New research supports sofosbuvir in combination with other antivirals for COVID-19

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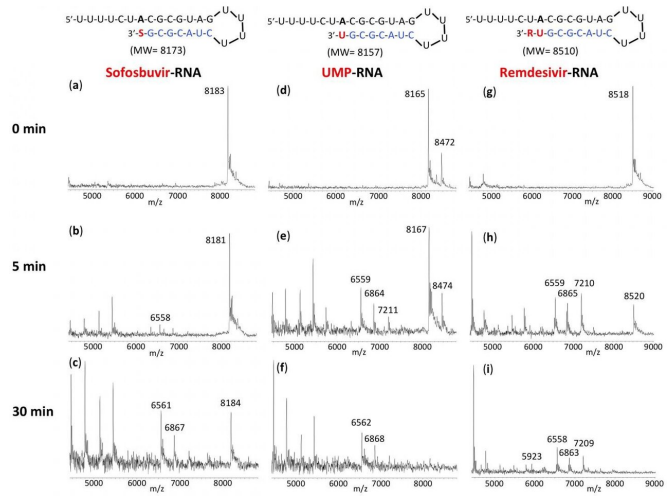

This figure shows that there is substantially more cleavage of Remdesivir-RNA (g, h, i) than Sofosbuvir-RNA (a, b, c) by SARS-CoV-2 exonuclease. It is also apparent that Remdesivir-RNA (g, h, i) is cleaved by the exonuclease more rapidly than RNA extended with UMP (d, e, f). The results were obtained by treatment of the RNA products with the SARS-CoV-2 exonuclease proofreader and analysis by MALDI-TOF mass spectrometry to determine relative excision of Sofosbuvir, UMP, and Remdesivir. Credit: Jingyue Ju/Columbia Engineering

Columbia Engineering researchers report that Sofosbuvir-terminated RNA is more resistant to the proofreader of SARS-CoV-2, the virus that causes COVID-19, than Remdesivir-terminated RNA. The results of the new study, published today by the Nature Research journal *Scientific Reports*, support the use of the FDA-approved hepatitis C drug EPCLUSA—Sofosbuvir/Velpatasvir—in combination with other drugs in COVID-19 clinical trials.

The SARS-CoV-2 exonuclease-based proofreader maintains the accuracy of viral RNA genome replication to sustain virulence. Any effective antiviral targeting the SARS-CoV-2 polymerase must therefore display a certain level of resistance to this proofreading activity.

"We found that the RNA terminated by Sofosbuvir resists removal by the exonuclease to a substantially higher extent than RNA terminated by Remdesivir, another drug being used as a COVID-19 therapeutic," says the team's lead PI Jingyue Ju, Samuel Ruben-Peter G. Viele Professor of Engineering; professor of Chemical Engineering and Pharmacology; director, Center for Genome Technology & Biomolecular Engineering.

The new study builds upon earlier work the researchers have conducted. Last January, before COVID-19 reached pandemic status, the team posited that EPCLUSA might inhibit SARS-CoV-2, the virus responsible for COVID-19. Their reasoning was based on the analysis of the molecular structures and activities of hepatitis C viral inhibitors and a comparison of hepatitis C virus and coronavirus replication.

In a subsequent study, the researchers demonstrated that the active drug Sofosbuvir triphosphate is incorporated by SARS-CoV and SARS-CoV-2 polymerases, shutting down the polymerase reaction. Other investigators have since demonstrated the ability of Sofosbuvir to inhibit SARS-CoV-2 replication in lung and brain cells; currently, COVID-19 clinical trials with a number of hepatitis C drugs such as EPCLUSA and the combination of Sofosbuvir and Daclatasvir (which is similar to Velpatasvir) are ongoing in several countries.

Ju notes that a recent preprint from UC Berkeley indicates that a combination of Remdesivir and

EPCLUSA increases Remdesivir's efficacy 25-fold in inhibiting SARS-CoV-2, the virus that causes COVID-19: "These results offer a molecular basis supporting the study of EPCLUSA in combination with Remdesivir for COVID-19 clinical trials."

More information: Steffen Jockusch et al, Sofosbuvir terminated RNA is more resistant to SARS-CoV-2 proofreader than RNA terminated by Remdesivir, *Scientific Reports* (2020). DOI: 10.1038/s41598-020-73641-9

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