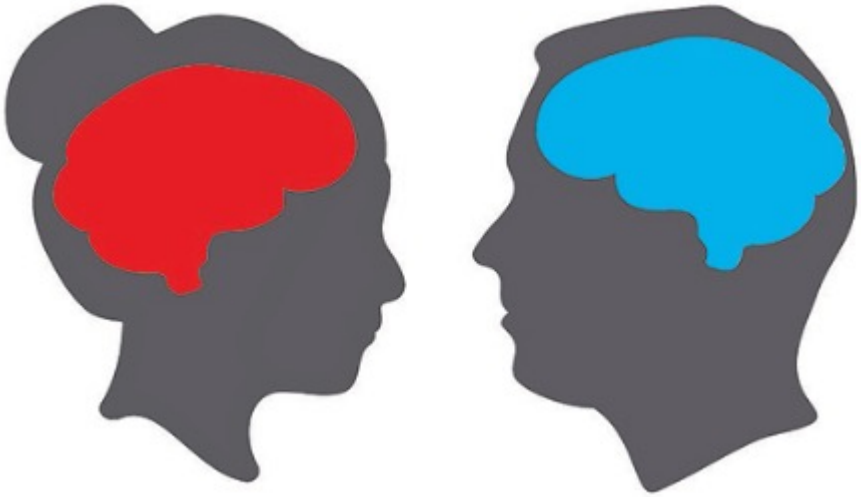


Molecular sex differences in Alzheimer's disease

Speaker: Enrico Glaab

Fondation Wivine project

Motivation:

Alzheimer's disease displays strong sex differences in incidence rates and brain pathology which are not yet understood at the molecular level

Project Goals:

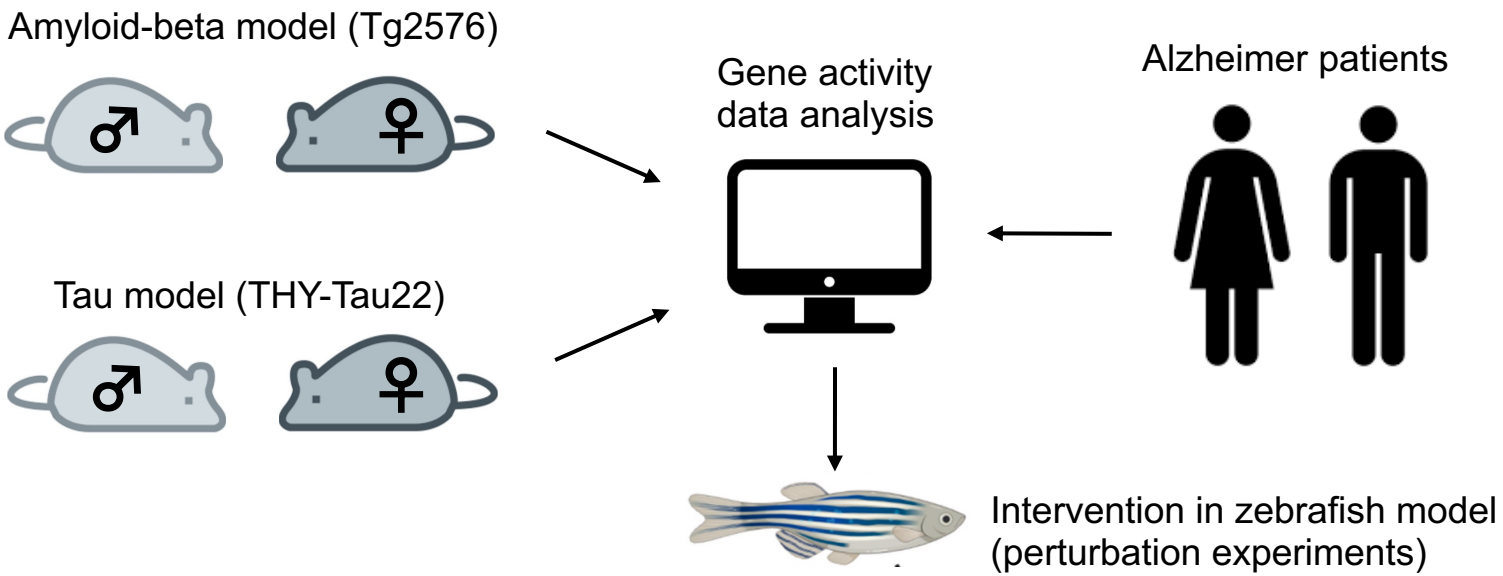
- Investigate animal models reflecting the early stages of Alzheimer's disease to better understand the mechanisms behind sex-specific molecular changes
- Identify key regulatory molecules that control sex-specific changes in Alzheimer's to investigate them as potential targets for pharmacological interventions

Project workflow

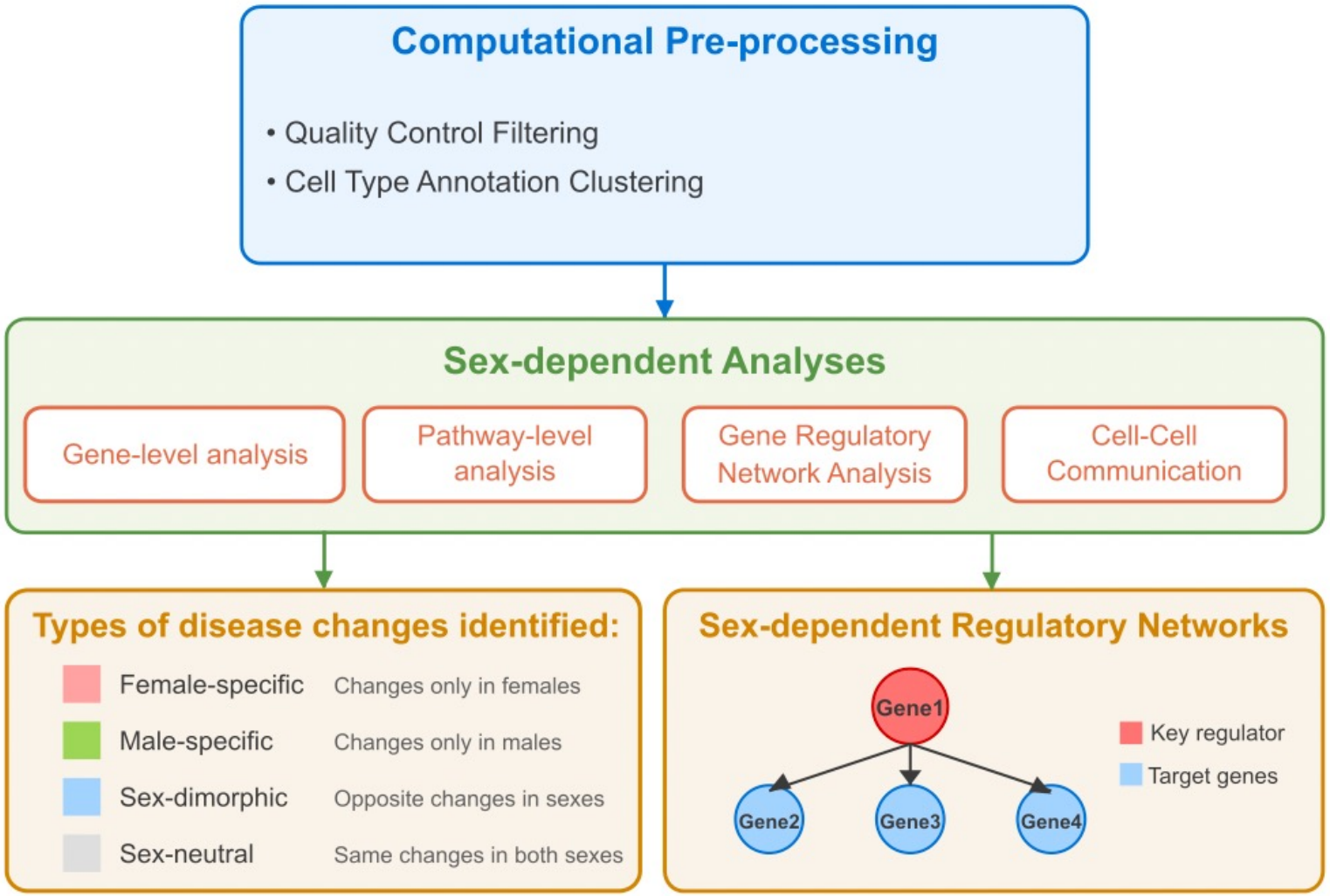
Step 1: Measure gene expression in the brains of Alzheimer mouse models and in *post-mortem* brains of Alzheimer patients

Step 2: Compare disease-associated sex-specific changes in mice & humans

Step 3: Characterize candidate genes in a zebrafish model (perturbation studies)

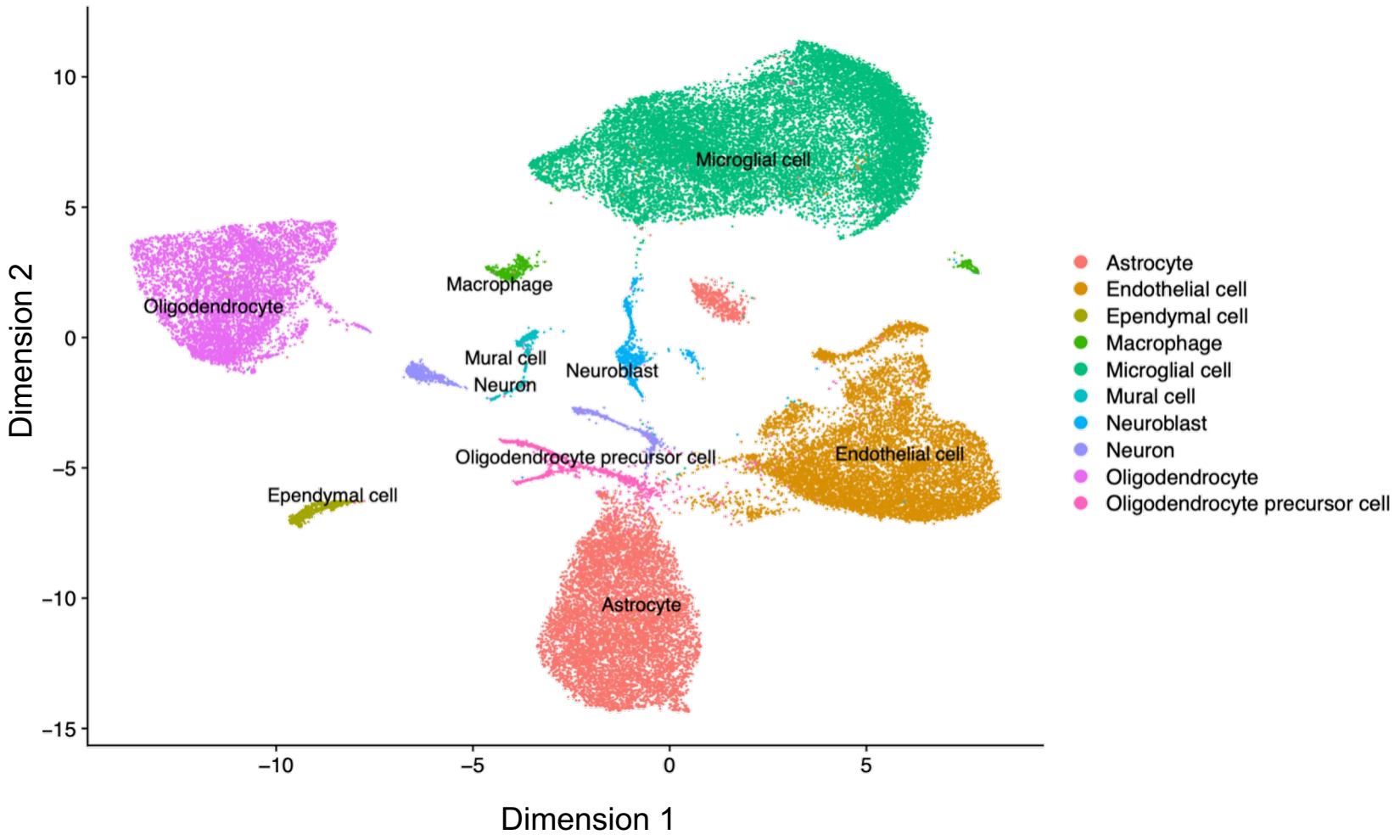


Computational data analysis



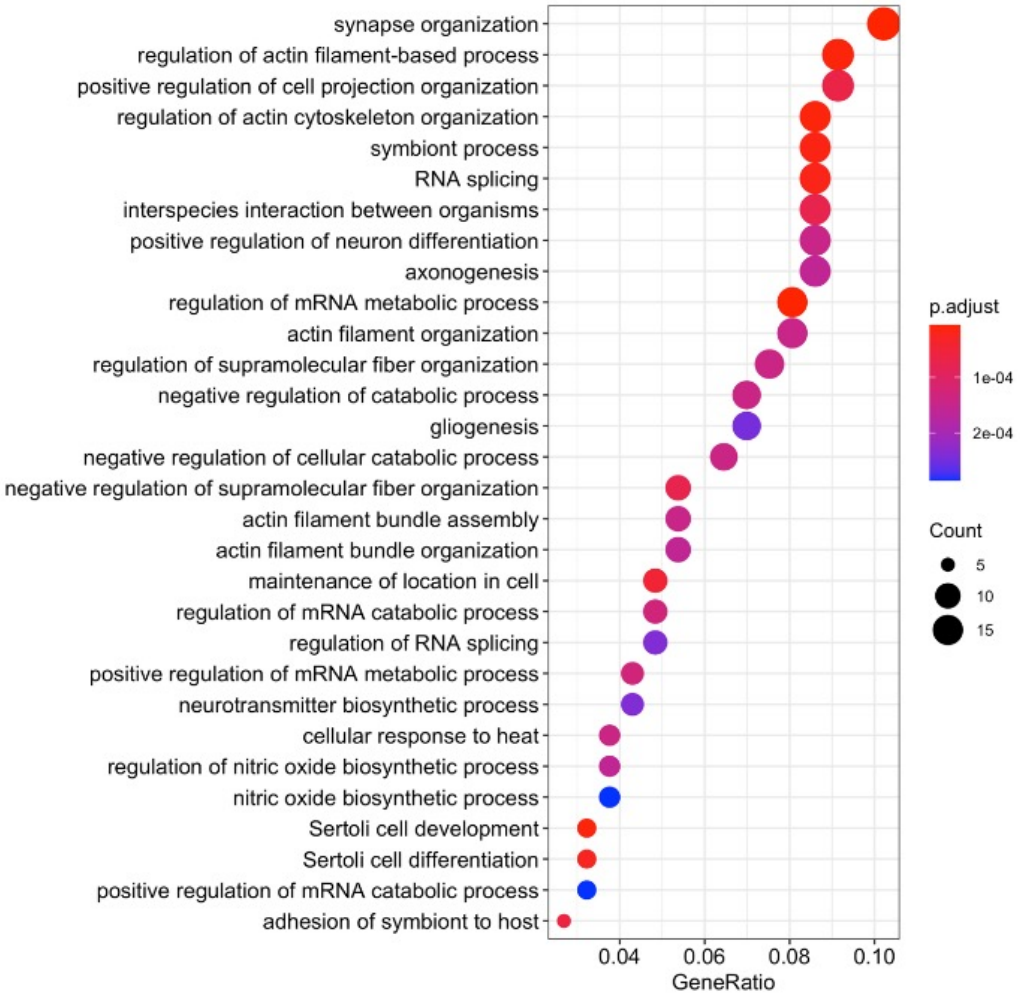
Visualization of the data

Cell type clusters (THY-Tau22 mouse model)



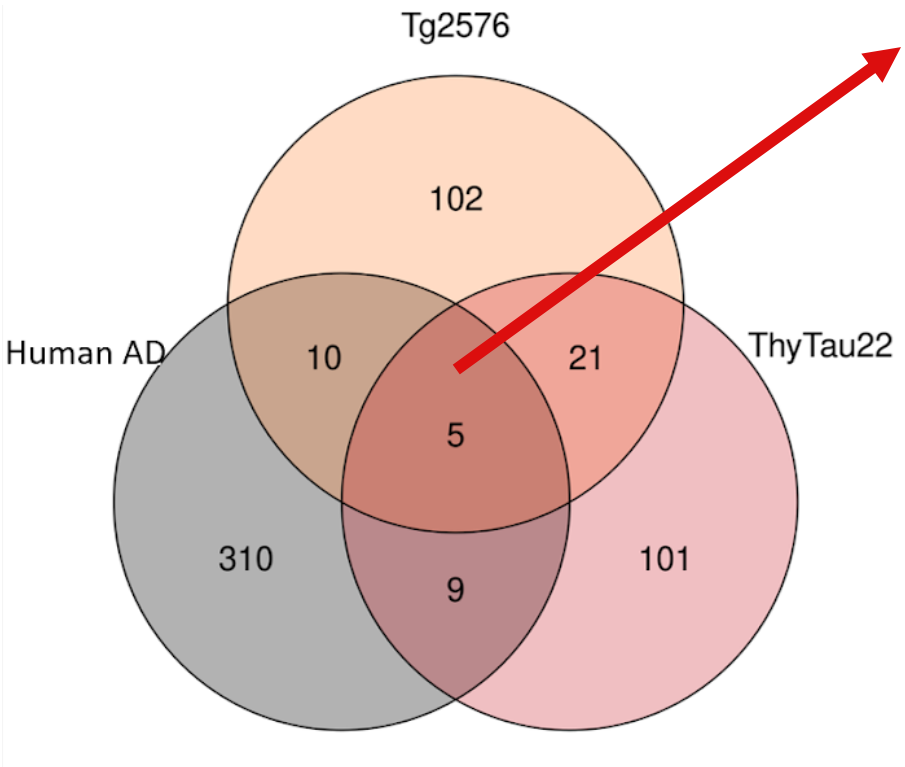
Sex-specific Alzheimer-associated changes in cellular processes

Cellular processes enriched in sex-specific changes (Tg2576 mice vs. wildtype):



Overlap between disease models and species

Shared sex-dependent gene changes across two mouse models and human patients:



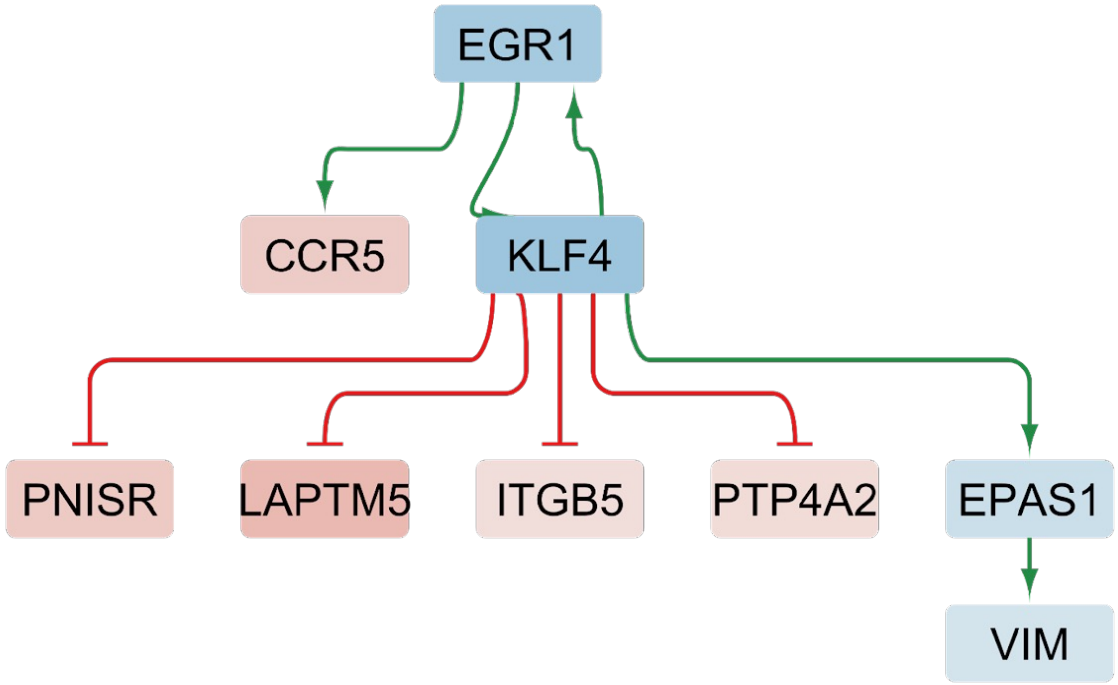
Genes with shared significance:

- *MBP* (myelin binding protein)
- *PLP1* (myelin proteolipid protein 1)
- *MALAT1* (lncRNA)
- *HSP90AA1* (heat shock protein)
- *ACTB* (actin beta)

Regulatory network analysis

Goal: Find coordinated and consistent activity changes in gene regulatory networks

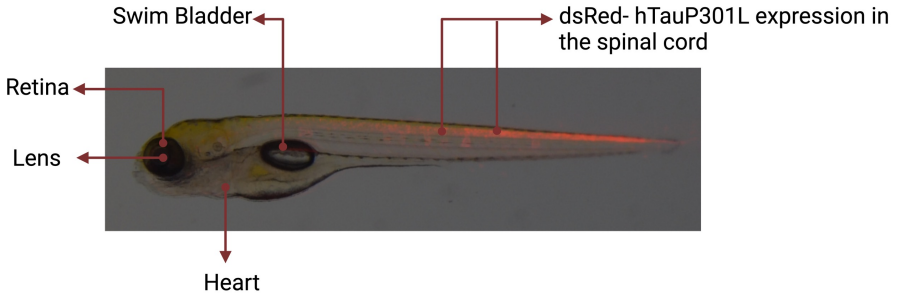
→ *EGR1* (early growth response 1) identified as key regulator of sex-dependent changes

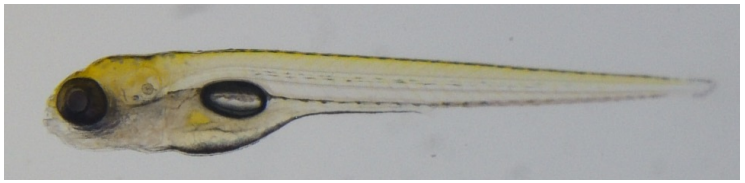


Zebrafish model analyses

- **Model**: Zebrafish larvae with tau pathology (TauP301L model)
- **Benefits**: rapid development, transparent embryos, genetic similarity to humans

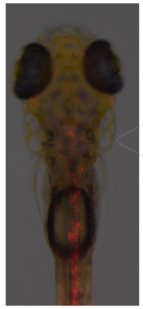
  → comprehensive analysis of candidate genes via intervention studies



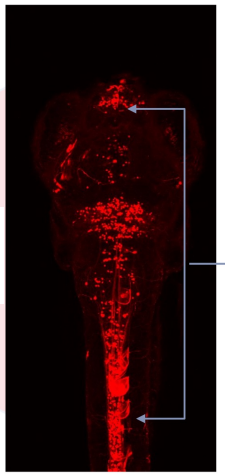


No fluorescence

No fluorescence



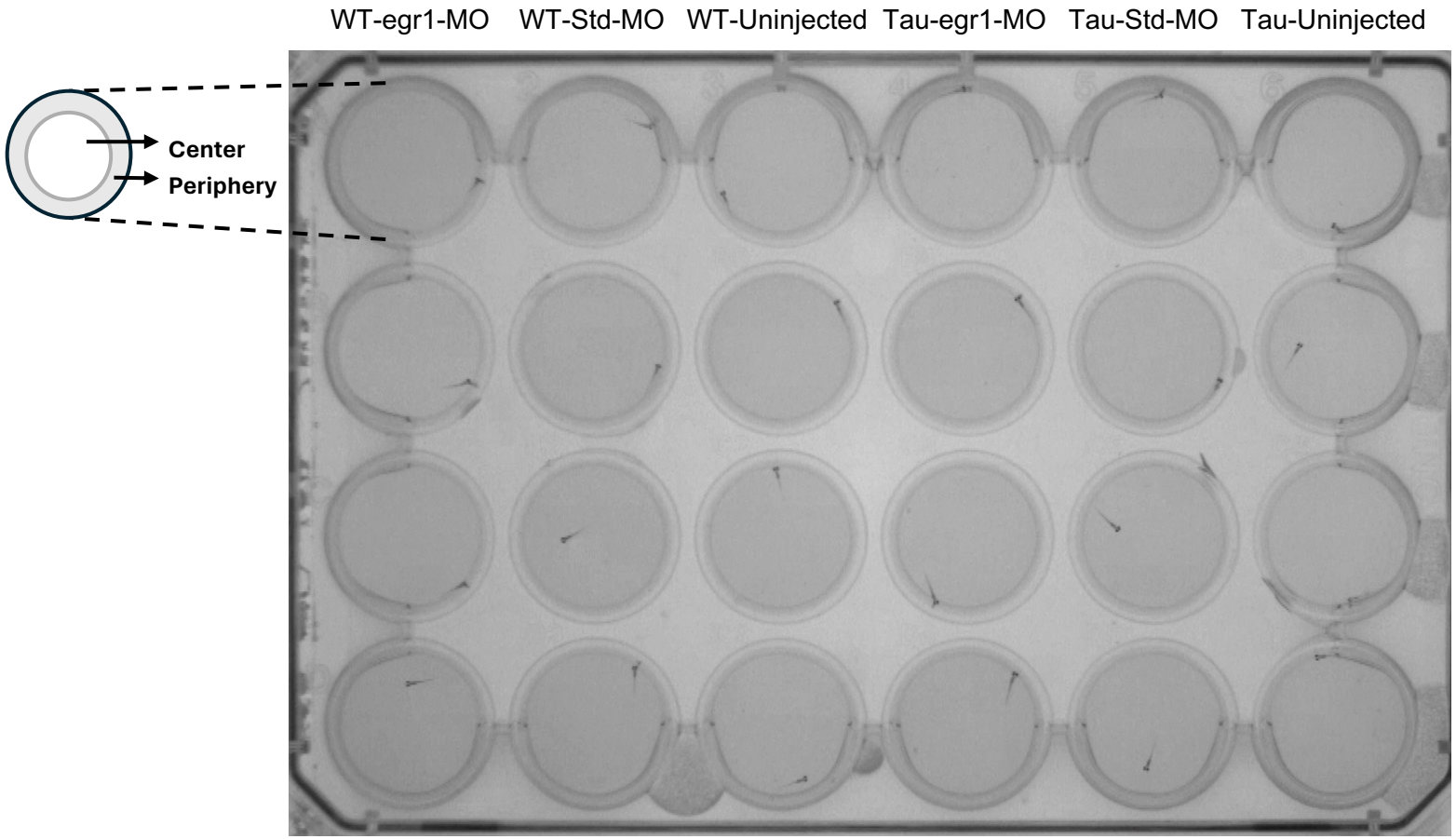
Confocal microscope



Mutant tau protein expression (red)

Zebrafish model analyses (2)

Locomotor activity: Track movement transitions between center and periphery



Zebrafish model analysis (2)

Experiment: Knockdown of candidate gene (*egr1*) in zebrafish model (TauP301L)

Molecular findings: Successful knockdown + mild effect on tau genes (*maptb*, *mapta*)

Behavioral findings: - Altered motor response in tau fish compared to wildtype

- Reduced adaptation to light/dark switches

- No significant behavioral change with *egr1* knockdown

Main conclusions:

→ Molecular effects of *egr1* knockdown insufficient for behavioral change

→ Model successfully validated for follow-up candidate genes analyses

Project progress overview (1)

2022:

- Publication of manuscript for the first mouse model (Tg2576 model)
- Pathway/network analyses of THY-Tau22 model data (hippocampus)
- Clustering & annotation of THY-Tau22 single cell data (cortex, age: 7M)
- Pathway analyses of THY-Tau22 single cell data (cortex, age: 7M)
- First network analyses of THY-Tau22 single cell data (cortex, 7M)
- Gene expression measurements for THY-Tau22 model at 17 months age

2023:

- Completed data analyses for THY-Tau22 mouse model (age: 7M)
- Comparative analysis of mouse models (Tg2576 & THY-Tau22, 7M)
- Comparison of mouse model data vs. human patient data
- First analyses of THY-Tau22 mouse model at 17 months of age
- First analyses of key regulatory genes derived from the mouse analyses in a zebrafish model of Alzheimer‘s disease

Project progress overview & next steps planned (2)

2024:

- Publication of findings on THY-Tau22 model (7-months)
- Completed analyses of THY-Tau22 mice at 17 months of age
- Submitted manuscript on temporal changes in THY-Tau22 mice (7 to 17 months, in revision stage)
- Publication on sex-dependent molecular changes in human Alzheimer's
- Publication of methodological framework for studying sex differences
- First gene knockdown experiments in the zebrafish model
- Molecular & behavioral assessments in the zebrafish model

Next steps:

- Compare findings to longitudinal molecular profiling data for human Alzheimer's disease, covering complementary biomolecules
- Test the effects of modulating identified disease-associated genes in human cell culture and zebrafish models

Thank you!

The Biomedical Data Science Group

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