A *Caenorhabditis elegans* model for ubiquitin-proteasome activity

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The ubiquitin-proteasome system is the primary pathway for intracellular ATP-dependent proteolysis of many short-lived and misfolded proteins. In recent years, the ubiquitin-proteasome pathway has been implicated in certain conformational diseases, such as Alzheimer's Disease (AD). For instance, proteasome activity has been shown to decrease with age and in addition, a mutant form of ubiquitin B (UBB+1) has been detected in postmortem brain tissue of AD patients. UBB+1 has also been shown to inhibit the proteasome, ultimately ending in cell death. Lindsten et al. (2003) have developed a transgenic mouse expressing a ubiquitin-GFP fusion protein with an active degradation signal in order to visualize proteasome activity. Under normal physiological conditions, the fusion protein is efficiently targeted to and degraded by the proteasome. The administration of a proteasome inhibitor shows a dose and time-dependent accumulation of GFP expression. The disease-significant UBB+1 also results in GFP accumulation due to UBB+1's effective blockage of the proteasome.

C. elegans is a highly beneficial genetic tool for further analysis of proteasome activity *in vivo* using the ubiquitin-GFP reporter. Also, expression of UBB+1 in *C. elegans* using cell-specific promoters can provide insights into how variant ubiquitin, an endogenous proteasome inhibitor, contributes to cellular toxicity. Preliminary data shows a locomotor, egg-laying, and defecation defect that progresses with age in worms with muscle-specific expression of UBB+1. Inducible promoter constructs have also been developed to test whether the UBB+1 phenotype can be induced at earlier stages. We are currently testing if we can visualize proteasome activity in *C. elegans* using the ubiquitin-GFP reporter. Co-expression of UBB+1 together with the ubiquitin-GFP reporter can demonstrate not only proteasome activity in *C. elegans*, but is also useful for the identification (i.e. through RNAi screens) of novel proteins and compounds, which can ameliorate UBB+1 toxicity.

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