Group 6 BCH242 Poster Project Outline Chee Ka Candice Lam, Peiqi Wang and Sai Kumar
Article: **Mutant huntingtin alters Tau phosphorylation and subcellular distribution**

Introduction - Background Knowledge and Unanswered Question

- Tau protein and tauopathies
- Huntington's disease (HD) and mutant huntingtin (mHtt)
- Does mHtt change (1)Tau phosphorylation and (2) subcellular localization individuals with HD?

Results - Important Data Figures, Experimental Methods, Controls (WT) and Weaknesses

- 2 HD models: R6/2 and KI140 (mutant 103QHtt); Control = littermate w/o HD (WT 25QHtt)
- Fig. 1+2: increase in Tau acidity correlating to hyperphosphorylation
  - 2D west. blot, SDS-PAGE, immunoblot analysis (IA) of WT littermates and two HD models
- Fig. 4: no change in expression of kinases and a significant decrease in phosphatase expression
  - SDS-PAGE and IA of diff. kinases + phosphatases (2 HD models + control WT littermates)
- Fig. 3: no co-localization of pS396 Tau and mutant Htt (pS396 Tau) *in vivo*
  - Confocal microscopy immunofluorescence detection of dsDNA(DAPI), mHtt and mTau
- Fig. 5: Shows aggregate compositions in vitro = mHtt and mTau found
  - SDS-PAGE + filter trap assay w/ Htt as expression control and GAPDH as loading control
- Fluorescence Recovery After Photobleaching (FRAP) shows dynamic properties of inclusions
  - No figure, full FRAP videos show constant turnover of mutant 103QHtt in aggregates
- Fig. 6: Co-localization patterns of different pairs (wild type 24QHtt, mutant 103QHtt and Tau)
  - Bimolecular fluorescence complementation assays in live cells
- Weaknesses (to be included in above slides): lack of controls, poorly-defined methods …

Conclusions - Contributions to the Field and a Model Figure

- mHtt leads to hypophosphorylation of Tau, most likely due to reduced phosphatases, resulting in:
  - Relocalization+sequestration of mHtt and mTau to inclusion compartments near the MTOC
  - Tau loss-of-function (i.e. impaired microtubule-stabilizing functions, reduced interaction with phosphatases, motor alterations, synaptic defects) = HD symptoms

Future Directions - New Questions Raised and Possible Future Experiments

- How can we reduce HD effects? Increase phosphatase in cells? Increase functioning Tau to promote recruitment to microtubules (regain function)? Gene therapy to treat HD?

Blum, D., Herrera, F., Francelle, L., Mendes, T., Basquin, M., Obriot, H., Demeyer, D., Sergeant, N., Gerhardt, E., Brouillet, E., Buee, L., and Outeiro, T.F. (2014) Mutant huntingtin alters Tau phosphorylation and subcellular distribution. *Hum. Mol. Genet*, **24**, 76-85.