

6TH ISRV AVG CONFERENCE

**Preclinical characterization of CC-42344, a broad spectrum,
potent influenza A PB2 inhibitor for potential triple route
(oral, inhalation, IV) treatment**

Sam Lee

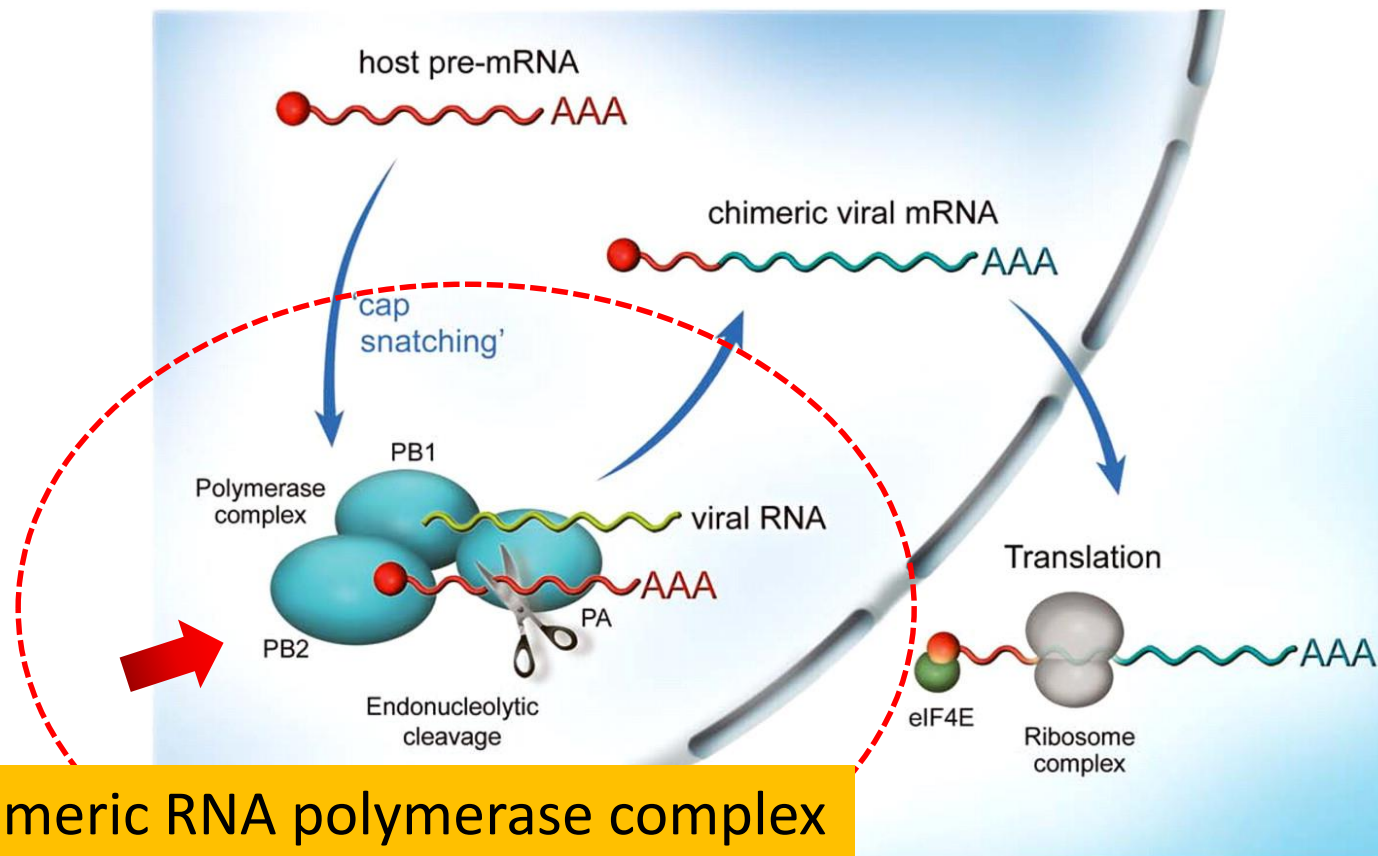
November 13, 2018

COCRYSTAL
PHARMA, INC.

Forward Looking Statements

This presentation contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. Forward-looking statements are prefaced by words such as "expect," "plan," "intend," "anticipate," 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. Our actual results may differ materially from those contemplated by the forward-looking statements for a variety of reasons. Also see the risk factors contained in the Prospectus Supplement dated April 30, 2018, and our Form 10-K for the year ended December 31, 2017. We caution you, therefore, against relying on any of these forward-looking statements. They are neither statements of historical fact nor guarantees or assurances of future performance. We do not intend to nor do we undertake any duty to update these forward-looking statements.

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

Influenza Replication Inhibitors

**Endonuclease
Domain (PA)**

Baloxavir marboxil

**Cap-binding
Domain (PB2)**

VX-787 (Pimodivir)

Cocrystal's PB2 inhibitors

Polymerase (PB1)

T-705 (Favipiravir)

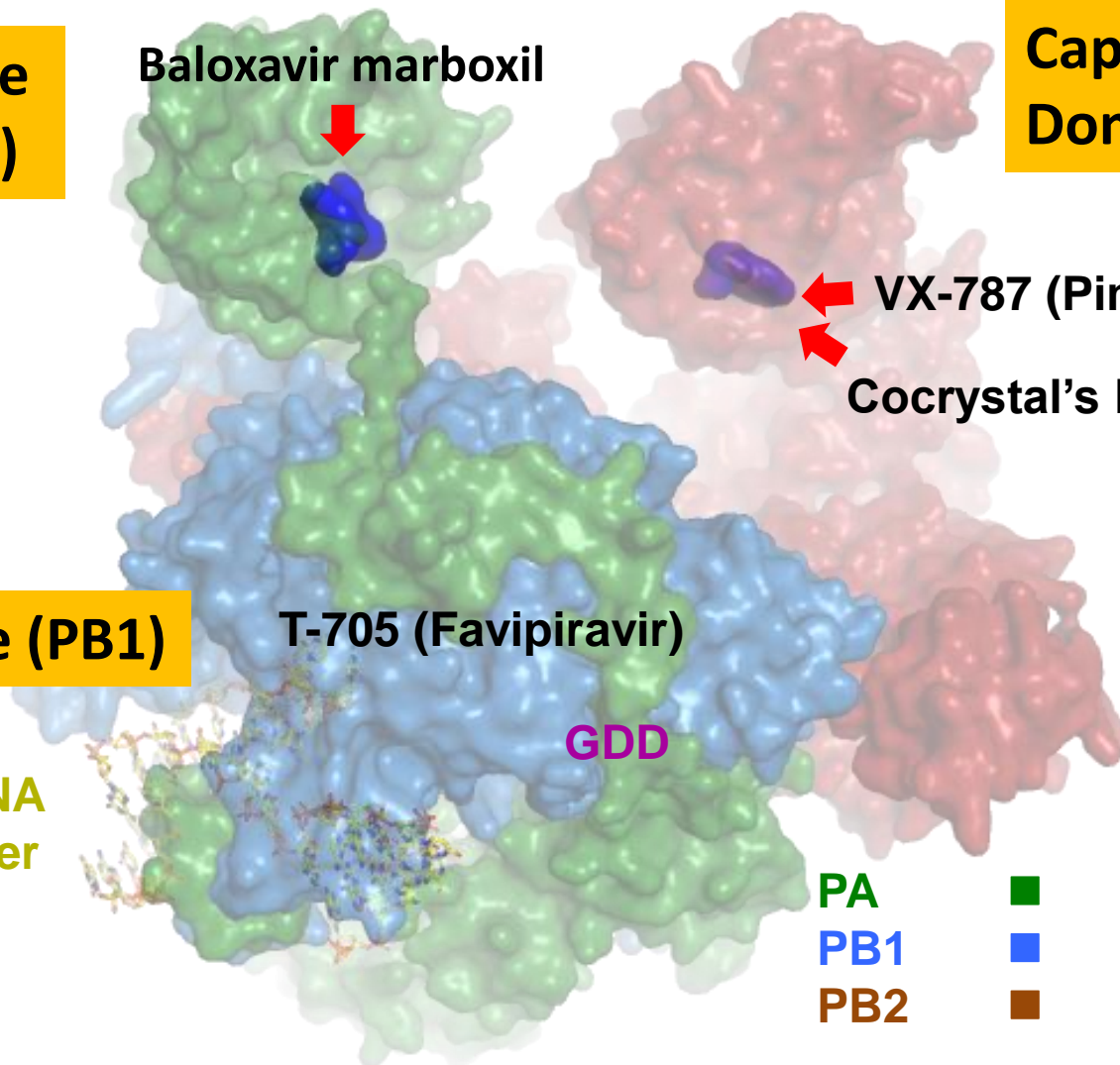
GDD

**Viral RNA
Promoter**

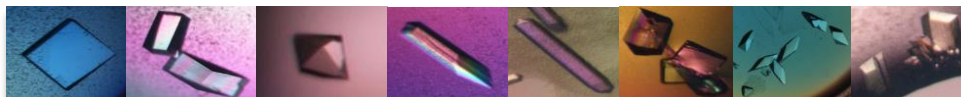
PA

PB1

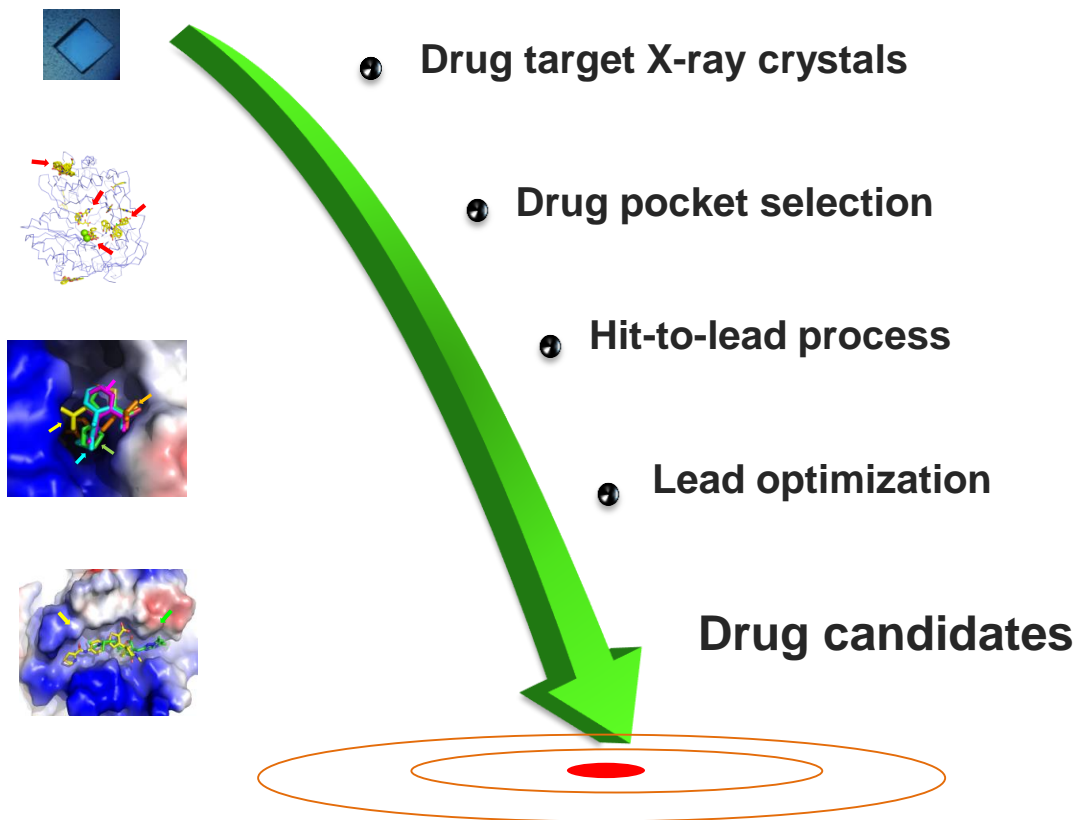
PB2



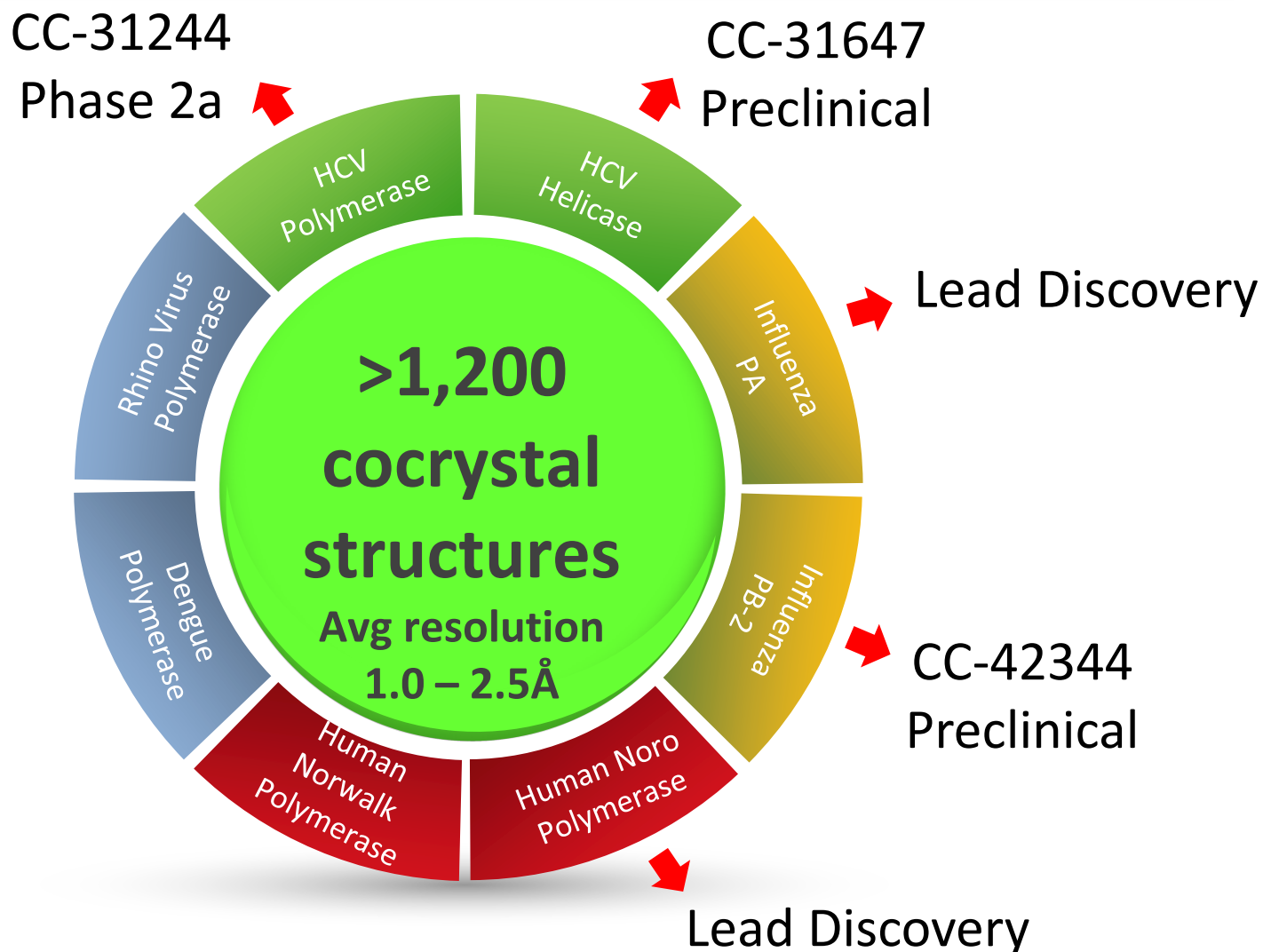
Cocrystal Drug Discovery Platform Technology For Developing Broad Spectrum Antiviral Therapeutics



Influenza PB2 crystals

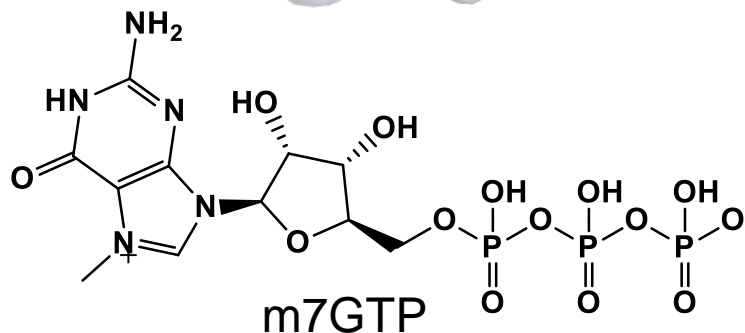
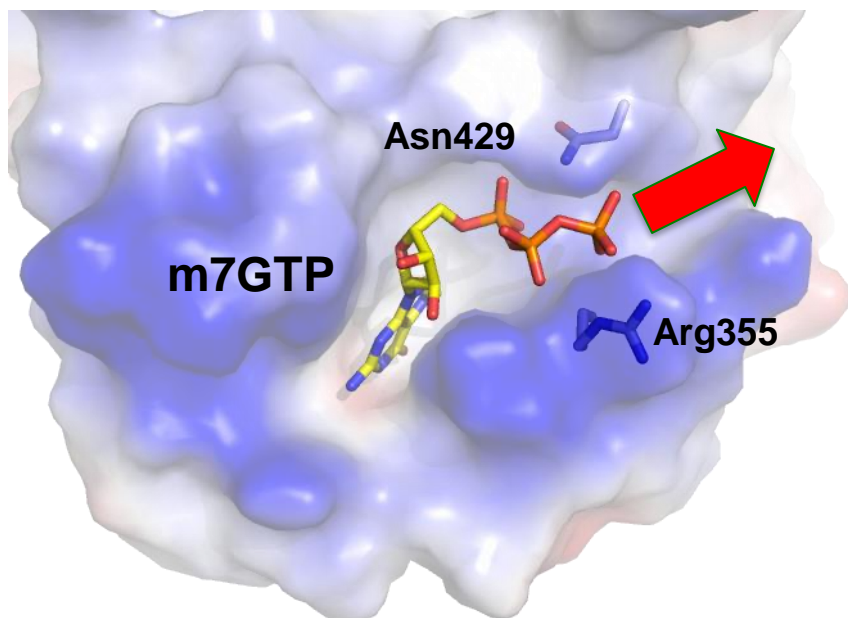


Cocrystal Technology Platform Focuses on Well Validated Drug Targets: Viral Replication Enzymes

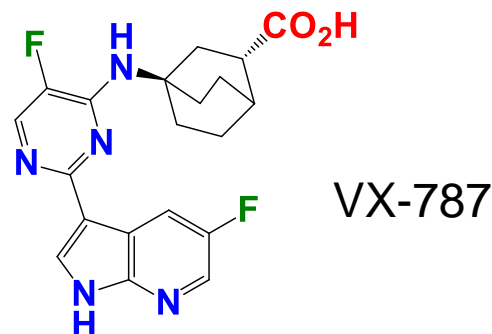
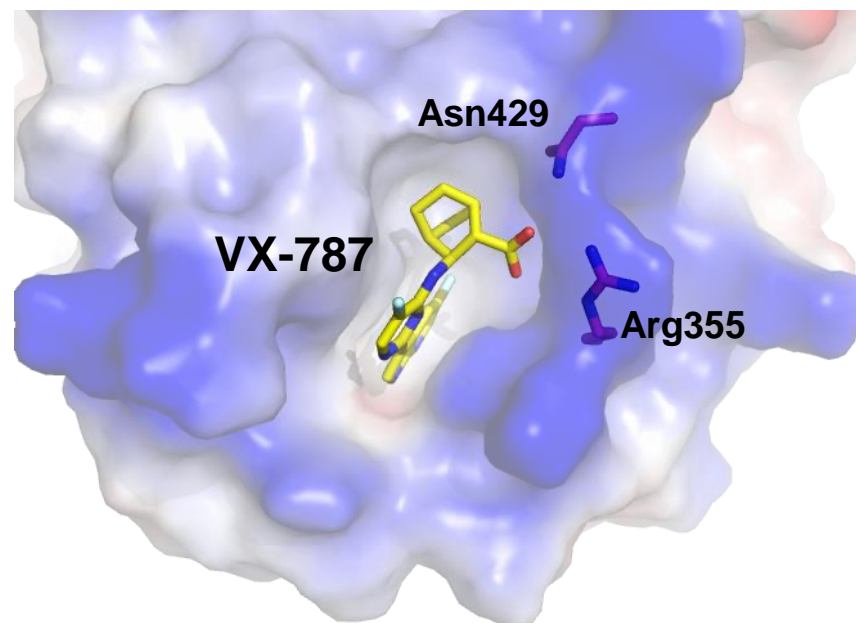


m7GTP Binds To Influenza Cap-Binding Domain

(A) m7GTP

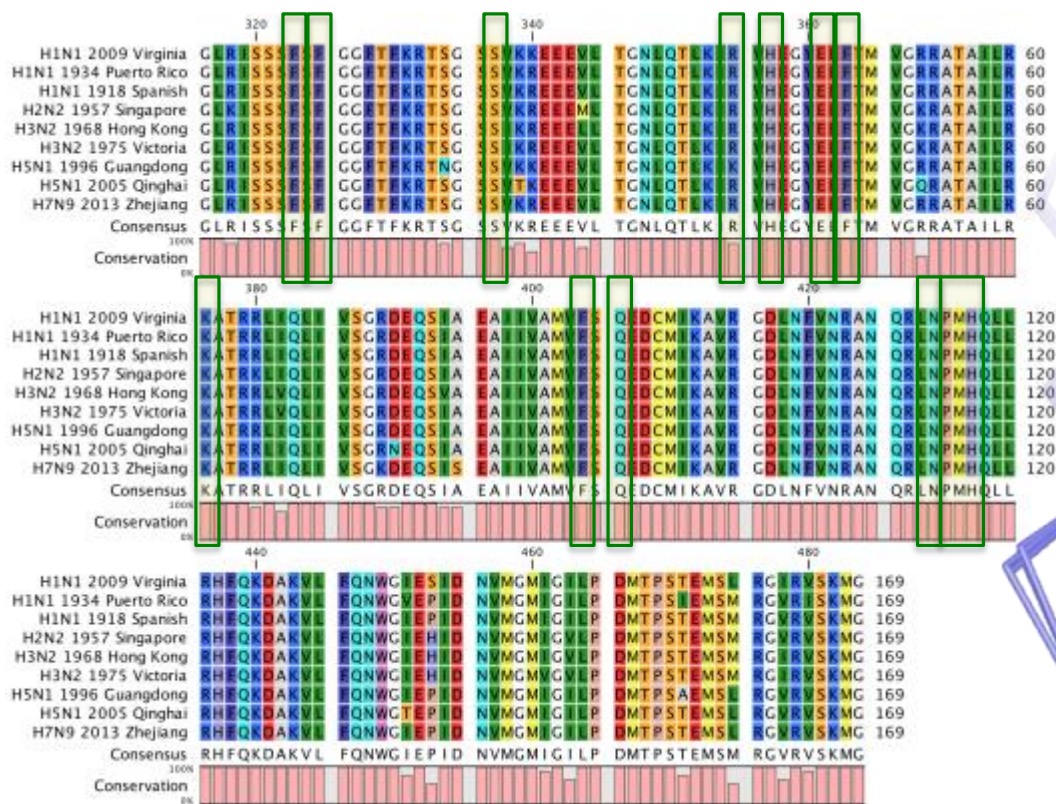


(B) VX-787

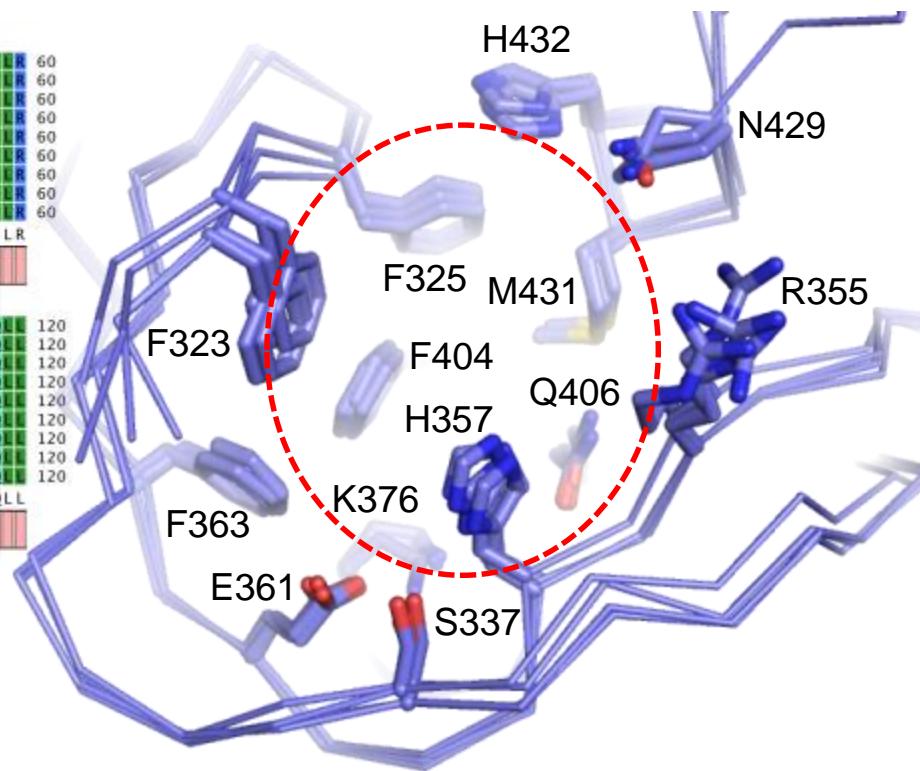


PB2 m7GTP Binding Site is Highly Conserved

(A) PB2 sequence comparison

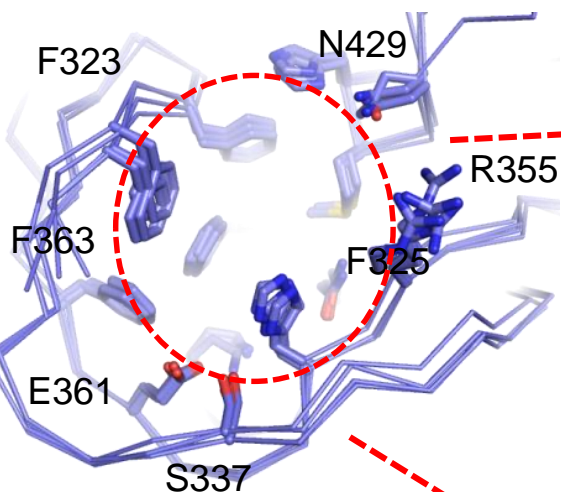


(B) m7GTP binding pocket

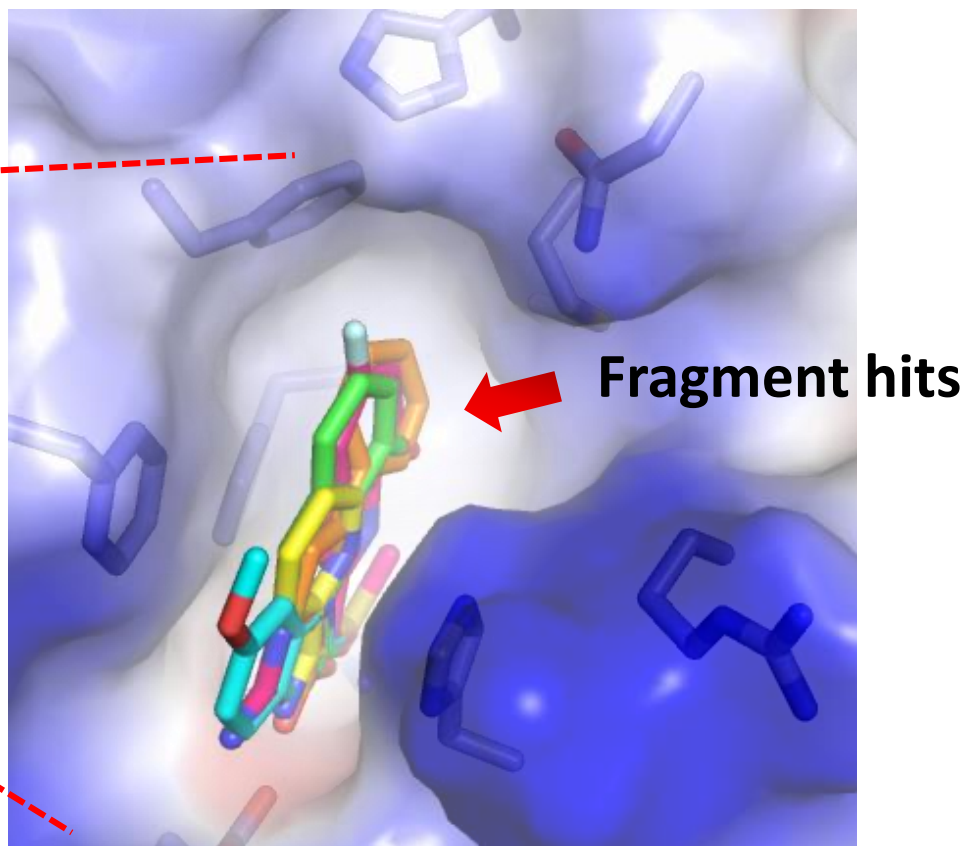


m7GTP Binding Pocket is a Fragment Hot Spot

(A) m7GTP binding pocket

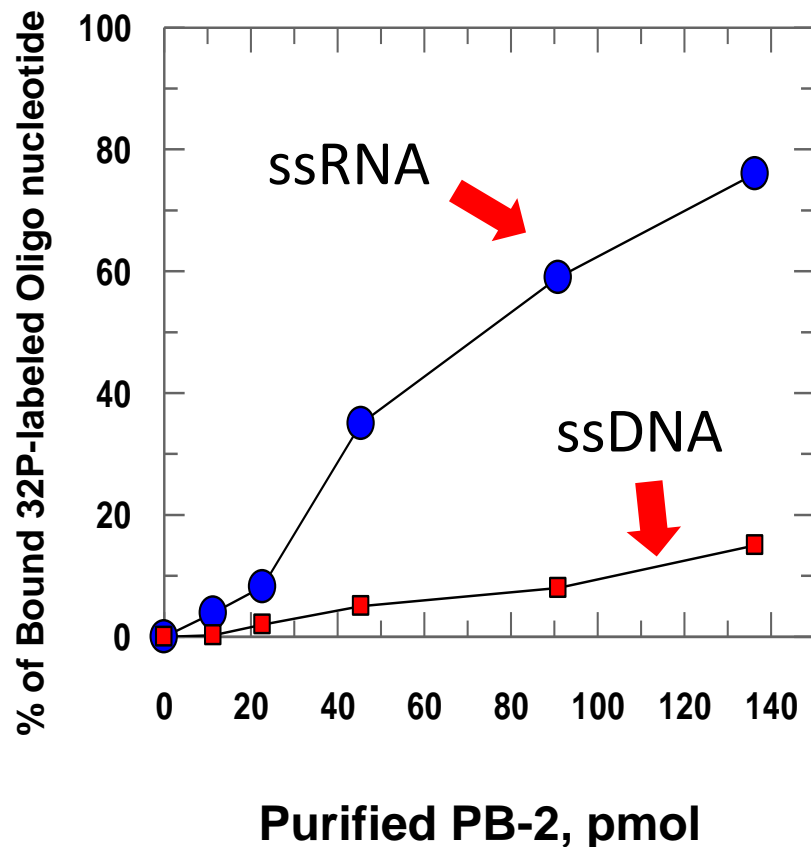


(B) Fragment hits

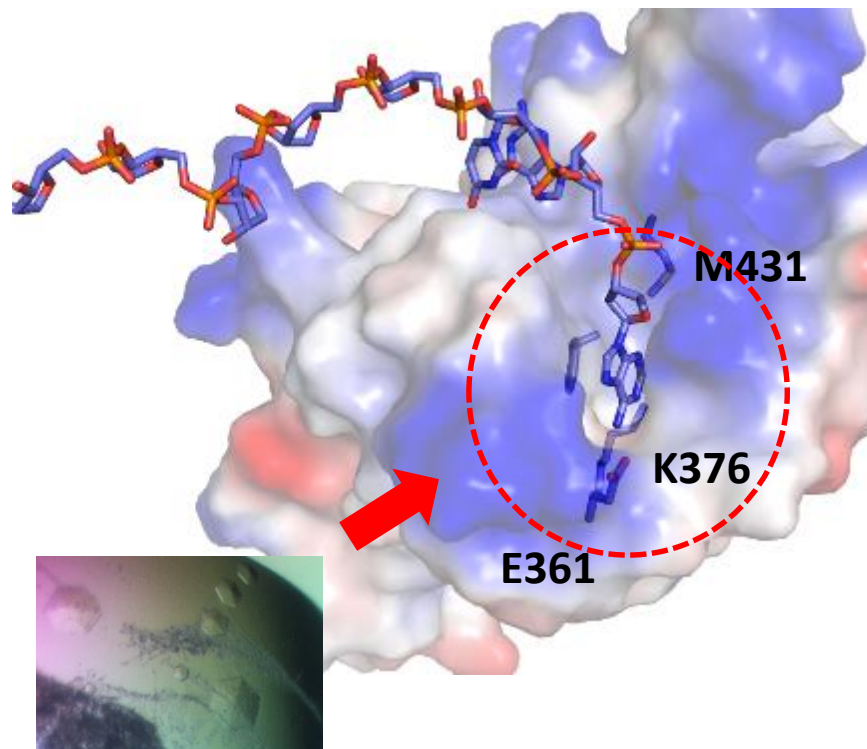


Crystal Structure of PB2-ssRNA Complex Determined

(1) ssRNA binding activity of PB2



(2) ssRNA binding activity of PB2



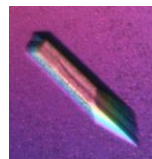
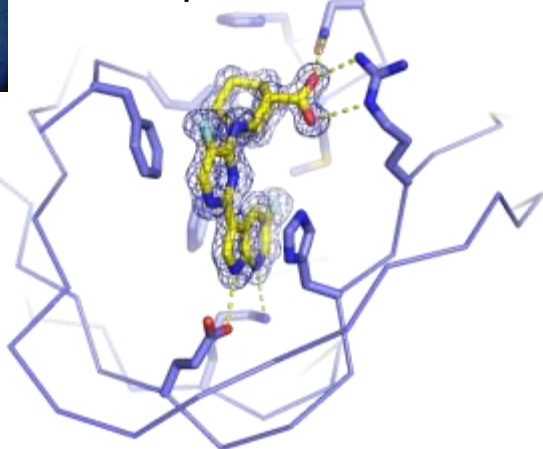
2.7 Å

Highly Conserved Binding Modes of PB2 Inhibitors



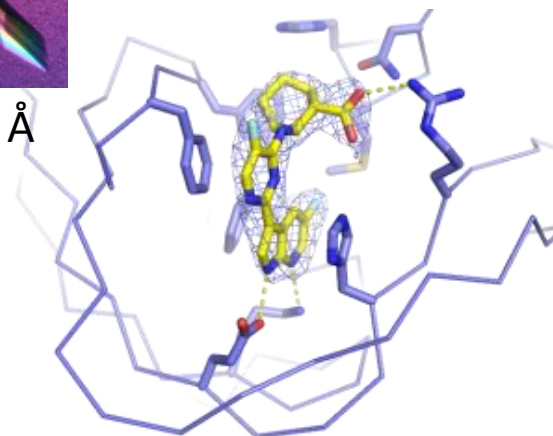
1.25 Å

H1N1 Spanish 1918



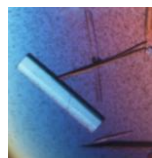
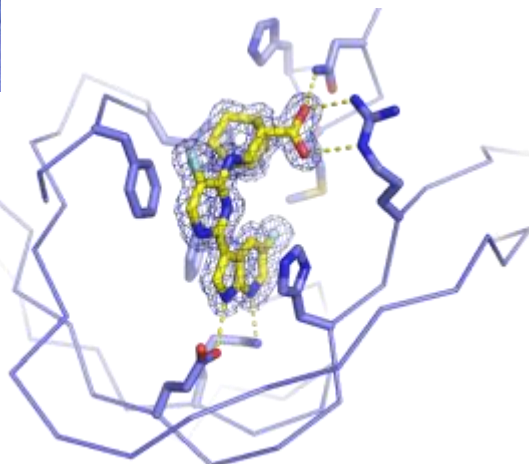
1.6 Å

H3N2 Victoria 1975



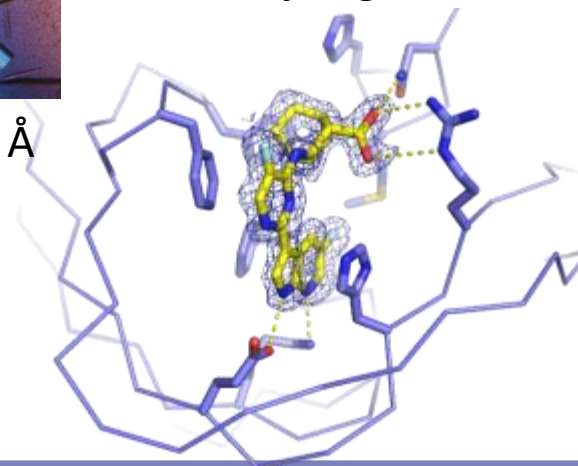
2.0 Å

H5N1 Guangdong 1996





1.5 Å

H7N9 Zhejiang 2013

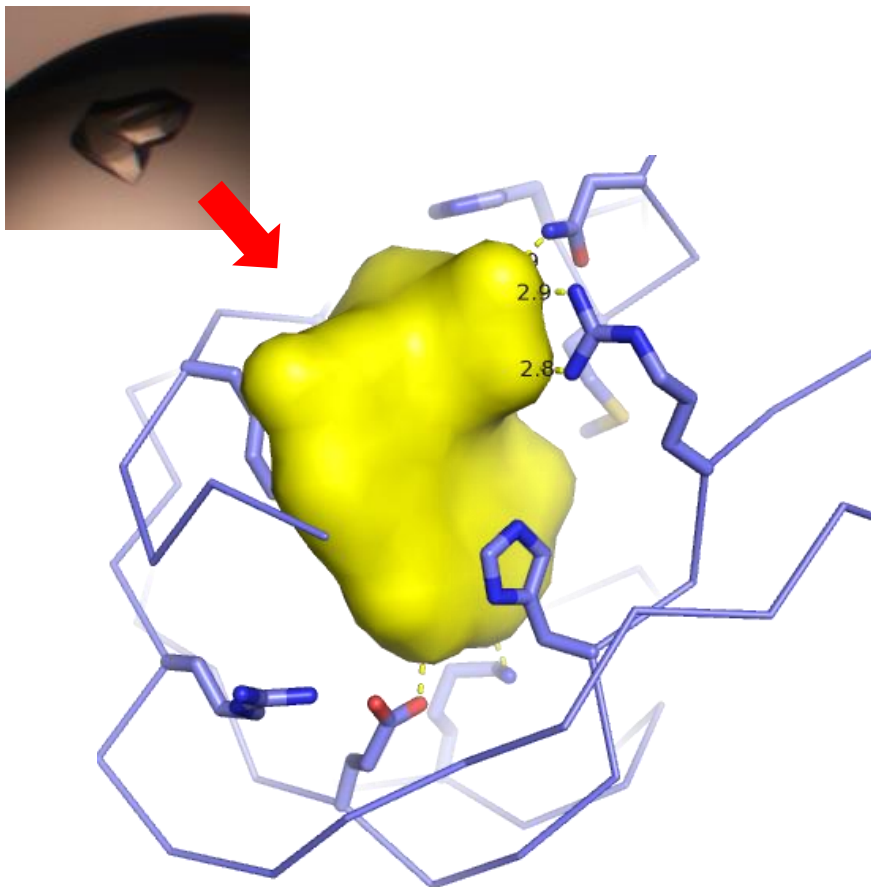


Cocrystal's PB2 Leads

		Cocrystal Preclinical Lead	Cocrystal's backup PB2 inhibitors			
Influenza strain	VX-787 EC50 nM	42344 EC50 nM	42343 EC50 nM	42487 EC50 nM	42500 EC50 nM	42530 EC50 nM
 Pandemic H1N1 Influenza A/CA/07/2009	2.4	 0.12	5	0.9	2.7	ND
H1N1 Influenza PR/8/34	1	1	1.2	1.2	2	0.5
Pandemic H5N1 Influenza A/VN/1193/ 2004	<3.2	<3.2	<3.2	<3.2	<3.2	<3.2

Influenza A Lead CC-42344 Properties

CC-42344 cocrystals



- 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

Cocrystal structure of CC-42344 (1.47 Å)

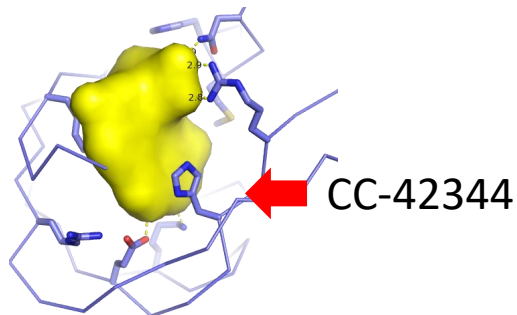
CC-42344 Shows Broad Spectrum Antiviral Activity Against Seasonal and Pandemic Strains

Influenza serotype	Strain	CC-42344, EC ₅₀ nM
H1N1	A/PR/8/34	1
H1N1	A1/Denver/1/57	3
H1N1	A/Fort Monmouth/1/47	2
H1N1	A/NY/18/09	5
H3N2	A/AICHI/2/68	0.2
H5N1	Duck/MN/1524/81	<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
H1N1- Tamiflu resistant	A/HK/2369/09 H274Y	9
H3N2-Tamiflu resistant	A/Wuhan/395/95	0.5
H5N1- Amantadine resistant	Duck/MN/1524/81	8.6

CC-42344: Pharmacological, Safety, Toxicity, and PK Evaluations Completed To Date

- ✓ In vitro antiviral profiling against seasonal and pandemic influenza A strains
- ✓ Cytotoxicity including larger screen: HepG2/high content analysis and 13 cell lines
- ✓ Caco-2 bidirectional permeability
- ✓ CYP inhibition (HLM): inhibition (2D6, 3A, 1A, 2B6, 2C8, 2C9, 2C19) & time dependent inhibition (2D6, 3A4)
- ✓ Thermodynamic/aqueous solubility
- ✓ pION solubility determination (at pH 7.4)
- ✓ Metabolic stability in rat and human microsomes (intrinsic clearance)
- ✓ Plasma protein binding (human)
- ✓ Plasma stability/half-life determination (human, rat)
- ✓ Pharmacokinetics: in rats (IV/PO), mouse (IV/PO) and dogs (IV/PO)
- ✓ In silico genotoxicity /carcinogenicity
- ✓ Off-target: kinase/receptor profiling; safety screen (CEREP)
- ✓ Mitochondrial toxicity (GLU/GAL)
- ✓ Mini Ames (genotox) screen
- ✓ Mini hERG (in vitro pharmacology) screen
- ✓ Exploratory 7-day mouse tox study (up to 500 mg/kg/day)

In Vitro and In Vivo Assessment of CC-42344



H1N1 EC50, nM	1
H1N1 EC90, nM	2
Cytotoxicity (HepG2) at 10 μ M	No
Cytotoxicity (13 cell lines) at 10 μ M	No
Mitochondria toxicity at 10 μ M	No
Off-target inhibition at 10 μ M	No
Solubility in PBS, μ M	90.8
Caco2 A-B, 10^{-6} cm/s	20
Caco2 B-A, 10^{-6} cm/s	2.5

Dose (Rat & Mouse, single dose)	PO 5mg/kg IV 1mg/kg
Oral bioavailability, %F	45% (rat); 57% (mouse)
Cl (ml/min/kg)	40 (rat); 27 (mouse)
Vd (L/kg)	18 (rat); 1.77 (mouse)
t _{1/2} (h)	5.24 (rat); 0.75 (mouse)
C _{max} (nM)	1,600 (rat), 1,600 x EC50; 9,544 (mouse), 9,544 x EC50
C _{min} (nM)	34 (rat); 148 (mouse)
hERG IC50	>10 μ M
Metabolic stability (liver microsomes)	rat, >60 min; Human, >60 min
CYP1A2, 2C19, 2C9, 2D6 & 3A4 IC50s	>10 μ M
Time-dependent CYP3A Time-dependent CYP2D	No inhibition at 10 μ M

Multiple Routes of Administration (Oral, Inhalation, IV) Explored

CC-42344

Oral administration

Vehicle 1: 40% Miglyol 812
40% VE TPGS
20% PEG400
Vehicle 2: 8% DMA, 37% PEG300,
5% poloxamer188,
50% pH 8 USP buffer
Vehicle 3: 2% PVP/0.5% Tween80

Inhalation administration



Dry powder
~2 μ m

IV administration



40% PEG300
10% Solutol H515 10%
50% Phosphate buffer
pH 7.45

In Vivo Assessment of CC-42344

Comparative maximum formulation single PO dose exposures in rat

<i>Test formulation</i>	<i>PO Dose (mg/kg)</i>	<i>Fed or fasted</i>	<i>T_{1/2} (hours)</i>	<i>Plasma C_{max} (ng/mL)</i>	<i>T_{max} (hours)</i>	<i>Plasma AUC_{0-last}^t (ng.h/mL)</i>
40% miglyol/40% VE TPGS/20% PEG400	300	Fed	3.82	2,333 (5.3 µM)	0.83	7,857
2% PVP/0.5% Tween80	500	Fed	2.15	30,633 (70 µM)	1.17	95,913
	800		1.96	65,300 (148 µM)	6.00	600,000
8% DMA/37%PEG300/ 5% poloxamer188/50% USP buffer, pH 8	200	Fed	1.78	39,067 (89 µM)	1.00	292,854

Comparative single dose IV pharmacokinetics

<i>Animal species</i>	<i>Dose (mg/kg)</i>	<i>T_{1/2} (hours)</i>	<i>V_d (L/kg)</i>	<i>Cl (mL/min/kg)</i>	<i>AUC_{0-last} (ng h/mL)</i>
Female BALB/C mouse	2.5	2.02	1.79	37.8	1097
Male Sprague-Dawley rat	1	5.24	17.9	39.9	385

In Vivo Assessment of CC-42344



- Single dose inhalation pharmacokinetics in the female Balb/c mouse

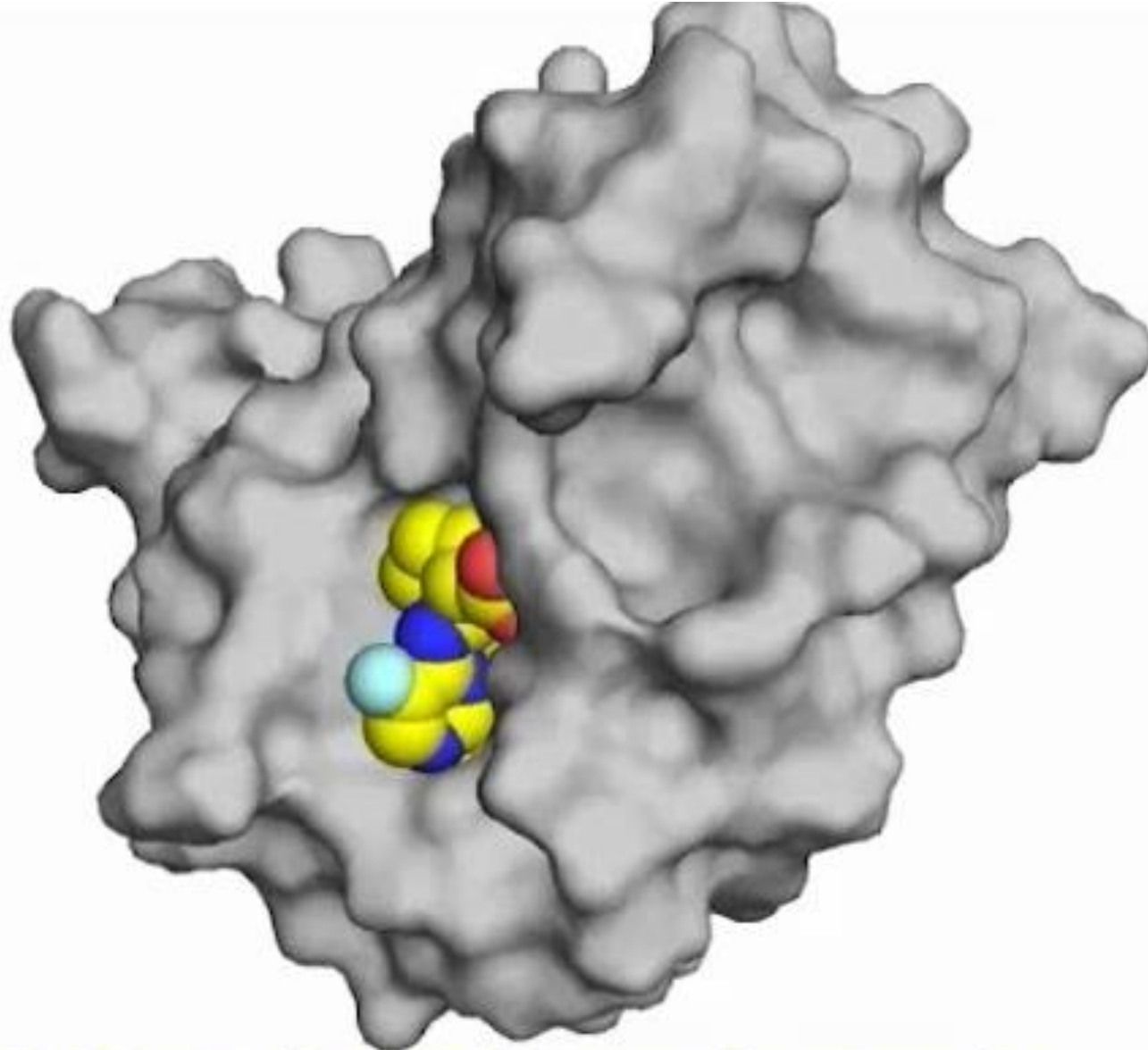
- ☐ Dry power formulation developed

- ☐ Dose 0.8-1.2 mg of dry power (~200 ug of CC-42344)



Dry powder
~2 μm

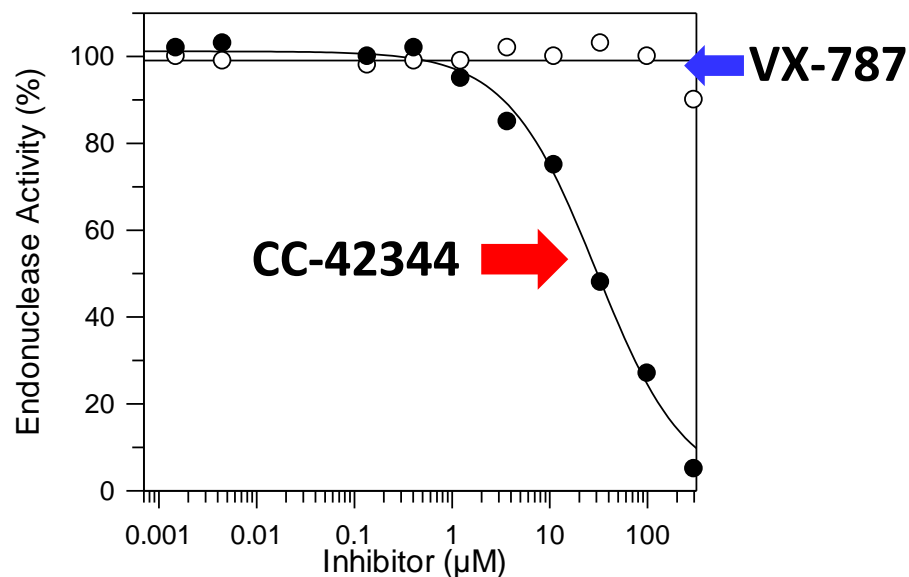
Time course	CC-42344 concentration Lung	CC-42344 concentration Plasma
1 hr	984 μM 	5.6 μM 
24 hr	218 μM	0.081 μM
48 hr	8.6 μM	0.052 μM
72 hr	0.63 μM	0
96 hr	0.35 μM	0



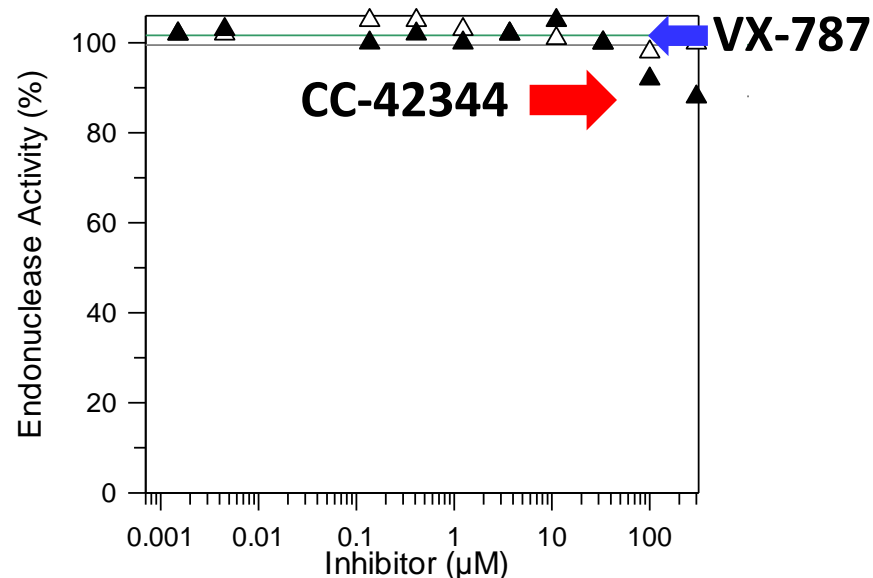
PB2 Cap binding domain

CC-42344 Inhibits The Endonuclease Activity of Influenza A Trimeric Complex (PA:PB1:PB2)

(A) PA:PB1:PB2 trimeric complex

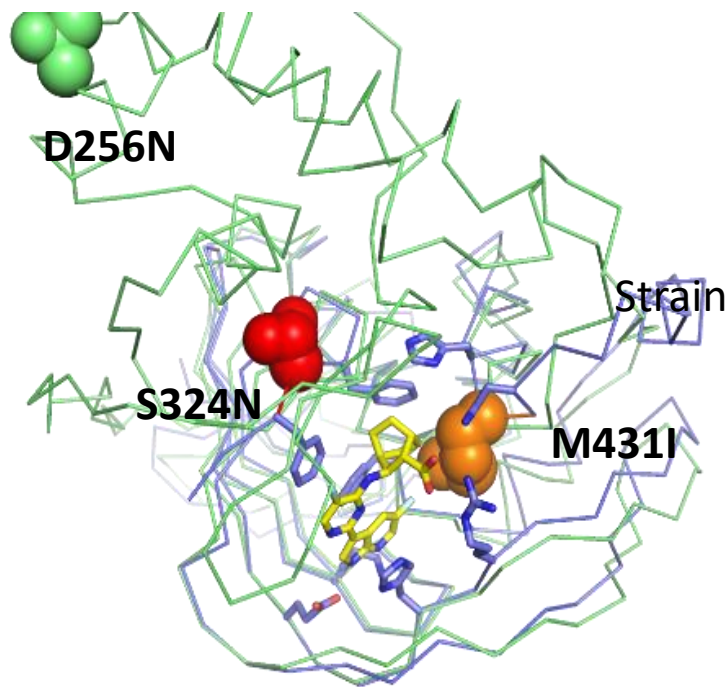


(B) PA endonuclease



Drug Resistant Profile of Cocystal PB2 Lead, CC-42344

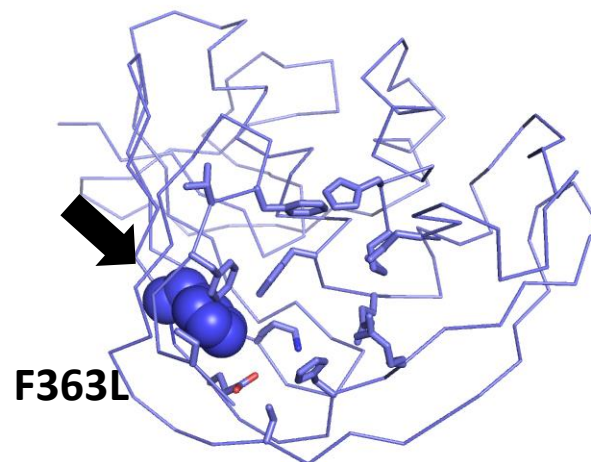
(A) VX-787: **3** resistant H1N1 viruses
D265N, S324N, M431I



**3 mutations identified after
treatment with VX-787**

Cocystal PB2 lead

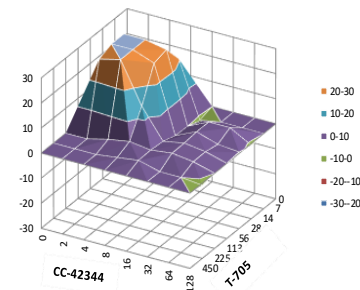
(B) CC-42344: **1** resistant H1N1 virus
F363L



**1 mutation identified after
treatment with CC-42344**

CC-42344 Shows Strong Synergistic Effects With Approved Influenza Antivirals

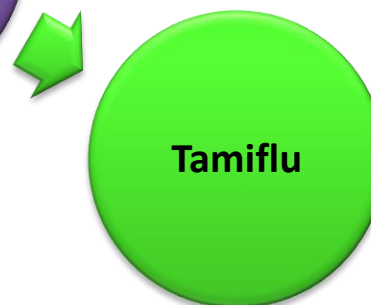
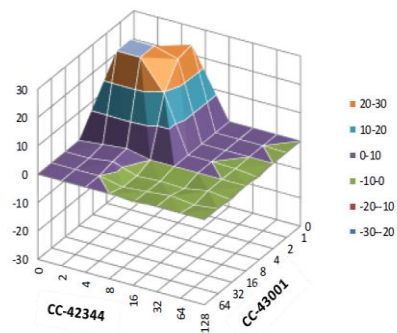
Polymerase inhibitor



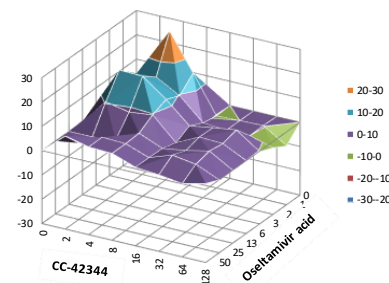
Cocystal
42344



PA inhibitor



Neuraminidase inhibitor



Summary

Property	Cocrystal CC-42344	Pimodivir (VX-787)
Antiviral activity against seasonal and pandemic influenza	Single digit nanomolar, Broad spectrum	Single digit nanomolar, Broad spectrum
Drug resistance profile	One mutation F363L	Three mutations D256N, S324N, M432I
Route of Administration	Inhalation, IV, and oral routes Currently explored	Oral, BID
Chemical stability (>12 months)	Yes	Data not available
Synergistic Effects with replication inhibitors	Yes	Data not available