Determinants of $\alpha$-Synuclein Toxicity
Biology of $\alpha$-Synuclein

Pathology of $\alpha$-Synuclein
α-Synuclein (Mis)Folding
Deep Mutational Scanning

Fowler, Fields. *Nat. Methods* 2014, 11, 801
The Model: Yeast

- Protein folding, quality control and degradation
  - Chaperone proteins (e.g. Hsp90)
  - Protein-remodelling factors (e.g. Hsp104)
  - Osmolytes (e.g. trehalose)
  - Proteolytic machineries (e.g. UPS, lysosomal and autophagic mechanisms)

- Lipid biology

- Vesicular trafficking and fusion

- Lysosomal and peroxisomal function

- Autophagy

- Apoptosis

- Mitochondria and oxidative stress

- Cell cycle

Deep Mutational Scanning

DNA Library Encoding All Missense Variants

Transform into Yeast

Induce Expression

Deep Sequencing

Variant Frequency

Less Toxic

More Toxic

Amino Acid Residue Number
\( \alpha \)-Synuclein (Mis)Folding

- Mitochondrial dysfunction
- ROS
- Blocking of the proteasome / ERAD
- Oligomer
- Aggregate
- Sequestration of chaperones
- Misfolding of metastable proteins
- Toxic gain-of-function
- Extracellular transport

Open Questions

• What cellular stresses would make a cell more susceptible to α-synuclein toxicity?

• Is the toxicity of α-synuclein dependent on its ability to engage different cellular factors?

• What features or properties of α-synuclein enable those cellular interactions?

• Is the cell targeting particular structures or residues of α-synuclein to mitigate toxicity?
A Chemical Biology Approach
Authorship Criteria

- Intellectual Contribution
  - Conceive/revise/develop approaches
  - Analyze/interpret data

- Technical Execution
  - Do something to help the study be accomplished

- Dissemination
  - Describe your work and its implications
  - Certify the manuscript
Goals for Today

• Meet your groups

• Come up with a name

• Choose the compound for your experiment, give 1 minute presentation justifying the compound selection

• Set up cluster access
Compound Choices

- MG132
- Brefeldin A
- Tunicamycin
- Geldanamycin
- Miconazole
- Menadione
- Spermidine
- TPCK
- Dopamine
- L-Dopa