

# Translatability of animal models for Alzheimer's disease using a machine learning based workflow

Alex Foster-Powell<sup>1</sup>, Guy Meno-Tetang<sup>2,3</sup>, Amin Rostami-Hodjegan<sup>1,4</sup>, Kayode Ogungbenro<sup>1</sup>, Donald E Mager<sup>5</sup>

<sup>1</sup>CAPKR, University of Manchester – Manchester UK.

<sup>2</sup>Neuroscience – Research and Development, AstraZeneca – Cambridge, UK. <sup>3</sup>Neurocrine Biosciences, London, United Kingdom. <sup>4</sup>Certara, Predictive Technologies, Certara Inc., Sheffield, United Kingdom. <sup>5</sup>Department of Pharmaceutical Sciences, University of New York at Buffalo, SUNY, Buffalo, USA. <sup>6</sup>Enhanced Pharmacodynamics, LLC, Buffalo, NY, USA. This research was funded by the BBSRC ICASE studentship award in collaboration with AstraZeneca.

## Background

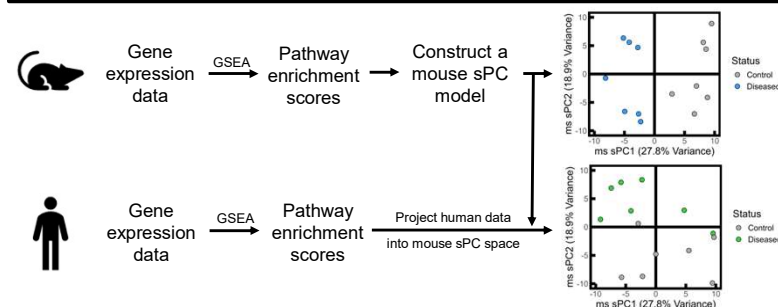
- Alzheimer's disease (AD) is a chronic neurodegenerative disease with almost no disease modifying treatment
- Testing in preclinical animal models, such as **APP/PS1**, **3xTg** and **5xFAD** transgenic mice, for many investigational compounds appear promising based on amyloid reduction or behavioural assessments.
- These findings are not replicated in the clinic
- Therefore, there is a need to assess the translatability of preclinical animal models
- Aim:** Build upon a previously developed machine learning-based workflow<sup>1</sup> to identify phenotype-defining pathways in both animal models and human patients.

## Methods

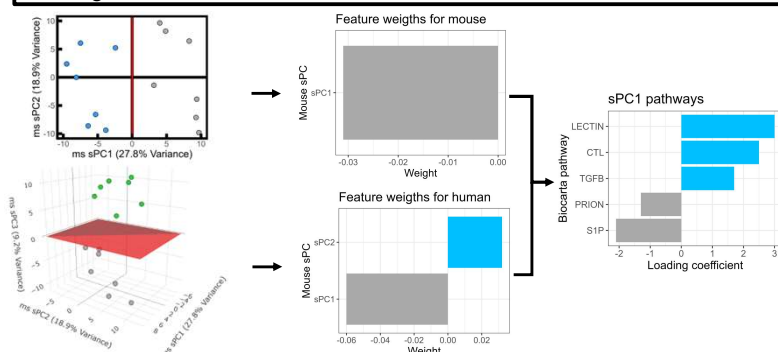
- Microarray datasets from APP/PS1, 3xTg and 5xFAD were obtained from the literature

| Brain Region | Organism | Model                 | N disease | N healthy | GEMMA score | GSE code |
|--------------|----------|-----------------------|-----------|-----------|-------------|----------|
| Hippocampus  | Human    | /                     | 7         | 10        | 0.7         | 36890    |
|              | Mouse    | APP/PS1               | 5         | 4         | 0.6         | 67306    |
|              |          | APP/PS1 (Ibu treated) | 5         | 4         |             |          |
|              |          | 3xTg                  | 3         | 3         | 0.4         | 36981    |
|              |          | 5xFAD                 | 3         | 3         | 0.9         | 50521    |

1. Train a sPC model using mouse pathway enrichment scores, and project human data into this mouse space



2. Train separate L1-regularised SVMs for each species to identify if there are any common sPCs or pathways which contain phenotype defining information



3. Further filter identified pathways through combining both mouse and human data, and training a new SVM on this combined data

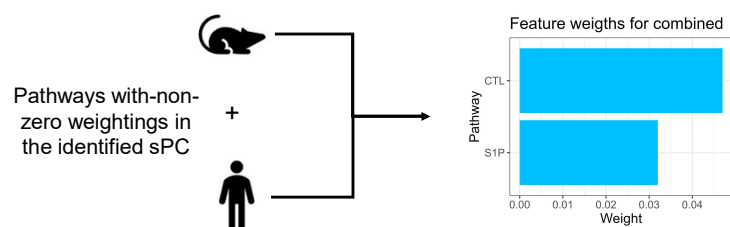


Figure 1: Overview of the methodology

## Results

- Similar sPCs were important for capturing variance in both the human and 5xFAD mouse data but not for the APP/PS1 and 3xTg (Figure 2)
- No common sPCs were utilised by the SVM classifier for the APP/PS1 and 3xTg models (Table 1)
- The SVM classifier utilised sPC1 for both the 5xFAD and human data (Table 1)
- An L1-regularised SVM using combined human and 5xFAD mouse loadings from sPC1 pathways (Figure 3) could classify data well irrespective of species source through inspecting....
- SREBP control of lipid synthesis pathway**
  - Known associated risk with AD in mice and humans<sup>2</sup>
- Cytotoxic T-lymphocyte pathway**
  - Lipid signalling plays an important role in CD8+ activation<sup>3</sup>
  - Potential use of the 5xFAD model for inflammatory treatments

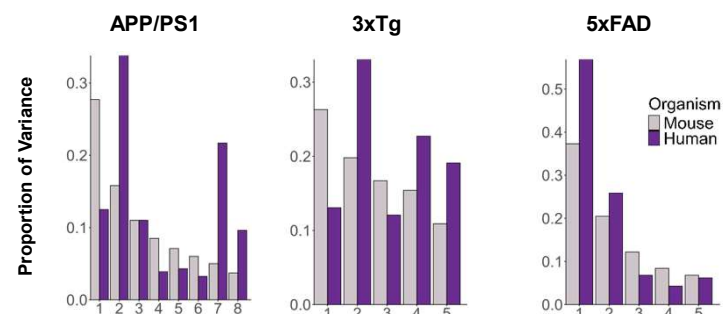


Figure 2: sPC loadings of mouse and human data projected into mouse sPC space

|       | APP/PS1 | 3xTg | 5xFAD |
|-------|---------|------|-------|
| Human | 2,3,4,6 | 4    | 1,3   |
| Mouse | 1       | 1,3  | 1     |

Table 2: sPCs utilised by the SVM classifier

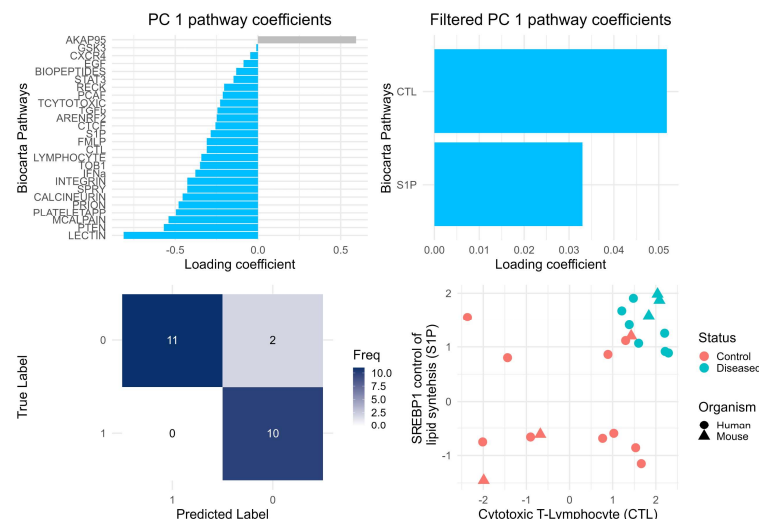


Figure 3: Further reduction of identified pathways in sPC1 for 5xFAD and human data

## Conclusions

- APP/PS1 and 3xTg models appear to be poor representations of human AD
- 5xFAD model contains phenotype relevant information for humans through inspection of the cytotoxic t-lymphocyte pathway, and SREBP control of lipid synthesis

## Reference(s)

- [1] Carroll et al, Inter Biol (2021) 10, 237-245
- [2] Picard et al, Neurobiol Aging. (2018), 66:180.e1-180.e9.
- [3] Baeyens et al., Trends Immunol. (2015) 12, 778-787