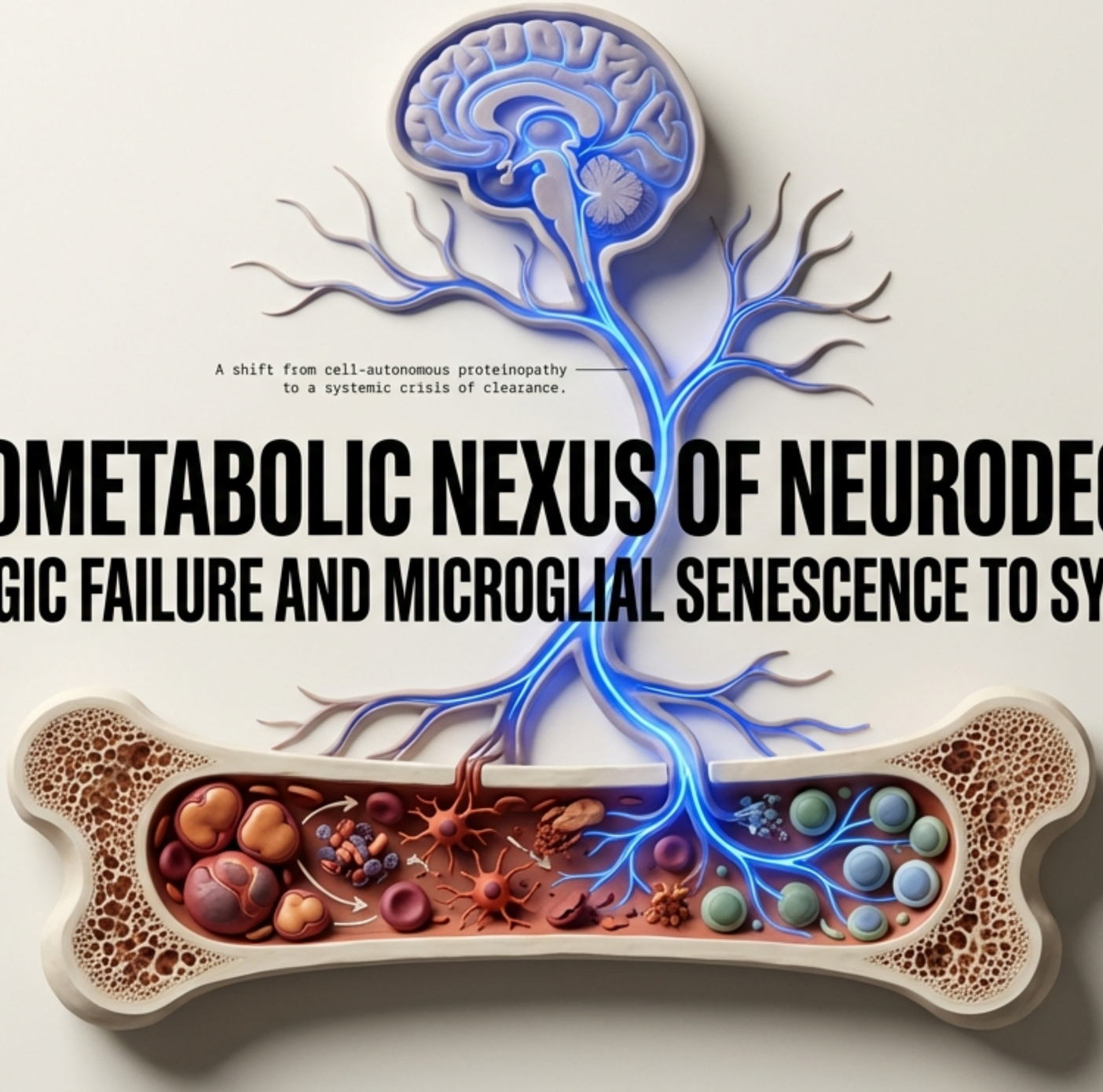


A shift from cell-autonomous proteinopathy
to a systemic crisis of clearance.

THE IMMUNOMETABOLIC NEXUS OF NEURODEGENERATION

FROM AUTOPHAGIC FAILURE AND MICROGLIAL SENESCENCE TO SYSTEMIC RESCUE

Prepared for Dr. James Truchard and Benjamin Gustafsson
Drafted by ChatGPT-5.2

SHATTERING THE ISOLATIONIST VIEW OF THE BRAIN

THE OLD PARADIGM: PROTEIN-CENTRIC MODEL

← Passive Plaque Accumulation

NEUROINFLAMMATION IS NOT A REACTION TO DISEASE; IT IS A DRIVER OF IT.

Roboto Mono

THE NEW REALITY: IMMUNOMETABOLIC FRAMEWORK

Microglial Activation & Cytokine Release →

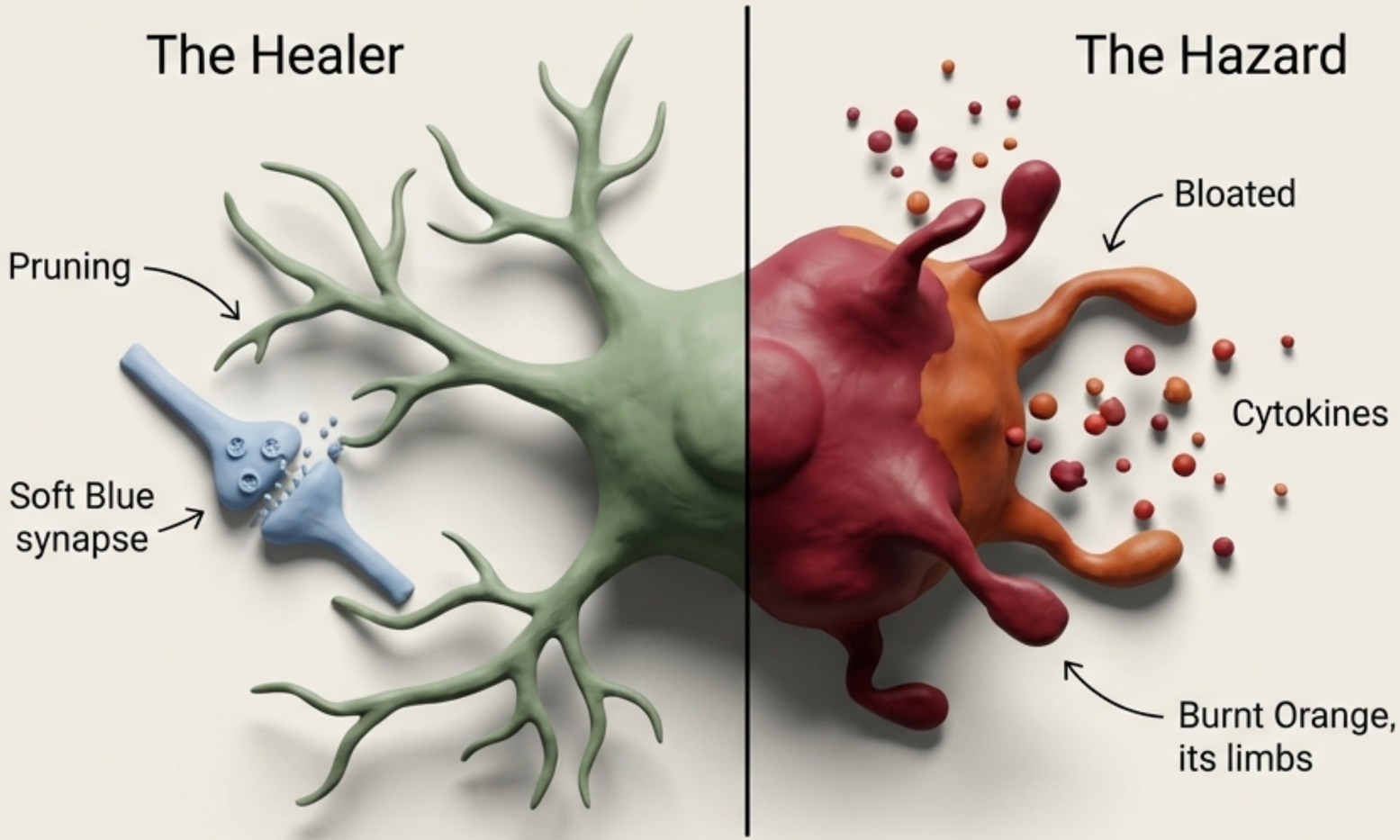
Microglial Activation & Cytokine Release →

THE OLD PARADIGM: PROTEIN-CENTRIC MODEL

THE NEW REALITY: IMMUNOMETABOLIC FRAMEWORK

Prepared for Dr. James Truchard and Benjamin Gustafson
Drafted by ChatGPT-5.2

THE SENTINELS THAT BECOME THE THREAT



Microglia: ~10% of CNS population.
Independent of peripheral hematopoiesis.

Prepared for Dr. James Truchard and Benjamin Gustafsson
Drafted by ChatGPT-5.2

THE ROOT OF THE CRISIS IS AUTOPHAGIC COLLAPSE

Aβ Aggregates

Stalled
Autophagic
Flux

>24hrs exposure to Aβ overwhelms lysosomal machinery.

Prepared for Dr. James Truchard and Benjamin Gustafsson
Drafted by ChatGPT-5.2

AUTOPHAGY FAILURE IGNITES THE INFLAMMASOME

Autophagy Blocked

Step 1:
Autophagy
Blocked

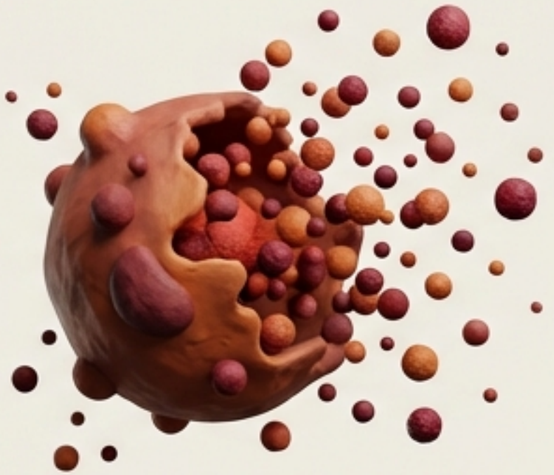
mtROS Accumulation

Step 2:
Damaged
mitochondrion
emits mtROS.

NLRP3 Assembly

Step 3:
NLRP3
inflammasome
assembly

Cytokine Storm

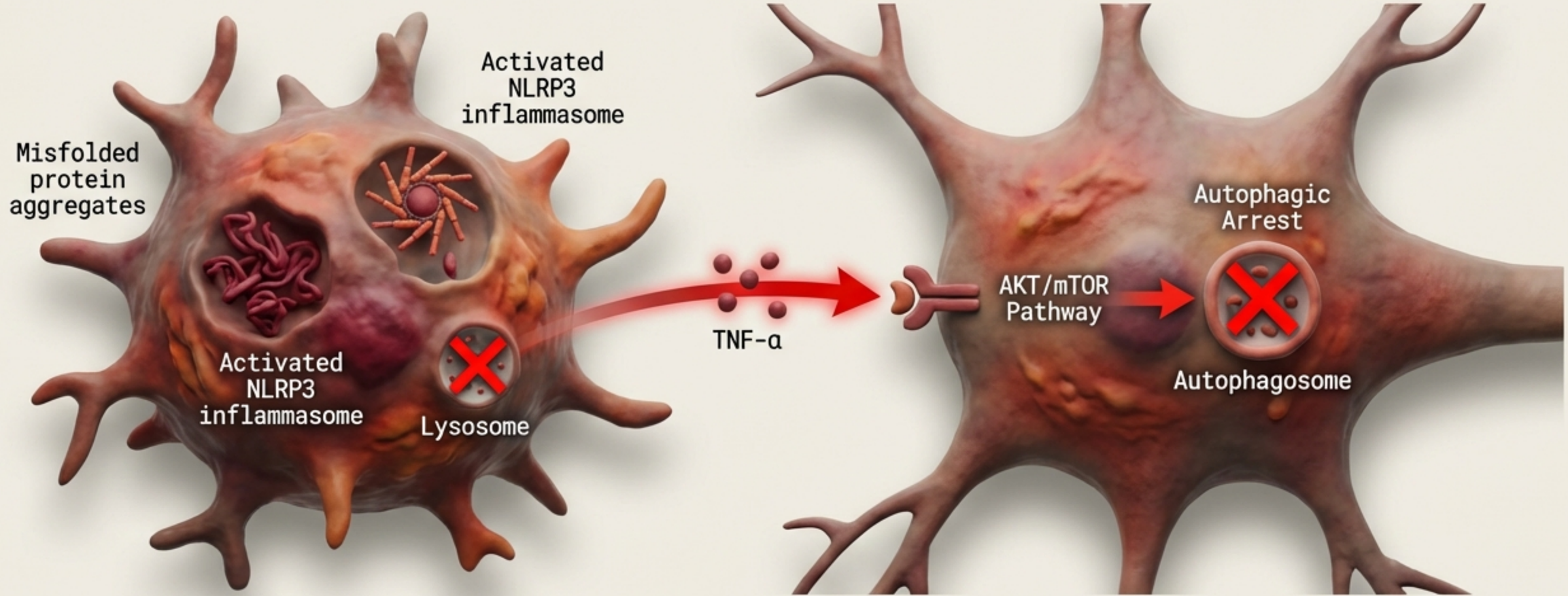


Step 4:
Explosion
of cytokines

When autophagy fails, the cell enters a hyper-inflammatory M1-like state.

Prepared for Dr. James Truchard and Benjamin Gustafsson
Drafted by ChatGPT-5.2

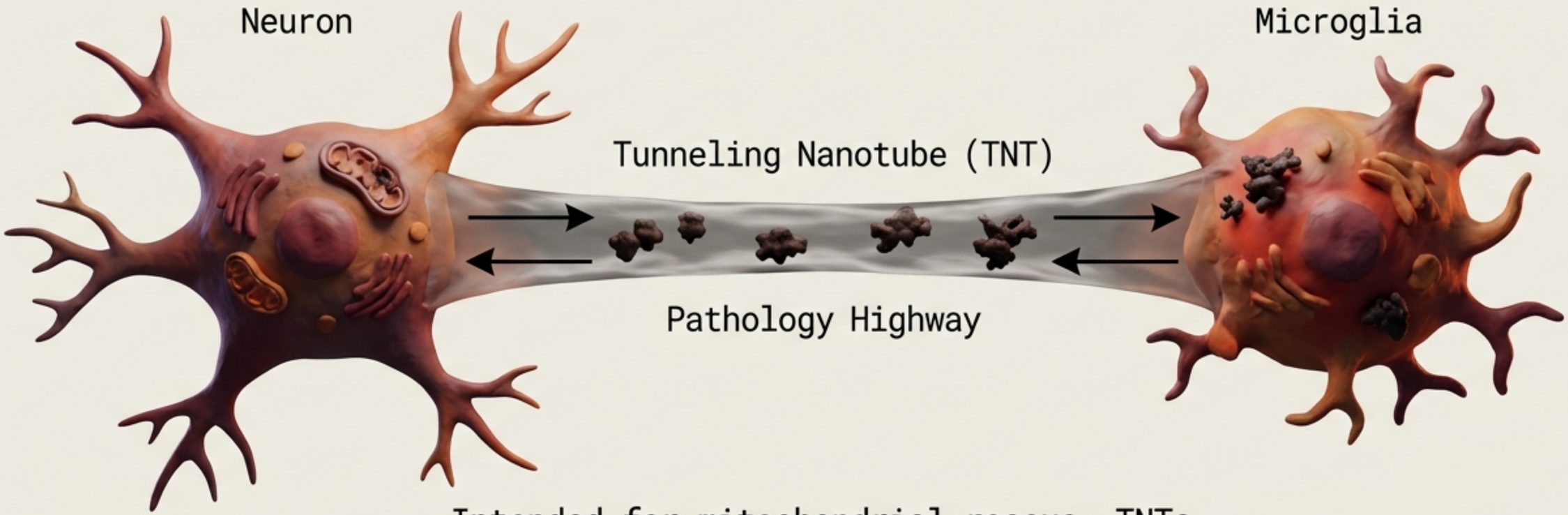
THE LETHAL HANDSHAKE: HOW MICROGLIA PARALYZE NEURONS



Misfolded proteins trigger microglial autophagy failure, leading to NLRP3 inflammasome activation and the release of TNF-α. This cytokine activates the neuronal AKT/mTOR pathway, suppressing neuronal autophagy and exacerbating protein aggregation.

Prepared for Dr. James Truchard and Benjamin Gustafsson
Drafted by ChatGPT-5.2

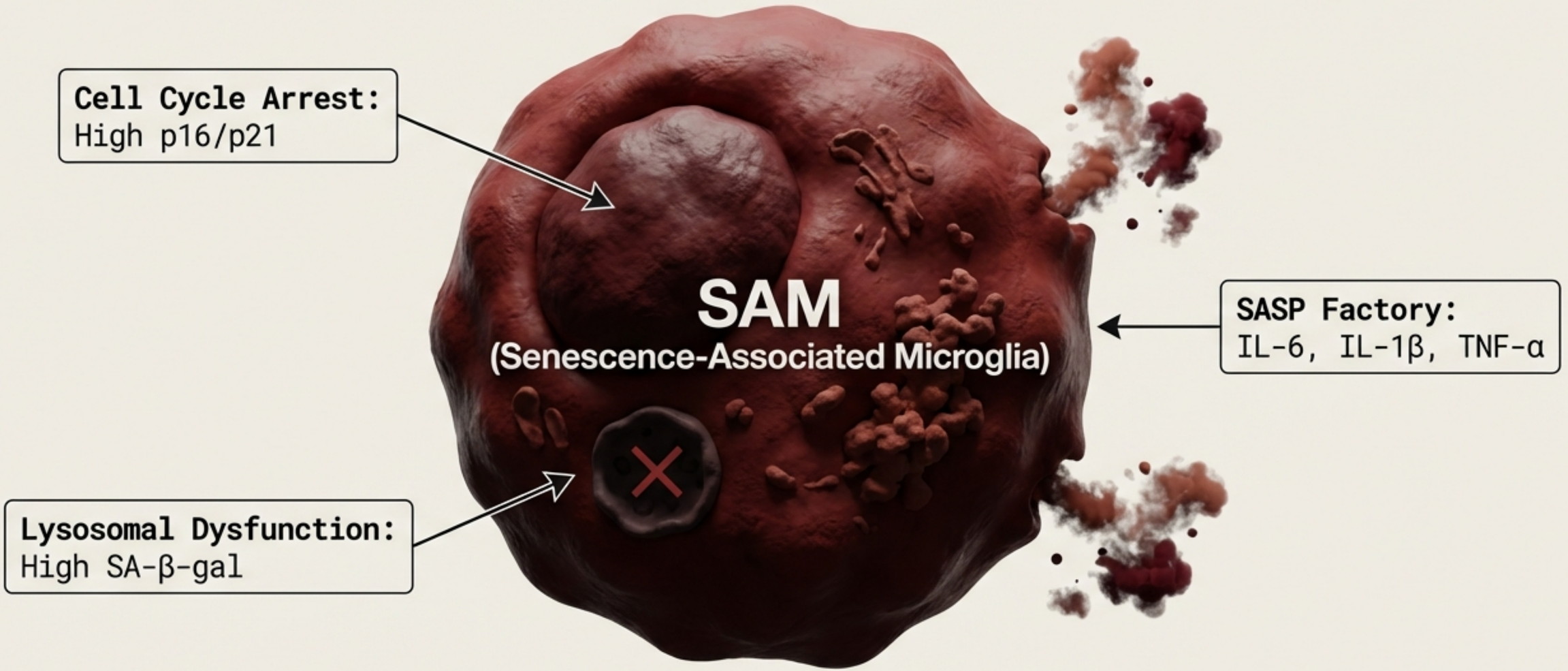
RESCUE CONDUITS TURNED VECTORS OF CONTAGION



Intended for mitochondrial rescue, TNTs become vectors for α-synuclein/Tau spread when microglial degradation fails.

Prepared for Dr. James Truchard and Benjamin Gustafsson
Drafted by ChatGPT-5.2

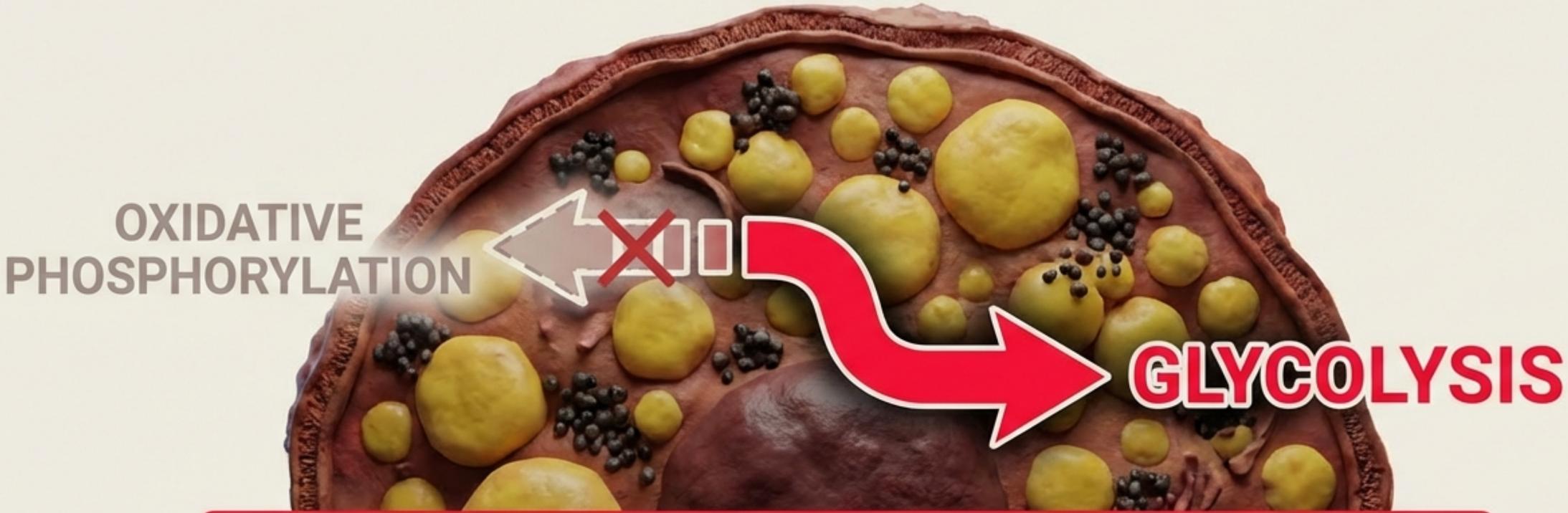
ENTERING THE SENESCENT STATE



These cells stop dividing, stop clearing, and refuse to die.

Prepared for Dr. James Truchard and Benjamin Gustafsson
Drafted by ChatGPT-5.2

METABOLIC REPROGRAMMING AND LIPID OVERLOAD



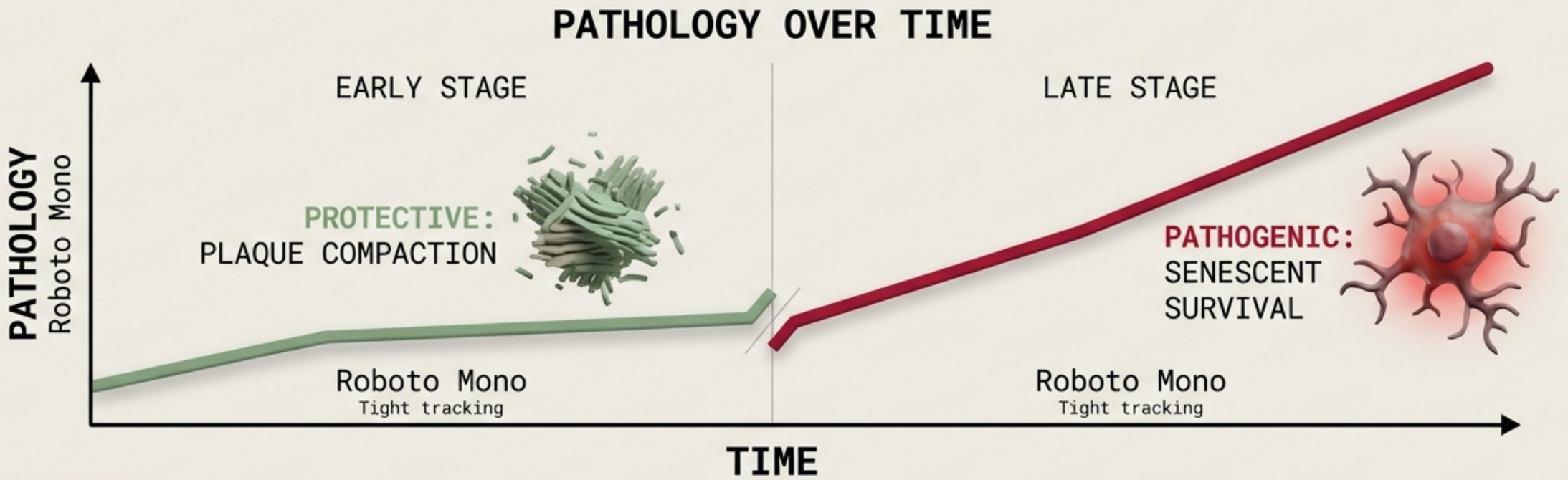
LDAM (Lipid-Droplet-Accumulating Microglia)

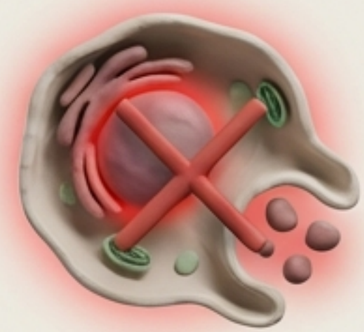
Genetically biased toward a viral-like, pro-inflammatory state.

Prepared for Dr. James Truchard and Benjamin Gustafsson
Drafted by ChatGPT-5.2

Helvetica Now Display

THE TREM2 PARADOX IN LATE-STAGE DISEASE

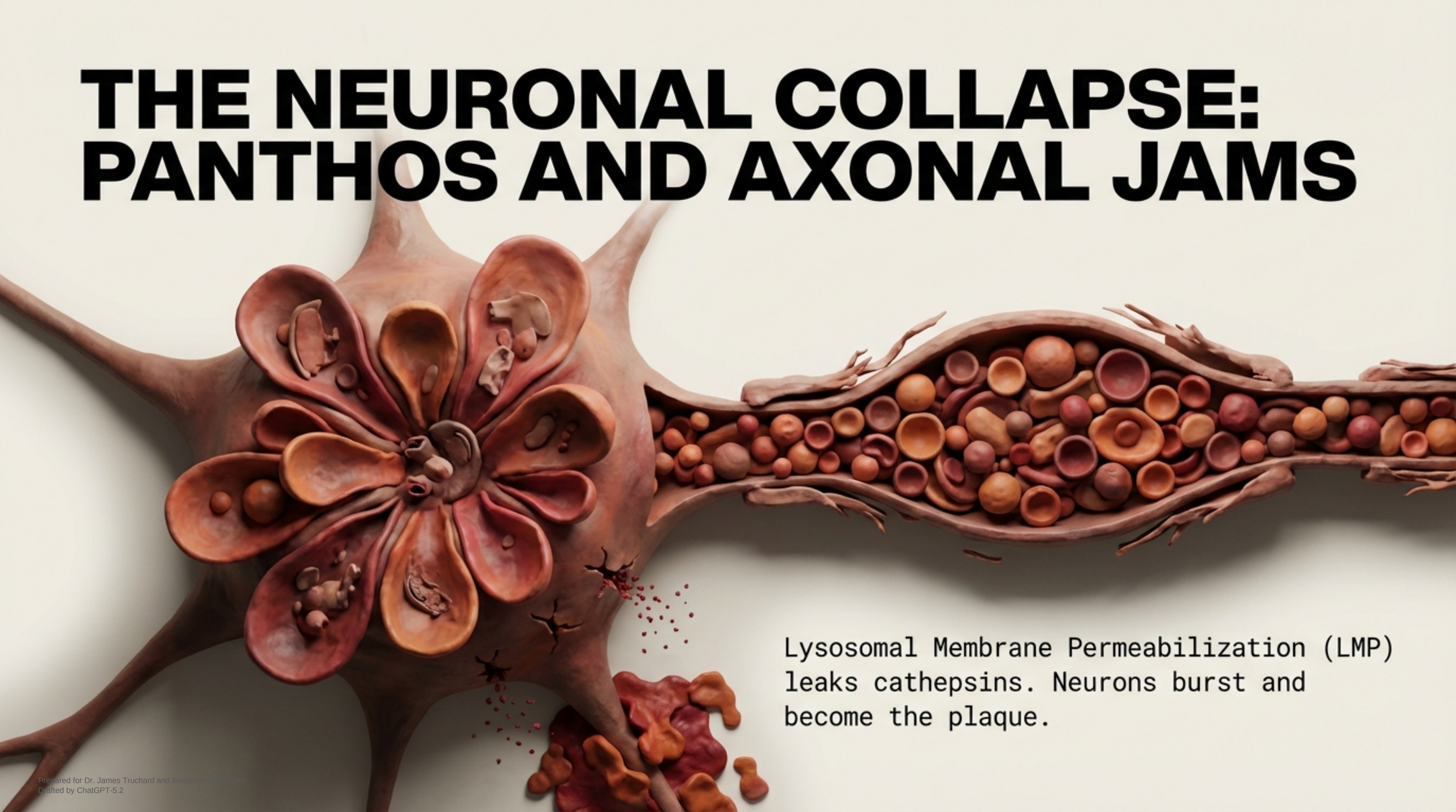




In senescence, TREM2 uncouples from phagocytosis and instead prevents the apoptotic clearance of the toxic cell itself.

Prepared for Dr. James Truchard and Benjamin Gustafsson
Drafted by ChatGPT-5.2

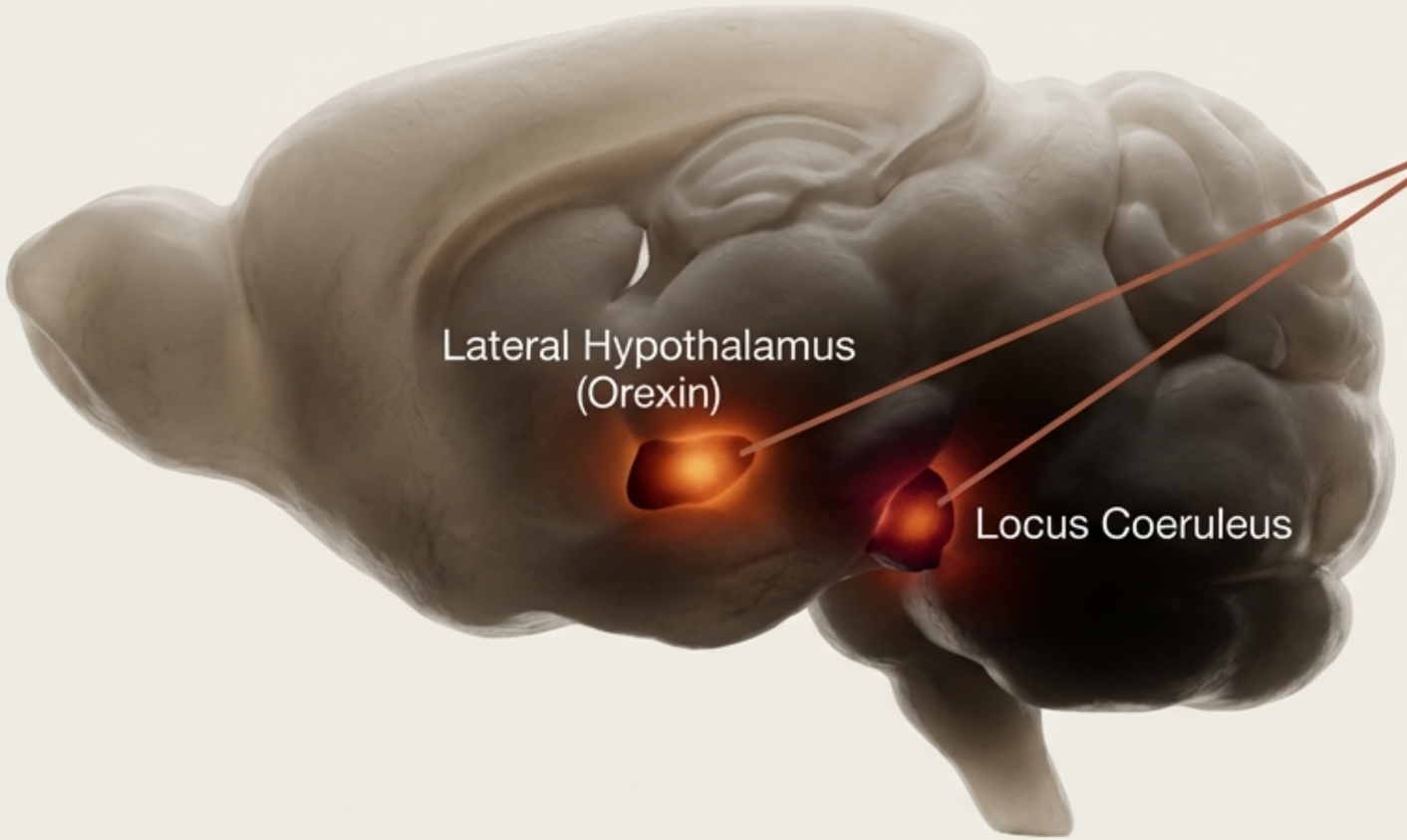
THE NEURONAL COLLAPSE: PANTHOS AND AXONAL JAMS



Lysosomal Membrane Permeabilization (LMP) leaks cathepsins. Neurons burst and become the plaque.

Prepared for Dr. James Truchard and Benjamin Carlson
Drafted by ChatGPT-5.2

THE GEOGRAPHY OF VULNERABILITY

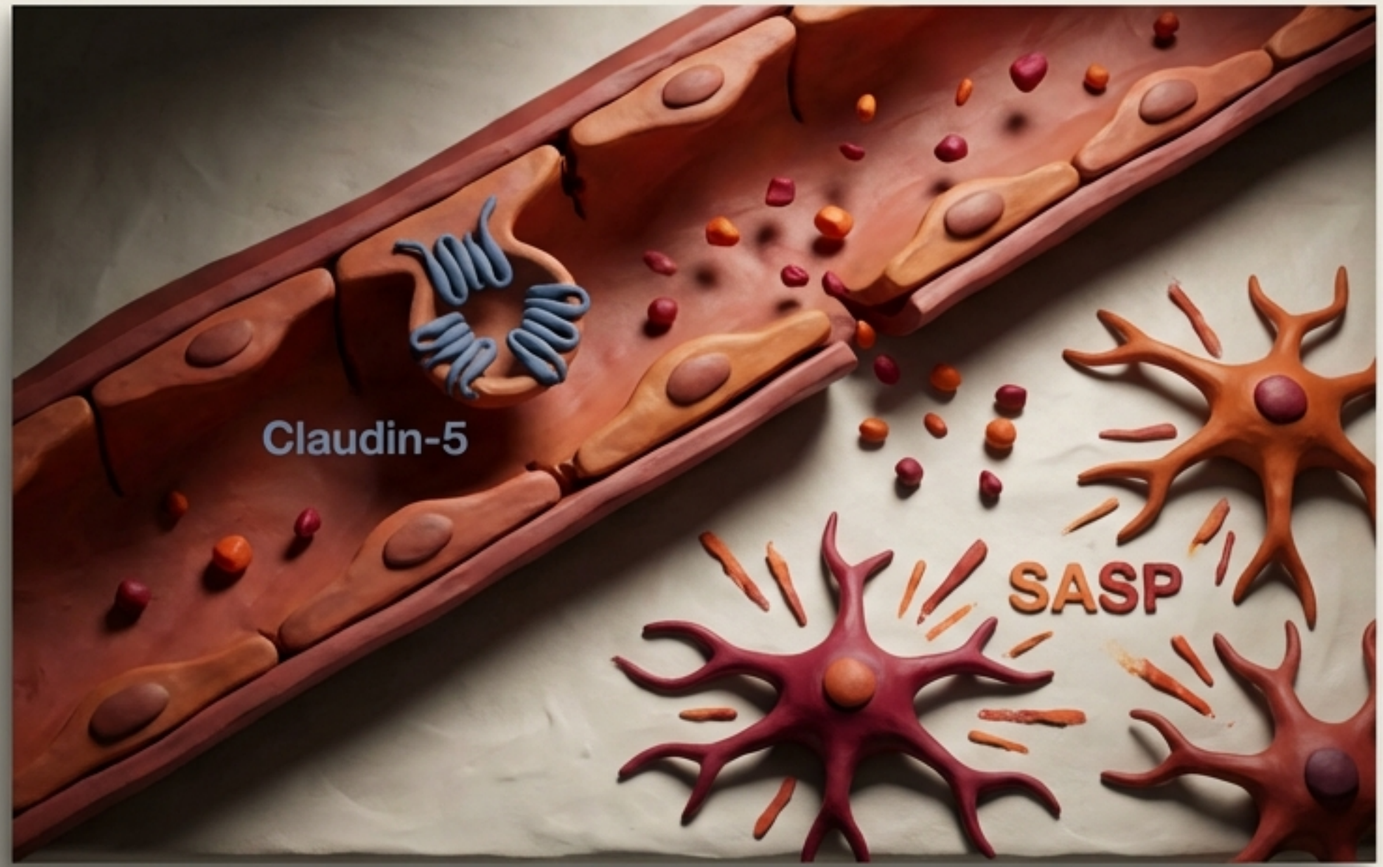


Autophagic failure occurs here before cortical plaque deposition.

Clinical Correlation: Explains early sleep-wake cycle fragmentation in AD.

Prepared for Dr. James Truchard and Benjamin Gustafsson
Drafted by ChatGPT-5.2

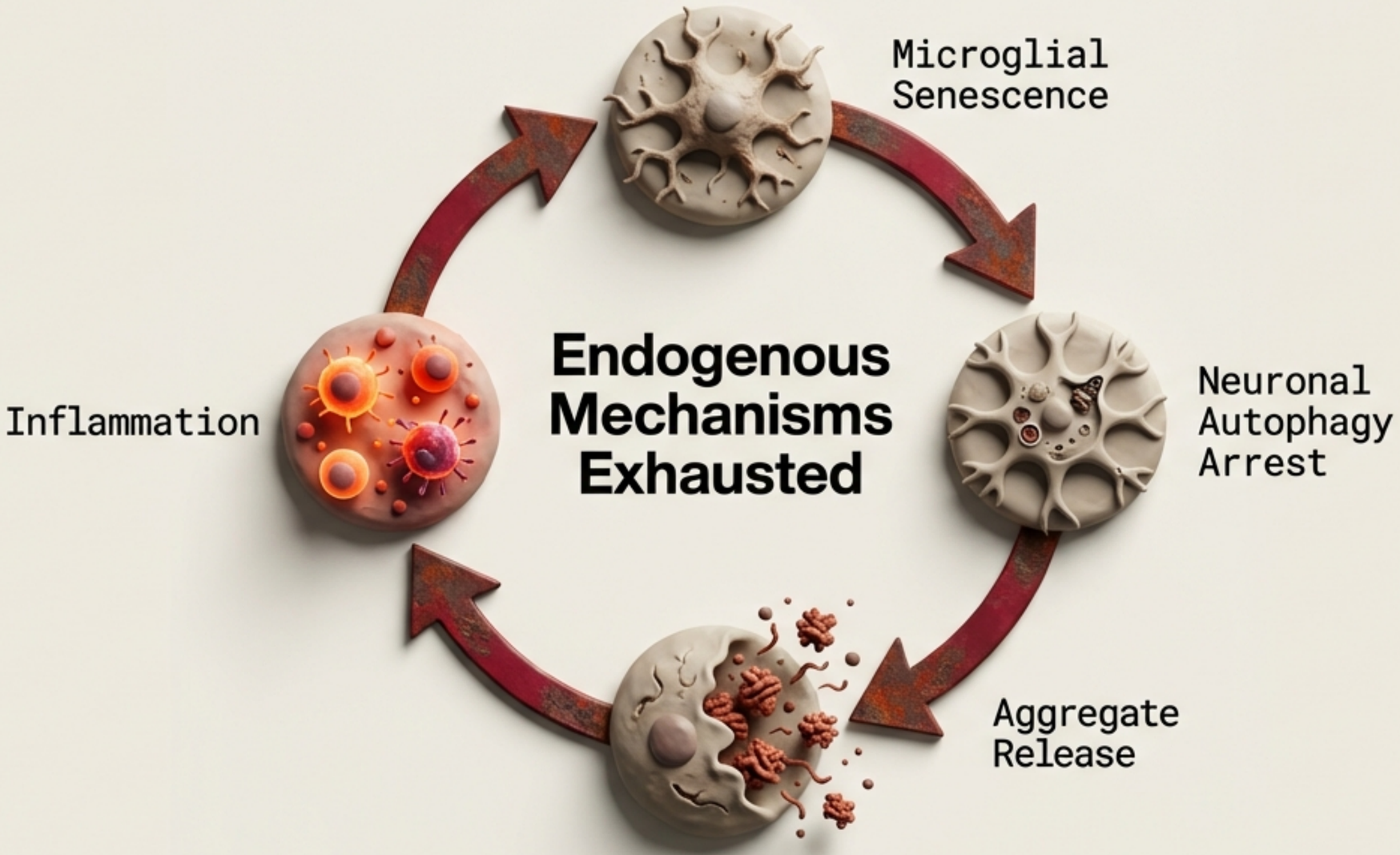
SYSTEMIC BREACH: GLIA AND THE BLOOD-BRAIN BARRIER



Loss of tight junctions.
The BBB becomes permeable
to peripheral toxins.

Prepared for Dr. James Truchard and Benjamin Gustafsson
Drafted by ChatGPT-5.2

The Deadlock of Local Repair



Targeting amyloid alone fails because the machinery to clear it is broken.

Prepared for Dr. James Truchard and Benjamin Gustafsson
Drafted by ChatGPT-5.2

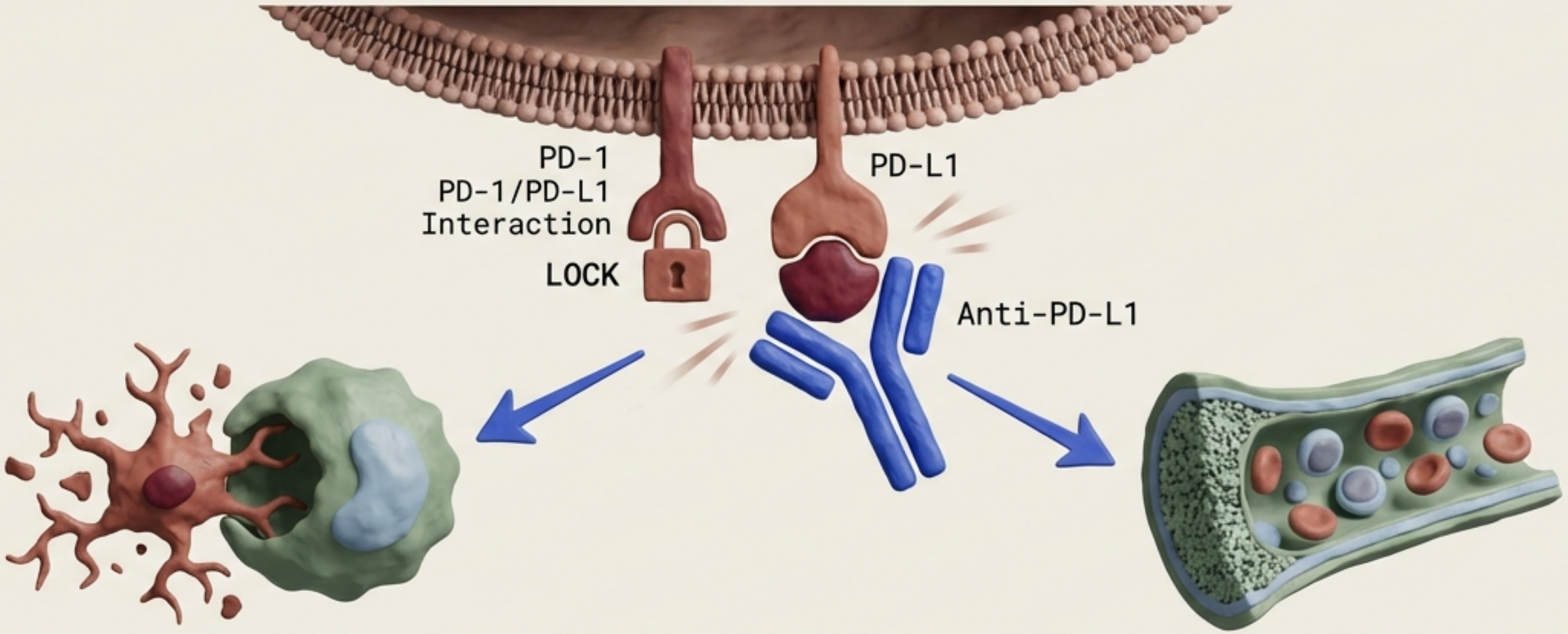
THE SYSTEMIC TOLL: BONE MARROW EXHAUSTION

HSCs forced out of quiescence leading to exhaustion.

Result: Production of low-quality, pro-inflammatory monocytes stuck in the marrow.

Prepared for Dr. James Truchard and Benjamin Gustafsson
Drafted by ChatGPT-5.2

BREAKING THE DEADLOCK: IMMUNE CHECKPOINT BLOCKADE



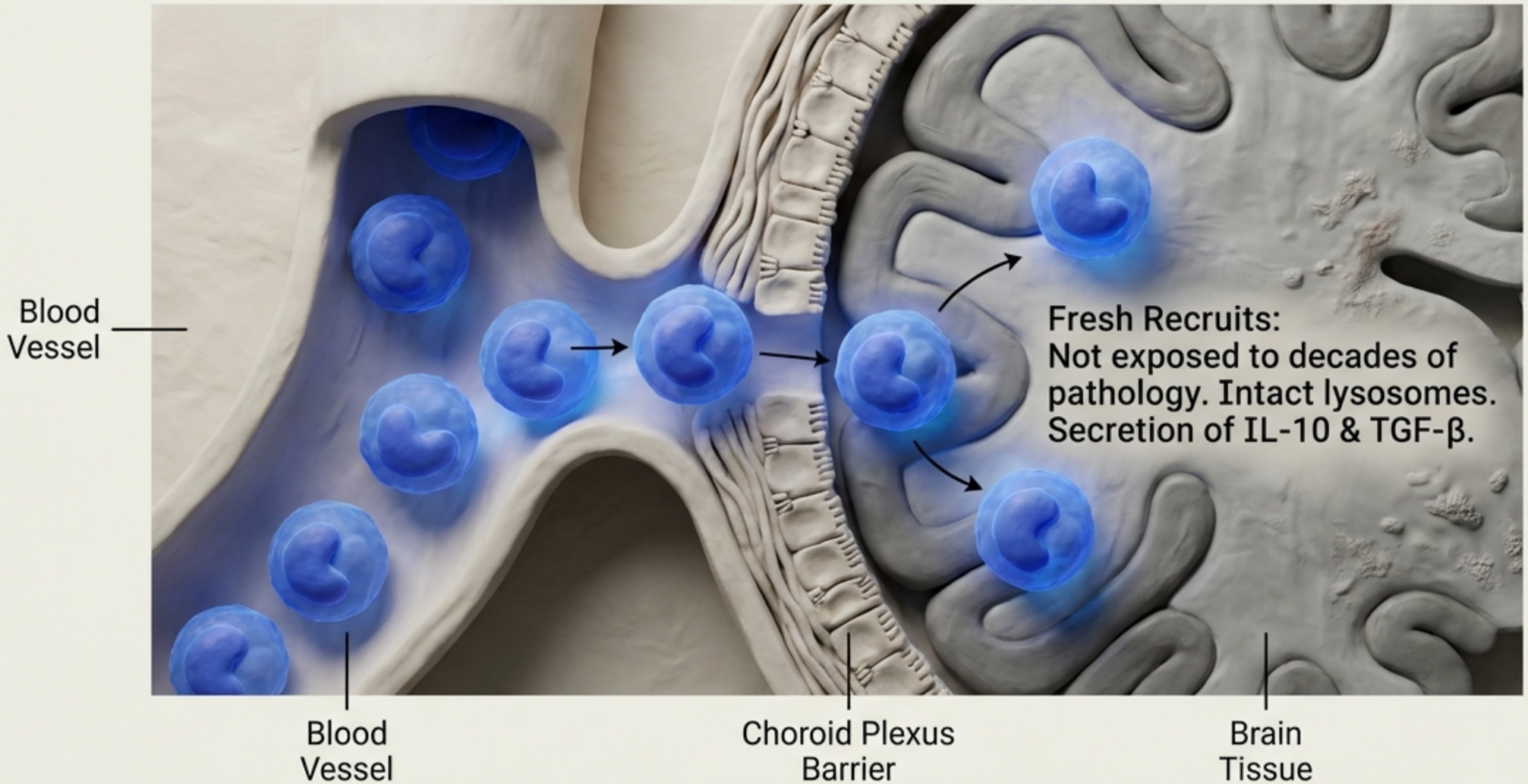
1. Clears Senescent Microglia
(Removes ‘Don’t Eat Me’ signal)

2. Restores Bone Marrow
Homeostasis

Rejuvenating the systemic immune system to rescue the CNS

Prepared for Dr. James Truchard and Benjamin Gustafson
Drafted by ChatGPT-5.2

THE CAVALRY ARRIVES: MONOCYTE-DERIVED MACROPHAGES (MDMs)



Prepared for Dr. James Truchard and Benjamin Gustafsson
Drafted by ChatGPT-5.2

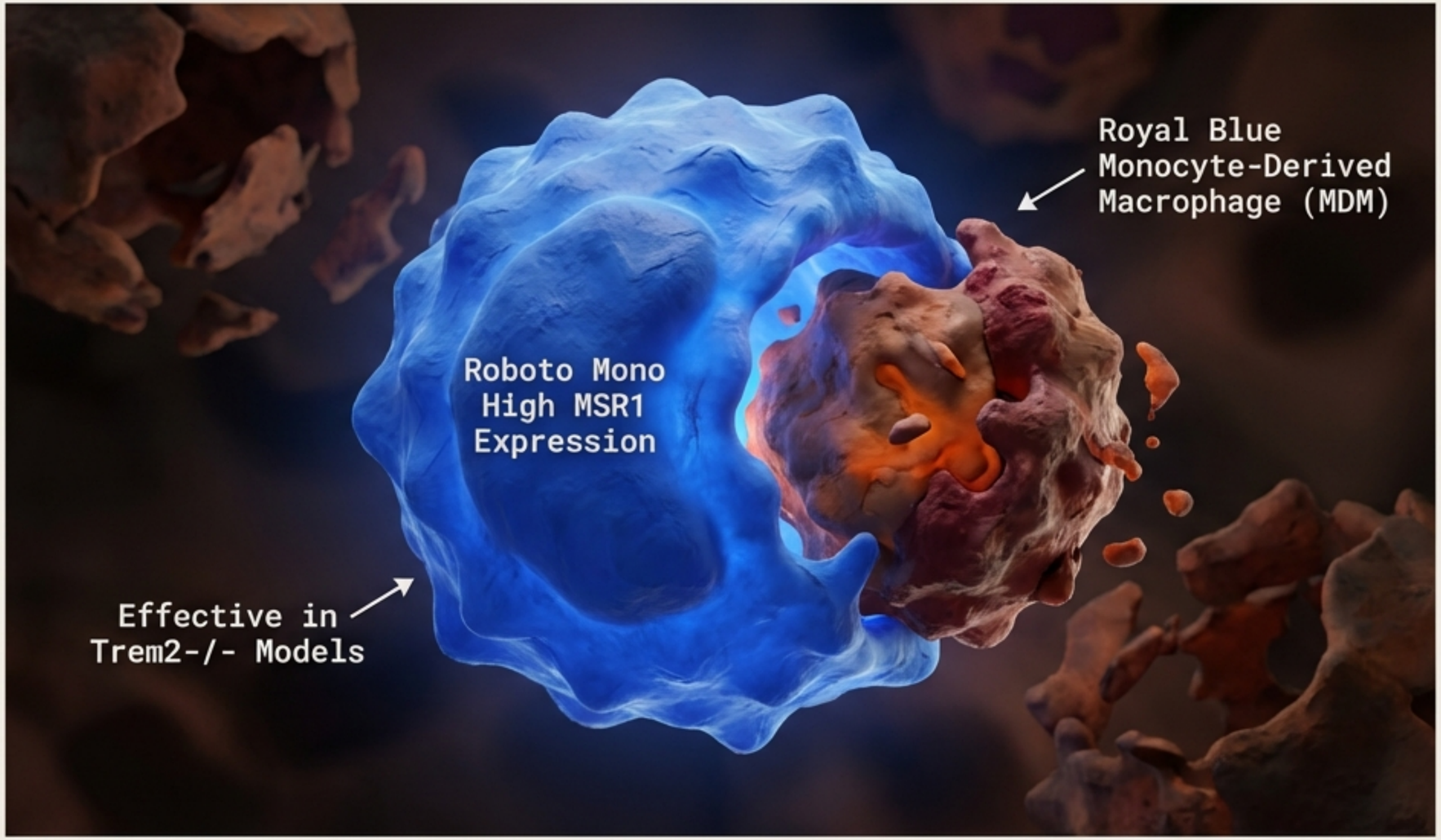
REINFORCEMENTS VS. RESIDENTS

BIOLOGICAL CATEGORY	Resident Senescent Microglia Local CNS Environment	Recruited MDMs Post PD-L1 Blockade
Origin & Environment	[COMPROMISED] Resident innate immune cells of the CNS. Subjected to prolonged exposure to hostile stimuli within the chronic diseased brain environment.	[FRESHLY MOBILIZED] Arise from circulating monocytes replenished by hematopoietic stem cells in the bone marrow or spleen. Freshly recruited from blood circulation.
Autophagic Flux & Metabolism	[IMPAIRED] Suffer from severe metabolic impairment. Characterized by lipid-drop accumulation and increased production of Reactive Oxygen Species (ROS).	[FUNCTIONAL] Act as essential reinforcements possessing high clearance capacity, contributing to the restoration of microglial autophagy flux.
Phenotypic State	[SENESCENT] Exhausted and senescent due to aging and sustained activation. Exhibit heavily reduced patrolling activity in the brain tissue.	[ACTIVE] Adopt an inflammation-resolving phenotype, actively fostering tissue repair and not subjected to long-term local stimulation.
Key Markers	[PATHOLOGICAL PROFILE] Loss of homeostatic receptors (P2RY12, TGFBR1). Show increased expression of genes such as TREM2, APOE, B2M, and CSF1.	[RESTORATIVE PROFILE] Express unique scavenger molecules, particularly high levels of macrophage scavenger receptor 1 (MSR1), required for disease modification.
Phagocytic Capacity	[DEFICIENT] Fall short in containing damage; frequently fail to clear accumulating proteins and escalating debris in chronic conditions.	[SUPERIOR] Perform highly efficient phagocytosis, rapidly clearing cellular debris and misfolded protein aggregates (e.g., amyloid-beta).
Cytokine Profile	[TOXIC] Contribute to inflammatory exacerbation through increased and sustained production of pro-inflammatory mediators.	[HEALING] Release crucial anti-inflammatory factors, creating a microenvironment that is permissive to recovery and neural regeneration.

Following PD-L1 blockade, freshly recruited Monocyte-Derived Macrophages (MDMs) bypass the exhausted local environment. Unlike senescent resident microglia, MDMs exhibit robust autophagic capacity, express high levels of scavenger receptors (MSR1), and secrete inflammation-resolving cytokines.
Data sources: PubMed, Nature Neuroscience, ResearchGate

Prepared for Dr. James Truchard and Benjamin Gustafsson
Drafted by ChatGPT-5.2

BYPASSING THE BROKEN MACHINERY

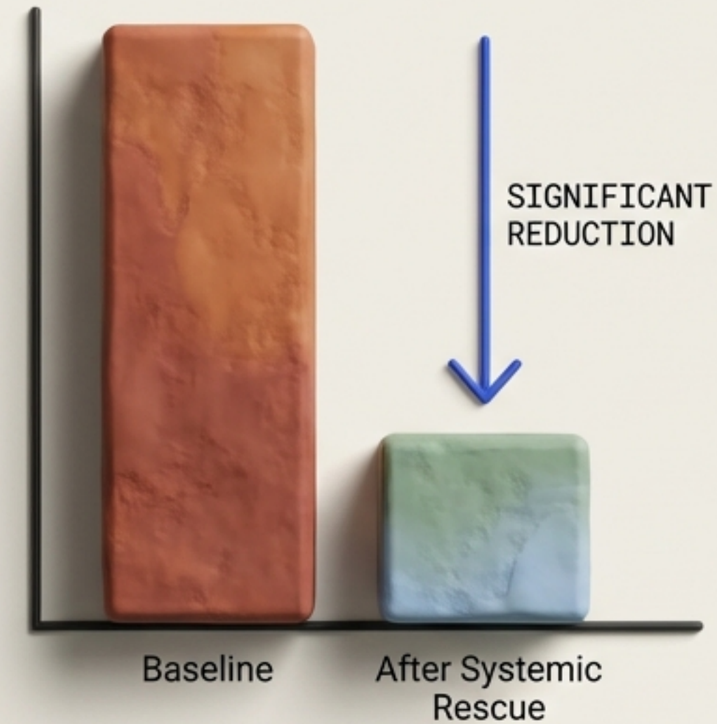


WE DO NOT NEED TO FIX THE BROKEN MICROGLIAL TREM2 PATHWAY; WE BYPASS IT ENTIRELY WITH PERIPHERAL IMMUNITY.

Prepared for Dr. James Truchard and Benjamin Gustafson
Drafted by ChatGPT-5.2

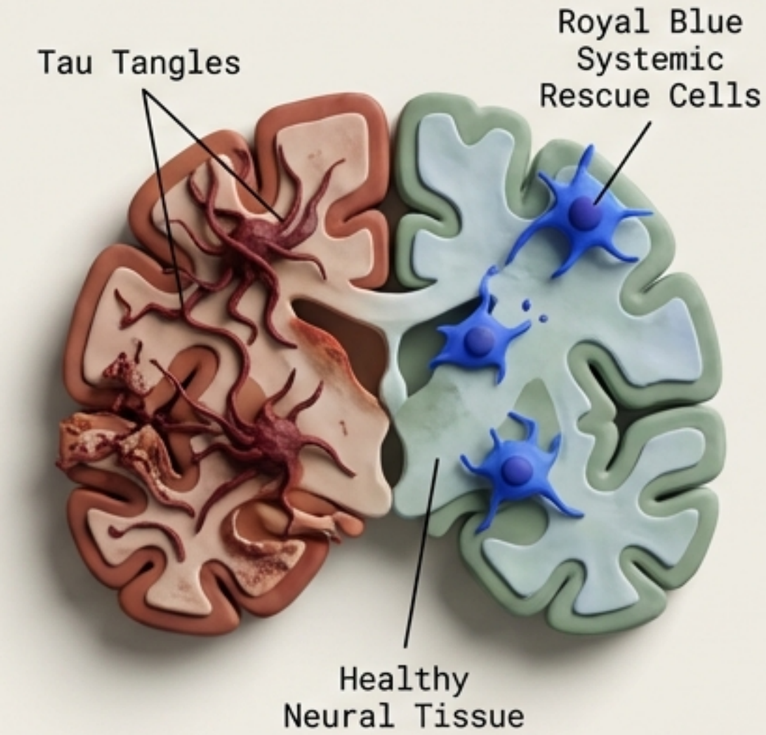
RESTORING HOMEOSTASIS AND FUNCTION

Reduced Plaque Load (5xFAD)



Cognitive Performance (Barnes Maze)

Clearance of Hyperphosphorylated Tau



Systemic rescue breaks the vicious cycle, allowing the brain to heal.

Prepared for Dr. James Truchard and Benjamin Gustafsson
Drafted by ChatGPT-5.2

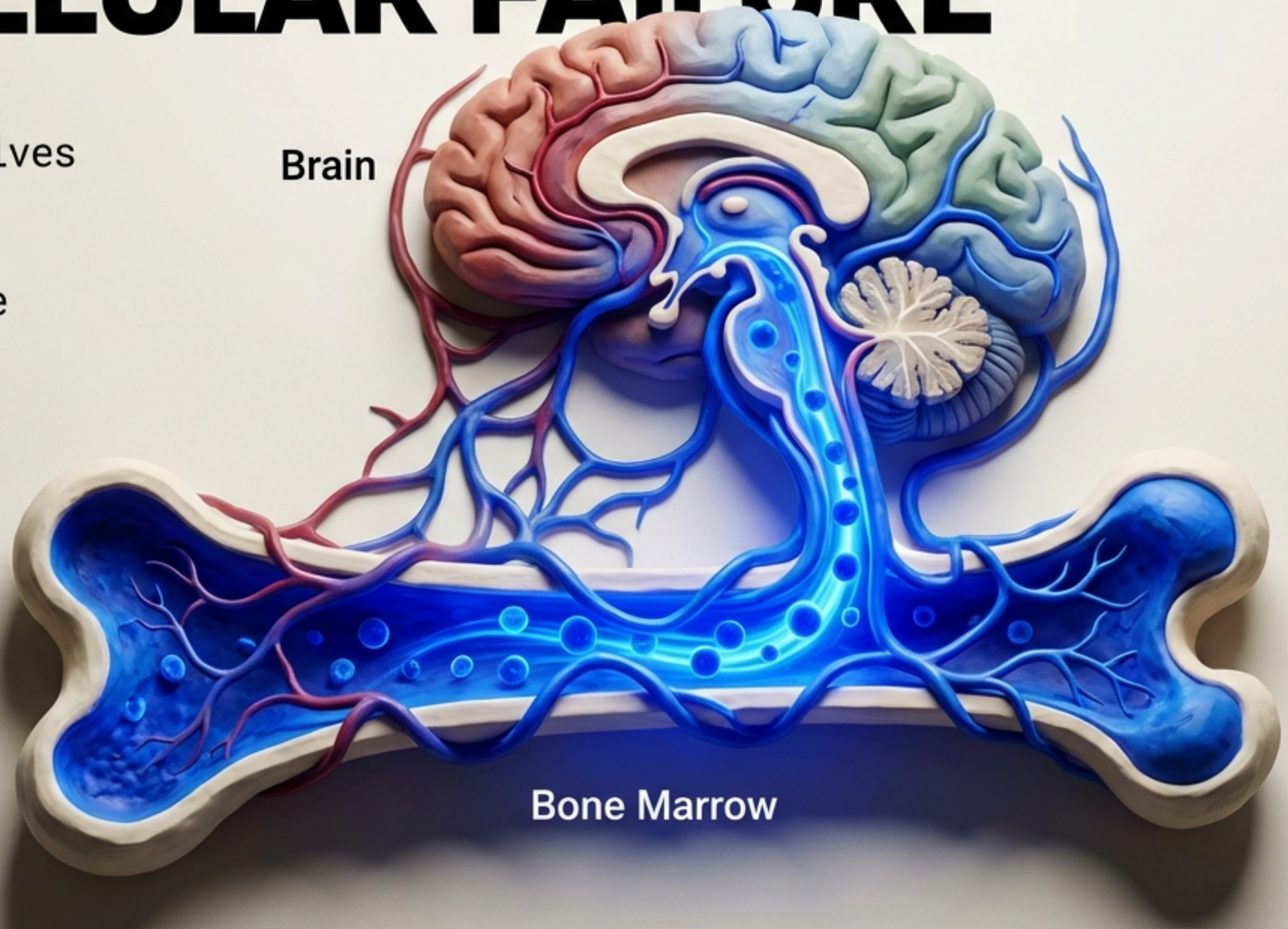
A SYSTEMIC SOLUTION TO A CELLULAR FAILURE

1. Autophagy failure drives neuroinflammation.

2. Microglial senescence acts as a vector of destruction.

3. Chronic pathology exhausts the bone marrow.

4. PD-L1 blockade mobilizes MDMs to restore order.



Prepared for Dr. James Truchard and Benjamin Gustafsson
Drafted by ChatGPT-5.2

THE MIND IS RESCUED BY THE BODY

We cannot treat neurodegeneration in isolation.
The cure lies in harnessing the body’s
wisdom to repair the brain.

Roboto Mono
BASED ON THE DOCTORAL THESIS: THE IMMUNOMETABOLIC NEXUS OF NEURODEGENERATION.

Prepared for Dr. James Truchard and Benjamin Gustafsson
Drafted by ChatGPT-5.2