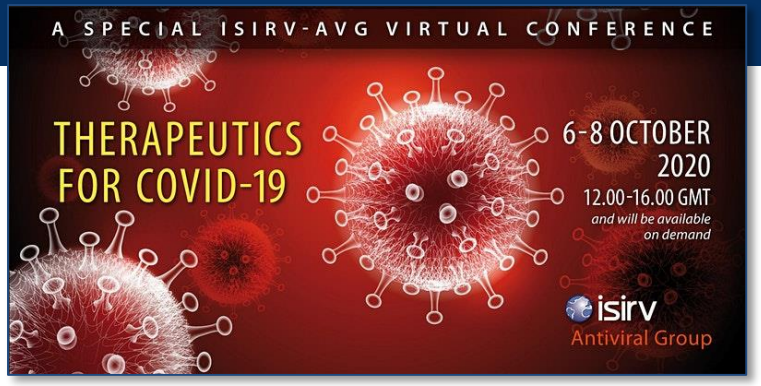
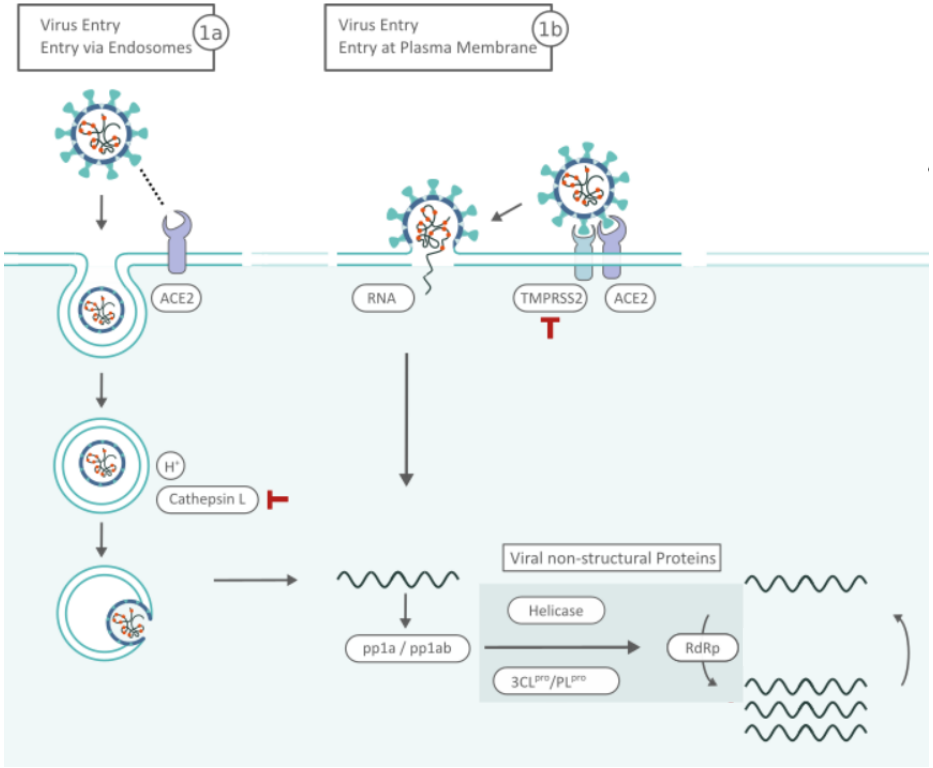


SELVA THERAPEUTICS

Blockage of Cathepsin L Activity by SLV213, a Novel Cysteine Protease Inhibitor, Prevents SARS-CoV-2 Viral Entry

Dr. Felix Frueh
Chief Science Officer
Selva Therapeutics

Host Protease Activity Is Needed for SARS-CoV-2 Cell Entry



- **Activation of the SARS-CoV-2 spike protein can be mediated via two host proteases:**
  - Cathepsin L, a cysteine protease
  - TMPRSS2, a serine protease

- ***In vitro* experiments have shown that:**
  - Blocking Cathepsin L can shut down viral entry completely,
  - Blocking TMPRSS2 partially shuts down viral entry,
  - Potential for synergy of blocking Cathepsin L and TMPRSS2

Source: https://www.antibodies-online.com/resources/18/5410/sars-cov-2-life-cycle-stages-and-inhibition-targets/

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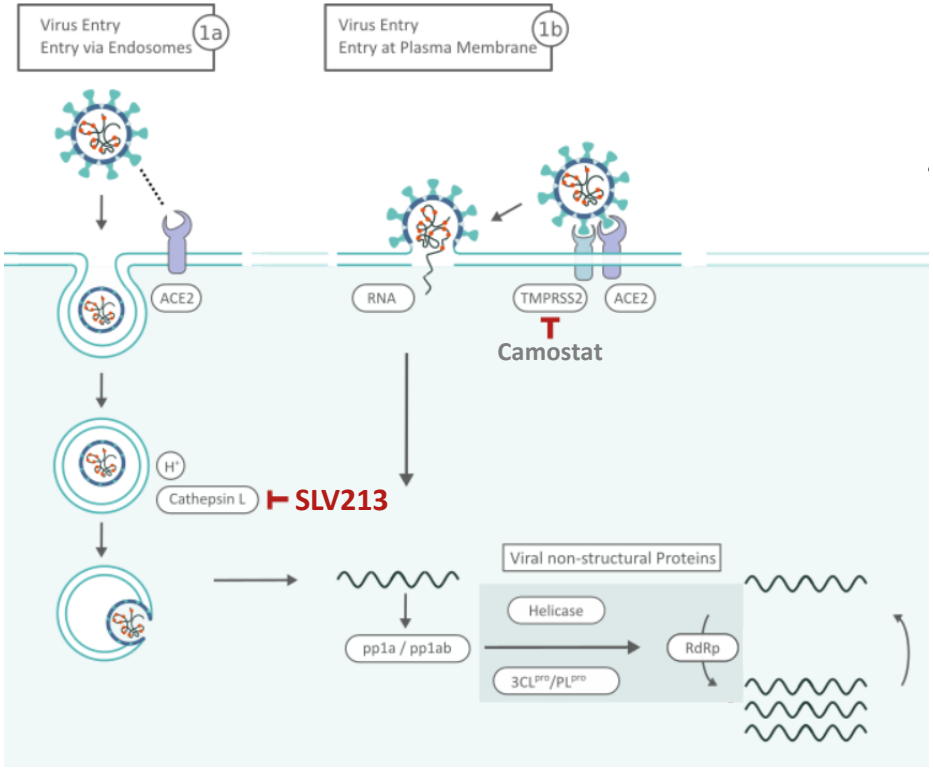

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SLV213 IS A POTENT INHIBITOR OF CATHEPSIN L

	Cruzain	Cathepsin L	Cathepsin B
Ki [nM]*	**0.23**	**0.25**	**14.4**
IC50 [nM]**		**0.2**	**5.7**
IC50 [nM]***		**<0.2**	**9**

* Selva internal data

** Chen et al. (2010, PLoS Neglected Tropical Diseases 4(9):e825)

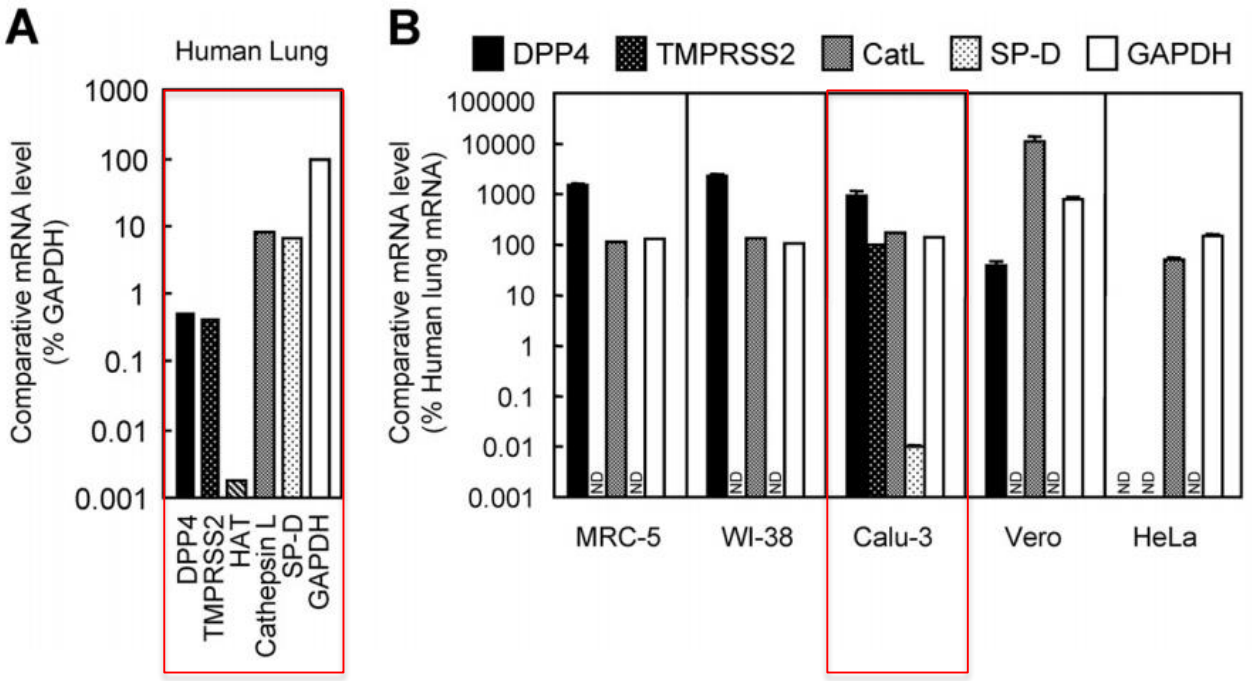
*** Ndao et al. (2014, Antimicrobial Agents and Chemotherapy 58(2):1167-1178)

Cathepsin L Cleaves Viral Spike Protein, SLV213 Prevents Cleavage

- Protein activity experiments demonstrate that Cathepsin L is cleaving the Spike protein in a dose-dependent manner (Cath L titration against fixed S protein)
- SLV213, when added, prevents Cathepsin L from cleaving the Spike protein
- Cathepsin B does NOT cleave the Spike protein

Thomas Meek, Texas A&M, pers. communication

CATHEPSIN L VS. TMPRSS2 EXPRESSION IN HUMAN LUNG

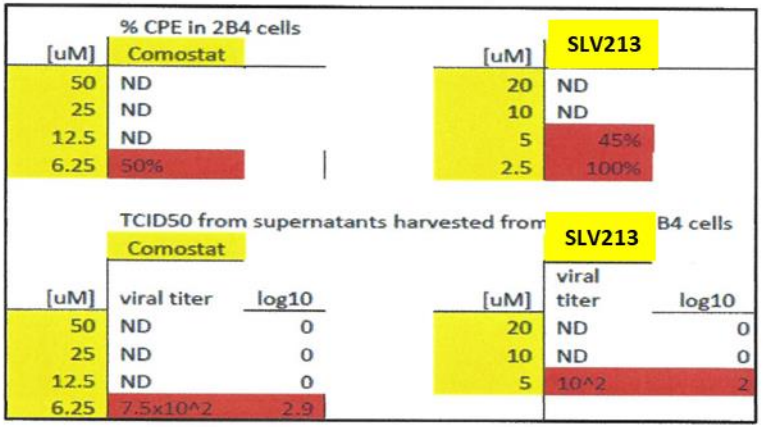


https://jvi.asm.org/content/87/23/12552

CALU-3 DATA FOR SLV213 AND CAMOSTAT

qRT-PCR cycle count

	Vero E6	A549	Calu-3
Cathepsin L	n/a	13.9	20.2
TMPRSS2	n/a	34.0	24.7



% CPE in 2B4 cells

[uM]	Comostat
50	ND
25	ND
12.5	ND
6.25	50%

[uM]	SLV213
20	ND
10	ND
5	45%
2.5	100%

TCID50 from supernatants harvested from B4 cells

Comostat

[uM]	viral titer	log10
50	ND	0
25	ND	0
12.5	ND	0
6.25	7.5x10^2	2.9

SLV213

[uM]	viral titer	log10
20	ND	0
10	ND	0
5	10^2	2

Selva (unpublished, data included in IND), Tseng et al. Univ. Texas Medical Branch

SLV213 In Vitro Activity Against SARS-CoV-2

Cell Line	Cell Type	Inhibition of Viral Infectivity EC_{50} (μM)
Vero E6	African Green Monkey kidney epithelial	0.62
A549	Human lung carcinoma transformed with ACE2 receptor	<0.08
Calu-3	Human lung carcinoma cells	~ 5

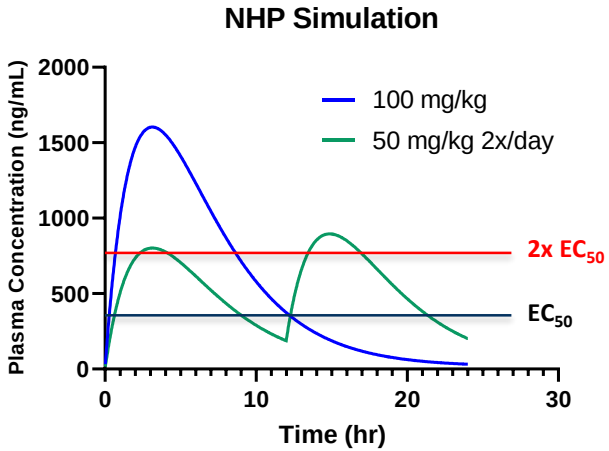
CPE-based assays
No cytotoxicity at >10μM

Selva (unpublished, data included in IND), Tseng et al. Univ. Texas Medical Branch

PRIMATE STUDY

- Pilot study to determine the potential for efficacy of SLV213 against SARS-CoV-2 in a non-human primate model (African Green Monkey)
- N=6 (2 controls, 4 on drug)
- Simple design:
  - Pretreatment of animals with SLV213 (100mg/kg) or placebo
  - Inoculation with virus at C_{max} (3-4 hours after first SLV213 dose)
  - Treatment of animals with SLV213 for 7 days (100mg/kg/day)
  - Necropsy on day 7
- Daily measurement of viral titers via BAL, nasal swabs, pharyngeal swabs
- Additional exams and organ assessment included

NHP Study: PK Model for QD vs. BID (100 mg/kg/day)



- PK simulation based on data from cynomolgus monkey study (200 mg/kg) assuming linear model
- EC_{50} values based on SARS-CoV-2 activity in Vero E6 cells

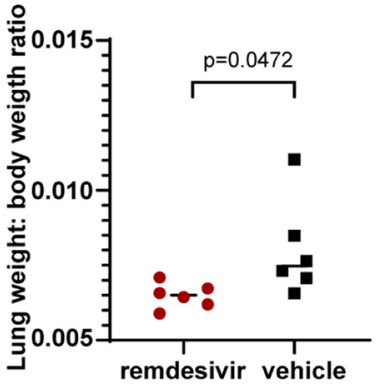
Key Observations:

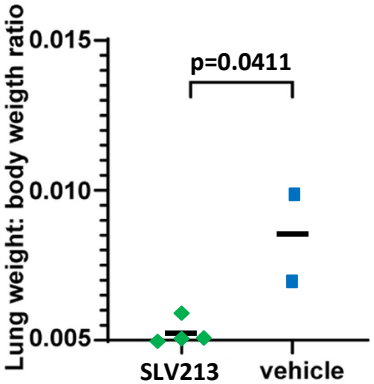
- QD dosing results in C_{max} >> 2x EC_{50}, whereas BID does not
- QD dosing has significantly higher AUC above 2x EC_{50} compared to BID dosing
- BID dosing results in C_{max} > EC_{50} twice per day, whereas QD does not
- BID dosing maintains concentrations above EC_{50} for a longer duration than QD

Selva data, unpublished

PRIMATE STUDY: PRELIMINARY FINDINGS FROM GROSS PATHOLOGY

	Animal ID	Weight [kg]	Lung weight [g]				Lymph enlargement [fold]
			Left lung	Right lung	Total	% of weight	
Vehicle	51	6.00	29.02	29.79	58.81	0.98%	3
	54	5.75	14.83	23.42	38.25	0.67%	3
SLV213	49	6.55	19.06	14.43	33.49	0.51%	2.5
	50	6.70	21.72	16.84	38.56	0.58%	2
	52	5.80	13.06	17.22	30.28	0.52%	2
	53	6.05	12.79	16.99	29.78	0.49%	2





https://www.nature.com/articles/s41586-020-2423-5

Selva data, unpublished

SLV213 Preclinical Safety Assessment Is Complete

- **Pharmacokinetics/ADME**
  - Readily absorbed after oral dosing (T_{max} ~1-4 hrs; bioavailability ~15-20%)
  - Half-life in monkeys (2-6 hrs) supports daily administration in humans
  - Liver is major organ of distribution/metabolism, with excretion primarily via feces
- **Safety Pharmacology**
  - hERG channel inhibition EC_{50} (18.3 µM) is 10 to 100-fold greater than concentrations expected *in vivo*
  - No significant effects on ECG, blood pressure, or body temperature.
  - No effects on pulmonary function or neurobehavioral assessment in rats (15, 50 or 150 mg/kg)
- **Toxicology**
  - Liver is target organ for toxicity – reversible elevation of transaminases observed at high doses
  - Emesis (dog, monkey) and effects on body weight (rat, dog) observed at high doses only
  - No genotoxicity signal in 3 different GLP studies
  - No unexpected observations in ongoing 28-day GLP oral toxicity study in dog (in-life completed)

SUMMARY

- SLV213 is a potent inhibitor of human Cathepsin L
- Strong *in vitro* inhibitory effect preventing SARS-CoV-2 viral infection
- *In vivo* non-human primate study ongoing; promising early results
- Clean safety profile
- IND filed
- Phase 1 clinical trial to start in late October
- Potential for synergistic effect with other host protease inhibitor (e.g. camostat)
- Potential for synergistic effect with antivirals targeting viral proteins (e.g. remdesivir)

Thank You.

ffrueh@selvarx.com