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"Navitoclax does not alter genes related to blood-brain barrier proteins, Aβ and tau production in the hippocampus of a porcine model of familial hypercholesterolemia"

Purpose: Preclinical evidence demonstrates that navitoclax (ABT263), a potent experimental senolytic, reduces atherosclerosis and stabilizes atherosclerotic plaques. Atherosclerosis is a condition characterized by plaque accumulation on arterial walls and mainly consists of lipids. This buildup can constrict arteries and impair blood flow to key organs such as the brain, potentially resulting in hypoxia which is associated with compromised blood-brain barrier (BBB) and may contribute to neurodegeneration. The hippocampus is highly vulnerable to hypoxia and high fat diet has been linked to neurodegenerative outcomes, including memory decline. Therefore, we hypothesized that Navitoclax will upregulate genes for BBB proteins and downregulate genes for Aβ and tau production in a porcine model of familial hypercholesterolemia and atherosclerosis.

Methods: A total of 15 female Rapacz Familial hypercholesterolemia pigs (*Sus scrofa*) were randomly allotted into 3 groups: i.) Basal control (i.e., subjected to high fat diet for only 3 months), ii.) Mock (i.e., subjected to high fat diet for 6 months and administered placebo after the initial 3 months on high fat diet) and iii.) ABT (i.e., subjected to high fat diet for 6 months and administered ABT263 following the initial 3 months on high fat diet). High fat diet was meant to accelerate atherosclerosis. ABT263 was administered in evening feed at 150 mg per day for 7 days, followed by a total of 3 cycles of 325 mg per day for 21 days with 7 days off between each cycle. After humane euthanasia, hippocampal tissue was harvested and processed for qPCR analysis of Claudin-5, Occludin, ZO1, BACE-1, APP, PSEN-1 and MAPT genes.

Results: When compared to Mock group, ABT treatment did not change gene expression for BBB proteins (Claudin-5, Occludin and ZO-1), Aβ production (BACE-1, APP and PSEN-1) as well as tau production (MAPT). Chronic high fat diet significantly ($p<0.05$) downregulated Claudin-5 gene in Mock and ABT groups when compared to basal control. However, the duration of high fat diet did not downregulate nor upregulate all other genes assayed. Results are underway for the hippocampal glia genes such as GFAP and Iba-1.

Conclusion: ABT263 in female Rapacz-FH pigs does not downregulate hippocampal genes related to BBB and neurodegeneration. Also, except for Claudin-5, chronic high fat diet does not alter genes related to BBB proteins, Aβ and tau production.

Keywords: Atherosclerosis, blood-brain barrier, neurodegeneration, and senolytic.