

## AB023. Characterization of a novel anti-angiogenic protein for the treatment of exudative age-related macular degeneration

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**Background:** Age-related macular degeneration (AMD) is a leading cause of blindness in Canada. The exudative (wet) form of AMD accounts for approximately 15% of AMD patients, but is responsible for the majority of severe vision loss associated with the disease. Wet AMD is characterized by choroidal neovascularization, the abnormal growth of blood vessels from the choroid into the sub-retinal space. Current therapies for exudative AMD directly target and inhibit the vascular endothelial growth factor (VEGF) signaling pathway, a signaling axis that promotes endothelial cell survival. While initially effective at restoring visual acuity, recent studies suggest that chronic use of anti-VEGF therapies can lead to further vision impairment through off-target effects on photoreceptors and other non-vascular tissues. These off-target effects of anti-VEGF therapy highlights the need for alternative treatments for this increasingly common disease. We have recently identified a novel anti-angiogenic protein, AAP1 that inhibits retinal angiogenesis during development. As a regulator of the vasculature, our current work aims to characterize the function of AAP1 in endothelial cells and determine the potential of AAP1 as a therapy for exudative AMD.

**Methods:** To address our aims, we used various *in vivo* and *in vitro* models of normal and pathological vascular growth. Mice were injected intravitreally with AAP1 to investigate its effects on developmental and pathological angiogenesis. Using HUVECs, we employed immunofluorescent quantifications to determine the impact of AAP1 on sprouting angiogenesis by measuring cellular proliferation, apoptosis and migration. To investigate the signaling events that mediate the actions of AAP1, we examined key signaling pathways involved in angiogenesis by western blotting and qPCR.

**Results:** We evaluated the role of AAP1 as a regulator of angiogenesis during retinal development and mouse models of AMD. Our pilot data show that AAP1 prevents angiogenesis *in vitro* and *in vivo*, and that it can also inhibit pathological neovascularization in experimental models of AMD. In spite of its anti-angiogenic effects, our data show that AAP1 does not adversely affect photoreceptors. Both *in vitro* and *in vivo* systems showed a decrease in cellular division, while apoptosis was not affected in response to AAP1 treatment. While cellular migration was reduced in AAP1-treated HUVECs, cellular polarity was not affected. Finally, gene and protein expression of key angiogenic factors were modified in response to AAP1.

**Conclusions:** AAP1 is a potent regulator of angiogenesis. However, in contrast to anti-VEGF agents, our data suggests that AAP1 does not adversely affect the photoreceptors—highlighting the therapeutic potential of this protein. Further data generated from our studies characterizing the mechanism of AAP1 action may lead to a novel treatment option for AMD patients preventing vision loss and improving their quality of life.

**Keywords:** Age-related macular degeneration (AMD); angiogenesis

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