DRIVE

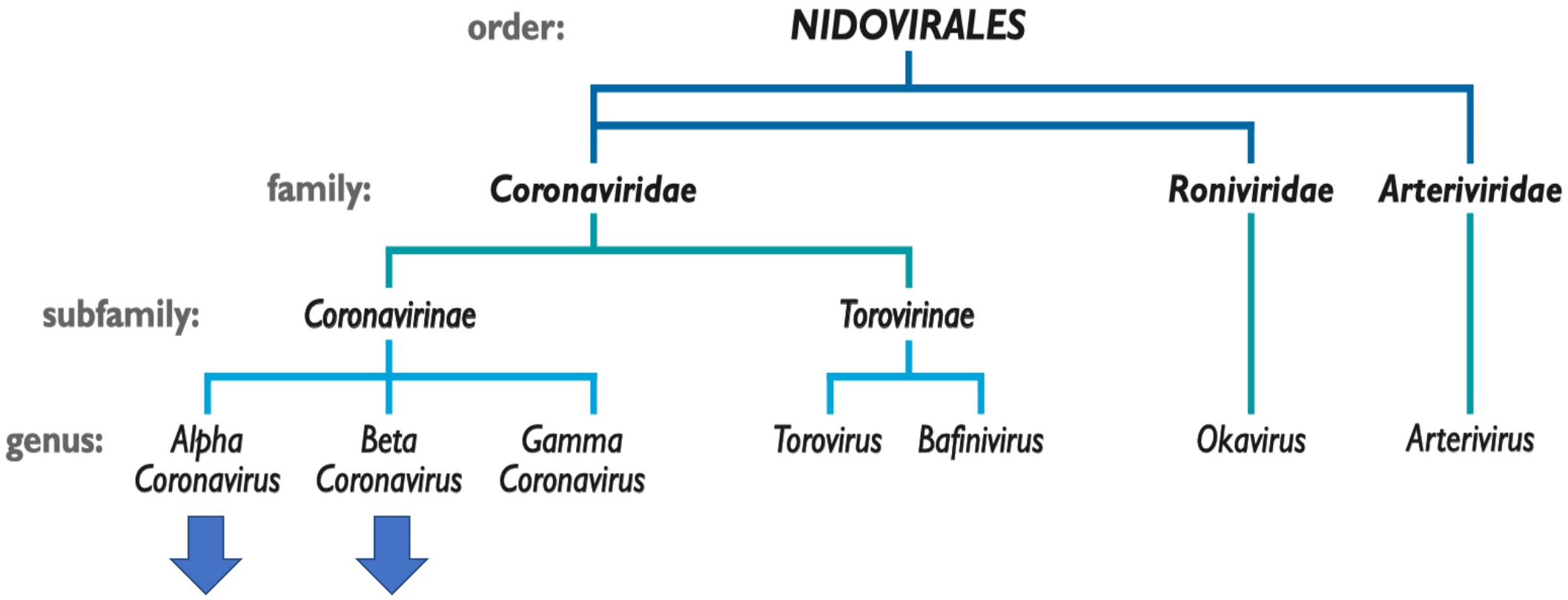
INFECTIOUS INNOVATION

ANTIVIRAL DRUGS THAT ARE APPROVED OR UNDER EVALUATION FOR THE TREATMENT OF COVID-19

INA Respond

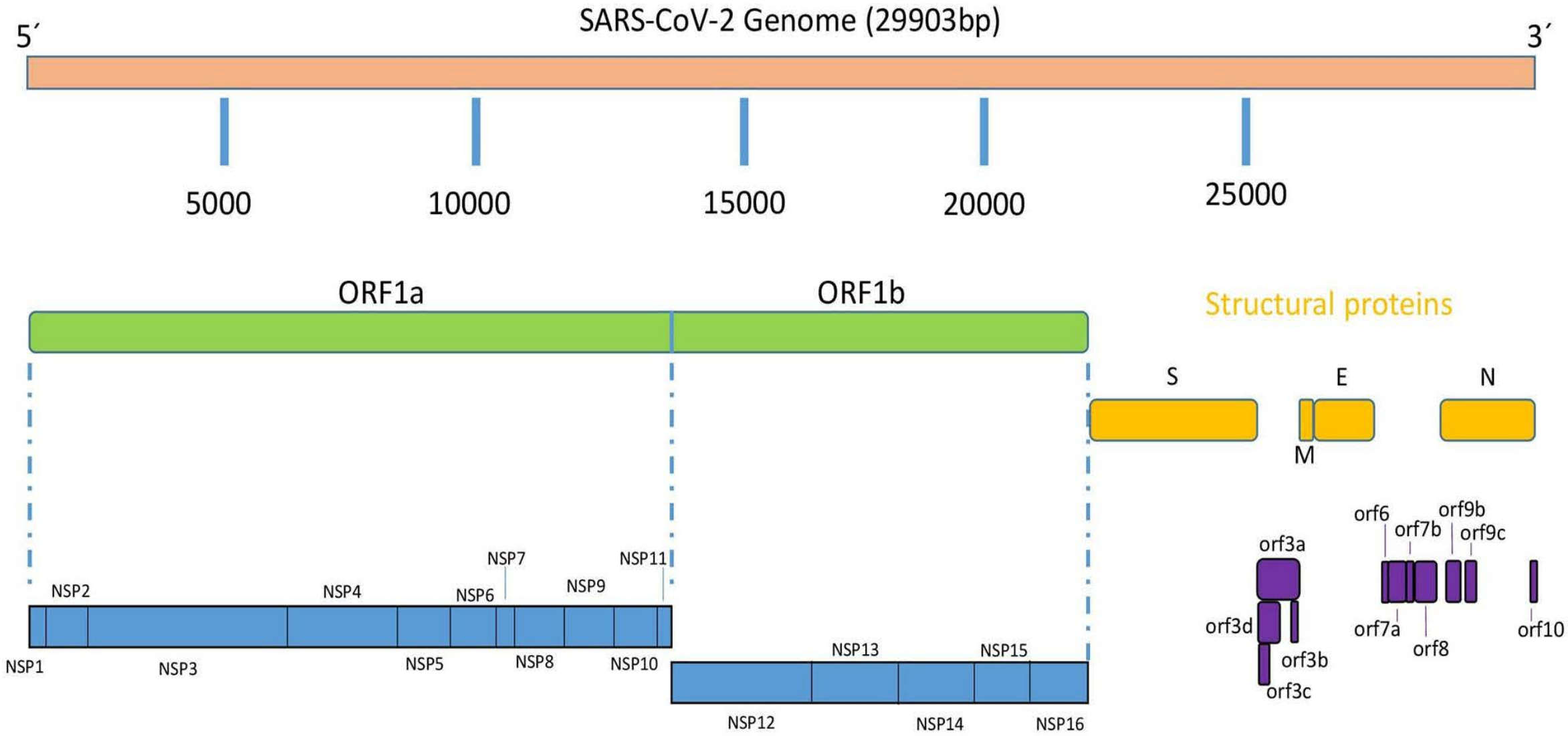
03 December, 2021

Coronaviruses that Cause Human Illness

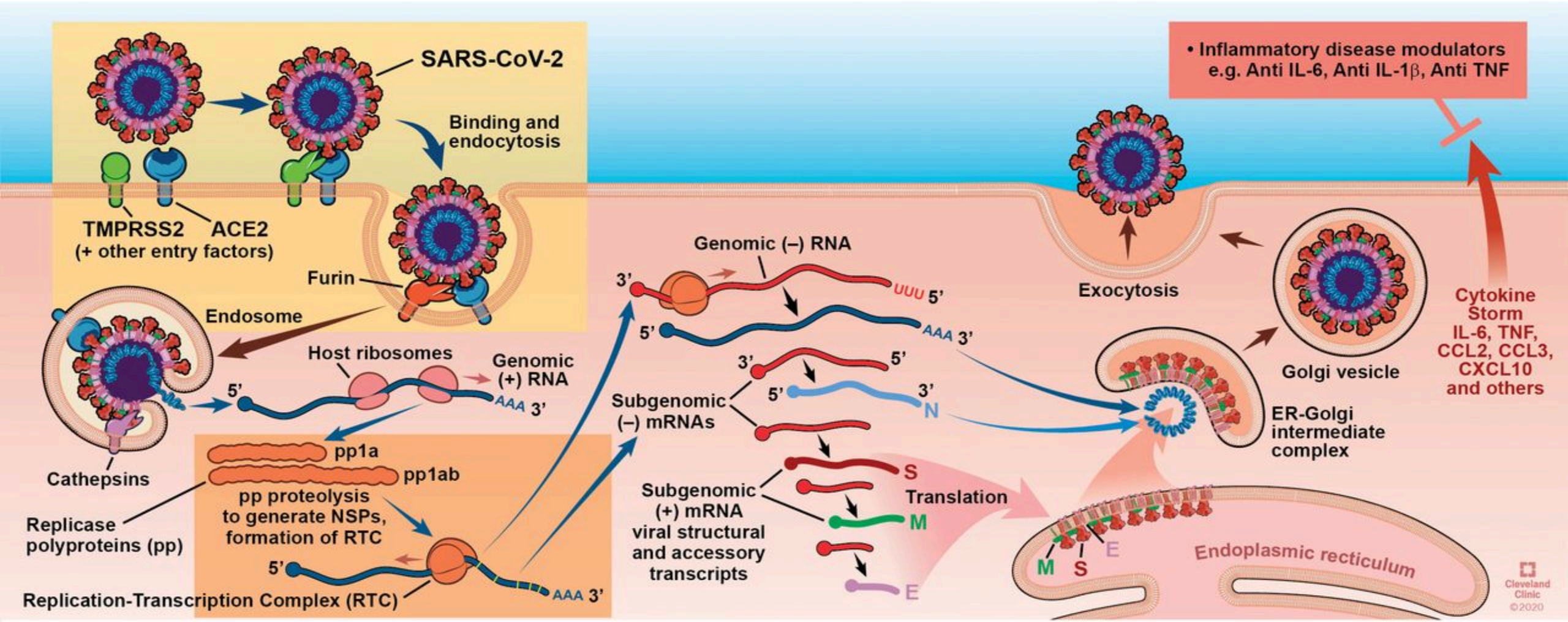


HCoV-229E, HCoV-NL63 **HCoV-HKU1, HCoV-OC43, MERS-CoV, SARS-CoV, SARS-CoV-2**

GENOMIC ORGANIZATION OF SARS-CoV-2



SARS-CoV-2 Replication Cycle



Blockade of Entry

- **Anti-spike Ab**
  convalescent serum
  vaccine expressing spike
- **Endocytosis inhibitor**
  chloroquine
  hydroxychloroquine
- **Inhibition of S1/S2 cleavage**
  e.g. TMPRSS2

Blockade of Replication

- **Interference with RdRP (Replicase)**
  Remdesivir (GS-5734)
  EIDD-1931
- **Viral protease inhibitor**
- **Ribavirin**

Innate Immune Response

- **MDA5**
- **IFN-I, IFN-III**
- **ISG effectors**
  OAS, PKR, ...

Enhancers of Antiviral Innate Immunity

- **Early treatment with IFN or IFN inducers**
- **Blockade of IFN antagonists**

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

Ideal Target Product Profile for COVID-19 Therapeutic

- Easily distributed, stable at room temperature, and widely available
- Self-administered
- Predictably bioavailable
- Distributed to appropriate tissues
- Rapidly reduced viral replication
- Generally safe and well tolerated
- Low risk of drug-drug interactions
- Low risk of developing resistance mutations
- Broad anti-RNA respiratory virus activity

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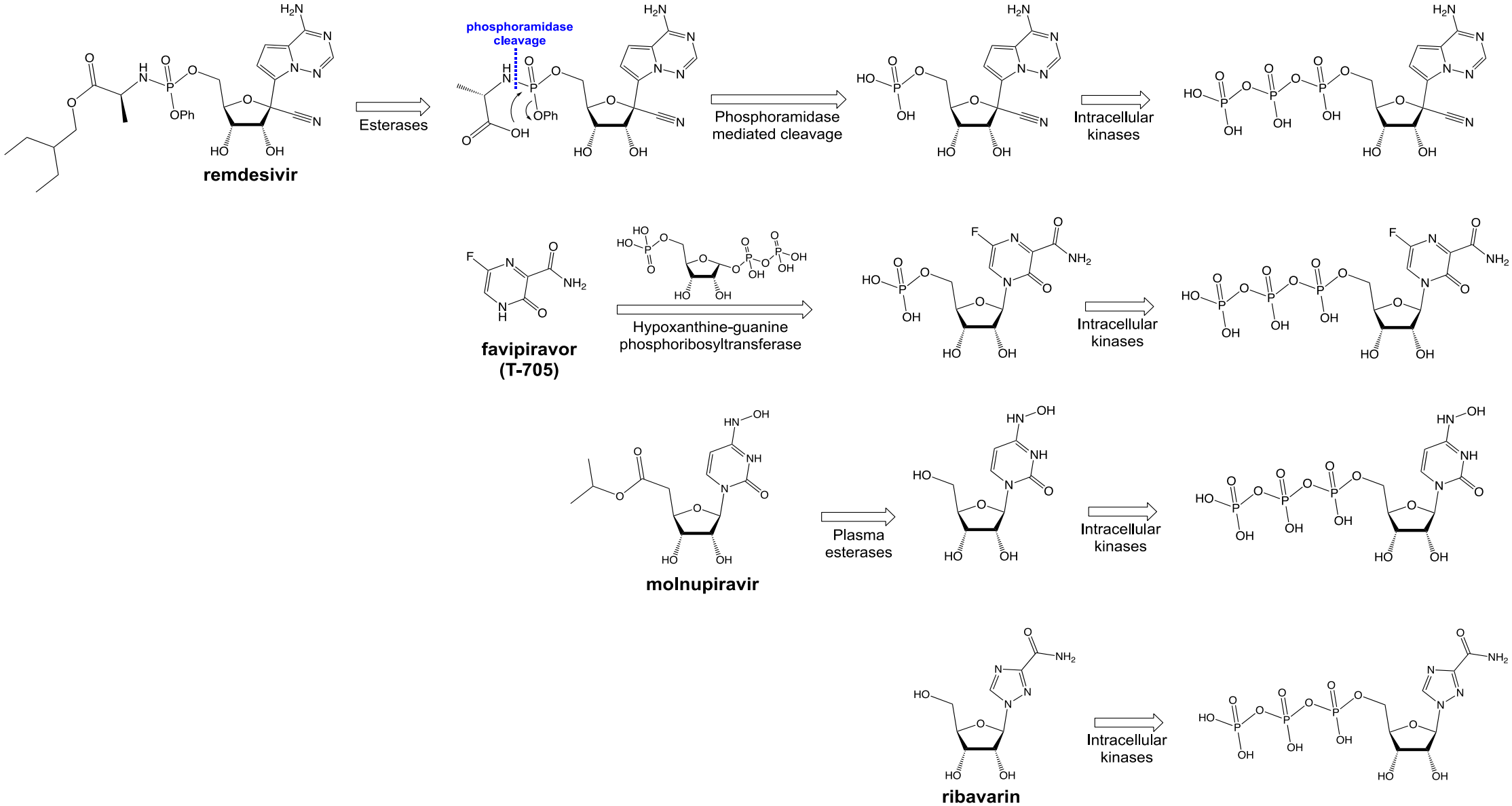
Nucleosides Play a Critical Role in Antiviral Therapy

- 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

Ribonucleoside Analogs Need to be Metabolically Activated



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EMORY UNIVERSITY | Emory Institute for Drug Development

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-68	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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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

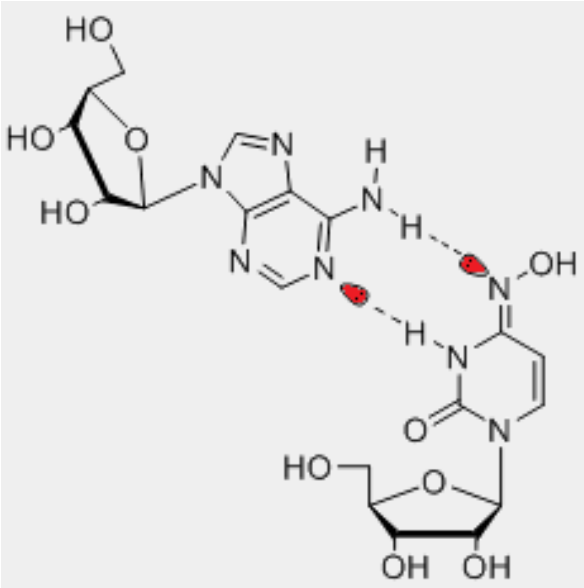
Agostini et al. (2019) showed that passage of coronaviruses in the presence of EIDD-1931 yields low-level resistance associated with multiple transition mutations and that EIDD-1931 mutagenesis may hinder emergence of robust resistance to EIDD-1931.

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

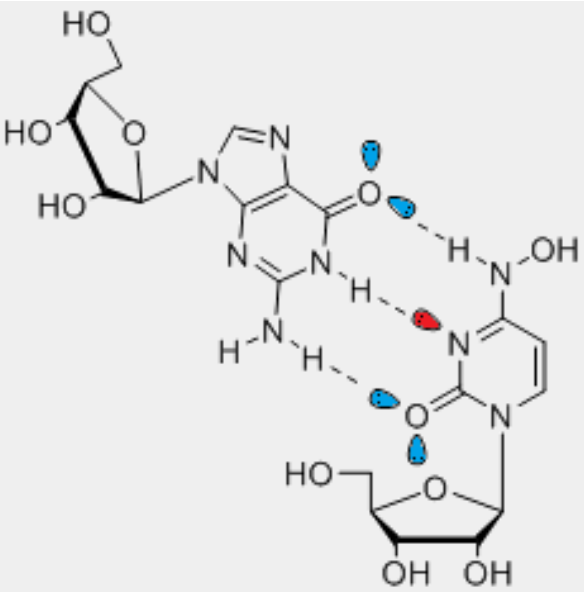
Mechanism of Action of Molnupiravir: Viral Error Catastrophe

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



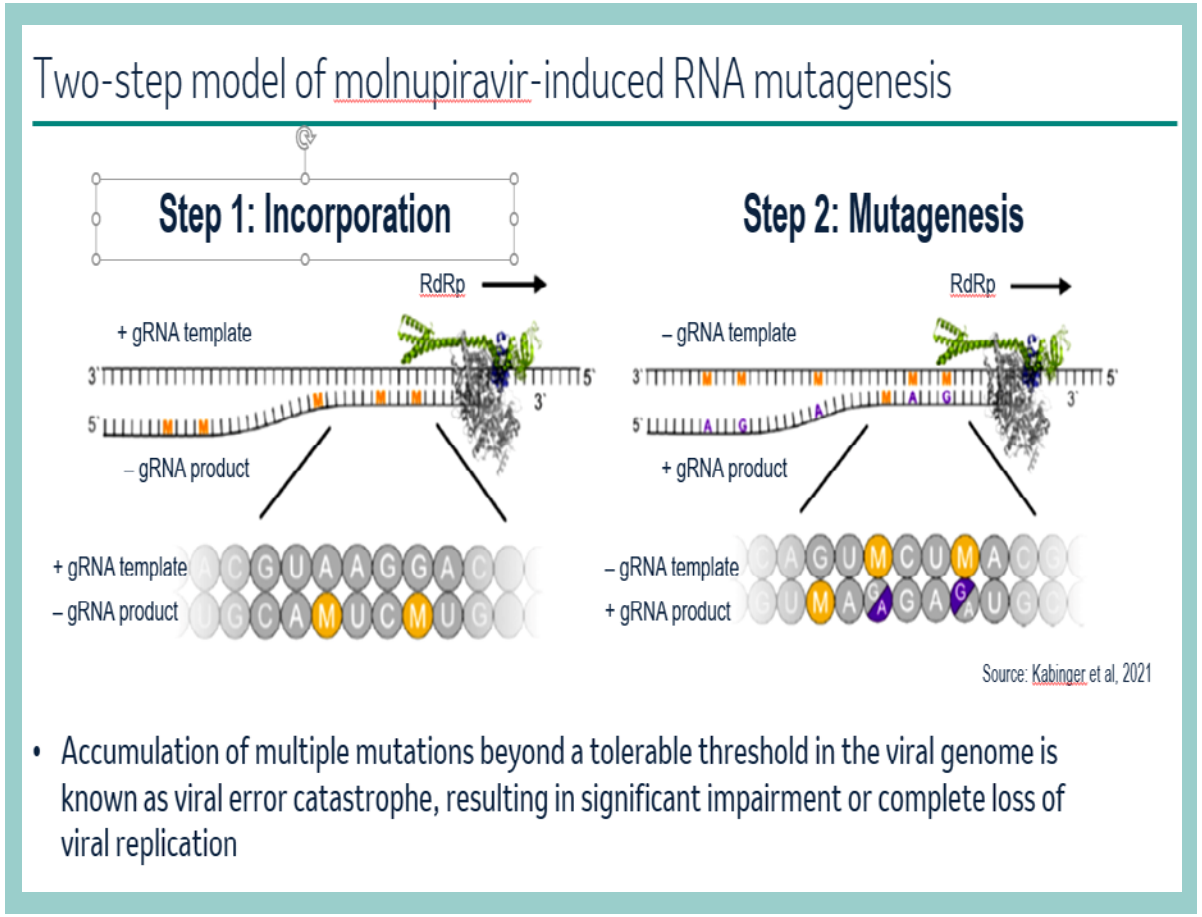
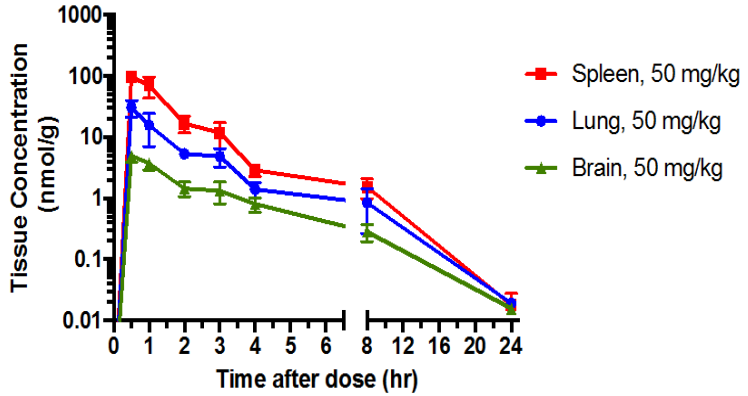


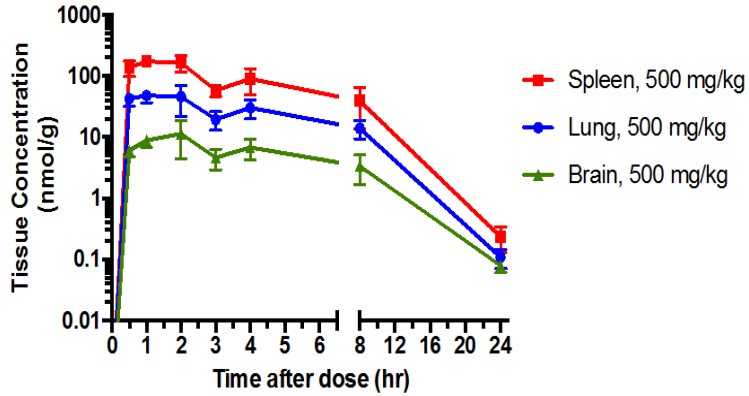
Figure adapted from: Moriyama et al. *Nucleic Acids Research* **1998**, 26 (9): 2015-2111

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

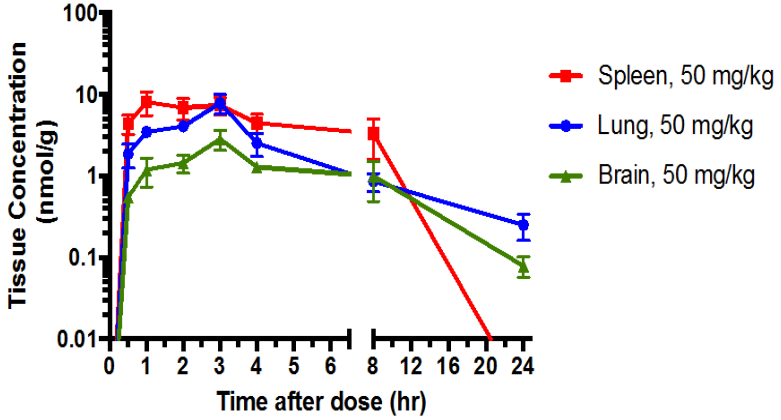
EIDD-1931 is Efficiently Distributed to and Anabolized in Key Tissues in the Pathogenesis of RNA Viral Diseases

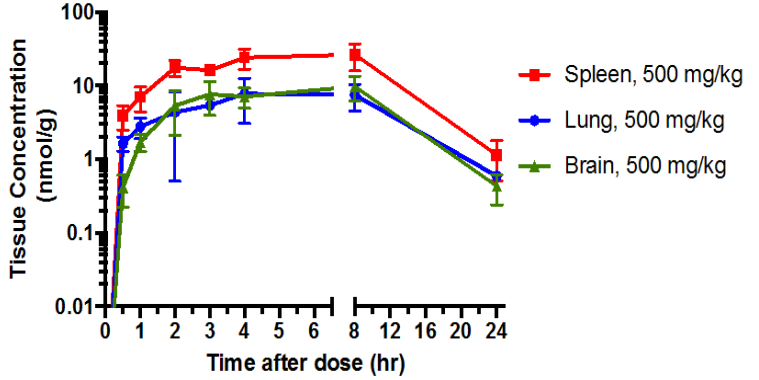
EIDD-1931 levels in mouse tissues after a single oral dose





EIDD-1931 5'-triphosphate in mouse tissues after a single dose of EIDD-1931

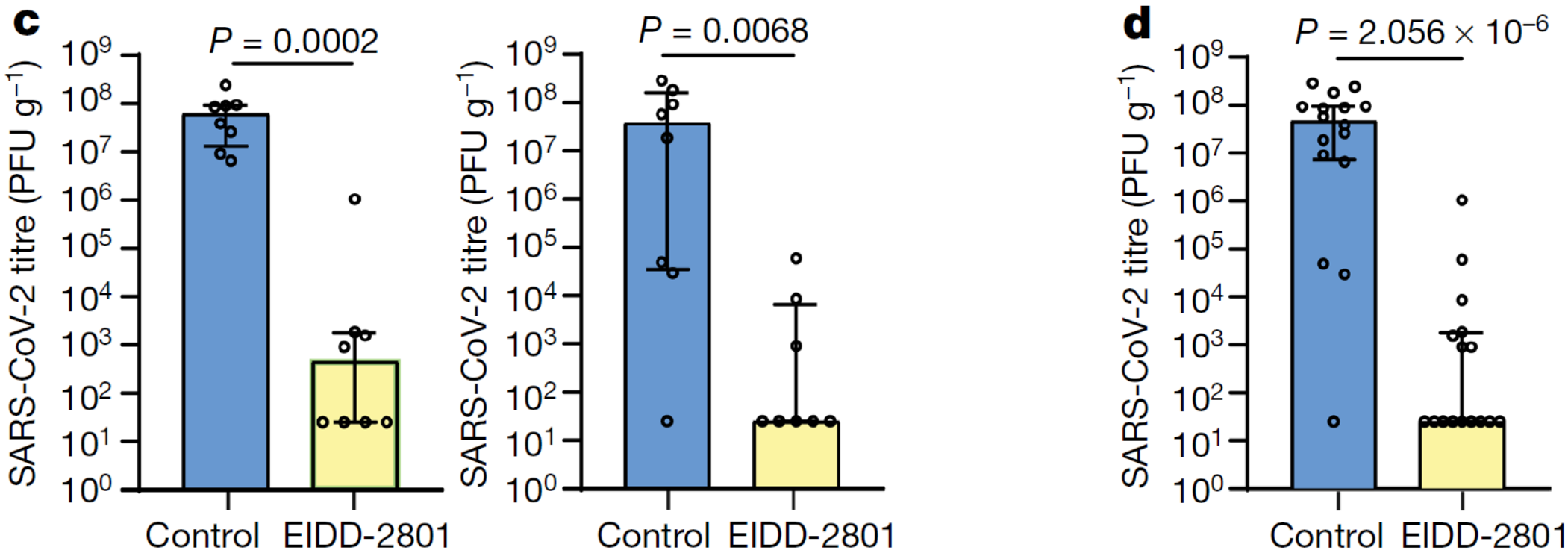




Painter et al., *Antiviral Res* **2019**, 171: 104597 doi: 10.1016/j.antiviral.2019.104597

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**)



Non-clinical Toxicology

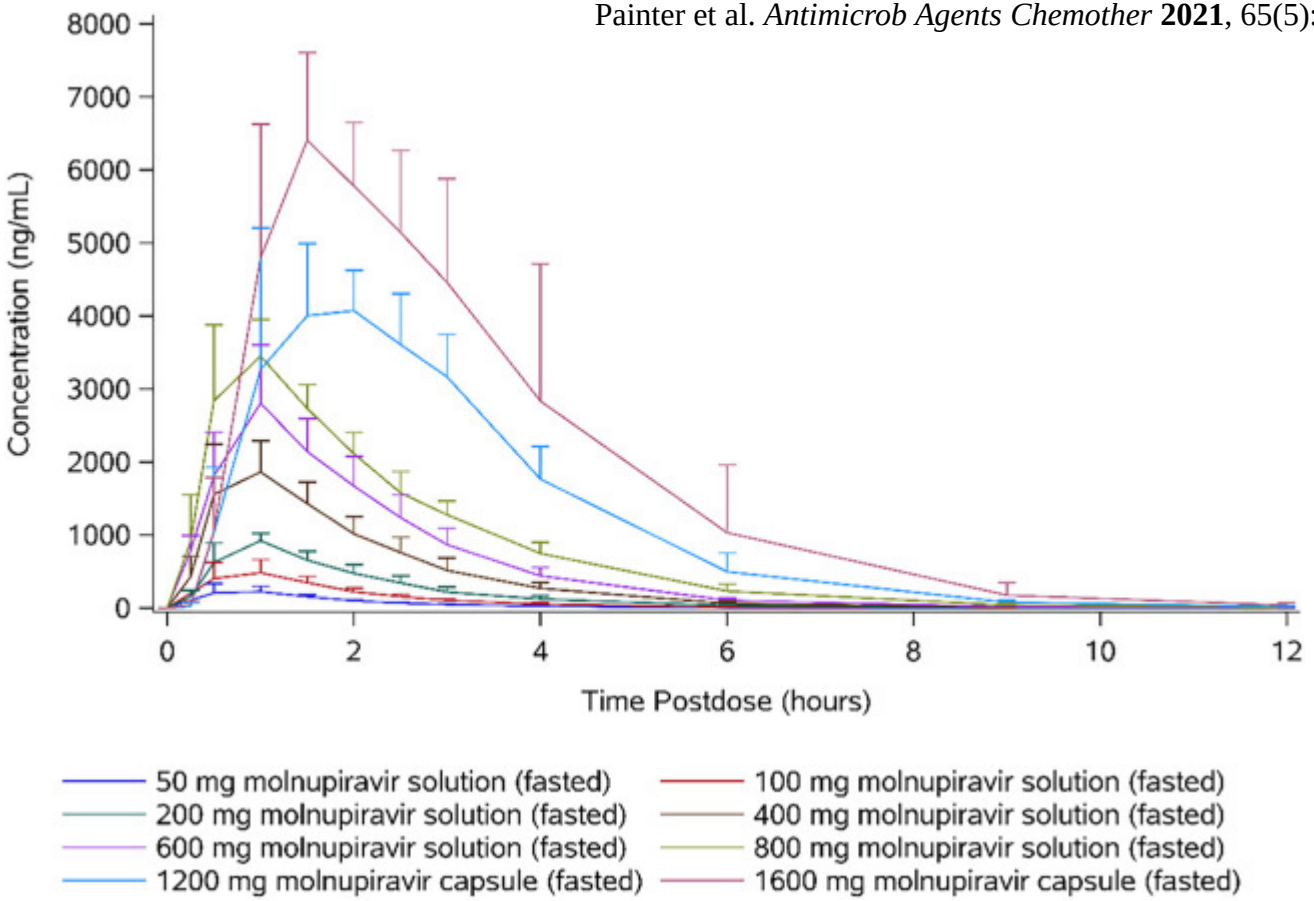
- Molnupiravir and NHC were positive in the in vitro bacterial reverse mutation assay (Ames assay) with and without metabolic activation.
- In 2 distinct in vivo rodent mutagenicity models (Pig-a mutagenicity assay and Big Blue® [cII Locus] transgenic rodent assay), molnupiravir did not induce increased 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

Single Dose Pharmacokinetics (PK) of EIDD-1931 after Oral Administration of Molnupiravir

- 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

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

A Phase 2/3, Randomized, Placebo-controlled, Double-blind Clinical Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of MK-4482 in Non-hospitalized Adults with COVID-19 (MOVe-OUT)

Interim efficacy analysis resulted in decision to stop recruitment:

- The planned interim analysis evaluated data from 775 patients who were initially enrolled in the MOVe-OUT trial. At the time of the decision to stop recruitment, more than 90% of the intended sample size had already enrolled.
- Molnupiravir treatment resulted in a 6.8% reduction in risk of hospitalization or death (approximately 50% relative risk reduction). All 8 subjects who died through Day 29 were in the placebo group and were hospitalized prior to their death.
- Molnupiravir reduced the risk of hospitalization and/or death across all key subgroups; efficacy was not affected by timing of symptom onset or underlying risk factor. Additionally, based on the participants with available viral sequencing data (approximately 40% of participants), molnupiravir demonstrated consistent efficacy across viral variants Gamma, Delta, and Mu.
- The incidence of any adverse event was comparable in the molnupiravir and placebo groups (35% and 40%, respectively). Similarly, the incidence of drug-related adverse events was also comparable (12% and 11%, respectively). Fewer subjects discontinued study therapy due to an adverse event in the molnupiravir group (1.3%) compared with the placebo group (3.4%). The most common adverse reactions reported during treatment and during the 14 days after last dose were diarrhea (3%), nausea (2%), dizziness (1%), and headache (1%), all of which were Grade 1 (mild) or 2 (moderate).

RIDGEBACKBIO

Molnupiravir Found to be Safe and Effective by Medicines and Healthcare Products Agency in Great Britain

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

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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.

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