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5th September, 2014

Brad Hoffman
President and Treasurer
SSADH Association
498 Lillian Court
Delafield, Wisconsin 53018

Re: Progress report and continuation request for the project "To determine if the induction of autophagy by rapamycin would remove surplus organelles, thus reducing oxidative stress and restoring cellular homeostasis which may lead to potential treatments for SSADH Deficiency"

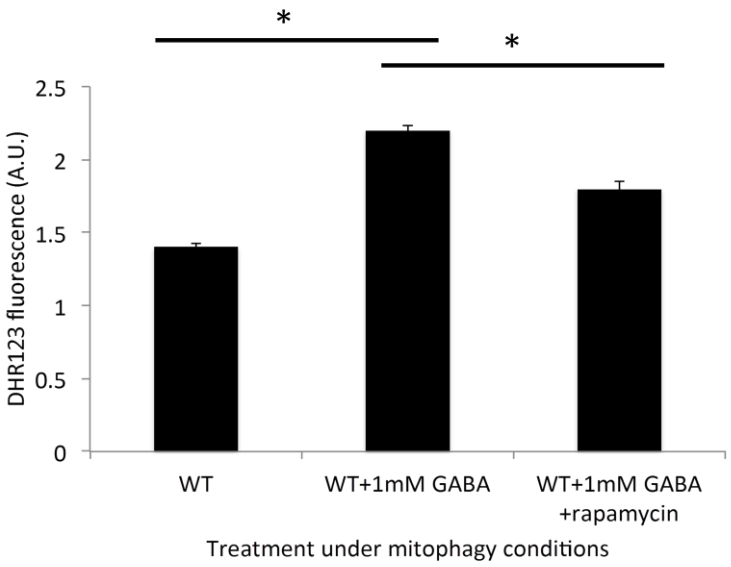
To the SSADH Association's Board of Directors,

Here is a summary of the progress achieved during the past six months investigating the role defects in autophagy-related pathways may cause the symptoms of SSADH deficiency and how rapamycin, or other autophagy-inducing or mTOR inhibiting drugs may alleviate the symptoms of this disease.

1. The manuscript sent to the high-impact journal "EMBO Molecular Medicine" was successfully accepted for publication.

2. Our re-submission of the NIH R21 grant (Which I wrote with Professor Suresh Subramani here at UCSD in collaboration with Professor Mike Gibson at Washington State University) was also successful, resulting in $275,000 of funding over the next two years. This funding will enable our research in the use of mTOR inhibitors to alleviate the symptoms of SSADH deficiency to continue, where the aim is to generate enough data to apply for a more substantial NIH R01 grant in the future.

3. We have also established a mammalian cell assay to measure oxidative stress, which shows that increased levels of GABA significantly increases oxidative stress in a human cell-line, and that the mTOR inhibitor, rapamycin, can significantly reduce the oxidative stress caused by elevated GABA (shown below). We can now use this assay to test the effect of other mTOR inhibitors, including Temsirolimus, Torin-1, Everolimus and others to establish which mTOR inhibitor is best able to reduce oxidative stress in human cells containing elevated levels of GABA.



4. I am also continuing research in yeast showing mechanistically exactly how autophagy-related pathways are inhibited in SSADH deficiency.

5. Finally, I have almost completed the analysis of organelle markers in human white blood cells to see if peroxisomes, ER or S6 phosphorylation is increased in SSADH-deficient patients, to see if what we see in yeast and SSADH-deficient mice is also conserved in humans with the disease.

I would again like to express my appreciation for the funding from the SSADH Association which has allowed me to continue this research, and believe the following 6 months will lead to even greater insights into the cause and potential treatments for SSADH deficiency.

Please let me know if you require any further information.

Regards,

Ronak Lakhani, PhD