Version June 27, 2025

NanoNewron™

New Treatments for CNS Diseases

NewroBus™

Carrying Biologics Across the Blood-Brain Barrier

A Novel Approach to Treat Alzheimer's Disease

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Forward-Looking Statements

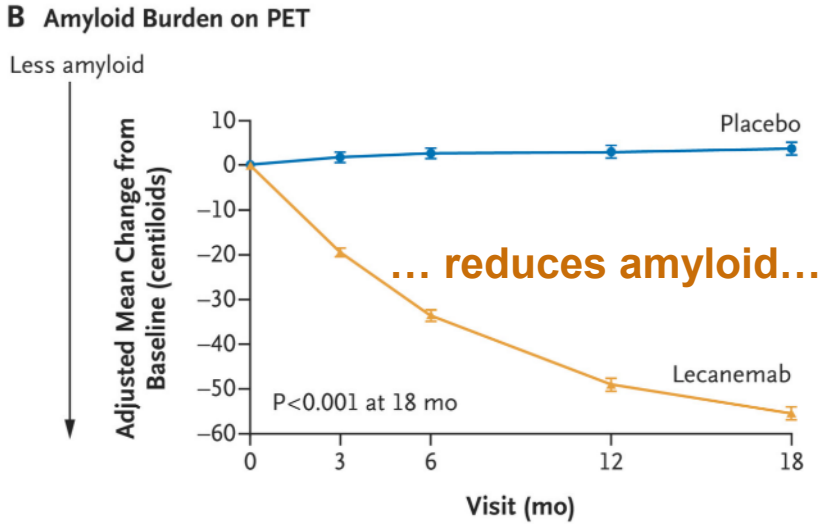
This presentation contains “Forward-Looking Statements” Forward-Looking Statements reflect our current view about future events. When used in this presentation, the words “anticipate,” “believe,” “estimate,” “expect,” “future,” “intend,” “plan,” or the negative of these terms and similar expressions, 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.

Table of Content

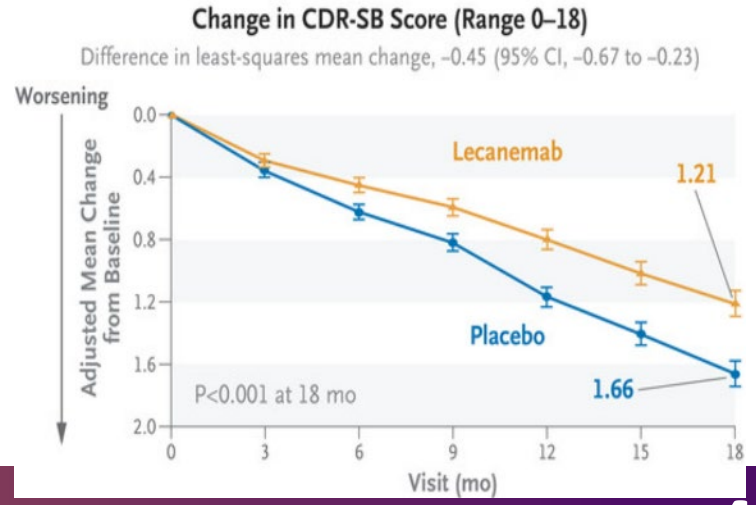
The Problem: Alzheimer's Disease Remains a Major Unmet Need

- >7 million Alzheimer's patients in the U.S.[1]
  - >40 million worldwide, expected to double in the next 20 years
  - A $14.5 billion market by 2029… **a large but unsatisfied market**
- 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 consistently failed, to date

Leqembi's biological effect…



… but with modest clinical effect!

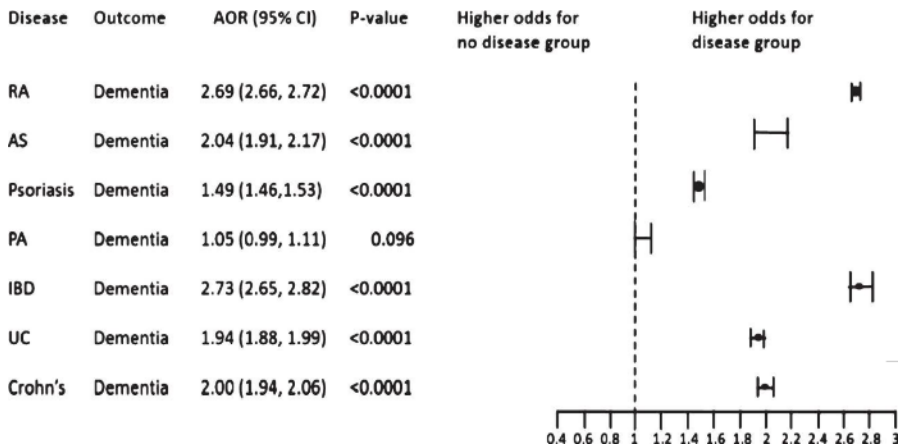


We need to target additional pathogenetic mechanisms!

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)**
- Higher risk of AD in patients with systemic inflammatory diseases such as Crohn's disease or rheumatoid arthritis which are mediated by TNF, but reduced risk when they are treated with TNFIs[1,2]



RA – Rheumatoid Arthritis
AS – Ankylosing Spondylitis
PA – Psoriatic Arthritis
IBD – Inflammatory Bowel Disease
UC – Ulcerative Colitis

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

- Cognitive improvements after peri-spinal administration of TNF-α inhibitor (etanercept, Enbrel)[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]

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

TNF-α Pathogenetic Changes Reversed with TNF-α Inhibition

Data in animal models

- TNF-α inhibitor XPro1595 decreases beta-amyloid plaque load in 5xFAD mice[1]
- TNF-α inhibition in a mouse AD model prevents pre-plaque amyloid-associated neuropathology[2]
- TNF-α increases excitatory transmission preceding Alzheimer's pathology in young Trem2R47H rats[3]
- *Trem2*^{R47H} rats produce human amyloid-β (Aβ) and high brain levels of TNF-α[3,4]
  - 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[4]

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) 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
3) 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
4) 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

TNF-α Inhibitors to Treat Alzheimer's Disease

- **TNF-α inhibitors (TNFI) could transform the treatment of Alzheimer's** as TNFI Remicade and Humira did with Crohn's Disease, Rheumatoid Arthritis and other diseases…

- **… but TNFI don't cross the Blood-Brain Barrier (BBB)!**

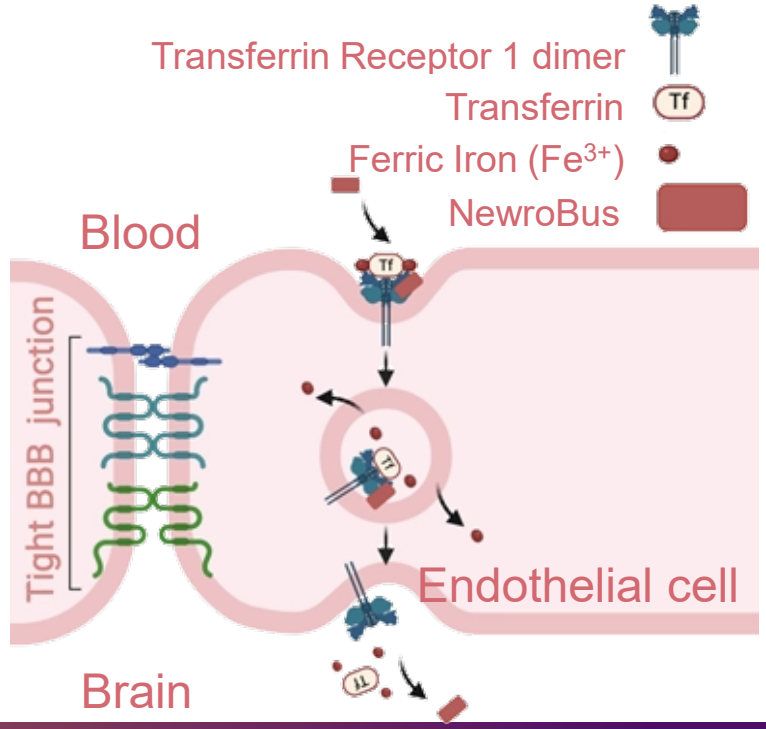
- **NanoNewron's Solutions: NewroBus™ and NN-841**
  - **NewroBus:** single-chain nanobody designed to transport biologics across the BBB
  - **NN-841:** our lead program is a potent TNF-α inhibitor crossing the BBB using NewroBus™

NewroBus™

Versatile Brain-Carrier Technology Platform Exploting TfR1

- The blood-brain barrier (BBB) keeps out from the brain large molecules, e.g. biologics
- NewroBus transports large molecules into the brain by exploiting the natural mechanism of **Transferrin Receptor 1 (TfR1)** to carry Transferrin (Tf) across the BBB
  - NewroBus shows no pharmacology activity by itself other than the ability to cross efficiently the BBB and carry pharmacologically active biologics with it

- **NewroBus: a Best-in-Class TfR1 Brain Carrier**
  - Four different NewroBus molecules are available
    - Selected from a large pool of >450 humanized nanoantibodies
    - No interference with Tf binding and uptake
  - High humanness with **low immunogenicity potential**
  - High specificity: bind exclusively to human TfR1, not rodent TfR1
  - High BBB permeability (**High CSF/Serum ratio >0.7**) tested in rat models with the human TfR1 gene
  - High tolerability, with **low risk for anemia** in humans, as tested in rats with humanized TfR1/Tf complex

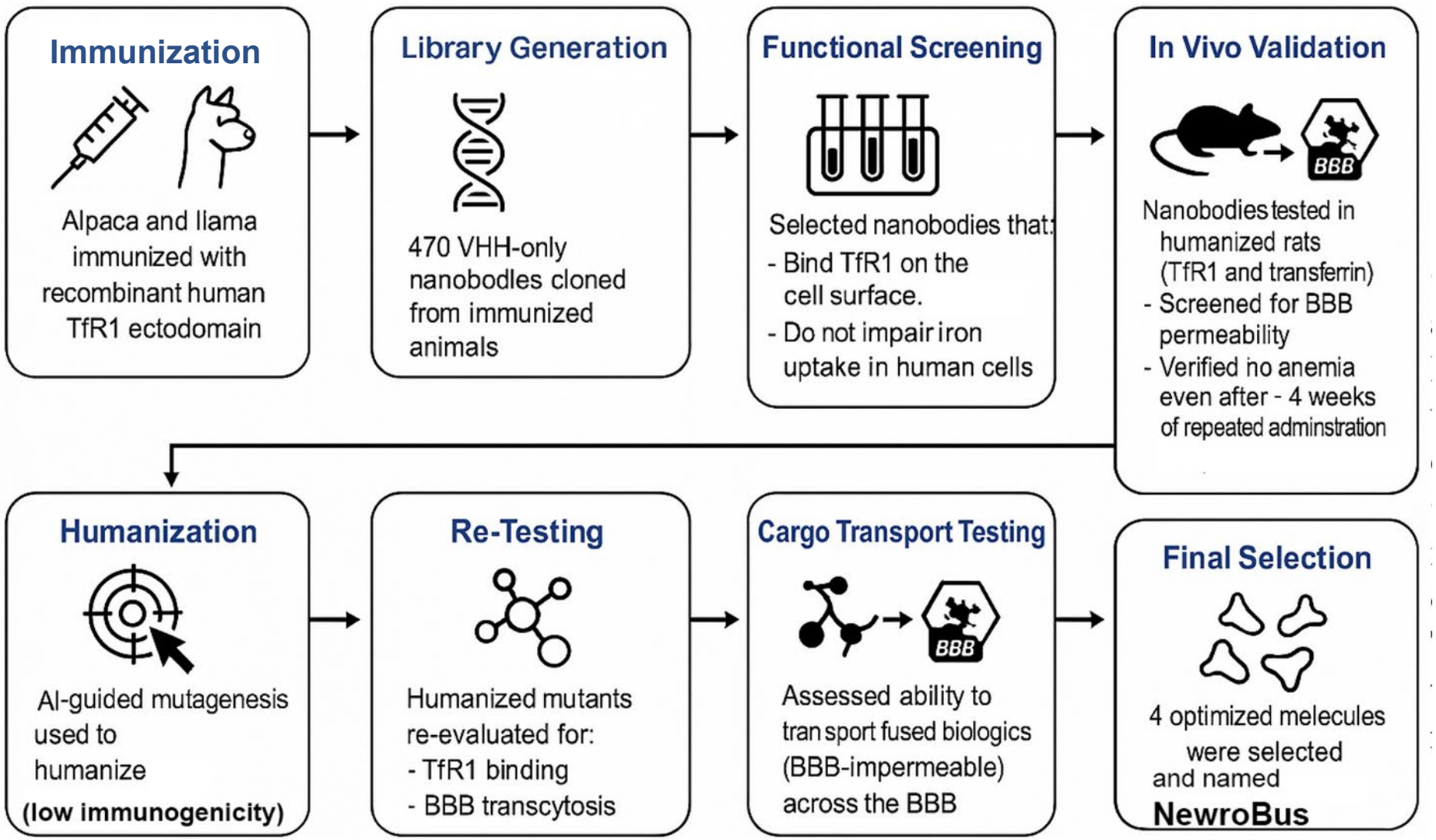


Why Using TfR1 for Blood-Brain Barrier Transcytosis?

TfR1 carriers remain the most efficient transcytosis mechanism to carry biologics into the CNS across the Blood-Brain Barrier (BBB)

- **TfR1 is highly expressed on endothelial cells at the BBB**
  - High expression of TfR1 on brain endothelial cells explains the distinctive CNS-trophism of TfR1 carriers
- **Favorable TfR1 receptor recycling**
  - TfR1 is recycled via clathrin-mediated endocytosis avoiding rapid lysosomal degradation, improving delivery efficiency and avoiding degradation of the therapeutic payload
- **Demonstrated broad and versatile payload compatibility**
  - TfR1 carriers can be fused to diverse therapeutic payloads, including proteins, antibodies, oligonucleotides, nucleic acids (DNA/RNA) and nanoparticles
  - **A TfR1 carrier was approved in Japan** for Hunter syndrome (MPS II) by JCR Pharma (IZCARGO, pabinafusp)
- **Availability of animal models (rat and mice) expressing human TfR1 for preclinical testing**
- **Well understood potential safety liabilities of TfR1 carriers**
  - Anemia and immunogenicity as major potential safety liabilities for TfR1 carriers, **but not for NewroBus!**

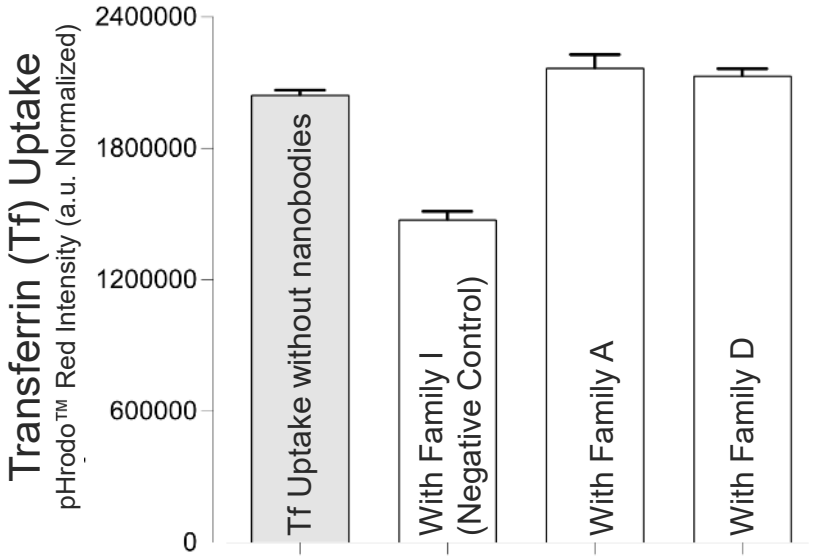
NewroBus™
Development Path of NewroBus — From Immunization to CNS Carrier



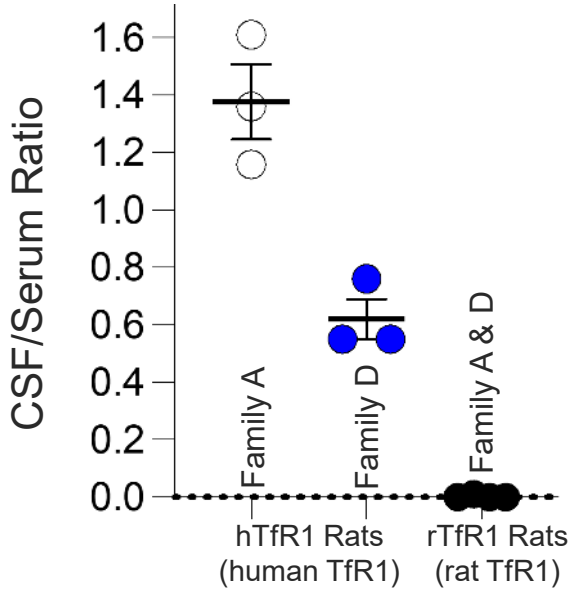
NewroBus™
Criteria to Select the Optimal NewroBus Carriers

- About 470 different nanobodies tested and divided in different “Families”
  - From Family “A” to Family “L” based on CDRs Sequence
- Four final NewroBus carriers were selected from Family A and D based on no interference with transferrin (Tf) uptake, high human specificity, and high BBB permeability

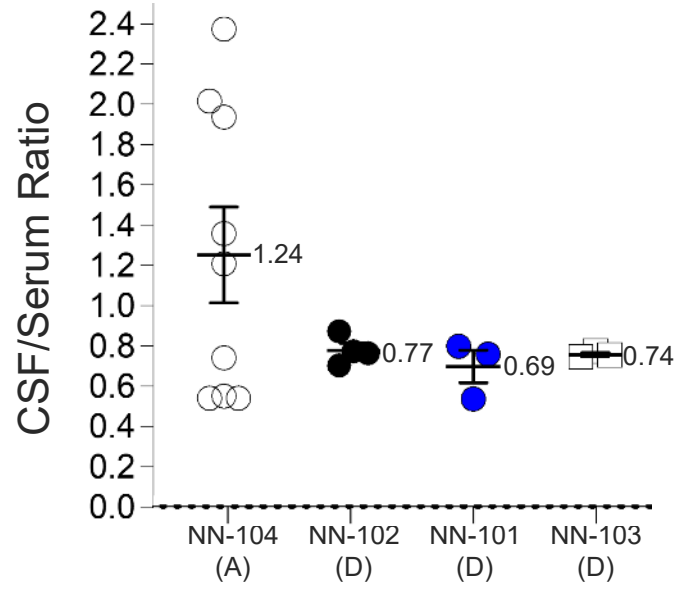
Family A and D showed no interference with Tf uptake



Family A and D crossed BBB only in rats with human TfR1



High BBB permeability of the four selected humanized NewroBus



(24 hour after SC administration of 0.4 mg/Kg)

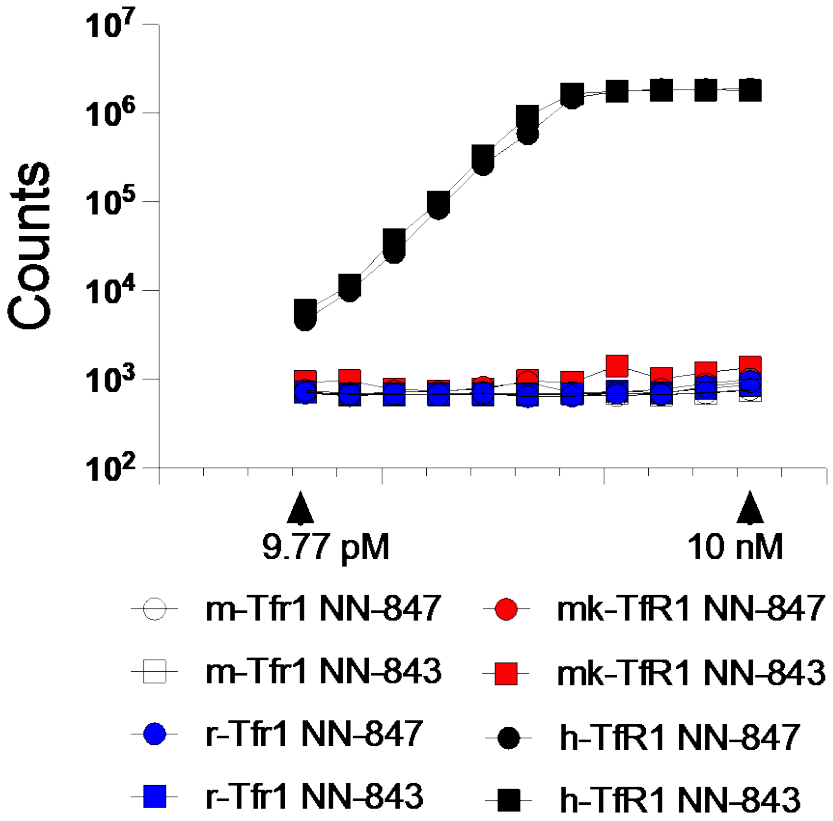
NewroBus Nanobodies Were Intentionally Selected to Be Human Specific

- To avoid interfering with TfR1's normal function, NewroBus doesn't bind to functionally important –and, therefore, more conserved– regions, like those involved in transferrin (Tf) binding and endocytosis regulation
- Species Differences in TfR1
  - Human vs. Monkey TfR1: ~80% identical
  - Human vs. Mouse/Rat TfR1: ~65–70% identical
  - The most conserved regions are where Tf binds — these are critical for Tf uptake and iron metabolism
  - The least conserved areas are surface-exposed loops not involved in TfR1 function
- NewroBus nanobodies screened to avoid the Tf-binding site to preserve iron metabolism and TfR1 recycling
  - No binding to rodent TfR1 and lower binding to monkey TfR1, due to divergence at the selected epitope
  - High specificity for human TfR1 without affecting Tf uptake and iron metabolism

The lack of cross-species binding is a beneficial, safety-driven feature that preserves TfR1 function and normal iron metabolism

NewroBus™
Strong Human TfR1 binding, Weak Monkey Binding, No Rodent Binding

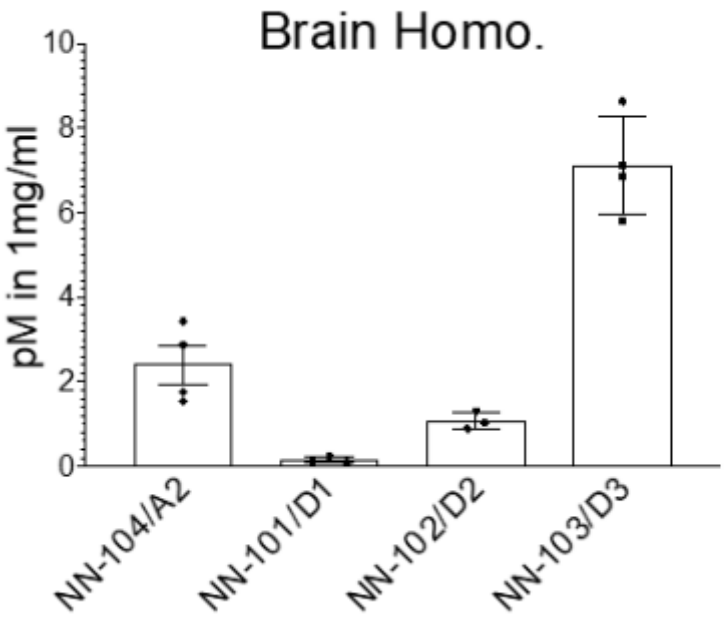
- Two TNFI constructs tested for TfR1 binding[1]:
  - NN-847 (Family D)
  - NN-843 (Family A)
- Tested concentrations ranged from 9.8 pM to 10 nM
  - Strong, dose-dependent binding to human hTfR1
  - No binding to monkey (mk), rat (r), or mouse (m) TfR1
  - Weak binding of monkey TfR1 observed at very high doses (>300 nM)

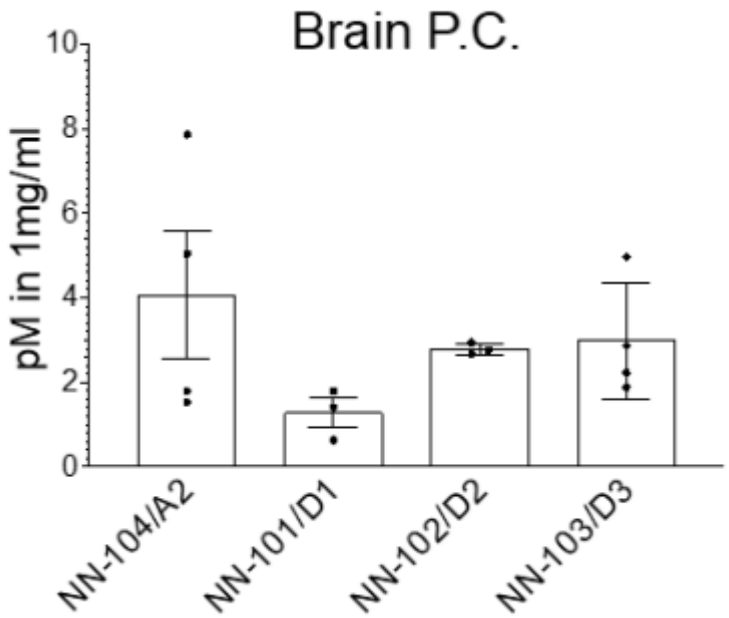


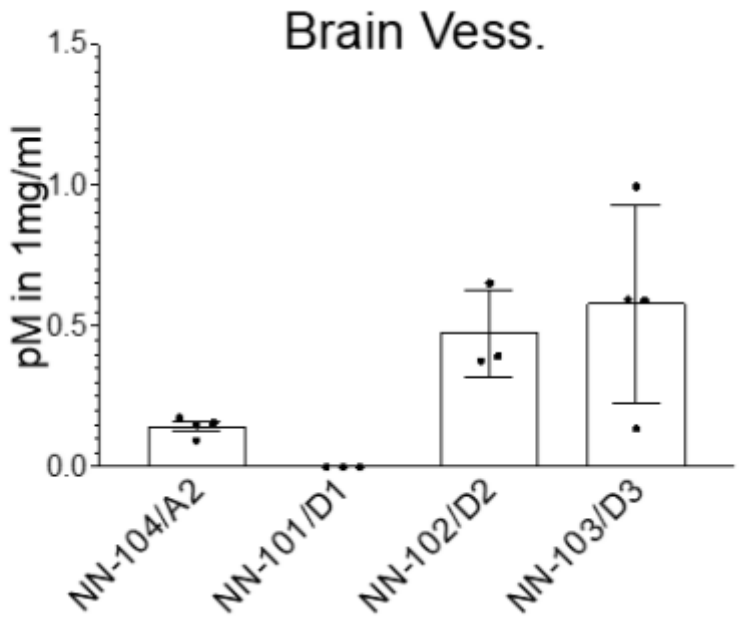
1) To assess species specificity, ELISA plates coated with human, monkey, mouse, or rat TfR1 were incubated with 2-fold serial dilutions of NN-843 or NN-847 across different concentration ranges.

NewroBus Levels in the Brain Parenchyma

- High NewroBus levels in brain homogenates (Homo.), parenchymal cells (P.C.) and vessels (Vess.) assessed using an established protocol[1]
  - Levels were assessed for the four different NewroBus compounds







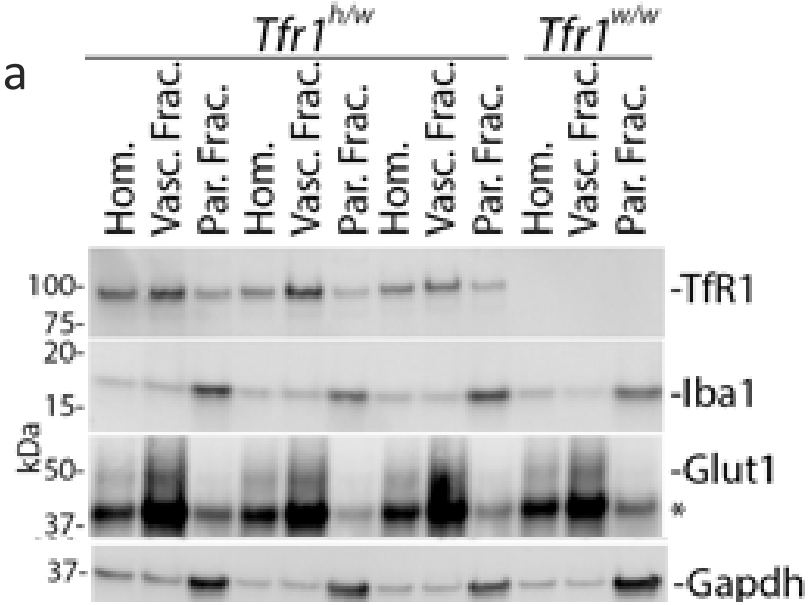
1) https://www.science.org/doi/10.1126/scitranslmed.aay1359

(24 hour after SC administration of 0.4 mg/Kg)

Method to Evaluate Parenchymal Distribution in the CNS

- Before CNS analysis, rats were perfused with PBS for ≥10 minutes, until the liver appeared blood-free, to remove circulating antibody
  - CSF was collected, serving as a reliable proxy for brain interstitial fluid (ISF) levels
- Brains homogenized and fractionated into vascular and parenchymal compartments following protocol used to evaluate BBB permeability of TfR1-based therapeutics[1]
- Validation of Brain Fractionation (Western Blot)
  - Western Blot confirms separation of CNS vasculature and parenchyma
  - Glut1 (endothelial marker) enriched in vasculature, depleted in parenchyma
  - Gapdh (general cellular marker) enriched in parenchyma
  - Parenchymal cell-type markers Iba1 detected

  Human TfR1 detected in all fractions, with strongest expression in vasculature—consistent with endothelial localization

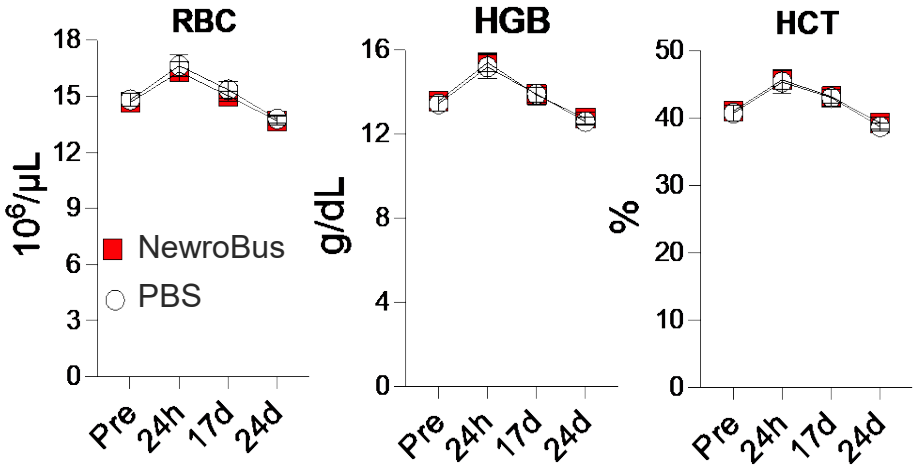


1) https://www.science.org/doi/10.1126/scitranslmed.aay1359

NewroBus™ Safety

No Hematologic Toxicity Observed with NewroBus

- **NewroBus is a safe TfR1 carrier** because of monovalent binding to TfR1, biologically inert
  - **No direct competition** with Tf that can block Tf binding
  - **No indirect (allosteric) competition** that can change the conformation of TfR1 hindering Tf binding
  - **No interference with cellular Tf uptake**, indicating that NewroBus does not induce Tf-independent endocytosis of TfR1 that could reduce physiological Tf transport
- NewroBus "hitchhikes" TfR1 **ONLY** when bound to an active TfR1/Tf complex
  - TfR1 transcytosis is triggered by Tf binding, not NewroBus binding
  - NewroBus preserves iron metabolism and homeostasis
- **No anemia observed with NewroBus**
  - Tested in rats with humanized TfR1 and Tf complex
  - No hematologic or gross toxicity observed for 24 days
  - 6 IV administration of 0.4 mg/kg every 4 days



NewroBus™ Safety

Low Immunogenicity Potential of NewroBus

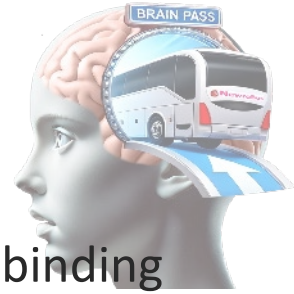
- **Immunogenicity potential of NewroBus lower than trastuzumab (Herceptin®)**
  - Trastuzumab is the current standard as a low-immunogenicity control for in-vitro testing[1]

- Comprehensive in-vitro/in-silico immunogenicity testing of NewroBus
  - **Donor Cohort:** 15 HLA-typed human donors representing global MHC class II diversity
  - **MAPPs (LC-MS/MS) assay:** Monocyte-derived dendritic cells from each donor were incubated with NewroBus constructs, and naturally processed peptides bound to MHC class II were isolated from the cell surface and identified by mass spectrometry
  - **iTope-AI assay:** *in-silico* prediction of peptide binding across 46 representative human MHC class II alleles
  - **TCEM assay:** Functional assay using dendritic cells and matched $CD4^+$ T cells from the same donors. Synthetic peptides identified by MAPPs were tested for T cell activation via IL-2 and IFNγ release.

	% Donors with Positive Response (Positive response: SI ≥ 2)	Mean SI (Stimulation Index) (Lower SI, lower Immunogenicity)
NN-101 (NewroBus D Family)	4/15 (26.7%) – all weak responses	2.60
NN-104 (NewroBus A Family)	2/15 (13.3%) – all weak responses	2.67
Trastuzumab (Herceptin®)	5/15 (33.3%) – moderate responses	3.31

1) Di Ianni A et al (2023) Assessing MAPPs assay as a tool to predict the immunogenicity potential of protein therapeutics. *LSA* 7(1), e202302095

NewroBus is a Best-in-Class TfR1 Brain Carrier

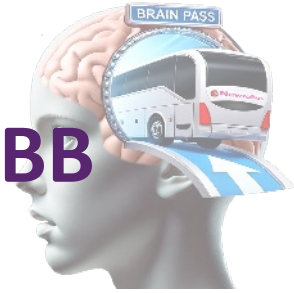


- **Why using nanobodies for NewroBus?**
  - Small (~13 kDa), highly specific, single-domain with optimal solubility, stability, and high-affinity binding
  - Lack of glycosylation makes efficient manufacturing with high-yield production in cell expression systems

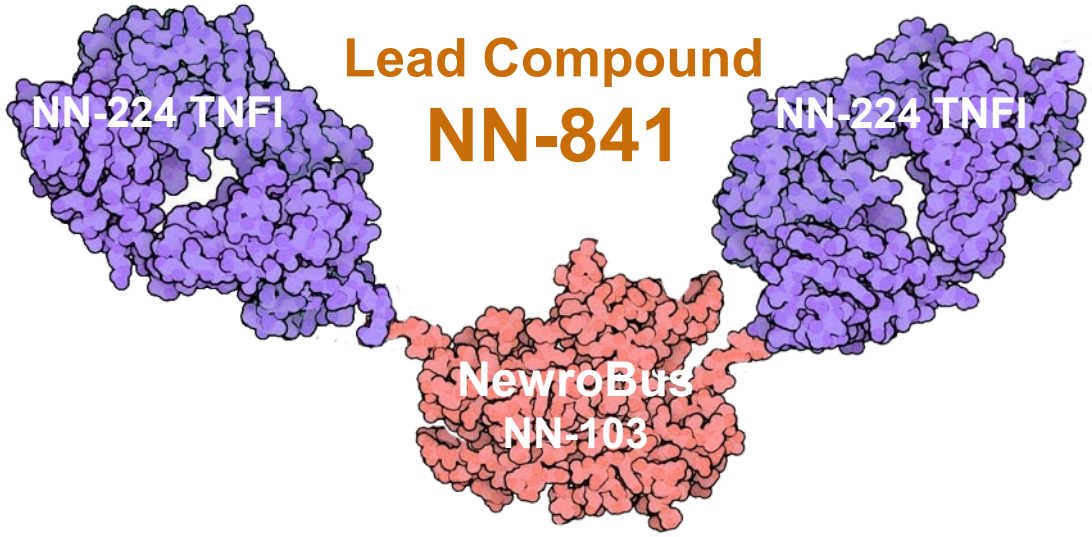
- **NewroBus engineered for transcytosis efficiency, safety, immunogenicity, and modularity**
  - High BBB permeability, with CSF/serum ratio higher than 0.7, after subcutaneous administration
  - Monovalent binding prevents engagement of both chains of TfR1 avoiding Tf-independent endocytosis.
  - Targeting a Tf-non-competing epitope allows normal Tf binding and uptake
  - Engineered to be human specific to avoid binding to functionally important –and, therefore, more conserved– epitopes interfering with normal function of TfR1, Tf and endocytosis process
  - No evidence of anemia after multiple doses in animals
  - Fully humanized to minimize immunogenicity, using AI-guided mutagenesis
  - Low immunogenicity shown with MAPPs, iTope-AI prediction, and $CD4^+$ T cell activation assays
    - Lower immunogenicity than trastuzumab (Herceptin®), the current standard as a low-immunogenicity control
  - Detectable plasma and CSF levels up to 72 hours with subcutaneous administration
    - Potential for using depot-formulations for subcutaneous injections to extend exposure
  - Well established processes to link NewroBus to protein, antibodies, oligonucleotides or other biologics

Lead Compound in Alzheimer Disease (NN-841)

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



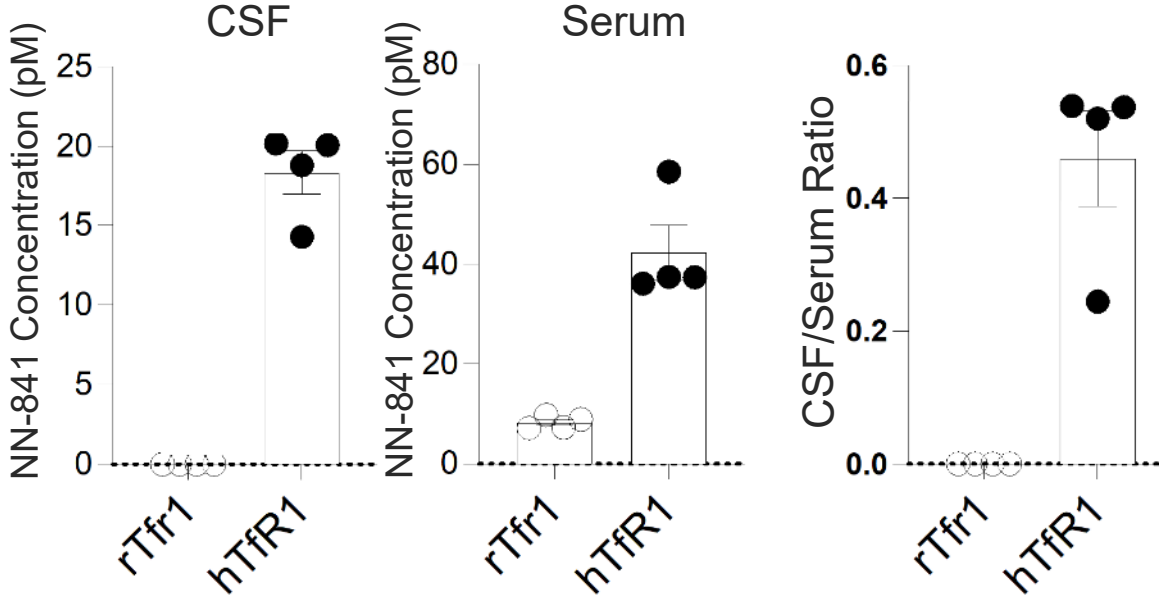
- **Lead compound NN-841 for the treatment of Alzheimer's Disease**
  - NewroBus NN-103 linked to two molecules of **proprietary TNF-α inhibitor (TNFI) NN-224**
  - Biological activity tested in rats with humanized TfR1, Tf, and TNF-α
  - NN-841 crosses the BBB via TfR1 in rats **after S.C. administration**
  - **High inhibition of TNF-α**
  - Excellent **CSF/Serum ratio (~1:2)**
  - Broad distribution in the brain tissue
  - High specificity to human TfR1
  - NN-841 does not cause hematotoxicity
  - Low immunogenicity potential



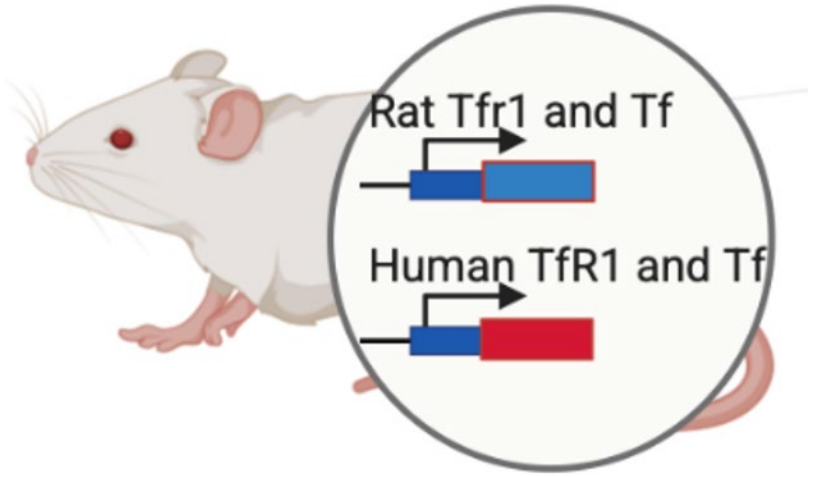
Lead Compound in Alzheimer Disease (NN-841)

Heterotrimer NN-841 Efficiently Crosses the BBB

- **High BBB Permeability of NN-841 in rats after subcutaneous administration**
  - CSF/Serum ratio ranging from 0.24 to 0.53 (average 0.46)
    Compare, for example, to the CSF/Serum ratio of small molecules like SSRI (~0.2) or benzodiazepines (~0.1)



(24 hour after SC administration of 0.6 mg/Kg)



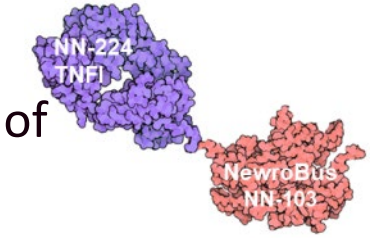
hTfR1: Rats with humanized TfR1 and Tf
rTfR1: Rats with rat TfR1 and Tf

Lead Compound in Alzheimer Disease (NN-841)

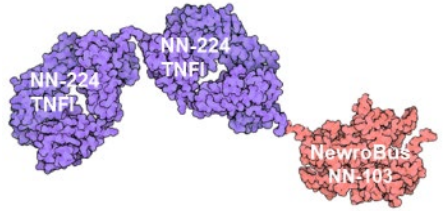
Why Heterotrimers and not Heterodimers?

- **… because arrangement matters!**
  - We tested many arrangements

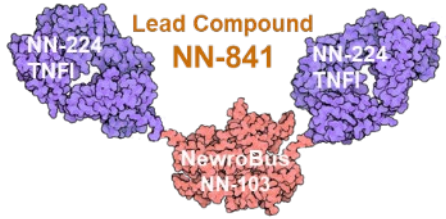
- **Heterodimers**
  - NewroBus linked to one molecule of TNFI (TNF-α inhibitor)



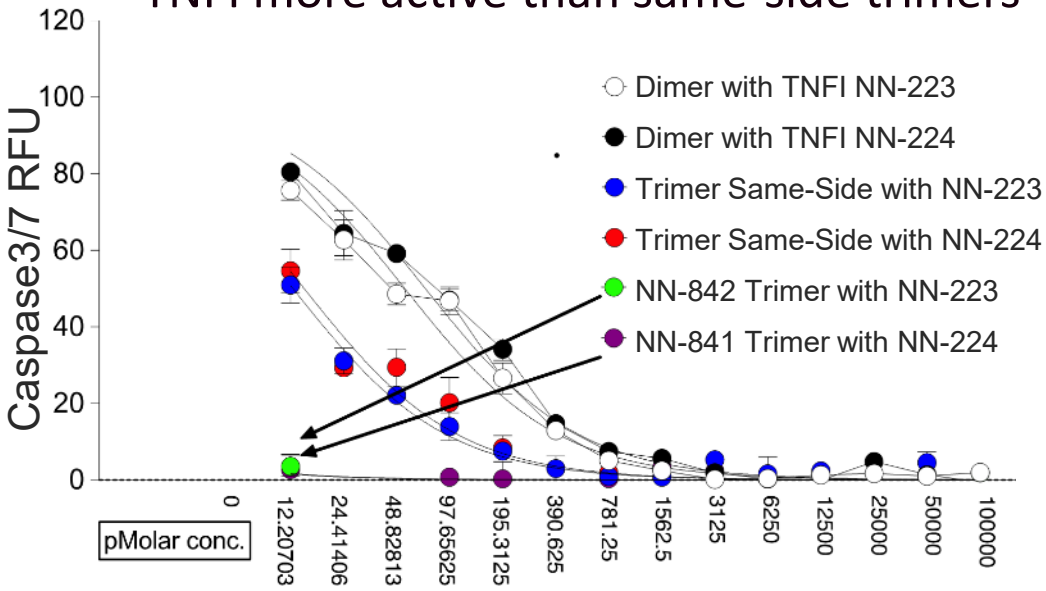
- **Heterotrimers Same-Side Linked**
  - NewroBus linked to two molecules of TNFI on one side



- **Heterotrimers Side Linked**
  - NewroBus linked between two molecules of TNFI



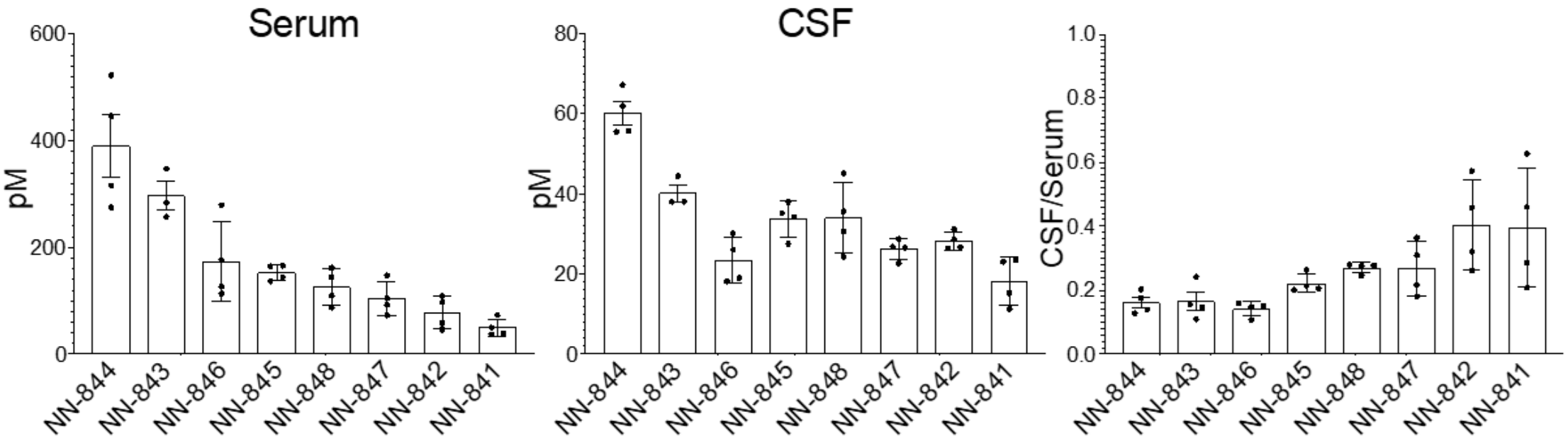
- Trimers more active than dimers
  - Trimers Achieve maximum TNF-α inhibition at lower concentrations than dimers
- Trimers with NewroBus linked between TNFI more active than same-side trimers



Lead Compound in Alzheimer Disease (NN-841)

All TNFI Heterotrimers Showed Excellent BBB Permeability

- The patented 840-series of TNFI Heterotrimers includes eight different compounds
  - Four NewroBus molecules and two TNFI allowed eight possible combinations
  - All compounds of series 840 showed excellent permeability with NN-841 showing one the highest CSF/Serum ratio

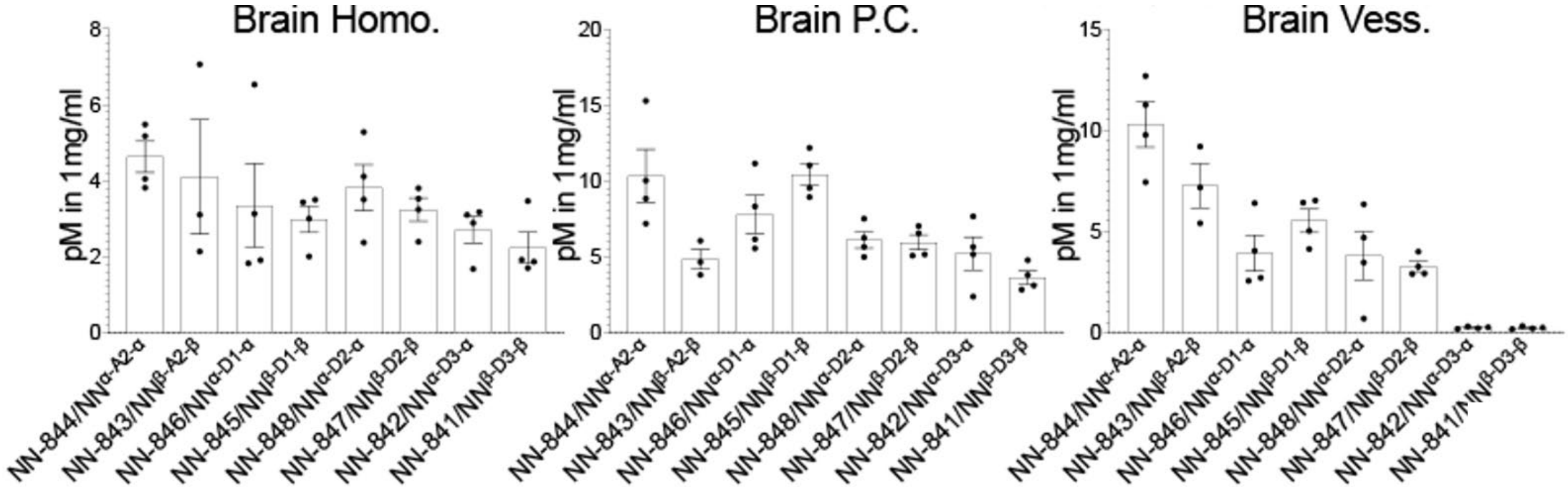


(24 hour after SC administration of 0.6 mg/Kg)

Lead Compound in Alzheimer Disease (NN-841)

Penetration of TNFI Heterotrimers in Brain Tissues

Levels in brain homogenates (Homo.), parenchymal cells (P.C.) and vessels (Vess.) assessed using well established protocols[1]



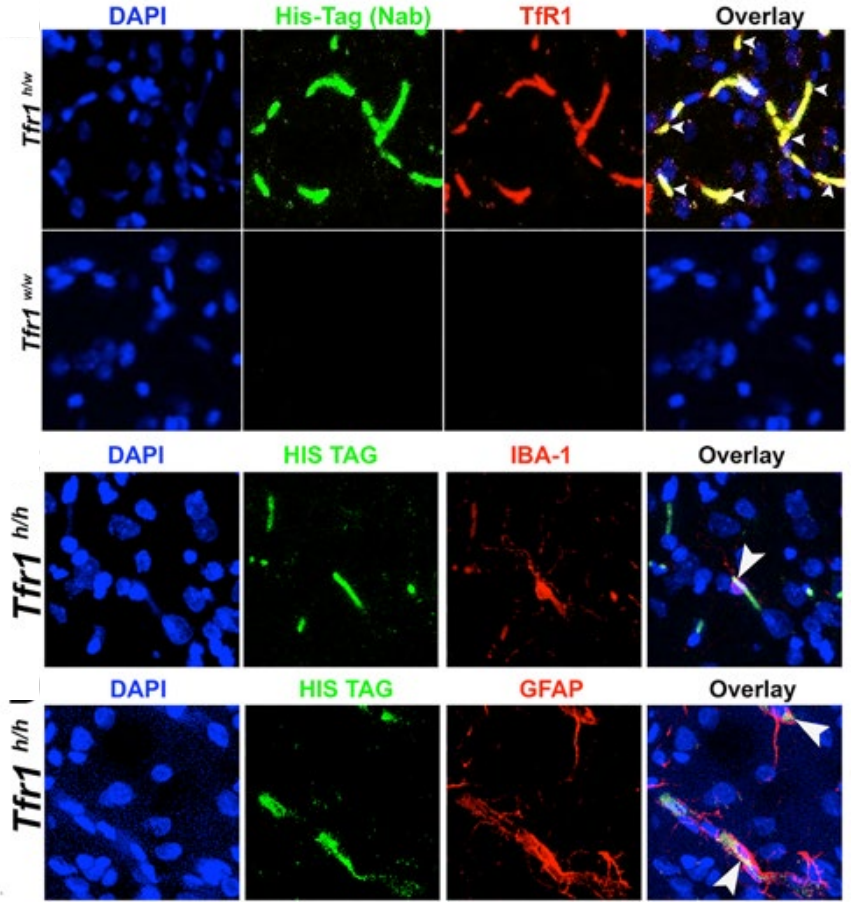
1) https://www.science.org/doi/10.1126/scitranslmed.aay1359

(24 hour after SC administration of 0.6 mg/Kg)

Lead Compound in Alzheimer Disease (NN-841)

Immunostaining Confirms Parenchymal Distribution of NN-841

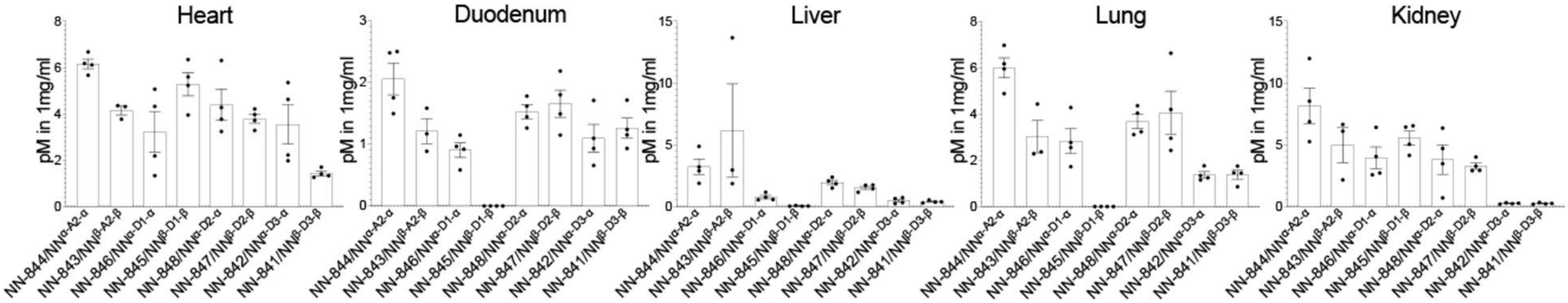
- NN-841 crossed BBB via hTfR1 but not wild-type TfR1
  - Anti-His tag staining confirmed NN-841 presence in Tfr1h/w brains, but not in Tfr1w/w controls
  - Reaches CSF/ISF and accumulates in parenchymal cells



- Colocalization observed with:
  - Human TfR1 (vessels)
  - IBA1 (microglia)
  - GFAP (astrocytes)

Lead Compound in Alzheimer Disease (NN-841)

Penetration of TNFI Heterotrimers in Other Body Tissues

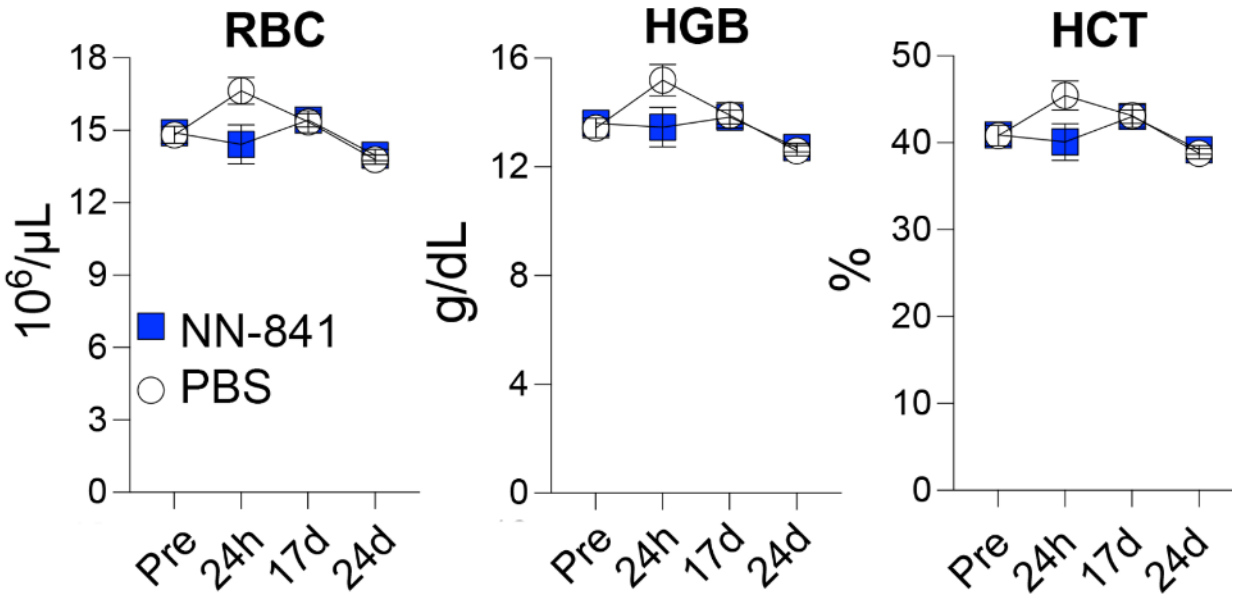


(24 hour after SC administration of 0.6 mg/Kg)

Lead Compound in Alzheimer Disease (NN-841)

No Safety Issues Observed with NN-841

- **No hematologic toxicity** observed in rats with humanized TfR1 and Tf complex
  - No gross toxicity observed for 24 days
  - 6 IV administration of 0.6 mg/kg every 4 days
  - Assessment on Day 1, 17 and 24



- **Low immunogenicity** detected in *ex-vivo* test

Two Groups of NanoNewron's Competitors

1. **TNF-α inhibitors** in development for Alzheimer's
   - They may provide additional evidence of TNF-α role in Alzheimer's
   - **InMune Bio** (Nasdaq INMB)
     - XPro1595 (pegipanermin)

2. **Brain Barrier Carrier** (but not against TNF-α) in development
   - Brain Carriers are a high-interest area of development
   - **Early preclinical products licensed for $100+M upfront, milestones and royalties**
   - **Denali** (Nasdaq DNLI)/**Takeda**
     - DNL919
   - **BioArctic** (Nasdaq Stockholm BIOA-B.ST)/**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

- **Weakness:** Reported modest penetration across the BBB in rats[4]
  - In rats, ratio of CSF levels (1 to 6 **ng/mL**) vs plasma levels (1 to 8 **µg/mL**) is **about 1:1,000,** with potential risk of off-target effects
  - Several positive animal models but administered doses are apparently 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
4) Barnum CJ et al (2014): Peripheral administration of the selective inhibitor of soluble tumor necrosis factor (TNF) XPro®1595. *J Parkinsons Dis.* 4(3):349-60

Competition — TfR1 BBB Carriers in CNS

TfR1 Constructs in Development

- TfR1 carriers remain the most used and effective BBB transcytosis mechanism
- TfR1 constructs fail clinically because of the wrong target, not brain permeability

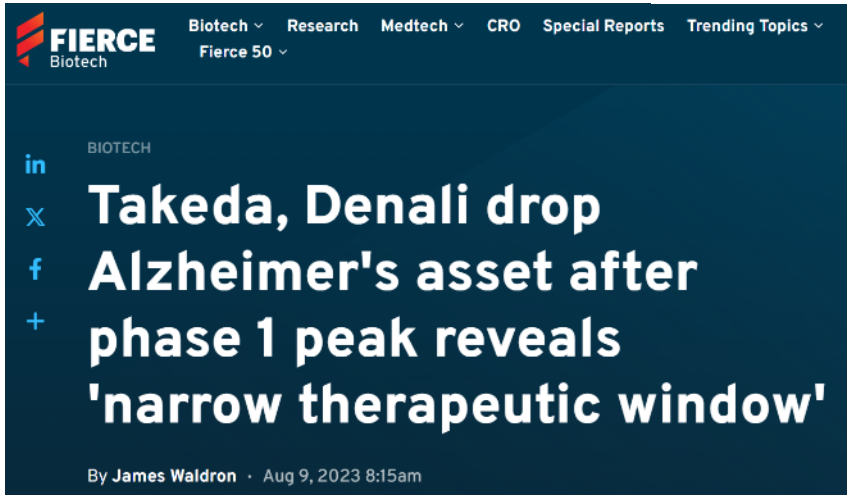
Company	Product	Payload	Target	Indication	Status
Roche	Gantenerumab	Antibody	Amyloid	Alzheimer	Failed
Eli Lilly	TfR-siRNA	siRNA	Tau	Alzheimer	Preclinical
Denali	DNL-919	Antibody	TREM2	Alzheimer	Failed
Bioarctic	BAN-1503	Antibody	Amyloid	Alzheimer	Pre-clinical
Denali	OTV-Tau	ASO	MAPT/Tau	Alzheimer	Pre-clinical
Denali	OTV-SNCA	ASO	α-Synuclein	Parkinson	Pre-clinical
Denali	DNL-593	Enzyme	Progranulin	FT Dementia	Phase 1b
Denali	DNL-310	Enzyme	IDS	MPS II	Phase 1b
Denali	DNL-126	Enzyme	SGSH	MPS IIIA	Phase 1b

Competition — TfR1 BBB Carriers in Alzheimer's

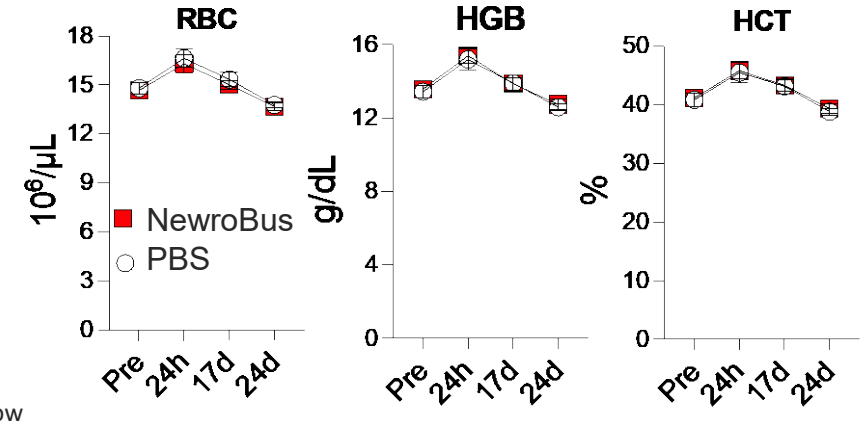
DNL919/TAK-920 by Denali (DNLI)/Takeda

- 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, anti-amyloid 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 for pre-clinical assets!**
  - $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

Effective and safe brain carriers, like NewroBus, can command highly valued transactions at an early stage of development

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

TfR1 Carriers vs. Other Types of Brain Carriers

- **TfR1 Carriers are the most established blood-brain barrier carriers**
  - Extensive experience and knowledge in exploiting TfR1-mediated transcytosis
  - **One approved TfR1 carrier** in Japan for Hunter syndrome (MPS II) by JCR Pharma (IZCARGO, pabinafusp alfa)
- Lipid Transporters for brain tumors
  - **LRP1** — Experience is mostly focused on carry oncologic drug (e.g. paclitaxel) with concerns about the widespread expression and essential functions in many tissues, including liver, kidney and lungs, not just the BBB
- Receptors for Insulin and Insulin-Like growth factors
  - **IR** — Since insulin receptors are also present in peripheral tissues, there is a risk of off-target effects, necessitating strategies to enhance CNS specificity
  - **IGFR1** — Because of the ubiquitous expression and mitogenic role of IGF1R in many peripheral tissues (e.g., liver, muscle, endothelium, tumors), there are concerns about interference with cell growth, survival, and metabolism
- Solute carrier transporters
  - **GLUT1** — Given the high metabolic need of glucose by the brain, GLUT1 is extremely highly expressed in the brain endothelial cells but its use as brain carrier may disrupt glucose uptake and brain function
  - **CD98hc** — An amino acid transporter is expressed in many peripheral tissues beyond brain, including kidney, intestine, immune cells, and tumors. It plays a critical role in amino acid transport and integrin signaling
- Other receptors
  - Other receptors are being investigated as potential brain carrier, including **Leptin**, **ITM2** and **FcRn**

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
  - More than $26M in NIH grants since 2004
  - 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 a favorable exit**

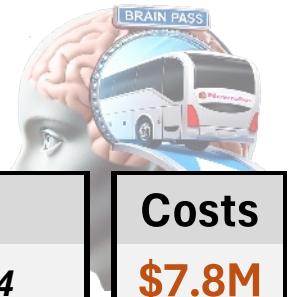
2) License NewroBus™ Technology to other companies
   - **Four different NewroBus molecules currently available for licensing**
   - Potential life-cycle management of commercial products
   - Enhancing brain penetration of other novel biologics
   - Potential for other therapeutic areas and combination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

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

- **All activities were supported with several NIH Grants totaling $5.7M**

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



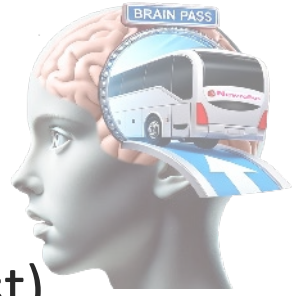
Workflow Activities	2025									2026												Costs
	Q2			Q3			Q4			Q1			Q2			Q3			Q4			$7.8M
	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	
1. CMC/Manufacturing Scale-Up																						**$1.75M**
PCB Selection and Generation																						$450K
Method Qualification and Validation, and Formulation																						$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					Five Different Models in Humanized Rats																	$550K
Neuropathology and synaptic activity studies					*in-vitro* 2D neurons/microglia cultures																	$450K
Human CNS organoids models							in vitro 3D human organoids															$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						Pre-IND								IND Preparation					IND			$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

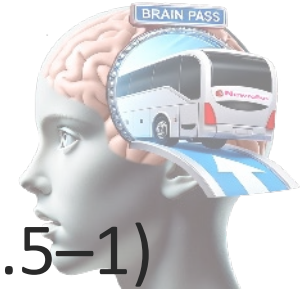
- 50-Liter productions expected to yield 500 g to 1,000 g of NN-841
  - 50-Liter Non-GMP in September 2025 for preclinical models and initial IND-enabling tox
  - 50-Liter GMP in November 2025 to complete IND-enabling tox and Phase 1

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

Clinical Phase 1/1b



- Target Population: Early-stage Alzheimer's Disease (MMSE ≥22; CDR 0.5–1)
- Biomarkers to Predict Response & Track Progression
  - Blood:
    - Cytokine: TNFα, IL-6, IL-8, GFAP
    - Neurodegeneration: p-Tau217, NfL
    - Composite: PrecivityAD2™ score (C2N Diagnostics)

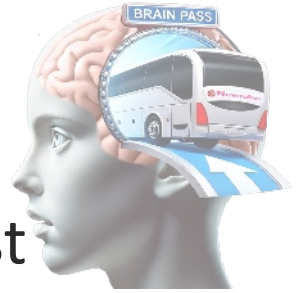
  CSF:
    - Cytokine: TNFα, CCL2, YKL-40, sTREM2
    - Core AD: Amyloid/Tau Index (ATI), MTBR-tau243
    - Disease progression: YWHAG:NPTX2 ratio

  - MRI white matter free water, a validated biomarker for neuroinflammation
  - Markers of cortical hyperexcitability (abnormal resting-state EEG, or task-based fMRI)
- Cognitive & Functional Assessments:
  - Inclusion Criteria: MMSE, CDR
  - Cognitive Testing: Logical Memory (WMS), RBANS
  - Primary Outcomes: iARDS, CDR-SB
  - Secondary Outcomes: NPI-Q for neuropsychiatric symptoms

Financing and Expenses

- **Past financing for work performed to date** **$5,700K**
  - Dr. D'Adamio's NIH Grants at Rutgers: $ 5,200K
  - NanoNewron's STTR Phase 1 NIH Grant (2023): $500K
- **Currently pursued financing** **$7,800K**
  - NanoNewron's STTR Phase 2 NIH Grant (expected) $2,500K (Intent-to-Fund received)
  - Financing (Investors, NJ Evergreen and/or partners) $5,300K
- **Use of proceeds and potential exit points**
  - $7.8M for activities to file IND in 4Q2026
    - Proceeds used for CMC, mechanistic Studies, IND-enabling tox and G&A
  - First possible exit point is IND filing in 4Q2026
    - Based on recent transactions in the sector with $100+M upfront, plus milestones and royalties
  - Second possible exit point is end of Phase 1/1B (additional financing of $12M-15M)

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.

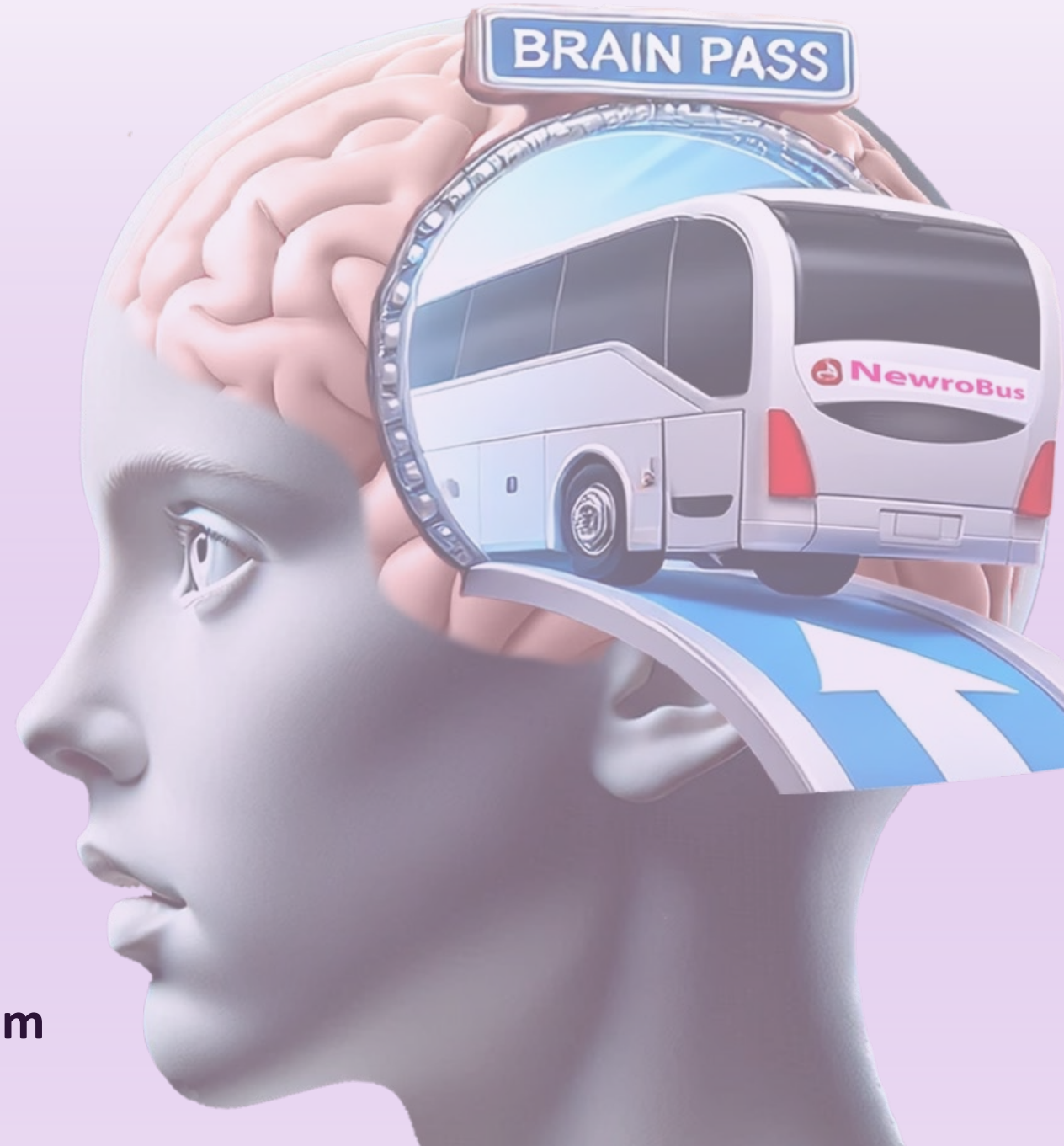
Five Key Takeaways/Conclusions

- Versatile, patented technology (NewroBus™) to carry biologics across the Blood-Brain Barrier (BBB) via TfR1, and available for licensing to companies with biologics requiring to cross the BBB
- Lead product (NN-841), based on NewroBus technology and developed in house, to treat Alzheimer's by reducing TNF-α induced neuroinflammation, with IND filing expected in 4Q2026
- Experienced scientific, clinical, regulatory and business team with successful track record in developing and licensing pharmaceuticals
- Brain carriers and Alzheimer's products, like NewroBus and NN-841, are currently commanding highly valued transactions, even at preclinical stage, allowing early, favorable strategic exits
- NanoNewron is looking for $7.8M (partially covered by an expected $2.5M NIH STTR grant), either as an investment transaction or a strategic partnership, to cover costs up to IND filing

NanoNewron™

New Treatments for CNS Diseases

Thank you!



For inquiries please contact:

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