WHITE PAPER

Research spotlight: New therapeutic targets focusing on aberrant lipid metabolism in Alzheimer's disease

As the global population ages and life expectancy increases, neurodegenerative disorders like Alzheimer's disease (AD) have the potential to overwhelm the healthcare system in the near future. Indeed, 50% of primary care physicians in the US believe medical professionals are not ready for this growth as well as the anticipated increase in cost to the US for AD and other dementias by more than 350% by 2050[1]. One issue is the lack of effective therapeutic treatments against AD. One of the major challenges we currently face is sparse drug discovery pipelines and low clinical trial success rates due to the variability of drug efficacy in individuals.

> "Indeed, compared to cancer research, the drug discovery pipelines for AD are very limited. A missing key ingredient that is needed to re-invigorate AD-related drug discovery is new, promising AD drug targets."
>
> - Dr. Maher, Sr Staff Scientist at Cellular Neurology, Salk Institute

Technological advances such as high-throughput phenotypic screens are also helping these endeavors to identify novel drugs. Dr. Pamela Maher, a Research Professor in Cellular Neurobiology Laboratory at the Salk Institute, notes on this point, "Promising drug targets must encode proteins whose activity is modifiable *in vivo* by small molecules or biologics in ways that alter disease onset, progression or outcome. However, currently our abilities to validate drug targets are mediocre at best."

Altogether, there is a steady migration from a reactive symptom-managing to a proactive disease-modifying stance

in regard to drug discovery. Basic researchers and biotech/pharma collaborate to understand both the genetic as well as phenotypic and physiological considerations that may ultimately lead to successful disease-modifying solutions to afford patients with higher quality of life for longer. The FDA recently granted priority review to an antibody therapy targeting amyloid beta proteins that form aggregates and plaques implicated in AD progression due to their toxic buildup in late 2020. AD's first pathological features were recognized in a signature case by Alois Alzheimer in 1906; from there, several hypotheses of disease pathogenesis was developed, including the amyloid hypothesis first proposed by John Hardy and David Allsop in 1991[3]. Complex disease research is never easy and takes time; however, some would agree that we are where fields such as immuno-oncology were only a few years ago: at the brink of medical breakthroughs for pressing, prevalent neurological disorders. Researchers are ceaselessly striving to explore novel pathways and elucidate drug targets. One of the exciting growing fields of study explores alterations in lipid metabolism implicated in neurological disorders; today we present key takeaways from a recent publication on exciting work targeting lipid peroxidation in AD.

revvity

Dr. Ates, in Dr. Maher's group, recently published their findings on CMS121, a small molecule derivative compound of the flavonoid fisetin for which they had been working on in the past decade that had shown initial potency against aspects of Alzheimer's cellular toxicities through a phenotypic screen assessing ischemia, inflammation, and oxidative stress. In their most recent publication, the lab shows the ability of CMS121 to modulate lipid metabolism by reducing inflammation and lipid peroxidation by targeting fatty acid synthase (FASN) in the brain, leading to alleviation of cognitive loss as displayed by several behavioral tests assessing spatial learning and memory (MWM), disinhibition phenotype, and contextual memory (fear conditioning assay) in a transgenic AD mice model APPswe/PS1Δ. The authors link CMS121's protective effect on cognitive loss to mitigation of lipid peroxidation and neuroinflammation in their mouse model, where they observed a decrease in hippocampal 4-hydroxynonenal (4HE) protein adduct levels, a cytotoxic by-product and marker of lipid peroxidation, in CMS121-treated AD mice back to wildtype mice levels (Figure 1).

Similarly, CMS121 treatment lowered the protein expression level of 15LOX2, a lipoxygenase (LOX) implicated in inflammation, lipid peroxidation, and cell death as well as glial fibrillary acidic protein (GFAP), a marker of inflammatory stress, back to wildtype levels in the hippocampus of AD mice. In the cortex, they saw that CMS121 treatment resulted in a decrease in total lipid-related metabolites compared to untreated AD mice, with relative levels of endocannabinoids, fatty acids, and PUFAs being significantly higher in these untreated AD mice using untargeted metabolomics mass spectrometry analysis via UPLC-MS/MS and GC-MS.

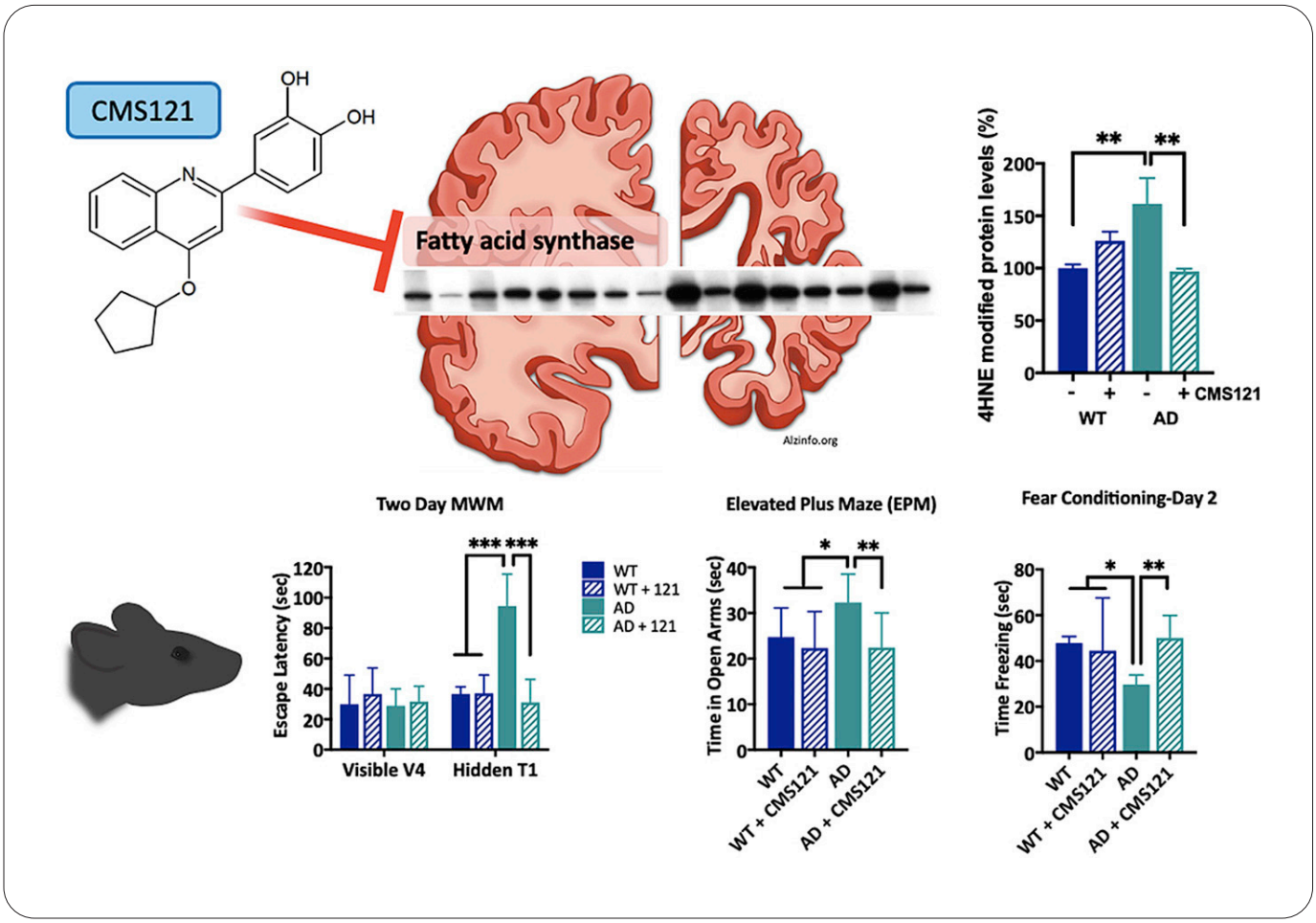

Figure 1: Graphical abstract from publication, summarizing the potential mode of action of CMS121 on improving cognitive decline in an transgenic AD mice model. Additional method details can be found in the method and figure legend of https://doi.org/10.1016/j.redox.2020.101648.

The lab performed numerous *in vitro* studies that not only strengthened their *in vivo* observations linking CMS121 to these pathways, but delved deeper into the mechanism by which CMS121 was having an effect. They observed its ability to counter the increase in eicosanoids – another marker of enzymatic and non-enzymatic lipid peroxidation – by intraneuronal amyloid-β, as well as resulting cell death, and performed a drug affinity responsive target stability (DARTS) analysis using mass spectrometry, which identified FASN as a top hit in two cell lines – HT22 neuronal cells and HeLa cells. Furthermore, they showed a CMS121 dose-dependent decrease in FASN activity, and subsequently explored the function of FASN using knockdown models for its impact on inflammation and oxytosis/ferroptosis, a cell death process linked to increases in lipid peroxidation.

> "In addition, by identifying fatty acid synthase as a target of CMS121, we open up a new avenue to explore and hopefully this will reinvigorate drug discovery in the field of AD."
>
> – Dr. Maher on her team's research

Thus, the importance and viability of novel targets associated with lipid peroxidation in AD cannot be understated during these times of exciting research discoveries in neuroscience. As altered lipid metabolism continues to be investigated as a hallmark of neurodegenerative diseases like AD, we anticipate seeing more diverse drug pipelines and promising therapies in the revvity. As lipids compose a majority of the makeup of the CNS and different brain disorders are tied to loss of mass in either the gray or white matter, one can muse that these findings centering around lipid metabolism may also have implications in other disorders as it pertains to myelin maintenance and protection such as in CMT1A and MS or sphingolipid deficits in psychiatric disorders like schizophrenia.

References

1. Alzheimer's association 2020 Alzheimer's infographic. (https://www.alz.org/media/Documents/alzheimers-facts-andfigures-infographic.pdf viewed 8/24/2020)
2. World Health Organization, detailed fact sheet Schizophrenia published Oct 2019. (https://www.who.int/news-room/factsheets/detail/schizophrenia viewed 8/24/2020)
3. Liu, P., Xie, Y., Meng, X. et al. (2019) History and progress of hypotheses and clinical trials for Alzheimer's disease. Sig Transduct Target Ther 4, 29. doi.org/10.1038/s41392-019-0063-8
4. Gamze Ates, Joshua Goldberg, Antonio Currais, Pamela Maher. (2020) CMS121, a fatty acid synthase inhibitor, protects against excess lipid peroxidation and inflammation and alleviates cognitive loss in a transgenic mouse model of Alzheimer's disease. Redox Biology 36: 101648. https://doi.org/10.1016/j. redox.2020.101648 (and references therein)

Revvity, Inc.
940 Winter Street
Waltham, MA 02451 USA
www.revvity.com