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Booklets

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Title: Modeling of human polyglutamine neurological disorders in Drosophila

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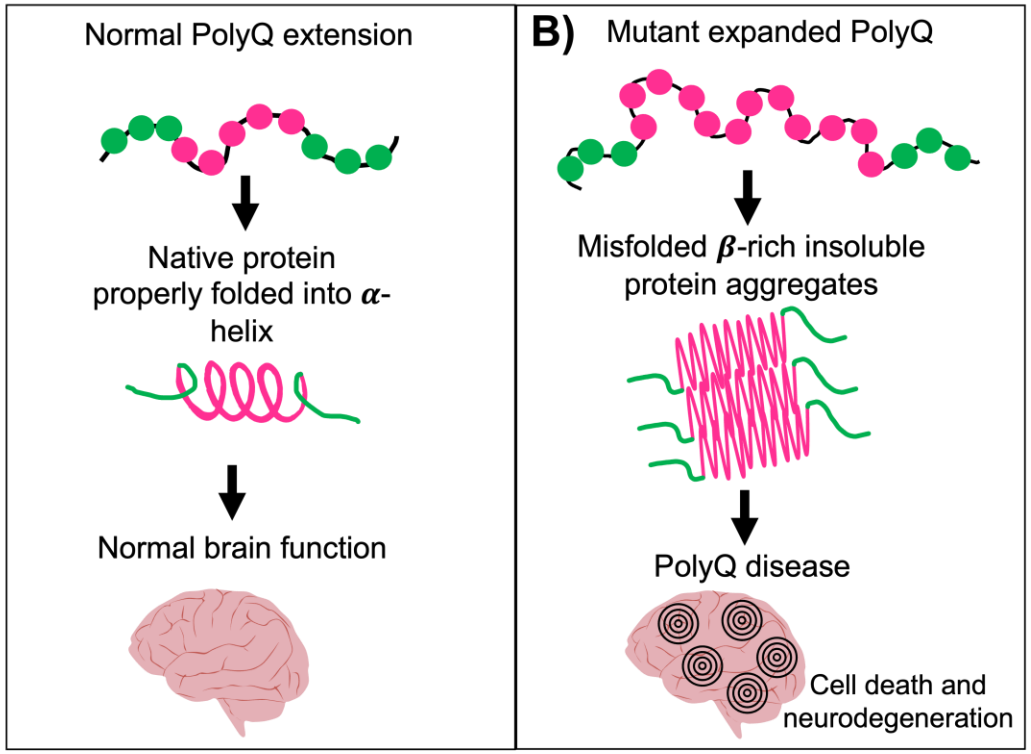
PolyQ Diseases

- Family of 40 autosomal dominant neurodegenerative disorders
  - Huntington’s disease and Spinocerebellar Ataxias (SCA) are among most common
- The affected neurons are in the cerebral cortex, basal ganglia, cerebellum, and retina
- Symptoms include chorea, ataxia, cognitive impairment, and eye degeneration

Shao and Diamond, 2007; Takahashi et al., 2010; McIntosh et al., 2021

Molecular Mechanism

- Increased number of CAG (glutamine) repeats in the affected genes
  - 35–50 glutamines in healthy proteins vs 40–100 in mutants
- Proteins involved have different function and mechanism
- Mutant proteins misfold and form aggregates
  - Aggregates may interfere with protein function or nuclear and celular mechanisms



Cohen-Carmon and Meshorer, 2012; McIntosh et al., 2021, Goswami et al., 2022

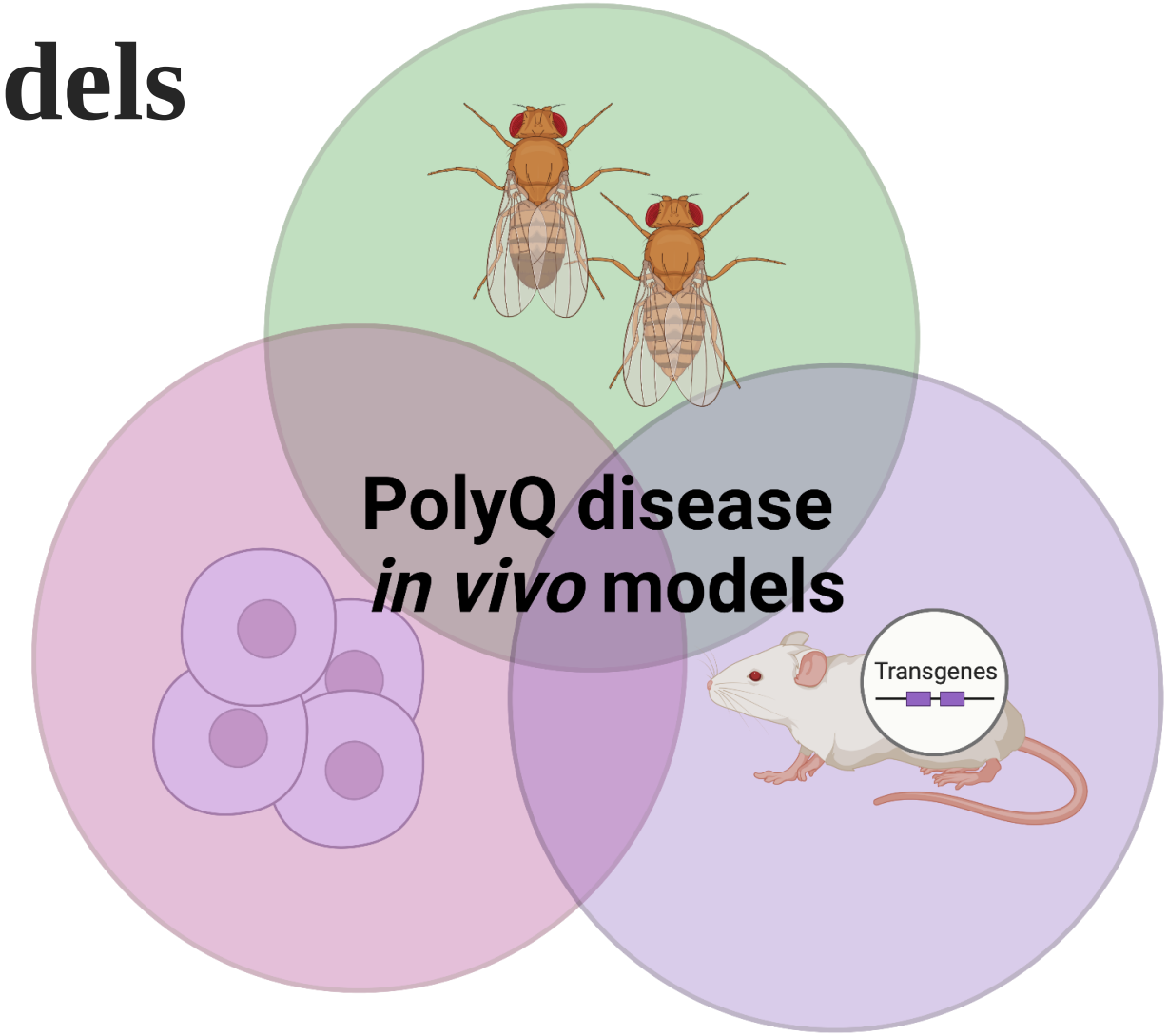
Molecular Mechanism (cont.)

- Huntington’s Disease (HD)
  - mutant hungtintin aggregates interfere with axonal transport, transcription, translation, and synaptic function in the affected neurons.
- Spinal and Bulbar Muscular Atrophy (SBMA)
  - toxicity is caused by aggregates of the mutant androgen receptor, affecting motor neurons and muscles, and causing endocrine issues.
- Spinocerebellar ataxias
  - Encompass 30 different diseases whose symptoms vary depending on the affected protein.
  - Mutant proteins accumulate in the nucleus and cytoplasm, affecting gene expression, cellular organization and other functions.

Orr and Zoghbi, 2007; McColgan and Tabrizi 2017; Breza and Koutsis, 2018; Chongtham and Agrawal, 2016

Models

- *In vitro*
  - Microarrays
  - FRET
- *In vivo*
  - Pluripotent stem cells
  - Transgenic mice
  - Transgenic fruit flies



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Luthi-Carter et al., 2002; Takahashi et al., 2010; Cohen-Carmon & Mesroher, 2012; Meierhofer et al., 2016; Naphade et al., 2019; Back et al., 2021; Koon & Chan, 2017; Rosas-Arellano et al., 2018

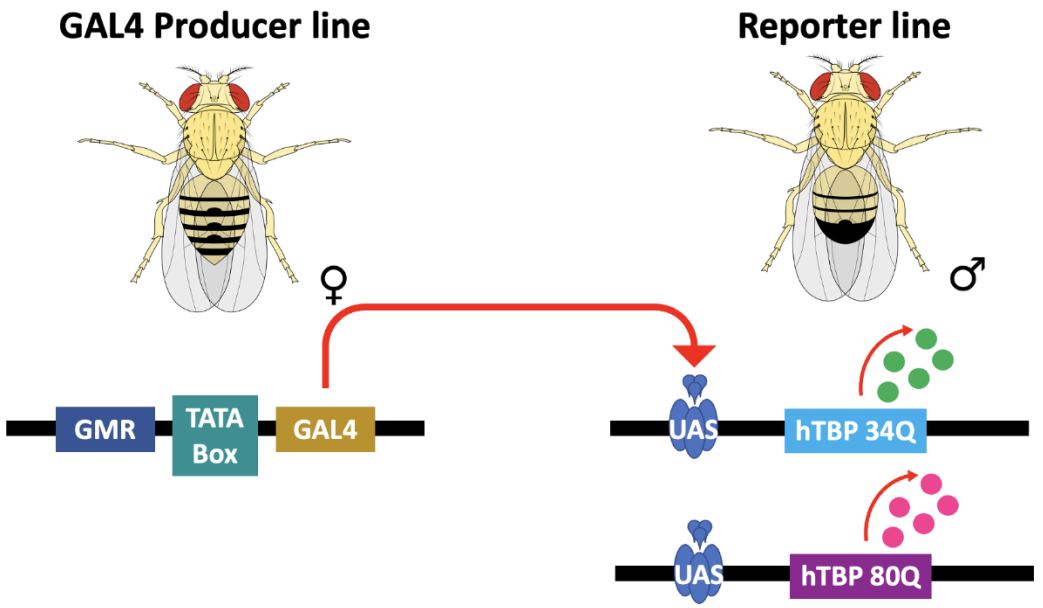
Drosophila as a model

- *D. melanogaster* has been used since the 1900s
- Small and easy to maintain and manipulate
- 75% of genes involved in human diseases have an homologue in fruit flies.
- Complex nervous system and behaviours makes it ideal to study neurodegenerative diseases.
    - Alzheimer, Parkinson, tauopathies, ALS, and PolyQ diseases

Sturtevant, 1959; Yamaguchi & Yoshida, 2018; Yamamoto et al., 2014; Xu et al., 2015; Tzou et al., 2022

Humanizing the fly

- The system consists of crossing a GAL4 producer line or driver and a UAS reporter line.
- The producer line encodes and expresses the GAL4 trans-activator protein under the control of a tissue-specific promoter or enhancer; the reporter line contains the gene encoding the protein of interest under the control of UAS sequences where GAL4 binds to activate transcription.
- When crossing both flies' lines, the progeny that contains both transgenes, in a tissue-specific manner, will express the GAL4 protein which in turn will bind to the UAS sequence and promote the transcription of the gene of interest only in the regions of the promoter's specificity.

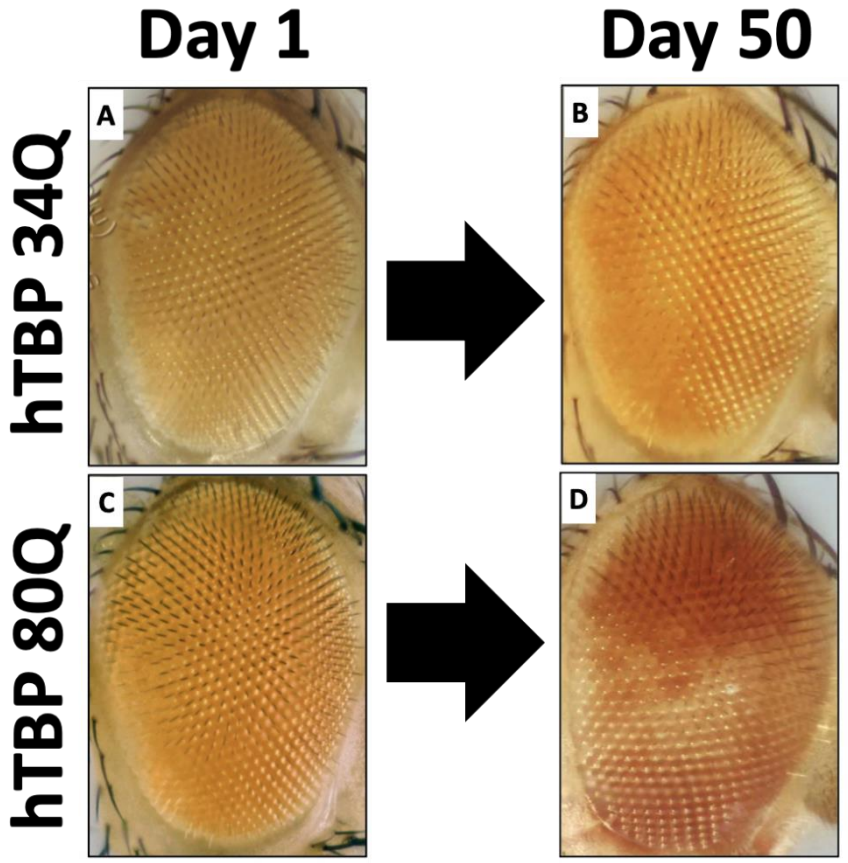


Brand & Perrimon, 1993; Marsh & Thompson, 2006

Drosophila and PolyQ Diseases

- Huntington's Disease
- SCA1
- SCA3
- SCA7
- SCA17

We developed a transgenic fly that expressed a mutated human TBP protein with 80Q in their eyes. After 50 days, the flies with the mutant protein degenerated with age, as shown by eye color and ommatidia degeneration.

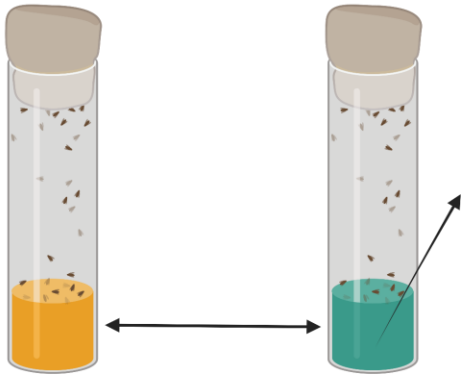


Warrick et al., 1998; Fernandez-Funez et al., 2000; Zhang et al., 2010, Ren et al., 2011, Cárdenas-Tueme, 2017

Drug screening and *Drosophila*

- *Drosophila* may be a useful model for testing new drugs
- "Humanized" *Drosophila* can help determine the adequacy of a drug, before reaching more expensive and time-consuming rodent assays or clinical trials
- Drug mechanism may be easier to elucidate in fruit flies, thanks to their reduced genetic redundancy

D. melanogaster with the desired genotype



Flies are kept until they reach the desired age

Drug being tested

Evaluation
- Toxicity
- Phenotype
- Behavior

Lawal et al., 2014; Wouters et al., 2018

Conclusions

- The common denominator of PolyQ diseases is the accummulation of abnormal proteins.
- Drosophila is a promising model for studying PolyQ diseases
- Our lab developed a model for SCA17 using fruit flies
- *Drosophila* and other animal models may open new and exciting avenues for therapeutics and diagnosis of PolyQ diseases

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