Repurposing of clinically-approved drugs for the treatment of COVID-19

Kris White, Romel Rosales, Elena Moreno, Thomas Kehrer, Lisa Miorin, David Gordon, Tia Tummino, Khushboo Bafna, B. Harish, C. Royer, Theresa Ramelot, Thomas Acton, Robert Krug, Gaetano T. Montelione, Brian Shoichet, Kevan Shokat, Nevan Krogan, Adolfo García-Sastre

Icahn School of Medicine at Mount Sinai

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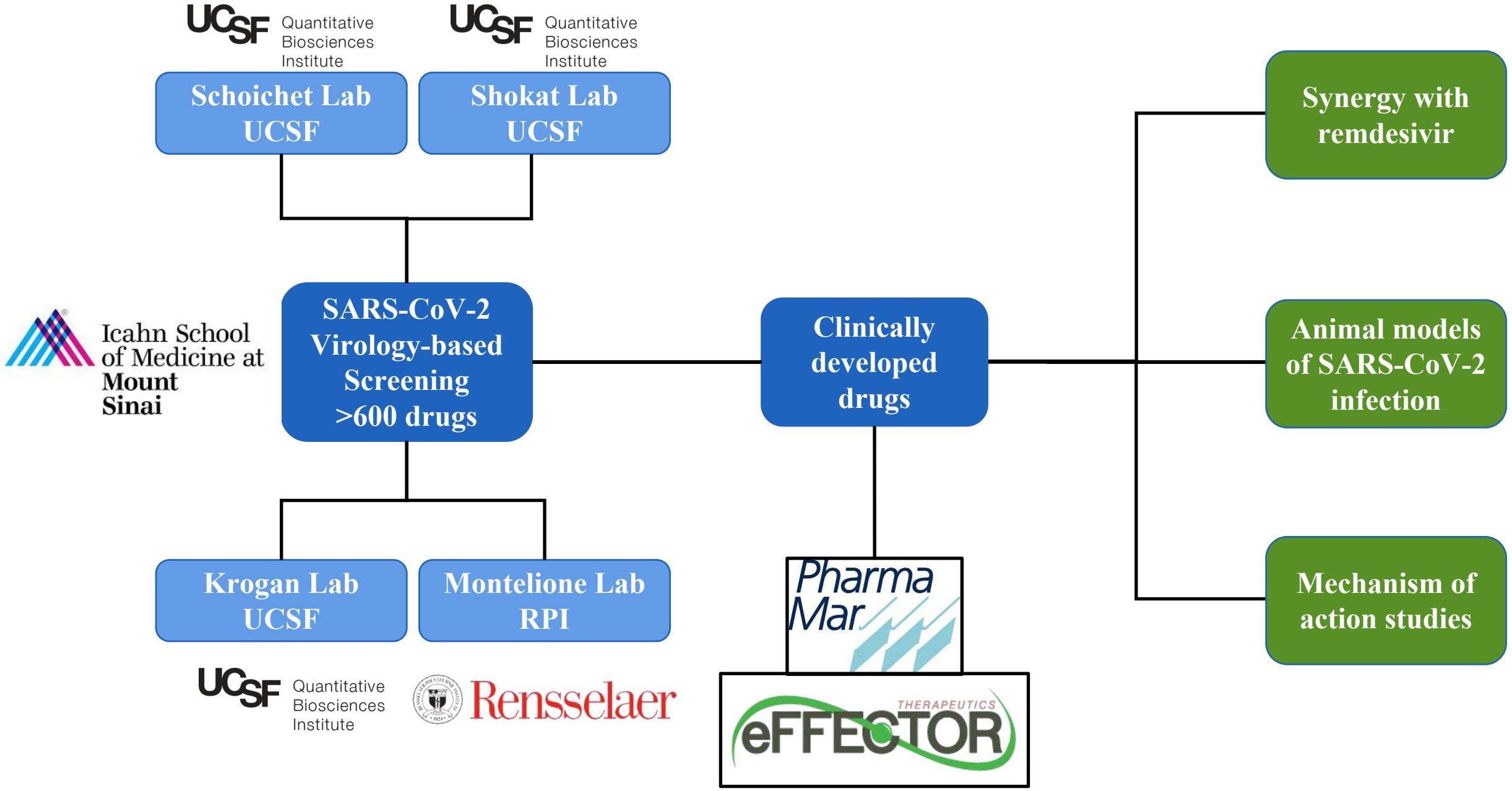
eFFECTOR THERAPEUTICS

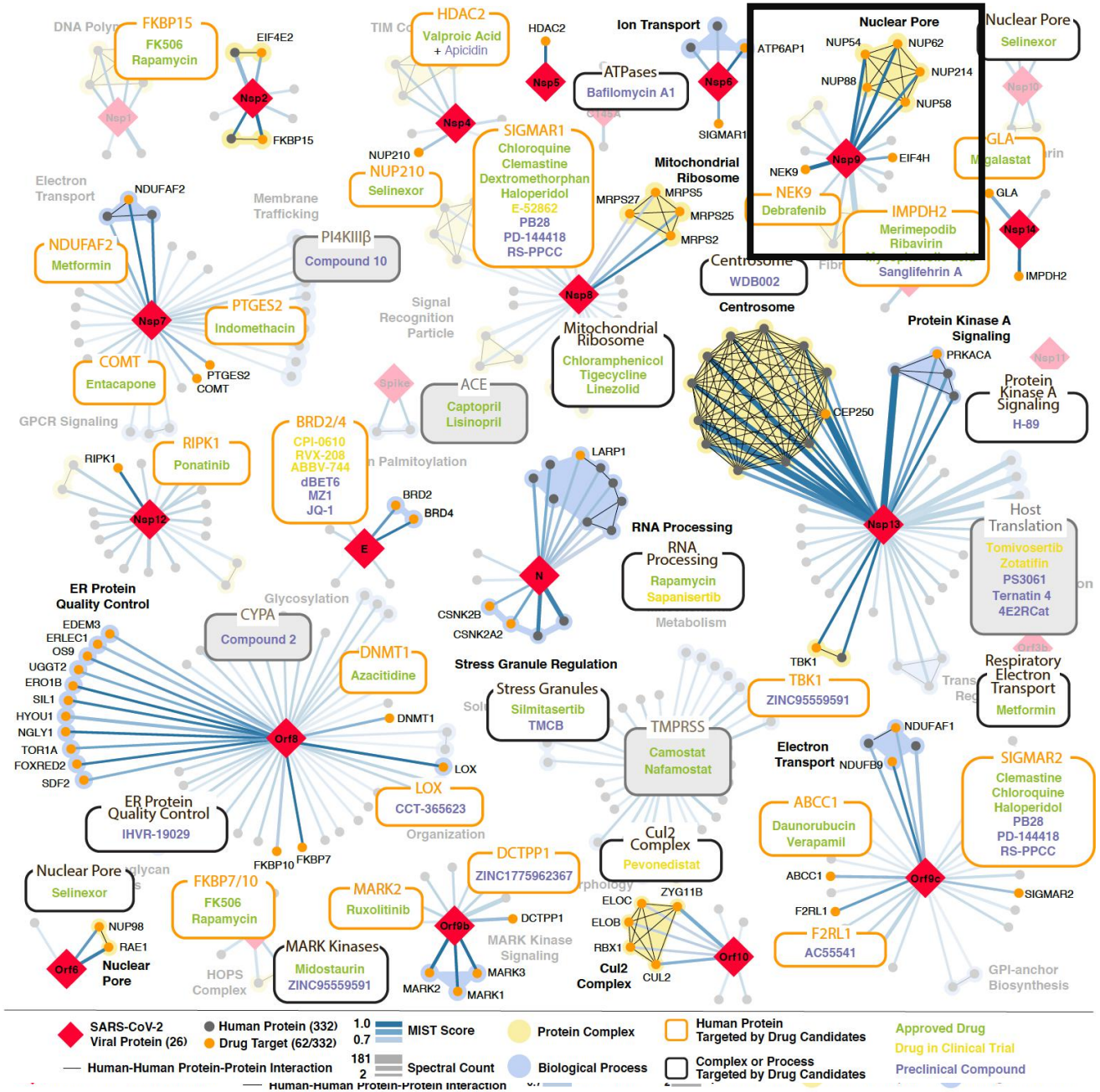
PharmaMar

Drug Repurposing for SARS-CoV-2 Antivirals



Protein-Protein Interaction Map

Proteomics
David Gordon
and
Nevan Krogan



Cheminformatics
Kevan Shokat
and
Brian Schoichet

Gordon DE, et al.
Nature. 2020

Protein-Protein Interaction Map

Proteomics
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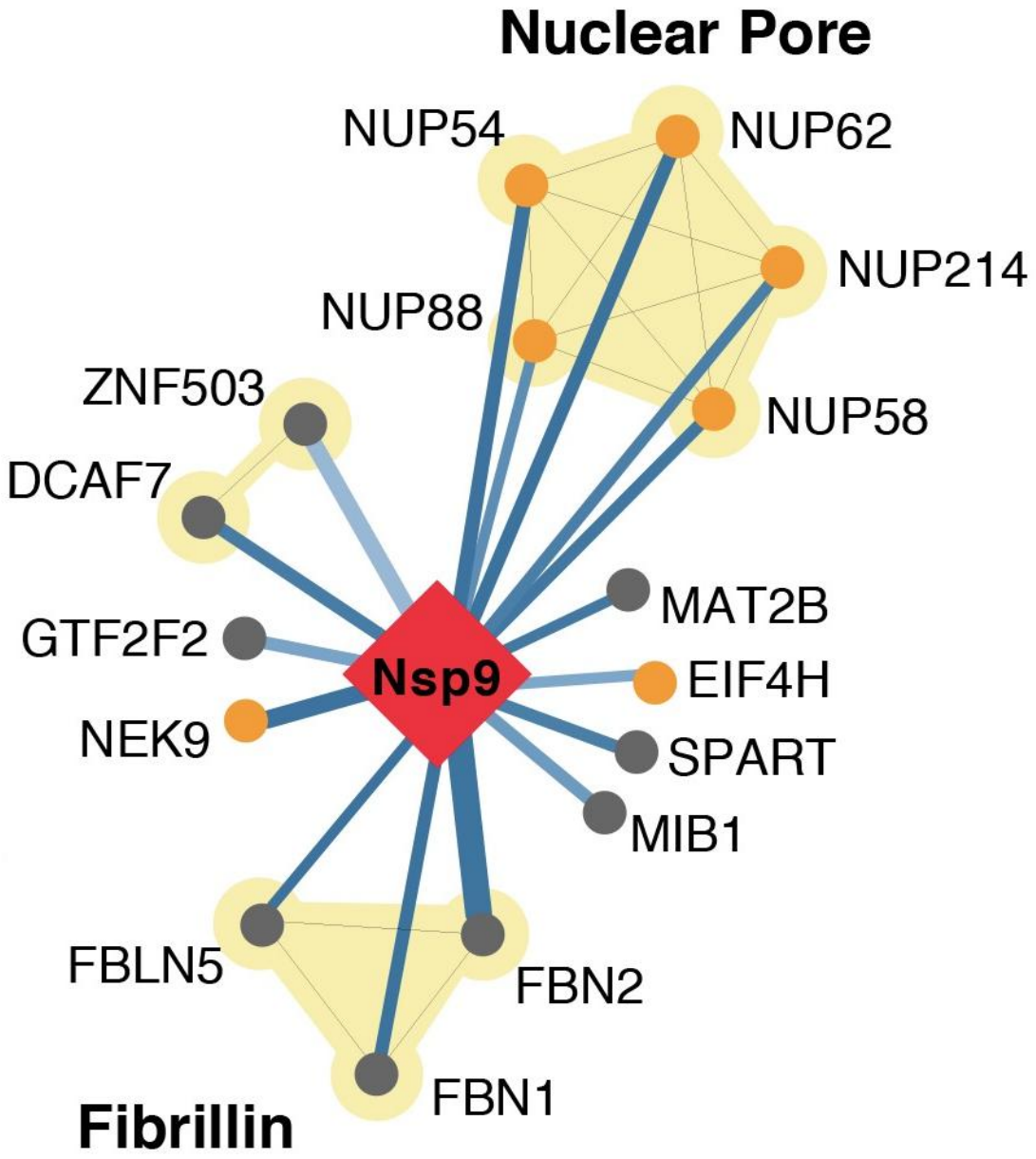
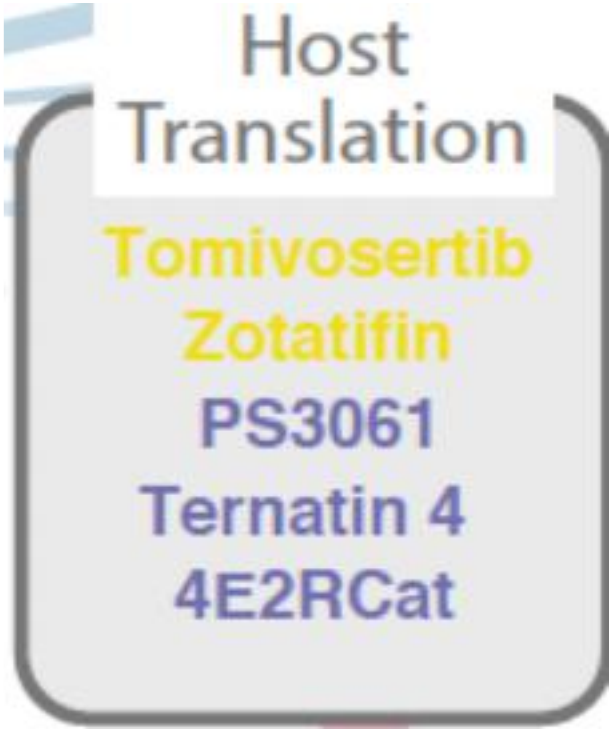
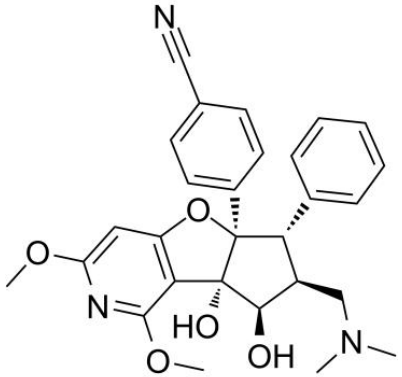




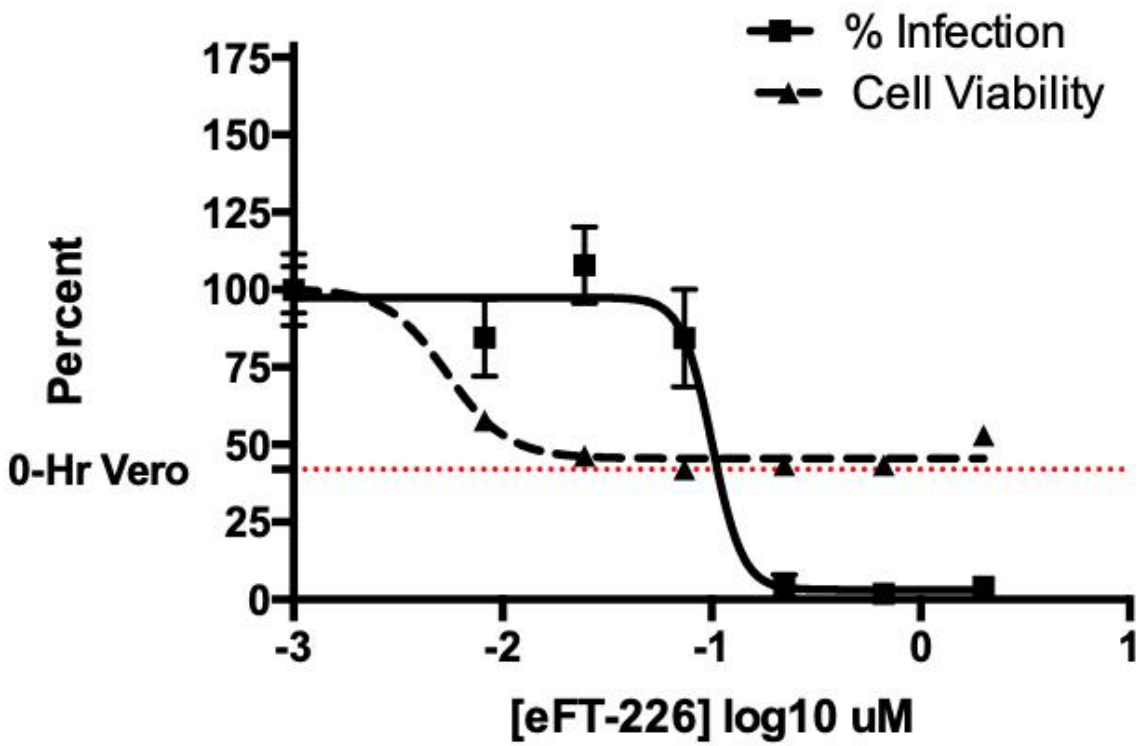
Cheminformatics
Kevan Shokat
and
Brian Schoichet

Translation Inhibitors

Zotatafin



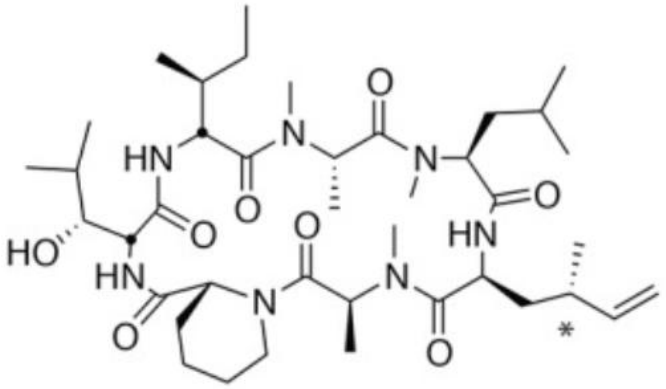
- **Target: eIF4A**
- **Phase I/II (Cancer)**



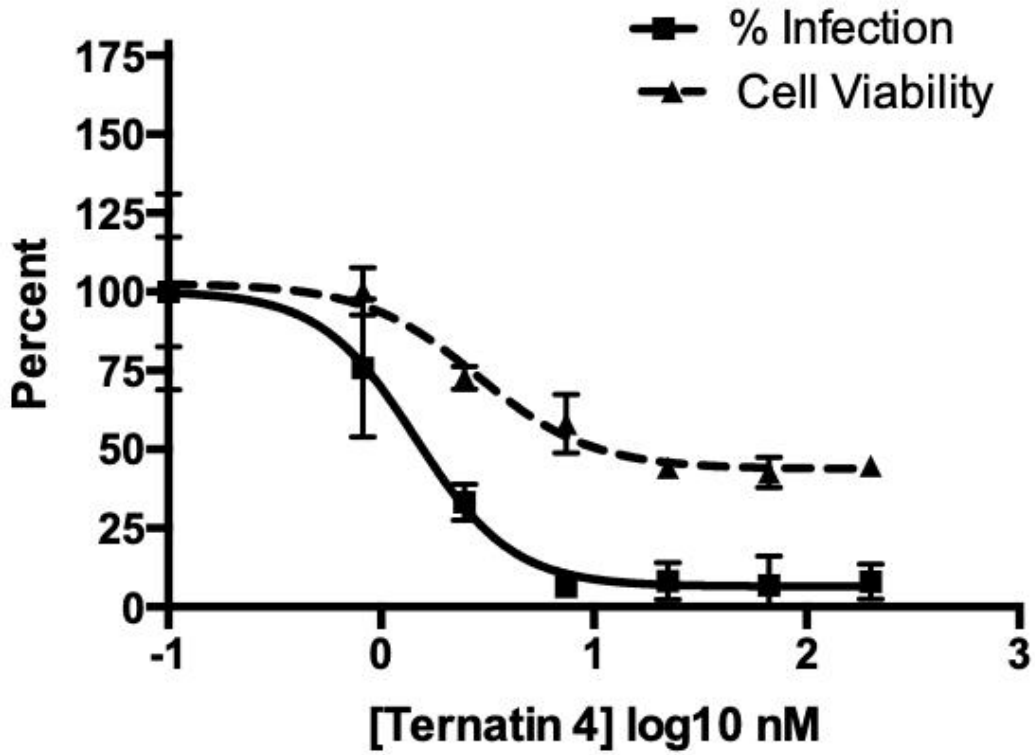
	IC50	IC90
Zotatafin	101 nM	154 nM
Remdesivir	10.4 nM	24.2 nM

Translation Inhibitors

Ternatin 4



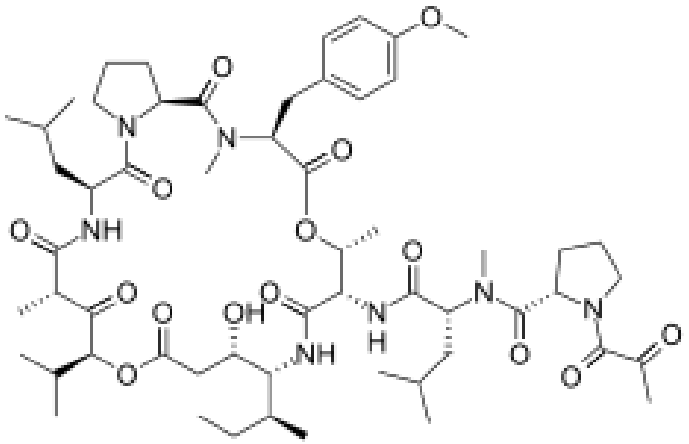
- Cyclic peptide
- Target: eEF1A
- Experimental



	IC50	IC90
Ternatin 4	1.6 nM	8.0 nM
Remdesivir	10.4 nM	24.2 nM

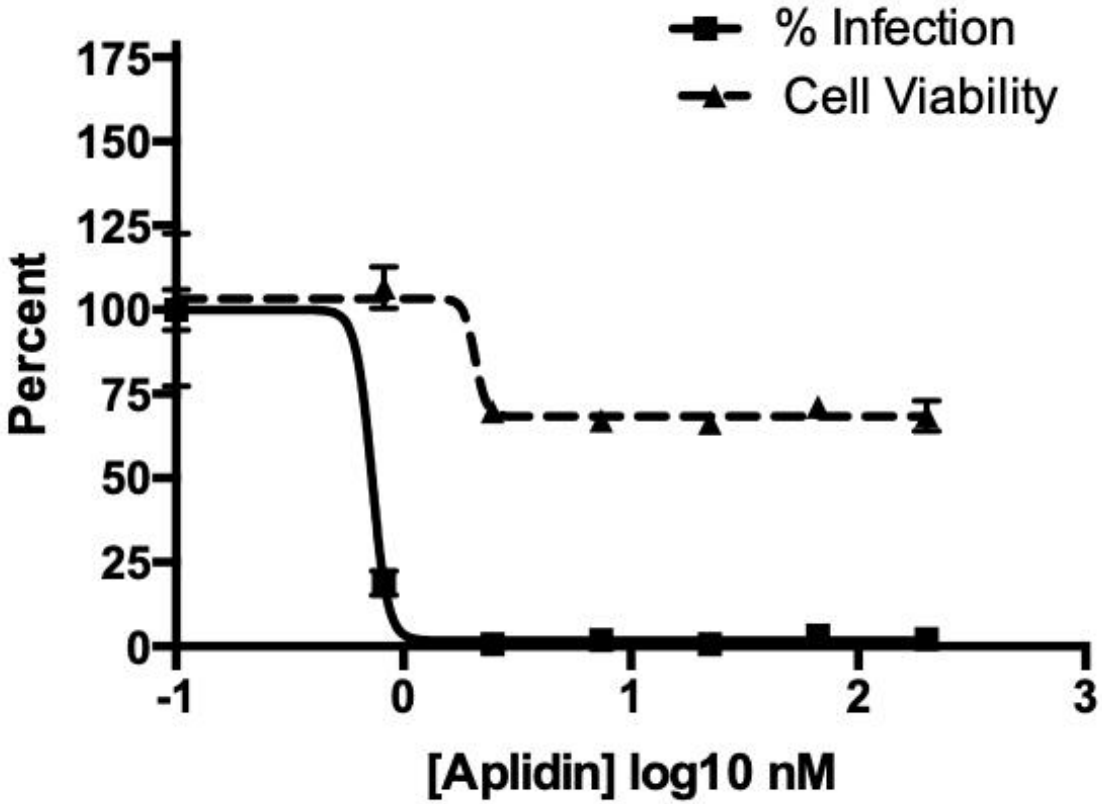
Translation Inhibitors

Aplidin

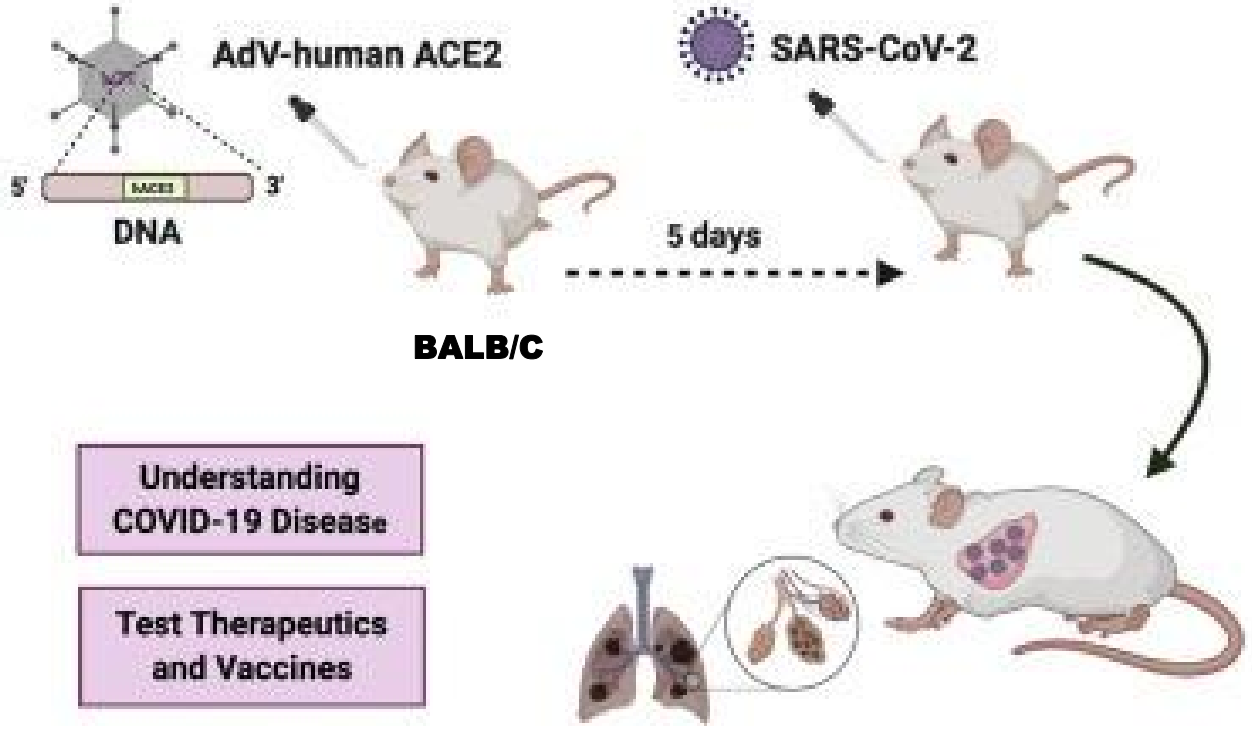


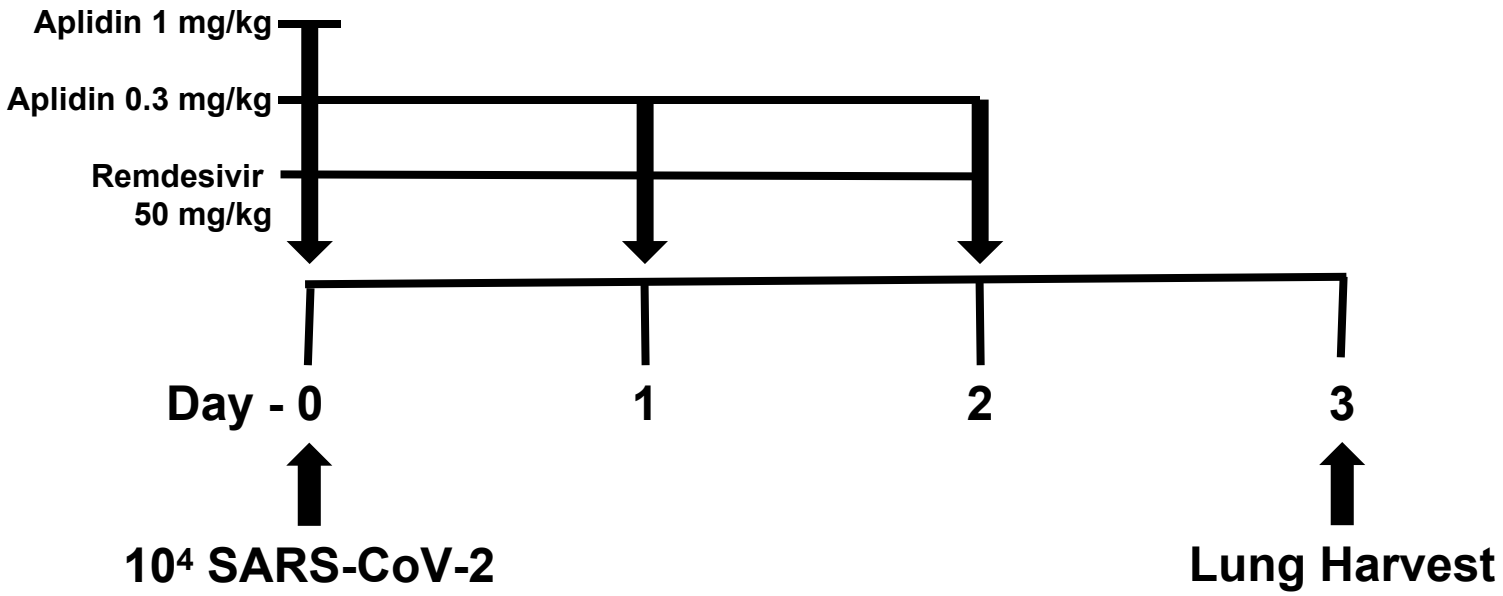
- **Cyclic peptide**
- **Target: eEF1A**

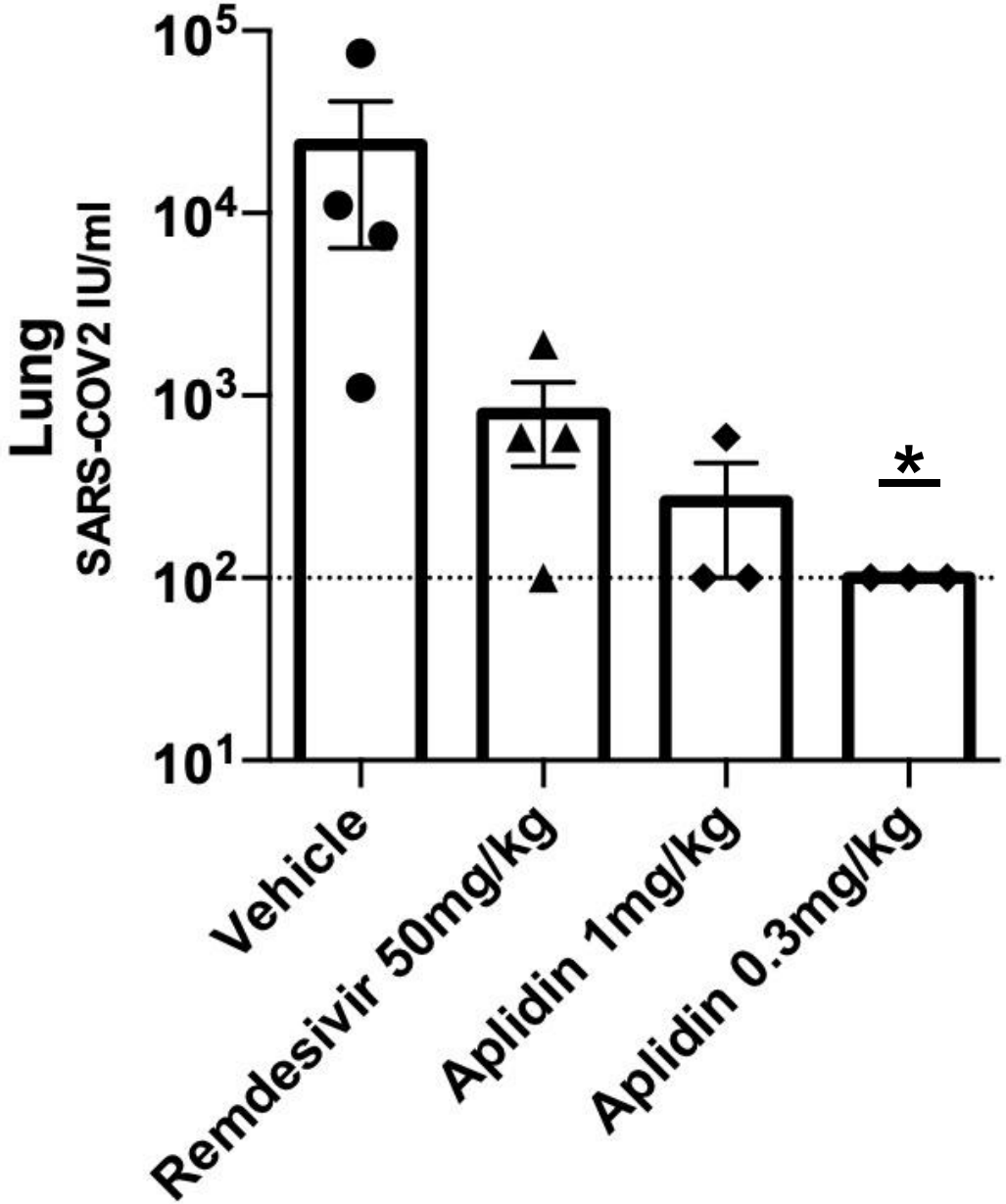
- **Approved (Australia) Multiple Myeloma**



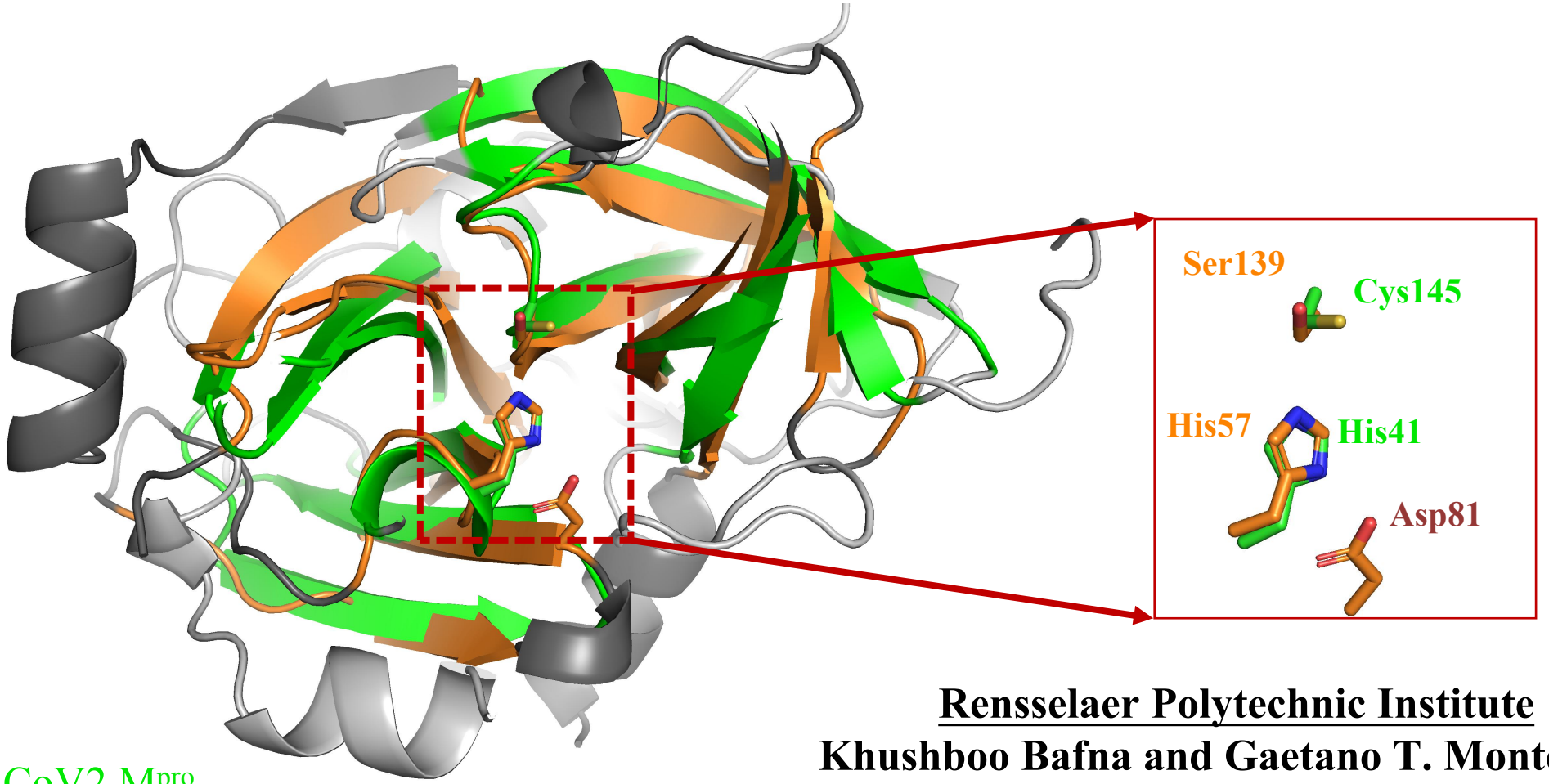
	IC50	IC90
Aplidin	0.7 nM	0.9 nM
Remdesivir	10.4 nM	24.2 nM


AdV-human ACE2
SARS-CoV-2
5'
3'
DNA
5 days
BALB/C
Understanding COVID-19 Disease
Test Therapeutics and Vaccines


Aplidin 1 mg/kg
Aplidin 0.3 mg/kg
Remdesivir 50 mg/kg
Day - 0
1
2
3
10⁴ SARS-CoV-2
Lung Harvest


Lung
SARS-COV2 IU/ml
10⁵
10⁴
10³
10²
10¹
*
Vehicle
Remdesivir 50mg/kg
Aplidin 1mg/kg
Aplidin 0.3mg/kg

SARS-CoV2 Main Protease



SARS-CoV2 M^{pro}

HCV protease NS3/4A

Rensselaer Polytechnic Institute

Khushboo Bafna and Gaetano T. Montelione

University of Texas at Austin

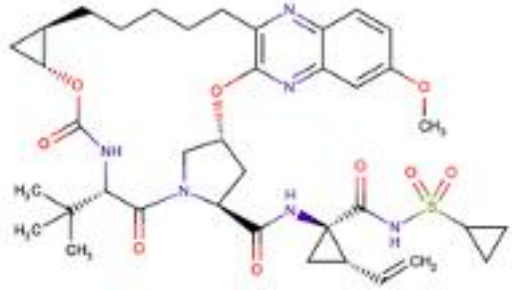
Robert M. Krug

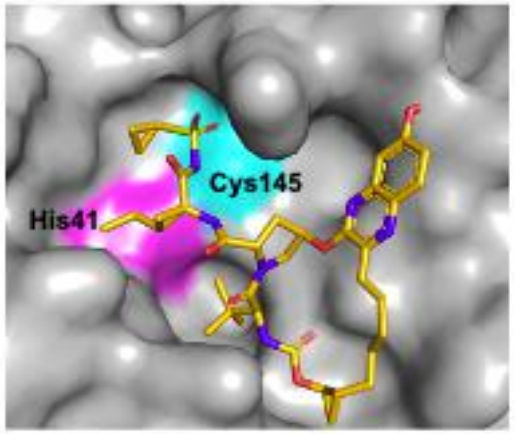
HCV 3C/4A Protease Inhibitors

Inhibitor	Identifier of Protease Inhibitor	*AutoDock* Score (kcal/mol) Lowest "Energy"
HCV NSP3/4A Protease Inhibitor Drugs		
Vaniprevir	VAN	-10.95
Simeprevir	SIM	-10.75
Paritaprevir	PAR	-10.71
Danoprevir	DAN	-9.99
Narlaprevir	NAR	-9.80
Grazoprevir	GRZ	-9.71
Glecaprevir	GLE	-9.51
inhibitor 13b	13b	-9.17
Boceprevir	BOC	-9.13
Telaprevir	TEL	-9.05
Asunaprevir	ASU	-8.37

Example of Docking Pose

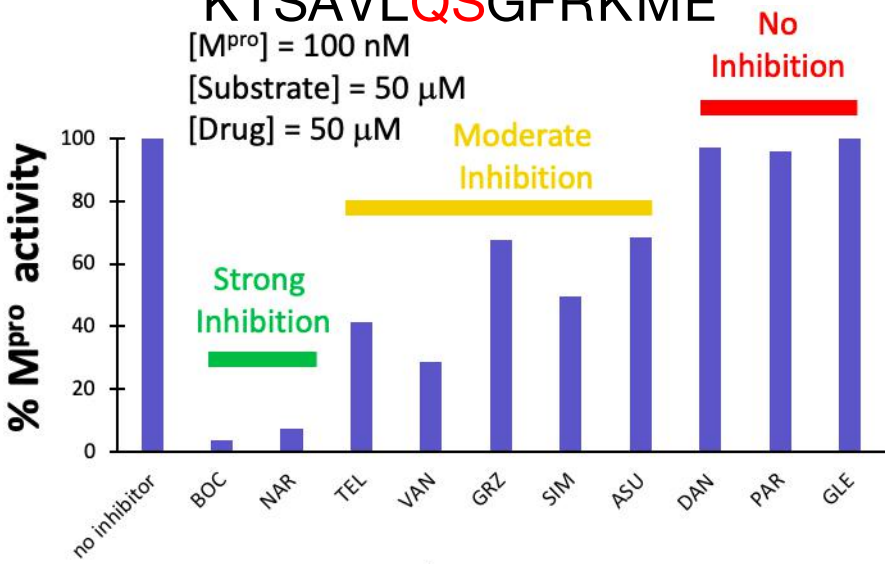
grazoprevir





1D ^{1}H-NMR Protease Assay

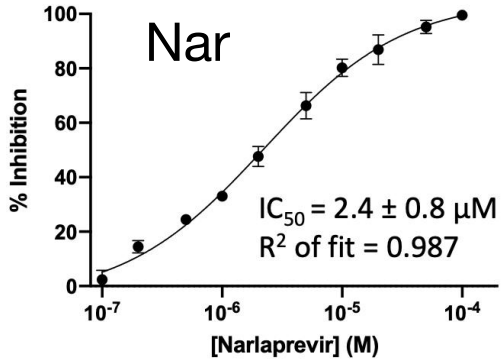
Substrate:
KTSAVLQSGFRKME



HCV NS3/4A protease inhibitors

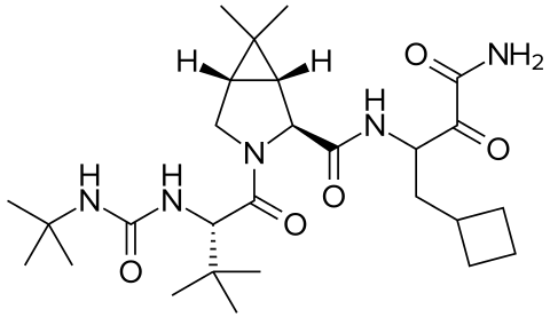
FRET Protease Assay

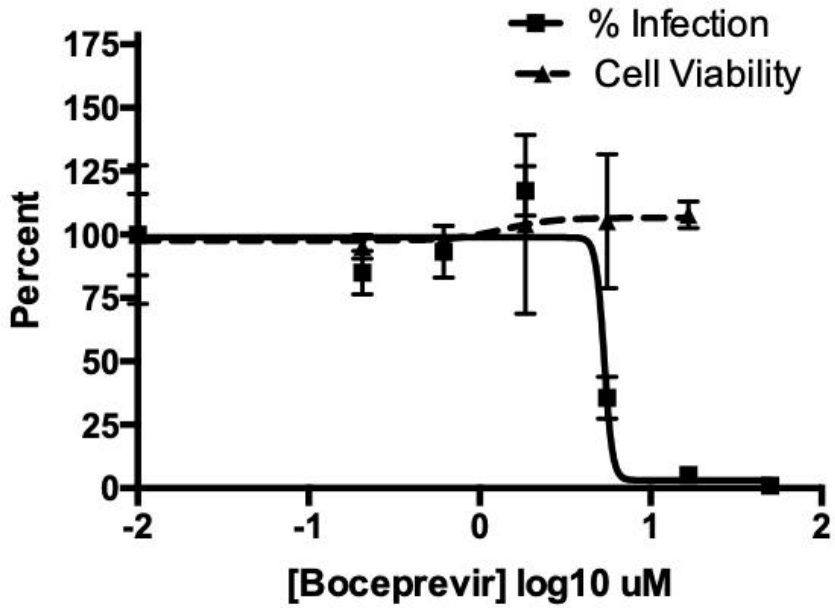
(Dabsyl)-DKTSAVLQSGFRKME-(Edans)



HCV Protease Inhibitors

Boceprevir

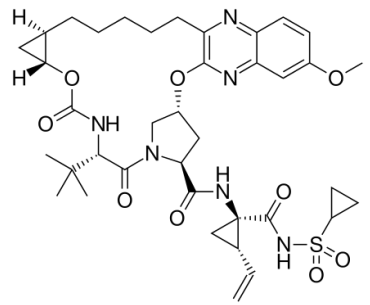


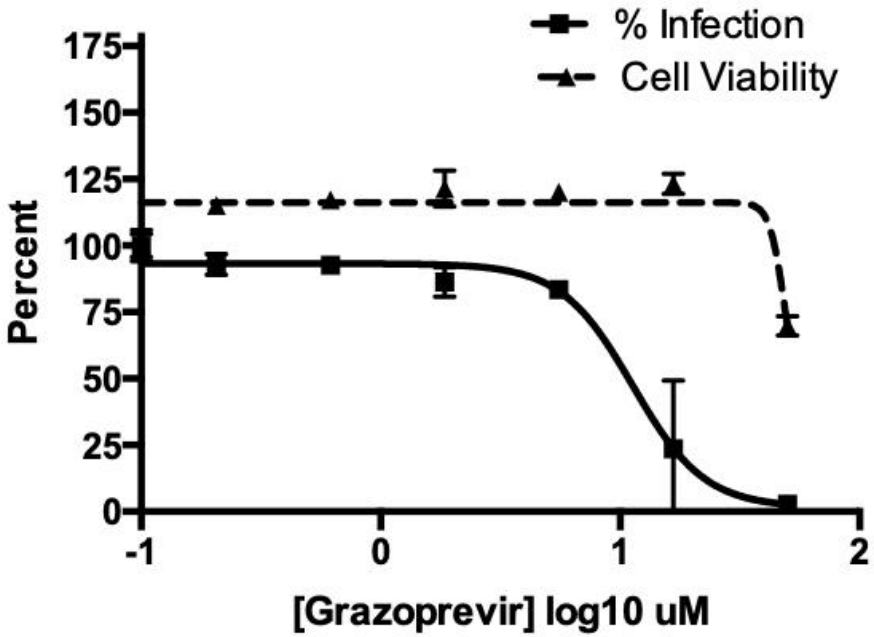


IC50	IC90
5.4 uM	6.2 uM

- **Predicted Target: Viral Main Protease (MPro)**
- **FDA-Approved HCV**

Grazoprevir

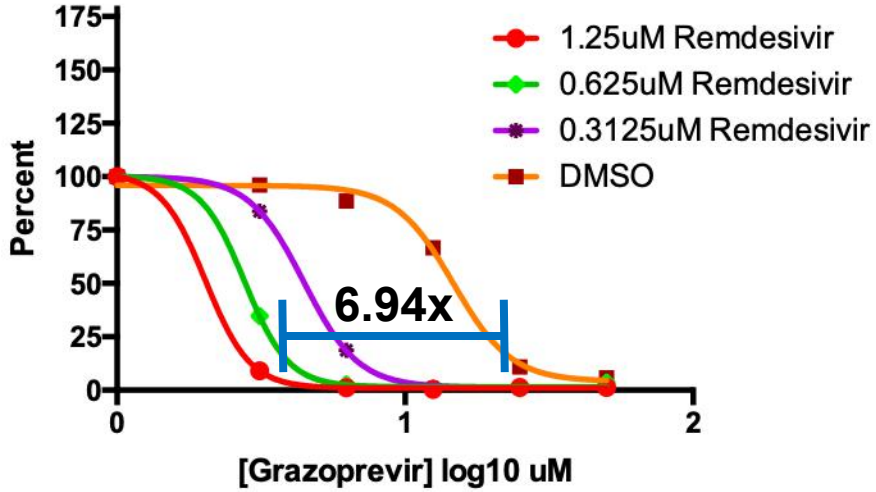


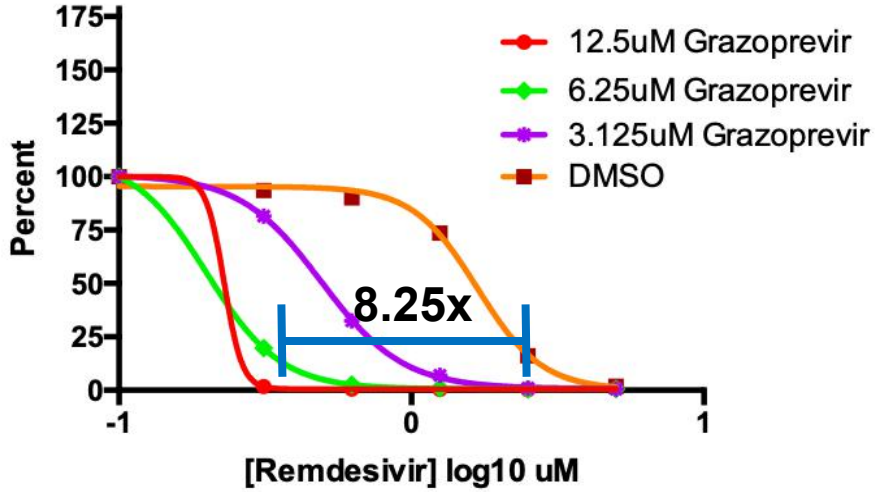


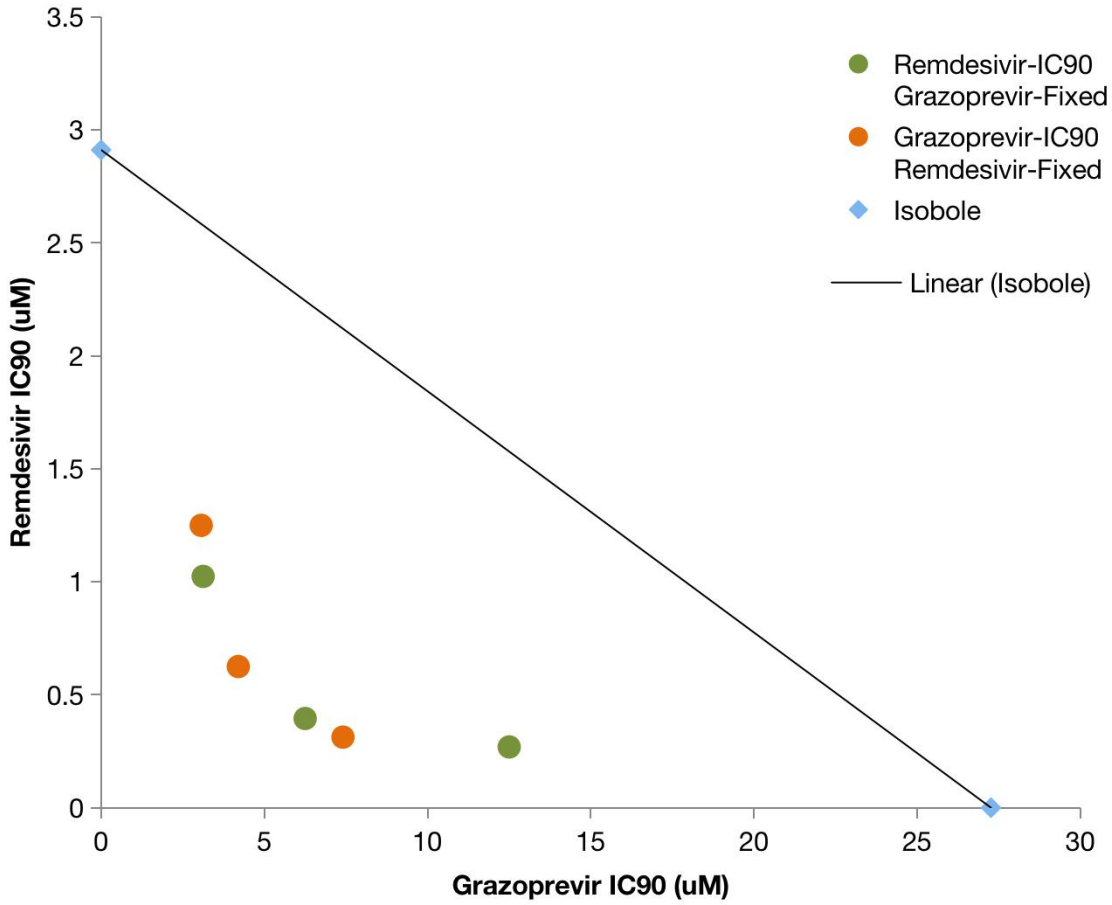
IC50	IC90
10.9 uM	24.8 uM

- **Predicted Target: Viral Main Protease (MPro)**
- **FDA-Approved HCV**

HCV Protease Inhibitors







Combination Index = 0.445±0.087

Synergistic

Icahn School of Medicine at Mount Sinai

UCSF Quantitative Biosciences Institute

Rensselaer

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Elena Moreno Del Olmo
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Romel Rosales
Carles Martinez-Romero
Nacho Mena
Maite Sanchez-Aparicio
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Beril Tutuncuoglu
Helene Foussard
Jyoti Batra
Kelsey Haas
Maya Modak
Minkyu Kim
Paige Haas
Benjamin Polacco
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