transportation, and engage therapeutic targets relevant to treatment of AD. Stability – (a) PEGylation. BBB transportation – (b) glutathione, (c) surface antibody, (d) PEG-peptide, (e) PEG-antibody, (f) lactoferrin, (g) glucose, (h) wheat germ agglutinin, (i) PEG-mApoE, (j) transferrin. Targeting systems for AD – (k) phosphatidic acid, (l) PEG-curcumin, (m) lipophilic peptide, (n) lipophilic drug, (o) hydrophilic peptide, (p) hydrophilic drug, (q) nucleic acid.
Abbreviations: AD, Alzheimer's disease; ApoE, apolipoprotein E; BBB, blood–brain barrier; PEG, polyethylene glycol.

Transport through the BBB

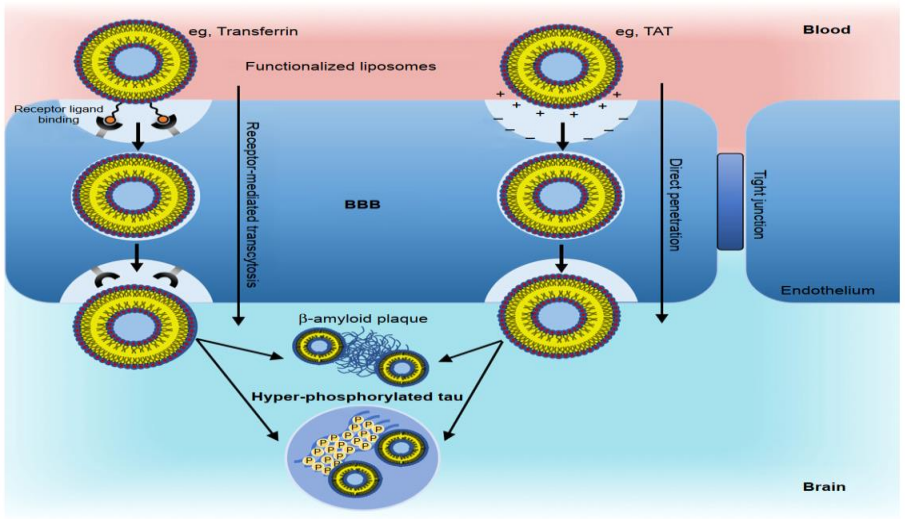


Figure 1 Promising liposomal BBB transport mechanisms.
Notes: Receptor-mediated transcytosis exploits receptors highly expressed at the BBB (eg, transferrin receptor). Receptor ligand binding triggers internalization and brain delivery. A relatively new mechanism, direct penetration, involves internalization primarily exhibited by CPPs (eg, TAT). Positively charged amino acids (+++) permit endocytosis by interacting with the negatively charged endothelial cell membrane (– – –). Once in the brain, multifunctional liposomes can be directed at an appropriate target (eg, at Aβ or tau) for AD therapy.
Abbreviations: BBB, blood–brain barrier; CPPs, cell-penetrating peptides; Aβ, amyloid-β; AD, Alzheimer's disease; TAT, transactivator of transcription of human immunodeficiency virus.

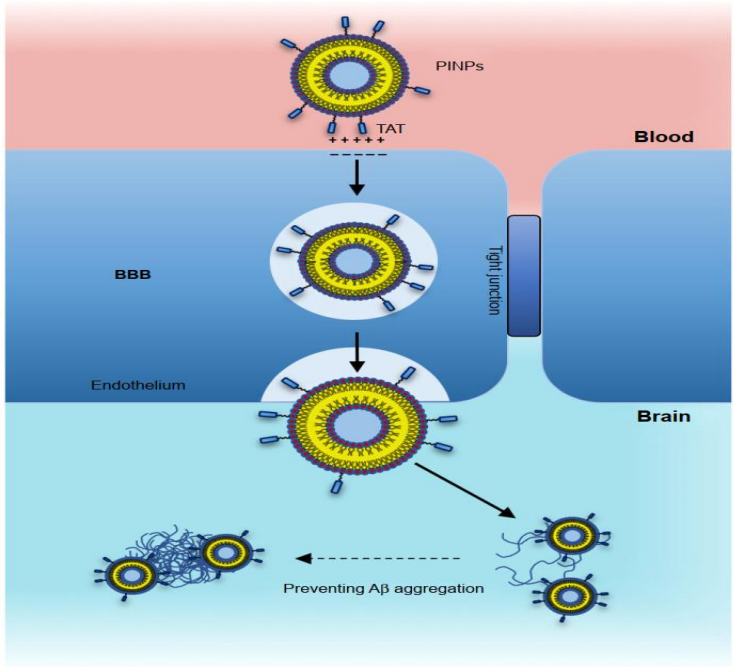
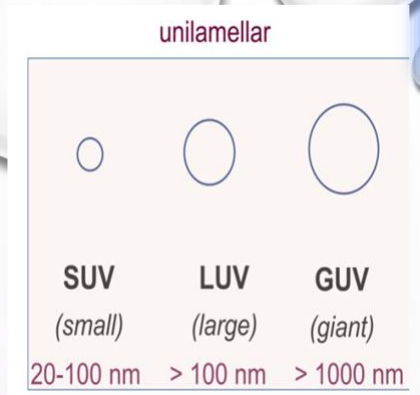
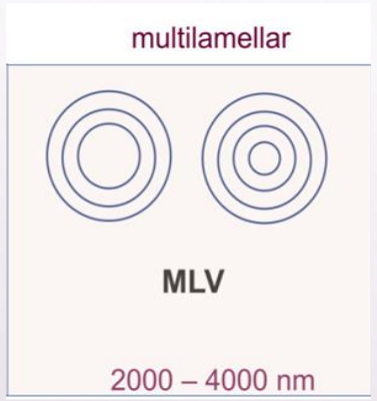
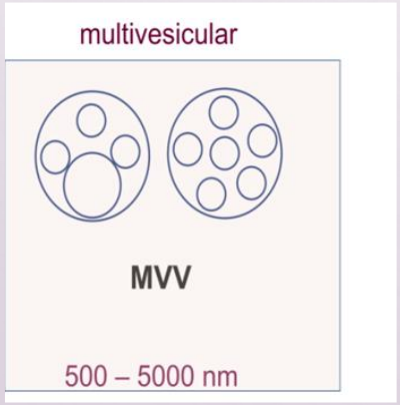


Figure 4 Targeting strategy with PINPs.
Notes: PINPs transport across the BBB by non-specific endocytosis, triggered by positively charged TAT interaction with the negatively charged membrane. RI-OR2-TAT inhibitor acts to prevent the aggregation of Aβ into oligomers and fibrils.
Abbreviations: Aβ, amyloid-β; BBB, blood–brain barrier; PINPs, peptide inhibitor nanoparticles; TAT, transactivator of transcription of human immunodeficiency virus.

Which method is better?







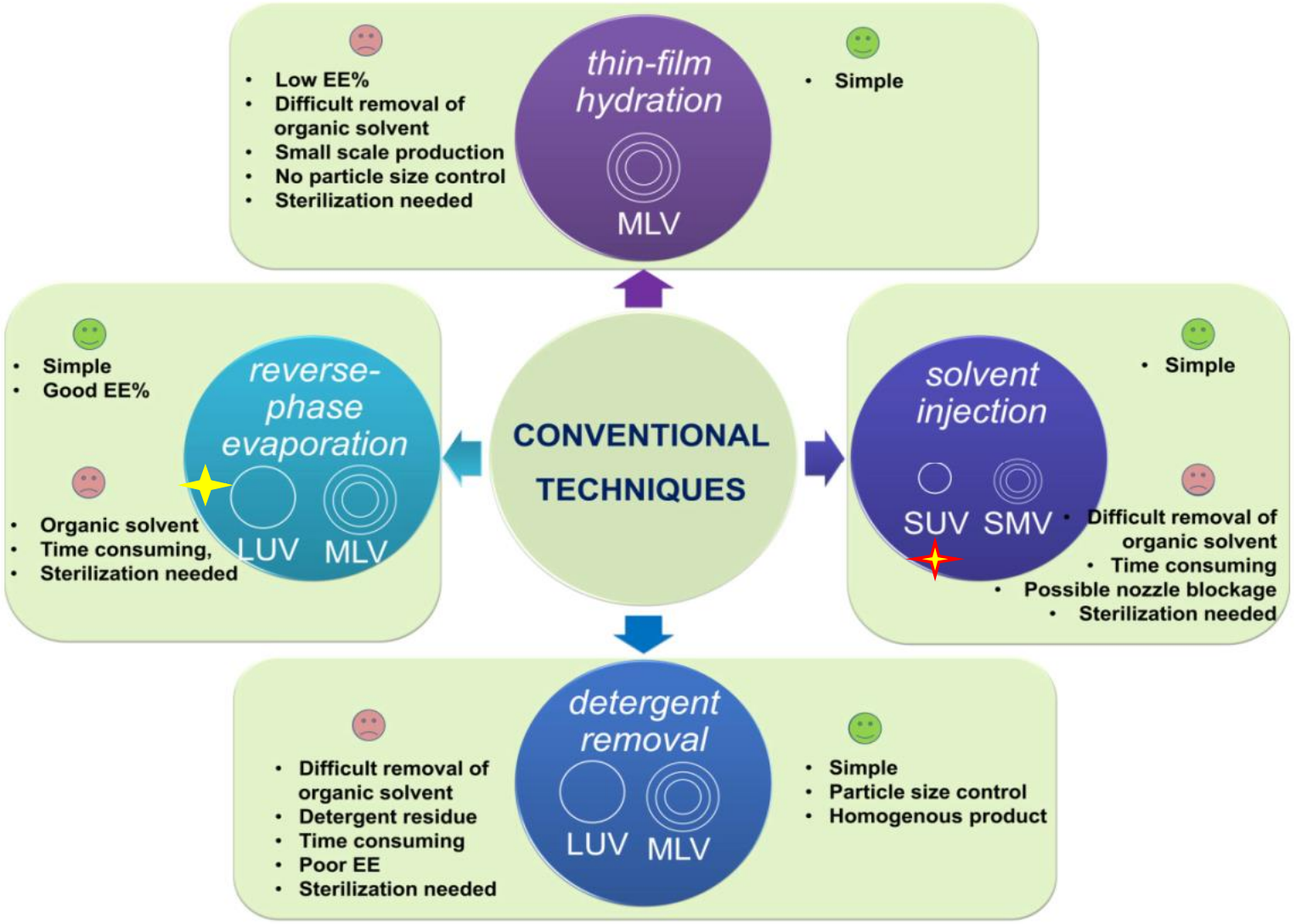


Figure 7. Main conventional techniques used for liposome preparation.

Facilitating DNAzyme Transport Across the Blood-Brain Barrier with Nanoliposome Technology

Mohammad Javad Hoseinifar[1], Faranak Aghaz[1]*, Zahra Asadi[2,3], Payman Asadi[1], Seyed Ershad Nedaei[4], Elham Arkan[1], Ali Pourmotabbed[4], Gholamreza Bahrami[5], Tayebeh Pourmotabbed[6]*

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[3] Department of Clinical Biochemistry, School of Medicine, Kermanshah University of Medical Sciences, Kermanshah, Iran

[4] Department of Physiology, School of Medicine, Kermanshah University of Medical Sciences, Kermanshah, Iran

[5] Medical Biology Research Center, Health Technology Institute, Kermanshah University of Medical Sciences, Kermanshah, Iran

[6] Department of Microbiology, Immunology, and Biochemistry, University of Tennessee, Health Science Center, Memphis, TN, USA

Professor · University of Tennessee Health Science Center

Our works in progress….

Cross of BBB 6%

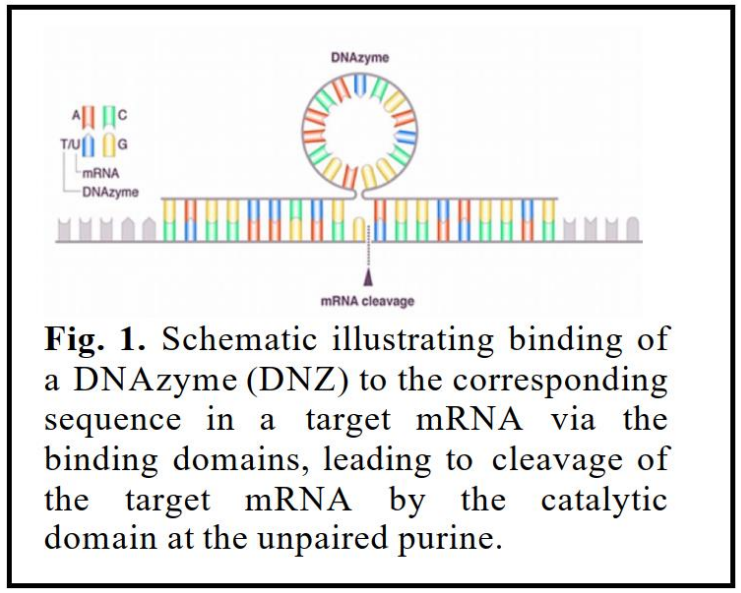


Fig. 1. Schematic illustrating binding of a DNAzyme (DNZ) to the corresponding sequence in a target mRNA via the binding domains, leading to cleavage of the target mRNA by the catalytic domain at the unpaired purine.

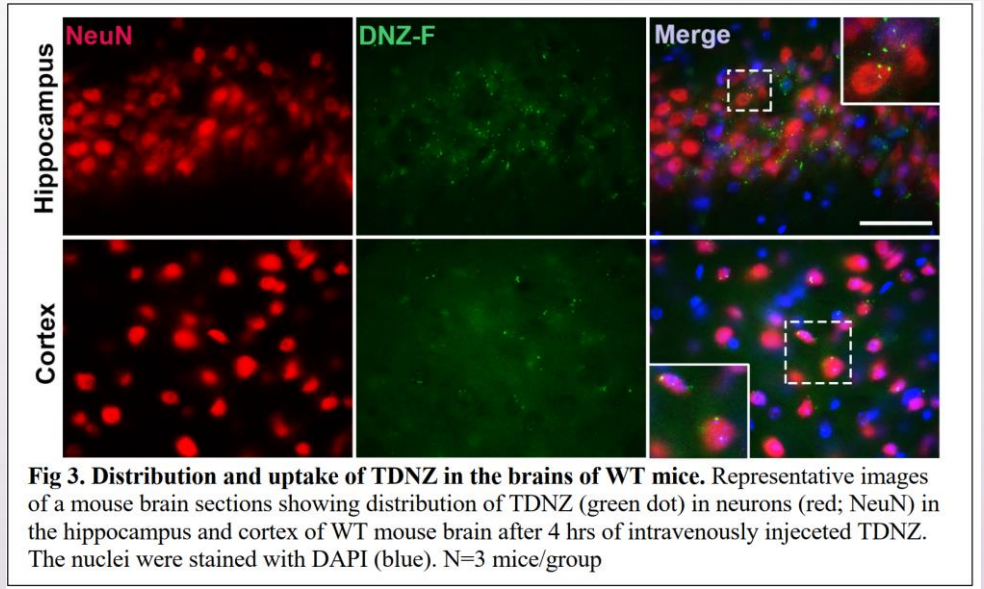
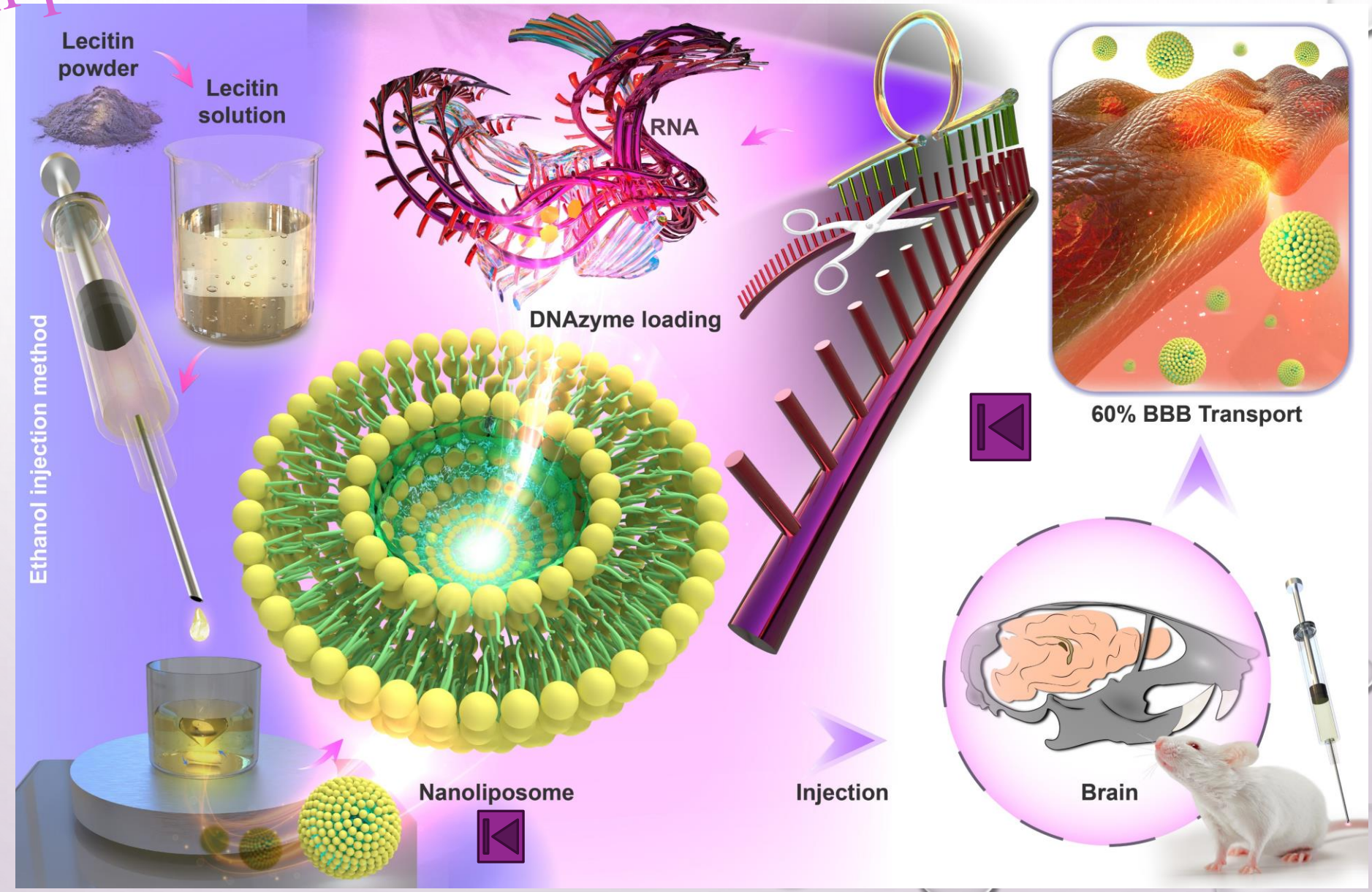


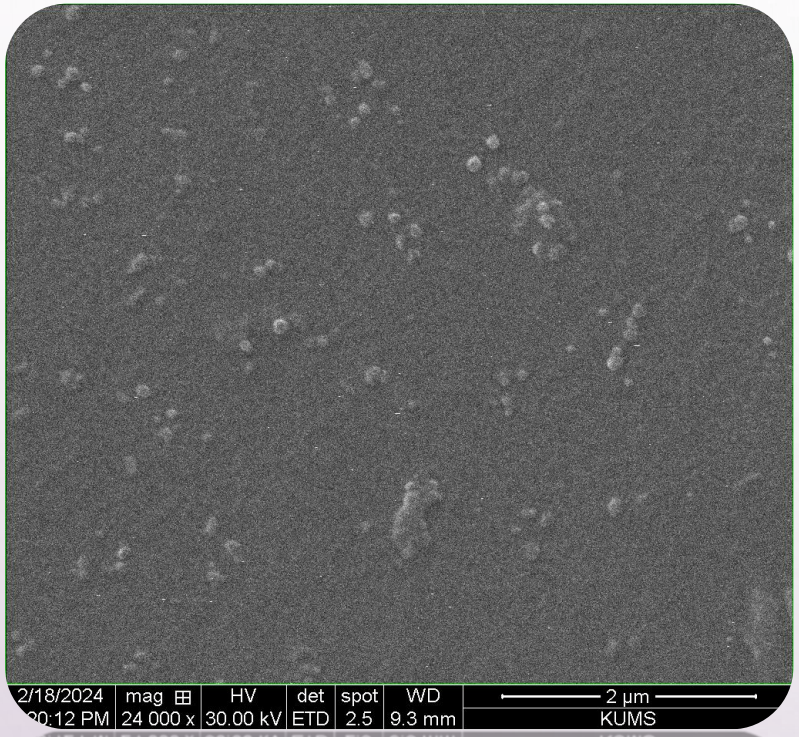
Fig 3. Distribution and uptake of TDNZ in the brains of WT mice. Representative images of a mouse brain sections showing distribution of TDNZ (green dot) in neurons (red; NeuN) in the hippocampus and cortex of WT mouse brain after 4 hrs of intravenously injeceted TDNZ. The nuclei were stained with DAPI (blue). N=3 mice/group

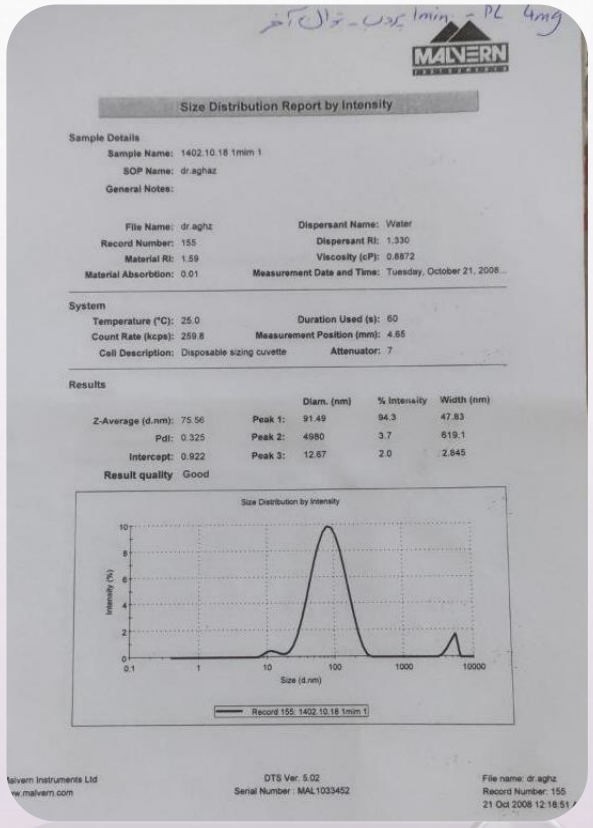
Our works in progress….



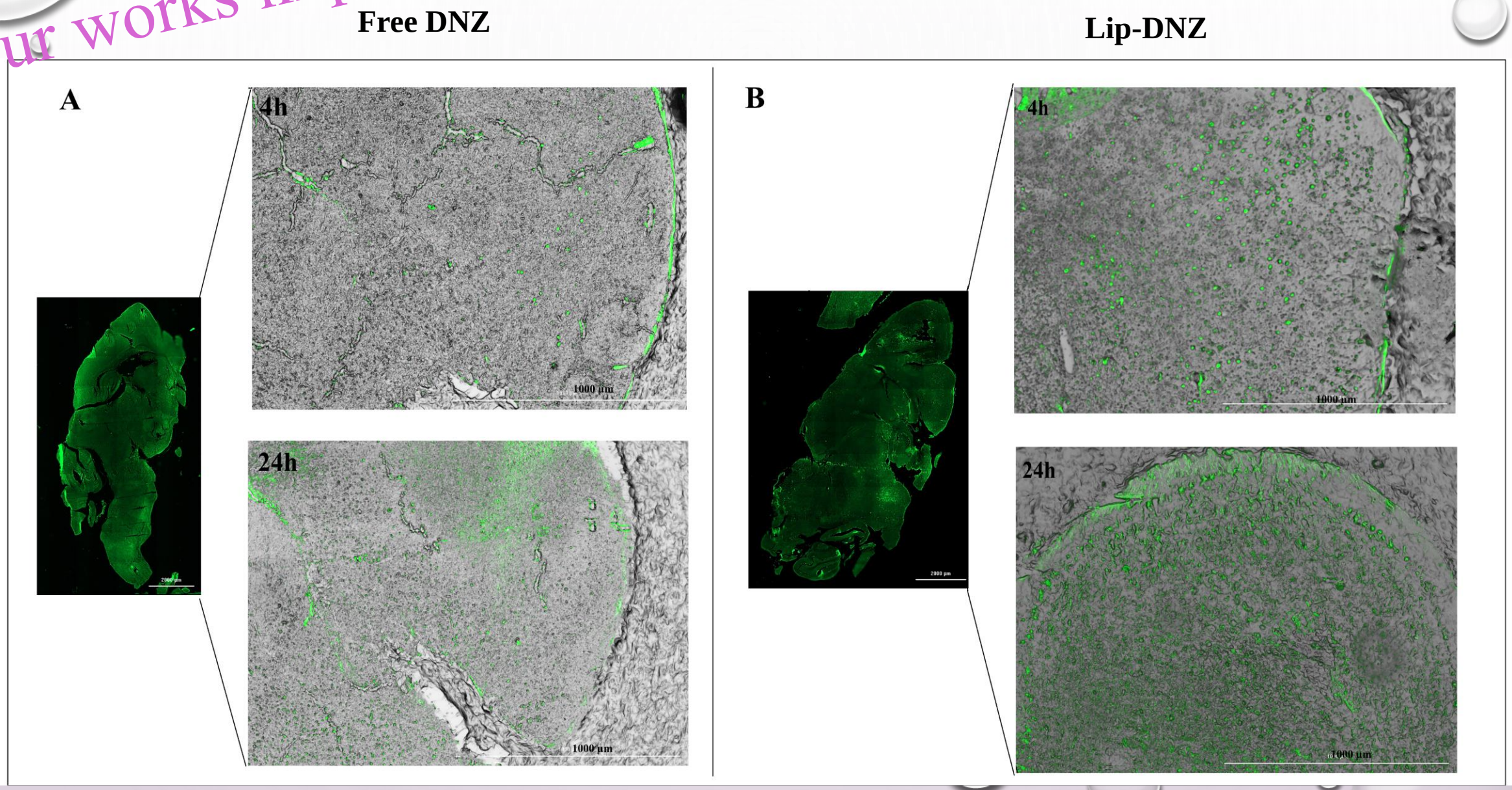
Our works in progress….

DLS= 75 nm
PDI:0.3
Control released: 48 h”””” 30%
Intra cellular uptake : More than 80%

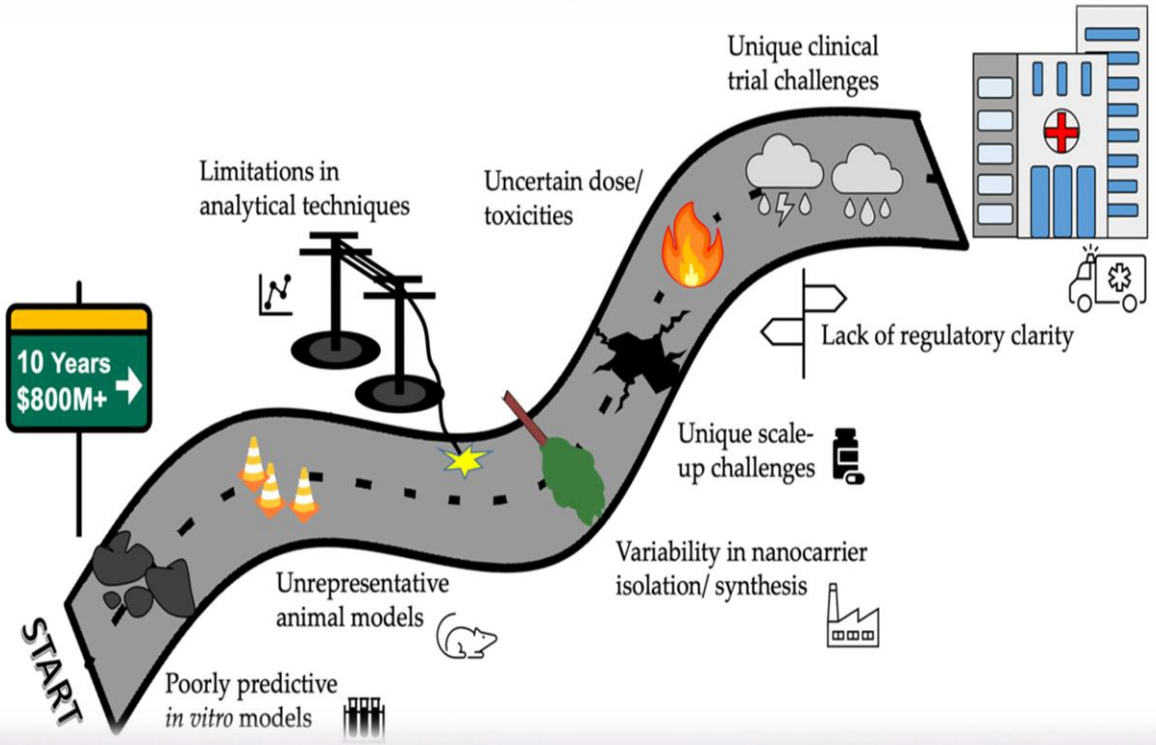




Our works in progress….



Summery



However, there are **still significant challenges**, particularly in creating solutions which are highly **efficacious, clinically feasible and realistic**

Most published research shows technologies **which produce moderate, but not transformative, improvements** in brain drug delivery.

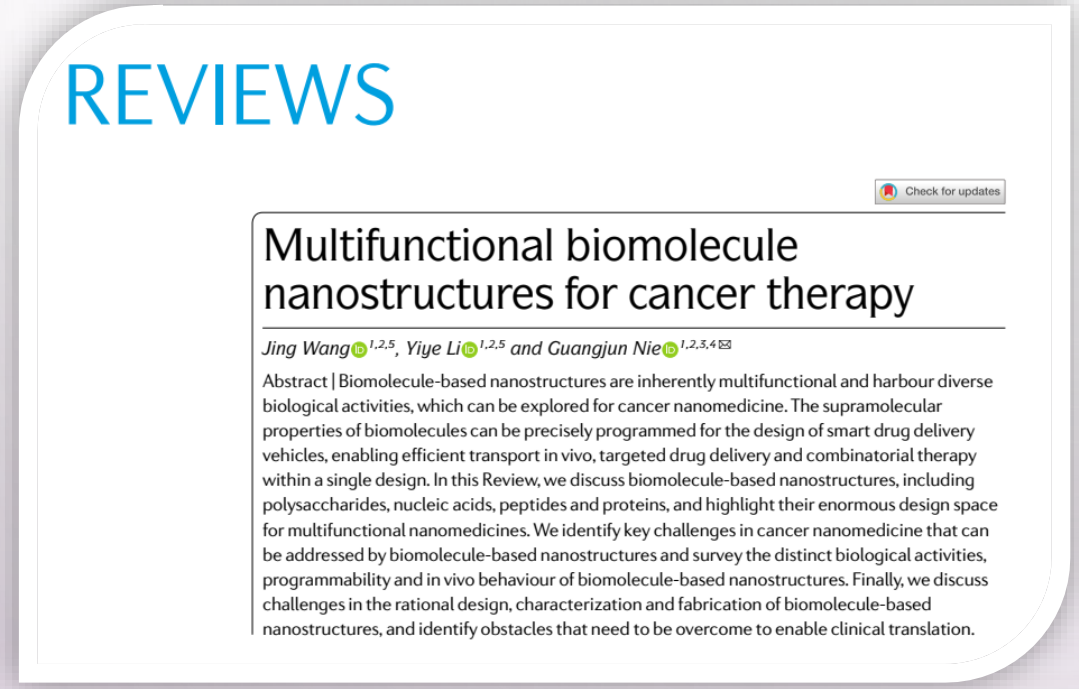
As a result, most of the promise of these technologies has **not yet been realized in the clinic.**

There are also significant obstacles with the translation of **nanomedicines to the clinic**, **including lack of regulatory clarity**.

Pre-clinical evidence needs **to be robust,** using several methods to fully characterize nanomedicines, understand the properties essential for function, and to demonstrate their efficacy in multiple in vitro and in vivo models.

Nevertheless, **we are positive** about the future direction of the field and believe that **the great promise will ultimately be realized**.

References



REVIEWS

Check for updates

Multifunctional biomolecule nanostructures for cancer therapy

Jing Wang[1,2,5], Yiye Li[1,2,5] and Guangjun Nie[1,2,3,4]✉

Abstract | Biomolecule-based nanostructures are inherently multifunctional and harbour diverse biological activities, which can be explored for cancer nanomedicine. The supramolecular properties of biomolecules can be precisely programmed for the design of smart drug delivery vehicles, enabling efficient transport in vivo, targeted drug delivery and combinatorial therapy within a single design. In this Review, we discuss biomolecule-based nanostructures, including polysaccharides, nucleic acids, peptides and proteins, and highlight their enormous design space for multifunctional nanomedicines. We identify key challenges in cancer nanomedicine that can be addressed by biomolecule-based nanostructures and survey the distinct biological activities, programmability and in vivo behaviour of biomolecule-based nanostructures. Finally, we discuss challenges in the rational design, characterization and fabrication of biomolecule-based nanostructures, and identify obstacles that need to be overcome to enable clinical translation.

pharmaceutics

MDPI

Review

Emerging Nano-Carrier Strategies for Brain Tumor Drug Delivery and Considerations for Clinical Translation

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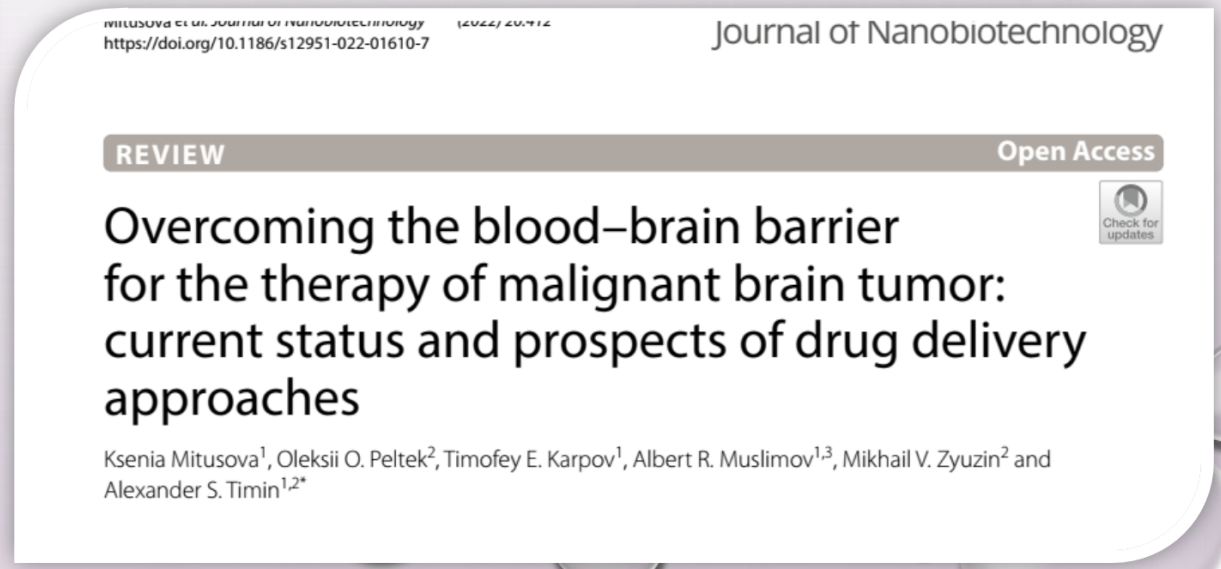

https://doi.org/10.1186/s12951-022-01610-7

Journal of Nanobiotechnology

REVIEW Open Access

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Overcoming the blood–brain barrier for the therapy of malignant brain tumor: current status and prospects of drug delivery approaches

Ksenia Mitusova[1], Oleksii O. Peltek[2], Timofey E. Karpov[1], Albert R. Muslimov[1,3], Mikhail V. Zyuzin[2] and Alexander S. Timin[1,2*]

Thank You

Have a Safe &
Happy Thanksgiving!