Characterization of the Anti-HCV Activities of the New Cyclophilin Inhibitor STG-175
Philipp A. Gallay¹, Udayan Chatterji¹, Michael D. Bobartd², Zhengyu Long¹, Shengli Zhang³, and Zhuang Su²

BACKGROUND & AIMS
Shortened current direct-acting antiviral (DAA) therapies while less expensive, have not provided satisfactory efficacy in naive cirrhotics, treatment experienced non-cirrhotics, and even genotype-3 (GT3)-infected patients. Since DAA regimens consist of the same classes of inhibitors - NSSA (NS5A) and NSSB (NS5B) +/- NS3 (NS3) inhibitors - it is likely that their costs will be high and will provide similar degrees of protection. Retreatment provides little therapeutic benefit with distinct mechanisms of action (MoA) into DAA regimens could provide the solution for shortening the period of treatment. One such class of agents is the cyclophilin inhibitors (Cyp), which has shown efficacy in patients. Resistance-associated variants persist for years post-treatment in patients exposed to NSSA or NS5B who fail to achieve a sustained virologic response, impairing their chance for cure on retreatment with existing DAA combinations. Because of their high barrier to resistance, they may be particularly useful as a rescue therapy for patients who have relapsed with DAA resistance-associated variants.

METHODS
In this study, we analyzed the anti-HCV properties of the novel cyclophiline A (Csa) derivative - STG-175 - using a panel of in vitro assays including mono- and co-infection assays, viral clearance and rebound assays, and viral resistance and cross-resistance assays.

RESULTS

In this study, we analyzed the anti-HCV properties of the novel Csa derivative - STG-175. The non-immunosuppressive STG-175 possesses a high (EC₅₀ 11.5-38.9 nM) multi-genotypic (GT1a to 4a) anti-HCV activity. STG-175 clears cells from HCV since no viral rebound was observed after cessation of drug treatment. It presents a higher barrier to resistance than other Cyp or selected DAA. HCV variants, which emerged under STG-175 pressure, are only ~2-fold resistant to the drug. No cross-resistance was observed with DAA STG-175 was efficacious against DAA-resistant HCV variants. Drug combination studies revealed that STG-175 provides additive and synergistic effects against GT1a and 4a. STG-175 inhibits the infection of HCV, HIV-1 and HBV in mono-, dual- and triple-infection settings.

CONCLUSIONS
In this study, we analyzed the anti-HCV properties of the novel Csa derivative - STG-175. The non-immunosuppressive STG-175 possesses a high (EC₅₀ 11.5-38.9 nM) multi-genotypic (GT1a to 4a) anti-HCV activity. STG-175 clears cells from HCV since no viral rebound was observed after cessation of drug treatment. It presents a higher barrier to resistance than other Cyp or selected DAA. HCV variants, which emerged under STG-175 pressure, are only ~2-fold resistant to the drug. No cross-resistance was observed with DAA STG-175 was efficacious against DAA-resistant HCV variants. Drug combination studies revealed that STG-175 provides additive and synergistic effects against GT1a and 4a. STG-175 inhibits the infection of HCV, HIV-1 and HBV in mono-, dual- and triple-infection settings.

ACKNOWLEDGMENTS
We thank the AIDS Repository for the primary HCV-1a virus JR-CSF, T. Chouat for the Huh7.5.1 cells, D. Rice for the JFH1 cells, B. Ho for the GT4a and GT4b Huh7 cells, F. Panchaud, T. Maillet and B. Garnier-Banger for the Luc-JFH1-1 plasmid and the Huh-Luc Neo/Coni cell line, W. Darley for the GT2a cell line, and Christoph Seeger for JFH1 for help with the cell expression. This work was supported by the U.S. Public Health Service grants no. AI078391 and AI083057 (to J. F. Gallay) from the National Institute of Allergy and Infectious Diseases (NIAID) and a special funding Project 2179 from the S. & T. Global Inc.

Contact Information
Philipp Gallay can be contacted via email at gallay@scripps.edu; Zhuang Su can be contacted via email at zhuang.su@globalinc.com

REFERENCES