Development of camostat-related compounds for COVID-19 and other coronavirus infections

Joseph M. Vinetz, M.D.
Professor of Medicine
Section of Infectious Diseases
Department of Internal Medicine

Yale SCHOOL OF MEDICINE

The Problem:
No outpatient treatment for COVID-19

- Supportive—isolation, quarantine, refer to hospital
- Vaccines on horizon—treatment still necessary
- Antivirals—none
  - Antibodies available; expensive and challenging to give
- Hoped-for outcomes of a new orally available drug—a **magic** pill
  - A pill to be taken outside of hospital
  - To treat sick people (feel better, prevent disease progression)
  - To prevent infection after exposure (prophylaxis)
  - To prevent transmission (public health approach)
- We need a rationale way to open up our country, our economy, our world

- <u>Cold viruses don't have treatments either</u>

Executive Summary

- SARS-CoV-2 (the virus) and COVID-19 (the disease) are causing untold global harm to human health
- There is no anti-viral treatment for early COVID-19 infection to forestall complications
  - A drug to prevent SARS-CoV-2 infection and transmission would have global importance including virus eradication
  - Such a drug might be active against **other and future coronaviruses** given known mechanism of action
  - Global interest in camostat, strong fundamental data
- **Yale has established a best-in-world outpatient clinical trial platform to test treatments of early COVID-19 infection**
- Camostat, a repurposed oral serine protease inhibitor is in Phase II clinical trial at Yale for early, outpatient, treatment of COVID-19, requires molecular optimization
- Global market for a safe and effective anti—coronavirus drug is in the many $billions

Experienced Scientific, Development and Business Team

Joseph M. Vinetz, M.D.

Professor of Medicine
Section of Infectious Diseases

Department of Internal Medicine

***Highly experienced medicinal chemists with long-term industry experience**

IP is Yale's

Harrington Discovery Institute Team

- Mukesh Jain, MD FAHA, Chief Scientific Officer
- Diana Wetmore, PhD, VP of Therapeutics Development
- ***Kaushik Dave, PhD, MBA, R.Ph, TD Strategic Advisor**
- Perry Molinoff, MD, TD Strategic Advisor
- Donald Stanski, MD, TD Strategic Advisor
- ***William Greenlee, PhD, TD Strategic Advisor**
- Vadim Bichko, PhD, TD Strategic Advisor
- Jeffrey Klein, PhD MBA, Project Manager, Therapeutics Development

David Lewin, PhD

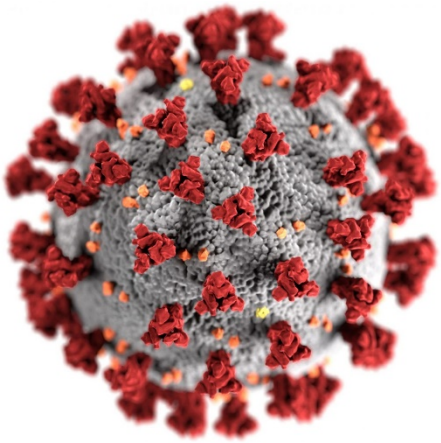
Director Bus. Dev.
Yale, OCR

Advisor/IP Management

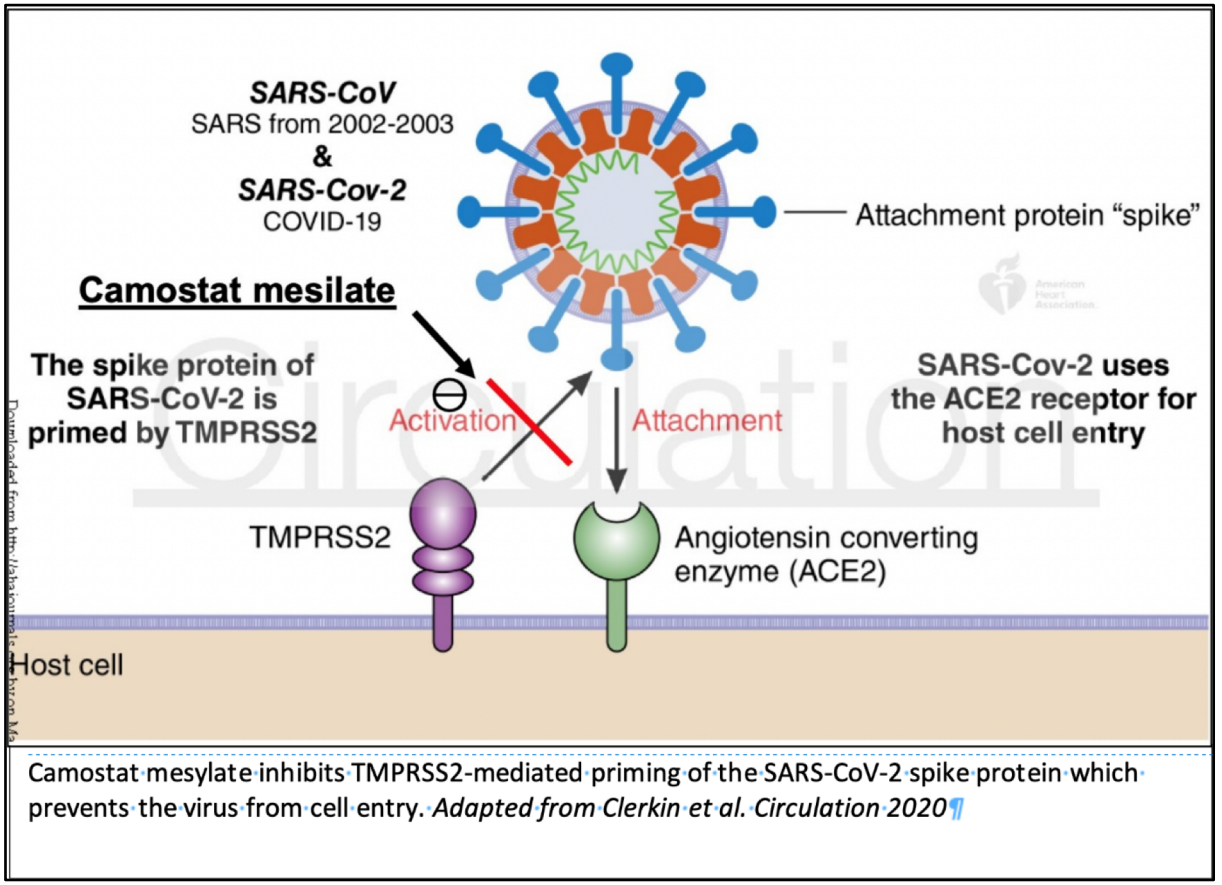
david.lewin@yale.edu

Mechanism of anti-viral action of **camostat** for SARS-CoV-2

The respiratory epithelial cell surface serine protease, TMPRSS2, is both necessary and sufficient for viral entry.



CDC, 2020



The idea is that camostat prevents virus from infecting respiratory lining cells

Repurposed drug, i.e. already available (Japan, used for pancreatitis)

Hoffmann et al., 2020, Cell *181*, 271–280
April 16, 2020 © 2020 Elsevier Inc.
https://doi.org/10.1016/j.cell.2020.02.052

Camostat protects mice *in vivo* against SARS-CoV

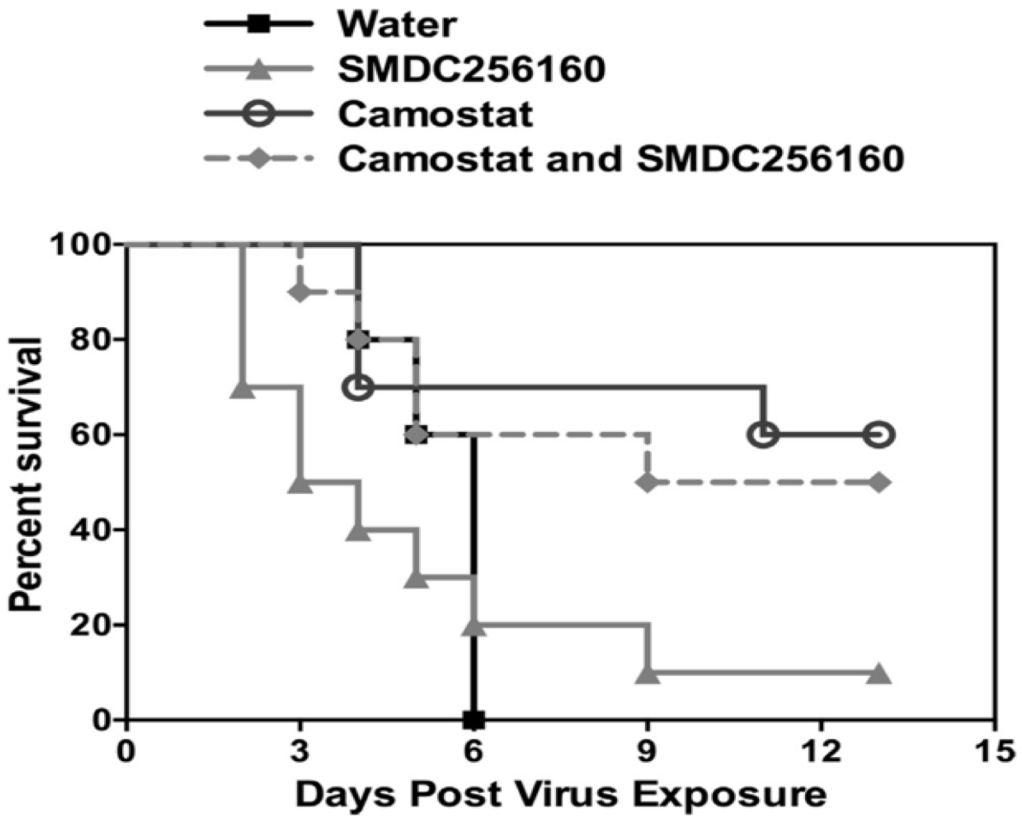


Fig. 3. Effects of per os administered SMDC256160 and/or camostat on survival of BALB/c mice infected with a lethal SARS-CoV. Ten mice per group were dosed twice a day by oral gavage with SMDC256160 and/or camostat or diluent alone (sterile water) for 9 days beginning 10 h prior to infection with 10,000 pfu of mouse-adapted SARS-CoV.

Y. Zhou et al. / Antiviral Research 116 (2015) 76–84

Yale's best-in-world outpatient clinical trial platform for COVID-19

Design: Randomized, double-blind, placebo-controlled

Hypothesis: Camostat mesylate will have an *in vivo* anti-viral effect on SARS-CoV-2 that will diminish clinical signs and symptoms of COVID-19 and reduce viral load in the respiratory tract

Study population:

- Ambulatory (outpatients)
- Early infection

Participants: COVID-19+ within 3 days of a positive report

- Pilot phase: N=114, viral load outcome; Clinical outcome phase, N=600
- Primary outcome: every other day NP swab or saliva tests
- Daily symptom score and clinical assessments; O2 levels (pulse oximeter)

Outcomes:

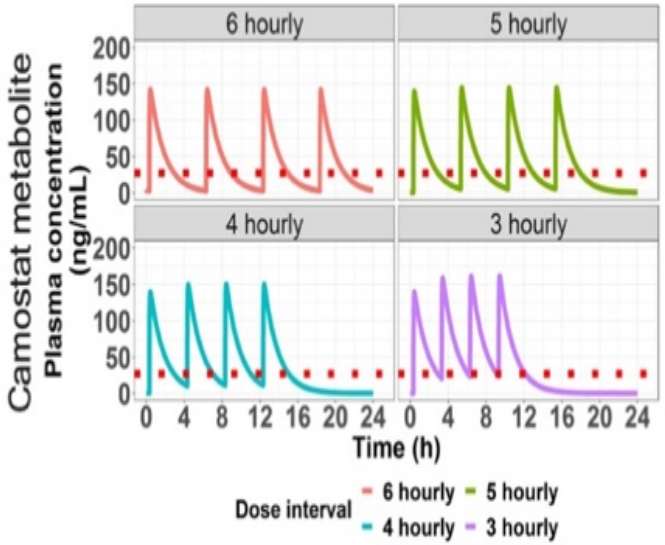
- Primary: Measurement of respiratory viral load (does drug reduce/eliminate virus?)
- Secondary: Risk for hospitalization, complications

Limitations of Camostat

- Designed for **local effect in the gut**:
  - Oral bioavailability, PK/PD not optimal
- Dosing frequency QID, compliance challenges
- PK/PD need to be improved via medchem

GOAL – A potent and selective TMPRSS2 inhibitor with robust anti-COVID-19 efficacy and PK/ for once-daily oral dosing in humans

Relationship between plasma concentration and viral inhibitory concentration



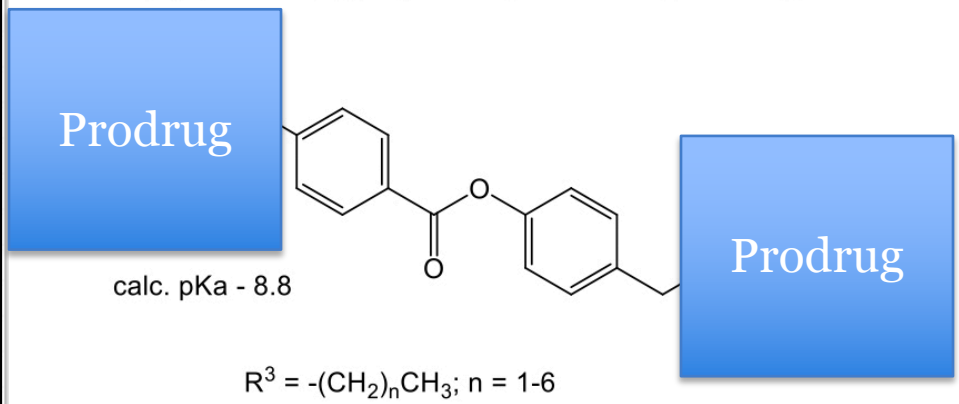
EC50 of camostat 0.087 μM

Hoffmann et al.(2020) AAC.

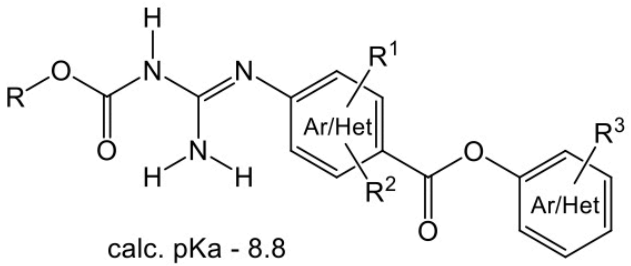
200mg QID Dose interval	Duration over 0.087 μM (hour/day)	Average concentration
6 hourly	10.4	0.12 μM
5 hourly	10.5	0.12 μM
4 hourly	10.6	0.12 μM
3 hourly	11.0	0.12 μM

Complementary medchem approaches to optimize TMPRSS2 Camostat-related inhibitors

Approach 1 - Improved Camostat Prodrug*



Approach 2 - Camostat Analogs with Improved Selectivity



R = -$(CH_2)_nCH_3$; n = 1-6

$R^{1,}$ R^2, R^3 = -alkyl, halogen, hydroxyl, alkoxy, cyano, amide

*Camostat mechanism of action: competitive antagonist, slow off rate; Unknown effect on TMPRSS2 expression levels

Approach 3 - Identify Novel Non-Covalent Inhibitors for TMPRSS2

Non-covalent inhibitors of serine proteases have been discovered and marketed.

Proposed Use of Blavatnik Funds

- Stage 1: 6 months
  - Preliminary medicinal chemistry ($100K) at Jubilant, Pirimal, or the like, inclusive of established TMPRSS2 activity assay*
- Stage 2: 9 months depending upon medchem product(s)
  - Preliminary IP & Oral PK/PD for top 5 compounds – $60K
  - PanLabs tox & microsomal stability for best 2-3 compounds - $20K
  - Test against other CoVs ($20K)
- Stage 3: 10-18 months
  - Animal efficacy model for SARS-CoV-2 and/or other CoV ($100K)
    - Charles River: hamster, ACE2-transgenic mice
- **Total: $300K**

*An Enzymatic TMPRSS2 **Assay** for Assessment of Clinical Candidates and Discovery of Inhibitors as Potential Treatment of COVID-19.
Shrimp JH, Kales SC, Sanderson PE, Simeonov A, Shen M, Hall MD.
ACS Pharmacol Transl Sci. 2020 Sep 7;3(5):997-1007.
doi: 10.1021/acsptsci.0c00106