reImagine HEALTH

Intervention and Prevention Symposium

Application of Structure-Based Drug Design Platform Technology For Developing Broad Spectrum COVID-19, Influenza, and HCV Antivirals

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January 21, 2021

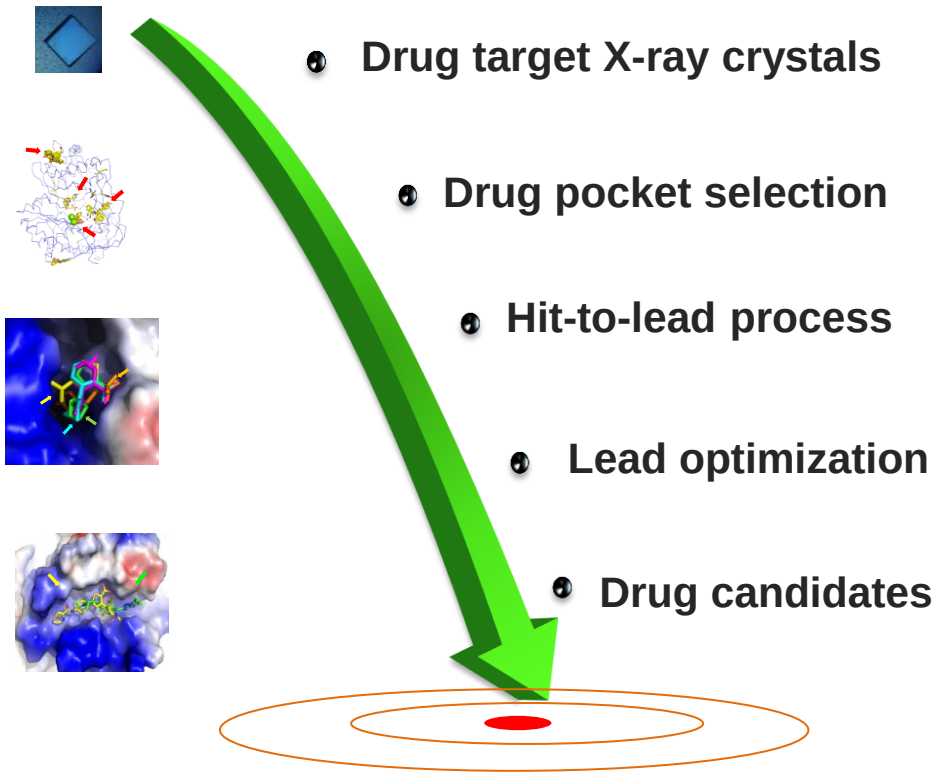
COCRYSTAL PHARMA, INC.

NASDAQ: COCP

Forward-Looking Statements

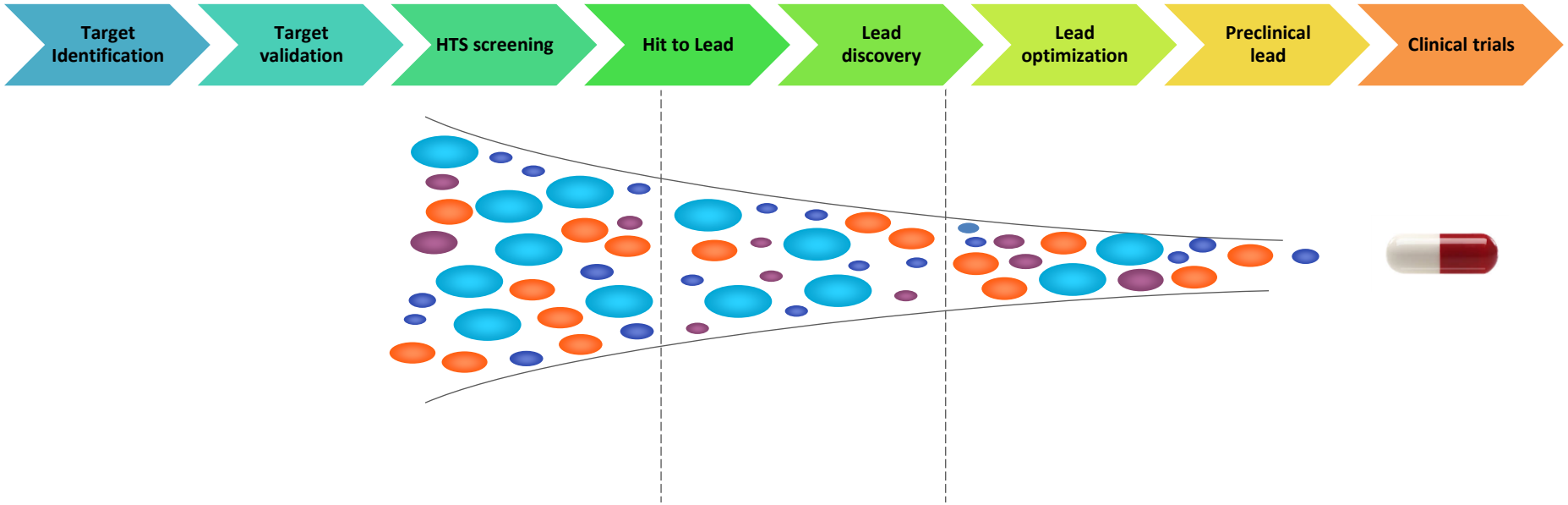
This presentation contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, including statements regarding expected results of our collaboration with Merck Sharp & Dohme Corp. ("Merck"), including the anticipated characteristics of the drug candidates developed as the result of this collaboration, expected funding by Merck of future research, development and commercialization of products derived from such collaboration, and the expected future payments and royalties in connection with the collaboration; the expected progress in developing a compound for the effective treatment and prevention of COVID-19 infections and the anticipated timing of achieving the value-driving milestones, including achieving pre-IND status and development of additional COVID-19 inhibitors with novel mechanism of action in 2021; the expected progress of our Influenza A program, including the initiation of Phase 1 study in Q3 2021; the expected synergetic effects of CC-42344 with approved Influenza antivirals; the expected progress of our HCV program, including future partnership for further development; the expected progress of our norovirus program and the anticipated timing of achieving the value-driving milestones, including completion of a proof-of-concept animal study in H1 2021; and our estimates with respect to market opportunities and development pipeline. Forward-looking statements are prefaced by words such as "anticipate," "expect," "plan," "could," "may," "will," "should," "would," "intend," "seem," "potential," "appear," "continue," "future," believe," "estimate," "forecast," "project," and similar words. Forward-looking statements are based on our current expectations and assumptions regarding our business, the economy and other future conditions. Because forward-looking statements relate to the future, they are subject to inherent uncertainties, risks and changes in circumstances that are difficult to predict. We caution you, therefore, against relying on any of these forward-looking statements. Our actual results may differ materially from those contemplated by the forward-looking statements for a variety of reasons, including, without limitation, the risks arising from the impact of the COVID-19 pandemic on our Company, including supply chain disruptions, our continued ability to proceed with our programs, receive necessary regulatory approvals and continue to rely on certain third parties, and on the national and global economy, risks arising from our reliance on continuing collaboration with Merck under the collaboration agreement, the future results of preclinical and clinical studies, general risks arising from clinical trials, receipt of regulatory approvals, development of effective treatments and/or vaccines by competitors, and our ability to find and enter into agreements with suitable collaboration partners. Further information on the risk factors that could cause actual results to differ materially from those expressed or implied by forward-looking statements, is contained in our filings with the Securities and Exchange Commission, including our Annual Report on Form 10-K for the year ended December 31, 2019, as amended and supplemented by the Quarterly Reports on Form 10-Q for the three months ended June 30, 2020 and the three months ended September 30, 2020. Any forward-looking statement made by us in this presentation speaks only as of the date on which it is made. Factors or events that could cause our actual results to differ may emerge from time to time, and it is not possible for us to predict all of them. We undertake no obligation to publicly update any forward-looking statement, whether as a result of new information, future developments or otherwise, except as may be required by law.

Cocrystal Drug Discovery Platform Technology For Developing Broad Spectrum Antiviral Therapeutics

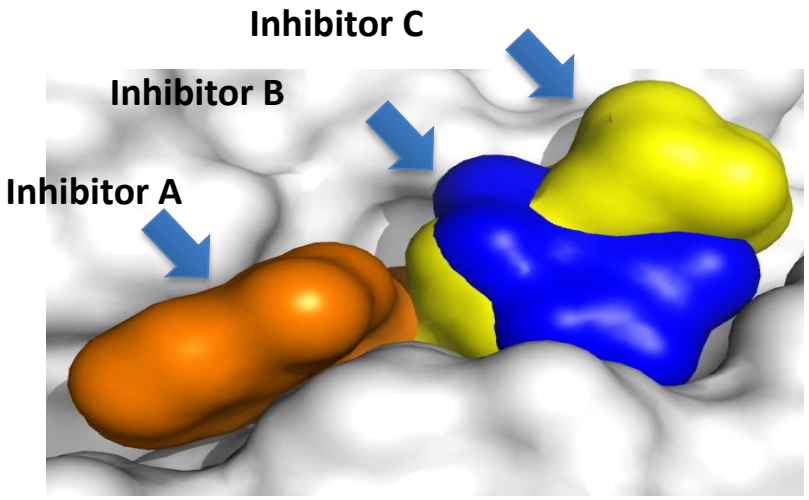


Traditional Drug Discovery and Development Process: Slow Process and High Attrition Rate

- Target identification and target validation process required
- Compound screening and hit identification yield high attrition rate



Advantages of Cocrystal's Structure-based Drug Discovery Platform Technology



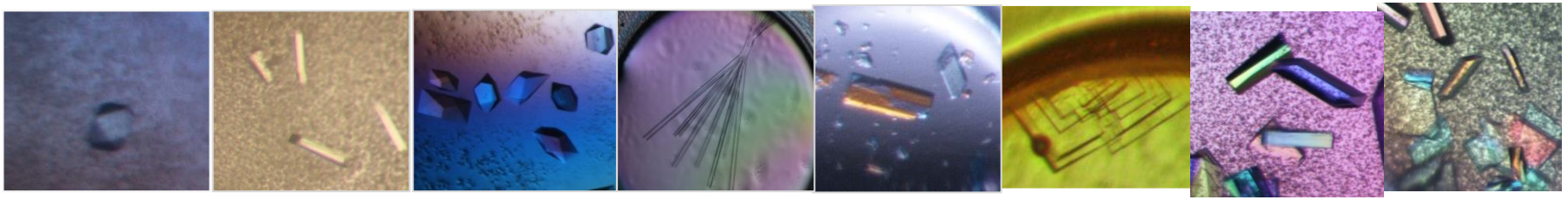
- Provide 3D structures of inhibitor protein complexes at near-atomic resolution with immediate insight to guide SAR
- Identify novel drug binding pockets
- Design and develop broad spectrum inhibitors with high barrier to drug resistance

Case Studies: Broad Spectrum Antiviral Development

HCV NS5B polymerase	▪ Broad spectrum NNI ▪ Phase 2a completed
HCV NS3 helicase	▪ Broad spectrum helicase inhibitors ▪ Preclinical stage
Influenza A PB2	▪ Broad spectrum influenza PB2 inhibitor ▪ Phase 1 in 2021
SARS-CoV 3CL (Main) protease	▪ Broad spectrum coronavirus protease inhibitors ▪ Preclinical stage

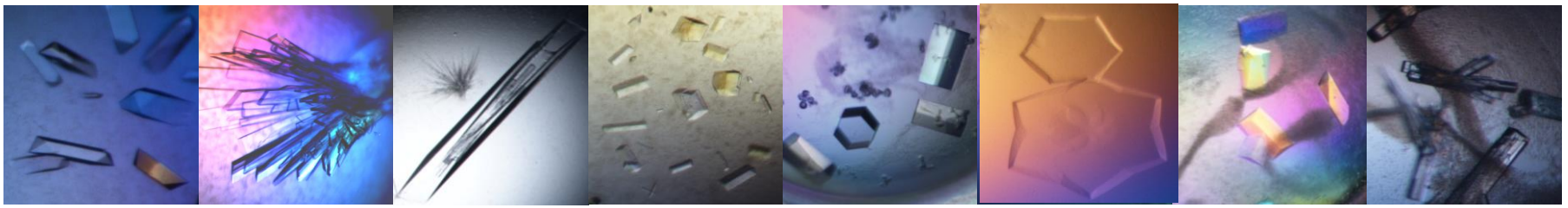
Large Scale X-ray Quality Crystal Production For High Throughput Protein Crystallography

HCV polymerase crystals (1.6-2.1 Å)



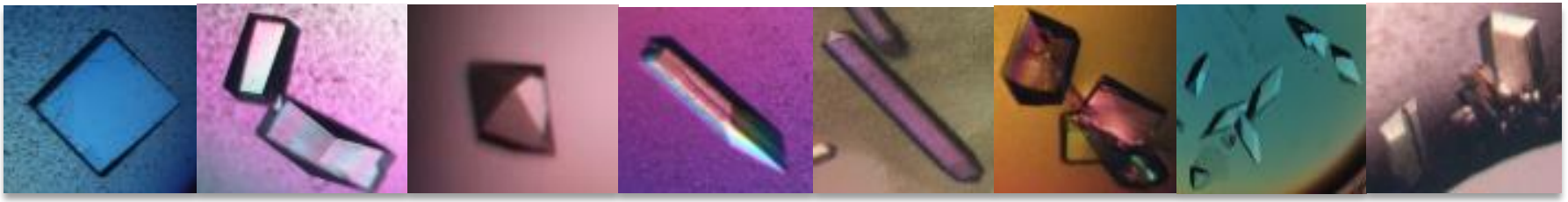
GT1a | GT1b | GT2a | GT4a | GT5a | GT6a | GT1b* S282T | GT1b* N316Y

HCV helicase crystals (1.7-2.6 Å)



GT1b | GT1a | GT1b FL | GT2a | GT3a | GT4a | GT5a | GT6a

Influenza PB2 crystals (1.0 – 2.5 Å)

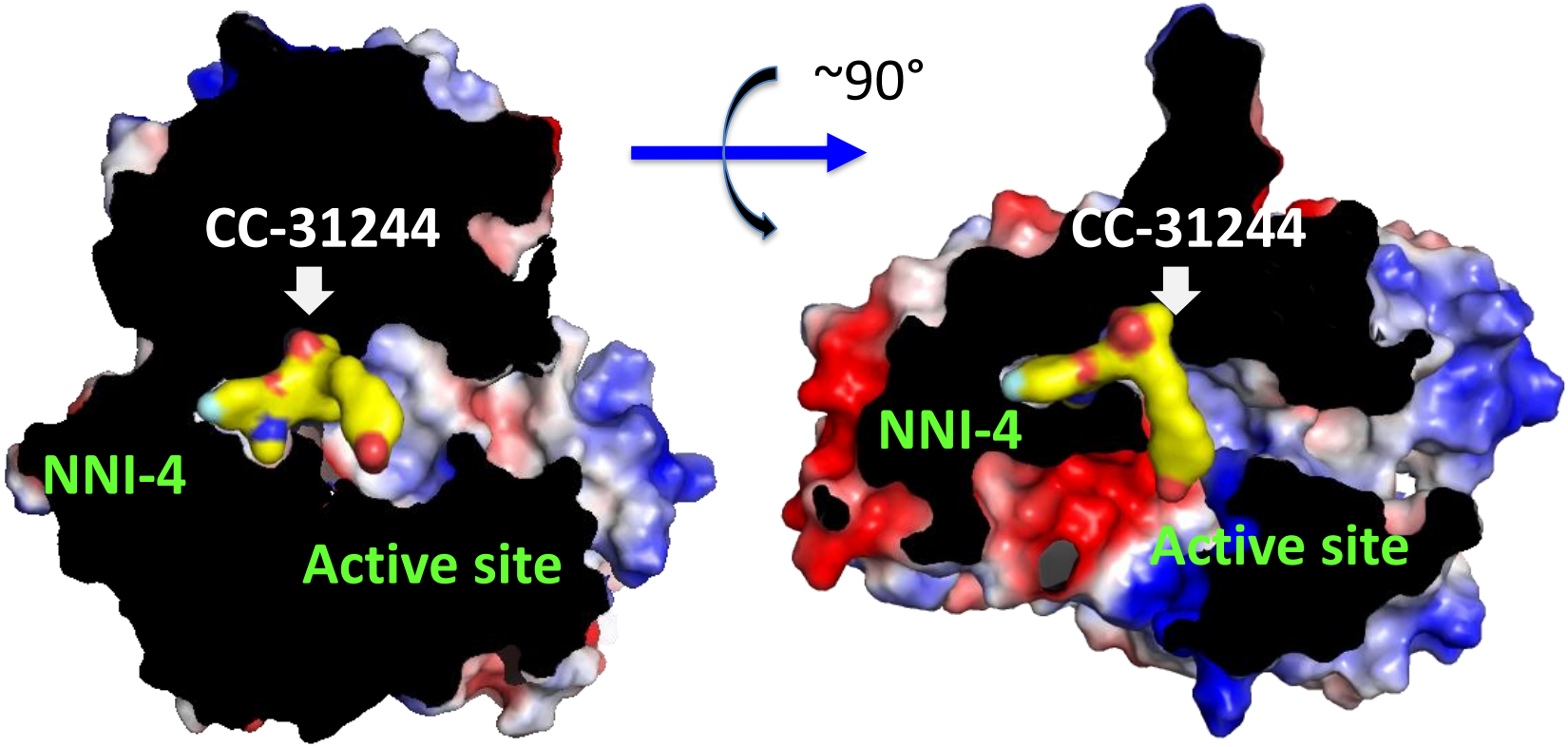


Technology Platform Focuses on Well Validated Antiviral Drug Targets

- Viral enzymes are essential for viral replication and transcription

Case Study 1: HCV NNI Pan-genotypic Inhibitor CC-31244

- CC-31244 extends from the NNI-4 site to the active site



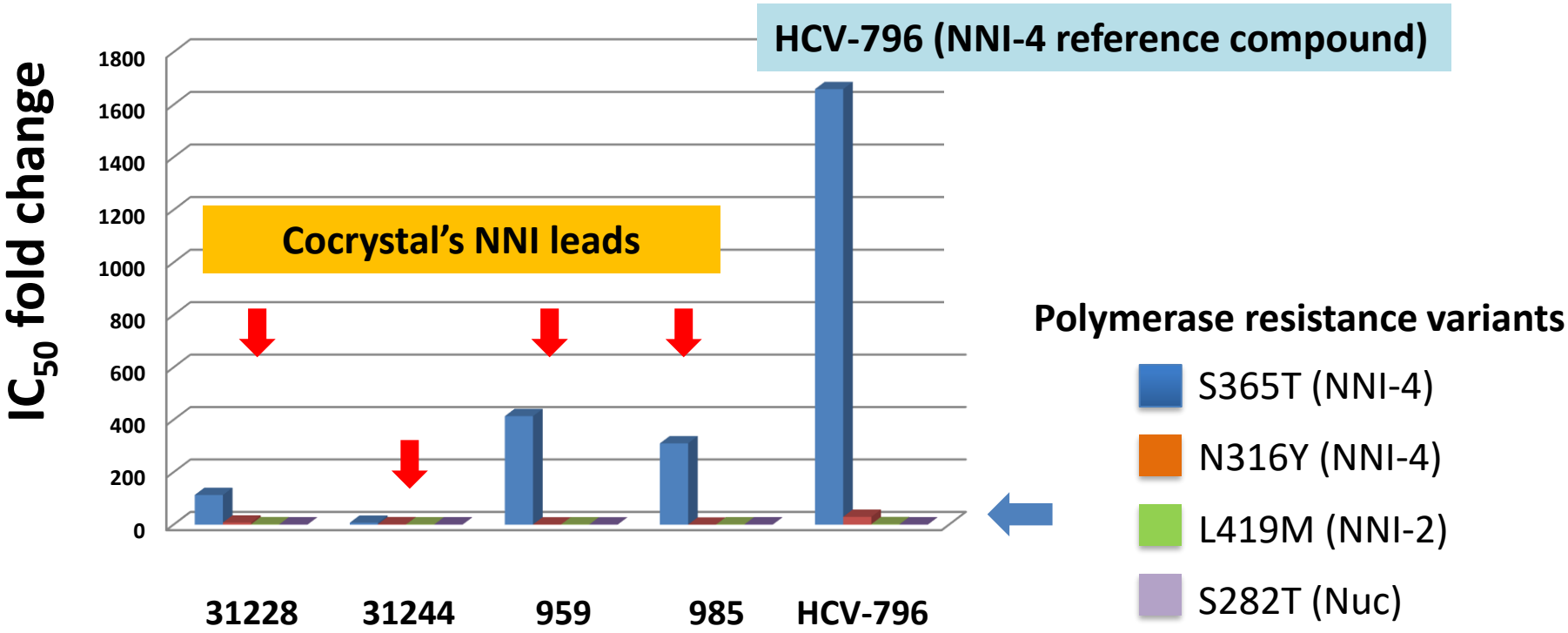
CC-31244: Potent, Broad Spectrum Non-nucleoside Inhibitor

- **CC-31244: HCV EC_{50} fold change, <6-fold**

Genotype	CDI-31244 EC_{50}, nM	EC_{50} Fold change	Sofosbuvir EC_{50}, nM	EC_{50} fold change
1b	5	1.0	42	1.0
1a	9	1.8	34	0.8
2b	26	5.2	28	0.66
3a	11	2.2	14	3.2
4a	21	4.2	47	1.1
5a	2	0.4	75	1.7

CC-31244 Shows Superior Activity Against All Known HCV Drug Resistant Polymerases

- CC-31244: IC_{50} fold-change against NNI drug resistant polymerases, **<5-fold**; Reference compound, HCV-796:IC_{50} fold-change, **>1,600-fold**
- Liver targeting of CC-31244 (>1,000 above EC_{50}) observed



CC-31244 Exhibits High Barrier to Drug Resistance

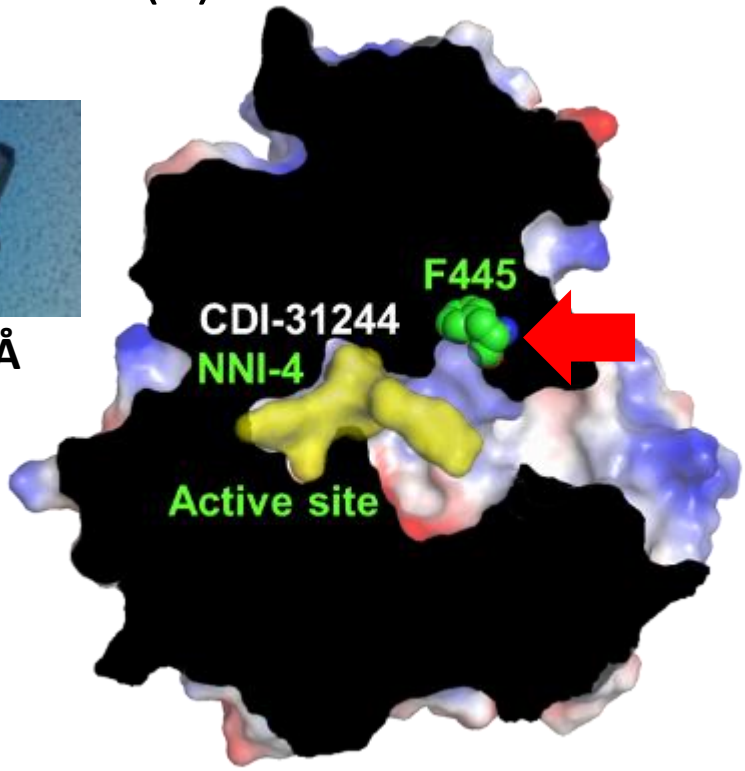
- **C445F**: only drug resistant variant isolated from *in vitro* screening
- Fold shift: **IC_{50} <2-fold and EC_{50} <7-fold**

(A) GT1b wild type

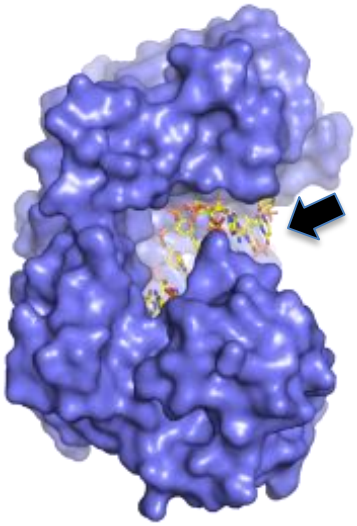
1.6 Å

(B) GT1b C445F

1.7 Å



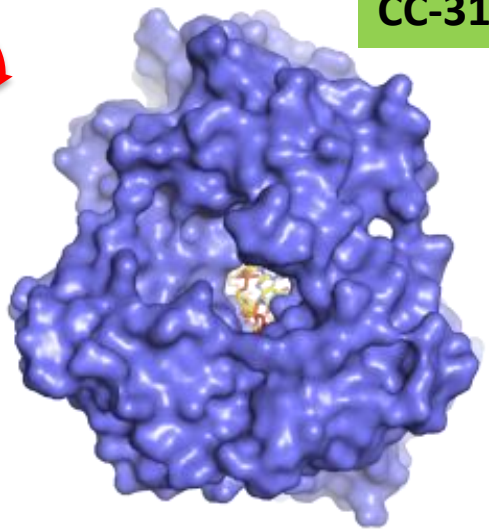
Novel Mechanism of Inhibition by CC-31244



RNA substrate

HCV polymerase
Back view

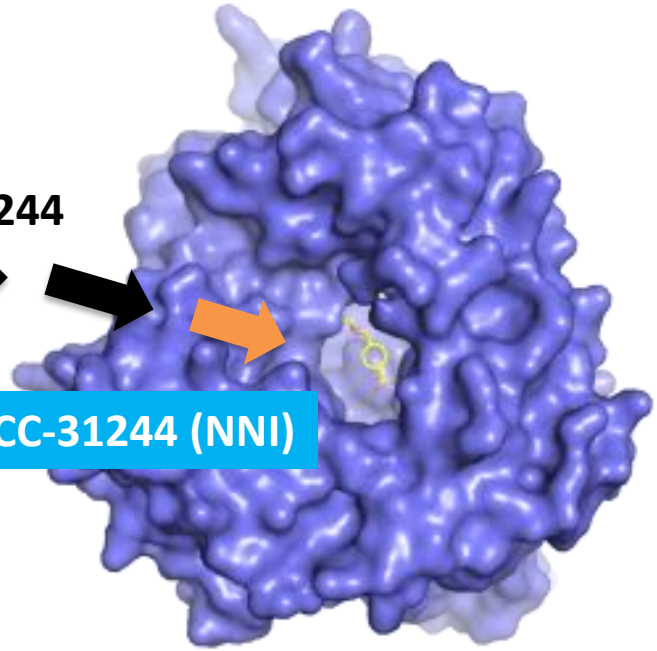
Rotate



HCV polymerase
Front view

CC-31244 blocks RNA entry into the active site

CC-31244

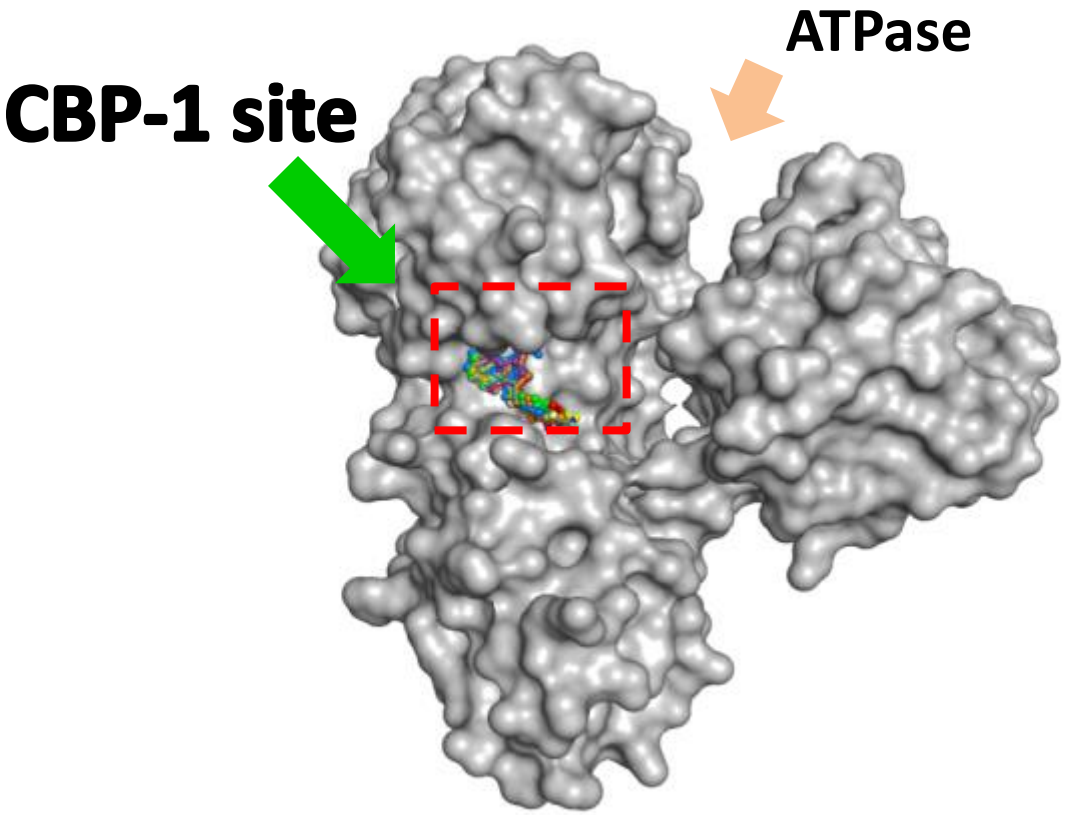


CC-31244 (NNI)

Case Study 2: HCV NS3 Helicase Inhibitors

Novel Drug Binding Pocket (CBP-1) Identified

(A) HCV NS3 helicase structure



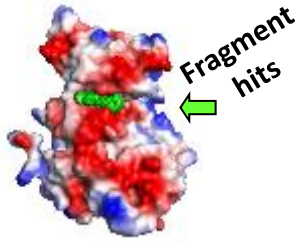
(B) Fragment screening

Proprietary ARTIST fragment libraries

4-8 fragments/cocktail

Soaked with protein crystals

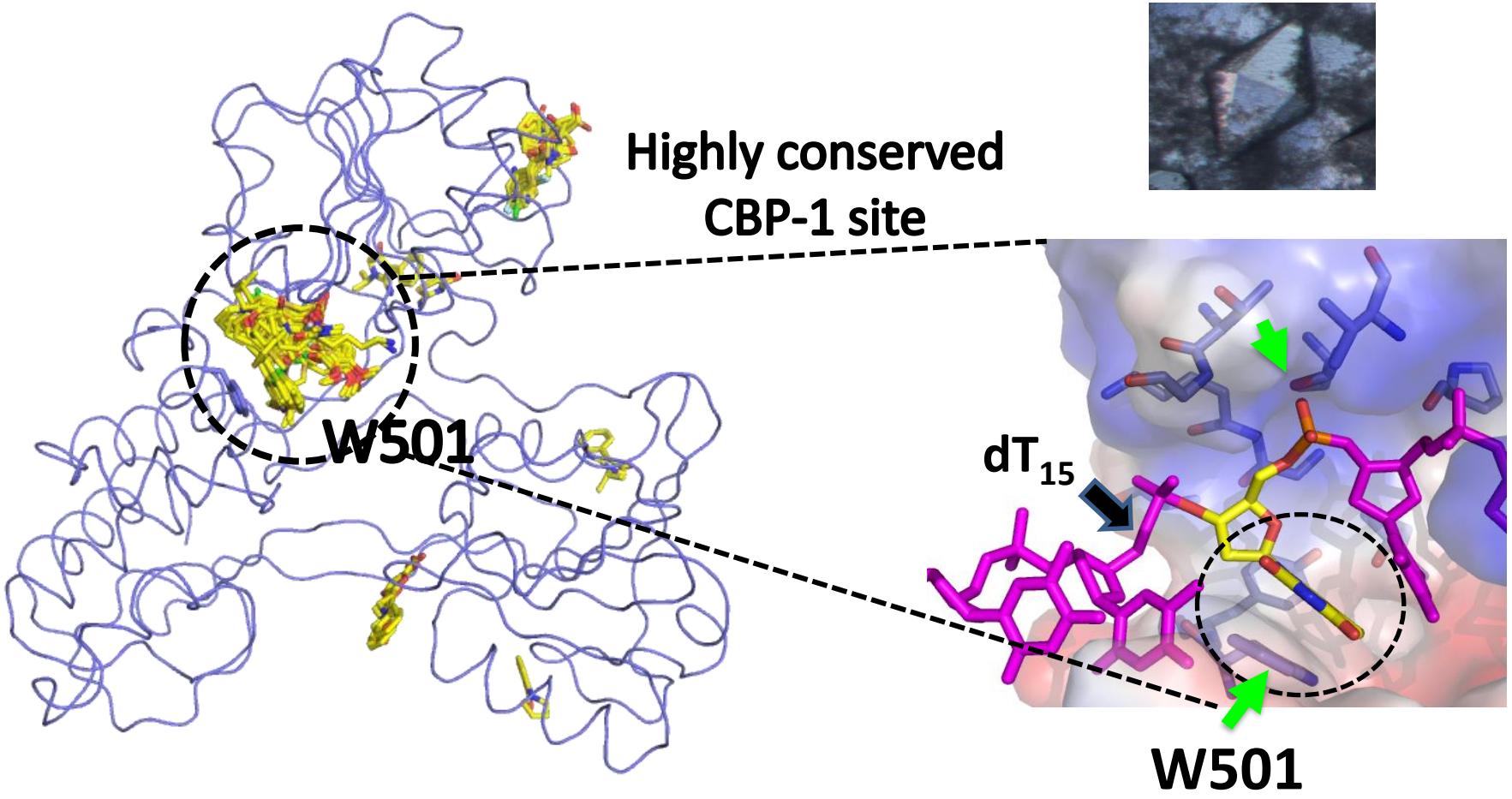
Cocrystals



Novel Mechanism of Inhibition by HCV NS3 3'-5' Unwinding Inhibitors

(A) HCV NS3 helicase fragment hits

(B) HCV NS3 helicase:dT_{15} structure

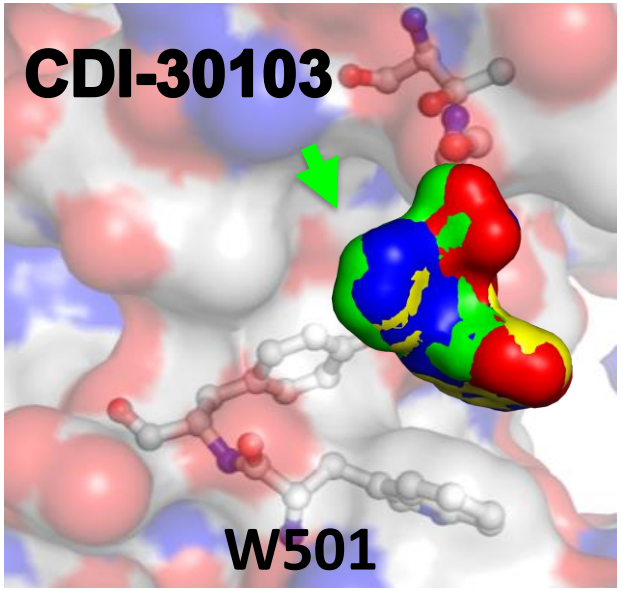


Pan-Genotypic Binding Mode of HCV Helicase Inhibitor

HCV helicase crystals

GT1b GT1a GT1b FL GT2a GT3a GT4a GT5a GT6a

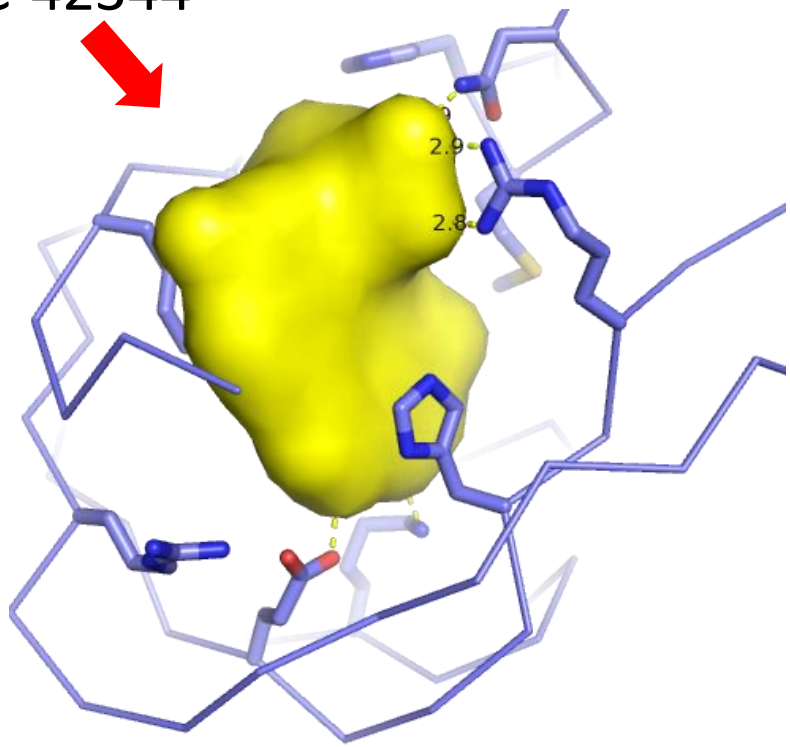
Overlay structure of HCV helicases (GT1-6) complexed with CDI-30103



Case Study 3: Influenza A PB2 Inhibitor, CC-42344

Broad Spectrum Pandemic and Seasonal Influenza Antiviral

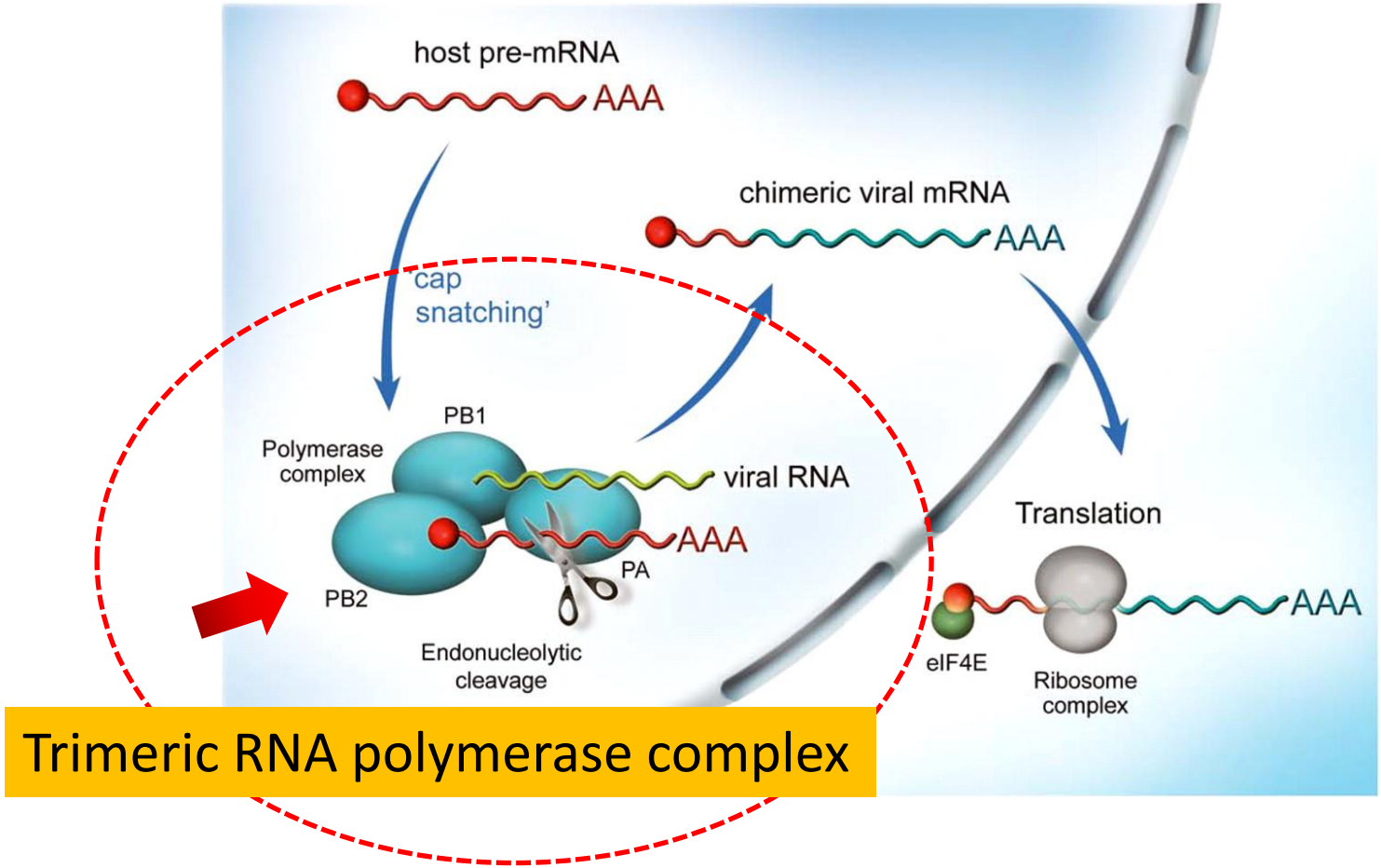
CC-42344



Cocrystal structure of CC-42344 (1.47 Å)

- Binds to the highly conserved m7GTP binding pocket of PB2
- Exhibits broad spectrum activity against seasonal and pandemic influenza strains, EC_{50} 0.12-9 nM
- Favorable preclinical safety profile and pharmacokinetic properties
- Phase 1 will be initiated in 2021

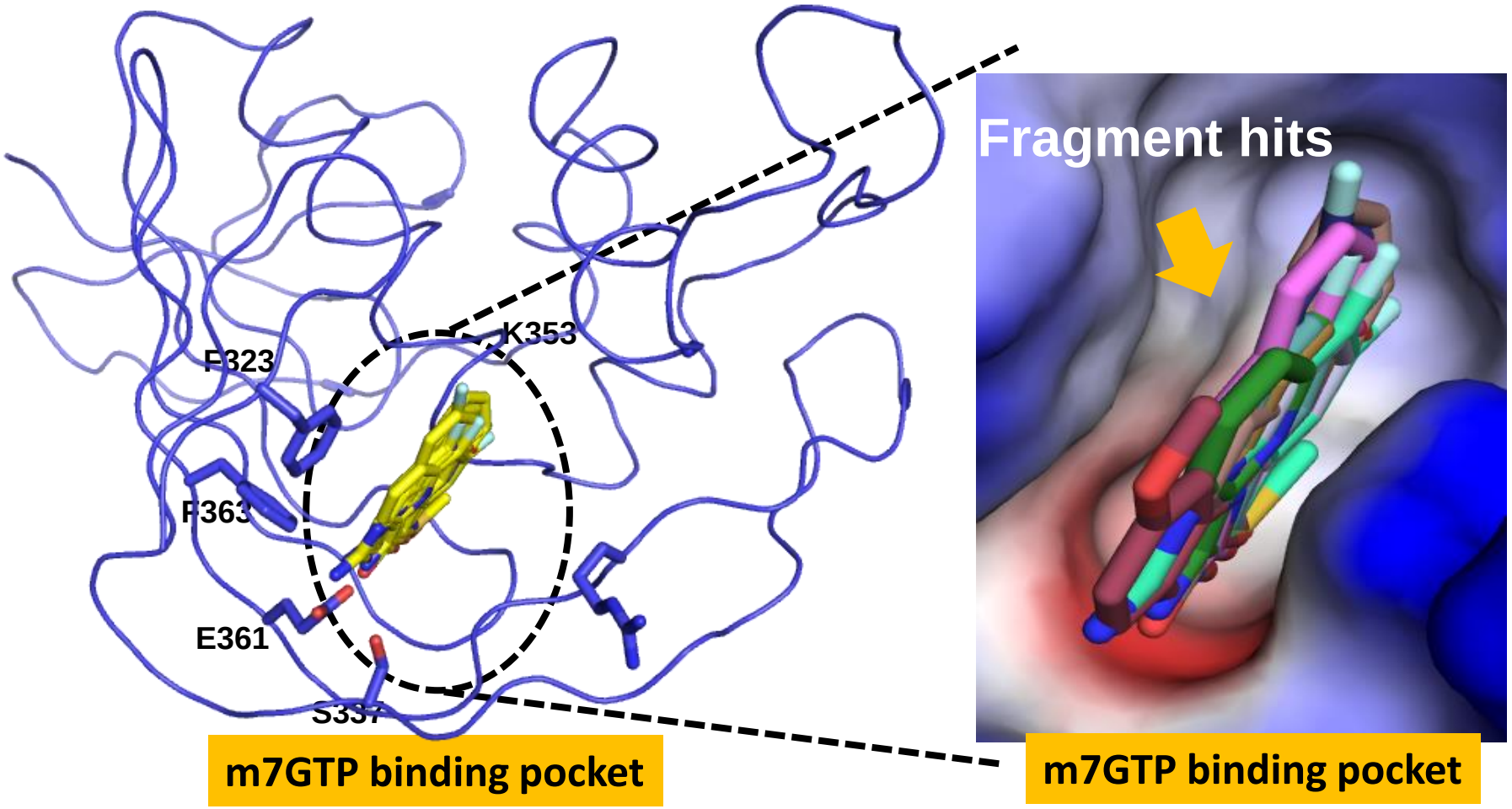
Cap Binding (PB2), Endonuclease (PA), and Polymerase (PB1) Are Essential For Influenza Viral Replication



Boivin S et al. J. Biol. Chem. 2010;285:28411-28417

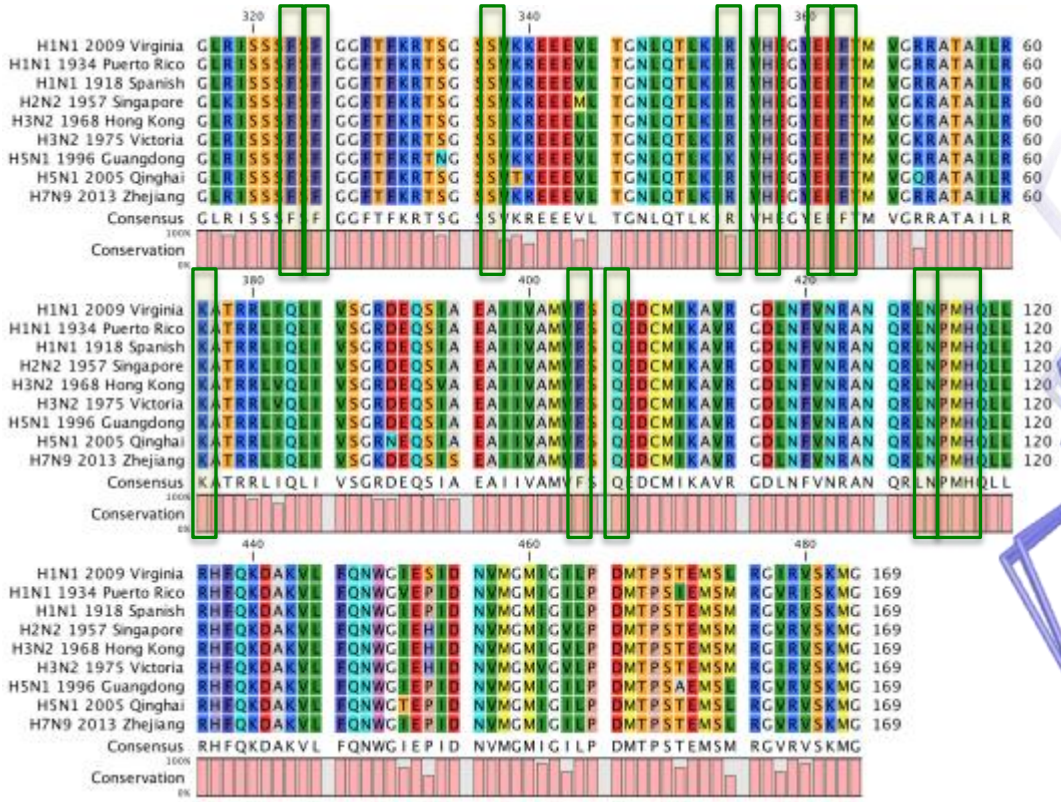
PB2 Fragment Screening Reveals Highly Conserved Pocket

- The fragment binding pocket confirmed to be m7GTP binding pocket

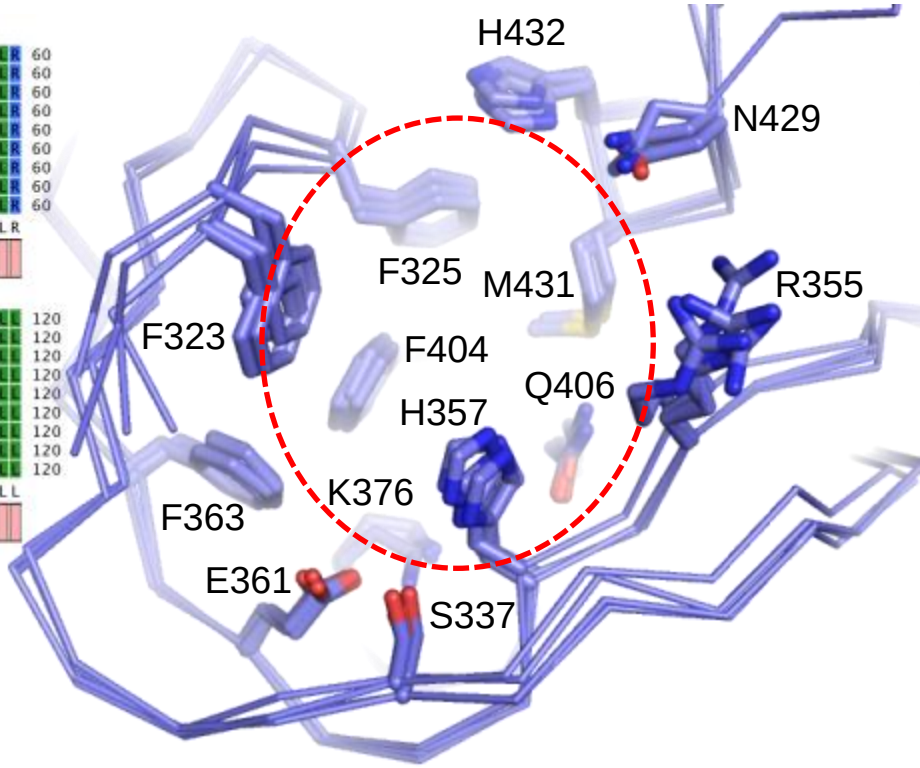


PB2 m7GTP Binding Pocket is Highly Conserved

(A) Influenza A PB2 sequence comparison

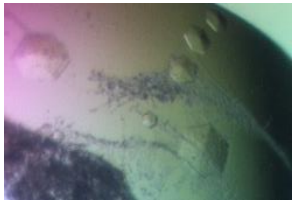


(B) m7GTP binding pocket of all influenza A strains

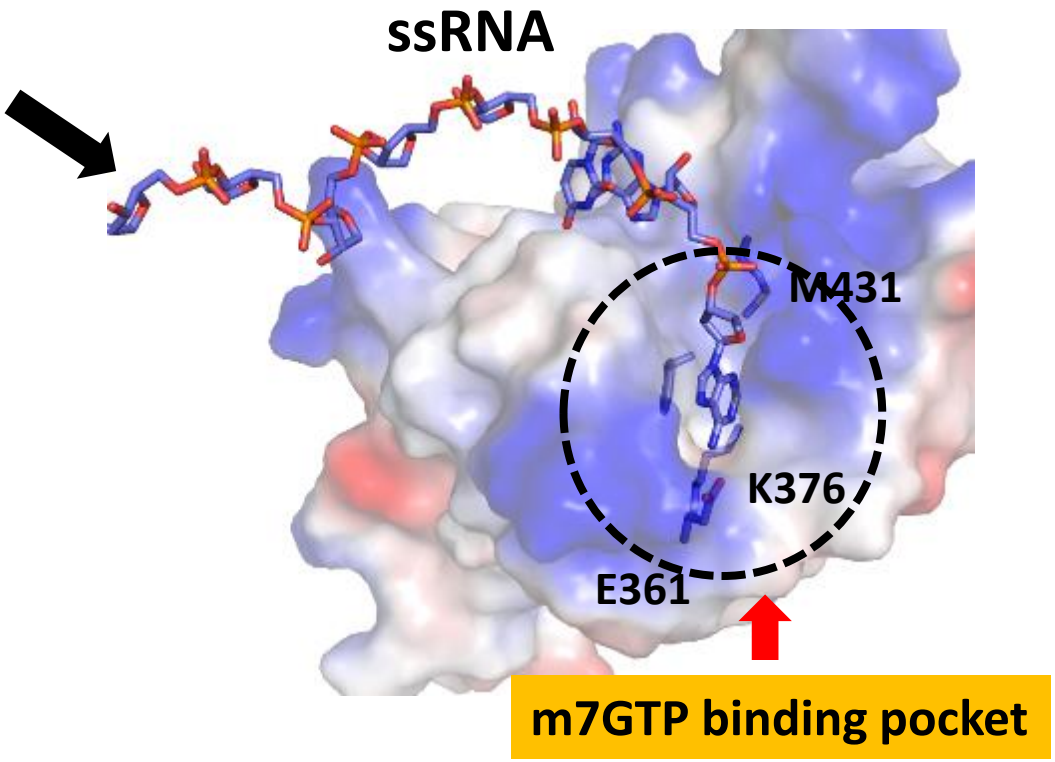


Crystal Structure of PB2:ssRNA Complex Further Revealed m7GTP Binding Pocket:ssRNA Interactions

PB2:ssRNA cocrystals



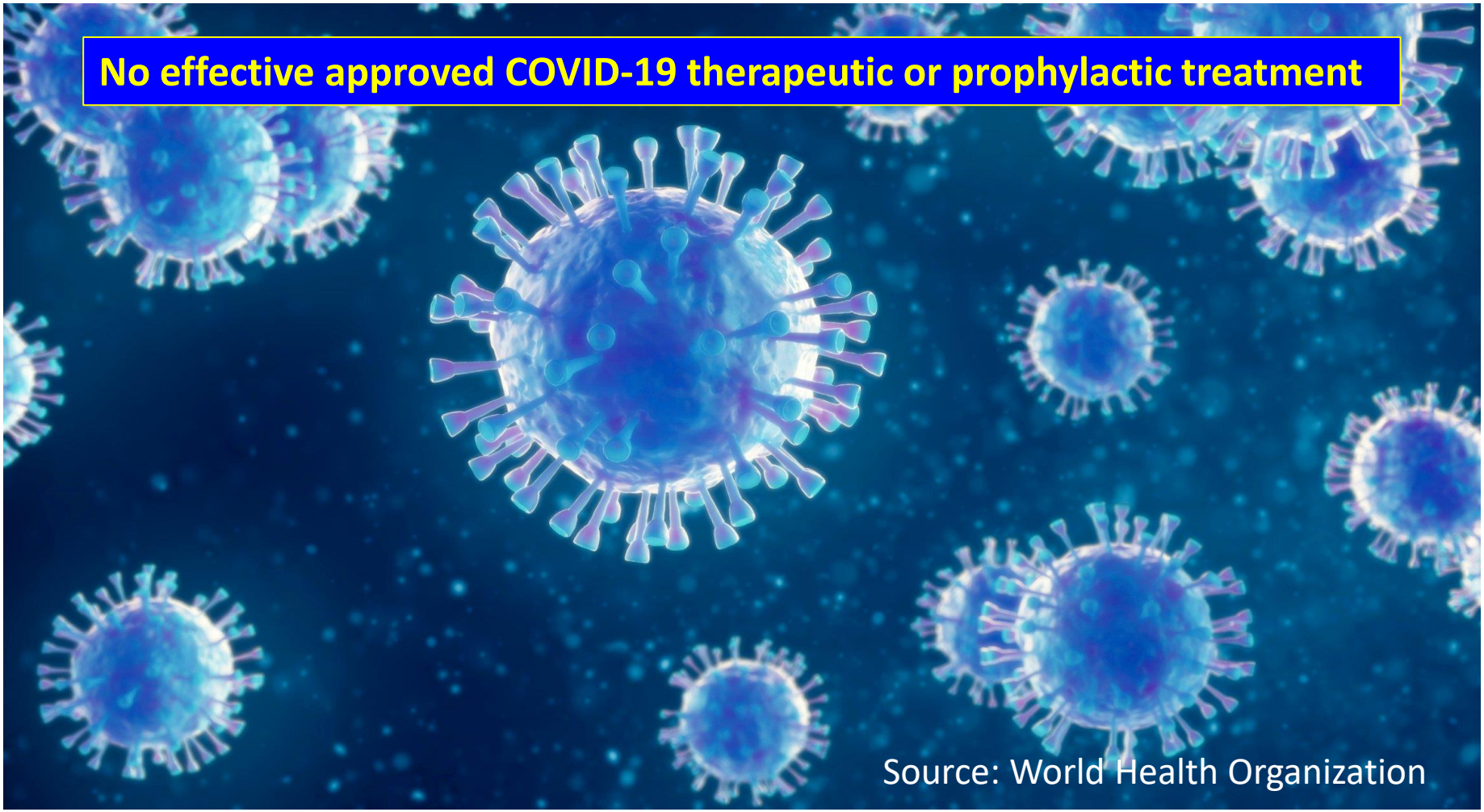
2.7 Å



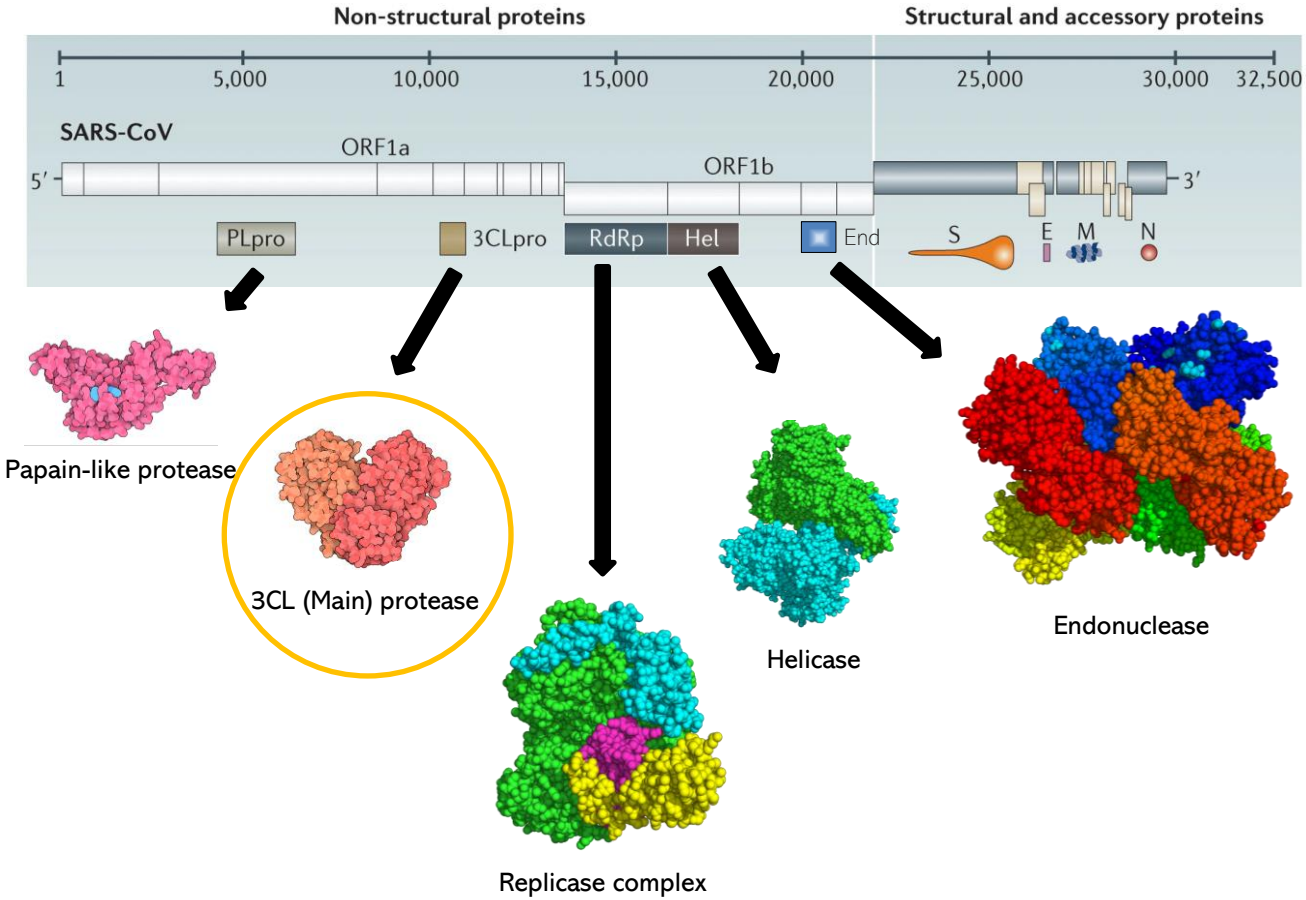
CC-42344 Shows Broad Spectrum Antiviral Activity Against Pandemic and Seasonal Influenza Strains

Influenza serotype	Strain	CC-42344, EC_{50} nM
H1N1	A/CA/07/2009	**0.12**
H1N1	A/PR/8/34	**1**
H1N1	A/Fort Monmouth/1/47	**2**
H1N1	A/NY/18/09	**5**
H3N2	A/AICHI/2/68	**0.2**
H5N1	A/VN/1193/2004	**<3.2**
H5N1	Hong Kong/213/2003	**4.5**
H5N1	Thailand/16/2004	**<3.2**
H7N7	Netherlands/219/2013	**5.6**
H7N9	Anhui/1/2013	**<3.2**
H3N2-tamiflu resistant	A/Wuhan/395/95	**0.5**
H1N1-baloxavir resistant	A/PR/8/34	**0.5**

Case Study 4: COVID-19 Direct-Acting Antivirals



Cocrystal Focuses On Multiple SARS-CoV-2 Drug Targets

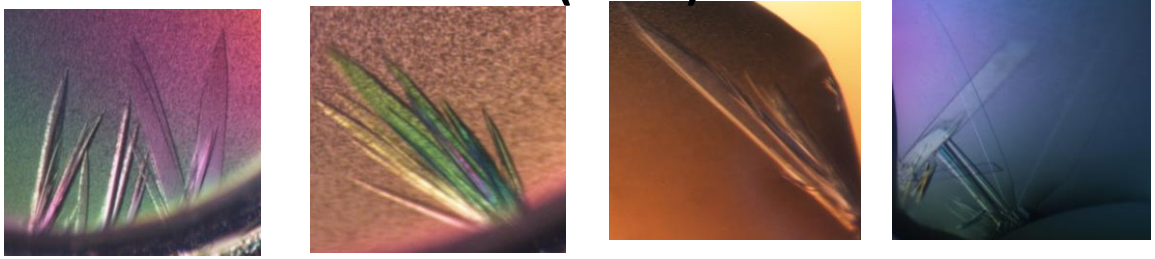


SARS-CoV-2, SARS-CoV-1, and MERS-CoV Protease Crystals

SARS-CoV-2 (1.8 Å)

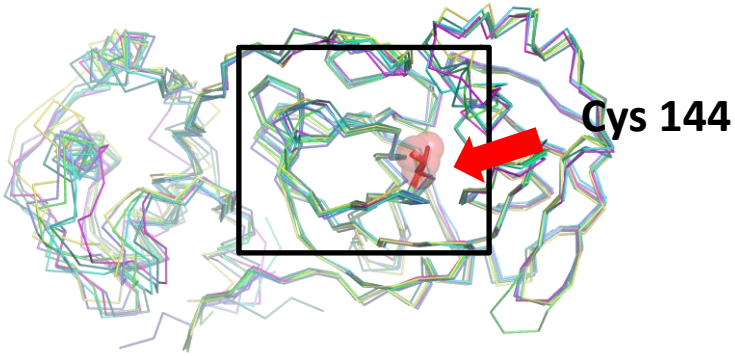
SARS-CoV-1 (1.56 Å)

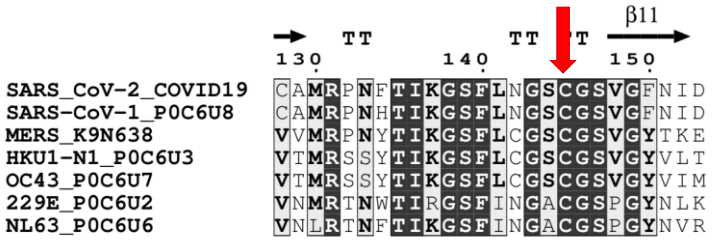
MERS-CoV (1.9 Å)



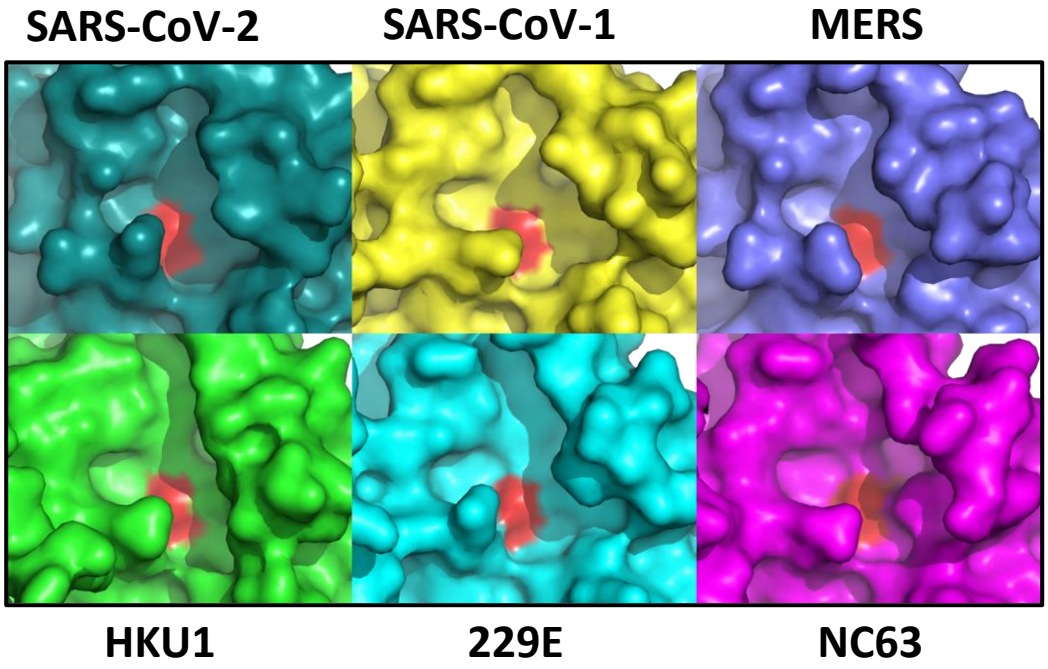
Cocrystal 3CL Protease Inhibitors Target a Highly Conserved Cysteine Residue of Coronavirus Proteases

(A) Overlay structures of coronavirus proteases

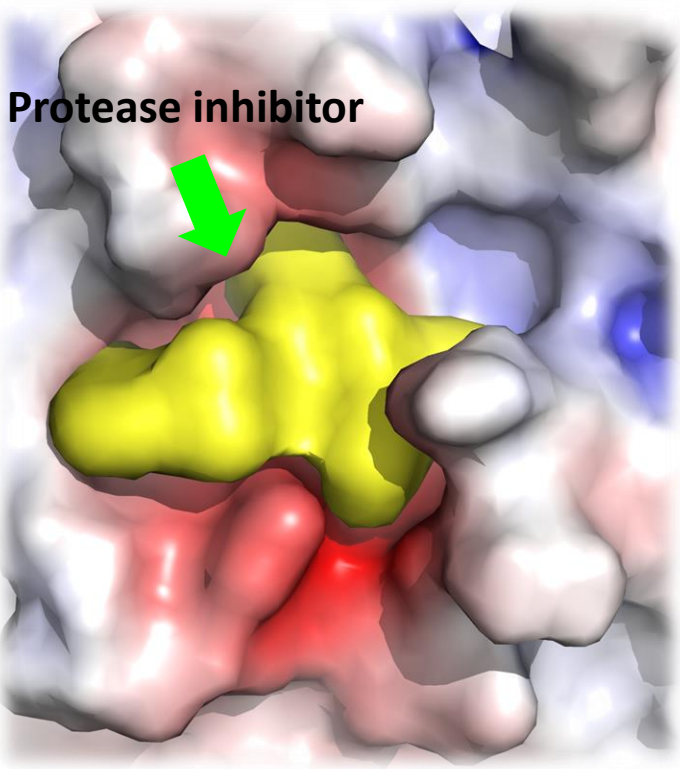




(B) Highly conserved Cys144 residue



SARS-CoV-2 3CL Protease Inhibitors



Cocrystal structure of SARS-CoV-2 3CL protease

- Exhibits broad spectrum activity against viral cysteine proteases including coronaviruses, noroviruses, and picornaviruses
- Binds to a highly conserved, essential residue (Cys144) of SARS-CoV-2 3CL (Main) protease
- Shows favorable ADMET properties and *in vivo* efficacy in MERS-CoV infected mouse model
- Initiated preclinical toxicology

Summary: Cocrystal's Drug Discovery Platform Technology For Developing Broad Spectrum Antivirals

HCV NS5B polymerase	▪ Potent, pan-genotypic NNI ▪ Phase 2a completed
HCV NS3 helicase	▪ Pan-genotypic helicase unwinding inhibitors ▪ Preclinical stage
Influenza A PB2	▪ Broad spectrum pandemic and seasonal inhibitor ▪ Phase 1 in 2021
SARS-CoV 3CL (Main) protease	▪ Broad spectrum coronavirus protease inhibitors ▪ Preclinical stage