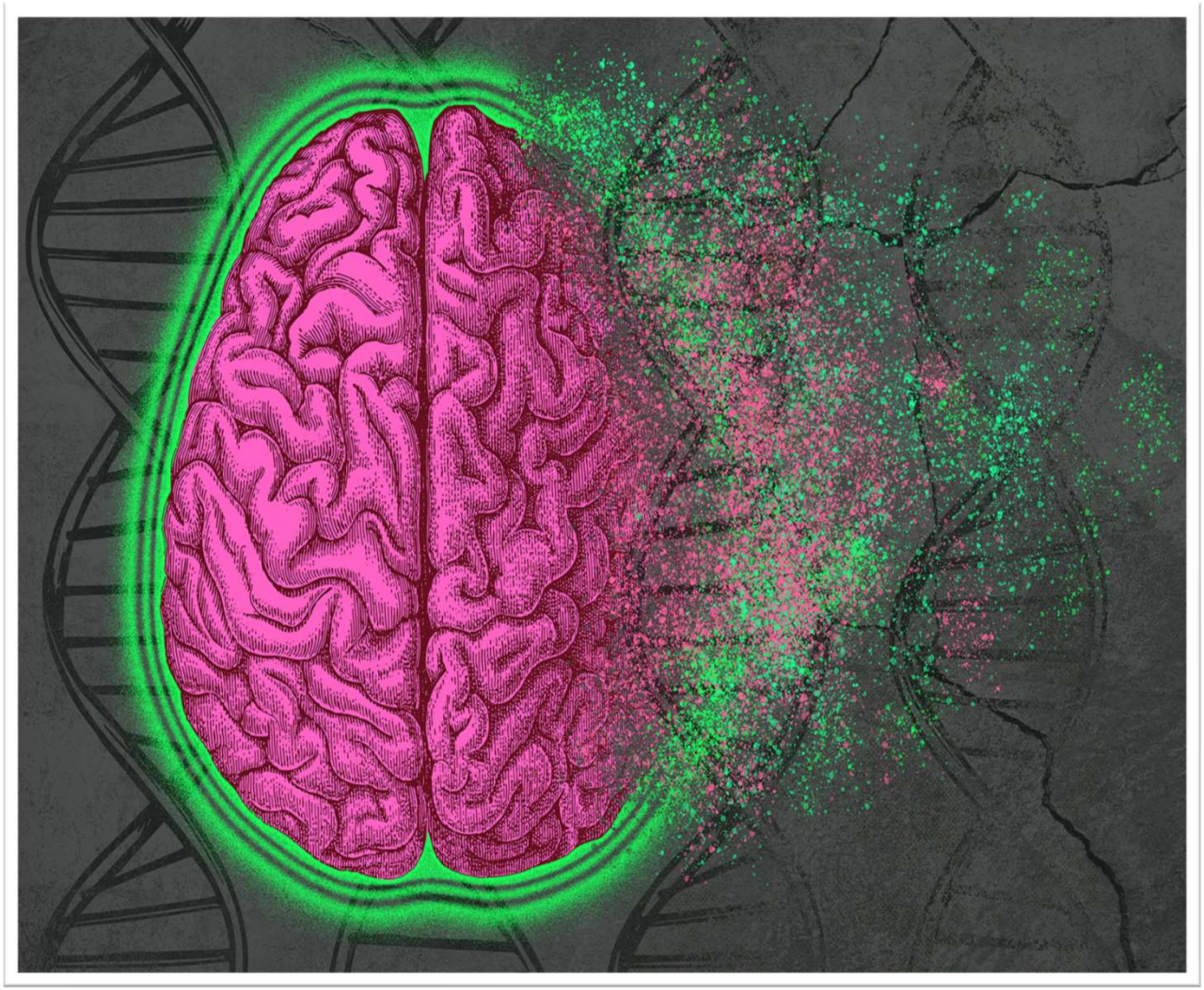

ALZHEIMER'S DISEASE CURRENT THERAPIES AND NOVEL DRUG DELIVERY SYSTEMS

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Physiology Class

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TABLE OF CONTENTS

Pathophysiology

Treatment Challenges & future Directions

Genetic Factors

Advanced Drug Delivery Systems

ALZHEIMER'S DISEASE (AD)

- First identified over a century ago by Dr. Alois Alzheimer
- Alzheimer's disease (AD) is regarded as the most common neurological condition in terms of cognition. The disease progresses gradually, begin with a slight memory loss and maybe lead to the lack of communication as well as environmental awareness.
- Has no proven effective drug and treatment of reversal

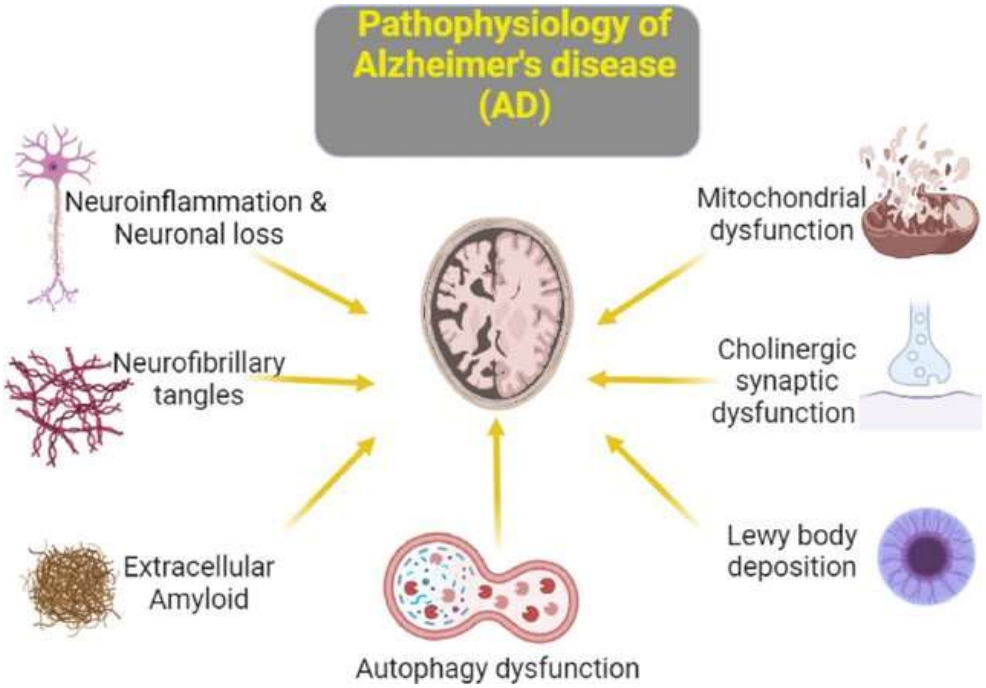
PATHOPHYSIOLOGY OF ALZHEIMER'S DISEASE

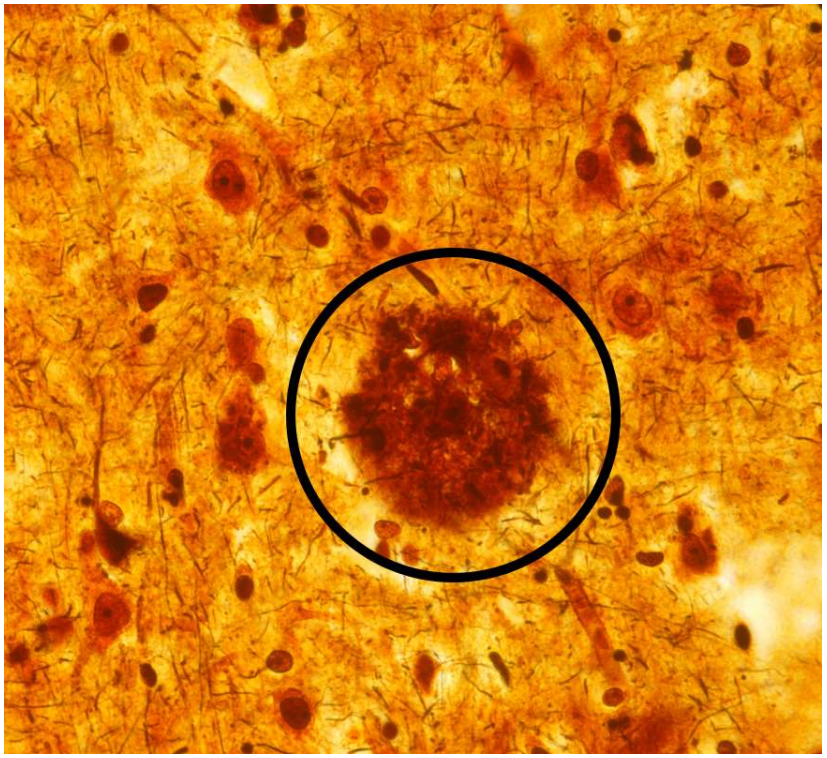
- Beta-Amyloid Plaques: Insoluble plaques that disrupt neuronal communication and trigger inflammation.
- Neurofibrillary Tangles: Hyperphosphorylated tau protein forms twisted filaments inside neurons, leading to instability and dysfunction.
- Amyloid Cascade Hypothesis: Abnormal beta-amyloid accumulation is a primary trigger.

PATHOPHYSIOLOGY OF ALZHEIMER'S DISEASE

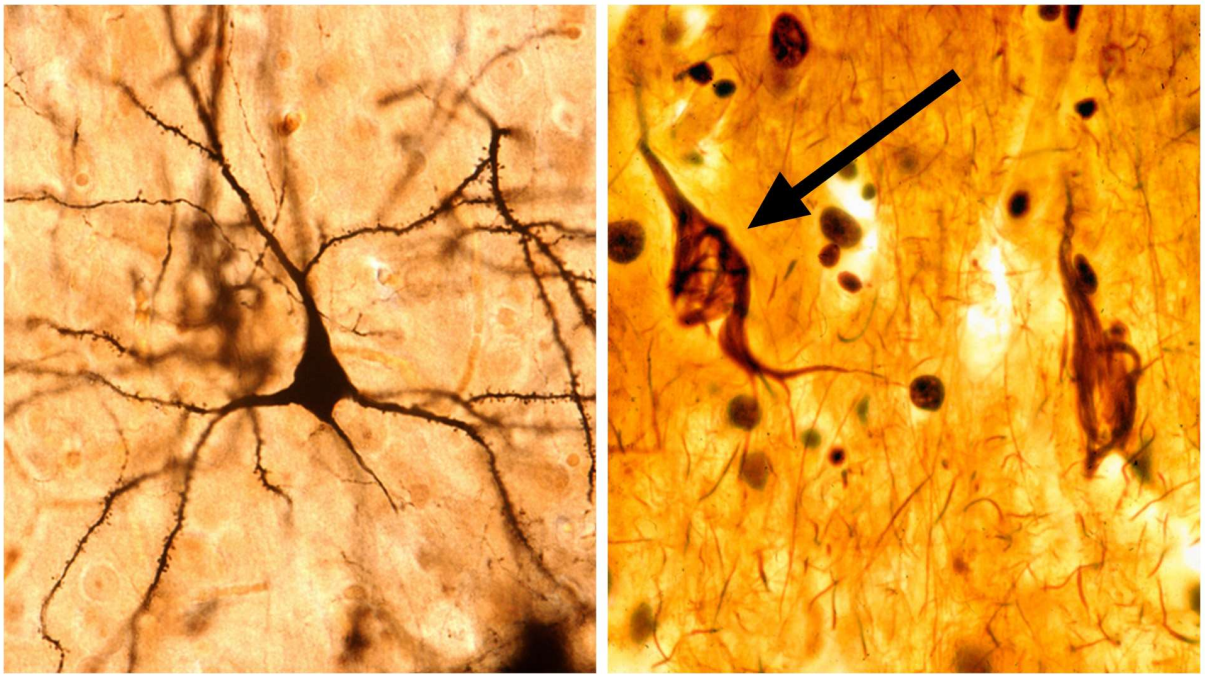
- Inflammation: Microglia activate in response to beta-amyloid, releasing pro-inflammatory cytokines, causing neuronal damage.
- Astrocyte Dysfunction: Loss of supporting function contributes to neuroinflammation.
- Synaptic Dysfunction: Accumulating beta-amyloid interferes with synaptic communication, leading to memory and learning impairments.
- Mitochondrial Dysfunction: Disrupts energy production, increases oxidative stress, and contributes to neuronal death.

PATHOPHYSIOLOGY OF ALZHEIMER'S DISEASE





A microscope image of an amyloid plaque in human brain tissue.

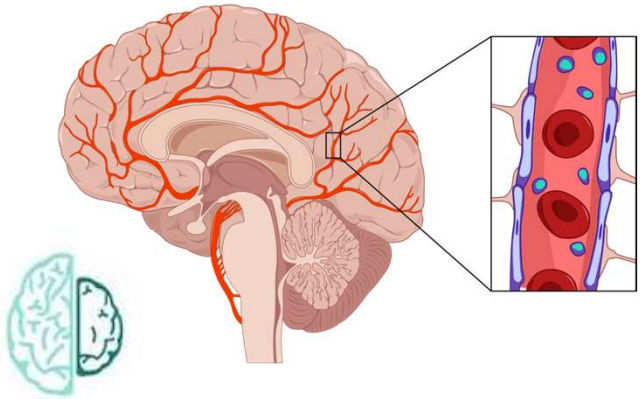


A microscope image of a healthy neuron (left) versus a neuron with neurofibrillary tau tangles (right).

GENETIC RISK FACTORS

- Mutations: In genes like APP, PSEN1, PSEN2, and APOE, increasing Alzheimer's risk. APOE also plays a role in beta-amyloid clearance.

BLOOD BRAIN BARRIER (BBB) DYSFUNCTION



- Compromised BBB allows harmful substances and immune cells into the brain, exacerbating inflammation and neuronal damage.

SUBTYPES OF ALZHEIMER'S DISEASE

- Early-Onset AD (EOAD): Characterized by rapid progression with severe neurocognitive symptoms and pronounced tau aggregation, leading to faster cognitive decline and brain atrophy, especially in temporal and parietal regions.

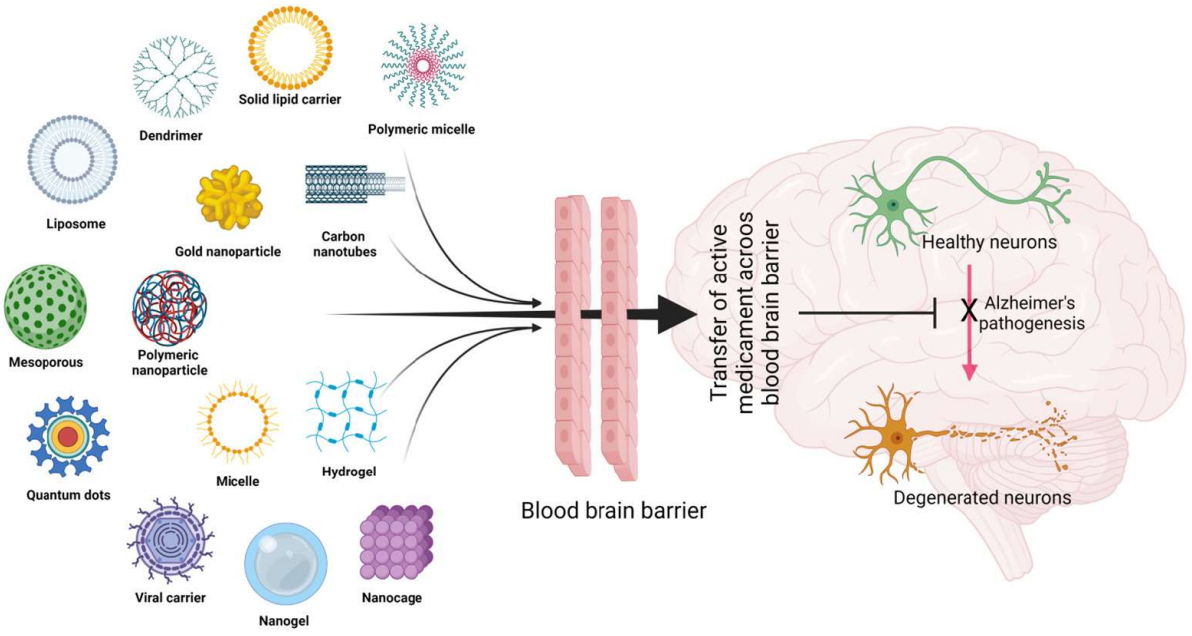
- Late-Onset AD (LOAD): More common, associated with extensive beta-amyloid build-up, slower progression, and reduced glucose metabolism. Atrophy occurs in the temporoparietal cortex, often following mild cognitive impairment (MCI).

- Autosomal Dominant AD (ADAD): Caused by mutations in PS1 gene, leading to beta-amyloid accumulation 15 years before symptoms appear. Characterized by early brain functionality loss, glucose hypometabolism, and tau accumulation in the striatum and parahippocampal gyrus.

CHALLENGES IN TREATING ALZHEIMER'S DISEASE (AD)

- Blood-Brain Barrier (BBB): Limiting drug delivery across the BBB.
- Drug Efficacy: Reduced effectiveness due to systemic side effects and poor bioavailability.
- Traditional Therapies: Conventional methods, such as oral tablets, face issues like first-pass metabolism and plasma protein binding.

ADVANCED DRUG DELIVERY SYSTEMS (ADDS)



Various Nanocarrier sytems

ADVANCED DRUG DELIVERY SYSTEMS (ADDS)

- Goals: Overcome BBB challenges, improve pharmacokinetics, and reduce toxicity.

Types of Systems:

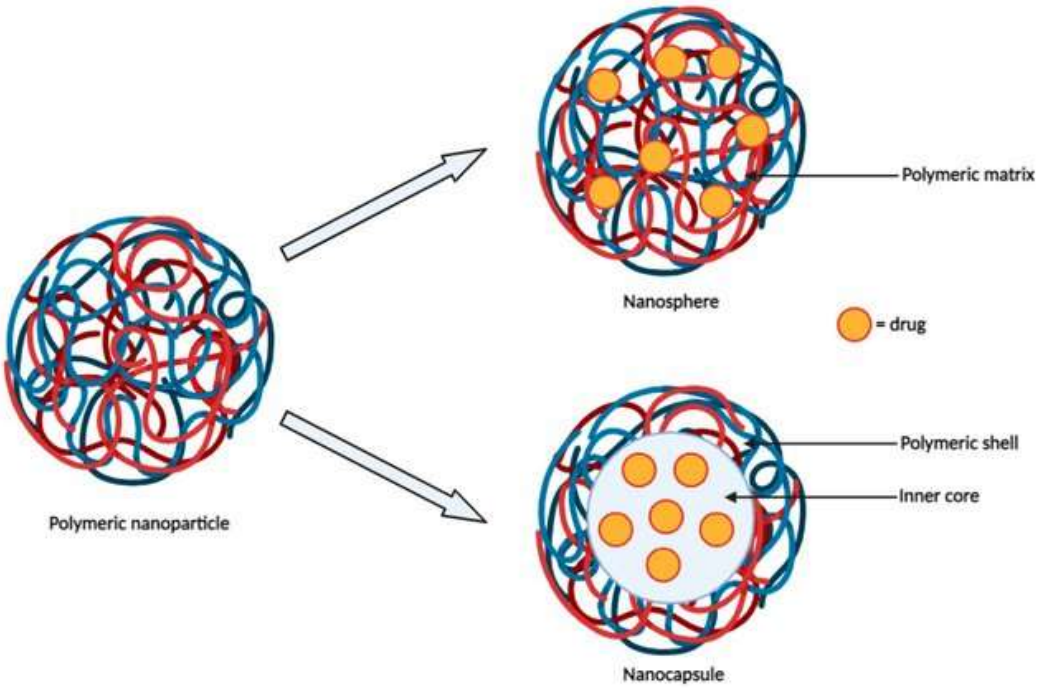
- Nanoparticles (NPs): Lipid-based (liposomes, solid lipid nanoparticles) and polymer-based (natural and synthetic polymers).

- Gel-based Systems: For controlled release.

- Drug Conjugates: For improved targeting and efficacy.

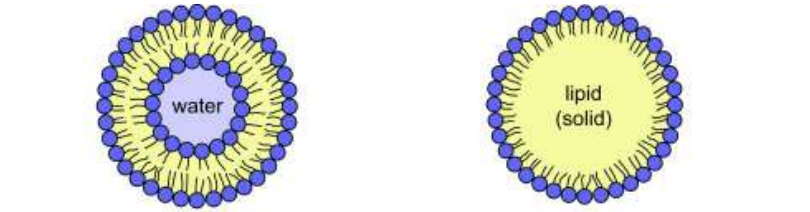
POLYMER BASED NANOPARTICLES (NPS)

- Examples: Self-assembling nanoscale scaffolds loaded with Memantine for slow drug release.
- Benefits: Improve long-term treatment effects, slow release, and disease-modifying properties.
- Preclinical Studies: Show promise for neurological disorders.



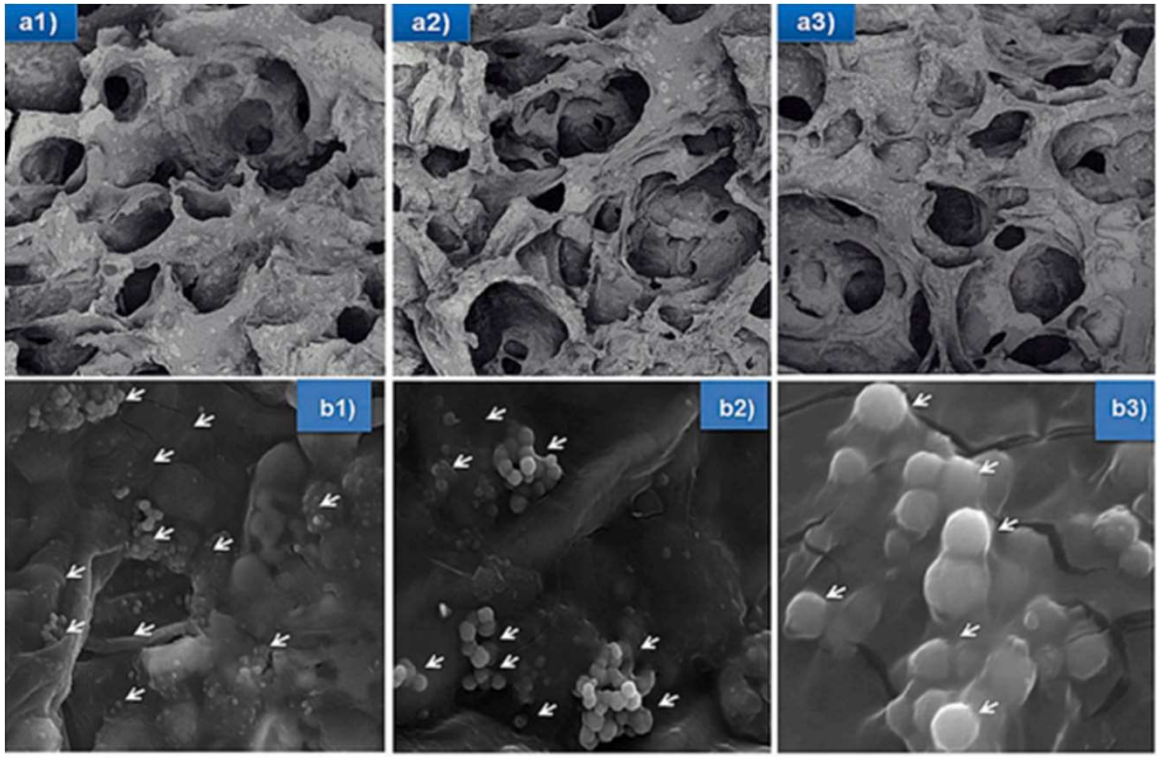
LIPID-BASED DELIVERY SYSTEMS

- Liposomes & SLNs: Improve stability and brain uptake.
- Drug Examples: Donepezil and Curcumin-loaded nanofibers show prolonged release profiles.



Liposome
(Lipid bilayer enclosing an aqueous core)

Solid lipid nanoparticle (SLN)
Lipid monolayer enclosing a solid lipid core



Label: SEM micrographs of (a1-a3) lyophilized CEP scaffold and (b1-b3) nanoliposomes embedded into the CEP scaffold.

Lyophilized CEP scaffold micrographs by SEM showed liposomes embedded into 3-D structure. “Reprint with permission from Mufamadi et al.”

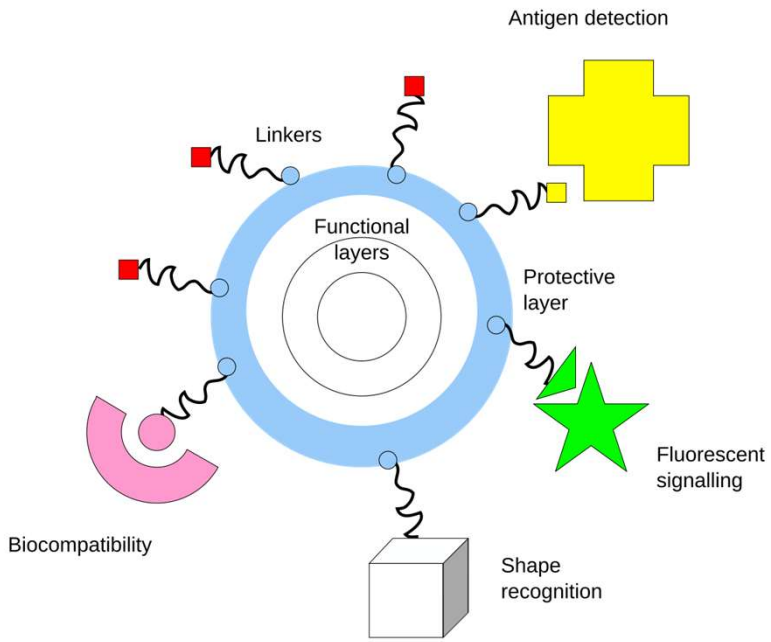
DRUG-CONJUGATED NANOCARRIERS

1.Memantine-Based Conjugates

2.Donepezil-Based Systems

3. Rivastigmine Delivery

4. Galantamine Delivery



MISCELLANEOUS DDS STUDIES

- Magnetic NEs with memantine, prepared using a microwave-assisted process, exhibited prolonged circulation time and controlled release.
- Hydroxyapatite NPs (HAP) demonstrated pH-dependent drug release and high biocompatibility.
- Mesoporous silica NPs (MSNs) showcased high drug-loading capacity, controlled release, and low toxicity.
- Nasal Drug Delivery: Shaghlil developed rivastigmine nasal inserts with promising permeation and sustained release profiles, positioning them as potential alternatives for AD

MISCELLANEOUS DDS STUDIES

- Transdermal drug delivery systems: These systems deliver drugs directly through the skin, which can improve patient compliance, reduce side effects, and increase the amount of medication that reaches the bloodstream. TDDSs can also be used to treat other chronic conditions, such as diabetes and hypertension.

advantages of TDDSs:

- Sustained drug release
- Reduced side effects
- Improved patient compliance
- Avoids first-pass metabolism

CONCLUSION

- The discussed nanocarriers represent significant advancements in targeted drug delivery for AD, offering controlled release, enhanced BBB penetration, and reduced systemic toxicity. However, most studies highlight the need for further in vivo evaluation to validate therapeutic efficacy and safety.

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THE END