INTERNATIONAL BRAIN

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RESEARCH ORGANIZATION

IBRO-APRC Georgian Associate School of Neuroscience

Tbilisi, Georgia
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IBRO-APRC Georgian Associate School of Neuroscience

الجامعة الإسلامية العالمية ماليزيا
INTERNATIONAL ISLAMIC UNIVERSITY MALAYSIA
Garden of Knowledge and Virtue

Considerations of Drug Formulations to Overcome the Blood Brain Barrier

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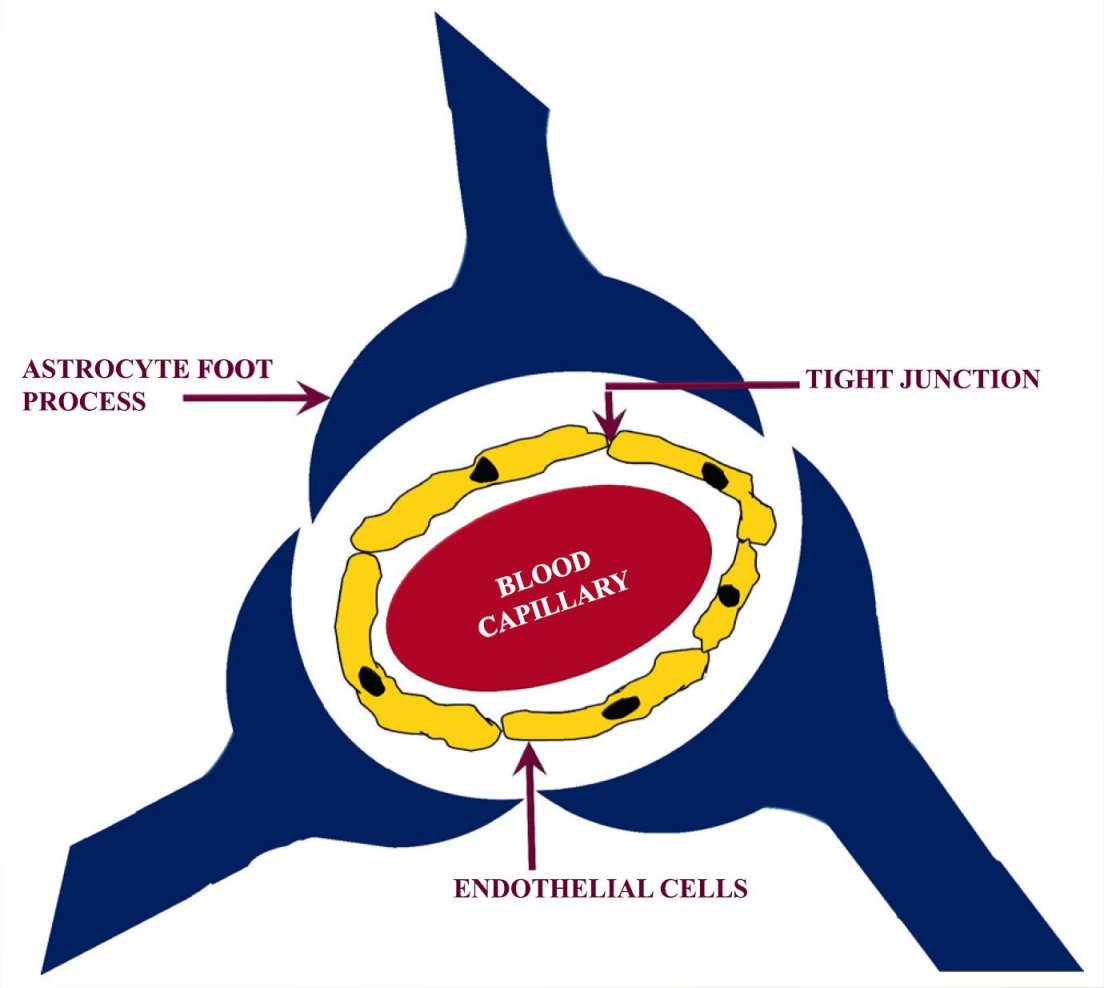
BLOOD–BRAIN BARRIER (BBB)

- BBB restricts the permeation of most drugs to the central nervous system (CNS).
- Despite the ability of a therapeutic molecule to achieve the therapeutic effect, its in vivo medical application is not met.
- The systemic administration of the drugs is often challenged by a well-versed biological impediment: the blood–brain barrier (BBB).

BBB…

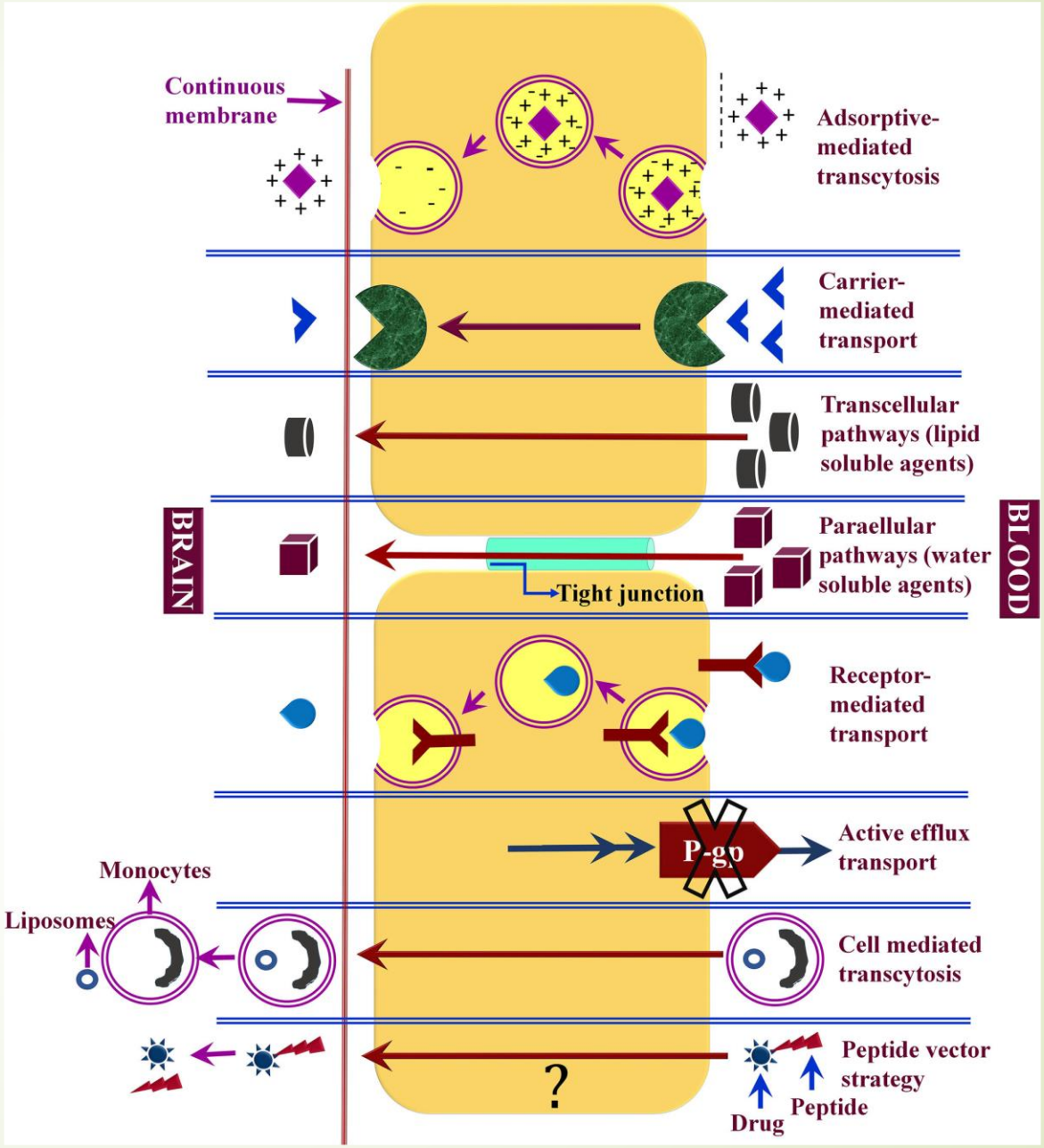
- Although the BBB is crucial for maintaining brain health against harmful and toxic agents that exist in blood, it also blocks the penetrance of many drugs.
- It is also the main reason why treatments for cancer that work elsewhere in the body fail routinely when directed at the brain.



Schematic representation of BBB

BBB…

- The passage of molecules across the BBB relies primarily on their structure, surface properties, and chemical composition.
- Only small molecular weight drugs (<400–500 Da) and lipophilic in nature can reach into the brain.
- Traversing the BBB is a particular challenge for the large, lipid-insoluble biological drugs.



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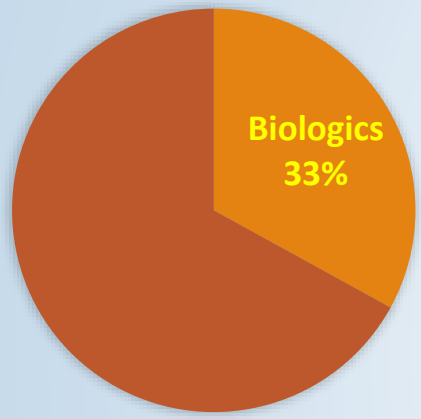
BBB…

Over 98% of small-molecule drugs and nearly 100% of large-molecule drugs such as recombinant proteins and monoclonal antibodies cannot enter the brain.



A 33% of the total new drugs approved by FDA in 2019 were biologic drugs: antibody-drug conjugates, an antisense oligonucleotide therapy, and a therapy based on RNA interference (RNAi).

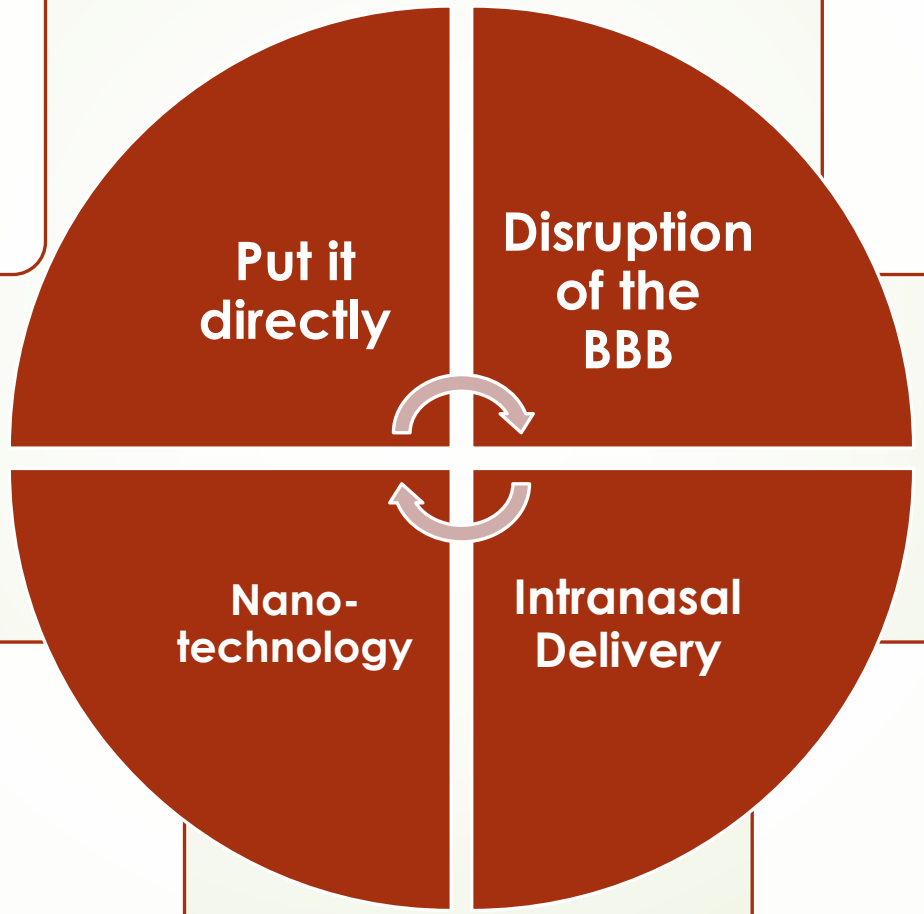
Figure 2: Percentage of Biologics Approved as New Molecular Entities (NMEs) by FDA's CDER, 2016–2020.

25%	21%	29%	26%	32%
2020: 53 NMEs approved: 13 were biologics	**2019**: 48 NMEs approved: 10 were biologics	**2018**: 59 NMEs approved: 17 were biologics	**2017**: 46 NMEs approved: 12 were biologics	**2016**: 22 NMEs approved: 7 were biologics

Biologic approvals include those approved as new molecular entities via an original biologics license application (BLA) by the US Food and Drug Administration's Center for Drug Evaluation and Research.

Source: US Food and Drug Administration's Center for Drug Evaluation and Research

HOW TO GO THROUGH THE BBB?



- Gliadel wafer
- Catheter infusion

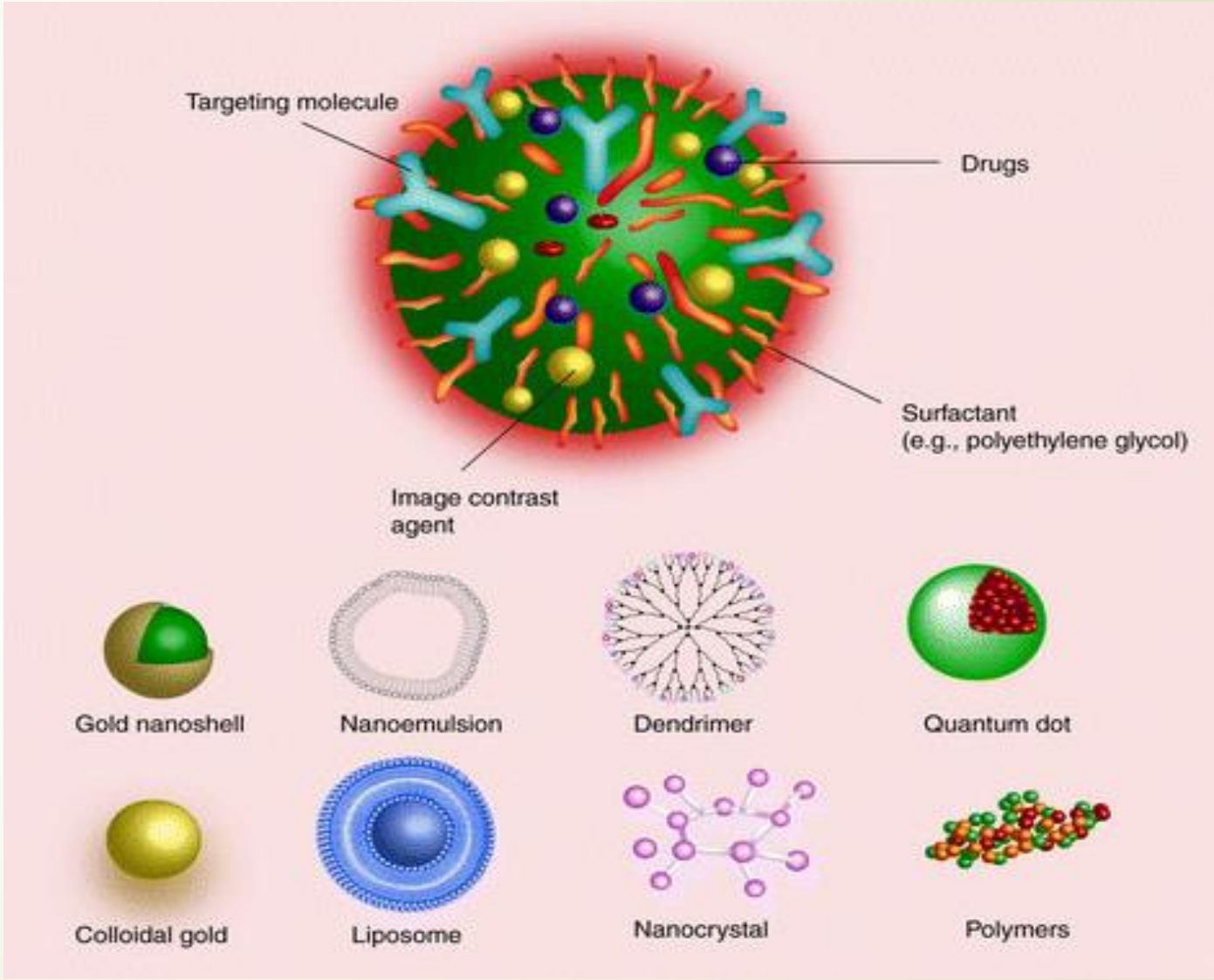
- Osmotic Shock
- Biochemical
- Alkylglycerols
- Ultrasound

- Liposomes
- Nanoemulsion
- Solid lipid nanoparticles
- Nanogel
- Polymer nanoparticles

- Solutions
- Hydrogel
- Nonomaterials

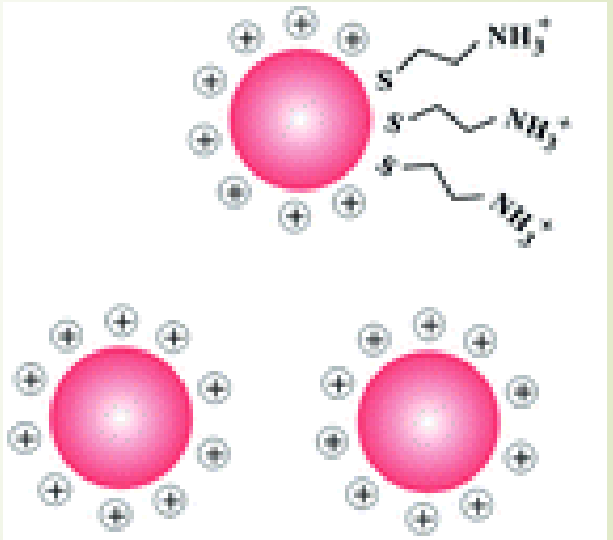
NANOPARTICLE DELIVERY TO THE BRAIN

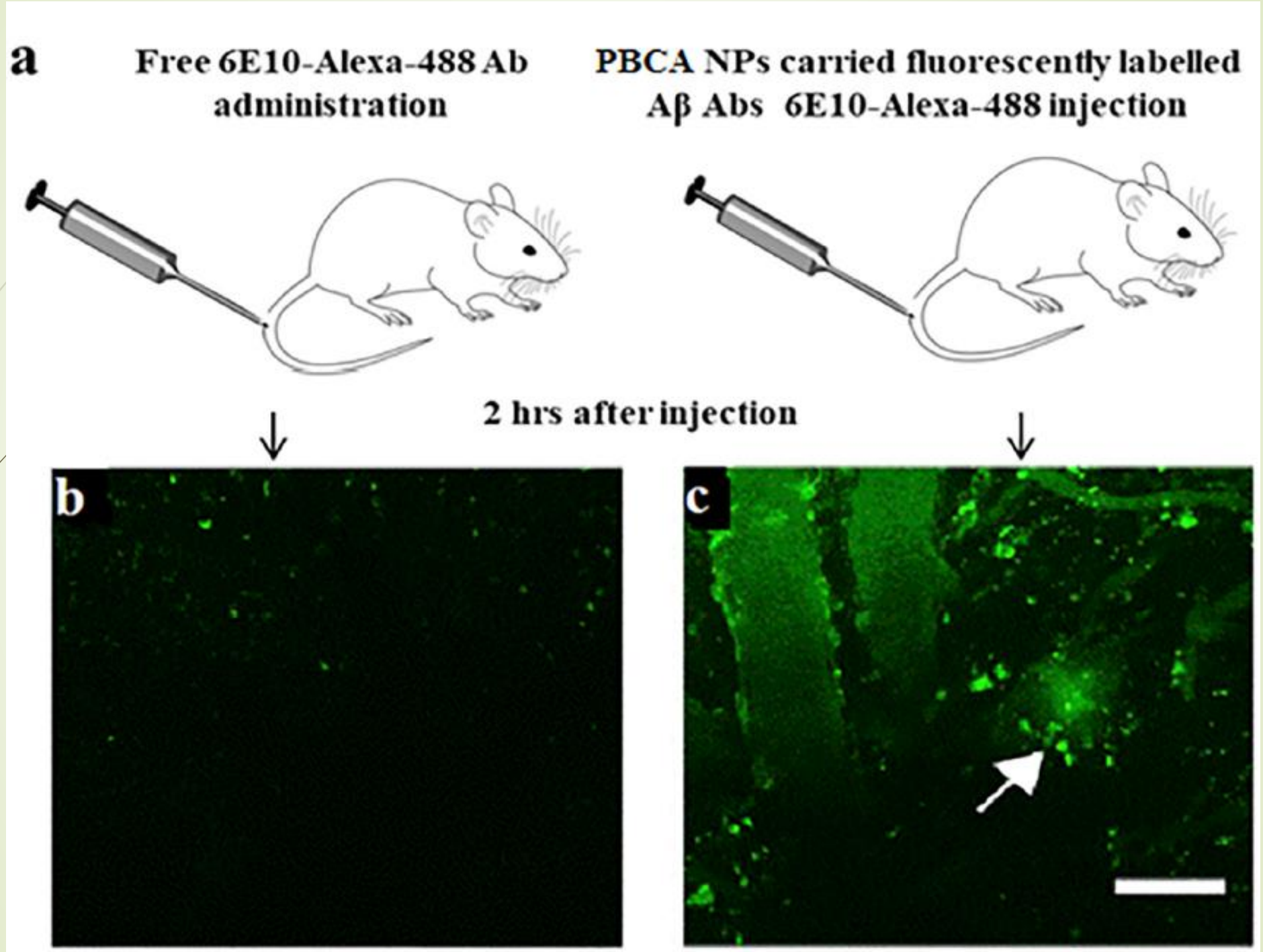
- Nanoparticles loaded with drugs (small molecules or macromolecules) have been intensively studied for the treatment of brain diseases with various successful rates in animal models.
- To cross the BBB, the surface of NPs has been crafted with various kinds of molecules to recognize the receptors and transporters expressed on BBB.



Nanoparticle delivery to the brain…

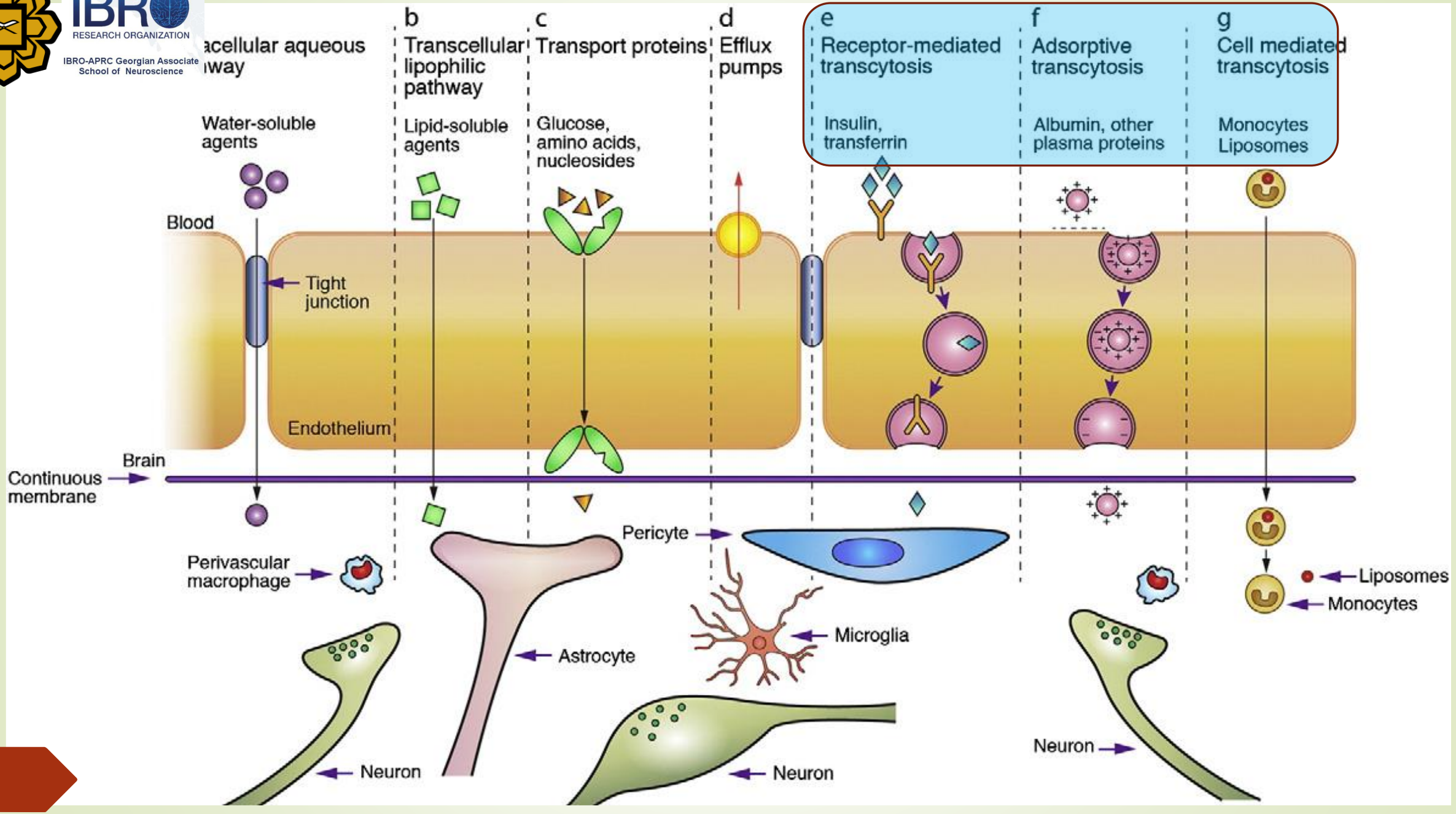
- Highly positive NPs were found to cross BBB.
- Cell penetrating peptides and positively charged albumin proteins were often used to coat NPs to enable electrostatic attachment to BBB and penetration.
- **Receptor-mediated transcytosis** is another way that NPs can cross BBB.




a
Free 6E10-Alexa-488 Ab
administration
PBCA NPs carried fluorescently labelled
Aβ Abs 6E10-Alexa-488 injection
2 hrs after injection
b
c

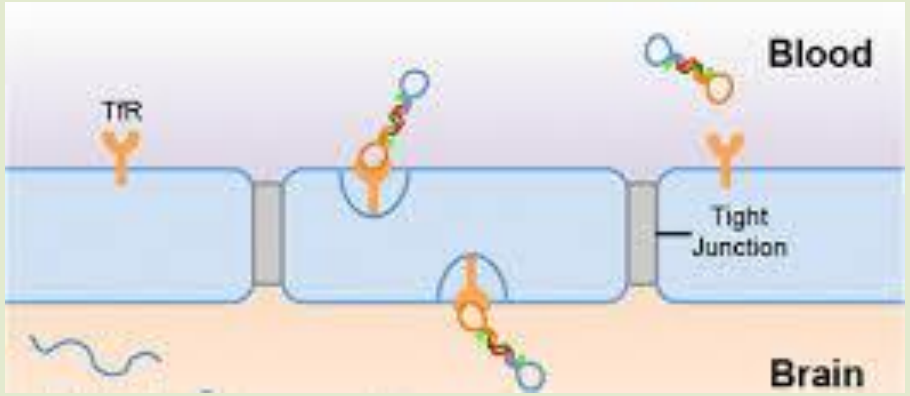
Cellular pathways for nanoparticle uptake by BBB

- It is well known that BBB communicates with the outer surface and obtains its nutrients by means of a highly regulated pathway, i.e. endocytosis.
- Such endocytic pathways include fluid-phase endocytosis, receptor mediated endocytosis and adsorptive endocytosis.
- Receptor mediated and adsorptive mediated endocytosis is the most explored modes for nano-formulation



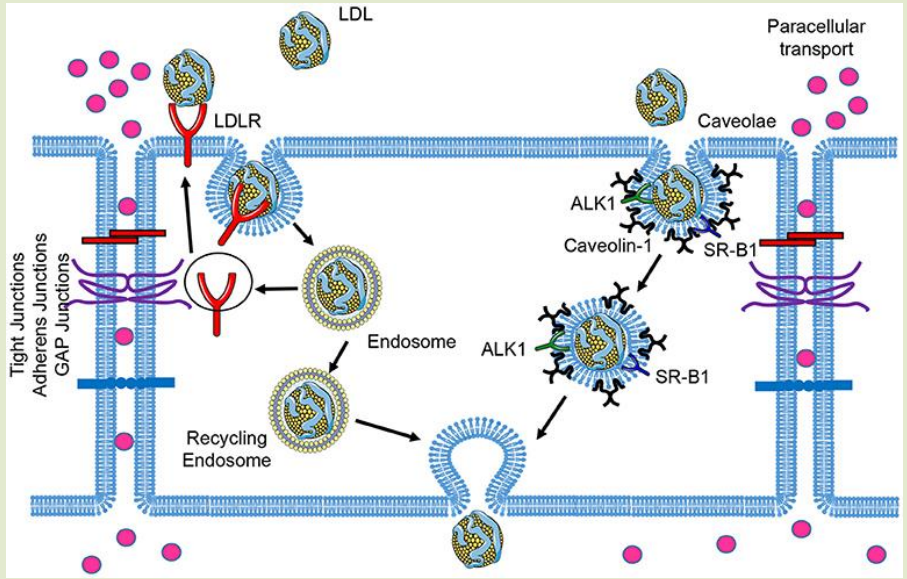
Receptor mediated transcytosis

1. Transferrin receptor (TfR) mediated transcytosis



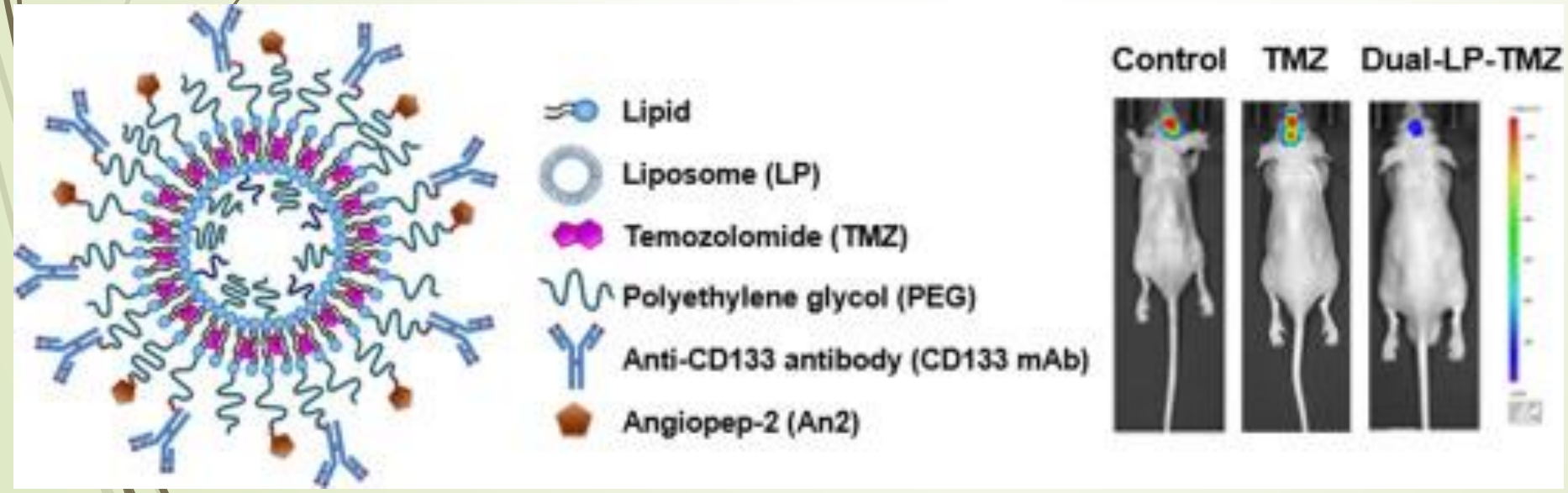
- High expression level of iron-transferrin receptors on brain endothelium, as opposed to peripheral endothelium.
- transferrin (Tf) functionalized fluorescein-loaded magnetic NPs were found located in the dendrites, synapse of neurons, cytoplasm and axons, indicating that they can efficiently cross the intact BBB through TfR (Yan et al., 2013).
- Since in physiological conditions, majority of TfR are saturated due to endogenous proteins, the use of mAbs, such as OX26, 8D3, T7 peptide, MYBE/4C1 and R17217, are suggested

2. Low density lipoprotein (LDL) receptor mediated transcytosis



- Apolipoprotein E (apoE) is responsible for transporting several nutrients into the blood.
- Polysorbate-80 coated poly(butylcyanoacrylate) (PBCA) NPs binds to apoE of blood plasma and interacts with LDL receptor on cerebral endothelial cells, serving as a drug delivery system.
- Two-to-twelve-fold increased uptake and decreased side effects of rivastigmine and temozolomide (TMZ) loaded polysorbate-80 NPs were reported for the treatment of AD and brain tumor, respectively (Tian et al., 2011; Wilson et al., 2008).

- Another most explored receptor mediated transcytosis via LDL receptors is angiopep-2 based ligand,
- It is present not only on BBB but also on brain cancer cells and neurons with Aβ peptide (Ulery et al., 2000).
- Thus, NPs functionalized with angiopep-2 can act as a specific ligand for LDL receptor related protein (LRP) and accomplish dual targeting i.e.,
  - first crossing BBB and thereafter
  - targeting the drug loaded NPs to the site expressing higher levels of LRP

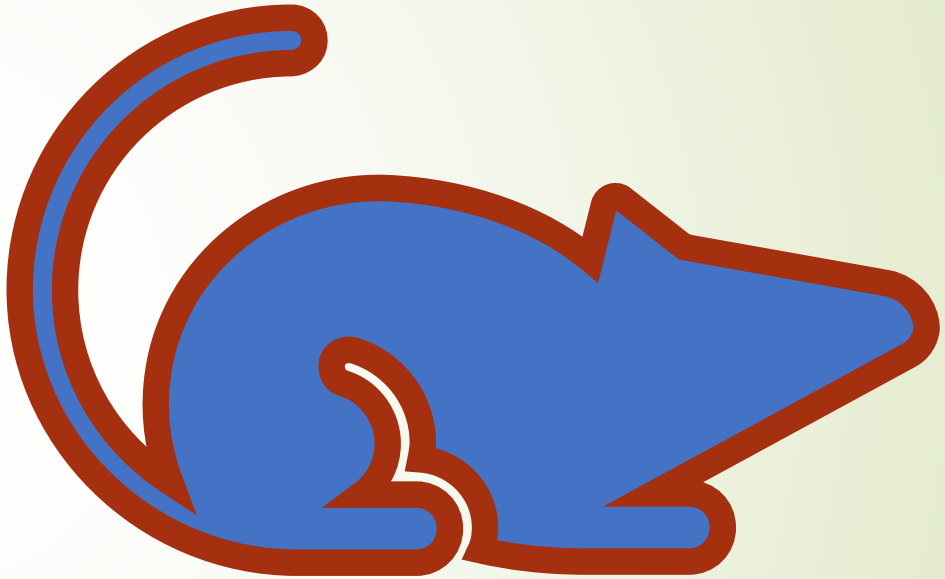


3. Nutrient receptors/transporter mediated transcytosis

- D-glucose transporter proteins are among the most abundant nutrient transporters present in brain micro vessels and glioma cells.
- Modification of poly(ethylene glycol)−poly(trimethylene carbonate) (PEG−PTMC) NPs by 2-deoxy-D-glucose served as a potential dual drug targeting delivery system and resulted in increased uptake of paclitaxel by glioma cells (Jiang et al., 2014).

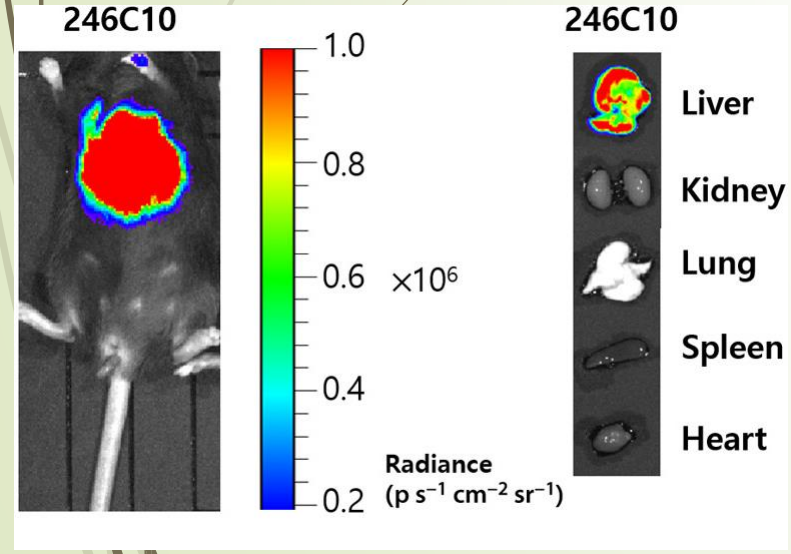
Insulin receptor mediated transcytosis

- In an *in vivo* study, intravenous administration of human serum albumin (HAS) NPs covalently attached with insulin or monoclonal antibody for antiinsulin receptor (29B4) demonstrated successful transport of loperamide across BBB (Ulbrich et al., 2011).



MPS (Mononulcear Phagocytic System)

BEFORE CONCLUSION, LET US NOT FORGET…



- The major barrier for nanoparticulate delivery systems.
- If not especially designed to escape from the MPS uptake, intravenously administered NPs are rapidly cleared from the blood stream (blood half-lives are generally in minutes) and mostly accumulate in liver and spleen.
- It is generally admitted that opsonization, the first step for MPS recognition, is favored by hydrophobic surfaces.
- In contrast, hydrophilic coating sterically stabilizes NPs and reduces opsonization and MPS uptake.
- To avoid the MPS uptake, size below 100 nm is preferred.

CONCLUSION

- In conclusion, with the emerging of biological drugs as effective therapeutic molecules, new advanced delivery systems are needed to facilitate the BBB penetration for effective clinical outcome.
- Nanomedicine designed to target specific receptors in the BBB has the potential to cross the BBB and deliver the cargo inside the brain.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Thank You