**Targeting Proteolytic Activity using protease inhibitors as natural therapeutics for human metapneumovirus (HMPV)** Amber Earlywine1,2, Tyler Kinder3, Dr. Rebecca Dutch1,3 1NSF REU program, Lexington, KY; 2Berea College Department of Chemistry, Berea, KY; 3Department of Cellular and Molecular Biochemistry, University of Kentucky Lexington, KY; The fusion protein (F protein) has shown to be the only surface protein necessary for viral transmission of the negative sense, ssRNA virus, Human Metapneumovirus (HMPV). The F protein is activated through cleavage by proteolytic activity. The cleavage event causes a conformational change in the F protein where Heptad Repeat A (HRA) moves from the globular head, attaches to the membrane of the target cell, and moves to the stalk domain, fusing the two membranes. Based on previous knowledge of how serine proteases cleave Hemagglutinin (HA) in Respiratory Syncytial Virus (RSV), it is believed that these proteases also cleave the Fusion protein in HMPV. The goal of this project was to test if different proteases such as HAT (TMPRSS11D), TMPRSS2, TMPRSS4**,** Matriptase, KLK5, or KLK12 cleave the F protein so that we can use a protease inhibitor and stop viral spread. However, there was a focus on TMPRSS2 and TMPRSS4. First, expression of TMPRSS4 was tested using Western Blot Analysis, using HA as a positive control. When no expression was seen, TMPRSS4 was sub-cloned into pcAGGS from pcDNA and cleavage was not seen. TMPRSS2 expression was also tested through Western Blot Analysis with trypsin as a positive control and cleavage of the F protein was observed, suggesting that the TMPRSS2 protease can be inhibited.