Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), represents an ongoing global crisis wreaking havoc on communities and economies. Key to SARS-CoV-2 therapeutic development is unravelling the mechanisms that drive high infectivity, broad tissue tropism, and severe pathology. We discovered a druggable pocket in SARS-CoV-2 spike (S) glycoprotein. Our cryo-EM structure revealed that the receptor-binding domains, which mediate viral infection, tightly bind the essential free fatty acid linoleic acid (LA) in three composite binding pockets locking S in a non-infective state. The pocket is highly conserved: a similar pocket is also present in the highly pathogenic SARS-CoV and MERS-CoV which caused the 2003 and 2012 outbreaks, respectively. Importantly, all SARS-CoV-2 Variants of Concern, including Omicron, contain this pocket which is thus evolutionary conserved since decades. LA binding to the pocket precludes binding of S to the cellular receptor ACE2 outside of cells, and inside of cells suppresses viral replication. These results set the stage for the development of an urgently needed, affordable and potent antiviral drug to inhibit infection and transmission of SARS-CoV-2.

**From Bench to Bedside: The Fortuitous discovery of a druggable pocket - and a drug - in SARS-CoV-2 Spike**

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