GliaCure, Inc.

Overview Presentation

Current Status of GliaCure & GC021109

- **Open IND, fast track designation granted** by FDA
- **Safe and well tolerated** in Phase 1 clinical trials
  - Phase 1a SAD trial in healthy volunteers completed
  - Phase 1b MAD trial in Alzheimer's patients completed
- Anti-inflammatory platform may enable **lower threshold for proof of concept** in patients relative to Alzheimer's disease (shorter trial duration, lower cost, objective end-points); e.g. psoriasis (IL-17) and asthma (IL-13)
- Efficient path to proof of concept for **oral standard of care in asthma**
- Easily synthesized, stable, and **exhibits excellent drug characteristics**

- Strong IP, with composition of matter and method of treatment coverage through at least 2032
- $8.5M raised to date from angels

Leadership with Deep Expertise in Neuroscience

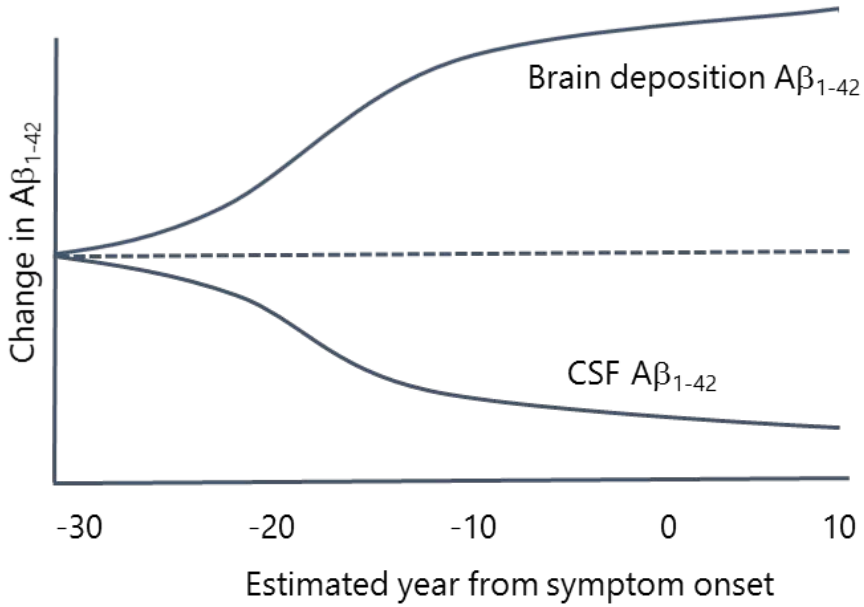
Philip Haydon, PhD, Co-founder

- Phil Haydon is the Annetta and Gustav Grisard Professor and Chair in the Department of Neuroscience at Tufts

Neuroscience Expertise

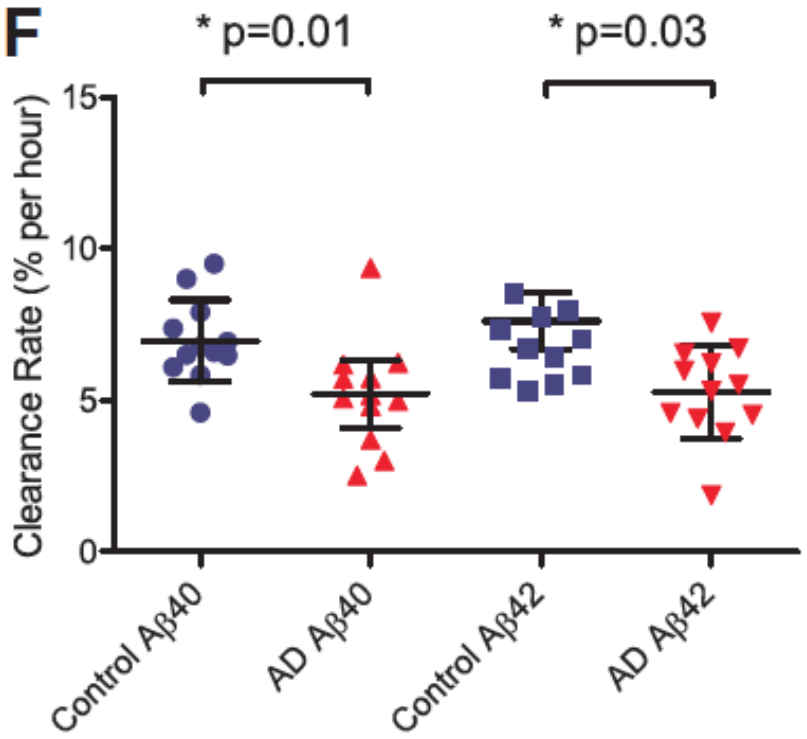
- Recently, Dr. Haydon's work has focused on microglia and emphasized identification of the mechanisms regulating phagocytosis by this subtype of glial cell. He pioneered the discovery of the importance of reactivation of the microglial phagocytotic pathway that normally declines in Alzheimer's disease.
- In 1994, Dr. Haydon's laboratory discovered that astrocytes can release the chemical transmitter glutamate in response to receptor-induced Ca2+ elevations, and that this glial-mediated signal can activate neighboring neurons. In 1999, he coined the expression "the tripartite synapse" to recognize the important role that astrocytes play in tuning and modulating synaptic transmission.
- In addition to his academic background Dr. Haydon has significant experience in commercial enterprises. He was a founding partner in three small businesses, including Prairie Technologies, which resulted from his need for new imaging technology to optimize neuroscience research.
- Previously, Phil had academic positions at the University of Iowa, Iowa State University, and the University of Pennsylvania School of Medicine.

Decades before symptom onset, Aβ accumulates in the brain and declines in the cerebrospinal fluid



GliaCure

Clearance of Aβ From the CNS Declines in Alzheimer's Disease: How is Clearance Regulated?

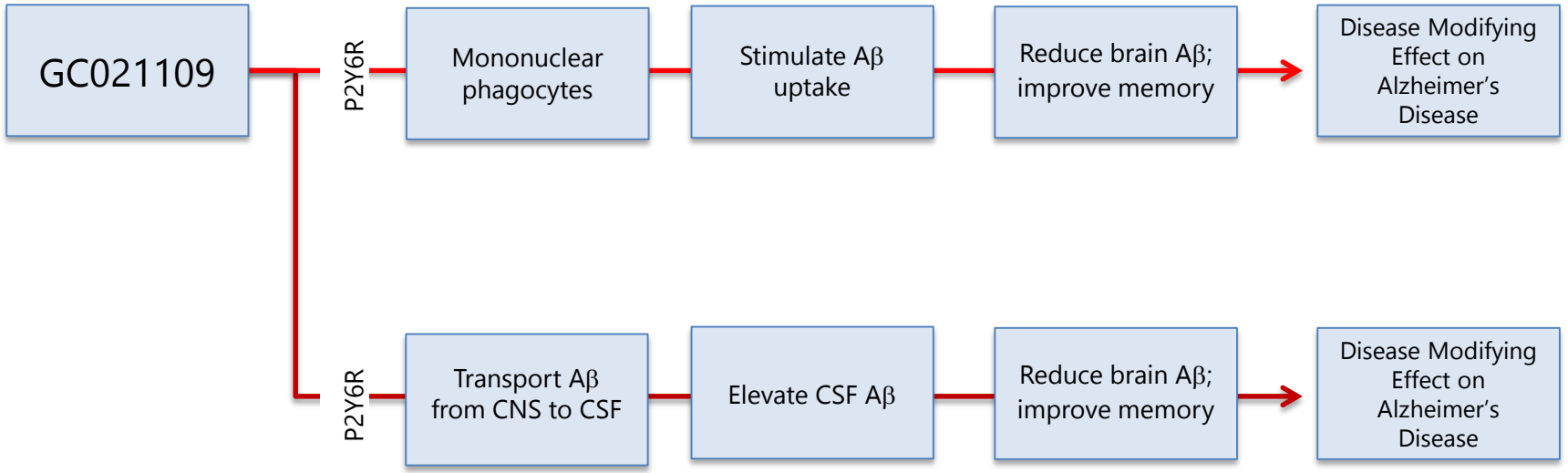


Mawuenyega et al., Decreased clearance of CNS amyloid-β in Alzheimer's disease. Science 2010

- It is known that there is reduced clearance of Aβ from the CNS in Alzheimer's disease (left)
- We propose that reduced clearance presumably results from
  - Reduced microglial clearance
  - reduced export to, and results in, reduced Aβ concentration in the CSF

GliaCure

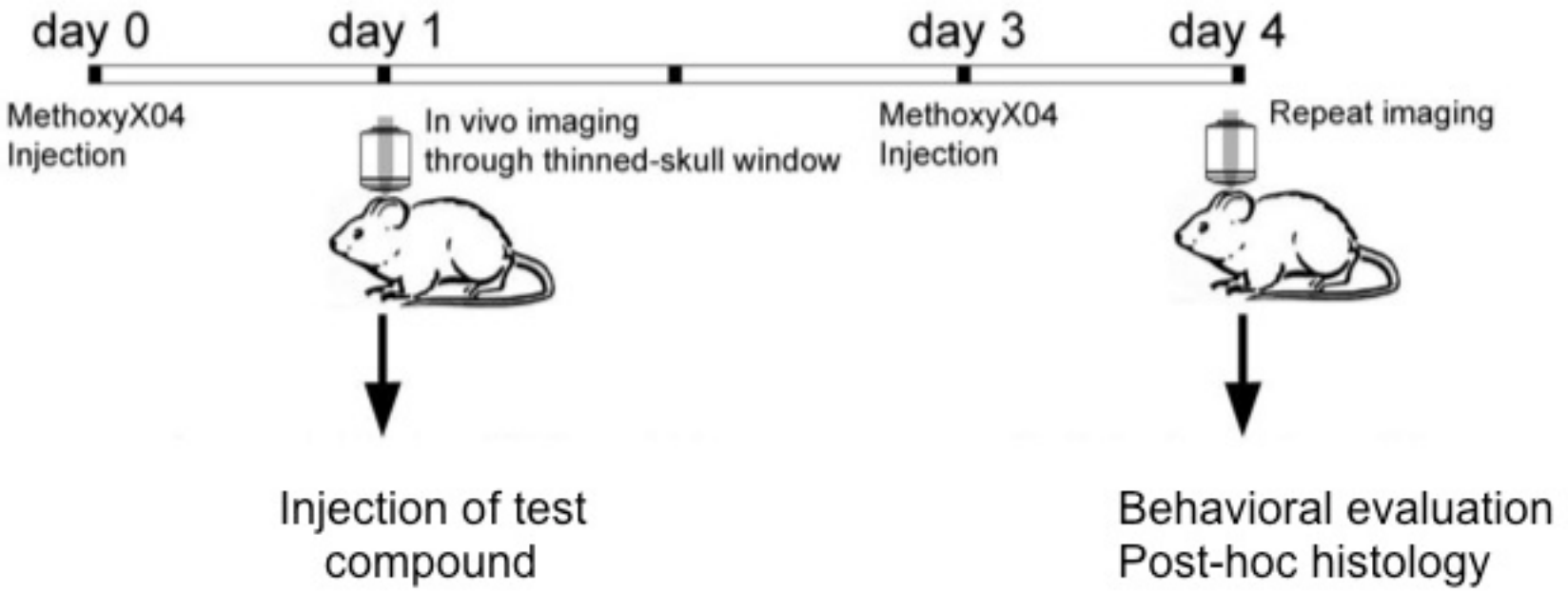
GC021109, our clinical compound, acts through the P2Y6 receptor to stimulate amyloid clearance



GliaCure

Linking UDP to Amyloid β Reduction

Experimental Design to Determine Whether UDP, the Endogenous P2Y6 Receptor Agonist, Reduces Amyloid β in Alzheimer's Mouse Model

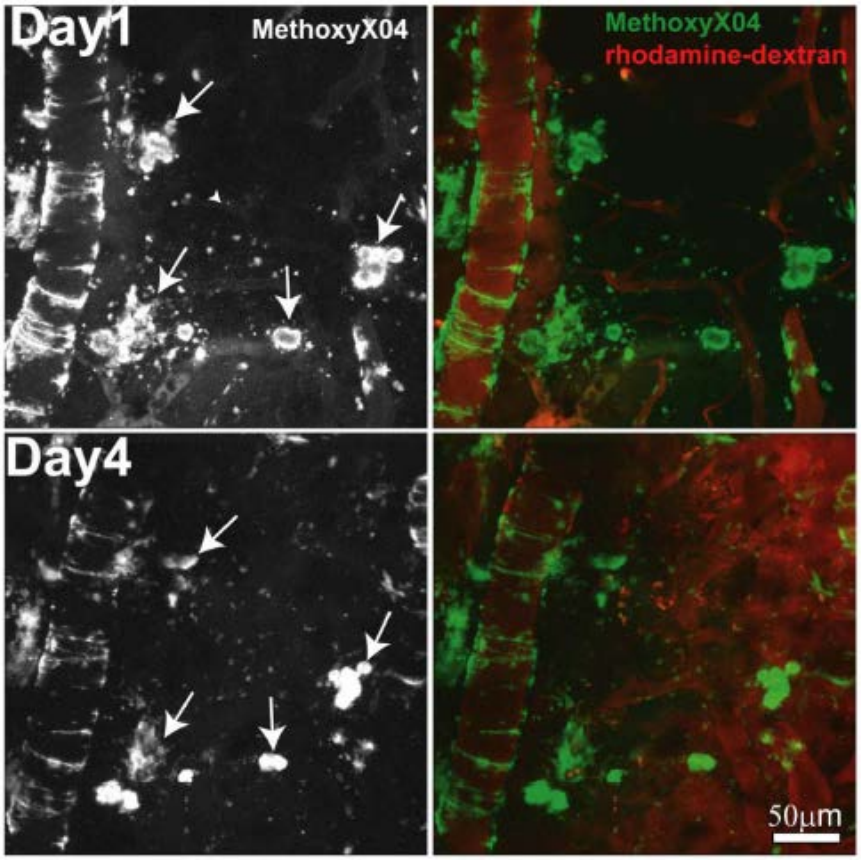


All studies were performed using 6-month-old PS1APP mice

GliaCure

Treatment with UDP Leads to Reduced Amyloid Plaques

Longitudinal Study of Plaques Using 2 Photon Microscopy Between Days 1 and 4



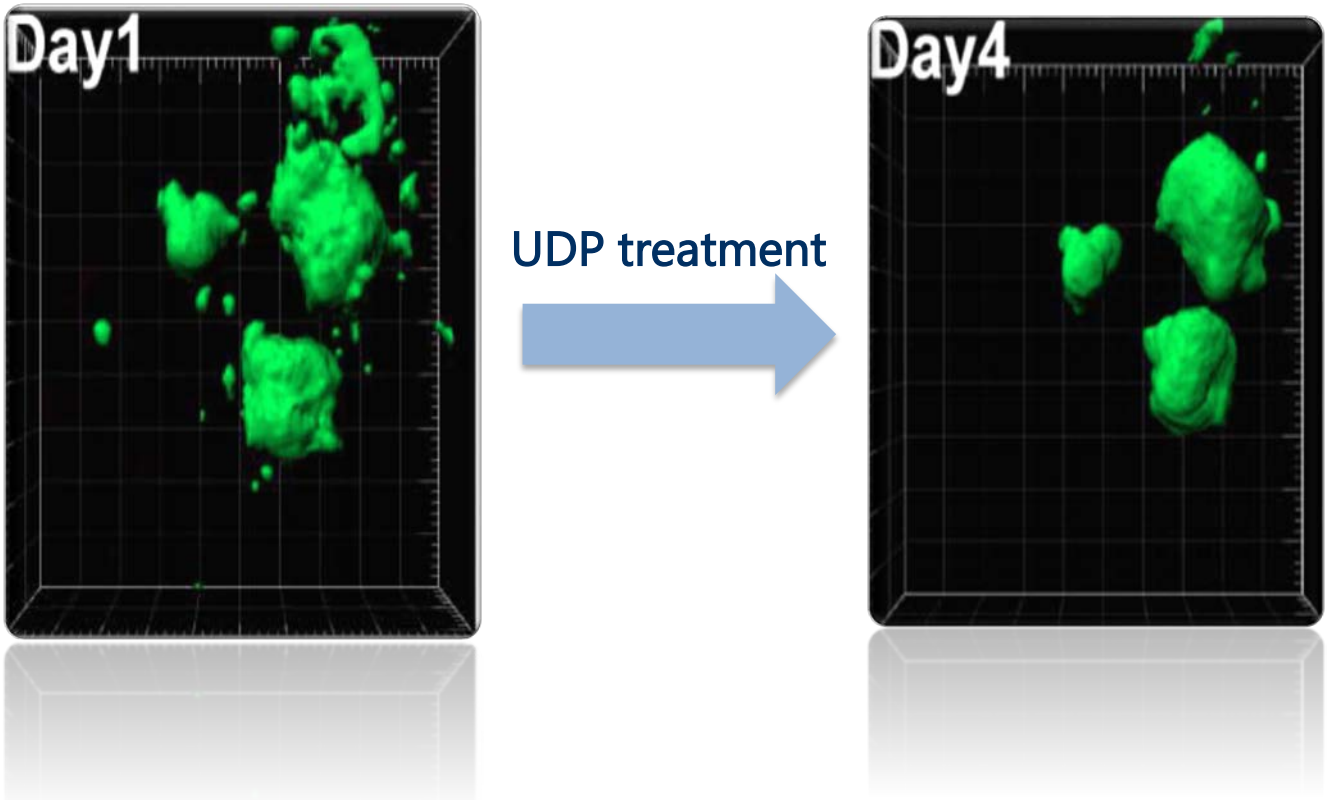
= vasculature

= amyloid

GliaCure

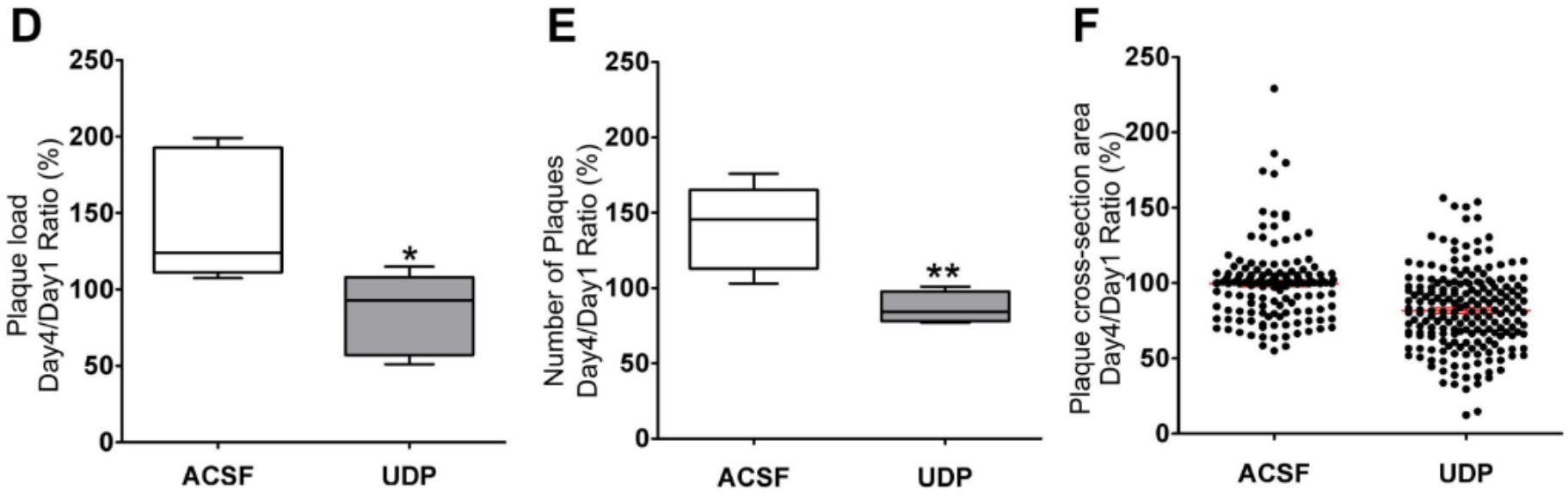
P2Y6 Receptor Agonist Reverses CNS Deposition of Amyloid

Longitudinal 2 Photon Imaging in a Mouse Model of Alzheimer's Disease



GliaCure

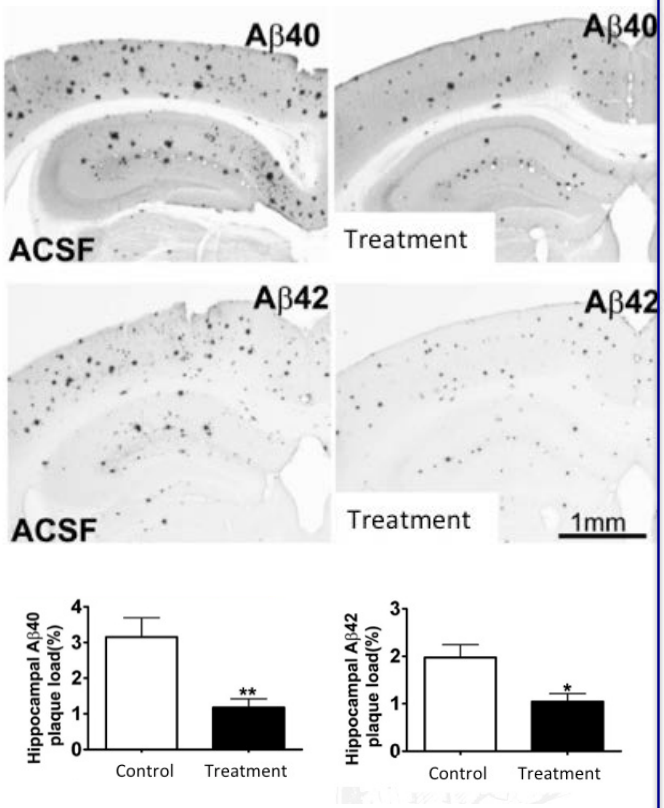
UDP Significantly Reduces Plaque Burden in Live Mice



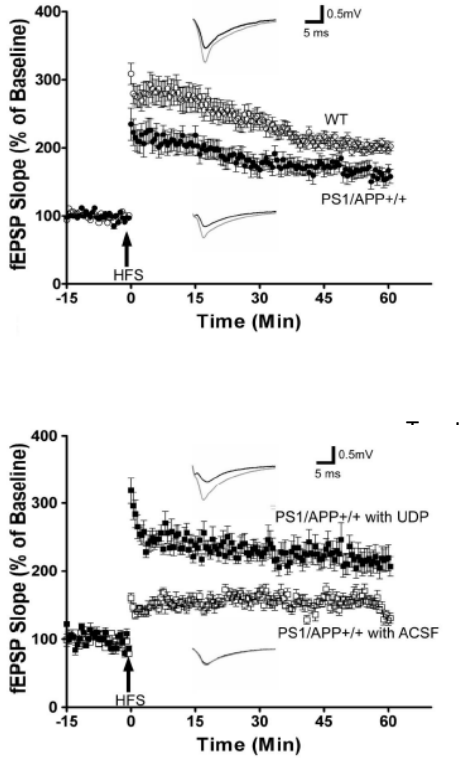
GliaCure

Reversal of Deficits in PSAPP Mice Following Treatment with P2Y6 Receptor Agonists for 3-7 Days

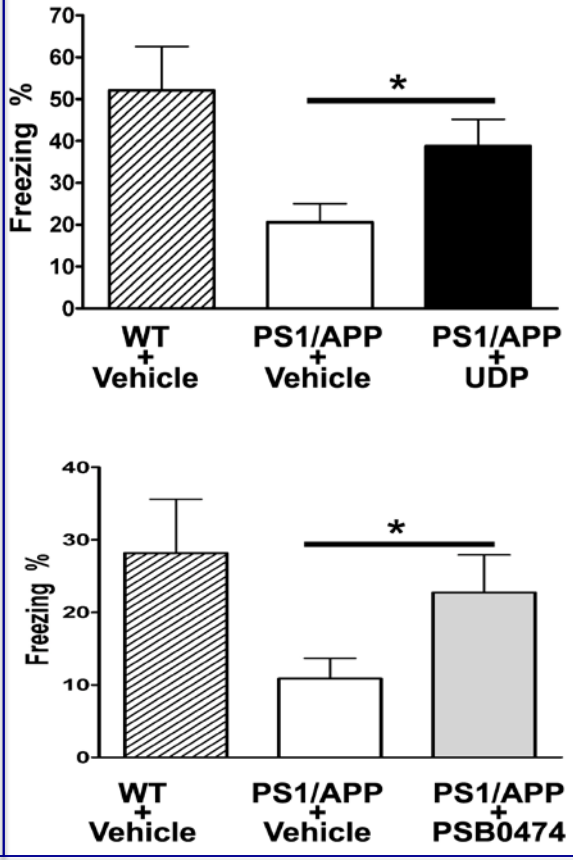
A) i.c.v administration UDP leads to a reduction in plaque burden assessed three days later



B) i.c.v administration of UDP leads to a reversal of a synaptic plasticity deficit assessed three days later



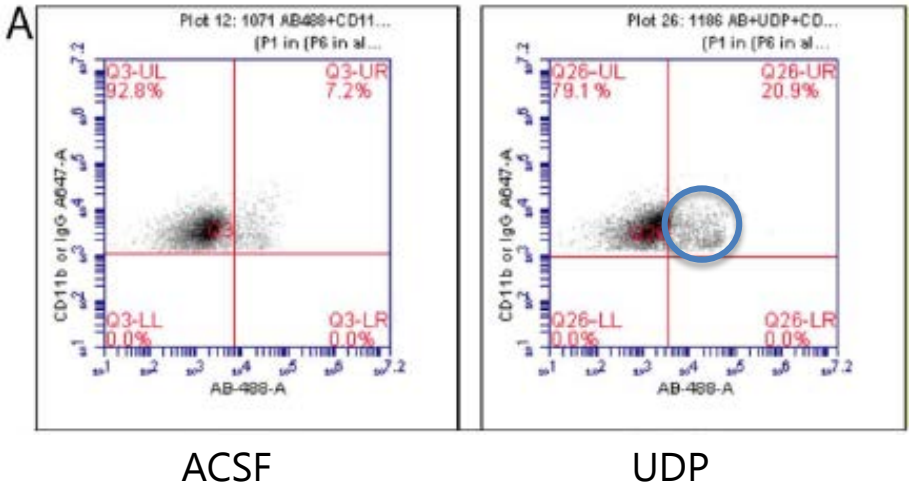
C) i.c.v administration of UDP or i.p. administration of PSB-0474 reverses deficits in memory

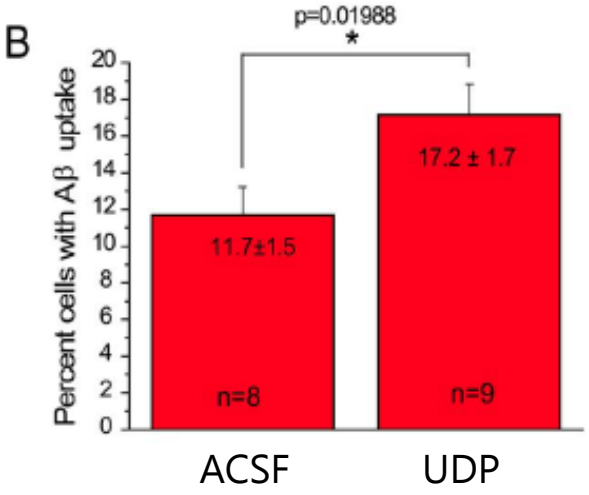


GliaCure

UDP Enhances Amyloid β Uptake, Validating Role of P2Y6R Target in Alzheimer's

- UDP is the endogenous ligand of P2Y6R
  - Uridine (UDP precursor) is reduced in the CSF of AD patients[1]
  - UDP is released as an activity-dependent signal[2], suggesting activation of the P2Y6R is reduced in Alzheimer's patients
- PSAPP mice were treated for 3 days with UDP, living hippocampal slices were cut and an *ex vivo* assay for amyloid β uptake was performed
- Fluorescently-tagged amyloid β (AB-488-A) was superfused over brain slices, then cells were dissociated and microglia (CD11b) were sorted using FACs
- The number of amyloid β-labeled microglia was increased by treatment with UDP

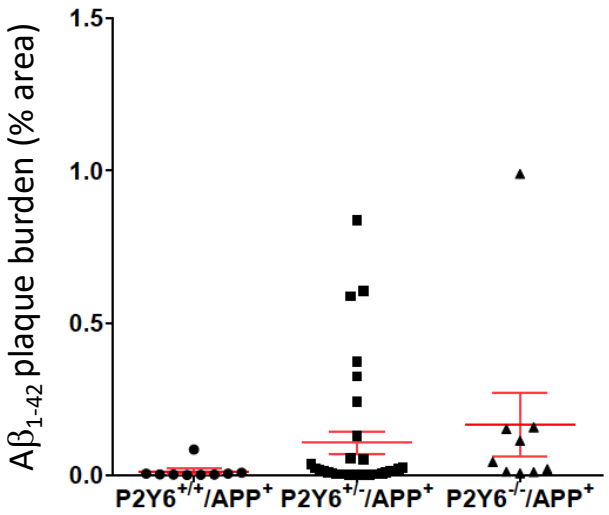


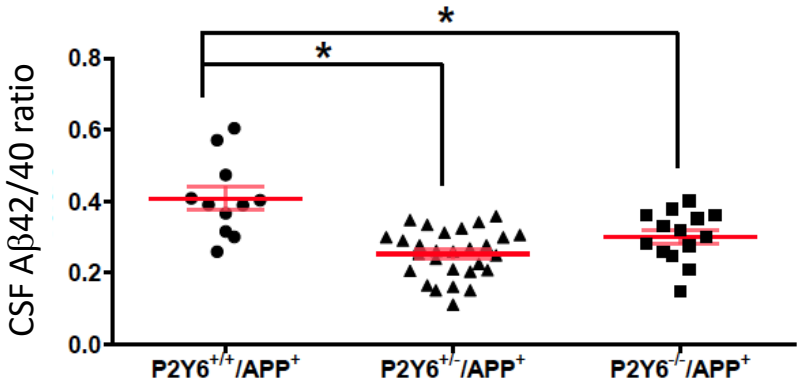


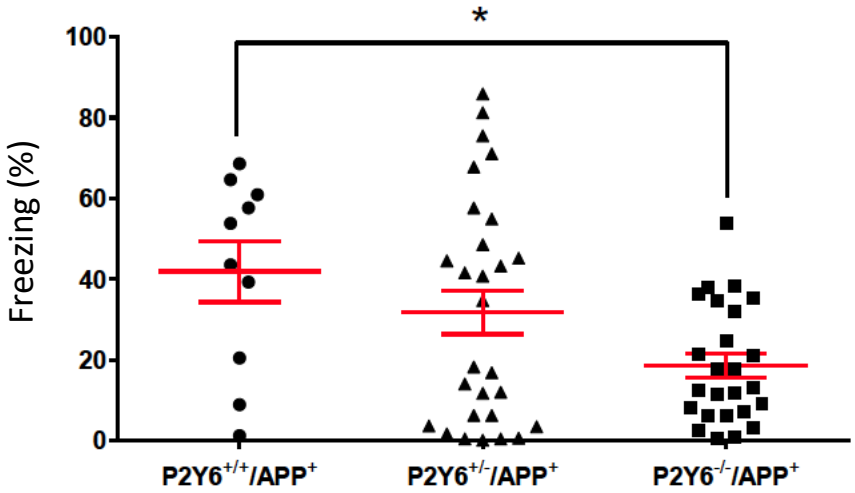
1 Czech, C. *et al.* Metabolite profiling of Alzheimer's disease cerebrospinal fluid. *PloS one* **7**, e31501, doi:10.1371/journal.pone.0031501 (2012).
2 Cansev, M. *et al.* Evidence for the existence of pyrimidinergic transmission in rat brain. *Neuropharmacology* **91**, 77-86, doi:10.1016/j.neuropharm.2014.12.019 (2015).

GliaCure

Deletion of the P2Y6R gene accelerates the Alzheimer's phenotype







Contextual fear memory is impaired when in P2Y6R$^{-/-}$ mice in an APP background

P2Y6R+/- X P2Y6R+/-,APP+

Offspring used at 3 months of age prior to an Alzheimer's (AD) phenotype normally developing. Deletion of the P2Y6R gene led to early accumulation of plaques (a), premature decline in CSF Aβ (b), and to accelerated memory impairment (c), fully supporting the hypothesis that the P2Y6R guard's against the development of AD.

GliaCure

Medicinal Chemistry Campaign

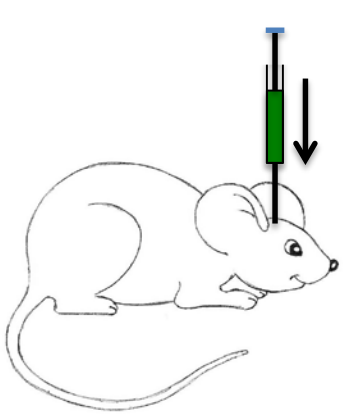
- We developed novel UDP analogs as agonists of the P2Y6R
- We developed agonist prodrugs for the P2Y6R
- One of these compounds, GC021109 was evaluated in pre-clinical studies and has been advanced through phase 1b studies in patients with Alzheimer's disease.
- (Composition of matter and method of use IP has been obtained)

Assay to Determine Whether GC021109 Stimulates Export of $A\beta_{1-42}$ From CNS to CSF

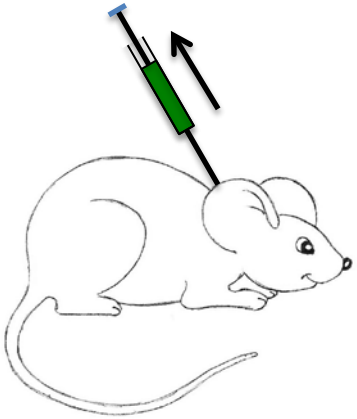
Inject $A\beta_{1-42}$ into CNS

Collect ~10µl CSF

Treat with:
Vehicle,
GC021109,
MRS2578
(P2Y6R antagonist)

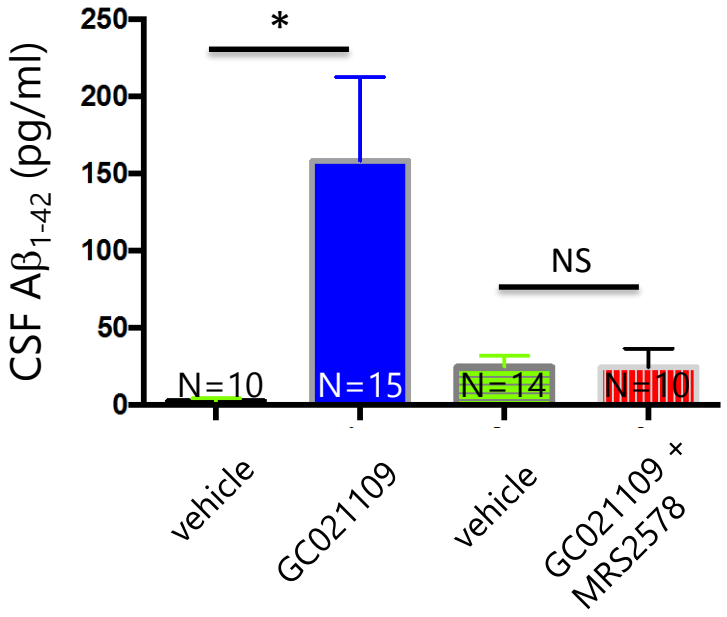


30 mins



ELISA assay to quantify $A\beta_{1-42}$ in CSF

GC021109 Stimulates a P2Y6R Dependent Efflux of $A\beta_{1-42}$ From CNS to CSF

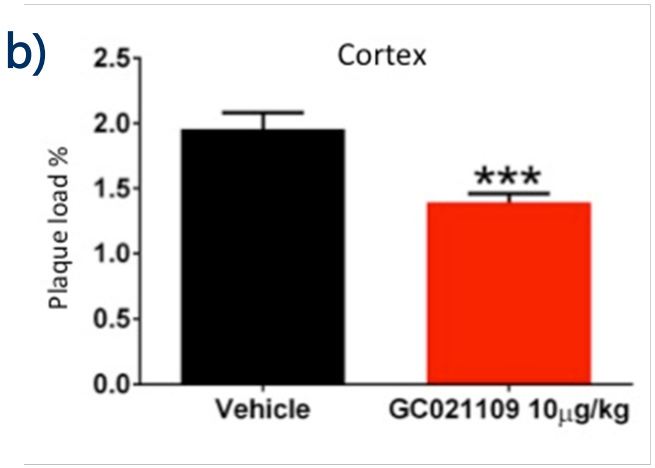


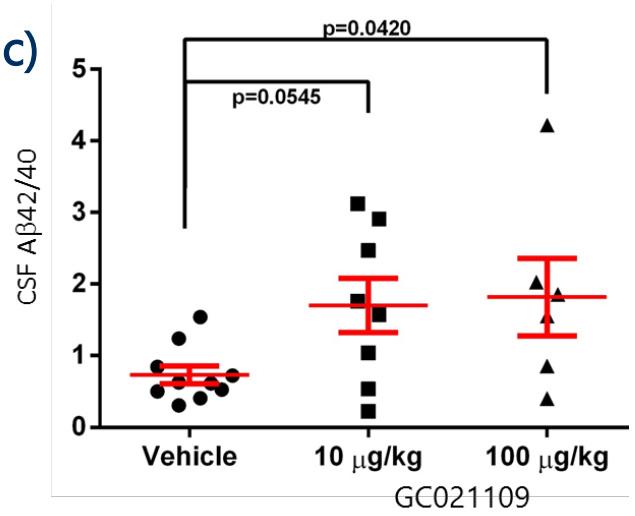
* P=0.029 2-tailed t-test

MRS2578 = P2Y6R antagonist

GliaCure

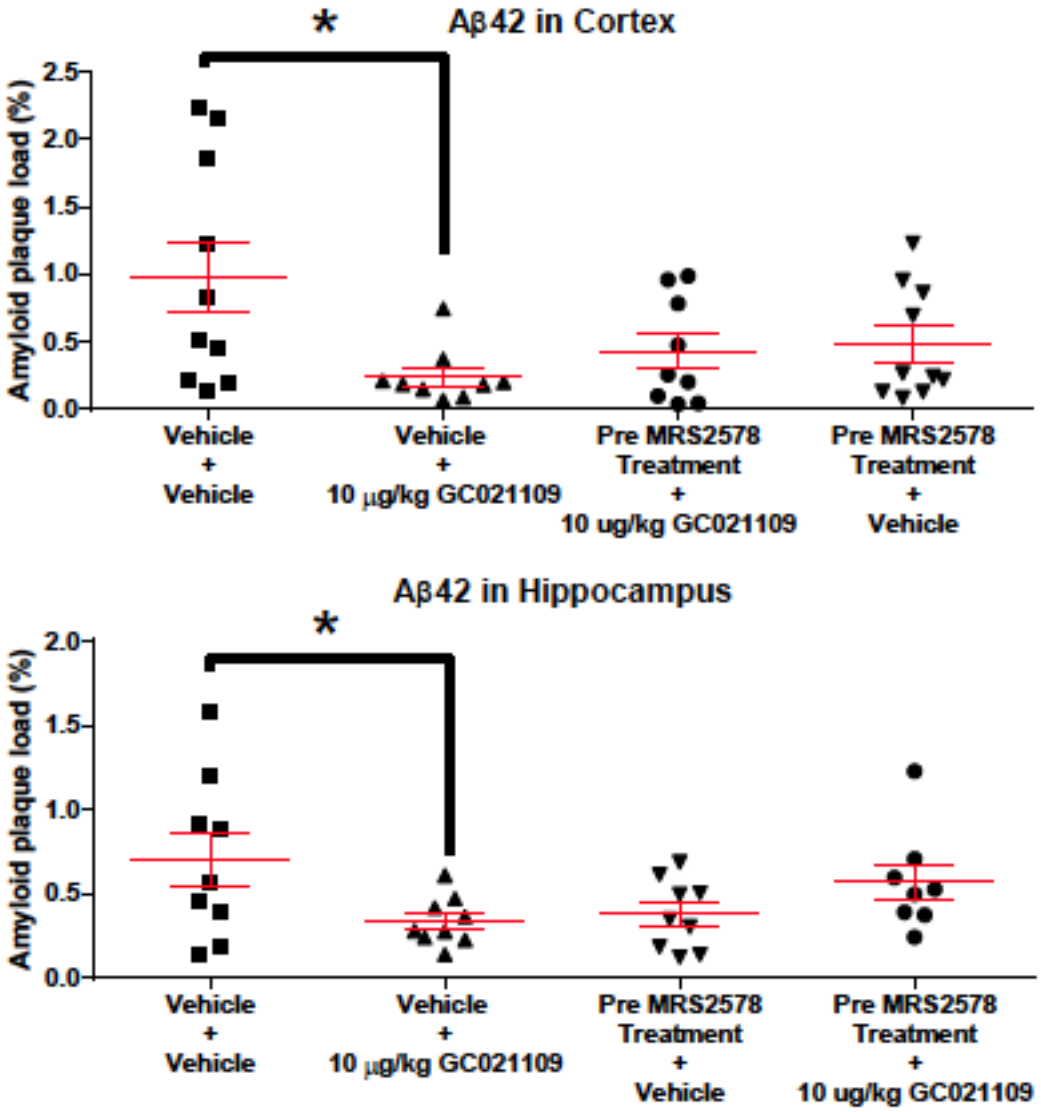
GC021109 Elevates Aβ in CSF Concomitant with Reducing Brain Aβ in Alzheimer's Model





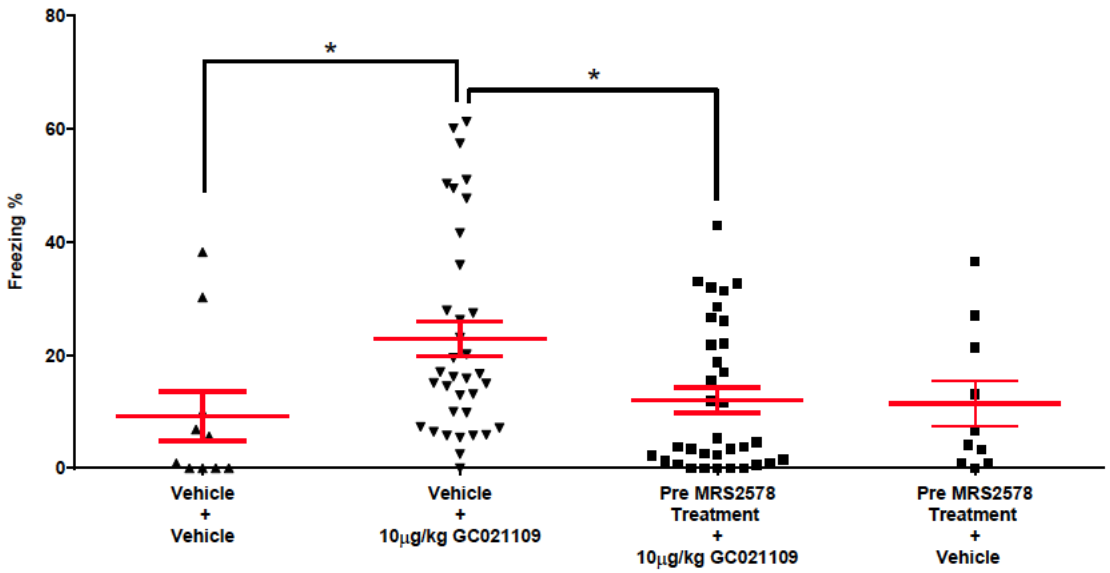
GliaCure

GC021109 causes a P2Y6R dependent reduction in $A\beta_{1-42}$ accumulation in the CNS (7 days of QD dosing)



GliaCure

GC021109 causes a P2Y6R dependent augmentation of memory formation (7 days of QD dosing in 6 month old PS1APP mice)



GliaCure

Phase 1b MAD Study in Patients with Alzheimer's Disease

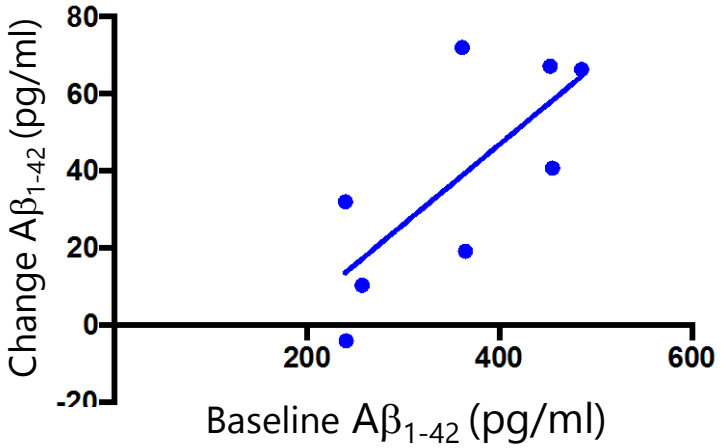
Primary Objective	▪ To evaluate the safety and tolerability of multiple oral daily doses of GC021109 administered to subjects with mild to moderate Alzheimer's disease
Secondary Objective	▪ Estimate the PK parameters of multiple, escalating dose levels of GC021109 ▪ Determine the effect of multiple, escalating dose levels of GC021109 on potential biomarkers of activities (e.g. IL-12, amyloid β, and tau) in CSF and plasma

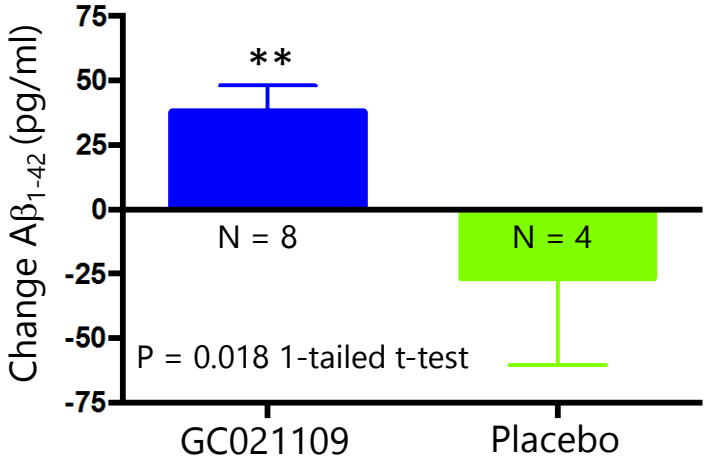
Design	▪ 36 patients with clinically diagnosed mild to moderate Alzheimer's disease
	  • 3 cohorts (1, 10, 30mg GC022109); 28 days treatment
	  • 12 patients per cohort (9 active, 3 placebo)
	▪ Plasma sampled on day 1, 14 and 28 for PK
	▪ CSF sampled pre-dose and on day 28 of dosing for biomarkers
	▪ Plasma sampled on days 1, 7, 14 and 28 for biomarkers

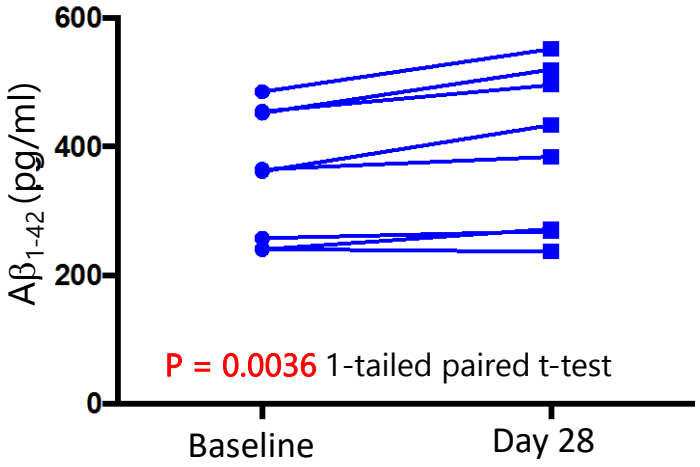
GC021109 Phase 1b Safety Summary

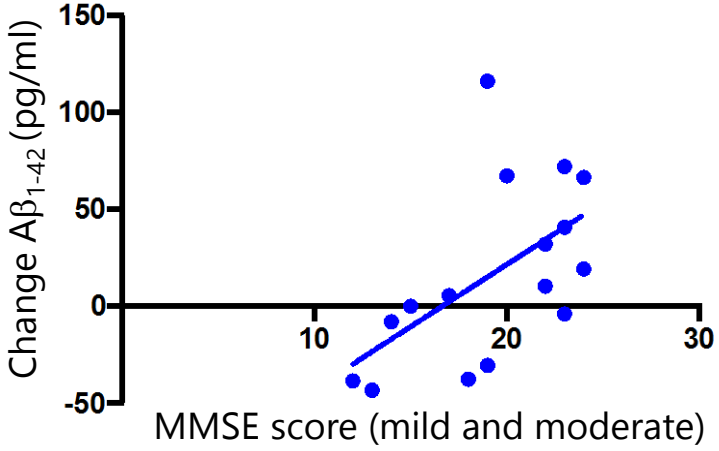
- 21 adverse events (AEs) in 11 of 28 (39.3%) patients treated with GC021109
  - No SAEs, grade 3 or higher AEs, or AEs leading to treatment discontinuation
    - Cohort 1 (1mg): 8 AEs
    - Cohort 2 (10mg): 10 AEs
    - Cohort 3 (30mg): 3 AEs
- 6 AEs in 4 of 11 (36.4%) patients treated with placebo
  - 1 SAE (TIA), patient discontinued
- There were a total of 6 AEs in 5 patients which were considered related to GC021109 treatment by the Investigator and 1 related AE in the Placebo group
  - Cohort 1 (1mg): 1 subject with leukopenia, neutropenia; 1 subject with somnolence; 1 subject with confusion
  - Cohort 2 (10mg): 1 subject with somnolence
  - Cohort 3 (30 mg): 1 subject with dizziness

28 days of treatment with GC021109 Reverses the 2+ Decade Progressive Decline in CSF $A\beta_{1-42}$ in Patients with Mild Alzheimer's Disease









GliaCure

Program Next Steps

- Align and finalize study design for next clinical trial
  - Optimal design and endpoint prioritization, duration, and sample size
- End of Phase 1 Meeting with FDA
  - Phase 2a study start and tox enabling plan
  - ARIA monitoring requirements(1)
  - Nonclinical toxicology program
  - Manufacturing plans
- Initiate chronic toxicology studies
  - 13 / 39 week dog
  - 13 / 25 week rat
- Program development plan refinement and initiation of clinical start up activities
- Further detail, including Phase 2a plans, available in further discussion

(1) Preliminary FDA feedback indicates that ARIA monitoring would not be required

Key Benefits of GC021109

- ✓ Orally administered
- ✓ Complimentary to / synergistic with other Alzheimer's therapies
- ✓ Safe and well tolerated
- ✓ Ability to target patient selection in future trials
- ✓ High margins (nominal annual production costs)
- ✓ Novel dual MOA enabling very positive results to-date