



Platform Therapy for Neurodegenerative Disease
TBI | Stroke | Alzheimer's Disease

Cerebral Protection & Neurologic Repair

LG3: Designed by Evolution
Developed by Stream

September 2025 | Non-Confidential Deck

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

Non-confidential disclosure



streambiomedical.com

Impact of Traumatic Brain Injury

TBI –Urgent Unmet Medical Need

- **No approved** pharmaceutical treatment to accelerate recovery from TBI
- **Children aged (0-4) and adults > 75** have highest rates of TBI Related hospitalization and death
- **Traumatic brain injury** is perhaps the best established environmental risk factor for dementia
- **Road Traffic Accidents** is the leading cause of TBI
- **>\$4 Trillion** Direct and indirect economic burden of TBI

>2.8M Traumatic Brain Injuries (TBI) annually in US *

69k TBI related deaths annually in US **

282k hospitalized for TBI related injuries in US **

69M annual global incidence of TBI **

* PLOS One May 9, 2019 <https://doi.org/10.1371/journal.pone.0216743>

** CDC <https://wonder.cdc.gov/mcd.html>

** JNS 2018; 130(4): 1080-1097

2-4x increased risk of dementia after mod/severe TBI*

5.3M individuals living with disability from TBI in US**

>200k veterans living with TBI related disability in US #

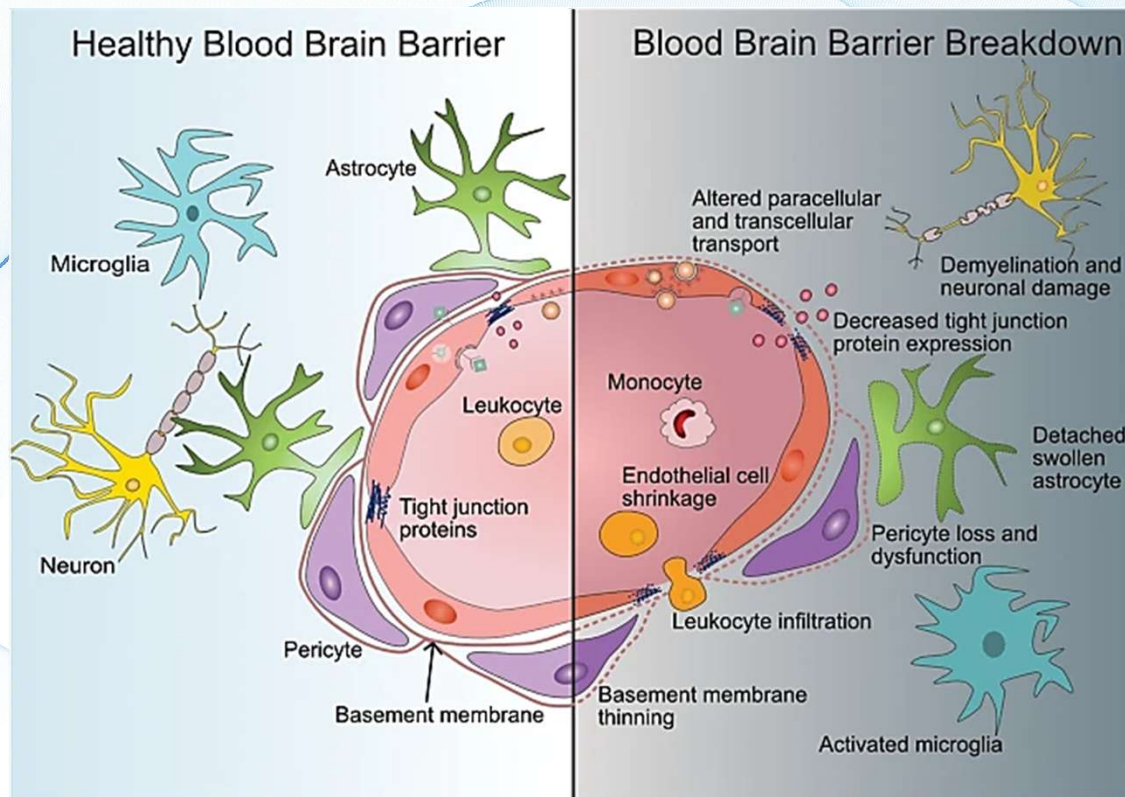
*Arch. Neurology; 2012; 69(10):1245-1251

**Arch. Phys Med Rehab 2003 84(2) 242-248

#;Matney C, Bowman K, Berwick D, National Academies Press (US); 2022 Feb 1.

The Challenge: Blood-Brain Barrier Breakdown in TBI

Induces multiple pathologic effects in TBI and across other neurodegenerative diseases

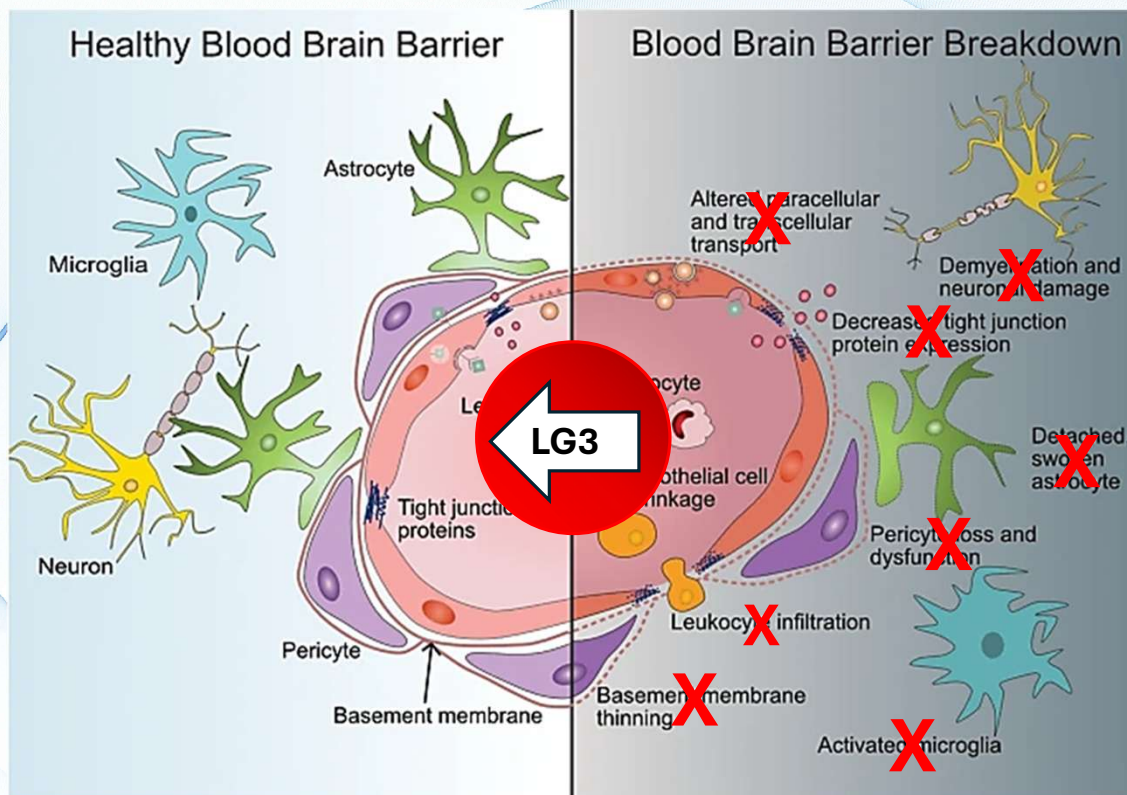


INITIAL INDICATIONS

- Traumatic brain injury
- Acute ischemic stroke
- Alzheimer's disease
- Other neurodegenerative diseases

Stream's Solution: Perlecan Domain V LG3 ("LG3")

Reverses blood-brain barrier breakdown and restores homeostasis to the entire neurovascular unit



- Seals the BBB
 - Restores endothelial tight junctions
 - Mobilizes pericytes
- Reduces tissue inflammation
- Anti-apoptotic for neurons
- Induces neurogenesis
- Induces angiogenesis
- Upregulated only following injury,
 - hypoxia, mechanical trauma
- Binds to upregulated integrin receptors
- Crosses the BBB
 - through active transport (caveolin)

Stream Scientists Developed LG3 To Generate A Novel, Powerful, Disruptive, 1st in class Neuroprotective Agent

Stream has exclusive intellectual property rights to LG3 and other matrikines

Translational Stroke Research (2023) 14:941–954
<https://doi.org/10.1007/s12975-022-01089-2>



RESEARCH

Recombinant Human Perlecan DV and Its LG3 Subdomain Are Neuroprotective and Acutely Functionally Restorative in Severe Experimental Ischemic Stroke

Ifechukwude Joachim Biose¹ · Ibolya Rutkai^{1,2} · Bryan Clossen³ · Gary Gage³ · Kenneth Schechtman⁴ ·
H. Davis Adkisson IV³ · Gregory J. Bix^{1,2,5}

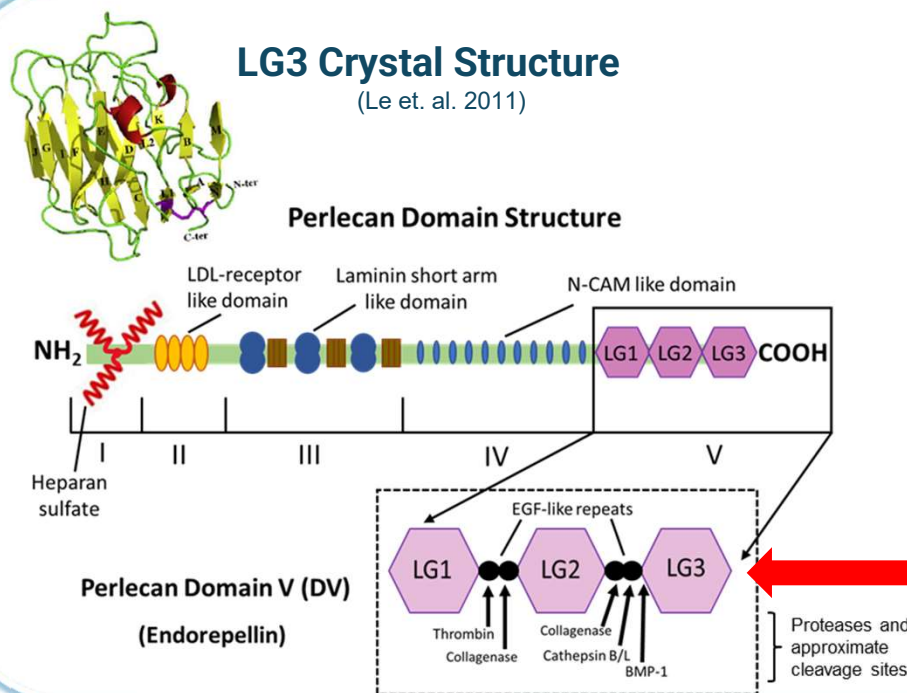
Received: 13 June 2022 / Revised: 1 September 2022 / Accepted: 20 September 2022 / Published online: 12 December 2022
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Abstract

Despite recent therapeutic advancements, ischemic stroke remains a major cause of death and disability. It has been previously demonstrated that ~85-kDa recombinant human perlecan domain V (rhPDV) binds to upregulated integrin receptors ($\alpha 2\beta 1$ and $\alpha 5\beta 1$) associated with neuroprotective and functional improvements in various animal models of acute ischemic stroke.

LG3: An Endogenous Repair Protein for the Brain and Vasculature

Designed by Evolution, Developed by Stream



- New therapeutic class: **Vascular Matrikines**
- 550M year-old protein highly conserved throughout all species
 - Fundamental to all vascular systems
- Elevated in the brain only following injury or ischemia
 - Critical role in the repair of the CNS/brain vasculature
- Endogenously produced in the brain from perlecan
 - Stream manufactured via microbial expression at Cytovance Biologics
- Clinical-stage asset: Phase 1 NHV Study Q2 2026
 - GMP Manufacturing/GLP Tox studies complete

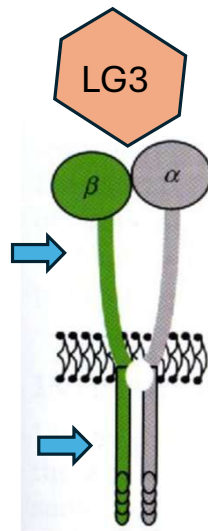
LG3 Targets Upregulated Integrin Receptors

Affects multiple NVU cell types - Paracrine signaling distance ≤ 25 microns

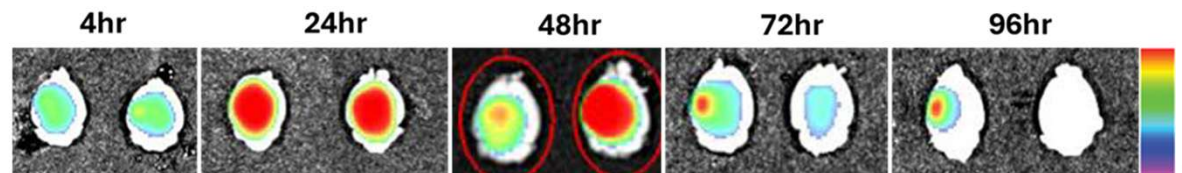
LG3 activates pro-survival pathways

Integrins are heterodimeric cell-surface molecules that mediate cell-ECM interactions

Interactions with all cell types of the neurovascular unit!



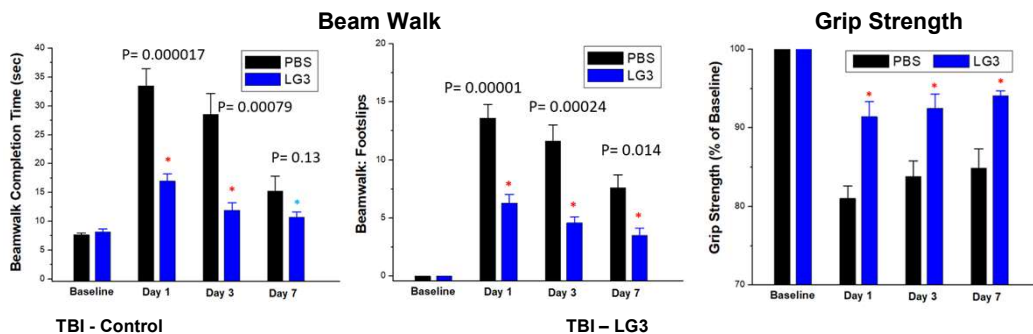
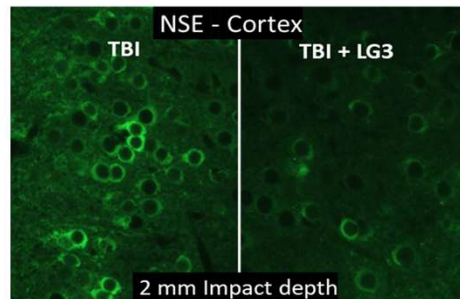
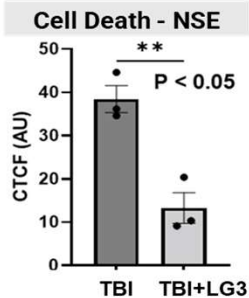
- Homes to, engages, and persistently occupies integrin receptors upregulated in response to tissue injury (see data below)
- Mediates cell survival and/or neurotrophic factor production via integrin-mediated signaling
- Net effect is restoration of NVU homeostatic function
- Integrin R-expressing cell types: **vascular endothelial cells, astrocytes & microglia, pericytes, and neurons**



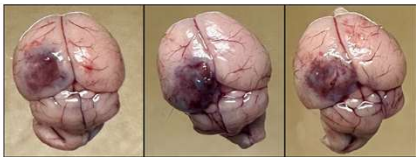
In-vivo imaging (IVOIS) of fluorescent-LG3 in mouse brains following stroke (left hemisphere)

LG3 Effective in Traumatic Brain Injury

Dramatic effects in multiple preclinical models and studies



TBI - Control



TBI - LG3

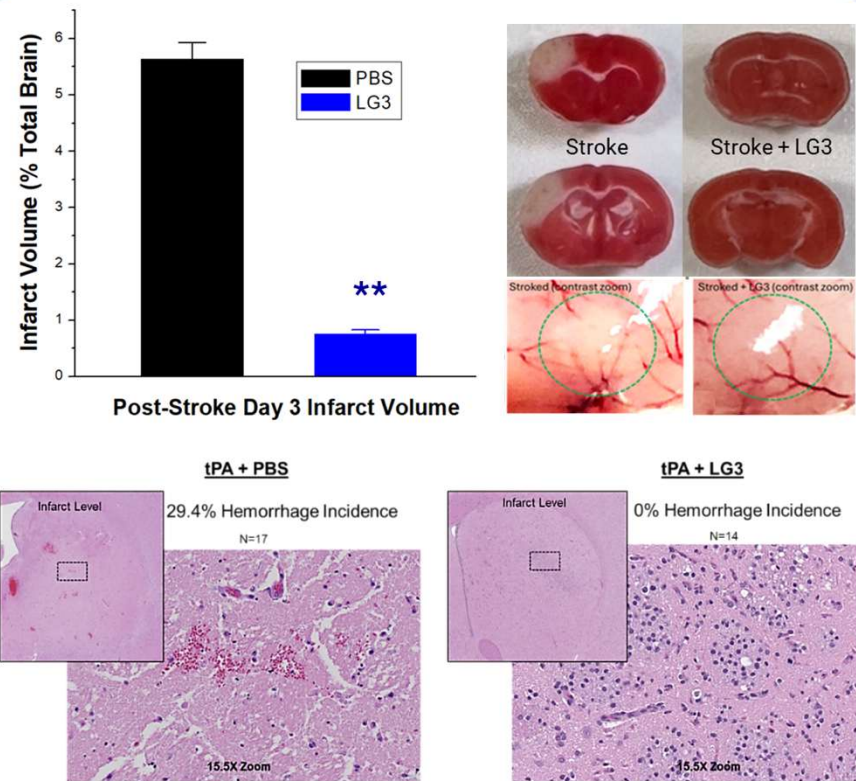


- Improves Function & Saves Brain following impact traumatic brain injury (TBI)
- Highly efficacious with a single dose
- Reduces cell death (NSE quantification)
- Rapidly improves functional performance
 - Beam walk/coordination
 - 4-limb grip strength
- Improves BBB integrity in impact region
- Improves function in repeat mild blast injury (data not shown)

Mouse Studies - UTHSC/Stream Internal Data. (top) Penetrating CCI-TBI young adult male mice. (bottom) 5xFAD Alzheimer's mice, 3mo females.

LG3: Demonstrates Efficacy in Acute Stroke and tPA-induced Hemorrhage

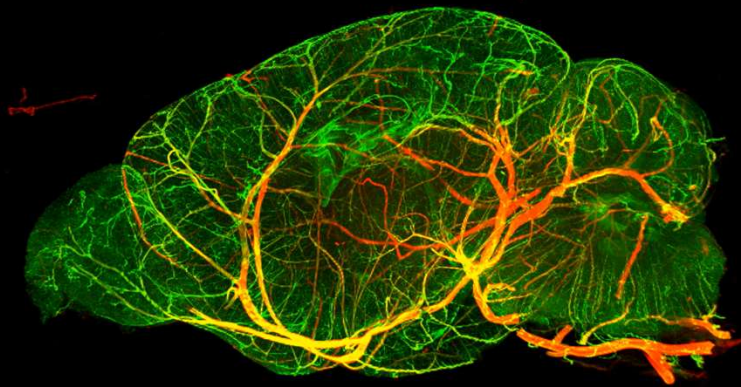
- **Highly efficacious neuroprotection with single dose**
- Directly homes to site of injury
- Reduces mortality & brain damage preclinically
- Improves tPA (tissue plasminogen activator) safety by reducing hemorrhage risk
- Compatible with commonly prescribed medications
- Multiple Indications: Positive data in preclinical TBI and Alzheimer's studies
- >25 Patents issued with global coverage



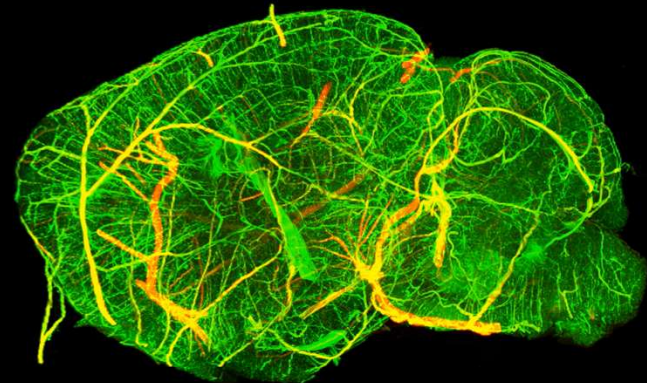
LG3 Restores Stroke-Injured Vasculature

A single dose after reperfusion provides profound clinical benefit

Stroke - Saline Treated



Stroke - LG3 Treated

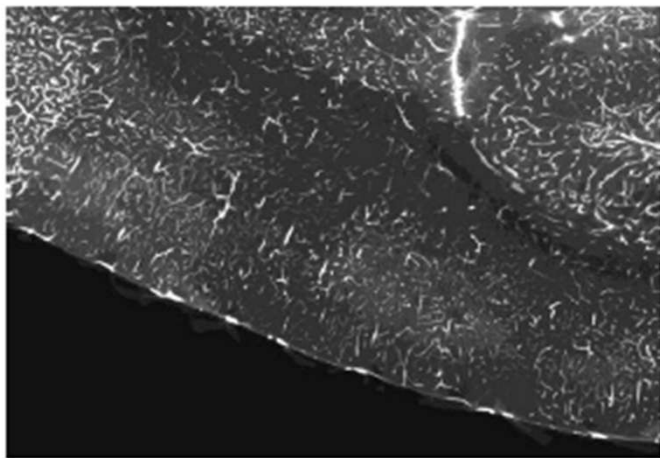


Brain Tissue Clearing + Light Sheet Microscopy 72hr Post 1-hour transient MCAO Stroke in mice

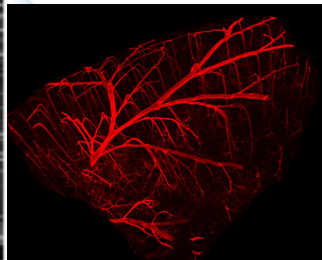
LG3 Restores Stroke-Injured Vasculature

A single dose after reperfusion preserves vascular network in infarct region

Stroke - Saline Treated

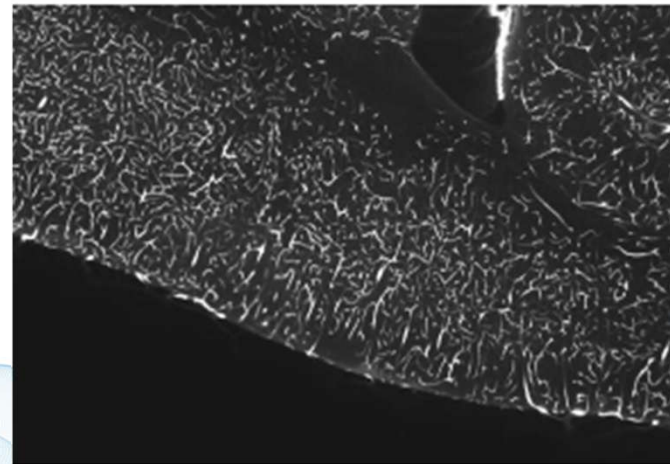


Penumbral
Core Focus

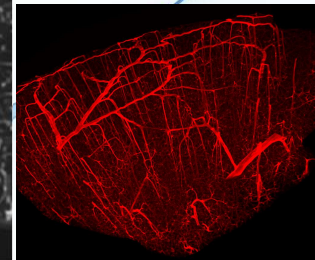


Vessel Density: 4.20%

Stroke - LG3 Treated



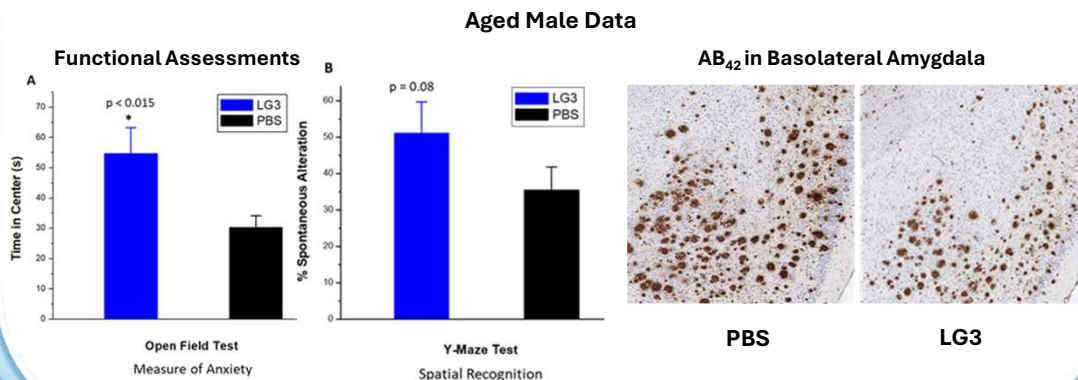
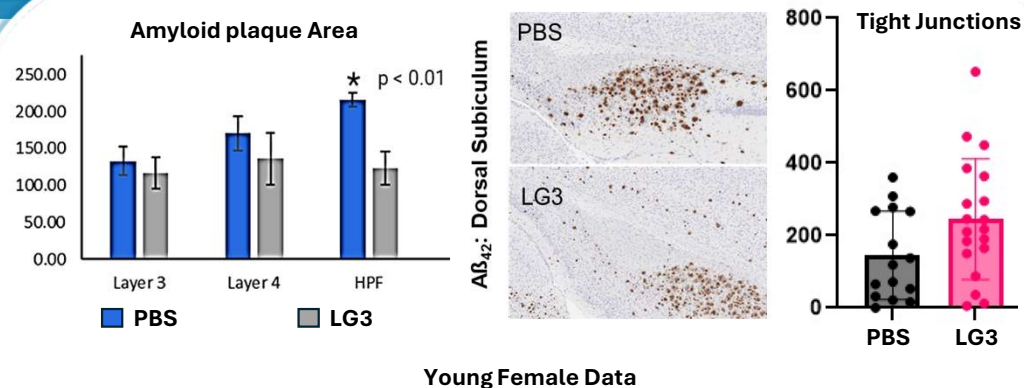
Penumbral
Core Focus



Vessel Density: 7.11%

LG3 Effective in Alzheimer's Model

Consistent with neurovascular hypothesis of cause of AD

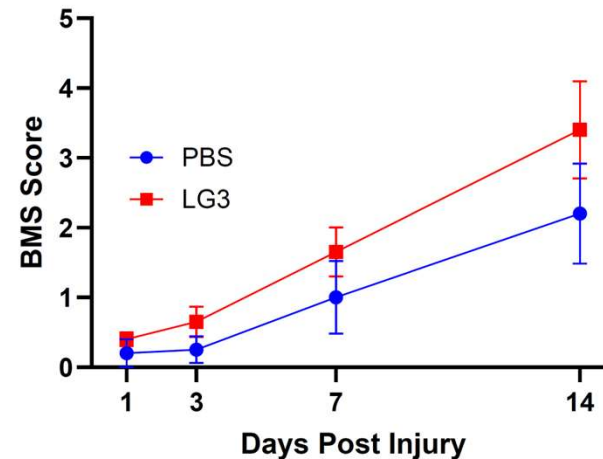


- **Reduces Alzheimer's (AD) plaque burden in key brain structures**
 - Brain-wide effect in Young Females
 - Greatest effect in Hippocampus
 - Amygdala specific in Aged Males
- **Improves blood-brain barrier integrity (tight junction protein expression)**
- **Improves Alzheimer's-related behavioral and functional deficits**
 - Rescues exploratory behavior
 - Improves spontaneous alternation
 - Trend toward improved object memory
 - (small n= for memory assessments)
- **Reduces amyloid burden in amygdala**

LG3 Effective in SCI and Diabetes Models

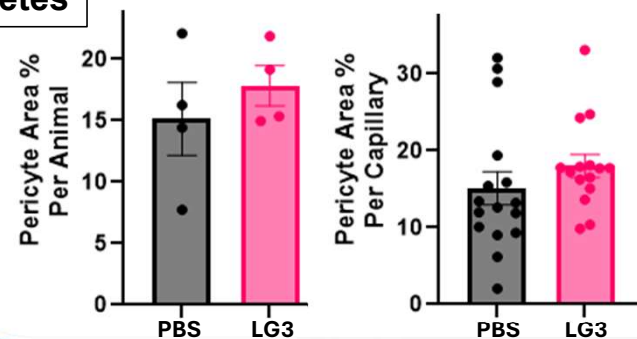
- Improves Limb Function & Weight Support following Impact Spinal Cord Injury (SCI)
- Accelerates Recovery Trajectory in SCI
- Enhances NVU Function via improved pericyte coverage of capillaries in Diabetes
- Repair and protection of NVU Function is reoccurring observation across indications
- Continuing research for these and other indications with serious unmet need

SCI



- **Pilot Study:** mouse model of crush injury
- Single Dose Following Injury
- Imaging in progress

Diabetes



- **Pilot Study:** mouse model of diabetes (db/db)
- 7 Doses over 30 days (1x/5 days)
- Imaging complete

Stream's Development Timeline and Capital Raise (\$10MM)

First-in-Man Studies (NHV and TBI) Establish Initial Safety and Efficacy

PATH TO THE CLINIC



- Completed Pre-IND Meeting for Stroke
- Completed Pre-IND Meeting for TBI
- Clinic-Ready, P1 trials starting Q1 2026
- Market Impact >\$10B
- Multiple Indications beyond TBI
- Potential Acquisition 2027+



TBI Clinical Trial: Establish Initial Safety / Efficacy

Trial Design

- Initial assessment of safety; pharmacokinetics; efficacy
- Design / Inclusion criteria:
 - Patients with moderate-to-severe TBI (Glasgow Coma Scale 3-12; one reactive pupil)
 - Placebo-controlled, N=40 (10 placebo; 30 drug). Single-ascending dose, 2 sites
- Dose regimen: n= 5 ascending dose-cohorts
 - 0.075 mg/kg; 0.15 mg/kg; 0.30 mg/kg; 0.60 mg/kg; 1.2 mg/kg
 - Single –dose administered in emergency room following diagnosis
- Outcome measures:
 - Safety and Tolerability: adverse events
 - Pharmacokinetics:
 - Efficacy:
 1. Clinical outcomes: Extended Glasgow Coma Scale
 2. Radiographic outcomes: BBB Permeability/Damage
 - DCE-MRI K-trans; baseline / post-treatment
 3. Serum biomarkers: neuroprotective & anti-inflammatory effects
 1. Nf-L, GFAP, PDGFR β , TNF- α , pro-inflammatory cytokines...

Strengths of the Study

- Using highly sensitive outcome measures (DCE-MRI* scans, serum biomarkers)
- Single-dose intravenous administration
- Results will provide basis for additional studies in other neurodegenerative diseases, e.g., acute Ischemic stroke, Alzheimer's disease, etc.

*Ware et al, Neuroimage Clin. 2022 Oct 17;36: 10326

**We are experts in drug development, translational neuroscience,
protein biochemistry, and regulatory affairs**



CEO - Bill Schwieterman, MD



CSO - Davis Adkisson, PhD



Dir. Research – Bryan Clossen, PhD



Dir. Manufacturing – Seth Fisher, BA

Field-Leading Neurodegeneration Collaborators:

Bix Lab – Tulane University Medical Center



University of Kentucky Stroke Core



Hubbard Lab – University of Kentucky

McCreedy Lab – Texas A&M University



Soto Lab – University of Texas Health Science Center



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