Investigating Mitophagy as a Therapeutic Intervention for Parkinson’s Disease
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Introduction

- Parkinson’s Disease is a multisystem neurodegenerative condition
- Main symptoms include tremor at rest, stiffness, slowness of movement, and postural instability
- Non-motor symptoms include autonomic dysfunction and psychiatric problems
- There is currently no disease-modifying therapeutic on the market for patients

Annual disease cost: $52 billion
Annual US diagnosis: 60,000 patients

Project Goal

- Genetic evidence that mitochondria play a role in Parkinson’s Disease
- Mitochondria are energy-producing organelles found within cells
- Mitochondrial toxins can create Parkinson-like symptoms by killing highly energy-dependent neurons in the brain
- The goal of this project is to create a small molecule oral therapy that encourages a mitochondrial recycling process known as mitophagy
- The therapy my team is designing will inhibit a specific mitophagy antagonist protein
- By encouraging mitophagy with a therapy, we can aim to replenish long-term energy production in the neurons of Parkinson’s patients
- This has potential to improve neuronal health and fulfill an unmet therapeutic need for the Parkinson’s community

Results

- To induce mitophagy in vitro, mitochondrial insults CCCP, Oligomycin A, and Antimycin A are used to disrupt energy production in mitochondria
- Software algorithm is designed and utilized to quantify results of high content imaging mitophagy experiments
- CCCP and Oligomycin A decreased mitochondrial area in neurons after treatment for at least 24 hours, while Antimycin A did not
- Cellular debris observed after 48 hours in all conditions, including control
- Moving forward, CCCP and Oligomycin A will be used to induce mitophagy

Future Directions

- Future experiments will determine optimal concentrations of mitochondrial insults that induce mitophagy but not widespread cell death
- Expand experimental paradigm in order to perform biochemical assays for mitophagy and test novel Amgen compounds on existing assays
- Determining the proper reaction kinetics is crucial to understanding the ideal endpoint for various in vitro experiments

Approach

1. Develop human neuronal assays
2. Find proper mitochondrial insults while optimizing assays
3. Measure effects of drug intervention

Results

- High-content cellular imaging assays are particularly suited to measure cellular mitophagy in human neurons
- High-content cellular imaging assays provide both qualitative and quantitative data for:
  - Cytotoxicity
  - Cell morphology
  - Mitochondrial migration/localization

Procedure for Mitophagy Imaging Experiments

- Stain for Glial cells and MAP2
- Use high-content imaging to quantify mitophagy
- Analyze the data

Impact

- We developed human neuron-based mitophagy assays, built imaging algorithm to detect mitochondria in human neurons, and evaluated high content images as tools to visualize and quantify mitophagy
- Creating a therapy to target mitophagy will hopefully provide patients with the first ever disease-modifying therapeutic