Toward Precision Medicine, June 3, 2019

Pierre D. Mourad, PhD. Professor. Engineering and Mathematics, UW Bothell and Neurological Surgery, UW Seattle. *Towards use of transcranial, near-diagnostic ultrasound to treat dementia*

Dr. Mourad presented on the potential of ultrasound therapy in treating Alzheimer's disease and related dementias. He presented preliminary evidence for the use of ultrasound therapy in the context of multiple prior studies in order to make a case for further research into this novel therapy.

Dr. Mourad explained that prior studies have shown that the use of light treatments of specific frequencies activates light-sensitive neurons and causes associated myelin re-growth or activated microglia with a reduction in amyloid beta plaque. He then proposed that ultrasound waves could be used to activate neurons and produce similar effects. He summarized relevant, prior research beginning with a study from 1950 showing de-activation of visual cortex by ultrasound in an anesthetized cat.

Dr. Mourad cited additional research, including some of his own studies, to highlight the capability of ultrasound to affect neurons and endothelial vasculature in different ways. He explained that outcomes of ultrasound treatment have included electrophysiological activation of neurons in vitro, blood brain barrier disruption and, presumably, plaque reduction by microglial activation, vasodilation of peripheral blood vessels, increased rate of re-myelination in de-myelinated mice, enhancement of endothelial NOS (eNOS), increased blood flow, and reduced concentrations of soluble amyloid beta.

He and his team have most recently used a 40Hz ultrasound treatment to activate targeted parts of the FAD mouse brain. Using canonical discriminant analysis sampling many methods to identify microglial activation, Mourad et al. found that a roundness in aspect ratio best differentiated some slides versus others, allowing Mourad to assess differences in the percent of activated microglia in populations throughout the mouse brain.

They found that the side of the mouse brain given the ultrasound treatment had increased percentages of activated microglia and reductions in amyloid beta plaque compared to the contralateral side without treatment and a "sham" group not given 40Hz ultrasound treatment. No reduction in amyloid beta plaque was observed, but concentrations of soluble amyloid beta were reduced.

While the mechanism for these changes is not known, Dr. Mourad suspects that ultrasound could be activating microglia by eNOS production or electrophysiological activity, or causing endothelial vasodilation, which allows microglia to access plaques more readily.

Dr. Mourad also reported unpublished findings from his current research where he has observed more active behavior in animals given ultrasound treatment compared to animals that did not receive treatment. Dr. Mourad's work is preliminary, and he aims to request a grant from the NIH to continue his work.

**Group Discussion:**

The group discussion pointed out that Dr. Mourad had not yet done a test to see if there was a difference in activated microglia morphology in mice without amyloid beta plaques present, and he has not verified that the ultrasound treatment does not disrupt the blood brain barrier.

Other discussion focused on Dr. Mourad's methods. The FAD mouse used in his research has not translated well into humans, presumably because of differences in plaque development and clearance. In

addition, his methods for measuring activated microglia were verified by present experts to be long-standing, but it was noted that recent data suggests a larger number of existing activated states.

Dr. Mourad's work is based upon the idea that the amyloid hypothesis is correct, and that efforts simply need to be taken earlier on in the disease process to yield real clinical benefits. Dr. Jeff Iliff suggested that this technology could be tested as a means to entrain neural frequency bands, such as delta waves, which become depleted with aging. Using this technology in such a way could prove important and would not depend on an assumption of the amyloid hypothesis.

While it would not be difficult to find human subjects with neurodegeneration to test this potential therapy on, finding amyloid positive non-symptomatic subjects would likely prove difficult, especially in the context of studies where amyloid was removed but patients either did not benefit or symptoms worsened. Researchers agreed that if operating under the amyloid hypothesis, an important goal must be to reduce amyloid burden without any adverse effects.

ADRC researchers then discussed the potential for collaboration with hospice centers. Such an effort could serve as a way to find human subjects that could be examined post-mortem. By doing so, these individuals could make a large contribution to the progress of Alzheimer's research.