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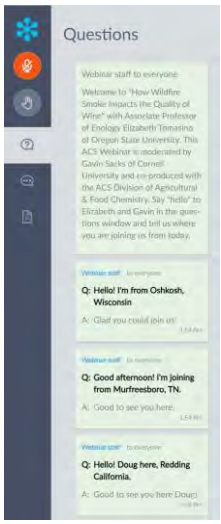

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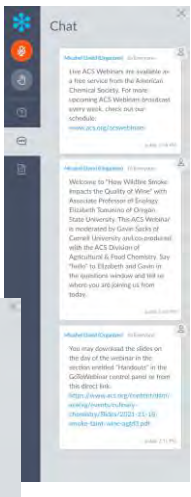

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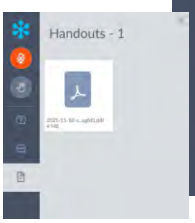

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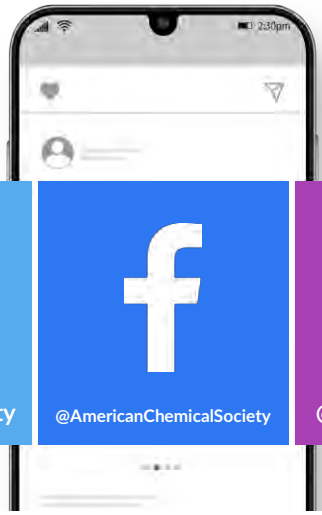

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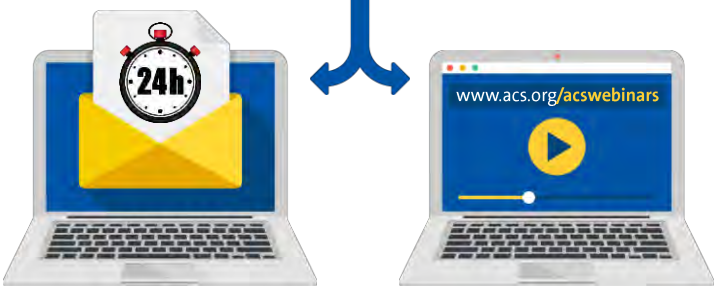

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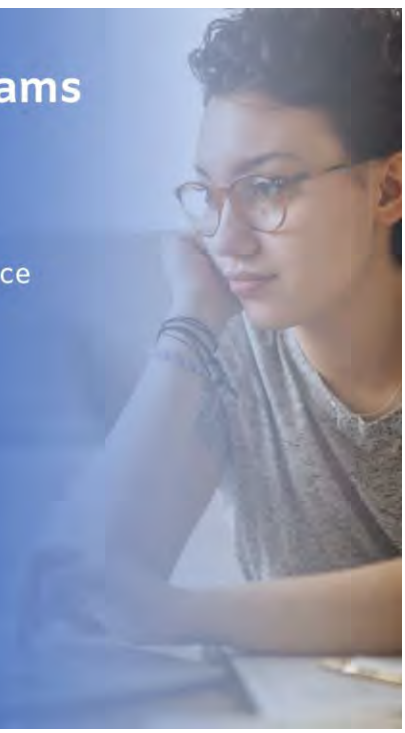

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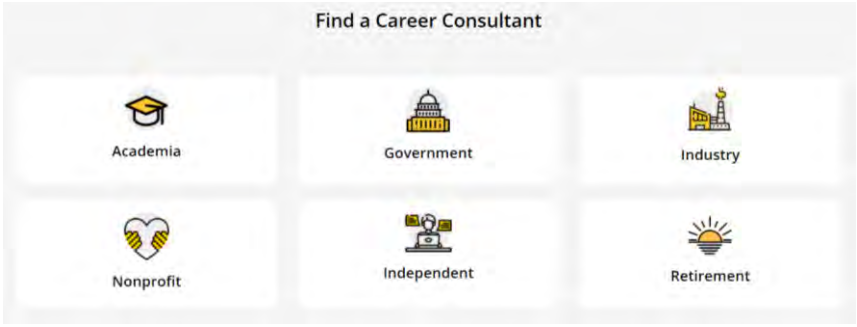

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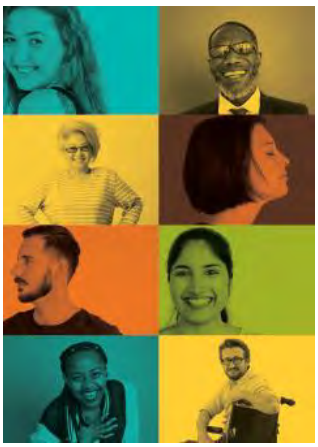

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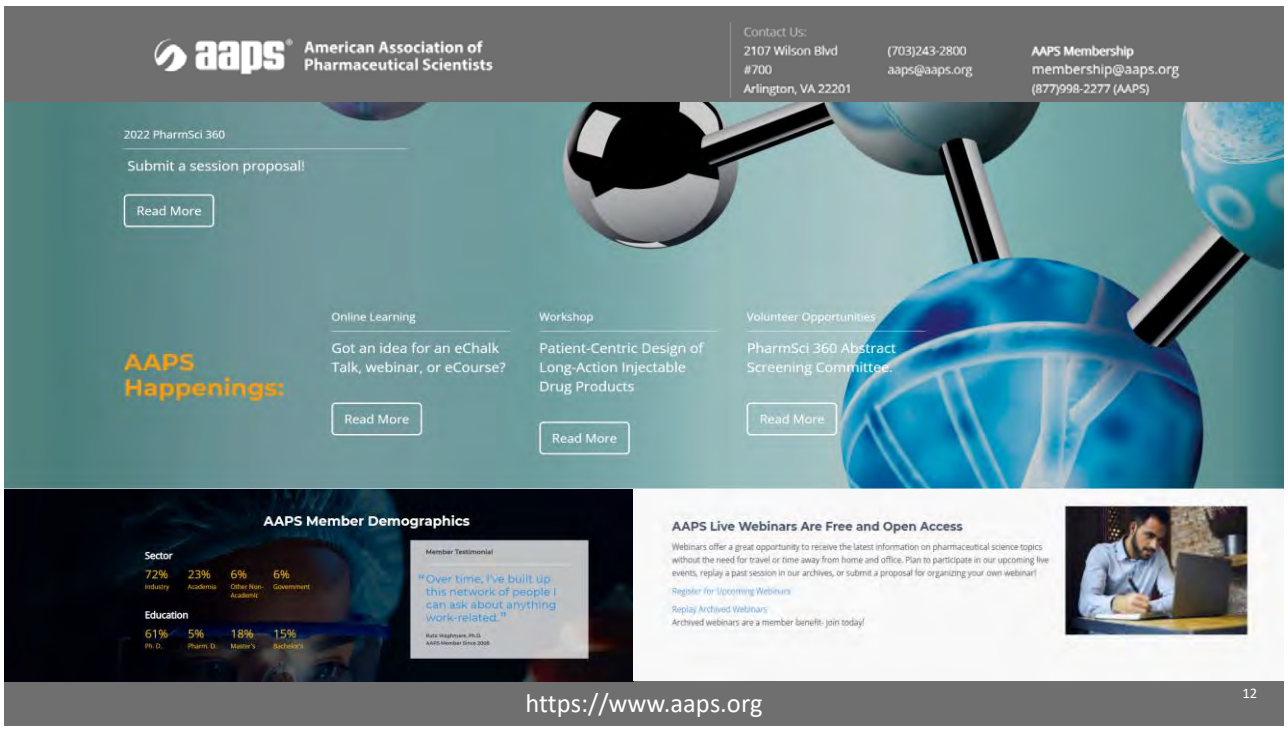
10



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12

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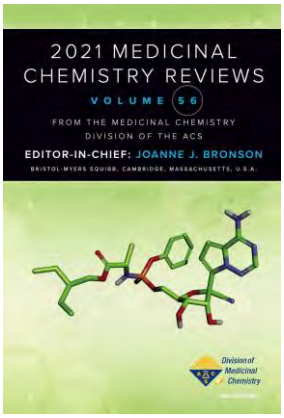

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Next Event in the Series is in April 2022!

The Discovery of Sotorasib (AMG 510): First-in-Class Investigational Covalent Inhibitor of KRAS G12C
Brian Lanman of Amgen outlines the strategies used to overcome these challenges of KRAS, one of the most frequently mutated oncogenes in human cancer.

An Integrated Approach: Oral Delivery of a Fatty Acid Acylated GLP-1 Peptide
Stephen Buckley of Novo Nordisk shares how this coformulation provides a unique, site-directed release and absorption in the stomach and effectively surmounts inherent challenges relating to solubility, molecular size, and proteolytic lability to achieve therapeutically relevant plasma exposure of semaglutide.

Online vs. In-Person: Networking as a Medicinal Chemist
With the suspension of in-person meetings due to the coronavirus pandemic, scientists need to shift to networking virtually in order to remain connected. Join our panel as they share how to make the most out of virtual networking opportunities.

How Computational Chemistry is Accelerating Drug Discovery
Scott Edmondson, the Sr. Vice President and Head of Chemistry at Nimbus Therapeutics, discusses how SBDD is leveraged to deliver clinical candidates that are differentiated from others in their class by their exquisite selectivity.

Targeted Delivery of RNA-targeted Therapeutics
Punit Seth of Ionis Pharmaceuticals discusses examples of different strategies for delivery of oligonucleotide drugs. Learn about the recent advances in receptor-mediated delivery which have greatly expanded the repertoire of cell types and tissues that are now accessible for antisense drug-discovery.

Designing around Structural Alerts in Drug Discovery
Nick Meanwell of BMS provides a synopsis of known alerts and their associated issues as well as the underlying mechanistic organic chemistry that will allow you to implement strategies to avoid potential problems in the design process.

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16

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Small Molecule COVID Antivirals:
New Game Changing Treatments for COVID-19

GEORGE PAINTER

Professor of Pharmacology and Chemical Biology, Emory University School of Medicine and Director, Emory Institute of Drug Development, CEO, Drug Innovation Ventures at Emory

JAMISON TUTTLE

Associate Research Fellow, Pfizer

CHRISTOPHER CUNNINGHAM

Associate Professor, Concordia University Wisconsin School of Pharmacy

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17

DRIVE

INFECTIOUS INNOVATION

THE DISCOVERY AND DEVELOPMENT OF MOLNUPIRAVIR FOR THE TREATMENT OF COVID-19

ACS Webinar
February 24, 2022

A COVID-19 Timeline

Status on 2-18-2022: 421,113,202 Cases and 5,912,871 Deaths

- **12/31/19**: WHO China country office notified of a number of cases of pneumonia of unknown etiology
- **1/7/2020:** The causative agent is identified as a novel coronavirus
- **1/22/20:** Human-to-human transmission confirmed as the virus rapidly spreads around the world. Disease resulting from the novel coronavirus (SARS-CoV-2) is named COVID-19
- **3/11/20: WHO declares COVID-19 a pandemic**
- **3/18/20:** Cases multiply exponentially and more countries begin to take measures to arrest spread of virus
- **1/2021:** Multiple vaccines are approved and the world begins a race to vaccinate. Several anti-SARS-CoV-2 antibodies and three direct acting antiviral agents become available. Death rates fall as countermeasures become available and physicians learn best practices for patient management
- **2021:** Concern increases as variants arise that are vaccine and monoclonal antibody resistant
- **3/16/22:** The world has experienced 5 waves (epidemiologically) of SARS-CoV-2 infection with the latest, and largest, wave fueled by emergence of the Omicron variant

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Audience Survey Question

ANSWER THE QUESTION ON THE INTERACTIVE SCREEN IN ONE MOMENT

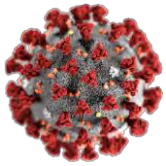
Some Human Coronaviruses cause mild respiratory disease and some are highly pathogenic. How many Human Coronaviruses exist?

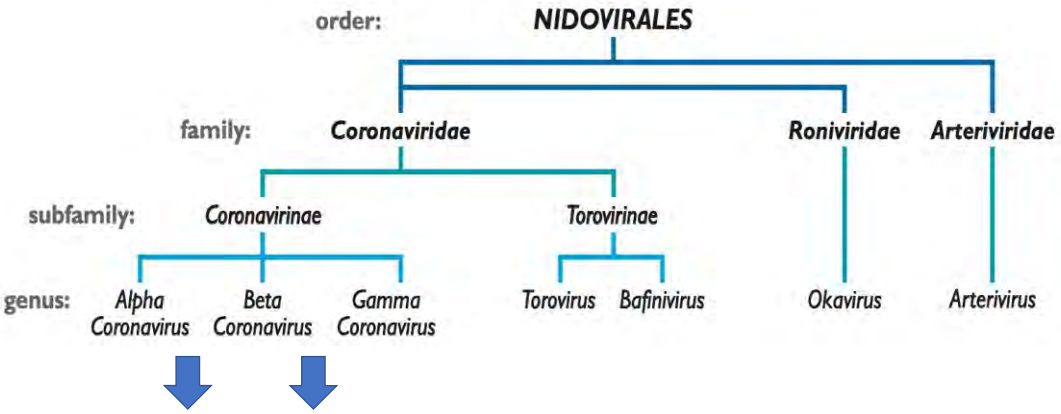
- One
- Three
- Four
- Five
- Seven

* If your answer differs greatly from the choices above **tell us in the chat!**

20

There are 7 Human Coronaviruses: Four that cause mild Respiratory Disease and Three Highly Pathogenic





Alpha: **HCoV-229E**, **HCoV-NL63** Beta: **HCoV-HKU1**, **HCoV-OC43**, **MERS-CoV**, **SARS-CoV**, **SARS-CoV-2**

A Focus Developing Therapeutics to Treat Viral Infections of Global Concern

- RNA viruses are a leading cause of epidemic/pandemic disease and at any given time are responsible for 80% of the viral disease burden worldwide. They are major contributors to the pool of emerging and reemerging infectious disease
- As of 2013, there were 180 recognized species of RNA viruses that infect humans and on average two new species are added every year
- Anthropogenic changes of ecosystems and population growth will likely continue to drive infection rates
- **There are no drugs available for the prophylaxis or treatment of the vast majority of RNA viral infections.** DRIVE is focused on the following families:

(+) Single-Stranded RNA Viruses

Flaviviradae: HCV, Dengue, West Nile, Zika, Tick Borne Encephalitis Complex
Togaviridae: EEEV, VEEV, WEEV, CHIKV
Coronaviridae: SARS-CoV, MERS-CoV and **SARS-CoV-2**
Picornaviridae: Rhinovirus and Enterovirus (68 and 71)

(-) Single-Stranded RNA Viruses

Paramyxoviridae: Respiratory syncytial virus (RSV)
Orthomyxoviridae: Influenza A and B
Filoviridae: Ebola
Arenaviridae: Lassa virus, Junin, Tacaribe

DRIVE

RNA-directed RNA-polymerases (RdRps): Ideal Targets for Antiviral Therapy

- Viral RdRps are essential enzymes with the dual roles of transcribing mRNA from templates and acting as a replicase to copy genomic RNA; there are no known host cell equivalents
- Viral RdRps share mechanistic similarities with all nucleic acid polymerases
- RdRps are the most conserved of the RNA virus encoded proteins
  - Crystal structures to date have shown that all RdRps adopt a canonical “right hand shape” with three conserved sub-domains referred to as fingers, thumb and palm
  - All RdRps contain a series of eight conserved primary sequence motifs, three of which are located in the palm domain and are critical to catalysis
- The overall structural similarity and the conservation of secondary and tertiary structural elements in the palm and thumb domains of RdRps has led to speculation that these enzymes may have evolved from a common ancestor

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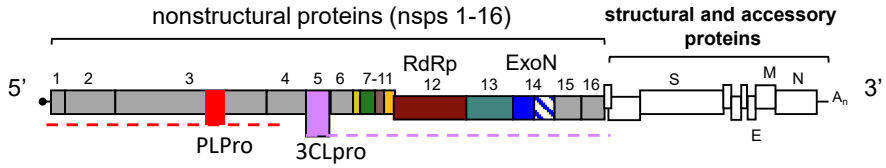
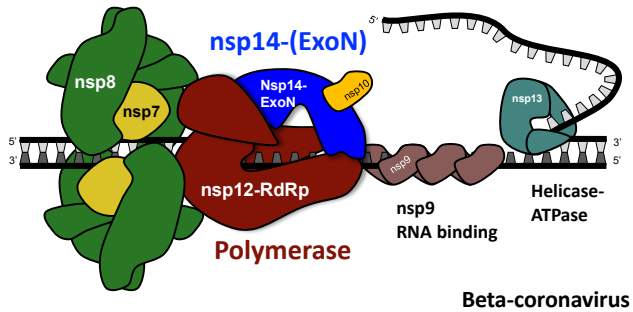
RNA Viruses Encode a Multiprotein Replicase Complex





Beta-coronavirus replicase model

Nucleosides Play a Critical Role in Antiviral Therapy

- Of the 55 approved antiviral therapeutics for the prophylaxis and/or treatment of viral infections, 28 are nucleoside/nucleotide analogs or include them in a combination dosage
- Nucleoside analogs act as competitive alternative substrates and block nucleic acid synthesis by the virally encoded polymerases
- In general, there is a high barrier to the development of resistance to nucleoside analog polymerase inhibitors. Consequently, they have become the backbone of modern antiviral therapy
- The toxicities of nucleoside analogs are well understood and generally derive from off-target activity against host polymerases: human DNA polymerase γ and mitochondrial DNA directed RNA polymerase are prime examples
- Nucleoside analogs are amenable to multiple prodrug strategies that can facilitate efficient distribution to the appropriate anatomical site of action

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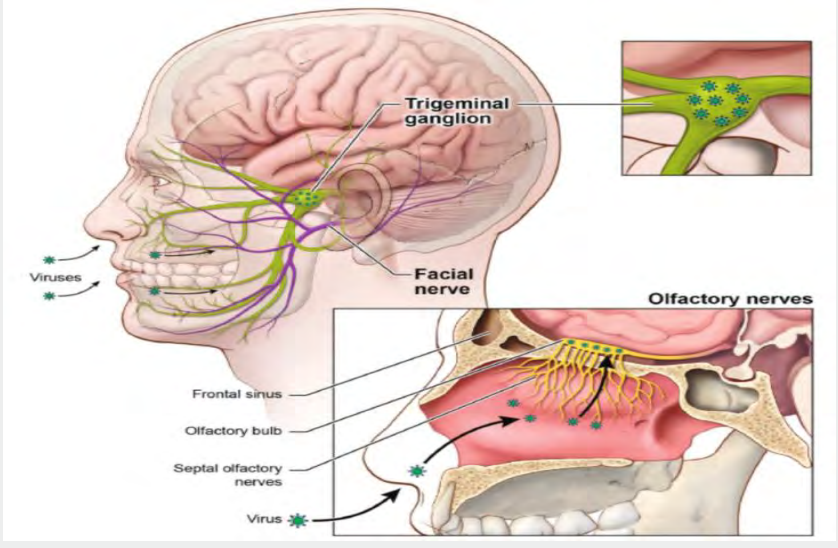
Pathway of Neuroinvasion by Aerosolized Venezuelan Equine Encephalitis Virus



Swanson II, Phillip A. & McGavern, Dorian. (2015). Portals of Viral Entry into the Central Nervous System. 23-47. 10.1201/b19299-3.

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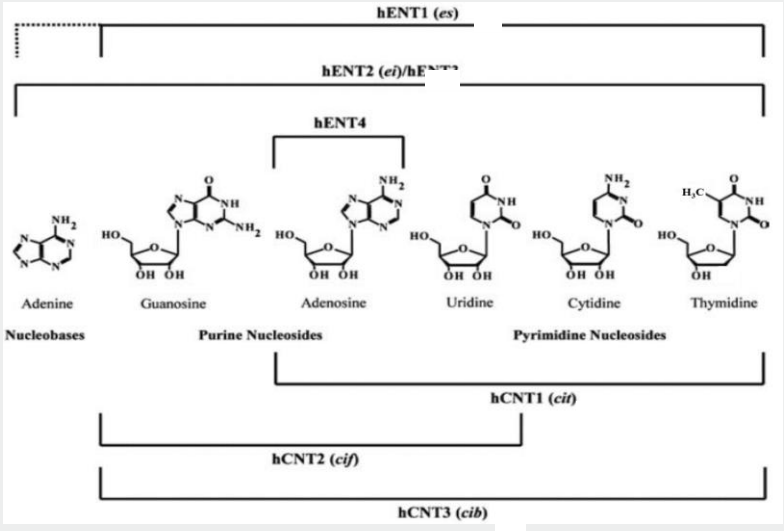
Transporters of Nucleosides and Nucleoside Analogs in the Blood Brain Barrier



Taken from: Parkinson, F. E.; Damaraju, V. L.; Graham, K.; Yao, S. Y.; Baldwin, S. A.; Cass, C. E.; Young, J. D. *Current Topics in Medicinal Chemistry* **2011**, *11* (8), 948–972.

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EIDD-2801/1931 is a Broadly Active Ribonucleoside Analog

Virus	EC_{50} (μM)	CC_{50} (μM)	Selectivity Index	Assay
CHKV	1.0	338	≥ 300	Plaque reduction assay in Vero cells
VEEV	1.4	> 500	≥ 300	Plaque reduction assay in Vero cells
WEEV	0.73	247	≥ 300	Neutral Red CPE assay in Vero 76 cells
EEEV	0.93	123	132	Visual CPE assay in Vero 76 cells
Human-CoV	0.20	224	≥ 1100	Neutral Red CPE assay in HEL cells
SARS-CoV	< 0.4	139	≥ 300	Neutral Red CPE assay in Vero 76 cells
SARS-CoV-2	0.08	> 125	≥ 1500	$TCID_{50}$ viral titer reduction assay in Calu-3 cells
MERS-CoV	< 0.8	20	> 25	$TCID_{50}$ viral titer reduction assay in Vero E6 cells
Ebola	4.7	> 100	> 21	Plaque reduction assay in Vero cells
RSV	2.5	> 300	> 120	Replicon assay in Huh-7 cells
Enterovirus-D68	2.3	52	23	Neutral Red CPE assay in RD cells
Rhinovirus	0.48	44	92	Neutral Red CPE assay in HeLa cells
Influenza A (H1N1)	1.1	> 300	> 270	HAU titer assay in MDCK cells
Influenza B (Yamagata)	0.015	> 100	≥ 6000	HAU titer assay in MDCK cells

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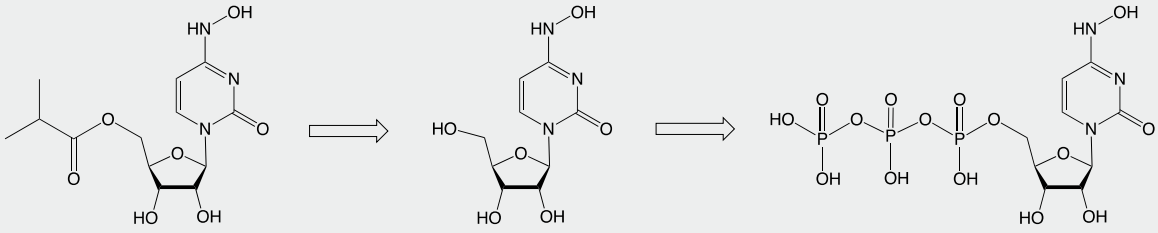
Structures of EIDD-2801, EIDD-1931 and the Active Antiviral Agent EIDD-1931 5'-Triphosphate

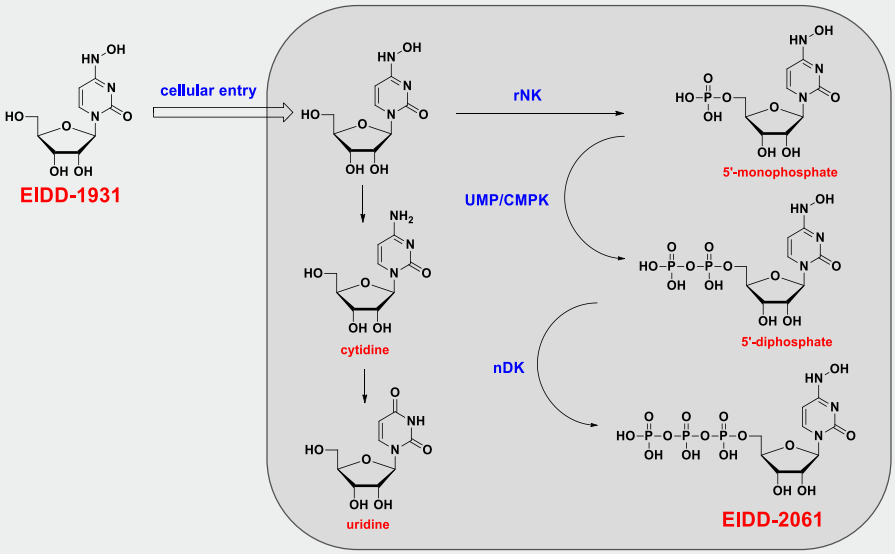


EIDD-2801 | EIDD-1931 | EIDD-1931-5'-Triphosphate

N4-hydroxycytidine

DRIVE

EIDD-1931 must be Phosphorylated by Host Cell Kinases to its Active 5'-Triphosphate



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Mechanism of Action of Molnupiravir: Viral Error Catastrophe

The triphosphate metabolite of molnupiravir can tautomerize and mimic both uridine and cytidine. Through tautomerization of the incorporated triphosphate, pairing can occur with adenosine or guanosine.

Adenosine with uridine mimic **Guanosine with cytidine mimic**

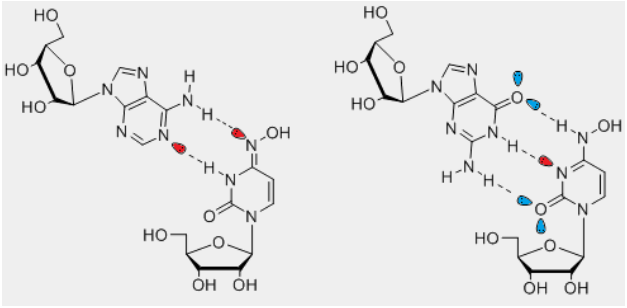
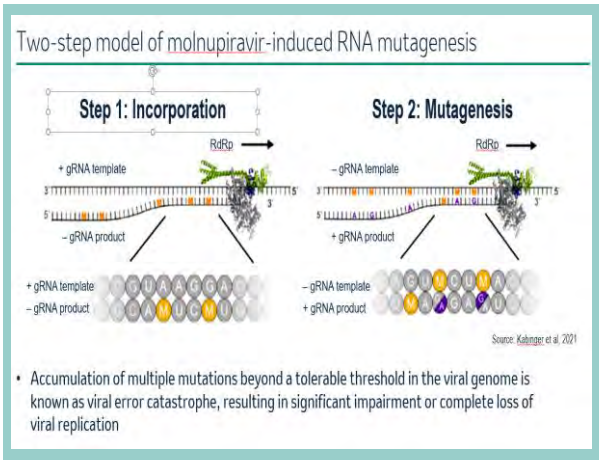
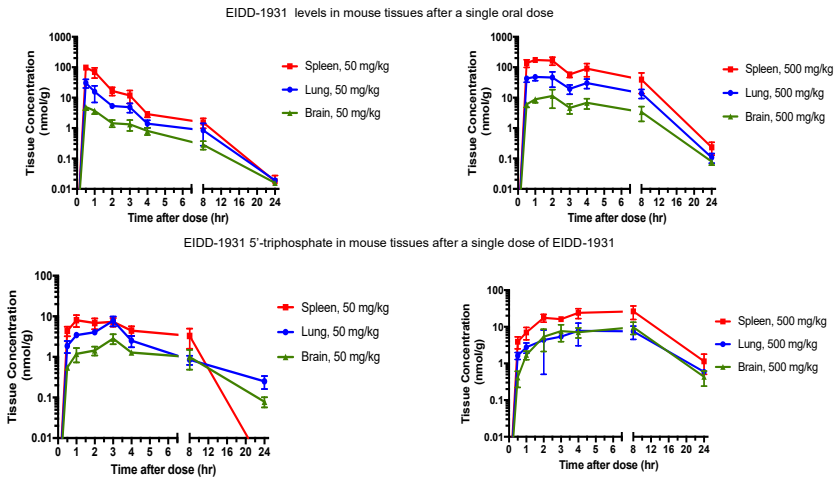


Figure adapted from: Moriyama et al. *Nucleic Acids Research* **1998**, 26 (9): 2015-2111



Kabinger et al. *Nature* **2021** https://doi.org/10.1038/s41594-021-00651-0

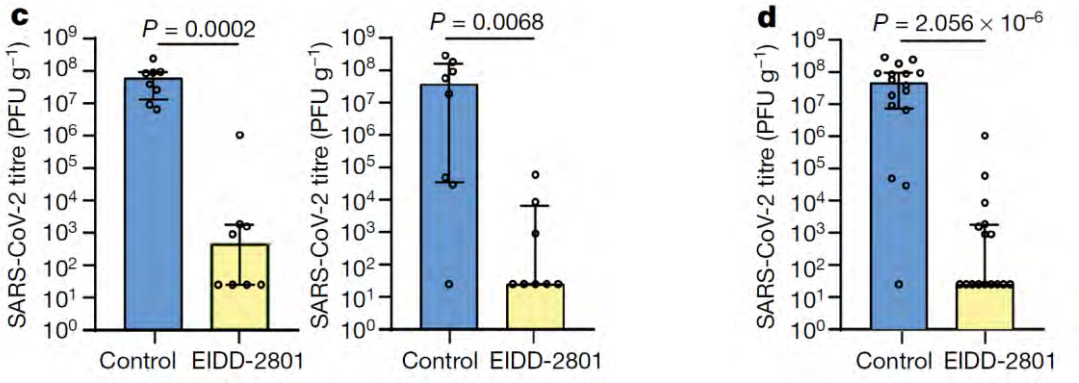
EIDD-2801 is Efficiently Distributed to and Anabolized in Key Tissues in the Pathogenesis of RNA Viral Diseases



Painter et al., *Antiviral Res* **2019**, 171: 104597 doi: 10.1016/j.antiviral.2019.104597

Prophylactic treatment with EIDD-2801 potently inhibit SARS-CoV-2 infection in vivo

- SARS-CoV-2 titers in the human lung tissue of LoM administered EIDD-2801 (*n* = 8 per experiment) or control vehicle (*n* = 8 per experiment) 12 h before exposure to virus in two independent experiments shown separately (**c**) and combined (**d**)



Wahl, A. et al. SARS-CoV-2 infection is effectively treated and prevented by EIDD-2801. Nature, Vol 591, March 2021

There Is a Very High Barrier to the Development of Resistance to Molnupiravir

Toots et al. (2019) employed both dose-escalation and fixed-dose passaging strategies to induce influenza A virus (IAV) resistance to NHC.

(i) Gradual dose-escalation consistently resulted in virus extinction at drug concentrations ≥4 μM, which is approximately 2-times the EIDD-1931 (NHC) EC_{50} concentration against representative IAVs in MDCK cells.

(ii) Serially passaged virus in the presence of fixed drug concentrations: 4 and 10 μM NHC doses were rapidly sterilizing; 1 and 2 μM were tolerated for >10 passages, however, virus replication efficiency was impaired even at sublethal NHC concentrations.

Toots et al. *Science Translational Medicine*. **2019,** 11(515) doi: 10.1126/scitranslmed.aax5866

Urakova et al. (2018) showed that only a low-level resistance of VEEV to EIDD-1931 (NHC) can be developed and became clearly detectable only after 15 passages in the presence of NHC; that resistance [up to 3.2 μM NHC] likely requires acquisition and cooperative function of more than one mutation.

Urakova et al. *Journal of Virology.* **2018,** 92(3):e01965-17, doi: 10.1128/JVI.01965-17

Agostini et al. (2019) showed that passage of coronaviruses in the presence of EIDD-1931 yields low-level resistance associated with multiple transition mutations and that EIDD-1931 mutagenesis may hinder emergence of robust resistance to EIDD-1931.

Agostini et al. *Journal of Virology*, **2019,** doi: 10.1128/JVI.01348-19

Non-clinical Toxicology

- Molnupiravir and NHC were positive in the in vitro bacterial reverse mutation assay (Ames assay) with and without metabolic activation.
- In 2 distinct in vivo rodent mutagenicity models (Pig-a mutagenicity assay and Big Blue® [cII Locus] transgenic rodent assay), molnupiravir did not induce increased mutation rates relative to untreated historical control animals, and therefore is not mutagenic in vivo.
- Molnupiravir was negative for induction of chromosomal damage in in vitro micronucleus (with and without metabolic activation) and in vivo rat micronucleus assays.
- Based on the totality of the genotoxicity data, molnupiravir is of low risk for genotoxicity or mutagenicity in clinical use.

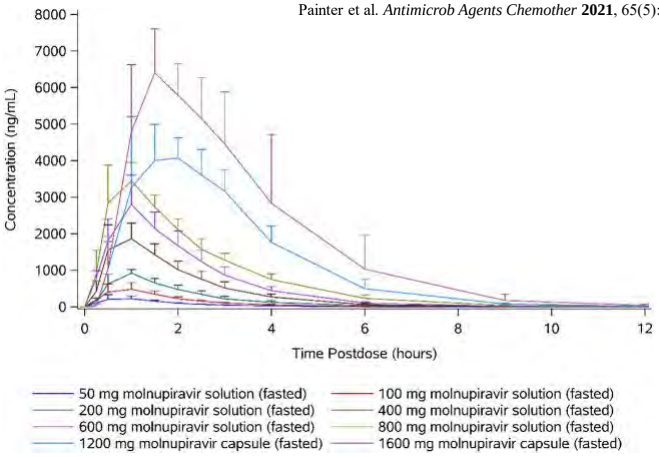
www.medicines.org.uk/emc/product/13044/smpc

DRIVE

A Randomized, Double-Blind, Placebo-controlled, First-in-Human Study Designed to Evaluate Safety, Tolerability, and Pharmacokinetics of EIDD-2801 Following Administration to Healthy Volunteers

- Concentrations of molnupiravir were generally below the limit of quantification (BLQ) at doses up to 800 mg. At doses of 1200 and 1600 mg, concentrations of molnupiravir were quantifiable at 1 or more time points between 0.25 and 1.5 hours postdose in all subjects.
- EIDD-1931 appeared rapidly in plasma.
- Median time of maximum observed concentration (T_{max}) of 1.00 to 1.75 hours.
- Geometric half-life of approximately 1 to 4.6 hours.
- Slower elimination phase apparent following higher doses.
- Mean maximum observed concentration (C_{max}) and area under the concentration versus time curve increased in a dose-proportional manner.

Painter et al. *Antimicrob Agents Chemother* **2021**, 65(5):e02428-20



Painter, W et al., Antimicrob Agts Chemother, February 2021, doi.org/10.1128/AAC.02428.20

PHASE 2 EIDD-2801-2003: Infectivity Key Virology Endpoint

- Viral cultures were done at Baseline, Day 3, and Day 5. Clearance of infectious virus was faster for participants treated with molnupiravir 800 mg compared with participants treated with placebo, molnupiravir 200 mg, or molnupiravir 400 mg.

- On Day 3, the proportions of participants with positive infectivity results had decreased to 1/53 (1.9%) in the molnupiravir 800 mg group compared with 9/54 (16.7%), 4/22 (18.2%), and 5/43 (11.6%) in the placebo, molnupiravir 200 mg, and molnupiravir 400 mg groups, respectively.

- On Day 5, none of the participants in the molnupiravir 400 mg or 800 mg groups had positive results compared with 11.1% of participants in the placebo group and 4.5% of participants in the molnupiravir 200 mg group

Fischer, W et al., Molnupiravir, an Oral Antiviral Treatment for COVID-19, doi.org/10.1101/2021.06.17.21258639

Emergency Use Authorization Has Been Granted in Multiple Countries Around the World

Therapeutic indications

- Lagevrio is indicated for treatment of mild to moderate COVID-19 in adults with a positive SARS-COV-2 diagnostic test and who have at least one risk factor for developing severe illness

Posology and method of administration

- The recommended dose of Lagevrio is 800 mg (four 200 mg capsules) taken orally every 12 hours for 5 days, with or without food.
- The safety and efficacy of molnupiravir when administered for periods longer than 5 days have not been established.
- Lagevrio should be administered as soon as possible after a diagnosis of COVID-19 has been made and within 5 days of symptom onset

Additional information:

- Elderly: No dose adjustment of Lagevrio is required based on age
- Pregnancy: Not recommended during pregnancy. Use contraception during treatment and for 4 days after last dose
- Renal impairment, hepatic impairment: No dose adjustment is required for patients with renal or hepatic impairment
- Paediatric population: The safety and efficacy of Lagevrio in patients below 18 years of age have not been established. No data are available
- Potential to interact with concomitant medications is considered unlikely

www.medicines.org.uk/emc/product/13044/smpc

Acknowledgements

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Zachary Sticher

Colorado State University

Richard Bowen

University of North Carolina

Ralph Baric
Tim Sheahan

Vanderbilt University

Mark Denison

Funding

DTRA – Seed Contract: HDTRA1-13-C-0072 HDTRA1-12-CHEM-BIO-BAA (CB-SEED-09)
Broadly Active, Antiviral Ribonucleoside Analogs Targeting the RNA Dependent RNA Polymerases (RdRps) Encoded by the Arboviral Encephalitides, WEEV, VEEV and EEEV

DTRA - Contract: HDTRA1-15-C-0075 Sole Source
Preclinical Development of a Broadly Active Antiviral for the Prophylaxis and Treatment of VEEV and other Alphavirus Infections

NIAID – Contract: HHSN272201500008C BAA NIH-AI-2014007
Targeting Therapeutics Development to Relieve Bottlenecks: Optimizing Lead Therapeutic Compounds against Infectious Pathogens

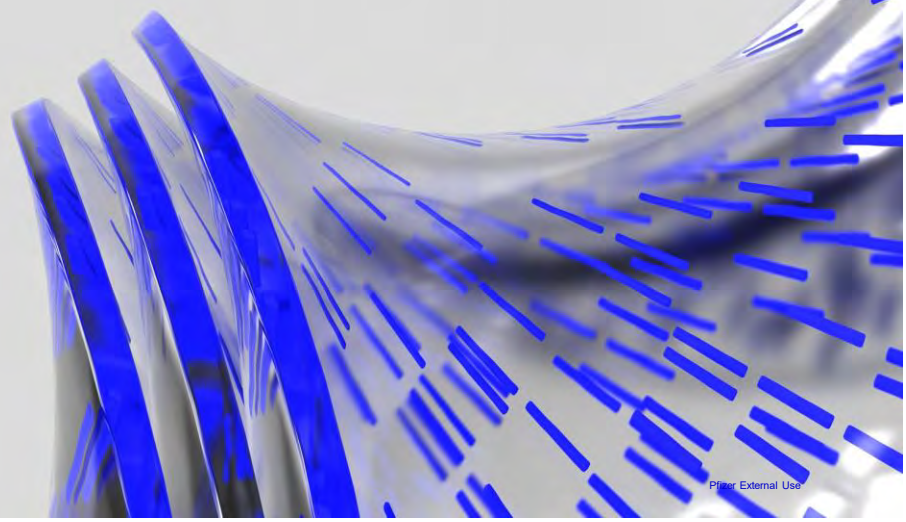
GP receives licensing fees and royalties based on Emory's sublicense of his technology to Ridgeback Biotherapeutics and a family member serves as the Chief Medical Officer of Ridgeback. This technology is the subject of the research described in this presentation. The terms of this arrangement have been reviewed and approved by Emory University in accordance with its conflict of interest policies.

DRIVE

Oral Inhibitors of the SARS-CoV-2 Main Protease for the Treatment of COVID-19

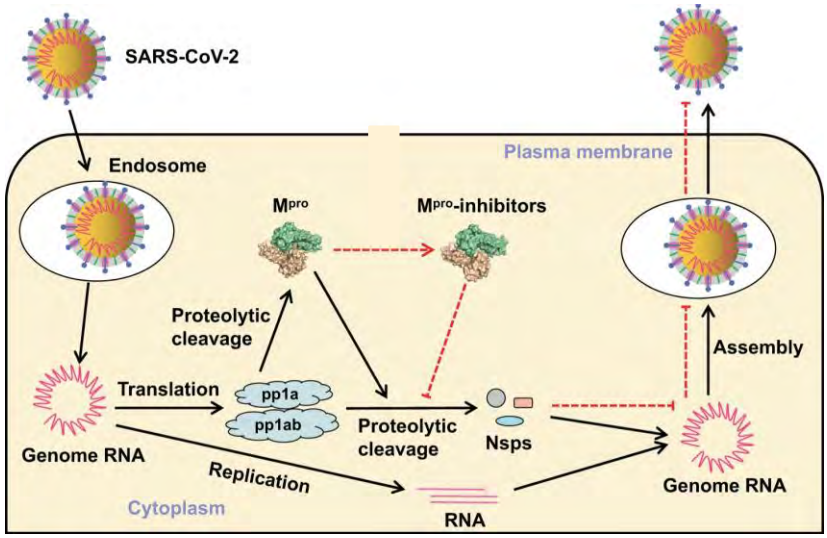
Jamison Tuttle
Medicine Design
Pfizer WRD&M
Cambridge, MA
USA

ACS Webinar 2022



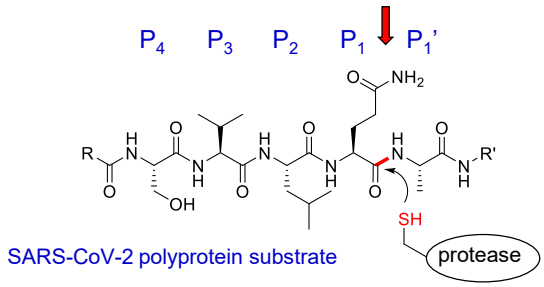
- PAXLOVID™ has not been approved, but has been authorized for emergency use by FDA under an EUA, for the treatment of mild-to moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS CoV-2 viral testing, and who are at high-risk for progression to severe COVID-19, including hospitalization or death.
- The emergency use of PAXLOVID™ is only authorized for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic under Section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the declaration is terminated or authorization revoked sooner.

Main protease (M^{pro}) has an Important Role in Viral Replication

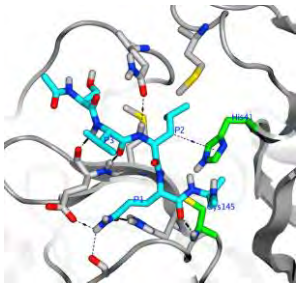


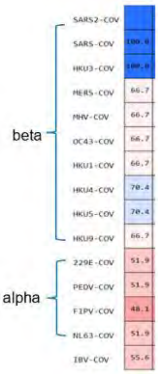
Mengist, H.M., Fan, X. & Jin, T. Designing of improved drugs for COVID-19: Crystal structure of SARS-CoV-2 main protease M^{pro}. *Sig Transduct Target Ther* **5,** 67 (2020). https://doi.org/10.1038/s41392-020-0178-y

SARS-CoV-2 Polyprotein Substrate and M^{pro} Function



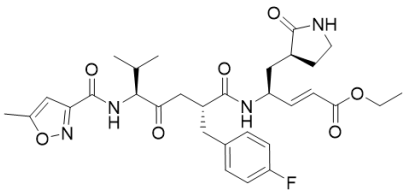
SARS-CoV-2 polyprotein substrate





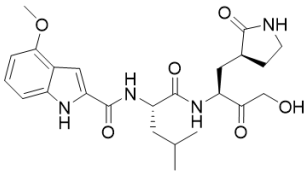
- M^{pro} exclusively cleaves polypeptide sequences at 11 **Gln** P_1 sites
- No human equivalent host cell proteases cleave at Gln. M^{pro} has selectivity attractions.
- Proximal P_2 from polyprotein cleavage site is a leucine >90% of the time

PF-7304814 is an IV SARS-CoV-2 Inhibitor in Clinical Trials



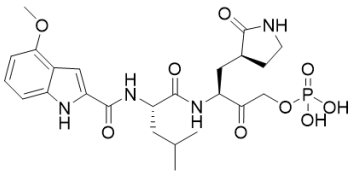
HRV: Rupintrivir

J. Med. Chem. 1999, **42**, 1213



SARS: PF-835231

J. Med. Chem. 2020, **63**, 12725

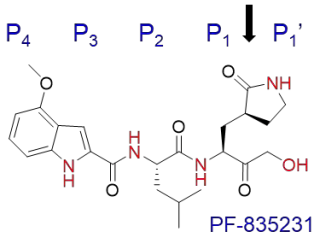


COVID-19: PF-7304814

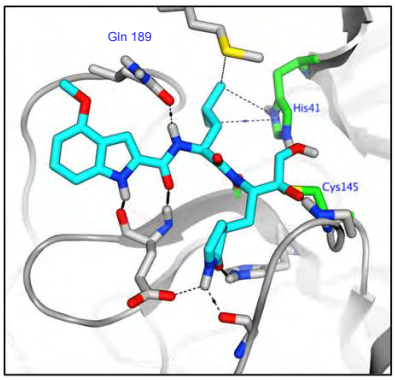
bioRxiv 2020.09.12.293498

- Human rhinovirus learnings from Rupintrivir identified attractive Gln mimetic - P_1 lactam
- IV Phosphate prodrug PF-7304814 entered clinical trials in September 2020

IV to Oral: Design Challenges

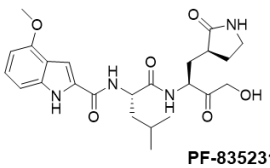


- Peptidomimetics are a tough challenge for oral drug space
- AV requires EC_{90} C_{min} and an associated therapeutic index
- 5 H-bond donors means <0.5% oral bioavailability for '231
- Need permeability, metabolic stability and anti-viral activity



- Crystal structure of PF-835231 bound to SARS 2 M^{pro}
- Extensive H bond network

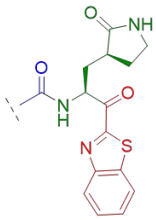
Tactics Employed to Increase Oral Bioavailability of M^{pro} Inhibitors



PF-835231

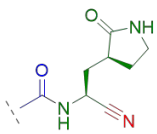
HBD = 5
RRCK < 0.2
Rat %F <1

- Too polar, improve permeability: remove unnecessary H-bond donors
- Preserve P1 lactam for speed
- Implement groups to improve RRCK/take risks on low RRCK compounds
- Choice of cysteine trap affects physicochemical properties
- Take advantage of modularity to progress multiple warheads



Benzothiazole ketone

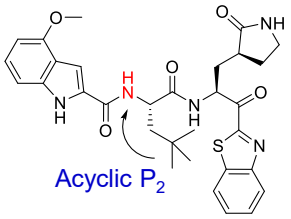
- Lipophilic, high MW
- Target small polar P2/P3



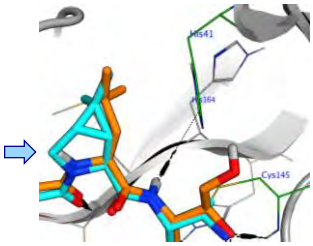
Nitrile

- Polar, low MW
- Options to incorporate lipophilic and higher MW P2/P3

Challenging Need For Certain H-Bonds in Benzothiazoles

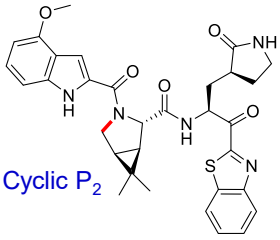


H Bonds	4
Enz IC_{50}	39nM
Cell EC_{50}	383nM
HLM	350 μl/min/mg
RRCK	4.3 P_{app} AB (10^{-6} cm/sec)
LogD	4.0
Rat F_{oral}	<1%



Design hypothesis: Can P_2 substituent be cyclized, eliminating an H-Bond?

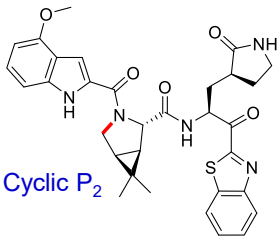
Model and screen cyclic P_2 contenders that are available, and scalable



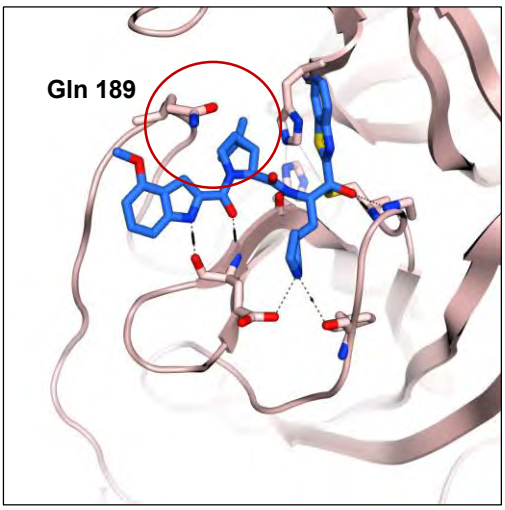
H Bonds	3
Enz IC_{50}	511 nM
Cell EC_{50}	4.1μM
HLM	388 μl/min/mg
RRCK	7.3 P_{app} AB (10^{-6} cm/sec)
LogD	4.2
Rat F_{oral}	NT

Incremental improvement to permeability but why the potency loss?

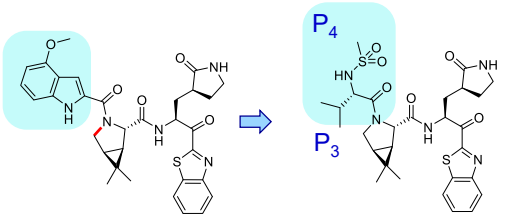
Xtal Structure Reveals Cyclic P2 Loses Gln 189 Interaction



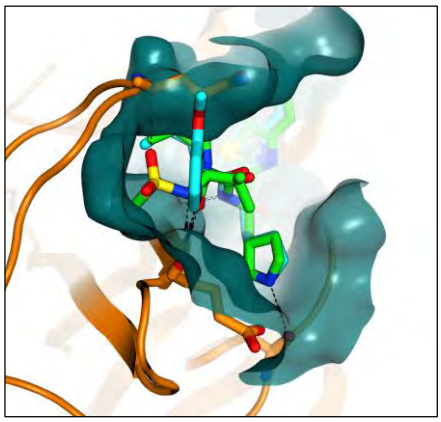
H Bonds	3
Enz IC_{50}	511nM
Cell EC_{50}	4.1μM
HLM	388 μl/min/mg
RRCK	7.3 P_{app} AB (10^{-6} cm/sec)
LogD	4.2
Rat F_{oral}	NT



Improving a Backbone Interaction and Engaging the S4 Pocket



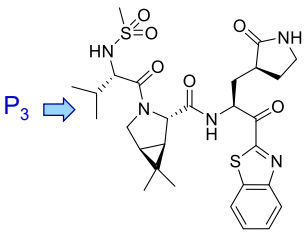
H Bonds	3	H Bonds	3
Enz IC_{50}	511nM	Enz IC_{50}	36nM
Cell EC_{50}	4.1μM	Cell EC_{50}	1.1μM
HLM	388 μl/min/mg	HLM	70 μl/min/mg
RRCK	7.3 P_{app} AB	RRCK	1.7 P_{app} AB
LogD	4.2	LogD	2.4
Rat F_{oral}	NT	Rat F_{oral}	7%

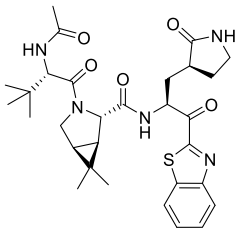


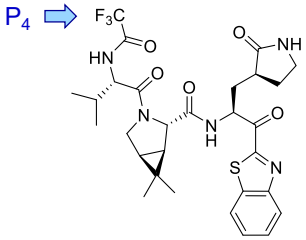
Xtal structure overlay with indole shows sulfonamide:

1) Fills the S4 protease pocket and
2) Improves the H bond interaction with the protease backbone

P_4 Cap Effect on Permeability

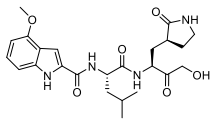






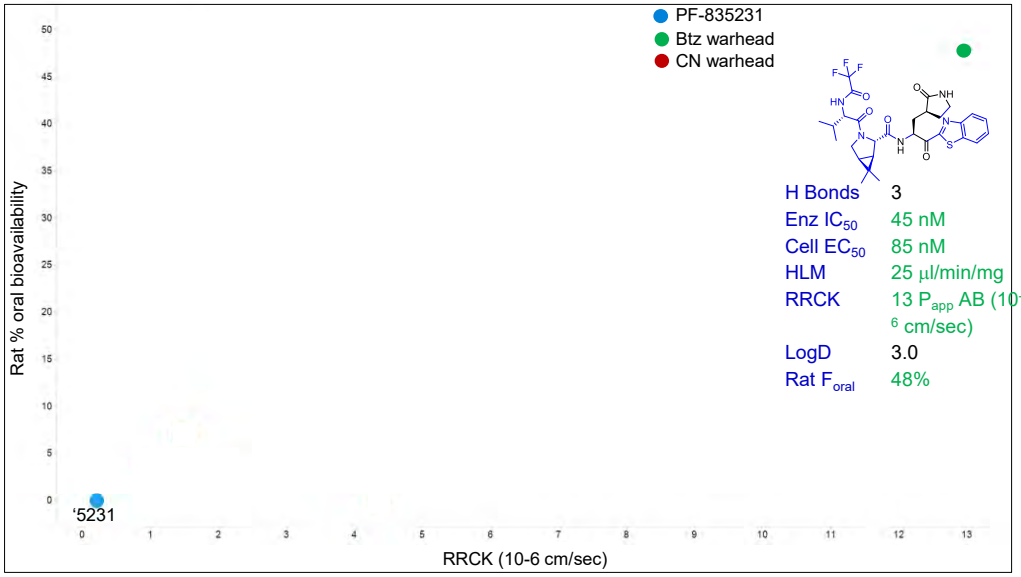
H Bonds	3	H Bonds	3	H Bonds	3
Enz IC_{50}	36nM	Enz IC_{50}	37nM	Enz IC_{50}	45nM
Cell EC_{50}	1.1μM	Cell EC_{50}	702nM	Cell EC_{50}	85nM
HLM	70 μl/min/mg	HLM	27 μl/min/mg	HLM	25 μl/min/mg
RRCK	1.7 P_{app} AB (10^{-6} cm/sec)	RRCK	0.7 P_{app} AB (10^{-6} cm/sec)	RRCK	13 P_{app} AB (10^{-6} cm/sec)
LogD	2.4	LogD	2.4	LogD	3.0
Rat F_{oral}	7%	Rat F_{oral}	NT	Rat F_{oral}	48%

Applying the Lessons Learned from the Btz to the Nitrile

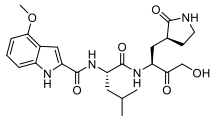


PF-835231

H Bonds	5
Enz IC_{50}	10 nM
Cell EC_{50}	231nM
HLM	7 µl/min/mg
RRCK	0.2 P_{app} AB (10^{-6} cm/sec)
LogD	1.7
Rat F_{oral}	<0.5%



Applying the Lessons Learned from the Btz to the Nitrile



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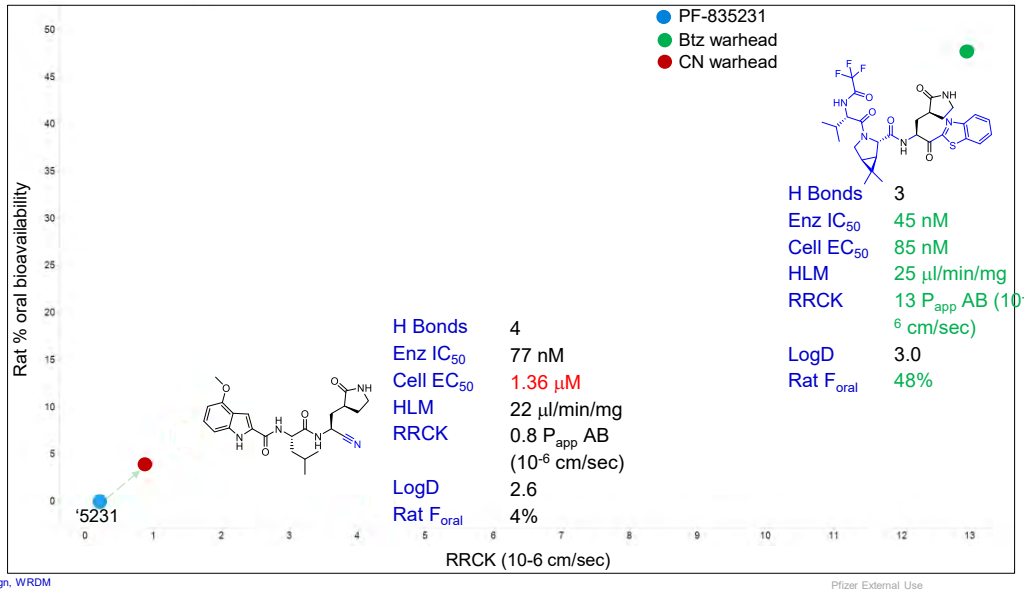
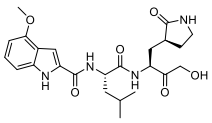
LogD	1.7
Rat F_{oral}	<0.5%



Pfizer Medicine Design, WRDM Pfizer External Use

Applying the Lessons Learned from the Btz to the Nitrile



PF-835231

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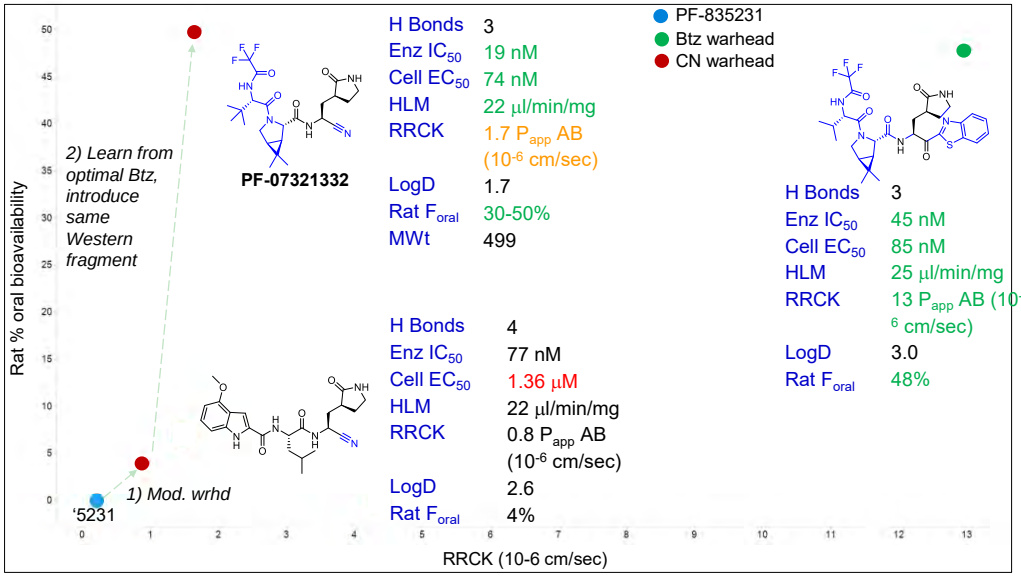
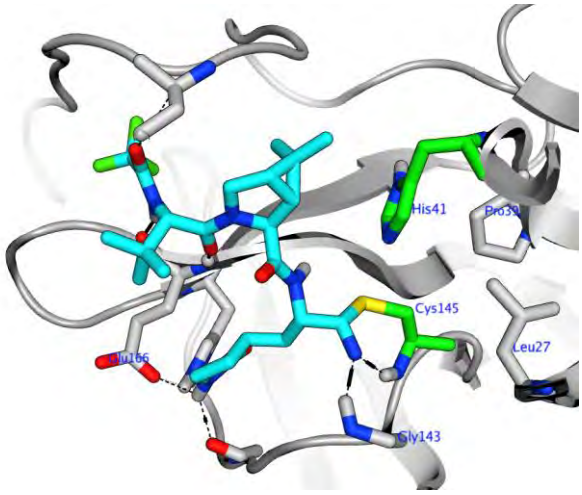
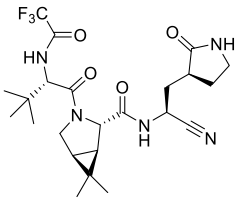
Cell EC_{50}	231nM
HLM	7 µl/min/mg
RRCK	0.2 P_{app} AB (10^{-6} cm/sec)
LogD	1.7
Rat F_{oral}	<0.5%



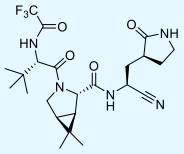
PF-7321332: Oral SARS-CoV-2 M^{pro} Inhibitor Candidate





H Bonds	3
Enz IC_{50}	19nM
Cell EC_{50}	74nM
HLM	22 µl/min/mg
RRCK	1.7 P_{app} AB (10^{-6} cm/sec)
LogD	1.7
Rat F_{oral}	30-50%
MWt	499

PF-7321332 Profile



PF-7321332

M^{pro} IC_{50} 19nM, Ki 3nM

SARS-CoV-2 Cell EC_{50}

Human Airway Epithelial Cell EC_{50} = 62 nM
Hela ACE2 Cell EC_{50} = 77 nM
A549 Cell EC_{50} = 56 nM
Vero Cell EC_{50} (+2μM EI) = 75 nM

Coronavirus Family Cell EC_{50}

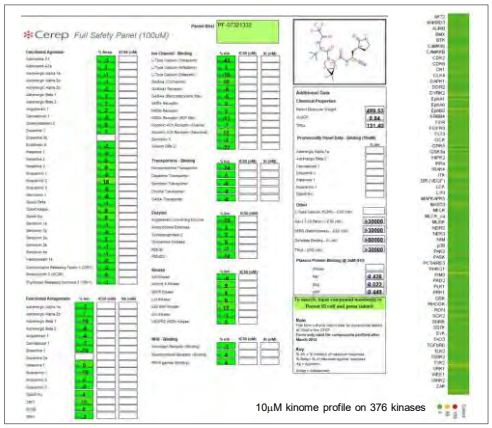
229E MRC5 Cell EC_{50} = 190 nM
SARS 1 Vero 61 Cell EC_{50} (+2μM EI) = 151 nM
MERS Vero 81 Cell EC_{50} (+1μM EI) = 166 nM

Coronavirus Family Main Protease Biochemistry IC_{50}

SARS-CoV-1 29nM, HKU1 39nM, OC43 78nM, 229E 113nM, MERS 402nM, NL63 479nM

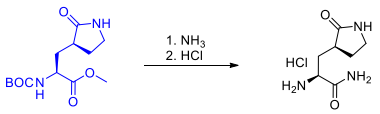
Human/HIV Protease Biochemistry Panel Selectivity IC_{50}

Cathepsin B, Cathepsin D, Chymotrypsin, Thrombin a, Caspase 2, Elastase, HIV >10μM



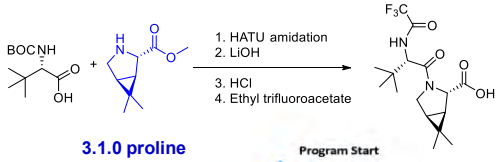
- Clean safety pharmacology mini panel & hERG
- Clean Gentox profile
- Stable to epimerization
- Highly soluble, developable solid form established
- Amenable to synthetic scale up
- Good gastric/intestinal stability

How to Make PF-7321332 on Scale

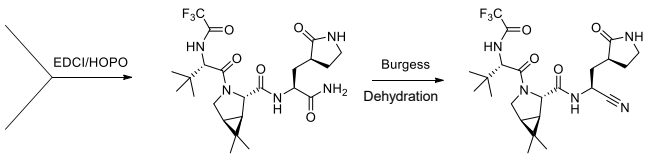


Used for IV candidate

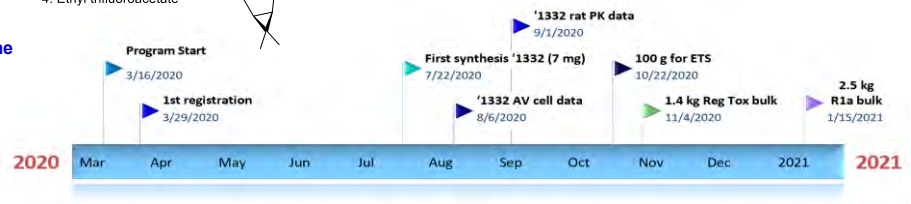
- With supply of key starting materials the route is peptide chemistry
- Lactam from IV candidate, 3.1.0 proline is commercial



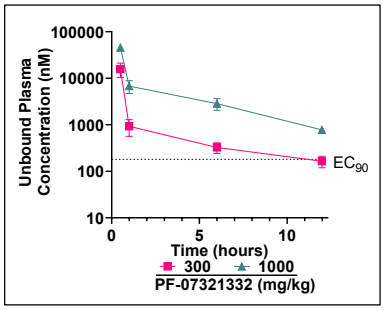
3.1.0 proline

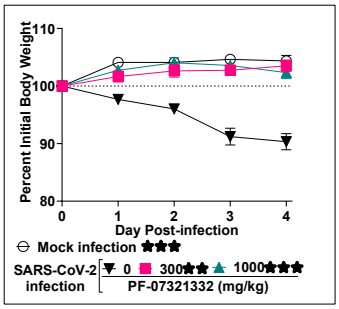


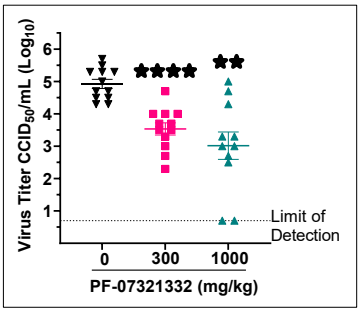
PF-7321332



In vivo efficacy of PF-07321332 in SARS-CoV2 MA 10 infected mice

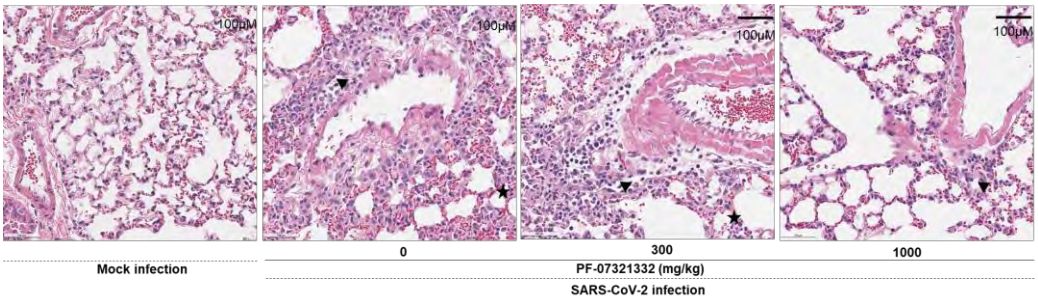


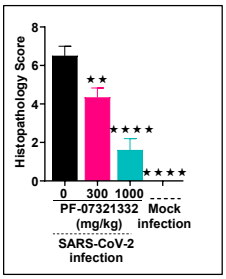




- 1000 and 300 mg/kg PF-07321332 dosed orally BID (n=6 mice/grp), 4h post infection
- Viral titers and lung histopath analyses performed on day 4
- PF-07321332 doses cover EC_{90}, prevents body weight loss and lowers viral titer in SARS CoV-2 infected mice

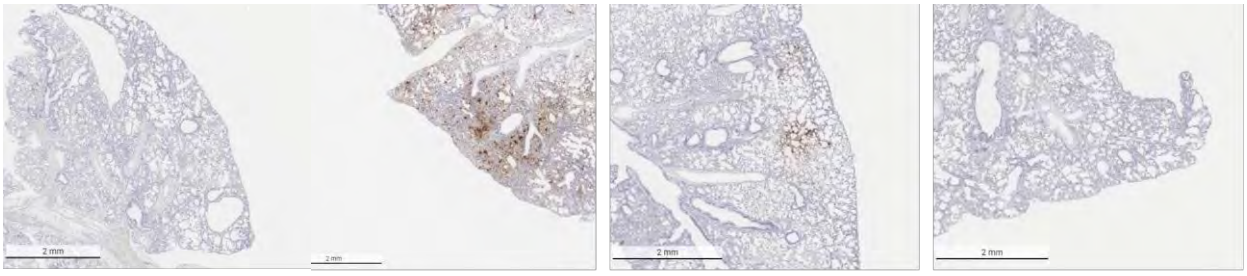
In vivo efficacy of PF-07321332 in SARS-CoV2 MA 10 infected mice





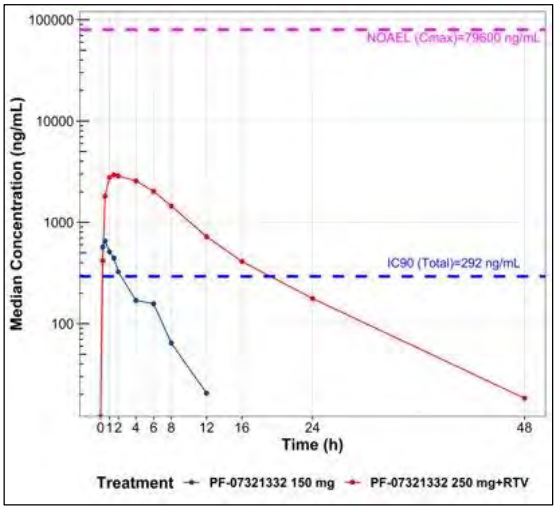
- Histopathological analysis of lung tissue from PF-07321332 treated mice
- Untreated mice show evidence of increased perivascular inflammation (▲) and alveolar thickening (★) compared to treated cohorts

In vivo efficacy of PF-07321332 in SARS-CoV2 MA 10 infected mice



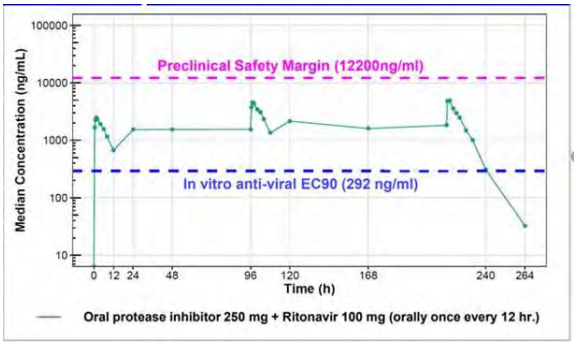
- Lung tissues from infected mouse-adapted SARS-CoV-2 at 4 days post infection, fixed and stained with antibody to the SARS-CoV-2 N protein
- Brown staining indicates the presence of replicating virus as demonstrated by expression of the N viral protein.

SAD Exposures of PF-07321332 +/- Ritonavir in healthy patients



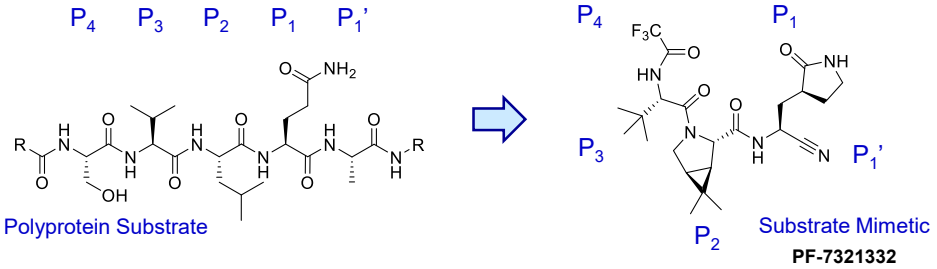
- Randomized, double-blind, placebo controlled study in healthy adults. 4 received 1332, 2 received placebo
- Co-dosing with Ritonavir (100 mg at t = -12 h, 0 h, and 12 h) increases exposure above the antiviral EC90 value
- Doses were safe and well tolerated

MAD Exposures of PF-07321332 + Ritonavir in Healthy Patients



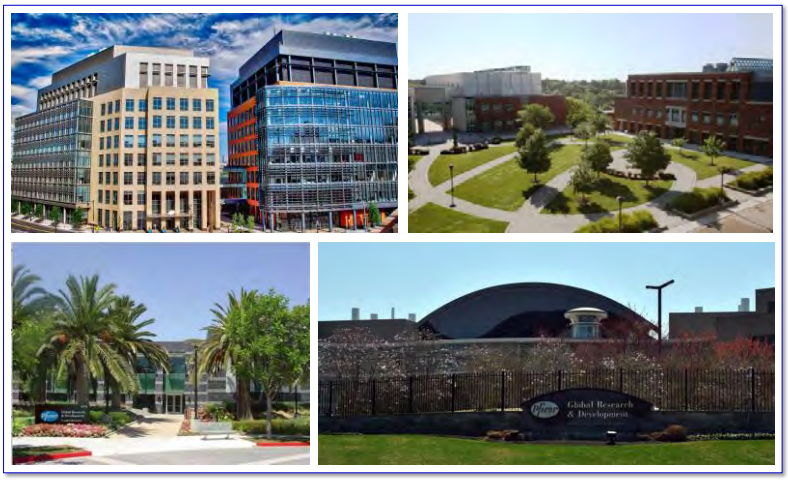
- 10 day MAD study
- Achieved 5x exposure over the antiviral EC90 value
- Safe and well tolerated

Summary



- Targeting H-bond donors, ↑oral PK studies and designing for scale-up paid off
- First oral SARS-CoV-2 protease inhibitor for COVID-19 to reach the clinic - 11 months
- *Science* (2021) 374, 1586-1593

Acknowledgements



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Brian Lanman of Amgen outlines the strategies used to overcome these challenges of KRAS, one of the most frequently mutated oncogenes in human cancer.

An Integrated Approach: Oral Delivery of a Fatty Acid Acylated GLP-1 Peptide
Stephen Buckley of Novo Nordisk shares how this coformulation provides a unique, site-directed release and absorption in the stomach and effectively surmounts inherent challenges relating to solubility, molecular size, and proteolytic lability to achieve therapeutically relevant plasma exposure of semaglutide.

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With the suspension of in-person meetings due to the coronavirus pandemic, scientists need to shift to networking virtually in order to remain connected. Join our panel as they share how to make the most out of virtual networking opportunities.

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Scott Edmondson, the Sr. Vice President and Head of Chemistry at Nimbus Therapeutics, discusses how SBDD is leveraged to deliver clinical candidates that are differentiated from others in their class by their exquisite selectivity.

Targeted Delivery of RNA-targeted Therapeutics
Punit Seth of Ionis Pharmaceuticals discusses examples of different strategies for delivery of oligonucleotide drugs. Learn about the recent advances in receptor-mediated delivery which have greatly expanded the repertoire of cell types and tissues that are now accessible for antisense drug-discovery.

Designing around Structural Alerts in Drug Discovery
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68