STREAM BIOMEDICAL

Platform Therapy for Alzheimer's and Related Neurodegenerative Conditions

Turning Irreversible Into Recoverable

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

August 2026 | Non-Confidential Deck

William D. Schwieterman, M.D.
CEO, Stream Biomedical Inc.
251-377-4828 | wds@streambiomed.com

streambiomedical.com

Non-confidential disclosure

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

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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.

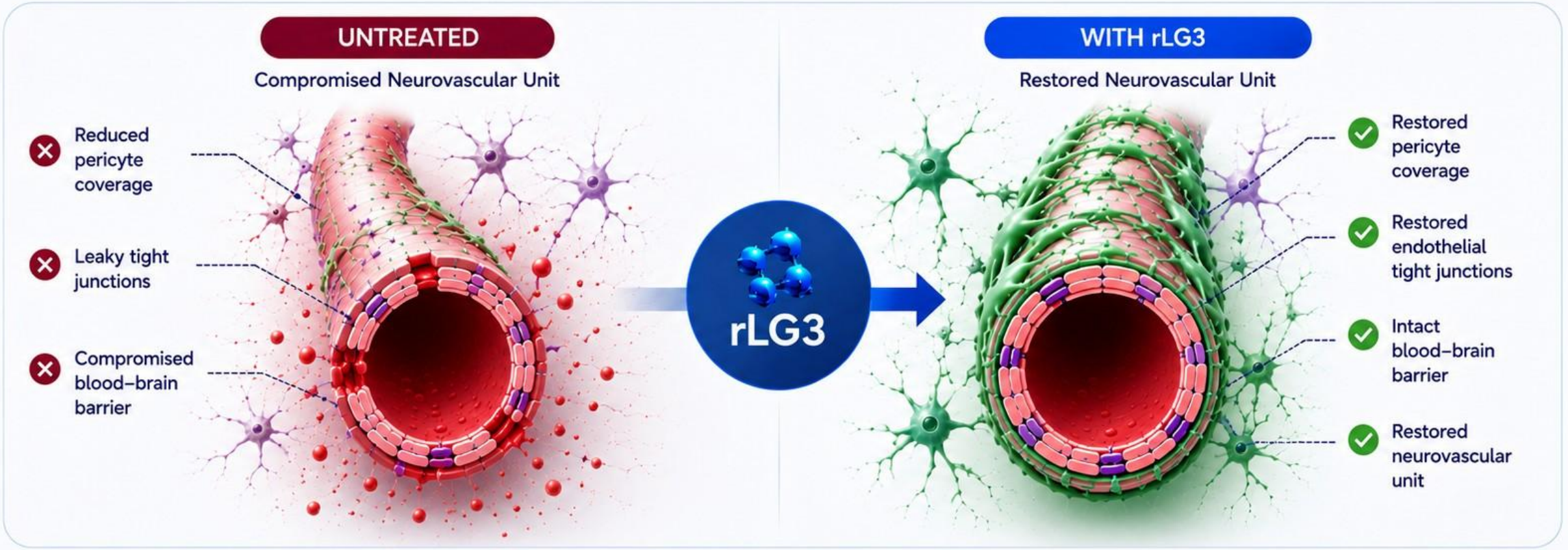
Targets shared upstream mechanisms
Addresses common drivers of neurodegeneration across multiple diseases.

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.



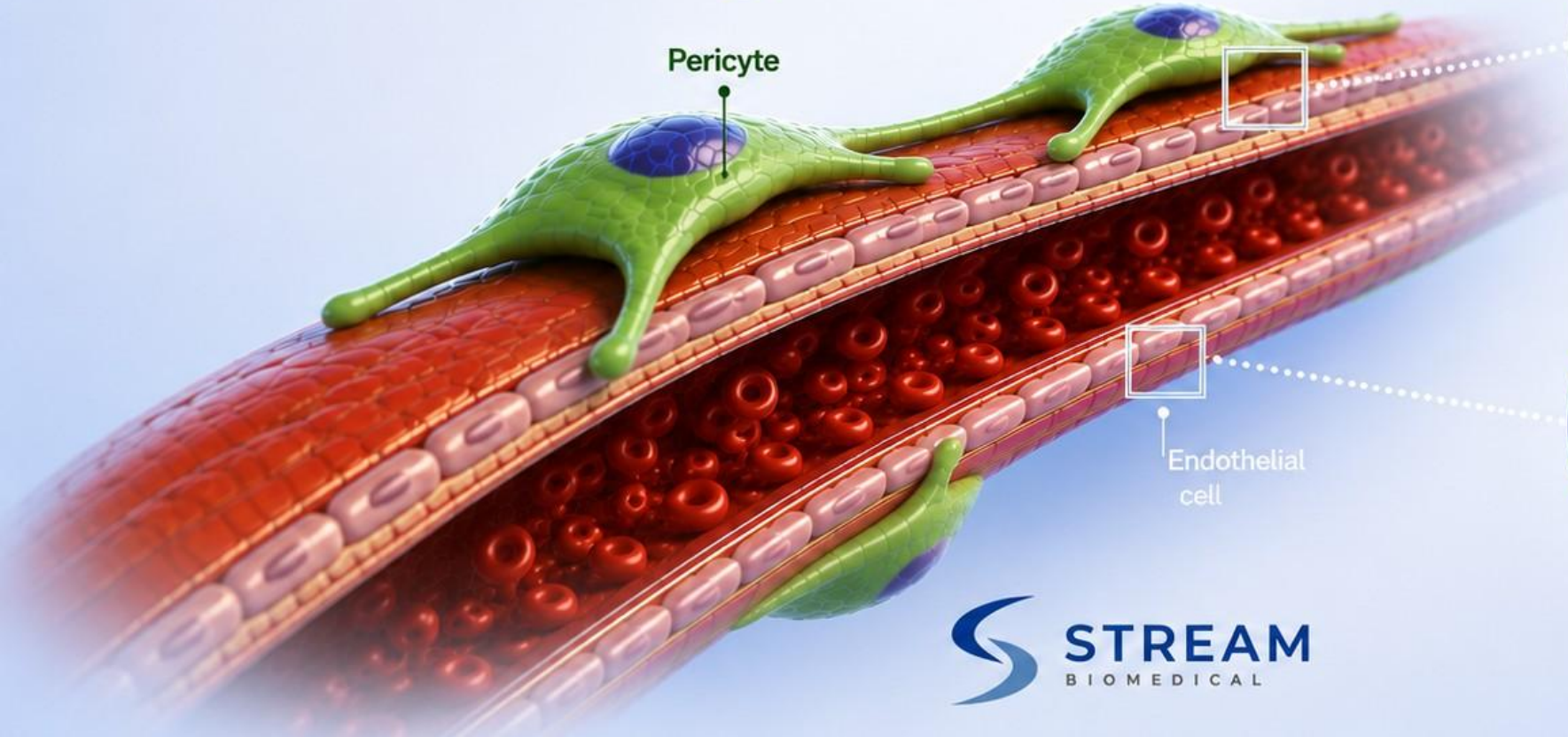
Restoring the brain's own repair mechanisms to **protect, heal and restore.**

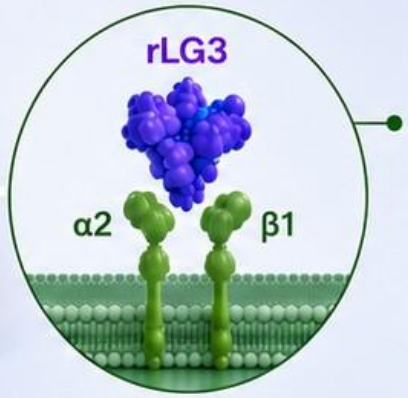
rLG3 MECHANISM OF ACTION

rLG3 restores pericyte coverage by engaging integrin receptors.

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

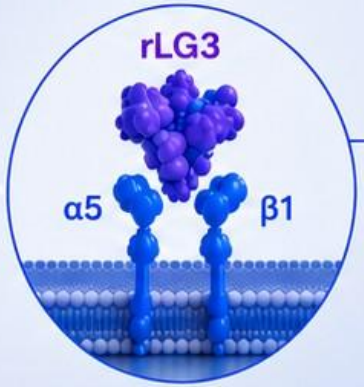
The result: Restored pericyte coverage. Stronger vessels. Healthier brain.





rLG3 binds to α2β1 integrin on pericytes

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



rLG3 binds to α5β1 integrin on endothelial cells

This interaction supports endothelial cell function and vessel integrity.

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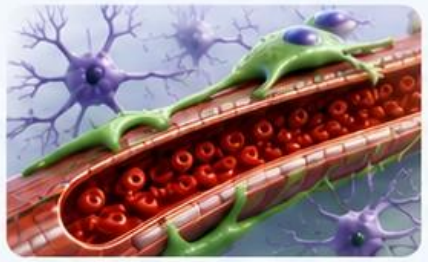
rLG3 acts early to restore the neurovascular foundation

In Alzheimer's disease, vascular dysfunction begins early—driving and accelerating pathology.
rLG3 targets the earliest vascular changes to restore pericyte coverage and support a healthy brain.

THE ALZHEIMER'S DISEASE CASCADE

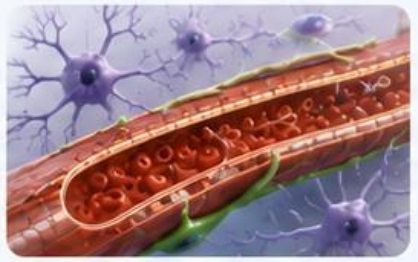
Vascular dysfunction occurs early—often before clinical symptoms.

1 HEALTHY NEUROVASCULAR UNIT



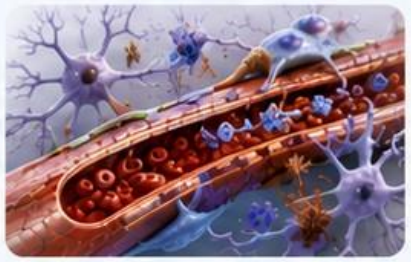
Pericytes wrap and stabilize brain capillaries. Blood-brain barrier (BBB) is intact.

2 EARLY VASCULAR DYSFUNCTION



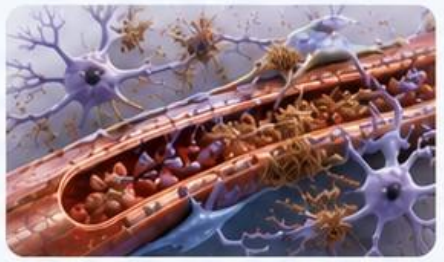
Pericyte loss begins.
BBB integrity is compromised.
Vessel stability declines.

3 AMPLIFIED PATHOLOGY

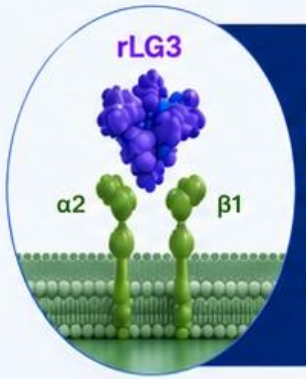


Impaired clearance and blood flow lead to amyloid-β accumulation and tau pathology, neuroinflammation and neuronal stress.

4 NEURONAL INJURY & COGNITIVE DECLINE



Progressive neuronal loss and synaptic dysfunction drive cognitive decline.



rLG3 engages integrin receptors on pericytes to act at the source of vascular dysfunction.

ACTING EARLY. RESTORING VESSELS. PROTECTING THE BRAIN.

Restores pericyte coverage

Stabilizes blood vessels and restores BBB integrity

Improves blood flow and waste clearance; reduces neuroinflammation

Slows pathology and supports cognitive function

HEALTHIER BRAIN. BETTER OUTCOMES.

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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.

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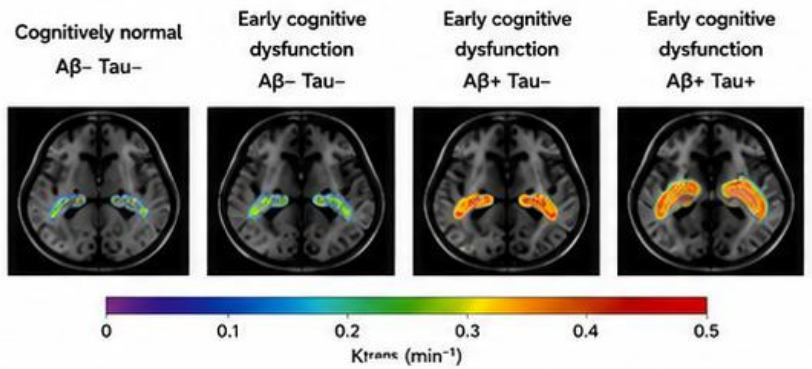
1 HUMAN EVIDENCE

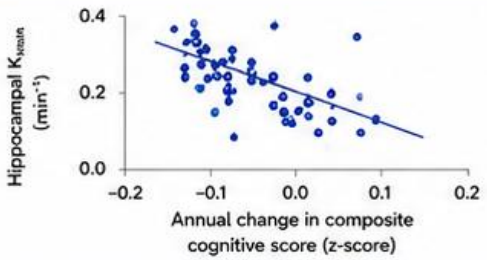
BBB breakdown occurs early and predicts cognitive decline

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.



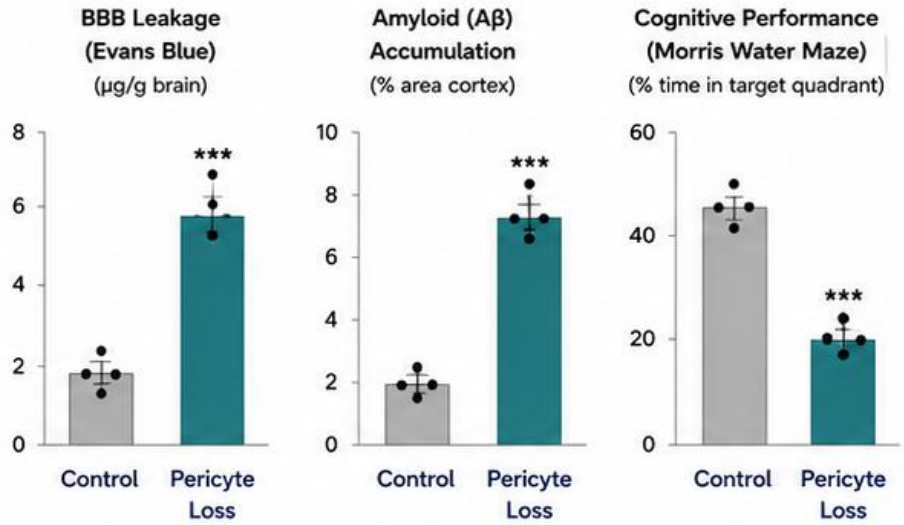
Higher hippocampal BBB permeability independently predicts future cognitive decline ($r = -0.52$, $p < 0.001$)

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.

1. Nation et al., Nature Medicine, 2019; 25:120–129.
2. Sagare et al., Neuron, 2013; 77:886–900.

rLG3 Restores Neurovascular Integrity Driving Amyloid Clearance and Cognitive Improvement

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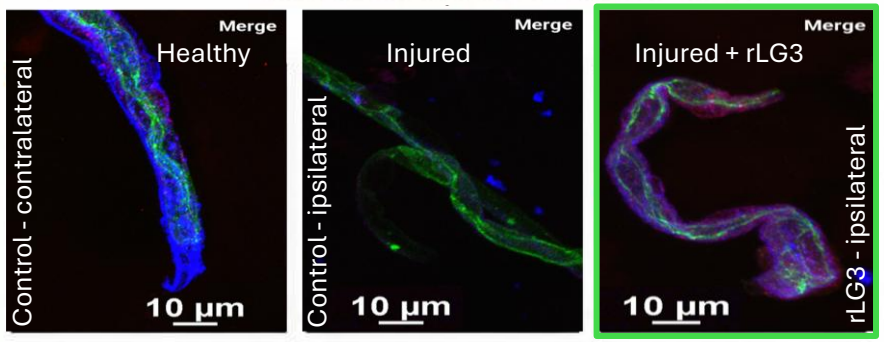
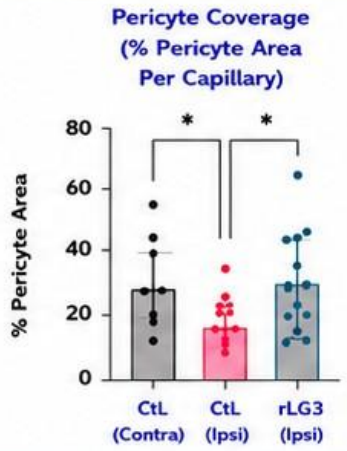
1. Restored Pericyte Coverage of Brain Capillaries

Acute Ischemic Stroke Murine Model

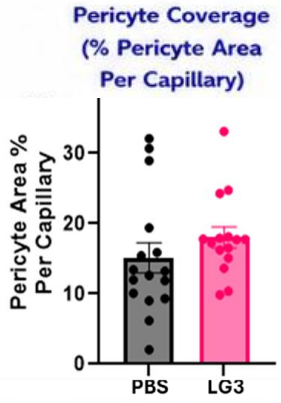


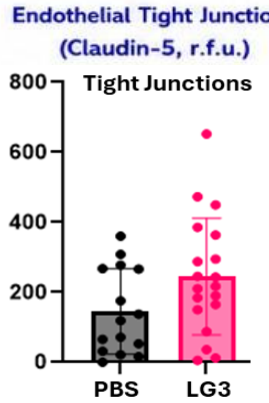
PDGFR-β (Pericyte) Claudin-5 (Endothelial) Lectin (Vessel)



2. Strengthened BBB Integrity

5XFAD Murine Alzheimer's Model

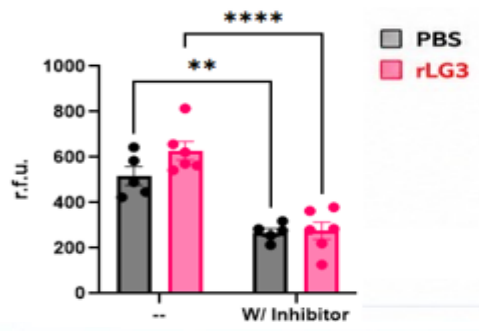


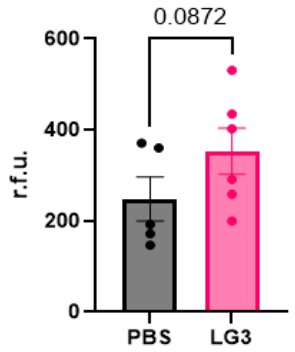


3. Increased Efflux of Amyloid Protein

db/db mice

Amyloid Efflux in Freshly Isolated Brain Capillaries



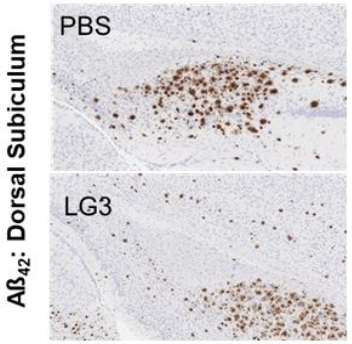


4. Downstream Impact: Reduced Amyloid Pathology

Hippocampus

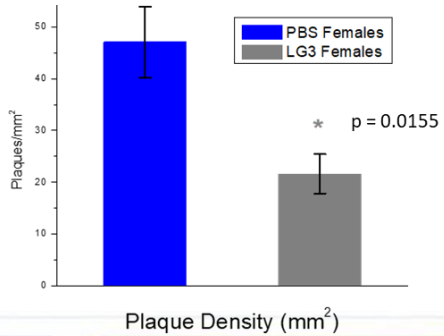
(Main site of AD pathology)

5XFAD Amyloid Model



Amyloid Protein Clearance

Amyloid (6E10) Immunofluorescence



Plaque Density (mm^2)

rLG3 Treatment
Restores Neurovascular Health and Function

→ Restores pericyte coverage → Strengthens BBB integrity → Increases amyloid efflux → Reduces amyloid pathology → Supports cognitive function

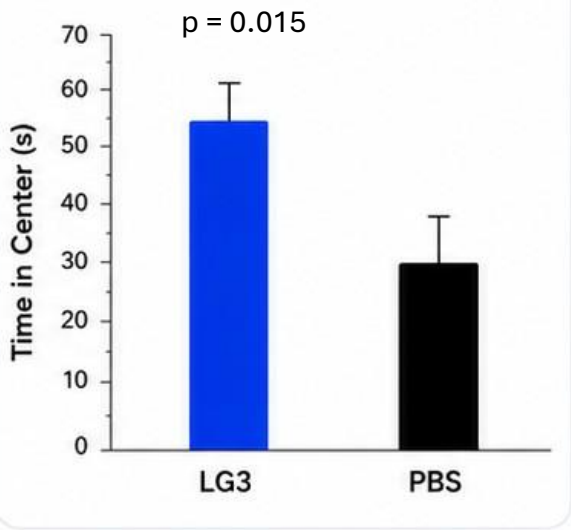
Broad neurovascular benefits with downstream impact

Data shown: mean ± SEM. *p < 0.05, **p < 0.01, ****p < 0.0001. ns = not significant.

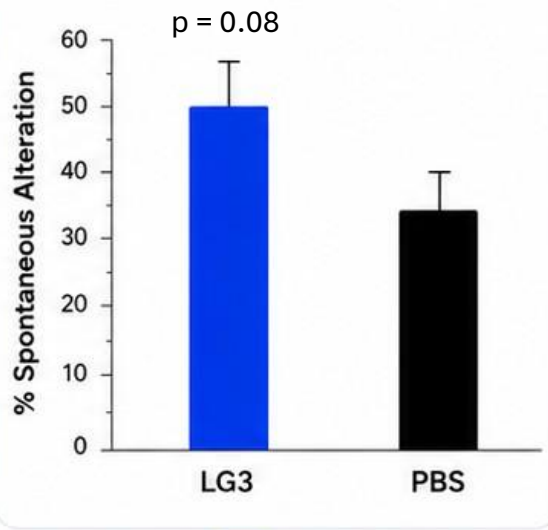
rLG3 Improves Cognitive Function in 5xFAD Mice

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

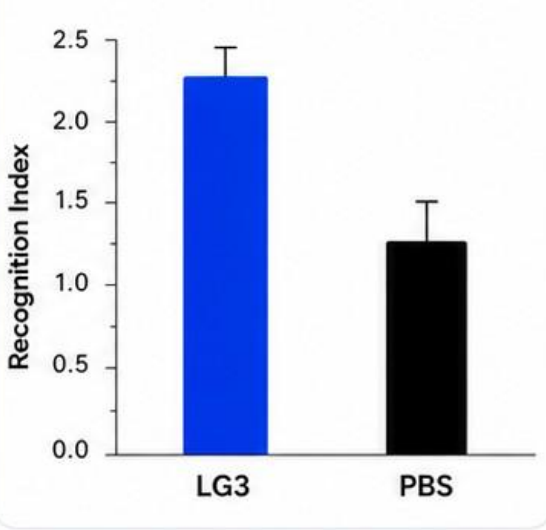
A Open Field Test
Measure of anxiety



B Y-Maze Test
Spatial recognition



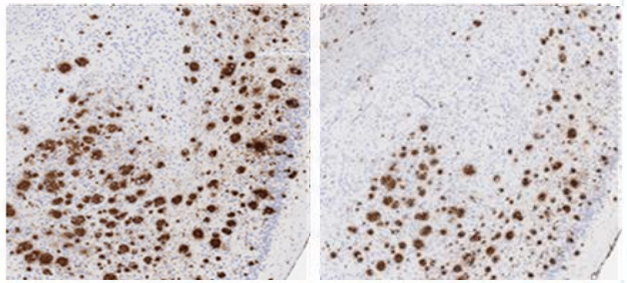
C Novel Object Recognition
Measure of cognition



LG3 PBS

Reduced Amyloid Pathology
5XFAD Amyloid Model

$A\beta_{42}$ 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

Data from 7mo males: In Vivo Assessment of $rhPDV_{LG3}$ for Disease Modification in Alzheimer's Mice, Stream/UTHSC/Premier: 2023

rLG3 Preserves Cerebrovascular Integrity

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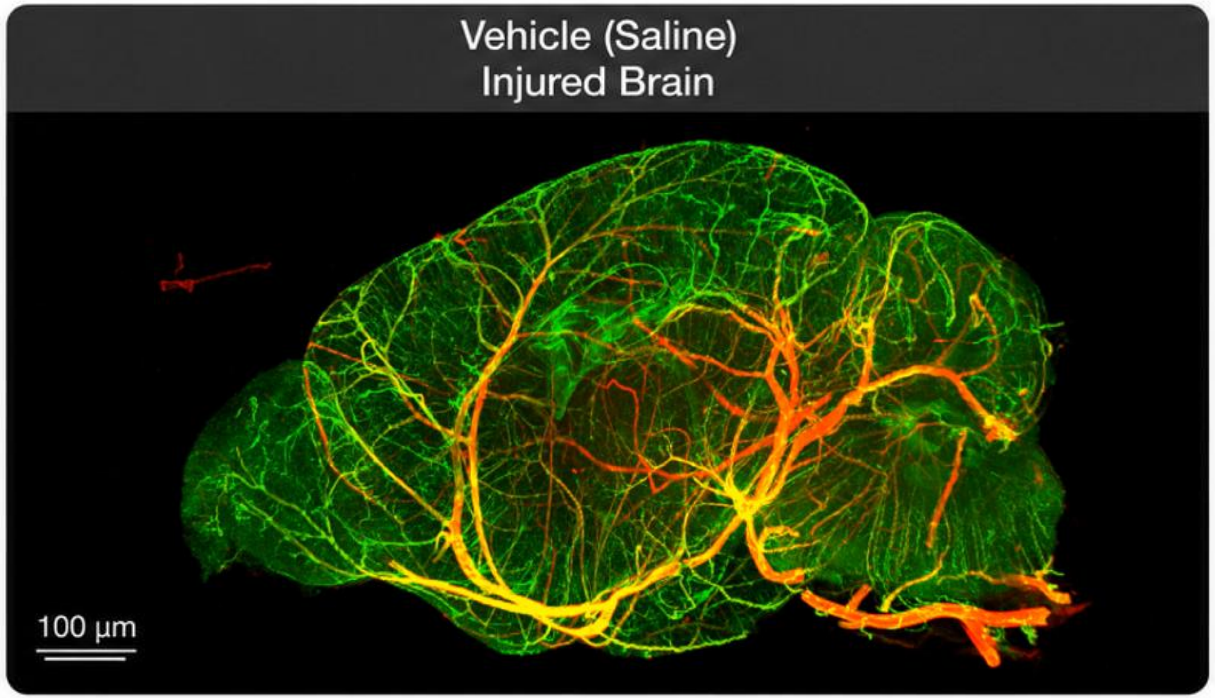
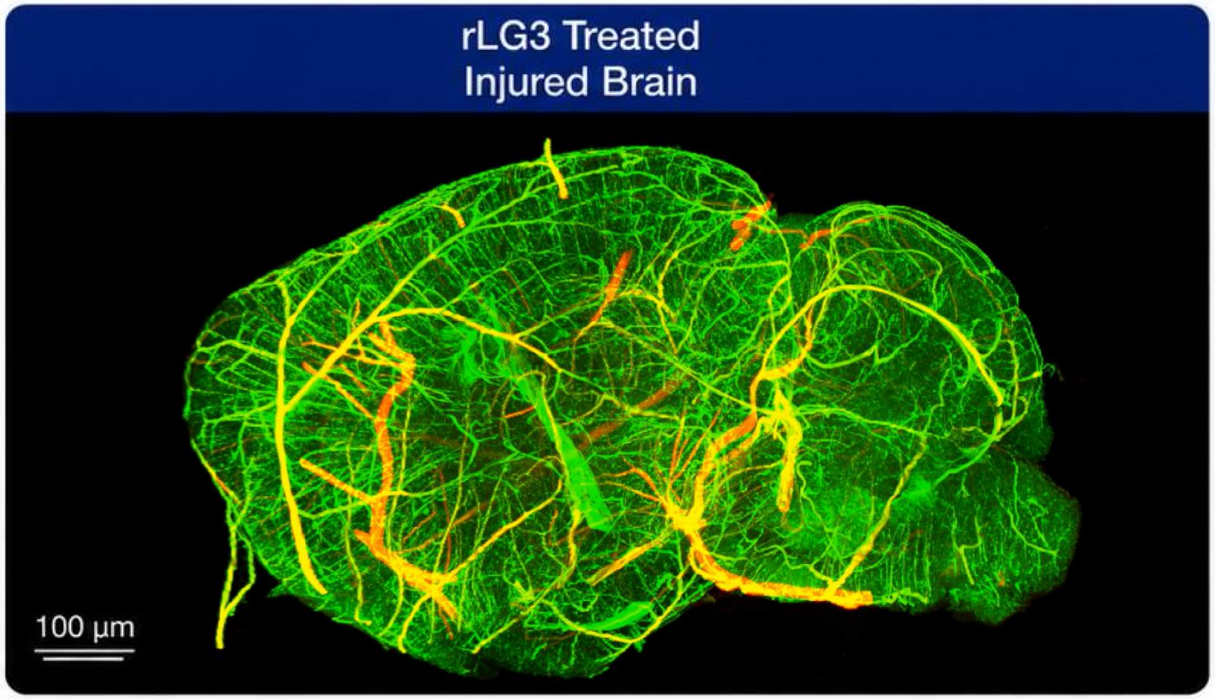
A single dose after reperfusion preserves microvascular structure and density.





Vessel Density: 8.25%
(57% loss vs. healthy tissue)

Vessel Density: 18.92%
(2% loss vs. healthy tissue)

Healthy Tissue Vessel Density: 19.19%

rLG3 treatment preserves cerebral microvascular architecture and density, supporting sustained blood flow and neurovascular function.

Representative images 72-hours following acute ischemic stroke in mice

rLG3: A Multi-Mechanism, Disease-Modifying Therapeutic

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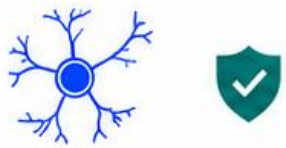
Powerful Biology. Broad Potential. Clinic-Ready.

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. 0% 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**
  Composition of matter to 2045
- **Clear path to first-in-human trials**
  IND-enabling package in preparation

Clinical Development Timeline

From CTA Submission to Patient Data

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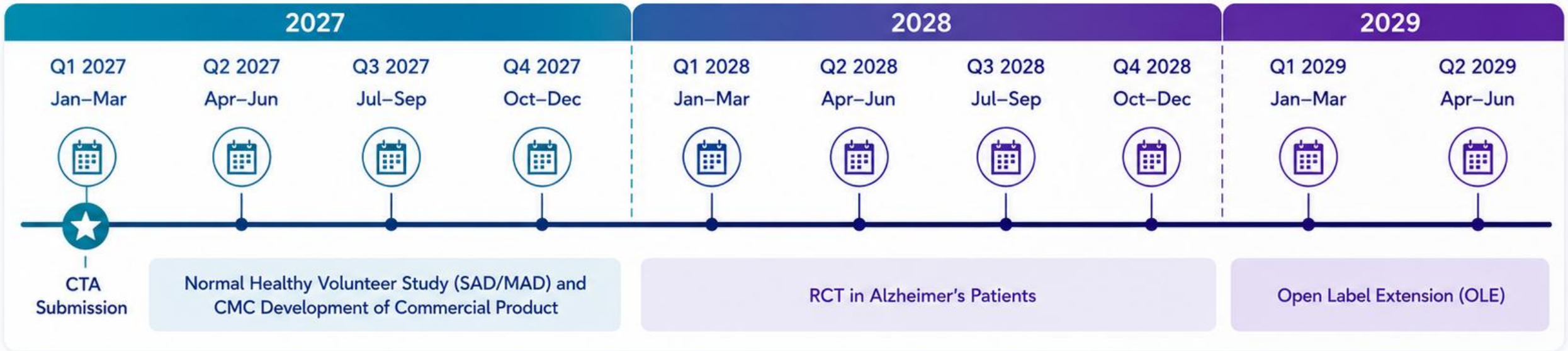

Normal Healthy Volunteer Study (SAD/MAD)

- Establish initial safety in humans
- Characterize PK and immunogenicity

CMC Development of Commercial Product

- For use in all future studies
- Scalable, GMP manufacturing and supply readiness

RCT in Alzheimer's Patients

- Initial target engagement using advanced MRI and serum/CSF biomarkers
- Evaluate safety, tolerability, and PK in patients
- Assess biomarker changes in vascular function and neurodegeneration
- Generate patient data to guide dose selection and future pivotal trials

Open Label Extension (OLE)

- Durable safety
- Durable effects on biomarkers
- Initial assessment of efficacy

Our goal: Generate robust safety and biological data to enable rapid transition from healthy volunteers to patient studies and advance rLG3 toward disease-modifying potential.

rLG3 Phase 2 Trial in Alzheimer's Disease Patients

Biomarker-Focused, Efficient Design to Establish Safety and Demonstrate Target Engagement

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OUR FOCUS

Restore vascular integrity in Alzheimer's patients with baseline vascular abnormalities by MRI and fluid biomarkers.

OUR APPROACH

Advanced MRI technology measures vascular function at baseline and 48 hours after LG3 therapy to detect early restoration of vascular integrity.

WHERE WE CONDUCT THIS TRIAL

Leveraging advanced MRI at one of the premier clinical sites in the world.

TRIAL SCHEMATIC

Randomized Placebo-Controlled Trial (3:1 allocation LG3:placebo)

~60 Participants

Alzheimer's Disease patients screened for baseline vascular abnormalities by MRI and fluid biomarkers

PART 1: SAD
Single Ascending Dose
5 Dose Cohorts
1 2 3 4 5

DSMB Review
- Safety
- Tolerability
- PK/PD
- Biomarkers

PART 2: MAD
Multiple Ascending Dose
5 Dose Cohorts
1 2 3 4 5

DOSING & IMAGING PLAN

SHORT, WELL-DEFINED EXPOSURE
3 intravenous doses over 6 days

Day 1 → Day 3 → Day 6

COMPREHENSIVE ASSESSMENTS

ADVANCED MRI ASSESSMENTS
Measuring vascular function
- **BASELINE** Pre-dose
- **48 HOURS AFTER FINAL DOSE**

BIOMARKER COLLECTION
Serum & CNS biomarkers
- **SERUM** Collected at Baseline and 48-hour post-dose
- **CNS** Collected at Baseline and 48-hour post-dose

Paired imaging and biomarker assessments detect early restoration of vascular integrity.

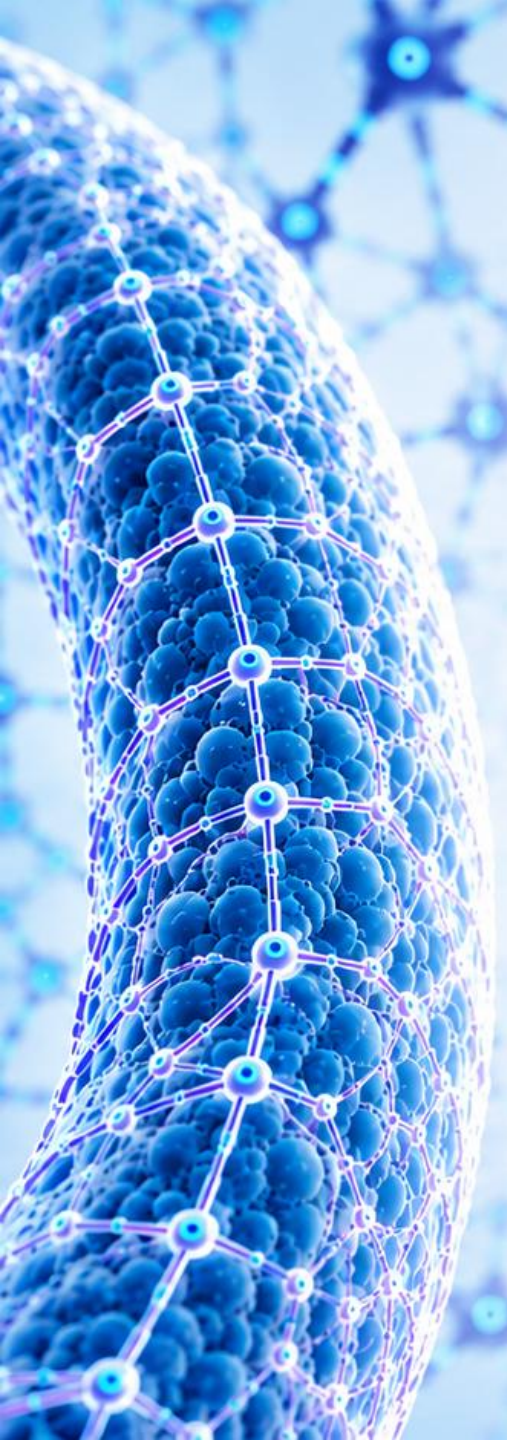
BIOMARKER READOUTS

VASCULAR (PRIMARY)
- DCE-MRI (K^{trans} in hippocampus [BBB leakage])
- Cerebral Blood Flow (ASL MRI)
- Vascular reactivity

CNS INJURY (SECONDARY)
- Serum & CSF biomarkers: NfL, GFAP, sTREM2, YKL-40, pTau181, etc.

COGNITION (EXPLORATORY)
- ADAS-Cog13
- CDR-SB
- Memory & executive function tests

SAD = Single Ascending Dose | **MAD** = Multiple Ascending Dose | **DCE-MRI** = Dynamic Contrast-Enhanced MRI | **ASL MRI** = Arterial Spin Labeling MRI | **MCI** = Mild Cognitive Impairment



rLG3: A Fundamental Solution for Alzheimer's and Other Related Dementias

TURNING IRREVERSIBLE INTO RECOVERABLE

rLG3

A RECOMBINANT BIOLOGICAL MOLECULE

DERIVED FROM AN **ENDOGENOUS REPAIR PROTEIN**

Harnessing the body's natural repair pathway to restore the brain from the vascular injury.

RESTORES
neurovascular integrity

REPAIRS
BBB dysfunction

ENABLES
brain recovery and resilience

A PROMISING PATH FORWARD

Upstream. Restorative. Clinical-ready.

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Appendix

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rLG3 Provides Potent Neuroprotection and Restores Function in Traumatic Brain Injury

Single-dose rLG3 reduces cell death, preserves brain tissue, and improves functional recovery.

KEY TAKEAWAYS

POTENT NEUROPROTECTION
Significant reduction in neuronal cell death in the cortex after TBI.

FUNCTIONAL RECOVERY
Rapid and sustained improvements in motor function and grip strength.

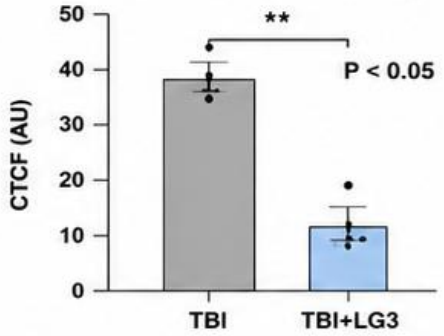
BBB INTEGRITY
Marked reduction of Evan's Blue leakage in the impact region.

SINGLE DOSE EFFICACY
Robust benefits achieved with a single administration of rLG3.

These data demonstrate that rLG3 protects brain tissue and restores function after TBI by preserving vascular integrity and reducing secondary injury.

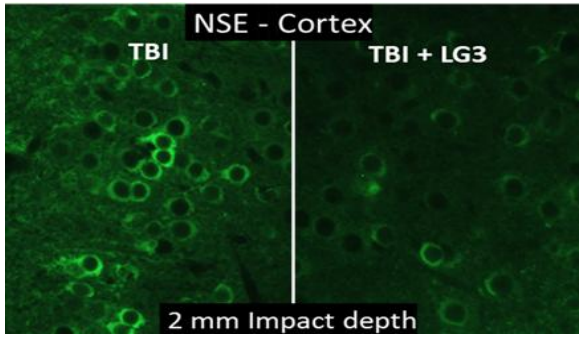
1 REDUCES CELL DEATH

Neuronal Cell Death (NSE)



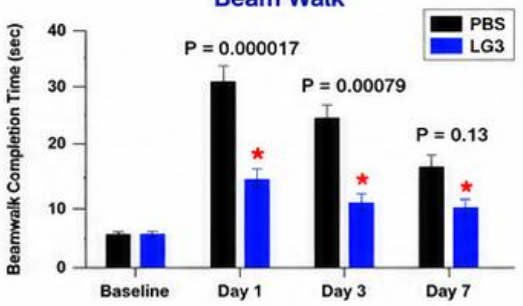
2 PRESERVES CORTICAL TISSUE

NSE – Cortex (Green Fluorescence)

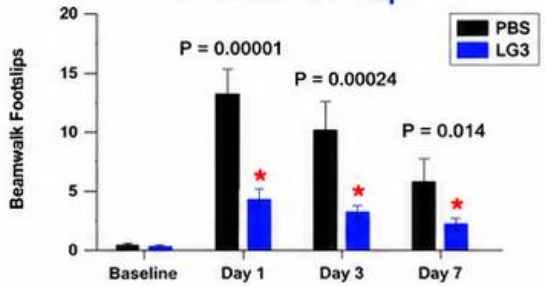


3 IMPROVES FUNCTIONAL PERFORMANCE

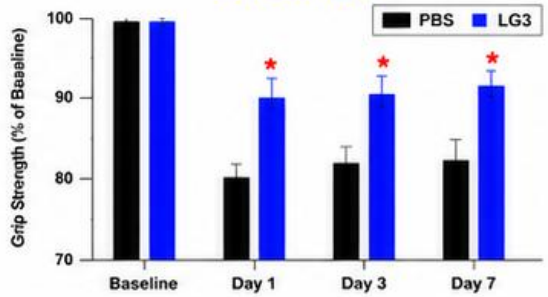
Beam Walk



Beamwalk: Footslips



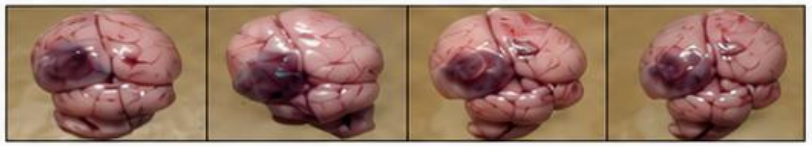
Grip Strength



4 IMPROVES BBB INTEGRITY

Evan's Blue BBB Leakage (Impact Region)

TBI – Control (PBS)



TBI – LG3

CCI = controlled cortical impact; NSE = neuron specific enolase (marker of neuronal injury); BBB = blood–brain barrier.
Mouse studies – UTHSC/Stream Internal Data. (top) Penetrating CCI-TBI young adult male mice.

rLG3 Delivers Potent Neuroprotection and Eliminates tPA-Associated Hemorrhage

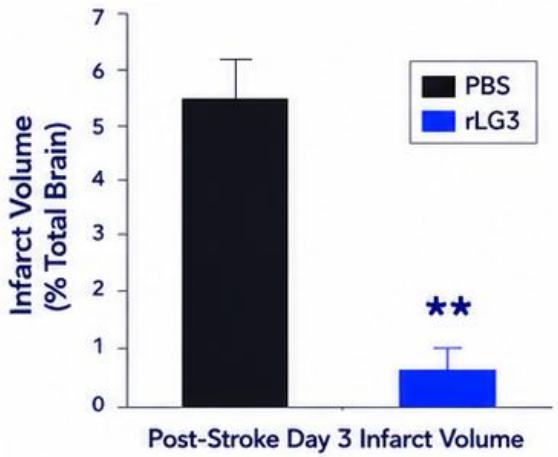
Restoring vascular integrity improves outcomes and broadens therapeutic potential.

1 ISCHEMIC STROKE MODEL (MCAO)

Profound Neuroprotection with Single Dose rLG3

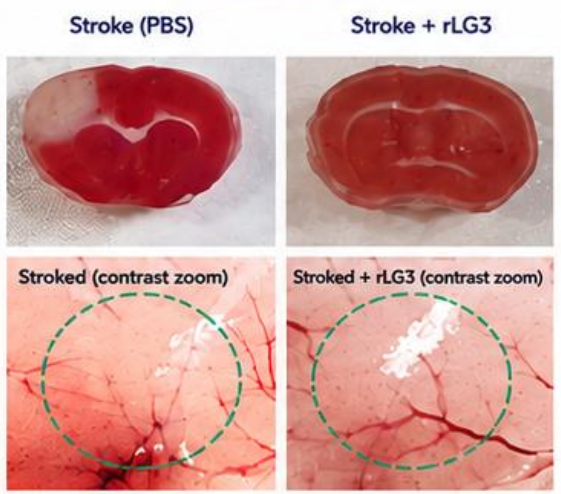
INFARCT VOLUME

Post-Stroke Day 3



REPRESENTATIVE BRAIN SECTIONS

(Post-Stroke Day 3)



rLG3 markedly reduces infarct volume and preserves brain tissue following ischemic stroke.

2 tPA MODEL OF ACUTE STROKE

rLG3 Eliminates tPA-Associated Hemorrhage

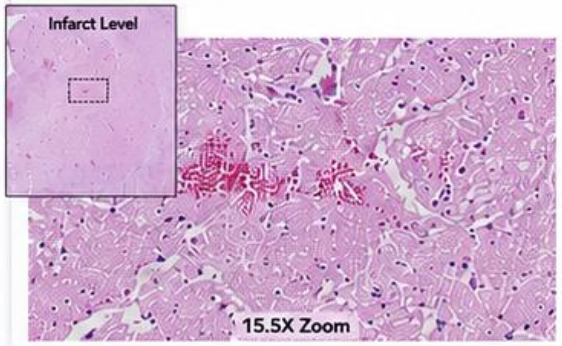
HEMORRHAGE INCIDENCE

(Post-Stroke)

tPA + PBS

29.4% Hemorrhage Incidence

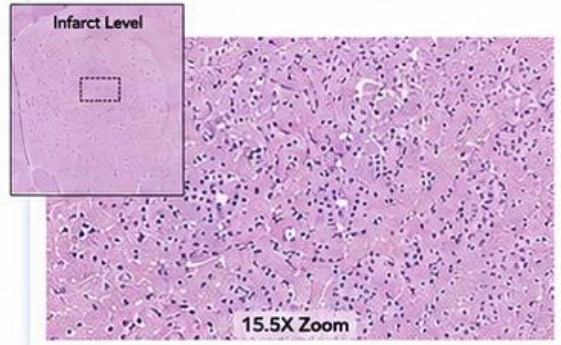
N=17



tPA + rLG3

0% Hemorrhage Incidence

N=14



rLG3 completely prevents tPA-associated hemorrhage, supporting vascular protection and enabling safer reperfusion therapy.

Across ischemic stroke models, rLG3 protects brain tissue and preserves vascular integrity—supporting its potential as a disease-modifying therapy for stroke.

MCAO = middle cerebral artery occlusion; tPA = tissue plasminogen activator.

Biose et al., 2022. Translational Stroke Research; Stream internal data. Preclinical observations in young adult male mice (MCAO) and aged male and female rats (tPA), 60′ MCAO, 90′ tPA.

The Molecular Genesis of Endogenous LG3

A Conserved, Injury-Induced Response for Neuroprotection and Repair

STREAM BIOMEDICAL

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

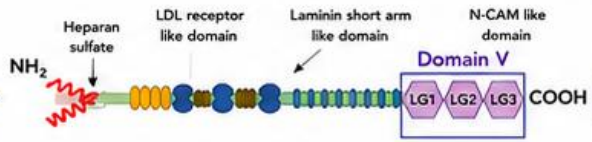
Traumatic or ischemic injury triggers a rapid biological response in the CNS.

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)

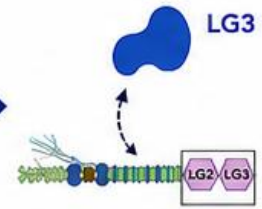


Perlecan (HSPG2)

- 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)

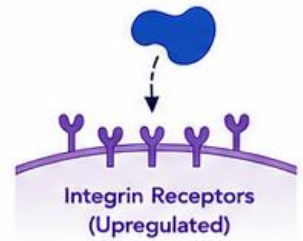
4 RELEASE OF LG3 DOMAIN



- 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

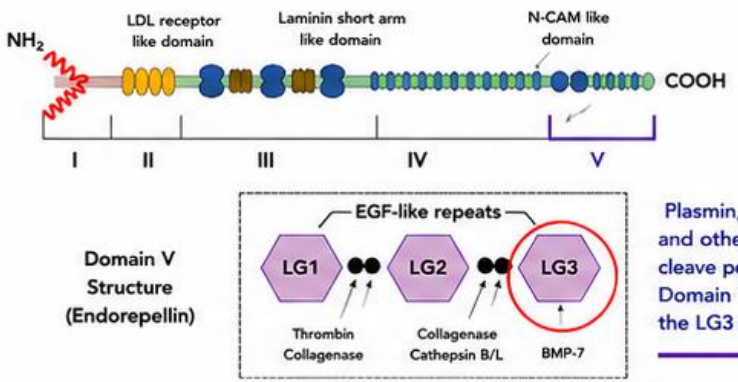
6 NEUROPROTECTION & REPAIR

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

Neuroprotection & Repair

PERLECAN DOMAIN V (SOURCE OF LG3)

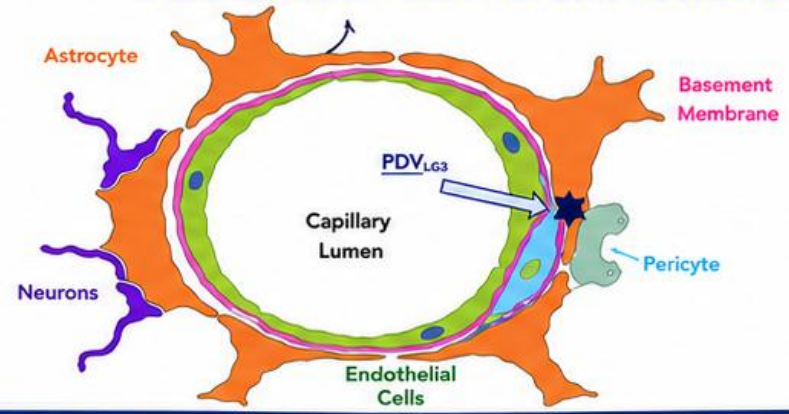
- ~550 million years evolutionary conservation
- 21 kDa C-terminus of Perlecan Domain V
- Elevated in the brain of stroke and TBI patients
- Pleiotropic & anti-apoptotic: interacts with all cell types of the neurovascular unit (through integrin R's)



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.

LG3

This is how endogenous LG3 is naturally generated and functions.

rLG3 therapeutically amplifies this intrinsic protective system.