COCRYSTAL PHARMA, INC.

Discovery of Potent, Broad-Spectrum SARS-CoV M^{pro} Inhibitors: Advancing to Clinical Development

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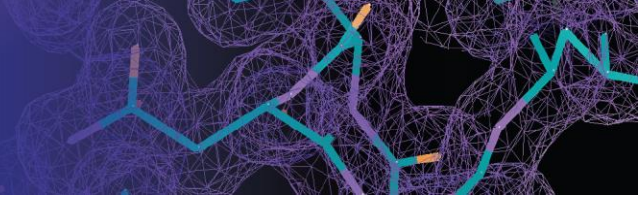
Nasdaq: COCP
www.cocrystalpharma.com

Forward-Looking Statements



This presentation contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, including statements regarding the market opportunities for the treatment of acute and chronic viral diseases which are the focus of our programs; the development pipeline; the expected future characteristics and 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 selecting a preclinical lead for an oral broad spectrum protease inhibitor by year end and initiating two IND-enabling studies in H1 2022; the expected progress of our Influenza A program, including the initiation of Phase 1 study in Q1 2022; and the expected progress of our norovirus program and the anticipated timing of achieving the value-driving milestones, including preclinical lead selection planned for 2022-2023.

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 the national and global economy, on our collaboration partners, CROs, CMOs, and on our Company, including raw material and test animal shortages and other supply chain disruptions, the ability of our CROs to recruit volunteers for, and to proceed with, clinical trials, possible delays resulting from the lockdown in Australia, the cooperation of the FDA in accelerating development in our COVID-19 program, our reliance on Merck for further development in the influenza A/B program under the license and collaboration agreement, our and our collaboration partners’ technology and software performing as expected, the results of future preclinical and clinical trials, general risks arising from clinical trials, receipt of regulatory approvals, regulatory changes, and development of effective treatments and/or vaccines by competitors, including as part of the programs financed by the U.S. government. 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, 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.

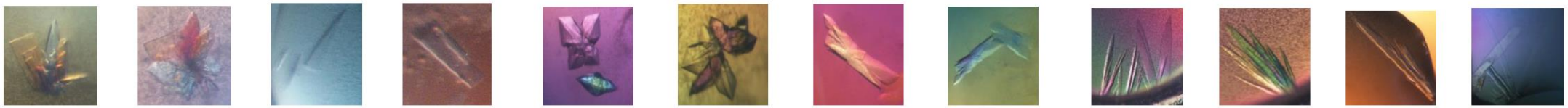
Cocrystal Focuses on Direct-Acting Antivirals

- Our focus is exclusively on inhibitors of **viral replication enzymes and proteases**

COVID-19	Influenza	Norovirus	HCV
Drug target ▪ Main protease (M^{pro}) ▪ Replication enzymes	Drug target ▪ Polymerase complex PB2 PB1 PA	Drug target ▪ Polymerase (NNI) ▪ Protease	Drug target ▪ Polymerase (NNI) ▪ Helicase

Cocrystal Pharma Structure-Based Drug Discovery Platform Technology Applied To Broad-Spectrum Antiviral Development

COVID-19 Program



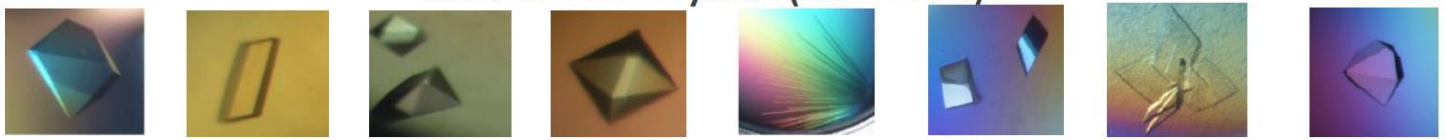
SARS-CoV-2 main protease (1.8 Å)

SARS-CoV-1 main protease (1.56 Å)

MERS-CoV main protease (1.9 Å)

Influenza Program

Influenza PB2 crystals (1.0 – 2.5 Å)



Influenza A/B crystals (1.4 – 2.3 Å)

Hepatitis C Program

GT1b GT1a GT1b FL GT2a GT3a GT4a GT5a GT6a

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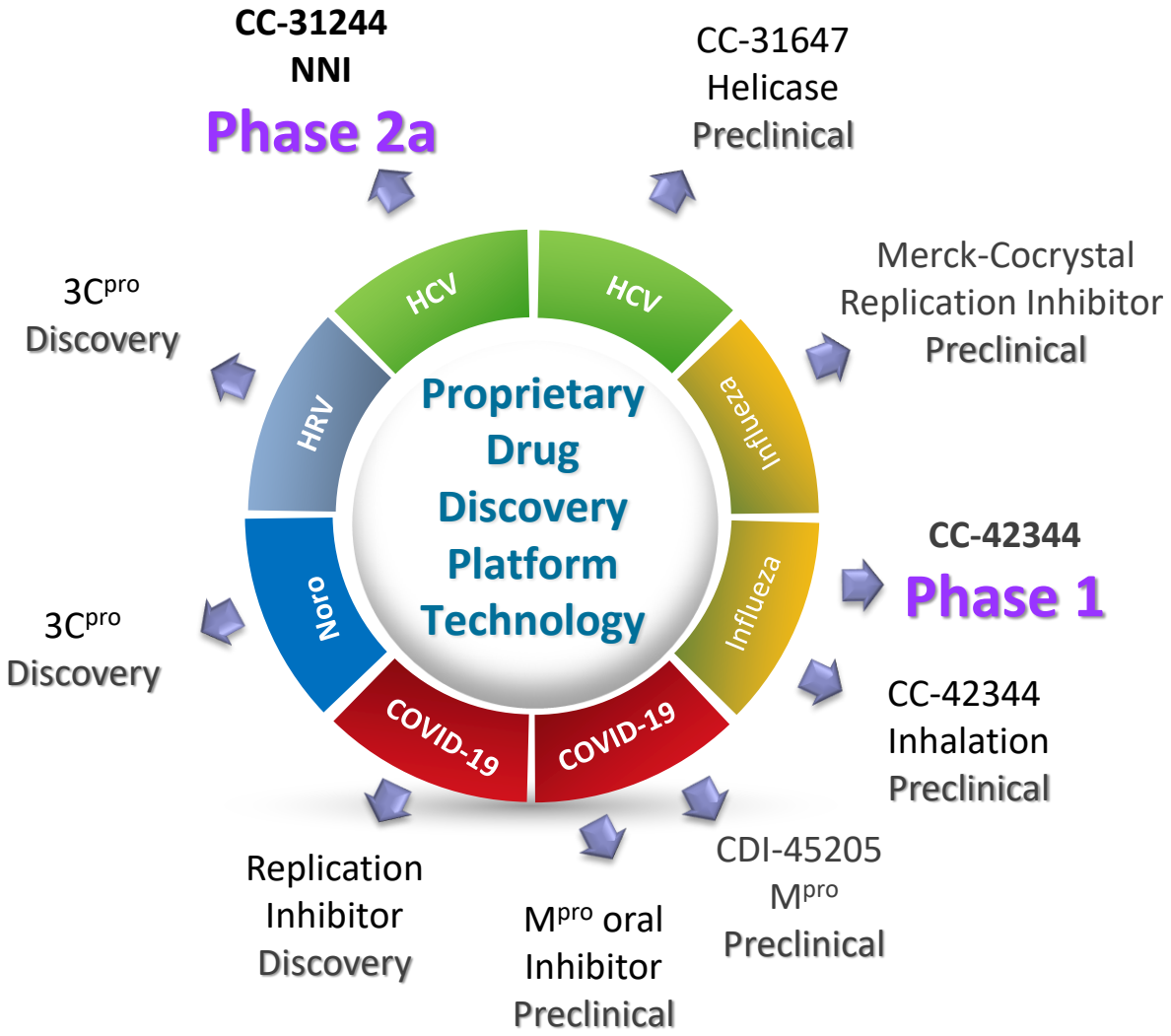
Cocrystal Structure-Based Drug Discovery Platform Technology Delivers Multiple Broad-Spectrum Antiviral Leads



Cocrystal technology uniquely offers:

1. Systematic analysis of drug binding pockets
2. Rapid cocrystal structure determination
3. Structural insight into drug resistance
4. Novel structural hits and pockets
5. Multiple leads

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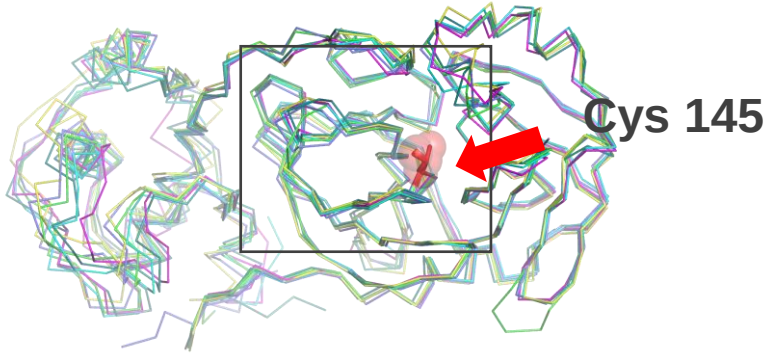
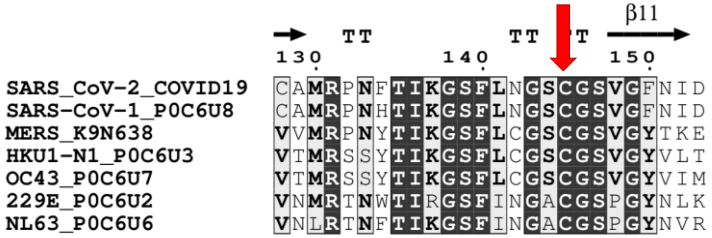
Robust Therapeutic Pipeline Addressing Unmet Medical Needs

Program		Discovery	Preclinical	Phase 1	Phase 2	Phase 3
COVID-19	Oral Protease Inhibitor			IND-enabling studies in H1 2022		
COVID-19	CC-7087 (intranasal) Protease Inhibitor			IND-enabling studies in H1 2022		
COVID-19	Replication Inhibitors		Discovery ongoing			
Influenza A	CC-42344 PB2 Inhibitor			Phase 1 trial initiation in Q1 2022		
Influenza A/B	Influenza A/B Inhibitor			In collaboration with MERCK		
Hepatitis C (HCV)	CC-31244 Pan-genotypic NS5B NNI				Available for partnering	
Norovirus Gastroenteritis	Replication and Protease Inhibitors			Preclinical lead selection planned for 2022-2023		

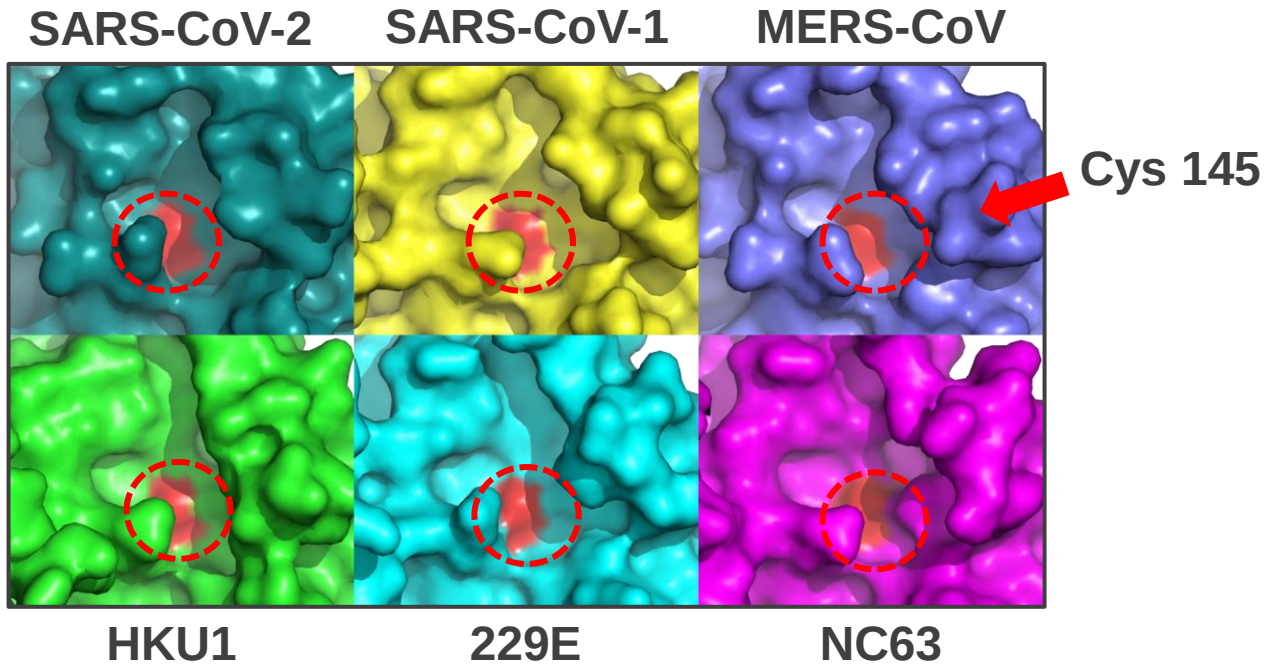
Coronavirus Main Protease is Essential For Viral Replication: Highly Conserved Active Site

(A) Overlay structures of coronavirus proteases





(B) Highly conserved Cys145 residue



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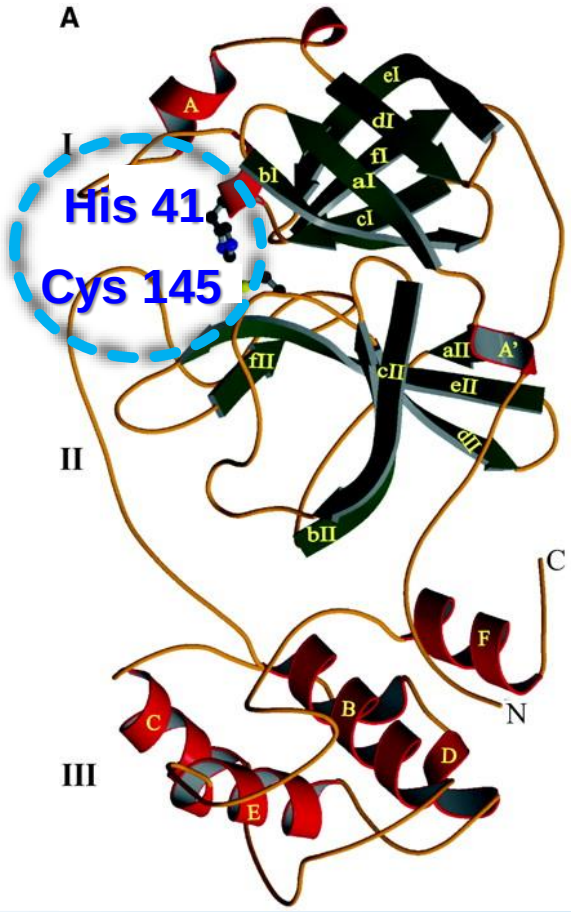
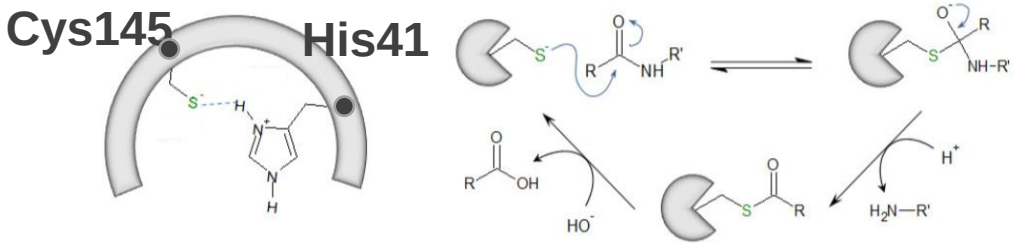
Cocrystal Inhibitors Target The Highly Conserved Cys145

Highly conserved Cys145 is required for the viral M^{pro} protease activity



Cysteine protease
Catalytic dyad -
Cys145 and His41



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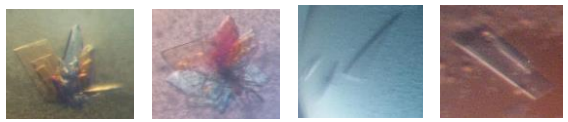
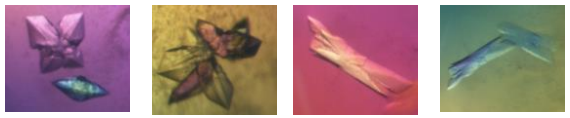
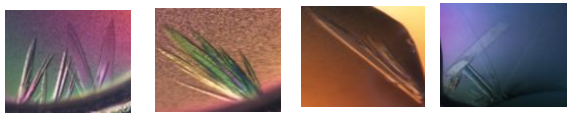
Cocrystal Is Developing Multiple SARS-CoV-2 M^{pro} Inhibitors For Multiple Routes of Administration (Oral, inhalation, and IV)



SARS-CoV-2 main protease (1.8 Å)

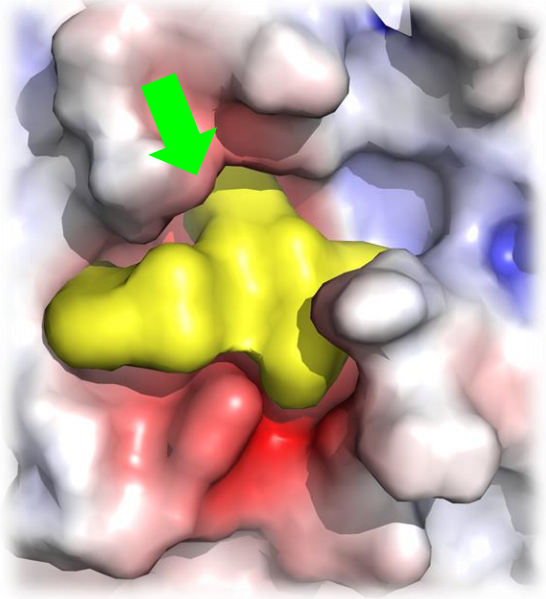


SARS-CoV-1 main protease (1.56 Å)



MERS-CoV main protease (1.9 Å)

Main (3CL) protease inhibitor



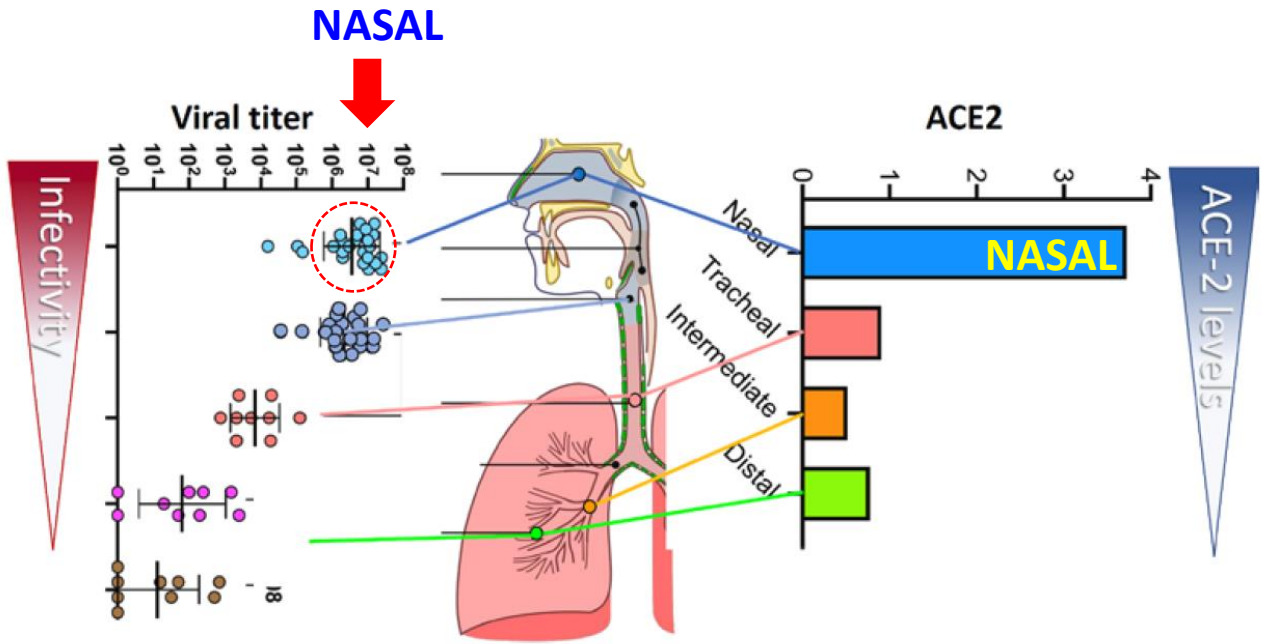
Cocrystal structure of SARS-CoV-2 Main(3CL) protease

Cocrystal SARS-CoV-2 M^{pro} inhibitors

- Bind to a highly conserved, essential residue (Cys145) of SARS-CoV-2 main protease and other coronavirus main proteases
- Exhibit broad-spectrum activity against SARS-CoV-2 and its variants
- In development for multiple routes of administration:
  (1) Oral
  (2) Intranasal
  (3) Intravenous

Intranasal/Pulmonary Main Protease (M^{pro}) Lead: CDI-45205

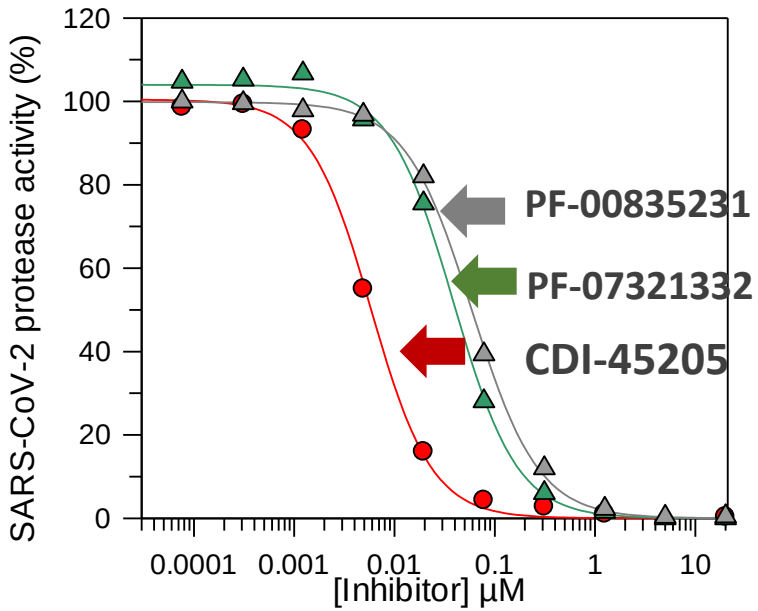
Nasal cavity cells express high level of SARS-CoV-2 entry receptor (ACE-2 receptor) and also show the highest SARS-CoV-2 viral load

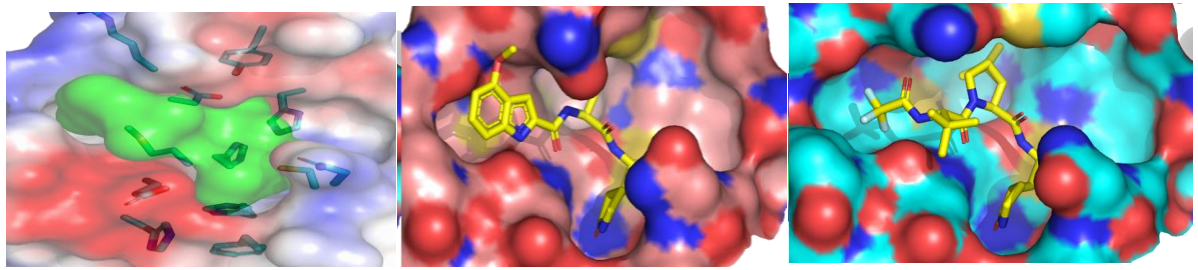


Reference: Hou et al., 2020, Cell 182, 429-446

PF-00835231(IV), PF-07321332 (Oral) *vs* CDI-45205

(A) SARS-CoV-2 M^{pro} IC50





CDI-45205 PF-00835231 PF-07321332

Assay	Cocrystal CDI-45205	PF-07321332 (Oral inhibitor)	PF-0085231 (IV inhibitor)
SARS-CoV-2 M^{pro} IC50	5 nM	59 nM	37 nM
SARS-CoV-2 EC50 (MEX-BC2/2020)	1.3 uM	4.7 uM	>20 uM
DSF* ΔTm	12^{0}C	8^{0}C	4^{0}C

*Differential Fluorimetry Scanning

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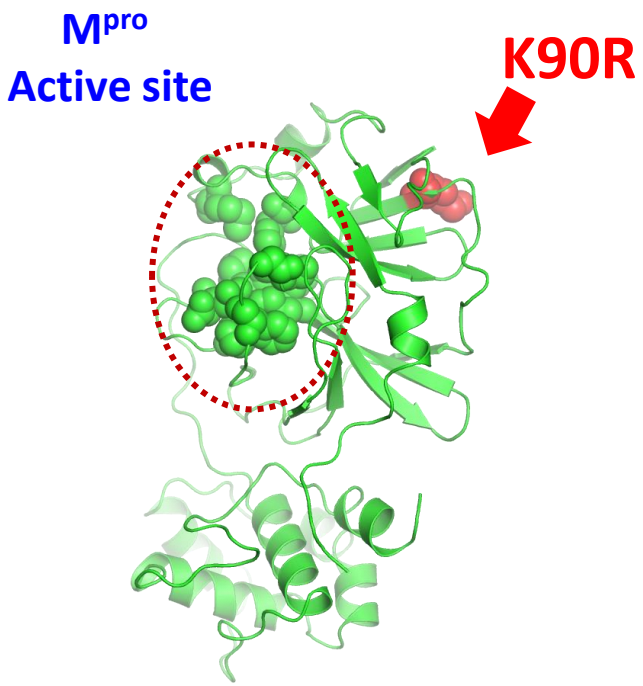
SARS-CoV-2 Antiviral Activity of CDI-45205 In The Presence of P-glycoprotein efflux inhibitor

Antiviral inhibitor	Wuhan strain* EC_{50} µM	Wuhan strain* EC_{50} µM
	Without P-glycoprotein efflux inhibitor	**With** P-glycoprotein efflux inhibitor
CDI-45205 (SARS-CoV-2 M^{pro} protease inhibitor)	**6.2**	**1.9**
PF-00835231 (SARS-CoV-2 M^{pro} protease inhibitor)	**>100**	**3.0**
GS-441524 (Nucleoside inhibitor, remdesivir plasma metabolite)	**1.2**	**0.8**

*: VeroE6 cells expressing enhanced GFP

Cocrystal's Unique Structure-Based Drug Design Approach Using Naturally Occurring Variants

(A) SARS-CoV-2 β variant M^{pro}



(B) CDI-45205 exhibits an excellent antiviral activity against SARS-CoV-2 β variant

Wuhan	Delta (B.1.617.2)	Alpha (B.1.1.7)	Beta (B.1.351)	Gamma P1/B.1.1.28
M^{pro}	No mutation	No mutation	K90R	No mutation
CDI-45205 IC_{50}, 5 nM	-	-	CDI-45205 IC_{50}, 0.9 nM	-

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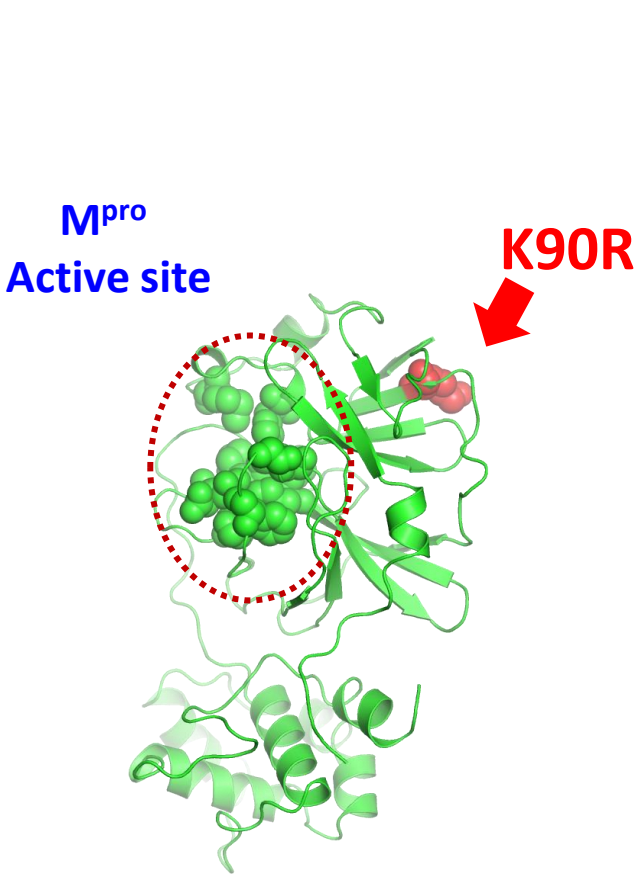
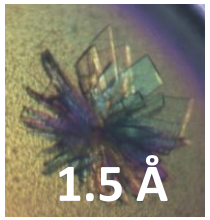
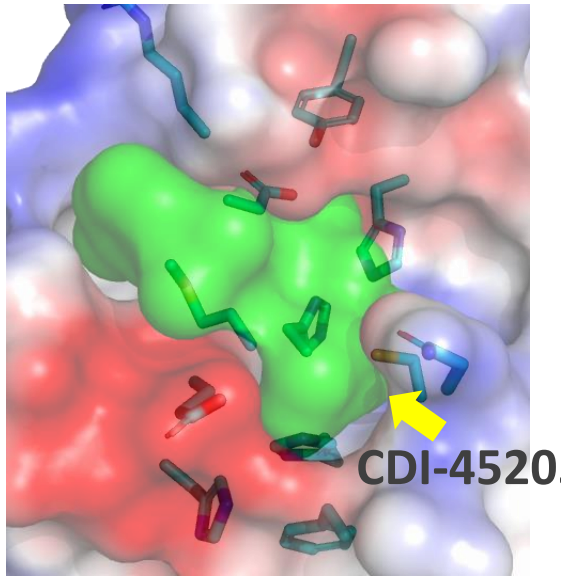
Cocrystal Lead, CDI-45205, Binds To SARS-CoV-2 β Variant M^{pro}

High resolution X-ray cocrystal structure of β variant M^{pro}:CDI-45205 complex

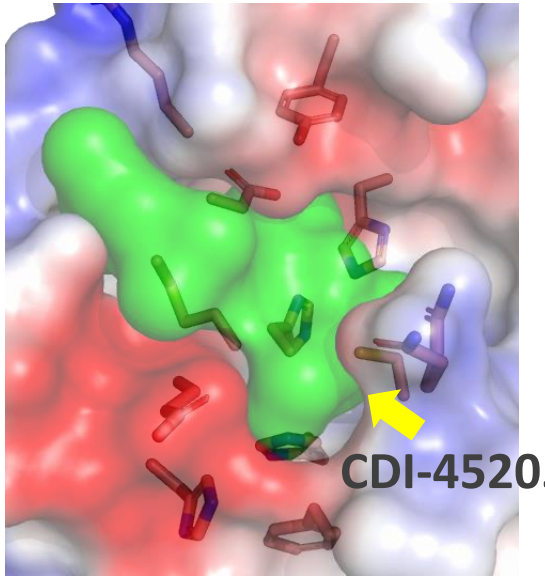


β variant M^{pro}





Wuhan M^{pro}



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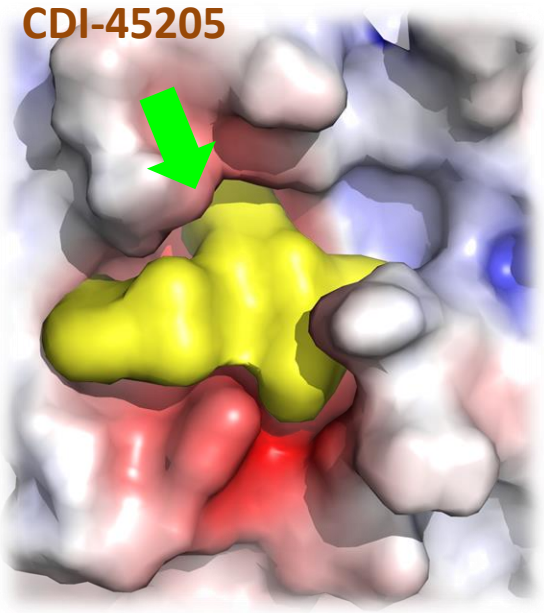
Broad-Spectrum SARS-CoV-2 Antiviral Activity of CDI-45205 Against COVID-19 Variants Including Delta Variant

Broad-spectrum antiviral activity of CDI-45205 against COVID-19 variants

Antiviral inhibitor	Wuhan EC_{50} µM	Delta (B.1.617.2) EC_{50} µM	Alpha (B.1.1.7) EC_{50} µM	Beta (B.1.351) EC_{50} µM	Gamma P1/B.1.1.28 EC_{50} µM
		With P-glycoprotein efflux inhibitor			
CDI-45205	**1.9**	**0.4**	**1.1**	**0.8**	**0.4**
GS-441524 (Nucleoside inhibitor, remdesivir plasma metabolite)	**0.8**	**1.1**	**0.8**	**0.9**	**1.4**

*VeroE6 cells expressing enhanced GFP

In Vitro and *In Vivo* Assessment of CDI-45205



Cocrystal structure of SARS-CoV-2 Main(3CL) protease

SARS-CoV-2, IC50	5 nM
SARS-CoV-2, EC50 (VeroE6)	460 nM
DSF	8^0C shift
Cytoxicity (HepG2) at 10 uM	No
Cytoxicity (13 cell lines) at 10 uM	No
AMES genotoxicity	No
hERG	No
Human nasal epithelia toxicity	No
Off-target inhibition (44 targets)	No
Caco2 A-B, 10^{-6} cm/s Caco2 B-A, 10^{-6} cm/s	0.39 7.1
Lung microsomal stability	>120 min

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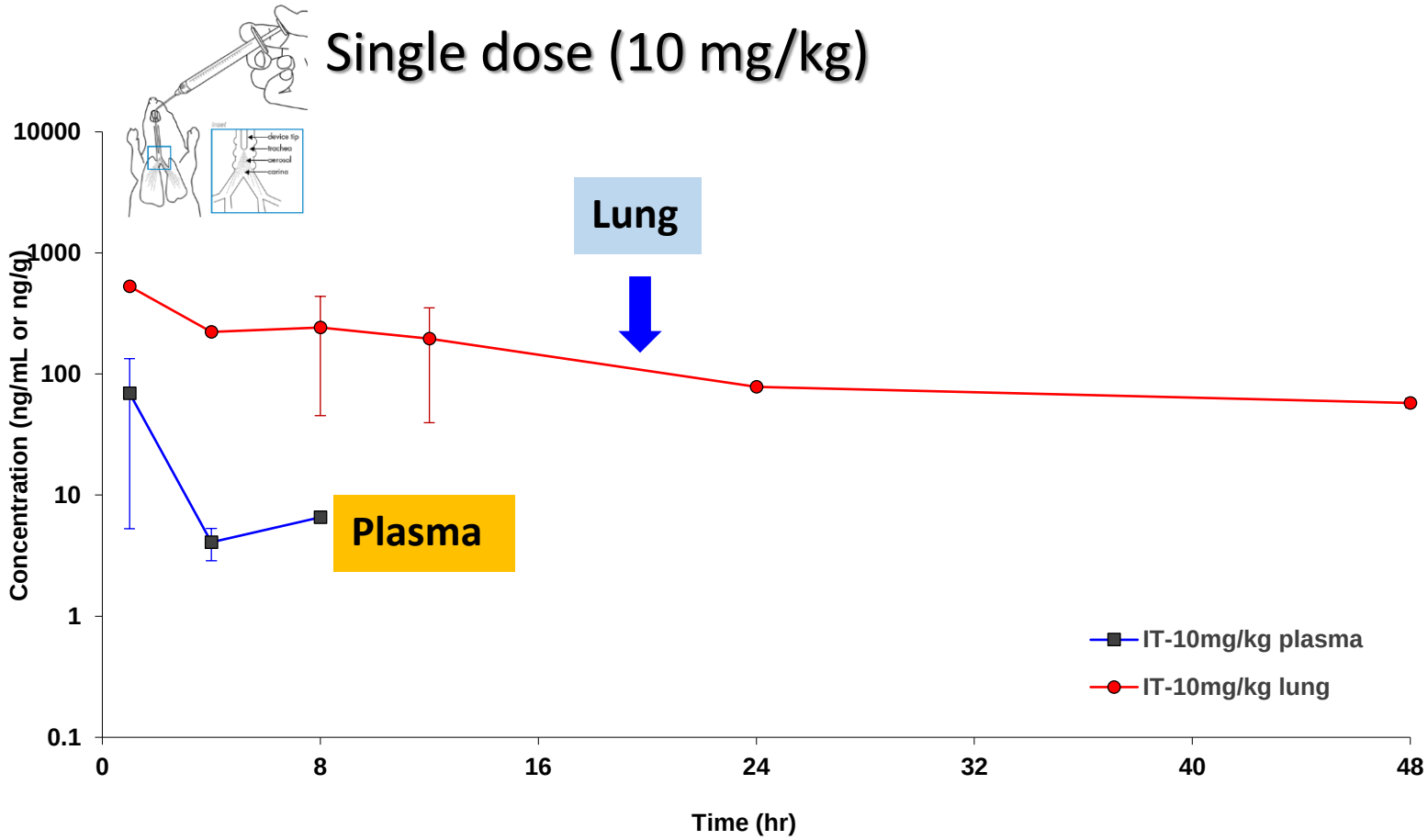
Intratracheal PK of CDI-45205: Potential COVID-19 Inhalation Treatment

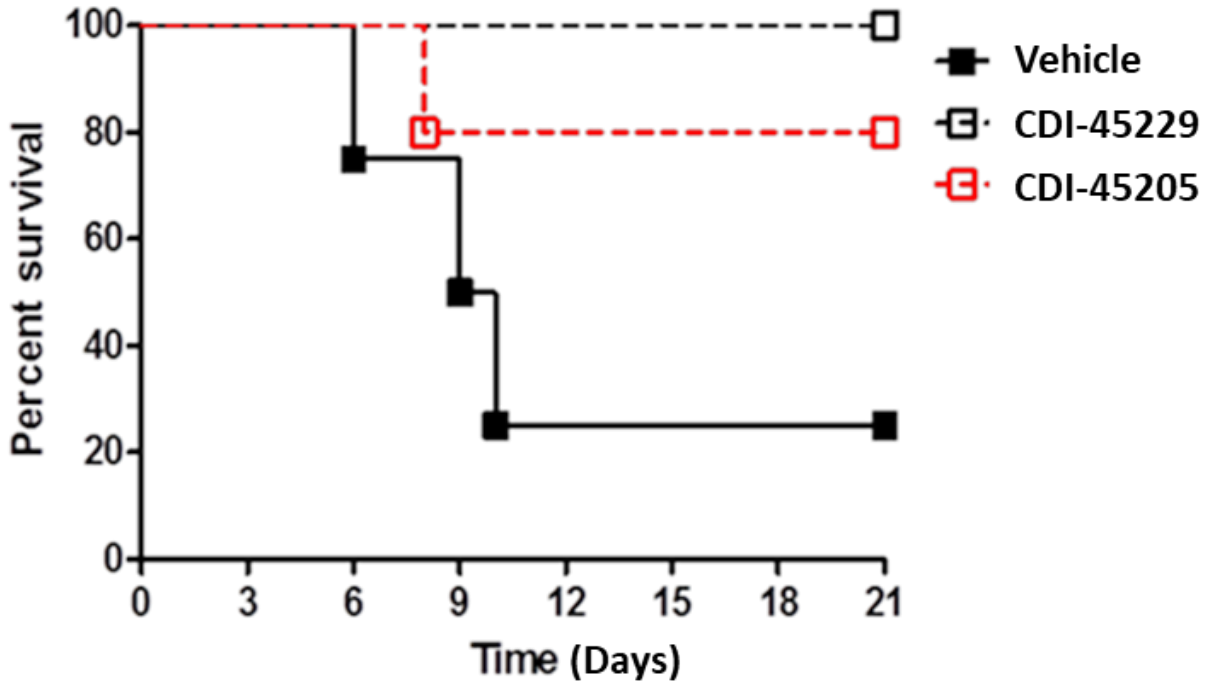
PK data demonstrated that intracheal delivery can significantly improve the half-life of CDI-45205 and also reduce systemic exposure



Cmax = 530 ng/mL
Cmin = 57.7 ng/mL
$T_{1/2}$ = 19.25 hrs
N =3

CDI-45205: Significantly Increased Survival Of MERS-CoV Infected Mice

- SARS-CoV-2 M^{pro} inhibitors reduced virus titer and decreased acute lung injury



- SARS-CoV-2 M^{pro} inhibitor or vehicle was given at one day post virus inoculation
- Therapeutic dose: 50 mg/kg, i.p. once per day, n=5
- MERS-CoV mouse study was conducted by Kansas State University and University of Iowa

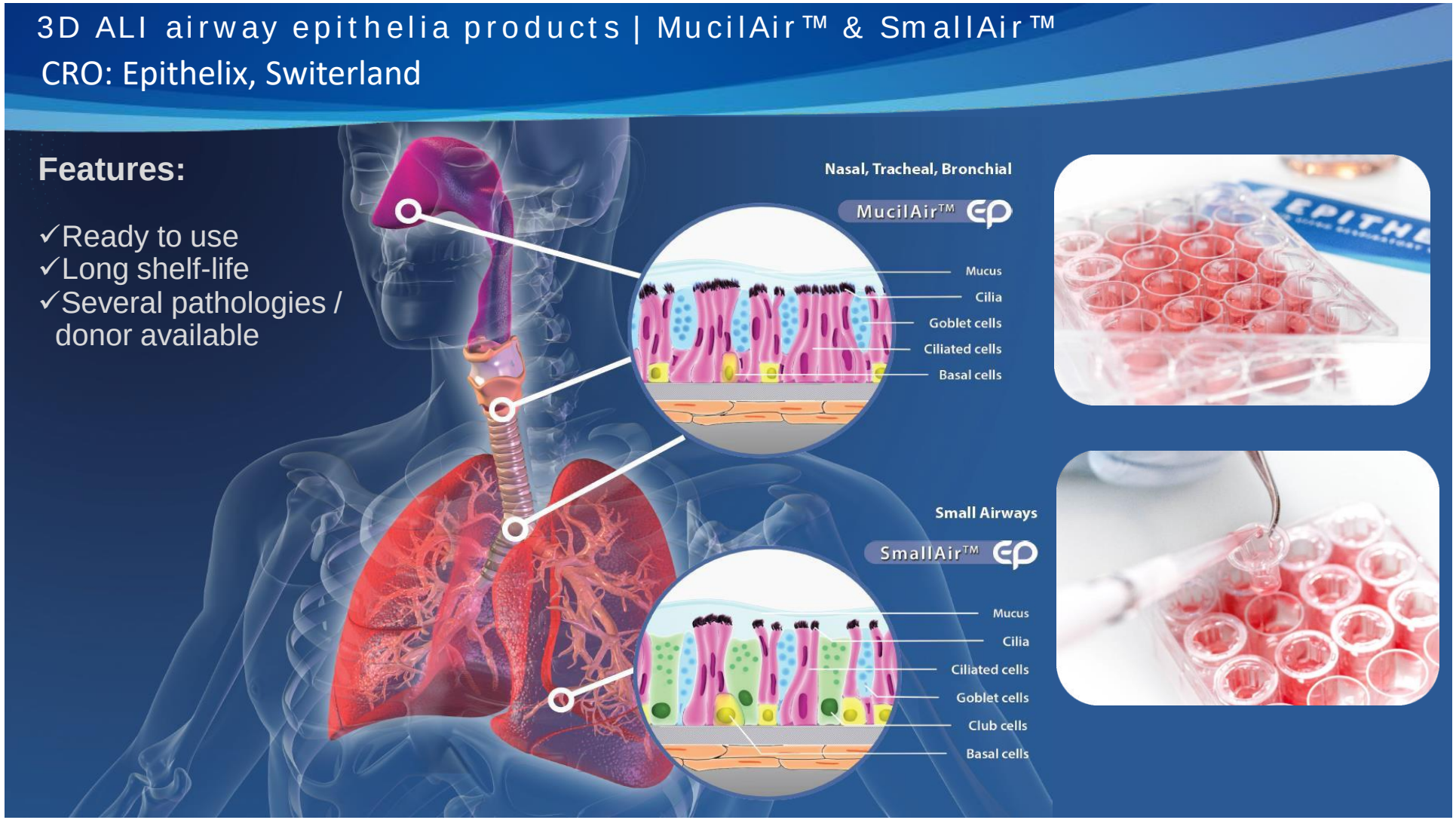
CDI-45205 :7-Day Exploratory Mouse Tox Studies Showed Favorable Safety Profile

Studies	Route	Animal	Dose	Mortality of Treated animals
7-day mouse tox	PO (oral)	CD1 mice	50, 150 , 500 mg/kg	No
7-day mouse tox	IV (intravenous)	CD1 mice	25, 80, 250 mg/kg	No

Both regimens were tolerated; no abnormal findings observed

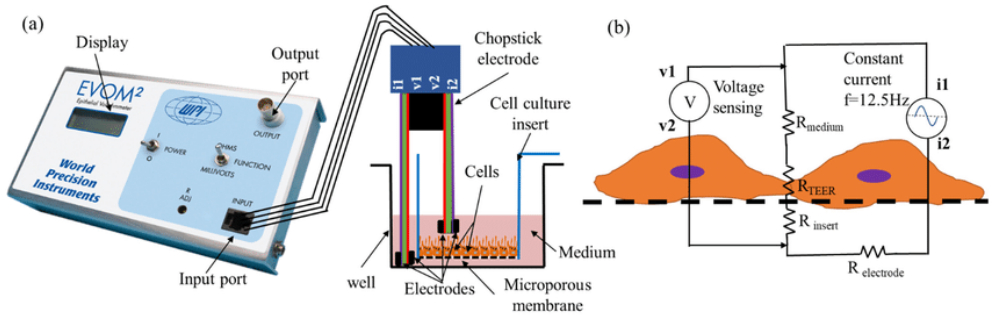
- ☑ Clinical signs
- ☑ Clinical pathology change
- ☑ Food consumption
- ☑ Body weight change
- ☑ Organ weight change
- ☑ Macroscopic observation (on necropsy)

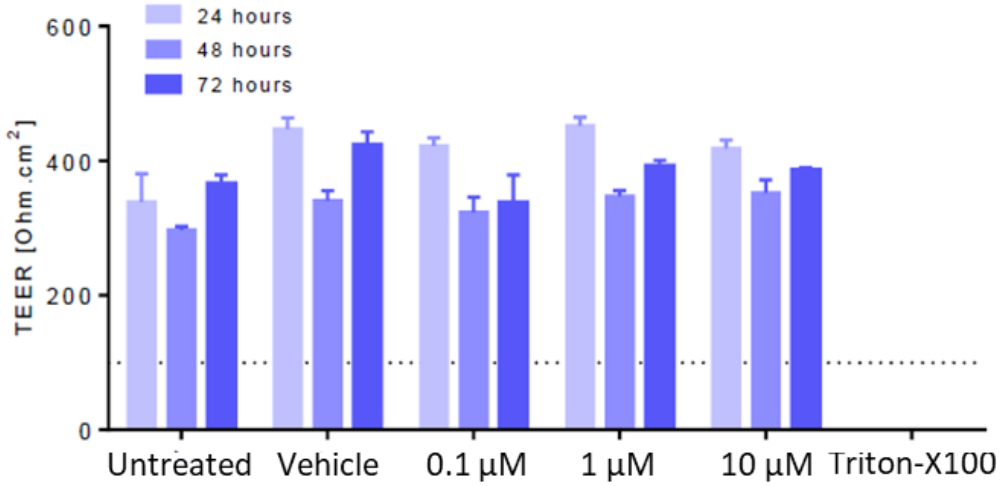
CDI-45205 Showed No Lung Toxicity in Human Nasal Airway Epithelia (HAE)



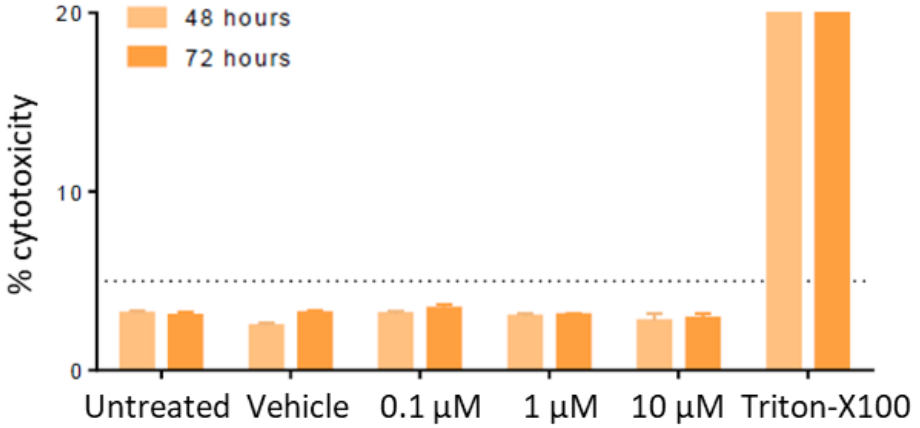
Favorable Safety Profile of CDI-45205 Demonstrated In Human Nasal Epithelia

(A) Trans-epithelial electric resistance: No toxicity

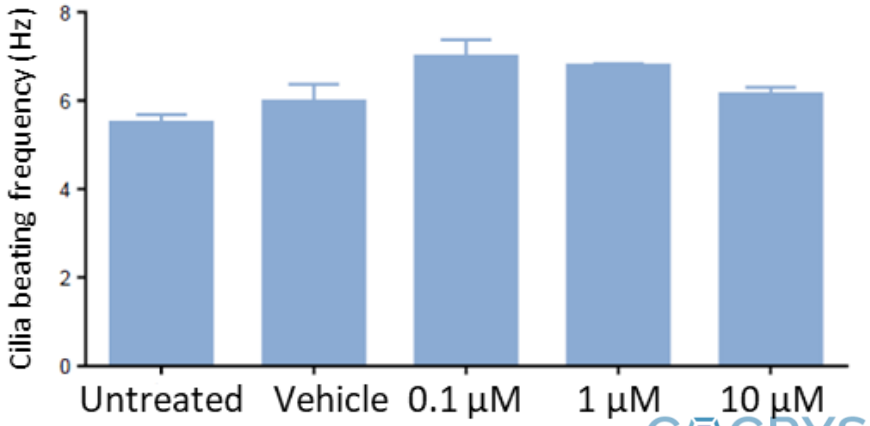




(B) Lactate dehydrogenase: No toxicity



(C) Cilia motility: No toxicity



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CDI-45205: Pharmacological, Safety, Toxicity, and PK Evaluations

- ☑ In vitro antiviral profiling against SARS-CoV-2 and its variants (delta, gamma, beta, alpha)
- ☑ Cytotoxicity: 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)
- ☑ Aqueous solubility
- ☑ Liver microsomal stability
- ☑ Lung microsomal stability
- ☑ Plasma protein binding
- ☑ Intracheal pharmacokinetics in mouse
- ☑ Pharmacokinetics: in rats (IV/PO/IP) and mouse (IV/PO/IP)
- ☑ In silico genotoxicity /carcinogenicity
- ☑ Off-target: kinase/receptor profiling; safety screen
- ☑ Human nasal epithelia toxicity
- ☑ Mini Ames (genotoxicity)
- ☑ Mini hERG
- ☑ Exploratory 7-day mouse tox study (up to 500 mg/kg/day)
- ☑ POC animal study (MERS-CoV-2 mouse model)

Cocrystal COVID-19 Direct Acting Antivirals

Main Protease inhibitor
Intranasal Lead
CDI-45205

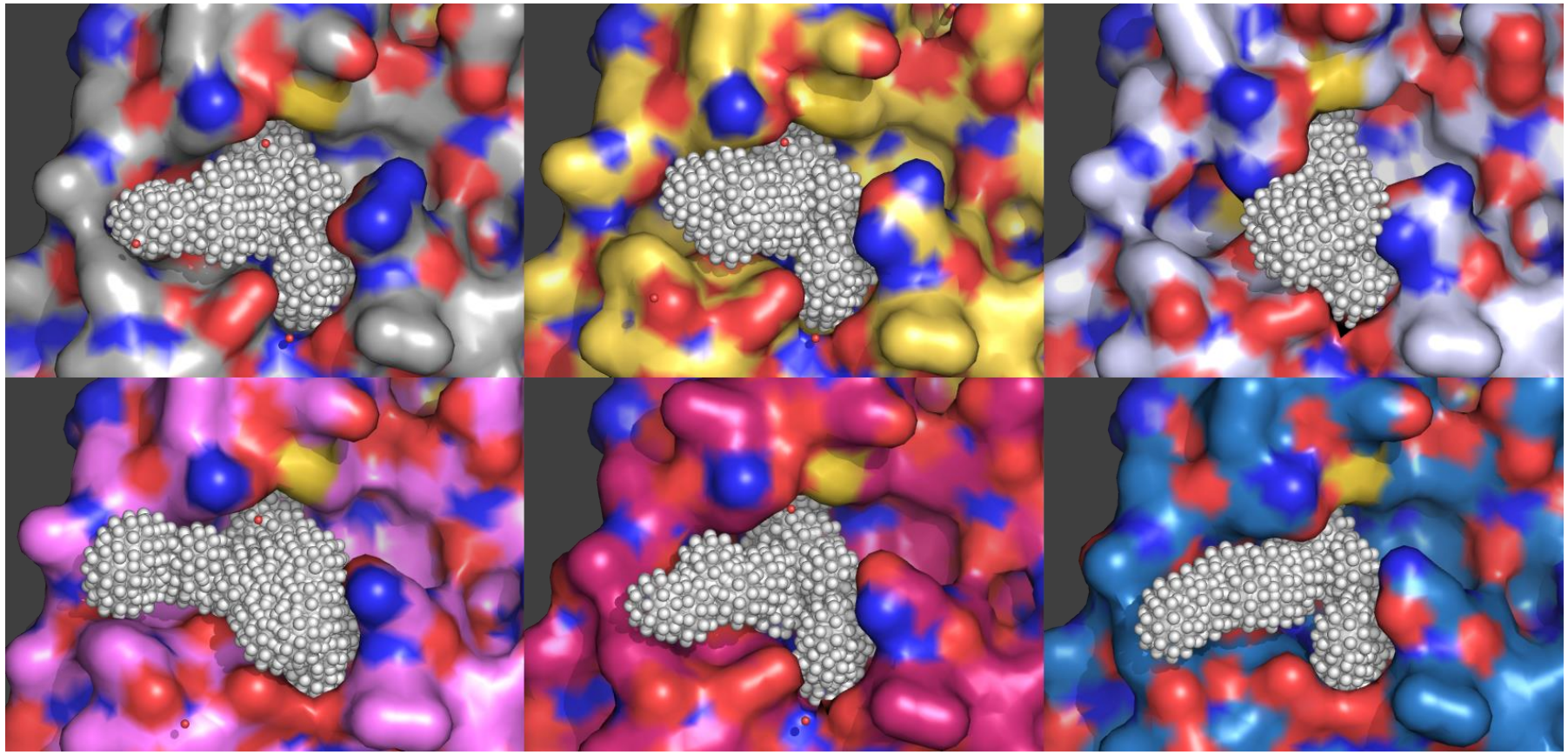
- Broad-spectrum SARS-CoV-2 M^{pro} inhibitor
- Intranasal/pulmonary administration (once or twice-daily)
- FDA pre-IND briefing package – awaiting response
- Phase 1 planned in 2022

Main protease inhibitor
Oral lead

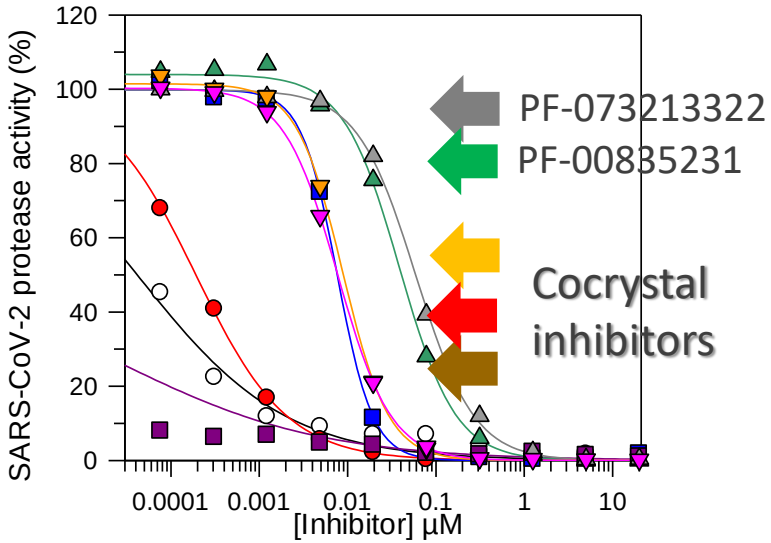
- Broad-spectrum SARS-CoV-2 M^{pro} inhibitor
- Oral administration (once or twice-daily)
- FDA pre-IND briefing package – Q1 2022
- Phase 1 planned in 2022

Multiple SARS-CoV-2 M^{pro} Oral Inhibitors Developed

- SARS-CoV-2 Main(3CL) protease structures complexed with inhibitors



Cocrystal M^{pro} Inhibitors Exhibit Excellent In Vitro Potency IC50 < 1nM



M^{pro} inhibitor	Route of administration	SARS-CoV-2 IC50
PF-0085231	IV inhibitor	37 nM
PF-07321332	Oral inhibitor	59 nM
	Cocrystal Inhibitors	
CDI-45205	Intranasal inhibitor	5 nM
CDI-50551	Oral inhibitor	0.2 nM
CDI-50559	Oral inhibitor	<0.1 nM
CDI-60523	Oral inhibitor	<0.1 nM

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Pharmacokinetic Parameters For Oral Inhibitors After a Single Dose Administration

Oral PK parameters	CC-055307 (40 mg/kg)	CC-055393 (40 mg/kg)	CC-055491 (40 mg/kg)	CC-055466* (10 mg/kg)	CC-055489* (10 mg/kg)
C_{max} (ng/mL)	1523	668	1173	1450	1778
$T_{1/2}$ (hr)	2.3	3.6	2.6	0.8	1.0
T_{max} (hr)	1.1	1.7	1.0	0.6	0.3
$AUC_{0\text{-last}}$ (ng·h/mL)	7325	2772	3809	2619	1322
Bioavailability	**48%**	**36%**	**29%**	**50%**	**41%**

*Pharmacokinetic study performed in mouse

COVID-19 Initial Clinical Development Trials For Intranasal and Oral Inhibitors

Phase 1 study design

- Randomized, placebo-controlled, double-blind, single-ascending dose/multiple-ascending dose design in healthy volunteers
- Safety, tolerability, PK, food effect

Phase 2 study design

- Randomized, double-blind, placebo-controlled
- Nonhospitalized patients with mild or moderate COVID-19
- Safety, tolerability, efficacy
- Primary endpoint: change from baseline to Day 15 in SARS-CoV-2 viral load
- Secondary endpoints: multiple clinical indices
- Key entry criterion: at least 1 underlying condition associated with ↑ risk of severe illness from COVID-19

Cocrystal COVID-19 Direct Acting Antivirals

Main Protease inhibitor Intranasal Lead

- Broad-spectrum SARS-CoV-2 M^{pro} inhibitor
- Intranasal/pulmonary administration (once or twice-daily)
- US FDA pre-IND briefing package – awaiting response
- Phase 1 planned in H2 2022

Main protease inhibitor Oral lead

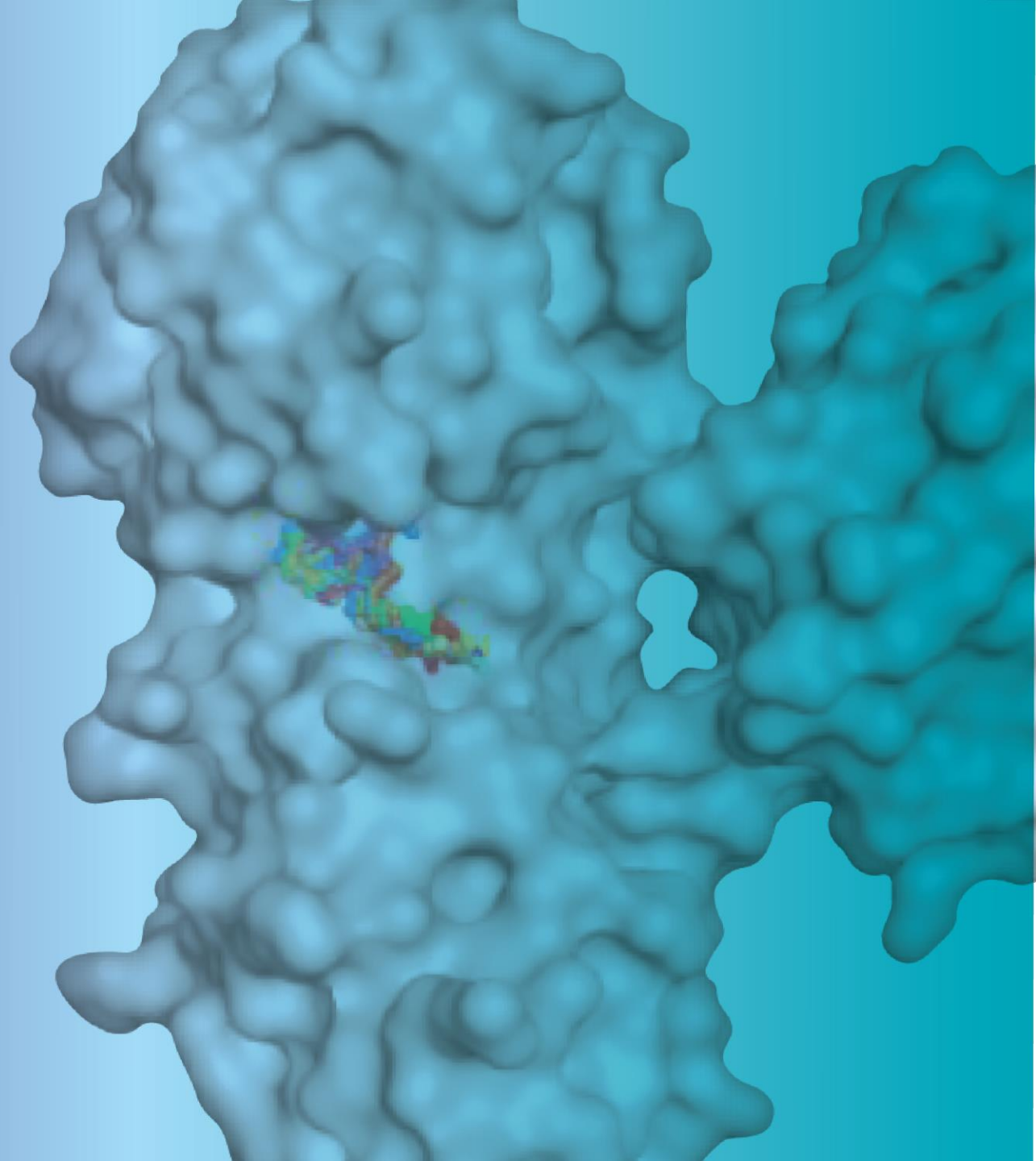
- Broad-spectrum SARS-CoV-2 M^{pro} inhibitor
- Oral administration (once or twice-daily)
- US FDA pre-IND briefing package – Q1 2022
- Phase 1 planned in H2 2022

Replication inhibitors

- Broad-spectrum SARS-CoV-2 replication inhibitors
- Oral combination therapy regimen
- Discovery stage

COCRYSTAL
PHARMA, INC.

Potent antivirals to combat some of the most serious diseases facing humanity



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