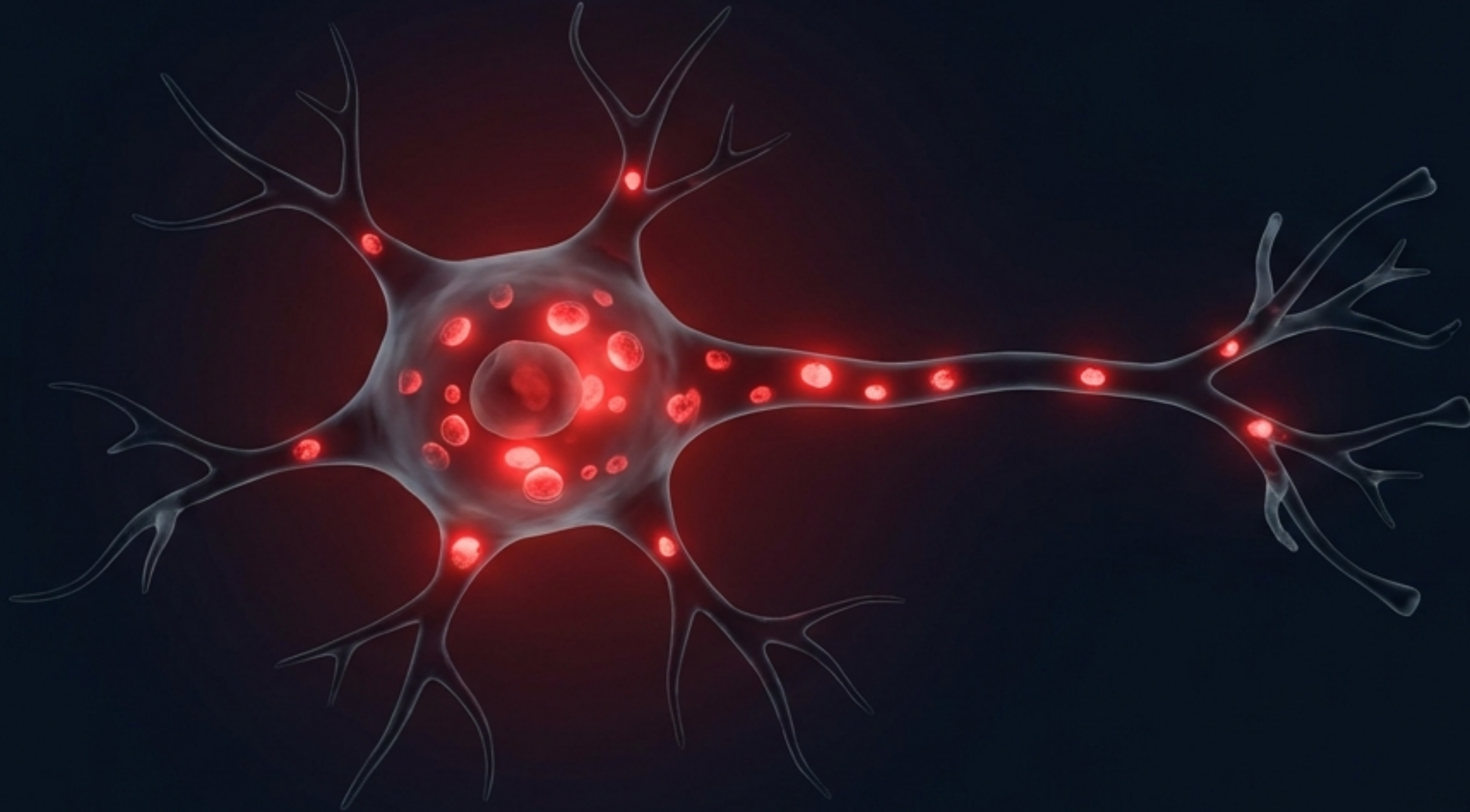


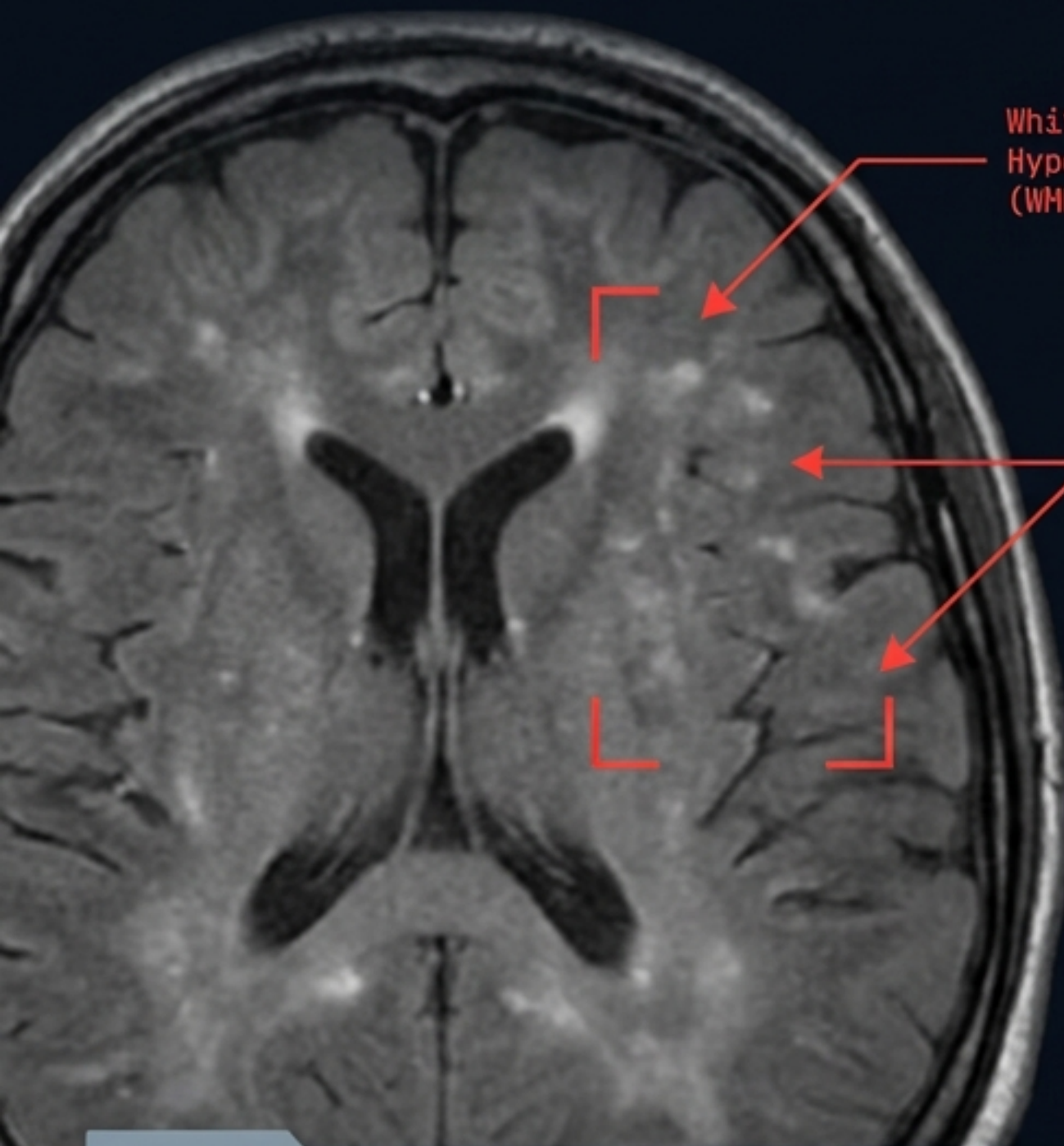
The Hypoxic-Lysosomal Axis in Vascular Dementia

Quantifying the Bioenergetic Crisis via Serum HIF-1 α and Exosomal LC3-II



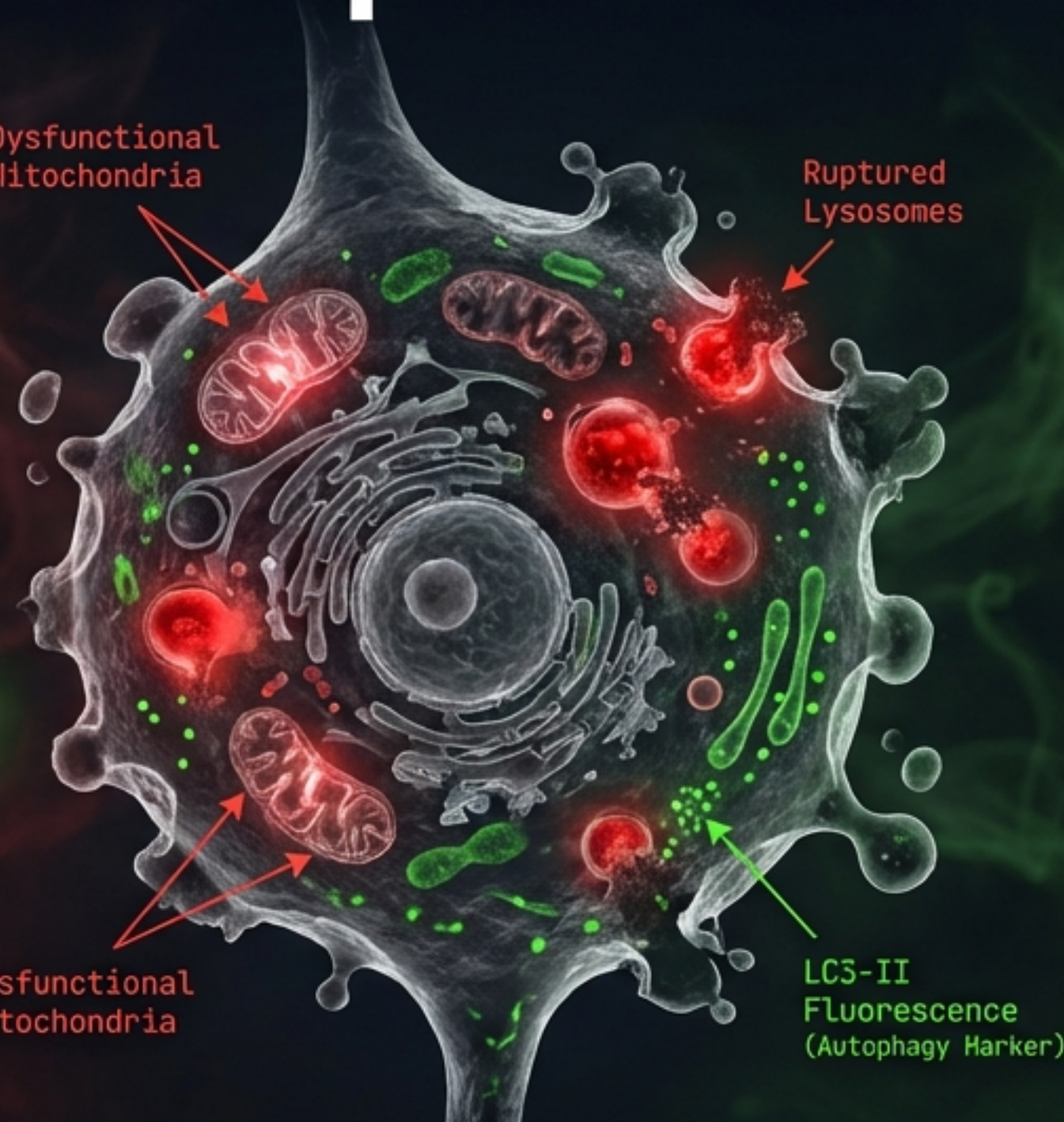
A COMPOSITE BIOMARKER ANALYSIS | MOVING FROM ANATOMICAL DAMAGE TO METABOLIC FAILURE

The Diagnostic Blind Spot



White Matter
Hyperintensities
(WMH) - Late Stage

**Viewing
the ashes,
but missing
the fire.**

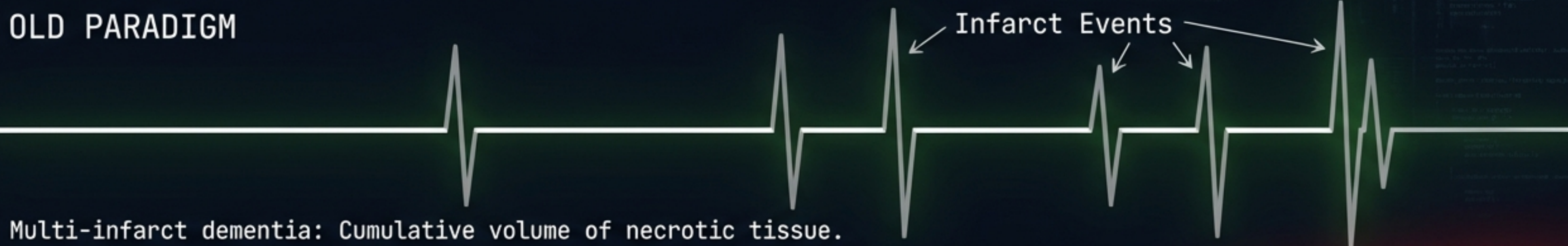


THE CURRENT STANDARD: Diagnosis relies on structural neuroimaging (MRI) of WMH and lacunes. By the time atrophy is visible, damage is irreversible.

THE GAP: We lack a fluid-based metric to quantify cellular stress before cell death occurs.

Reframing Vascular Dementia: A Bioenergetic Crisis

OLD PARADIGM



NEW PARADIGM



REALITY: A specific metabolic failure mode links reduced blood flow to neurodegeneration.

HIF-1 α : The Saboteur of the Aging Brain

ACUTE ISCHEMIA (Stroke)

Adaptive
Response:
Triggers VEGF
& GLUT1.
Survival Mode.

HIF-1 α

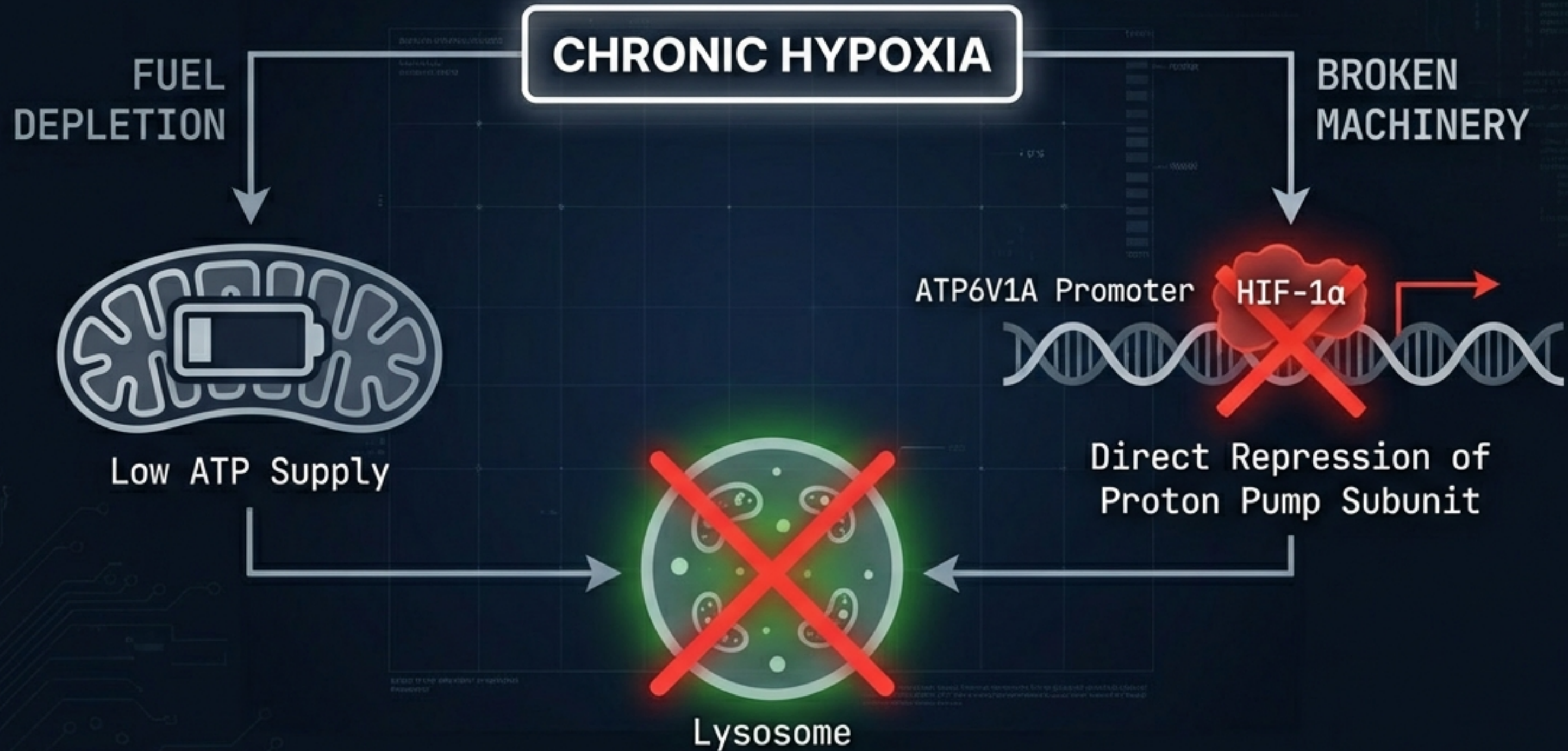
**STABILIZATION
> 12 HOURS**

CHRONIC HYPOXIA (VaD)

Maladaptive
Response:
Triggers
Inflammation &
BBB Breakdown.
Neurotoxicity.

DATA: Persistent elevation observed in 2VO models from 12 hours to 56 days.

The Mechanism of Sabotage: Transcriptional Repression

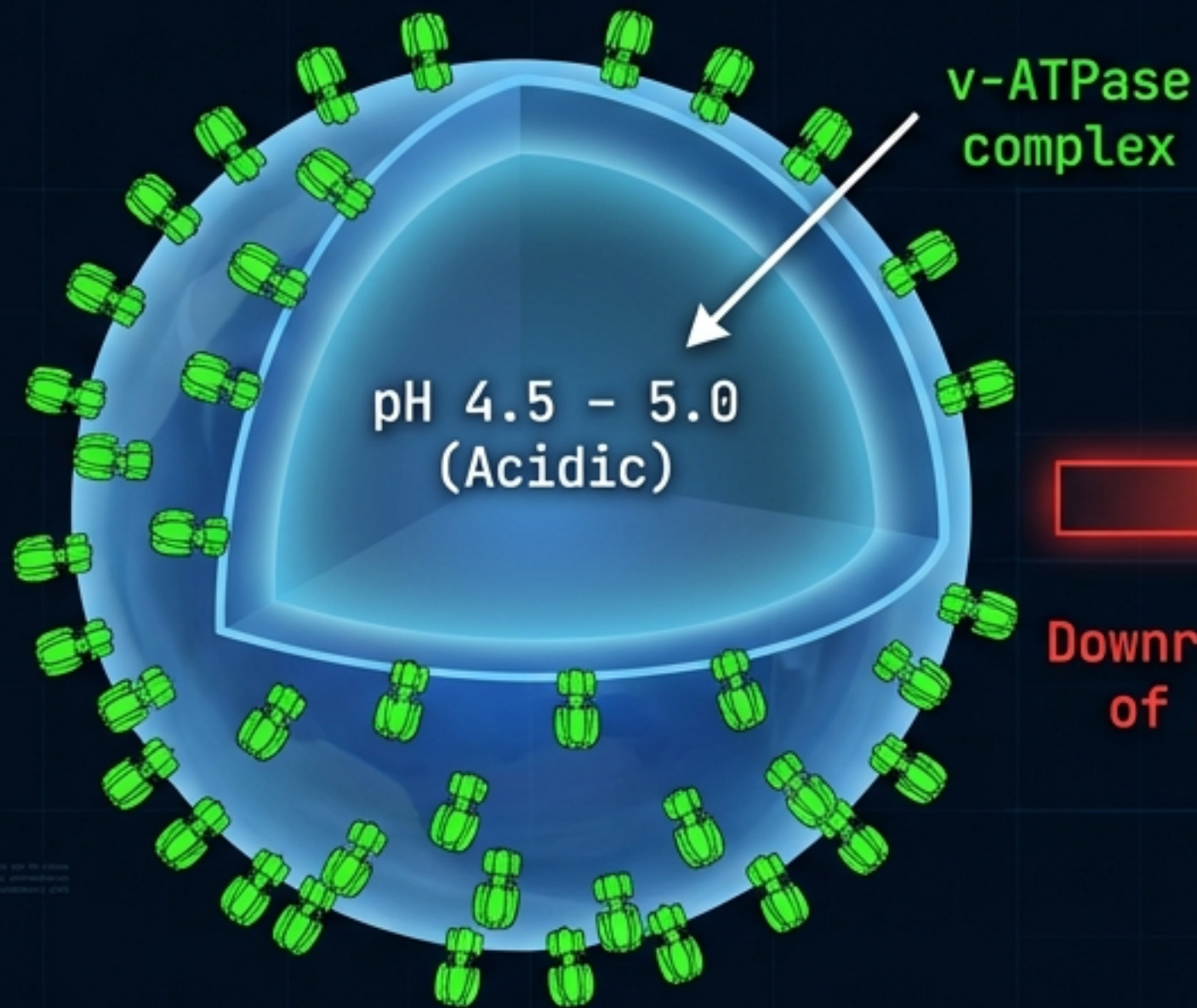


THE DOUBLE HIT: The pump is starved of fuel AND transcriptionally suppressed.

Lysosomal De-acidification

Before and After

HEALTHY

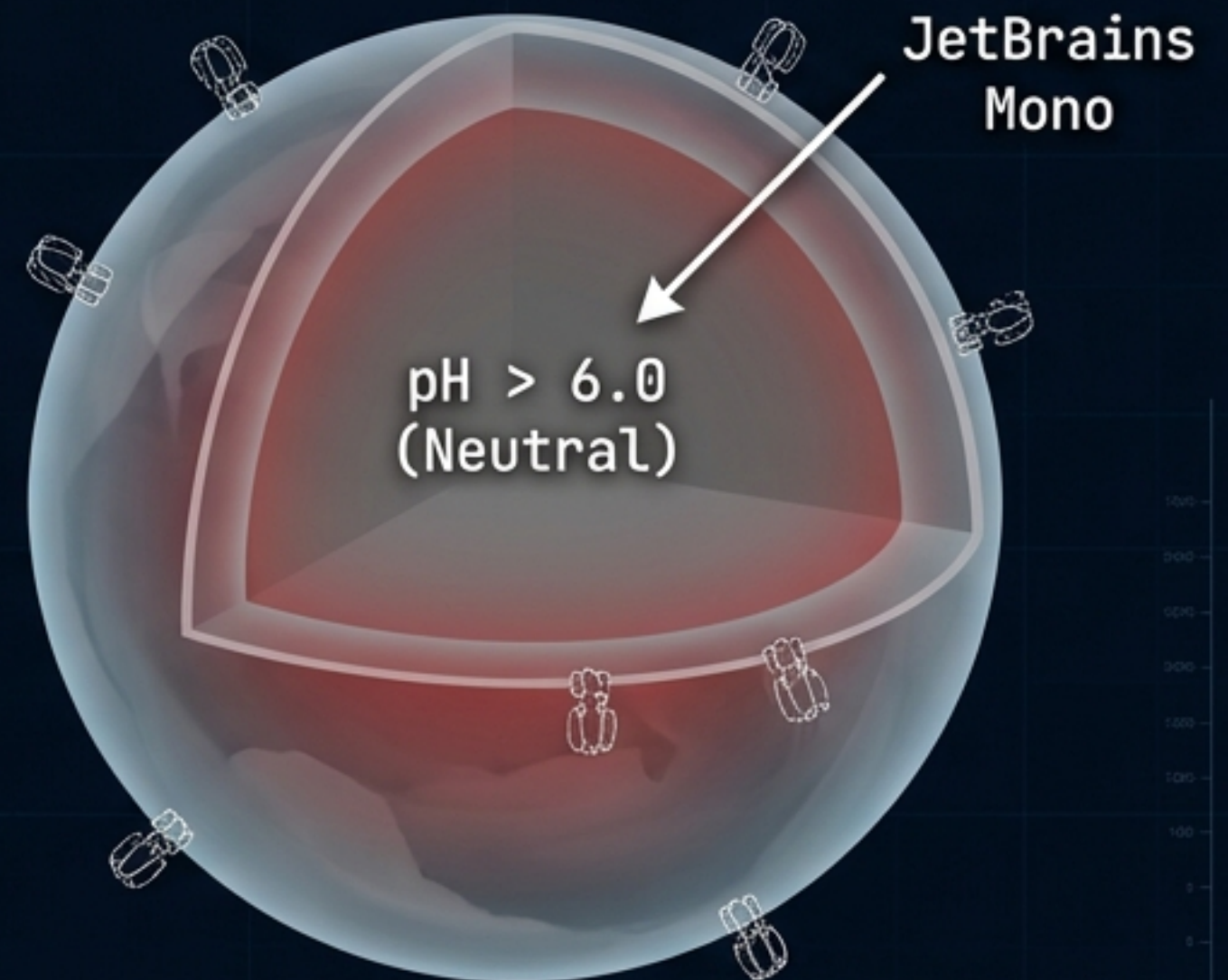


Active Enzymes
Degrading Waste.



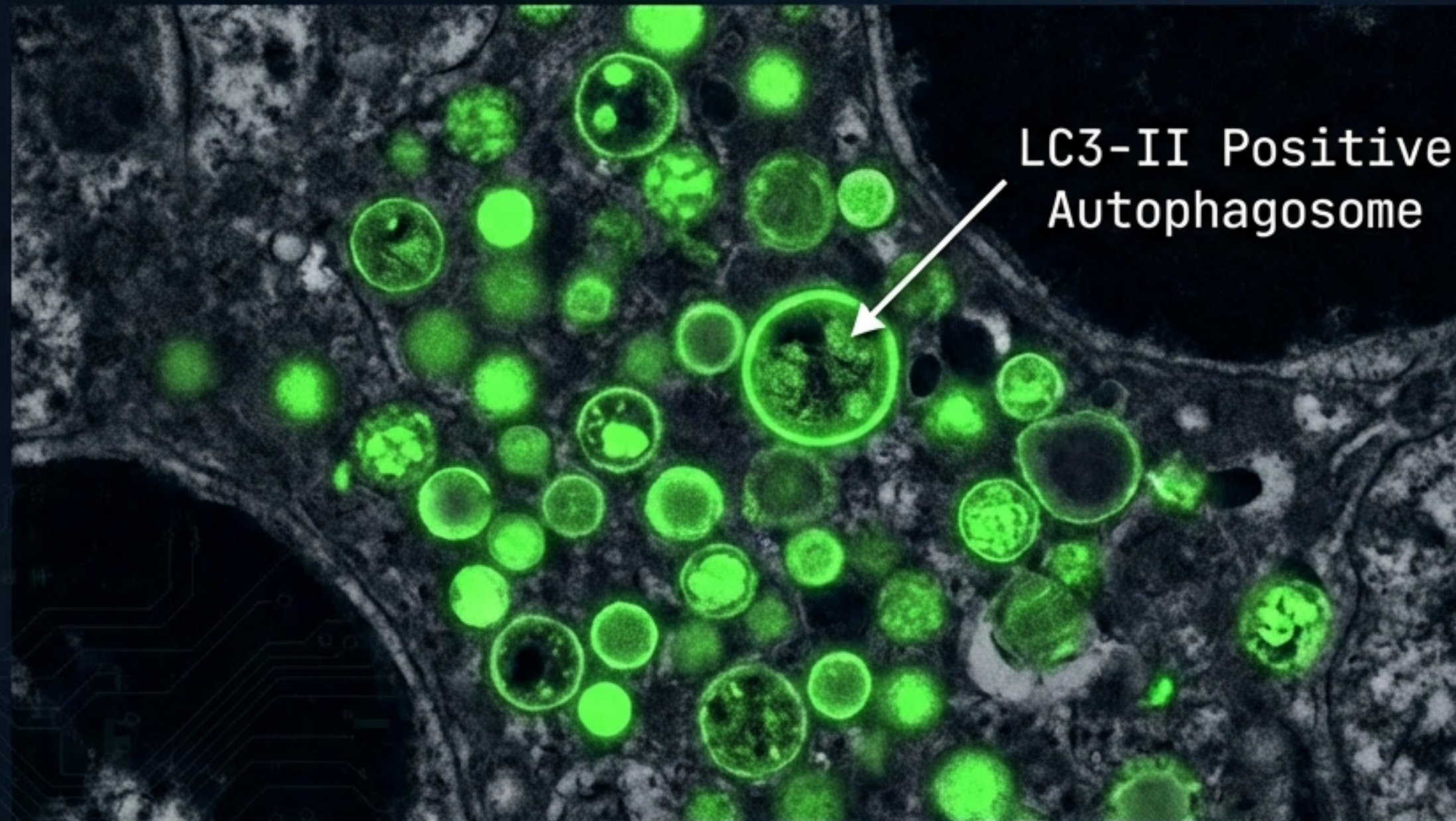
Downregulation
of ATP6V1A

VaD CRISIS



Enzyme Inactivation.
Stagnant Container.

Downstream Consequence: Autophagic Stagnation

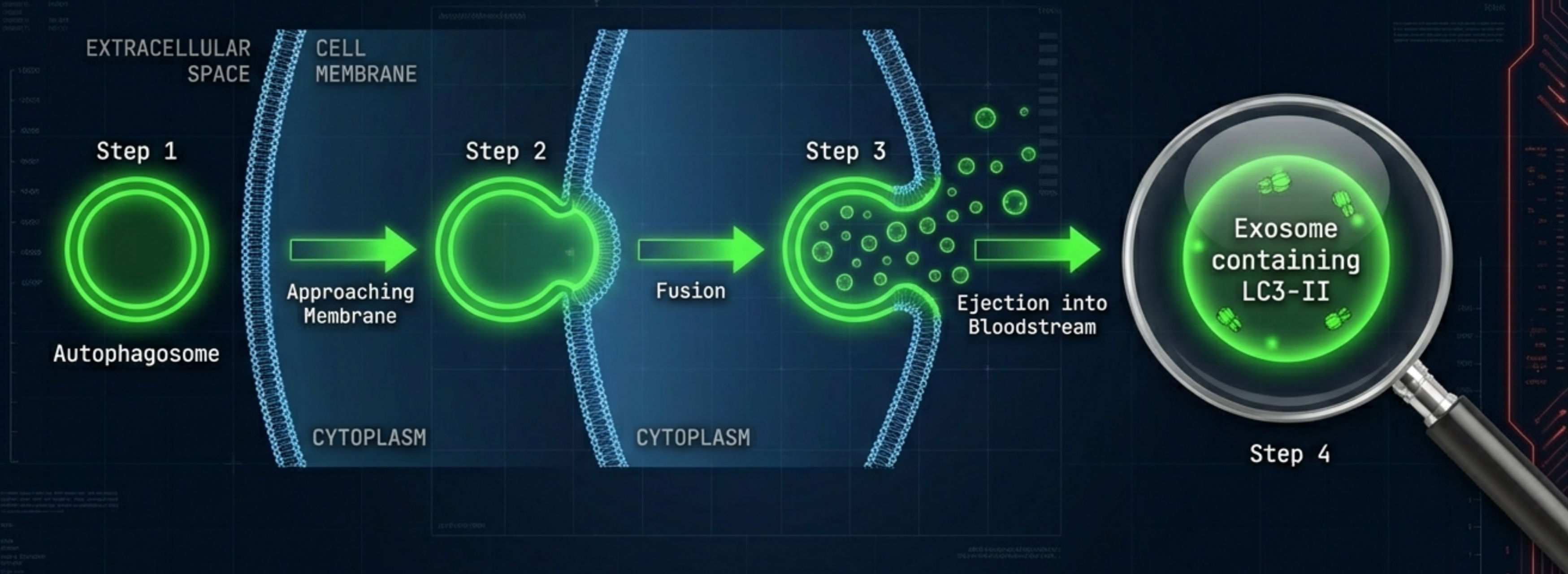


THE MARKER: LC3-II
(Microtubule-associated Protein 1 Light Chain 3-II)

THE BLOCKADE:
Lysosomal failure prevents degradation.

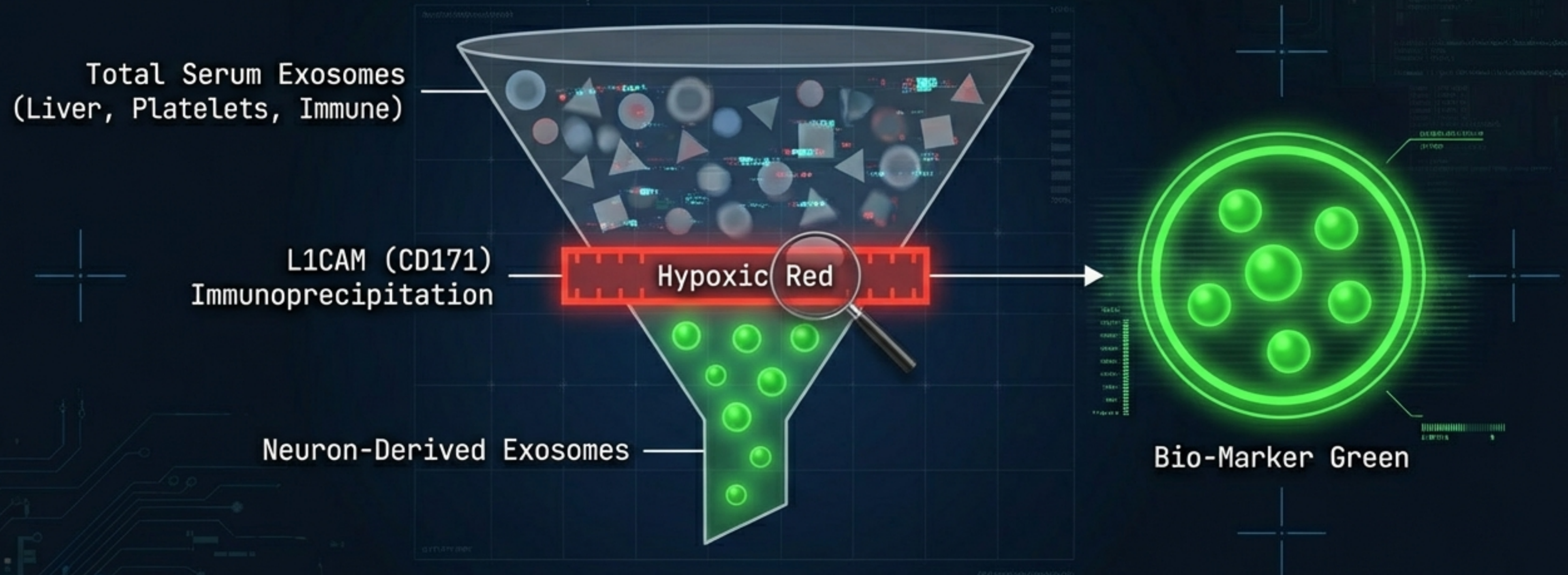
KEY CONCEPT:
High LC3-II signals a traffic jam (Flux Blockade), not increased activity.

The Relief Valve: Secretory Autophagy



When degradative pathways stall, neurons divert cargo to the plasma membrane. Intracellular stasis becomes extracellular evidence.

Isolating the Signal: Neuron-Derived Exosomes (NDEs)



THE PRECISION:
A liquid biopsy of the neuronal state, comparable to CSF analysis.

The Composite Biomarker Index

$$\left[\text{Serum HIF-1}\alpha \right] + \left[\text{Exosomal LC3-II} \right] = \text{Bioenergetic Crisis Score}$$

Systemic Hypoxia Proxy
(The Trigger)

Neuronal Autophagy Stasis
(The Effect)

Synergy: The correlation between these two markers fingerprints the specific etiology of Vascular Dementia.

Differential Diagnosis: VaD vs. AD

CONDITION	HIF-1α (HYPOXIA)	LC3-II (AUTOPHAGY)
VASCULAR DEMENTIA (VaD)	HIGH (Primary Driver)	HIGH
	Strong Correlation ($r > 0.7$)	
ALZHEIMER'S DISEASE (AD)	LOW/MOD (Secondary)	HIGH
	Amyloid Driven	
HEALTHY CONTROL	LOW	LOW

VaD Pathology:
Autophagy fails
due to
bioenergetic
pump failure;
hypoxia is
primary.

Clinical Correlations: The Bioenergetic Scale



**Biomarkers
(High)**



**MRI
(High WMH Volume)**



**Cognition
(Low MoCA Score)**

INTERPRETATION: High biomarkers indicate active, ongoing metabolic failure. Correlates with executive dysfunction and rapid progression.

A New Window into Neurodegeneration

THE OLD WORLD

- Anatomical Damage
- Focus on Stroke/Infarct
- Tool: MRI
- Timing: Too Late

THE NEW WORLD

- Metabolic Failure
- Focus on Lysosomal pH/ATP
- Tool: Composite Biomarker
- Timing: Early/Preventative

From counting dead neurons to monitoring cellular stress.

Implications for Therapy and Staging

1. MOLECULAR STAGING: Identifying 'Bioenergetic Crisis' before atrophy.
2. THERAPEUTIC TARGETS: v-ATPase agonists, mTOR modulators, perfusion enhancement.
3. CLINICAL TRIALS: A surrogate endpoint for vascular interventions.

Looking into the blood to see the brain
starving—and intervening before it dies.