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Structure of SARS-CoV-2 papain-like protease PLpro reveals a framework for antiviral inhibitor design

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The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) papain-like protease (PLpro) is essential for the virus replication. PLpro has the additional function of removing ubiquitin and ISG15 (Interferon-stimulated gene 15) from host-cell proteins to aid coronaviruses in their evasion of the host innate immune responses. PLpro is thus an excellent drug target for a two-fold strategy to develop antiviral compounds that both inhibit viral replication and strengthen the immune response of the host. To provide a structural framework for efficient screening of inhibitor compounds, we expressed, purified and crystallized PLpro (Fig.1). The crystals are stable, reproducible, have a high solvent content of 66% suitable for soaking experiments and diffract to a high resolution of 1.5Å (Fig.2). Bioinformatics analysis of the active site based on the PLpro crystal structure coordinates showed interestingly high similarities to the proteasome and we screened 37 proteosome inhibitors by soaking and co-crystallization experiments. The PLpro crystals complexed with these compounds diffracted in the resolution range of 1.5Å-2.5Å and structural efforts to identify new antiviral compounds to combat the coronavirus spread will be presented.**strong text**

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