
بسم الله الرحمن الرحيم

Neuropharmacokinetic:

Transport of Drugs Across The Blood–Brain Barrier by **Nanocarriers**

By:

Mehrdad Hamidi, *Pharm.D., Ph.D.*

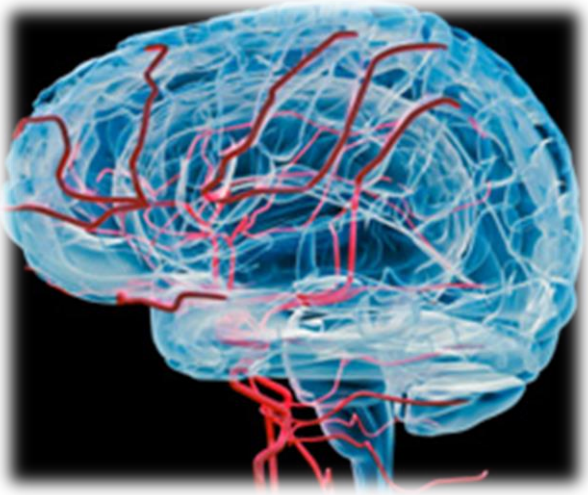
Professor of Pharmaceutics and Dean
Zanjan School of Pharmacy
Zanjan, IRAN

hamidim@zums.ac.ir

Drug delivery to brain

The blood circulation is the most important gateways to enter brain parenchyma.

- 20% of cardiac output goes to the brain
- 600 km of capillaries
- 20 m^2 surface area
- 1 km blood vessel per cm3

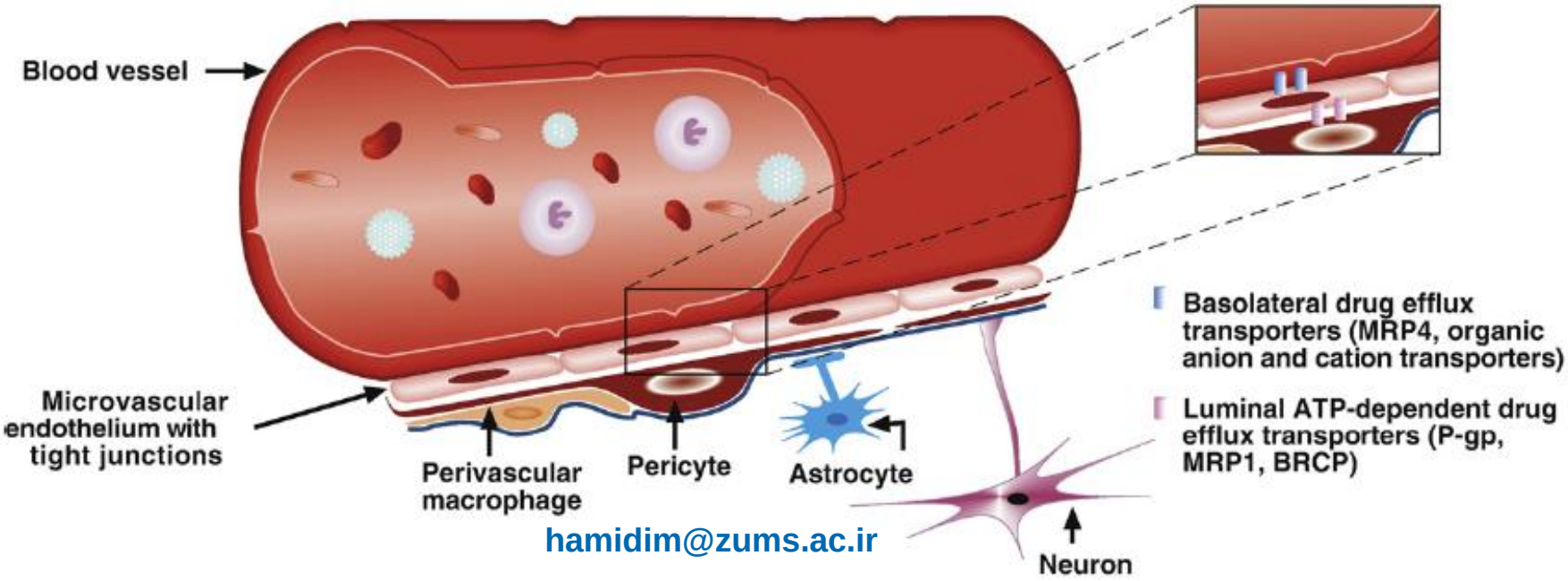


hamidim@zums.ac.ir

Blood-Brain Barrier

The blood–brain barrier (BBB) is a dynamic barrier protecting the brain against invading organisms and unwanted substances.

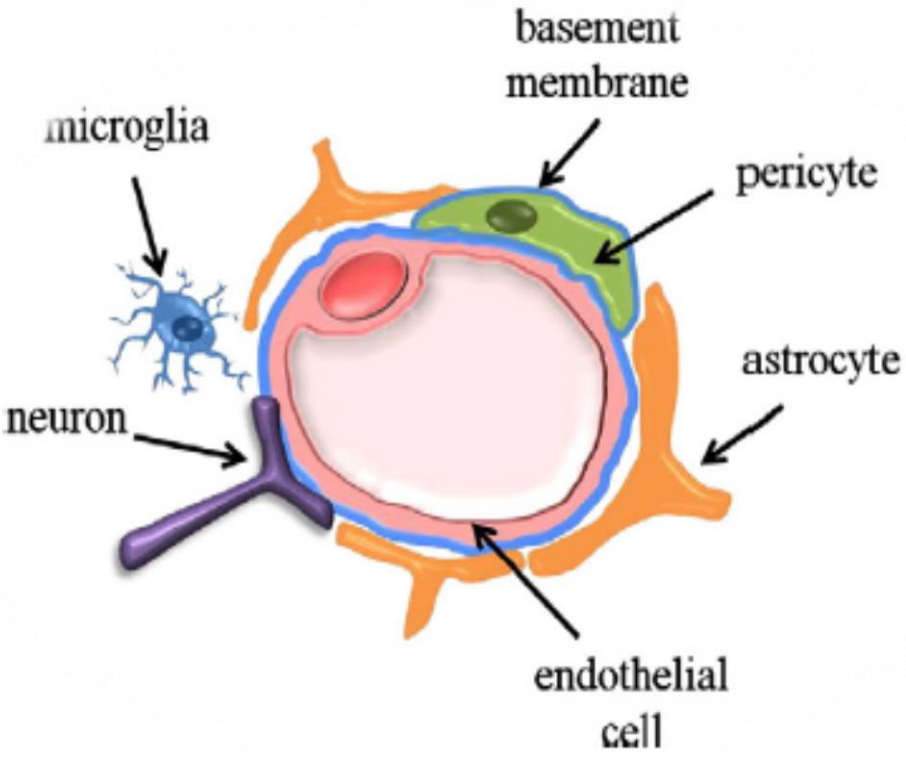
- ✓Physiology of BBB
- ✓Transport routes across the BBB
- ✓Available delivery technologies



hamidim@zums.ac.ir

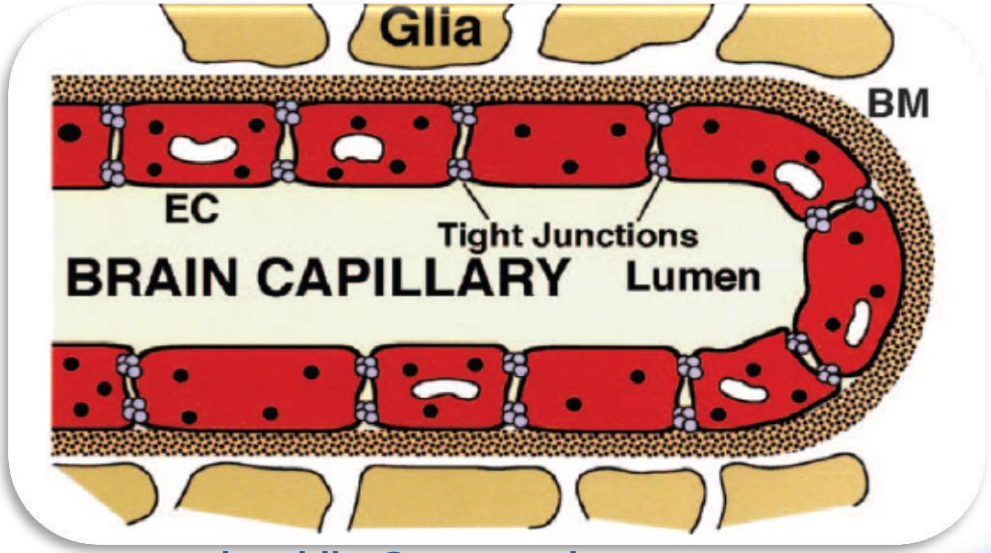
Neurovascular unit

- Brain microvascular endothelial cells (BMVEC)
- Basement membrane
- Microglia
- Astrocytes
- Pericytes
- Neuron



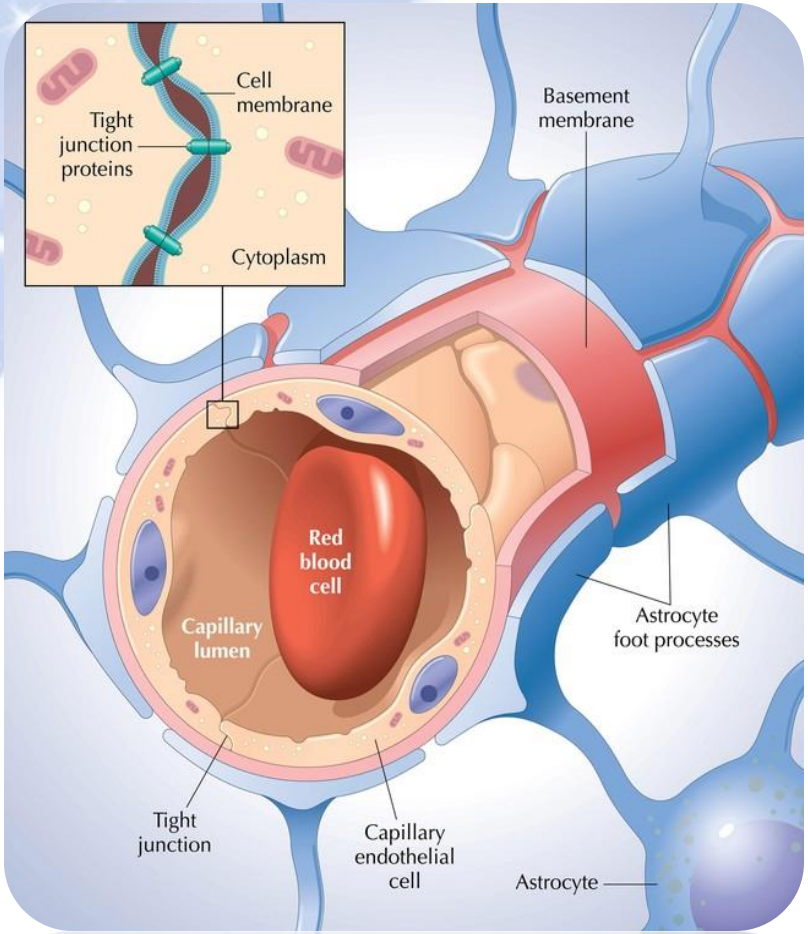
Neurovascular unit: Endothelial cells

- Key role in BBB properties
- High electric impedance
- Interact intimately with other brain cells of the NVU
- 50–100 times tighter than peripheral microvessels
- Uniform thickness with no fenestrae, low pinocytotic activity and a continuous basement membrane of EC cytoplasm
- Higher number and volume of mitochondria



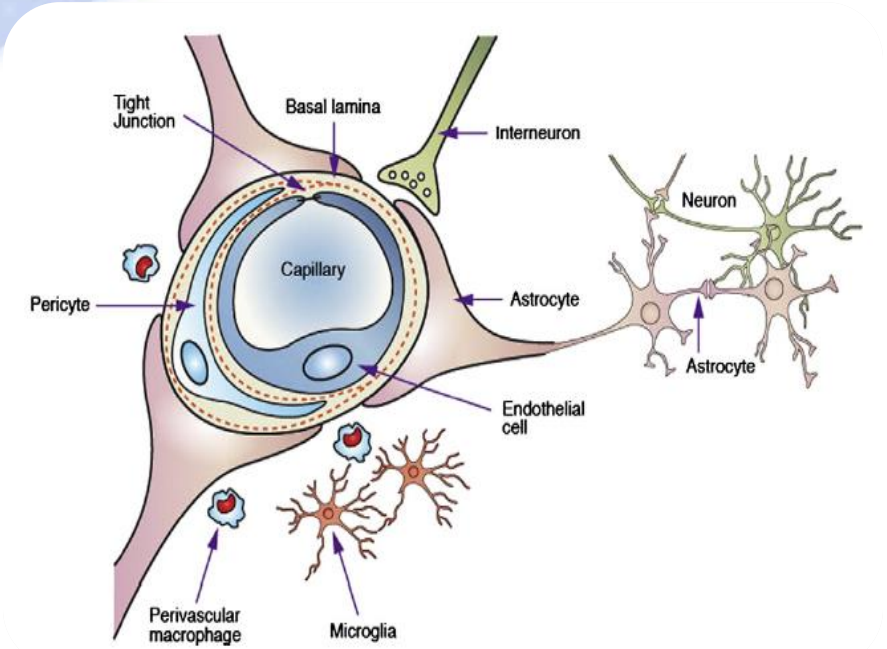
hamidim@zums.ac.ir

Neurovascular unit: Basement Membrane



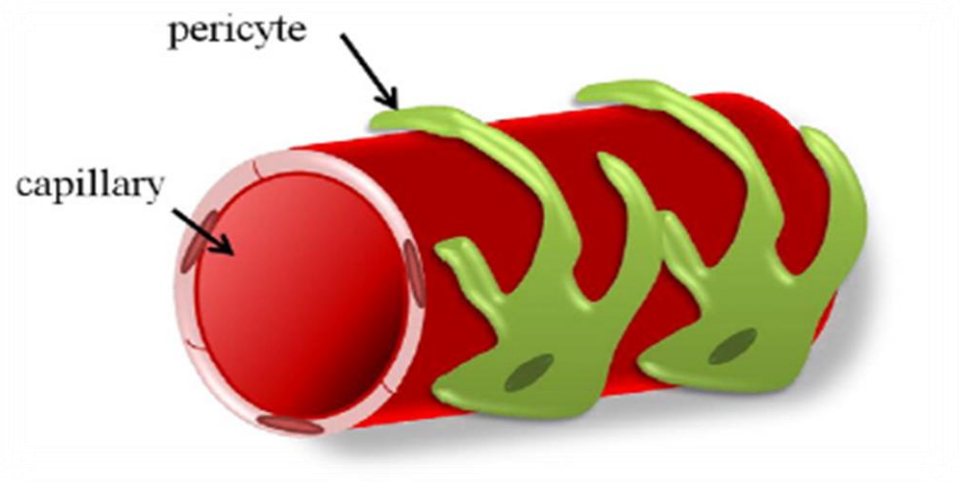
- Essential part of the BBB
- Surrounds BMVEC
- Engulfs pericytes
- Composed of different extracellular matrix classes of molecules:
  - Structural proteins (collagen and elastin),
  - Specialized proteins (fibronectin and laminin)
  - Proteoglycans

Neurovascular unit: Microglia



- Play a very important role in immune responses of the CNS
- Surveying local microenvironment
- Changing the phenotype in response to homeostatic disturbance of the CNS
- Present in two forms: resting and activated microglia.

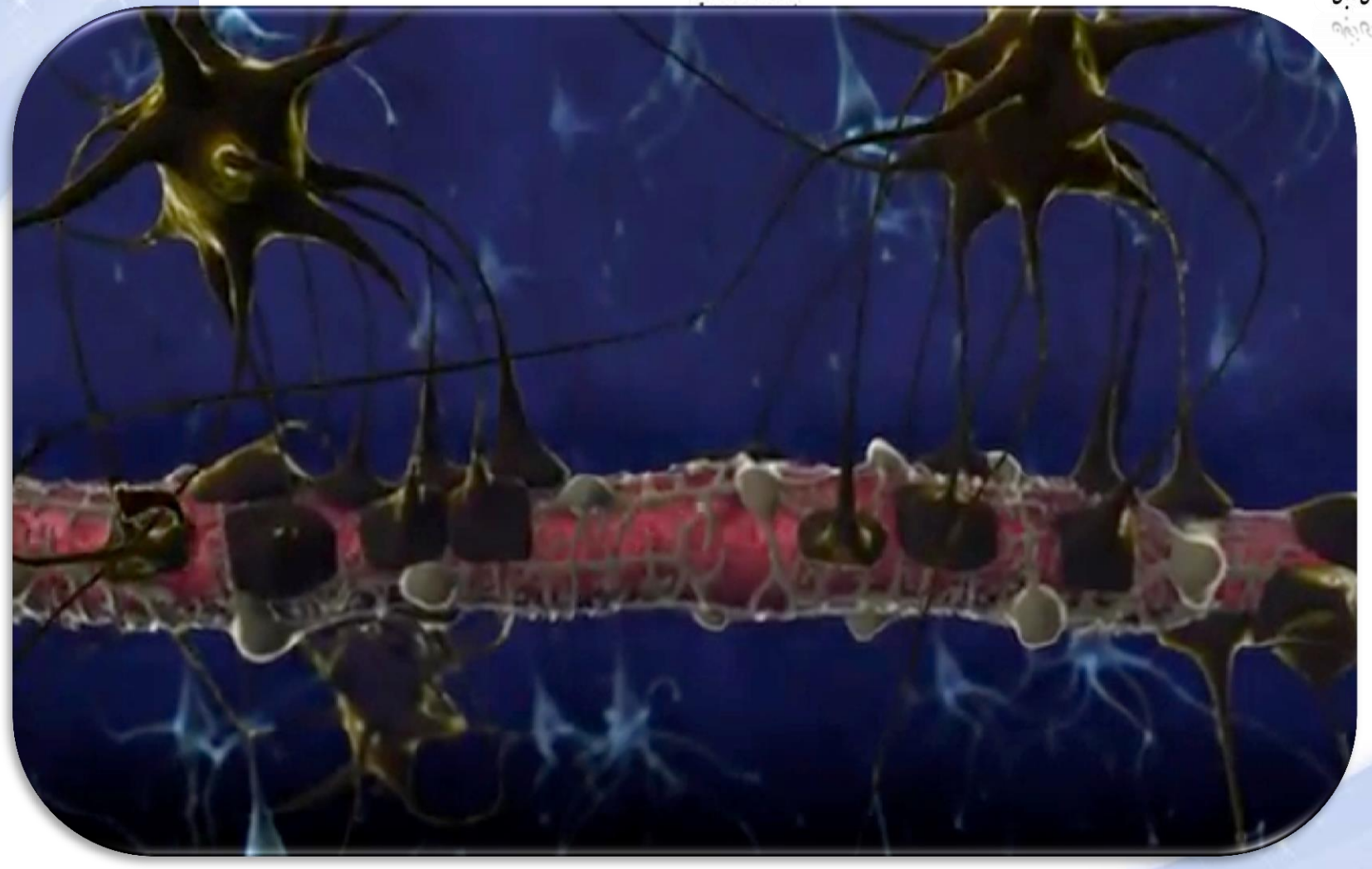
Neurovascular unit: Pericytes



- Cover 22 to 32% of the capillaries
- Synthesizes most elements of the basement membrane (proteoglycans)
- Essential to maintain structural support and junctional integrity

hamidim@zums.ac.ir

Neurovascular unit: Astrocyte



hamidim@zums.ac.ir

The unique biological characteristics of BBB

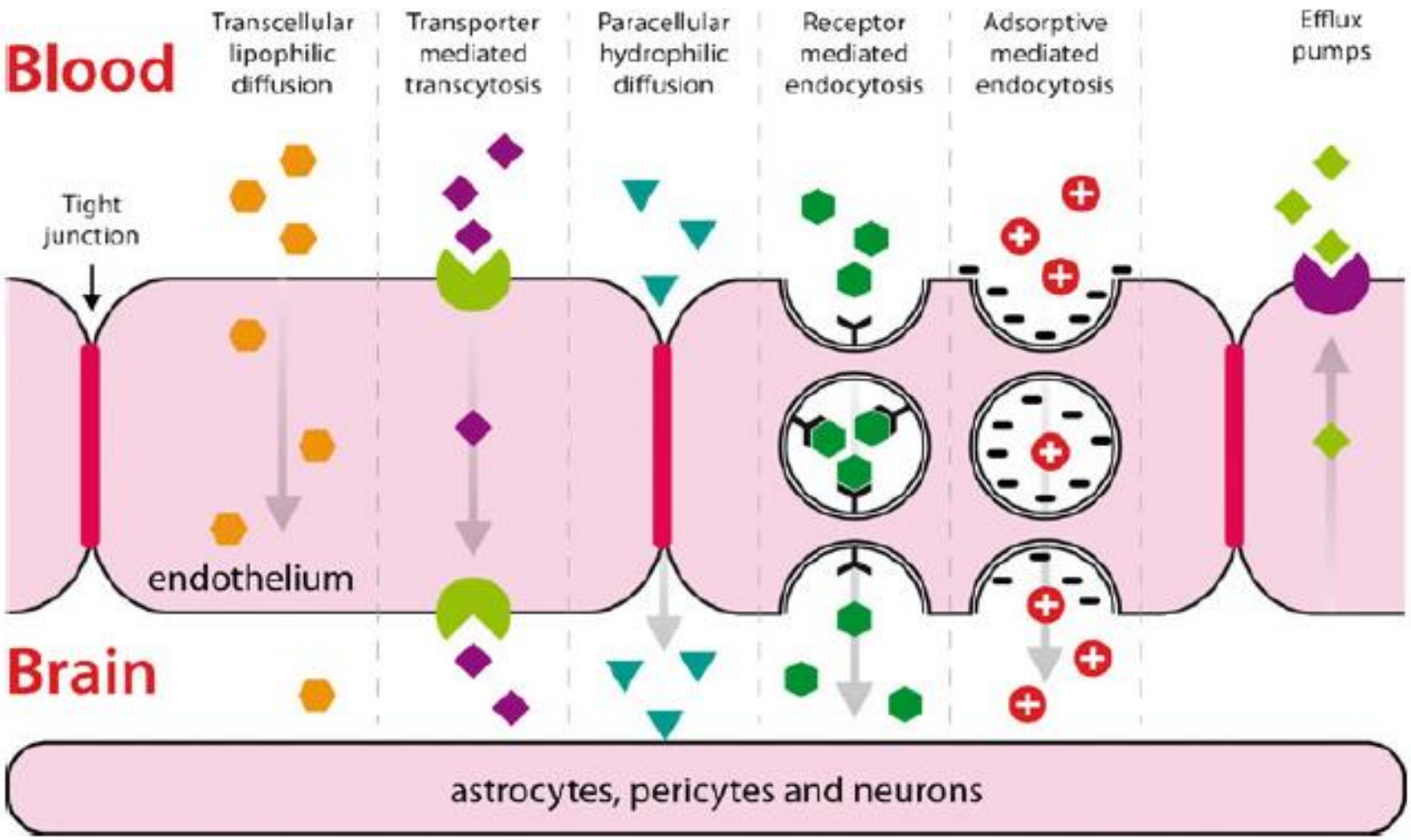
1. The lack of fenestrations , very few pinocytotic vesicles, higher number and volume of mitochondria in endothelial cells

2. The presence of tight junctions (TJ) between adjacent endothelial cells

3. The expression of various transporters including:
- GLUT1 glucose carrier
- amino acid carrier LAT1
- transferrin receptors
- insulin receptors
- lipoprotein receptors
- ATP family of efflux transporters such as p-glycoprotein and MRPs

4. The synergistic inductive functions and upregulating of BBB features by astrocytes, astrocytic perivascular endfeet, pericytes, perivascular macrophages and neurons.

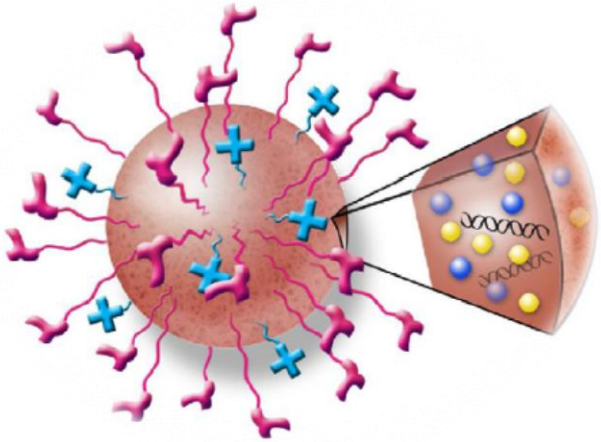
Transport routes across the blood–brain barrier

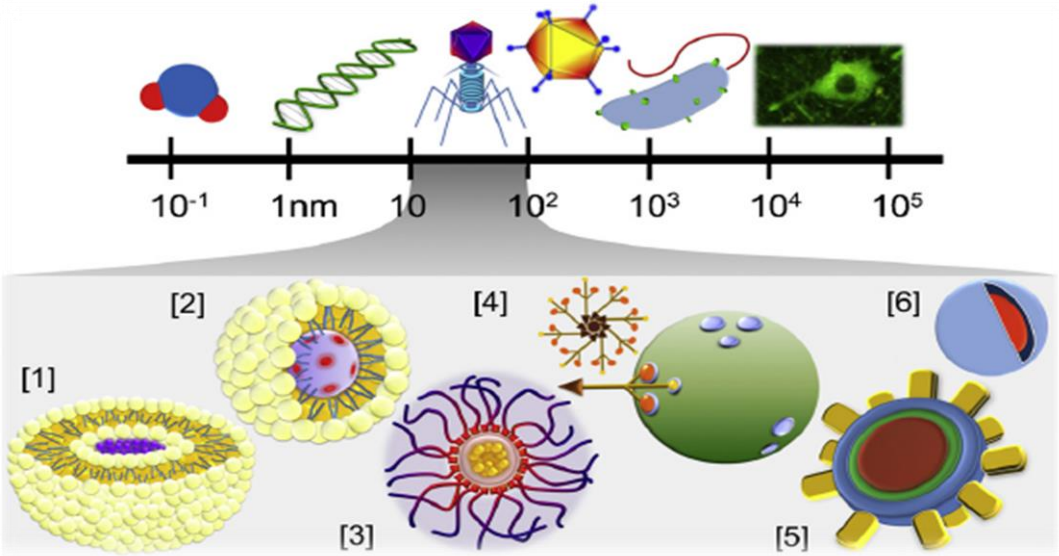


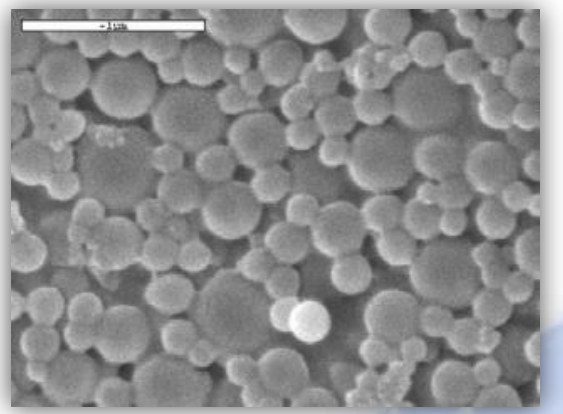
hamidim@zums.ac.ir

Nanocarriers for brain drug delivery

- Mean diameter: 10-200 nm
- Ability of carrying a variety of drugs
- Improved therapeutic agent circulation
- Targeted drug delivery
- Controlled drug release
- High loading capacity
- Co-delivery of more than one therapeutic agent

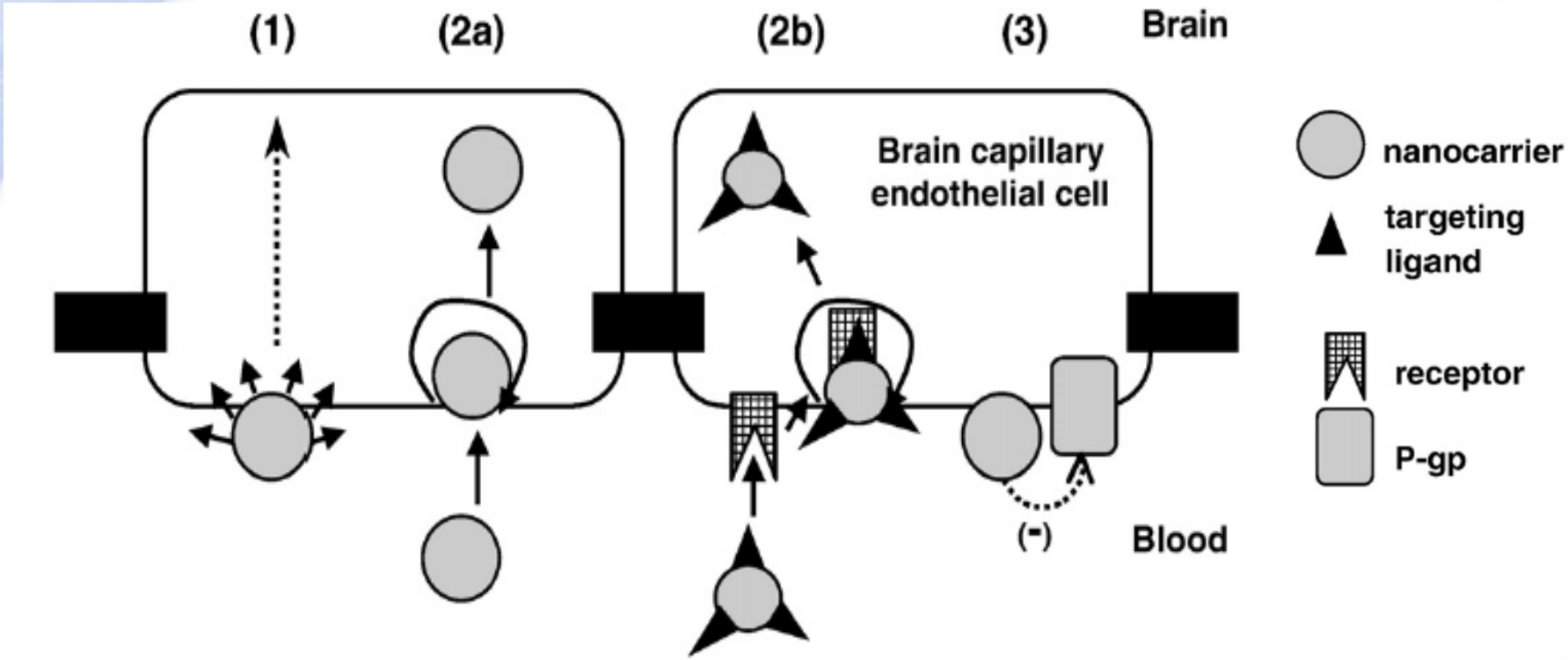






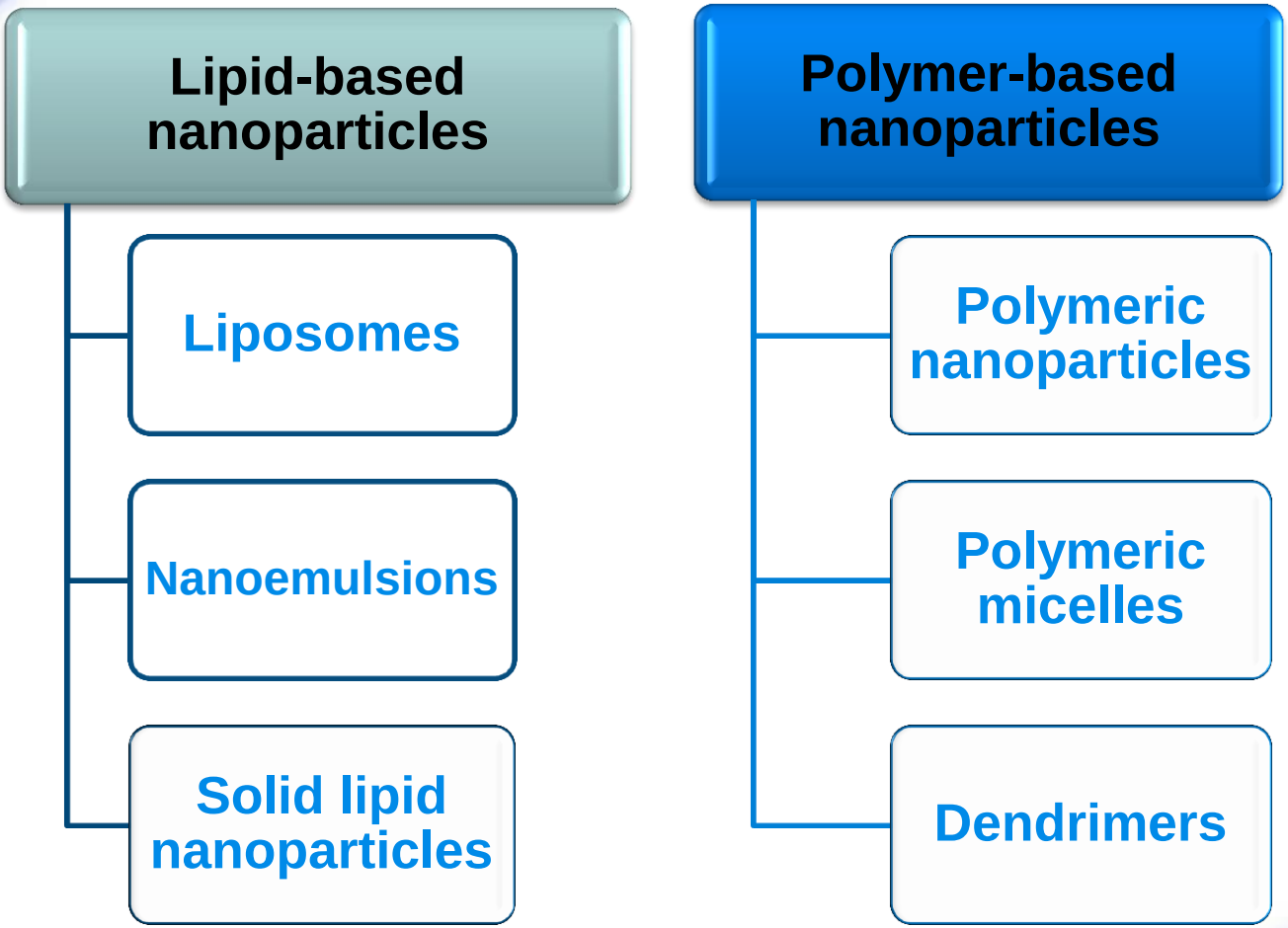
hamidim@zums.ac.ir

Major pathways used by nanocarrier systems to improve drug penetration across the blood-brain barrier



(1) Increasing the local drug gradient at the BBB by passive targeting (2a) and (2b) allowing drug-trafficking by endocytosis (non-specific or receptor-mediated), (3) blocking drug efflux transporters. : inhibitory effect.

Classification of naocarriers for brain drug delivery

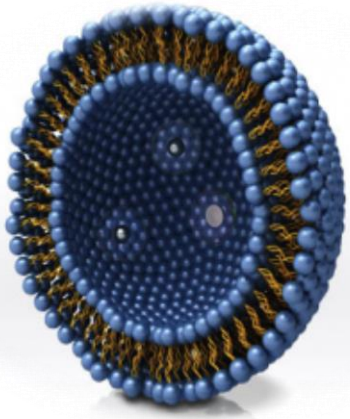


hamidim@zums.ac.ir

Liposomes

- Bilayered vesicles of phospholipids
- Biocompatible and biodegradable
- The most studied colloidal systems; **cancer**, **HIV**, **strokes.**

- Transport by **passive diffusion** through the lipophilic endothelial cells, by **endocytosis** or by **fusion** with brain capillary endothelial cells
- The endocytic pathway for smaller liposomes with diameter not larger than 80–100 nm



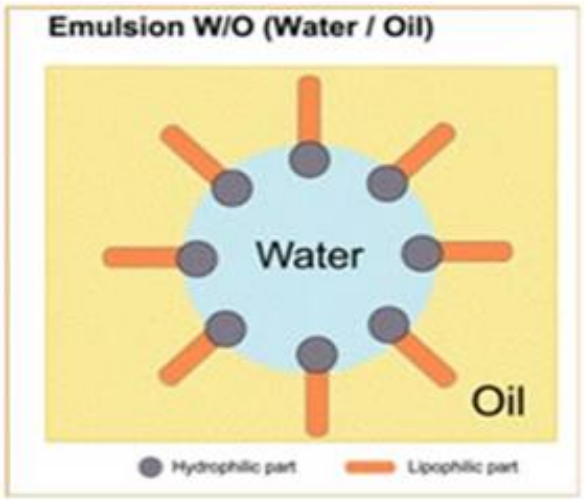
Liposomes (contd.)

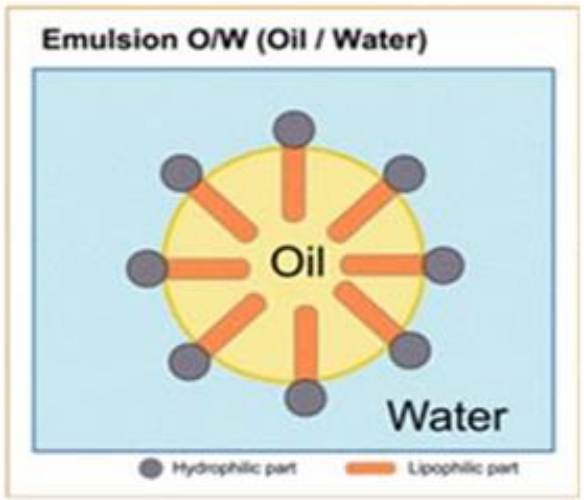
The drawbacks:

- Very fast elimination and degradation when injected into the bloodstream
- The metabolism of lipids which are constituents of the liposomes
- Unable to maintain therapeutic drug concentrations for a prolonged time

Nanoemulsions

- Dispersed systems consisting of nanoscale oil droplets
- In the range of 20–200nm
- Ability of solubilizing lipophilic compounds
- Biocompatible
- The selective uptake of essential polyunsaturated fatty acids, omega-6 fatty acids





hamidim@zums.ac.ir

Solid Lipid Nanoparticles (SLN)

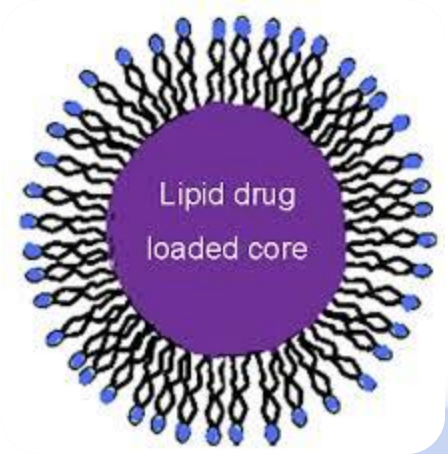
- A matrix of physiological lipid (fatty acids, mono-, di- or triglycerides, glycerine mixtures and waxes)

- Remain solid at room and body temperature

- Solid hydrophobic core containing the drug dissolved or dispersed

- Smaller size (around 10–200 nm) allows them to cross tight endothelial cells of the blood–brain barrier (BBB)

- Escape from the reticuloendothelial system (RES)



Polymeric nanoparticles

- A matrix type, solid colloidal particles
- Drugs can be dissolved, entrapped, encapsulated, chemically bound or adsorbed to the constituent polymer matrix
- Typically larger than micelles
- Having diameters between 100 and 200 nm
- Display more polydispersity

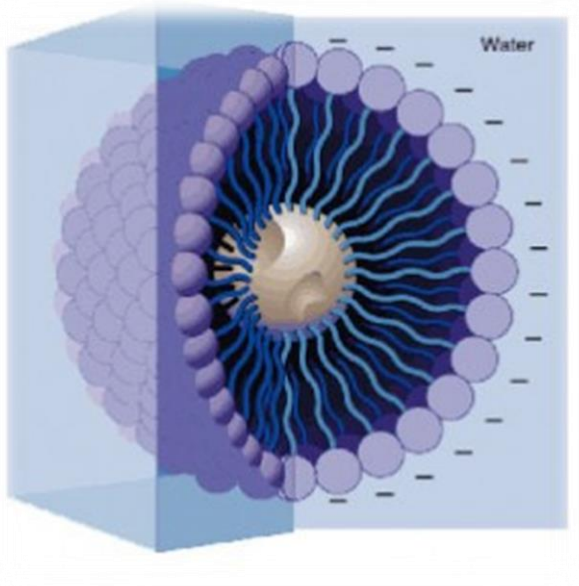
The mechanisms of passing through the BBB:

A central role to endothelial cells in the process of nanoparticle adhesion and subsequent:

- Endocytosis
- Transcytosis
- Tight junction modulation
- P-glycoprotein inhibition

Polymeric micelles

Nanostructures formed by amphiphilic copolymers having an A–B diblock structure with (A) the hydrophilic (shell) and (B) the hydrophobic polymers (core).



Advantages

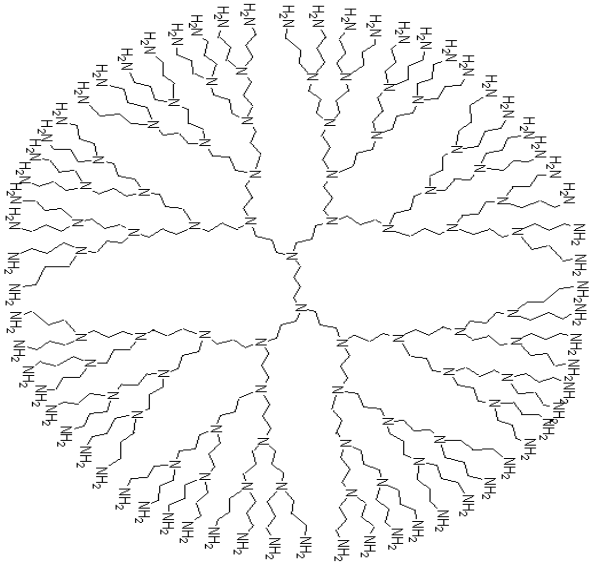
1. Very small size (diameter ; 10-100 nm)
2. High structural stability
3. Large amount of drug loading
4. High water solubility
5. Incorporation of various chemical species
6. Additional crosslinking in the core/shell leads to novel nanostructures with different drug delivery properties
7. Attachment of homing device(s) is possible – biotin, folic acid, antibodies

hamidim@zums.ac.ir

Dendrimers

Dendrimers are globular, nano-scaled macromolecules with a particular architecture constituted of three distinct domains:

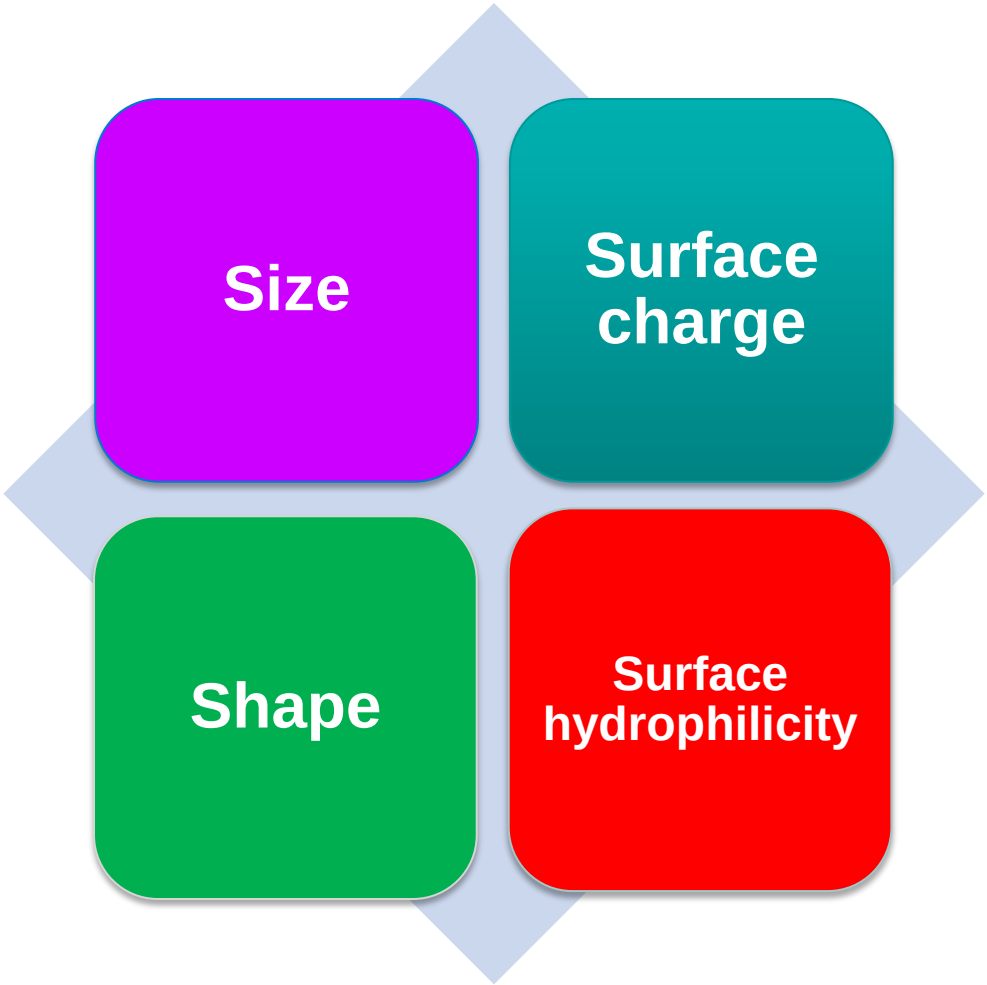
I. A central core: a single atom or a group having at least two identical chemical functionalities
II. Branches composed of repeat units having at least one junction of branching
III. Many identical terminal functional groups



Uptake: polyether-copolyester (PEPE)
dendrimers / Clathrin and aveolin pathway

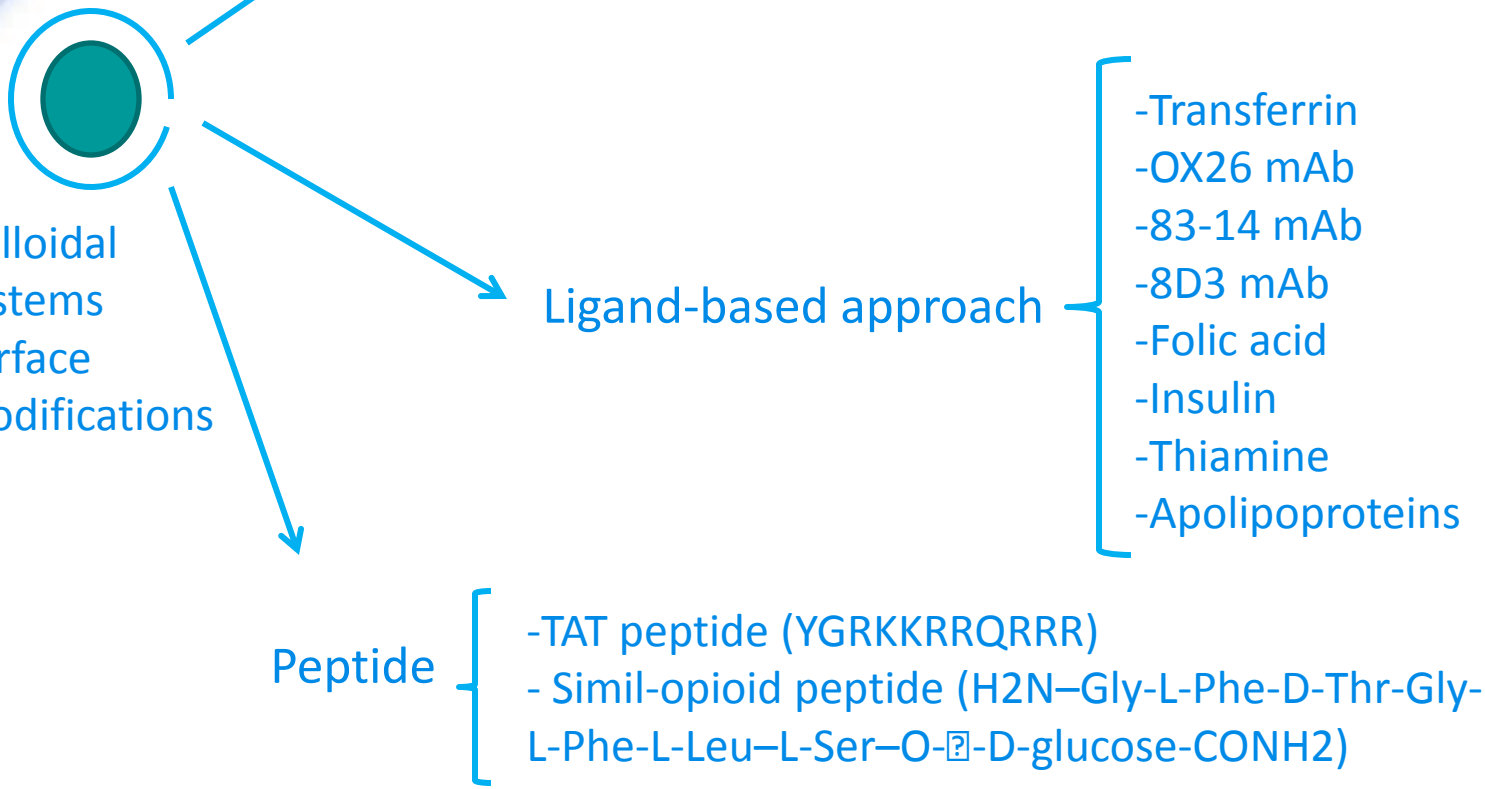
hamidim@zums.ac.ir

Parameters of colloidal systems involved in the interaction with Blood-Brain Barrier



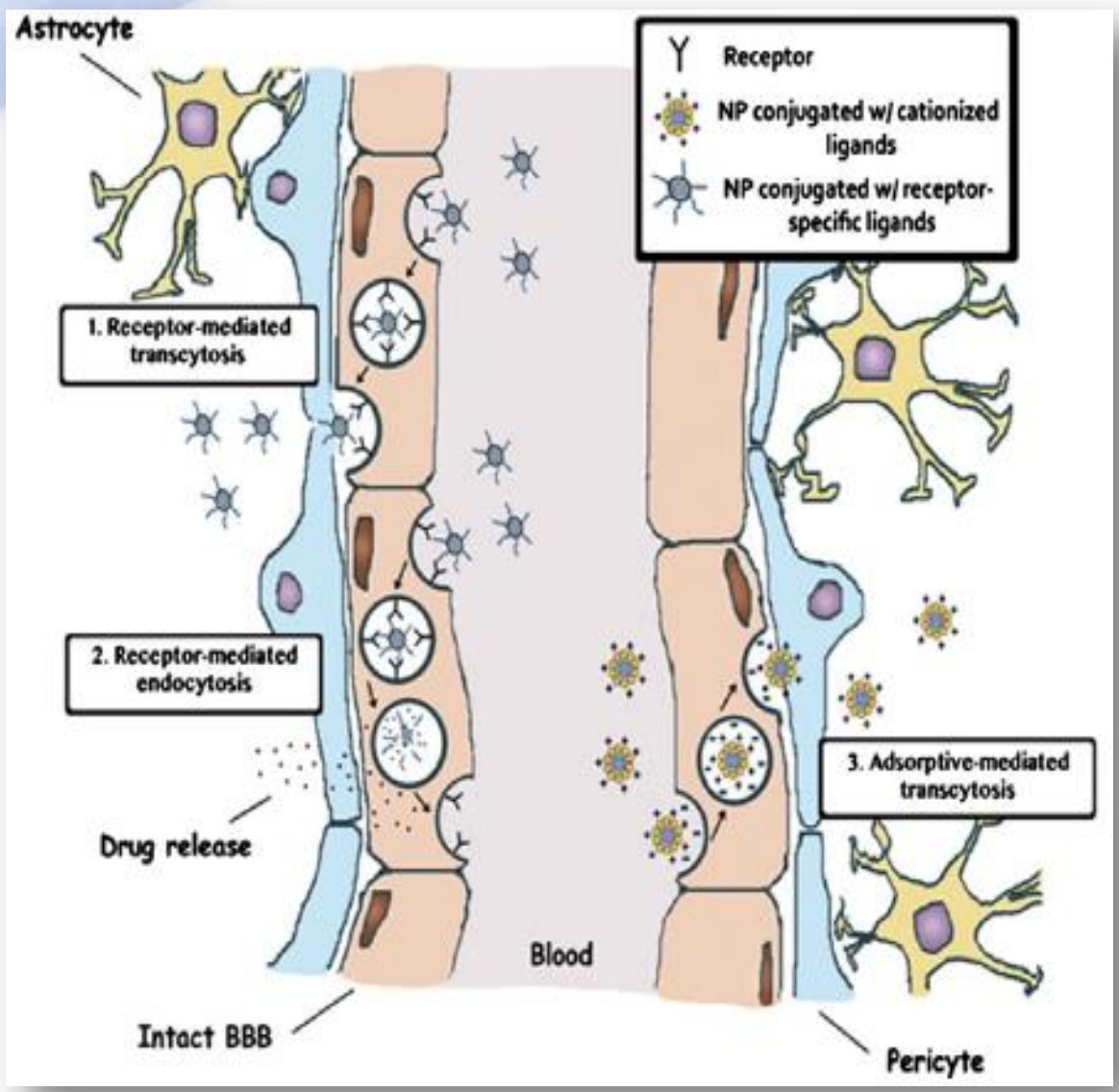
hamidim@zums.ac.ir

Surface modification of colloidal carriers for brain drug delivery



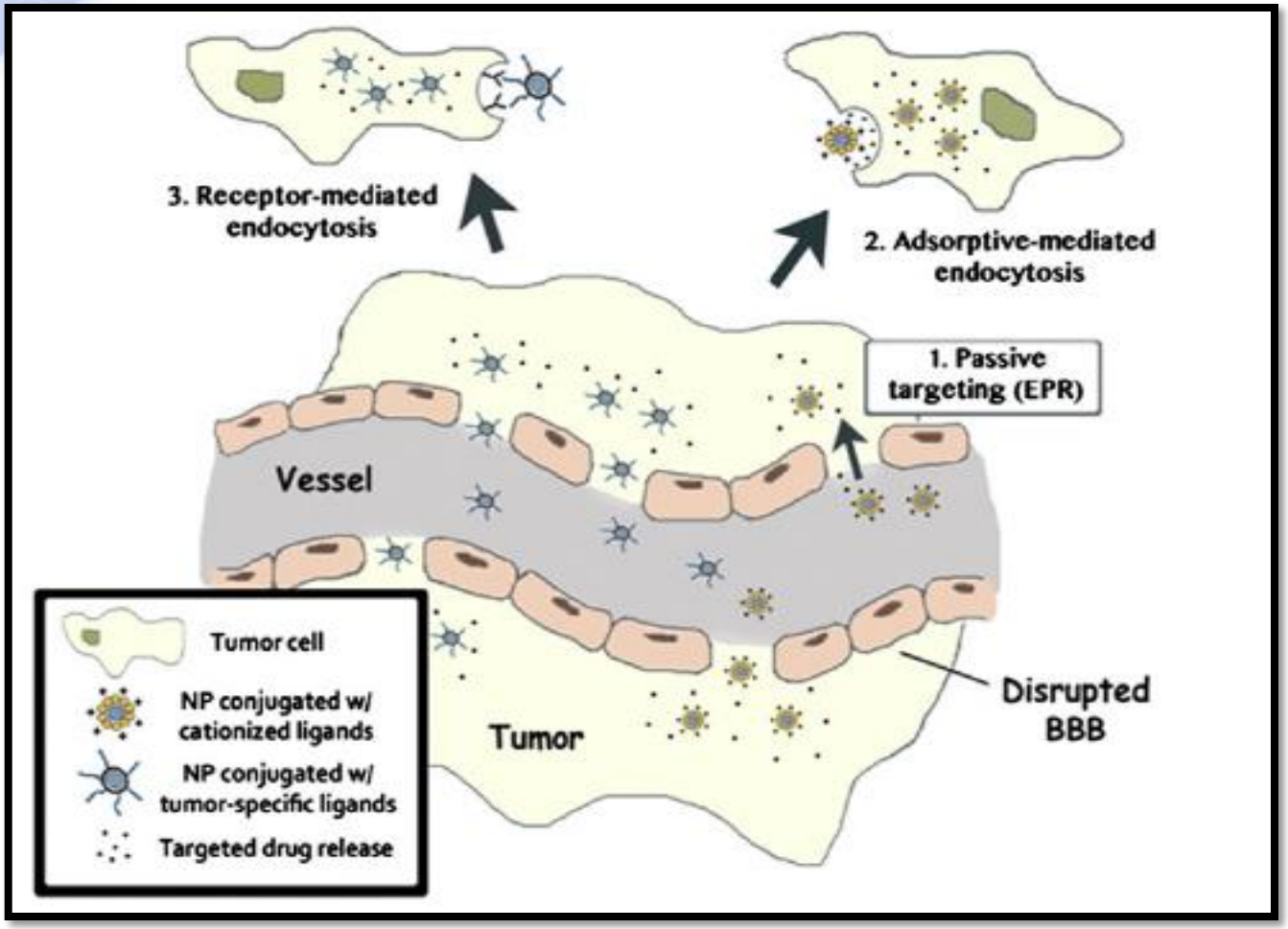
hamidim@zums.ac.ir

Targeted delivery of brain



hamidim@zums.ac.ir

Passive targeting of brain tumors



Lessons learnt so far

1. Different cell types do not behave comparably

2. How much is enough?

3. Specific versus universal?
   Receptor-mediated targeting

4. First comes, first serves!

5. Opsonization – enemy or friend?

hamidim@zums.ac.ir

Neurotoxicity of NPs

○ **Effects on BBB**

- Allowing the brain influx of toxins, vasoactive material, ..
- Entry of proteins, causing edema formation, cell injury and eventually cell death

○ **Effects on neurons**

- Cell shrinkage
- Morphological changes
- Gene expression

○ **Effects on cellular components**

-Impairment in the mitochondrial functions
- Autophagic-lysosomal system
- Cytoplasmic proteins

○ **Effects on glial cells and inflammation in the brain**

-Glial cell activation and heat shock protein upregulation, neuronal cell injuries, astrocyte swelling

Challenges of nanotechnology in neurological disorders

- **The selective passage** of candidate NP-based therapeutic agents cross the BBB is still a challenge.

- Once the drug is inside the brain, it has to be **maintained at a therapeutic level and should not be rapidly degraded**.

- The NP-derived drug should be **effective at a relatively low concentration**.

- **Toxicity** must be taken into consideration of nano-enabled drug delivery systems.

- NPs may invoke **unexpected immune responses**.

- Tissue cells may adapt to NPs, **modifying the behavior of the organ in unforeseen ways**.

Ideal properties of nanocarriers for drug delivery across the BBB

- ✓ Nontoxic, biodegradable and biocompatible
- ✓Particle size less than 100 nm
- ✓Stable in blood (no aggregation and dissociation)
- ✓Prolonged blood circulation time
- ✓Non-immunogenic
- ✓BBB-targeted moiety
- ✓Well maintained parent drug stability
- ✓Tunable drug release profiles
- ✓Applicable to carry small molecules, proteins, peptides or nucleic acids

Future trends and conclusions

✓Providing exciting opportunities for improved therapeutic management of CNS diseases;

✓Several issues should be resolved before CNS nanomedicine becomes useful in clinical setting;

✓Considering the complexity of the brain, in-depth and comprehensive toxicological studies are needed on brain targeting of nanodrugs;

✓Evaluation of nanocarrier formulations: with and without drug;

✓The chronic and cumulative effects of nano-drugs on brain tissues need to be clarified;

✓Targeted delivery is likely the main research direction of CNS nanotechnology;

✓In addition, the species-specificity issues need to be considered.

hamidim@zums.ac.ir

With Special Thanks To:

My Past and Prsent Students

Who Made This Possible

With My Warmest Appreciations to:

Amir and Samira

For the

LESSON THEY THAUGHT ME

یاد و خاطره دکتر سعید کاظمی آشتیانی گرامی باد.

هرگزم نقش تو از لوح دل و جان نرود
هرگز از یاد من آن سرو خرامان نرود