UNIVERSITY OF WATERLOO

TECHNOLOGY SUMMARY

Novel Therapeutically Viable Conformation of SARS-CoV-2 Main Protease

Background

The global COVID-19 therapeutics market size is expected to grow from USD $10.2 billion in 2021 to USD $25.6 billion in 2030 at a CAGR of 10.7%. This growth is largely due to the coronavirus pandemic, which resulted an increase in the global demand for vaccines/therapeutics and in healthcare expenditures. Concerns regarding future Coronavirus outbreaks at regular intervals and the need to protect vulnerable populations globally from known as well as unencountered virus strains also drive this market growth.

The COVID-19 pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in a global health crisis and the evolving variants of SARS-CoV-2 have reduced the efficacy of the vaccines developed to date. Furthermore, as there have been two other coronavirus epidemics: SARS-CoV and MERS-CoV within the past two decades, there is an urgent need to develop antiviral drugs against a variety of coronaviruses. The viral main protease, known as Mpro, plays an essential role in the polyprotein processing of viral replication. Therefore, Mpro is an attractive target for the design and development of antiviral drugs.

Description of the invention

Waterloo's novel, non-naturally occurring, conformational state of SARS-CoV-2 main protease (Mpro) enzyme reveals new druggable sites and offers an ideal platform to develop small molecule therapeutics to inactivate the enzyme and, thus, control the replication and spread of the SARS-CoV-2 virus. The novel method uses a site-specific engineering strategy at an allosteric lateral site of the enzyme. In this structural state of Mpro, conformation of the functionally important cysteine residue (C145) is altered, and it forms a disulfide bond with a nearby cysteine (C117). This change reshapes the catalytic site and inactivates the enzyme, resulting in a novel composition of matter.

While COVID-19 vaccines target the spike protein of SARS-CoV-2, oral drugs silencing other enzymes of the virus, mainly the Mpro, has emerged as a promising therapeutic strategy. A current market-approved drug, paxlovid, through its nirmatrelvir composition, targets the active site of Mpro to inhibit its enzymatic activity associated with viral polyprotein processing. While this therapy is proven efficient, there are accumulating reports of resumption of SARS-CoV-2 infection. This necessitates an alternative strategy to silence Mpro.

Waterloo's innovative site-engineering methodology has resulted in a novel composition of matter (a resolved 3D structure of an inactive oxidized state of SARS-CoV-2 Mpro). These discoveries enable the development of drug candidates that can lock Mpro from SARS-CoV-2 and homologous Mpro from other coronaviruses in an inactive state.

Advantages

- Novel conformational state of Mpro enzyme offers a new platform to design drugs to lock the enzyme in its inactive state.
- Novel site-specific engineering approach offers a very efficient route to synthesize the non-native enzymatic form(s) of Mpro.
- Engineering strategy can help with developing broad-spectrum drugs against all coronaviruses.

Potential applications

Pharmaceutical industry -> specifically for drug development against Mpro from SARS-CoV-2 and homologous Mpro from other coronaviruses.

Reference
10220

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Stage of development
Prototype developed and currently being validated.

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