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Great Chemistry Cures

EDP-235, an Oral 3CL Protease Inhibitor for the Treatment of COVID-19, Suppresses Viral Replication and Transmission in SARS-CoV-2-Infected Ferrets

Michael H. J. Rhodin, Anand Balakrishnan, Archie Reyes, Michael Vaine, Tessa Cressey, Miranda Crepeau, Nicole McAllister, Ruichao Shen, Kellye Daniels, Daniel Leonard, Indy Zang, Lijuan Jiang, Richard K. Plemper, Guoqiang Wang, Yat Sun Or, and Bryan Goodwin

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Disclosures: Michael H. J. Rhodin, Anand Balakrishnan, Archie Reyes, Michael Vaine, Tessa Cressey, Miranda Crepeau, Nicole McAllister, Ruichao Shen, Kellye Daniels, Daniel Leonard, Indy Zang, Lijuan Jiang, Guoqiang Wang, Yat Sun Or, and Bryan Goodwin are/were employees of Enanta Pharmaceuticals. Richard K. Plemper is affiliated with Georgia State University and performed ferret studies under a fee-for-service collaborative agreement.

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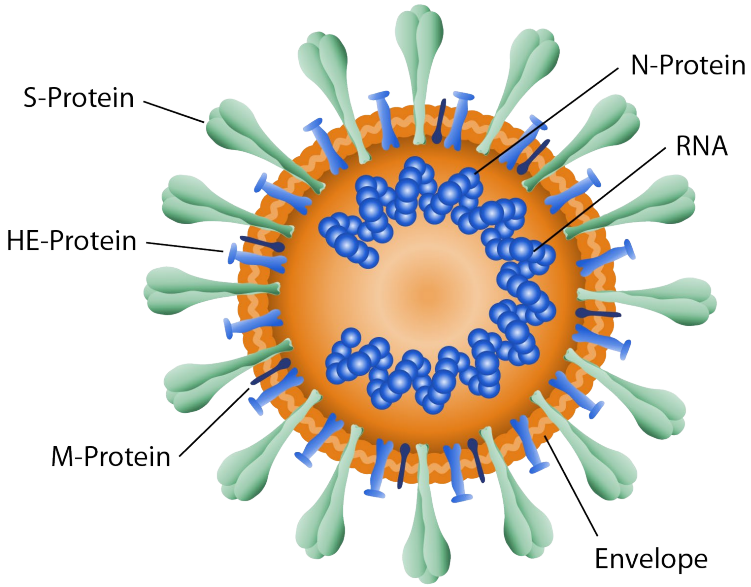
EDP-235: A Novel, Oral Protease Inhibitor Designed for COVID-19

- Potent and selective inhibition of SARS-CoV-2 3CLpro enzyme
- Potent inhibition of SARS-CoV-2 replication in multiple cellular models
- Activity retained against SARS-CoV-2 variants, including Omicron variants
- Other human coronaviruses susceptible to EDP-235
- High barrier to resistance observed preclinically
- Human efficacious dose predicted as 100 to 500 mg once-daily
  - Good oral bioavailability (95% in rats)
  - Long half-life (13 - 22 hours in humans)
  - Good target tissue distribution (e.g. lung to plasma AUC ratio >4)
  - Supported by Phase 1 PK data at 200 mg and 400 mg QD
- Phase 2 study (SPRINT*) data readout targeted for May 2023

SARS-CoV-2



*ClinicalTrials.gov Identifier NCT05616728

EDP-235: Highly Potent 3CLpro Inhibitor that Retains Activity Against SARS-CoV-2 Variants

Assay		Variant / Lineage *(mutation)*	Potency [nM]
Biochemical Activity	3CLpro FRET (**IC_{50}**)	**Omicron** *(P132H)* [B.1.1.529, BA.2, BA.5, BA.2.75, BQ.1, BQ1.1, XBB.1]	**4.1** ± 0.8
		Alpha [Original] / **Delta*** [B.1.617.2]	**5.8** ± 3.7
		B.1.1.318 *(T21I)*	**2.0** ± 0.1
		Beta [B.1.351] *(K90R)*	**2.8** ± 0.9
		Beta [B.1.351.2] *(K90R/A193V)*	**5.4** ± 1.0
		B.1.617.3 *(A194S)*	**5.7** ± 0.5
		C.36.3 *(G15S)*	**4.7** ± 2.5
		Zeta [P.2] *(L205V)*	**3.4** ± 1.0
Live Virus	Vero E6 +PGPi, CPE readout (**EC_{90}**)	**Omicron** [B.1.1.529]	**5.1** (n=1)
		Delta [B.1.617.2]	**9.1** ± 2.9
		Alpha [Original]	**11** ± 8

Values average of replicate experiments except where noted
*3CLpro sequences for the ancestral A lineage and B.1.617.2 (Delta) variant are identical
FRET: fluorescence resonance energy transfer, P-gpi: P-glycoprotein inhibitor CP-100356 (2 μM), CPE: cytopathic effect

Animal Models of COVID-19

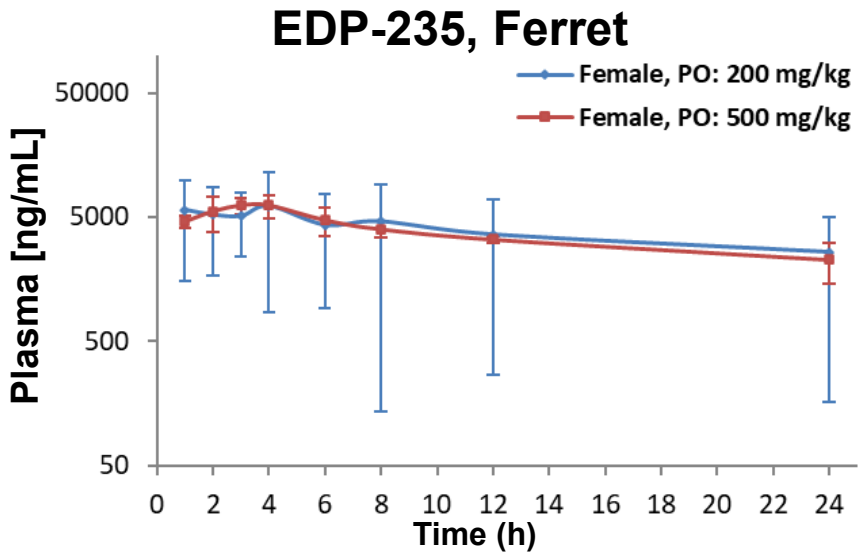
- Animal models of COVID-19 are indispensable for the discovery and characterization of novel antiviral agents targeting SARS-CoV-2
- Variation in the structure of the SARS-CoV-2 host receptor (ACE2) limits the animal species that can be used to study this virus
  - SARS-CoV-2 cannot productively infect mice without adaptation of the virus to mice or introduction of human ACE2 into the animals [so-called transgenic mice]
- Spill-over transmission of SARS-CoV-2 to farmed mink and mink-to-mink transmission suggested mustelids of the weasel genus can be naturally infected and transmit the virus[1]
- Ferret ACE2 contains favorable SARS-CoV-2 spike protein-interacting amino acids[2]
- Ferrets have emerged as an important model of SARS-CoV-2 infection and transmission[3,4]
- The ability of EDP-235 to inhibit SARS-CoV-2 replication and transmission was examined in ferrets in collaboration with Dr. Richard Plemper at Georgia State University

[1] https://www.science.org/doi/10.1126/science.abf6097#body-ref-R3
[2] https://journals.asm.org/doi/full/10.1128/JVI.00127-20
[3] https://www.nature.com/articles/s41467-020-17367-2
[4] https://www.nature.com/articles/s41564-020-00835-2

EDP-235 Ferret Pharmacokinetics

Ferret drug exposure levels well-aligned with human Ph1 PK data

- Single dose ferret PK study with 200 mg/kg and 500 mg/kg



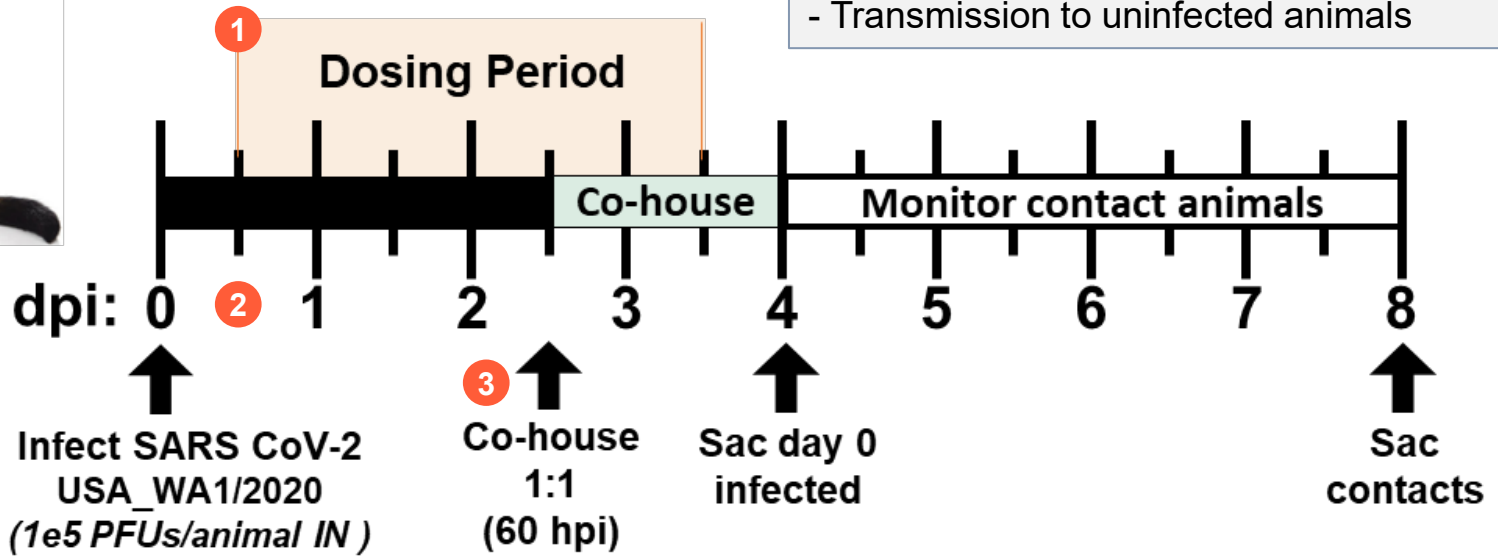
PO Dose	Sex	N		C_{24} (ng/mL)	C_{max} (ng/mL)	T_{max} (hr)	$t_{1/2}$ (hr)	AUC_{0-24} (hr•µg/mL)
200 mg/kg	F	3	Mean:	2597	9410	4.3	6.7	92.2
			SD:	2436	2421	1.5	0.6	50.5
500 mg/kg	F	3	Mean:	2270	6523	4.7	16.0	87.2
			SD:	811	1036	1.2	6.2	2.8

- EDP-235 exposures in ferrets were comparable to human phase 1 clinical EDP-235 plasma exposures, representing strong multiples over EC_{90}
  - For full details, visit ICAR poster #524: **EDP-235, an Oral, Once Daily, Ritonavir-Free, 3CL Protease Inhibitor for the Treatment of COVID-19: Results from Phase 1 Study in Healthy Subjects**
    - *Dr. Guy De La Rosa presenter*
- No dose effect observed, 200 mg/kg QD and BID selected for efficacy study

Ferret Model: Study Design

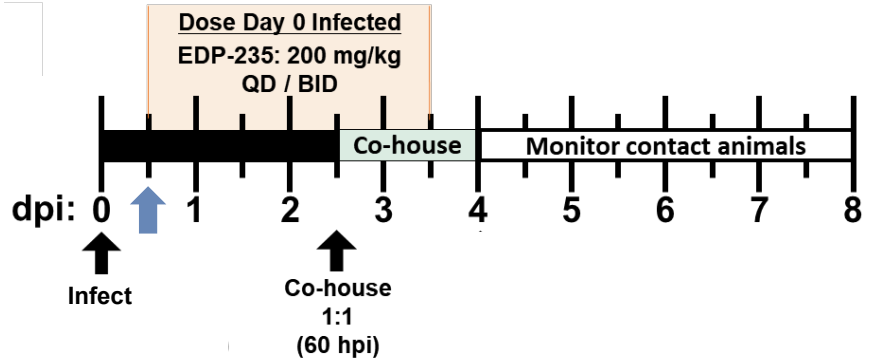
Primary Readouts:
- Nasal lavages: live virus + qPCR
- Nasal turbinate tissues: end of study live virus + qPCR
- Transmission to uninfected animals

N = 6
/ Cohort



1. 3 Cohorts: Vehicle Control (placebo), 200 mg/kg EDP-235 **QD**, and 200 mg/kg EDP-235 **BID**
2. Therapeutic dosing study (12 h post infection)
3. Transmission study (co-house naïve animals with infected ferrets 60 h post infection (48 h post treatment))
   - Co-housed naïve animals do not get drug; only there to ascertain if virus transmits from original infected animals to naïve co-housed animals, and if treatment of infected animals prevents this transmission

EDP-235 is Efficacious in a Ferret Model of COVID:
Robust Antiviral Treatment Effect & Prevention of Transmission



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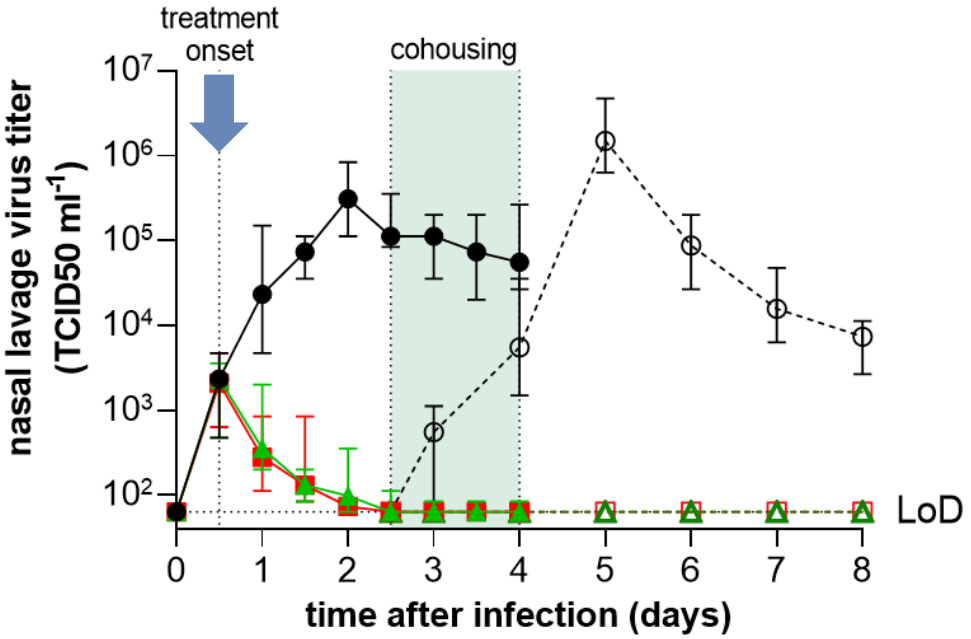
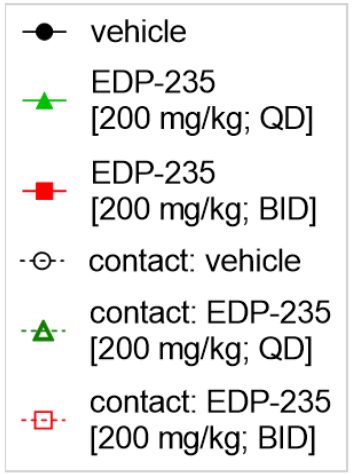
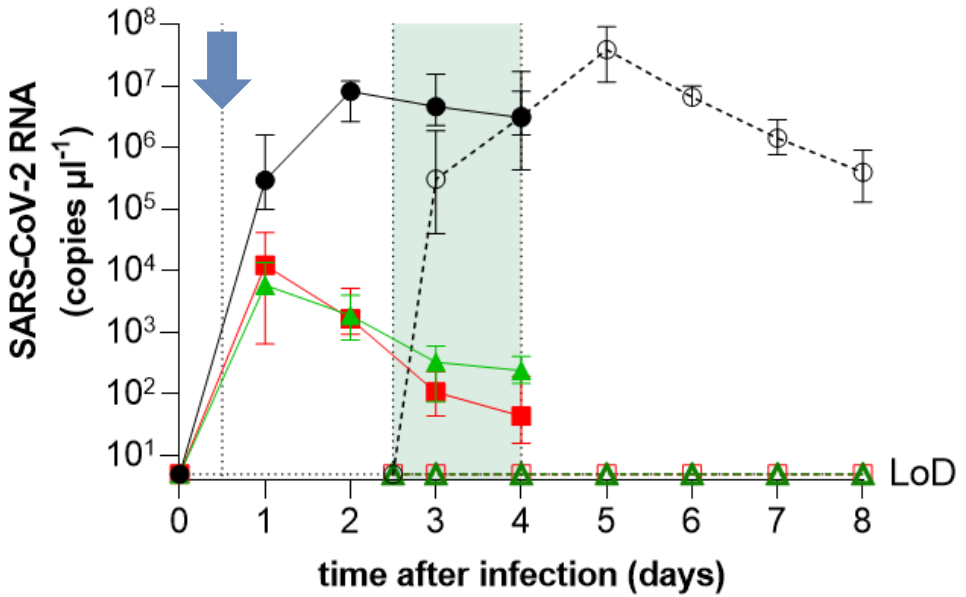
Daily Nasal Lavage: Live Virus





Daily Nasal Lavage: qPCR [RNA]



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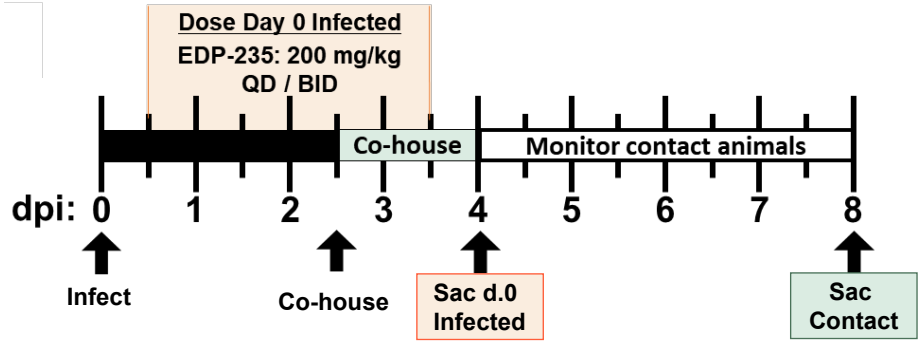

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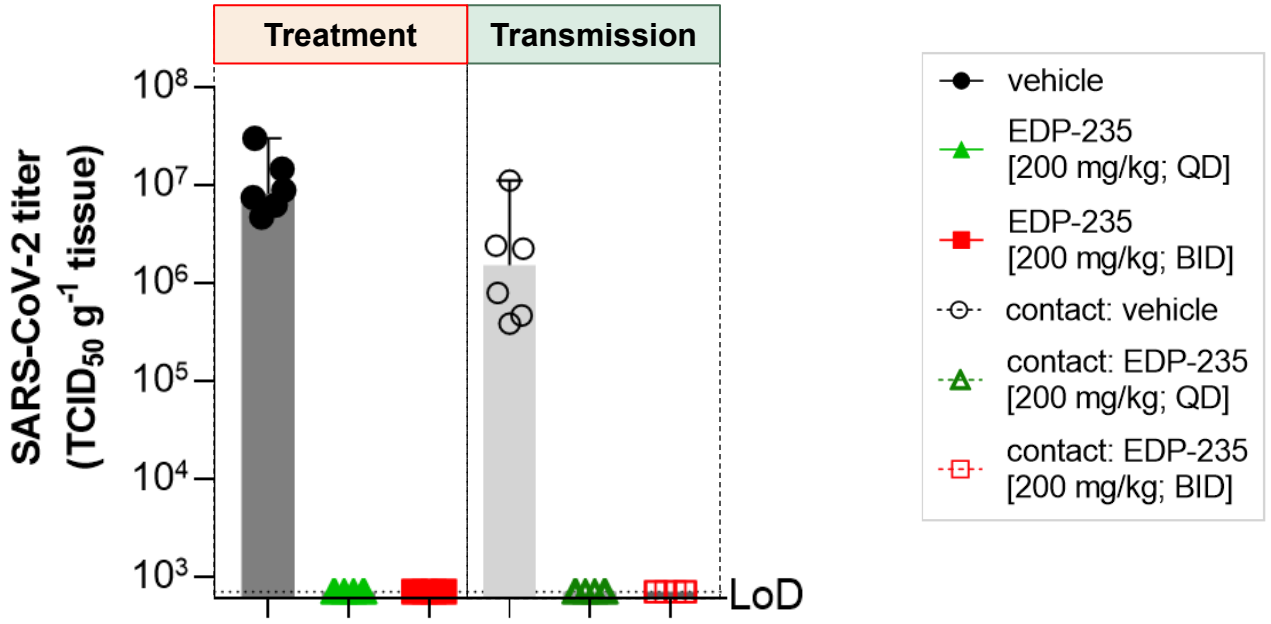
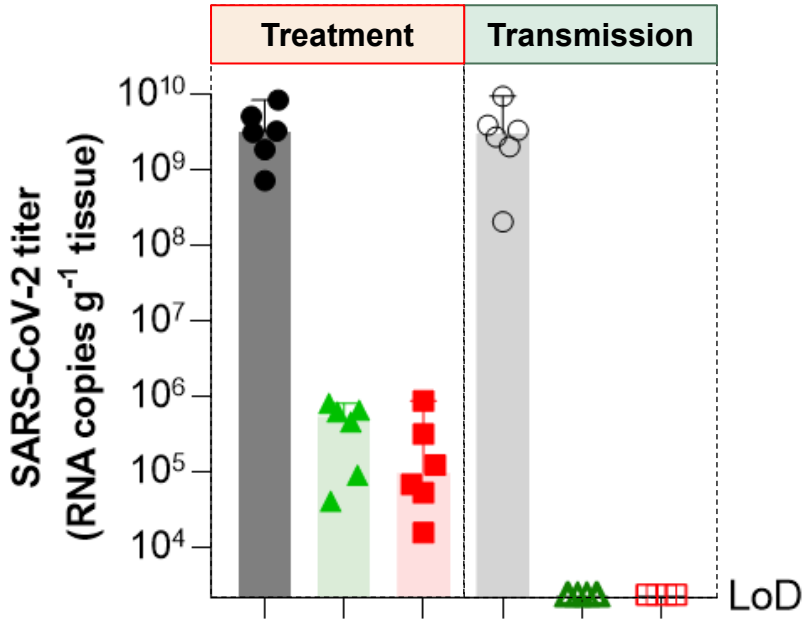
Nasal Turbinates: Live Virus



Nasal Turbinates: RNA



Summary

Antiviral Treatment Effect:

- EDP-235 treatment of SARS-CoV-2 infected animals resulted in a rapid and robust decline in viral replication and viral RNA levels

Transmission Prevention:

- Infected, untreated animals went on to infect healthy co-housed contact animals
- Infected, EDP-235-treated animals **did not** infect healthy co-housed contact animals
- Data supports the potential for EDP-235 to prevent or reduce household transmission

EDP-235 Profile Suggests Potential for Best-in-Class Antiviral Treatment for SARS-CoV-2 Infection

- Potent antiviral activity *in vitro* against SARS-CoV-2 variants, including Omicron variants
- Generally safe and well-tolerated in adult healthy volunteers up to 400 mg for up to 7 days
- Targeting an efficacious dose of 200 mg or 400 mg once-daily, without the need for boosting (e.g., ritonavir)
  - 200 mg: human free drug plasma levels 7x higher than EC_{90} of Omicron
  - 400 mg: human free drug plasma levels 13x higher than EC_{90} of Omicron
- 4x higher drug levels projected in lung tissue compared to plasma
- Good distribution into other key target tissues[a], providing the potential to impact post-treatment rebound and/or possible sites of ongoing replication linked to long COVID
- Phase 2 study in standard risk adults (SPRINT[b]) readout targeted for May 2023

Emerging data supports convenient dosing regimen, targeting a one pill, once-a-day treatment, active against COVID-19 variants of concern

[a] adipose, heart, liver, salivary gland, and lung alveolar macrophages
[b] ClinicalTrials.gov Identifier NCT05616728

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