# CALIFORNIA STATE SCIENCE FAIR
# 2016 PROJECT SUMMARY

**Name(s)**

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**Project Number**

36657

**Project Title**

## Novel Interactions between Parkinson's Risk Genes and a-synuclein Reveal Disease Mechanisms and Pathway-Based Therapies

**Abstract**

**Objectives/Goals**

Parkinson's Disease (PD) is characterized by the death of dopaminergic (DA) neurons. The hallmark of PD is toxic aggregates of a-synuclein (a-syn) that induce degeneration of DA neurons. It is unclear how a-syn becomes toxic, which has hindered development of therapies. To elucidate PD, we studied its genetic forms, which provide insight into mechanisms of a-syn toxicity. We identified interactions between PD gene mutations and a-syn in yeast. The goals of our study were to 1) identify mechanisms of a-syn toxicity, and 2) identify potential therapies that target these pathways for treatment.

**Methods/Materials**

Deletions: We transformed yeast so that each strain contained a-syn and a PD gene deletion.
Overexpressions: We transformed yeast so that each strain contained a PD gene overexpression and a-syn.
Both: All yeast strains were grown as spotting assays. After growth, each strain was assigned a toxicity score to identify genes that enhanced or suppressed a-syn toxicity.

**Results**

Enhancers: Genes Swa2 and INP53 enhanced a-syn toxicity when deleted.
Suppressors: Genes Sno4 and HSP31 suppressed toxicity when overexpressed.

**Conclusions/Discussion**

Enhancers: DA neurons fire after using vesicle recycling and ER->Golgi trafficking to transport dopamine. Swa2 and INP53 enable vesicle recycling, and a-syn inhibits ER->Golgi trafficking. Swa2 and INP53 may have enhanced toxicity because both mechanisms of vesicle trafficking were inhibited.
Suppressors: Misfolded proteins cause oxidative stress, which damages cells. Neurons use chaperones to ensure proper folding. Sno4 and HSP31 are chaperones, and a-syn induces oxidative stress. Sno4 and HSP31 may have suppressed toxicity because the increased chaperones prevented oxidative stress.
Validation of targets: We validated drugs that target these mechanisms. The compound curcumin promotes endocytosis, and nicotinamide prevents oxidative stress. Last year, we found that both compounds decreased toxic a-syn in *C. elegans*, confirming our results.
Conclusions:
1) Novel PD mechanisms: i) Impaired vesicle recycling and ER->Golgi transport cause defects in synaptic vesicle trafficking/transmission, and ii) shortage of stress resistance chaperones causes oxidative stress due to misfolded protein accumulation.
2) Potential PD therapies: Treatments that i) promote vesicle trafficking, or ii) protect cells from misfolded proteins or oxidative stress.

**Summary Statement**

This project showed that impaired vesicle trafficking and oxidative stress are two novel mechanisms of a-syn toxicity, and that therapies targeting these mechanisms may effectively treat Parkinson's disease.

**Help Received**

We would like to thank Noori Chai and Dr. Aaron Gitler for their help and providing yeast strains.