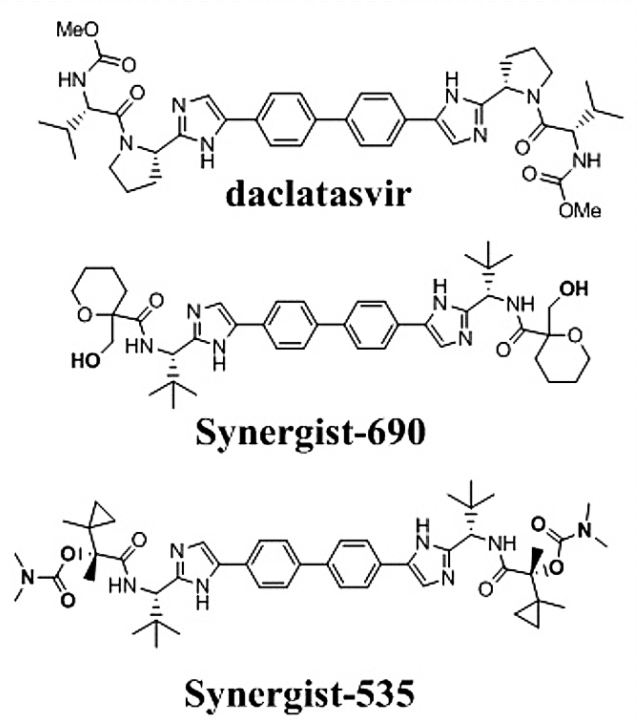
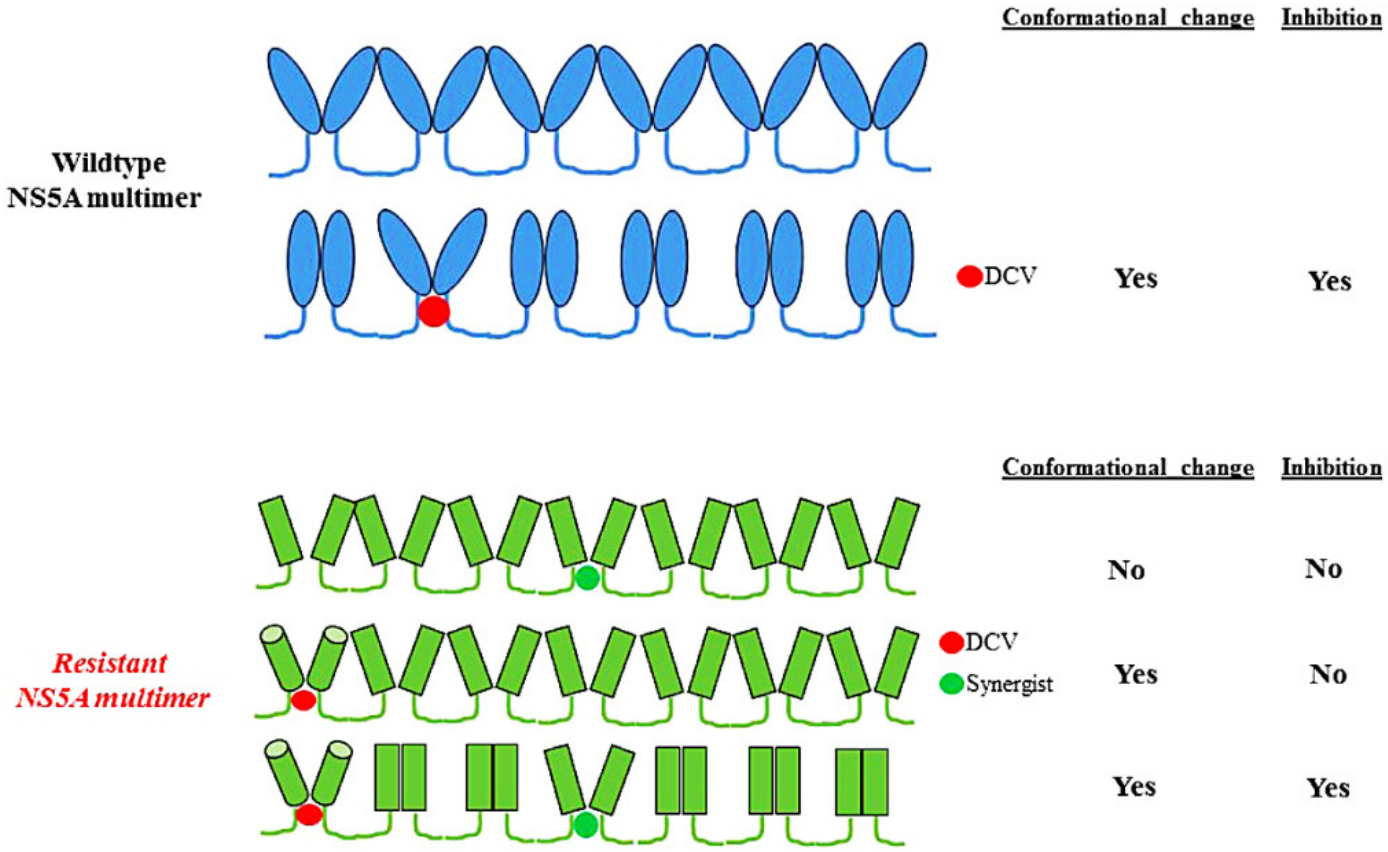
Making a good drug against a bad virus better

Recent advances in the treatment of chronic Hepatitis C virus (HCV) have led to a number of treatment options using only pills taken once-a-day that can lead to the elimination of the virus – a cure. Using only pills to totally eliminate a chronic viral infection is a first in the history of mankind. However, with all antiviral drugs, there is the potential for the virus to develop resistance which makes the drug much less effective. To overcome this problem, combinations of drugs have been developed resulting in very effective treatments with cure rates approaching 100% for chronic HCV infections.



One class of HCV drug used in these combinations are the most potent drugs ever described for HCV and are known as NS5A replication complex inhibitors (NS5A RCIs). The potency of these drugs are about a 1,000-times more potent than typical drugs and are in the pico-molar range (10^{-12}) for certain variants of HCV known as genotypes, including the one that is most prevalent in North America. When NS5A RCIs, such as daclatasvir (DCV, Fig. 1) are combined with other antivirals these combinations are highly efficient at curing patients. To try and find out why DCV is so potent, our group used techniques that looked at DCV binding to the viral protein along with related compounds to try and block the binding to the NS5A protein during an HCV infection. The HCV we used was modified so that it could make copies of itself but could not escape from inside liver cells in culture and is known as a replicon. To make the experiment easier to interpret, we used a replicon resistant to DCV that could allow binding of DCV to NS5A but lacked antiviral activity. When performing these experiments we found that certain pairs regained antiviral activity on the resistant virus: neither DCV nor related compounds by themselves were active but the

combination could recover picomolar potency. This type of synergistic activity using related compounds is, to our knowledge, a first for antiviral drugs. We published this initial observation in *Nature* using combination of compounds with the drug daclatasvir on a number of types of HCV replicons, infectious virus and chimeric mice.



To extend and further confirm this finding, the current publication used 6 different HCV replicons, 3 of the most difficult to cure HCV infectious viruses along with new synergists to explore the utility of this treatment (DCV + Synergist-690 or 535, Fig. 1). When compared to combinations of HCV drugs that bind to different proteins (ie the HCV protease or polymerase) and have been clinically evaluated, these combinations were shown to also be highly effective, spurring additional interest in these compounds. The data presented in this manuscript supports the use of these combinations as a promising replacement for other classes of HCV inhibitors targeting either the HCV protease or NS5B polymerase. Furthermore, the combination is shown to be highly effective on HCV populations that are fully-resistant to NS5A RCIs while still eliminating the virus from liver cells. These compounds provide additional tools to explore NS5A function and define a new class of HCV antivirals termed “NS5A synergists”. The mechanism(s) of how this effect is achieved is thought to involve a conformational change of an NS5A multimer upon binding of drug and NS5A synergist leading to inhibition of function(s) necessary for HCV growth (Fig. 2). The application of a similar screening methodology toward targets beyond HCV is possible and could lead to other potential synergistic inhibitors distinct from antivirals.

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Publication

Resensitizing daclatasvir-resistant hepatitis C variants by allosteric modulation of NS5A.
Sun JH, O'Boyle DR 2nd, Fridell RA, Langley DR, Wang C, Roberts SB, Nower P, Johnson BM, Moulin F, Nophsker MJ, Wang YK, Liu M, Rigat K, Tu Y, Hewawasam P, Kadow J, Meanwell NA, Cockett M, Lemm JA, Kramer M, Belema M, Gao M
Nature. 2015 Nov 12

Synergistic Activity of Combined NS5A Inhibitors.
O'Boyle DR 2nd, Nower PT, Gao M, Fridell R, Wang C, Hewawasam P, Lopez O, Tu Y, Meanwell NA, Belema M, Roberts SB, Cockett M, Sun JH
Antimicrob Agents Chemother. 2015 Dec 28