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Updates in the Treatment of Alzheimer's Disease, Nothing to Forget About

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Updates in the Treatment of Alzheimer's Disease: Nothing to Forget About

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Baptist Hospital of Miami

Disclosures

The author of this presentation has no relevant financial or non-financial relationships in the products described and reviewed in this presentation

Objectives

- Review pathophysiology and current therapeutic management of patients with Alzheimer's disease
- Discuss new drug targets and therapies for the treatment of dementia in patients with Alzheimer's disease
- Evaluate clinical impact of new drug therapies on disease progression in early/late phases of Alzheimer's disease

Prevalence

- **5.7 million** Americans are living with Alzheimer's
- **By 2050**, this number is projected to rise nearly to nearly **14 million**
- In 2018, the cost of Alzheimer's disease to the United States was **$277 billion** with costs expected to rise as high as **$1.1 trillion by 2050**

Alzheimer's Association Facts and Figures. 2018.

Prevalence

- Alzheimer's disease is the **6th leading cause of death** in the United States
- Deaths from Alzheimer's have **increased by 123%** from 2000 to 2015
- **1 IN 3** Senior citizens die from Alzheimer's or another dementia, killing more than prostrate and breast cancer combined

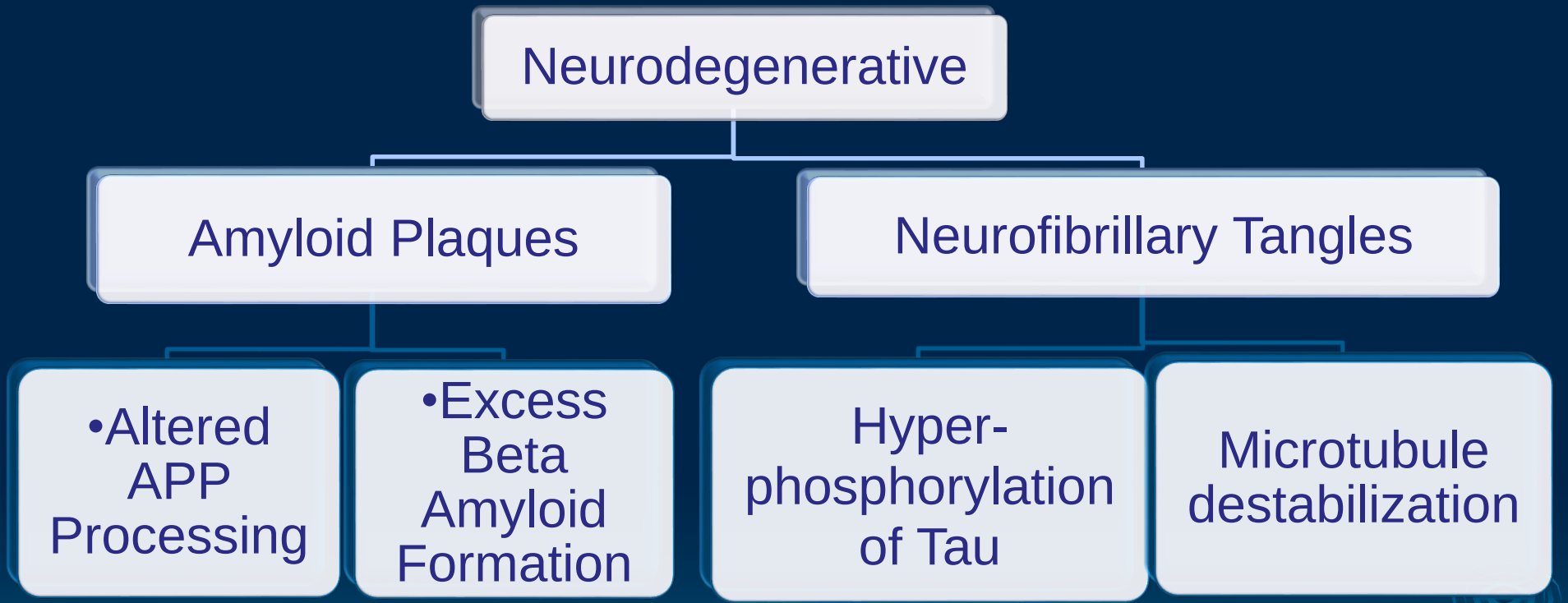
Alzheimer's Association Facts and Figures. 2018.

Risk Factors

- Age > 65 years
- Family History
- Head Injury
- Poor cardiovascular health
- Ethnicity
  - African American and Latino
- Genetics
  - Apolipoprotein E ε4 allele
  - Presenilin 1 (PSEN-1) & Presenilin 2 (PSEN-2) mutation
  - Trisomy 21 (Down Syndrome)

Alzheimer's Association. 2018.

Pathophysiology



APP= Amyloid Precursor Protein

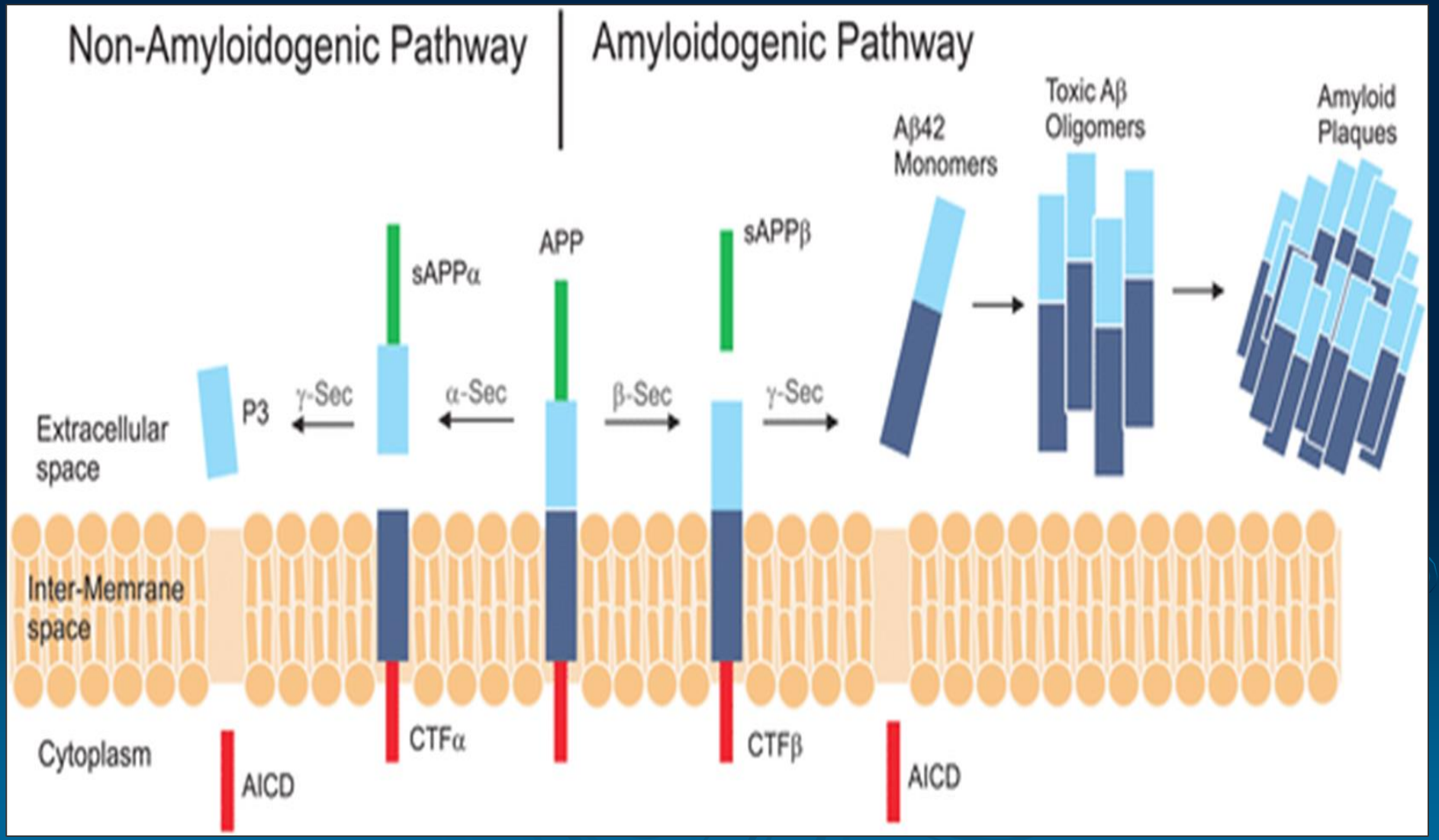
Scarpini E, Galimberti D, Ghezzi L. *Drug Design, Development and Therapy*. 2013:1471.

Pathophysiology

- Amyloid Precursor Protein (APP) is a transmembrane protein expressed at high levels in the brain
  - Primary function unknown
  - Implicated in the regulation of synapse formation, neuronal plasticity, and iron export
  - Plays a crucial role in the development of amyloid plaques

Scarpini E, Galimberti D, Ghezzi L. *Drug Design, Development and Therapy*. 2013:1471.

Pathophysiology

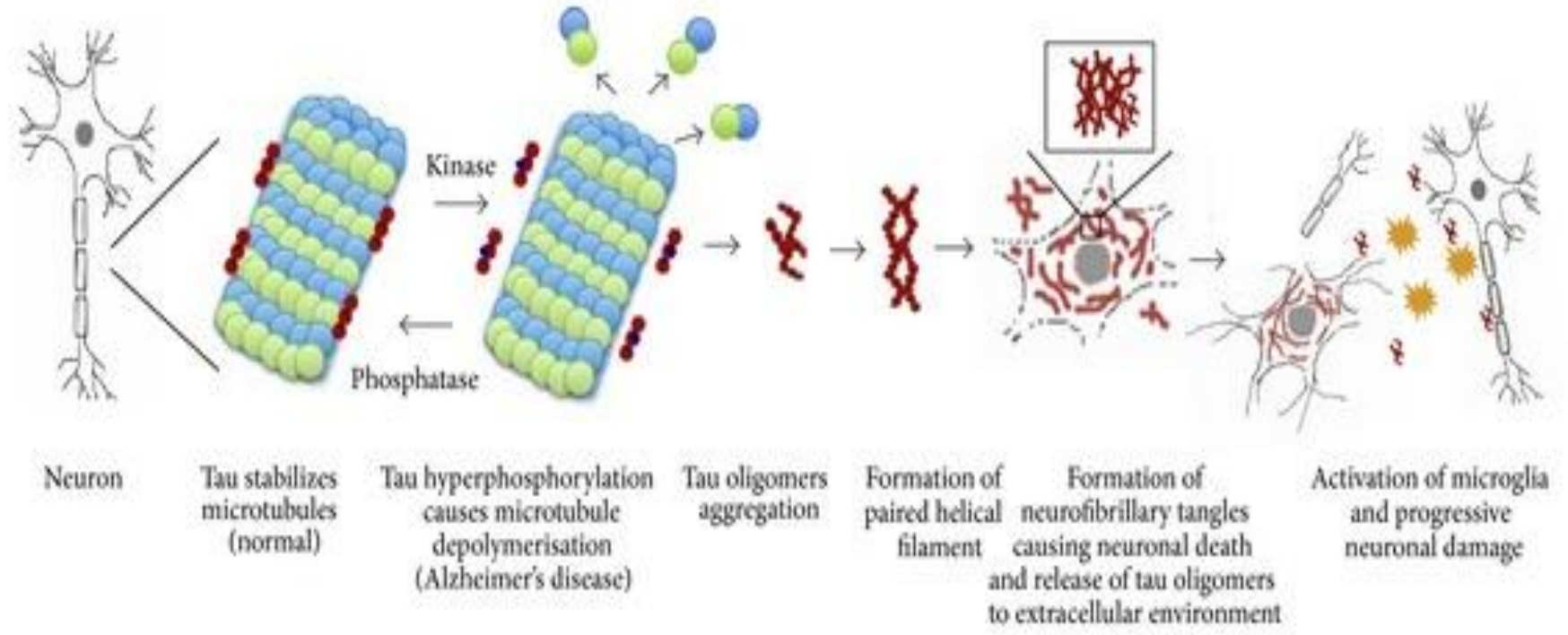


Pathophysiology

- APP is cleaved by either α-secretase, β-secretase, or γ-secretase
  - Cleavage by α-secretase and γ-secretase→ soluble monomer
  - Cleavage by β-secretase and γ-secretase → insoluble monomer → toxic oligomers → amyloid plaques

Scarpini E, Galimberti D, Ghezzi L. *Drug Design, Development and Therapy*. 2013:1471.

Pathophysiology

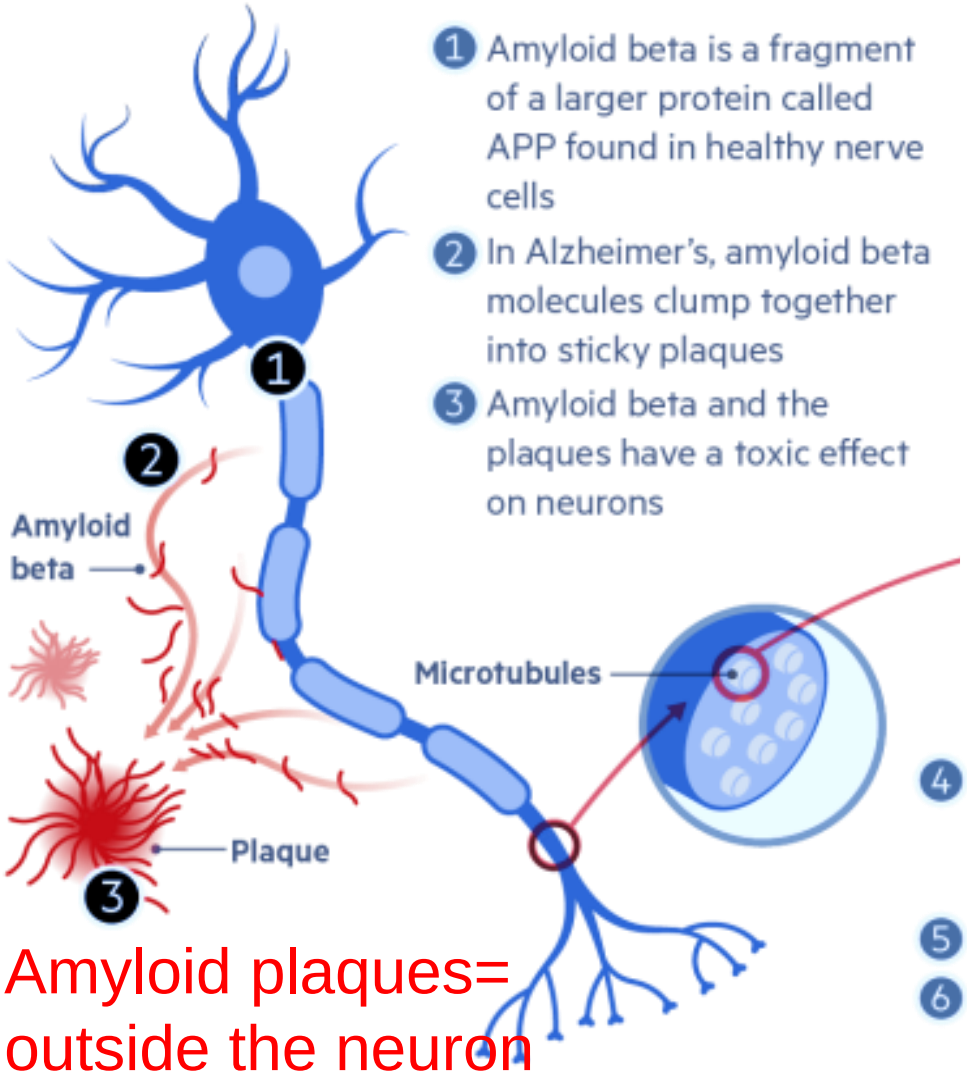


Pathophysiology

- Microtubules play a crucial role in organelle/nutrient transport and in maintaining the architecture of the neuron.
- Tau proteins help to maintain the structure of the microtubules
- Hyperphosphorylation of the tau protein causes de-stabilization of microtubules
- Overtime the tau protein develop into tangles and the neuron dies

Scarpini E, Galimberti D, Ghezzi L. *Drug Design, Development and Therapy*. 2013:1471.

Pathophysiology



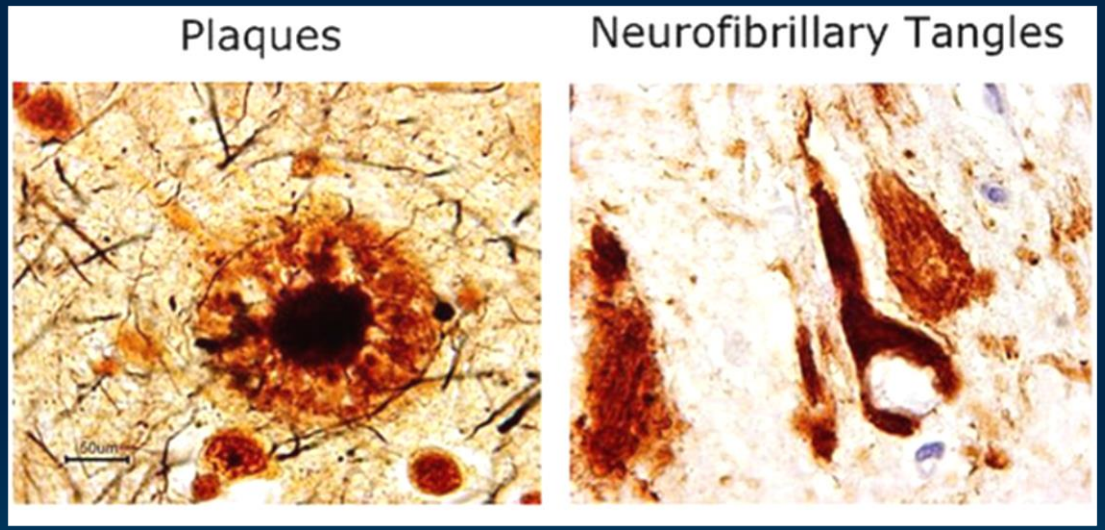
1. Amyloid beta is a fragment of a larger protein called APP found in healthy nerve cells
2. In Alzheimer's, amyloid beta molecules clump together into sticky plaques
3. Amyloid beta and the plaques have a toxic effect on neurons

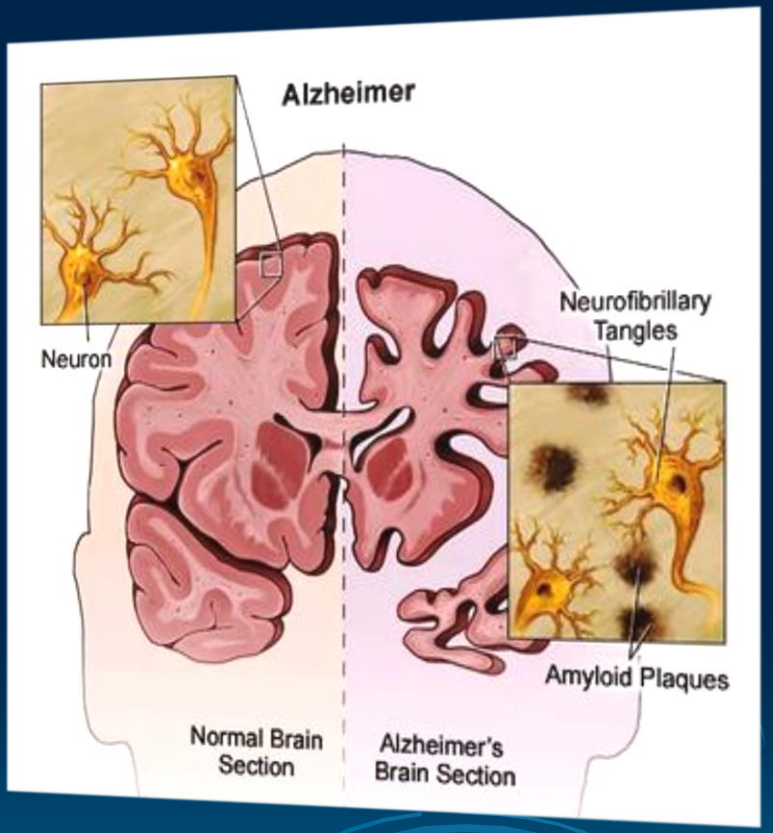
Amyloid plaques= outside the neuron

Neurofibrillary tangles= within the neuron

4. Another protein called tau helps maintain structure and stability of the microtubules in which nutrients and other matter are moved around the cell
5. In Alzheimer's the tau breaks down to form tangles
6. The microtubules also break down. Without a means of transporting matter around the cell, it will eventually die

Pathophysiology





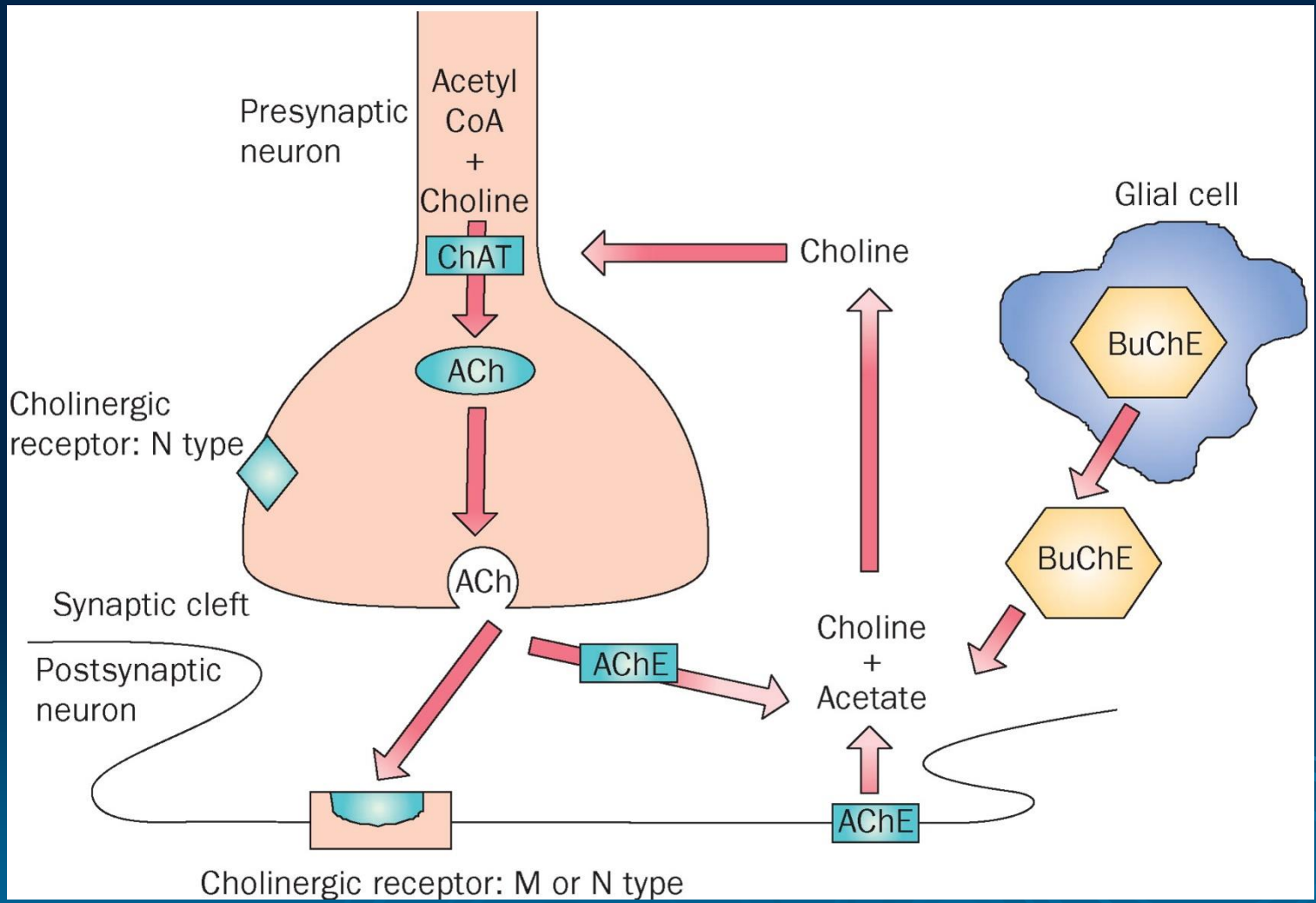
Scarpini E, Galimberti D, Ghezzi L. *Drug Design, Development and Therapy*. 2013:1471.

Pathophysiology

- Cholinergic neurons located in the basal forebrain are severely lost
- Synaptic loss is the principal correlate of disease progression
- Loss of Cholinergic neurons contributes to memory and attention deficits

Ferreira-Viera TH, et al. *Alzheimers disease* 2016; 14: 101-115

Pathophysiology

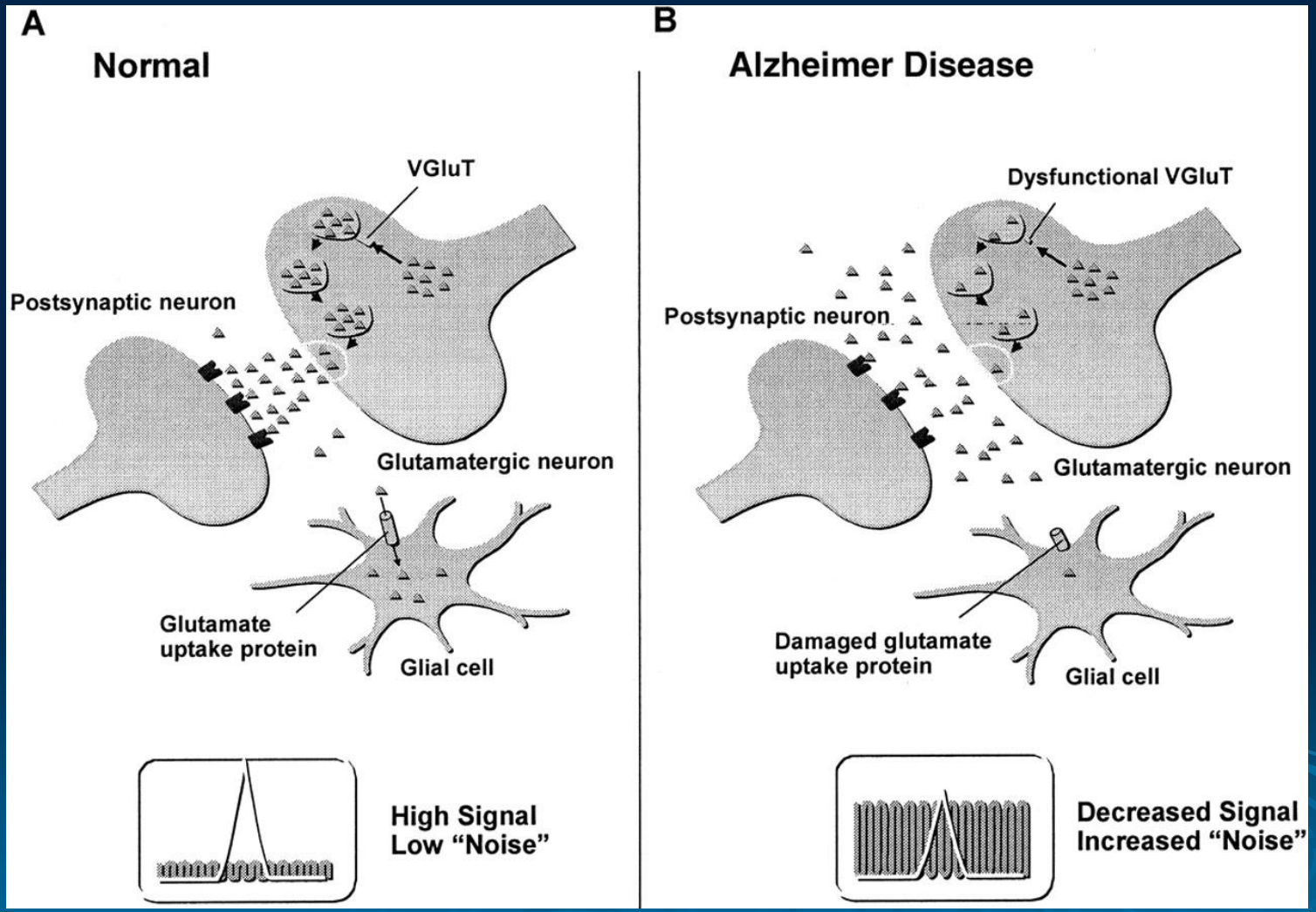


Pathophysiology

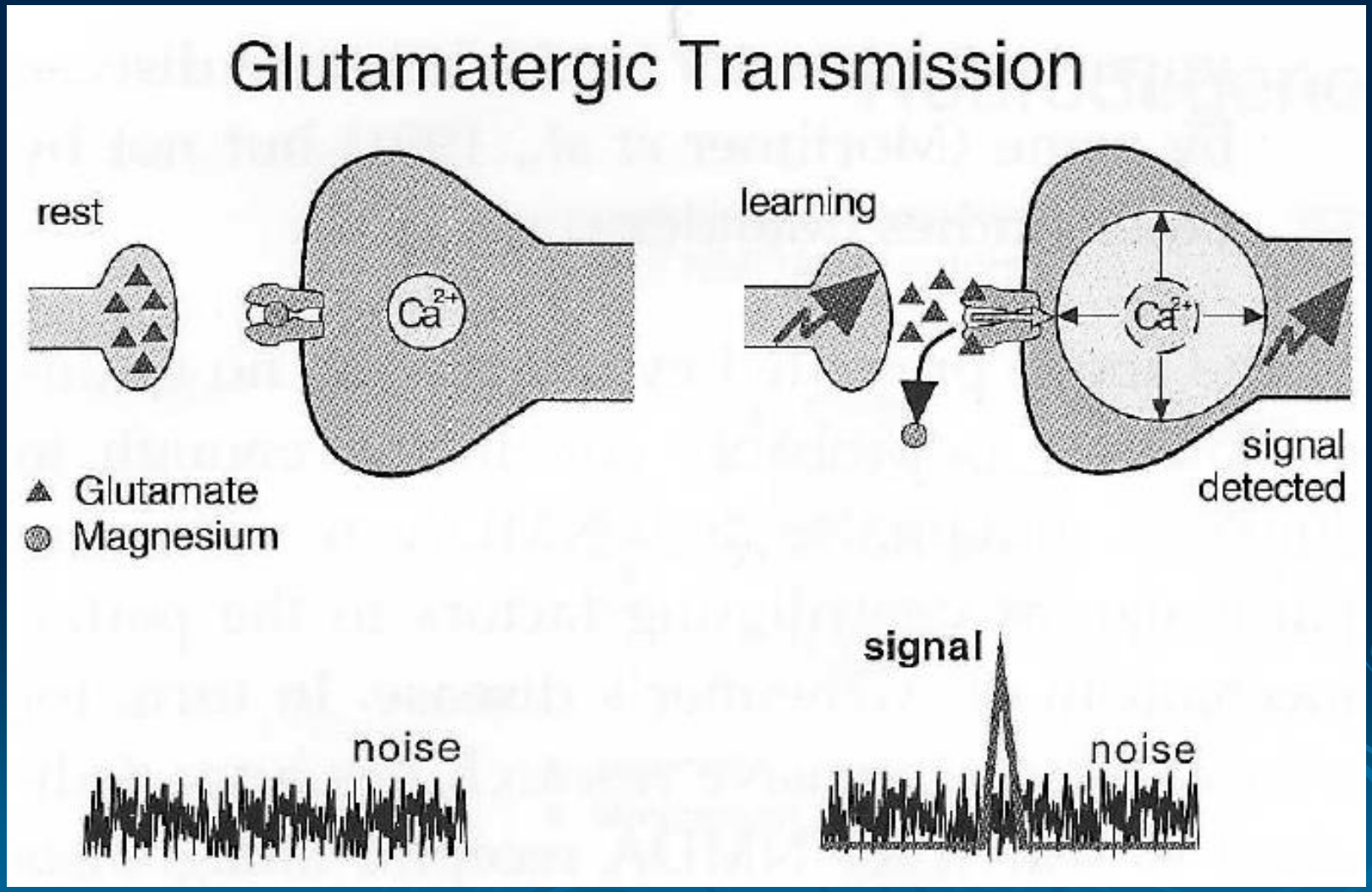
- Excitatory glutamatergic neurotransmission via N-methyl-d-aspartate (NMDA) receptor is critical for synaptic plasticity and survival of neurons
- Excessive NMDA receptor activity causes excitotoxicity and promotes cell death
- Potential mechanism of neurodegeneration

Wang R, et al. *Journal of Alzheimers Disease*. 2017;57 :1041-1048.

Pathophysiology



Pathophysiology



Current Therapeutic Management

Donepezil
(Aricept®)

Rivastigmine
(Exelon®)

Galantamine
(Razadyne®)

Memantine
(Namenda®)

Donepezil &
Memantine
(Namzaric®)

Birks J, Harvey R. *Cochrane Database of Systematic Reviews*. 2018;(6).

Scarpini E, Galimberti D, Ghezzi L. *Drug Design, Development and Therapy*. 2013:1471.

Current Therapeutic Management

Donepezil (Aricept®)

- Indicated for treatment of mild, moderate, or severe dementia of Alzheimer's disease
- Reversible Acetylcholinesterase Inhibitor
  - Prevents the breakdown of acetylcholine in the synaptic cleft
- Available as ODT or tablet

Aricept [prescribing information]. *Pfizer*. 2015.
Birks J, Harvey R. *Cochrane Database of Systematic Reviews*. 2018;(6).
Scarpini E, Galimberti D, Ghezzi L. *Drug Design, Development and Therapy*. 2013:1471.

Current Therapeutic Management

Donepezil (Aricept®)

- Adverse Reactions:
  - > 10%: Insomnia, nausea, diarrhea, infection, accidental injury
  - ≥ 1% to 10%: Headache, pain, abnormal dreams, dizziness, personality disorder, weight loss, vomiting, anorexia, dyspepsia, gastrointestinal hemorrhage, bruises
- Monitoring parameters: mental status, weight, symptoms of GI intolerance, symptoms of active or occult GI bleeding

Aricept [prescribing information]. *Pfizer*. 2015.
Birks J, Harvey R. *Cochrane Database of Systematic Reviews*. 2018;(6).
Scarpini E, Galimberti D, Ghezzi L. *Drug Design, Development and Therapy*. 2013:1471.

Current Therapeutic Management

Rivastigmine (Exelon®)

- Indicated for treatment of mild or moderate dementia of Alzheimer's disease
- Reversible Acetylcholinesterase Inhibitor
  - Prevents the breakdown of acetylcholine in the synaptic cleft
- Available as capsule or transdermal patch

Exelon [prescribing information]. *Novartis* 2015.

Birks J, Harvey R. *Cochrane Database of Systematic Reviews*. 2018;(6).

Scarpini E, Galimberti D, Ghezzi L. *Drug Design, Development and Therapy*. 2013:1471.

Current Therapeutic Management

Rivastigmine (Exelon®)

- Adverse Reactions:
  - > 10%: Dizziness, headache, agitation, falling, weight loss, tremor, nausea, vomiting, abdominal pain, anorexia, diarrhea
  - ≥ 1% to 10%: Fatigue, insomnia, confusion, depression, exacerbation of Parkinson disease, urinary tract infection
- Monitoring parameters: mental status, weight, symptoms of GI intolerance

Exelon [prescribing information]. *Novartis* 2015.
Birks J, Harvey R. *Cochrane Database of Systematic Reviews*. 2018;(6).
Scarpini E, Galimberti D, Ghezzi L. *Drug Design, Development and Therapy*. 2013:1471.

Current Therapeutic Management

Galantamine (Razadyne®)

- Indicated for treatment of mild to moderate dementia of Alzheimer's disease
- Reversible Acetylcholinesterase Inhibitors
  - Prevents the breakdown of acetylcholine in the synaptic cleft
  - Modulates nicotinic acetylcholine receptors to increase release of acetylcholine
- Available as extended release capsule, tablet, or solution

Razadyne [prescribing information]. *Janssen* 2016.
Birks J, Harvey R. *Cochrane Database of Systematic Reviews*. 2018;(6).
Scarpini E, Galimberti D, Ghezzi L. *Drug Design, Development and Therapy*. 2013:1471.

Current Therapeutic Management

Galantamine (Razadyne®)

- Adverse Reactions:
  - > 10%: Nausea, vomiting
  - ≥ 1% to 10%: Dizziness, headache, depression, fatigue, falling, weight loss, decreased appetite, diarrhea, abdominal pain, tremor
- Monitoring parameters: mental status, weight

Razadyne [prescribing information]. *Janssen* 2016.
Birks J, Harvey R. *Cochrane Database of Systematic Reviews*. 2018;(6).
Scarpini E, Galimberti D, Ghezzi L. *Drug Design, Development and Therapy*. 2013:1471.

Current Therapeutic Management

Memantine (Namenda®)

- Indicated for treatment of moderate to severe dementia of Alzheimer's Disease
- NMDA Antagonist
  - Binds to the intra-pore magnesium site of the glutamate NMDA receptor blocking the channel under conditions of excessive stimulation
- Available as extended release capsule, tablet, or solution

Memantine [prescribing information]. *Apotex.* 2017.

Scarpini E, Galimberti D, Ghezzi L. *Drug Design, Development and Therapy*. 2013:1471.

Kishi T, Matsunaga S, Oya K, Nomura I, et al. *Journal of Alzheimers Disease.* 2017;60(2):401-425.

Current Therapeutic Management

Memantine (Namenda®)

- Adverse Reactions:
  - ≥ 1% to 10%: Dizziness, headache, depression, hallucination, fatigue, confusion, diarrhea, constipation, weight gain,
- Monitoring parameters: cognitive function, functional such as activities of daily living (ADLs), periodic ophthalmic exam (Canadian labeling)

Memantine [prescribing information]. *Apotex.* 2017.

Scarpini E, Galimberti D, Ghezzi L. *Drug Design, Development and Therapy*. 2013:1471.

Kishi T, Matsunaga S, Oya K, Nomura I, et al. *Journal of Alzheimers Disease.* 2017;60(2):401-425..

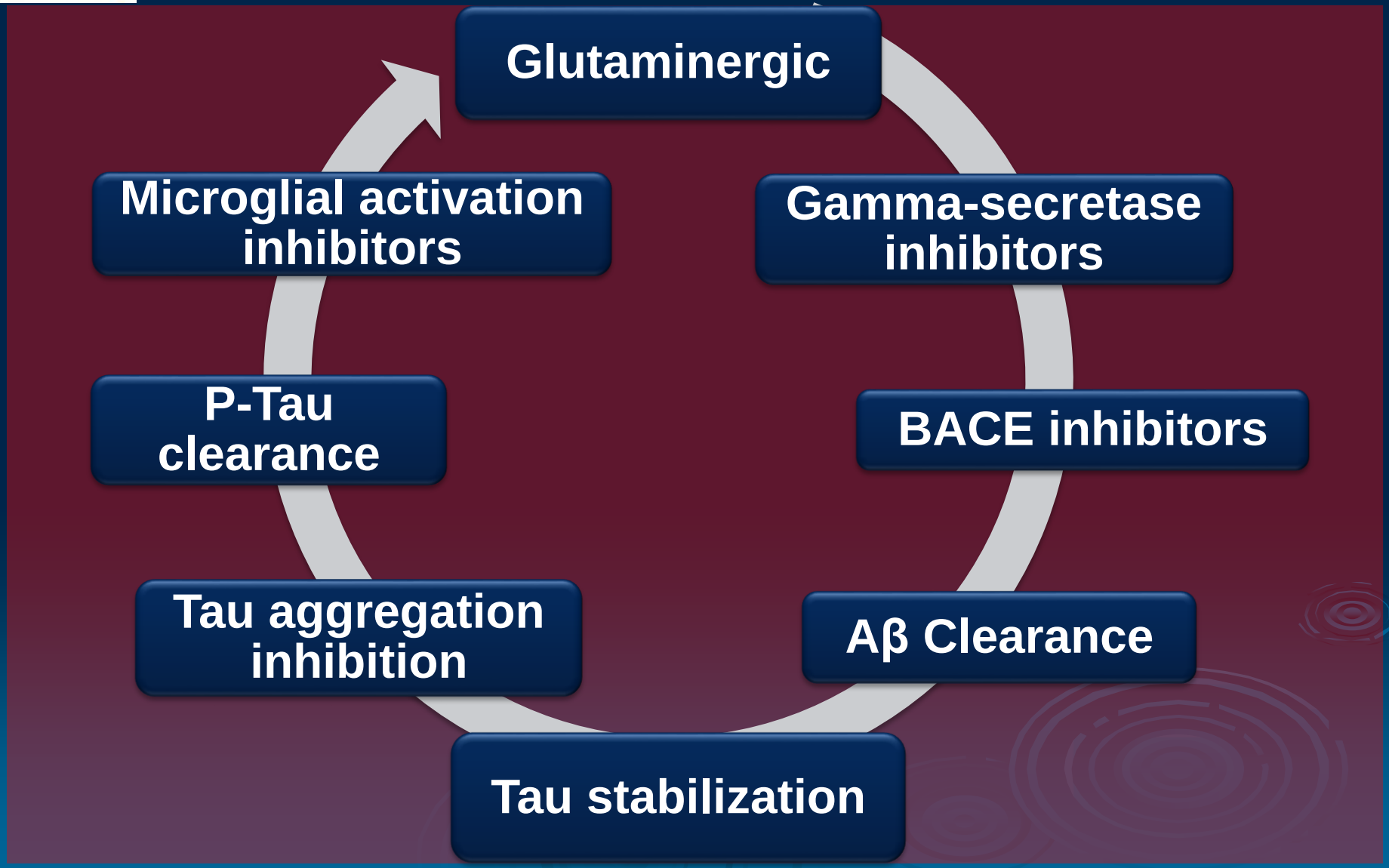
Current Therapeutic Management

- Combination Product: Donepezil & Memantine (Namzaric®)
- Indicated for treatment of moderate to severe dementia of Alzheimer's Disease
- For patient stabilized on donepezil 10 mg once daily
- Available as extended release capsule
- See individual agents for adverse reactions and monitoring

Namzaric [prescribing information]. *Allergan.* 2016.

Scarpini E, Galimberti D, Ghezzi L. *Drug Design, Development and Therapy*. 2013:1471.

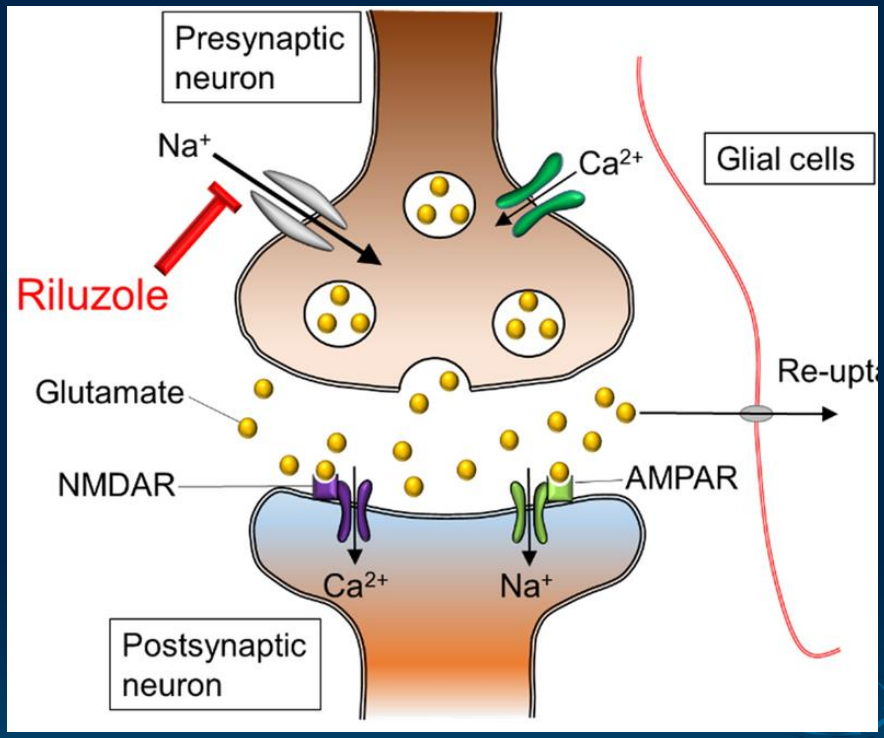
New Drug Targets



Graham WV, Bonito-Oliva A, Sakmar TP et al. *Annual Review of Medicine*. 2017;68(1):413-430.

New Drug Targets: Glutaminergic

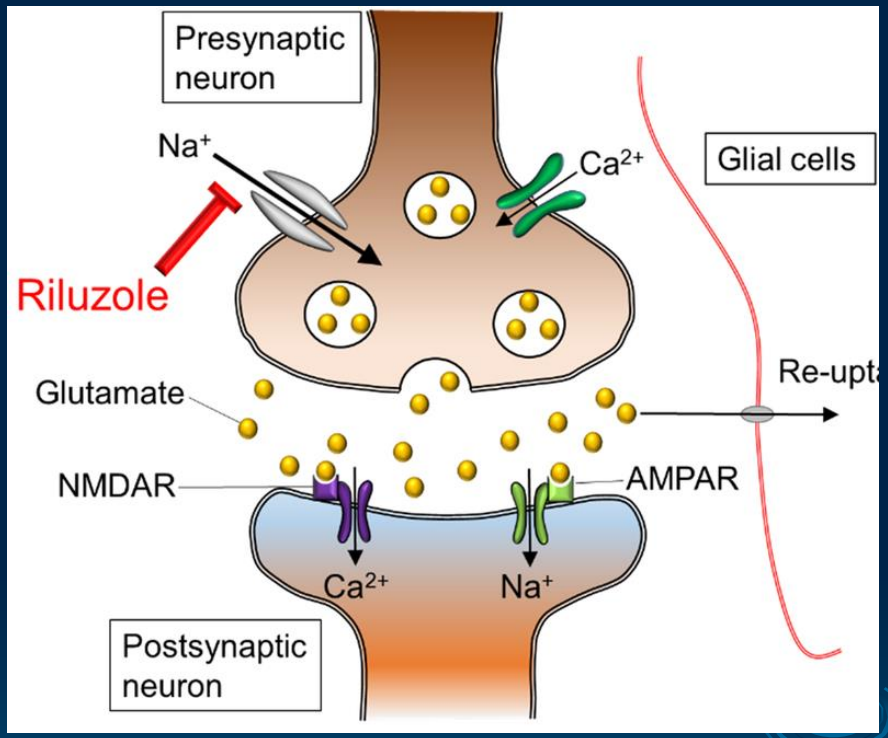
- Probable pathophysiological mechanism of Alzheimer's disease:
  - Excess glutamate at excitatory synapses with associated cytotoxicity, possibly due to decreased glutamate reuptake from microglia



Graham WV, Bonito-Oliva A, Sakmar TP et al. *Annual Review of Medicine*. 2017;68(1):413-430.

New Drug Targets: Glutaminergic

- Riluzole
  - Inhibitor of glutamate release
  - Inhibitor of postsynaptic glutamate receptor signaling
  - In Phase II trials for mild AD patients



Graham WV, Bonito-Oliva A, Sakmar TP et al. *Annual Review of Medicine*. 2017;68(1):413-430.

New Drug Targets: Gamma Secretase Inhibitors

- Gamma secretase is responsible for cleaving up to 50 different type I transmembrane protein substrates including APP and Notch Receptors

- Inhibition of proteolysis of Notch receptors can lead to toxic effects such as gastrointestinal bleeds and immunosuppression

Graham WV, Bonito-Oliva A, Sakmar TP et al. *Annual Review of Medicine*. 2017;68(1):413-430.

New Drug Targets: Gamma Secretase Inhibitors

- Semagacestat: discontinued
  - Failed to slow disease progression and worsen patient symptoms
- Avagacestat: discontinued
  - Adverse effects: cerebral microbleeds, dose-dependent glycosuria, and nonmelanoma skin cancer
- EVP-0962: phase II
  - Does not affect the Notch receptor

Graham WV, Bonito-Oliva A, Sakmar TP et al. *Annual Review of Medicine*. 2017;68(1):413-430.

New Drug Targets: BACE Inhibitors

- β-site APP cleaving enzyme 1 (BACE1) is the first enzyme to cleave the APP protein

- **First generation BACE inhibitors failed**
  - Low bioavailability and blood-brain barrier penetration
- BI 1181181: discontinued

Graham WV, Bonito-Oliva A, Sakmar TP et al. *Annual Review of Medicine*. 2017;68(1):413-430.

New Drug Targets: BACE Inhibitors

- **Second generation BACE Inhibitors failed**
  - More lipophilic
  - Able to cross the blood brain barrier and endosomal membranes
  - Liver toxicity
- RG7129: discontinued
- LY2811376: discontinued
- LY2886721: discontinued

Graham WV, Bonito-Oliva A, Sakmar TP et al. *Annual Review of Medicine*. 2017;68(1):413-430.

New Drug Targets: BACE Inhibitors

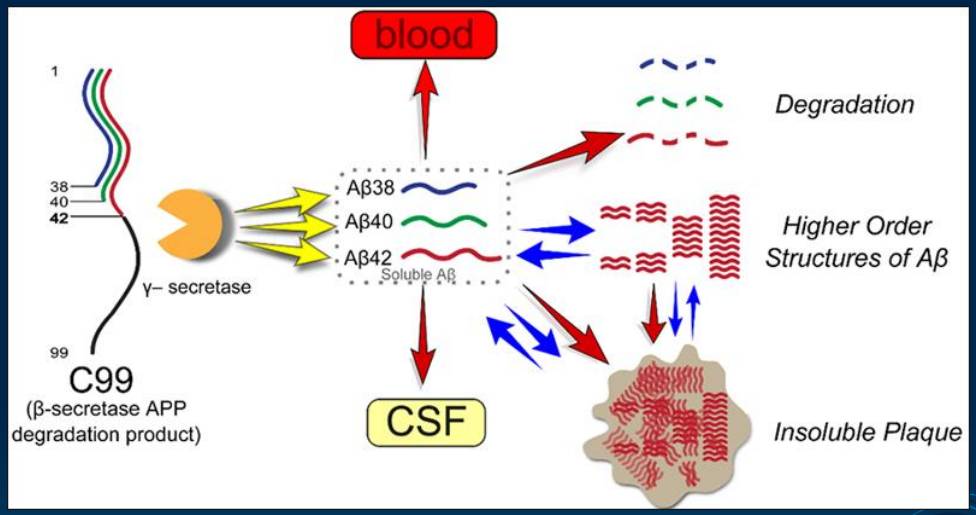
- **Third generation BACE inhibitors**
- E2609: phase II
- AZD3293: phase III
- CNP520: phase II/III
- JNJ-54861911: phase II/III
- Verubecestat: phase III

- **Anti-BACE antibodies (Abs)**
  - High target specificity and in animal models reduced Aβ concentrations in periphery and brain
- **Site directed Abs for BACE-APP complex**
  - Targets the β-secretase cleavage site of APP

Graham WV, Bonito-Oliva A, Sakmar TP et al. *Annual Review of Medicine*. 2017;68(1):413-430.

New Drug Targets: Aβ Clearance

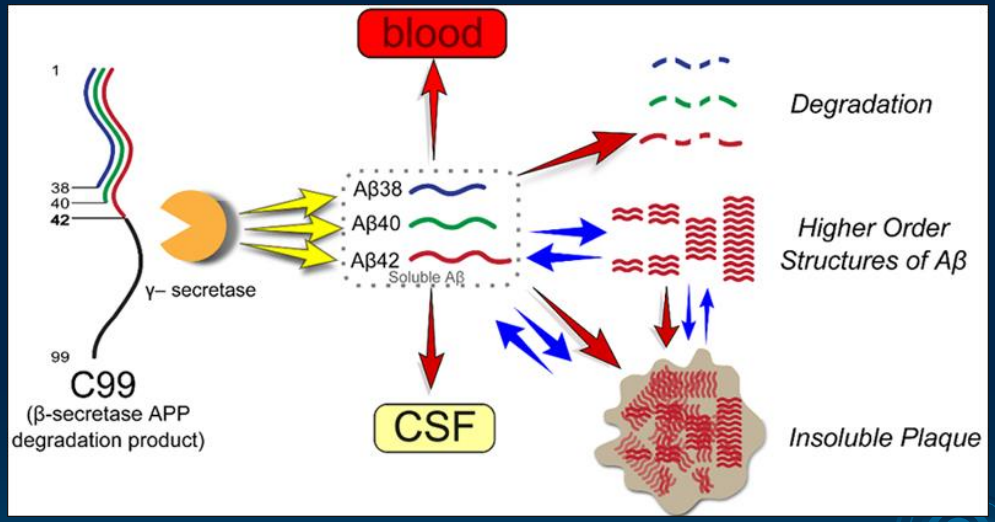
- **Defective-Clearance Hypothesis:**
  - Net Aβ content in the brain is determined by the equilibrium between the rate of production and clearance
  - Deficient cerebrospinal fluid clearance of Aβ has been found in cases of AD



Graham WV, Bonito-Oliva A, Sakmar TP et al. *Annual Review of Medicine*. 2017;68(1):413-430.

New Drug Targets: Aβ Clearance

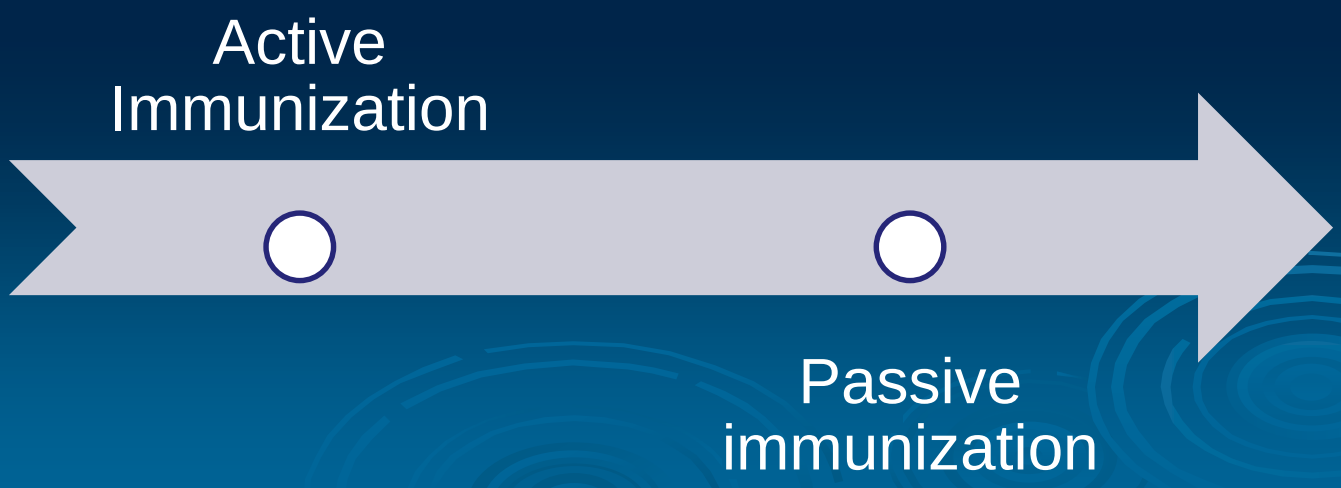
- **Defective-Clearance Hypothesis:**
  - Aβ-degrading proteases (AβDPs)- collective group of peptidases and proteinases that clear the Aβ
  - Pharmacologic treatment to stimulate expression of AβDPs or inhibit endogenous inhibitors of AβDPs



Graham WV, Bonito-Oliva A, Sakmar TP et al. *Annual Review of Medicine*. 2017;68(1):413-430.

New Drug Targets: Aβ Clearance

- Immunotherapy to increase Aβ clearance
- AN-1792: discontinued
  - Full length synthetic human Aβ42 reduced Aβ formation
  - Active immunization
  - 6% of patients developed severe meningoencephalitis



Graham WV, Bonito-Oliva A, Sakmar TP et al. *Annual Review of Medicine*. 2017;68(1):413-430.

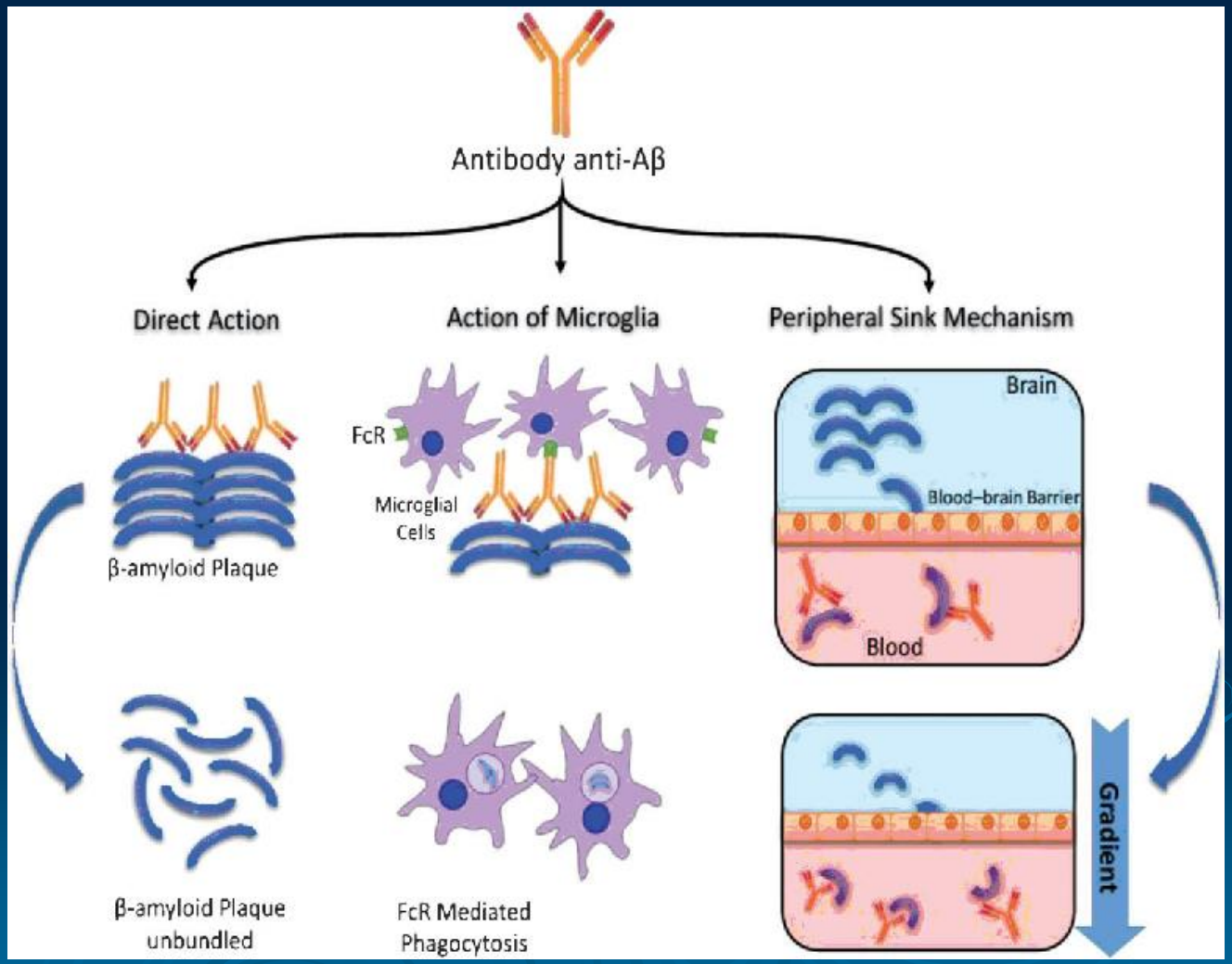
New Drug Targets: Aβ Clearance

- Immunotherapy to increase Aβ clearance
- Passive Immunization
  - Systemic infusion of monoclonal Abs (mAbs)
  - Prevents oligomerization and fibril formation and dissolves aggregates
  - Low blood brain barrier penetration, high specificity, affinity toward their antigen, low toxicity, and good plasma pharmacokinetics

Graham WV, Bonito-Oliva A, Sakmar TP et al. *Annual Review of Medicine*. 2017;68(1):413-430.

New Drug Targets: Aβ Clearance

- How does it work?
  - Microglia activation through Fc receptors
  - Peripheral sink effect



Graham WV, Bonito-Oliva A, Sakmar TP et al. *Annual Review of Medicine*. 2017;68(1):413-430.

New Drug Targets: Aβ Clearance

N-terminal Epitope

- AAB-003: phase I
- Bapineuzumab: discontinued
  - Dependent on ApoE4 genotype
  - Risk of vasogenic cerebral edema
- GSK933776: discontinued

Central Epitope

- Aducanumab: phase III
- Ban2401: phase II
- Crenezumab: phase III
  - No vasogenic cerebral edema
- Gantenerumab: phase III
  - Recognizes N-terminal tail and central region
- Solanezumab: discontinued

Graham WV, Bonito-Oliva A, Sakmar TP et al. *Annual Review of Medicine*. 2017;68(1):413-430.

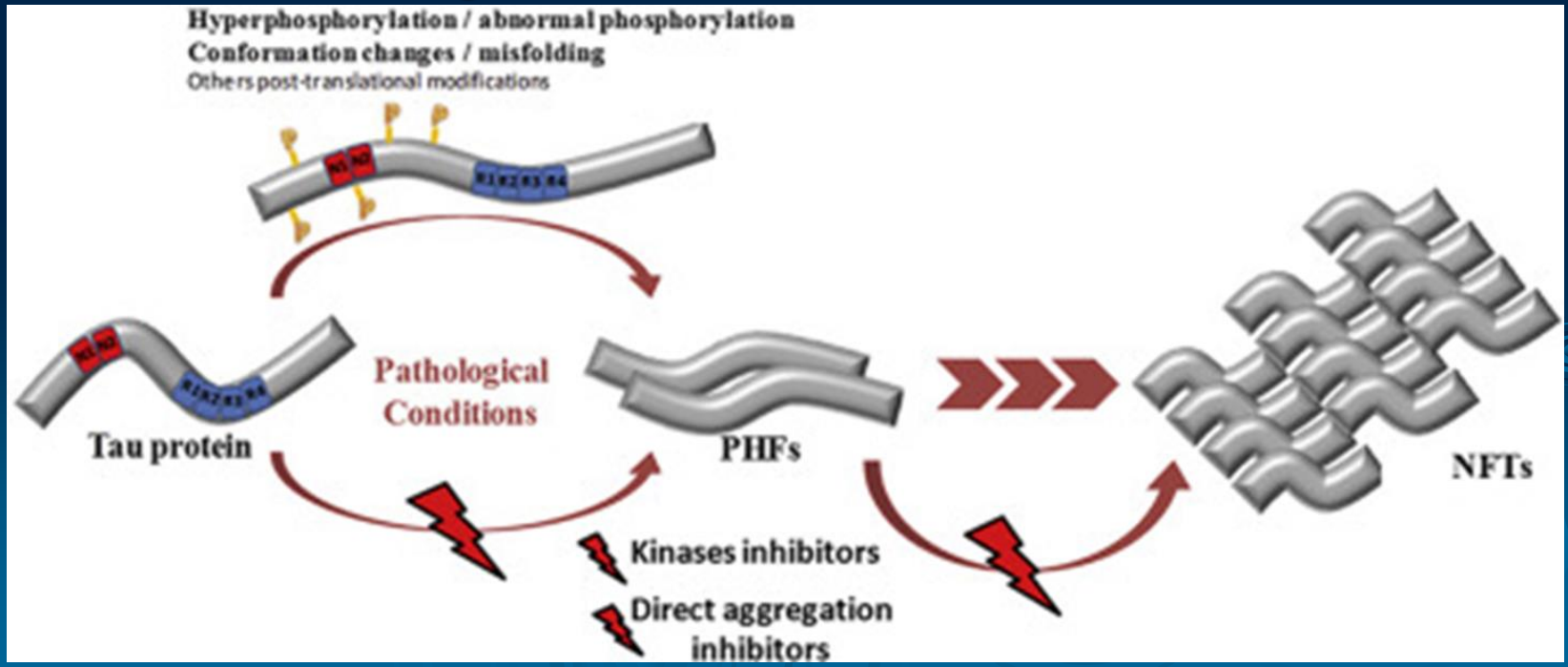
New Drug Targets: Tau Stabilization

- Hyperphosphorylated tau leads to cytoskeleton disruptions along axons
- Therapeutic approach to re-stabilize microtubules
- Epothilone D: discontinued
  - Paclitaxel-derived product
  - Reduced transport deficits and cognitive impairment in tau transgenic mice
  - Good penetration into brain
  - Evaluated in phase I, but not being pursued

Graham WV, Bonito-Oliva A, Sakmar TP et al. *Annual Review of Medicine*. 2017;68(1):413-430.

New Drug Targets: Tau Aggregation Inhibitor

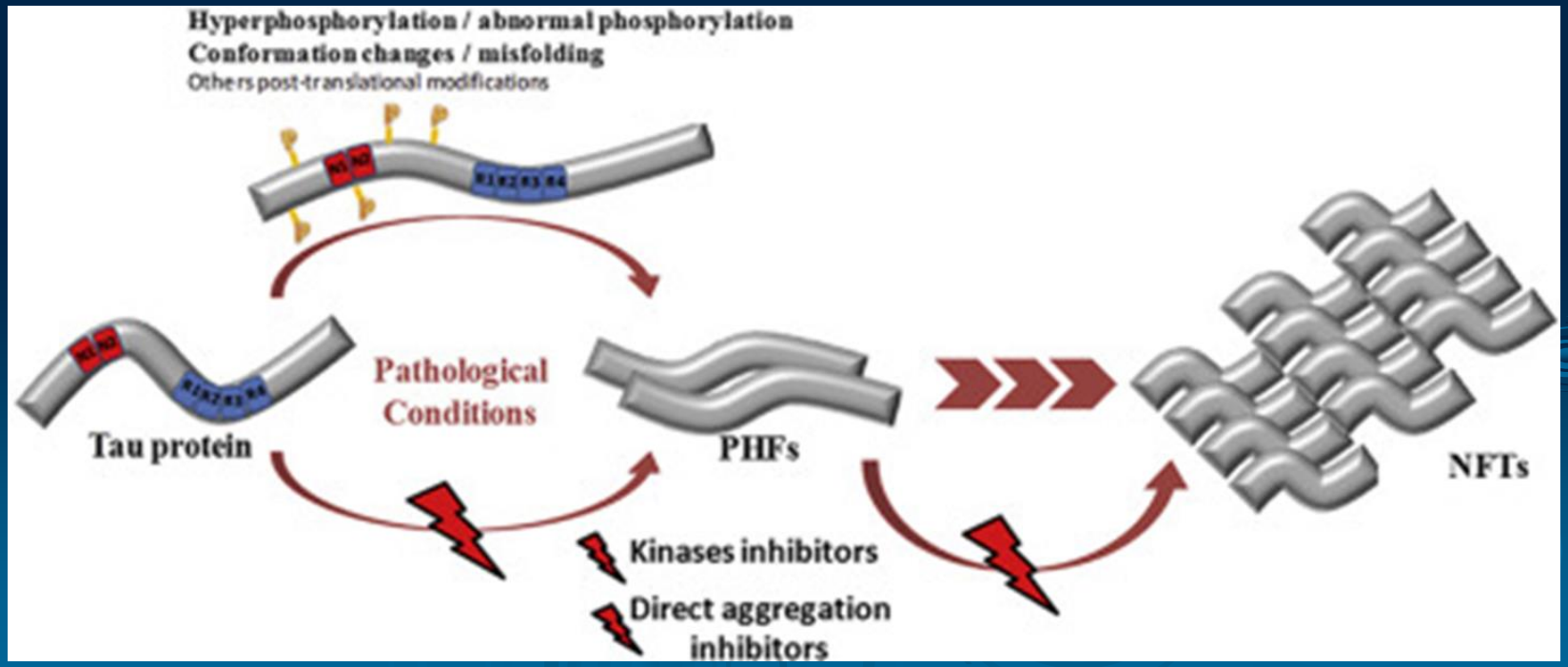
- Derivatives of methylene blue have been shown to disrupt the aggregation of tau
- Reduces oxidative stress
- Prevents mitochondrial damage
- Preserves cognitive function in mice



Graham WV, Bonito-Oliva A, Sakmar TP et al. *Annual Review of Medicine*. 2017;68(1):413-430.

New Drug Targets: Tau Aggregation Inhibitor

- Rember TM: discontinued
  - First generation
- TRx0237: phase III
  - Second generation



Graham WV, Bonito-Oliva A, Sakmar TP et al. *Annual Review of Medicine*. 2017;68(1):413-430.

New Drug Targets: P-Tau Clearance

Active Immunization Vaccines

- AADvac-1: phase II
- ACI-35: phase I

Passive Immunization

- Generalized into four categories
  - Hyperphosphorylated tau
  - Conformation of tau
  - Fragments of tau
  - Total tau

Graham WV, Bonito-Oliva A, Sakmar TP et al. *Annual Review of Medicine*. 2017;68(1):413-430.

New Drug Targets: Microglia Inhibitors

- Neuroinflammation in response to Aβ induces the activation of microglia and the recruitment of astrocytes to the sites where Aβ deposits occur
- Microglia enters a hyper-reactive state in neurodegenerative conditions and aging
- Sustained over-production of microglial pro-inflammatory mediators is neurotoxic

Graham WV, Bonito-Oliva A, Sakmar TP et al. *Annual Review of Medicine*. 2017;68(1):413-430.

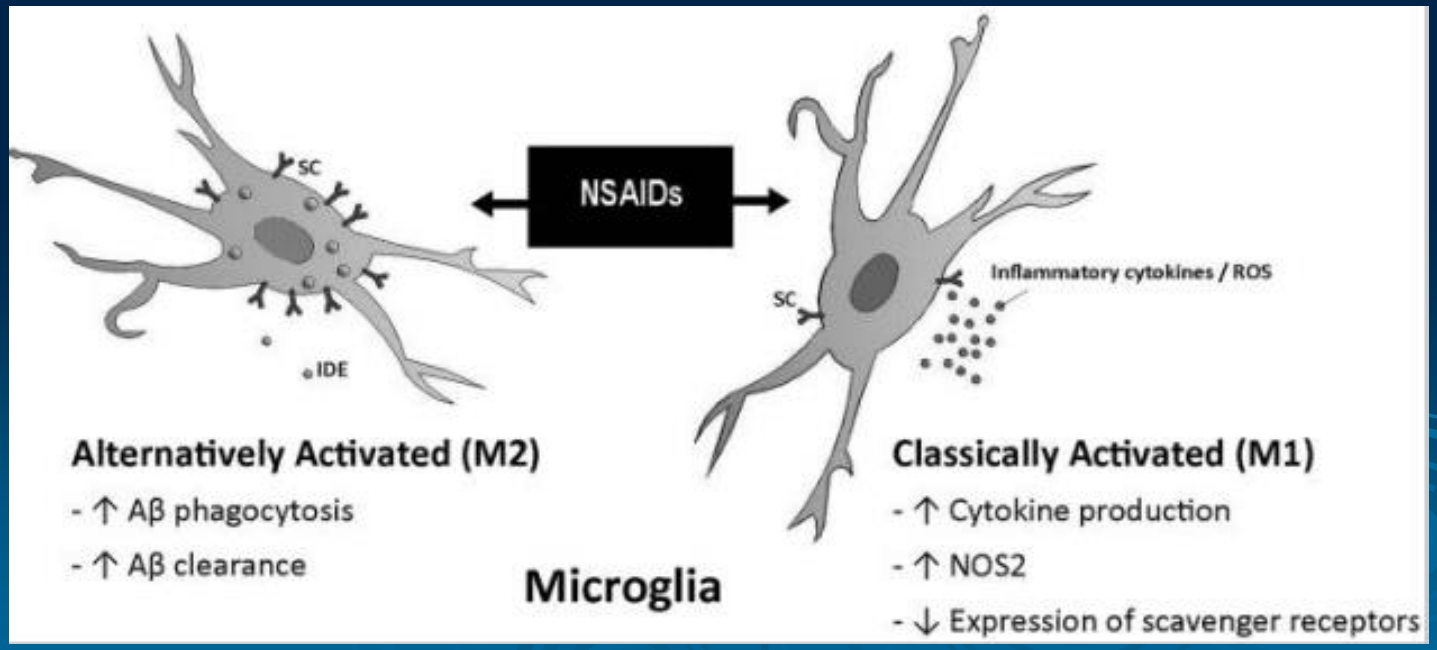
New Drug Targets: Microglia Inhibitors

- Alzhemed: discontinued
  - Phase III trial showed tolerability & safety→ study inactive
- Azeliragon: phase III
  - Inhibitor of receptor for advanced glycation end products (RAGE) preventing inflammation and oxidative damage

Graham WV, Bonito-Oliva A, Sakmar TP et al. *Annual Review of Medicine*. 2017;68(1):413-430.

New Drug Targets: Microglia Inhibitors

- No evidence supports the use of NSAIDs in reducing neuroinflammation
- Ibuprofen: discontinued
- Flurizan: discontinued



Graham WV, Bonito-Oliva A, Sakmar TP et al. *Annual Review of Medicine*. 2017;68(1):413-430.

New Drug Targets: Glycogen Synthase Kinase Inhibitor

- Glycogen Synthase Kinase 3 (GSK-3) leads to the hyperphosphorylation of tau
- Lithium is a GSK-3 inhibitor
- Lithium is a narrow therapeutic drug and not well tolerated
- Studies of micro-doses of lithium have demonstrated improvement in cognitive studies
- Studies limited by sample sizes and not FDA approved for treatment in AD

Allgaier M. *Frontiers in Bioscience*. 2014;19(8):1345.

New Drug Targets: Phase II/III or III

BACE Inhibitors

- AZD 3293
- CNP520
- JNJ-54861911
- Verubecestat

Immunotherapy Aβ Clearance

- Crenezumanb
- Gantenerumab
- Aducanumab

Tau Aggregation Inhibitors

- TRx0237

Microglial Inhibitors

- Azeliragon

Allgaier M. *Frontiers in Bioscience*. 2014;19(8):1345.

New Drug Targets: Phase II

Glutaminergic

- Riluzole

Gamma Secretase Inhibitor

- EVP-0962

BACE Inhibitor

- E2609

Immunotherapy Aβ Clearance

- Ban2401

Active Immunization Vaccines: P-Tau Clearance

- AADvac-1

Allgaier M. *Frontiers in Bioscience*. 2014;19(8):1345.

Clinical Impact of Current Medications

- Current FDA approved medications for Alzheimer's disease only manages symptoms and does not slow or prevent the progression of neurodegeneration
- Cognitive decline of Alzheimer's disease commonly appear years after the pathophysiological progression
- Once Alzheimer's disease has severely progressed the use of FDA approved medications, such as the ACEI and NMDA antagonists, may not benefit the patient

Birks J, Harvey R. *Cochrane Database of Systematic Reviews*. 2018;(6).

Clinical Impact of Current Medications

- Dependent on the clinical manifestation of cognitive impairment
- Used during the late stages of Alzheimer's disease
- Limited evidence on the specific time frame to discontinue treatment
- Reasonable to stop a medication when….
  - No noticeable benefit after the first three months of treatment
  - Dementia progresses to a point where there would be no meaningful benefit from continued therapy

Birks J, Harvey R. *Cochrane Database of Systematic Reviews*. 2018;(6).

Kishi T, Matsunaga S, Oya K, Nomura I, et al. *Journal of Alzheimers Disease.* 2017;60(2):401-425.

Clinical Impact of New Drug Targets

- New Drug targets intended to use as disease-modifying treatment
- Limitation
  - Benefit expected to be seen if used during early stages of Alzheimer's disease prior to development of cognitive impairment
  - Requires ability to find biomarkers to detect development of Alzheimer's disease
    - PET Scanning
    - CSF

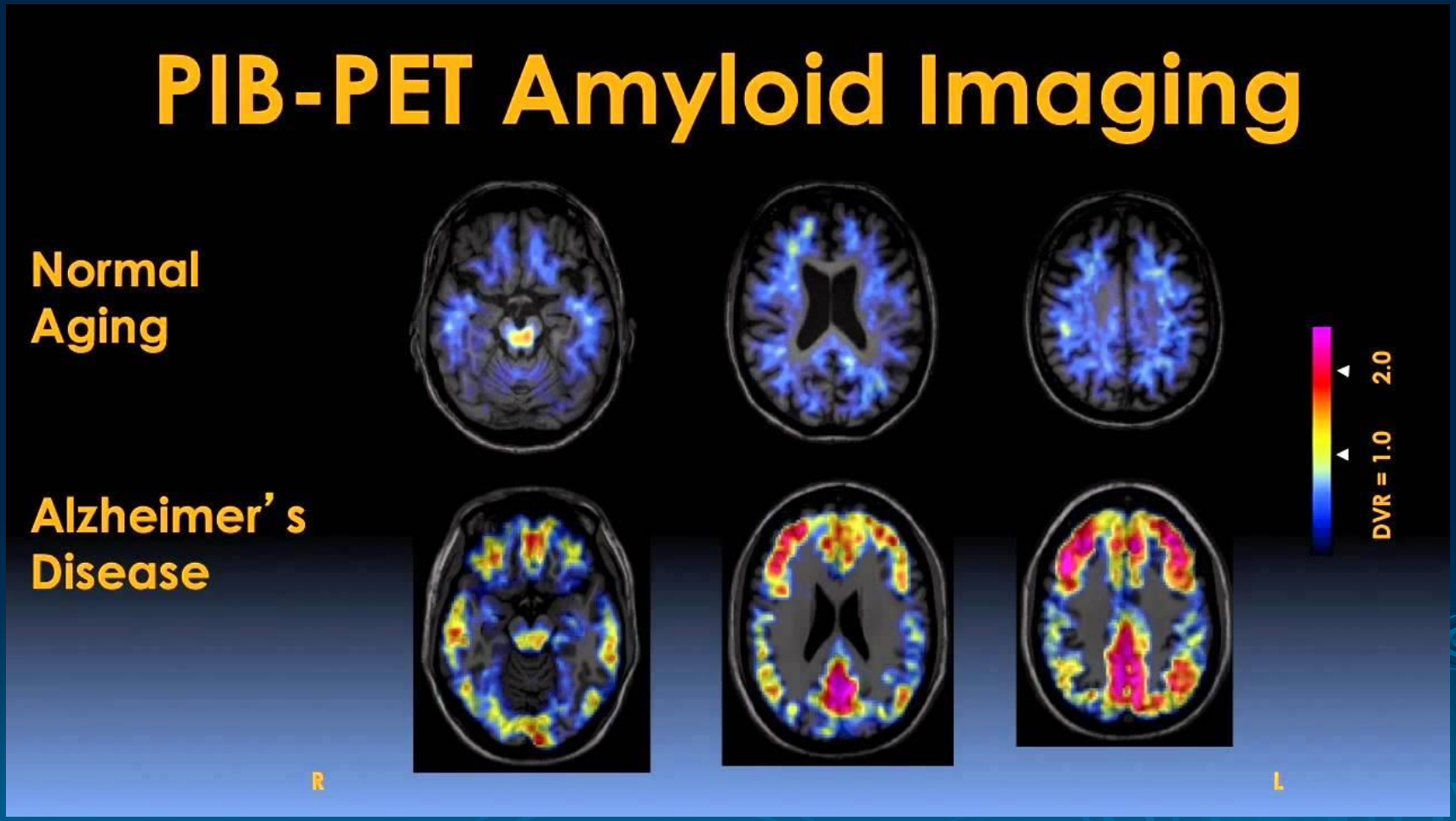
Khoury R, Patel K, Gold J, et al. *Drugs & Aging*. 2017;34(11):811-820.

Clinical Impact: Brigham & Women's Trial

- A4 Trial
  - **A**nti-**A**myloid treatment in **A**symptomatic **A**lzheimer's disease
  - Targeting early detection of amyloid plaques for prevention of cognitive impairment associated with Alzheimer's disease
  - Positron emission tomography (PET) scans that can identify plaque buildup
  - Multi-site, randomized double-blind study, enrolling 1000 patients ages 65-85
  - Half randomized to solanezumab vs. placebo

Brigham and Women's Hospital. *A4 study*. 2017.

Clinical Impact- PET SCANNING

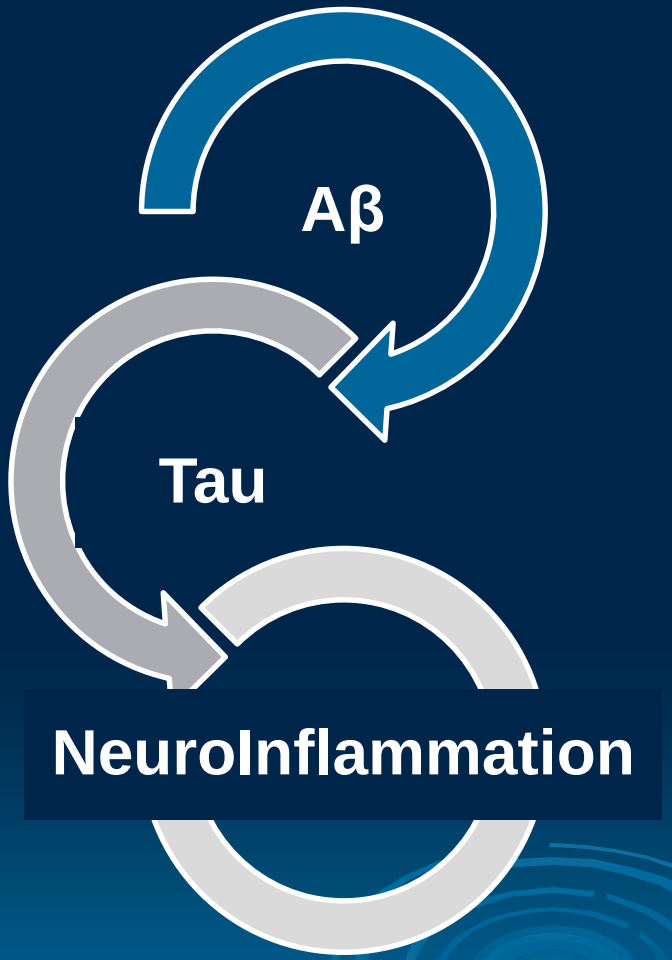


Brigham and Women's Hospital. *A4 study*. 2017.

Khoury R, Patel K, Gold J, et al. *Drugs & Aging*. 2017;34(11):811-820.

Clinical Impact

- Use multiple medications with varying targets to prevent progression of Alzheimer's disease
- Will changes in concentration of amyloid plaques or use of biomarkers be indicative of clinical outcomes?



Khoury R, Patel K, Gold J, et al. *Drugs & Aging*. 2017;34(11):811-820.

Conclusion

- As life expectancy increases, Alzheimer's disease will become more of an epidemic
- All causes of Alzheimer's disease are still not known, but associated with amyloid plaques and neurofibrillary tangles
- Current treatment for Alzheimer's disease are only symptomatic and often used in response to cognitive impairment

Conclusion

- Development of multiple new drug targets for Alzheimer's disease are entering phase II/III clinical trials

- New drug targets intended for use as disease modifying treatments and will require early detection of Alzheimer’s disease

True or False Questions

- Once initiated, donepezil and memantine should be given indefinitely for the treatment of Alzheimer's disease regardless of cognitive function.
- Lithium in microdoses is FDA approved for prevention of Alzheimer's disease, it works by reducing hyperphosphorylation of tau through glycogen synthase inhibition
- Amyloid directed active immunotherapy treatment reduces β-amyloid plaque formation but can lead to the development of meningoencephalitis

True or False Questions

- FALSE: Once initiated, donepezil and memantine should be given indefinitely for the treatment of Alzheimer's disease regardless of cognitive function.
- FALSE: Lithium in microdoses is FDA approved for prevention of Alzheimer's disease, it works by reducing hyperphosphorylation of tau through glycogen synthase inhibition
- TRUE: Amyloid directed active immunotherapy treatment reduces β-amyloid plaque formation but can lead to the development of meningoencephalitis

THANK YOU
Questions?

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