

- **Alzheimer's disease (AD)** is particularly devastating since there is no cure, no way to prevent it and no proven way to slow its progression.
- Management of AD represents a huge unmet **need**; thus, discovery and development of more effective therapies are critical for worldwide public health and health-care systems.
- **Novel strategy** for symptomatic treatment of Alzheimer's disease.
 - Novel target: GPCR-X (not yet related to AD)
 - Discovery of GPCR-X antagonists
 - *Target validated using a novel animal model (KOGPCR-X/APPswe" mice)*

Scope of the problem

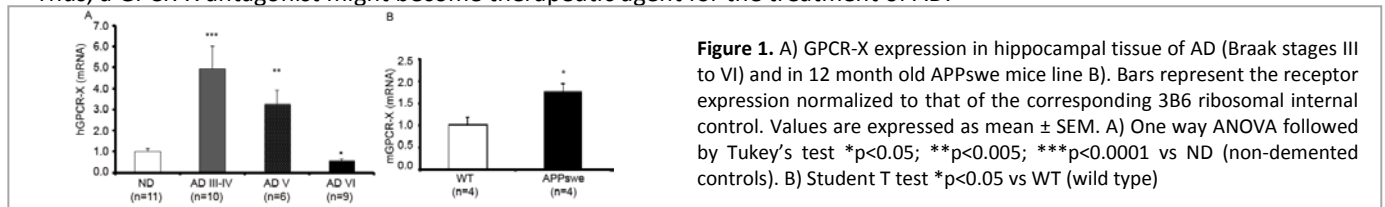
- Currently, approximately 18 million people worldwide are afflicted with this disease and it is projected to reach over 30 million by 2025.
- The current treatment options are only moderately effective. There is an unmet need for therapies that halt or substantially slow disease progression.
- Recent clinical trials of various disease-modifying therapies for AD failed to demonstrate benefit.

Patient need addressed Substantially improve symptoms of Alzheimer's disease.

Therapeutic Hypothesis (from experimental facts)

- *hGPCR-X* is over-expressed in AD patients (Figure 1A)
- *mGPCR-X* is over-expressed in AD transgenic mice model Tg2576 (APPswe) (Figure 1B)

Thus, a GPCR-X antagonist might become therapeutic agent for the treatment of AD.



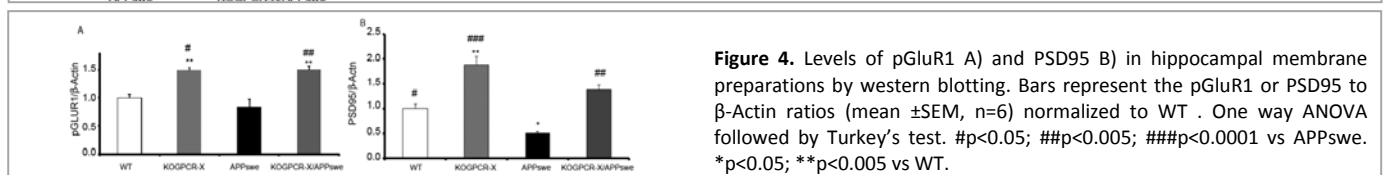
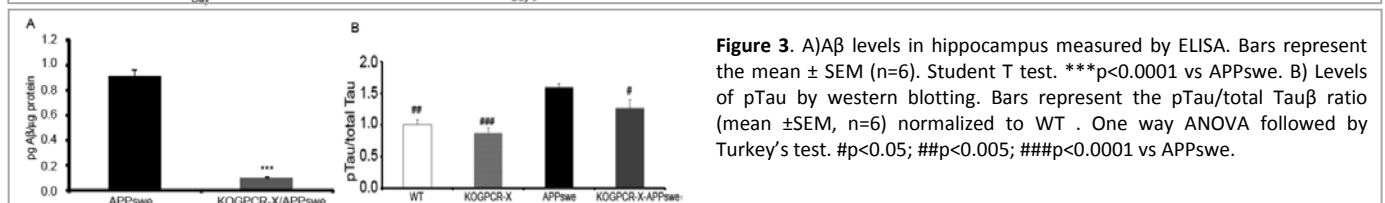
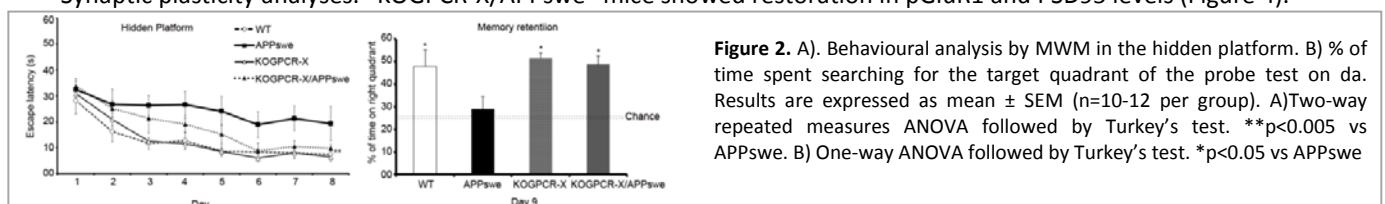
Target

- Although it is a decade since this Gi coupled GPCR-X was deorphanized, few ligands have been reported for the receptor; just weak agonists ($EC_{50} > 10 \mu M$).
- Only 6 antagonists have been reported so far, patent focused on a different therapeutic area (2004 as priority date), and no IC_{50} values were described.

Project Status

Validation process using a new animal model:

- *mGPCR-X* knock-out (KO) in Tg2576 (APPswe) mice was achieved: "KOGPCR-X/APPswe" mice
- "KOGPCR-X/APPswe" mice showed a restoration of memory deficits in Morris Water Maze (MWM) test vs APPswe mice (Figure 2) – behavioural task
- AD pathological marks analysis. "KOGPCR-X/APPswe" mice showed a reduction in amyloid and Tau pathology (Figure 3)
- Synaptic plasticity analyses. "KOGPCR-X/APPswe" mice showed restoration in pGluR1 and PSD95 levels (Figure 4).



Screening Assay

hGPCR_X1 stable cell line HEK293 is available; then, Fluorometric Imaging Plate Reader (FLIPR) assay can be performed for the measurement of intracellular calcium mobilization. Thus, high-throughput screening campaign can be run to identify *hGPCR_X1* antagonists; as confirmation, further hit validation may be performed using cAMP assay.