Development of a novel class of pan-genotypic HCV inhibitors for HCV combination therapy

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INTRODUCTION

Combination therapy has been the cornerstone of the treatment of chronic HCV infection. Further shortening of treatment duration could have significant benefits to HCV patients, including reducing viral breakthrough and toxicity. HCV NS3 protease/helicase is required for viral replication and is a dual functional enzyme with a serine protease domain and an ATP-dependent helicase domain. There are no approved HCV DAAs targeting the NS3 helicase domain.

AIM

Cocrystal Pharma, Inc. applied a unique structure-based drug design platform technology to develop pan-genotypic NS3 helicase inhibitors.

METHODS

HCV NS3 helicase domain (GT1-6) was purified for protein crystallization and IC50 determination. The NS3 helicase crystals and cocrystals diffracted to 1.9-2.5 A. Antiviral activity was determined using HCV replicon and chimeric replicon assays. X-ray data collection was done at ALS, SSRL, and APS.

RESULTS

We identified novel inhibitors that bind to a highly conserved drug binding pocket (CBP-1) located within the RNA binding channel of the GT-1b NS3 helicase domain. High resolution X-ray cocrystal structures confirmed that the CBP-1 binding pocket is highly conserved among all six HCV genotypes (GT1-6). The CPB-1 inhibitors block the unwinding activity of the NS3 helicase, and do not inhibit the ATPase. We also demonstrated pan-genotypic antiviral activity of these helicase inhibitors in the HCV replicon assays.

Figure 1: HCV Helicase Antivirals For HCV Combination Regimen

- HCV NS3 plays an essential role for the viral replication and consists of two domains, helicase and protease
- No approved DAA targeting the NS3 helicase activity
- Potential DAA for HCV combination regimen with NNI, Nuc, PI, and/or NS5A inhibitors

(A) HCV NS3 helicase-protease structure (B) Potential new combination regimen

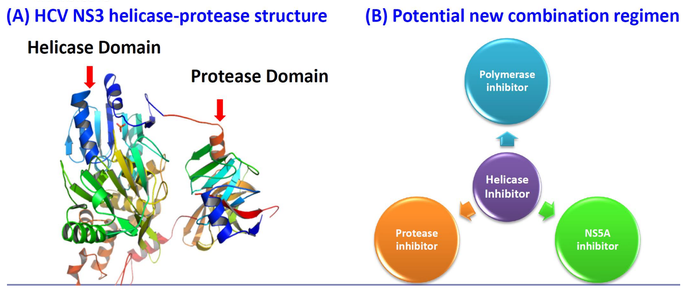


Figure 2: Cocrystal Drug Discovery Platform Technology For Developing Broad Spectrum Antiviral Therapeutics

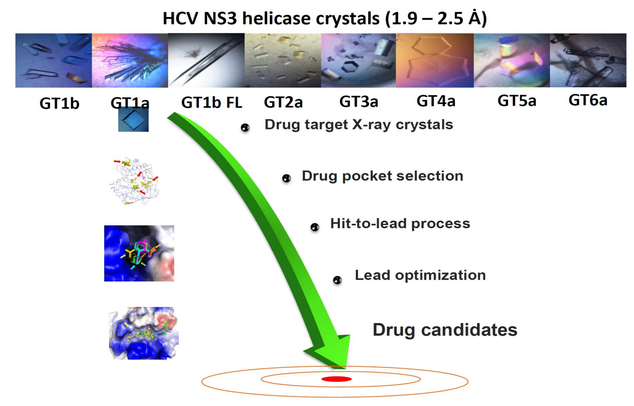


Figure 3: Discovery of Novel Drug Pocket Pocket, (CBP-1) By Fragment-based Screening

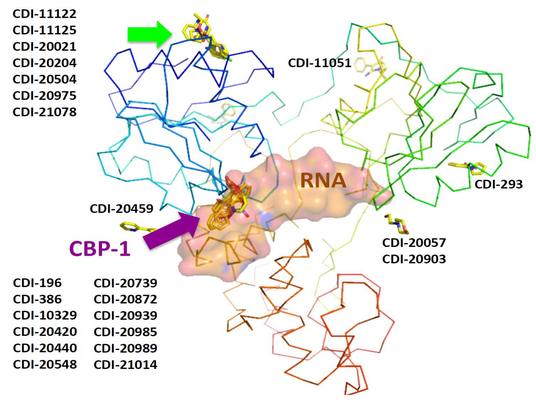


Figure 4: CBP-1 Site: Highly Conserved Among All Genotypes

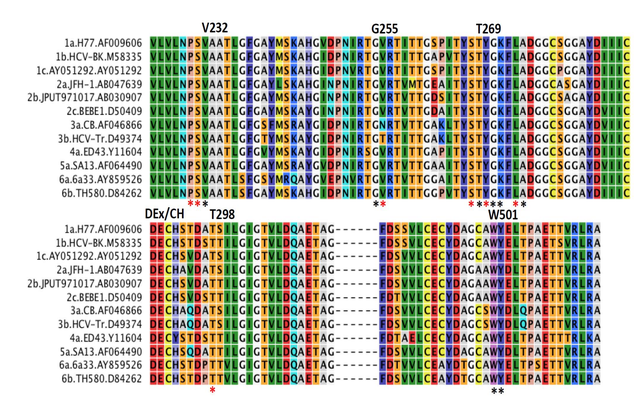


Figure 5: Overlay Structures of CBP-1 Pocket of HCV GT 1-6

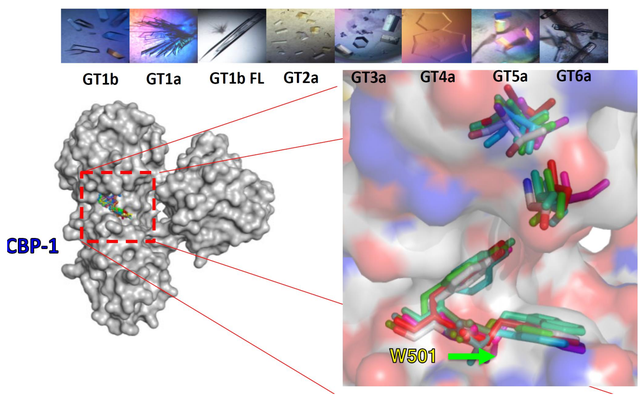


Figure 6: NS3 Helicase Inhibitors Bind to Highly Conserved CBP-1

- Overlay cocrystal structures of NS3 helicase (GT1-6):CDI-30103 complex

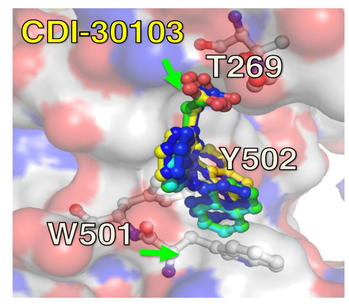


Figure 7: Pan-Genotypic Activity Of CDI-30103 Demonstrated

- HCV NS3 inhibitors specifically inhibit 3'-5' helicase activity
- No ATPase inhibition was observed

Genotype	IC50 (μM)
1b (Full length)	130
1a	54
1b	56
2a	13
3a	23
4a	13
5a	10
6a	21

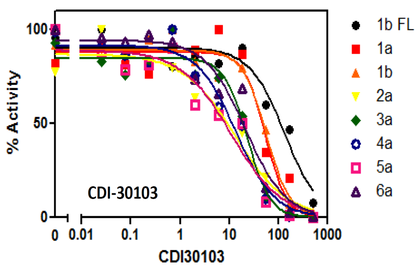
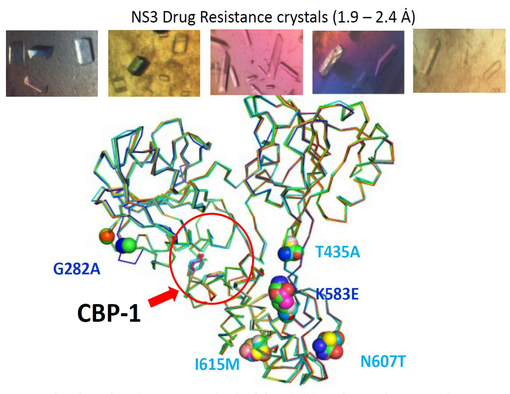


Figure 8: Pan-Genotypic Activity of Helicase Inhibitors Demonstrated

- Antiviral activity was measured in HCV replicon assays
- CC-31647 lead series developed by using Cocrystal's proprietary structure-based drug discovery technology platform
- NS3 helicase leads exhibit synergistic/additive effects with approved HCV antivirals and pan-genotypic NNI (CC-31244)

	GT1b μM	GT1a μM	GT2a μM	GT3a μM	GT4a μM	GT5a μM
CC-31647	3.9	5.3	0.99	5.4	3.66	6.5
EC50 fold change	1	1.4	0.3	1.4	0.9	1.7
CC50, uM	>100	>100	>100	>100	>100	>100

Figure 9: HCV Helicase Drug Resistance Structures Determined



Two lead molecules were selected for HCV replicon drug resistance screening

CONCLUSION

Cocrystal Pharma, Inc. has developed a novel class of HCV antivirals targeting the NS3 helicase that can be studied for the treatment of chronic HCV infection.

CONTACT INFORMATION

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