## Characterizing the Role of Nuclear Flap Endonuclease 1 as a Mitochondrial Long Patch DNA Base Excision Repair Enzyme in vitro

Ye, Tong (School: Half Hollow Hills High School East)

Neurodegenerative disorders represent a global healthcare crisis impacting over 60 million individuals worldwide at an estimated cost of over 800 billion dollars, that is exacerbated by a relative absence of disease altering therapies. Prevalent in an aging population, neurodegenerative disease can be attributed to mitochondrial dysfunction and oxidative stress resulting in an accumulation of mitochondrial DNA damage. To combat this oxidative damage, organisms utilize a pathway termed Long Patch Base Excision Repair (LP-BER) that is implemented to repair both nuclear and mitochondrial DNA. While specific endonucleases required for nuclear repair are known, those involved in mitochondrial repair have not been established. To this end, a mitochondrial LP-BER assay was developed utilizing both tetrahydrofuran-incorporated and tetramethylrhodamine (TAMRA) labeled DNA substrates. FEN1, a nuclear flap endonuclease which has been shown to migrate to mitochondria during repair, was assayed to determine if it was competent in the mitochondrial LP-BER pathway. Results indicated that increasing FEN1 concentration yielded concomitant increases in mitochondrial DNA repair on both 3'- and 5'-TAMRA labeled substrate following assay optimization. These results suggest that FEN1 is capable of functioning in mitochondrial LP-BER and may have a critical role in preventing the accumulation of damaged DNA. Ultimately, these results further our understanding of mitochondrial DNA repair pathways and suggest strategies that may ameliorate potential defects in these pathways which lead to debilitating dementias and associated neuropathies. Specifically, upregulation of FEN1 and/or enhanced FEN1 activity may serve as an effective therapy to mitigate a variety of neurodegenerative disorders.

## Awards Won:

American Chemical Society: Fourth Award of \$1,000