A4M | MEDICINE REDEFINED

Galectin-3:

Target for Neuroinflammation Prevention

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- Academic Co Chair A4M
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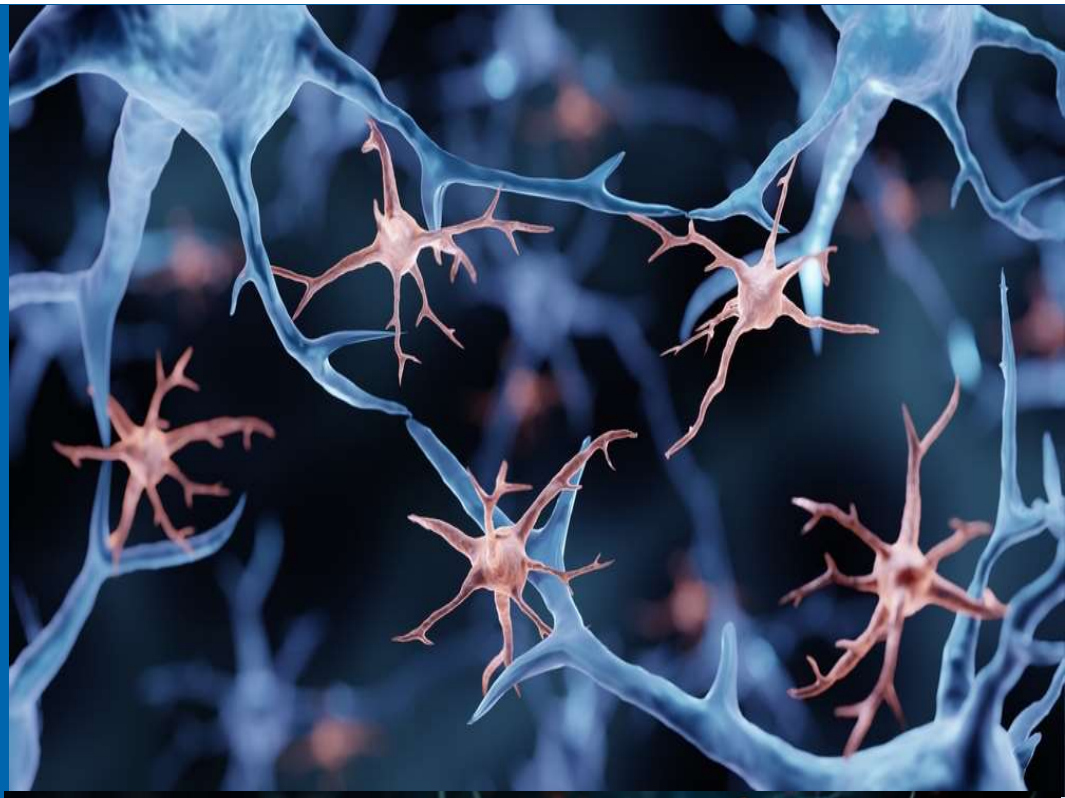

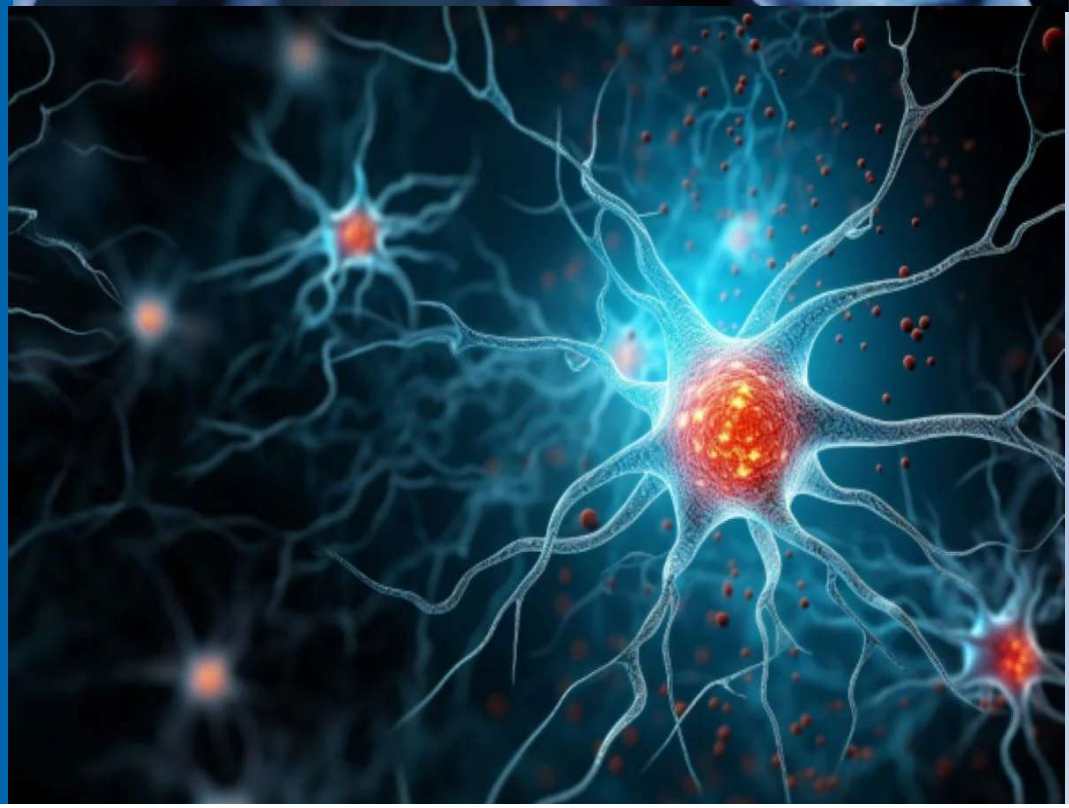

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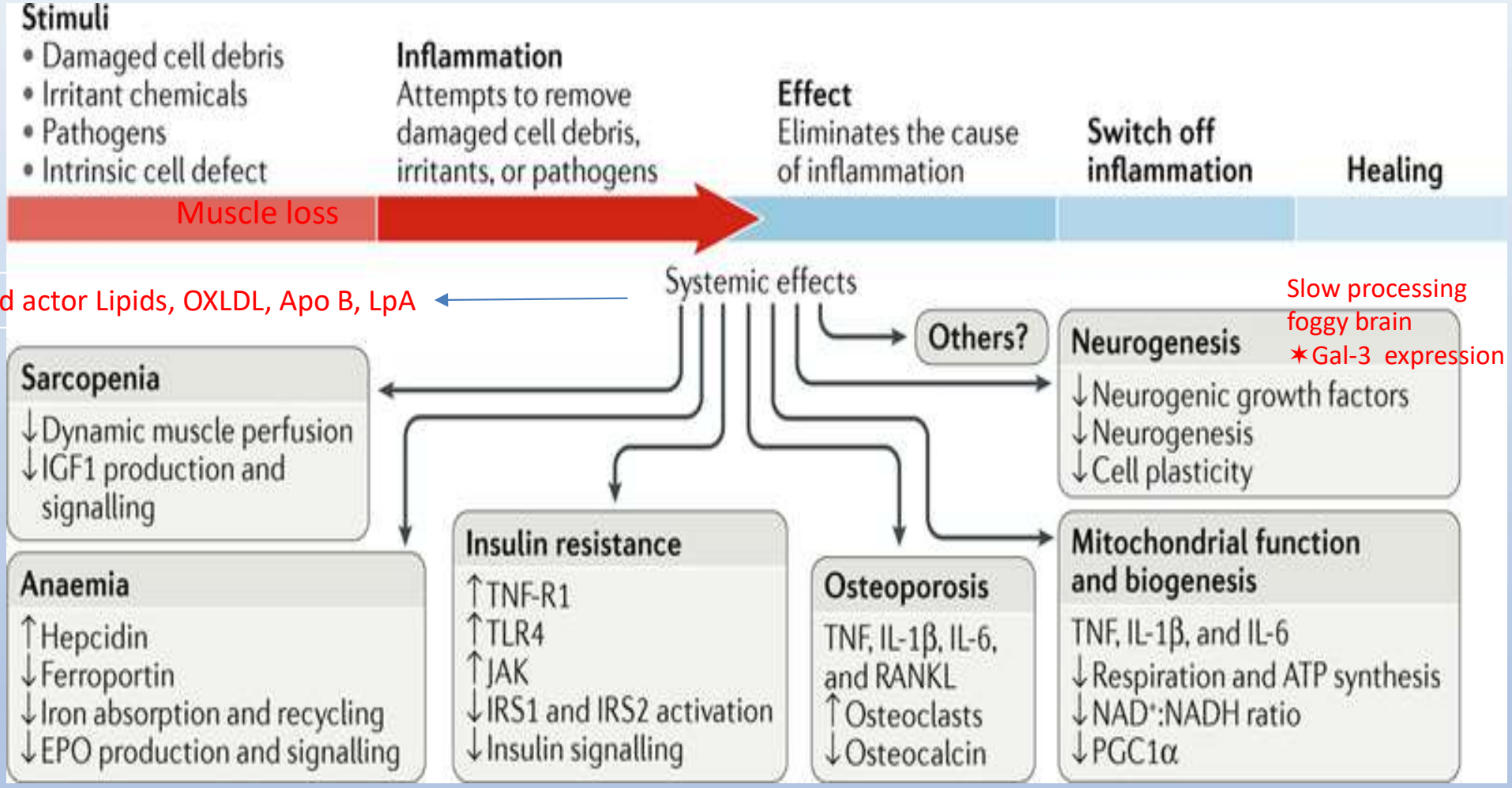
Metaflammation Leads to Inflammaging

Connecting The Downward Spiral to Dementia/AD



- Fatigue
- Palpitation
- Ferroptosis

- Weight Gain
- diabetes
- CVD, PVD,HTN, CHF
- Dementia

- Fractures

- Loss of Energy Capacity
- Damage DNA
- Cytokine Storm

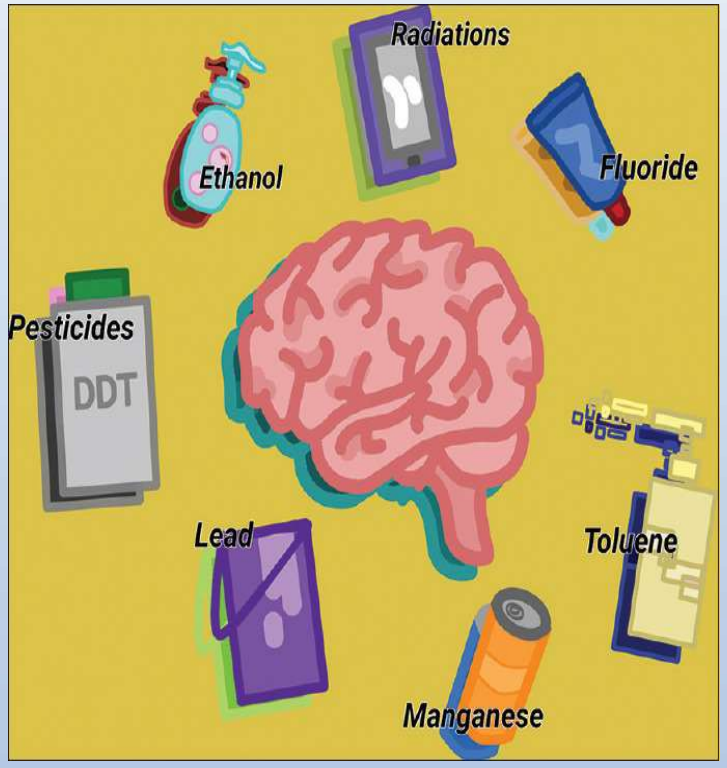
- Ferrucci L, et al. Inflammageing: chronic inflammation in ageing, cardiovascular disease and frailty. Nat Rev Cardiol. 2018;15(9):505-22.

Key Tenants: Aging and Performance

- Oxidative Stress / Inflammation
- Sex Hormonal Balance
- Stress Hormones
- Glucose / Insulin Regulation
- Immune Balance
- Gut Integrity/Microbiome
- Environmental Burden
- Individuality

Environmental Burden and Neurotoxicity

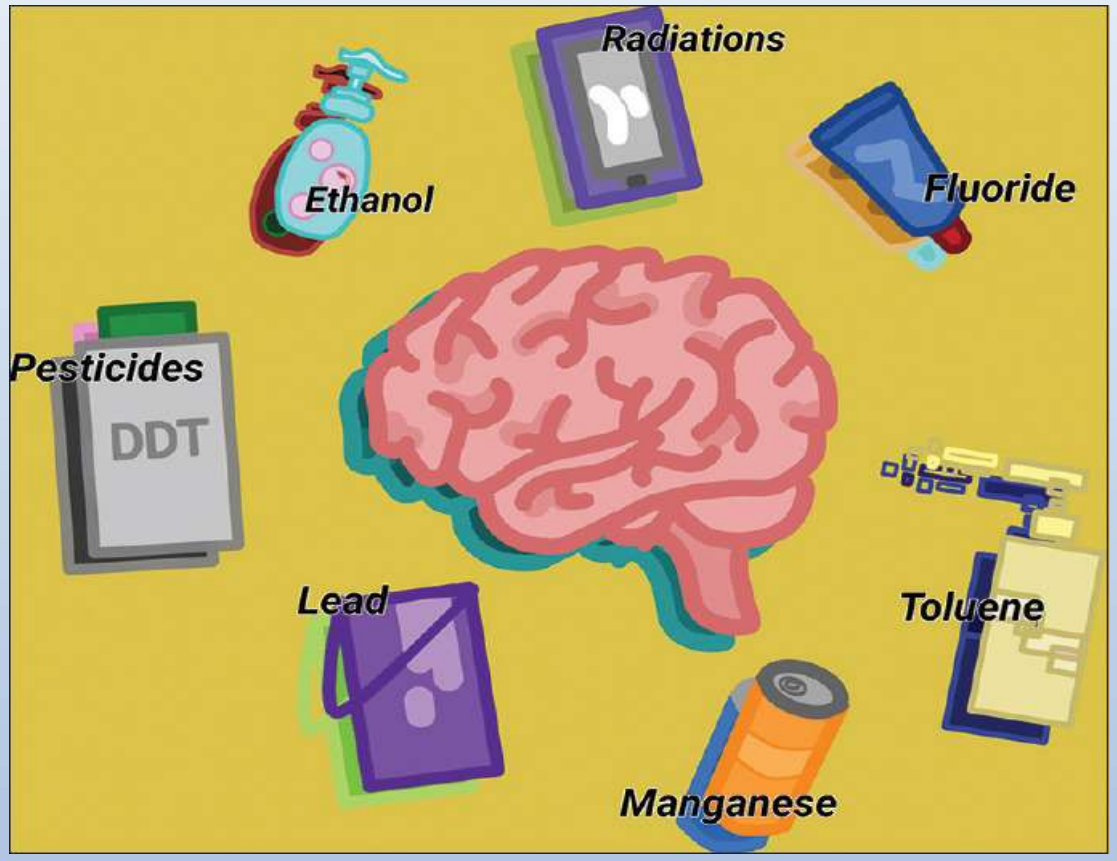
- Manganese - Excessive occupational exposure to Mn as a component of welding fumes and mining associated with neuronal damage in PD
  - In addition, Mn-exposed patients do not respond well to the classic PD levadopa therapy
- Diesel exhaust – increased microglial neuroinflammation
- PCBs (polychlorinated biphenyls) – increased peripheral neuropathies



Kraft AD, et al. Features of Microglia and Neuroinflammation Relevant to Environmental Exposure and Neurotoxicity. Int J Environ Res Public Health. 2011;8(7):2980-3018.
Aggarwal V, et al. Environmental toxins and brain: life on earth is in danger. Ann Indian Acad Neurol. 2022;25(Suppl 1):S15-S21.

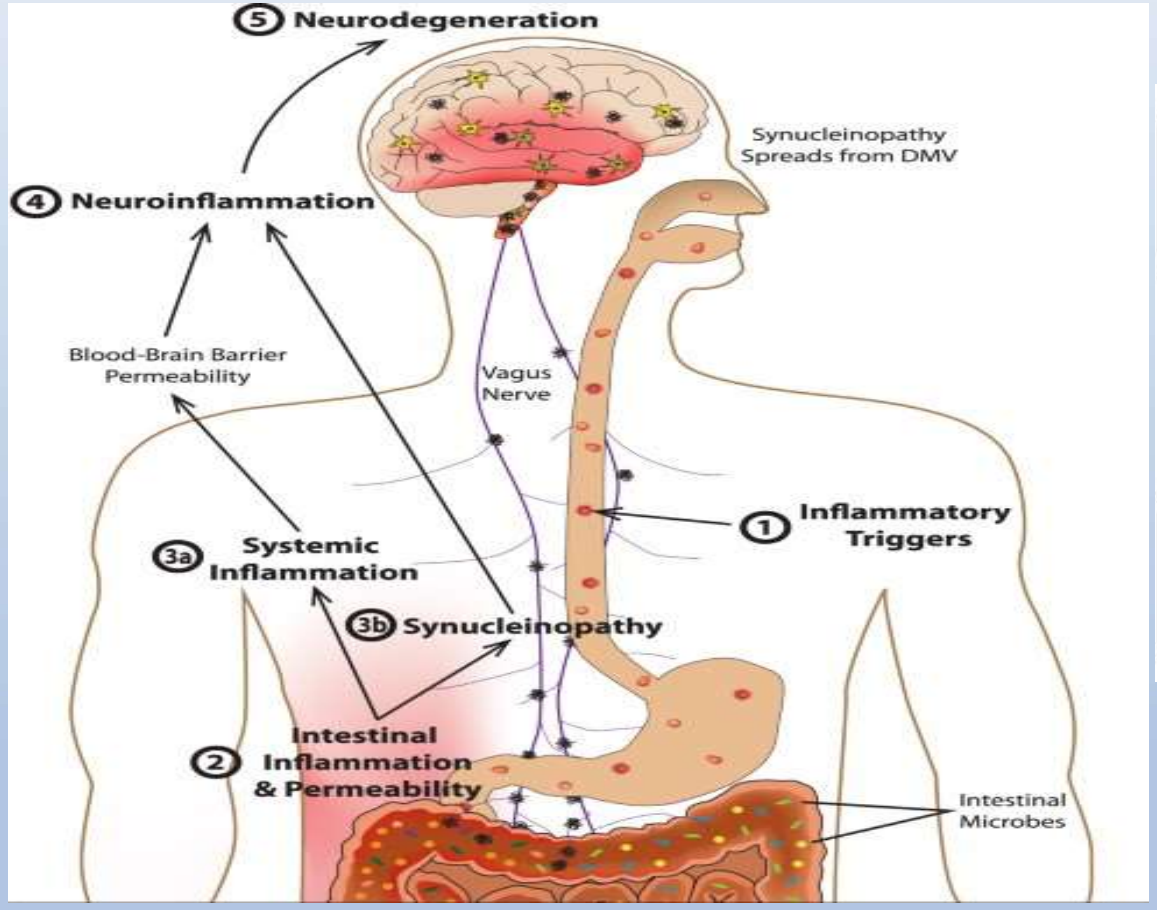
Environmental Burden and Neurotoxicity

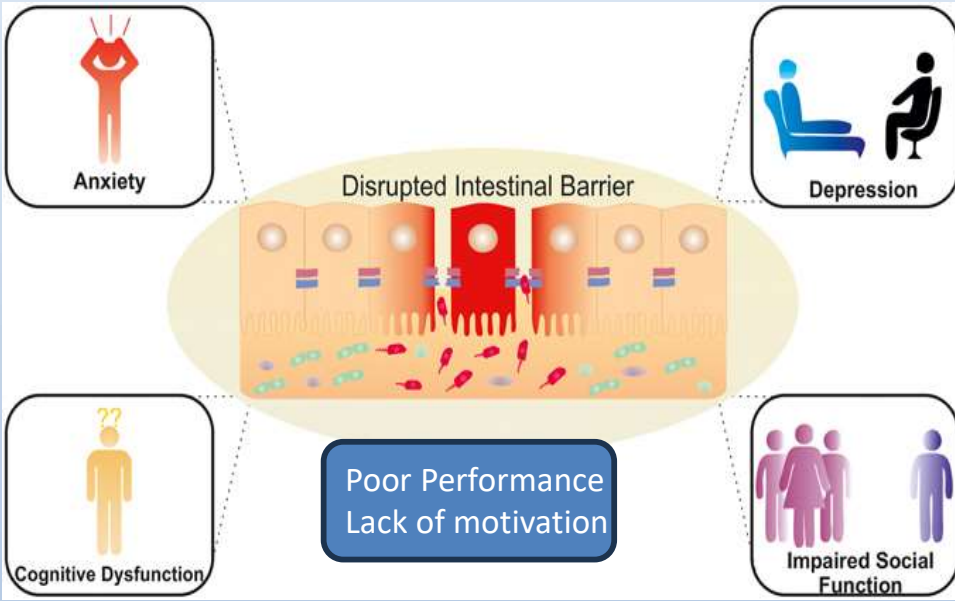
- BPA/phthalates
- Pesticides
- Mycotoxins
- Lead, mercury, cadmium
- Ozone
- Fluoride



Kraft AD, et al. Features of Microglia and Neuroinflammation Relevant to Environmental Exposure and Neurotoxicity. Int J Environ Res Public Health. 2011;8(7):2980-3018.
Aggarwal V, et al. Environmental toxins and brain: life on earth is in danger. Ann Indian Acad Neurol. 2022;25(Suppl 1):S15-S21.

GUT Barrier Dysfunction Can Lead to Neuroinflammation and Resulting Pathology





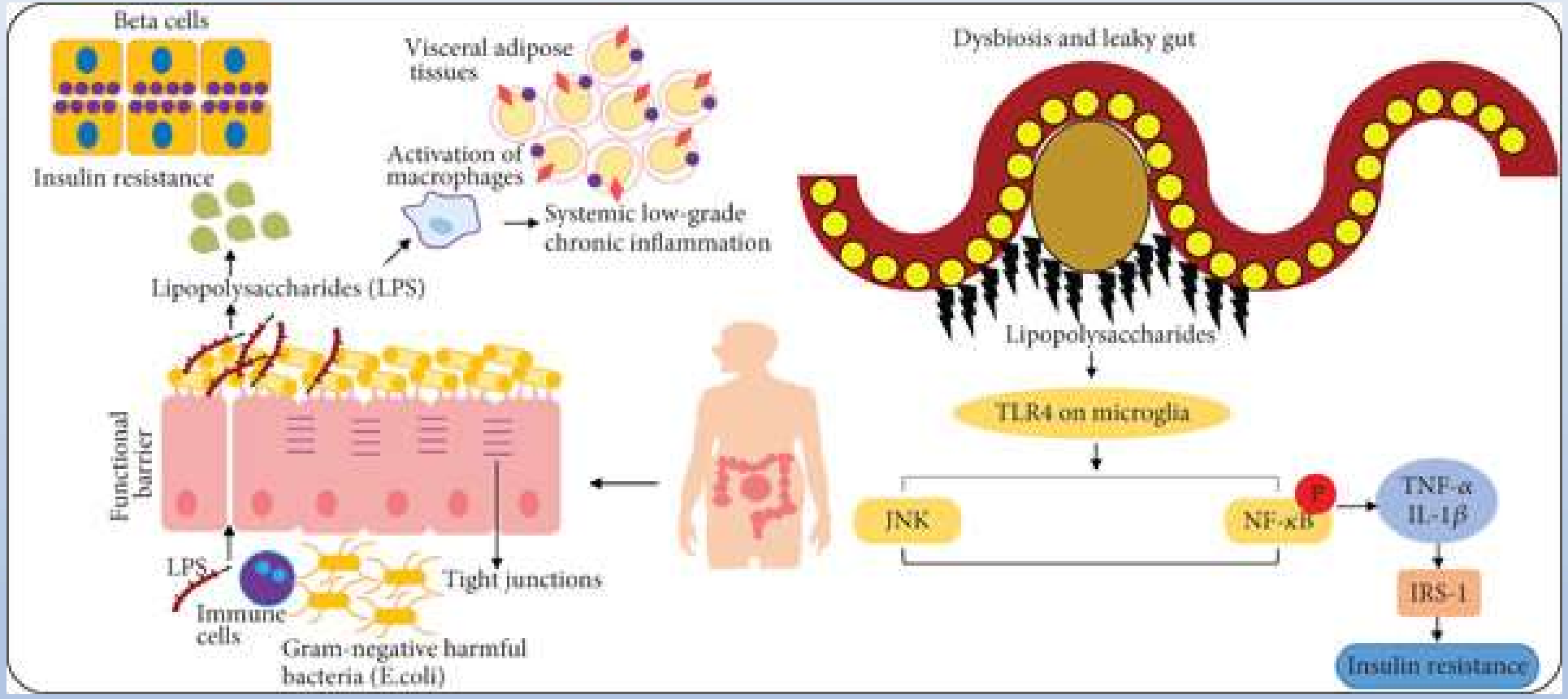
Kelly JR, et al. Front Cell Neurosci. 2015;2015:9

LPS Upregulation in Neuroinflammation

- LPS = potent endotoxin
- Activates innate immunity – Toll-like receptor 4 (TLR4) signaling
- Activates pro-inflammatory cytokines – like TNF-alpha, IL-6
- Chronic LPS = increases oxidative stress, synaptic dysfunction and neuronal damage/death
- Leads to neurodegeneration - contributes to conditions like Parkinson's and Alzheimer's

Batista CRA, et al. Lipopolysaccharide-Induced Neuroinflammation as a Bridge to Understand Neurodegeneration. Int J Mol Sci. 2019;20(9):2293.

Dysbiosis, Leaky GUT, LPS ⟹ IR



Khan MS, et al. Pathology, Risk Factors, and Oxidative Damage Related to Type 2 Diabetes-Mediated Alzheimer's Disease and the Rescuing Effects of the Potent Antioxidant Anthocyanin. Ox Med Cell Longev. 2021;4051207.

LPS – Lipopolysaccharide

- Endotoxin = large, heat stable lipopolysaccharides LPS
  - Major glycolipid component of the outer membrane of gram-negative bacteria
  - Comprises approximately 70% of the total bacteria in the gut
- LPS contains a PAMP– Lipid A
  - Initiates signaling cascade activating pro-inflammatory pathways when bound to receptor TLR4 - Toll-Like Receptor 4
- Endotoxin can enter the blood by either local or systemic infection by exogenous gram-negative bacteria

Mohammad S, et al. Front Immunol. 2020;11:594150

What is Galectin-3 (Gal-3)

- Gal-3 = pleiotropic protein
- Binds to B-galactoside residues in glycoproteins
- Mainly expressed and released in damaged brain by reactive microglia
- Interacts w/ immune receptors including TREM2 and TLR4

Siew JJ, et al. Neurosci. 2024;134(2):e165523.

GAL-3 and LPS

- GAL-3 (galectin-3) – mainly expressed and released in damaged brain by reactive microglia
- GAL-3 levels can be increased in athletes, esp. endurance
- **GAL-3 binds to LPS**
- Amplifies LPS-induced inflammation by activating inflammatory signaling pathways

Yubin L, et al. Galectin-3 is a negative regulator of lipopolysaccharide-mediated inflammation. J Immunol. 2008;181(4):2781-9.

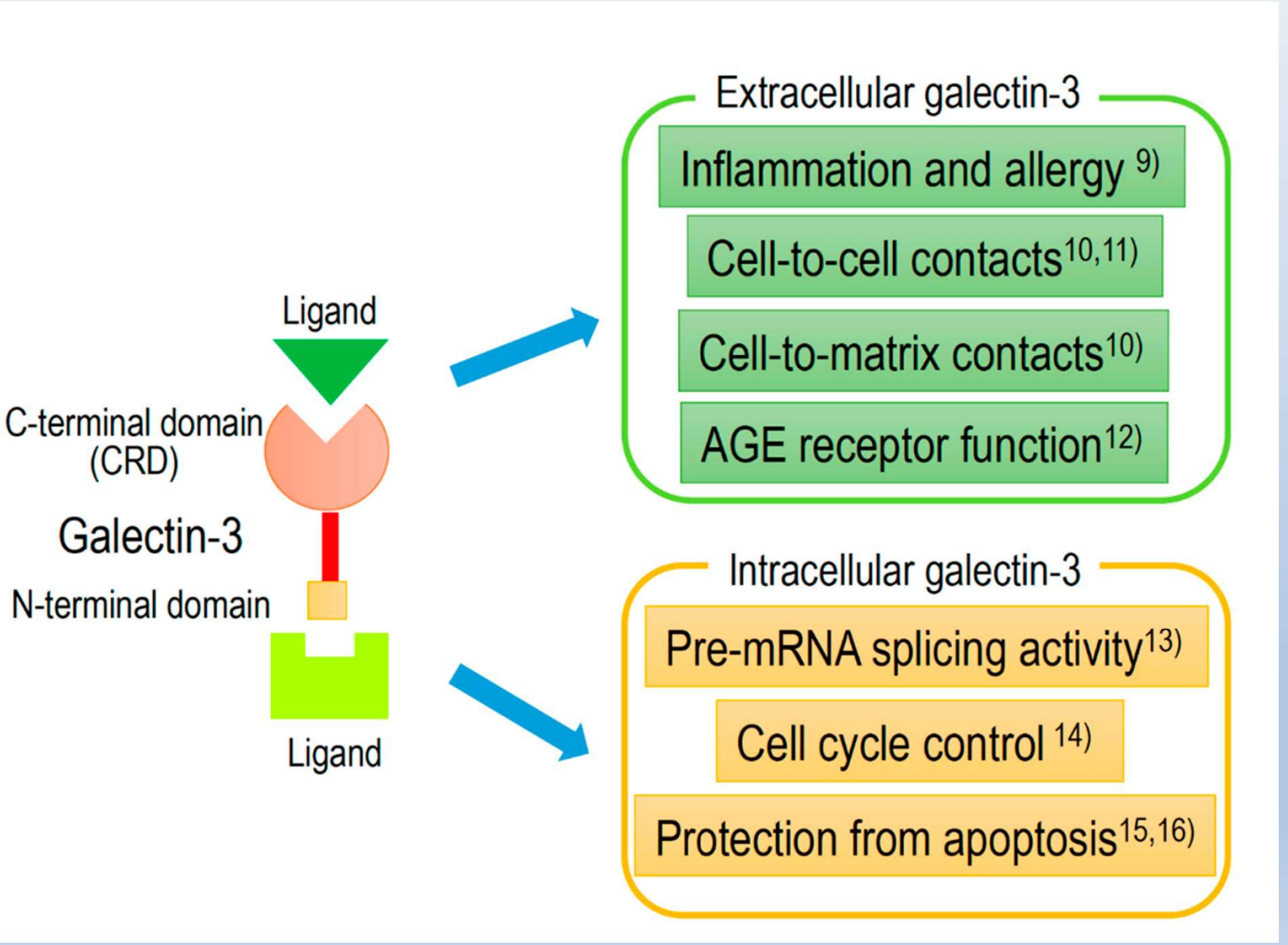
Galectin-3 (Gal-3)

- Plays role in :
  - Cell growth
  - Inflammation/neuroinflammation
  - Fibrosis – including heart failure progression
  - Involved in microglial activation in CNS
  - Expression of both M1 &M2 macrophages

- Levels may be increased in cancer and other conditions associated w/ organ fibrosis including cardiac failure, TBI, stroke, AD/dementias

Siew JJ, et al. Neurosci. 2024;134(2):e165523.

Gal-3 Intra- and Extracellular Functions



Hara A, et al. Biomolecules. 2020;10:389.

Gal-3: Systems Biology Implications

Galectin-3: A Single Protein with Systemic Implications

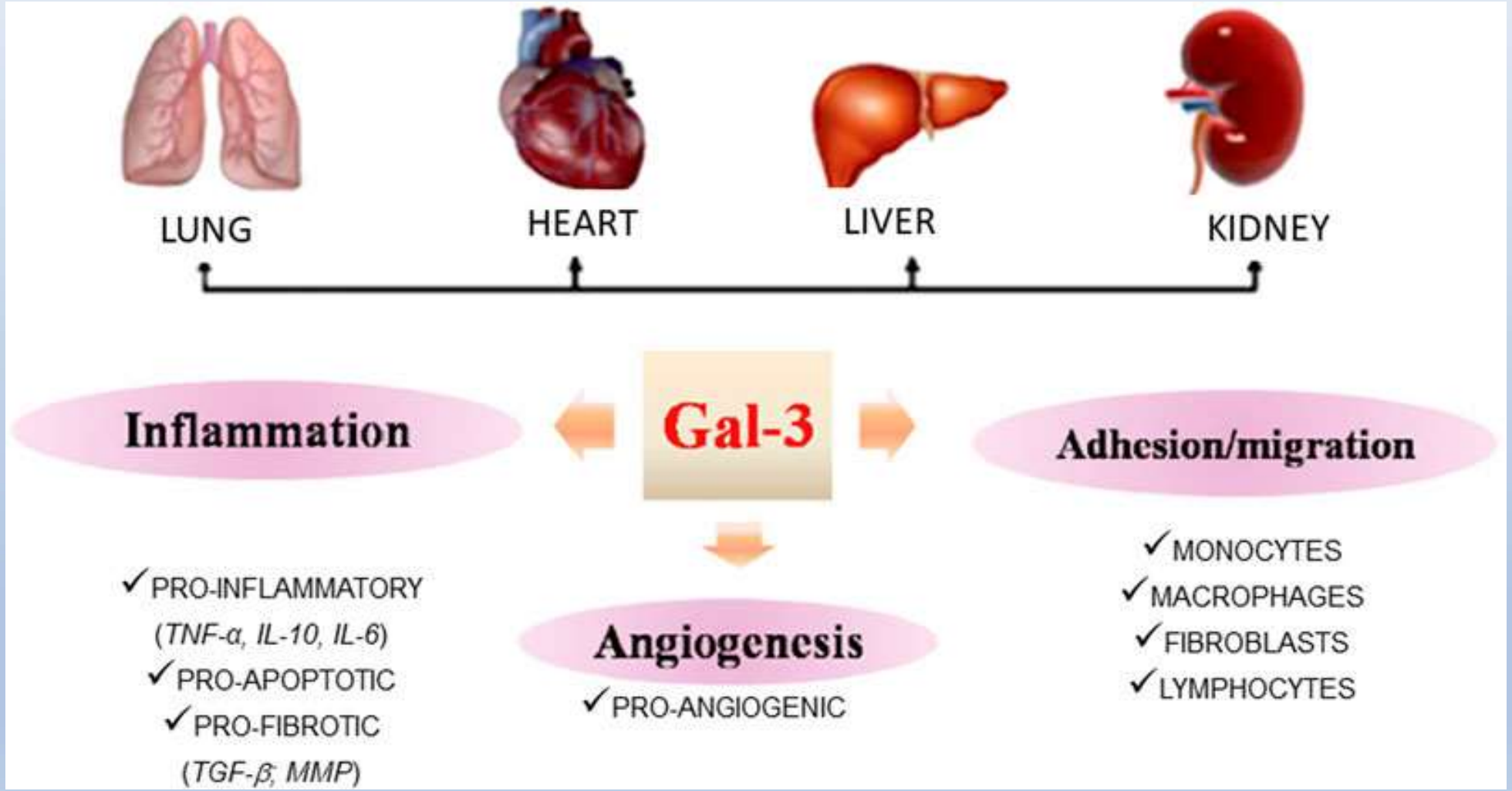
Review

Galectin-3: One Molecule for an Alphabet of Diseases, from A to Z

Aa	Bb	Cc	Dd	Ee	Ff	Gg	Hh	Ii	Jj	Kk	Ll	Mm
Asthma Atherosclerosis Atopic Dermatitis	Blood test	Cancer Cerebral infarction COPD	Degenerative Aortic Stenosis Diabetes Mellitus	Endometriosis Enteric nervous system Encephalitis	Fibrosis	Gastritis	Heart HIV Infection	Inflammation Interstitial lung disease	Juvenile Idiopathic Arthritis	Kidney	Liver Fibrosis	Mortality

Nn	Oo	Pp	Qq	Rr	Ss	Tt	Uu	Vv	Ww	Xx	Yy	Zz
NASH	Obesity	Pneumonia Pulmonary hypertension Plaque Psoriasis	Q Fever	Rheumatoid Arthritis	Sepsis Systemic Sclerosis	Target therapy	Urinary tract infections	Venous Thrombosis	Wound Healing	X syndrome of the heart	Yeast infection – Candidiasis	Zoster-related pain

Tissue Expression of Gal-3 and Role in Inflammation



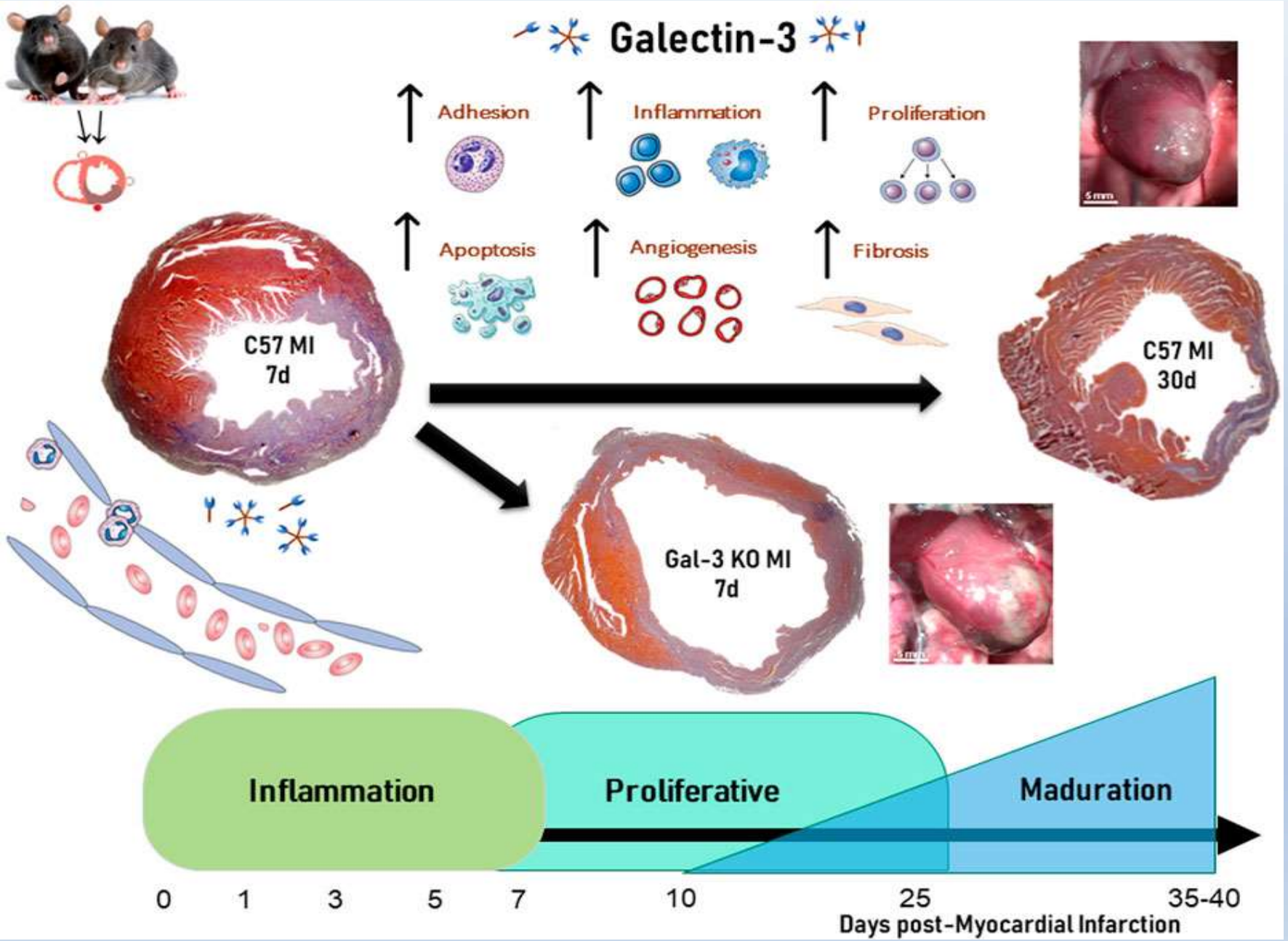
Seropian IM, et al. Front Physiol. 2023;14:1304735.

Gal-3 - Diabetes

- Gal-3 levels elevated in chronic inflammatory diseases including obesity, diabetes and its complications
- Gal-3 levels significantly higher in T2D patients
- **Elevated Gal-3 levels associated w/ increased HbA1c, FPG and hsCRP**
- Study findings suggests Gal-3 may play a role in the progression of prediabetes stage to diabetes stage

Li Y, et al. Rev Endocr Metabol Disorders. 2022;23:569-77.

Gal-3 CVDs


Galectin-3
Adhesion
Inflammation
Proliferation
Apoptosis
Angiogenesis
Fibrosis
C57 MI
7d
C57 MI
30d
Gal-3 KO MI
7d
Inflammation
Proliferative
Maduration
0
1
3
5
7
10
25
35-40
Days post-Myocardial Infarction

Key Concept

A doubling in galectin-3 level over the course of 6 months, irrespective of baseline value, identifies a high-risk patient in whom additional care management efforts and advanced therapies are warranted

McCullough PA, et al. Rev Cardiovasc Med. 2011;12(4):200-10.

Gal-3 Lab Testing

- Gal-3 lab range : < 22.2 ng/ml (LabCorp)
  - Levels ≤ 17.8 ng/ml – low risk of adverse outcomes
  - 17.8 – 22.2 ng/ml – moderate risk of adverse outcomes
  - > 22.2 ng/ml = high risk of adverse outcomes
- Studies report levels of Gal-3 > 25.9 predict patients likely to rapidly progress to heart failure

Siew JJ, et al. Neurosci. 2024;134(2):e165523.

Gal-3 COVID-19

- Severe COVID-19 associated w/ systemic hyperinflammation leading to acute respiratory distress syndrome, multi-organ failure and death

- 2022 study n= 156 patients Sars-CoV-2 positive
- Increased Gal-3 levels reported to correlate well between severe and non-severe outcomes

- Also correlated w/ other markers of COVID-19 severity (hs-CRP, NLR, D-dimer, neutrophil count)

- Authors concluded Gal-3 levels independent predictor of severe outcome

Cervantes-Alvarez E, et al. Sci Reports. 2022;12:1856.

Gal-3 Neurological Issues

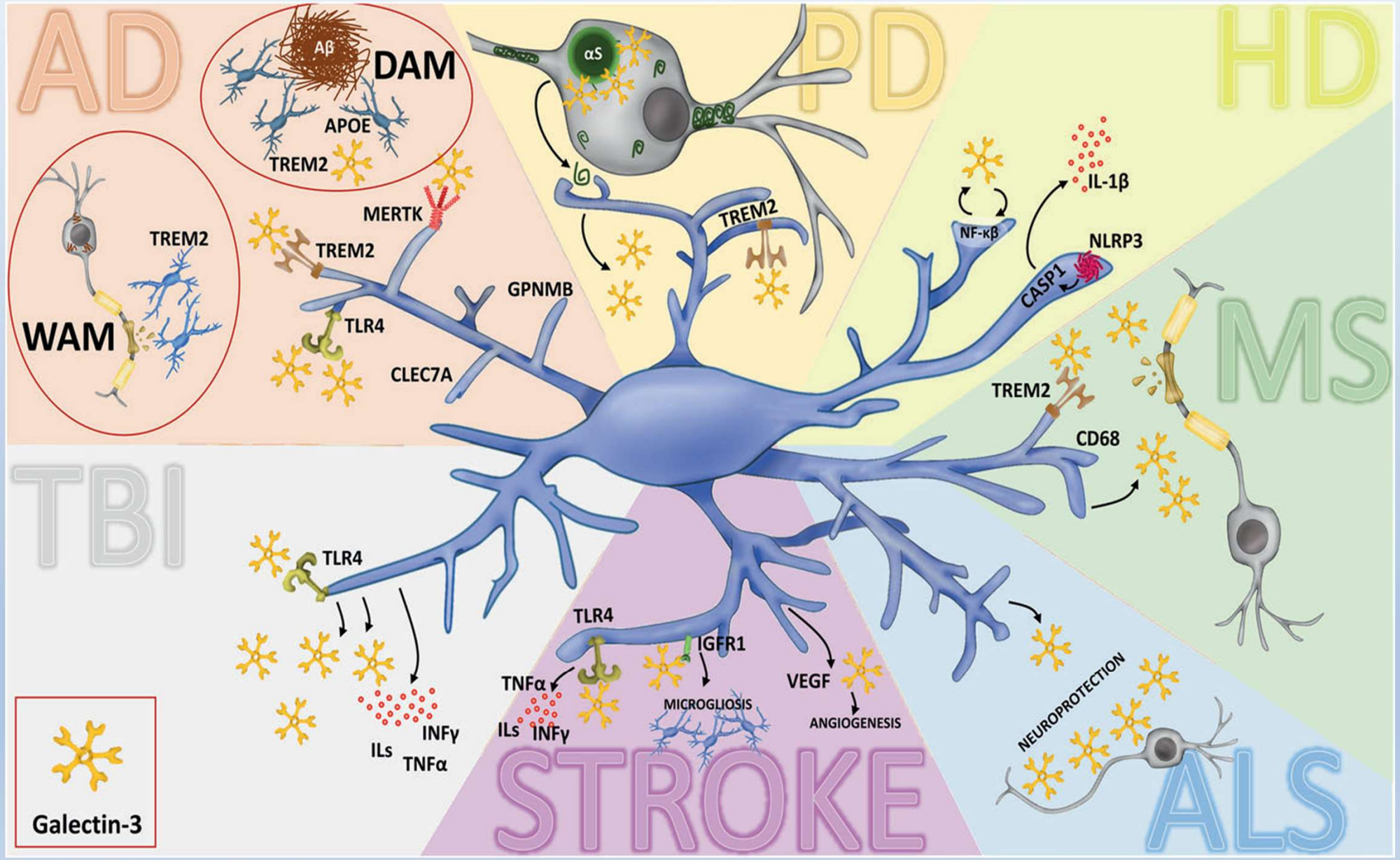
- Dysregulated microglial activation and altered homeostatic functions contribute to neurodegeneration

- Microglia express multiple types of lectins (e.g., galectins)
  - Serve as critical checkpoints for microglial activation
  - Contribute to neurodegeneration

- **Gal-3 is a proinflammatory autocrine mediator that can**:
  - Bind toll-like receptor 4 (TLR4)
  - And the receptor expressed on myeloid cells-2 (TREM2)
  - **KEY PLAYER in microglial mediated neuroinflammation**

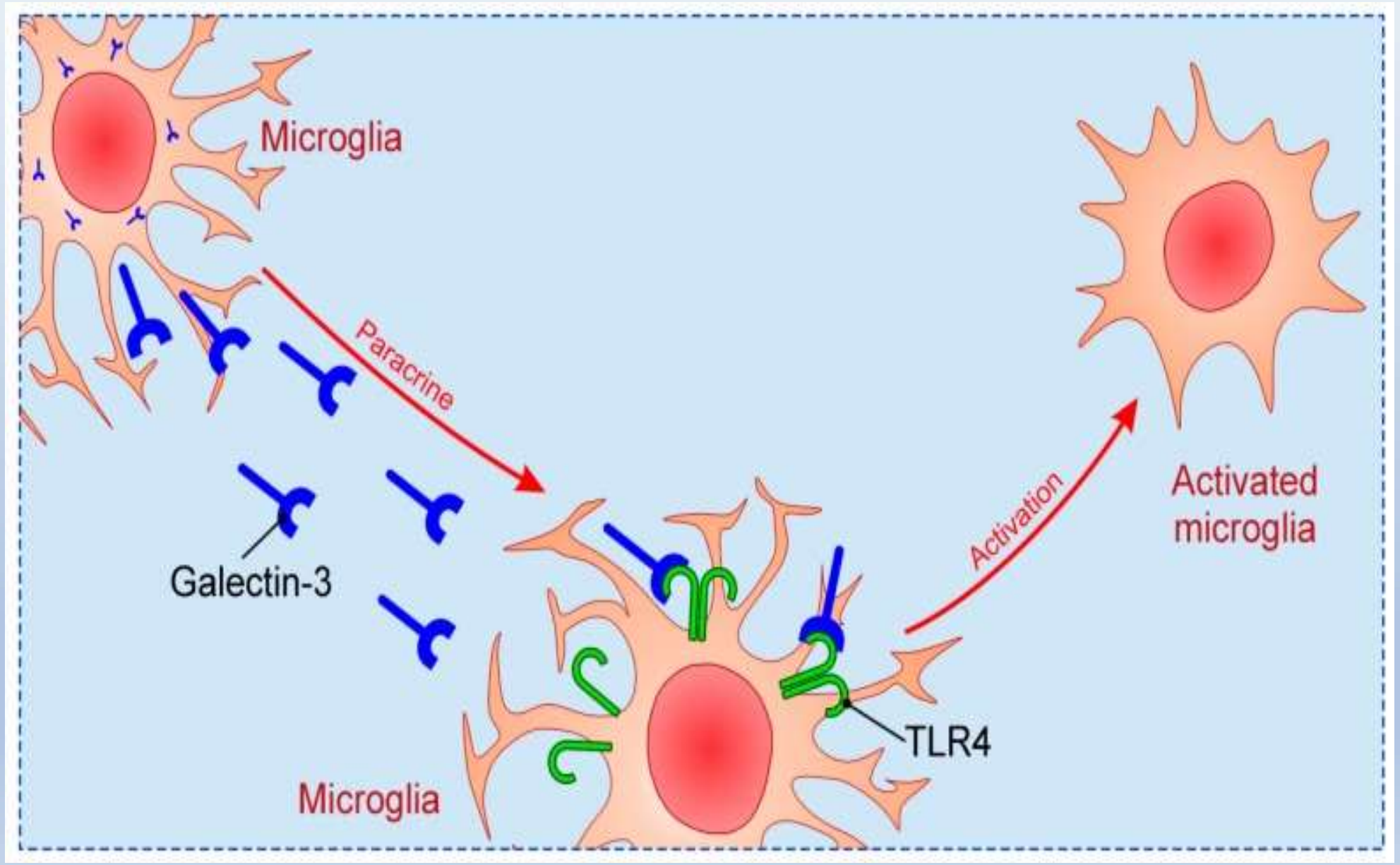
Weigand AJ, et al Brain Commun. 2020;**2**(1):fcz046.

Gal-3 in Microglia-Associated Neurodegenerative Diseases



Garcia-Revilla J, et al. Cell Death Dis. 2022;13:628.

Gal-3 Influence on Neuroinflammation



Srejovic I, et al. Glactin-3: Roles in Neurodevelopment, neuroinflammation, and behavior. Biomolec. 2020;10(5):798.

Gal-3 Dementia/Alzheimer's

- Large-scale proteomic analysis of brains in individuals with AD recently identified Gal-3 in a microglial metabolism module enriched with genetic risk factors of AD

- Alzheimer's disease - characterized by:
  - Accumulation of amyloid-β plaques,
  - Aggregation of hyperphosphorylated tau (pTau) - tauopathy
  - **Microglia activation and inflammation**

- **Gal-3 plays crucial deleterious role in microglial activation in Alzheimer's disease (AD) and other forms of dementias**

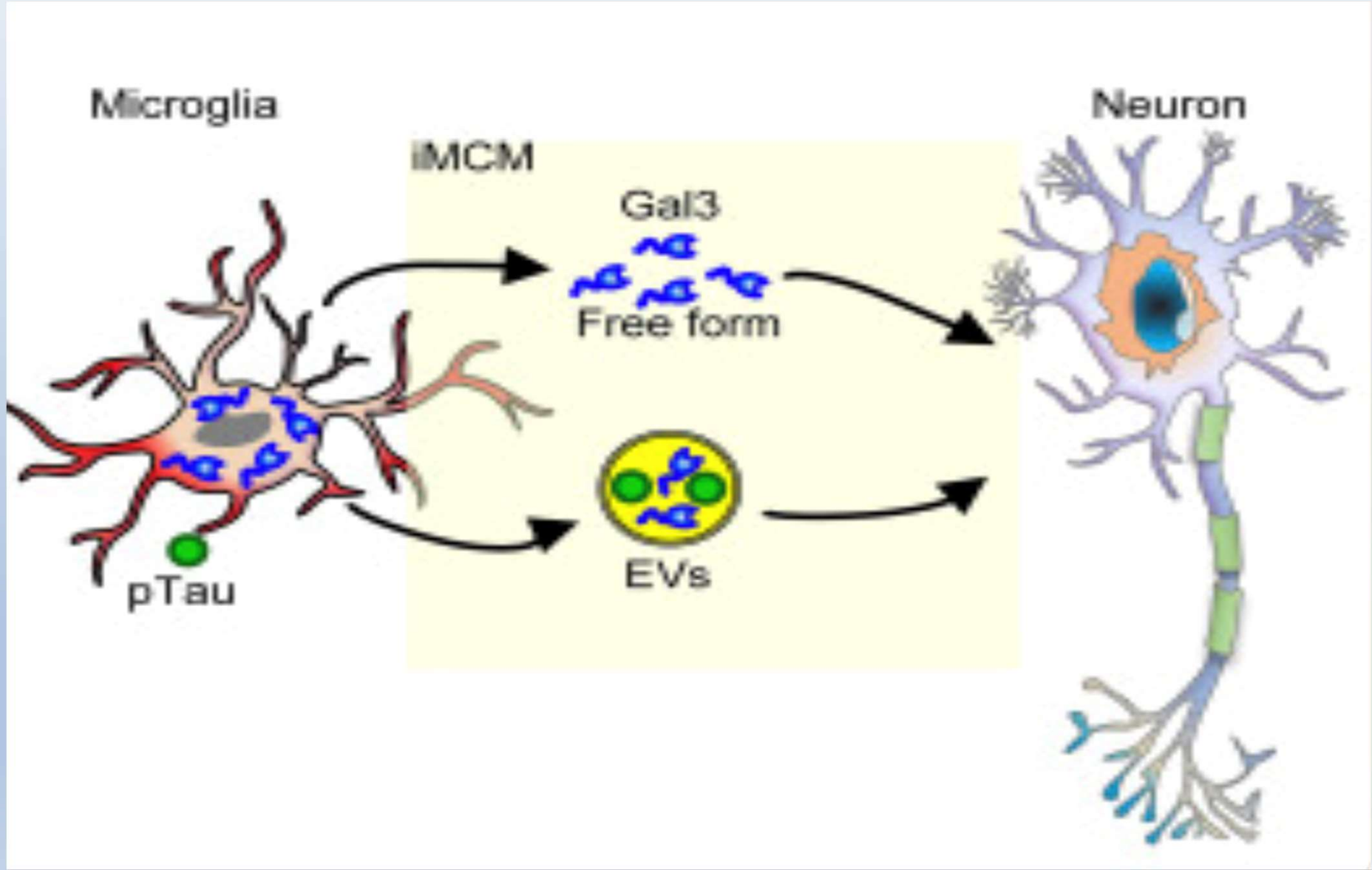
Siew JJ, et al. Neurosci. 2024;134(2):e165523.

Gal-3 Dementia/Alzheimer's

- Gal-3 upregulated in microglia with tauopathy
  - Both forms of GAL-3 upregulated - free and extracellular vesicular–associated (EV-associated) – see illustration next slide
- pTau reported to trigger release of Gal-3
- **Gal-3 suppression reported to reduce plaque burden and improve cognitive behaviors in lab animals**

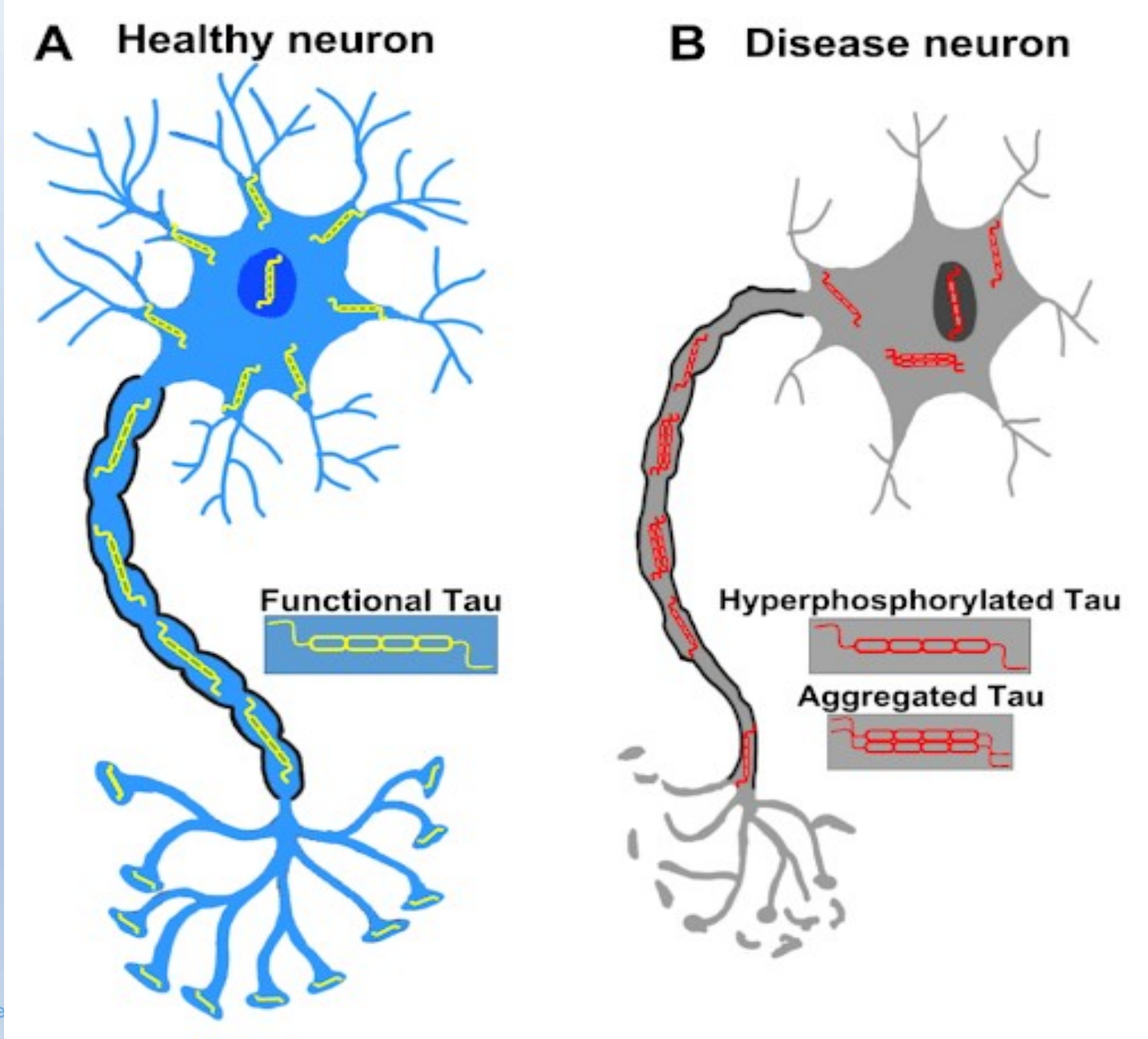
Siew JJ, et al. Neurosci. 2024;134(2):e165523.

Gal-3 in free form and in EVs exacerbates the effect of pathological tau



Siew JJ, et al. Neurosci. 2024;134(2):e165523.

Tauopathy and Effects on Neurons

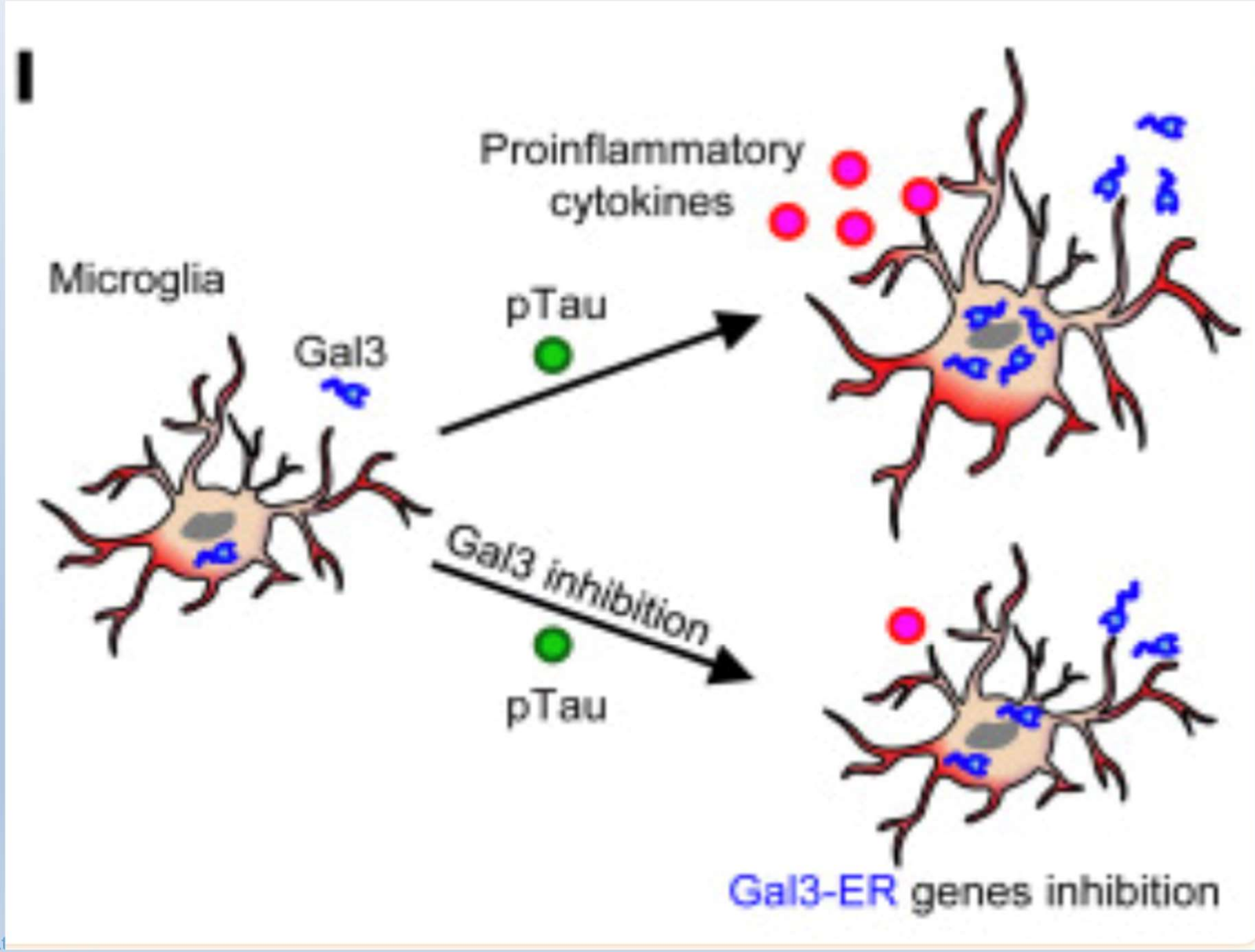


Study

- A 2020 neuroimaging study of 513 participants demonstrated that individuals with both amyloid and tau pathologies exhibited a 27% prevalence of AD
- In contrast, those with only amyloid pathology had just 6% prevalence of AD
- Genetic and epigenetic studies of patients with AD reveal that many genes associated with AD risk are enriched in microglia and are related to immune responses

Weigand AJ, et al. Is tau in the absence of amyloid on the Alzheimer's continuum?: A study of discordant PET positivity. *Brain Commun.* 2020;**2**(1):fcz046.

Gal-3 Influence on Neuroinflammation



GAL-3 Levels Correlate w/ Neurodegenerative Diseases

Authors, year	Disease	Sample	Galectin-3 levels	Main clinical findings
Ashraf and Baeesa, 2018	Alzheimer's disease	Serum CSF	↑	↓CF
Ashraf and Baeesa, 2018	Amyotrophic Lateral Sclerosis	Serum CSF	↑	No impact on CF
Yazar et al., 2021	Alzheimer's disease	Serum	↑	↓CF (↓MMSE) ↑Duration of disease
Wang et al., 2015	Alzheimer's disease	Serum	↑	↓CF (↓MMSE)
Cengiz et al., 2019	Parkinson's disease	Serum	↑	A good predictor for advanced-stage disease
Yazar et al., 2019	Idiopathic Parkinson's disease	Serum	↑	↑UPDRS scores ↑duration of disease
Siew et al., 2019	Huntington's disease	Serum	↑	↓CF (↓MMSE) ↑Disease burden Correlation with UHDRS scores
Yan J. et al., 2016	Amyotrophic Lateral Sclerosis	Serum	↑	↑Duration of disease
Zhou et al., 2010	Amyotrophic Lateral Sclerosis	CSF spinal cord tissue	↑	Disease biomarker
Wang et al., 2021	Acute ischemic stroke	Serum	↑	↓CF (↓MoCA)
Yan X.J. et al., 2016	Intracerebral hemorrhage	Serum	↑	↑Inflammation ↑Injury severity ↑Mortality
Liu et al., 2016	Subarachnoid hemorrhage	Serum	↑	↑Disease severity Poorer prognosis
Sävman et al., 2013	Birth asphyxia	CSF	↑	Severe clinical course poorer prognosis

CSF, cerebro-spinal fluid; CF, cognitive functions; MMSE, Mini Mental State Examination; UPDRS, Unified Parkinson's Disease Rating Scale; UHDRS, Unified Huntington's disease Rating Scale: MoCA. Montreal Cognitive Scale.

Microglial Activation in Parkinson's Disease (PD)

- Microglia in PD models exhibit activation and neuroinflammation
  - Particularly in response to α-synuclein – protein linked to neurodegeneration
- Inflammation mediated by microglia is considered a contributory factor in PD pathogenesis
- Dysfunctional, neuroinflammatory astrocytes also play a role in PD

Subramaniam SR, et al. Targeting microglial activation states as a therapeutic avenue in Parkinson's Disease. Front Aging Neurosci. 2017;9:176.

Gal-3 Parkinson's

- Parkinson's disease (PD) = neurodegenerative and progressive disorder
  - Characterized by Lewy Bodies and degeneration of dopaminergic neurons in substantia nigra

- Gal-3 reportedly found in the outer layer of the Lewy bodies in post-mortem brains

- Studies suggest prominent role for Gal-3 in the aggregation process Lewy Body formation

Garcia-Revilla J, et al. Galectin-3 shapes toxic alpha-synuclein strains in Parkinson's disease. Acta Neuropathol. 2023;146(1):51-75.

Gal-3 Parkinson's

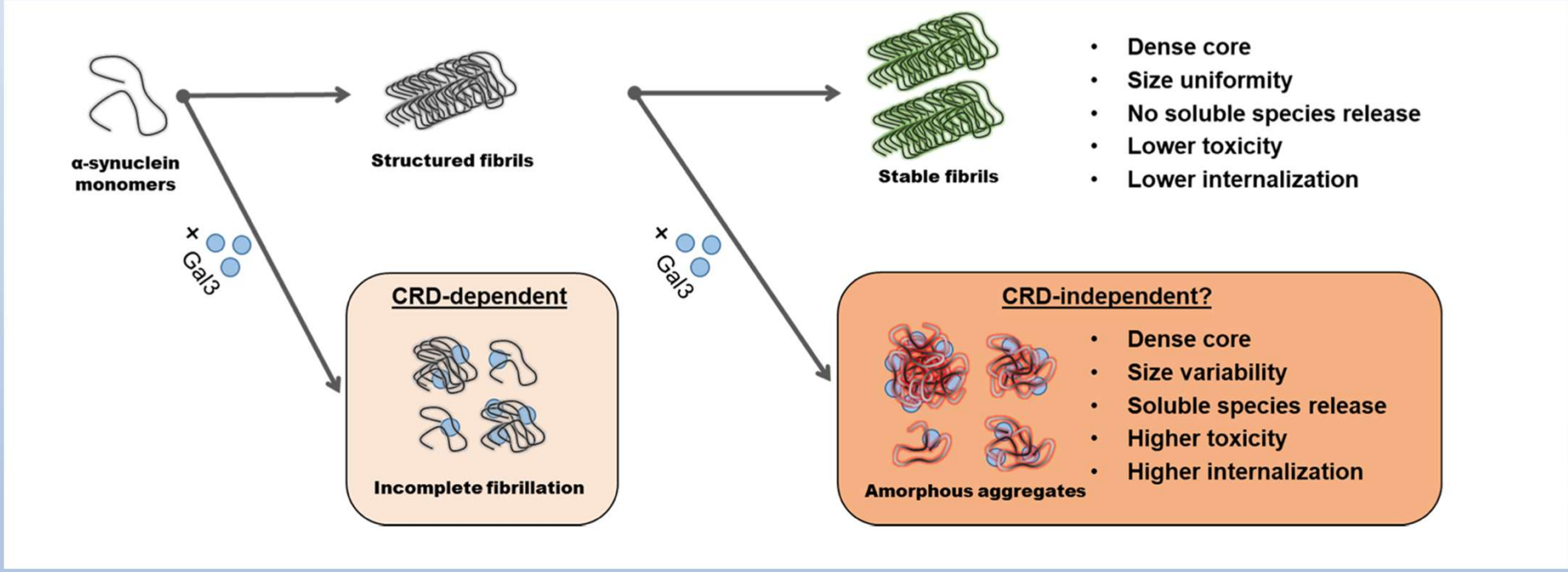
- In vitro studies report gal-3 interacts with α-synuclein (αSYN) fibrils in PD
  - Leads to formation of short, amorphous toxic fibril strains
  - Process is linked to disrupted lysosomes and increased αSYN accumulation within dopaminergic neurons
  - Increased dopaminergic damage

- Serum levels of gal-3 associated with severity of motor performance in PD patients
  - Studies indicate a higher serum gal-3 correlate with more severe motor performance impairment in PD

Garcia-Revilla J, et al. Galectin-3 shapes toxic alpha-synuclein strains in Parkinson's disease. Acta Neuropathol. 2023;146(1):51-75.

Gal-3+α Synuclein

Galectin-3 shapes toxic alpha-synuclein strains in Parkinson's disease



Juan García-Revilla, Antonio Boza-Serrano · Yiyun Jin · Devkee M. Vadukul · Jesús Soldán-Hidalgo · Lluís Camprubí-Ferrer · Marta García-Cruzado · Isak Martinsson · Oxana Klementieva · Rocío Ruiz · Francesco A. Aprile · Tomas Deierborg · José Luis Venero Received: 24 November 2022 / Revised: 11 May 2023 / 11 May 2023 / Published online: 18 May 2023

Why TB006 is a Promising Therapeutic for Parkinson's

- **Targets a master regulator of Parkinson-related neuroinflammation**
  - Gal-3 drives M1 microglia, α-syn aggregation, and neurotoxic cascades.
- **Reduces both inflammation AND proteinopathy**
  - Unlike dopamine-replacement therapies, TB006 acts upstream on the pathology.
- **May slow or halt disease progression**
  - By reducing α-syn spread and protecting dopaminergic neurons.
- **Strong translational rationale**
  - Gal-3 knockout models show dramatic neuroprotection.
  - TB006 reduces the same pathways in human neurodegenerative trials.

Boza-Serrano et al, *Acta Neuropathol*. 2019;138:251-273.

TB006 Mechanisms

- TB006 = experimental antibody-based drug targeting Gal-3
  - **Blocks Gal-3 binding**
  - **Reduces Gal-3 induced α-synuclein protein aggregation and microglial activation**
  - **Suppresses NLRP3 inflammasomes**
  - **Decreases neuroinflammation and neuronal apoptosis**
  - **Improves synaptic function**
  - **Improves BBB integrity**

    Improves cognitive performance

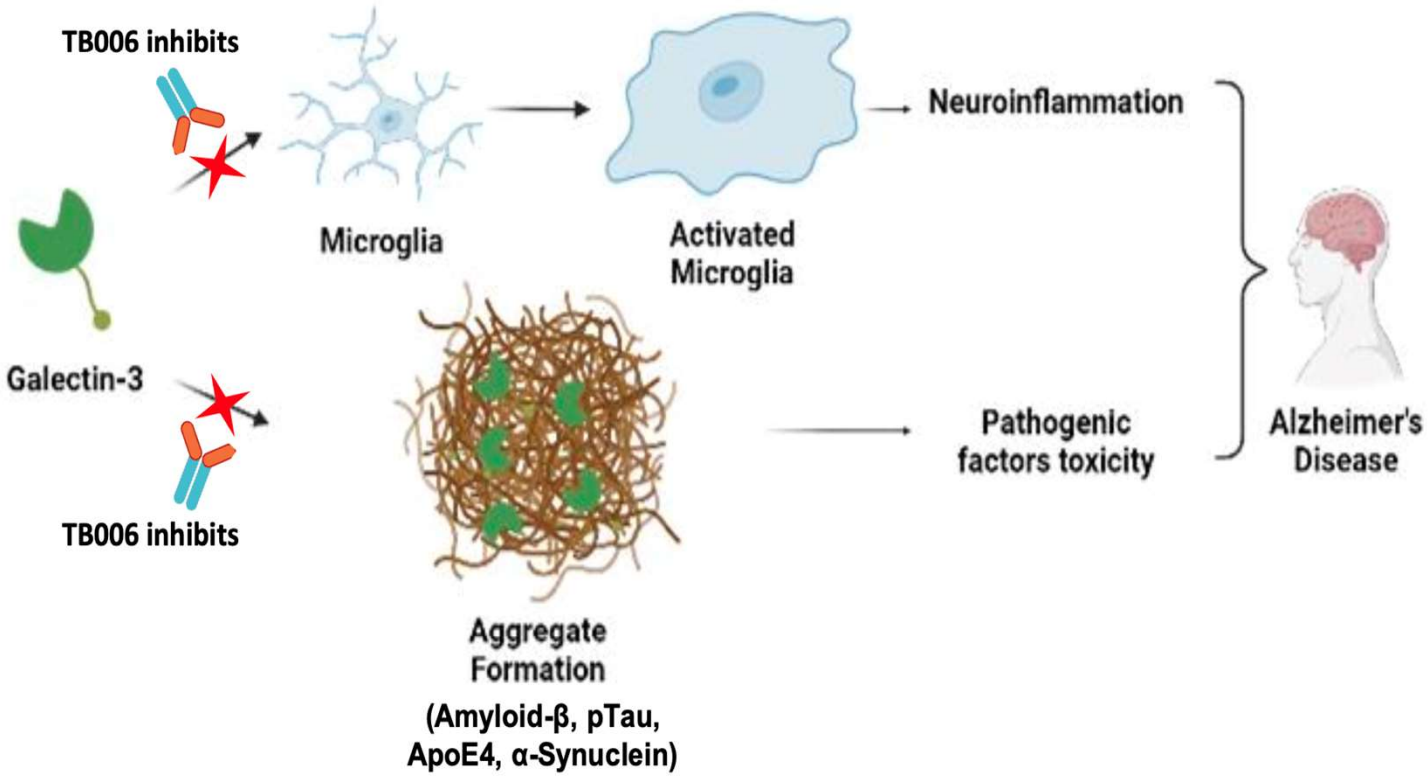
TB006

- Phase 1b/2a clinical trials are complete for use in dementias including Alzheimer's
- Promising therapeutic for neuroinflammatory conditions – like Alzheimer's, Parkinson's, TBI, stroke
- TB006 dosing in trials:
  - **2 mg/kg, 20 mg/kg, or 40 mg/kg IV every 2–4 weeks**
  - Generally well-tolerated
  - No major immune-related adverse events reported
  - Mild infusion reactions seen

TB006 and Alzheimer's Progression

Proposed Mechanisms of Action for Alzheimer's Progression

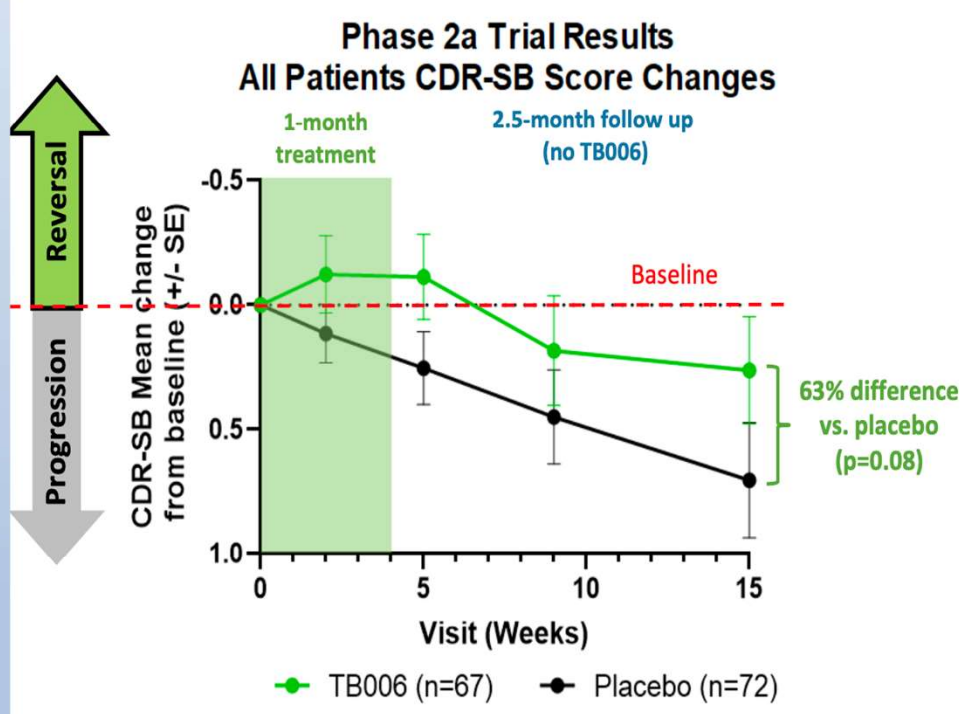
Gal-3 regulates the neuroinflammatory response via microglia activation

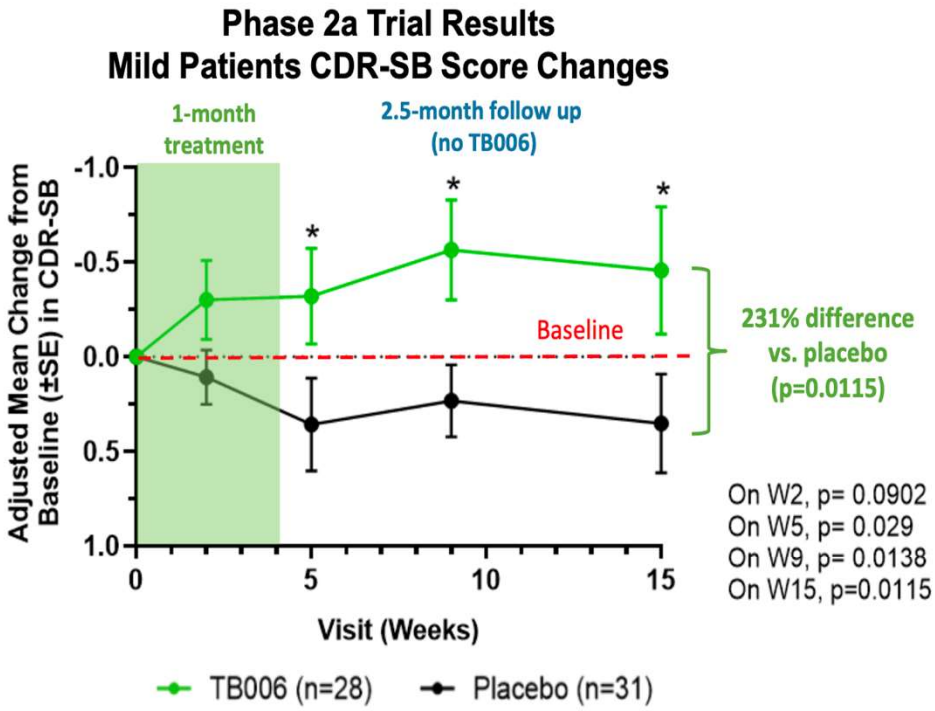


Gal-3 correlates with pathogenic factor toxicity via aggregation/oligomerization

TB006 Phase 2a Study – 1 month

Phase 2a: Significant Improvements in CDR-SB after One Month

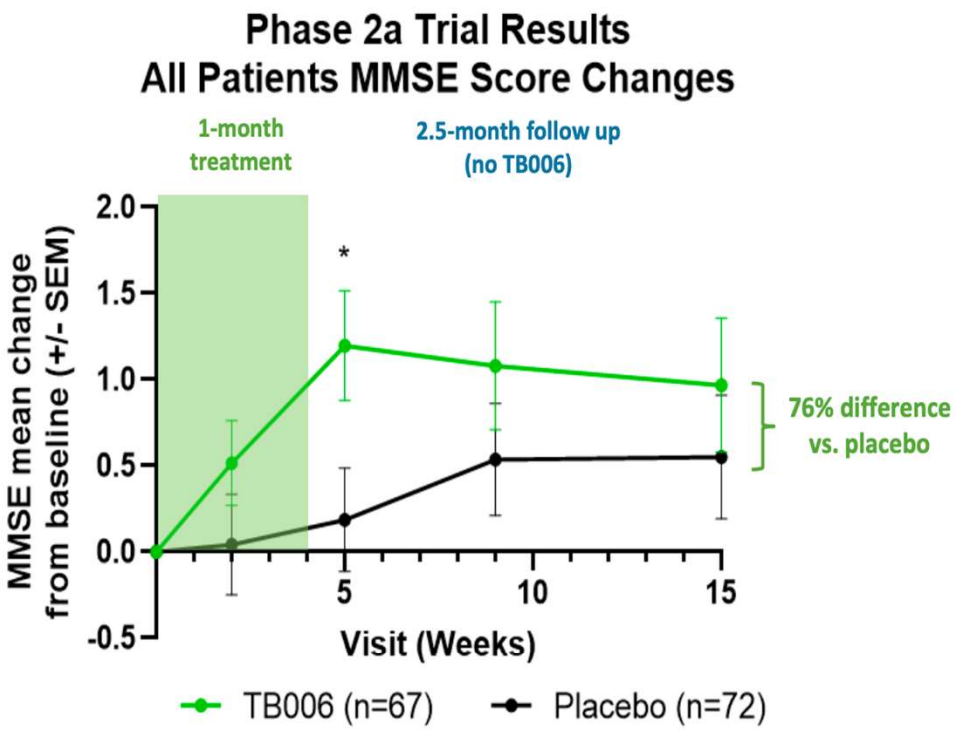


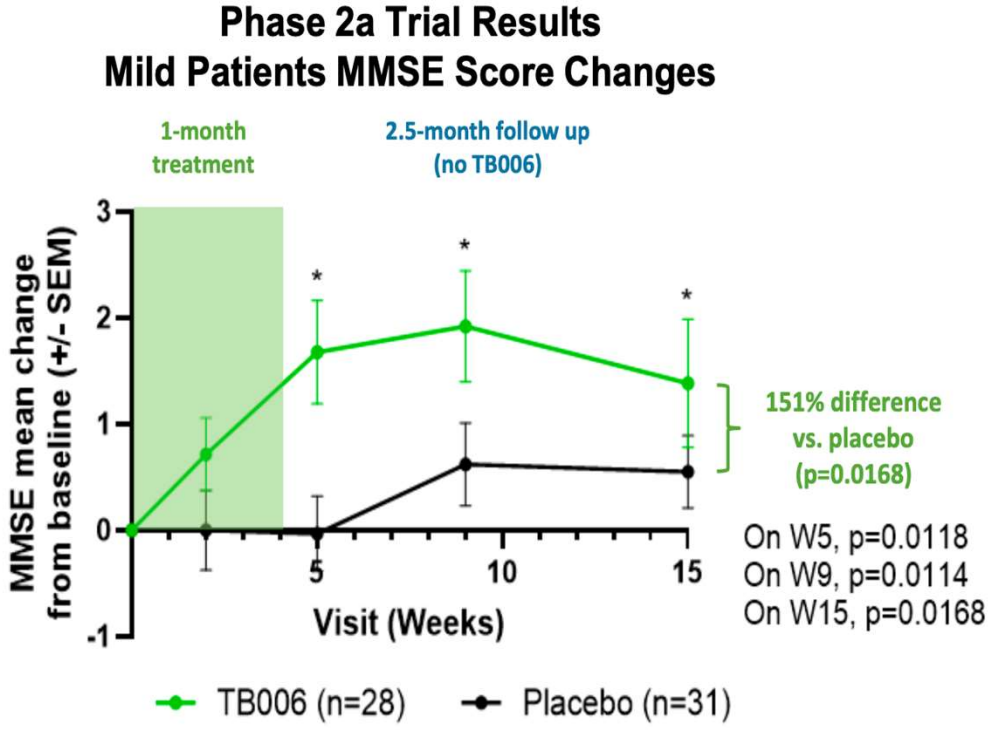


- Whole patient population included mild, moderate, and severe dementia (initial CDR-SB range 0.5 - 16)
- Signs of reversal observed in one month of treatment
- Statistically significant, sustained reversal and/or improvement in mild patients (231% difference by the end)

TB006 Phase 2a Study – MMSE Improvements after 1 month

Phase 2a: Significant Improvements in MMSE after One Month

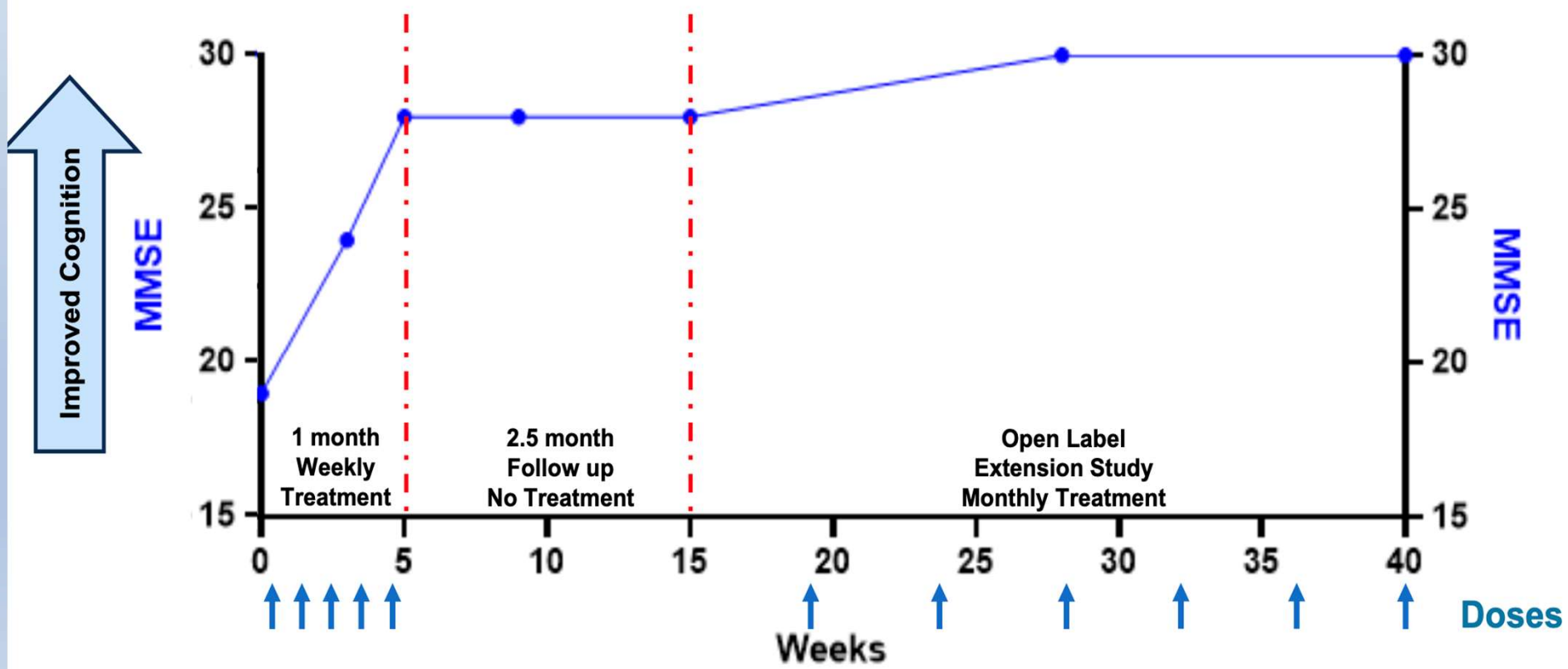




- Whole patient population included mild, moderate, and severe dementia (initial MMSE range 2 - 24)
- Statistically significant improvement observed in one month of treatment
- In mild patients, improvement in MMSE scores was maintained during the 2.5 month follow-up period

TB006 Phase 2a Study – MMSE 6 months

One Patient Improved MMSE from 19 to 30 in Six Months



TB006 Phase 2a Study – Adverse Events

TB006-related Adverse Events: Low Incidence, All Non-serious

TB006-related Adverse Events From Phase 2a Trials

Description	TB006 1000 mg/week dose (n=63)	Placebo (n=66)
Infusion-related reaction	2	0
Dizziness	1	0
Phlebitis	1	0

- All reported TB006-related adverse events were non-serious
  - Resolved with little to no intervention
  - Many could be infusion-related
- No amyloid-related imaging abnormalities (ARIA) in phase 2a trials
- Over an average 8-month treatment period, 1 of 119 patients from Open Label Extension study had asymptomatic ARIA (incidence rate of 0.8%)

Anecdotal Date Collection

Providers shared their observational results when renewing their annual IRB form. 76.5% of mild dementia patients (MMSE from 20-24) treated n=52 of 68 patients in the EAP. 82.6% of Moderate dementia (MMSE 13-19) treated n=38 of 46.

As of 11/14/2025	Treated + reported : n=145 (out of 290 treated)		
	Reported to be improved/stabilization n=108	Reported to be not working* n=27	Unknown results n=10
Mild (screening MMSE>=20) n=68	n=52; 76.5%	n=9; 13.2%	n=7; 10.3%
Moderate (scr-MMSE 19 to 13) n=46	n=38; 82.6%	n=7; 15.2%	n=1; 2.2%
Severe (scr-MMSE 0-12) n=30	n=18; 60%	n=10; 33.3%	n=2; 6.7%
Unknown scr-MMSE n=1		n=1, 100%	

75% of all severities treated showed improvement or stabilization. 108 out of 144. One patient with unreported MMSE score brings patient total reported as n=145.

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