SCIENCE SPOTLIGHT™

THE 3CL$_{pro}$ INHIBITOR ALG-097111 POTENTLY INHIBITS SARS-CoV-2 REPLICATION IN HAMSTERS

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Disclosure: Koen Vandyck is an employee of Aligos Belgium BV

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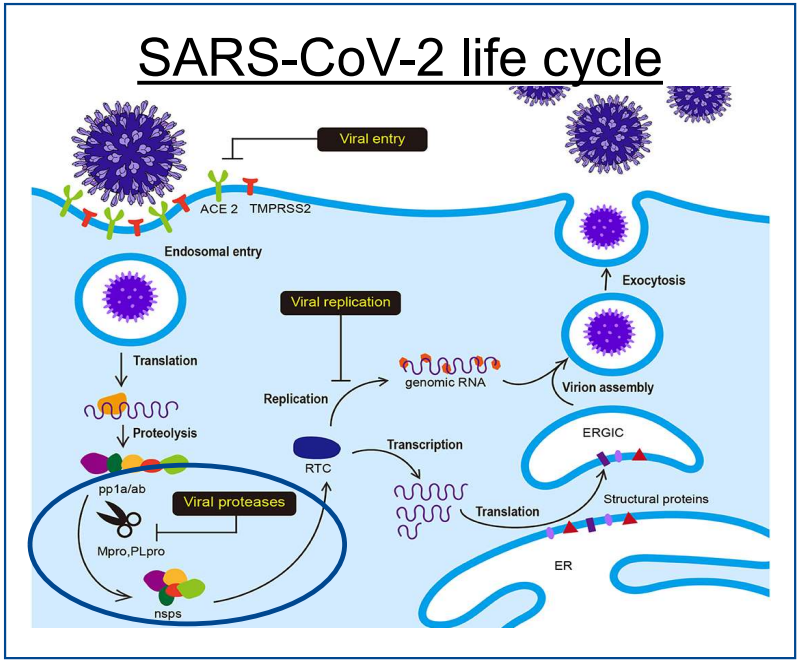
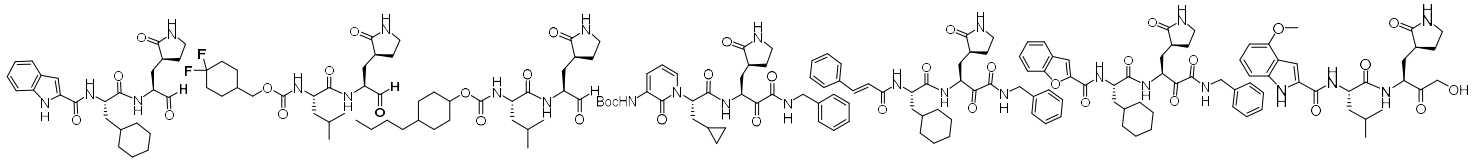
SARS-CoV-2 $3CL_{pro}$ Represents an Attractive Target

- The main protease of SARS-CoV-2 $3CL_{pro}$ is conserved among coronaviruses (including SARS-CoV-1, 2 and MERS-CoV)
- $3CL_{pro}$ cleaves at multiple sites on the large polyprotein 1ab
- No human homolog of $3CL_{pro}$
- Collaboration on Coronavirus Protease Inhibitors between Aligos and CD3/Rega at KU Leuven



https://www.frontiersin.org/articles/10.3389/fmicb.2020.01723/full

Other Reported $3CL_{pro}$ Inhibitors also Inhibit Cathepsin L



	Cpd 11a	6j	6e	Cpd 13b	Cpd 11r	A9	PF-00835231
Cathepsin L IC_{50} (nM)	**0.21** (n=2)	**<0.5** (n=2)	**<0.5** (n=2)	**291** (n=2)	**<0.5** (n=2)	**<0.5** (n=2)	**146** (n=13)
SARS-CoV-2 3CLpro IC_{50} (nM)	**8** (n=28)	**7** (n=2)	**10** (n=3)	**472** (n=2)	**1154** (n=2)	**4891** (n=2)	**5** (n=5)

- Cathepsin L is involved in SARS-CoV-2 entry and inhibitors block replication in several cell lines
- The SARS-CoV-2 inhibitory activity of Cathepsin L inhibitors is reduced upon expression of TMPRSS2 and might not translate *in vivo*

Increasing the selectivity of SARS-CoV-2 $3CL_{pro}$ inhibitors over Cathepsin L is considered important

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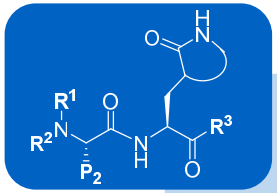
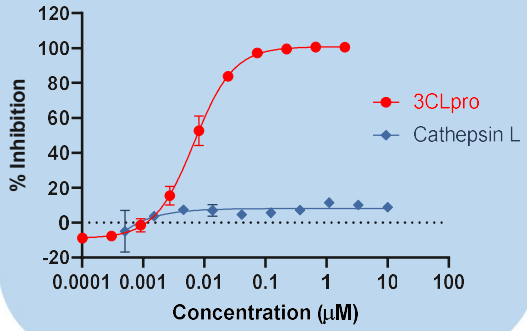
https://doi.org/10.1101/2021.02.14.431129; https://doi.org/10.1101/2020.11.21.392753

ALG-097111 is a Selective SARS-CoV-2 3Cl$_{pro}$ Inhibitor



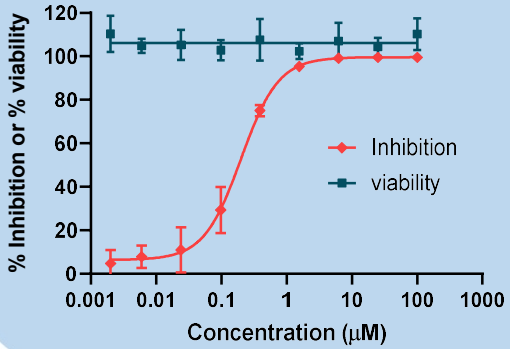
Biochemical

SARS-CoV-2 3CLpro (**IC_{50} = 7 nM**)
human cathepsin L (IC_{50} > 10 µM)

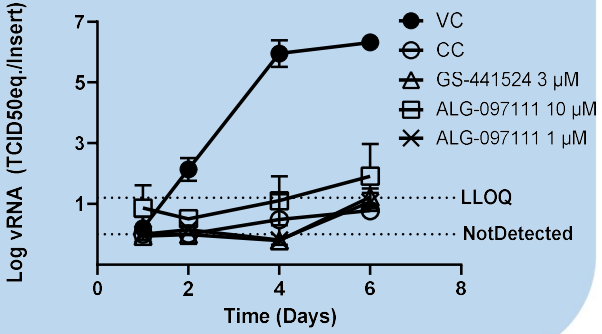


Cellular

SARS-CoV-2 (A549+ACE2): **EC_{50}= 200 nM**
(similar potency confirmed for β-CoV OC43 (HeLa) and α-CoV 229E (Huh-7))



SARS-CoV-2 inhibition in human small airway epithelial cell cultures
>3 log_{10} viral RNA reduction



ALG-097111, a selective SARS-CoV-2 3Clpro inhibitor, does not inhibit Cathepsin L, and shows cellular potency vs. alpha and beta coronaviruses

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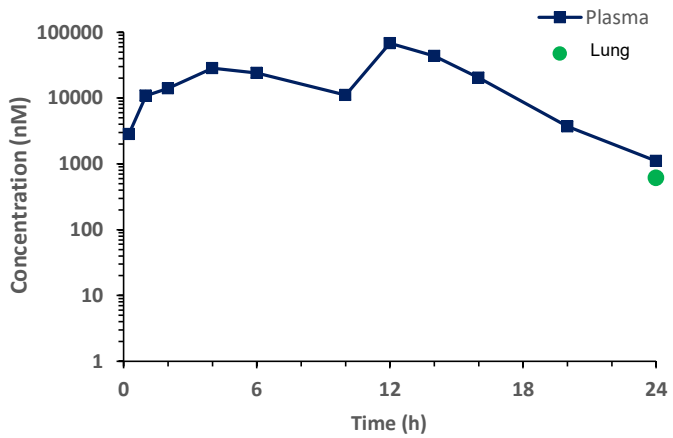
ALG-097111 Dosing in Female Syrian Hamster

- ALG-097111 is stable in human and dog liver microsomes ($t_{1/2}$ >60 min) and hepatocytes ($t_{1/2}$ >360 min)
- ALG-097111 is stable in hamster liver microsomes only in the presence of ritonavir ($t_{1/2}$ >60 min)
- Dose in hamsters: 200 mg/kg/dose BID SC co-dosed with ritonavir PO 50 mg/kg/dose BID
- Hamster plasma and lung C_{trough}: 5.5 and 3.0-fold above SARS-CoV-2 A549-ACE2 EC_{50}

ALG-097111 Plasma PK profile and lung concentration in female hamsters



SC administration of ALG-097111 when co-dosed with ritonavir, resulted in significant systemic exposure in female Syrian hamsters

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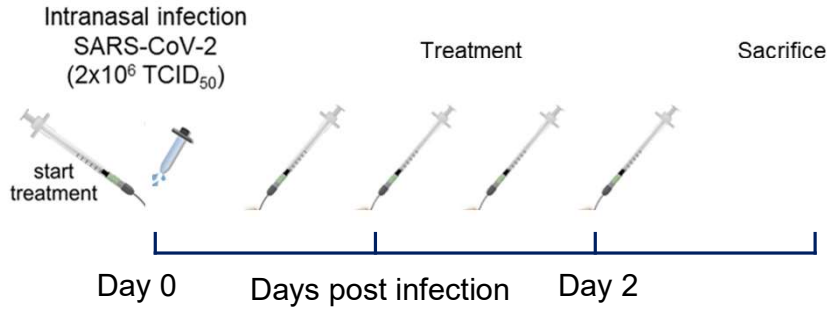
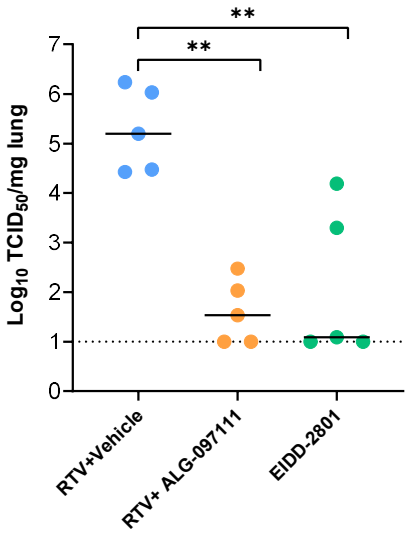
ALG-097111 Efficacy in SARS-CoV-2 Hamster Model



	SARS-CoV-2 on Day 2 versus control in lung	
	log_{10} ($TCID_{50}$/mg)	log_{10} (RNA copies/mg)
ALG-097111	-3.7	-3.5
Molnupiravir EIDD-2801	-4.1	-2.0

Infectious viral loads *in the lungs of SARS-CoV-2–infected hamsters at day 2 post-infection*



ALG-097111, a selective SARS-CoV-2 $3CL_{pro}$ inhibitor efficiently inhibits viral replication in the lungs of infected hamsters

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