



A SARS-CoV-2 Protein Interaction Map Reveals Targets for Drug-Repurposing

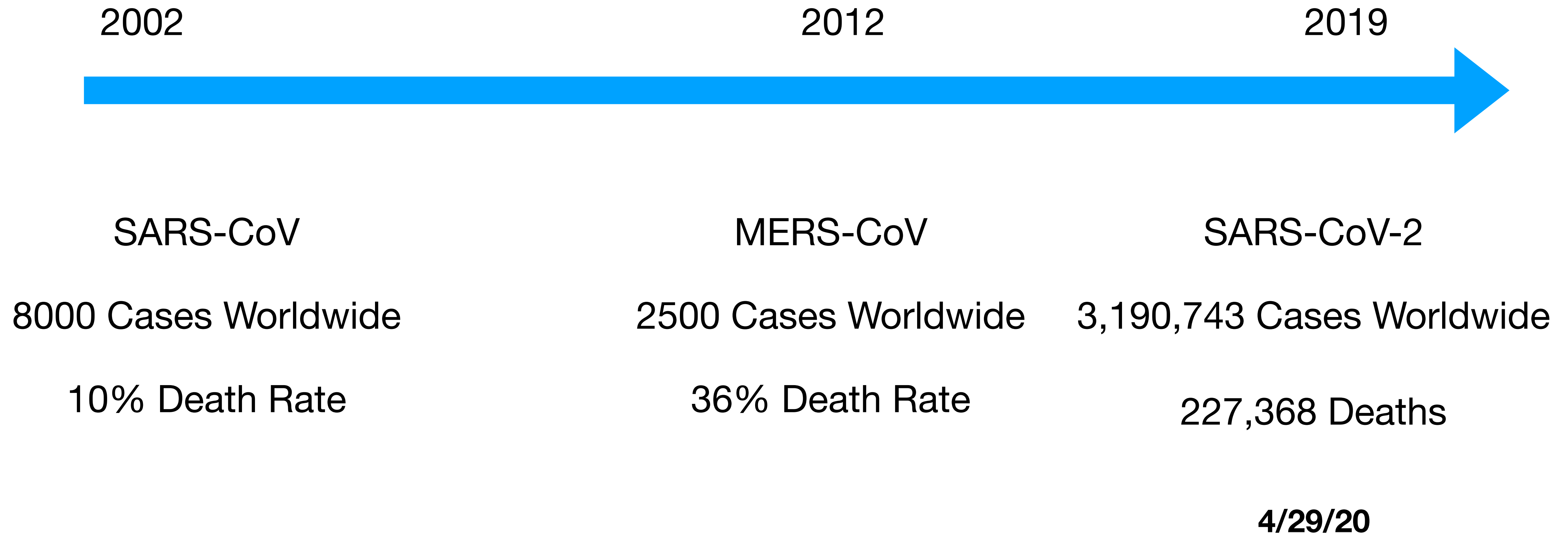
QBI Coronavirus Research Group
QCRG

<http://qbi.ucsf.edu/COVID-19>

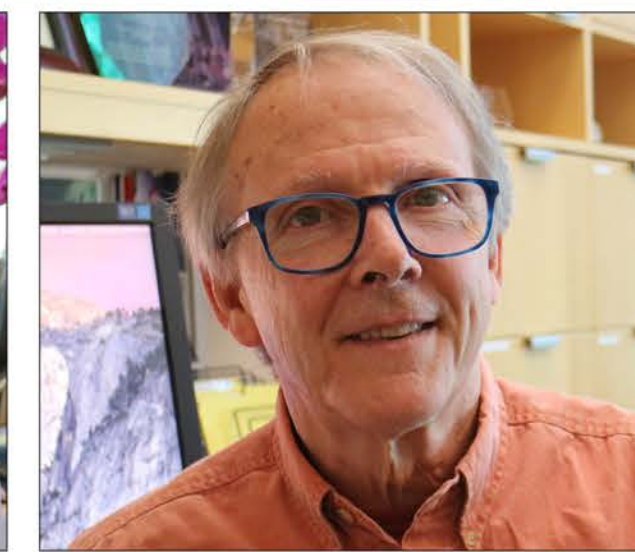
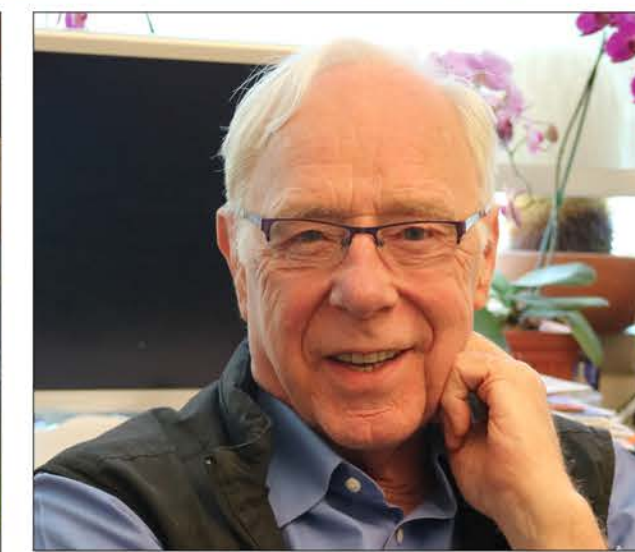
Overview

- Created the first-ever blueprint of how SARS-2 hijacks human cells using all 30 viral proteins
- Using this map, uncovered key drug classes with high potential to fight COVID-19
- Identified an over-the-counter medicine that appears to promote infection
- Spurring the initiation of several clinical trials

Emergence of Highly Pathogenic Human Coronaviruses: Enveloped, positive-sense single- stranded RNA genome



QCRG:
*A non-profit
research group*



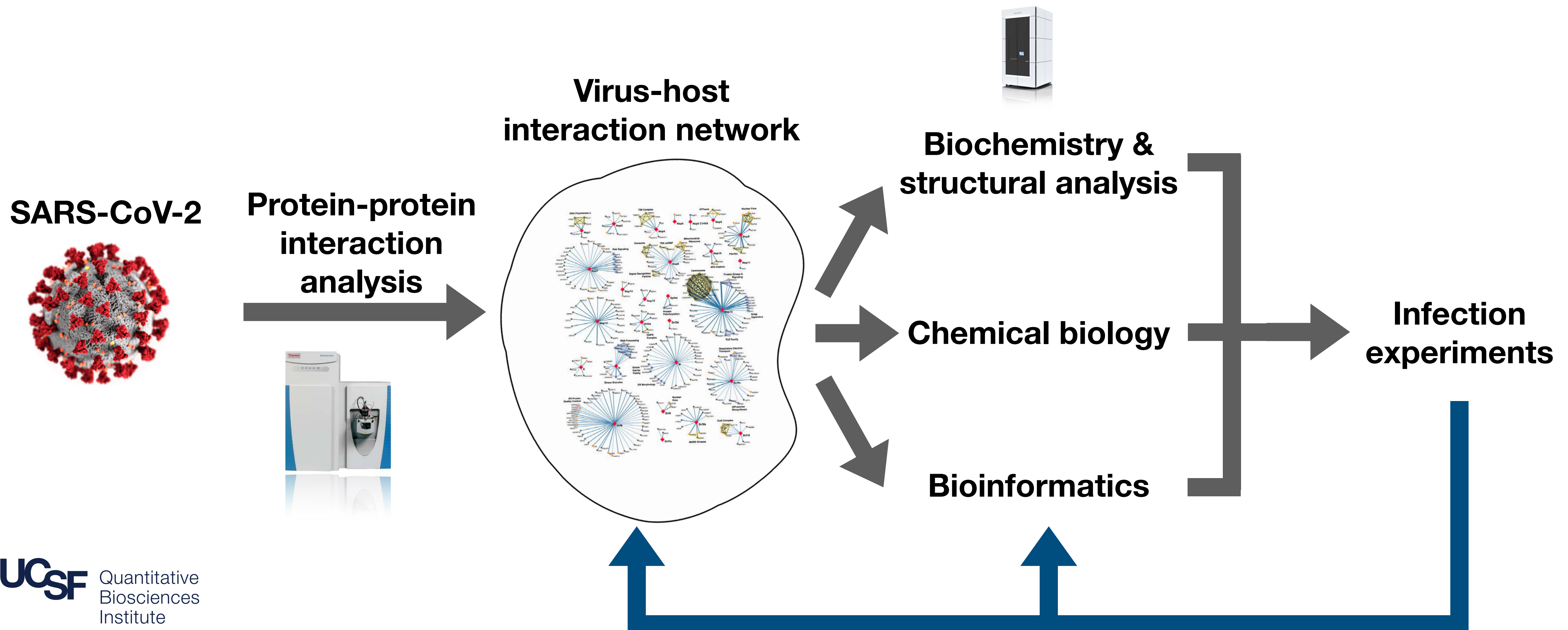
QCRG Members Across UCSF/MSSM/Institut Pasteur

A SARS-CoV-2 Protein Interaction Map Reveals Targets for Drug-Repurposing

David E. Gordon^{*1,2,3,4}, Gwendolyn M. Jang^{*1,2,3,4}, Mehdi Bouhaddou^{*1,2,3,4}, Jiewei Xu^{*1,2,3,4}, Kirsten Obernier^{*1,2,3,4}, Kris M. White^{*5,6}, Matthew J. O'Meara^{*7}, Veronica V. Rezelj^{*8}, Jeffrey Z. Guo^{1,2,3,4}, Danielle L. Swaney^{1,2,3,4}, Tia A. Tummino^{1,2,9}, Ruth Huettenhain^{1,2,3,4}, Robyn M. Kaake^{1,2,3,4}, Alicia L. Richards^{1,2,3,4}, Beril Tutuncuoglu^{1,2,3,4}, Helene Foussard^{1,2,3,4}, Jyoti Batra^{1,2,3,4}, Kelsey Haas^{1,2,3,4}, Maya Modak^{1,2,3,4}, Minkyu Kim^{1,2,3,4}, Paige Haas^{1,2,3,4}, Benjamin J. Polacco^{1,2,3,4}, Hannes Braberg^{1,2,3,4}, Jacqueline M. Fabius^{1,2,3,4}, Manon Eckhardt^{1,2,3,4}, Margaret Soucheray^{1,2,3,4}, Melanie J. Bennett^{1,2,3,4}, Merve Cakir^{1,2,3,4}, Michael J. McGregor^{1,2,3,4}, Qiongyu Li^{1,2,3,4}, Bjoern Meyer⁸, Ferdinand Roesch⁸, Thomas Vallet⁸, Alice Mac Kain⁸, Lisa Miorin^{5,6}, Elena Moreno^{5,6}, Zun Zar Chi Naing^{1,2,3,4}, Yuan Zhou^{1,2,3,4}, Shiming Peng^{1,2,9}, Ying Shi^{1,2,4,11}, Ziyang Zhang^{1,2,4,11}, Wenqi Shen^{1,2,4,11}, Ilsa T. Kirby^{1,2,4,11}, James E. Melnyk^{1,2,4,11}, John S. Chorba^{1,2,4,11}, Kevin Lou^{1,2,4,11}, Shizhong A. Dai^{1,2,4,11}, Inigo Barrio-Hernandez¹², Danish Memon¹², Claudia Hernandez-Armenta¹², Jiankun Lyu^{1,2,9}, Christopher J.P. Mathy^{1,2,13,14}, Tina Perica^{1,2,13}, Kala B. Pilla^{1,2,13}, Sai J. Ganesan^{1,2,13}, Daniel J. Saltzberg^{1,2,13}, Ramachandran Rakesh^{1,2,13}, Xi Liu^{1,2,9}, Sara B. Rosenthal¹⁵, Lorenzo Calviello^{1,16}, Srivats Venkataramanan^{1,16}, Jose Liboy-Lugo^{1,16}, Yizhu Lin^{1,16}, Xi-Ping Huang¹⁷, YongFeng Liu¹⁷, Stephanie A. Wankowicz^{1,2,11,18}, Markus Bohn^{1,2,9}, Maliheh Safari^{1,2,19}, Fatima S. Ugur^{1,2,4,9}, Cassandra Koh⁸, Nastaran Sadat Savar⁸, Quang Dinh Tran⁸, Djoshkun Shengjuler⁸, Sabrina J Fletcher⁸, Michael C. O'Neal²⁰, Yiming Cai²⁰, Jason C.J.Chang²⁰, David J. Broadhurst²⁰, Saker Klippsten²⁰, Phillip P. Sharp⁴, Nicole A. Wenzell^{1,2,4}, Duygu Kuzuoglu^{1,2,4,21,22}, Hao-Yuan Wang^{1,2,4}, Raphael Trenker^{1,2,23}, Janet M. Young²⁴, Devin A. Cavero^{3,26}, Joseph Hiatt^{3,25,26}, Theodore L. Roth^{3,25,26}, Ujjwal Rathore^{3,26}, Advait Subramanian^{1,2,26}, Julia Noack^{1,2,26}, Mathieu Hubert¹⁰, Robert M. Stroud^{1,2,19}, Alan D. Frankel^{1,2,19}, Oren S. Rosenberg^{1,2,19,27}, Kliment A Verba^{1,2,9}, David A. Agard^{1,2,19}, Melanie Ott^{1,2,3,27}, Michael Emerman²⁸, Natalia Jura^{1,2,4,23}, Mark von Zastrow^{1,2,4,29}, Eric Verdin^{1,27,30}, Alan Ashworth^{1,2,21}, Olivier Schwartz¹⁰, Christophe d'Enfert³¹, Shaeri Mukherjee^{1,2,26}, Matt Jacobson^{1,2,9}, Harmit S. Malik²⁴, Danica G. Fujimori^{1,2,4,9}, Trey Ideker^{1,32}, Charles S. Craik^{1,2,9,21}, Stephen N. Floor^{1,16,21}, James S. Fraser^{1,2,13}, John D. Gross^{1,2,9}, Andrej Sali^{1,2,9,13}, Bryan L. Roth¹⁷, Davide Ruggero^{1,2,4,21,22}, Jack Taunton^{1,2,4}, Tanja Kortemme^{1,2,13,14}, Pedro Beltrao^{1,12}, Marco Vignuzzi^{†8}, Adolfo García-Sastre^{†5,6,33,34}, Kevan M. Shokat^{†1,2,4,11}, Brian K. Shoichet^{†1,2,9}, Nevan J. Krogan^{†1,2,3,4,5}

Breakthrough Approach Enables Rapid and Focused Identification of Agents Directed at Proteins Critical for Disease Progression

Homes in on most relevant therapeutics; enables prediction of other related but seemingly different types of drugs

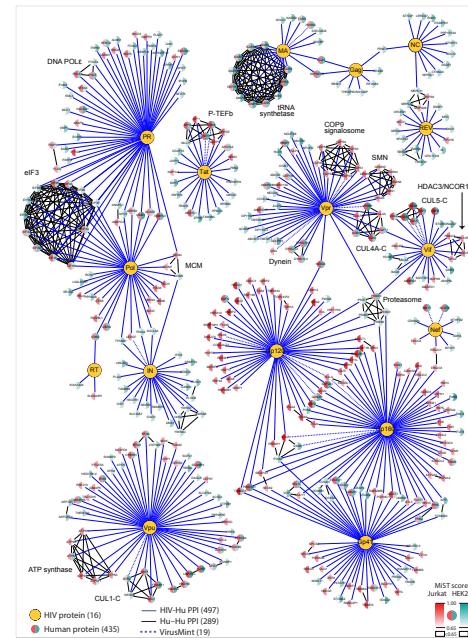


Previous Host-Pathogen Protein-Protein Interaction Networks

Time to completion: 2-3 years/map

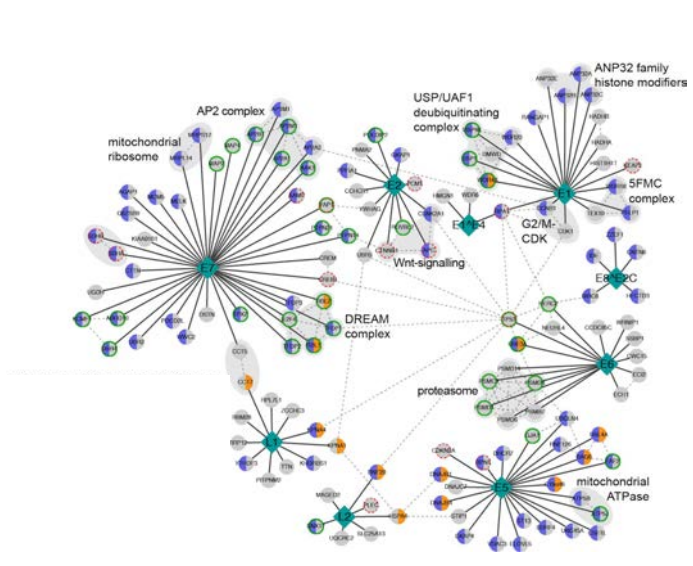
HIV-1

Jäger et al, Nature, 2012



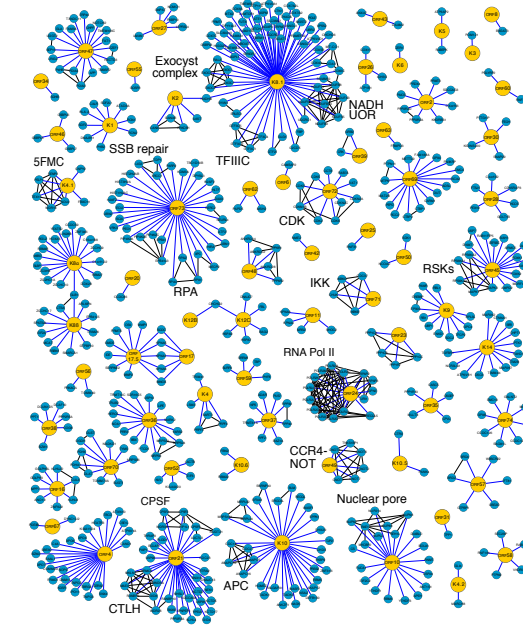
HPV

Eckhardt et al., Cancer Discovery, 2018



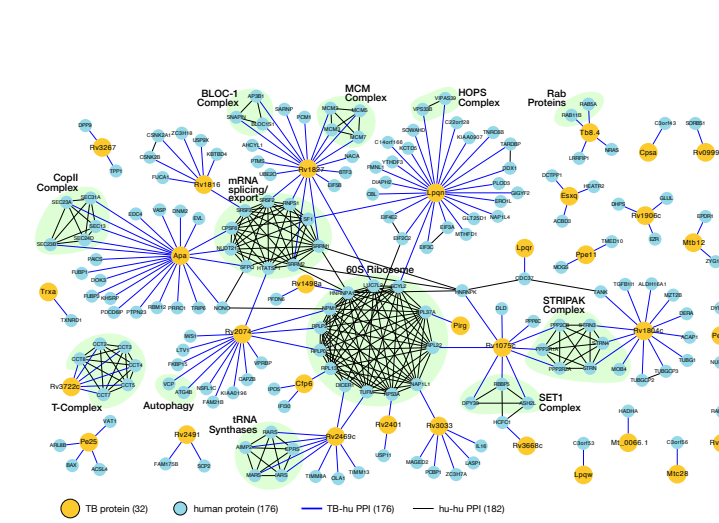
Kaposi Sarcoma's Herpes

Davis et al., Molecular Cell, 2015



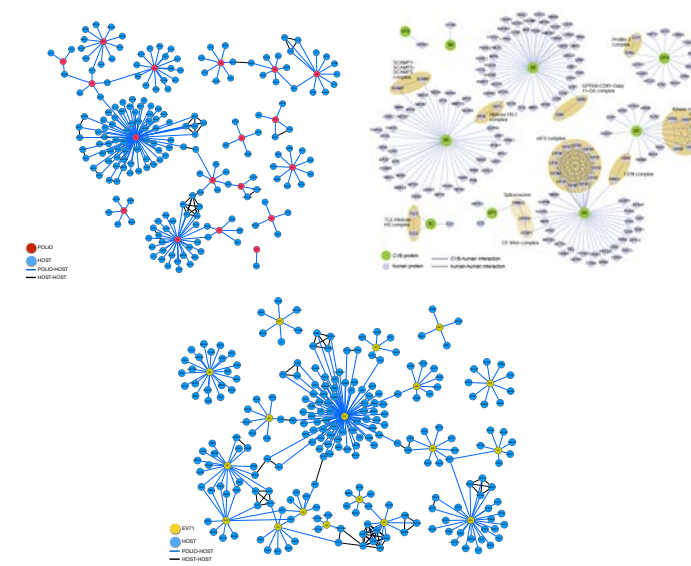
Tuberculosis

Penn et al., Molecular Cell, 2018



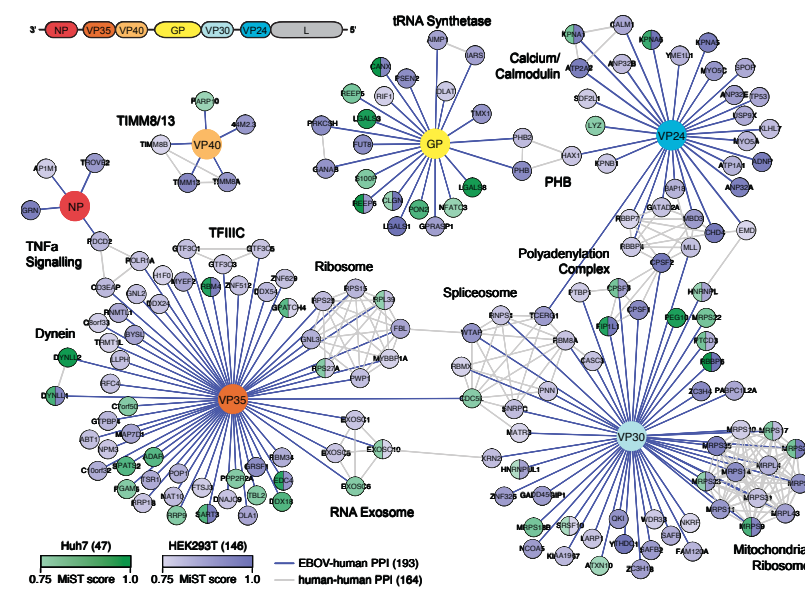
Enteroviruses: Polio vs Cox-B vs EV-71

CVB: Diep et al., Nature Microbiology, 2019

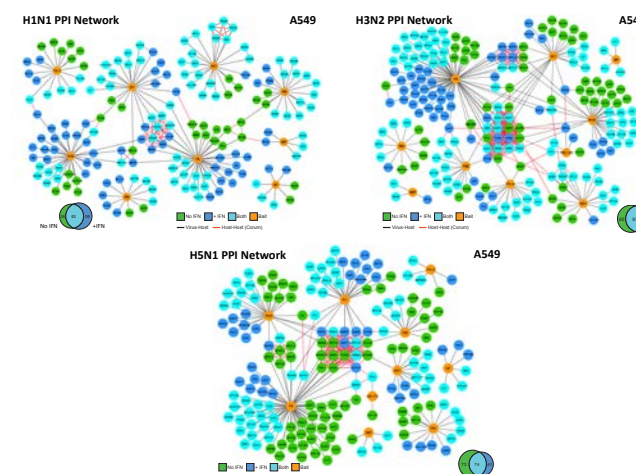


Ebola

Batra et al., Cell, 2018

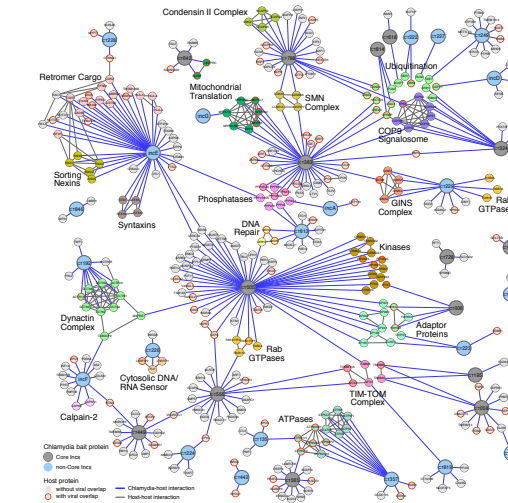


Influenza-A: H1N1 vs H5N1 vs H3N2



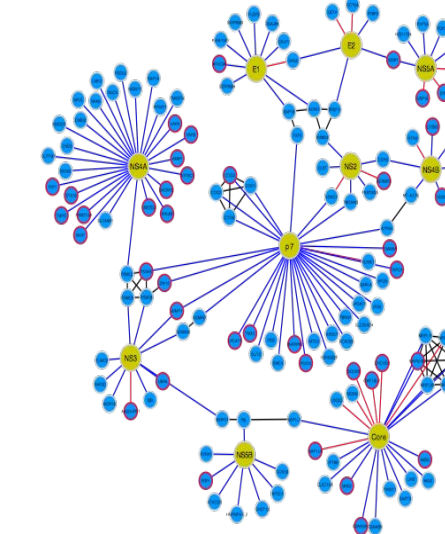
Chlamydia

Mirrahshidi et al., Cell Host and Microbe, 2015

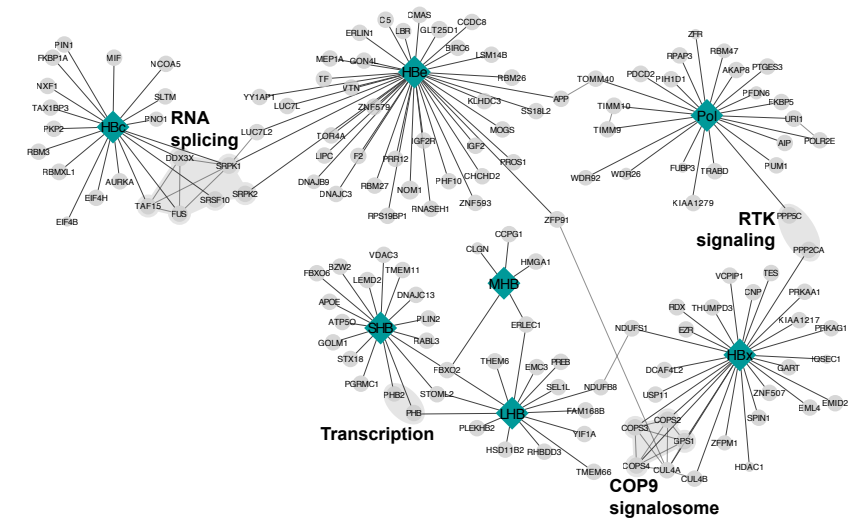


Hepatitis-C

Ramage et al., Molecular Cell, 2015

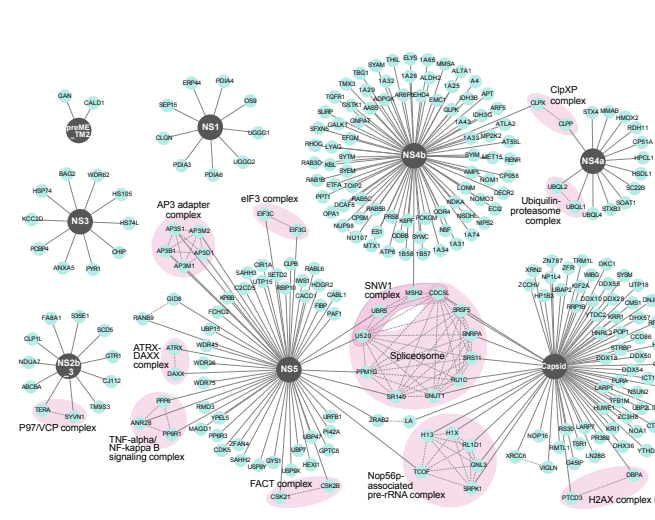


Hepatitis-B



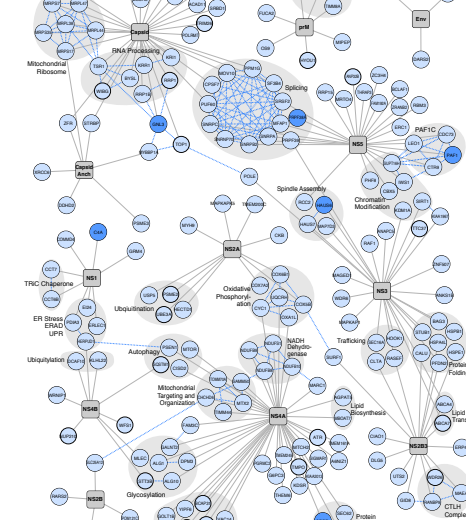
West Nile Virus

Li et al., Nature Microbiology, 2019



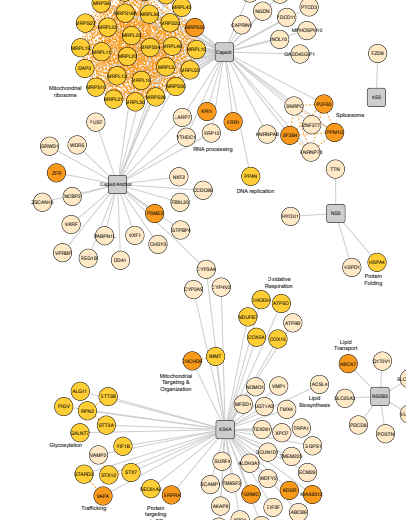
Dengue (human)

Shah et al., Cell, 2018



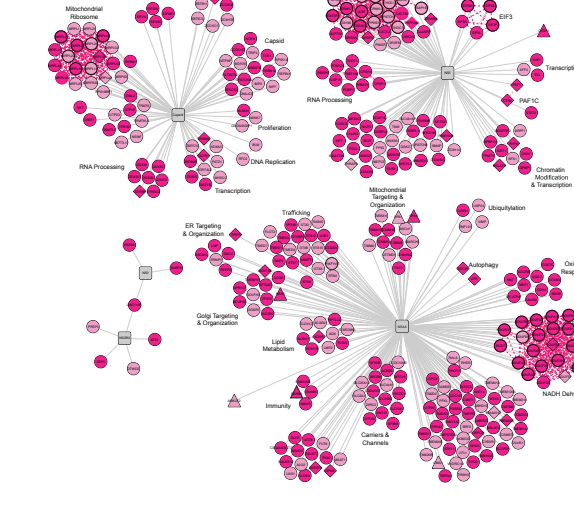
Dengue (mosquito)

Shah et al., Cell, 2018



Zika

Shah et al., Cell, 2018



SARS-CoV-2 Pandemic Project Timeline

12/31/19 Cluster of 41 Patients Reported to WHO

1/24/20 Cloning of 26/29 ORFs and start of

3/6/20 Draft Host Map

3/17/20 SF Shelter in Place Order—Lab shutdown except SARS-CoV-2 Related Research Projects

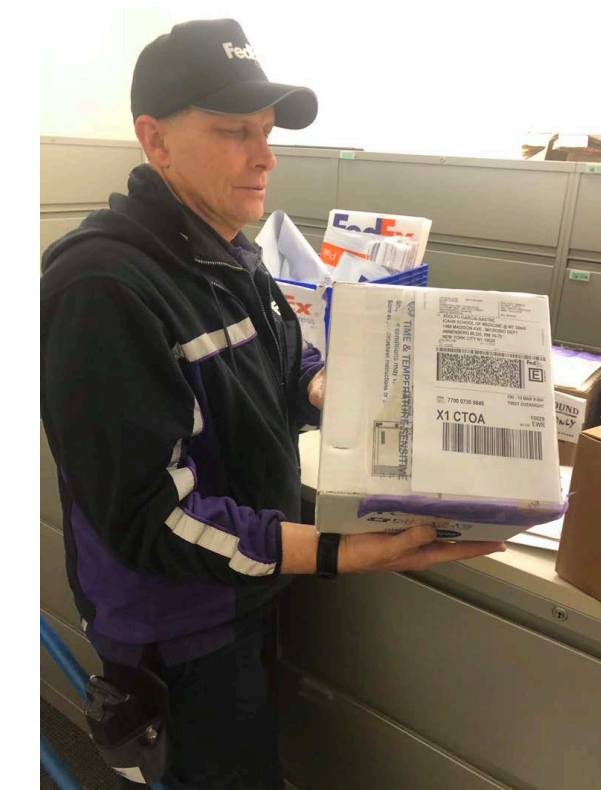
1/7/20 Virus Identified

2/6/20 First Death in US

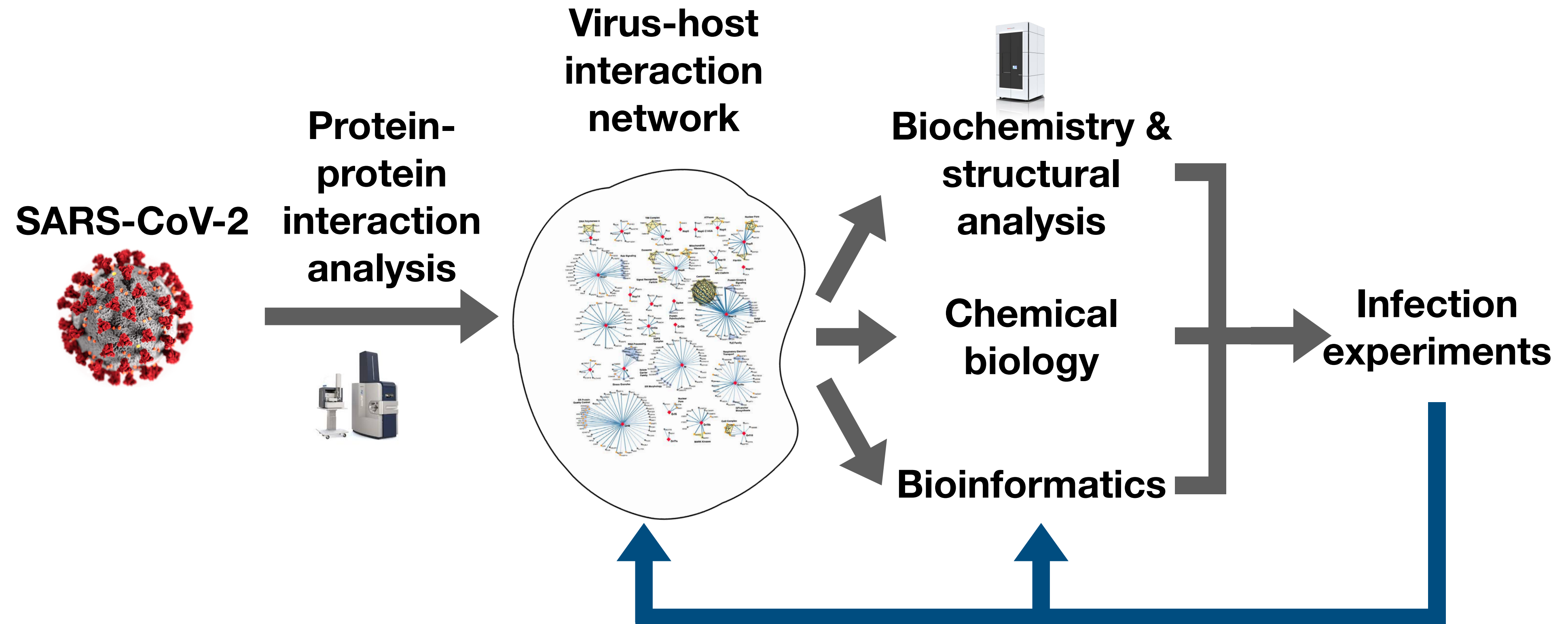
3/12/20 First Drug Candidates Sent to NY/Paris

3/22/20 bioRxiv

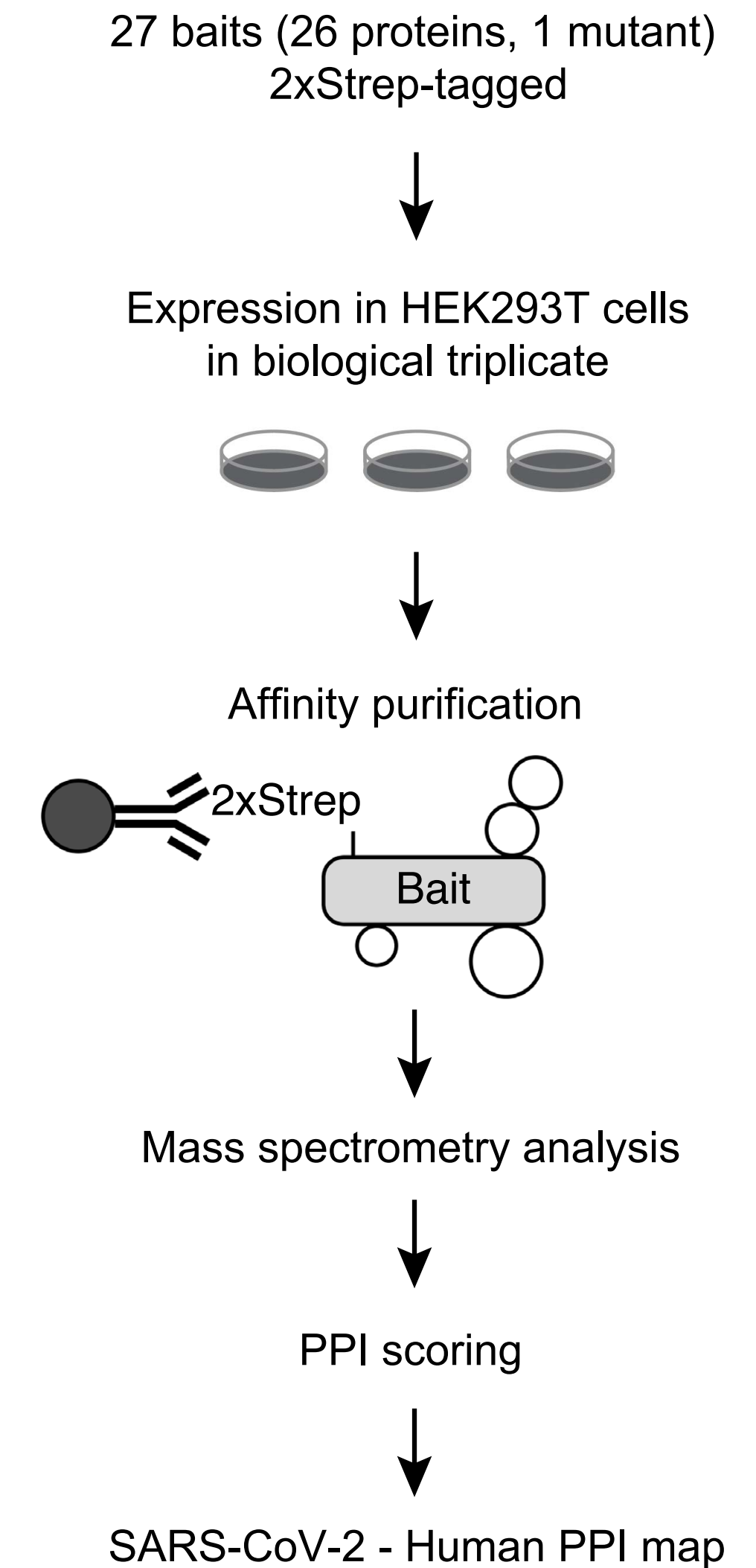
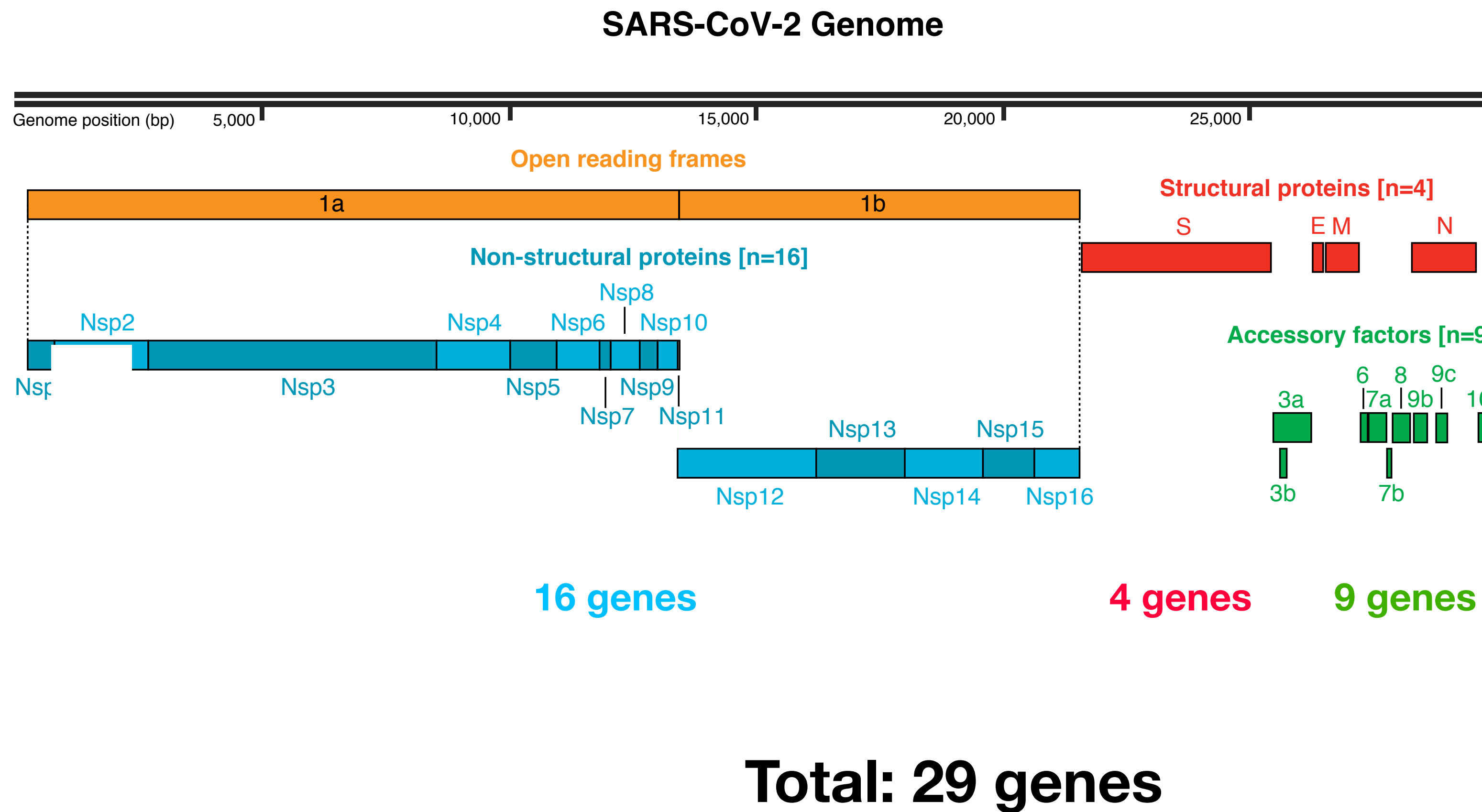
Expression constructs sent to 300 laboratories in 35 countries.



Targeting host factors a therapeutic strategy

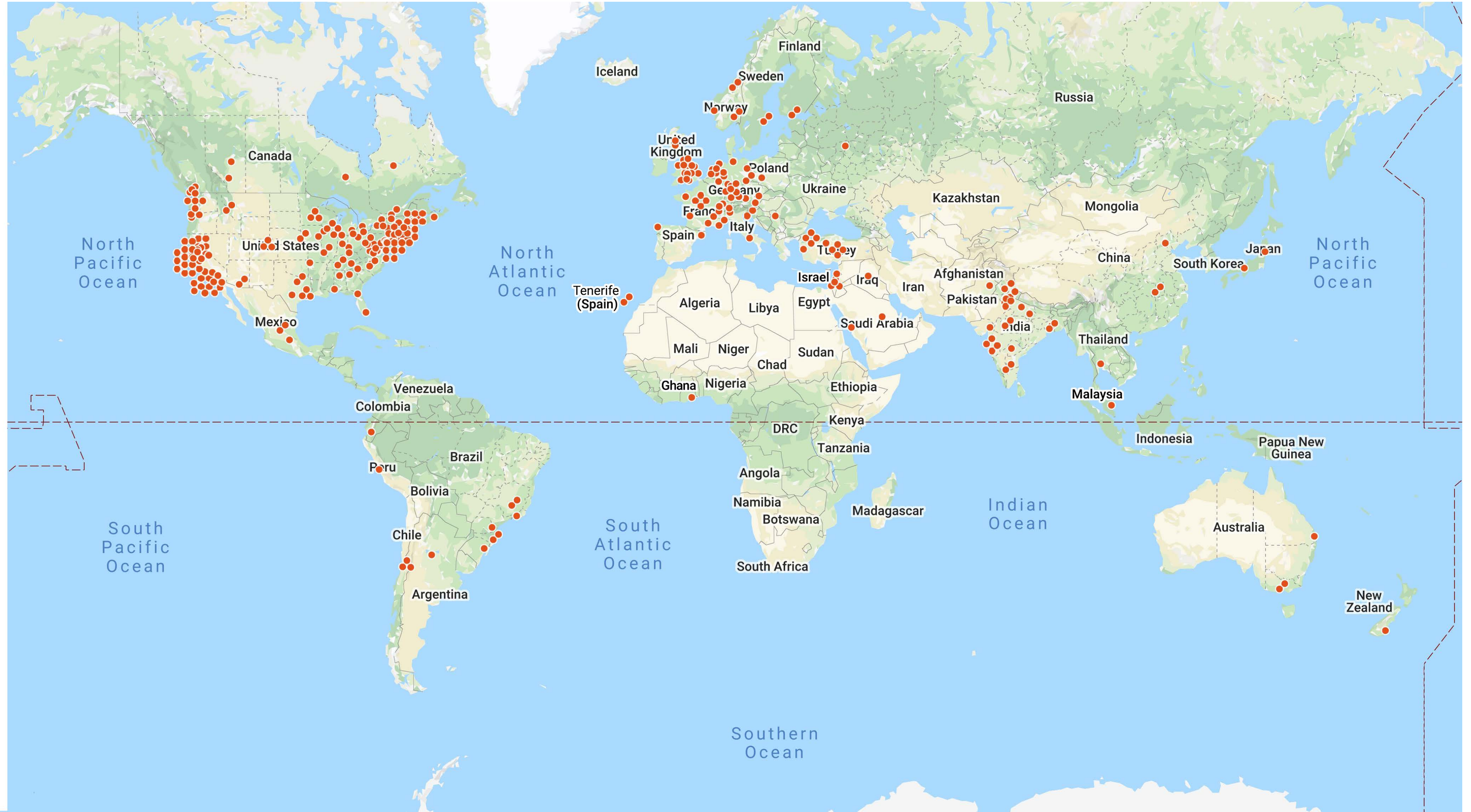


Cloning and expression of SARS-CoV-2 proteins

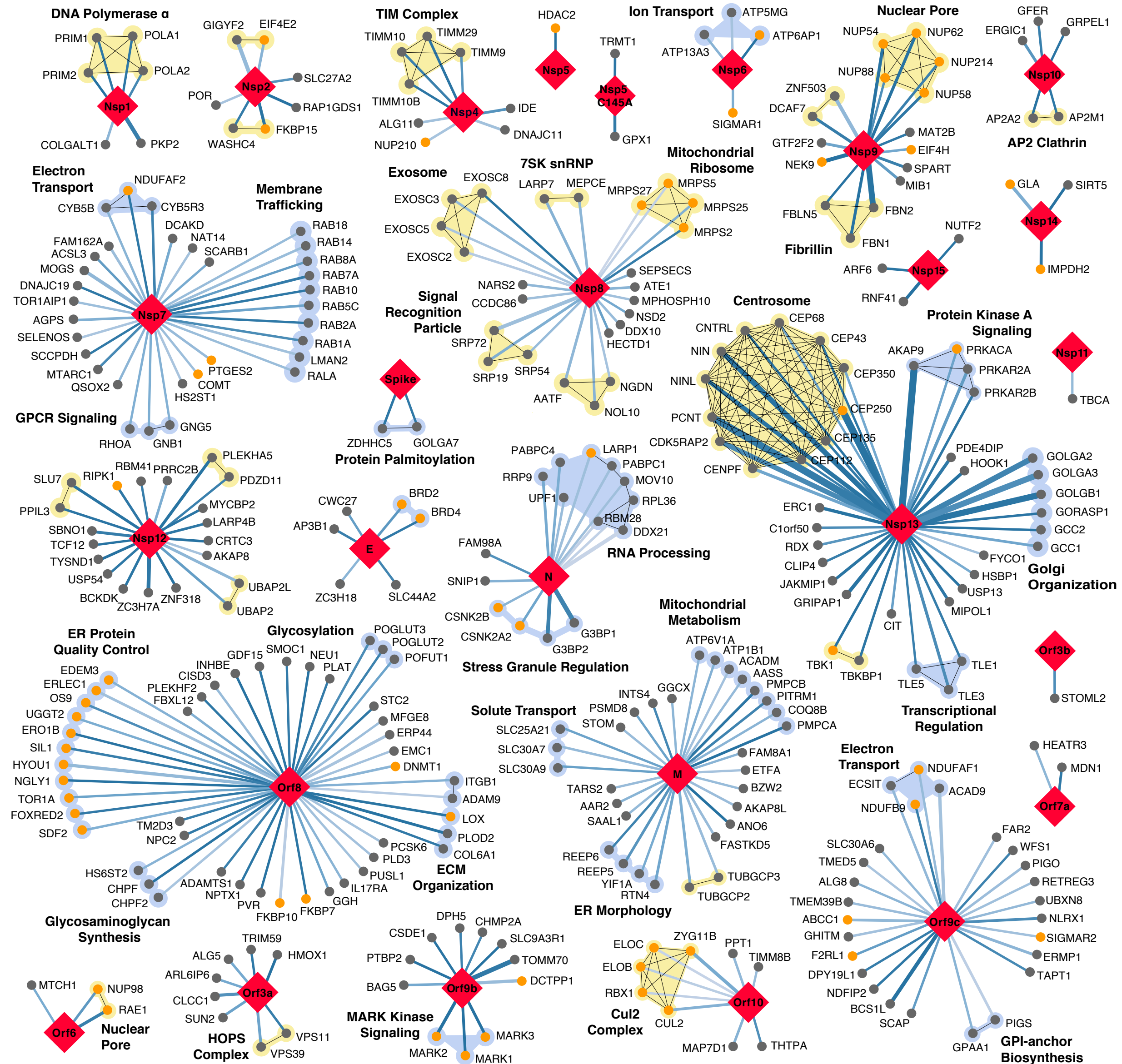


Plasmids to 314 Labs in 38 Countries

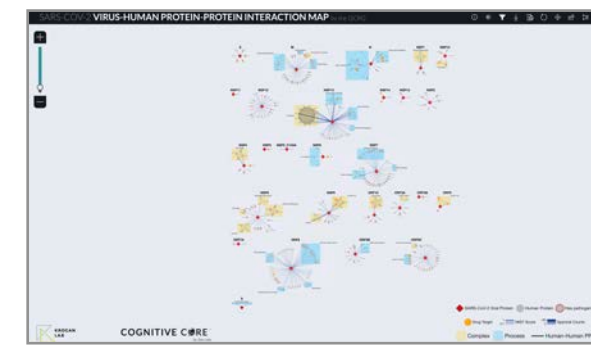
Nation	Shipments
Argentina	1
Australia	4
Austria	3
Brazil	7
Canada	12
Chile	3
China	3
Ecuador	1
Finland	2
France	11
Germany	18
Ghana	1
India	22
Iraq	1
Israel	4
Italy	2
Japan	2
Lebanon	1
Malaysia	1
Mexico	3
New Zealand	1
Norway	5
Pakistan	1
Palestine	1
Peru	1
Poland	1
Russia	1
Saudi Arabia	2
Serbia	1
Slovenia	2
Spain	4
Sweden	2
Switzerland	4
Thailand	1
The Netherlands	5
Turkey	10
UK	19
US	155
total	318



332 SARS-CoV-2-human PPIs include 69 druggable host factors



- ◆ SARS-CoV-2 Viral Protein
- Human Protein
- Drug Target

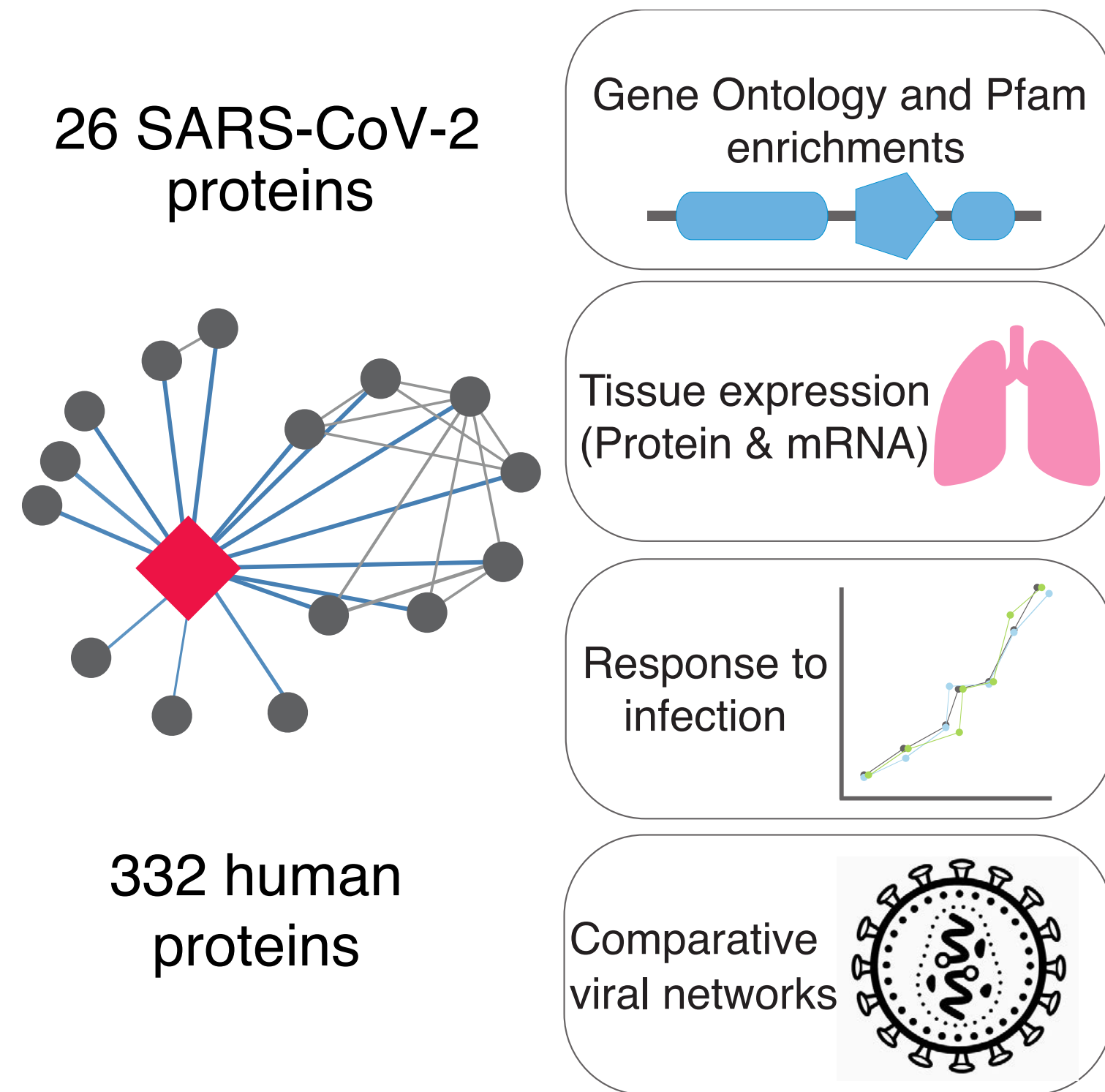


ZOIC LABS

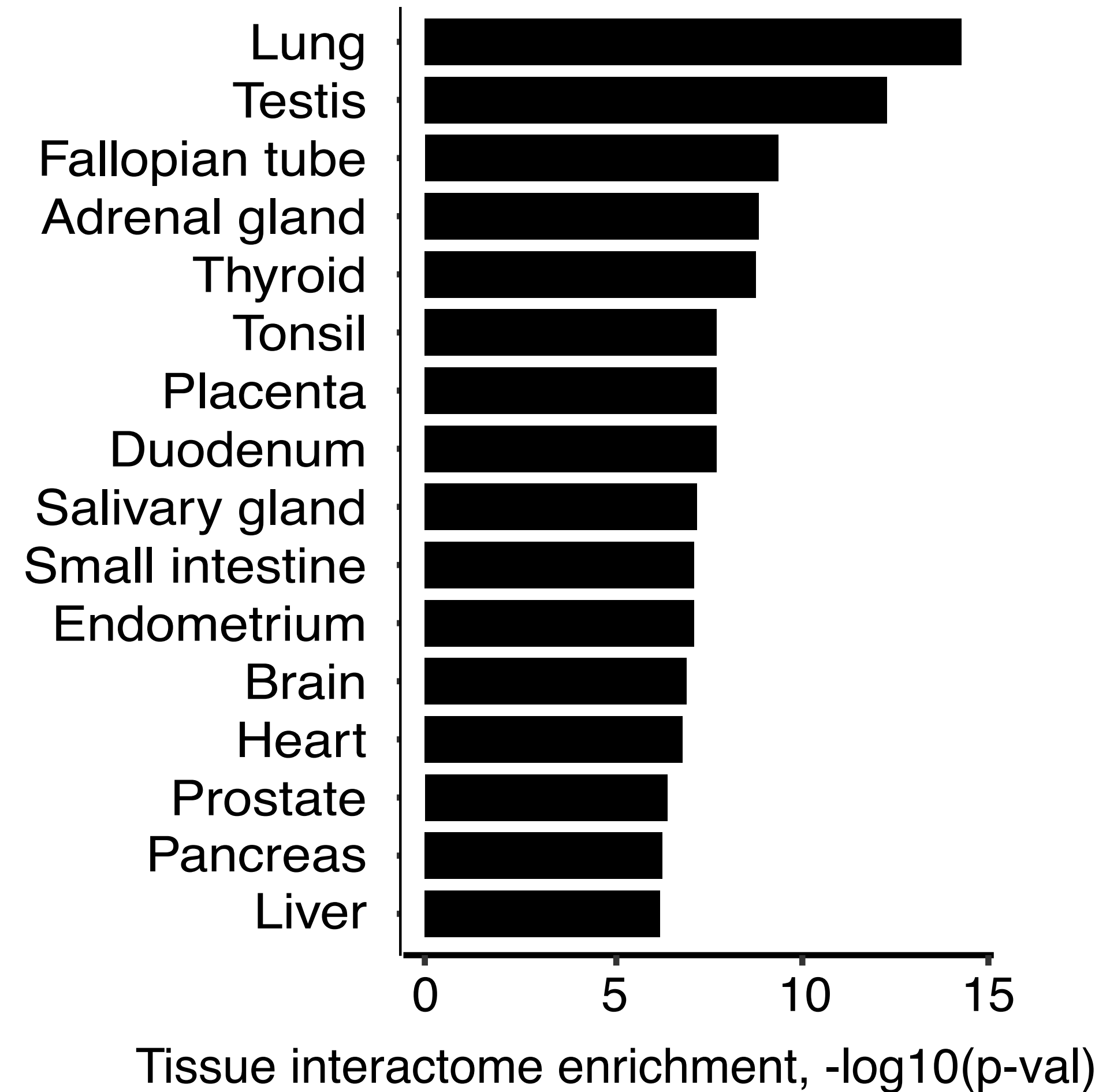
<https://ppi.zoiclabs.io/#/>

The Host Factor List From HEK293T Cells Show Bias for Lung Expression

a

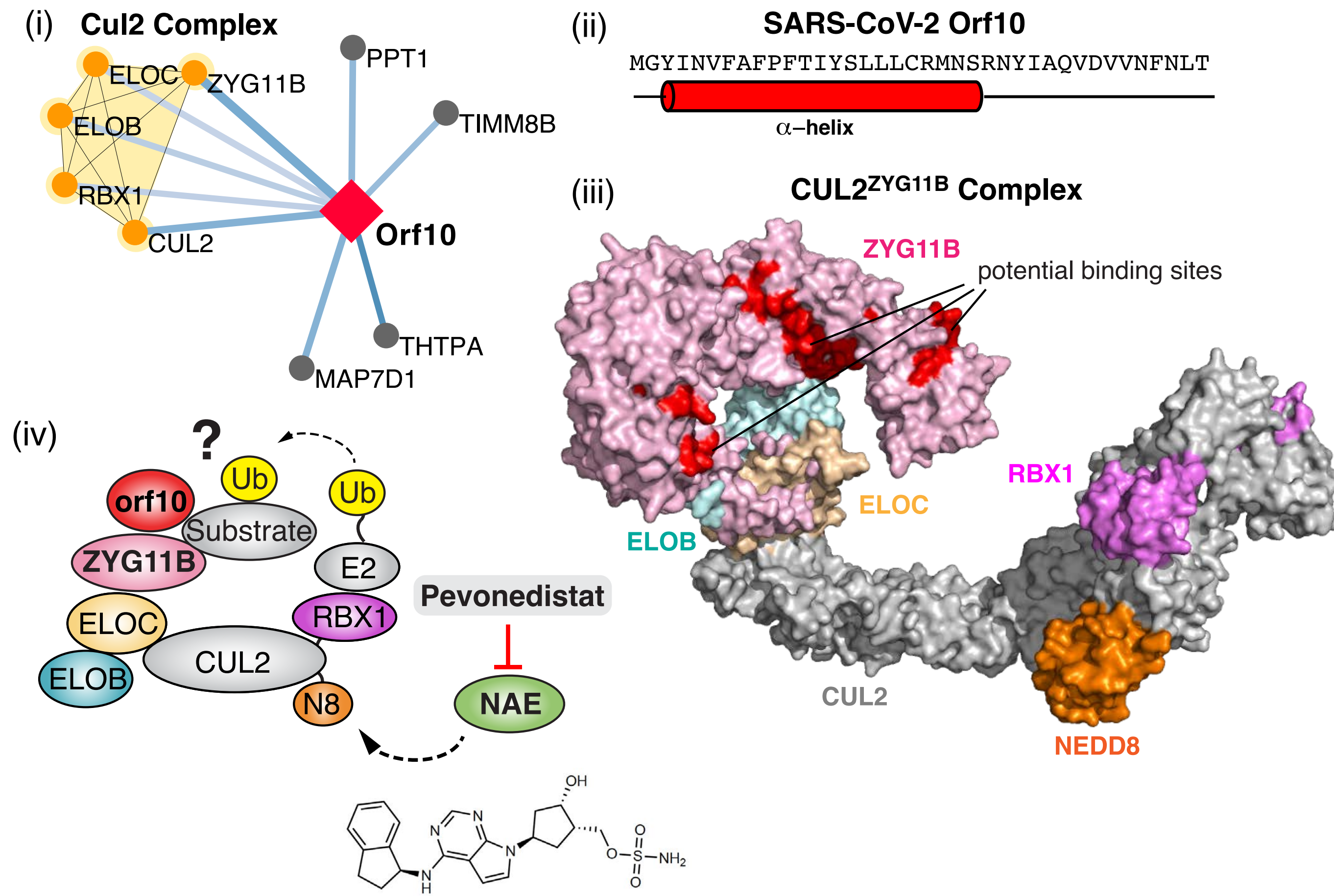


c



Novel aspects of SARS-CoV-2 biology

Orf10 - CUL2^{ZYG11B} E3 ligase



Drug discovery

- Nature and mechanism of drugs
- Costs and success-rate of drug development
- Drug side effects
- Classic drug discovery for antiviral delectasvir
- Turning the tables on SARS-Cov-2
 - Repurposing drugs for the human proteins that the virus subverts

A drug is a chemical or protein that changes the function of a cell (human or infectious)



NON-DROWSY

Daytime

Cold/Flu ALCOHOL-FREE & ANTIHISTAMINE-FREE

ACETAMINOPHEN.....Pain reliever/Fever reducer
DEXTROMETHORPHAN HBr...Cough suppressant
PHENYLEPHRINE HCl.....Nasal decongestant

For relief of

- aches, fever, cough
- nasal congestion

SEE NEW WARNINGS



actual size

20 DAYTIME SOFTGELS

Nighttime

Cold/Flu

ACETAMINOPHEN.....Pain reliever/Fever reducer
DEXTROMETHORPHAN HBr...Cough suppressant
DOXYLAMINE SUCCINATE.....Antihistamine

For relief of

- aches, fever, cough
- sneezing, runny nose

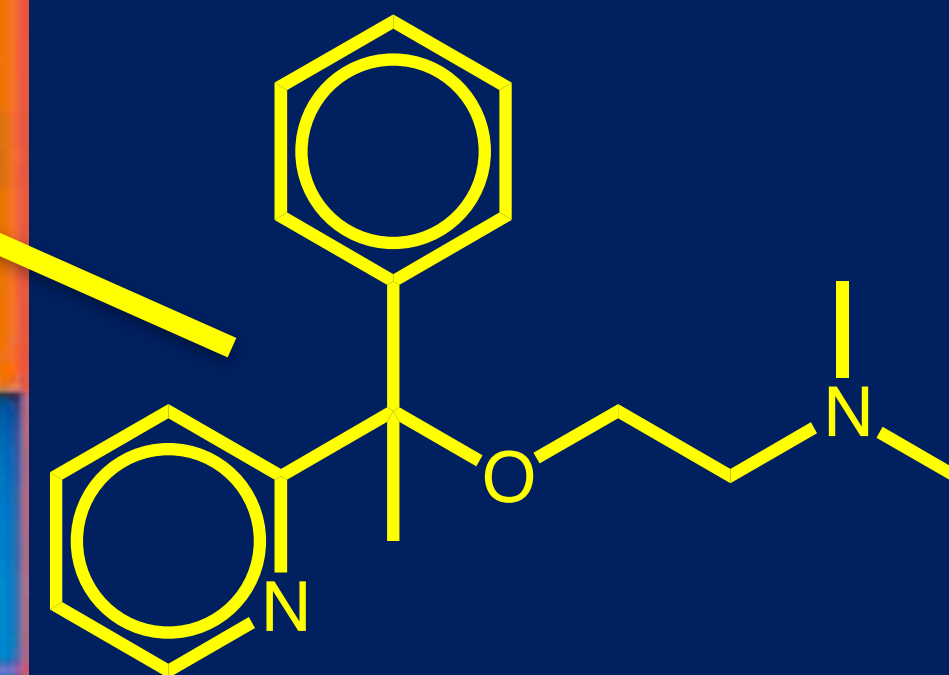
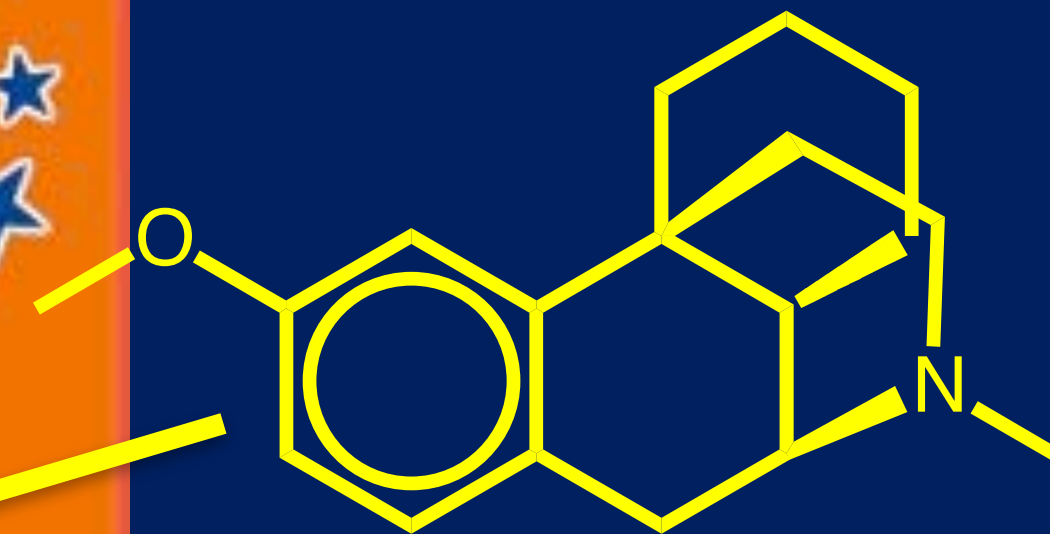
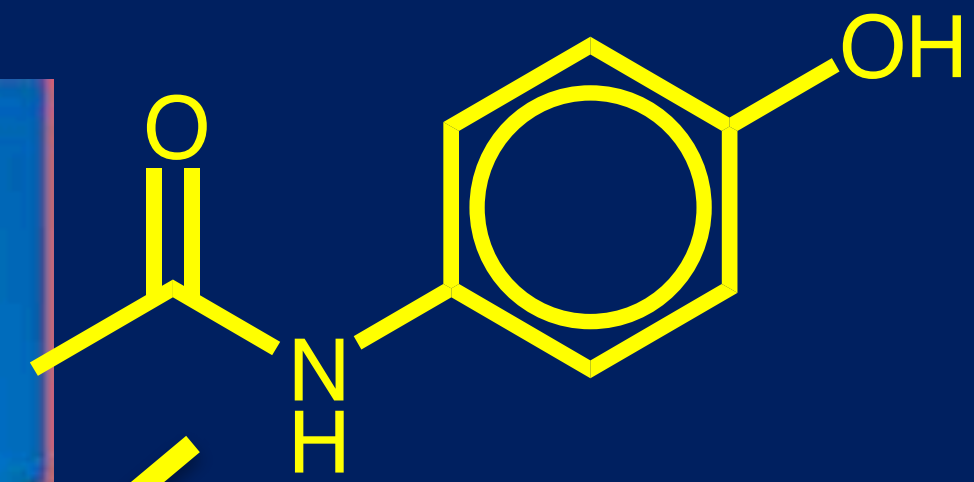
SEE NEW WARNINGS



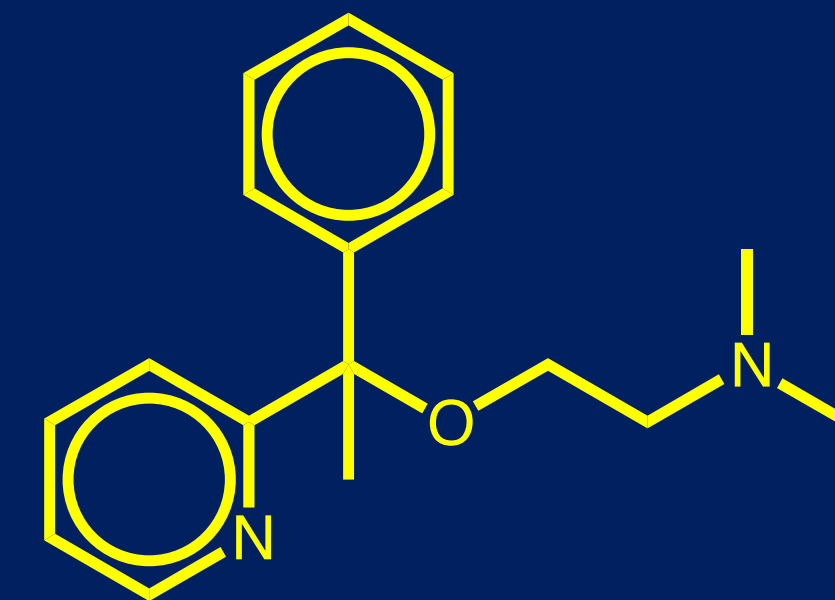
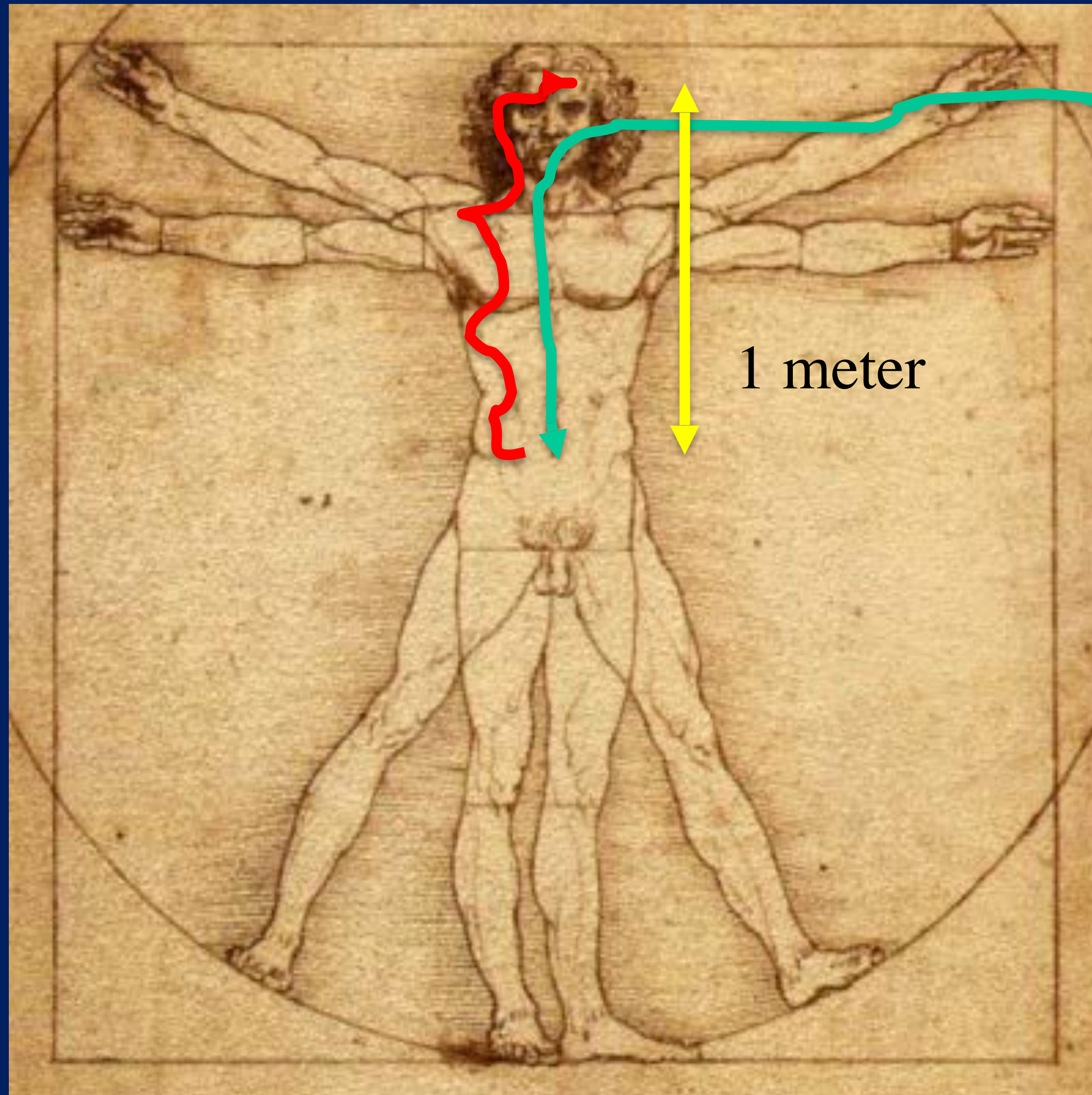
actual size

20 NIGHTTIME SOFTGELS

COMBO PACK 40 TOTAL SOFTGELS



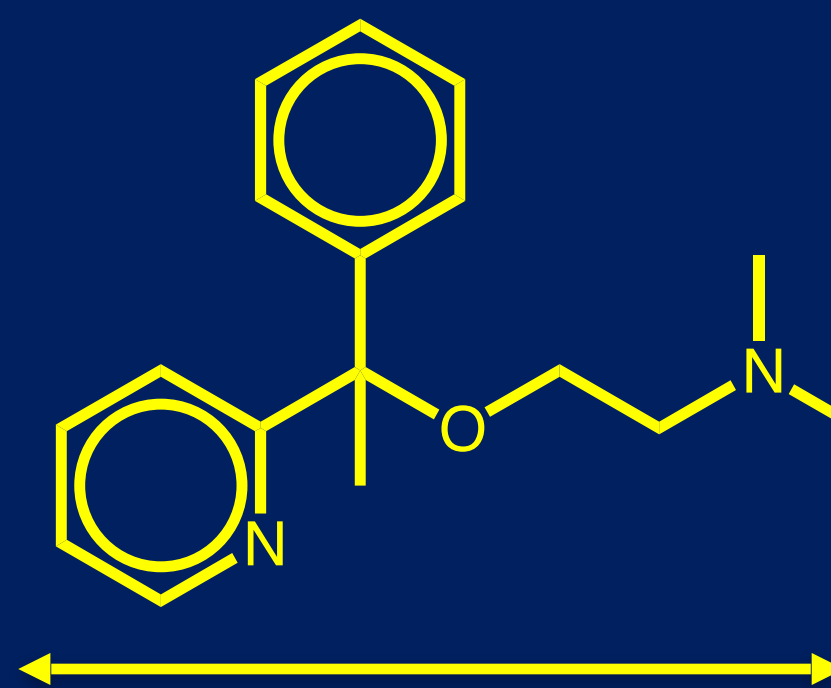
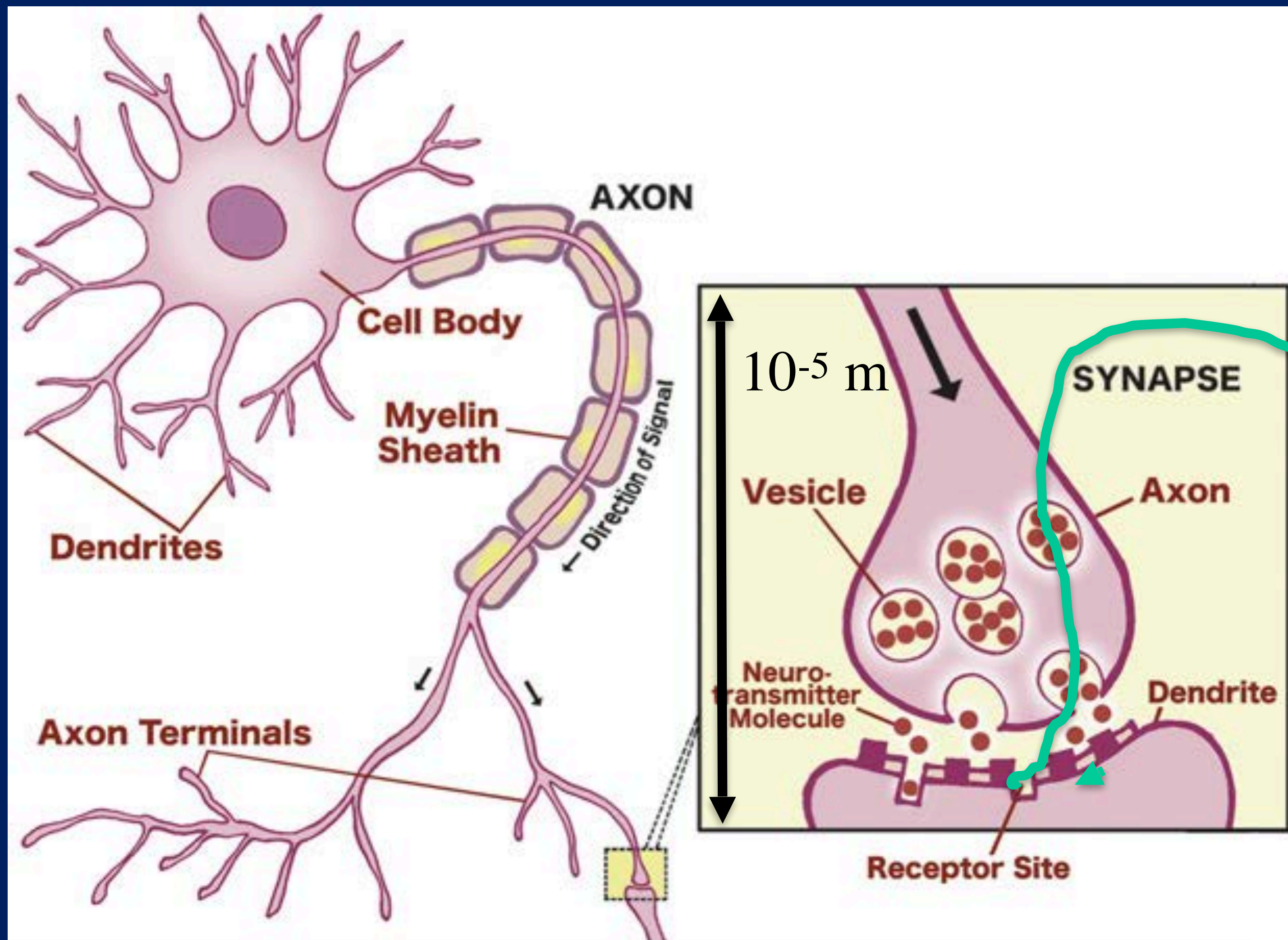
Drugs modulate “receptors” in tissues



10^{-9} meter

10^{19} drug molecules/pill

The rheostats are receptors on cells, in doxylamines case, neurons

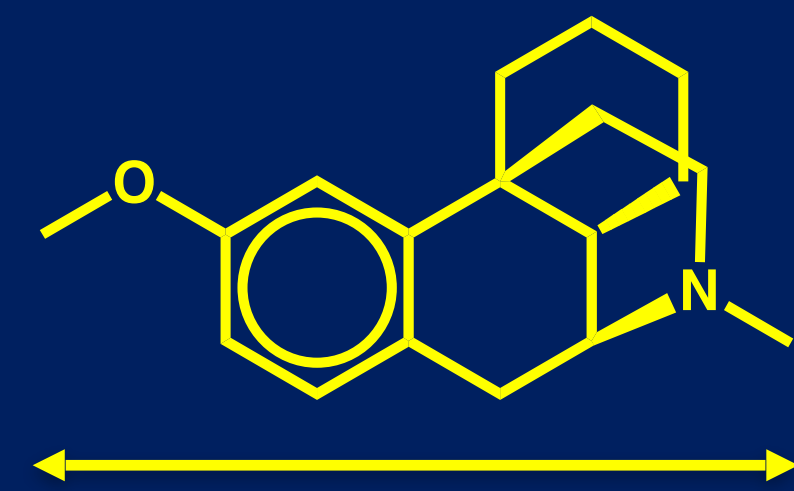
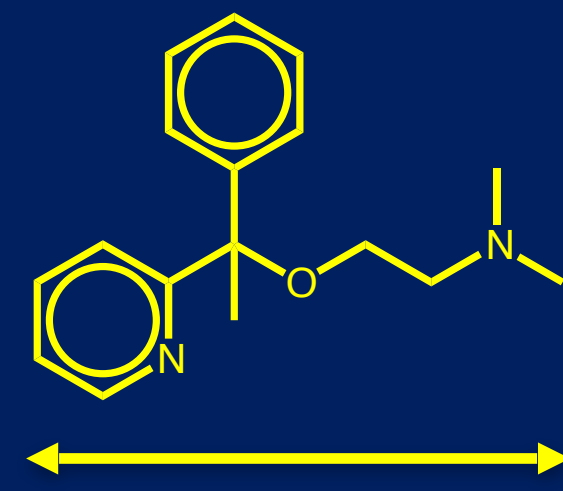
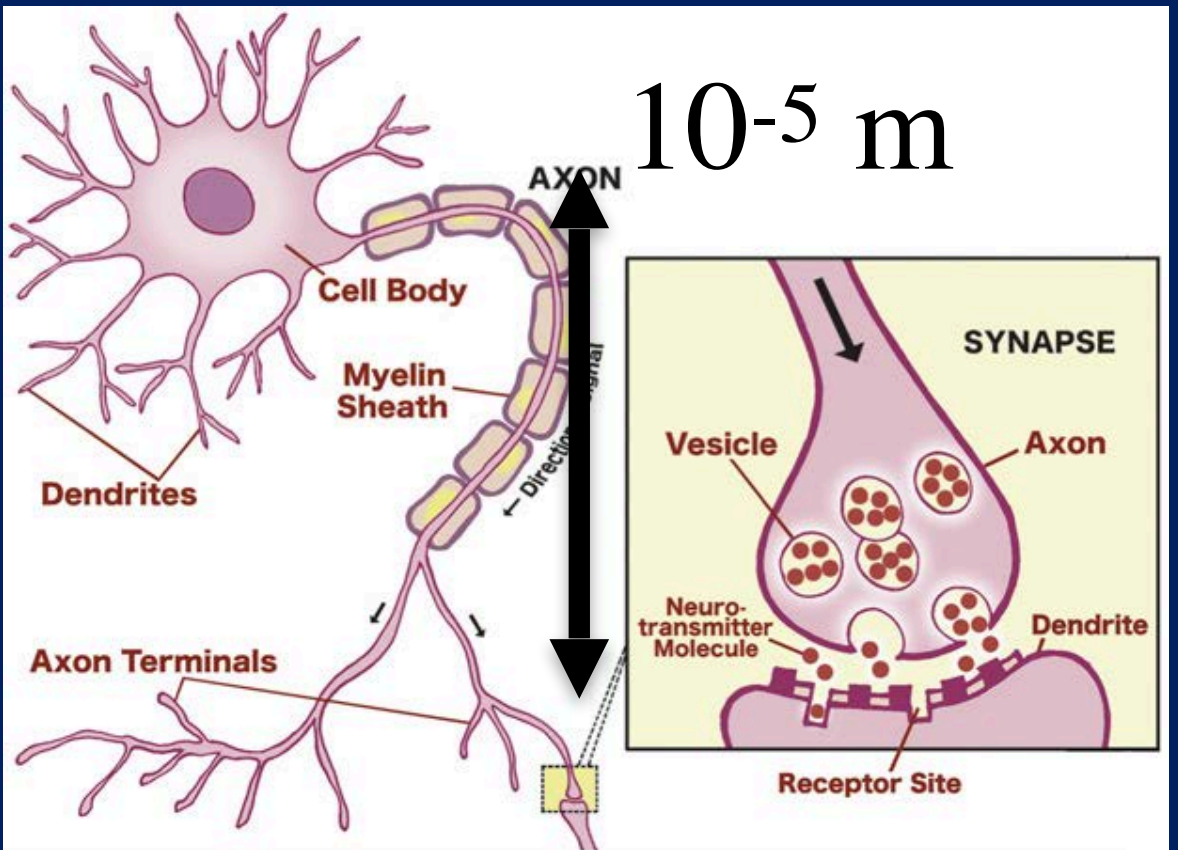


10^{-9} meter

10^{19} molecules/pill

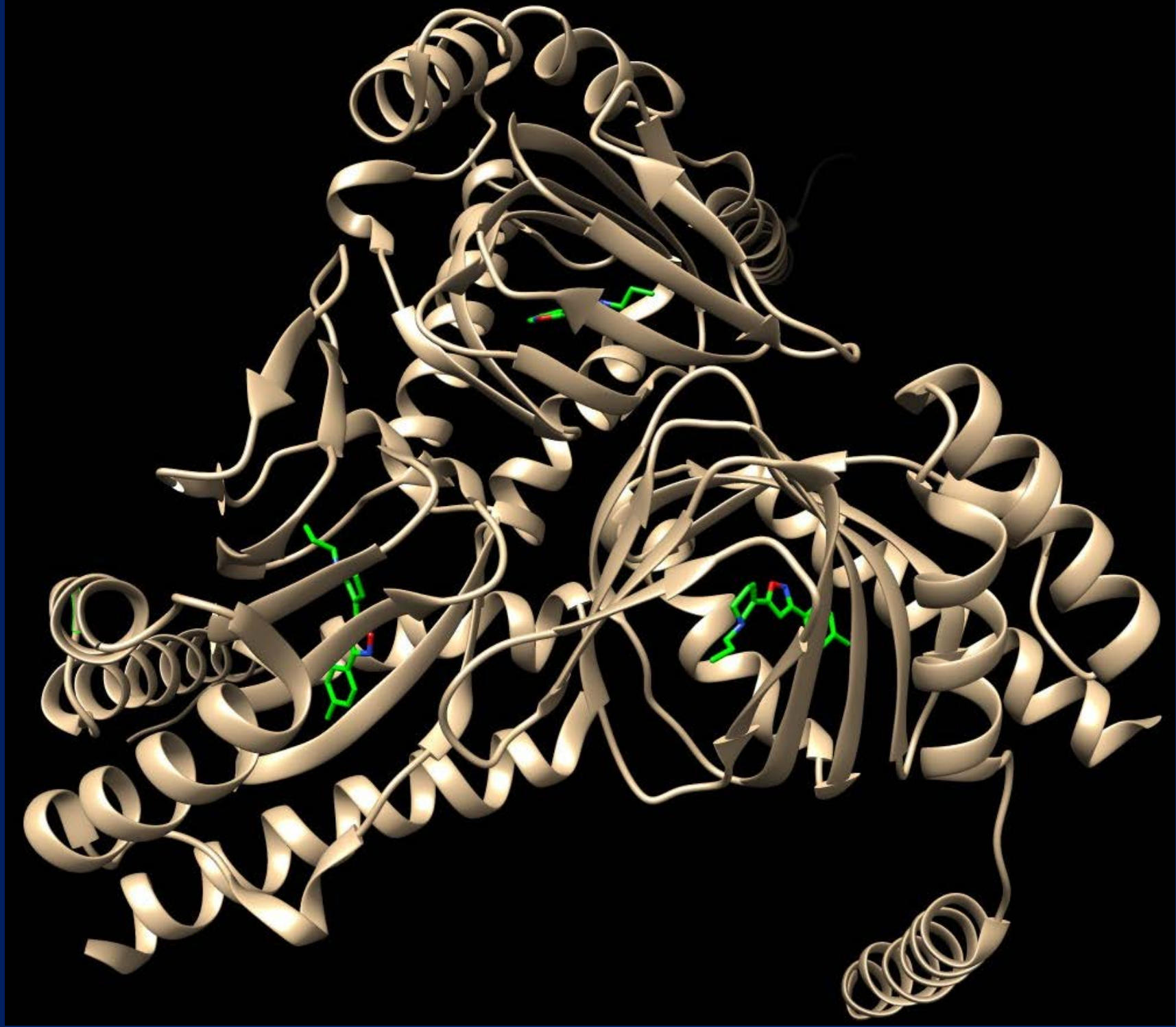
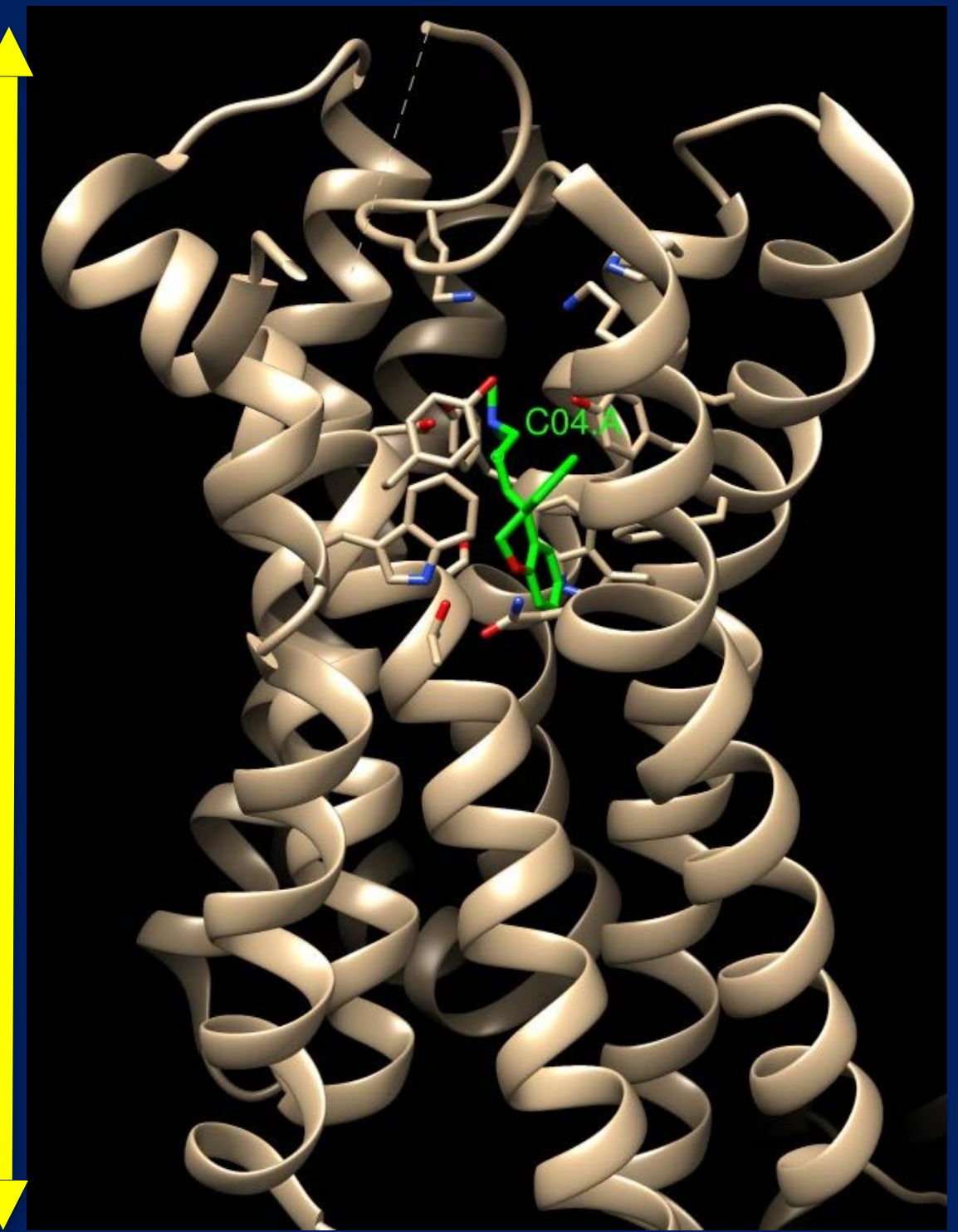
10^{11} neurons/brain

doxylamine blocks the histamine H₁ receptor
dextromethorphan activates the Sigma₁ receptor

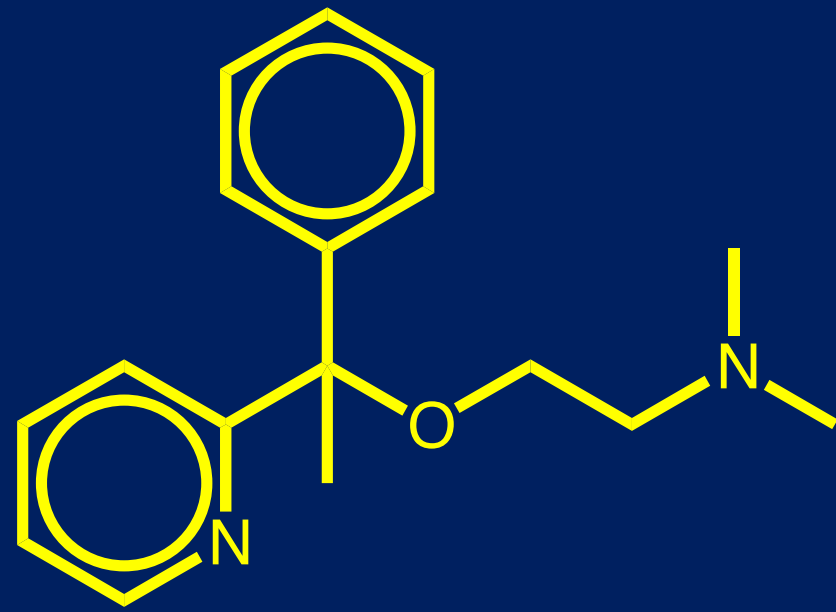


10⁻⁹ meter

6x10⁻⁹ m

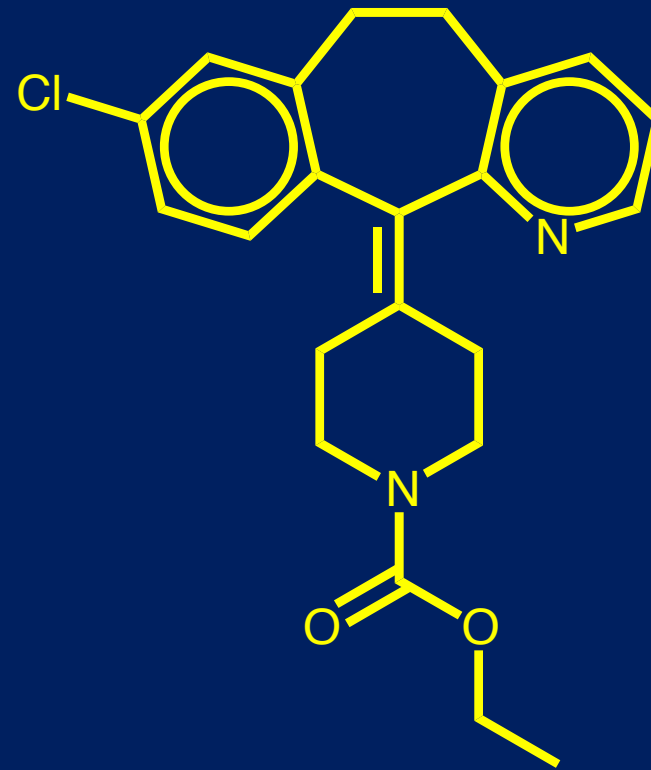


Side effects & alternative targets



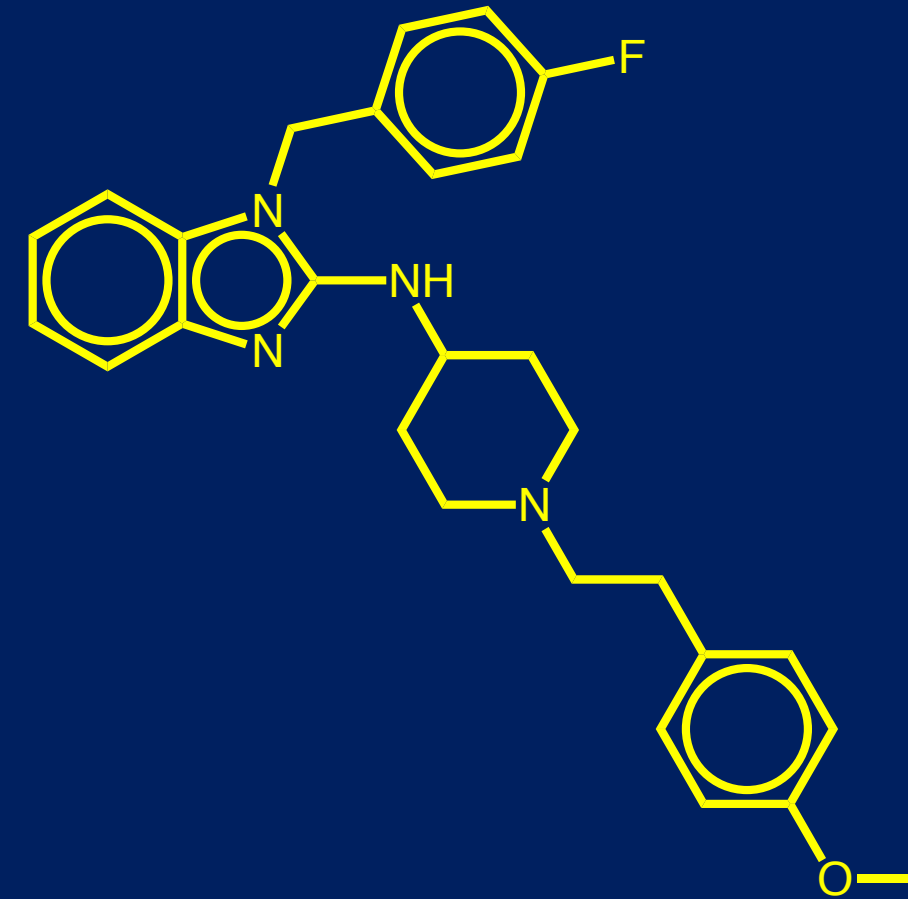
H1: strong
M1/2: decent
Sigma: decent
HERG: weak

sedation, lurid
dreams,
tachycardia, dry
mouth



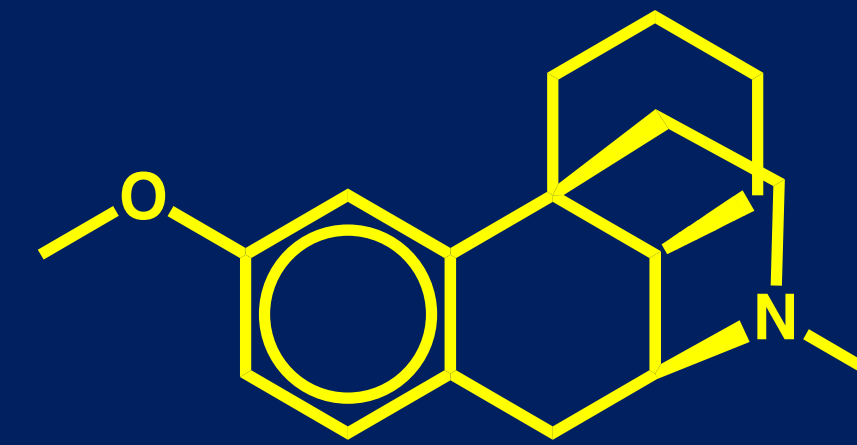
H1: very strong
M1/2: decent
HERG: weak

Dry mouth, low
sedation



H1: strong
M1/2: modest
Sigma: decent
HERG: strong (!)

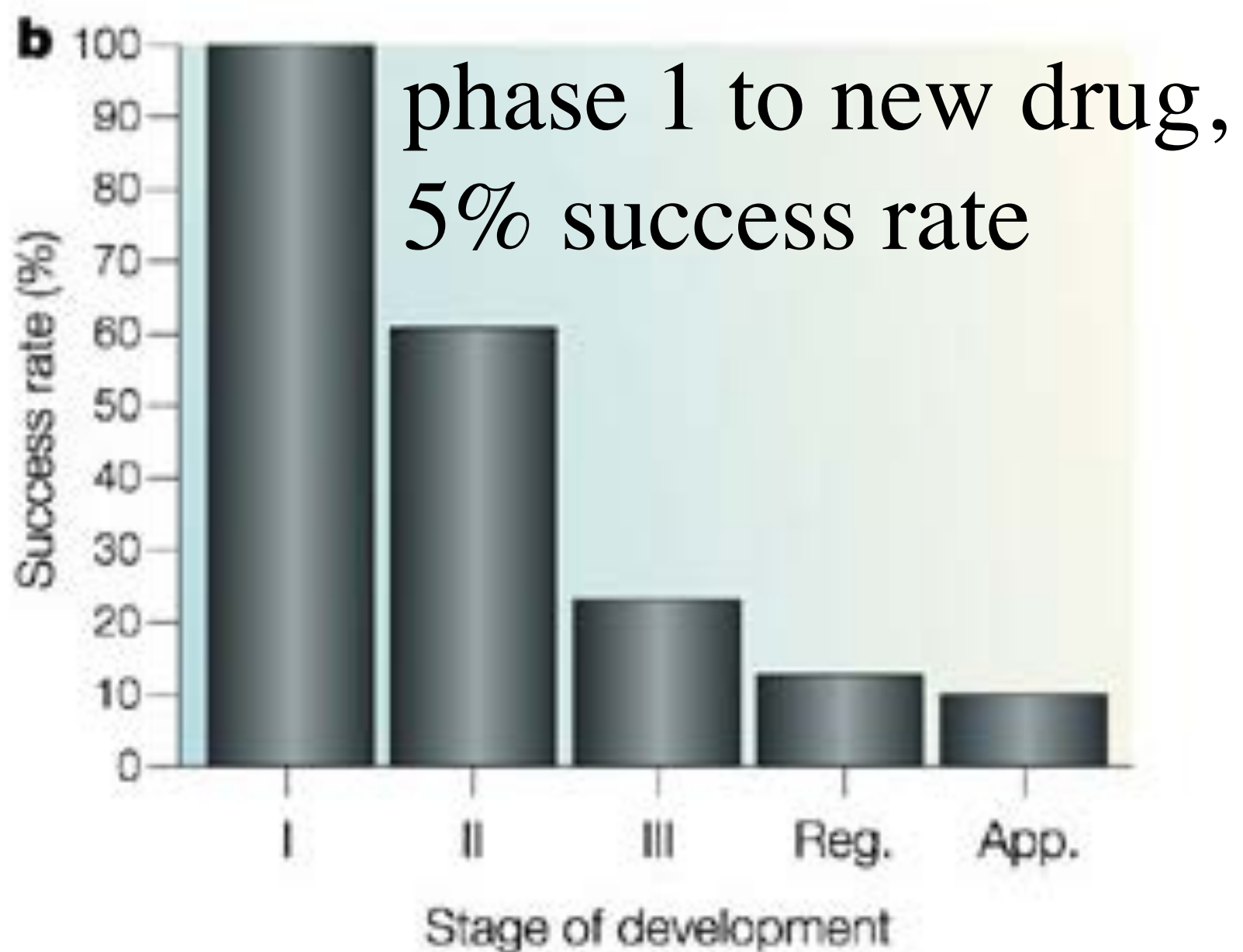
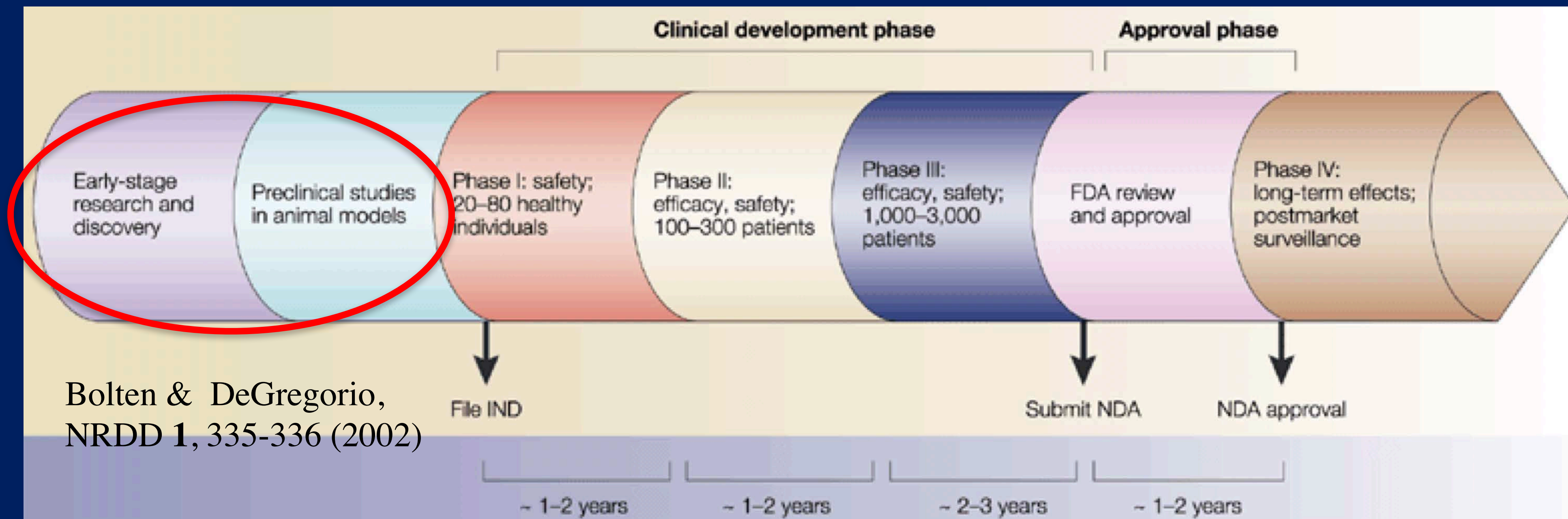
Heart attack



Sigma: decent
SERT: decent
NMDA: decent

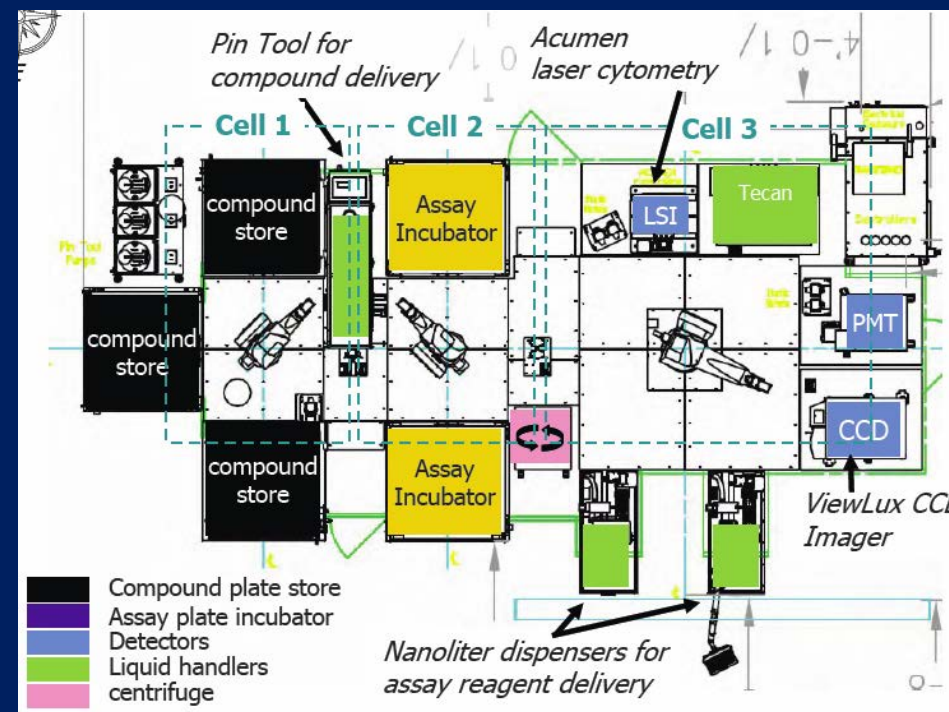
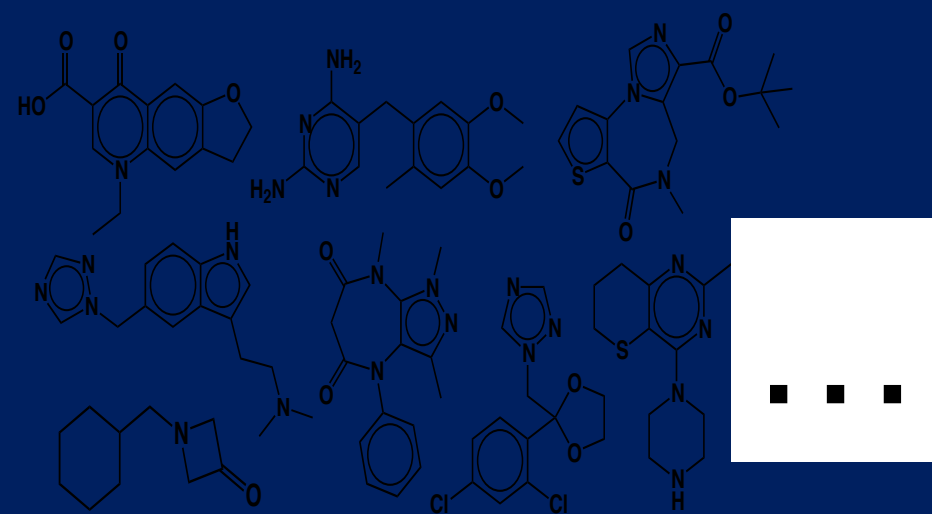
Dependence,
sleep disturbance

The drug discovery pipeline

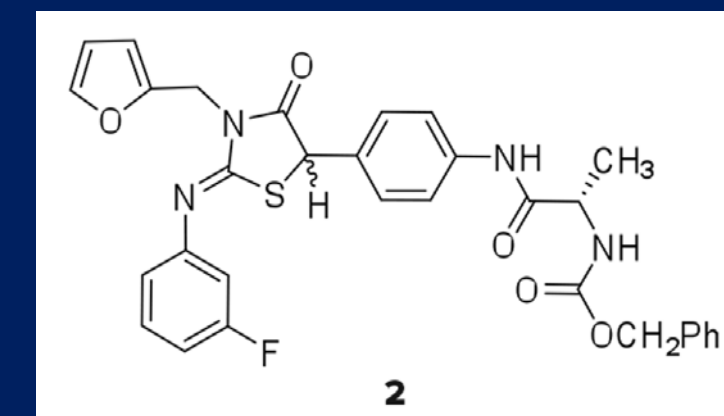


Anti HCV Daclatasvir: 2003 to 2015

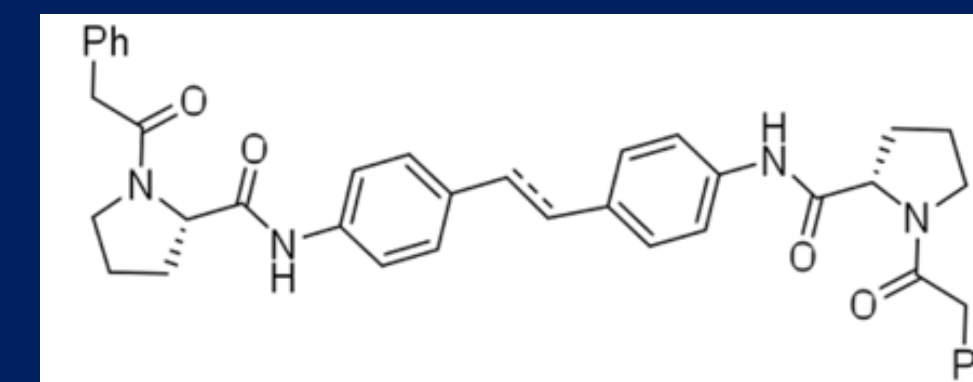
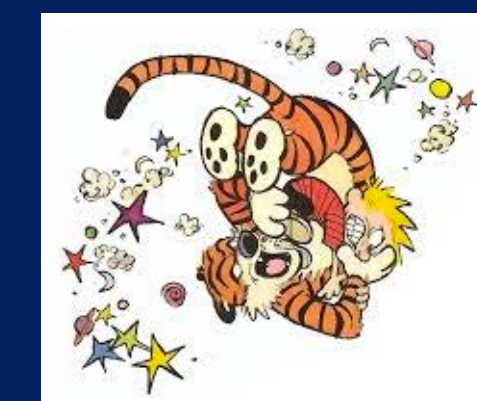
> 10⁶ molecules



1 (!) confirmed hit



chemistry
in vitro biology



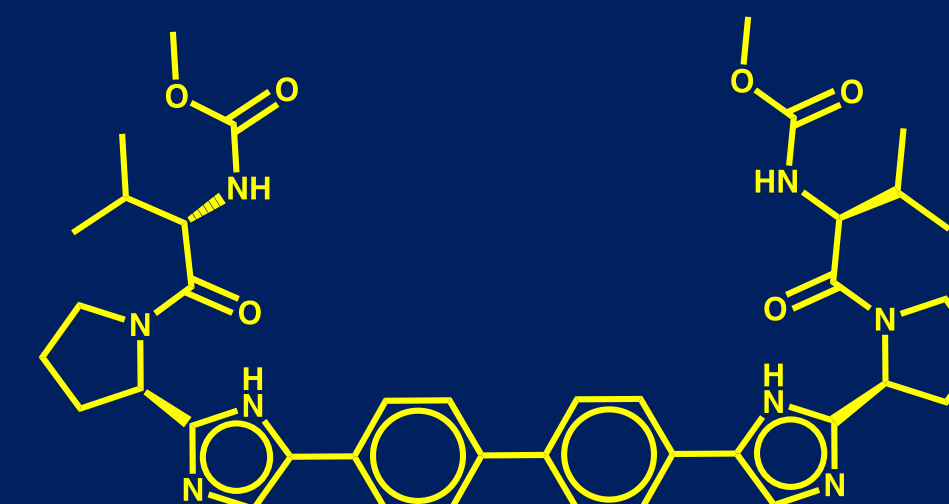
chemistry
pharm tox
Animal efficacy



Daclatasvir
12 years



IND application
Phase 1 (2007/8)
Phase 2
Phase 3



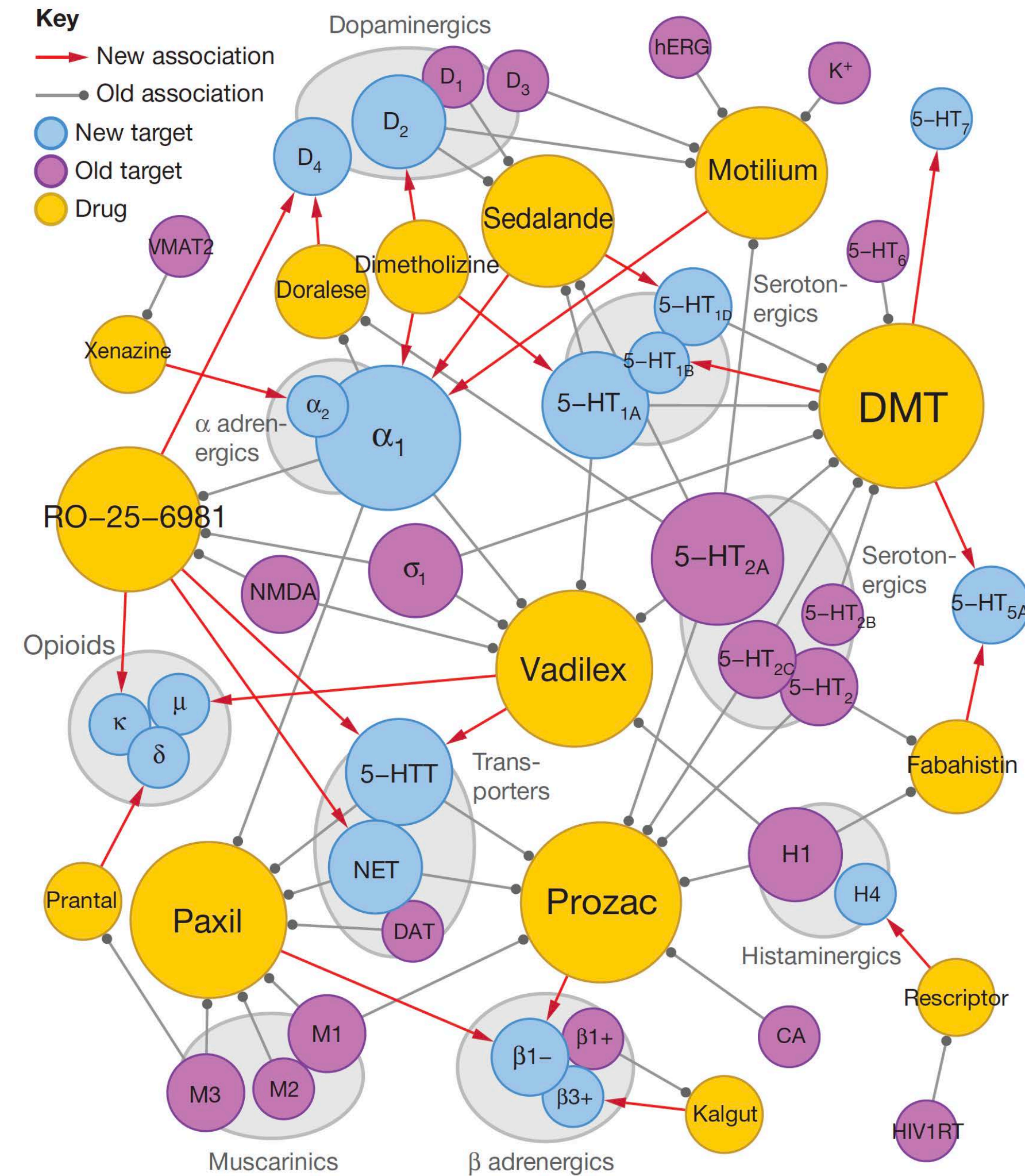
Statistics Based Chemoinformatics

Ligand Similarity Ensemble Approach (SEA)

Predicting new molecular targets for known drugs

Michael J. Keiser^{1,2*}, Vincent Setola^{3*}, John J. Irwin¹, Christian Laggner¹, Atheir I. Abbas⁴, Sandra J. Hufeisen⁵, Niels H. Jensen⁵, Michael B. Kujjer³, Roberto C. Matos³, Thuy B. Tran³, Ryan Whaley³, Richard A. Glennon⁶, Jérôme Hert¹, Kelan L. H. Thomas^{1,7}, Douglas D. Edwards¹, Brian K. Shoichet¹ & Bryan L. Roth^{3,5}

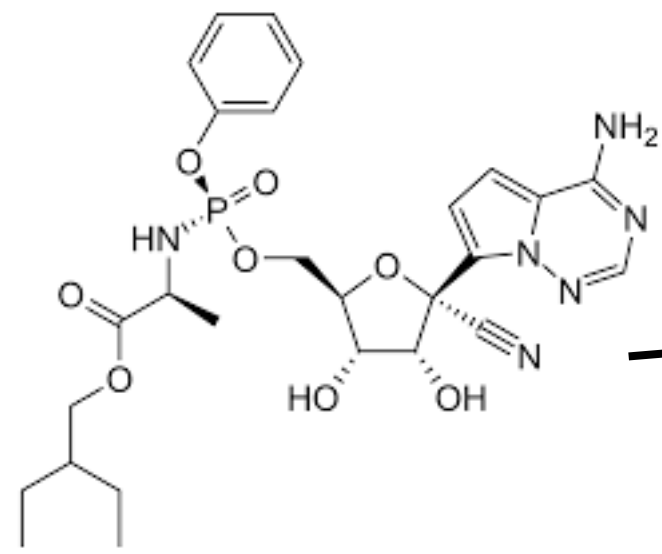
≈ 2,000 FDA Approved Drugs
≈ 10,000 Clinical Stage Drugs
>>>> Pre-clinical Drug Candidates



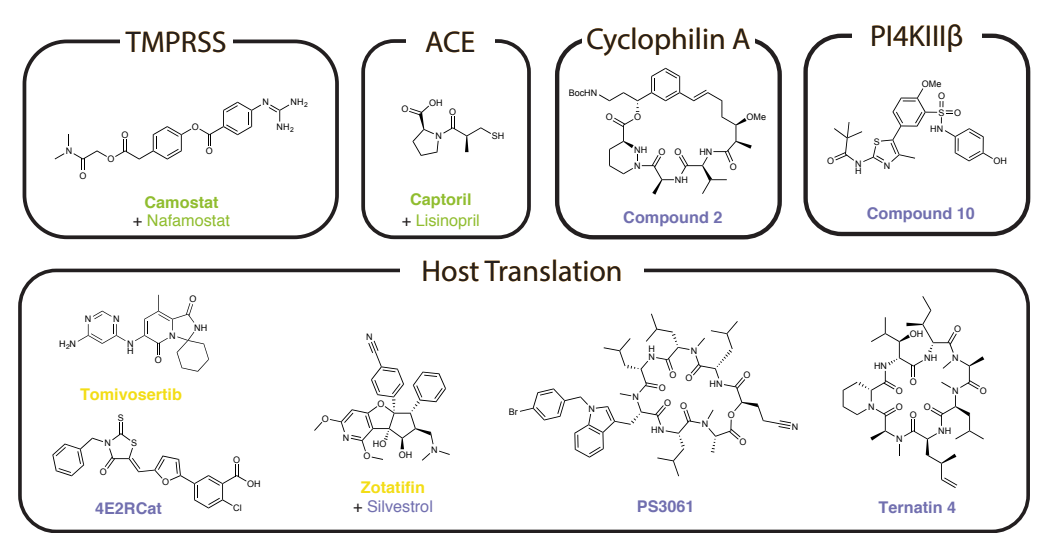
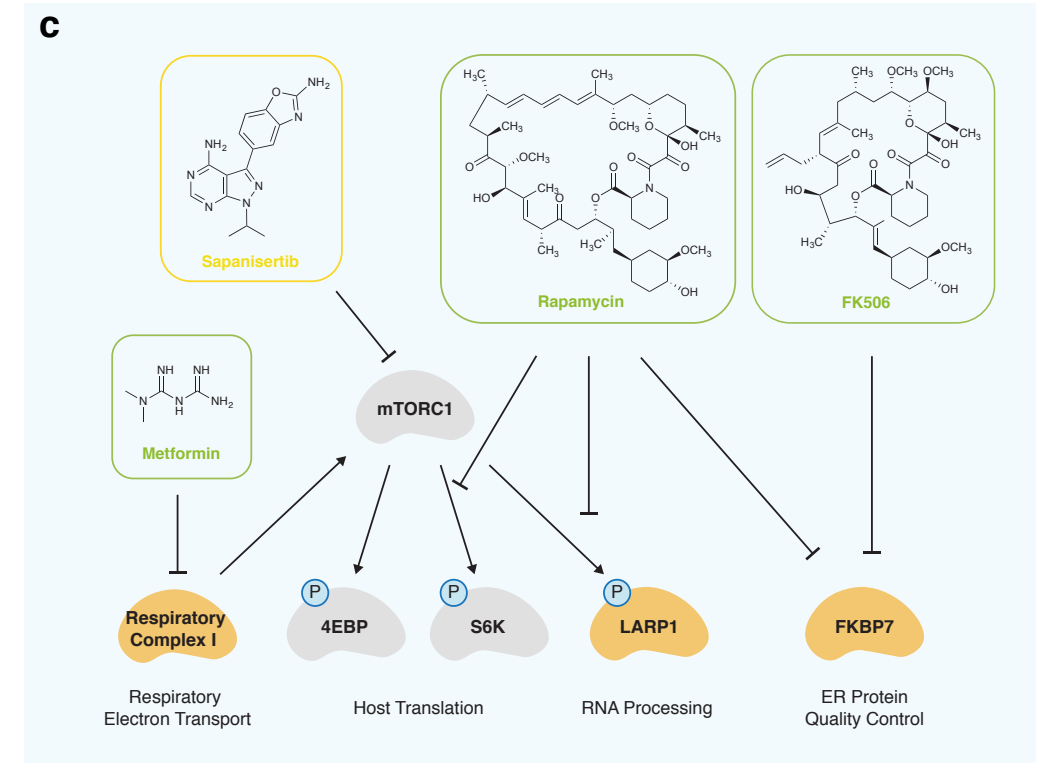
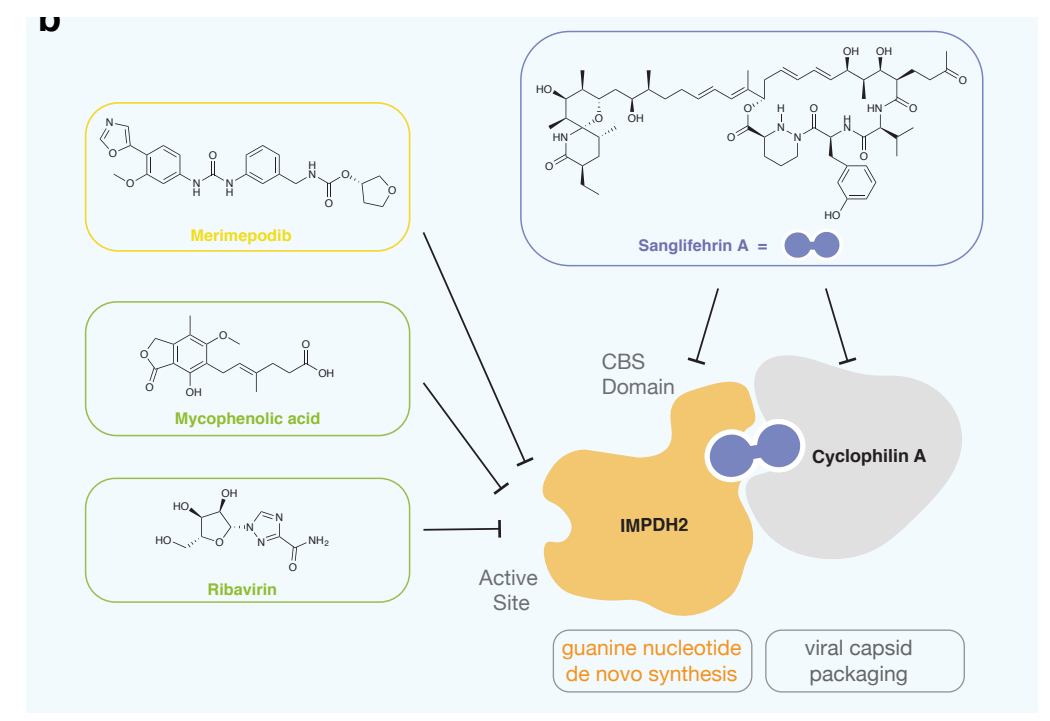
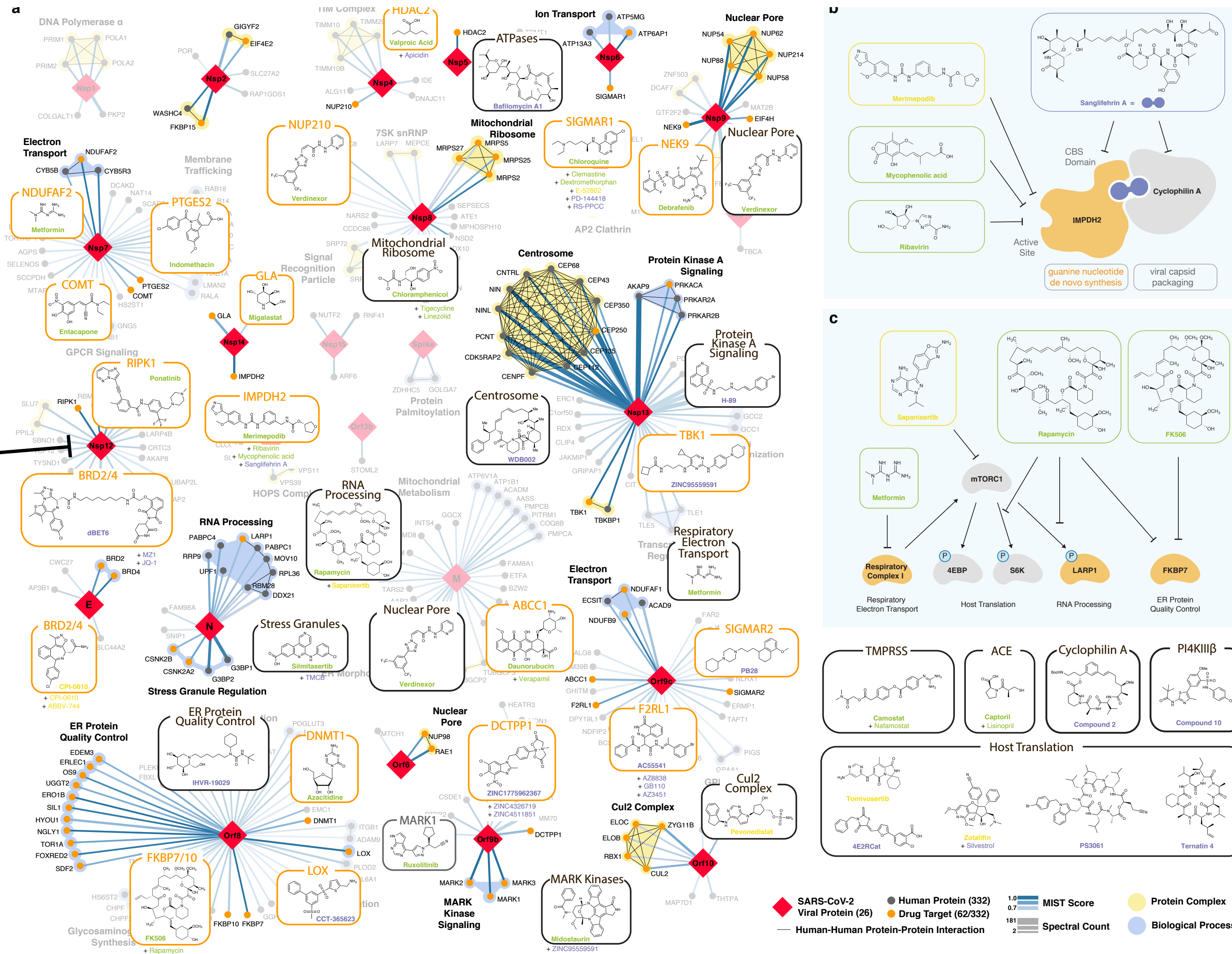
69 Candidates Identified

Approved Drugs + Drugs in Clinical Trials + Preclinical Compounds

Remdesivir
Direct Acting
Antiviral inhibitor of
Nsp12:
RNA-dependent
RNA Polymerase



Will become
standard of care
based on
NIAID sponsored
COVID trial results
released yesterday



◆ SARS-CoV-2
● Human Protein (332)
● Drug Target (62/332)
— Human-Human Protein-Protein Interaction
▬ MIST Score
▬ Spectral Count
● Protein Complex
● Biological Process

69 Existing drugs targeting SARS-CoV-2 human host factors

Camostat1	Linezolid1	Ruxolitinib	Pevonedistat	Apicidin	JQ1	ZINC4326719
Captopril	Lisinopril	S-verapamil	RVX-208	AZ3451	MZ1	ZINC4511851
Chloramphenicol	Metformin	Silmitasertib	Sapanisertib	AZ8838	PB28	ZINC95559591
Chloroquine	Midostaurin	Tigecycline	Tomivosertib	Bafilomycin A1	PD-144418	
Dabrafenib	Migalastat	Valproic Acid	Verdinexor	CCT 365623	PS3061	
Daunorubicin	Mycophenolic acid	ABBV-744	WDB002	Compound 10	RS-PPCC	
Entacapone	Nafamostat1	CPI-0610	XL413	Compound 2	Sangliferin A	
FK-506	Ponatinib	E-52862	Zotatifin	dBET6	Ternatin 4	
Haloperidol	Rapamycin	IHVR-19029	4E2RCat	GB110	TMCB	
Indomethacin	Ribavirin	Merimepodib	AC-55541	H-89	ZINC1775962367	

Approved
 Clinical Trial
 Pre-Clinical

Paper and authors



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bioRxiv is receiving many new papers on coronavirus SARS-CoV-2. A reminder: these are preliminary reports that have not been peer-reviewed. They should not be regarded as conclusive, guide clinical practice/health-related behavior, or be reported in news media as established information.

New Results

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A SARS-CoV-2-Human Protein-Protein Interaction Map Reveals Drug Targets and Potential Drug-Repurposing

[3 comments](#)

Posted March 22, 2020.

David E. Gordon, [Gwendolyn M. Jang](#), [Mehdi Bouhaddou](#), [Jiwei Xu](#), [Kirsten Obernier](#), [Matthew J O'Meara](#), [Jeffrey Z. Guo](#), [Danielle L. Swaney](#), [Tia A. Tummino](#), [Ruth Huttenhain](#), [Robyn Kaake](#), [Alicia L. Richards](#), [Beril Tutuncuoglu](#), [Helene Foussard](#), [Jyoti Batra](#), [Kelsey Haas](#), [Maya Modak](#), [Minkyu Kim](#), [Paige Haas](#), [Benjamin J. Polacco](#), [Hannes Braberg](#), [Jacqueline M. Fabius](#), [Manon Eckhardt](#), [Margaret Soucheray](#), [Melanie Brewer](#), [Merve Cakir](#), [Michael J. McGregor](#), [Qiongyu Li](#), [Zun Zar Chi Naing](#), [Yuan Zhou](#), [Shiming Peng](#), [Ilsa T. Kirby](#), [James E. Melnyk](#), [John S Chorbha](#), [Kevin Lou](#), [Shizhong A. Dai](#), [Wenqi Shen](#), [Ying Shi](#), [Ziyang Zhang](#), [Inigo Barrio-Hernandez](#), [Danish Memon](#), [Claudia Hernandez-Armenta](#), [Christopher J.P. Mathy](#), [Tina Perica](#), [Kala B. Pilla](#), [Sai J. Ganesan](#), [Daniel J. Saltzberg](#), [Rakesh Ramachandran](#), [Xi Liu](#), [Sara B. Rosenthal](#), [Lorenzo Calviello](#), [Srivats Venkataramanan](#), [Yizhu Lin](#), [Stephanie A. Wankowicz](#), [Markus Bohn](#), [Raphael Trenker](#), [Janet M. Young](#), [Devin Caverio](#), [Joe Hiatt](#), [Theo Roth](#), [Ujjwal Rathore](#), [Advait Subramanian](#), [Julia Noack](#), [Mathieu Hubert](#), [Ferdinand Roesch](#), [Thomas Vallet](#), [Björn Meyer](#), [Kris M. White](#), [Lisa Miorin](#), [David Agard](#), [Michael Emerman](#), [Davide Ruggero](#), [Adolfo GarcíSastre](#), [Natalia Jura](#), [Mark von Zastrow](#), [Jack Taunton](#), [Olivier Schwartz](#), [Marco Vignuzzi](#), [Christophe d'Enfert](#), [Shaeri Mukherjee](#), [Matt Jacobson](#), [Harmit S. Malik](#), [Danica G Fujimori](#), [Trey Ideker](#), [Charles S Craik](#), [Stephen Floor](#), [James S. Fraser](#), [John Gross](#), [Andrej Sali](#), [Tanja Kortemme](#), [Pedro Beltrao](#), [Kevan Shokat](#), [Brian K. Shoichet](#), [Nevan J. Krogan](#)

doi: <https://doi.org/10.1101/2020.03.22.002386>

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The authors have not filed for patent protection on the SARS-CoV-2 host interactions or the use of predicted drugs for treating COVID-19 to ensure all the information is freely available to accelerate the discovery of a treatment.

Collaborators



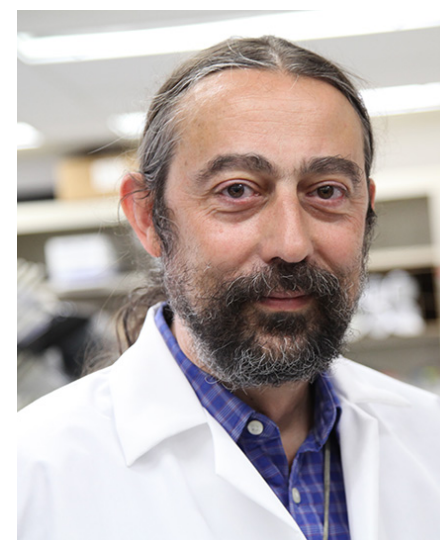
Marco Vignuzzi



Olivier Schwartz



Institut Pasteur, Paris



Adolfo Garcia-Sastre

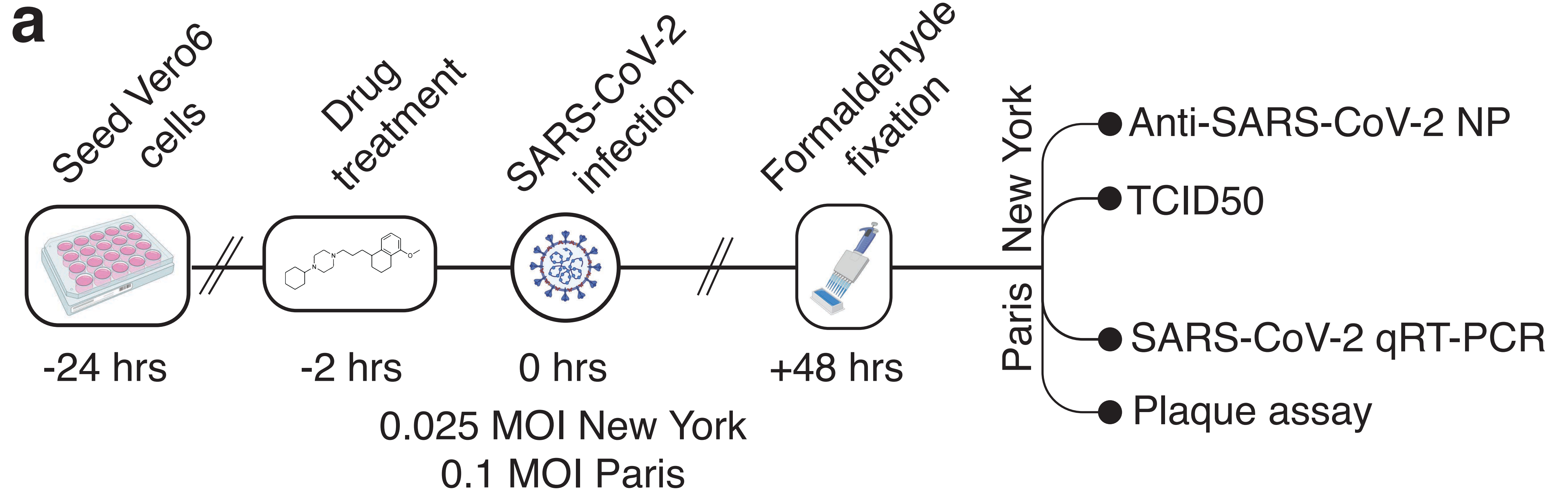


Kris White



Mount Sinai, New York

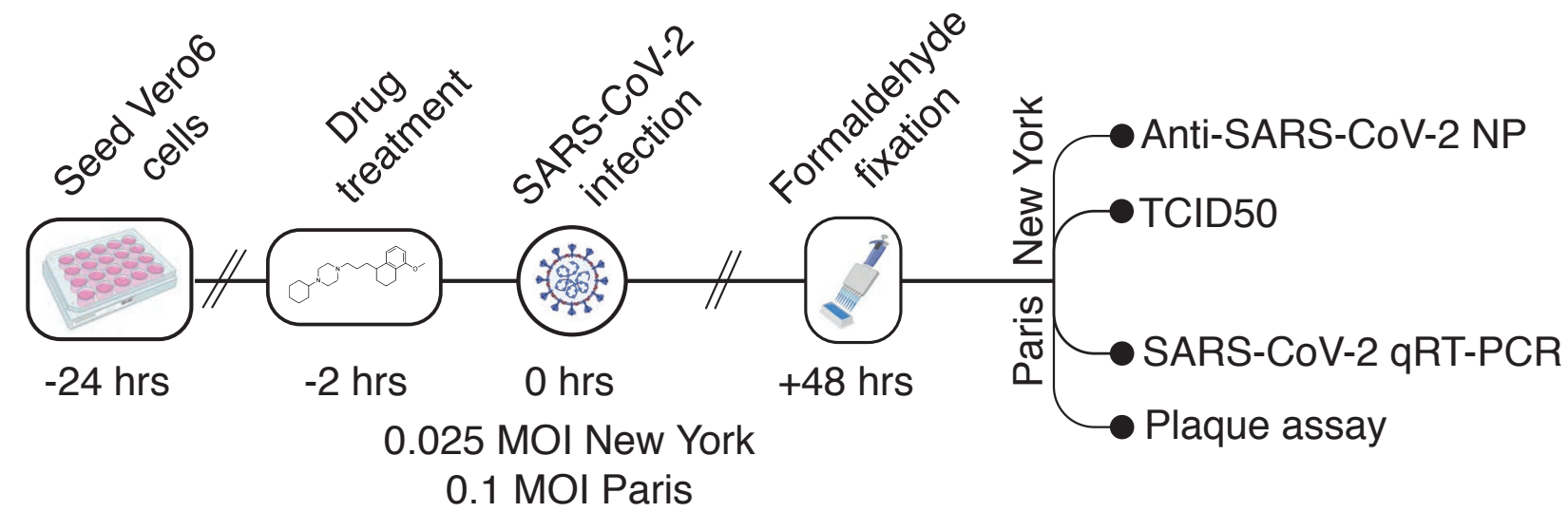
SARS-CoV-2 Replication Assays



The SARS-CoV-2 Infectible Vero E6 Cell line characteristics

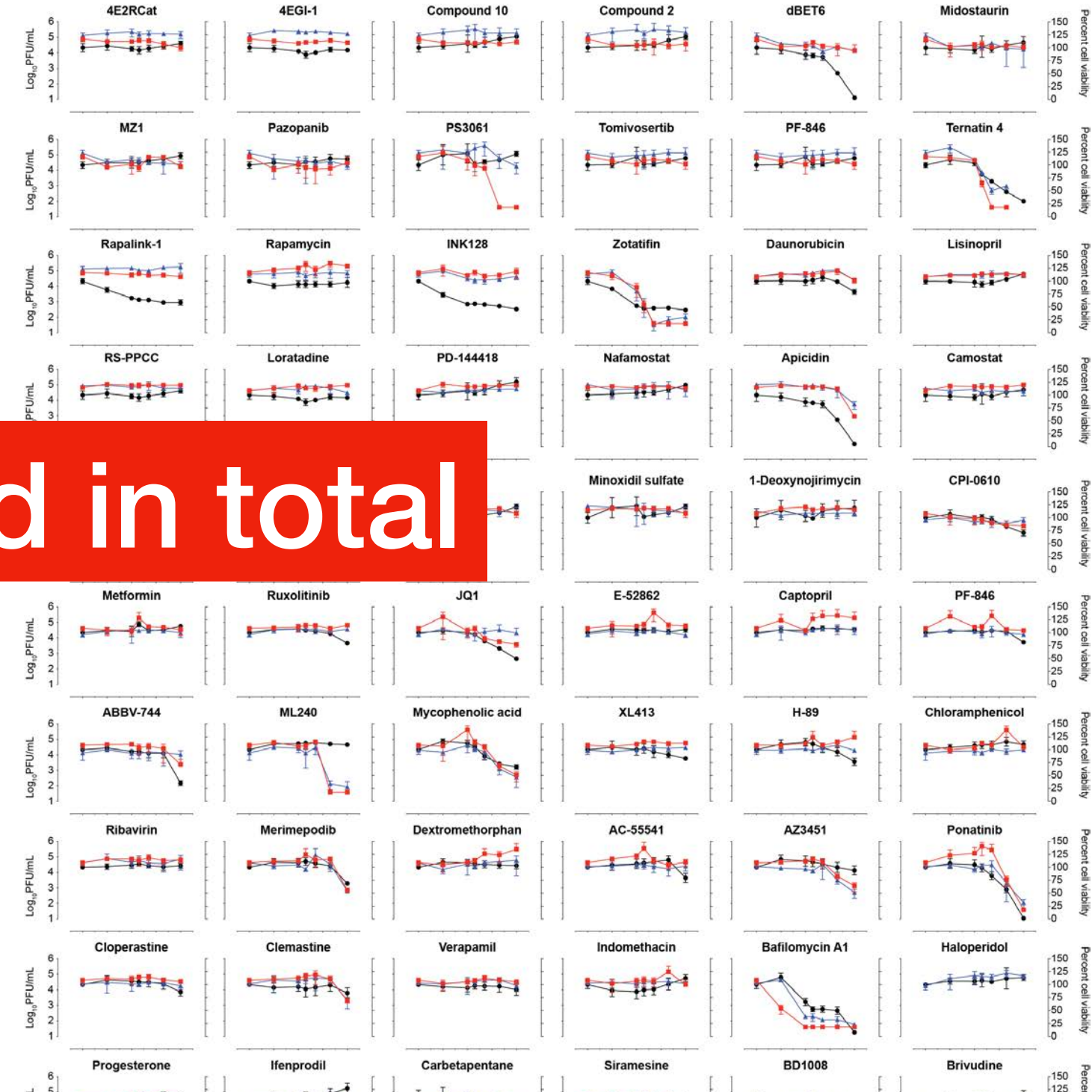
- Cell line model of choice for culture of emerging pathogens.
- Female African Green Monkey Bladder Cells primary culture started 1962 (Chiba Japan)
- Found to be highly susceptible to various viruses (SV-40, measles, rubella, arbo-, adenoviruses)
- Express Receptor for SARS-CoV-2 Ace2
- Pseudo-diploid. —immortalized but not transformed if kept at low passage
- Contains a homozygous deletion in Chromosome 12: loss of alpha- and beta-1 Interferon genes, and CDKN2A/CDKN2B (tumor suppressor locus for inhibitor of CDK4 and activator of p53)

Antiviral activity of host-directed drugs and compounds

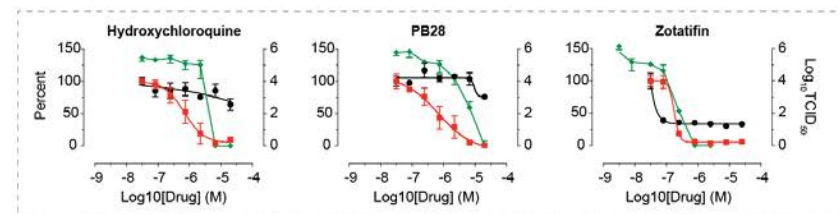


Mt Sinai: 37 drugs/compounds

Institut Pasteur: 44 drugs/compounds



47 tested in total



● Viral Titer (Plaque Assay) ● Viral RNA (qRT-PCR) ● Cell Viability (Alamar Blue)

Ten Agents Showed Efficacy in Killing Virus

Results Consistent in Different Assays Across Two Labs and Continents

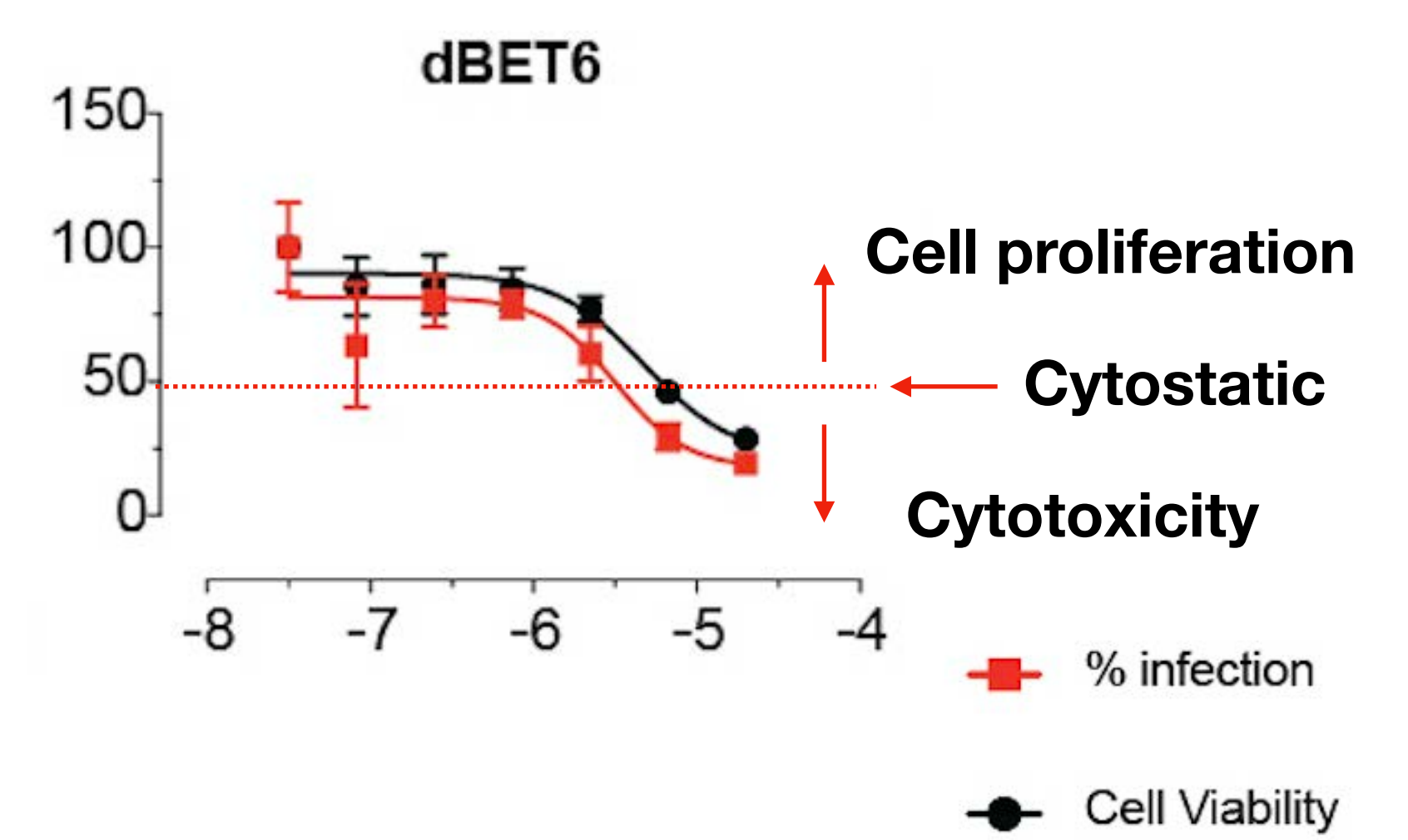
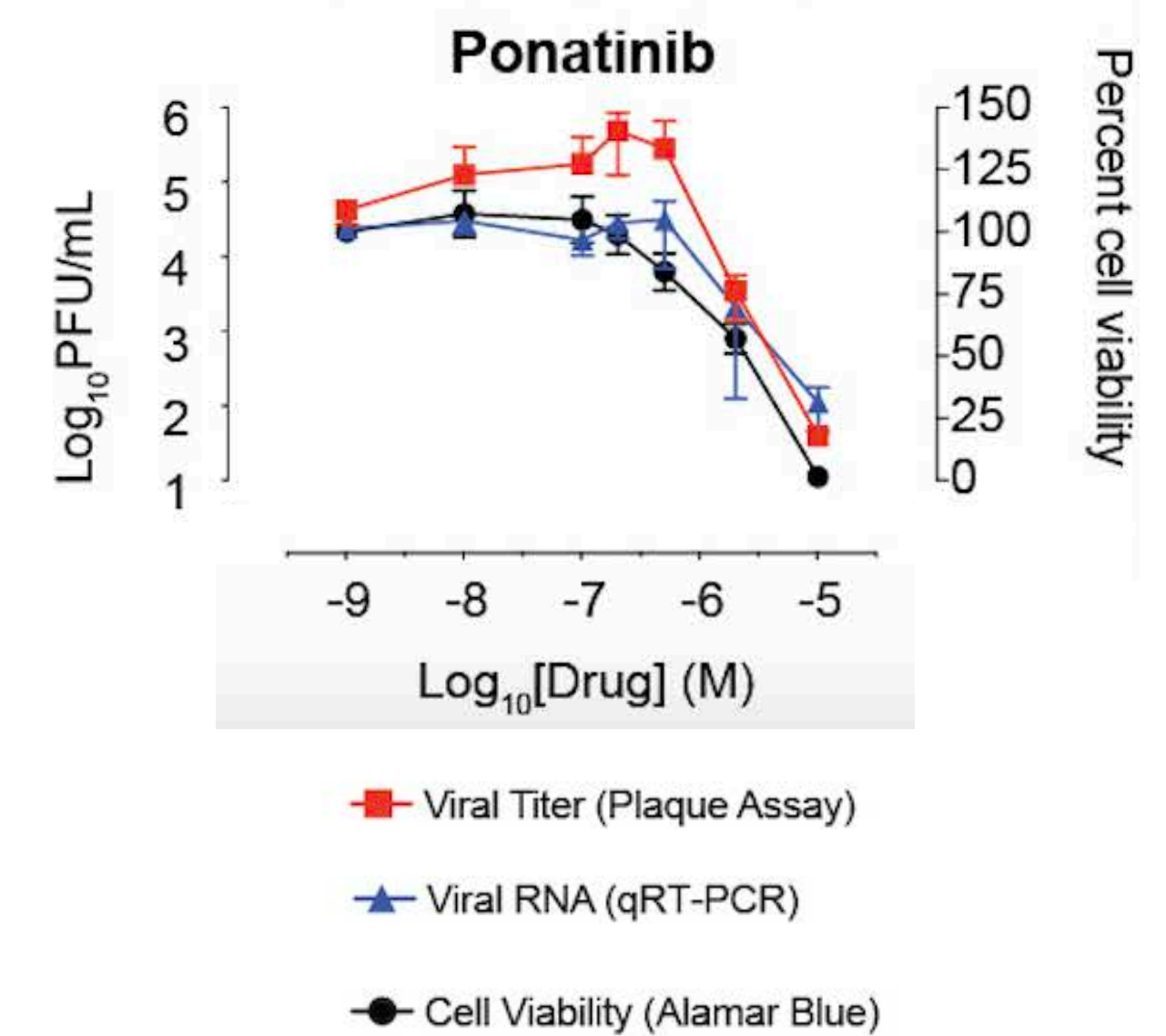
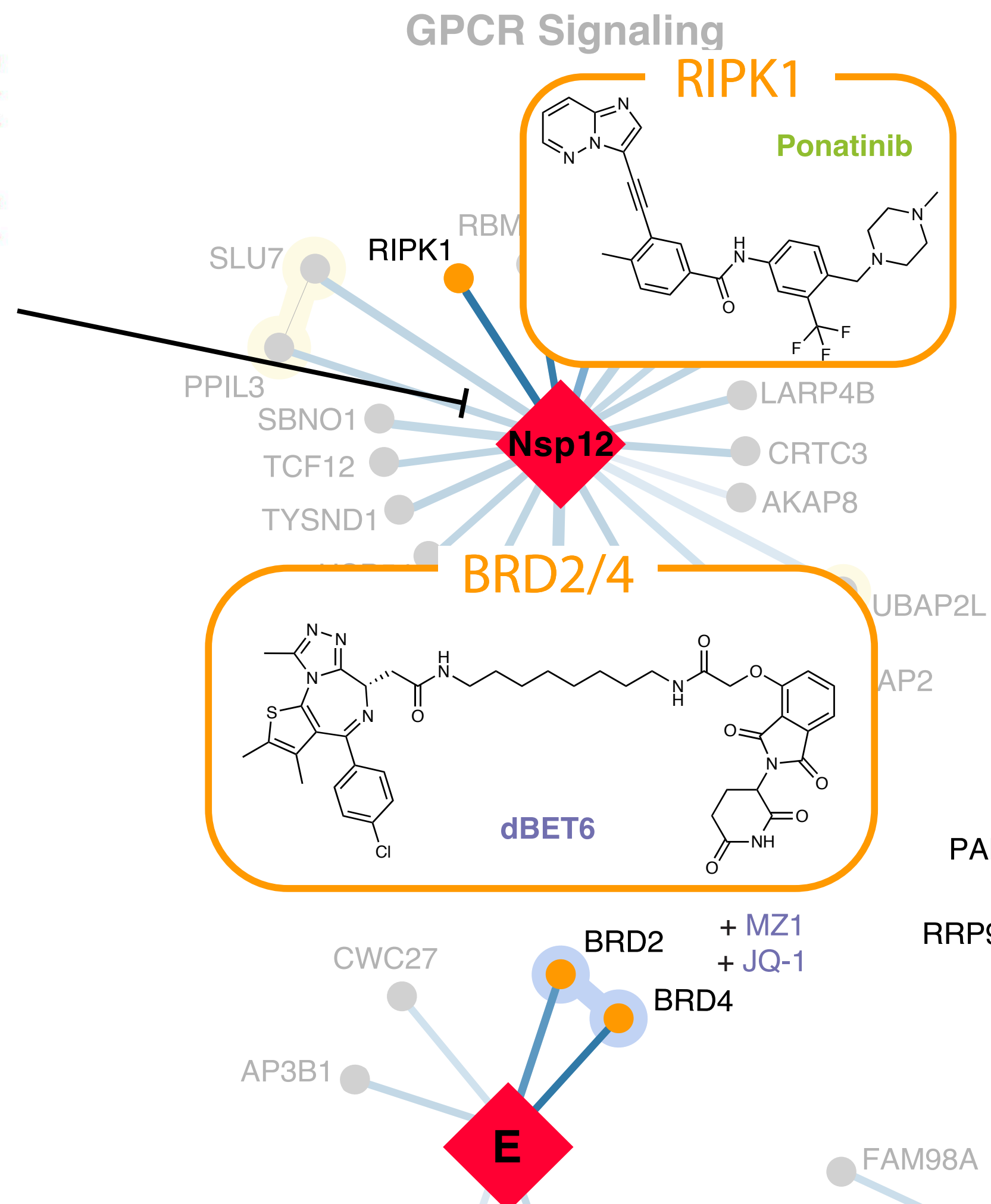
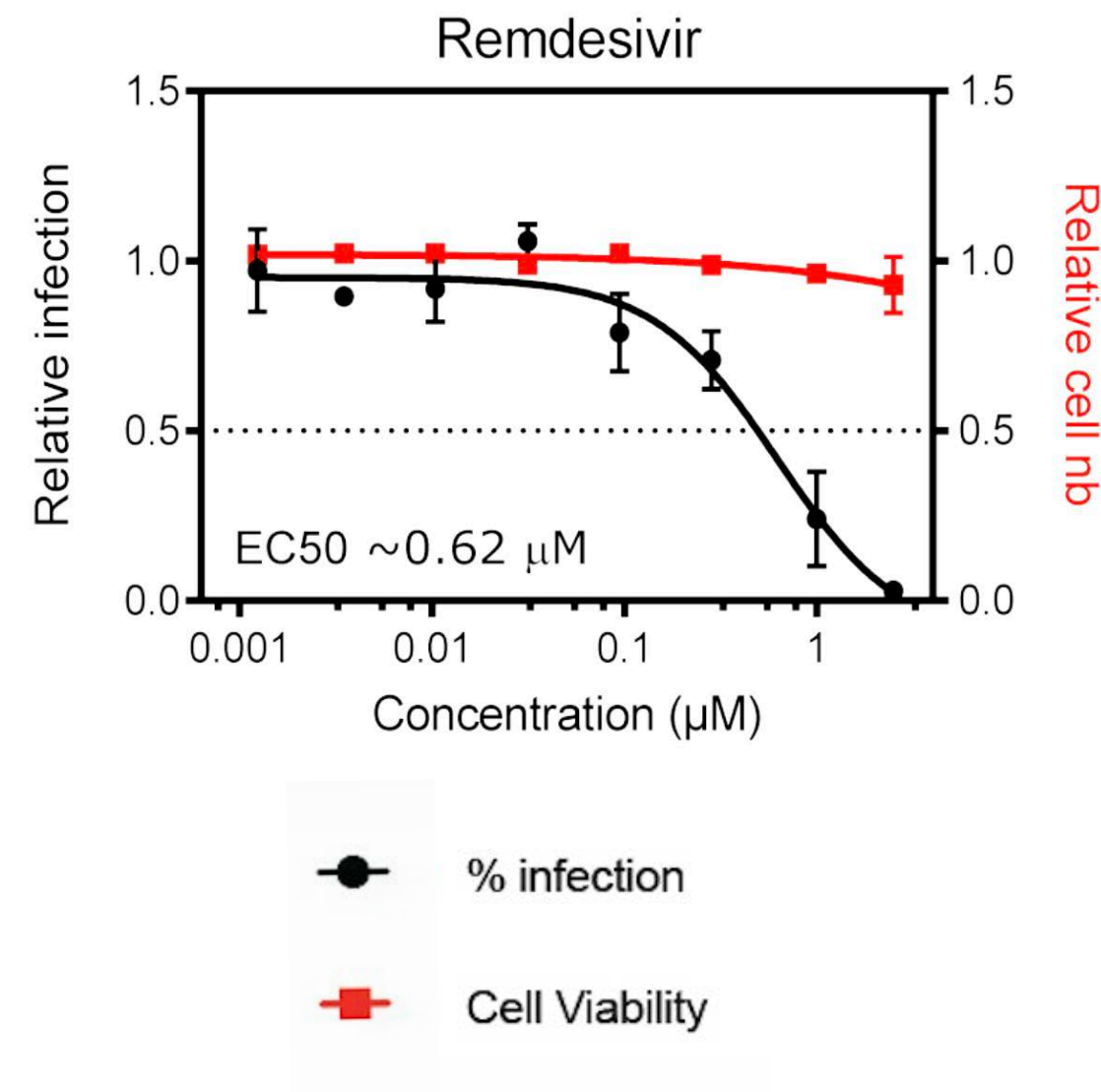
Protein Translation/Biogenesis Inhibitors:

- Zotatifin
- Ternatin-4/plitidepsin

SigmaR1 and SigmaR2 Modulators:

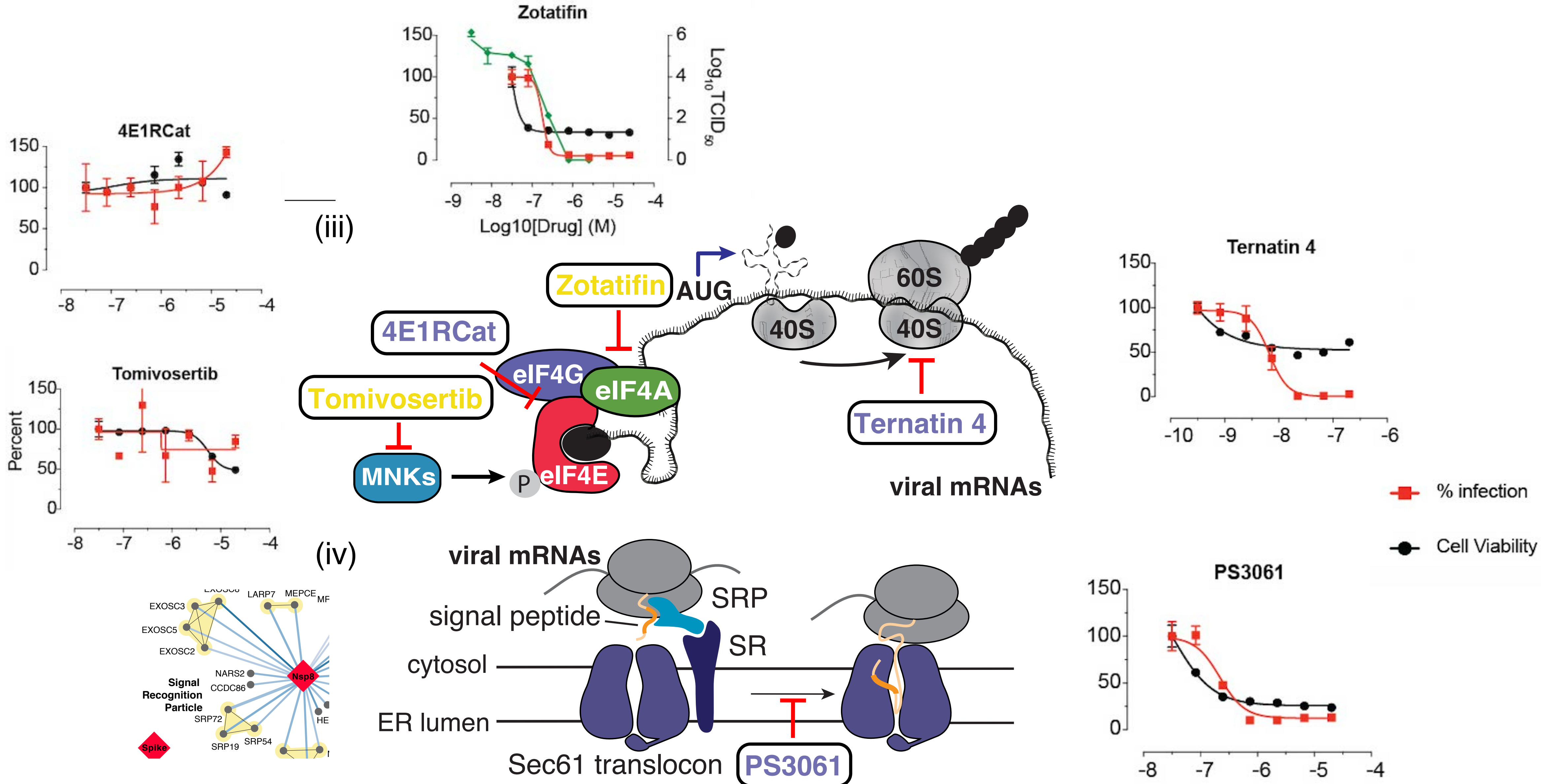
- *Antihistamines*
 - Cloperastine
 - Clemastine
- *Antipsychotics*
 - Haloperidol
 - **Melperone**
- *Antimalarials*
 - Hydroxychloroquine
 - *Hormone*
 - Progesterone
- *Antianxiety*
 - Siramesine
 - *Preclinical*
 - PB28 and PD-144418

Direct Acting and Host Factor Targeting Agents

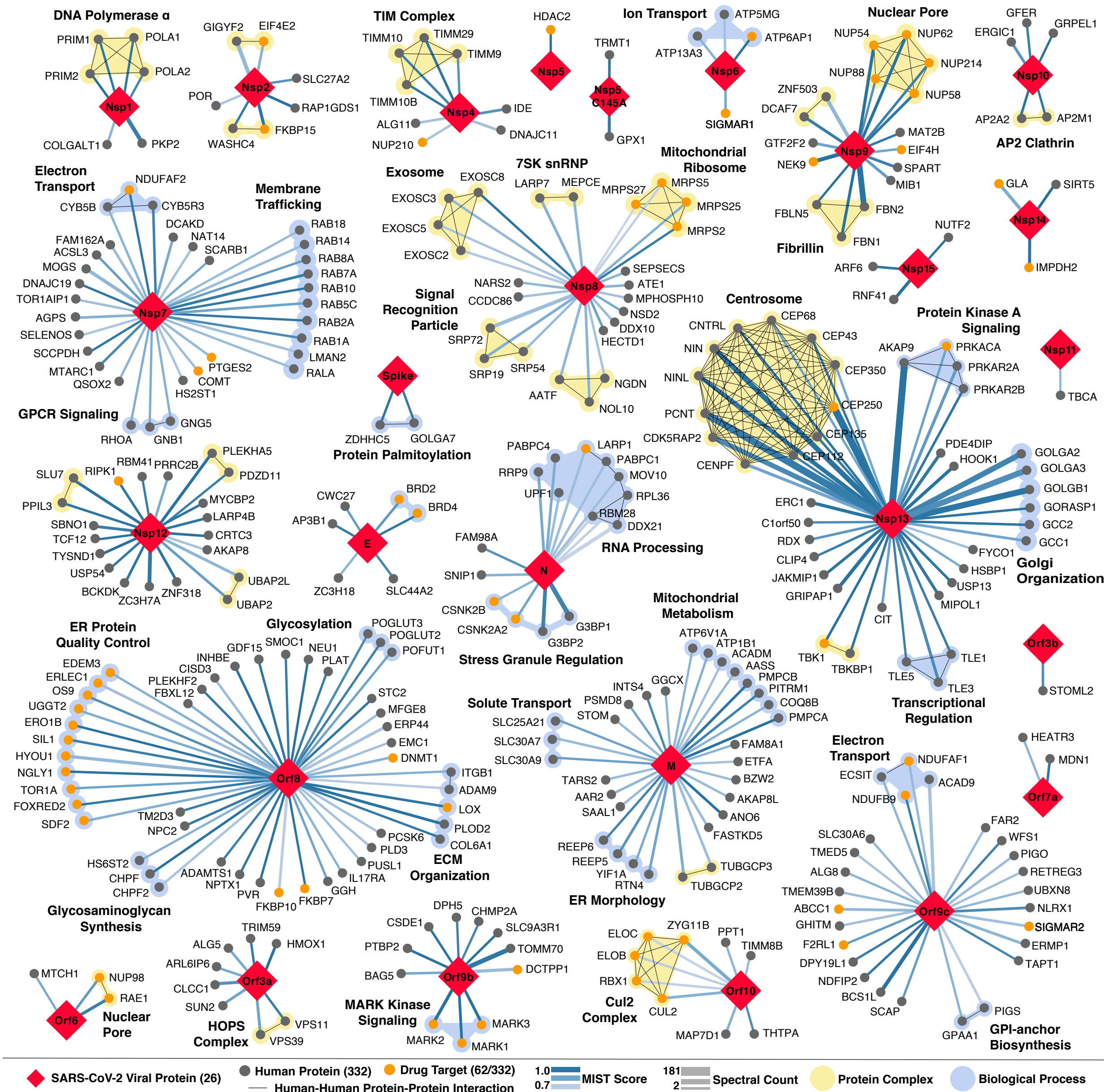


Riva et. al.
 bioRxiv preprint doi: <https://doi.org/10.1101/2020.04.16.044016>.

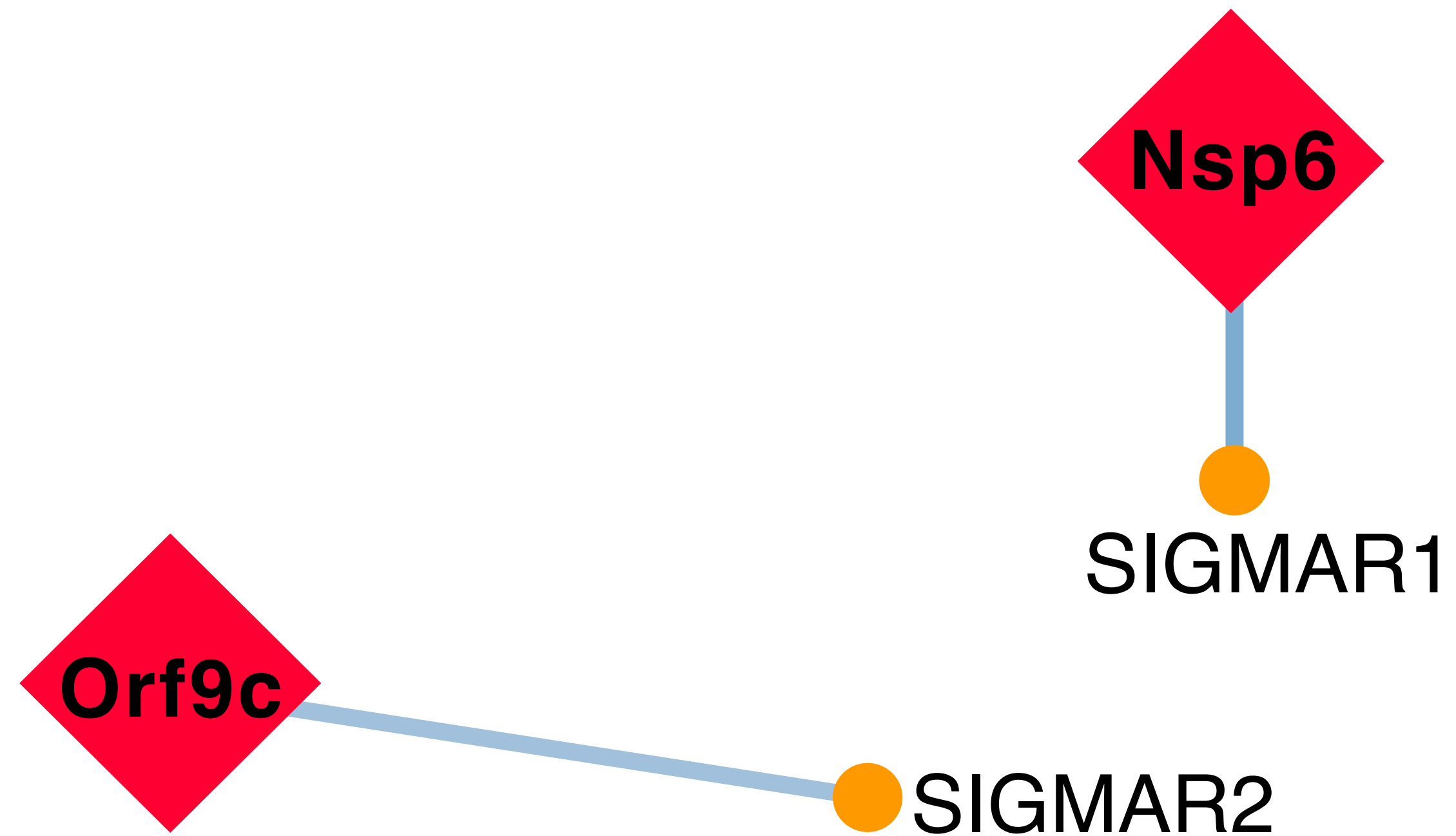
Protein Biogenesis as a Selectively Targetable Vulnerability



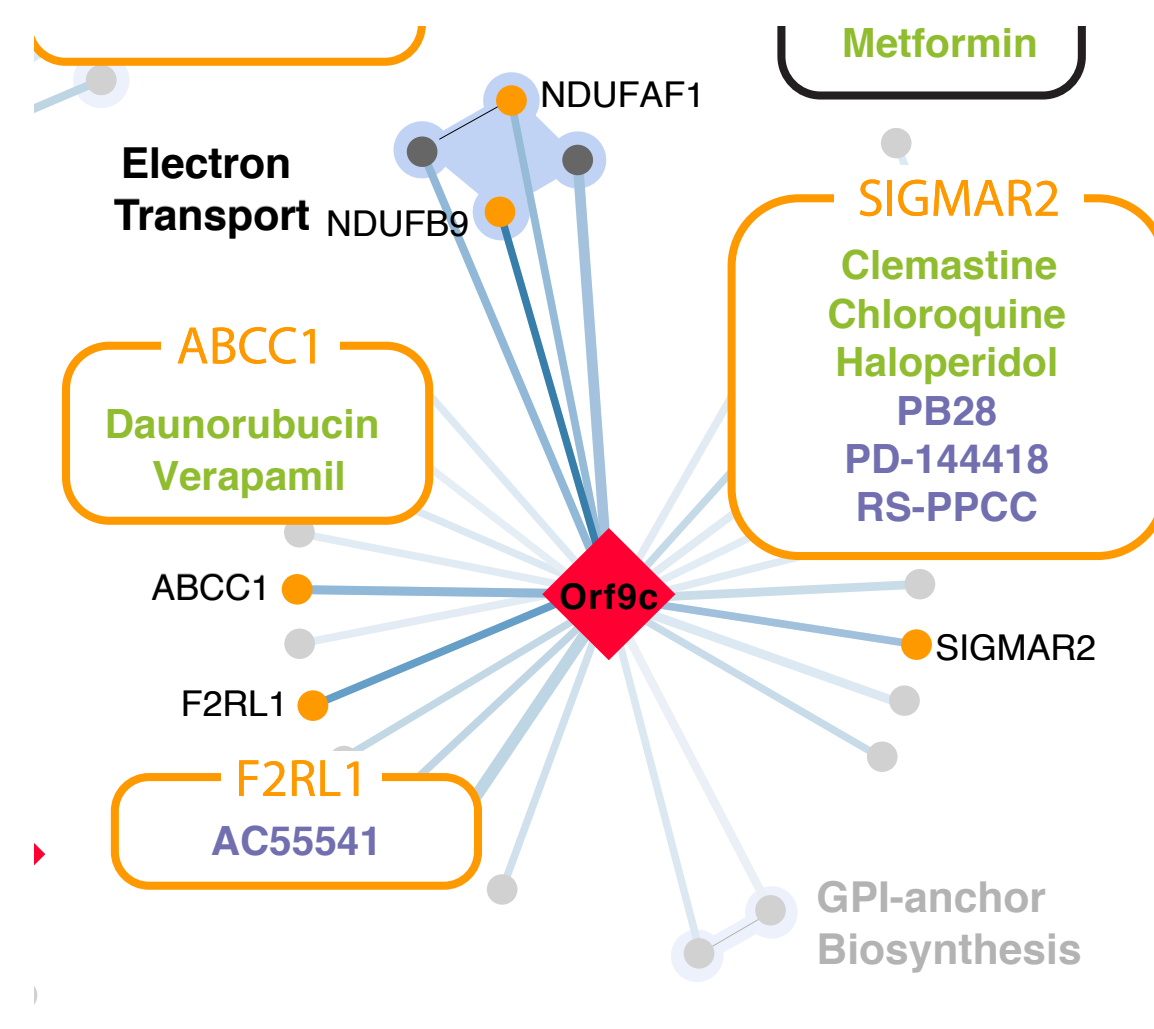
332 SARS-CoV-2-human PPIs include 69 druggable host factors



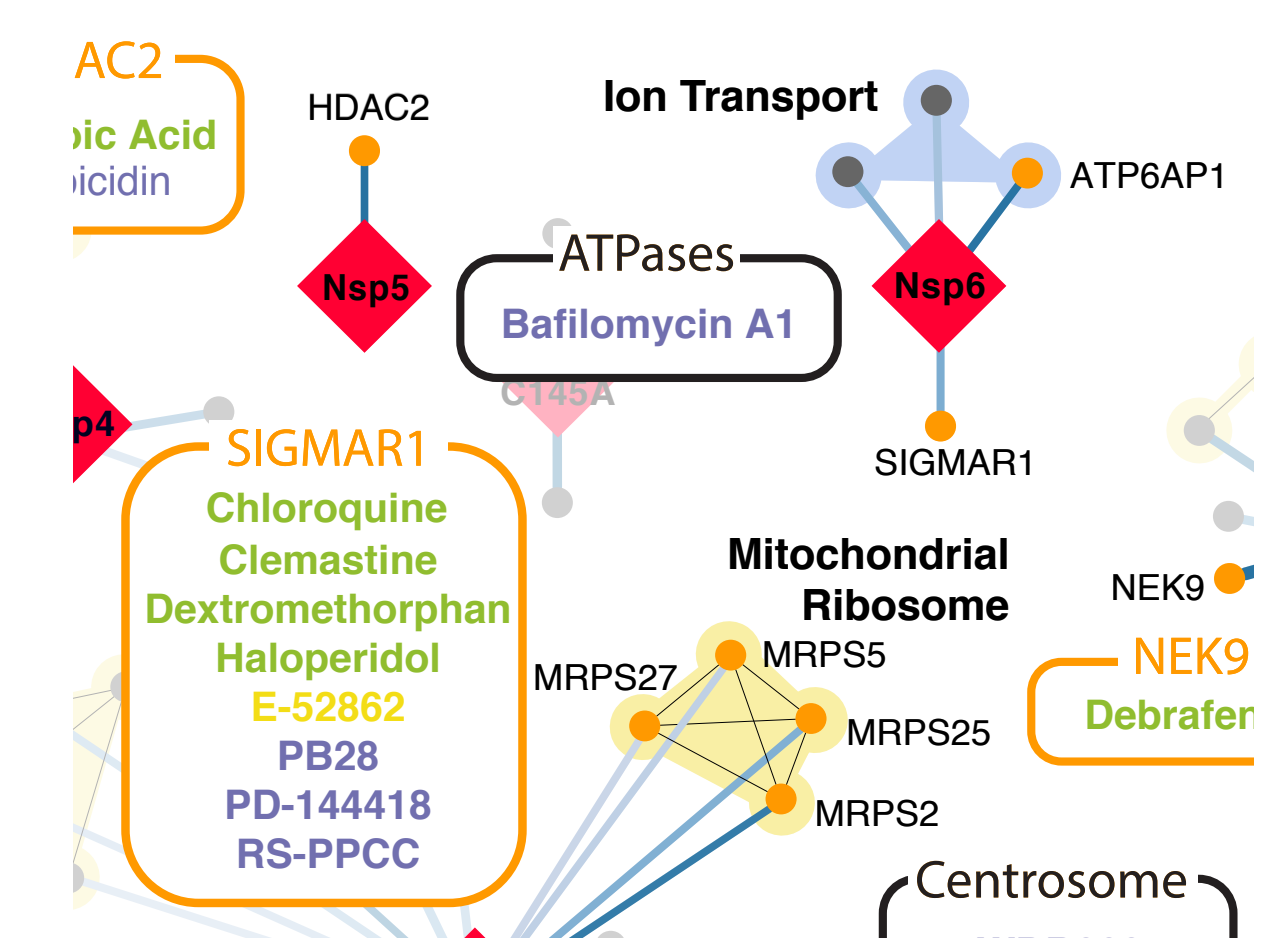
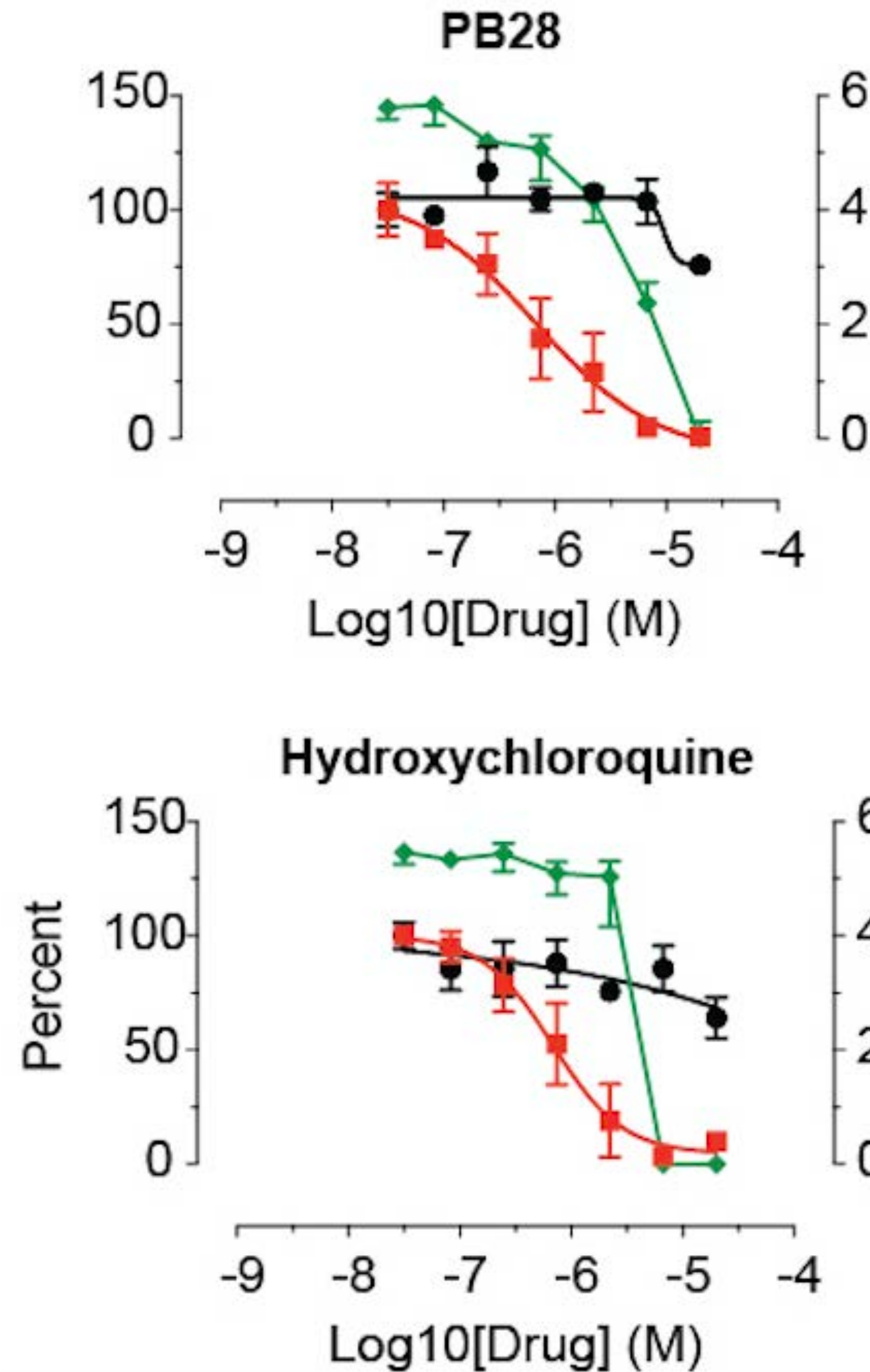
332 SARS-CoV-2-human PPIs include 69 druggable host factors



Hydroxychloroquine and Sigma R1 & Sigma R2 Receptors Are Very Attractive Host Factor Targets



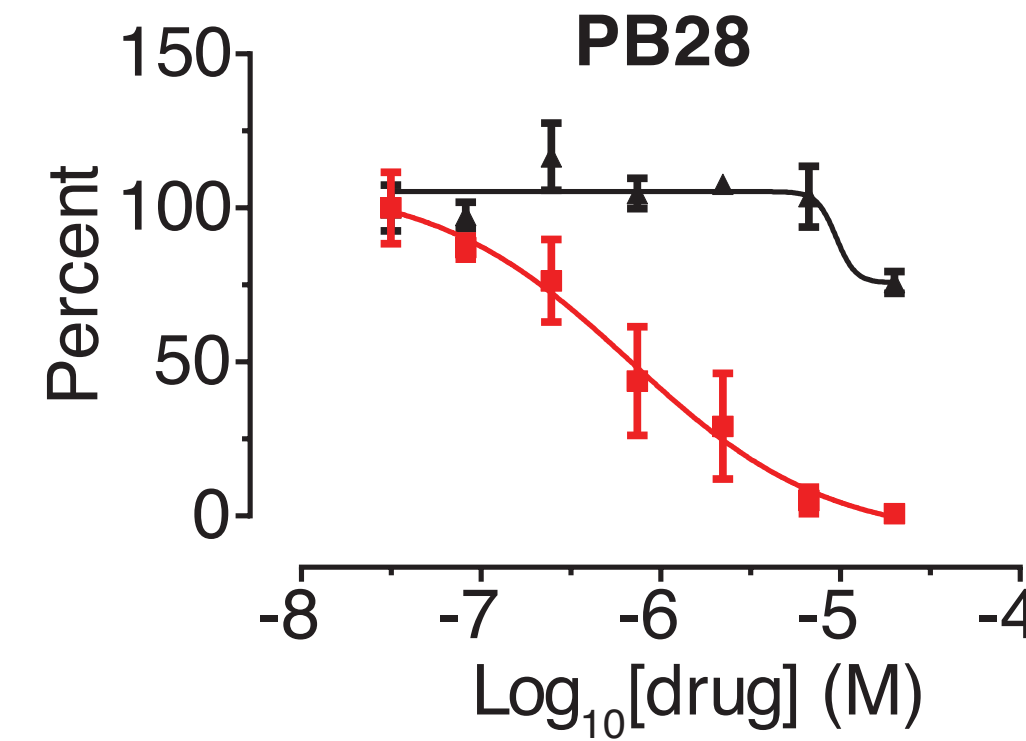
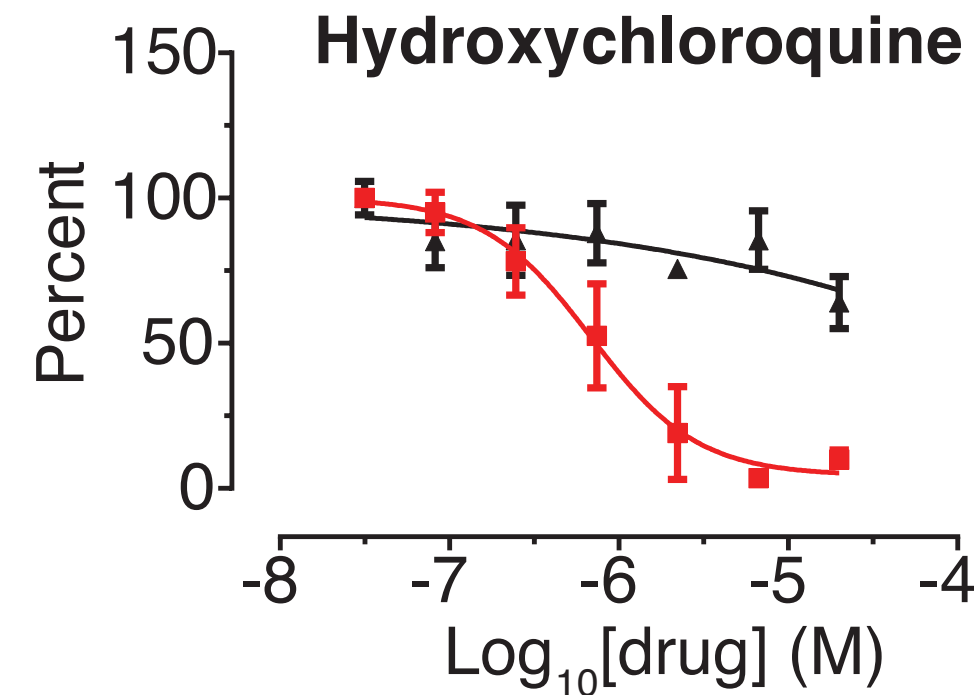
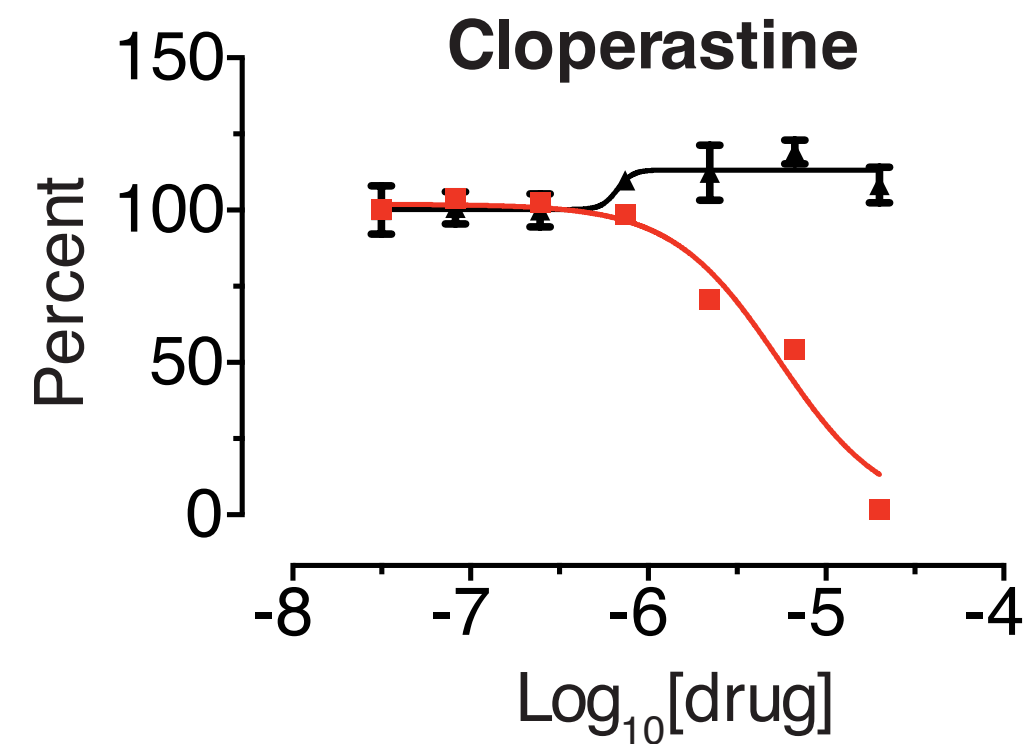
Mitochondria + ER



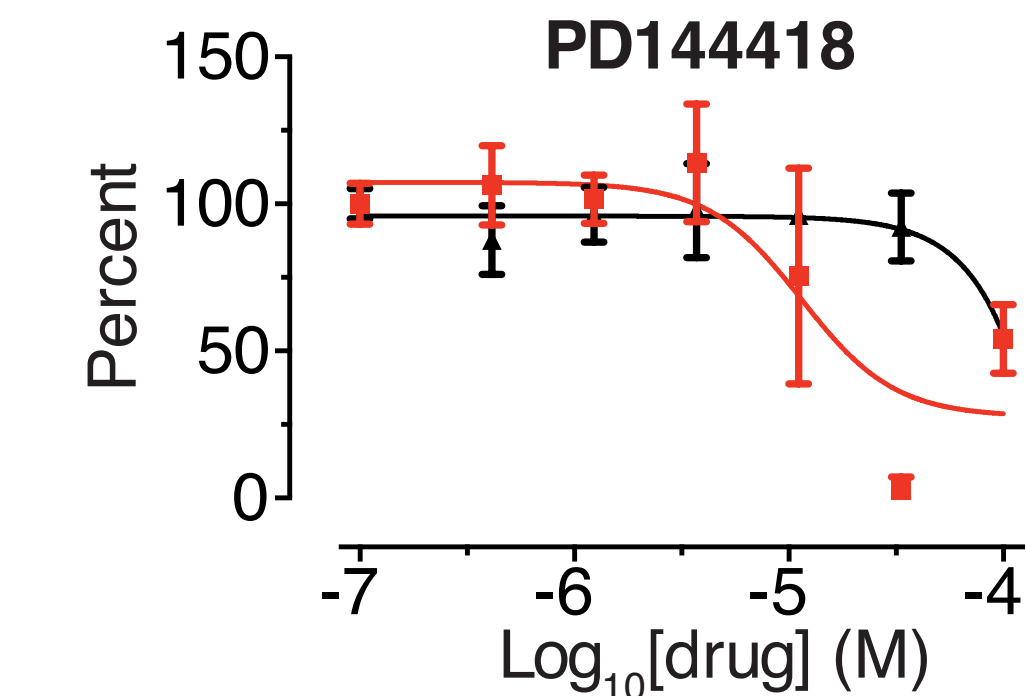
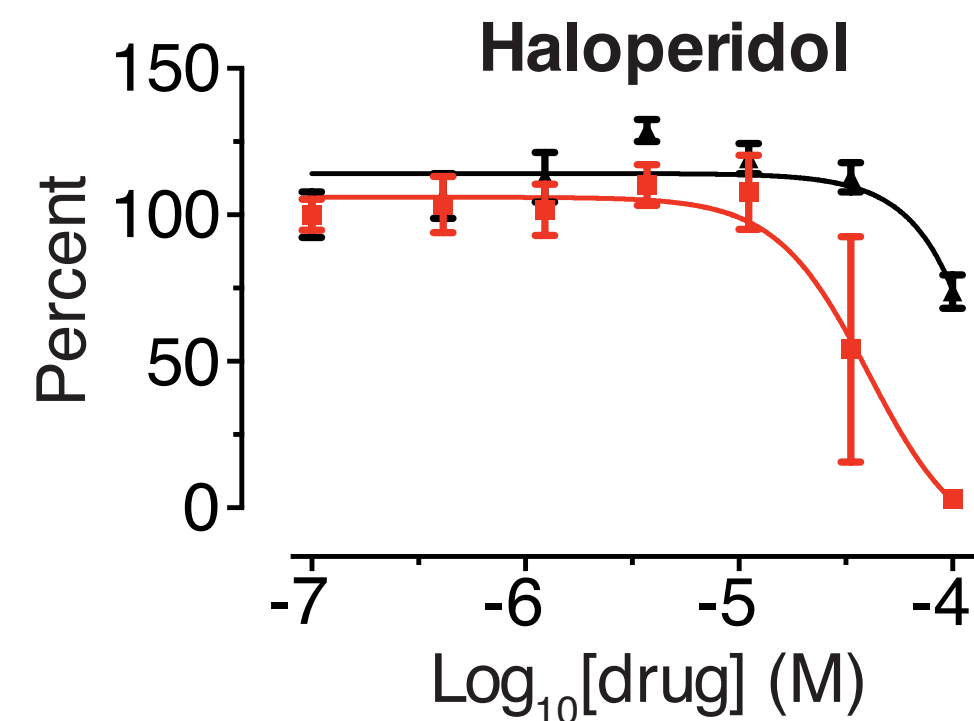
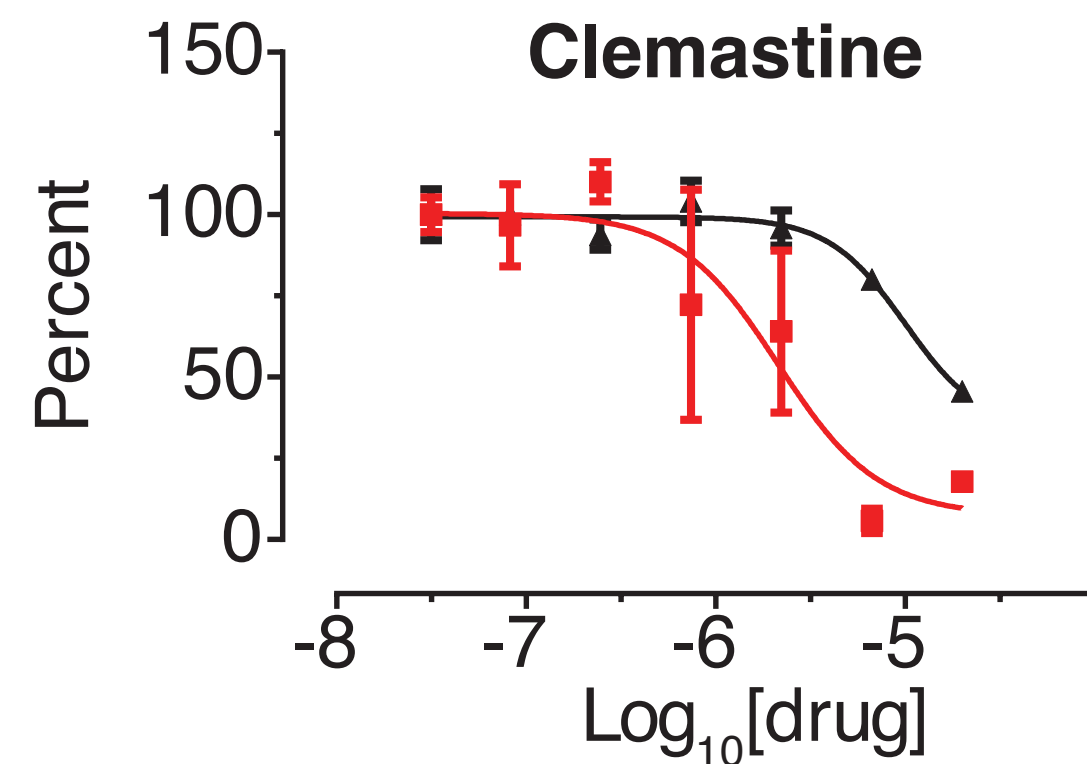
Vesicle Trafficking

- % infection
- Cell Viability
- ◆ TCID₅₀

Drugs/Compounds that Bind SigmaR1/R2



■ SARS-CoV-2 (Anti-NP)
▲ Cell viability



Antihistamines

Cloperastine
Clemastine

Antipsychotics

Haloperidol
Melperone

Antimalarials

Hydroxychloroquine

Hormone

Progesterone

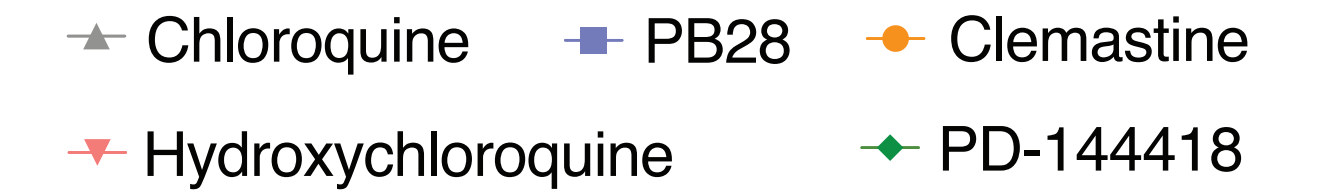
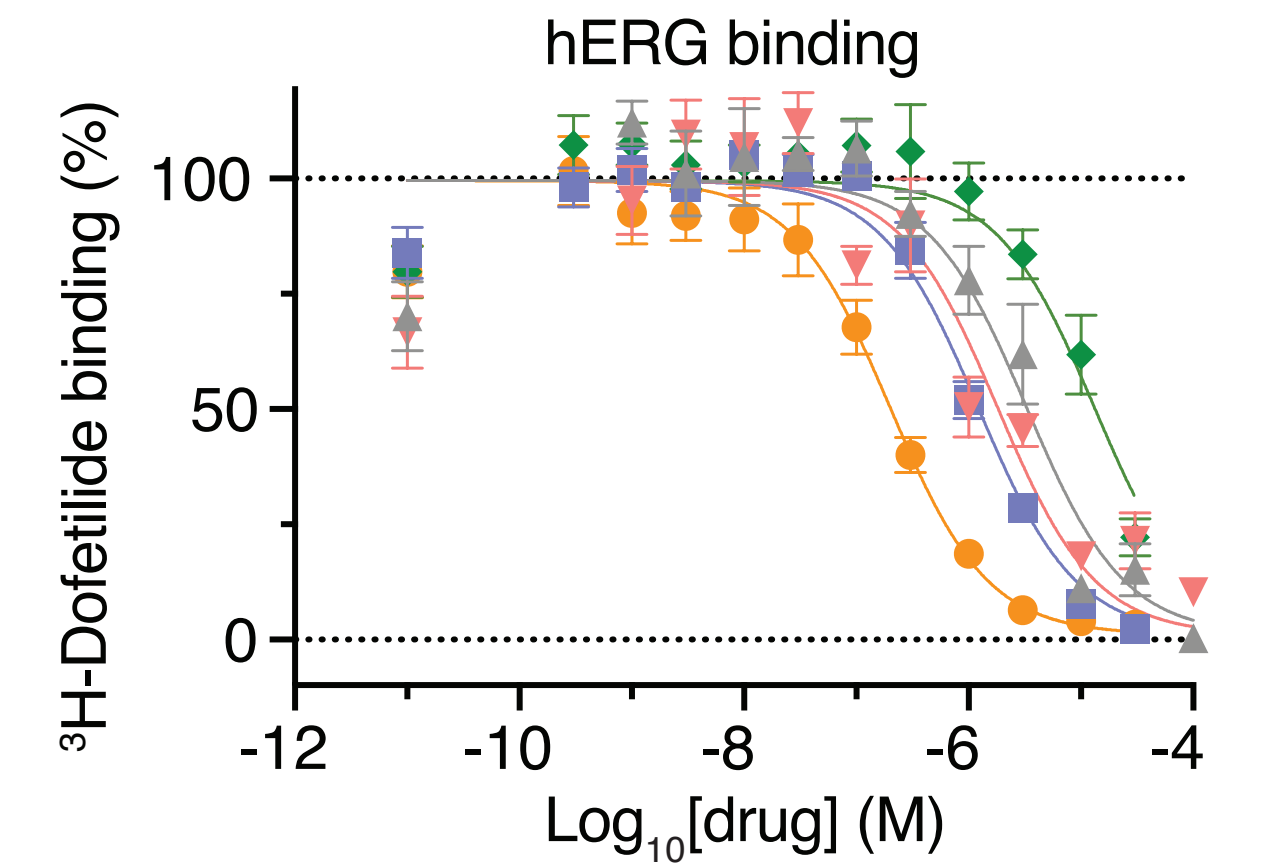
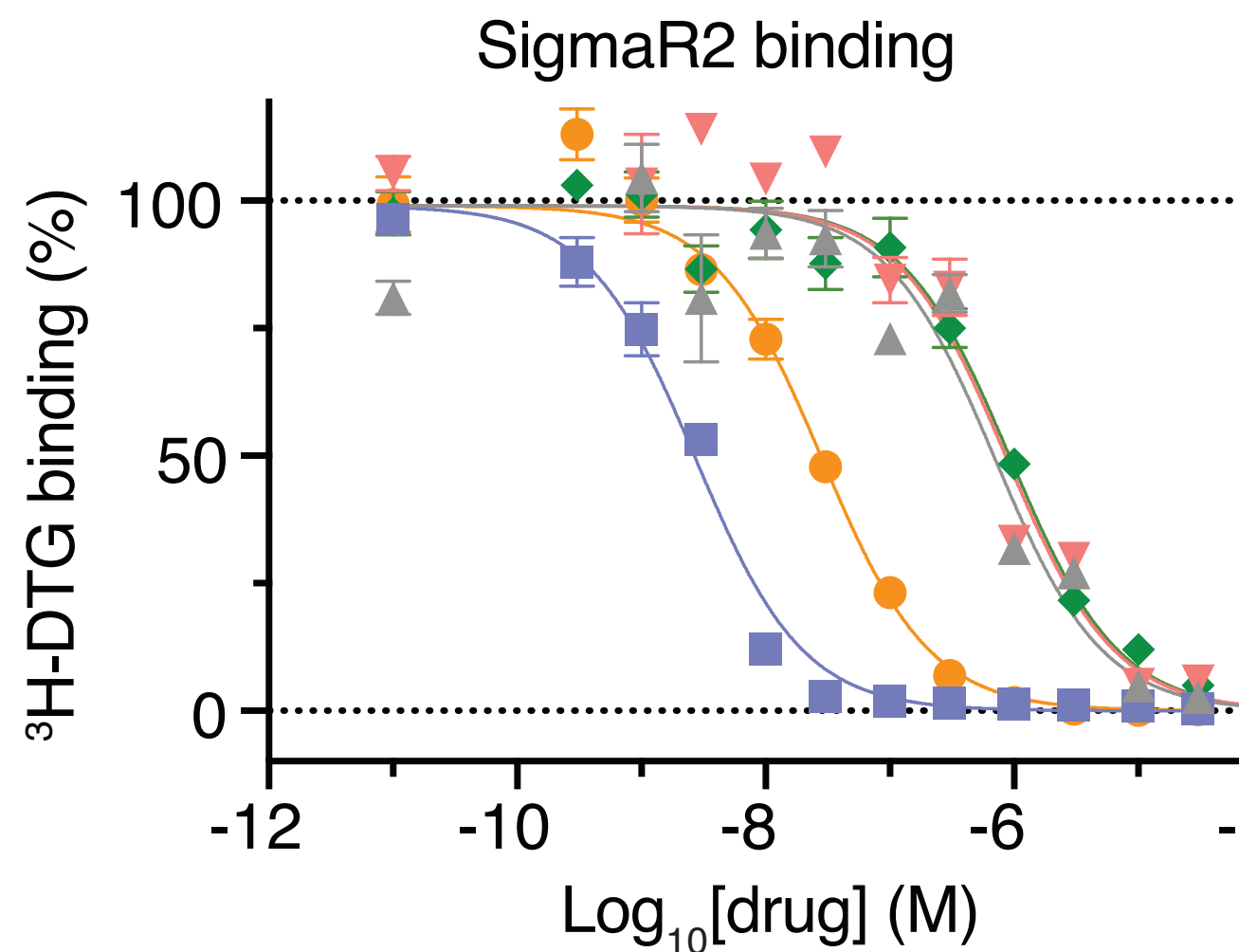
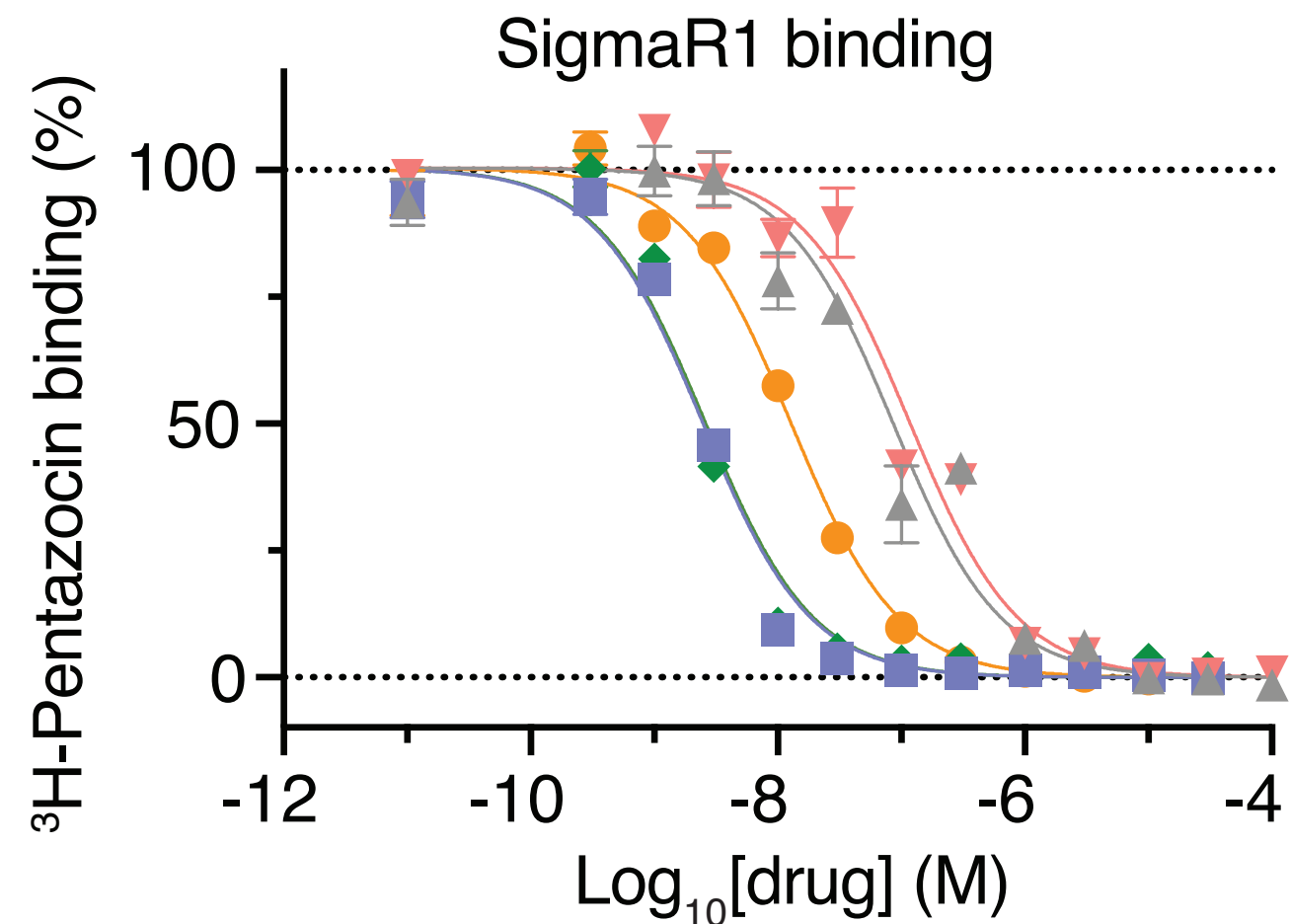
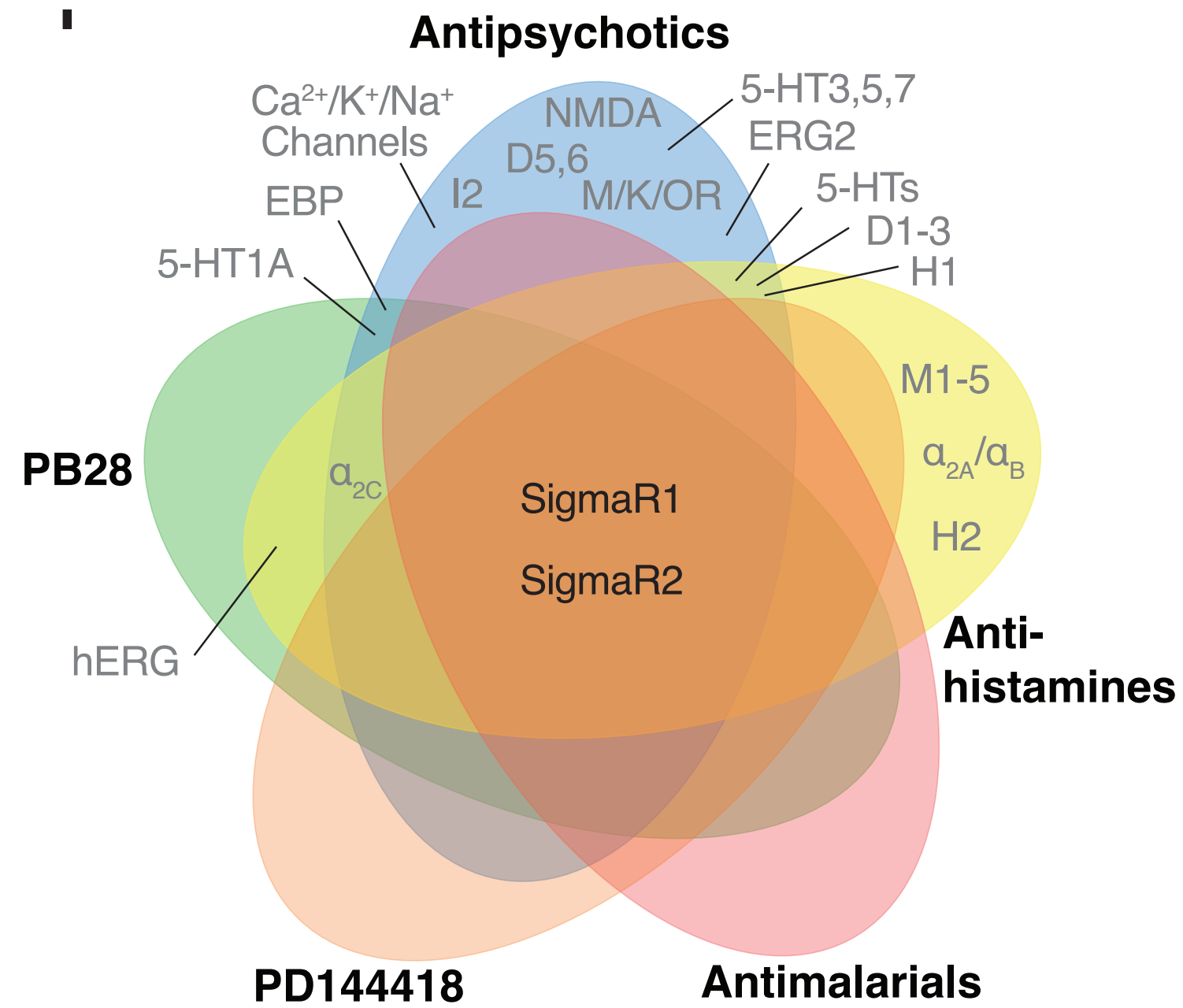
Antianxiety

Siramesine

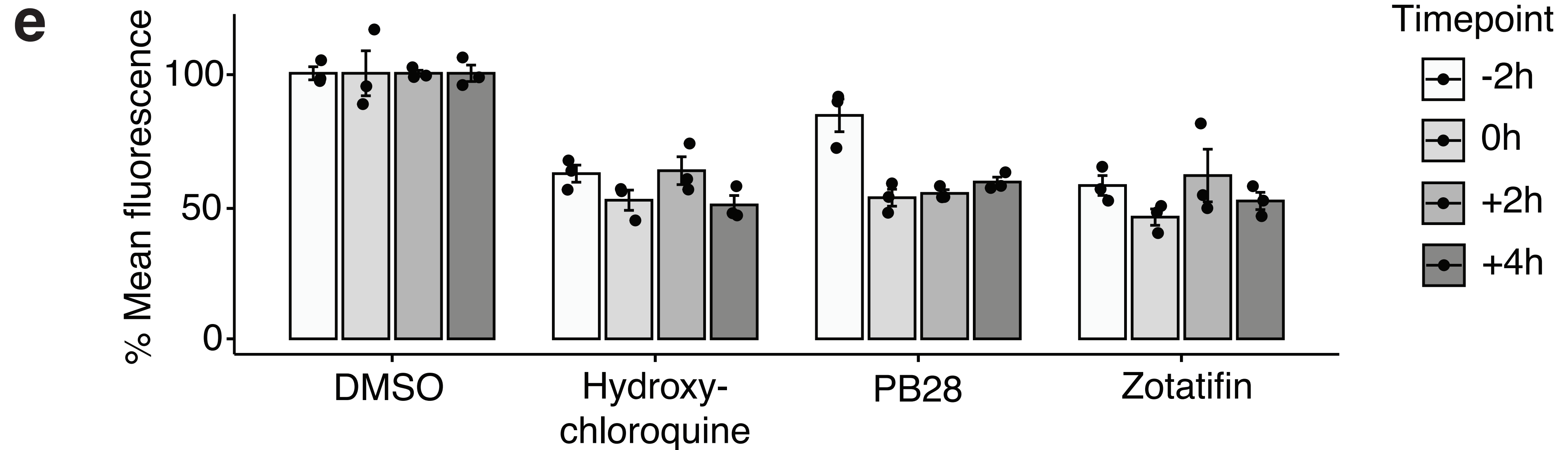
Preclinical

PB28
PD144418

Homing in on Sigma R1/R2 and Avoiding the known Toxicity of the HERG Channel (Causes sudden cardiac death)



Time to treatment test of mechanism



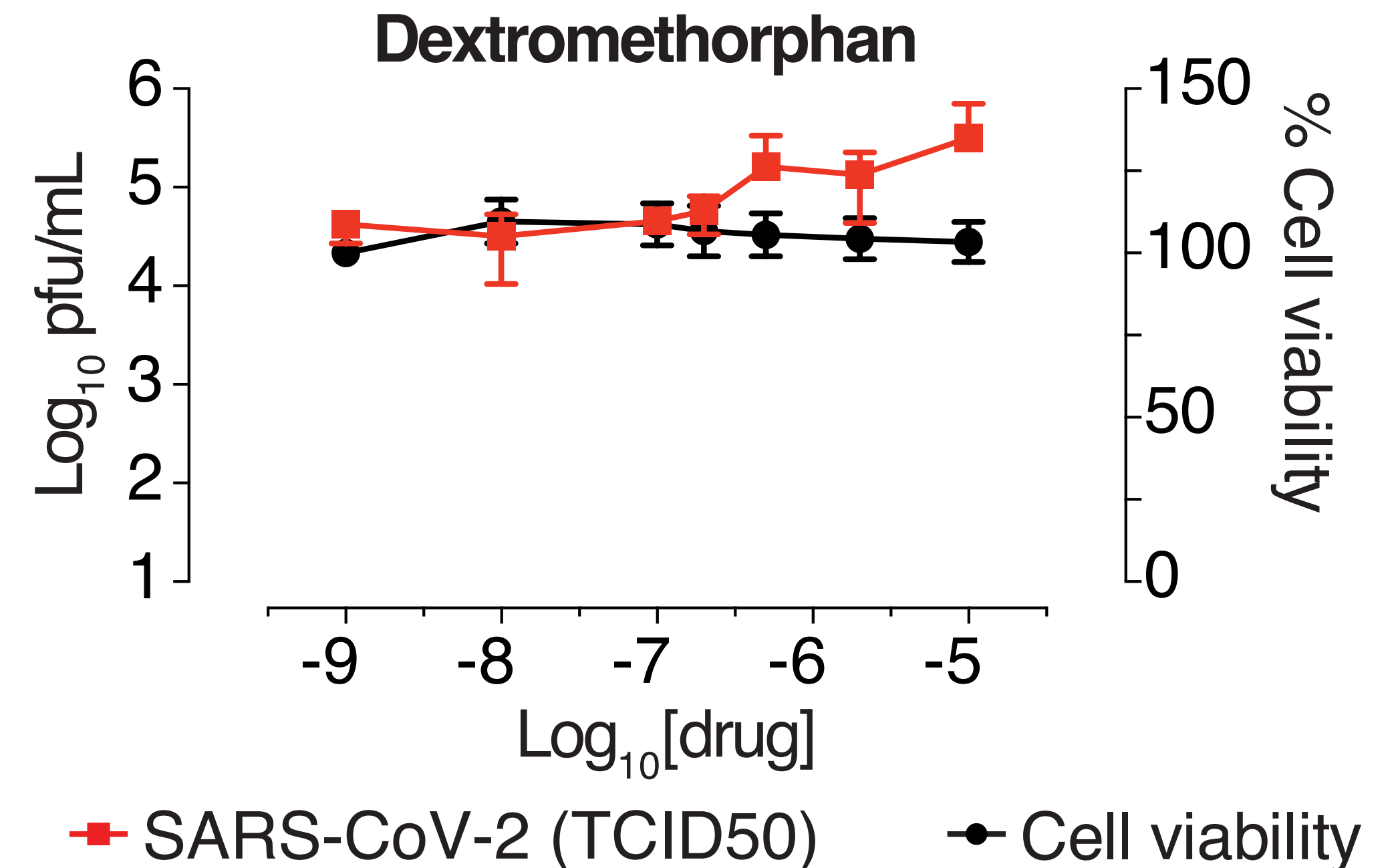
MOI = 2, Agent added up to 4 hours after virus

Additional Observations

- Molecules that target the Sigma1 and Sigma2 receptors perturb the virus through different mechanisms than the translation inhibitors, potentially including through cell stress response
- It may be that a combination approach is warranted, including combination with antivirals (remdesivir)

Dextromethorphan Appears to be Pro-Viral

- Used in many over-the-counter cough syrups
- During the pandemic, should caution against its use until further study



What's Next?

- Data shared with drug makers, government authorities and public health officials
- Several companies are taking agents into clinical trials to evaluate their anti-viral effectiveness and therapeutic index
- Continuing our research on COVID-19
- Unique and groundbreaking approach has pan-pathogenic applications
- Following COVID-19 response, research will resume in a number of disease areas
- Independent from institutional/corporate affiliations or barriers; breaking scientific silos and accelerating data results

Scientific Silos

Different Laboratories

Different Institutions

Academia and Pharma

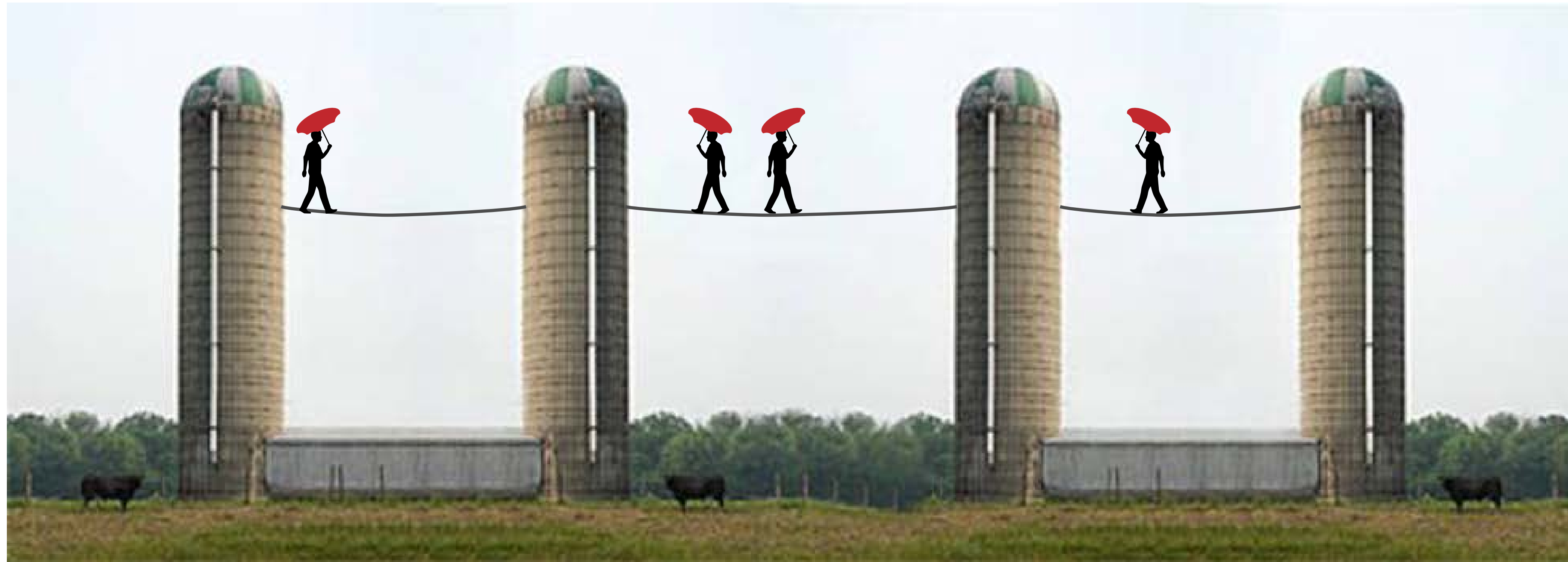


Scientific Silos

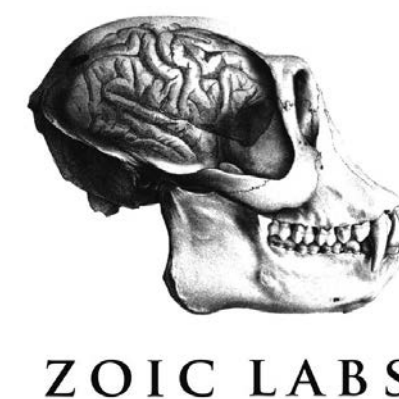
Different Laboratories

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Academia and Pharma



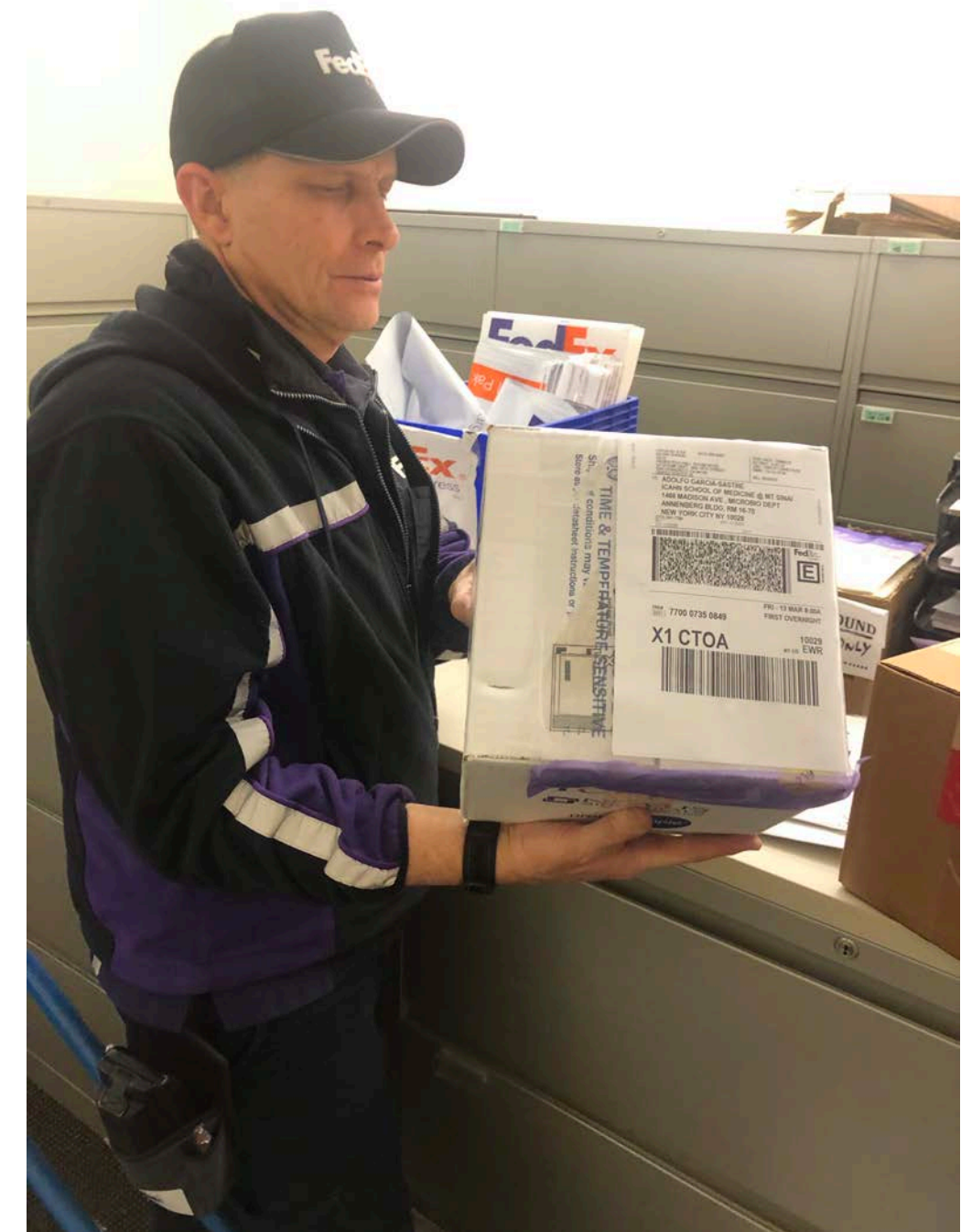
QCRG Collaborators, Partners

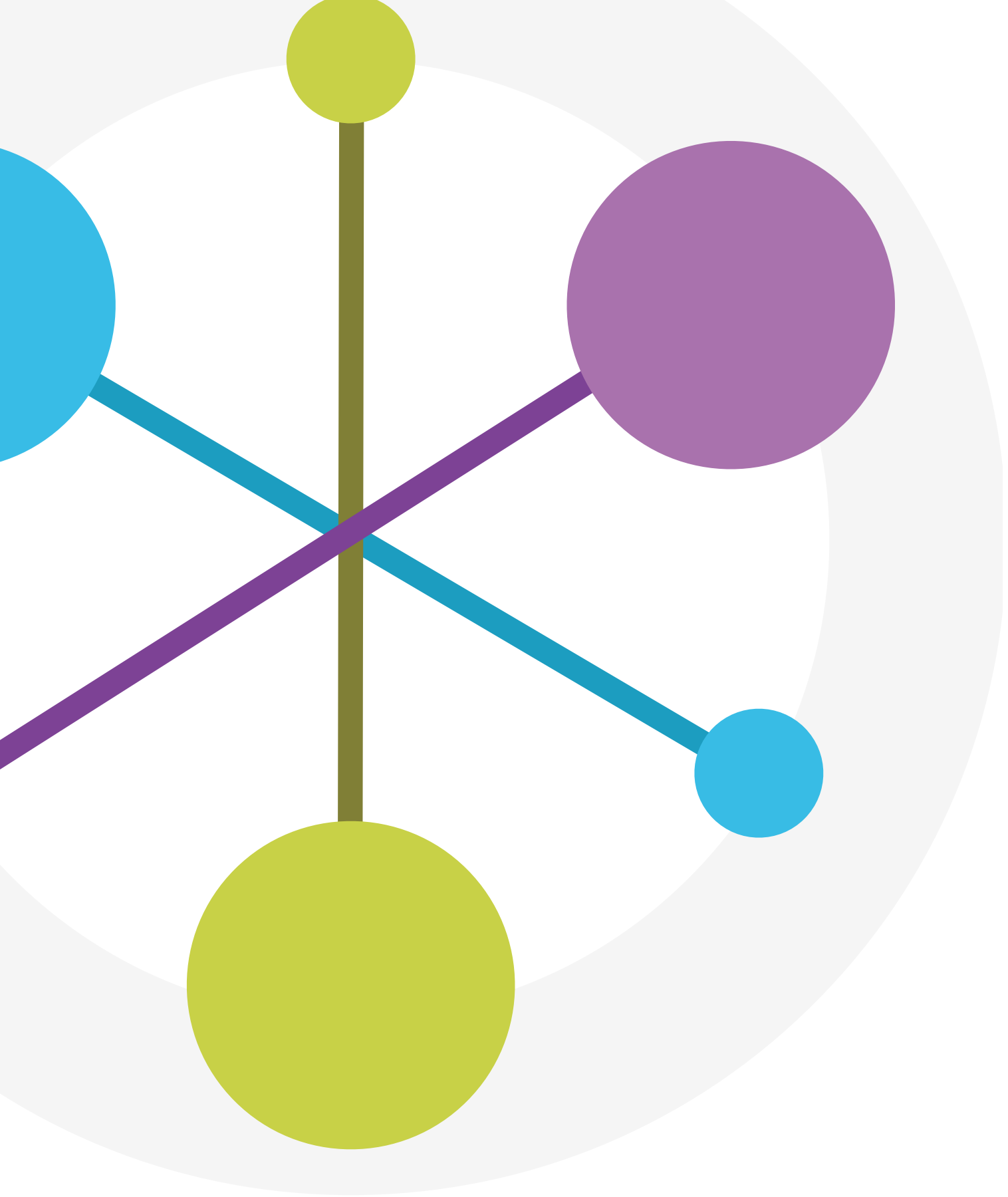


ACKNOWLEDGEMENTS

The authors would like to thank Todd from FedEx for his heroic effort helping us to ship out drugs and SARS-CoV-2 expression constructs across the globe. We thank Randy Albrecht for support with BSL3 procedures. The authors acknowledge their partners and families for support in child care and other matters during this time.

David E. Gordon^{*1,2,3,4}, Gwendolyn M. Jang^{*1,2,3,4}, Mehdi Bouhaddou^{*1,2,3,4}, Jiewei Xu^{*1,2,3,4}, Kirsten Obernier^{*1,2,3,4}, Kris M. White^{*5,6}, Matthew J. O'Meara^{*7}, Veronica V. Rezelj^{*8}, Jeffrey Z. Guo^{1,2,3,4}, Danielle L. Swaney^{1,2,3,4}, Tia A. Tummino^{1,2,9}, Ruth Huettenhain^{1,2,3,4}, Robyn M. Kaake^{1,2,3,4}, Alicia L. Richards^{1,2,3,4}, Beril Tutuncuoglu^{1,2,3,4}, Helene Foussard^{1,2,3,4}, Jyoti Batra^{1,2,3,4}, Kelsey Haas^{1,2,3,4}, Maya Modak^{1,2,3,4}, Minkyu Kim^{1,2,3,4}, Paige Haas^{1,2,3,4}, Benjamin J. Polacco^{1,2,3,4}, Hannes Braberg^{1,2,3,4}, Jacqueline M. Fabius^{1,2,3,4}, Manon Eckhardt^{1,2,3,4}, Margaret Soucheray^{1,2,3,4}, Melanie J. Bennett^{1,2,3,4}, Merve Cakir^{1,2,3,4}, Michael J. McGregor^{1,2,3,4}, Qiongyu Li^{1,2,3,4}, Bjoern Meyer⁸, Ferdinand Roesch⁸, Thomas Vallet⁸, Alice Mac Kain⁸, Lisa Miorin^{5,6}, Elena Moreno^{5,6}, Zun Zar Chi Naing^{1,2,3,4}, Yuan Zhou^{1,2,3,4}, Shiming Peng^{1,2,9}, Ying Shi^{1,2,4,11}, Ziyang Zhang^{1,2,4,11}, Wenqi Shen^{1,2,4,11}, Ilsa T. Kirby^{1,2,4,11}, James E. Melnyk^{1,2,4,11}, John S. Chorba^{1,2,4,11}, Kevin Lou^{1,2,4,11}, Shizhong A. Dai^{1,2,4,11}, Inigo Barrio-Hernandez¹², Danish Memon¹², Claudia Hernandez-Armenta¹², Jiankun Lyu^{1,2,9}, Christopher J.P. Mathy^{1,2,13,14}, Tina Perica^{1,2,13}, Kala B. Pilla^{1,2,13}, Sai J. Ganesan^{1,2,13}, Daniel J. Saltzberg^{1,2,13}, Ramachandran Rakesh^{1,2,13}, Xi Liu^{1,2,9}, Sara B. Rosenthal¹⁵, Lorenzo Calviello^{1,16}, Srivats Venkataramanan^{1,16}, Jose Liboy-Lugo^{1,16}, Yizhu Lin^{1,16}, Xi-Ping Huang¹⁷, YongFeng Liu¹⁷, Stephanie A. Wankowicz^{1,2,11,18}, Markus Bohn^{1,2,9}, Maliheh Safari^{1,2,19}, Fatima S. Ugur^{1,2,4,9}, Cassandra Koh⁸, Nastaran Sadat Savar⁸, Quang Dinh Tran⁸, Djoshkun Shengjuler⁸, Sabrina J Fletcher⁸, Michael C. O'Neal²⁰, Yiming Cai²⁰, Jason C.J.Chang²⁰, David J. Broadhurst²⁰, Saker Klippsten²⁰, Phillip P. Sharp⁴, Nicole A. Wenzell^{1,2,4}, Duygu Kuzuoglu^{1,2,4,21,22}, Hao-Yuan Wang^{1,2,4}, Raphael Trenker^{1,2,23}, Janet M. Young²⁴, Devin A. Caverio^{3,26}, Joseph Hiatt^{3,25,26}, Theodore L. Roth^{3,25,26}, Ujjwal Rathore^{3,26}, Advait Subramanian^{1,2,26}, Julia Noack^{1,2,26}, Mathieu Hubert¹⁰, Robert M. Stroud^{1,2,19}, Alan D. Frankel^{1,2,19}, Oren S. Rosenberg^{1,2,19,27}, Kliment A Verba^{1,2,9}, David A. Agard^{1,2,19}, Melanie Ott^{1,2,3,27}, Michael Emerman²⁸, Natalia Jura^{1,2,4,23}, Mark von Zastrow^{1,2,4,29}, Eric Verdin^{1,27,30}, Alan Ashworth^{1,2,21}, Olivier Schwartz¹⁰, Christophe d'Enfert³¹, Shaeri Mukherjee^{1,2,26}, Matt Jacobson^{1,2,9}, Harmit S. Malik²⁴, Danica G. Fujimori^{1,2,4,9}, Trey Ideker^{1,32}, Charles S. Craik^{1,2,9,21}, Stephen N. Floor^{1,16,21}, James S. Fraser^{1,2,13}, John D. Gross^{1,2,9}, Andrej Sali^{1,2,9,13}, Bryan L. Roth¹⁷, Davide Ruggero^{1,2,4,21,22}, Jack Taunton^{1,2,4}, Tanja Kortemme^{1,2,13,14}, Pedro Beltrao^{1,12}, Marco Vignuzzi⁸, Adolfo Garcia-Sastre^{5,6,33,34}, Kevan M. Shokat^{1,2,4,11}, Brian K. Shoichet^{1,2,9}, Nevan J. Krogan^{1,2,3,4,5}



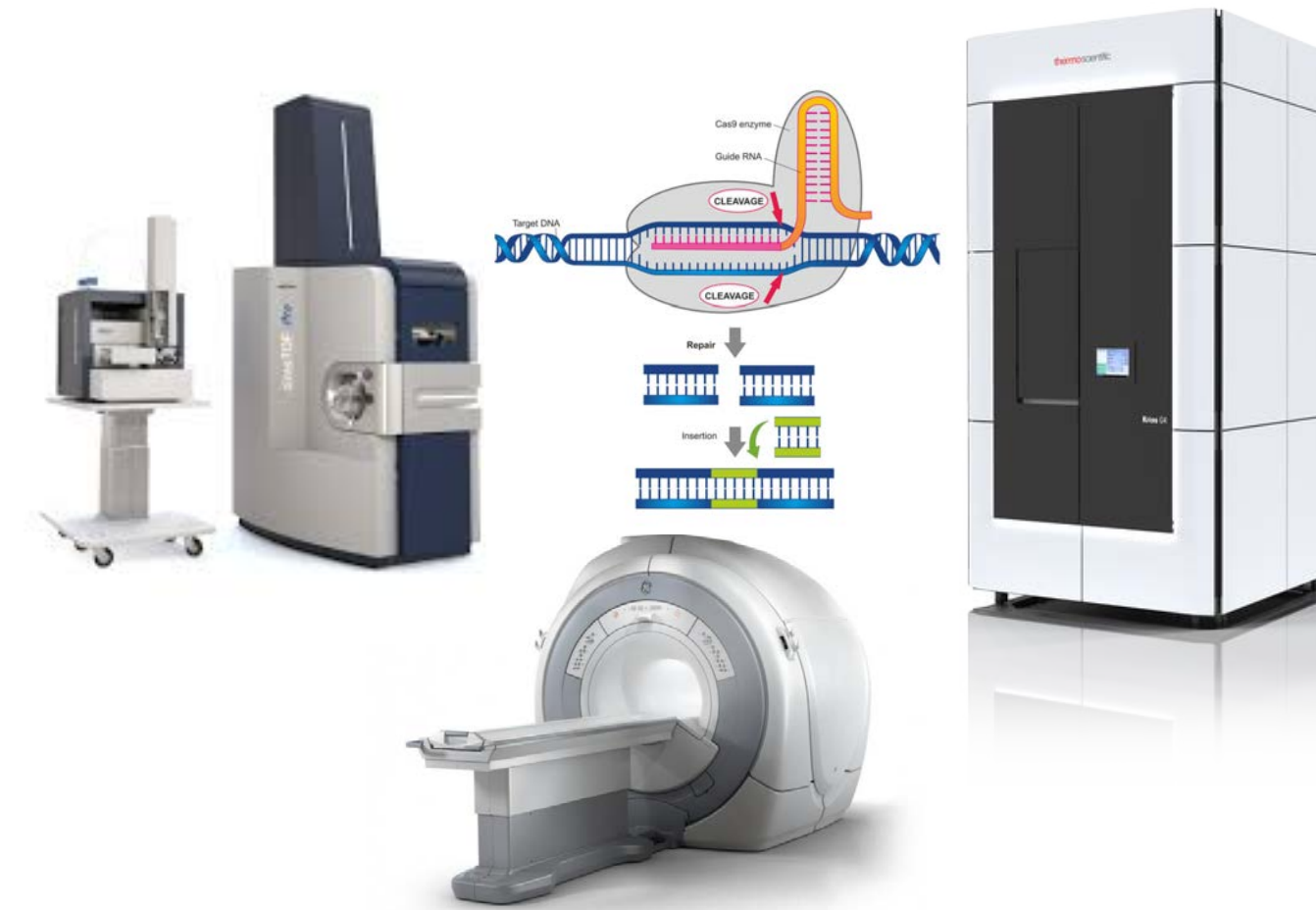


UCSF Quantitative
Biosciences
Institute

Breaking down silos

103 Labs

Collaborative Research
 Quantitative
 Basic science
 Disease agnostic
 Experimental & Computational



Cell Mapping Initiatives

HPMI | Host Pathogen Map Initiative

CCMI | Cancer Cell Map Initiative

PCMI | Psychiatric Cell Map Initiative

Investing in the young

QBI Scholarship for Women from Developing Nations



QBI Fellowship
 2-year fellowships



Education Outreach

QBI-UCSF HACKATHON
 October 4-5, 2019

Locked in a glass room for 48 hours?
QBI UCSF Hackathon
 October 4-5, 2019

UCSF Quantitative Biosciences Institute

QBI/UCSF COMPUTATIONAL BIOLOGY & DRUG DISCOVERY

QBI/MASS SNEC SYMPOSIUM

QBI/INFECTIOUS DISEASE SYMPOSIUM

CELL MAPPING

QBI/PASTEUR SYMPOSIUM ON INFECTION

QBI SYMPOSIUM SPRING

QBI/INTEGRATIVE STRATEGIC MEET

QBI/ARTHROPOD-BORNE DISEASES

QBI/QUANTITATIVE APPROACHES TO CANCER RESEARCH

QBI/SIGNALING ACROSS SCALES

Symposia
 13 scheduled for 2020

be bold & basic
 25k grants
 applications: rfa \$1.1m
 deadline: May 12, 2019

bold & basic
 25k grants
 applications: rfa \$900K
 deadline: May 12, 2019

RFAs
 2018 - \$1.1M
 2019 - \$1.2M
 2020 - \$300K

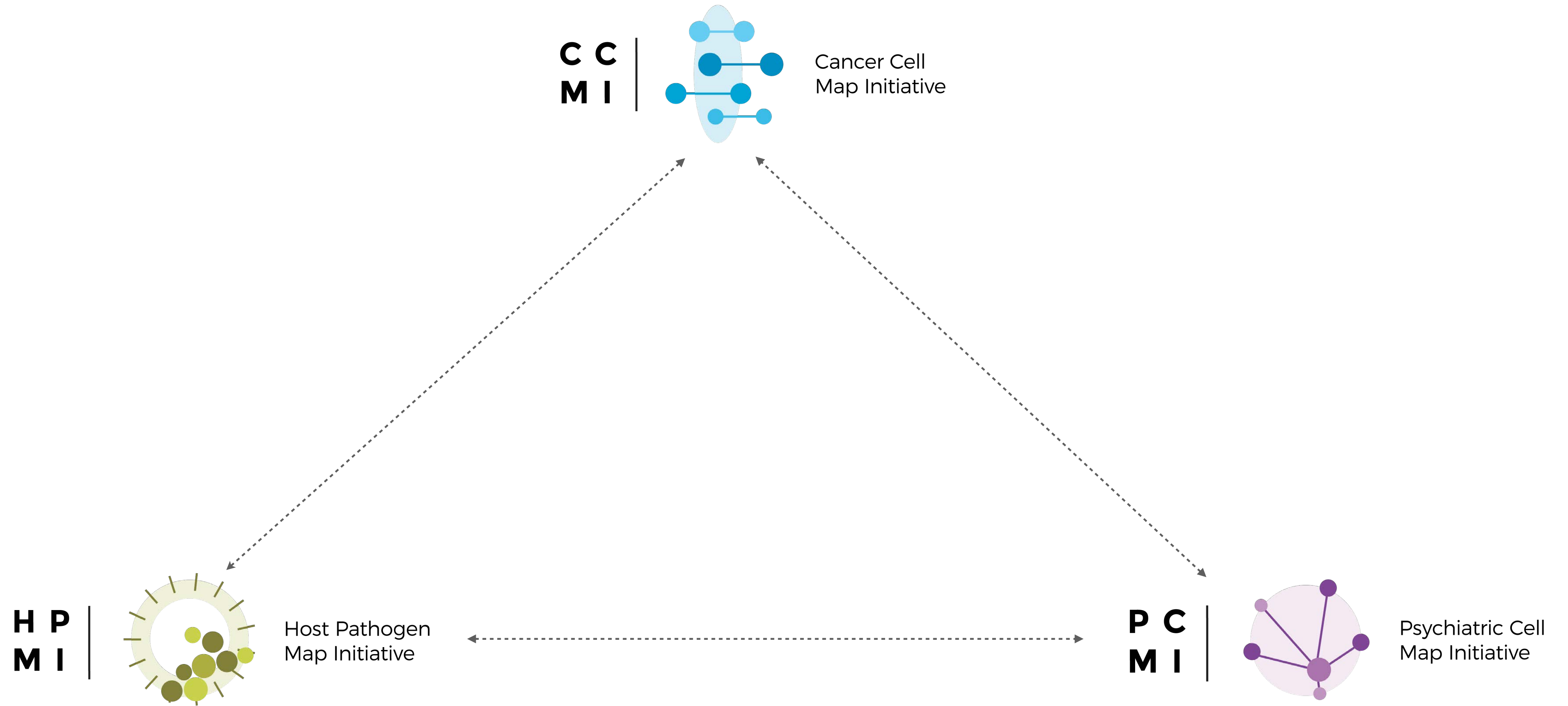
Media outreach
 Web, Instagram, Twitter, Facebook

Seminar series
 2018 - 8 seminars
 2019 - 10 seminars

QBI International Collaborations

Establishing a culture of collaboration

QBI Initiatives: Cell Mapping



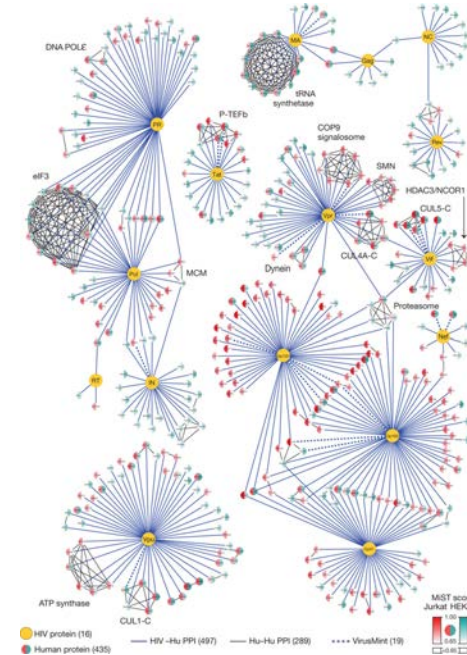
What if?

- What if in the same way we map the cells, we started mapping the world with collaborative interactions?
- Cell mapping = World mapping
- Protein Protein Interactions = People People Interactions

Host-Pathogen Protein-Protein Interaction Networks

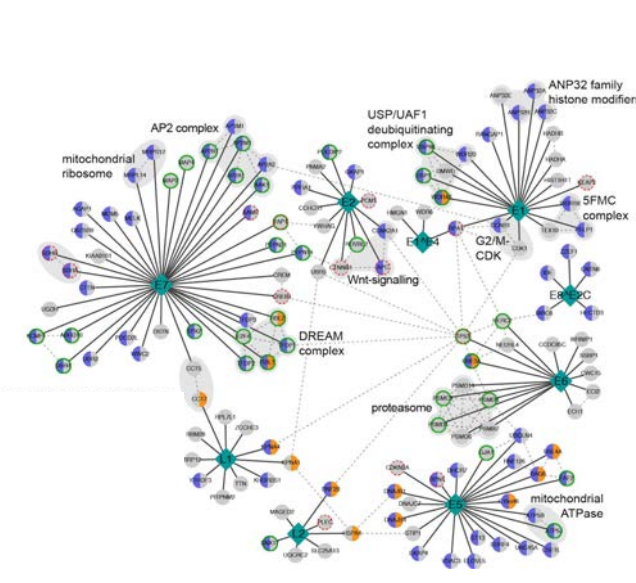
HIV-1

Jäger et al, Nature, 2012



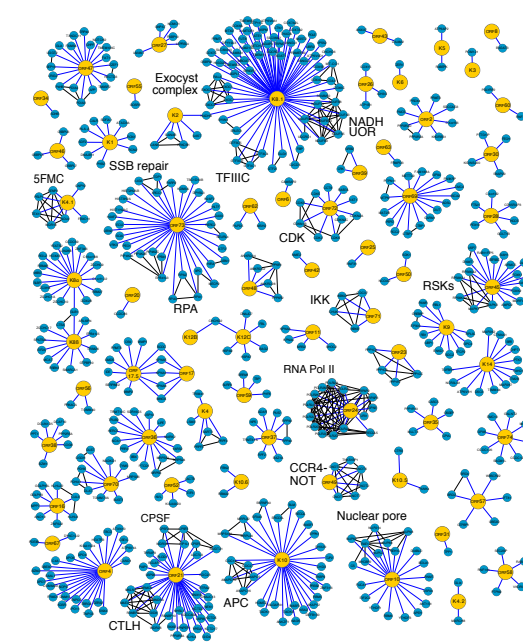
HPV

Eckhardt et al., Cancer Discovery, 2018



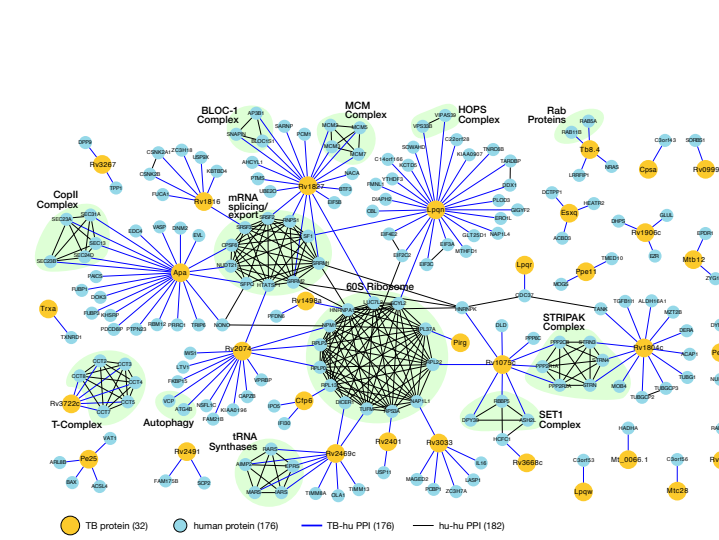
Kaposi Sarcoma's Herpes

Davis et al., Molecular Cell, 2015



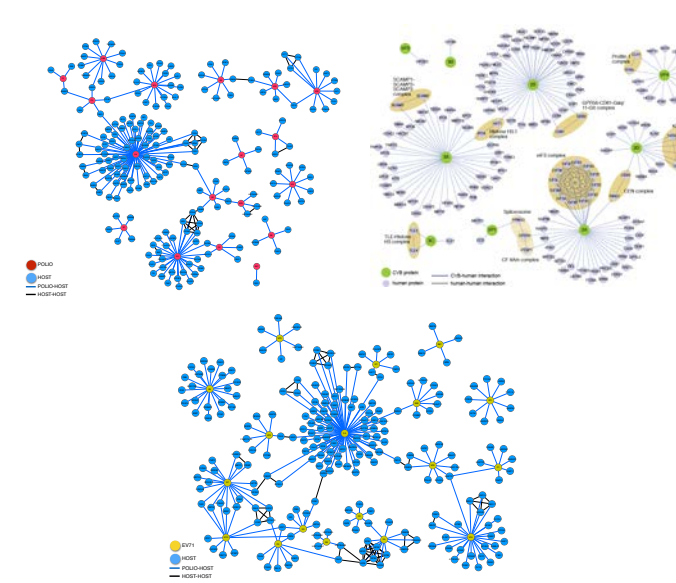
Tuberculosis

Penn et al., Molecular Cell, 2018



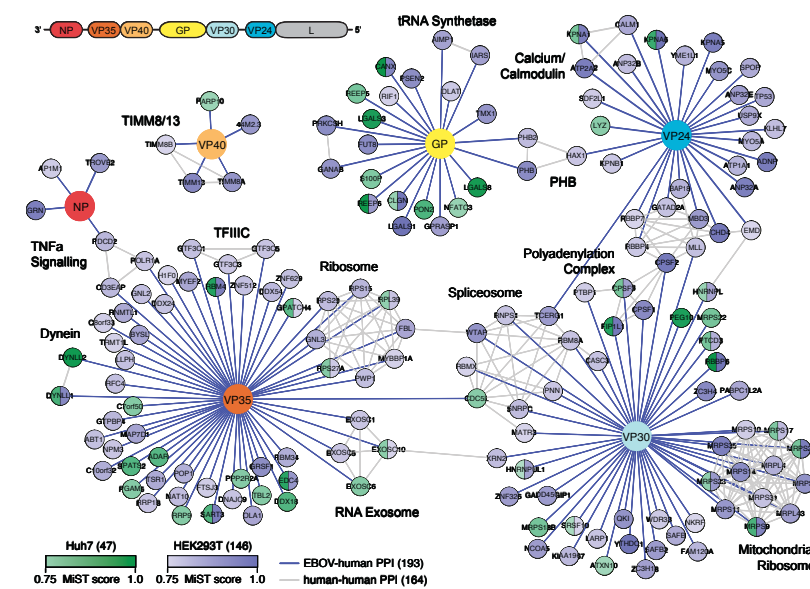
Enteroviruses: Polio vs Cox-B vs EV-71

CVB: Diep et al., Nature Microbiology, 2019

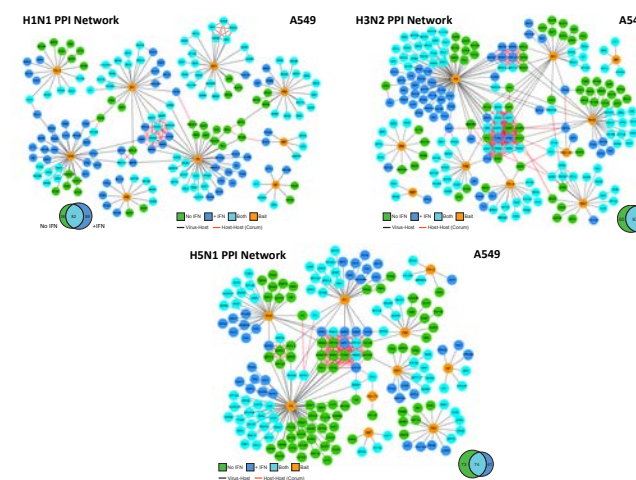


Ebola

Batra et al., Cell, 2018

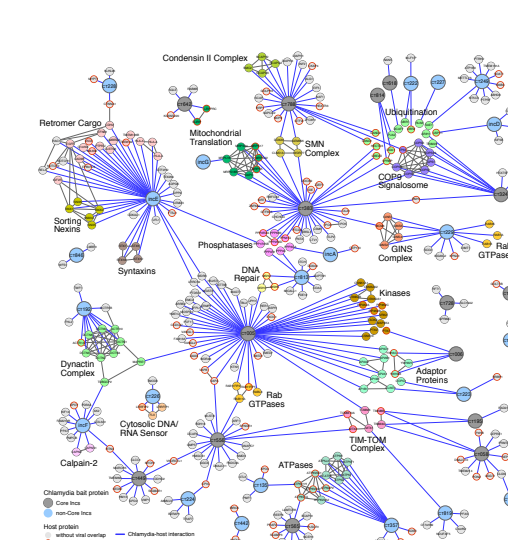


Influenza-A: H1N1 vs H5N1 vs H3N2



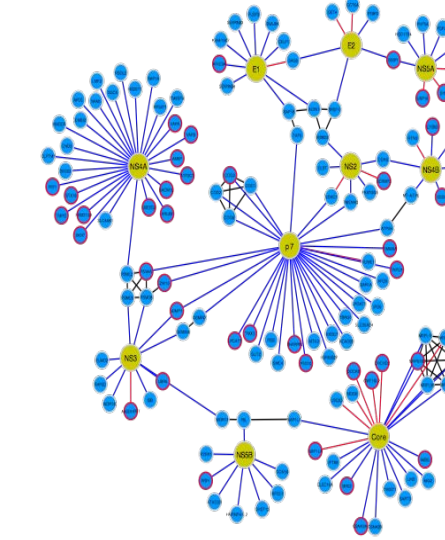
Chlamydia

Mirrahshidi et al., Cell Host and Microbe, 2015

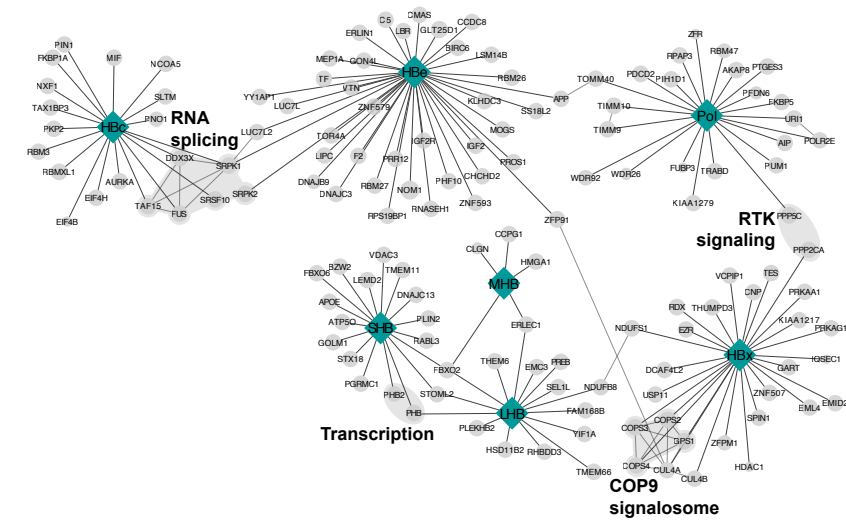


Hepatitis-C

Ramage et al., Molecular Cell, 2015

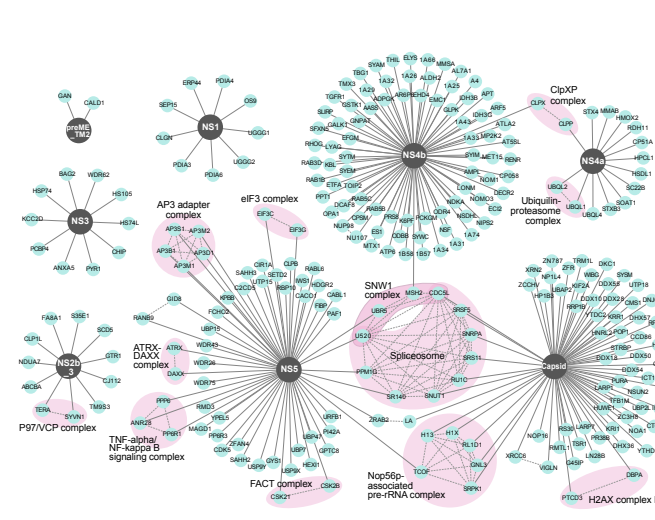


Hepatitis-B



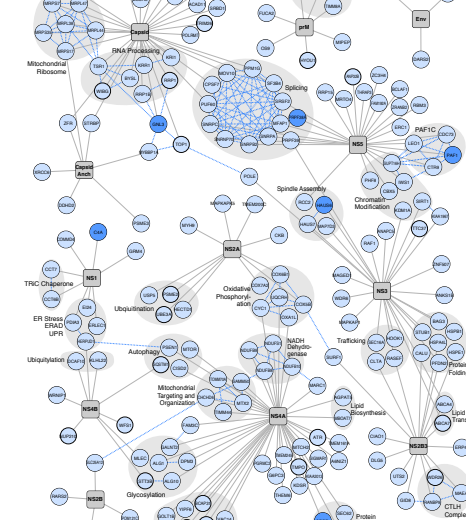
West Nile Virus

Li et al., Nature Microbiology, 2019



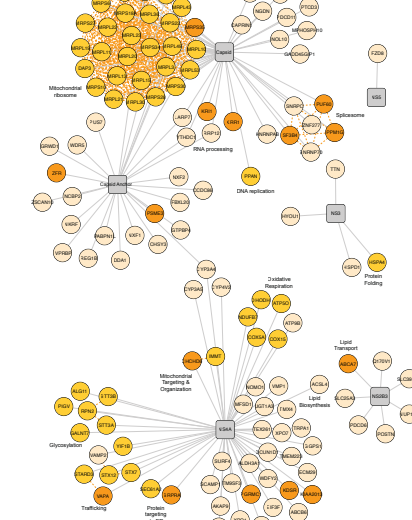
Dengue (human)

Shah et al., Cell, 2018



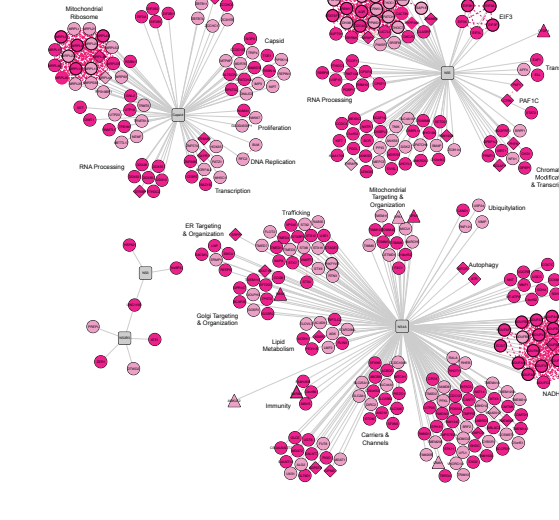
Dengue (mosquito)

Shah et al., Cell, 2018

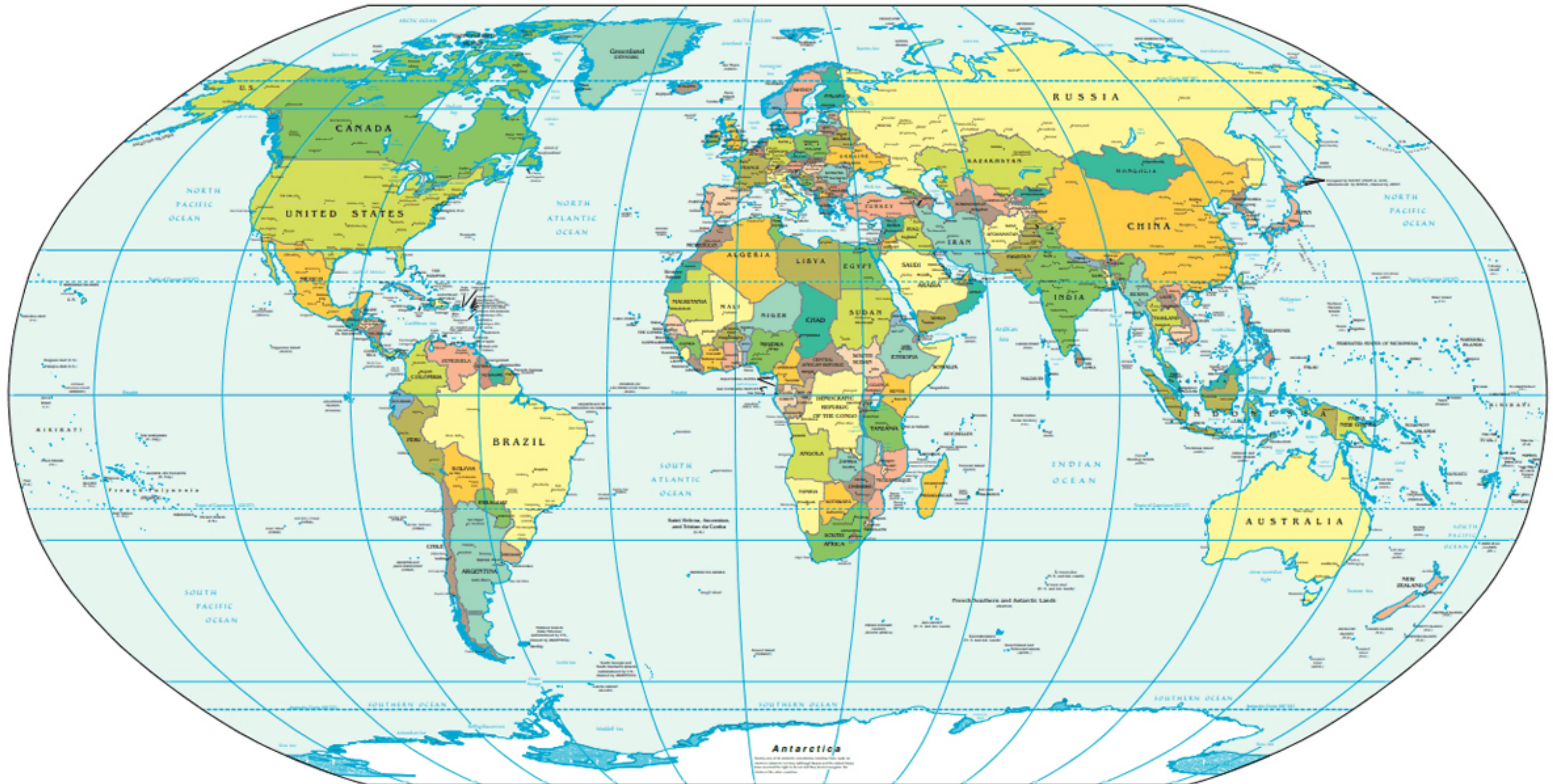


Zika

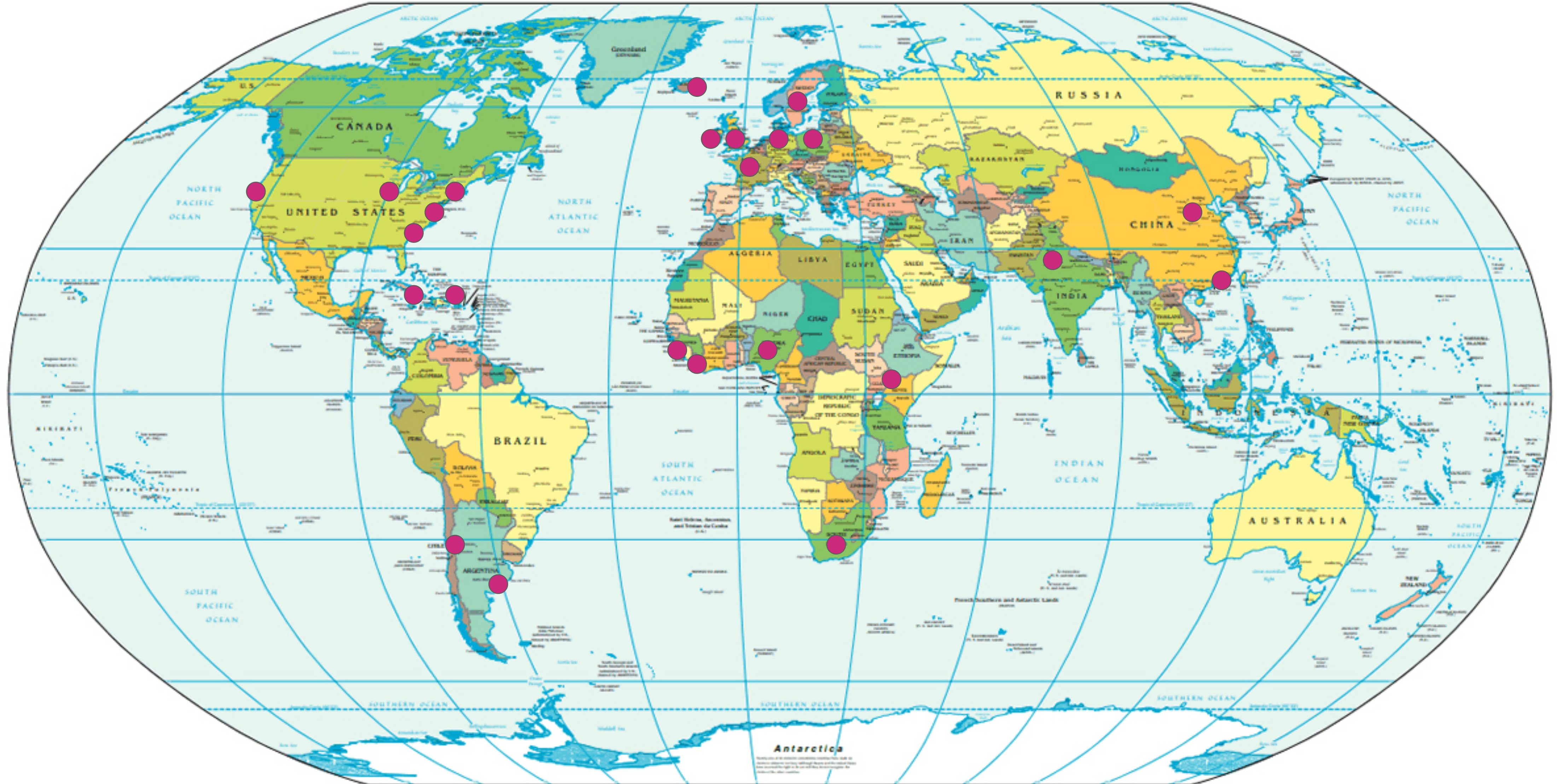
Shah et al., Cell, 2018



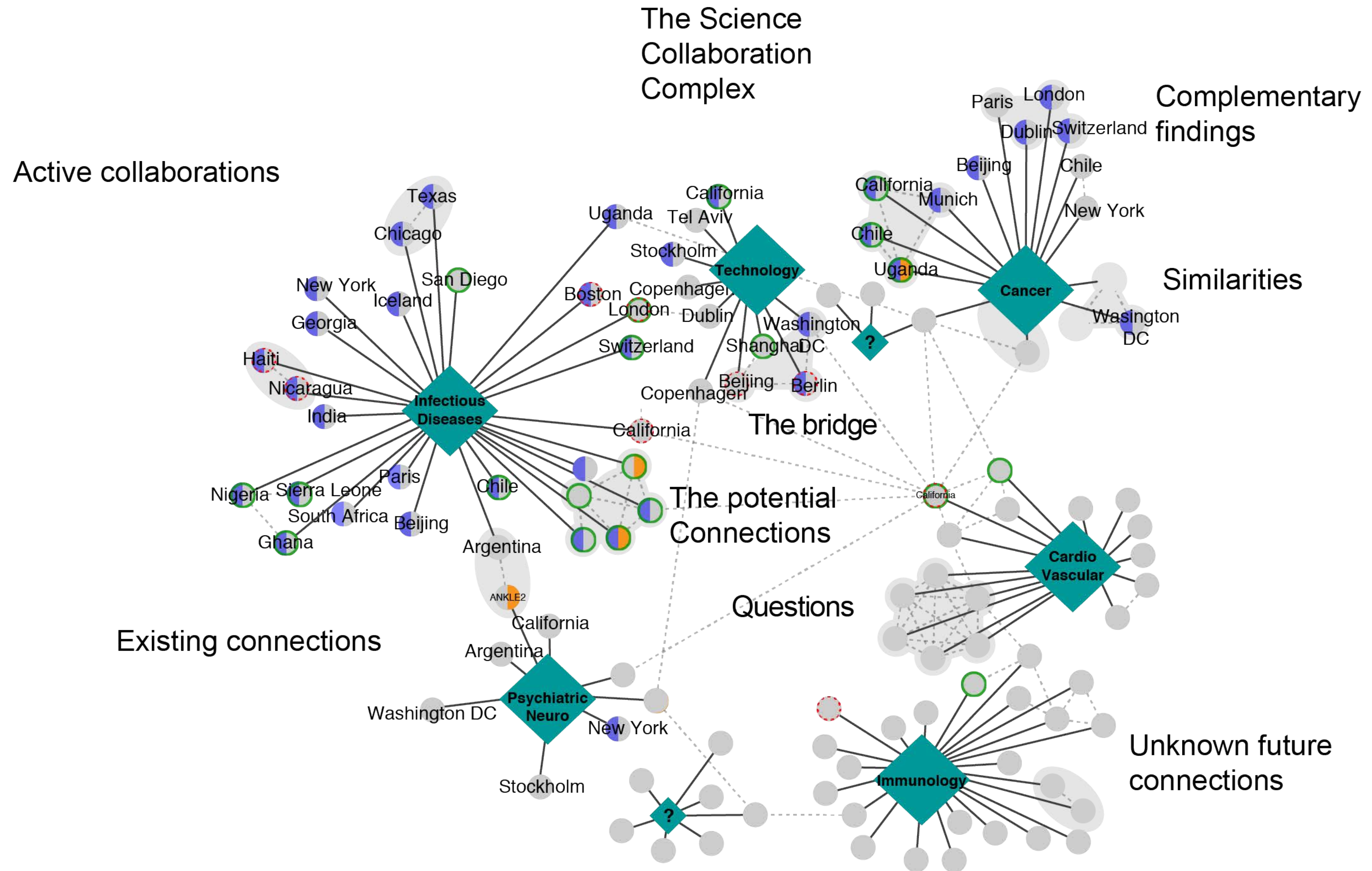
QBI International Collaborations



QBI International Collaborations

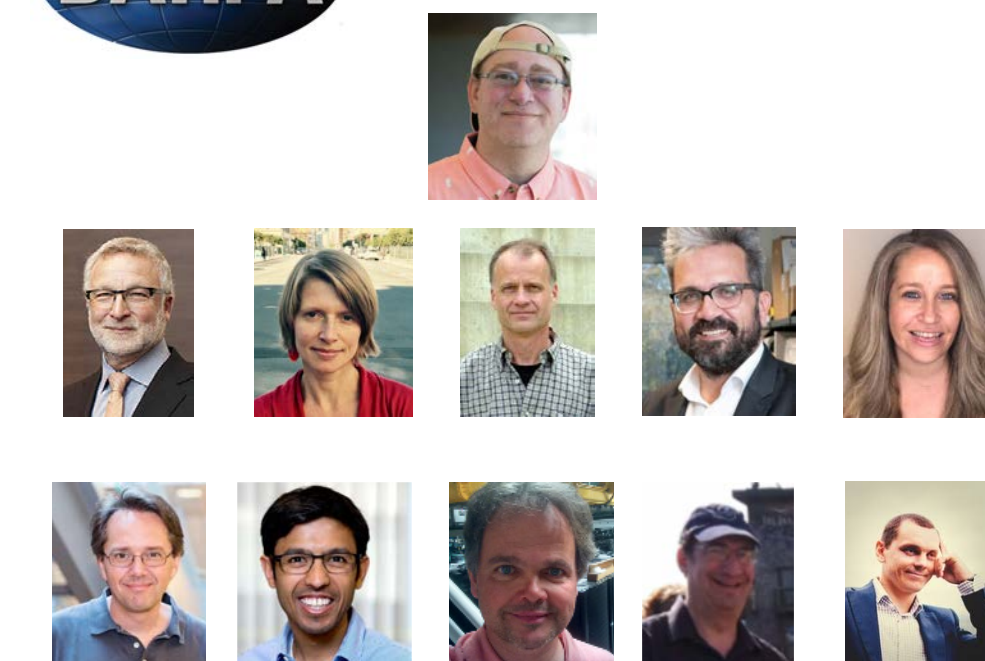
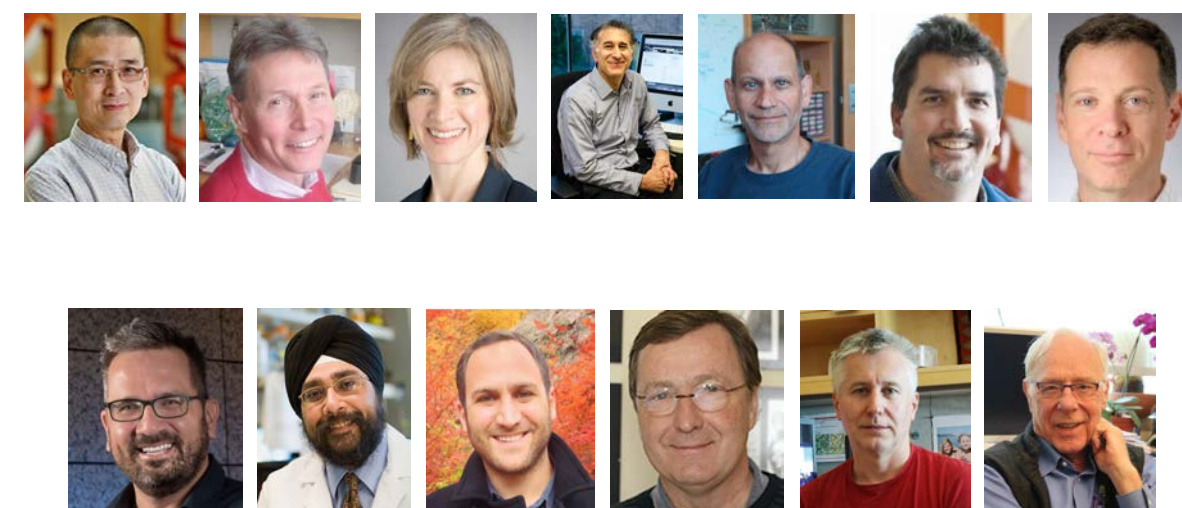
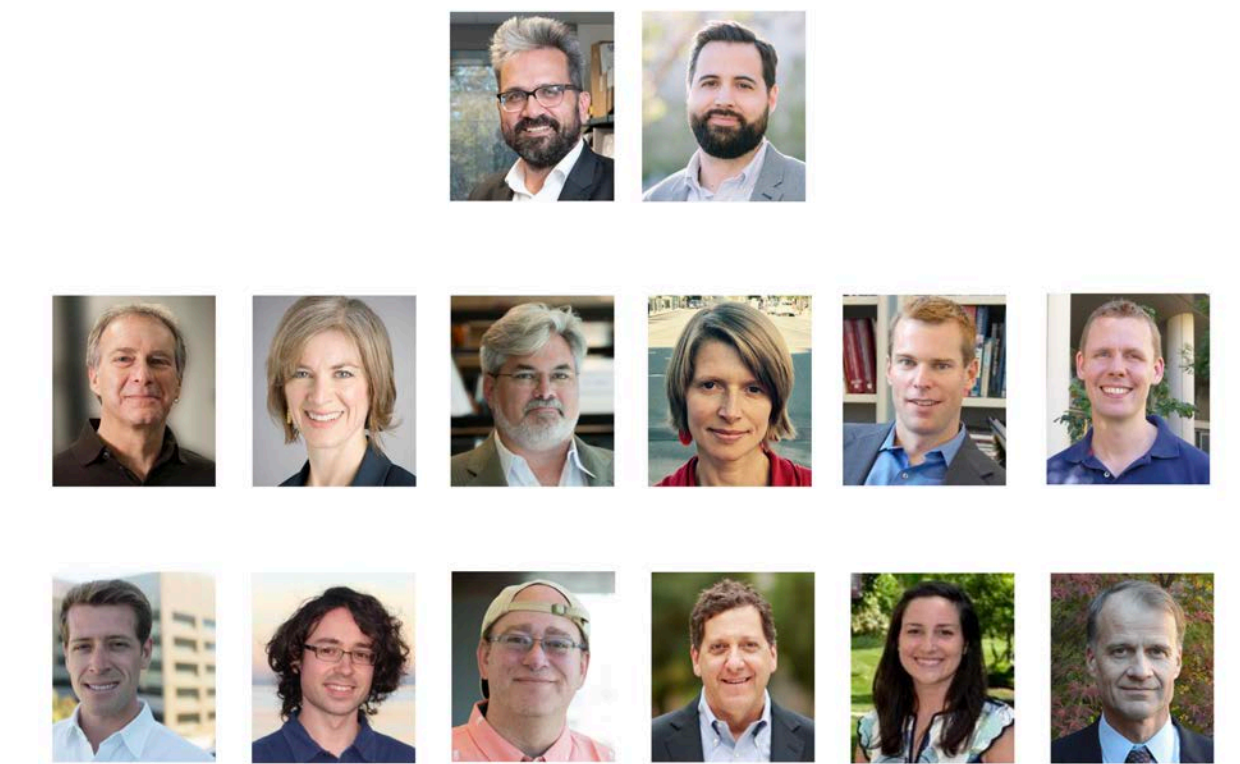
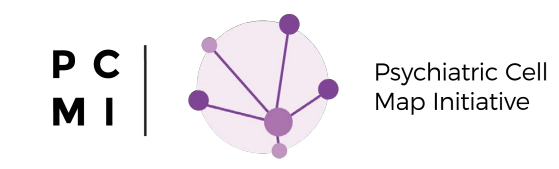
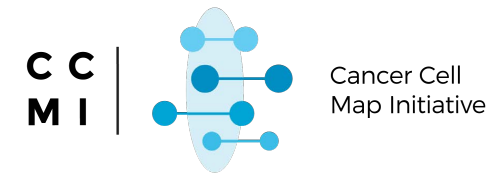


QBI Collaborative Network



QBI Center Grants - \$85M

Collaborative science at UCSF and beyond



Collaborative Meetings and MOUs



- International Relationships built on science
- Fostered with collaborative symposia
- Formalized with MOUs & RFAs for collaborative research

QBI International Collaborations

Breaking down silos



- Freie Universität Berlin, Germany**
Integrative Structural Biology
- University College Dublin, Ireland**
Quantitative Biology and Cancer
- Institut Curie / PSL, France**
Quantitative Biosciences
- Redeemer's University, Nigeria**
Hemorrhagic Fevers and viruses
- Jagiellonian University, Poland**
Structural Biology and Exchanges
- Tel Aviv University, Israel**
Bioinformatics and Drug Discovery
- Crick Institute, UK**
Cell Mapping
- Institut Pasteur, France**
Infectious Diseases

The formation of QCRG

Understanding the context of a coming pandemic and taking action

QCRG - The Beginning

Late Friday night, early March



Prepping MS



The team forms



Discussing immediate action



Mad rush to finish all mass spec experiments to create **the map** before the campus shutdown



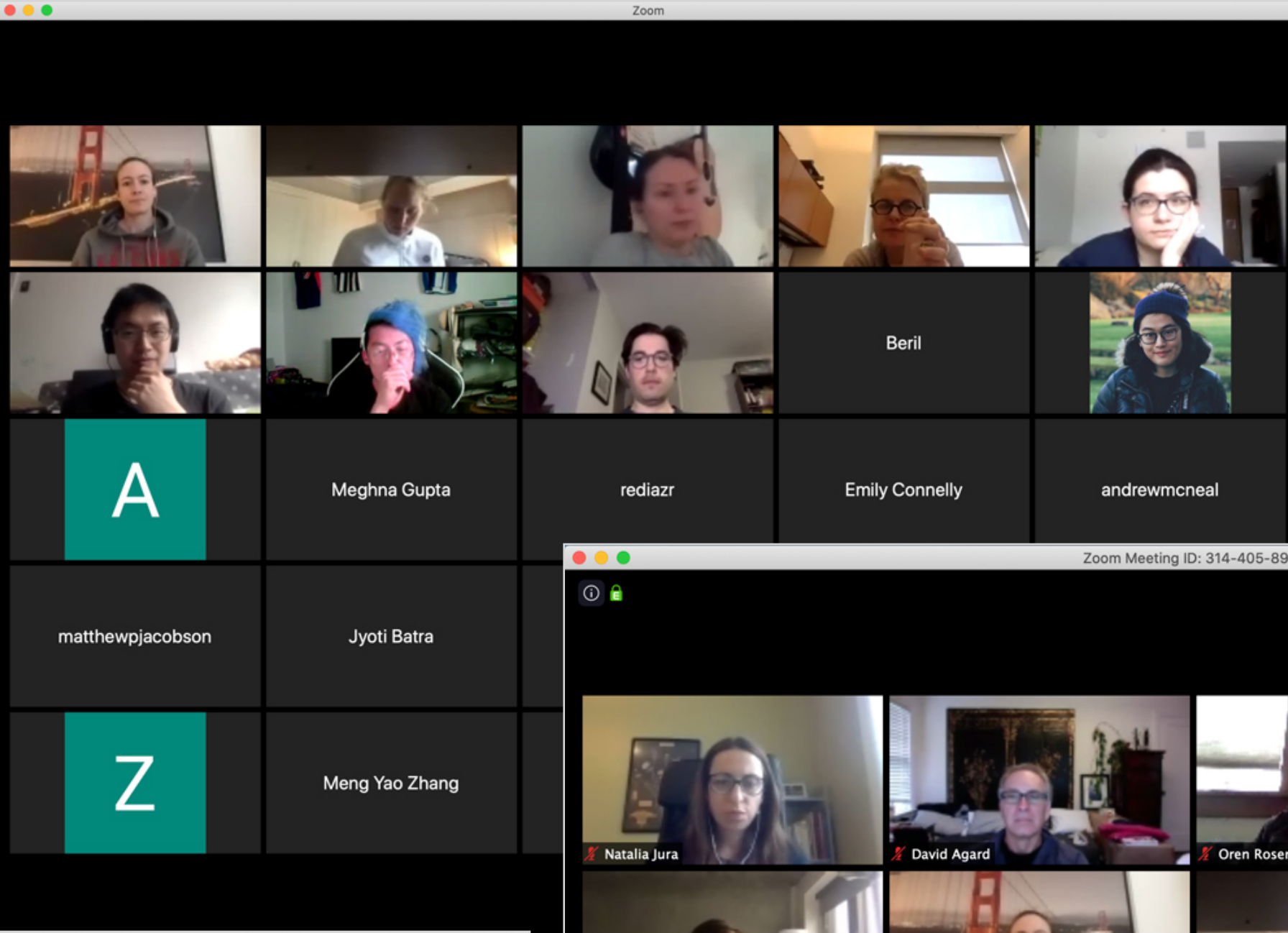
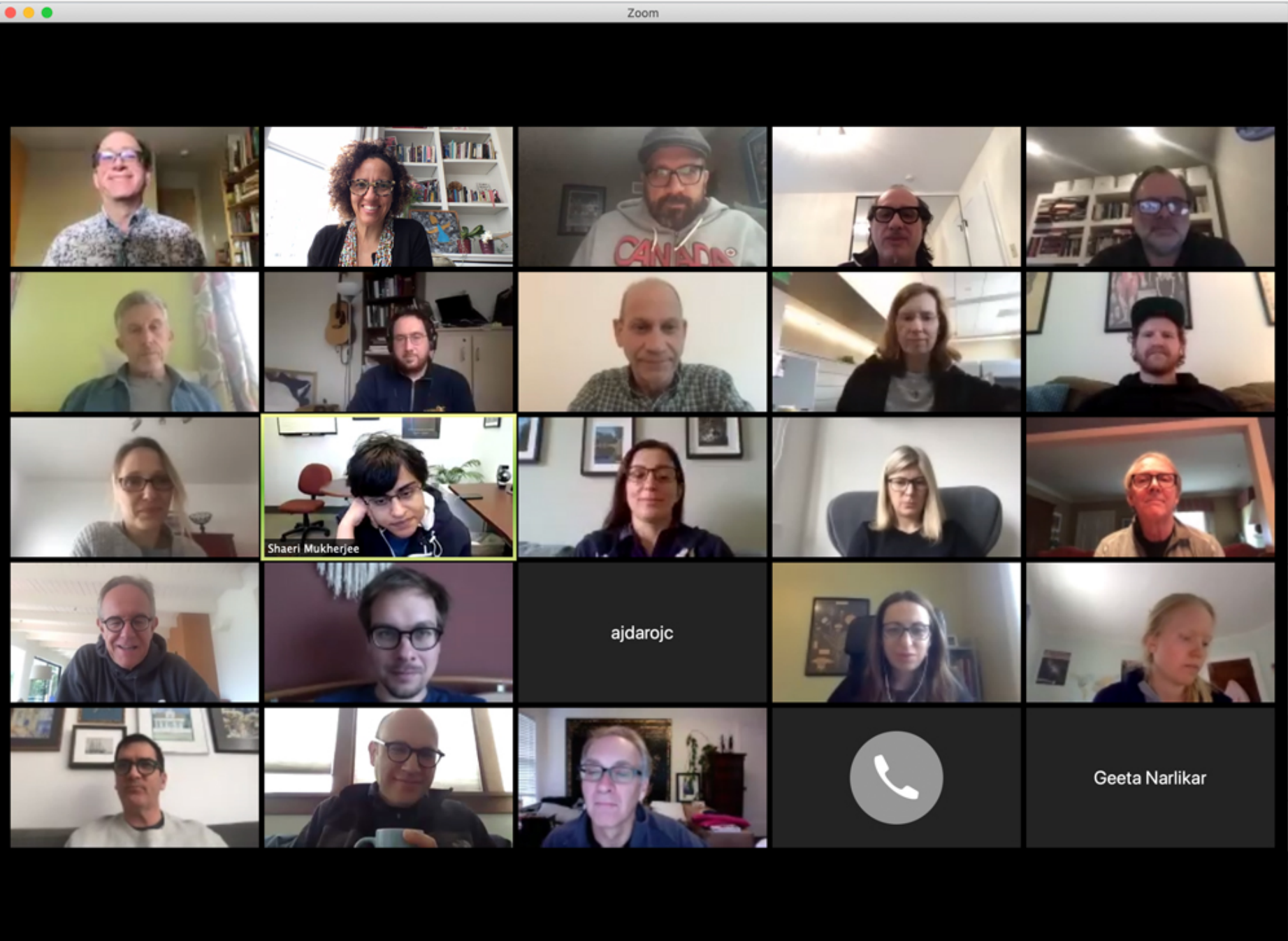
Running MS samples



Suddenly everyone working from home

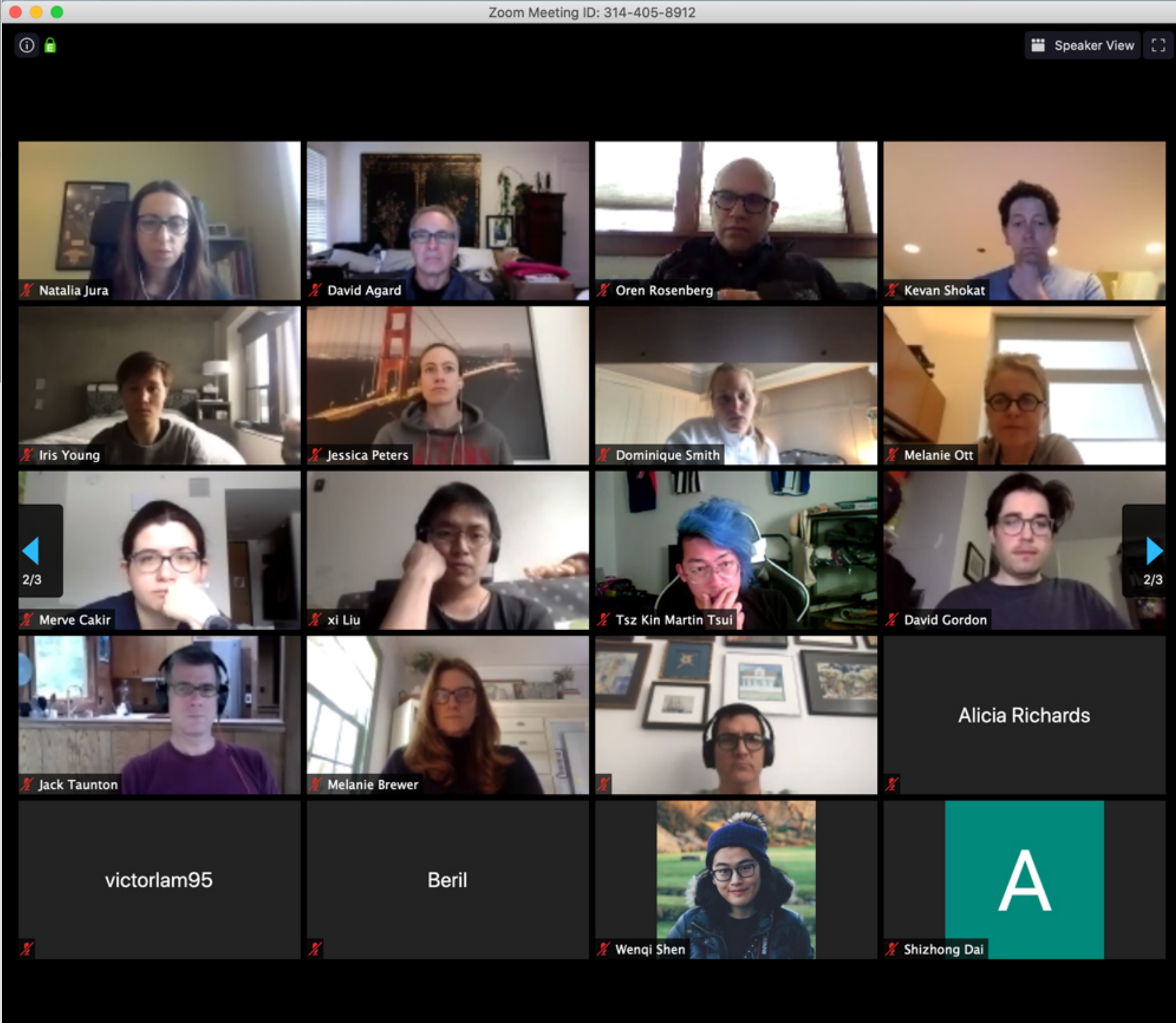
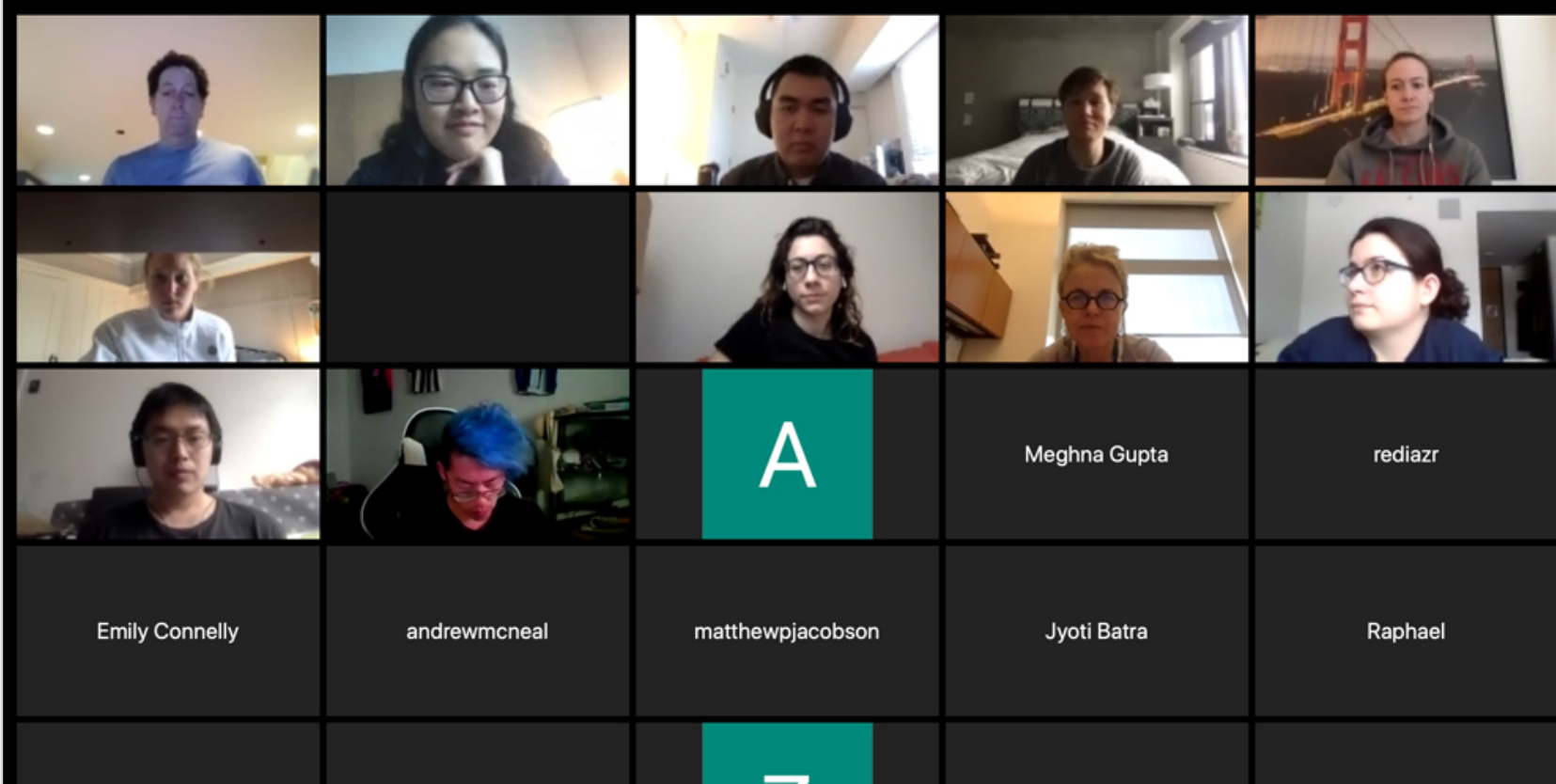
COVID-19, Quarantine 2020

Extensive Teamwork - Science on Zoom



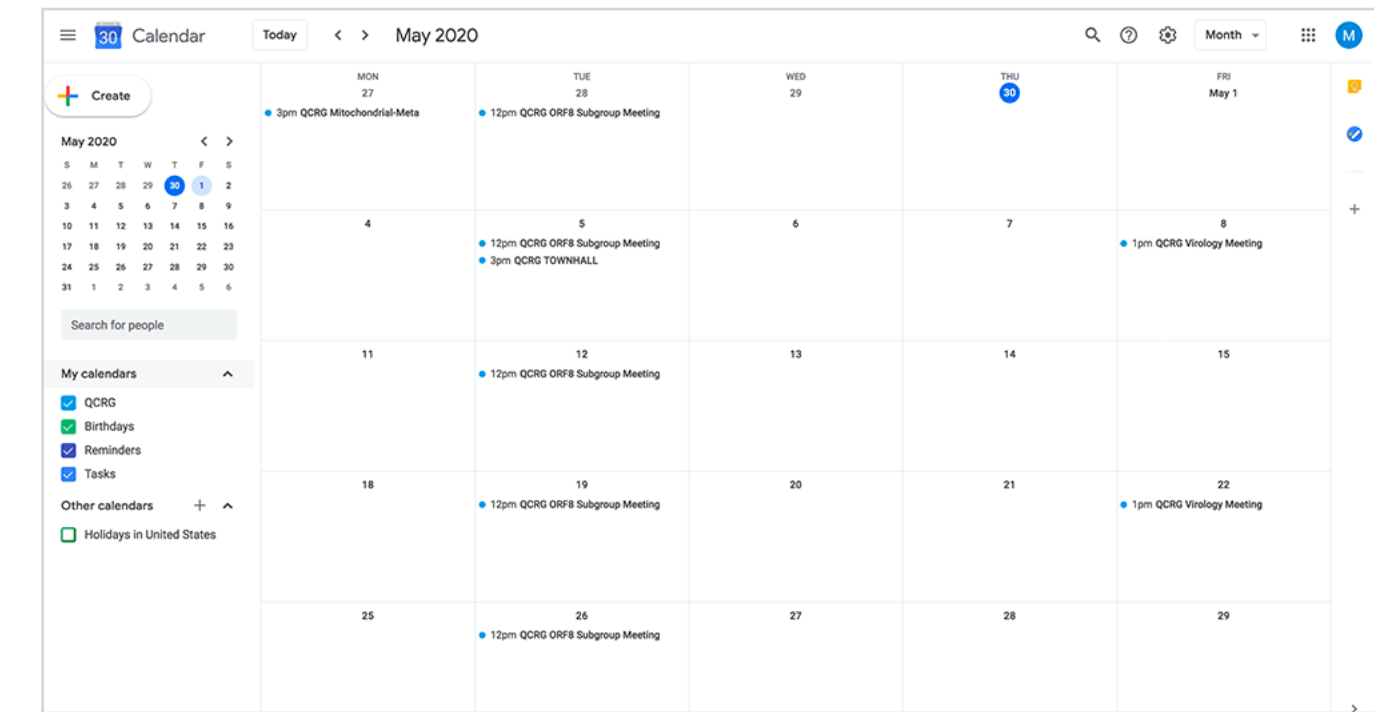
Science communication lends itself well to Zoom: people used to presentation and Q & A format.

- 178 scientist on one call
- Multiple calls a week
- Subgroups formed



Tools for the team

Google Calendar



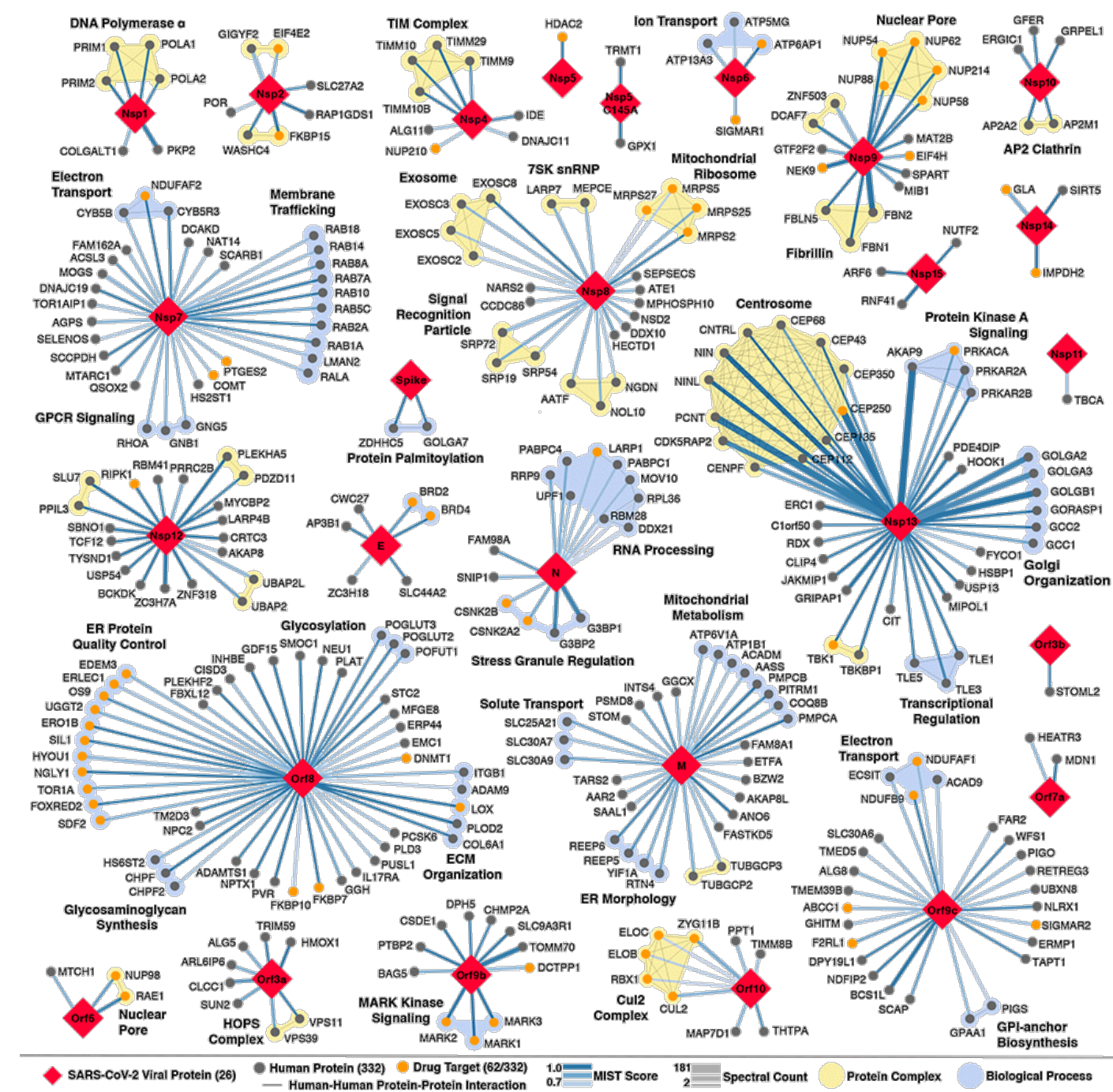
QCRG Wiki

Zoom

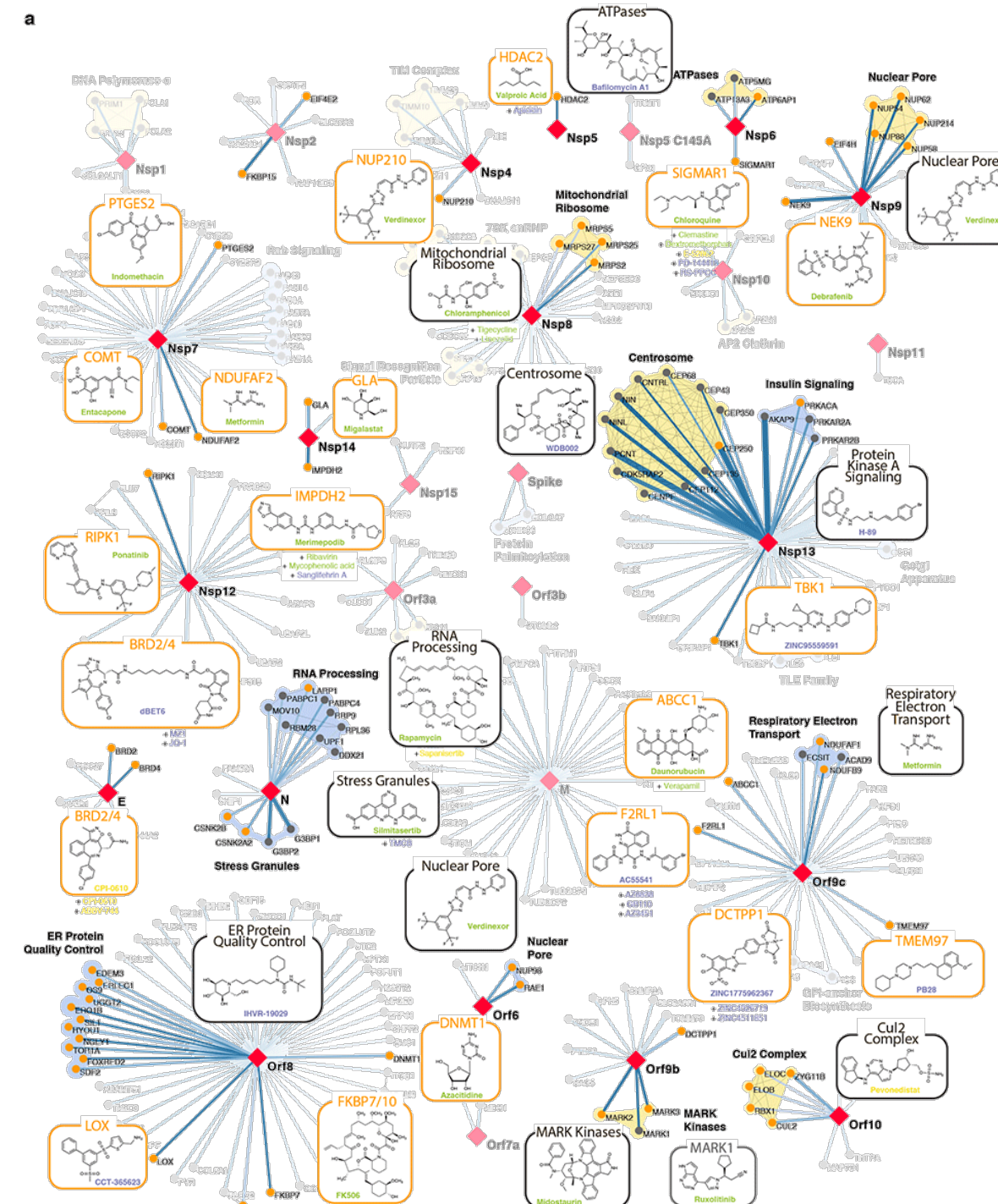
Slack

- Communication and exchange of findings in real time
- Connect calendars
- Upload files

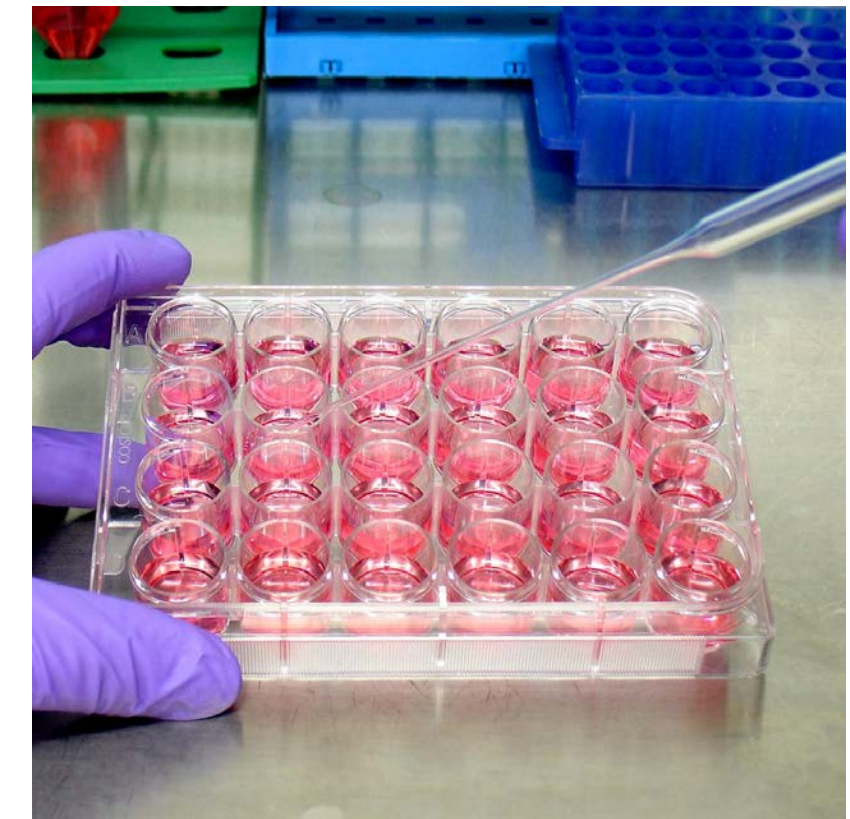
Map to Drug Identification to Virus Testing



Map

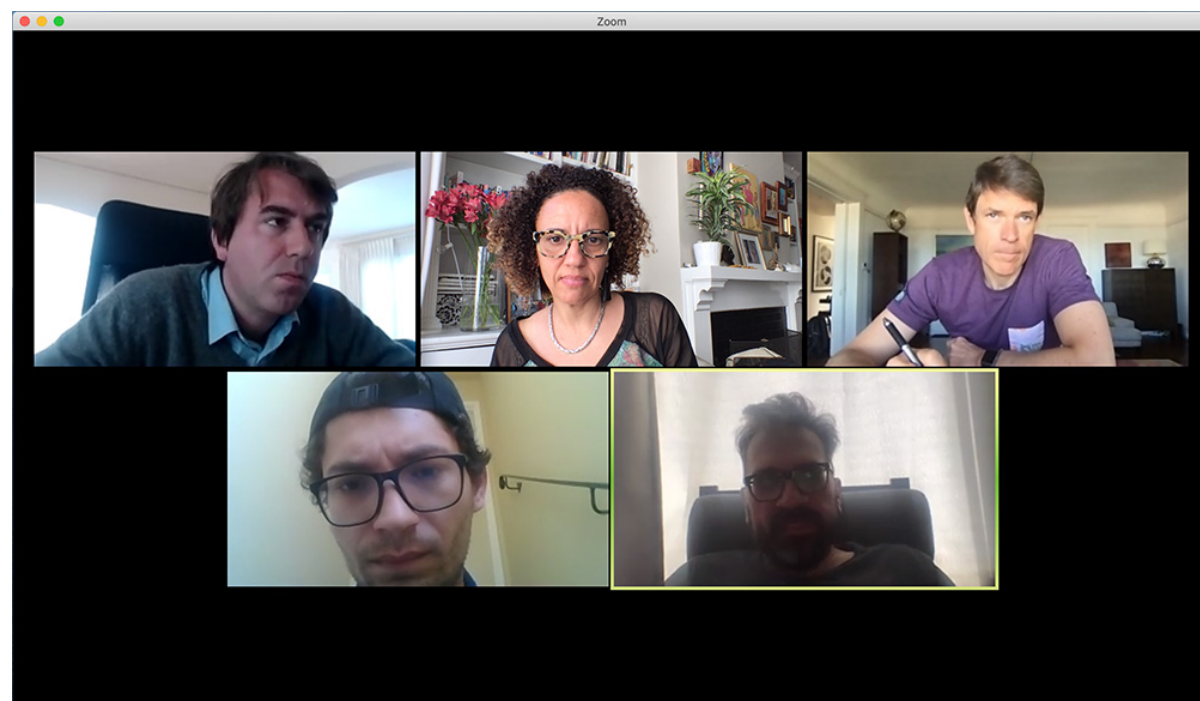


Map with drug & compounds overlaid

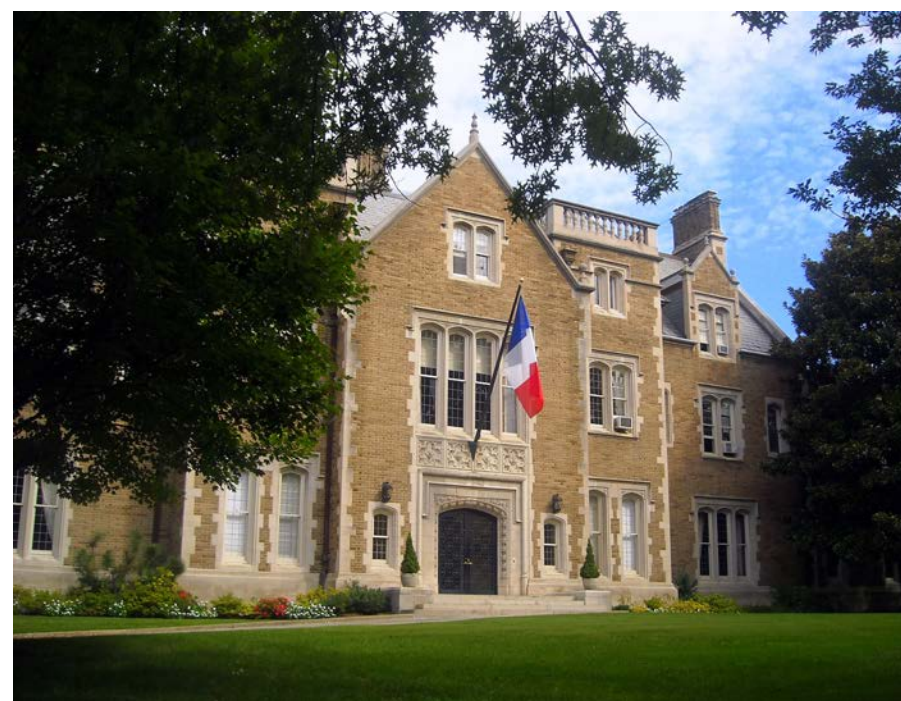


Experiments in NY & Paris
In virus

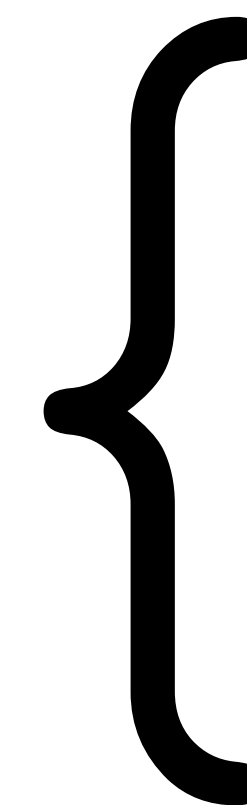
Support From All Sides



SF French Consulate



French Ambassador



FedEx



French Customs



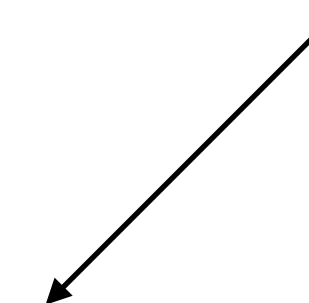
Institut Pasteur



Todd @ FedEx

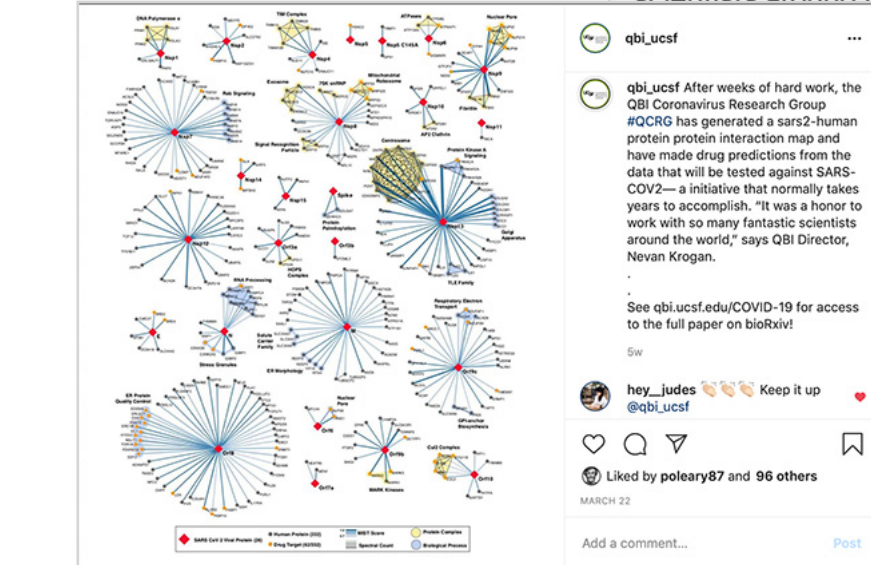
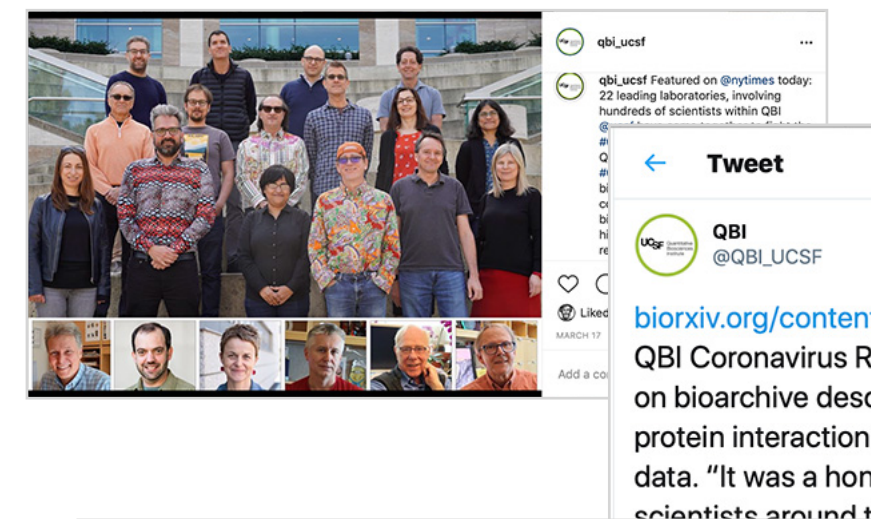
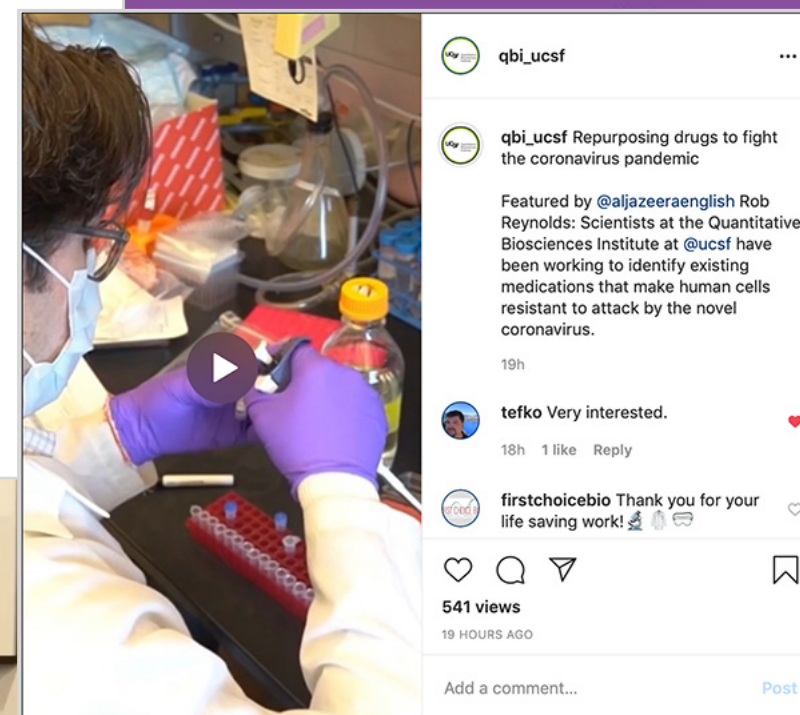
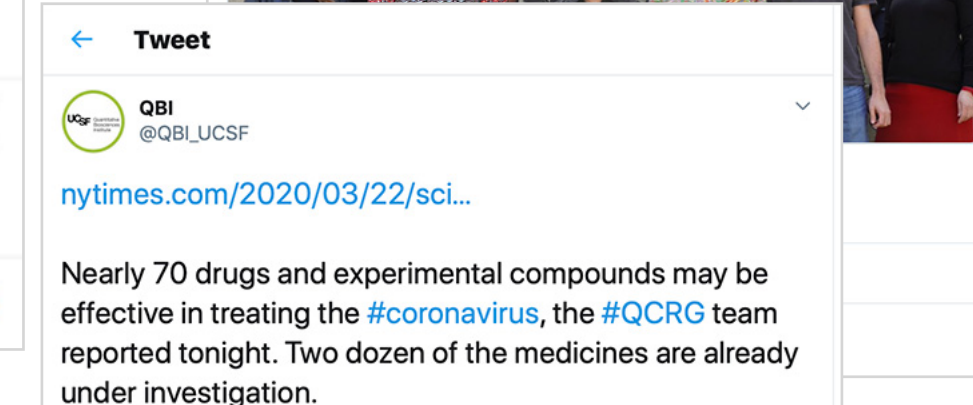
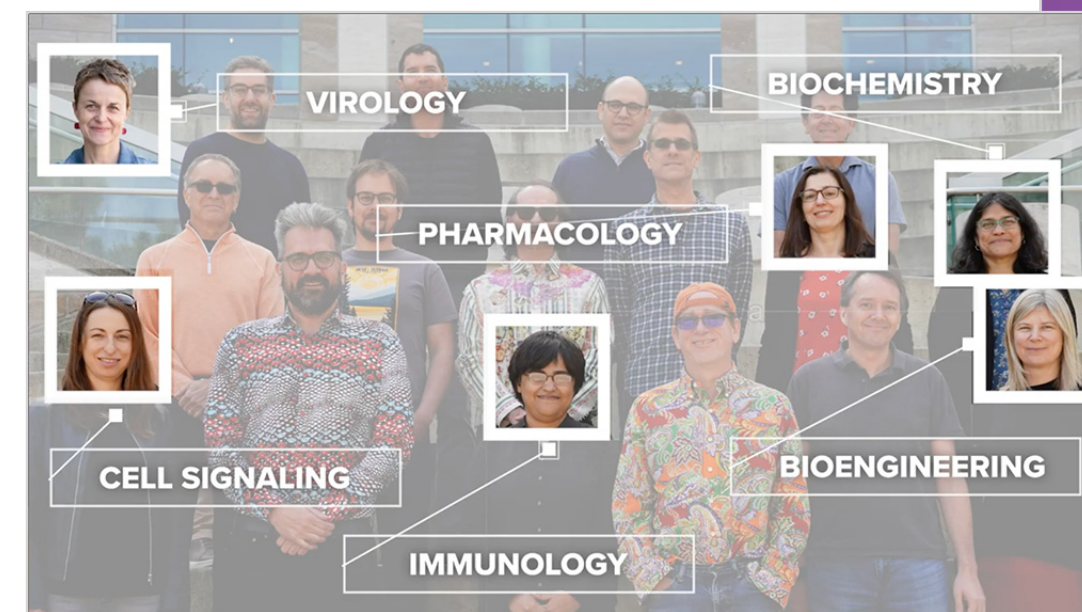


Compounds



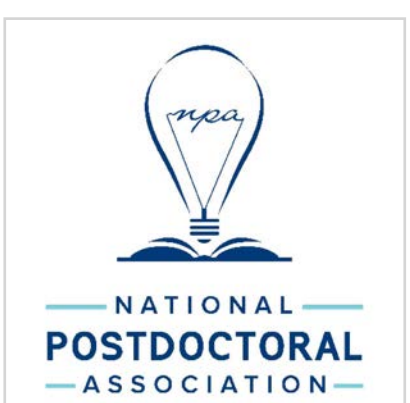
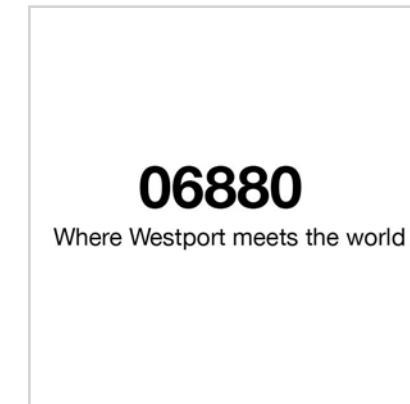
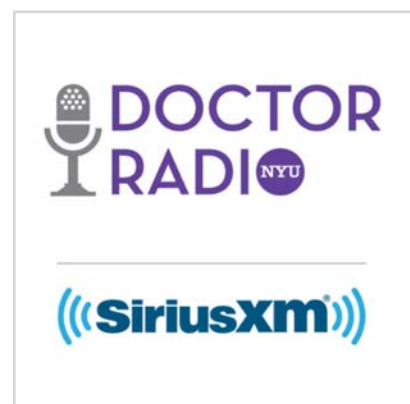
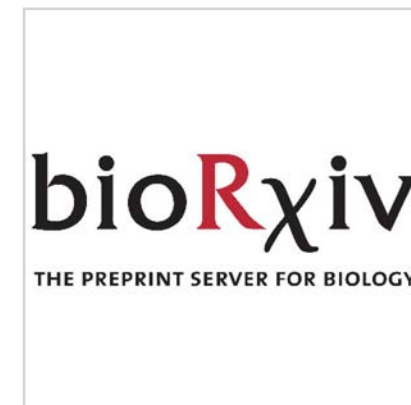
Building Our Narrative - Engaging People

- Public
- Donors
- Staff
- Government agencies, NIH, DARPA, etc.
- Biotech / Pharma
- Media



Keep people informed - often

Sudden Media Explosion



Write Our Story

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COVID-19 treatment might already exist in old drugs – we're using pieces of the coronavirus itself to find them

March 20, 2020 9:09am EDT Updated March 23, 2020 3:06pm EDT

There are 20,000 FDA approved drugs. One of them might fight COVID-19. If we can find it. Peter Dinkov/the image bank via Getty Images

Why don't we have drugs to treat COVID-19 and how long will it take to develop them?

SARS-CoV-2 – the coronavirus that causes the disease COVID-19 – is completely new and attacks cells in a novel way. Every virus is different and so are the drugs used to treat them. That's why there wasn't a drug ready to tackle the new coronavirus that only emerged a few months ago.

As a systems biologist who studies how cells are affected by viruses during infections, I'm especially interested in the second question. Finding points of vulnerability and developing a drug to treat a disease typically takes years. But the new coronavirus isn't giving the world that kind of time. With most of the world on lockdown and the looming threat of millions of deaths, researchers need to find an effective drug much faster.

This situation has presented my colleagues and me with the challenge and

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Disclosure statement
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Scientists Map the SARS-CoV-2-Human Interaction Network

Posted by Guest Blogger on Apr 9, 2020 9:15:00 AM

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This post was contributed by Manon Eckhardt and Melanie Brewer from the QBI Coronavirus Research Group at UCSF.

It's been only a few months since we all became acutely aware of the threat of SARS-CoV-2. Like many in the science community, we've been motivated to do anything and everything we can to help find a cure -- and quickly. Normally drug discovery is a process that would take years and millions, if not billions, of dollars, but by approaching it from a new direction, we hope to do it much faster.

Years of science, done in weeks

Our approach is to discover key human proteins that can be targeted (hopefully by existing therapeutics that are safe, effective, and already FDA-approved). This is a big job, but under the leadership of **Nevan Krogan** at UCSF we've brought together a network of scientists from more than 20 labs to form the **QBI Coronavirus Research Group (QCRG)** to do just this.

Figure 1: Sending out 80 FedEx envelopes in a single day -- all while maintaining social distance. From front to back: David Gordon, Jeff Guo, Fengbo Zhou, Paddy O'Leary (UCSF).

In under a month's time, we've published an [article on BioRxiv](#) describing a comprehensive SARS-CoV-2 virus-human interaction network in which we expressed 26 of the 29 SARS-CoV-2 viral proteins in human cells and used these viral "bait" proteins to fish for human "prey" proteins that interact with the virus. As a result, we identified 332 human proteins that the virus interacts with in cells. Because viruses rely on the help of human proteins in their lifecycle, identifying these potential human helpers of SARS-CoV-2 (especially the ones that are druggable) is a key step in our strategy to throw a therapeutic monkeywrench into the virus' hijacking of human cells. Even better, more than half the drugs hitting these proteins are FDA-approved or in clinical trials or preclinical studies already. We are following up on these leads as we speak, with collaborators in Paris and New York.

We want YOU to join the fight against coronavirus

We are just at the beginning of understanding how SARS-CoV-2 interacts with human proteins. For example, we used HEK293T cells in our first study, but we're planning to soon expand to other cell types, including more physiologically-relevant systems, to catch all the important interactions. It's also important to determine if the

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Hunting for a cure for COVID-19: an insider's story

As UCSF's Quantitative Bioscience Institute mobilizes researchers to fight a global pandemic, QBI's administrator shares the saga

By UCSF School of Pharmacy Editorial Staff / Sat Mar 21, 2020

Jacqueline Fabius is not a scientist. She doesn't have a PhD in physics or computational biology or virology. As the chief operating officer of the Quantitative Bio-

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We found and tested 47 old drugs that might treat the coronavirus: Results show promising leads and a whole new way to fight COVID-19

April 30, 2020 2:26pm EDT

Testing in cells is an important and exciting first step. vch0011 - via Getty Images

The more researchers know about how the coronavirus attaches, invades and hijacks human cells, the more effective the search for drugs to fight it. That was the idea my colleagues and I hoped to be true when we began building a map of the coronavirus two months ago. The map shows all of the coronavirus proteins and all of the proteins found in the human body that those viral proteins could interact with.

In theory, any intersection on the map between viral and human proteins is a place where drugs could fight the coronavirus. But instead of trying to develop new drugs to work on these points of interaction, we turned to the more than 2,000 unique drugs already approved by the FDA for human use. We believed that somewhere on this long list would be a few drugs or compounds that interact with the very same human proteins as the coronavirus.

We were right.

I am going full nerd and even going to put in links. Get a glass of wine and get ready for a

Author
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Professor and Director of Quantitative Biosciences Institute & Senior Investigator at the Gladstone Institutes, University of California, San Francisco

Disclosure statement
Nevan Krogan receives funding from NIH, DARPA and Roche Pharmaceuticals.

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An Army of Willingness

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Paul Graham @paulg · 3/23/20
The @QBI_UCSF's Coronavirus Research Group is making rapid progress. They've identified 69 existing drugs that might kill it, and their collaborators are already testing 22 of them in vitro.



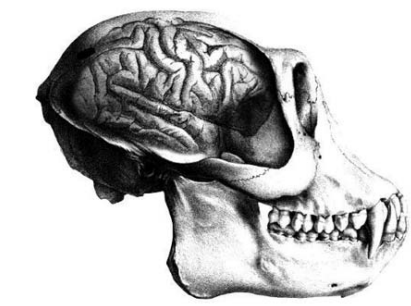
Scientists Identify 69 Drugs to Test Against the Coronavirus
nytimes.com

Paul Graham @paulg · 3/23/20
Want to help the Coronavirus Research Group go faster? Donate here: bit.ly/2UwHcup

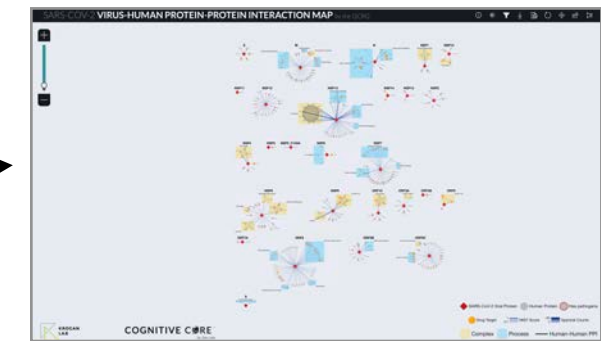


Biz Stone @biz
I am supporting the new @QBI_UCSF #Coronavirus Research Group to find solutions that will save lives. Please join me and DONATE bit.ly/33osvO5

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I'm supporting the new @QBI_UCSF #Coronavirus Research Group -- finding solutions that will save lives. Please donate: bit.ly/33osvO5



Hundreds of Scientists Scramble to Find a Coronavirus Treatment
nytimes.com

11:55 AM · 3/19/20 · Twitter Web App

9 Retweets 59 Likes

Todd @FedEx



Another shout out to Todd and @FedEx for shipping @QBI_UCSF Coronavirus Research Group drug candidates a few weeks ago to our collaborators @IcahnMountSinai and @institutpasteur @UCSF @HHMINEWS



A shout out to Todd and @FedEx, superheros working behind the scenes during this #COVID19Pandemic to pick up our #SARSCoV2 protein plasmids to send to all of you for your #COVID19 research!



3, 2020 · Twitter for iPhone

191 Likes

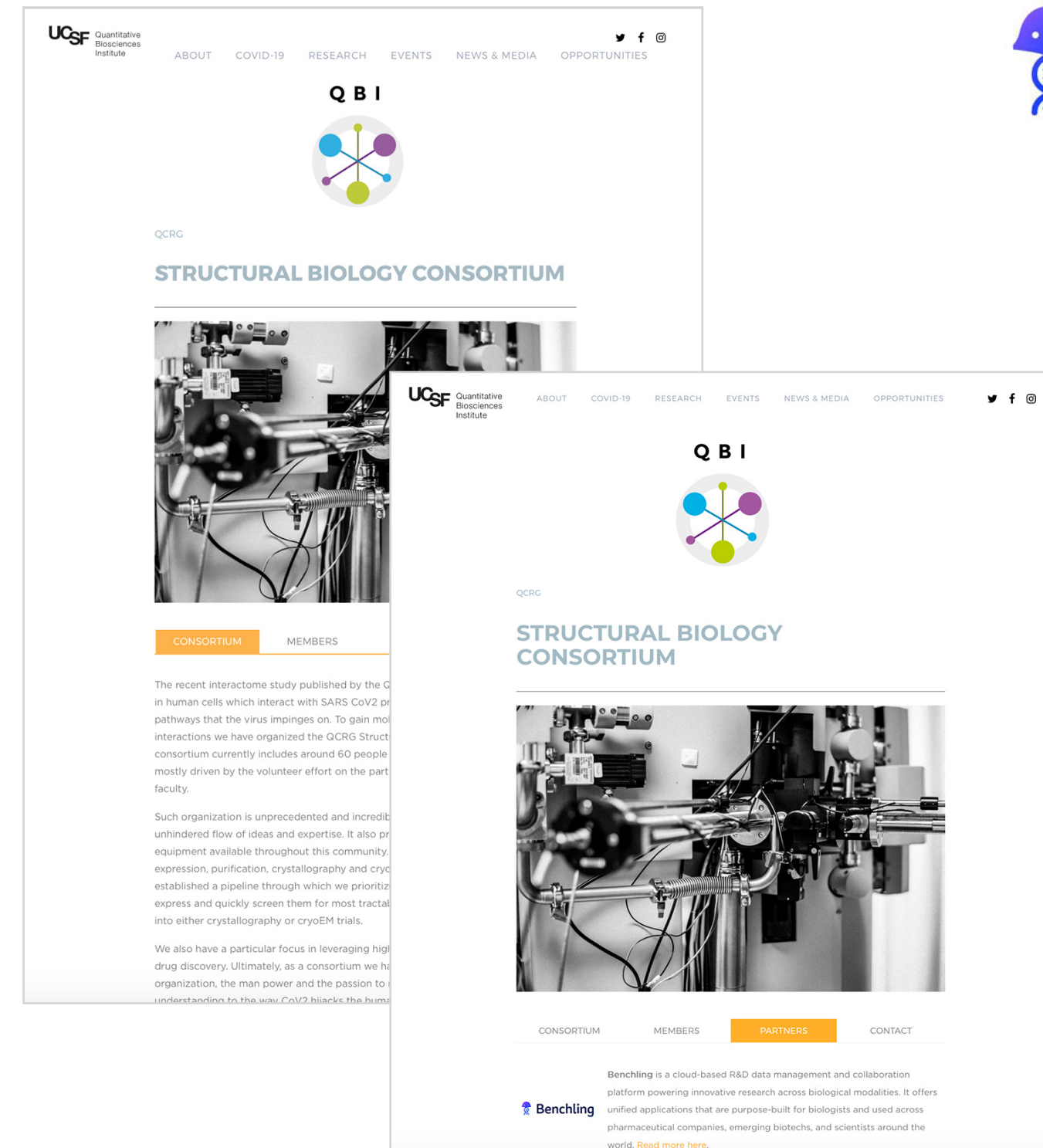
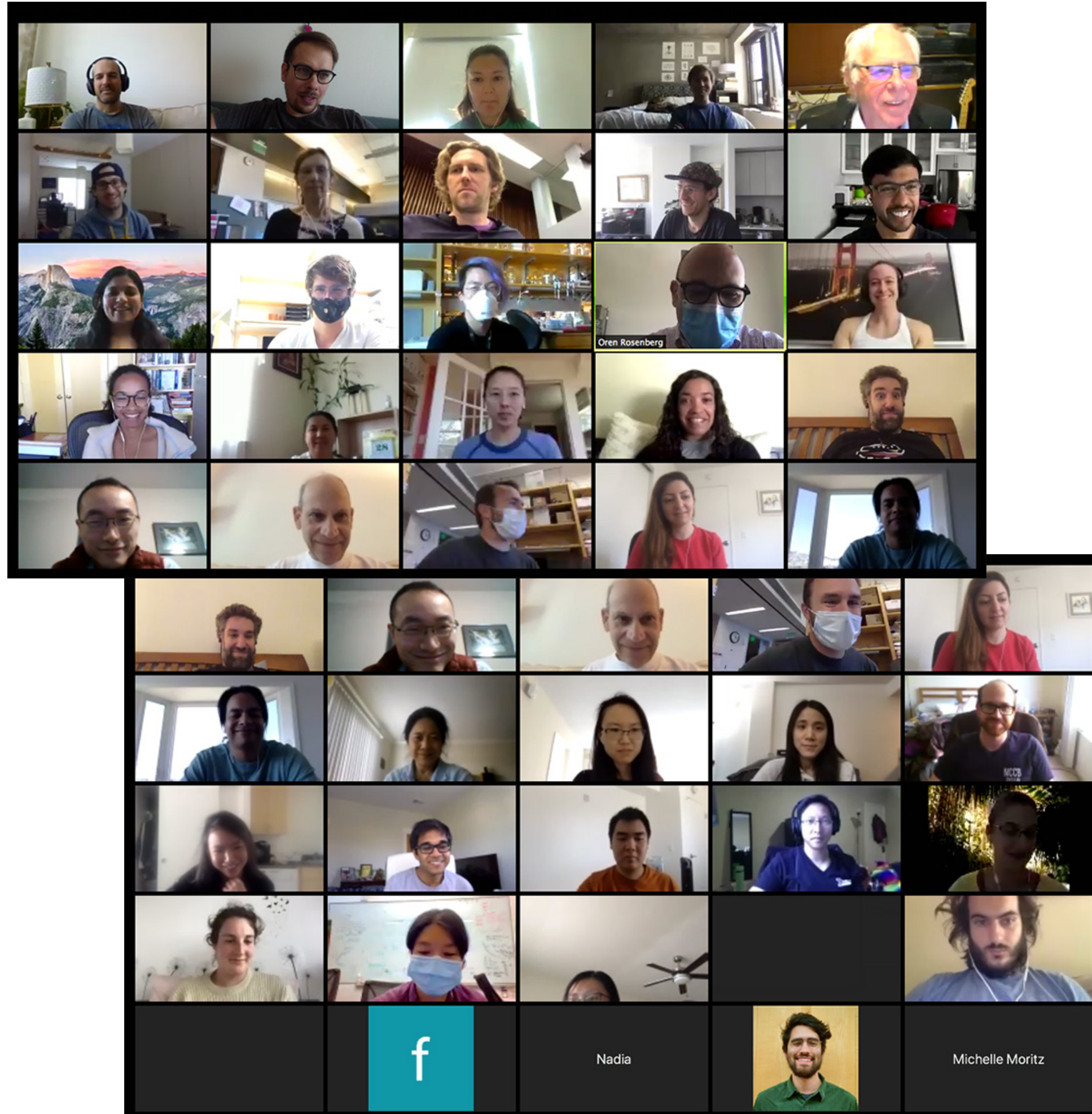


Y Combinator

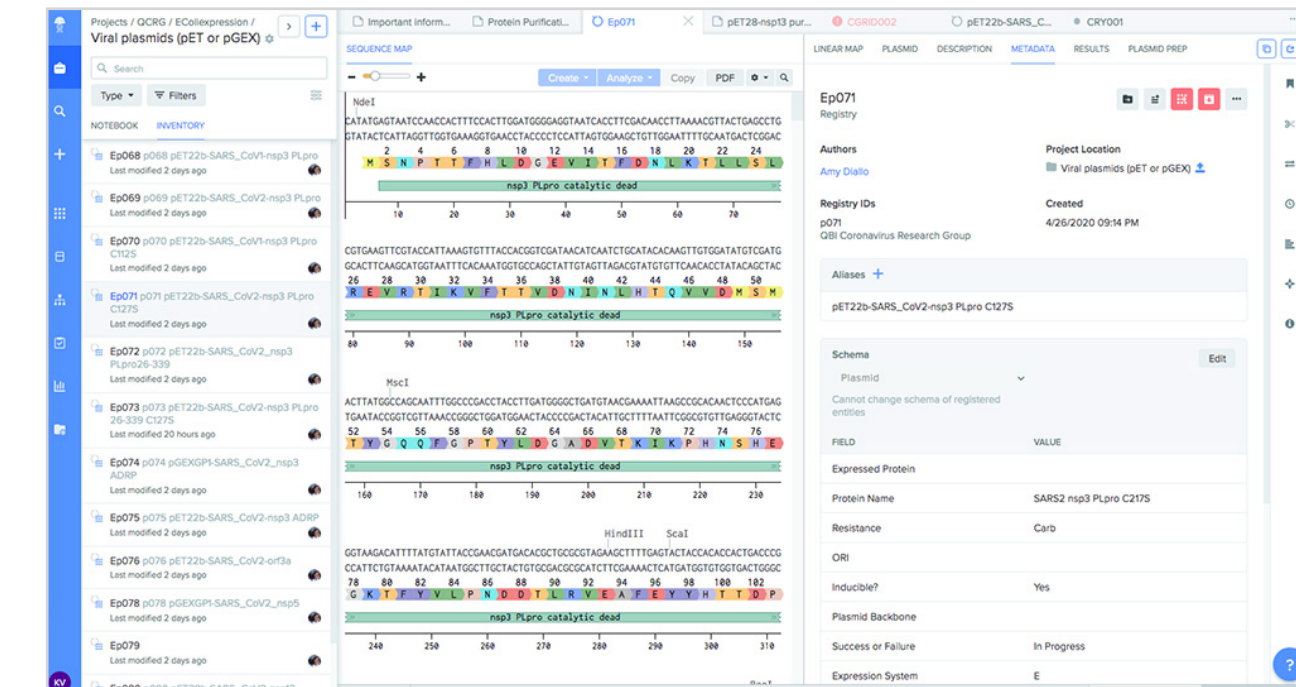
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Being Open to Resulting Innovation: Structural Biology Consortium



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Ready to support innovation and partnerships born from it

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