Title: “From the COVID-19 fog a new pain target emerges”

Abstract: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causative agent of COVID-19, a coronavirus disease that, as of February 4, has infected more than 104 million people and caused over 2.2 million deaths worldwide and paralyzed global economies. The pandemic continues unabated and certain aspects of the disease continue to baffle clinicians and researchers. It has been suggested that transmission of the SARS-CoV-2 by asymptomatic or mildly symptomatic individuals could be responsible for up to half of the spread, which may be why the virus has been so difficult to contain. Emerging evidence suggests that the Spike protein of SAR-CoV-2 is antinociceptive through subversion of a signaling pathway involving vascular endothelial growth factor-A (VEGF-A) and a host surface receptor (neuropilin-1, NRP-1). We leveraged this atypical pain-relieving function of the SARS-CoV-2 Spike interaction with NRP1 to perform a virtual screen of nearly 0.5 million compounds (diverse small molecules and commercially available natural products) against the VEGF-A binding site on the NRP-1 b1 domain. Nine chemical series emerged with identified chemotypes covering both small synthetic molecules and natural products. Predicted physico-chemical properties of all small molecule hit series fall within ranges of lead- or drug-like molecules. We identified two modes of binding that span the entire pocket at the VEGF-A/NRP-1 interface. Key binding elements were used to build a hybrid pharmacophore model which will guide the future design of synthetic molecules that fully occupy the available binding pocket. Our series of lead compounds represent a first step in a renewed effort to develop small molecule inhibitors of the VEGF-A/NRP-1 signaling pathway for the treatment of neuropathic pain and cancer and towards preventing or reducing SARS-CoV-2 viral entry. Prior to the ‘surprise’ emergence of the COVID-19 pandemic in December of 2019, the United States and parts of the World were mired by the opioid epidemic. Thus, the findings presented here are relevant to two current global health crises as emerging data suggest that the COVID-19 pandemic is likely to compound the opioid epidemic.

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