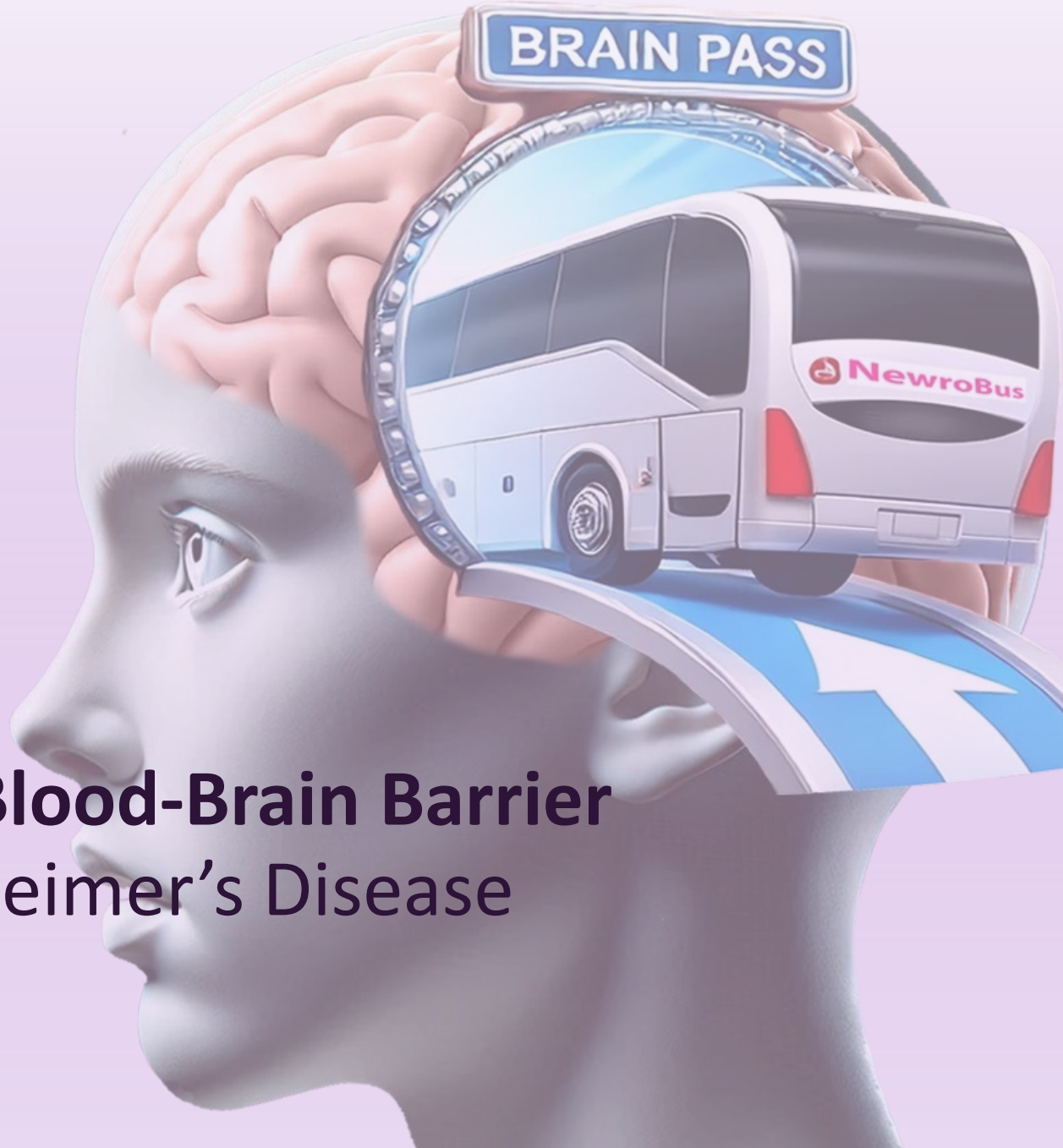
NanoNewron™

New Treatments for CNS Diseases



NewroBus™

Carrying Biologics Across the Blood-Brain Barrier

A Novel Approach to Treat Alzheimer's Disease

For inquiries please contact:
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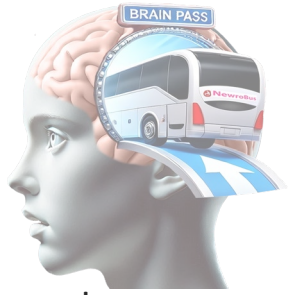
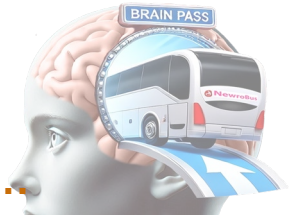
Townsend Hall T217, 1000 Morris Ave, Union, NJ 07083

Forward-Looking Statements



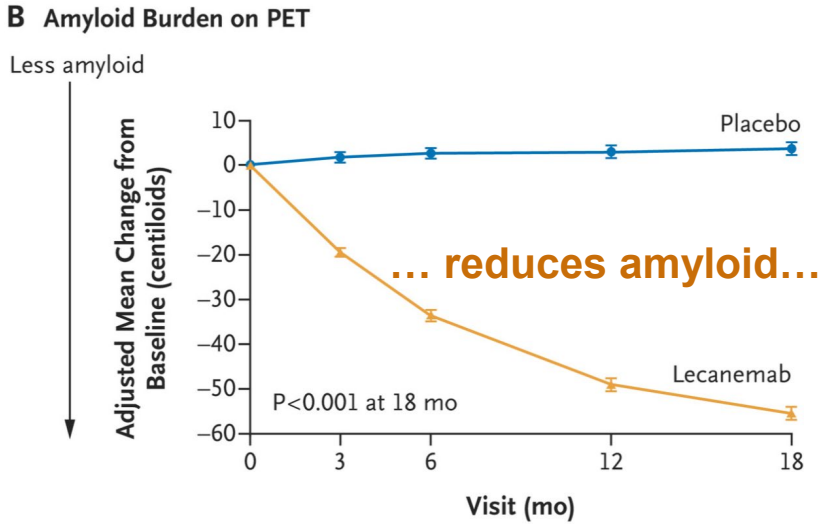
This presentation contains “Forward-Looking Statements” Forward-Looking Statements reflect our current view about future events. When used in this presentation, the words “anticipate,” “believe,” “estimate,” “expect,” “future,” “intend,” “plan,” or the negative of these terms and similar expressions, as they relate to us or our management, identify forward-looking statements. Such statements, include, but are not limited to, statements contained in this presentation relating to our business strategy, our future operating results and liquidity and capital resources outlook. Forward-looking statements are based on our current expectations and assumptions regarding our business, the economy and other future conditions. Because forward–looking statements relate to the future, they are subject to inherent uncertainties, risks and changes in circumstances that are difficult to predict. Our actual results may differ materially from those contemplated by the forward-looking statements. They are neither statements of historical fact nor guarantees of assurance of future performance. We caution you therefore against relying on any of these forward-looking statements. Important factors that could cause actual results to differ materially from those in the forward-looking statements include, without limitation, our ability to raise capital to fund continuing operations; our ability to protect our intellectual property rights; the impact of any infringement actions or other litigation brought against us; competition from other providers and products; our ability to develop and commercialize products and services; changes in government regulation; our ability to complete capital raising transactions; and other factors relating to our industry, our operations and results of operations. There is no guarantee that any specific outcome will be achieved. Investment results are speculative and there is a risk of loss, potentially all loss of investments. Actual results may differ significantly from those anticipated, believed, estimated, expected, intended or planned. Factors or events that could cause our actual results to differ may emerge from time to time, and it is not possible for us to predict all of them. We cannot guarantee future results, levels of activity, performance or achievements. Except as required by applicable law, including the securities laws of the United States, we do not intend to update any of the forward-looking statements to conform these statements to actual results.

Alzheimer's Disease Remains a Major Unmet Need

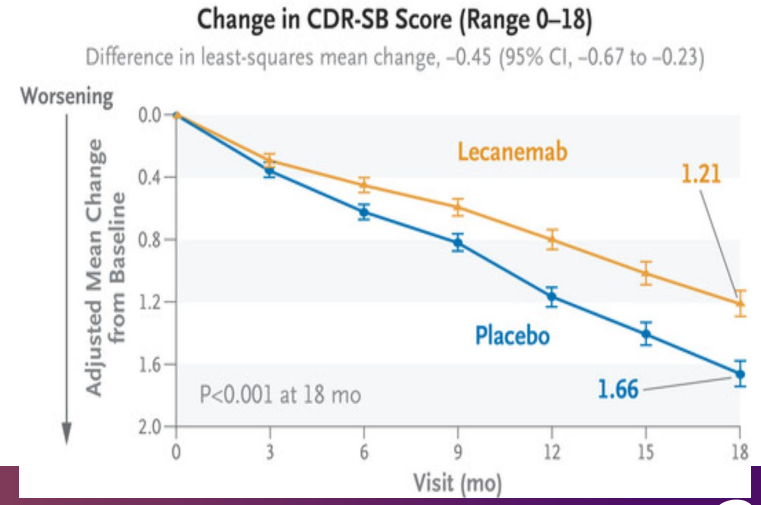


- >7 million Alzheimer's patients in the U.S.[1]
  - >40 million worldwide
  - A $14.5 billion market by 2029…
- Only partial success of **anti-amyloid biologics** [2]
  - **Strong biological effect** with reduction of amyloid…
  - … but only **temporary** improvements in symptoms
  - **Modest** slowdown of cognitive decline
  - **Inability** to block the progression of cognitive deterioration
- … and **Anti-Tau** products have failed, to date

Leqembi's biological effect…



… but with modest clinical effect!



We need to target additional pathogenetic mechanisms!

1) 2023 Alzheimer's Disease Facts and Figures, *Alzheimers Dement* 2023, 19(4) 1598-1695
2) https://www.nejm.org/doi/full/10.1056/NEJMoa2212948

Inflammatory Cytokine TNF-α May Drive Brain Inflammation

- **Growing evidence that excessive or dysregulated TNF-α drives brain inflammation and plays a role in Alzheimer's Disease (AD)**

Odd Ratio[1] of developing AD compared to the general population	
TNF Inhibitor	**Odd Ratio**
etanercept	0.3
etanercept	0.36
etanercept	0.34
adalimumab	0.65
adalimumab	0.28
infliximab	0.73
infliximab	0.64

- Data in humans
  - Reduced risk of AD in patients treated with TNFI for other conditions[1]
  - Cognitive improvements after peri-spinal administration of TNF-α inhibitors[2]
    - Open-label, small (N=15) study showed 5-point improvement in ADAS-Cog score at 6 months
  - Trend for elevated TNF-α levels in blood and CNS in Alzheimer's patients[3]
- Data in animal models
  - TNF-α inhibitor XPro1595 decreases beta-amyloid plaque load in 5xFAD mice[4]
  - TNF-α inhibition in a mouse AD model prevents pre-plaque amyloid-associated neuropathology[5]
  - TNF-α increases excitatory transmission preceding Alzheimer's pathology in young Trem2R47H rats[6]

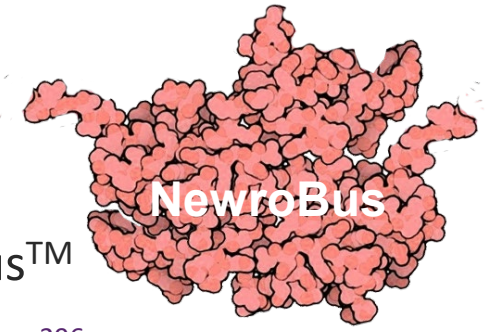
1) Torres-Acosta N. et al (2020) Therapeutic Potential of TNF-α Inhibition for Alzheimer's Disease Prevention. *Journal of Alzheimer's Disease, 78(2)*, 619-626
2) Tobinick E et al (2006) TNF-alpha Modulation for Treatment of Alzheimer's Disease: A 6-Month Pilot Study. *MedGenMed, 8(2)*, 25
3) Plantone D. et al (2023) The Role of TNF-α in Alzheimer's Disease: A Narrative. *Cells, 26;13(1)*, 54
4) MacPherson KM et al (2017) Peripheral administration of the soluble TNF inhibitor XPro1595 modifies brain immune cell profiles, decreases beta-amyloid plaque load, and rescues impaired long-term potentiation in 5xFAD mice. *Neurobiol Dis, 102*, 81-95
5) McAlpine FE et al (2009) Inhibition of soluble TNF signaling in a mouse model of Alzheimer's disease prevents pre-plaque amyloid-associated neuropathology. *Neurobiol Dis 34(1)*, 163-177
6) Ren S et al (2021) TNF-α-mediated reduction in inhibitory neurotransmission precedes sporadic Alzheimer's disease pathology in young Trem2R47H rats, J Biol Chem, 296

TNF-α Pathogenetic Changes Reversed with TNF-α Inhibition

- *Trem2*^{R47H} rats produce human amyloid-β (Aβ) and high brain levels of TNF-α[1,2]
  - TNF-α increases excitatory transmission preceding Alzheimer's pathology in young Trem2^{R47H}
    - Excitatory (glutamatergic)/Inhibitory (GABAergic) imbalance favoring excitotoxic neuronal cell death
    - Impaired Long-Term Potentiation (LTP), a surrogate of learning and memory
    - Increased Aβ production over Aβ clearance
  - **TNF-α inhibition** reversed the excitatory/inhibitory changes in *Trem2*^{R47H} rats[2]

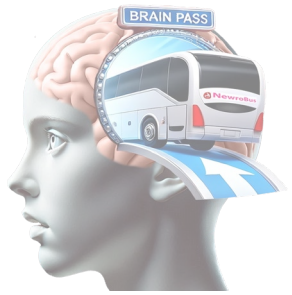
- **TNF-α inhibitors (TNFI) could transform the treatment of Alzheimer's** as TNFI Remicade and Humira did with Crohn's Disease or Rheumatoid Arthritis
  - **But TNFI don't cross Blood-Brain Barrier (BBB)!**

- **NanoNewron's Solution: NewroBus™ and NN-841**
  - **NewroBus:** single-chain nanobody designed to transport biologics across the BBB
  - **NN-841:** our lead program is a potent TNF-α inhibitor crossing the BBB using NewroBus™



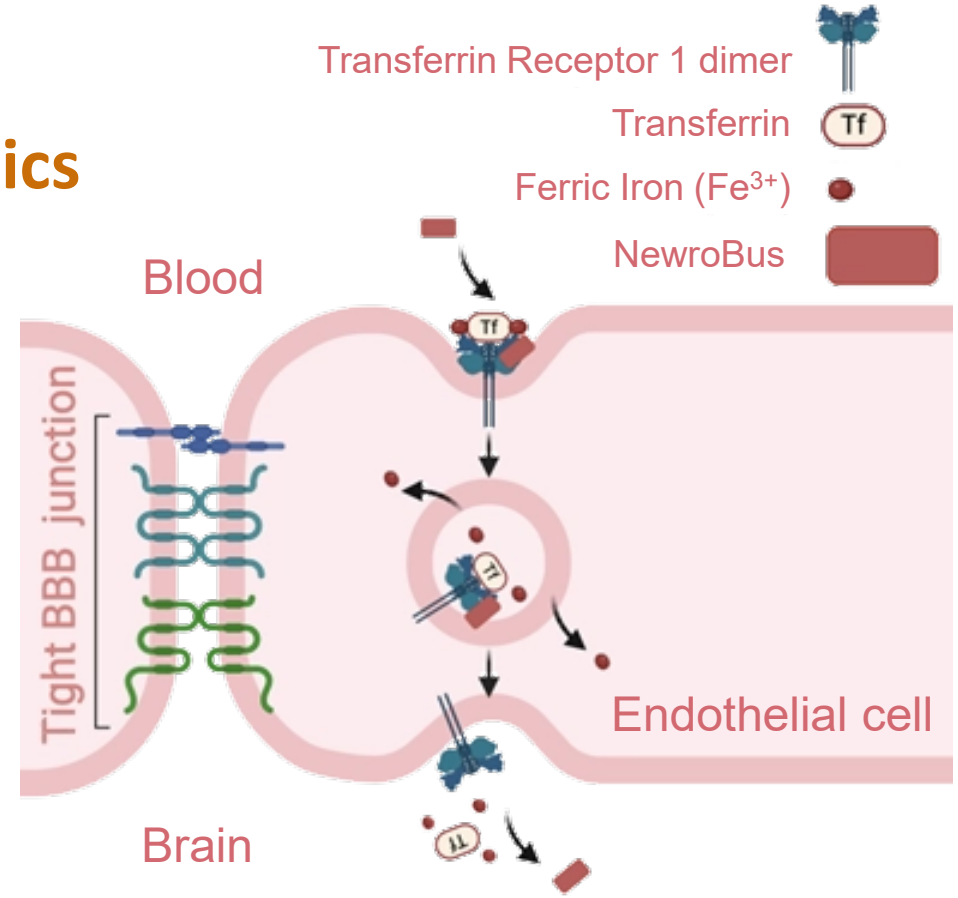
1. Ren S et al (2021) TNF-α-mediated reduction in inhibitory neurotransmission precedes sporadic Alzheimer's disease pathology in young Trem2R47H rats, J Biol Chem, 296
2. Ren S et al (2020) Microglia TREM2 R47H Alzheimer-linked variant enhances excitatory transmission and reduces LTP via increased TNF-α levels. Elife 24(9) 57513

Versatile Technology Platform – The NewroBus

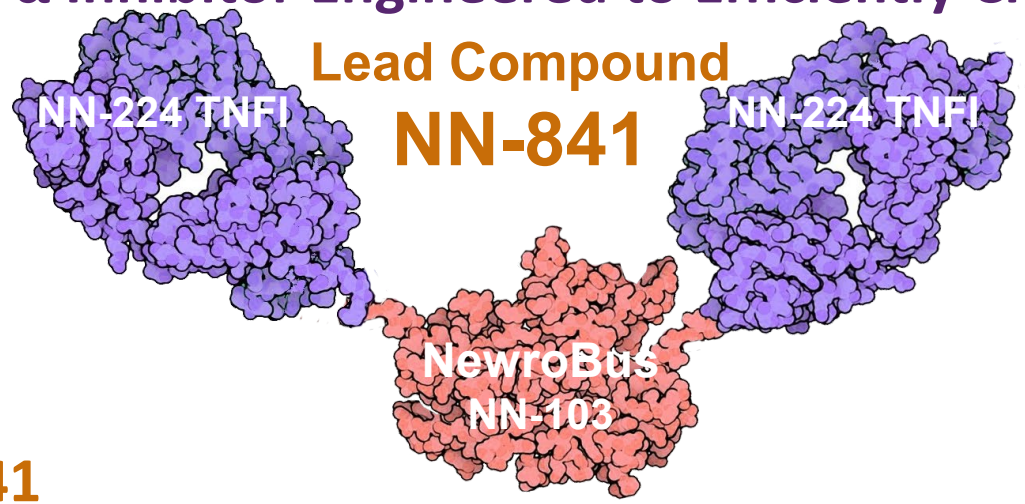


- The blood-brain barrier keeps out from the brain large molecules, e.g. biologics
- NewroBus exploits **Transferrin Receptor 1 (TfR1)** mediated transcytosis to transport large molecules across the BBB

- **NewroBus: Multipurpose Brain Carrier for Biologics**
  - Selected four different humanized nanobodies
    - Selected from a large pool of nanoantibodies
    - No interference with Tf binding and uptake
  - High humanness with **low or no immunogenicity**
  - High specificity: bind exclusively to human TfR1, not rodent TfR1
  - High BBB permeability (**CSF/Serum ratio >.90**) tested in rat models with the human TfR1 gene
  - High tolerability, with **low risk for anemia** in humans, as tested in rats with a human TfR/Tf complex

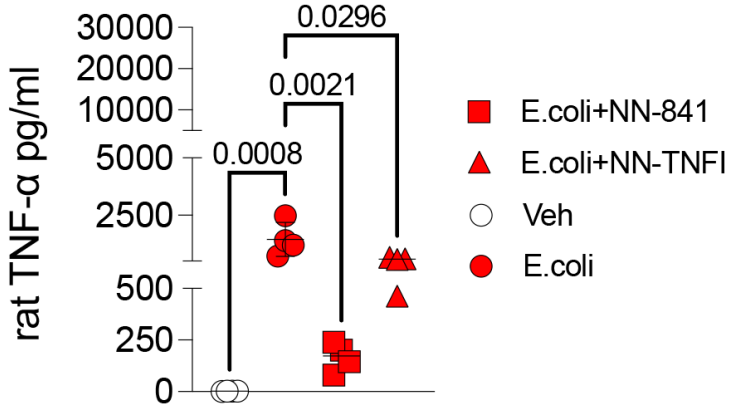


NN-841: A Potent TNF-α Inhibitor Engineered to Efficiently Cross the BBB



- **Lead Compound NN-841**
  - NewroBus NN-103 linked to two molecules of **proprietary TNF-α inhibitor (TNFI) NN-224**
  - Therapeutic activity tested in rats with humanized TfR1, Tf, and TNF-α
  - NN-841 crosses the BBB via TfR1 in rats **after S.C. administration**
  - **High Inhibition of TNF-α by NN-841**, higher than our TNFI NN-224 alone
  - Excellent **CSF/Serum ratio (~1:2)** and broad brain distribution
  - High specificity to human TfR1 (it doesn't bind to rat TfR1)
  - NN-841 administration does not cause hematotoxicity

Effect on TNF-α
of NN-841 vs TNFI NN-224



	NN-841	TNFI NN-224
IC50 (pM)	3-4	57-76

Two Groups of NanoNewron's Competitors

1. **TNF-α inhibitor** for Alzheimer's in development
   - Provides additional evidence of TNF-α role in Alzheimer's
   - **InMune Bio** (Nasdaq INMB, Mkt cap $200M)
     - XPro1595 (pegipanermin)

2. **Brain Barrier Carrier** (but not against TNF-α) in development
   - Brain Carriers are a high-interest area of development
   - **Denali** (Nasdaq DNLI, Mkt cap $2.1B)/**Takeda**
     - DNL919
   - **BioArctic** (Nasdaq Stockholm BIOA-B.ST, Mkt Cap ~$1.7B)/**BMS**
     - BAN1503 and BAN2803

Competition — TNF-α Inhibitors in Alzheimer's

XPro1595 (pegipanermin) by INmuneBio (Nasdaq INMB)

- **Technology:** A pegylated TNF-α modified monomer inhibiting soluble TNF-α
  - XPro1595 forms an inactive TNF-α heterotrimer and showed promising data in animal models:
    - Decreased β-amyloid plaque and rescued impaired long-term potentiation in 5xFAD mice[1] (10 mg/kg SC twice weekly for 8 weeks)
    - Prevented synaptic deficits in Alzheimer's model in TgCRND8 mice[2] (10 mg/kg SC daily for 4 weeks)
    - Improved synaptic alterations and cognitive performances in Fisher 344 rats[3] (0.08 mg/kg intracranially day for 6 weeks)

- **Stage of Development:** Ongoing global Phase 2 in Alzheimer's (MINDFuL, NCT05318976)
  - N=201, 2:1 randomization of 1 mg/kg of XPro1595 weekly SC vs placebo for 24 weeks
  - Topline expected mid-2025

- **Weaknesses:** Modest penetration across the BBB in rats
  - Ratio of CSF levels (1 to 6 **ng/mL**) vs plasma levels (1 to 8 **µg/mL**) in rats is **about 1:1,000** with higher risk of immunosuppression and off-target effects
  - Several positive animal studies but with doses 20 to 50 times higher than in humans

Ratio of CSF-to-Plasma Levels (SC administration)	
INMB XPro1595	~1:1000
NanoNewron NN-841	~1:2

1) MacPherson KM et al (2017) Peripheral administration of the soluble TNF inhibitor XPro1595 modifies brain immune cell profiles, decreases beta-amyloid plaque load, and rescues impaired long-term potentiation in 5xFAD mice. *Neurobiol Dis, 102*, 81-95
2) Cavanagh C et al (2016) Inhibiting tumor necrosis factor-α before amyloidosis prevents synaptic deficits in an Alzheimer's disease model. Neurobiol Aging 47, 41-49
3) Sama et al (2012) Inhibition of soluble tumor necrosis factor ameliorates synaptic alterations and Ca2+ dysregulation in aged rats. PLoS One 7(5), e38170

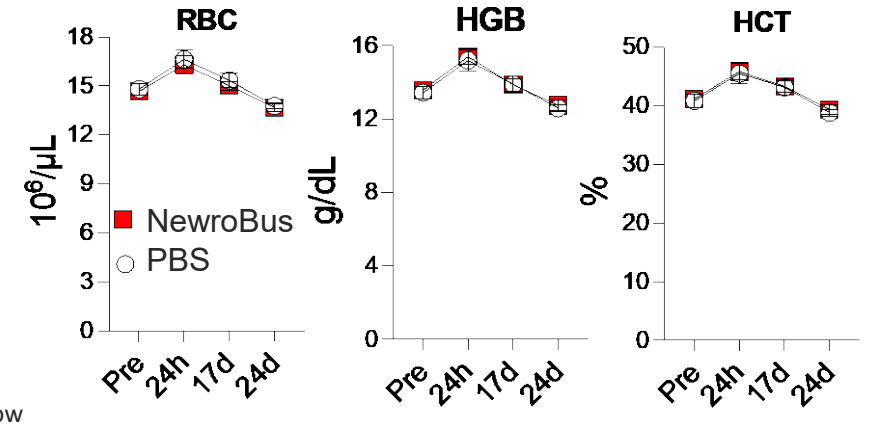
Competition — TfR1 BBB Carriers in Alzheimer's

DNL919/TAK-920 by Denali (DNLI)/Takeda

- A TREM2 activator
  - Crosses BBB efficiently with Denali's ATV technology
    - ATV (Antibody Transport Vehicle) exploits TfR1 transcytosis
  - Licensed at preclinical stage to Takeda for $150M upfront plus undisclosed milestones and royalties
  - Development of DNL919/TAK **stopped** because of **hematologic toxicity (anemia)**
    - **Anemia in a Phase 1, single-ascending-dose trial**
    - **Anemia observed also in rodent tox studies**

- **No hematologic toxicity with NewroBus™**
  - Tested in rats with humanized TfR1 and Tf complex
  - No gross toxicity observed for 24 days
  - 6 IV administration every 4 days
  - Assessment on Day 1, 17 and 24

No hematologic side effects with NewroBus



https://www.fiercebiotech.com/biotech/takeda-denali-drop-alzheimers-asset-after-phase-1-peak-reveals-narrow-therapeutic-window

Competition — TfR1 BBB Carriers in Alzheimer's

BAN1503 and BAN2803 by BioArctic

- BioArctic, the Swedish company that developed and licensed Leqembi to Eisai
- BAN1503 and BAN2803 for Alzheimer's
  - BioArctic's PyroGlutamate-amyloid-beta (PyroGlu-Aβ) antibody program in Alzheimer's
  - Crossing BBB efficiently with BioArctic BrainTransporter™ technology exploiting TfR1 transcytosis
  - **Program is preclinical, pre-IND**

- **Global license to BMS for BAN1503 and BAN2803**
  - $100 million upfront
  - $1.25 billion in milestones
  - Tiered low double-digit royalties

BIOARCTIC

En / Sv

BioArctic announces global license agreement with Bristol Myers Squibb for BioArctic's PyroGlutamate-amyloid-beta antibody program

December 19, 2024 07:30 | Regulatory

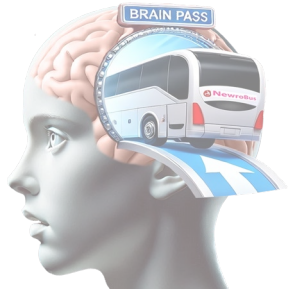
https://www.bioarctic.com/en/bioarctic-announces-global-license-agreement-with-bristol-myers-squibb-for-bioarctics-pyroglutamate-amyloid-beta-antibody-program/

Management

- Marco Taglietti, M.D., Chief Executive Officer, Investigator
  - Dr. Taglietti has brought more than 30 different products to market
  - President and Chief Executive Officer of Scynexis (Nasdaq:SCYX) from 2015 to 2022
  - President and Chief Medical Officer at Forest Laboratories (Nasdaq:FRX) from 2007 until 2014
  - Head of Global Research at Stiefel Laboratories from 2004 to 2007
  - Vice President, Clinical Development, Schering-Plough from 1992 to 2004

- Luciano D'Adamio, M.D., Ph.D., Founder, Chief Scientific Officer and Investigator
  - Distinguished neuroscientist and professor at Rutgers, the State University of New Jersey
  - Herbert C. and Jacqueline Krieger Klein Endowed Chair since 2017
  - Irene Diamond Professor of Immunology at the Albert Einstein College of Medicine
  - Professor of Clear Fame, University of Naples, Federico II
  - Alzheimer's Medal and the Zenith Award from the Alzheimer's Association.
  - On editorial boards of leading journals and has been recognized for his groundbreaking work in neurodegenerative diseases and translational neuroscience

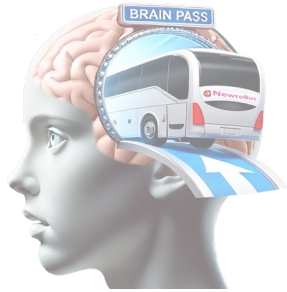
Business Plan Based on Two Strategies



1) Continue aggressive development of NN-841 for Alzheimer's
   - Novel approach targeting TNF-α inflammation
   - High brain penetration and TNF-α inhibition with excellent tolerability
   - Animal models in humanized TfR1 rats available to establish preclinical proof of concept
   - Early Alzheimer's disease as initial target population, an estimated market of 3 to 5 billion dollars
   - Expand use of NN-841 (or a follow-up compound) into additional CNS disorders
     - Parkinson's, Traumatic Brain Injury, Multiple Sclerosis, ALS
   - **Multiple short-(18-24 months), medium- and long-term inflection points for exit**

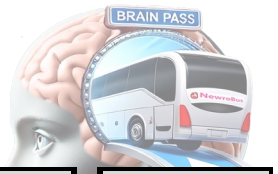
2) License NewroBus™ Technology to other companies
   - **Four different NewroBus molecules currently available for licensing**
   - Potential life-cycle management of commercial products
   - Enhancing brain penetration of other novel biologics
   - Potential for other therapeutic areas and combination therapy
   - **Additional source of income**

Our Achievements to Date by the Numbers



- Clinical candidate selection
  - **940** nanobodies were cloned, produced, and tested for antigen binding
  - **85** anti-TNF-α nanobodies were tested for TNF-α inhibitory activity
  - **106** anti-TfR1 nanobodies were tested for binding to human TfR1
- Rat models development
  - **3 different rat models** were generated with humanized TfR1, TF, and TNF-α
- Animal studies
  - **40 germline** and humanized TfR1b nanobodies tested in vivo for BBB permeability.
  - **32 heterotrimers**, heterodimers, and heterotetramers evaluated for TNFα inhibitory activity and in vivo BBB permeability
- Additional studies
  - **2 tox studies** in humanized rats to assess hematological side effects
  - ***ex-vivo* human dendritic cells and T cells immunogenicity** assessment of nanobodies
  - **Crystallography** studies

Key Milestones for NN-841 IND Filing in 4Q2026
(Total Cost: $7.8M)



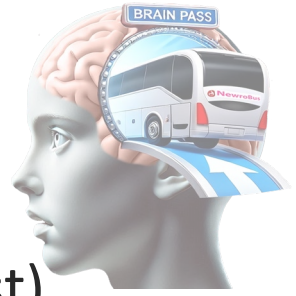
Workflow Activities	2025									2026												Costs
	Q2			Q3				Q4		Q1			Q2			Q3				Q4		$7.8M
	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	
1. CMC/Manufacturing Scale-Up																						**$1.75M**
PCB Selection and Generation																						$450K
Method Qualification and Validation, and Formulation																						$350K
NN-841 Non-GMP and GMP Production					Non GMP			GMP														$600K
Stability Studies																						$350K
2. Preclinical Mechanistic Studies																						**$1.50M**
Cognition and behavior studies																						$550K
Neuropathology and synaptic activity studies																						$450K
Human CNS organoids models																						$500K
3. IND Enabling Study																						**$2.60M**
Toxicology and safety studies (Assuming no primate studies)																						$1,850K
PK/PD validation studies and metabolism																						$750K
4. Regulatory/Operations																						**$1.95M**
Pre-IND meeting (12/2025), eCTD and IND preparation																						$600K
Operational and administrative costs																						$900K
Clinical Phase 1 preparation																						$450K

CMC and Manufacturing of NN-841

- Scalable NN-841 production with high-yield CHO Clones
  - Same CDMO used for previous 1-Liter pilot production
  - Based on previous experience, expected yield of NN-841 is 10 g to 20 g per liter

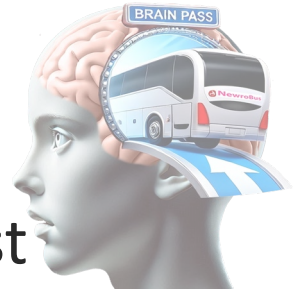
- 50-Liter productions expected to yield 500 g to 1,000 g of NN-841
  - 50-Liter Non-GMP in September 2025 for preclinical models and initial IND-enabling tox
  - 50-Liter GMP in November 2025 to complete IND-enabling tox and Phase 1

Preclinical Models



- **Rat models** with animals humanized for TfR1, Tf and TNF-α
  - Cognitive efficacy of NN-841 assessed using dPAL (Paired Associate Learning Test)
  - Biologic efficacy measuring amyloid and tau, synaptic function and neuroinflammation
  - Multiple Rat models to capture disease heterogenicity
    - $TREM2^{R47H}$ LOAD (Late Onset AD) model
    - LOAD APOE4 mutation with strongest genetic risk factor for LOAD.
    - LOAD ABCA7 Belgian mutation with Loss-of-function linked to increased LOAD risk
    - FAD (Familial AD) PSEN1-L435F mutation altering γ-secretase activity and Aβ processing
    - FAD APP Swedish mutation with increased β-secretase cleavage, leading to elevated Aβ and early-onset FAD
- **Human models *in vitro***
  - 3D organoids and 2D cultures of neurons, astrocytes and microglia
  - Readout Systems for AD in Human Organoid/Cellular Models
    - Aβ and Tau Pathology
    - Synaptic Activity and LTP-like plasticity.
    - Neuroinflammation with cytokine profiling
    - Microglial Function

Status of $2.5M NIH STTR Phase II Grant Status



- Email received on March 31st, 2025 from NIH about our $2.5M grant request
  - Notice of Intent to fund

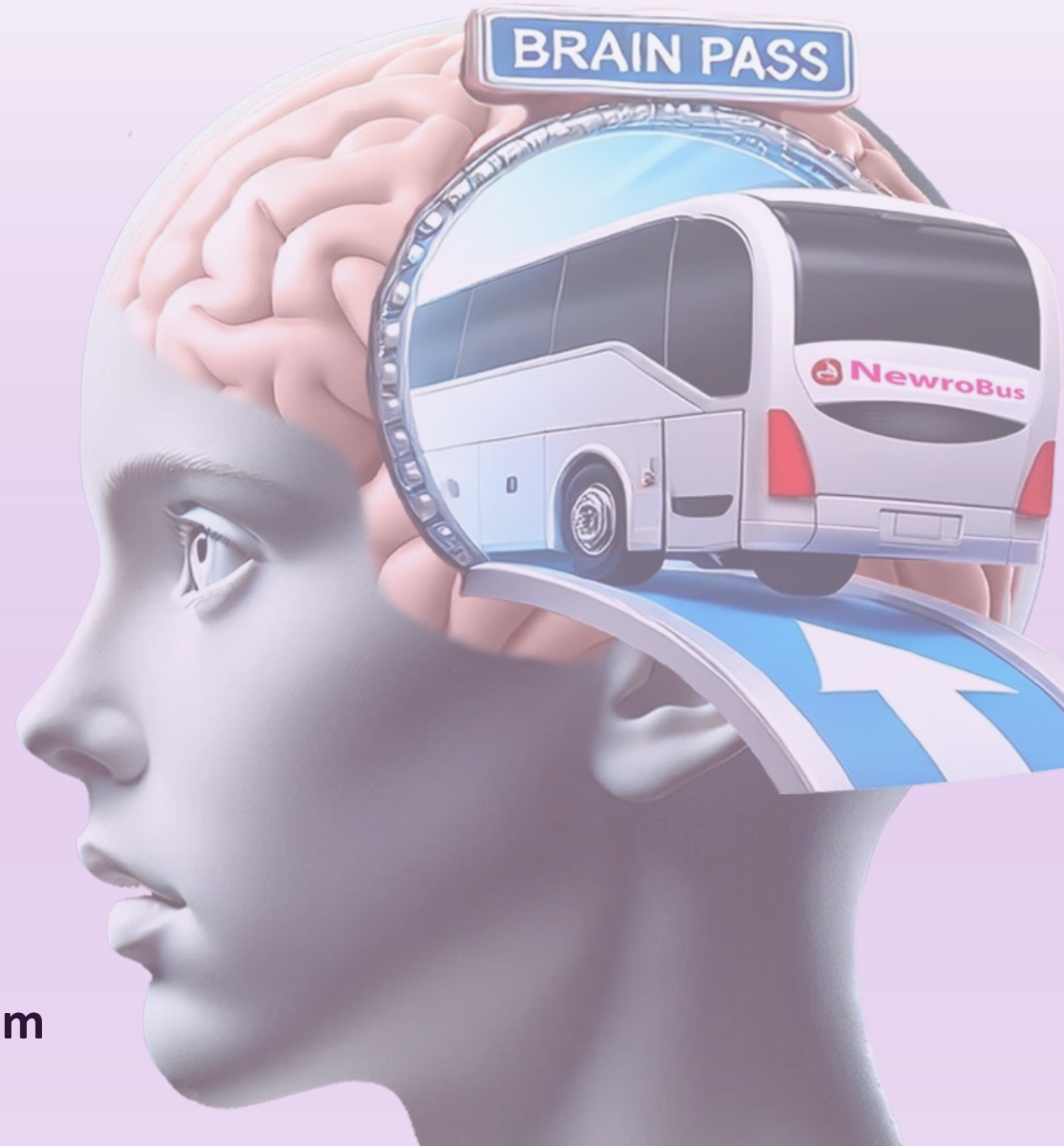
From: era-notify@mail.nih.gov
Sent: 03/29/2025 05:30 AM
To: pg@nanonewron.com
CC: AGeRANotifications@mail.nih.gov
Subject: SBIR/STTR Funding Decision for 2 R42 AG080864-02

This email serves as notification that application, 2 R42 AG080864-02, has been selected for probable funding by NATIONAL INSTITUTE ON AGING. This is not the official Notice of Grant Award, but a Notice of Intent to fund the application. A final decision on funding will be based upon further NATIONAL INSTITUTE ON AGING staff review of the application, and the receipt and review of any additional information that may be requested by NATIONAL INSTITUTE ON AGING staff.

NanoNewron™

New Treatments for CNS Diseases

Thank you!



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