



Platform Therapy for Alzheimer's and
Related Neurodegenerative Conditions

Turning Irreversible Into Recoverable

Restoring neurovascular integrity with a first-in-class biologic therapy

October 2026 | Non-Confidential Deck

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streambiomedical.com

Non-confidential disclosure



— Prix Galien USA Best Startup Nominee



Why Stream Was Nominated

Three innovations behind Stream's recognition

Discovery of a Hidden Repair Pathway

- Discovered a previously unrecognized endogenous ECM repair pathway.
- Injury-triggered perlecan cleavage releases LG3 within the neurovascular unit.
- This pathway helps restore BBB integrity, vascular stability, and tissue homeostasis.

A New Class of Therapeutics

- rLG3 amplifies a natural repair signal rather than blocking pathology.
- Selectively engages damaged neurovascular tissue through integrin receptors.
- Across CNS disease models, it improved neurovascular function and outcomes.

Redefining Biomarker-Driven Development

- Stream built a framework to directly measure neurovascular restoration in patients.
- The program integrates advanced DCE-MRI, cerebrovascular reactivity, and circulating biomarkers.
- This creates an early readout of safety, target engagement, and biological activity.

The Team Turning Irreversible into Recoverable

Scientific Advisory Board



Lennart Mucke, MD

Founding director of the Gladstone Institute of Neurological Disease, UCSF



Ramon Diaz-Arrastia, MD, PhD

Presidential Professor of Neurology at the University of Pennsylvania Perelman School of Medicine in Philadelphia



Andrew Shih, PhD

Professor at the Norcliffe Foundation Center for Integrative Brain Research at Seattle Children's Research Institute.

Stream Leadership



CEO

Bill Schwieterman, MD



CSO

Davis Adkisson, PhD



Dir. Research

Bryan Clossen, PhD



Dir. Manufacturing

Seth Fisher, BA

For millions living with neurodegenerative disease,
recovery may finally be within reach.



A GLOBAL HEALTH CRISIS

Neurodegenerative diseases impact tens of millions worldwide and remain one of the greatest unmet needs in medicine.



THE LIMITS OF CURRENT APPROACHES

Current approaches primarily target downstream pathology while leaving the underlying neurovascular dysfunction unresolved.



A DIFFERENT KIND OF THERAPY

Stream Biomedical is developing rLG3, a novel recombinant protein designed to restore brain function through **neurovascular repair**.

Failure of neurovascular repair drives neurodegeneration

Growing evidence shows that dysfunction of the neurovascular unit is a central driver across neurological diseases.



Pericyte loss and vascular instability



Impaired cerebral perfusion



Blood-brain barrier dysfunction



Chronic neuroinflammation
and impaired repair

Over time, breakdown of these systems leaves the brain **unable to maintain or repair itself.**



Neurovascular
Restoration



Vascular Integrity
& Repair



Enhanced Perfusion
& Support



Targeted, Systemic
Neuroregeneration

What if the brain could recover?

Stream is developing a new class of biologics — **vascular matrikines** — designed to restore neurovascular integrity by amplifying endogenous repair signaling.



Restores neurovascular stability and repair
Reinforces the brain's capacity to maintain and heal its own vascular network.



Enhances vascular integrity and neuronal support
Improves perfusion and the microenvironment that neurons depend on.



Targets shared upstream mechanisms
Addresses common drivers of neurodegeneration across multiple diseases.



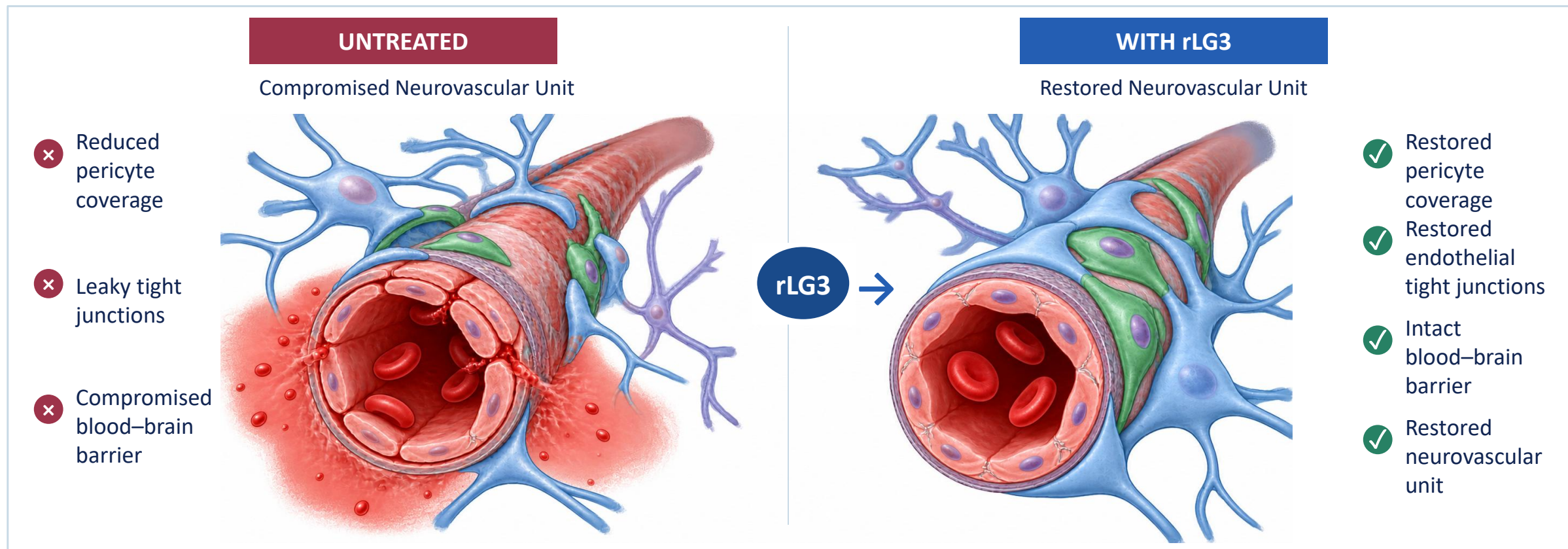
A unified **neurovascular approach to neurodegenerative disease.**

Introducing rLG3:

A First-in-Class Recombinant Biologic

Derived from a Natural Endogenous CNS Repair Protein

rLG3 restores neurovascular integrity and CNS homeostasis following injury by restoring pericyte coverage and endothelial tight junctions.



Restoring the brain's own repair mechanisms to protect, heal and restore.

rLG3 restores pericyte coverage by engaging integrin receptors.

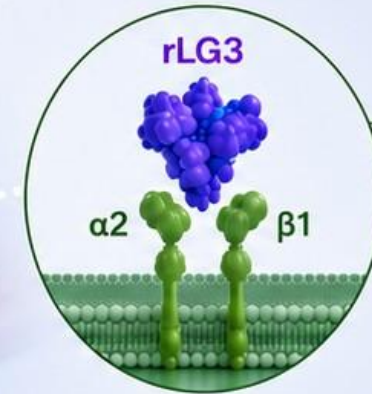
rLG3 is a vascular matrine that binds to integrin receptors on pericytes and endothelial cells to promote pericyte recruitment, adhesion, and stabilization on blood vessels.



The result: Restored pericyte coverage.
Stronger vessels. Healthier brain.

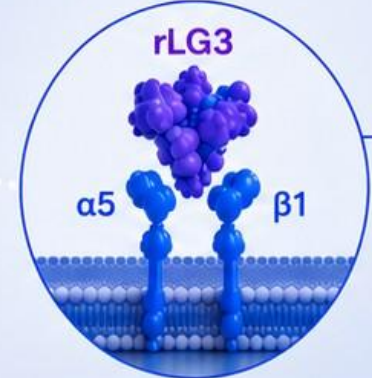
Pericyte

Endothelial cell



rLG3 binds to $\alpha2\beta1$ integrin on pericytes

This interaction promotes pericyte recruitment, adhesion, and stabilization on the vessel wall.



rLG3 binds to $\alpha5\beta1$ integrin on endothelial cells

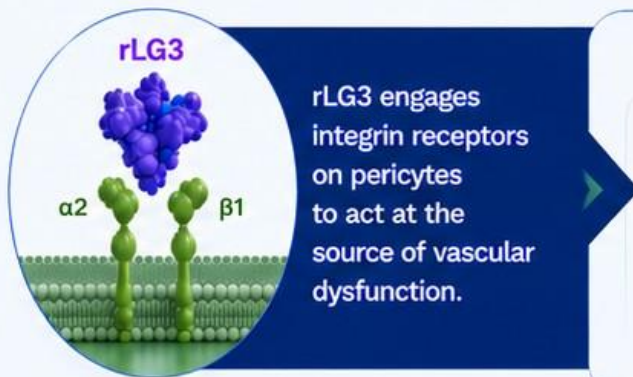
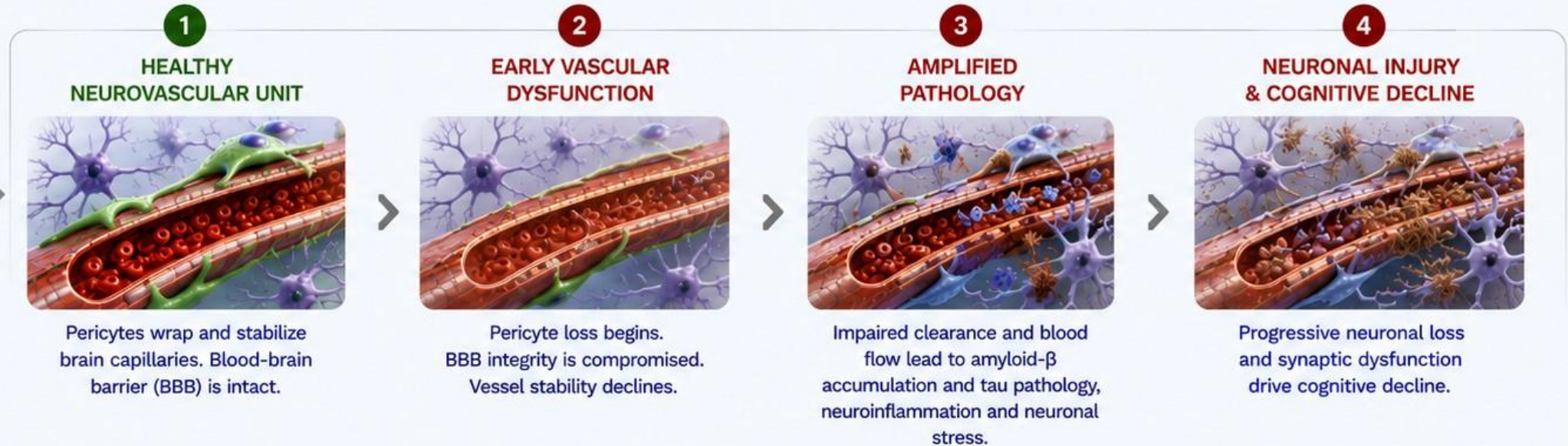
This interaction supports endothelial cell function and vessel integrity.

rLG3 acts **early** to restore the neurovascular foundation

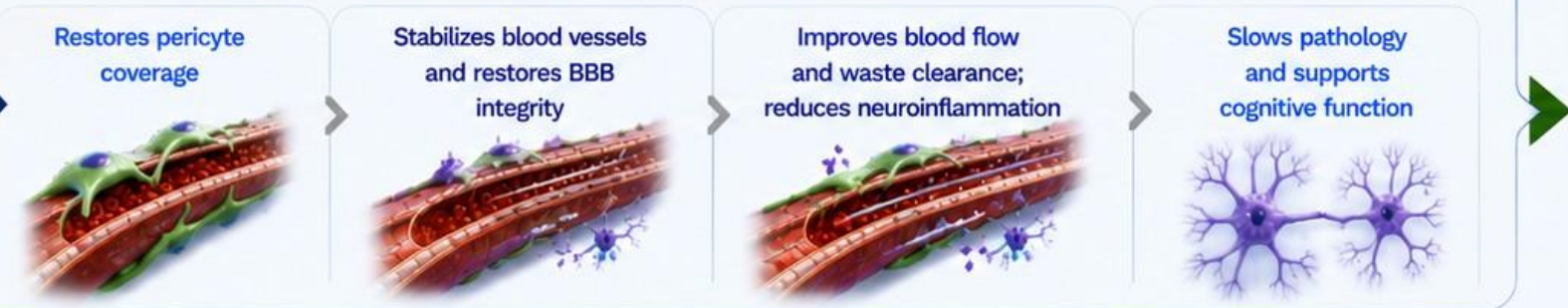
In Alzheimer's disease—and following brain injury—vascular dysfunction can emerge early and persist, amplifying downstream pathology. rLG3 targets the earliest vascular changes to restore pericyte coverage and support a healthy brain.

NVU Failure Cascade

Vascular dysfunction occurs early—often before clinical symptoms.



— ACTING EARLY. RESTORING VESSELS. PROTECTING THE BRAIN. —



**HEALTHIER
BRAIN.
BETTER
OUTCOMES.**

Why Pericytes Matter: Published Human and Preclinical Data Show Neurovascular Dysfunction Drives Downstream Pathology

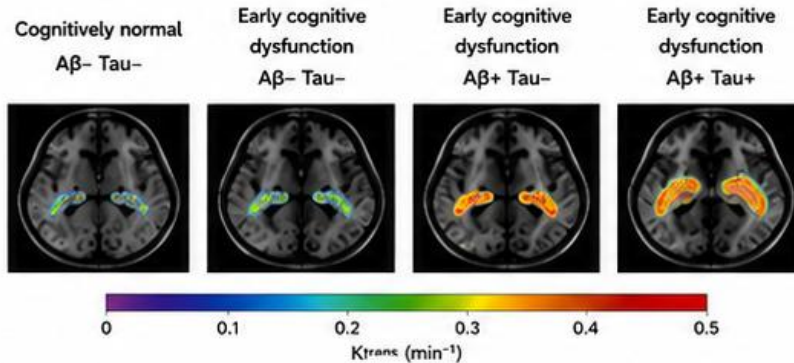
Pericyte injury and BBB breakdown occur early, predict cognitive decline, and cause downstream pathology.

1 HUMAN EVIDENCE

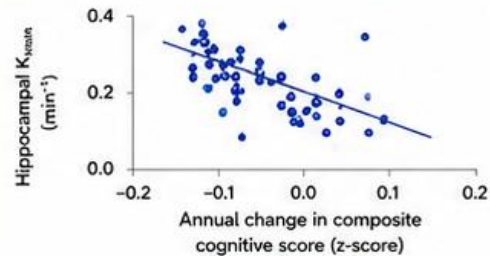
BBB breakdown occurs early and predicts cognitive decline

Nation et al., Nature Medicine, 2019

Hippocampal BBB Permeability (DCE-MRI)



BBB leakage is present in early cognitive dysfunction, before substantial amyloid or tau pathology.



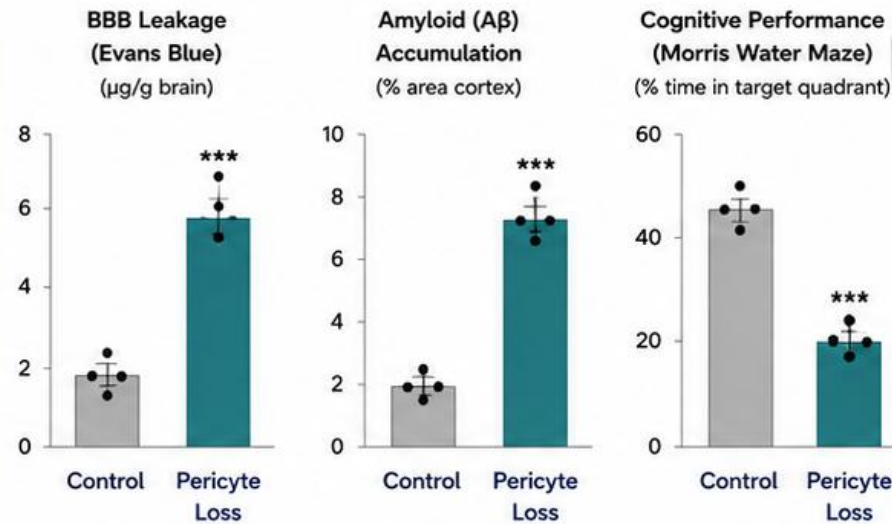
Higher hippocampal BBB permeability independently predicts future cognitive decline ($r = -0.52, p < 0.001$)

2 PRECLINICAL EVIDENCE

Pericyte loss causes BBB breakdown, pathology, and cognitive deficits

Sagare et al., Neuron, 2013

Mouse model: Pericyte depletion in APP mice



Pericyte loss is sufficient to drive BBB breakdown, increased amyloid accumulation, and cognitive impairment.

KEY TAKEAWAYS



Occurs Early

BBB dysfunction and pericyte injury are detectable in early cognitive dysfunction, before amyloid or tau accumulation.



Predicts Decline

Neurovascular dysfunction independently predicts future cognitive decline, even after controlling for amyloid and tau.



Drives Pathology

Pericyte loss causes BBB breakdown, increases amyloid accumulation, and leads to cognitive deficits.



Published human and preclinical studies support pericyte / BBB dysfunction as an upstream driver of neurodegenerative processes.

Preclinical Evidence



University of Texas Health
Science Center

TBI and Alzheimer's



University of Kentucky
Stroke Core

Stroke



Hubbard Lab
University of Kentucky

TBI and Alzheimer's



McCreedy Lab
Texas A&M University

SCI and Stroke



Bix Lab
Tulane Medical Center

Stroke

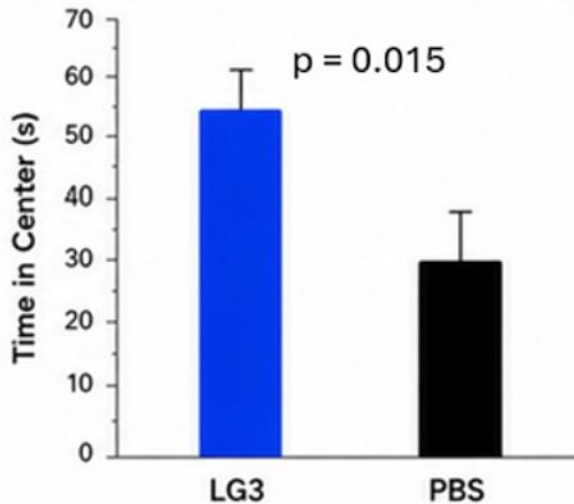
rLG3 Improves Cognitive Function in Alzheimer's Mice



LG3 treatment significantly improved cognitive and emotional function across multiple behavioral domains, concurrent with **reduced amyloid burden in the basolateral amygdala**.

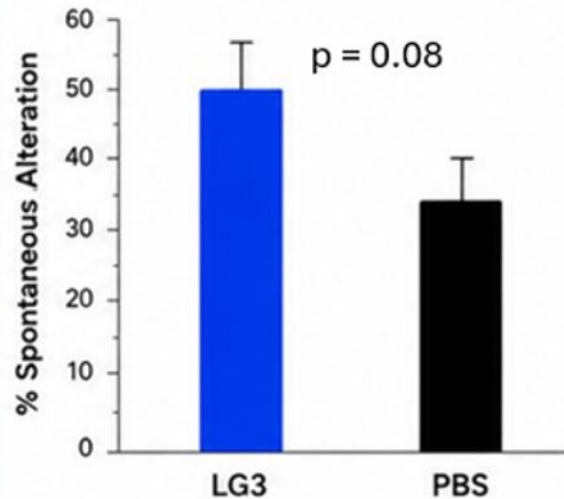
A

Open Field Test
Measure of anxiety



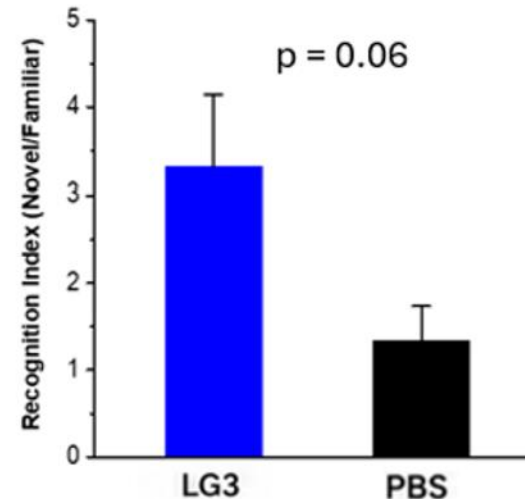
B

Y-Maze Test
Spatial recognition



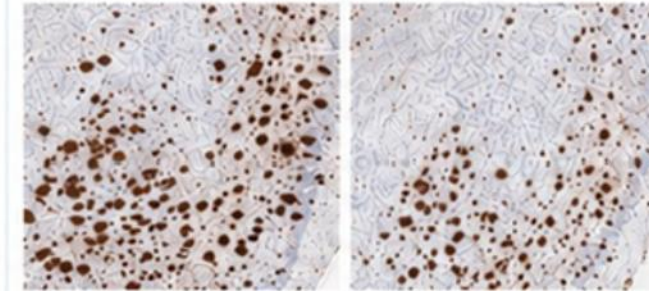
C

Novel Object Recognition
Measure of cognition



Reduced Amyloid Pathology
5XFAD Amyloid Model

A β ₄₂ in Basolateral Amygdala



PBS

LG3



Visibly reduced amyloid burden
in LG3-treated mice



LG3 increased time in the center of the arena, indicating reduced anxiety



LG3 improved spatial working memory as measured by Y-maze



LG3 enhanced novel object recognition, indicating improved cognition



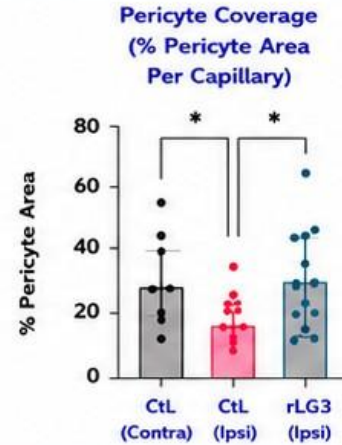
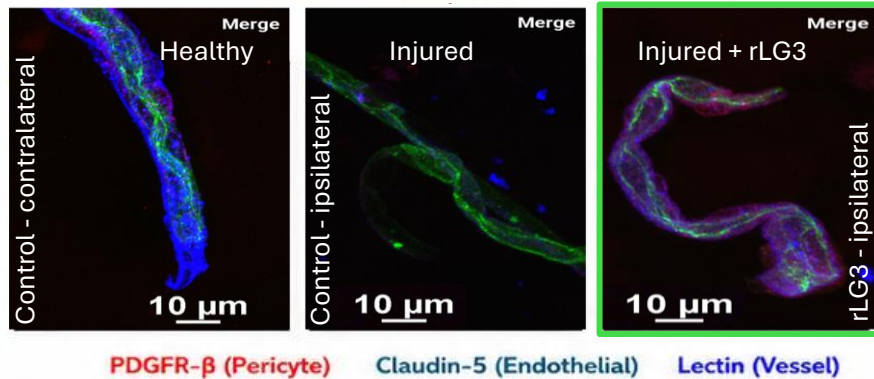
Improvements in behavior coincide with reduced amyloid burden in the basolateral amygdala

n=7-8/group

rLG3 Restores Neurovascular Integrity in Multiple Preclinical Models

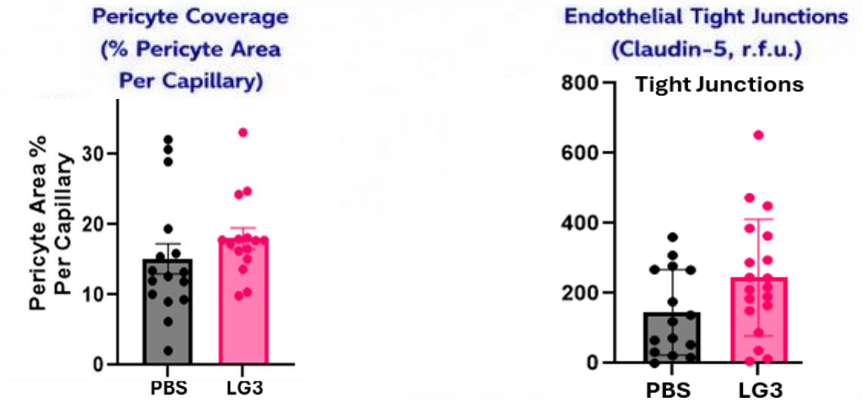
1. Restored Pericyte Coverage of Brain Capillaries

Acute Ischemic Stroke Murine Model



2. Strengthened BBB Integrity

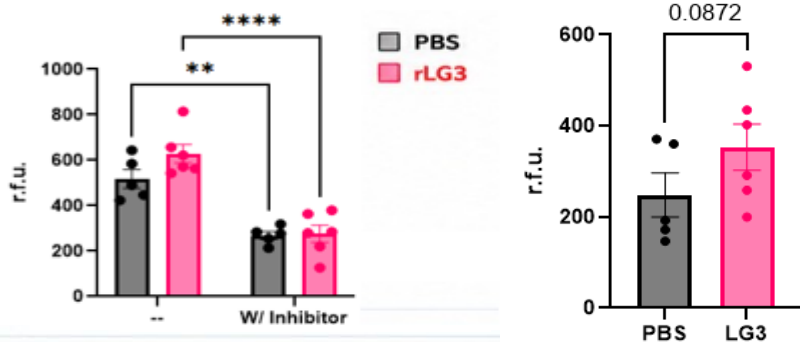
5XFAD Murine Alzheimer's Model



3. Increased Efflux of Amyloid Protein

db/db mice

Amyloid Efflux in Freshly Isolated Brain Capillaries

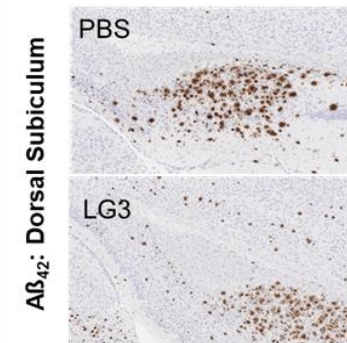


4. Downstream Impact: Reduced Amyloid Pathology

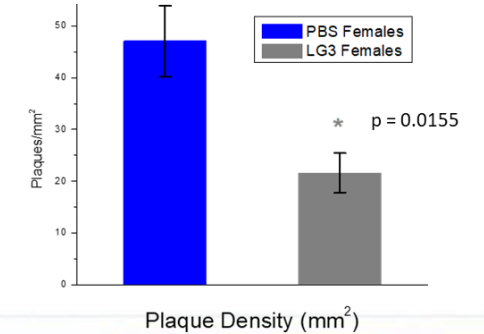
Hippocampus (Main site of AD pathology)



5XFAD Amyloid Model



Amyloid Protein Clearance Amyloid (6E10) Immunofluorescence



rLG3 Treatment
Restores Neurovascular
Health and Function



Restores
pericyte
coverage



Strengthens
BBB
integrity



Increases
amyloid
efflux



Reduces
amyloid
pathology



Supports
cognitive
function

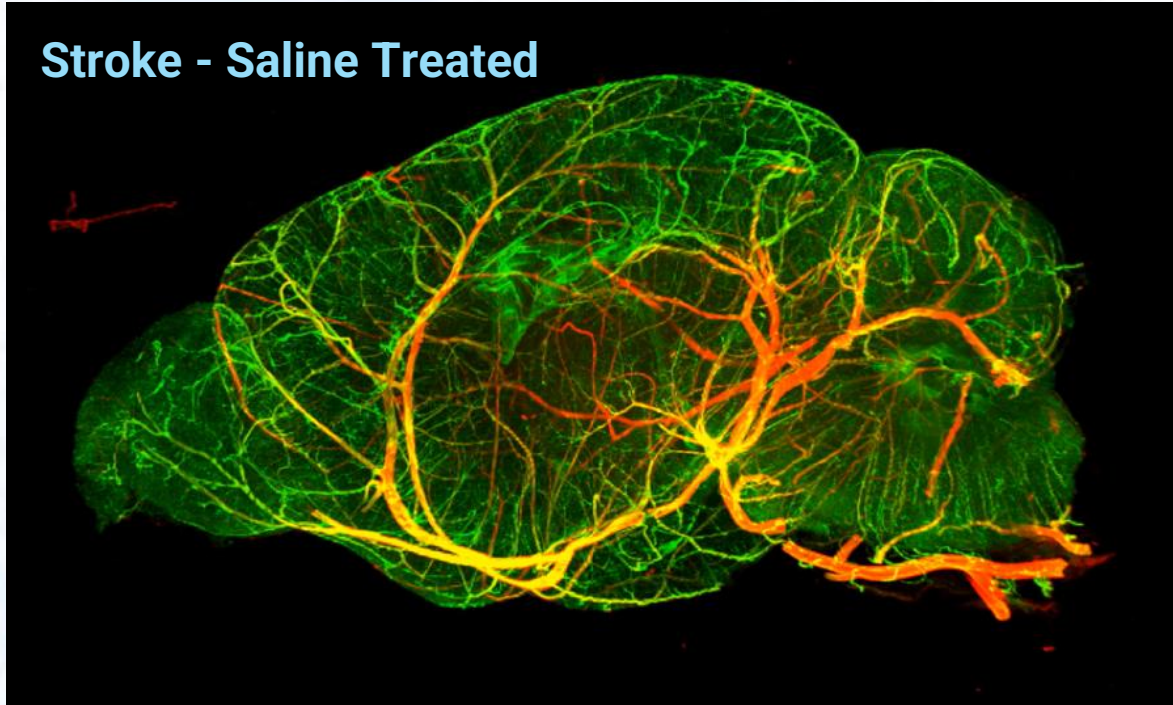


Broad neurovascular
benefits with
downstream impact

rLG3 Prevents Loss of Brain Vasculature

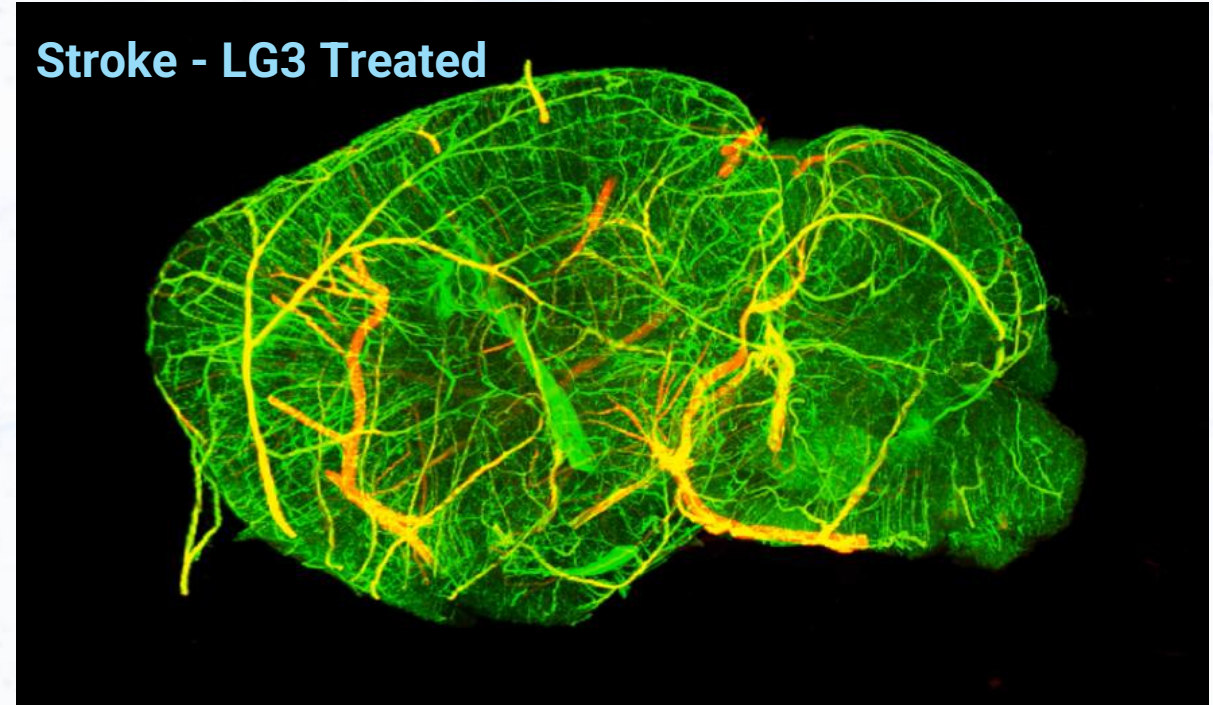
A single dose after reperfusion eliminates vascular rarefaction

Stroke - Saline Treated



Vessel Density: 8.25% (57% loss)

Stroke - LG3 Treated



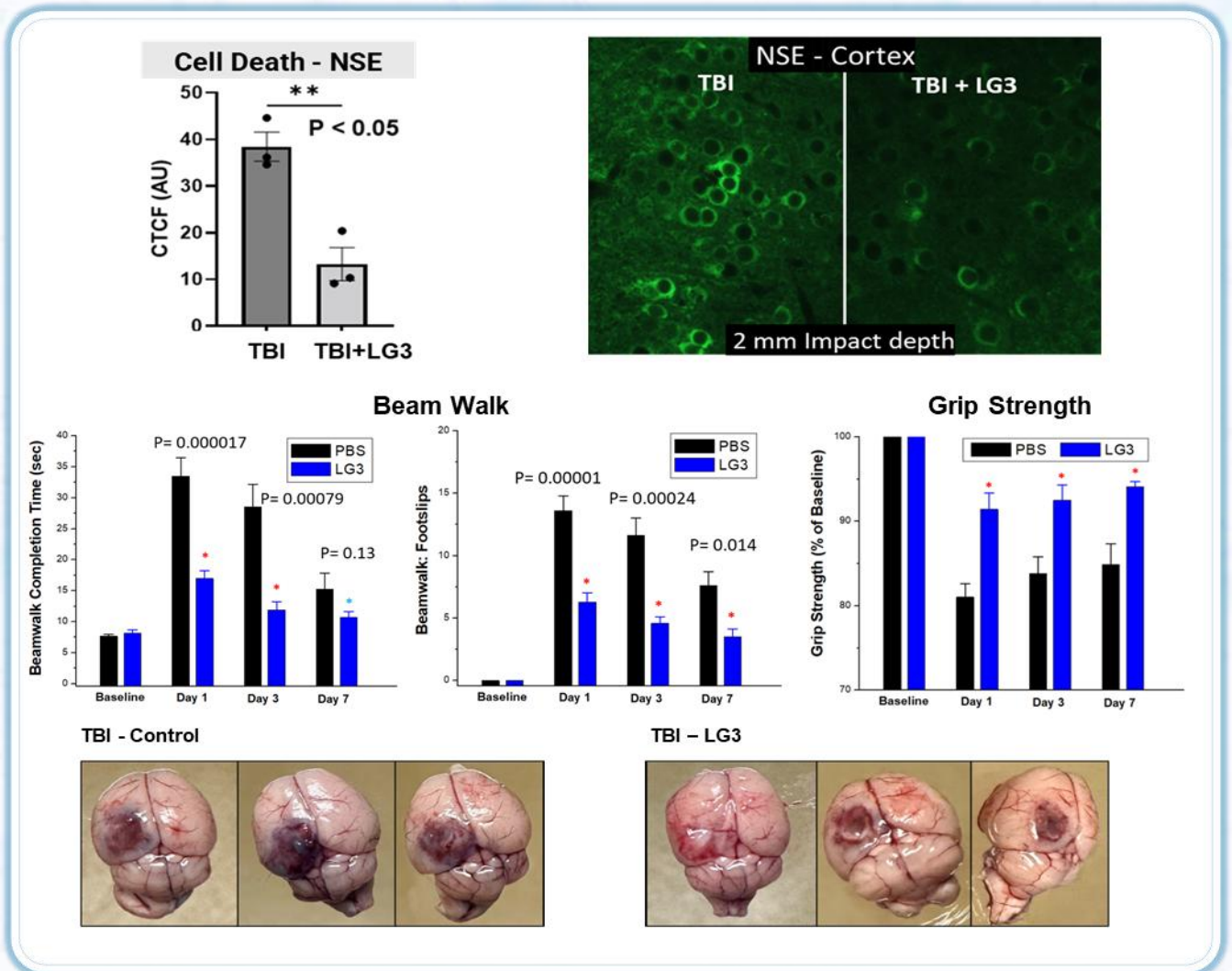
Vessel Density: 18.92% (2% loss)

Healthy Tissue Vessel Density: 19.19%

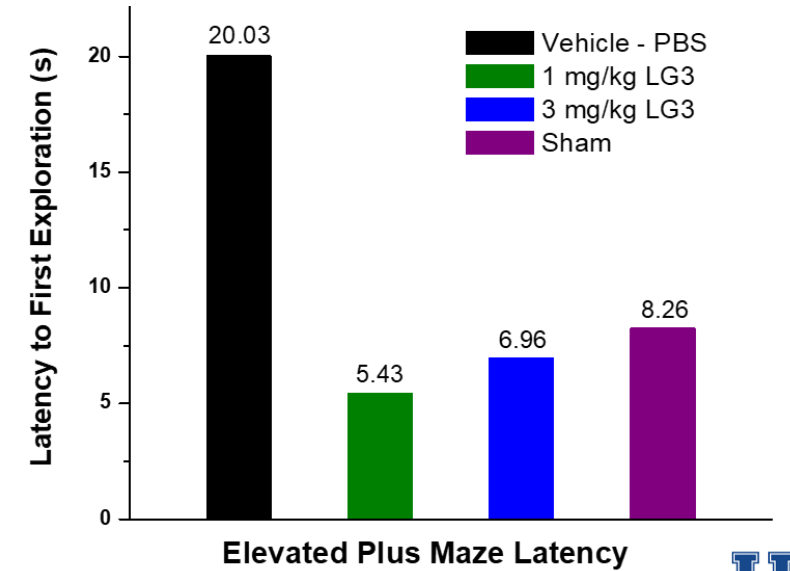
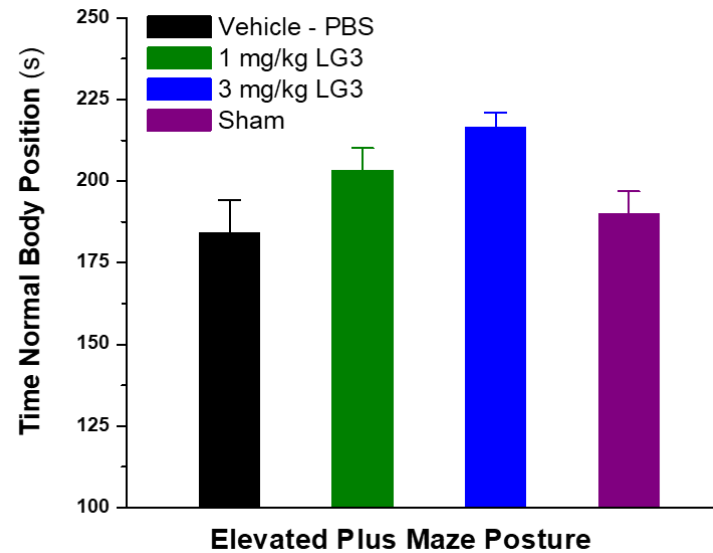
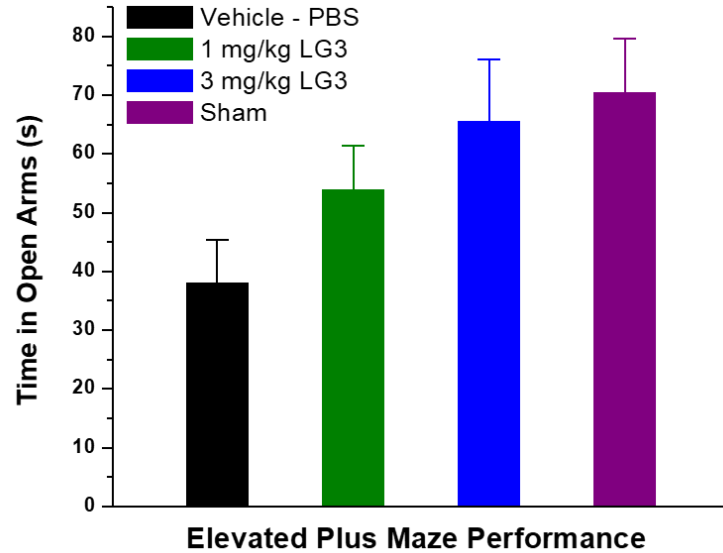


rLG3 Highly Effective in Traumatic Brain Injury

- Highly efficacious with a single dose
- Reduces cell death
- Rapidly improves functional performance
- Improves BBB integrity in impact region

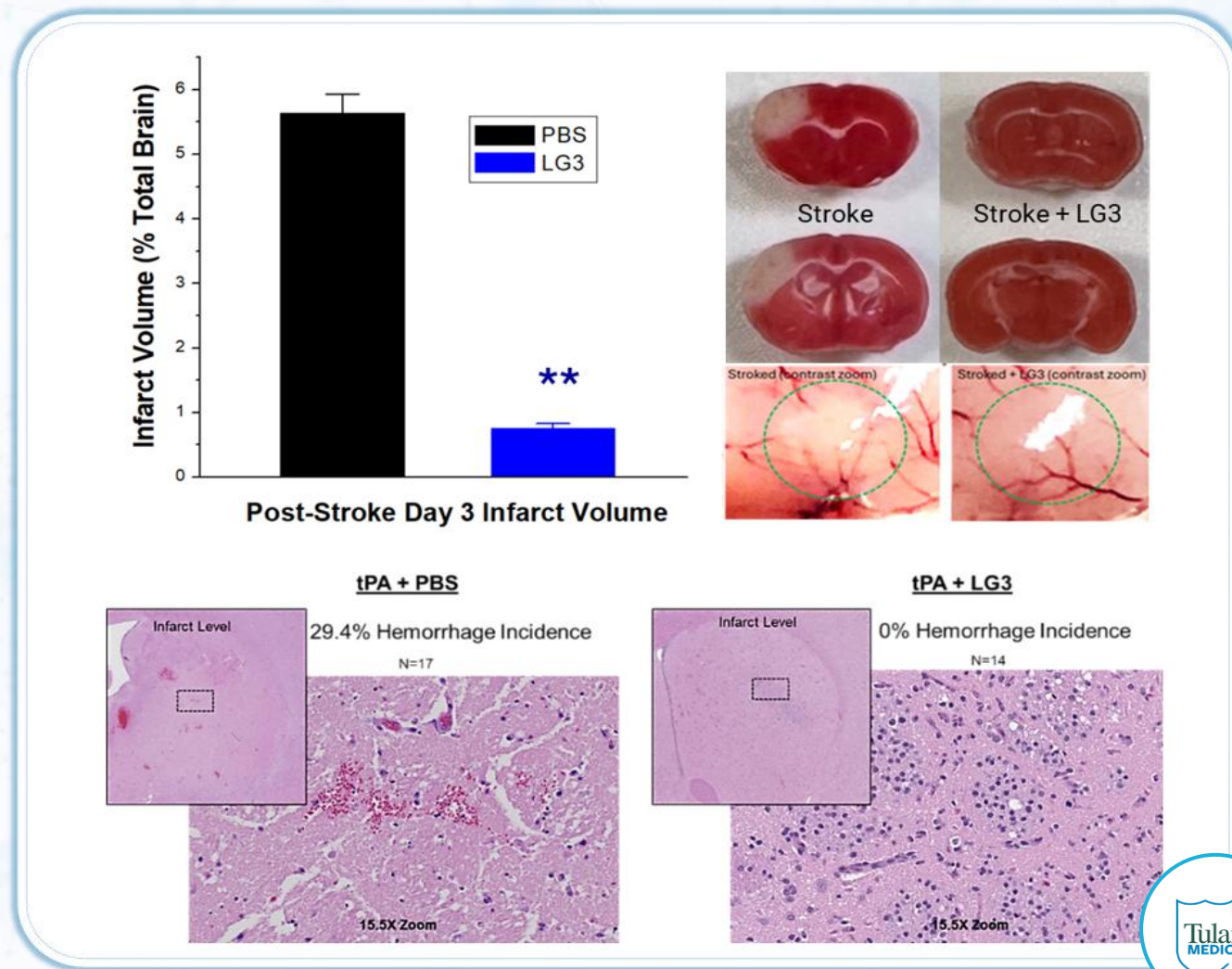


rLG3 Pre-treatment Improves Performance After Repeat Blast Injury



rLG3 is Neuroprotective and Reduces Hemorrhage

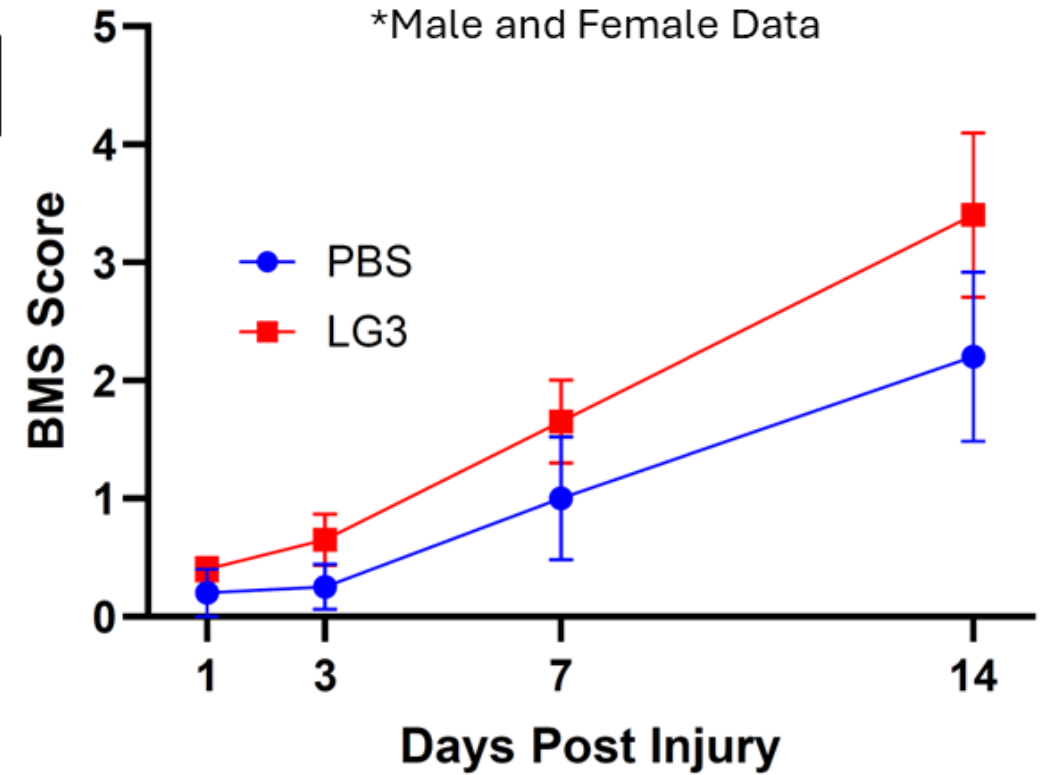
- Highly efficacious neuroprotection with single dose
- Reduces mortality & brain damage preclinically
- Eliminates hemorrhage in severe stroke models
- Improves tPA (tissue plasminogen activator) safety by reducing hemorrhage risk



rLG3 Improves Recovery in a Spinal Cord Injury Model

- Improves Limb Function & Weight Support
- Accelerates Recovery Trajectory
- Effective in males and females

Acute



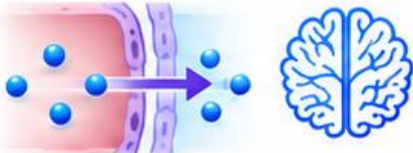
TAMU/Stream Internal Data. Basso Motor Score

rLG3: A Multi-Mechanism, Disease-Modifying Therapeutic



Powerful Biology. Broad Potential. Clinic-Ready.

rLG3 PROPERTIES

- 

1 Quickly crosses the BBB through Active Transport
- 

2 Profound Neuroprotection
- 

3 Restores the Blood Brain Barrier
- 

4 Reduces Biomarkers of CNS Injury
- 

5 Eliminates tPA Hemorrhage Risk

CLINIC-READY

- 

Recombinant human protein
Manufactured under cGMP
- 

High purity and batch consistency
Robust analytical characterization and QC
- 

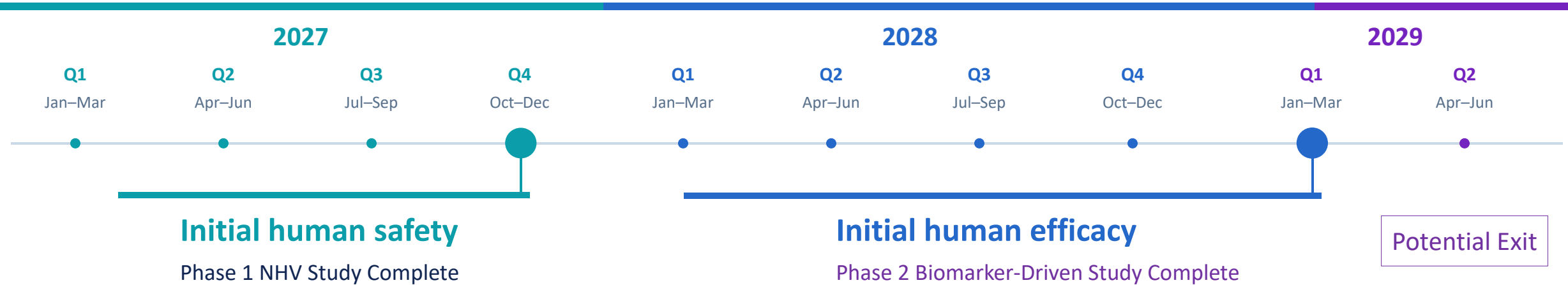
Favorable preclinical toxicology
GLP studies complete
- 

Strong intellectual property position
Patent Coverage to 2045
- 

Clear path to first-in-human trials
IND-enabling package in preparation

Clinical Development Timeline for rLG3

Efficient path to initial human safety and efficacy



Phase 1 NHV Study

- Establish safety, tolerability and PK in healthy volunteers
- Define dose range for patient studies

+

Mechanistic/CMC Readiness

- Mechanistic preclinical studies further validate rLG3 biology
- Advance CMC and manufacturing readiness for Phase 2 and beyond



Phase 2 AD/ADRD Patient Study

- Randomized, placebo-controlled, biomarker-rich design
- **Validates target engagement using advanced MRI**

Establishing a Foundation for Multiple Indications

AD/ADRD BIOMARKER STUDY



Demonstrate rLG3's
effect on neurovascular
health in humans

Phase 1 NHV + AD/ADRD
biomarker study



CONFIRM NEUROVASCULAR RESTORATION



Validated neurovascular
restoration creates a clear path
to expand rLG3 into additional
CNS indications where
restoring neurovascular health
may improve outcomes.

ALZHEIMER'S DISEASE & RELATED DEMENTIAS



Early disease intervention
to preserve brain health

BLAST EXPOSURE & TRAUMATIC BRAIN INJURY



Improve recovery and
long-term outcomes

TRAUMATIC ENCEPHALOPATHY SYNDROME (TES)



Address consequences
of concussion and
repetitive brain injury

Stroke and Hemorrhage

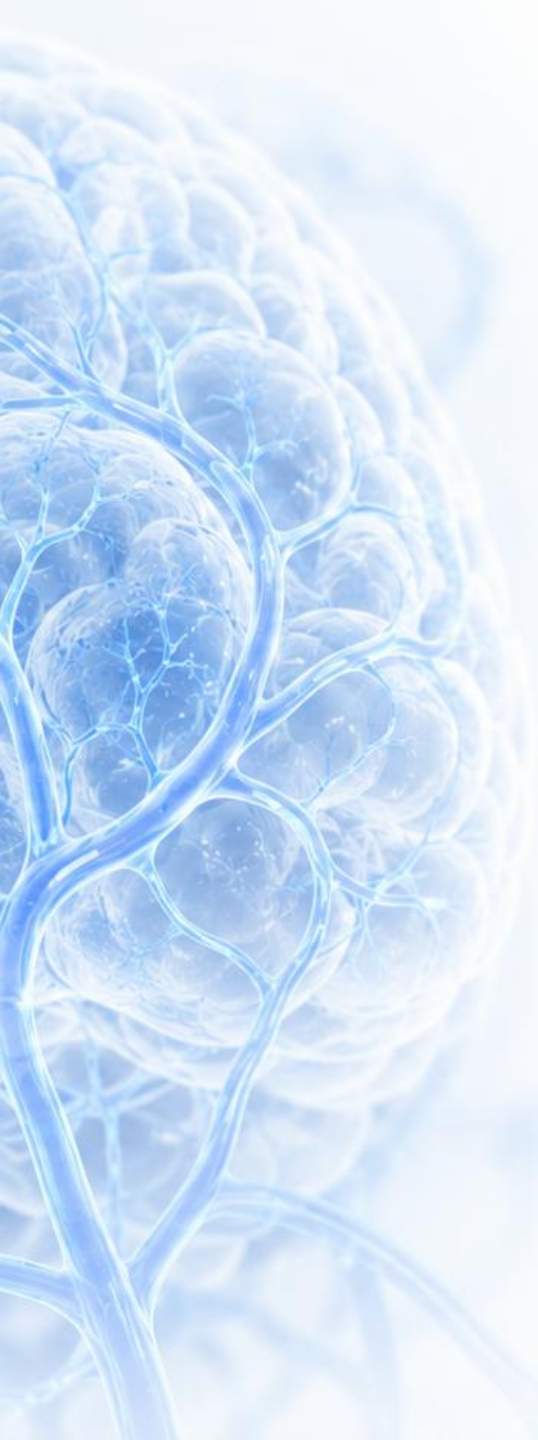


Protect brain tissue and
enhance functional recovery

ADDITIONAL NEUROVASCULAR INDICATIONS



Broad potential across
CNS disorders driven by
neurovascular dysfunction

A stylized, blue-tinted illustration of a human brain, showing the cerebral cortex and underlying vascular network. The brain is positioned on the left side of the slide, with the vasculature highlighted in a lighter blue, creating a sense of depth and focus on the neurological theme.

rLG3: A Foundational Platform for Alzheimer's and Related Brain Disorders

Designed to restore neurovascular health and support recovery across multiple CNS indications

rLG3

A recombinant biologic derived from the brain's natural repair system.

What it does

Helps restore neurovascular integrity, supports blood-brain barrier repair, and improves the brain environment for recovery.

Why it matters

This mechanism may support therapeutic benefit across Alzheimer's disease and related dementias, traumatic brain injury, traumatic encephalopathy syndrome, stroke, and other disorders linked to neurovascular dysfunction.

One restorative mechanism. Multiple clinical opportunities.

Upstream. Restorative. Clinical-ready.

Appendix

LG3 is released inside the receptor-bearing vascular basement membrane

Apoptotic endothelial cells liberate LG3 from perlecan within the same nanometer-scale matrix that supports endothelial–pericyte signaling

ANATOMICAL SEQUENCE

1

Endothelial injury

Caspase-3 activation drives extracellular cathepsin L release from an apoptotic endothelial cell.

2

Matrix cleavage

Cathepsin L cleaves perlecan at the abluminal endothelial surface and liberates LG3 into the vascular basement membrane.

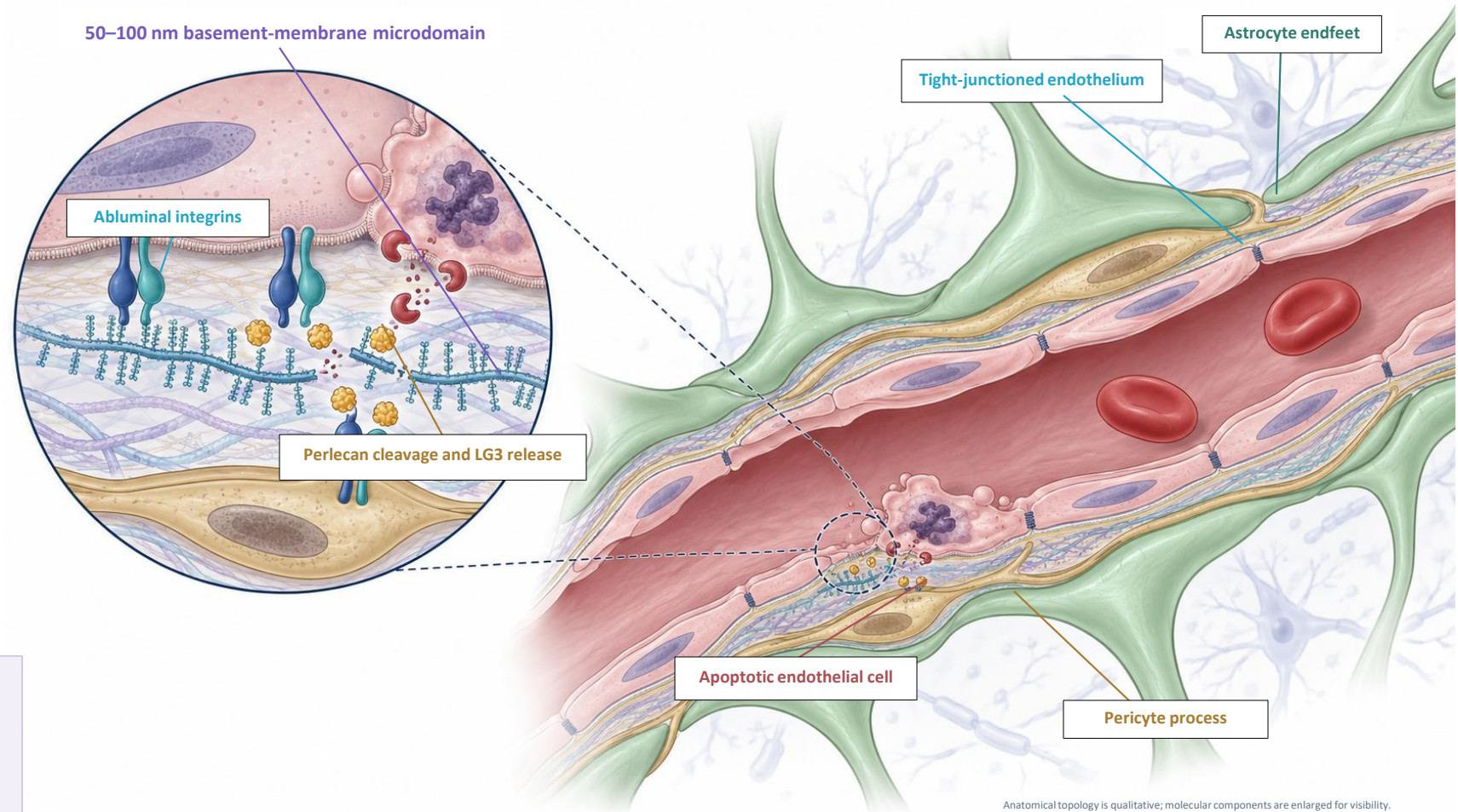
3

Receptor access

LG3 enters a 50–100 nm matrix compartment containing abluminal integrins on neighboring vascular cells.

Spatial implication

Release and receptor engagement occur at the same injured NVU interface, supporting a local matrix-derived repair signal.



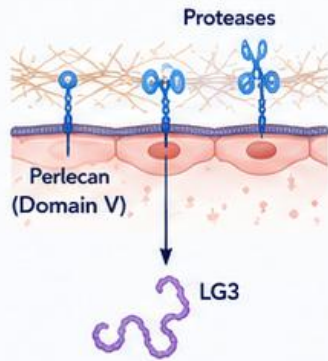
rLG3 Mechanism of Action:

Trophic Signaling to Pericytes Promotes Vascular Survival and Repair

Liberated LG3 (or administered rLG3) binds to pericyte receptors and initiates pro-survival signaling that preserves pericyte function, stabilizes the neurovascular unit, and supports recovery.

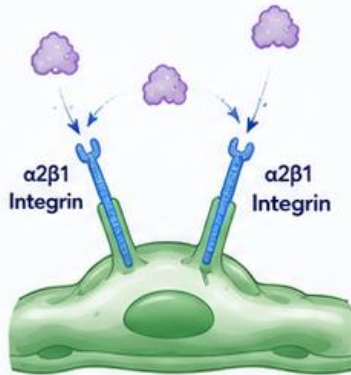
MECHANISM: rLG3 SIGNALING IN PERICYTES

1 Injury Triggers LG3 Release



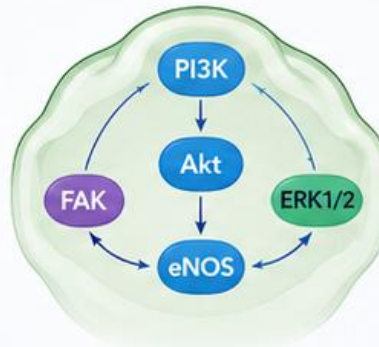
Neurovascular injury activates proteases that cleave perlecan Domain V to release LG3.

2 LG3 Binds to Pericyte Receptors



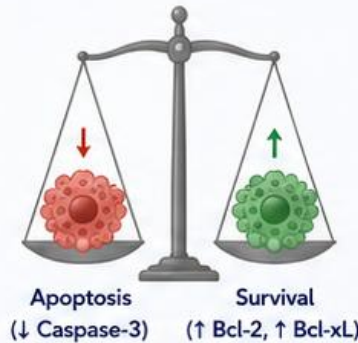
LG3 engages α2β1 integrin on pericytes, initiating, intracellular signaling.

3 Activation of Pro-Survival Signaling Pathways



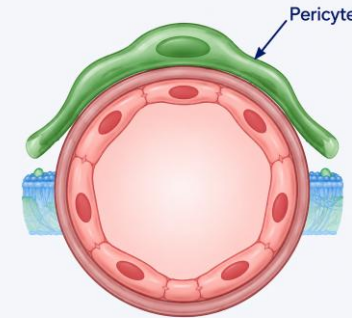
LG3 activates PI3K/Akt, FAK, and ERK1/2 pathways, enhancing survival signaling and cytoprotection.

4 Inhibition of Apoptosis and Stress Pathways



Pro-survival signals inhibit caspase-3 activation and shift the balance toward cell survival.

5 Pericyte Stabilization and NVU Support



Pericyte survival and contractile function are preserved, maintaining capillary stability and neurovascular integrity.

BIOLOGIC OUTCOMES



Pericyte Survival & Function
Preserved coverage and contractility



BBB Integrity
Reduced permeability and leakage



Improved Cerebral Perfusion
Restored microvascular blood flow



Neuroprotection & Functional Recovery
Reduced neuronal injury and improved outcomes



By acting upstream at the level of pericytes, **rLG3 preserves the neurovascular unit** and addresses a root cause of neurodegeneration.

The Molecular Genesis of Endogenous LG3

A Conserved, Injury-Induced Response for Neuroprotection and Repair

Endogenous LG3 is generated through a tightly regulated, injury-induced proteolytic process that liberates the LG3 domain from Perlecan Domain V and delivers it to sites of CNS injury where it binds to cell surface integrin receptors to initiate neuroprotective and repair pathways.

1 CNS INJURY



Traumatic or ischemic injury triggers a rapid biological response in the CNS.

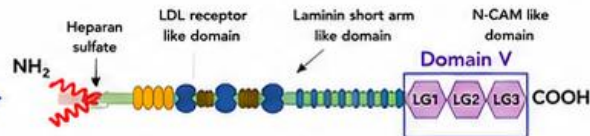
2 ACTIVATION OF PLASMINOGEN

tPA/uPA

- Injury induces release of tPA and/or uPA.
- These serine proteases convert plasminogen to plasmin.



3 CLEAVAGE OF PERLECAN (DOMAIN V)

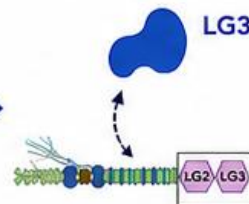


Perlecan (HSPG2)

- Perlecan is a large heparan sulfate proteoglycan in the extracellular matrix and basement membranes.
- Domain V at the C-terminus contains three laminin G (LG) modules (LG1, LG2, LG3).
- Plasmin, caspases and other proteases cleave perlecan within Domain V, releasing the LG3 domain.

Source of LG3:
Perlecan Domain V (C-terminus)

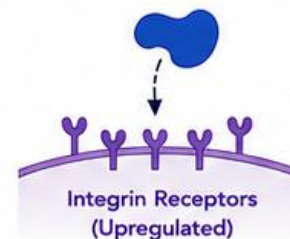
4 RELEASE OF LG3 DOMAIN



- The LG3 domain is liberated from perlecan as a soluble glycoprotein (~19 kDa).
- This is the endogenous form of LG3.

Endogenous LG3
(~19 kDa)

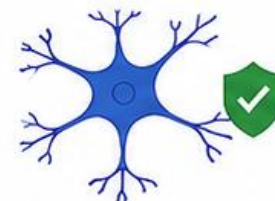
5 HOMING TO THE INJURY SITE



- LG3 homes to the site of injury by binding to upregulated integrin receptors on cells.

Targeted Localization
to Injury Site

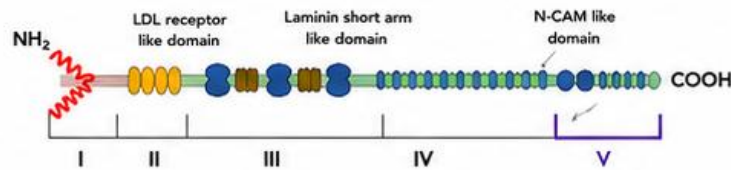
6 NEUROPROTECTION & REPAIR



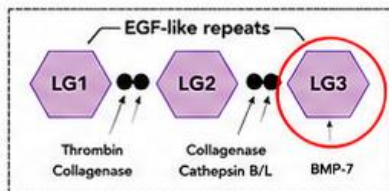
- LG3 binding initiates potent neuroprotective and repair pathways.
- Supports cell survival, BBB integrity, and functional recovery.

Neuroprotection
& Repair

PERLECAN DOMAIN V (SOURCE OF LG3)

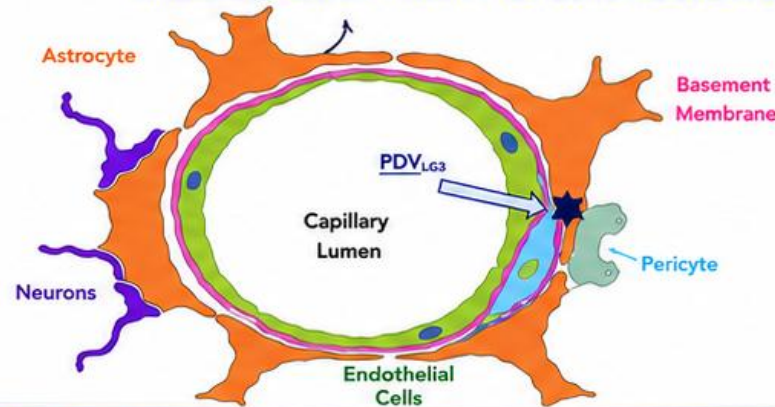


Domain V
Structure
(Endorepellin)



Plasmin, caspases and other proteases cleave perlecan within Domain V, releasing the LG3 domain.

PARACRINE ACTION WITHIN THE NEUROVASCULAR UNIT



Endogenous LG3 acts as a paracrine signal (~40 nm distance) between cells of the neurovascular unit to coordinate survival, inflammation control, and repair.



This is how endogenous LG3 is naturally generated and functions.

rLG3 therapeutically amplifies this intrinsic protective system.

Six separable NVU functions fail together in Alzheimer’s disease

Each domain has a human readout and a distinct therapeutic consequence

NVU domain	Primary biology	Human evidence	Clinical consequence
Barrier / transport	Tight junctions; transcytosis; endothelial selectivity	DCE-MRI Ktrans; albumin quotient	Toxic plasma entry; edema; altered drug distribution
Pericyte support	Capillary stability; endothelial signaling; flow control	CSF sPDGFRβ; capillary pathology	Leakage; stalls; reduced oxygen delivery
Perfusion / NVC	Activity-driven flow; vasodilatory signaling	ASL / fUS; CVR; tau PET relationships	Synaptic energy mismatch; cognitive vulnerability
Basement membrane	ECM signaling; vessel anchorage; repair cues	Proteolysis; vessel remodeling; cSVD markers	Fragile vessels; impaired repair after stress
Immune interface	Leukocyte traffic; complement; plasma proteins	GFAP; YKL-40; fibrinogen; complement	Microglial activation; synaptic injury; ARIA
Protein clearance	LRP1 transport; perivascular drainage	Aβ / tau kinetics; CAA; perfusion	Protein accumulation and feed-forward vascular injury

rLG3 addresses the complete neurovascular failure state

Human evidence defines the target domains; Stream data support a multi-domain restorative pharmacology

NVU domain	Stream evidence	Evidence status	Planned Human readout
Barrier / transport	Reduced leakage; claudin-5 preservation; endothelial protection; injury-selective uptake	Demonstrated preclinically	DCE-MRI Ktrans
Pericytes	Increased or preserved PDGFRβ-positive coverage in 5xFAD, db/db and injury models	Demonstrated structural effect	sPDGFRβ; DCE-MRI
Perfusion / NVC	Preserved capillary architecture; reduced dropout	Functional effect pending	ASL / CVR
Immune interface	Reduced reactive astrogliosis and neuroinflammation; hemorrhage protection	Demonstrated preclinically	GFAP; YKL-40; MMP9
Protein clearance	Increased microvascular Aβ efflux; lower amyloid burden	Demonstrated in model systems	Aβ42/40; amyloid imaging
Matrix repair	Endogenous injury-triggered LG3 biology; integrin-linked survival and repair	Mechanistically supported	No direct clinical assay

The development thesis depends on coordinated restoration across domains, not attribution to a single downstream target.