Has Developed a Compound for treating Alzheimer’s Disease

About GliaCure

- Development of a discovery by Professor Philip Haydon, PhD., Chairman of Neuroscience at Tufts University.

- Holds an Exclusive License Agreement with Tufts University for composition of mater and it uses in treatment of multiple disorders.

About GliaCure

- Successful P1 Human Safety Trial.
  - Awarded NIH fast track status.
- Positive outcomes in P1b test with Alzheimer's patients.
  - Changes in cytokines that are associated with Alzheimer's disease
- The compound is a small molecule that is taken orally.

Why is Our Compound Different?

To date, most of the failed Alzheimer's trials have focused on the chemistry to stop or reduce factors involved with the production of beta amyloid plaques or other chemistry associated with either build up or breakdown (neurofibrillary tangles) of the structures that are essential to preserve the neurons in the brain.

Why is Our Compound Different?

The GliaCure Compound targets the P2Y6 receptor which stimulates microglia which:

- Reduces Inflammation in the brain,
- Increases the clearance of the amyloid plaques and returns the beta-amyloid back to the central nervous system. (enhancing a natural process which starts to slow down as we age).

Glial Cells in Alzheimer's Disease

- GliaCure identified the role of glia in brain function in health and disease
  - Initial discoveries out of Tufts University
- Developed a orally bioavailable molecule (GC021109) to reduce amyloid plaque burden, restore memory formation and reduce circulating levels of inflammatory cytokine IL-12 via the P2Y6 receptor
- Interleukins, microglia and phagocytosis are gaining significant recognition as critical in Alzheimer's Disease
- This target has not been studied by drug development groups

Target validated by numerous third-party scientific papers

- Inhibition of IL-12/IL-23 signaling reduces Alzheimer's disease-like pathology and cognitive decline. *Vom Berg, J., et al., Nat Med. (2012)*
- IL-10 deficiency rebalances innate immunity to mitigate Alzheimer-like pathology. *Guillot-Sestier MV, et al., Neuron (2015)*
- IL-10 immunoproteostasis in APP mice, increasing plaque burden and worsening cognitive behavior. *Chakrabarty P, et al,. Neuron (2015)*
- Hippocampal expression of murine IL-4 results in exacerbation of amyloid deposition. *Chakrabarty P, et al., Mol Neurodegeneration (2012)*
- Variant of TREM2 associated with the risk of Alzheimer's disease. *Jonsson T et al., N. Engl. J. Med. (2013)*
- TREM2 variants in Alzheimer's disease. *Guerreiro R et al., N Engl J Med. (2013)*
- Alzheimer's disease risk gene CD33 inhibits *microglial uptake* of amyloid beta. Griciuc A, et al., Neuron. (2013)

Current Status of GC021109

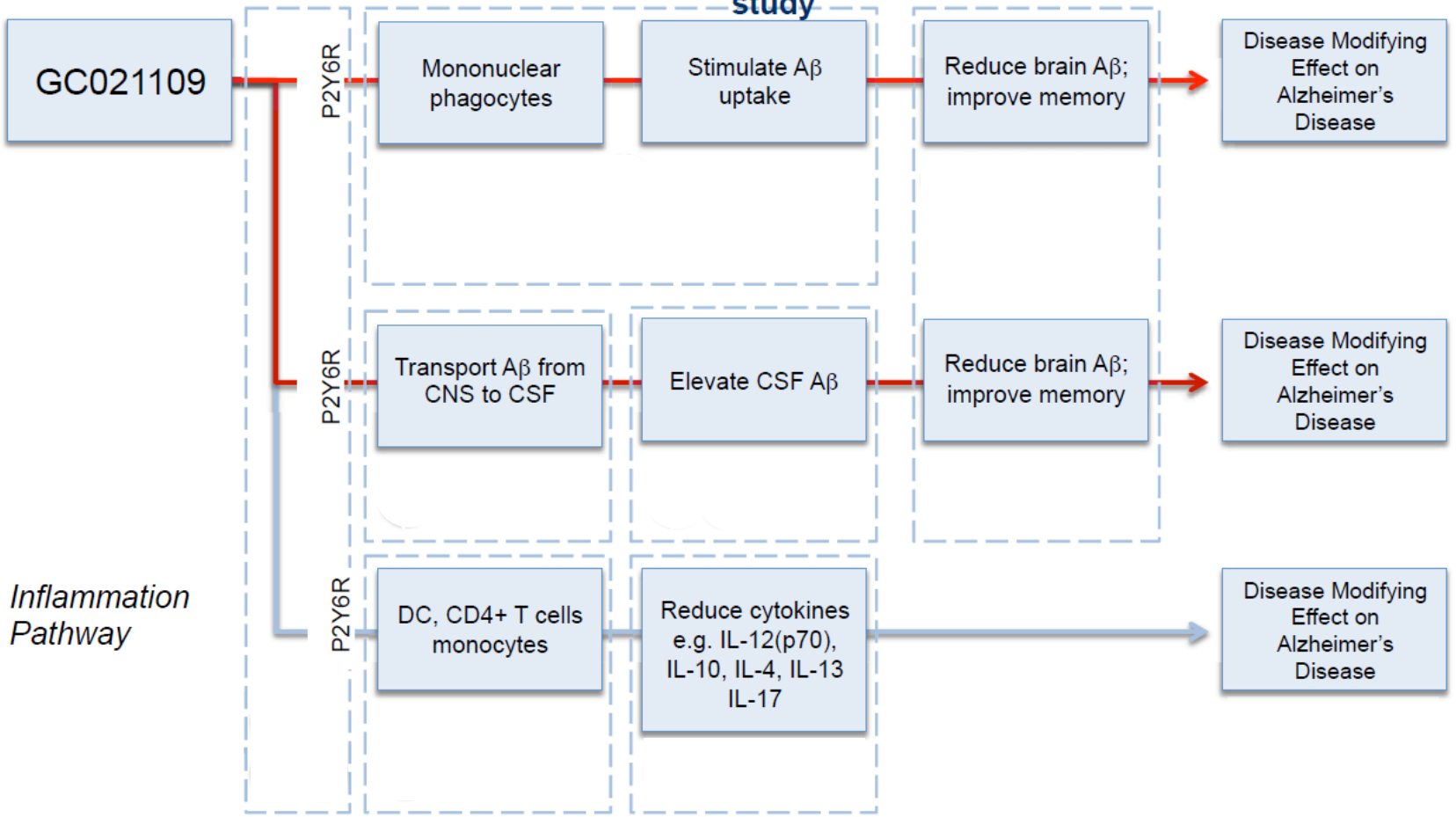
- **Open IND, fast track designation granted** by FDA
- **Safe and well tolerated** in Phase 1 clinical trials
  - Phase 1a SAD trial in healthy volunteers completed
  - Phase 1b MAD trial in Alzheimer's patients completed
- Anti-inflammatory platform may enable **lower threshold for proof of concept** 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**

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

Validated Novel Multi-Pronged Mechanism of Action

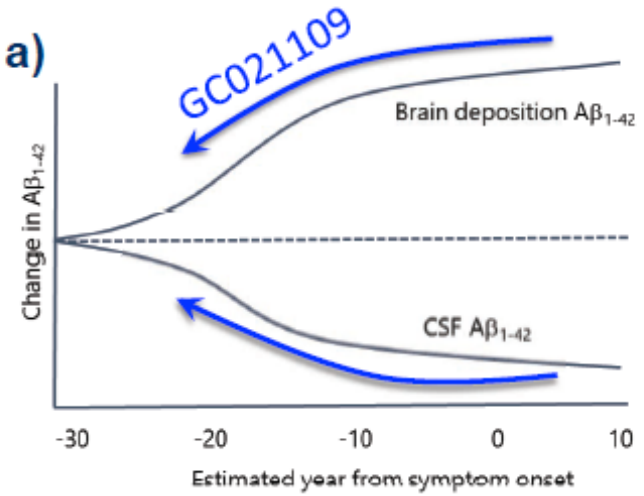
Each component of GC021109's mechanism-of-action is validated and supported by at least one study



Numbered circles refer to the studies on the previous slide

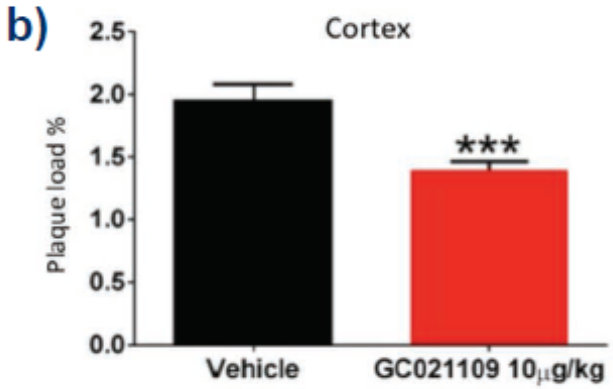
GC021109 Elevates Aβ in CSF Concomitant with Reducing Brain Aβ in Alzheimer's Model

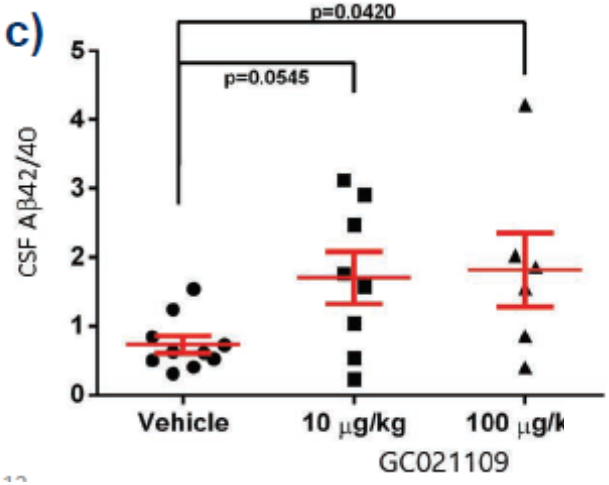
Untreated, $A\beta_{1-42}$ Declines in CSF Concomitant with Brain Accumulation in Alzheimer's Disease



(**a**) GC021109 Reverses age Dependent Changes in Distribution of $A\beta_{1-42}$

(**b**) GC021109 reduced brain plaque burden in parallel with reversing the decline in CSF Aβ in an Alzheimer's mouse model, resulting in (**c**) an elevation of Aβ in CSF compared to placebo control





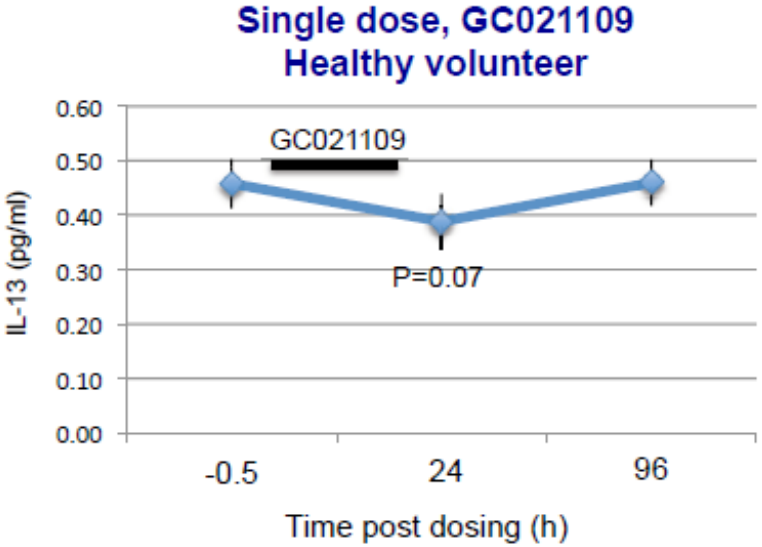
Preclinical and Clinical Studies Validate Method of Action

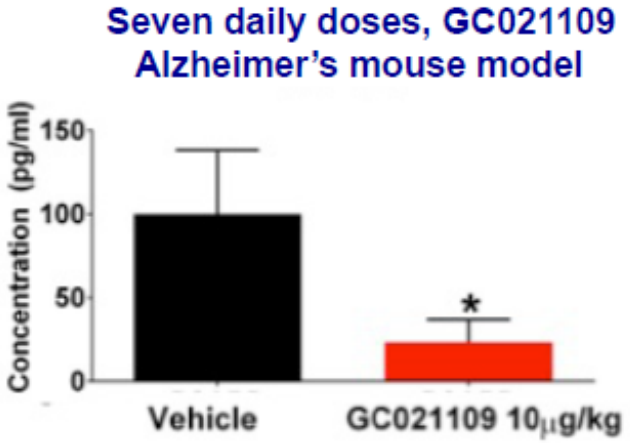
- Experimental design to determine whether UDP, an endogenous activator of P2Y6Rs, reduces amyloid a in Alzheimer's mouse model **completed**
  - Longitudinal study of plaques using 2 photon microscopy
    - Between Days 1 and 4, treatment with UDP leads to reduced amyloid plaques
  - Reversal of Deficits in PSAPP Mice Following Treatment with UDP and PSB0474 for 3-7 Days
  - UDP enhances amyloid uptake into microglia
  - GC021109 reduces amyloid in the brain, elevates cerebrospinal fluid amyloid . reduces cytokines and improves memory in PSAPP mice
  - GC021109 requires P2Y6R to reduce cytokine release from human THP-1 cells *in vitro*
  - Tests validated in multiples labs
- IND enabling toxicology studies **completed**
  - No significant effects of GC021109, even at maximum feasible dose (600 mg/kg - rats) and maximum exposure (300 mg/kg - dog)
- GMP manufacturing campaign **completed**
  - Met all specs & comparable to GLP tox material; released and used in FIH SAD study *wino* FDA questions
  - API stability ongoing at variety of storage conditions; scheduled to continue for 36 months
- FIH SAD healthy volunteer safety/tolerability and PK study **completed**
  - 5 cohorts (with an optional 6th and 7th if needed)
  - 4 cohorts of 8 subjects each and 1 food effect cohort of 12 subjects
  - Food effect was carried out in Cohort 4
    - 4a Fasted
    - 4b Fed
- Double blind placebo-controlled MAD safety and tolerability study in patients with mild to moderate Alzheimer's disease **completed**
  - Ascending doses of 1, 10 or 30 mg daily
  - 3 cohorts of 12 subjects each (9 on drug, 3 placebo)
  - 28 day duration each cohort

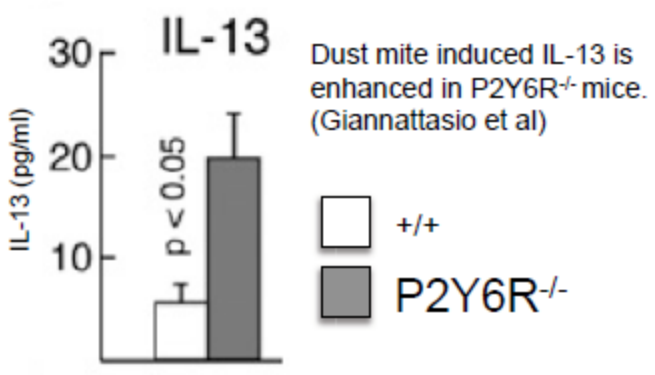
GC021109 Phase 1b Safety Summary

- 21 adverse events (AEs) in 11 of 28 (39.3%) patients treated with GC021109 at any dose level (1, 10, 30 mg)
  - 6 AEs in 4 of 11 (36.4%) patients in the Placebo group
- No Serious Adverse Events (SAEs), Grade 3 or higher AEs, or AEs leading to treatment discontinuation in any of the GC021109 treated patients
- One subject in the 10 mg group had moderate Leukopenia and Neutropenia which were considered AEs related to GC021109 treatment
  - No other clinically significant post-baseline changes in any laboratory parameter in any of the GC021109 treated patients or Placebo patients
- There were no clinically significant post-baseline changes in any vital sign or ECG parameter considered related to treatment with GC021109 or Placebo
- There were a total of 6 AEs in 5 patients which were considered <u>related to GC021109 treatment</u> by the Investigator and 1 related AE in the Placebo group

GC021109's Activity on IL-13 Makes Asset a Strong Candidate for Treatment of Asthma







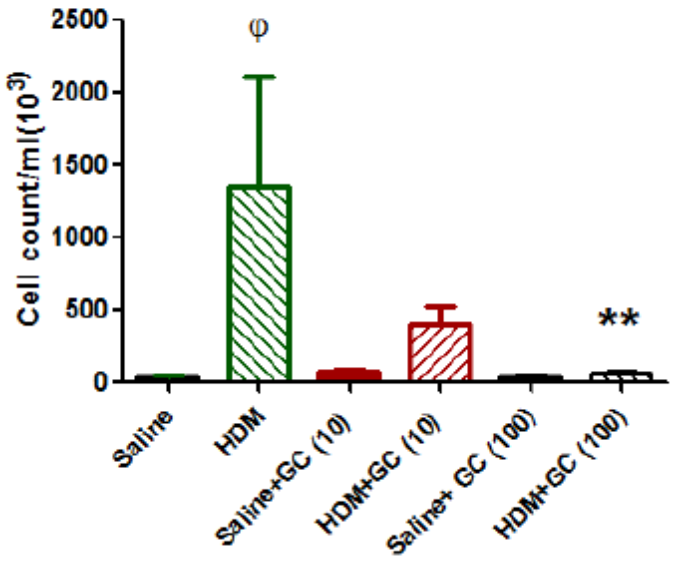
Dust mite induced IL-13 is enhanced in P2Y6R$^{-/-}$ mice. (Giannattasio et al)

- **P2a ready asset** (pending approval from FDA)
- Given the acknowledged importance of IL-13 in asthma and the importance of P2Y6R in this condition, we have the potential to develop an oral asthma medication with GC021109 or its related compounds

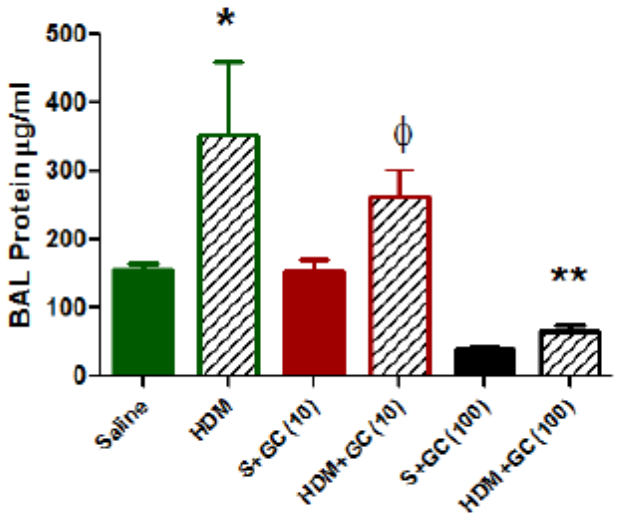
Compelling Preclinical Results in Dust Mite Models

- Intra-nasal house dust mite (HOM) purified antigen (40 micrograms) (or saline control) given 5 days per week for 6 weeks
- Treatment- GC021109 (or vehicle control) delivered 5 days per week for 6 weeks via an intraperitoneal route (10 and 100 µg/kg)

GC021109 reduces cell count in bronchoalveolar lavage (BAL)



GC021109 reduces BAL protein



*** P = 0.03 compared to saline; ** P = 0.008 compared to HDM**

Mean + SEM; N = 4 - 5

Strong Intellectual Property Coverage

- Three patent families exclusively licensed from Tufts with claims covering lead and back-up compounds, and their use
  - PCT/US12/58080 (WO2013/049686)
    - cases pending/granted in US, AU, CA, CN, EP, IL, IN, & JP
  - PCT/US13/62413 (WO2014/052896)
    - cases pending/granted in US, AU, CA, EP, & JP
  - PCT/US14/26865 (WO2014/160502)
    - cases pending in US, AR, AU, CA, CN, EA, EP, IL, JP, KR, NZ & TW
- Granted U.S. patents and allowed U.S. patent application covering lead and back-up compounds, and their use
  - U.S. Patent No. 8,598,141 (exp. 2032)
  - U.S. Patent No. 8,785,620 (exp. 2032)
  - U.S. Patent No. 9,163,055 (exp. 2033)
  - U.S.S.N. 14/323,690 (allowed)

Summary

- Robust statistically significant Phase 1b MAD data demonstrating elevated levels of amyloid r1 in CSF, correlating to increased clearance of amyloid in the brain.
- Extensive pre-clinical data supporting a novel target for the treatment of Alzheimer's Disease.
- Two-pronged disease-modifying MOA to treat Alzheimer's Disease: anti-inflammatory and stimulation of amyloid clearance.
- Demonstrated to be safe and well tolerated.
- Open IND, fast track designation granted by the FDA.
- Phase 1a SAD trial in healthy volunteers complete.

Summary

- Platform potential beyond Alzheimer's Disease (asthma, psoriasis, RA), with potential for lower threshold to demonstrate proof-of-concept.
  - Asthma indication is Phase 2a ready.
- Patent protection for lead and back-up compounds and their use through at least 2032.