Unique Novel Drug Shows Promise against SARS-CoV-2

SARS-CoV-2 is an RNA virus that caused a three-year long pandemic with millions of reported deaths worldwide.[1,2] Despite the unprecedented speed of development and approval of SARS-CoV-2 vaccines and oral antivirals especially Paxlovid (co-administered Nirmatrelvir with ritonavir), there remain risks for emerging variants of concern (VOCs) with increased virulence and infectivity, and clinical challenges especially for population at risk who cannot benefit from existing drugs due to potential drug-drug interactions (DDIs). Continued development of oral antiviral drugs with improved antiviral potency and safety are needed to address current challenges in clinical practice for treatment of COVID-19.

Olgotrelvir (STI-1558) is designed as a potent standalone antiviral drug with excellent oral bioavailability, limited drug-drug interactions, and antiviral efficacy at doses with low safety concerns. Olgotrelvir and its parent drug AC1115 potently inhibit activities of SARS-CoV-2 main protease (M^{pro}) including M^{pro} mutants found in SARS-CoV-2 VOCs, as well as M^{pro} mutants such as E166 found to be resistant to Paxlovid. In addition, olgotrelvir inhibits activity of human cathepsin L (CTSL), the major host cysteine protease aiding in virus entry through the endosomal pathway.[3-5] The dual inhibition of both virus entry and virus replication pathways may enhance the robustness of the antiviral effect and reduce potential drug resistance. Indeed, olgotrelvir and AC1115 displayed potent antiviral activities against SARS-CoV-2 variants in cell-based models and in humanized transgenic mouse models. In phase 1 clinical trials, orally administered olgotrelvir demonstrated effective plasma exposure, limited mild adverse events, and a positive trend of reducing the SARS-CoV-2 viral RNA copy loads. Considering the favorable efficacy and pharmacokinetic profile along with data supporting the positive safety profile of the compound, olgotrelvir is a promising anti-SARS-CoV-2 drug candidate, which warrants further development as a next-generation therapeutic intervention for COVID-19 and potentially other coronaviruses.

To gain insight into the dual mechanisms, high resolution co-crystal structures of AC1115 with SARS-CoV-2 M^{pro} and human CTSL were determined at 1.8 Å and 1.4 Å resolution, respectively, using crystallographic data collected on SSRL BL12-1 and data collected at the ALS. The co-crystal structures of SARS-CoV-2 M^{pro} or human CTSL in complex with AC1115 (Figure 1) illustrates a covalent linkage between the aldehyde warhead and the sulfur atom of Cys145 at M^{pro} or Cys25 at human CTSL catalytic active sites.[6] Additionally, AC1115 fits well in the catalytic active site pockets, forming multiple favorable hydrophobic and hydrophilic interactions with M^{pro} or Human CTSL. These co-crystal structures and the bindings of the drug molecule into the catalytic active site pockets explain the high inhibitory activities of the drug against M^{pro} and human CTLS, as well as potentially reducing drug (Paxlovid) resistance.

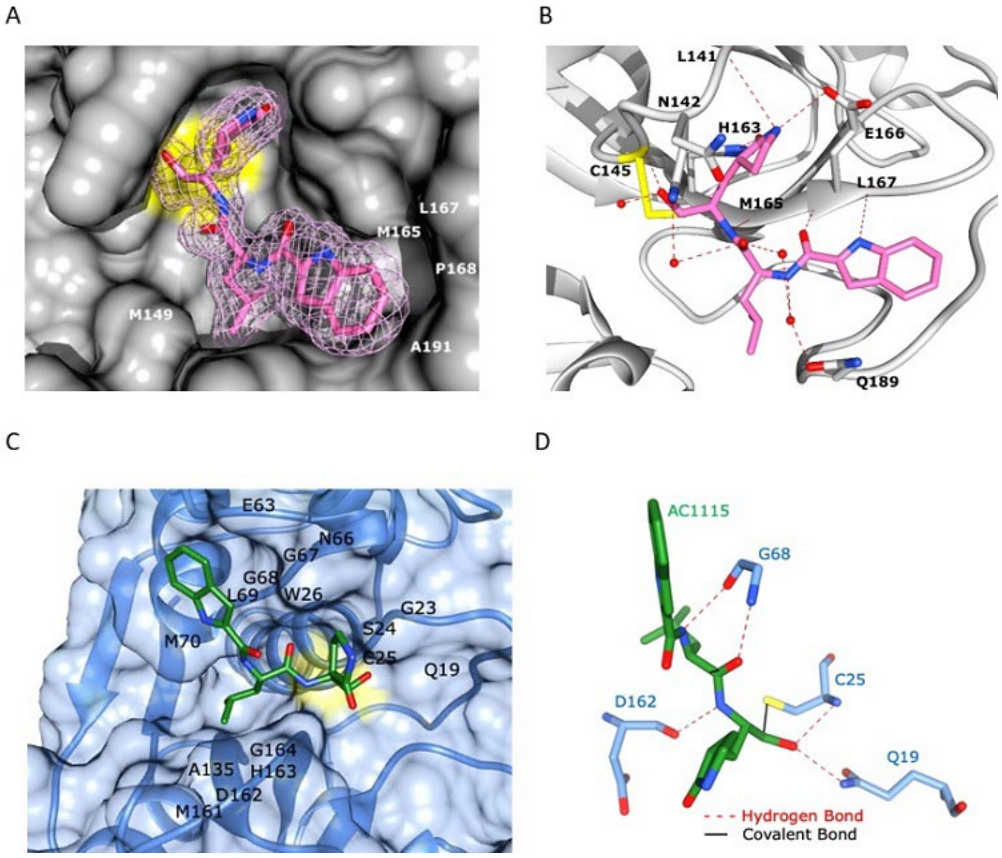

Figure 1. High resolution of co-crystal structure of SARS-CoV-2 M^{pro} or human cathepsin L complexed with AC1115. (**A**) SARS-CoV-2 M^{pro} (gray surface) bound with AC1115 (pink sticks). Electron density corresponding to AC1115 is shown in pink mesh. Hydrophobic residues of the M^{pro} catalytic active site binding pocket are labeled; with the active site cysteine shown in yellow. (**B**) Hydrogen bond interactions between AC1115 and M^{pro} are denoted with black lines. AC1115 forms 7 direct hydrogen bonds with M^{pro} residues, with additional polar interactions mediated by water molecules (red spheres). (**C**) CTSL protein (surface and cartoon) with covalently bound AC1115 (green sticks). Amino acid residues contacting AC1115 are labeled; the catalytic cysteine (Cys25) is additionally indicated by the yellow protein surface. **(D**) AC1115 hydrogen bonds with CTSL amino acids are shown (red dashed lines), along with the covalent bond to the Cys25 side chain sulfur atom (black line). The two structures were deposited to PDB with IDs of 8UAB and 8UAC.

In conclusion, the researchers at ACEA Therapeutics discovered and developed a new generation antiviral, olgotrelvir, that demonstrated potent inhibition of both virus entry and virus replication by targeting both M^{pro} and cathepsin L. Especially, the team also demonstrated that olgotrelvir can be used safely as a standalone treatment for COVID-19 without ritonavir as a booster, which reduces the drug-drug interactions.

At the time of preparing this summary, the clinical phase III study with 1212 patients has been successfully completed. The study demonstrated that olgotrelvir as standalone treatment significantly improved clinical recovery and reduced the viral RNA load in COVID-19 patients (pending for publication). Looking forward, the company is currently preparing

for new drug application (NDA) and seeking for approval of olgotrelvir from agencies in several countries. Furthermore, since olgotrelvir hits dual targets, the team is also exploring other indications and therapeutic fields for olgotrelvir beyond COVID-19.

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Primary Citation

L. Mao, N. Shaabani, X. Zhang, C. Jin, W. Xu, C. Argent, Y. Kushnareva, C. Powers, K. Stegman, J. Liu, H. Xie, C. Xu, Y. Bao, L. Xu, Y. Zhang, H. Yang, S. Qian, Y. Hu, J. Shao, C. Zhang, T. Li, Y. Li, N. Liu, Z. Lin, S. Wang, C. Wang, W. Shen, Y. Lin, D. Shu, Z. Zhu, O. Kotoi, L. Kerwin, Q. Han, L. Chumakova, J. Teijaro, M. Royal, M. Brunswick, R. Allen, H. Ji, H. Lu and X. Xu, "Olgotrelvir, a Dual Inhibitor of SARS-CoV-2 M^{pro} and Cathepsin L, as a Standalone Antiviral Oral Intervention Candidate for COVID-19", *Med* **5**, 42 (2024) doi: 10.1016/j.medj.2023.12.004

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SSRL is primarily supported by the DOE Offices of Basic Energy Sciences and Biological and Environmental Research, with additional support from the National Institutes of Health, National Institute of General Medical Sciences.