# Evaluating Alzheimer's Disease Therapeutics on mitoNEET Expression

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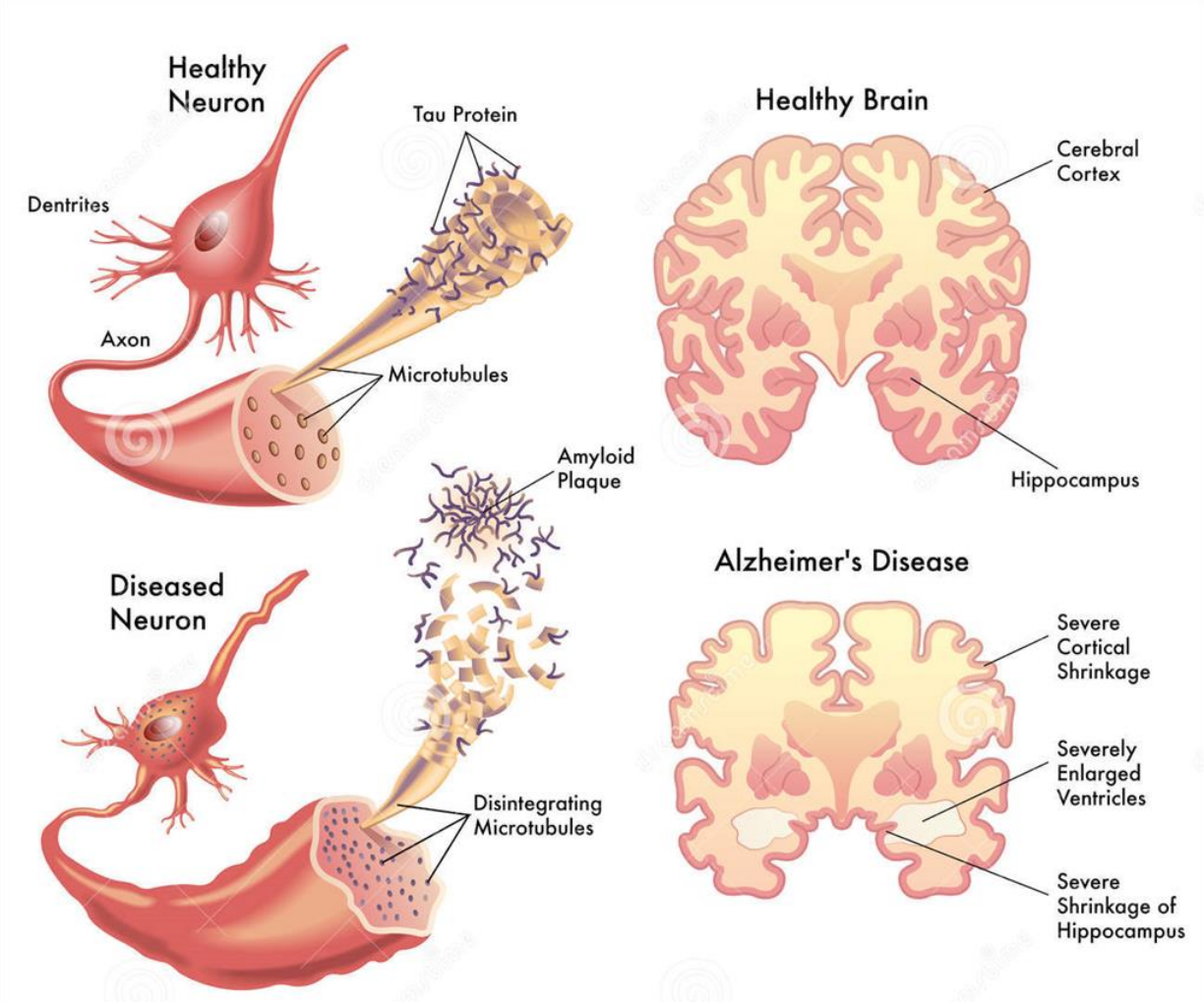
# Hallmarks of Alzheimer's Disease (AD)

- Neurodegenerative disease
- Common symptoms include dementia, cognitive impairment, and progressive memory loss
- Hallmarks of AD include the formation of senile plaques and neurofibrillary tangles

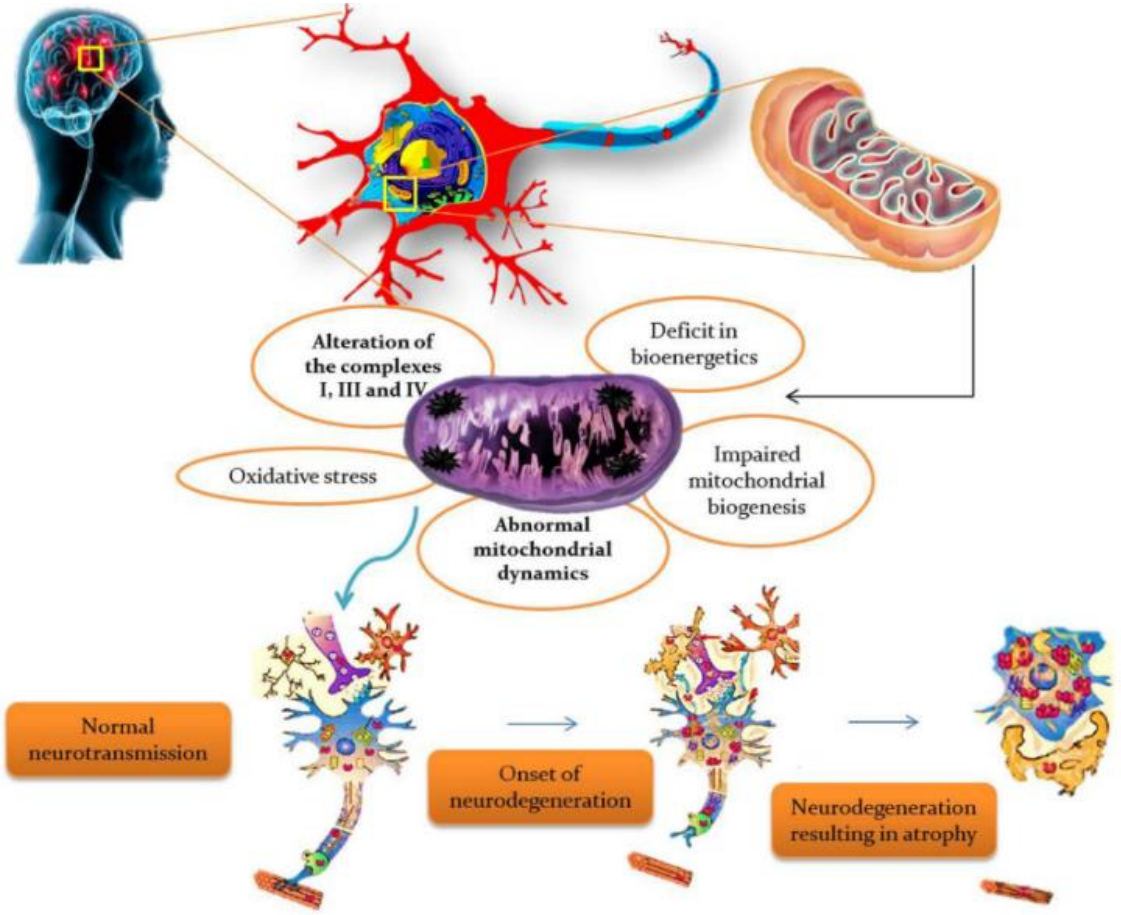


# Mitochondrial dysfunction and its role in cells

- Mitochondria play a role in many cell cycles including energy metabolism, antioxidant production, and cell survival

- Mitochondrial dysfunction leads to the formation of reactive oxygen species (ROS)

- Impaired mitochondrial pathways include ATP generation, ROS formation and defense, calcium buffering, morphology and dynamics, mPTP opening, and cytochrome c release.



# Current AD therapeutics

- AD therapeutics are cholinesterase inhibitors which inhibit acetylcholinesterase (AChE) and therefore increase the level of available acetylcholine

- They are limited to alleviating the symptoms of AD by trying to counterbalance the neurotransmitter disturbance

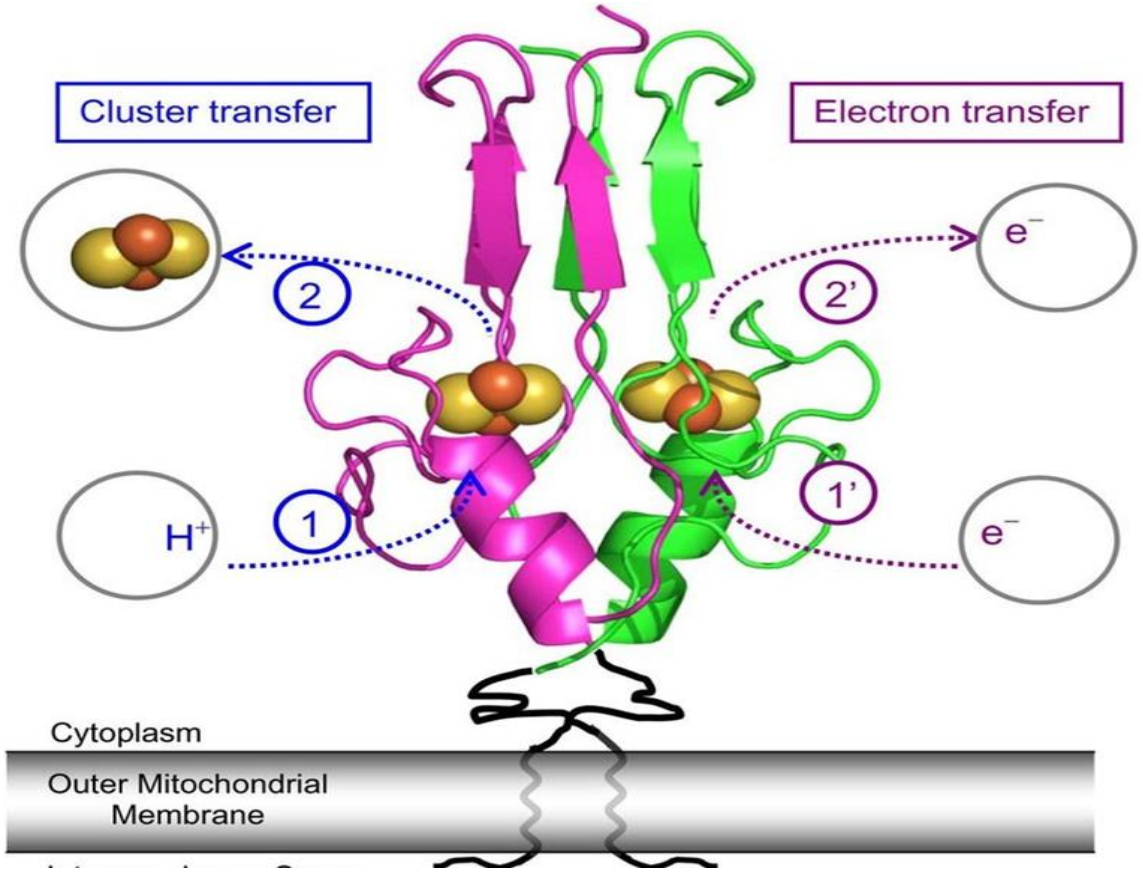
Table 1. FDA-Approved Drugs for Alzheimer's Disease

| Drug (Brand) | Class and Indication | Mechanism of Action | Common Adverse Effects |
|---|---|---|---|
| Donepezil (Aricept) | Cholinesterase inhibitor prescribed to treat symptoms of mild-to-moderate and moderate-to-severe AD | Prevents the breakdown of acetylcholine in the brain | Nausea, vomiting, diarrhea |
| Galantamine (Razadyne) | Cholinesterase inhibitor prescribed to treat symptoms of mild-to-moderate AD | Prevents the breakdown of acetylcholine and stimulates nicotinic receptors to release more acetylcholine in the brain | Nausea, vomiting, diarrhea, loss of appetite, weight loss |
| Memantine (Namenda) | NMDA antagonist prescribed to treat symptoms of moderate-to-severe AD | Blocks the toxic effects associated with excess glutamate and regulates glutamate activation | Dizziness, headache, constipation, confusion |
| Rivastigmine (Exelon) | Cholinesterase inhibitor prescribed to treat symptoms of mild-to-moderate AD | Prevents the breakdown of acetylcholine and butyrylcholine in the brain | Nausea, vomiting, diarrhea, loss of appetite, weight loss, muscle weakness |

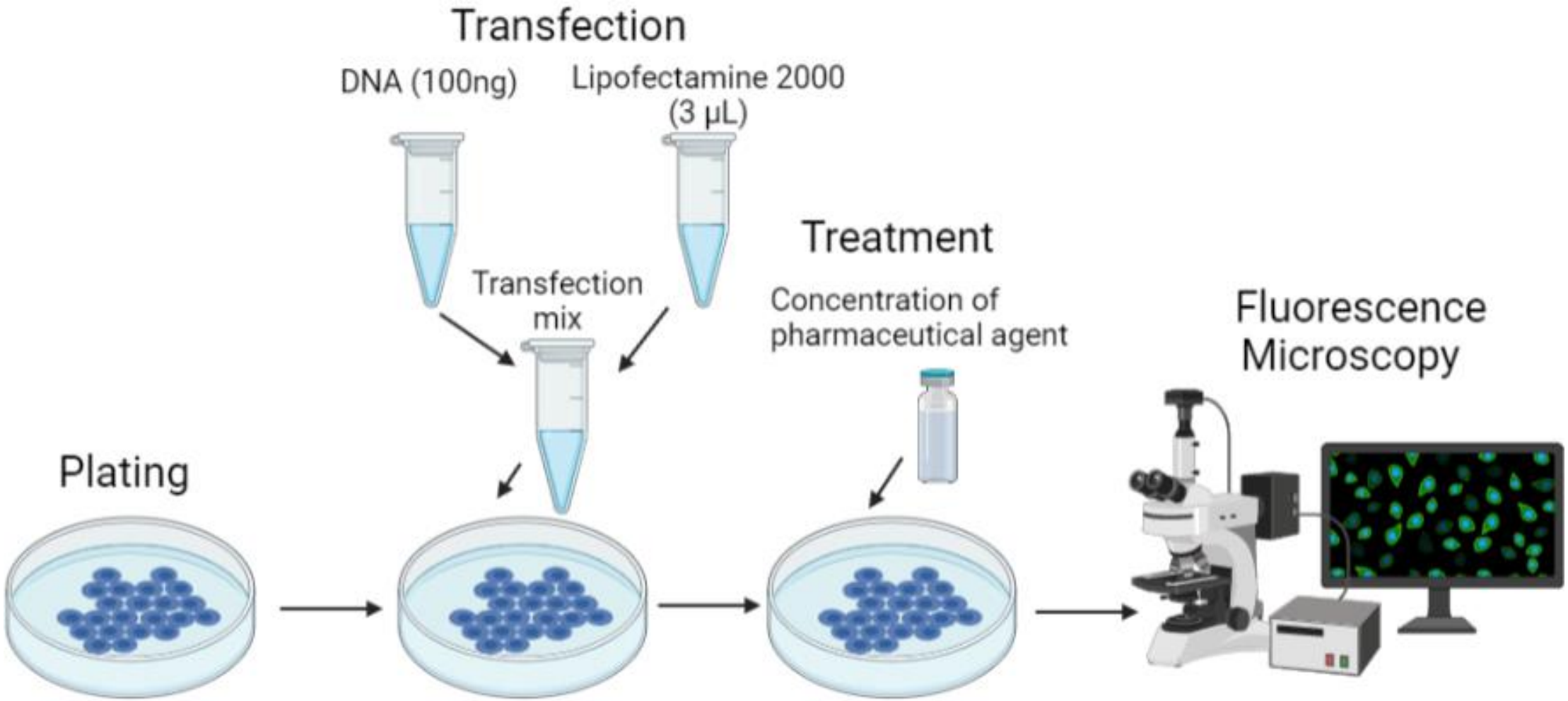
*AD: Alzheimer's disease; NMDA: N-methyl-D-aspartate.*
*Source: Reference 4.*

# What is mitoNEET and its role in cells

- Outer mitochondrial membrane protein with iron sulfur clusters
- Plays a role in iron homeostasis, regulating energy metabolism, formation of inter-mitochondrial junctions, and production of ROS
- Novel target for treating mitochondrial dysfunction and associated diseases



# Experiment Scheme



# Imaging using Fluorescence Microscopy

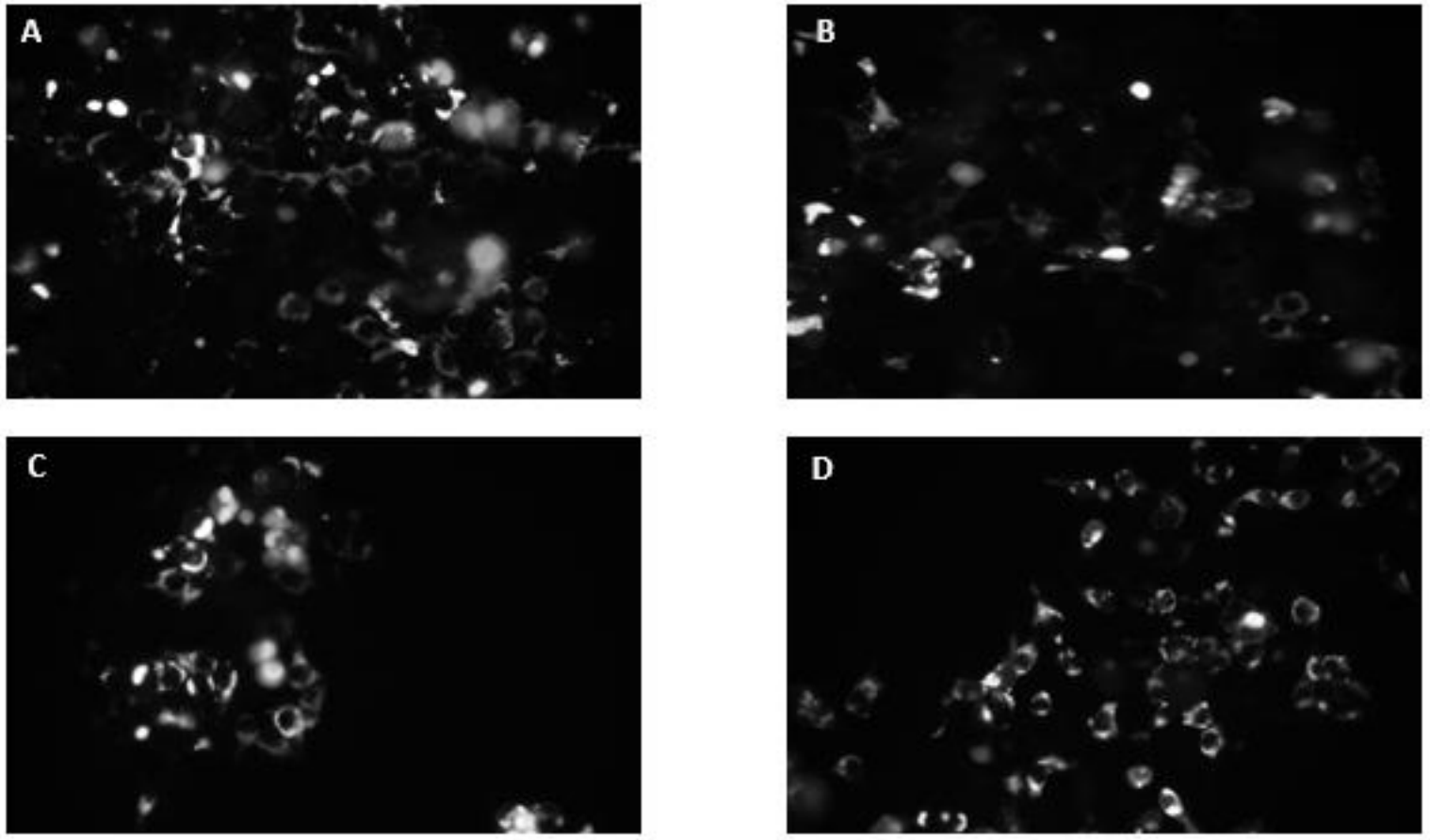
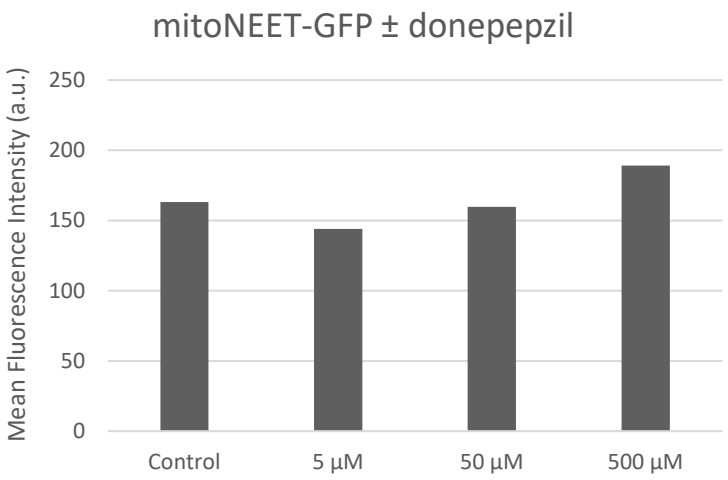
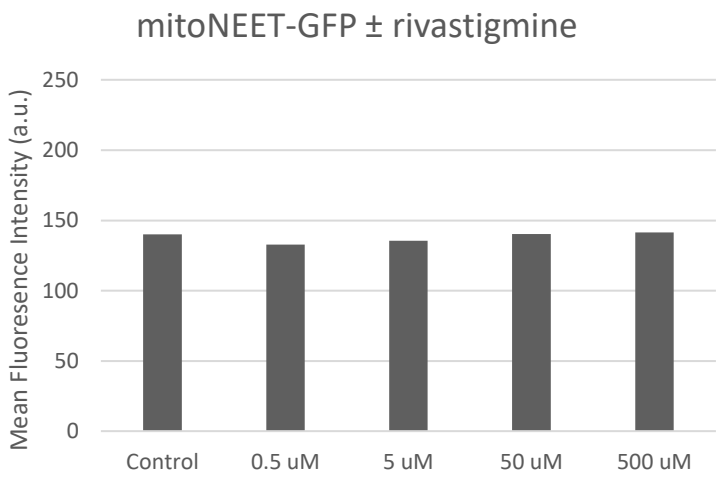
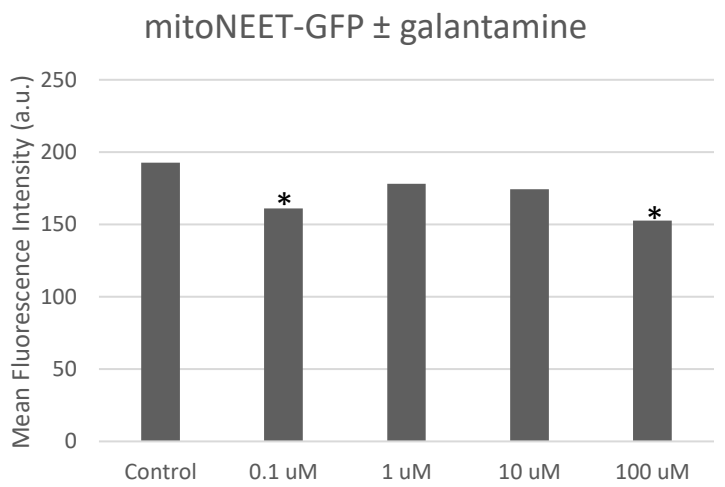


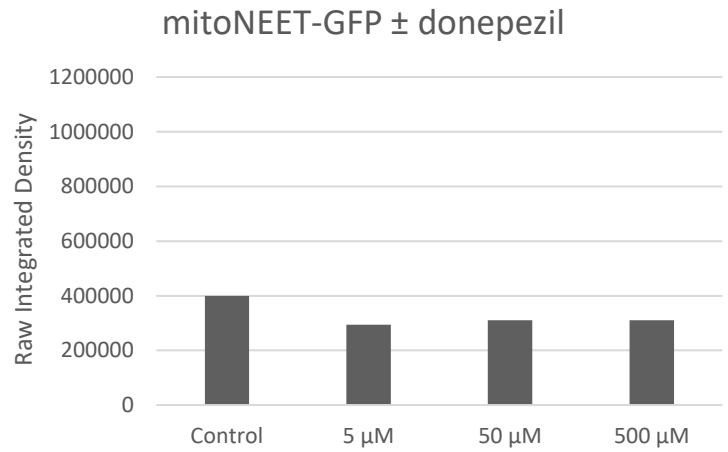

**Figure 1**. $N_2$a cells expressing mitoNEET-GFP (a) exposed to 5 µM (b), 50 µM (c), or 500 µM (d), donepezil for 24 hours.

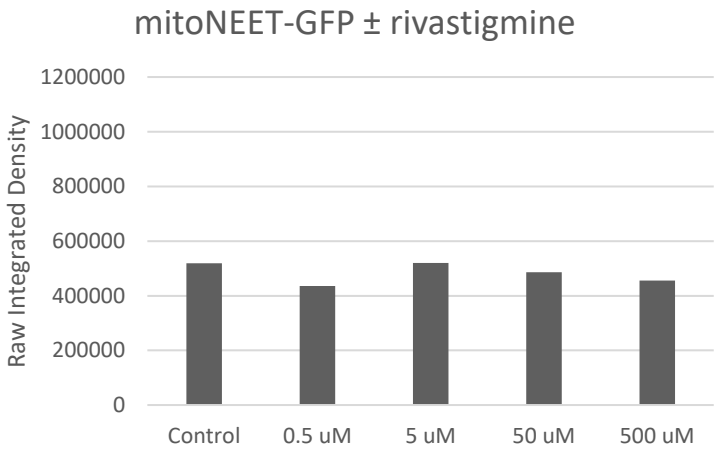
# Expression of mitoNEET in response to donepezil, rivastigmine, and galantamine

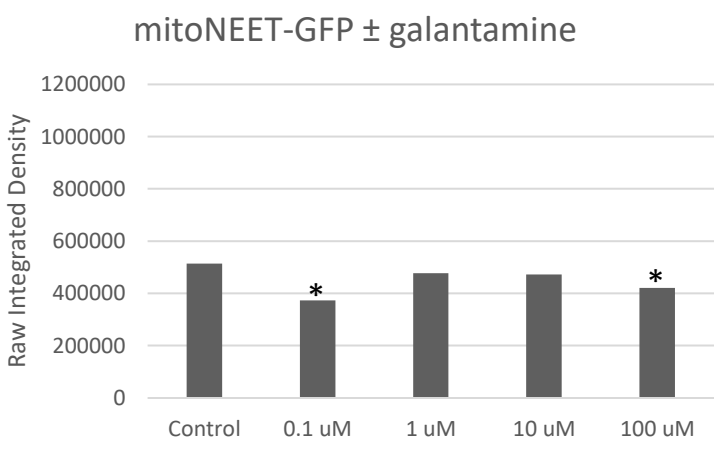


# Conclusion and Future Direction

- Donepezil and rivastigmine did not statistically impact the expression whereas certain concentrations of galantamine slightly statistically down regulated mitoNEET expression.

- These finding suggest that current AD drugs do not change mitoNEET expression and therefore do not target or impact mitochondrial dysfunction in cells.

- Future studies will explore the expression of mitoNEET in response to Aβ and oxidative stress.

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