**Prescott Cover Letter**

Dear Editor,

I would like to submit my original research manuscript titled “SARS-CoV-2 3CLpro whole human proteome cleavage analysis prediction and enrichment/depletion analysis” for consideration by PLOS ONE.

The structure of SARS-CoV-2 main protease (3CLpro) has been studied mainly to screen potential small molecule inhibitors and other interactions via molecular dynamics and docking, yet many variables determining its ability to cleave viral or host proteins remain poorly characterized. The recent explosion of publicly available coronavirus genomes has allowed me to create a 3CLpro putative cleavage dataset far larger than those used in previous publications. For the most part, my predecessors have limited applications of their cleavage prediction methods to designing peptide or peptidomimetic 3CLpro inhibitors, and few publications screen human proteins let alone speculate the broader impacts of these virus-host interactions. In this manuscript, I surpass accuracies of previously published cleavage prediction methods, apply the classifying neural networks to the entire human proteome, perform enrichment/depletion analysis on the 4,460 putatively cleaved proteins, discuss the viral benefits and host consequences of affecting many tissues and cellular pathways, and propose more than a dozen potential therapeutic targets against coronaviruses. I believe this analysis will open the door to similar investigations of all pathogenic proteases in all hosts.

I have no conflicts of interest, and this manuscript has not been submitted to any journal before. I believe any of your academic editors studying virology and host-pathogen interactions would be great reviewers, and it would be a privilege to have this manuscript accepted into PLOS ONE. Thank you for your time and consideration.

Sincerely,

Lucas Prescott

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