OFFICIAL ABSTRACT and CERTIFICATION

Evaluation of the Therapeutic Potential of Orlistat on a Mouse Model of Hereditary Hemorrhagic Telangiectasia

Seunguk (John) Baek
Herricks High School, New Hyde Park NY, United States

Hereditary hemorrhagic telangiectasia (HHT) is a genetic vascular disorder that is a highly debilitating disorder caused by loss-of-function mutations in bone morphogenetic protein 9 (BMP9)-ALK1-Smad1/5/9 signaling. Currently, there is no cure for this disease, however, it is characterized by Arteriovenous malformations (AVMs) around the brain, gastric-intestinal tract, liver, lungs, and skin. Sirolimus, an immunosuppressant drug used in liver transplant surgery has also shown to have possible links to treat AVMs; yet it is limited by its toxicity. Orlistat and Nintendonib are a class of FDA-approved drugs that are shown to have similar effects on the liver and organs associated with HHT as Sirolimus. Through the use of western blotting and vasculature analysis in the retina, the effect of Orlistat and nintedanib on mouse with BMP9/10 inhibition was tested to study the effectiveness of Orlistat in reducing HHT pathology. Results showed that Orlistat reversed the inhibitory effect of BMP9/10 antibodies in HHT model phosphorylation of Smad ($p<0.05$). However, although transmammary transfer of BMP9 and BMP10 blocking antibodies induces AVMs in the neonatal retina, Orlistat does not improve vascular pathology in the BMP9/10-immunoblocked retina. Therefore, my data highlights a beneficial interaction and synergy between Orlistat and Nin treatments in HHT mice. Further molecular mechanism studied can be made, and results can be supported through analysis through a bleeding assay and an increased dosage of the drugs.

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