

Kinase Inhibitors in the Fight against COVID-19

Worldwide efforts to develop preventative and therapeutic treatments for coronavirus associated disease of 2019 (COVID-19), caused by SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2), are intensely focused on identification of potential targets based on its molecular virology and disease biology. Given it could be a considerable time before an effective vaccine is widely available, it's crucial to find drugs providing symptomatic and life-saving relief as soon as possible.

As of April 13, 2020 more than 160 potential drug candidates were under evaluation to treat COVID-19 patients¹⁾. These include monoclonal antibodies, anti-virals, anti-malarials in combination with antibiotics, interferon therapies and small molecule enzyme inhibitors such as kinase inhibitors. FDA approved kinase inhibitors under investigation for off-label use in SARS-CoV-2 include those targeting **Bruton's Tyrosine Kinase (BTK)** and **Janus Kinases (JAK1, JAK2)** as examples. The newest compound in this category is AstraZeneca's Calquence (acalabrutinib), a BTK inhibitor, administered by the NCI to a select group of ventilated COVID-19 patients at Walter Reed Army Medical Center. Its promising results have warranted expanded controlled clinical trials²⁾. BTK inhibitors block the BTK protein in a key signaling pathway that when dysregulated, leads to the excessive white blood B-cell production seen in chronic lymphocytic leukemia (CLL). BTK inhibitors also have anti-inflammatory properties. The rationale of applying a BTK inhibitor to SARS-CoV-2 is that it may dampen the cytokine storm seen in critically ill COVID-19 patients with advanced lung involvement (pneumonia), which can lead to death. Other BTK inhibitors such as ibrutinib, (Janssen & JabbVie's Imbruvica®) and the monoclonal antibody Actemra® (Roche) used to treat rheumatoid arthritis, are under consideration for evaluation in advanced lung disease patients with the virus.

Janus Kinase (JAK) inhibitors approved as rheumatologic and/or auto-immune therapies and now

under consideration or in clinical trials to treat the severe inflammatory response seen in seriously ill COVID-19 patients include baricitinib (Lilly's Olumiant®), tofacitinib (Pfizer's Xeljanz®), and ruxolitinib (Novartis & Incyte's Jakafi®).

Preclinical research recently published in Nature reported that the spike glycoprotein of SARS-CoV-2 interacts with hACE2 (human angiotension converting enzyme 2), a host receptor of the virus used for entry, and that **PIKfyve** is critical for virus entry. This has created interest in the potential of PIKfyve inhibitors to treat COVID-19. Using HEK293/hACE2 cells as a pseudotype viral system and 2 PIKfyve kinase inhibitor research reagents, apilimod and YM201636, the researchers were able to demonstrate the compounds' effect on significantly limiting entry of SARS-CoV-2 S pseudovirions in a dose dependent manner, suggesting that PIKfyve might be a potential drug target for viruses that enter cells through endocytosis in general³⁾. Apilimod had been in development as treatment for B-cell non-Hodgkin lymphoma and amyotrophic lateral sclerosis/frontotemporal dementia, under the name LAM-002 by AI Therapeutics. It is thought to hold promise for targeting the viral replication mechanism associated with SARS-CoV-2 host cell entry and as a potential combination therapy with anti-viral drugs such as Gilead Sciences' remdesivir¹⁾. While apilimod currently has no approved clinical role, it is another example where targeting the mechanism of intracellular trafficking associated with SARS-CoV-2 is hoped to result in finding effective therapies.

Because kinases represent integral signaling molecules in such a wide array of key cellular functions, undoubtedly additional kinases could emerge as therapeutic targets in the fight against COVID-19 and possibly other viruses going forward.

Carna Biosciences - The Kinase Company - offers [activity-based biochemical assays](#), [cell-based assays](#) and [residence time analysis services](#) with kinome-wide coverage where BTK, Janus, and lipid

kinase family members such as PIKfyve are among the many [kinase targets](#) available for interrogation. Our products and services have been used globally by drug development teams for more than 15 years. It is our hope that the high quality reagents and services we provide will assist research institutes, pharma and biotech companies in the fight against COVID-19, the coronavirus family as well as other viral diseases of the future.

To learn more, please feel free to [contact us](#).

References :

- 1) Genetic Engineering News, “Vanquishing the Virus-160+ covid-19 drug and vaccine candidates in development” , Philippidis, A, 13 April 2020
- 2) Forbes, “AstraZeneca’ s Calquence shows early promise for Covid-19 patients” , Vardi, N. 2020, 14 April 2020
- 3) Qian, Z. & Wang, J., et al, Nature Communications, 2020; 11(1):1620, pgs 1-12, Characterization of spike glycoprotein of SARS-CoV-2 on virus entry and its immune cross-reactivity with SARS-CoV.