NCI Deputy Director's Report

Douglas R. Lowy, M.D.

1st Virtual Joint Meeting of NCI Board of Scientific Advisors & National Cancer Advisory Board

April 9, 2020

@NCIDrDougLowy
@TheNCI

Frederick National Laboratory for Cancer Research

- The only Federally-Funded Research and Development Center (FFRDC) dedicated exclusively to biomedical research

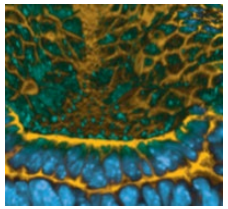
  Operated in the public interest by Leidos Biomedical Research, Inc. on behalf of the National Cancer Institute

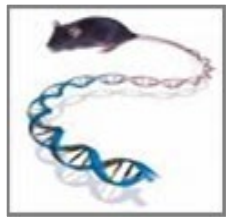
Mission

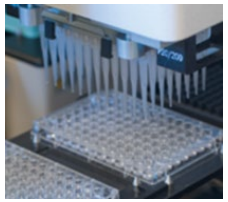
Provide a unique national resource for the development of new technologies and the translation of basic science discoveries into novel agents for the prevention, diagnosis and treatment of cancer and AIDS.

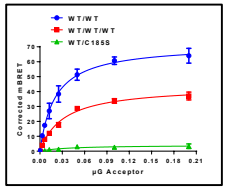
Science and Technology at FNLCR

The Frederick National Lab is dedicated to improving human health through discovery and innovation in the biomedical sciences, focusing on cancer, AIDS, and emerging infectious diseases.

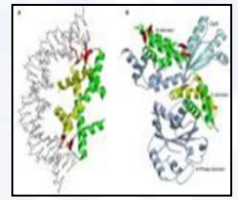


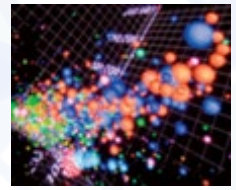


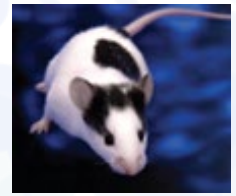




- Basic, translational, and clinical science
- Biopharmaceutical development
- Animal models and biomedical imaging
- Cancer, HIV/AIDS, and cancer viruses
- Drug discovery
- Nanotechnology characterization and formulations
- Data sciences
- Reagent validation and characterization
- Optical & Electron microscopy, Cryo-EM



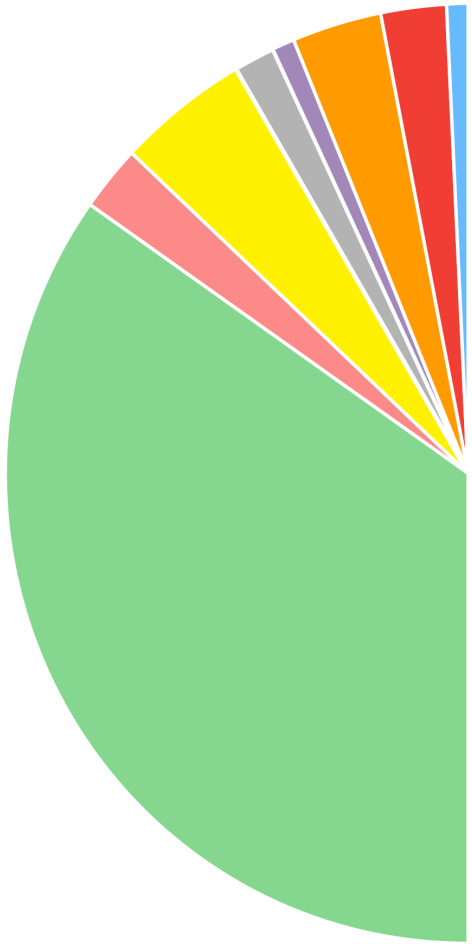




NCI and NIAID are the major users of FNLCR

- **NIAID has made extensive use of FNLCR in responding rapidly to other epidemics:** Examples include SARS (2003), Ebola (2013), Zika (2015)
- **One example from current SARS-CoV-2 epidemic:** Developing a global therapeutic trial of **Remdesivir** in COVID-19 patients
  - A nucleoside analog, functions as an RNA chain terminator
  - Originally developed for treatment of Ebola and Marburg virus infections,
  - Subsequently found to inhibit replication of other RNA viruses, including coronaviruses

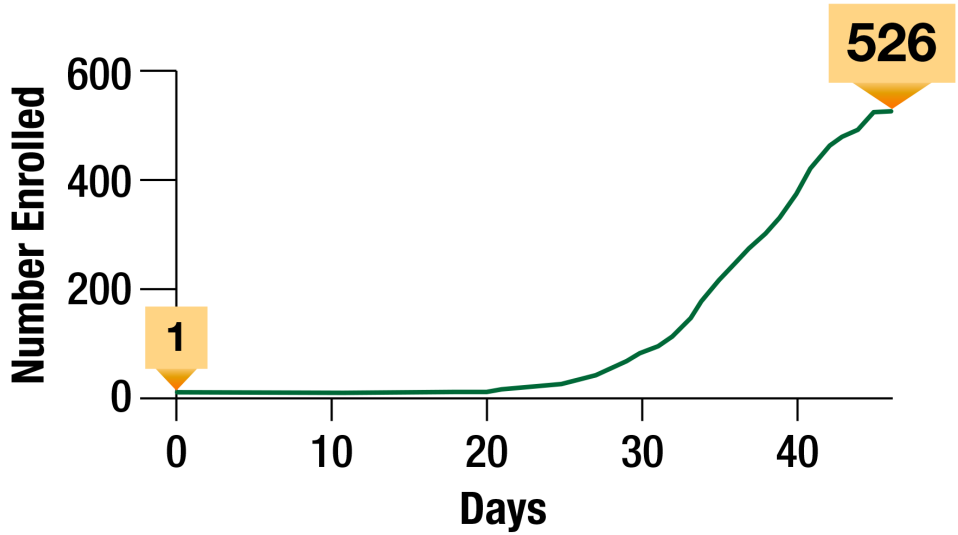
Adaptive Coronavirus Treatment Trial



Country Sites

1	Denmark	2	S. Korea
3	Germany	6	Singapore
4	Greece	3	United Kingdom
1	Japan	46	United States

Current Enrollment



Pivoting some cancer research activities at FNLCR to SARS-CoV-2 research

- **Identifying genetic determinants of SARS-CoV-2 susceptibility and outcomes:** Cancer Genomics Research Laboratory
- **Testing and validating serologic assays for SARS-CoV-2:** Serology laboratory of Vaccine, Immunity, and Cancer Program
- **High throughput screening for small molecule inhibitors of SARS-CoV-2 proteins:** Technology developed by RAS Initiative

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Genetic Determinants of Susceptibility and Outcomes of COVID-19

GOALS

1. Rapidly identify variants

- Targets for therapy
- Insights into biology of COVID-19 pathogenesis
- Use for screening/public health
  - Sets of SNPs or mutations

2. Immediately share data with community

- Cloud-based availability with dbGap ‘front-door’
- NCI/NIAID/NHGRI working together
  - Verily/Terra (Broad) and others

HIV: Genetic polymorphisms of CCR5 receptor can increase or decrease risk of infection and rate of disease progression

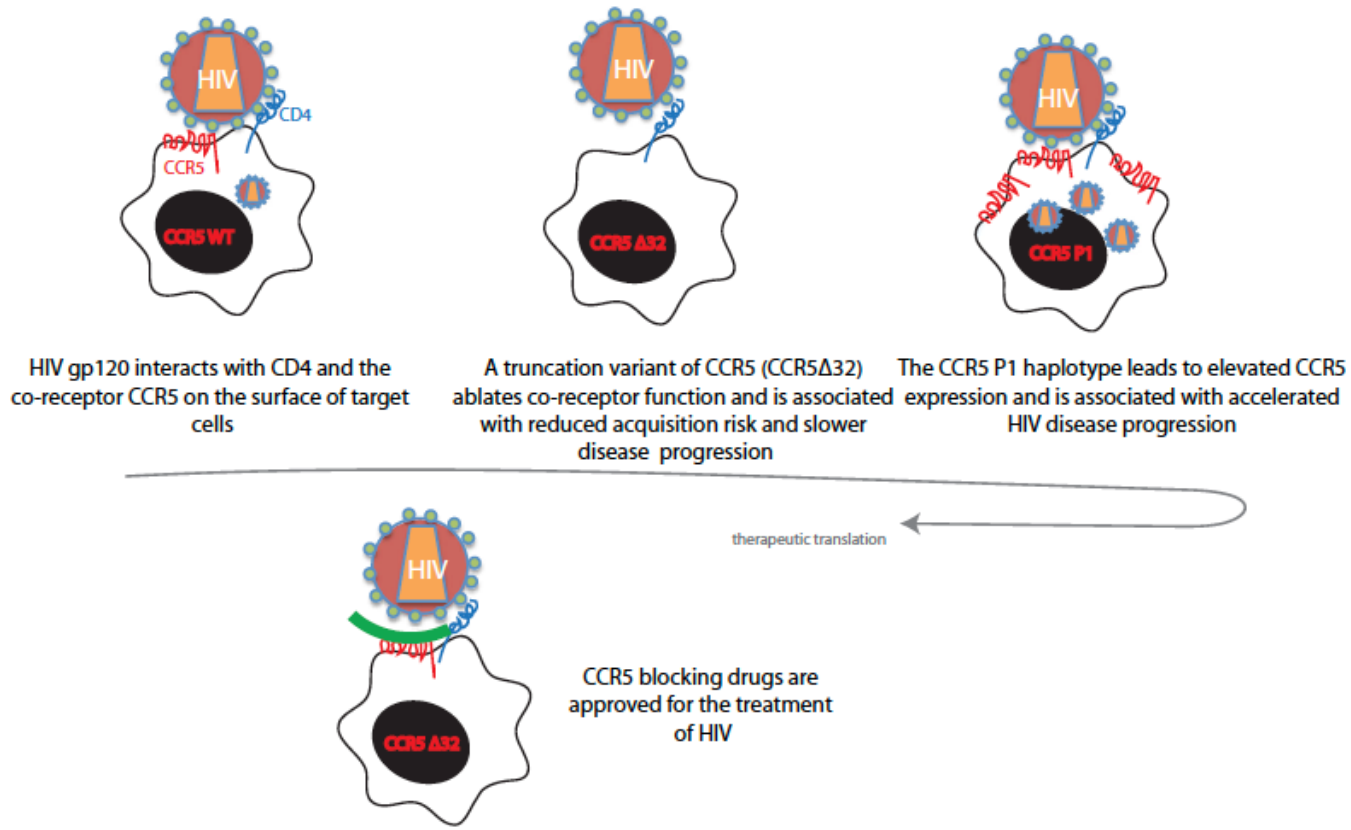

Fig. 1 CCR5 is a key co-receptor for HIV entry. CCR5Δ32 individuals in whom CCR5 expression is lost have reduced HIV acquisition risk and disease progression while individuals with the CCR5P1 haplotype have higher CCR5 expression and accelerated disease progression. These and other observations led to drugs that block CCR5, which are licensed for the treatment of HIV

Naranbhai & Carrington, Immunogenetics, 2017

Current planned studies of genetic determinants of SARS-CoV-2 susceptibility and outcomes

(Cancer Genomics Research Laboratory; immediately share data with scientific community)

- **Italian epidemic cohort:** collaboration with NIAID, up to 2500 samples, likely to be skewed to patients with poor outcome
- **NIH Clinical Center cohort:** collaboration with NHGRI, NIAID; COVID-19 patients at Clinical Center; planning to expand to extramural centers
- **Longitudinal cancer cohort (Dr. Doroshow will discuss):** COVID-19 infections in cancer patients, a group with increased risk of poor outcomes; will include patients with benign course and poor outcomes; detailed prospective information

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Frederick National Laboratory
for Cancer Research

sponsored by the National Cancer Institute

HPV Serology at FNL

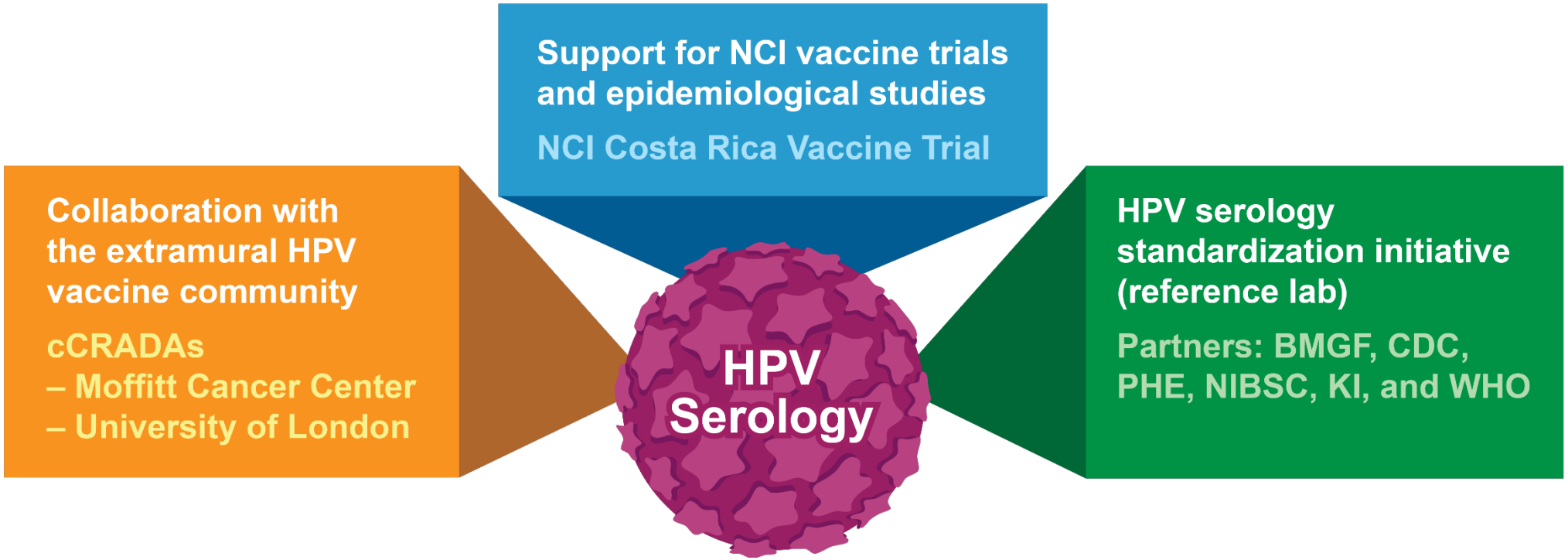
Ligia A. Pinto, PhD

Director, Vaccine, Immunity and Cancer Program

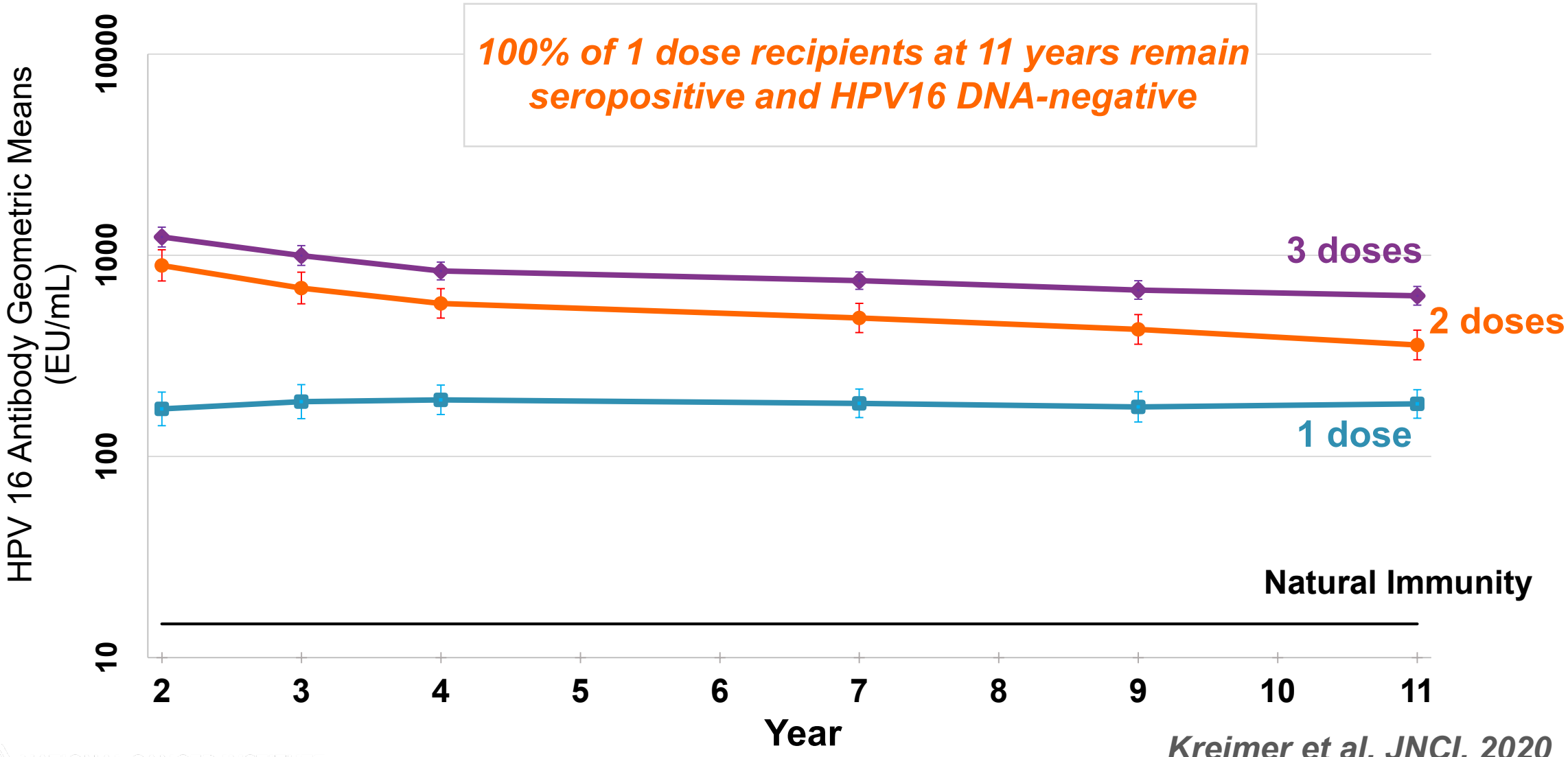
DEPARTMENT OF HEALTH AND HUMAN SERVICES • National Institutes of Health • National Cancer Institute

Frederick National Laboratory is a Federally Funded Research and Development Center operated by Leidos Biomedical Research, Inc., for the National Cancer Institute

Vaccine, Immunity and Cancer Program: HPV Serology Efforts



Stable HPV16 serum antibodies 11 years after one dose of the bivalent HPV vaccine (post-hoc analysis)



Kreimer et al, JNCI, 2020

Convert part of HPV serology lab to SARS-CoV-2 serology

- A collaborative research effort with several labs: NIAID, CDC, Mt. Sinai, others
- **Shorter term goals:** 1) Characterize performance of different serologic assays, correlate with neutralization assays, understand possible cross-reacting sera from prior to epidemic; 2) correlations with serologic tests submitted to FDA
- **Longer term goals:** Understand implications of being seropositive (e.g., resistance to reinfection), duration of seropositivity
- **Cohort oriented research projects:** COVID-19 longitudinal trial of cancer patients (to be discussed by Dr. Doroshow), others

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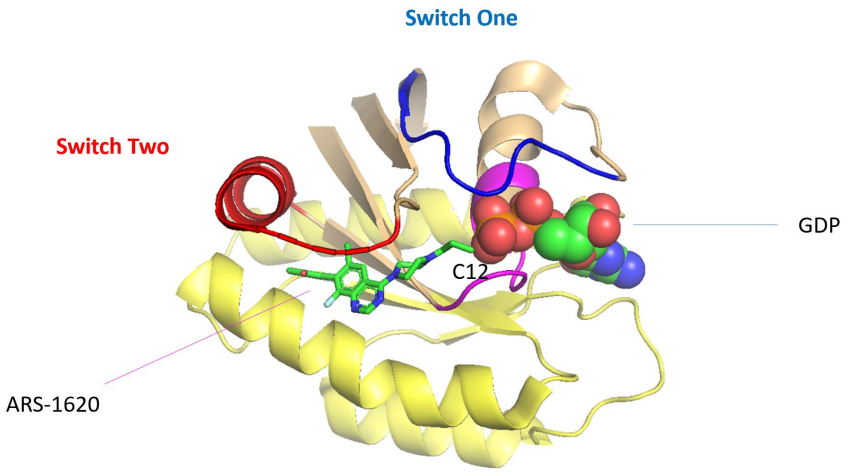
Development of RAS G12C mutant allele-specific inhibitors that attach covalently (tethered) to Cysteine-12 mutation

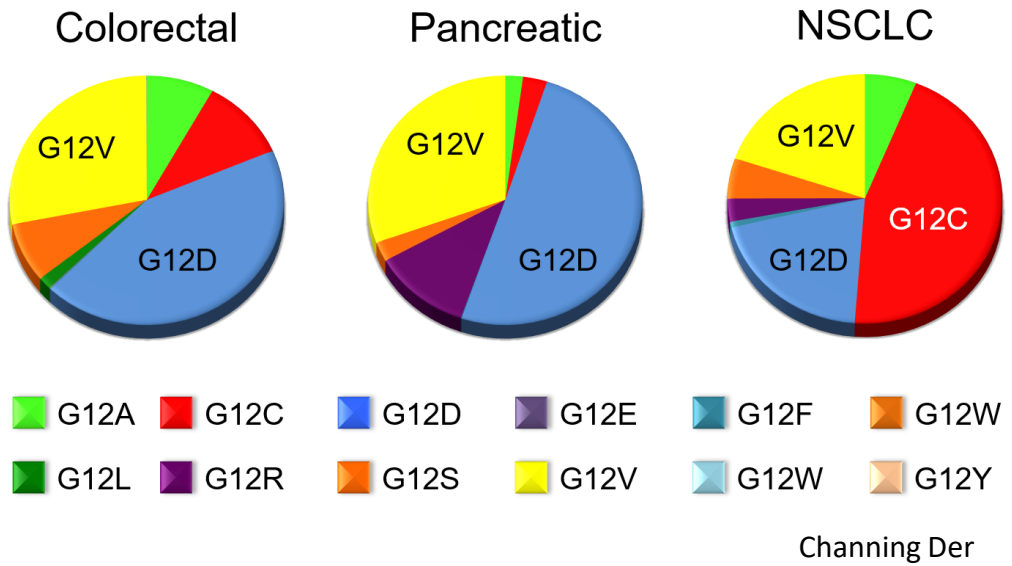
LETTER

doi:10.1038/nature12796

K-Ras(G12C) inhibitors allosterically control GTP affinity and effector interactions

Jonathan M. Ostrem[1]*, Ulf Peters[1]*, Martin L. Sos[1], James A. Wells[2] & Kevan M. Shokat[1]





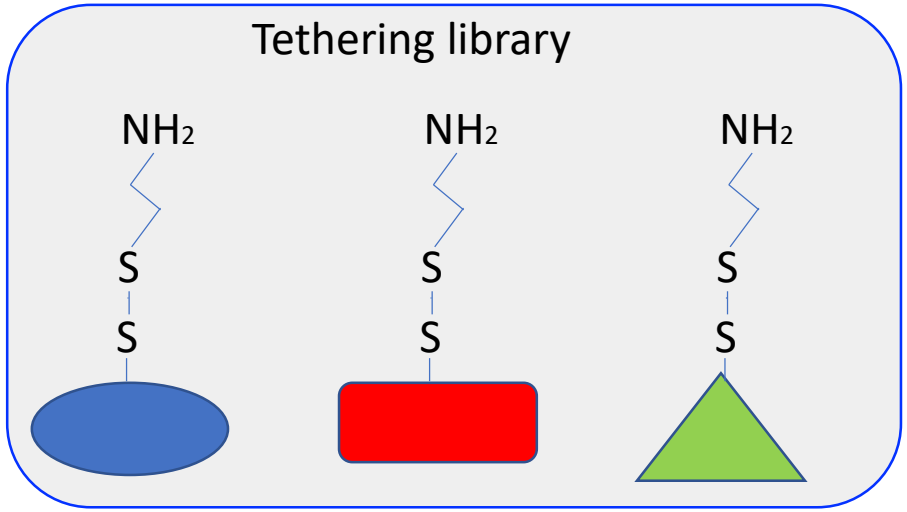
Channing Der

Evaluating several KRASG12C inhibitors in US-based clinical trials

Agent(s)/Mechanism	Phase	Company	Setting	N of pts
AMG 510 (+/− PD1/L1)/KRASG12inhibitor	1/2	Amgen/Carmot Therapeutics	AMG 510 monotherapy in KRASG12C advanced solid tumors and in combination w/PD1/L1 in KRASG12C advanced NSCLC	158
MRTX 849/KRASG12inhibitor	1/2	Mirati	MRTX 849 in KRASG12C advanced solid tumors	200
ARS-3248 (JNJ-74699157)/KRASG12inhibitor	1	Wellspring Biosciences and Janssen	ARS-3248 (JNJ-74699157) in KRASG12C advanced solid tumors	140
LY3499446/KRASG12inhibitor +/− abemaciclib, cetuximab, erlotinib vs docetaxel (phase 2)	1/2	Eli Lilly and Company	Advanced solid tumors including NSCLC and CRC	230

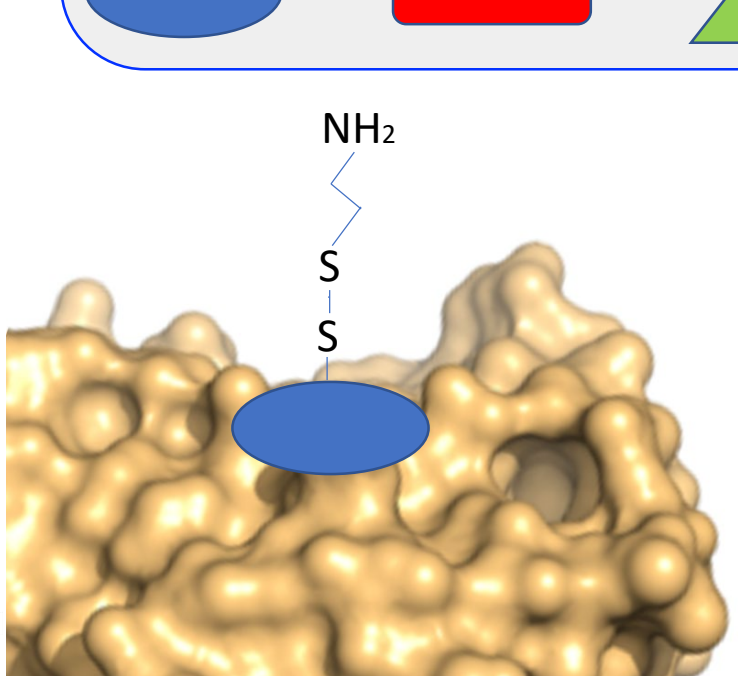
Nagasaka et al, Cancer Treat Rev 2020

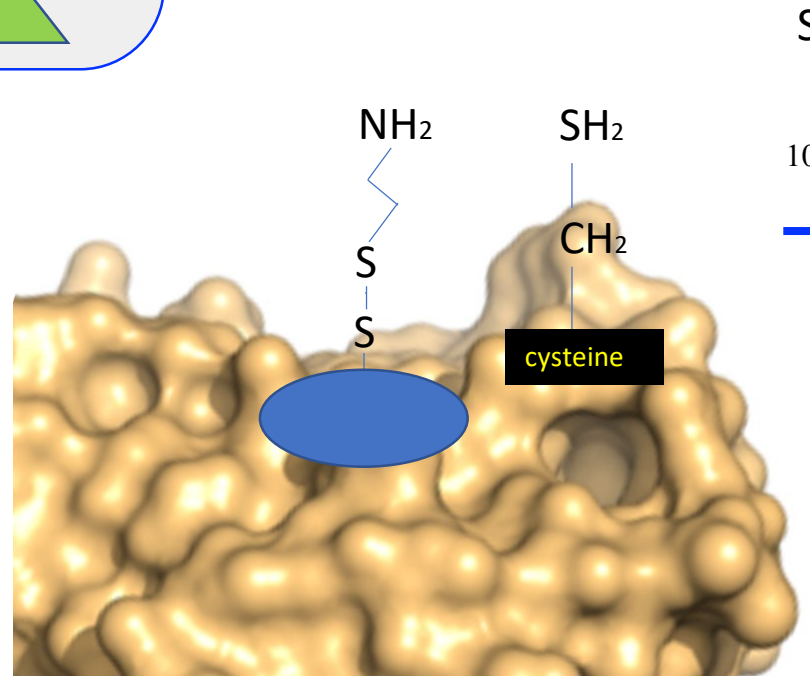
Tethering can identify fragment binding pockets adjacent to cysteines

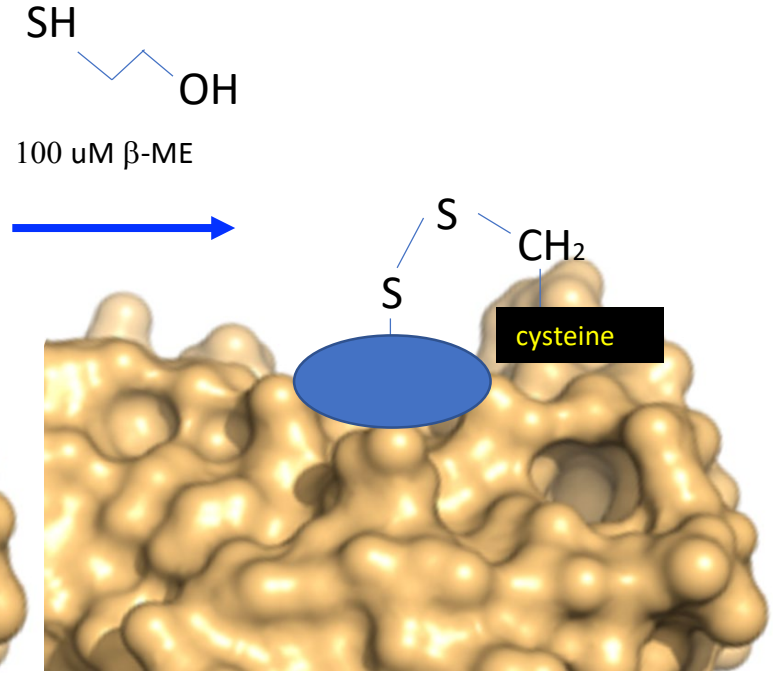


TETHERING: Fragment-Based Drug Discovery

Daniel A. Erlanson, James A. Wells,
and Andrew C. Braisted
Sunesis Pharmaceuticals, Inc., 341 Oyster Point Boulevard, South San Francisco, California 94080; email: erlanson@sunesis.com; jaw@sunesis.com







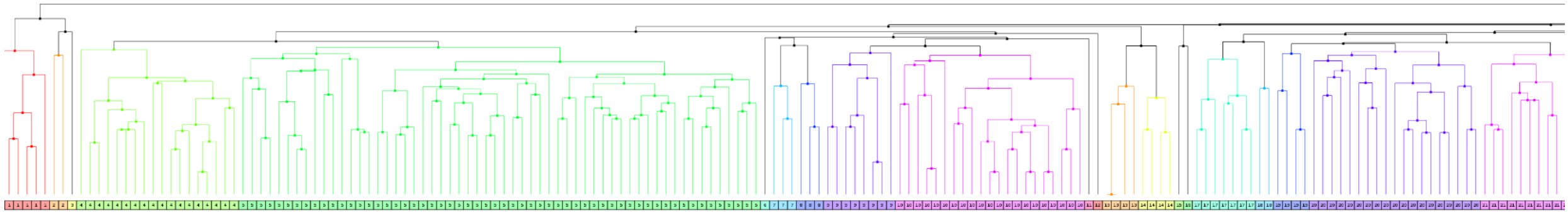
FNL Disulfide tethering library

Assessed library of 13,000 carboxylic acid building blocks – compounds selected through computational analysis based on R-group diversity:

- k-mean clustering (Lloyd's algorithm)
- Hierarchical clustering (Tanimoto similarity metric)
- Diversity-based selection (Soergel distance metric)

Total = 1158 unique disulfide fragments

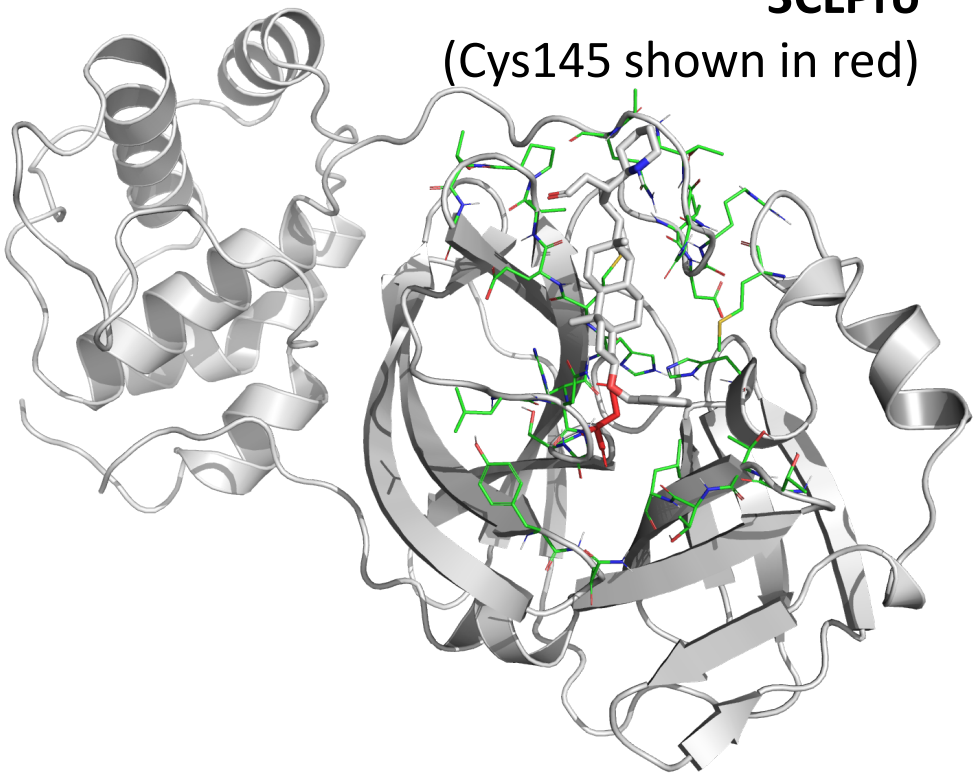
- Good fragment-like properties (MW <300, ClogP ≤ 3, $_n$(H-bond donors/acceptors) ≤3 etc.)
- Minimal overly complex molecules
- Exclusion of compounds with unnecessary stereochemistry (e.g. racemizable groups)
- Exclusion of PAINS / reactive groups



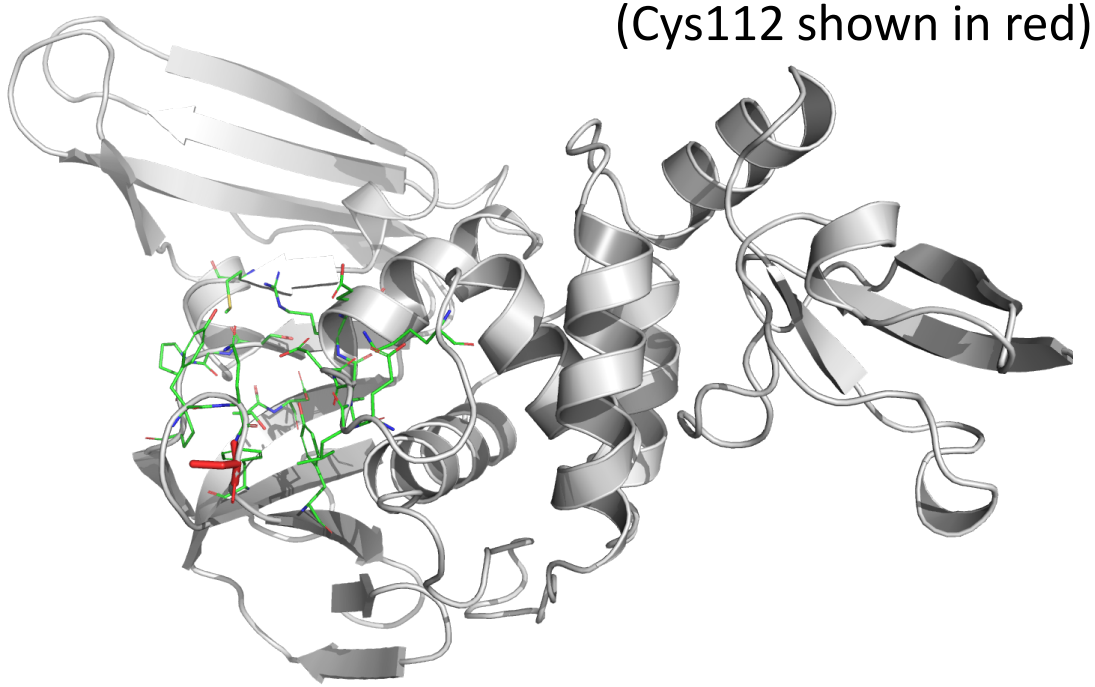
Hierarchical clustering example (different clusters represented by color)

3CLPro and PLPro: Two SARS-Cov-2 protease targets involved in viral life cycle

3CLPro
(Cys145 shown in red)



PLPro
(Cys112 shown in red)



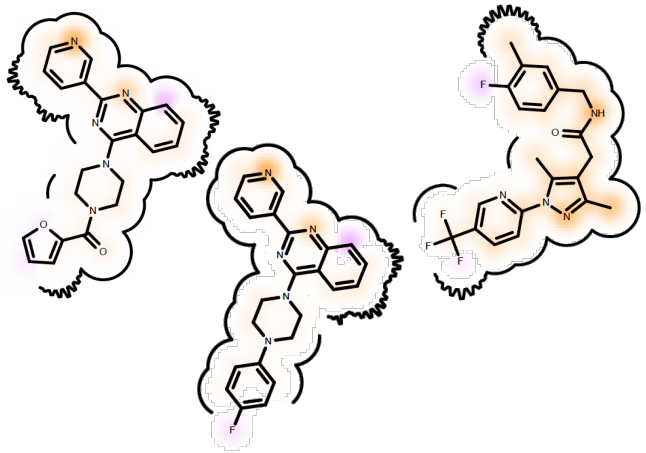
- Both proteins have at least 10 exposed cysteine residues that can be targeted for covalent inhibition
- Covalent inhibitors can have better antiviral activity
- AI-methods provide rapid “leads” that can test for inhibition across both targets

Iterative design: Argonne National Laboratory (ANL), FNLCR, and University of Chicago

ANL (AI Approaches)

Docking @ Scale across supercomputing facilities

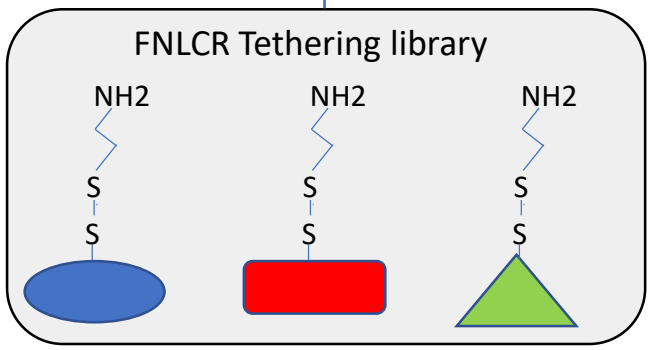
AI-based consensus ranking/ scoring



University of Chicago

Lead refinement / medchem / biochemical experiments

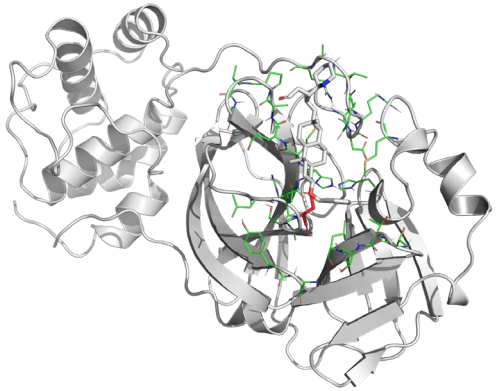
Screening against 3CLPro and PLPro



ANL (Crystallography)

Hits that can be co-crystallized / crystal soaks

Leads are deposited in the public domain (websites)



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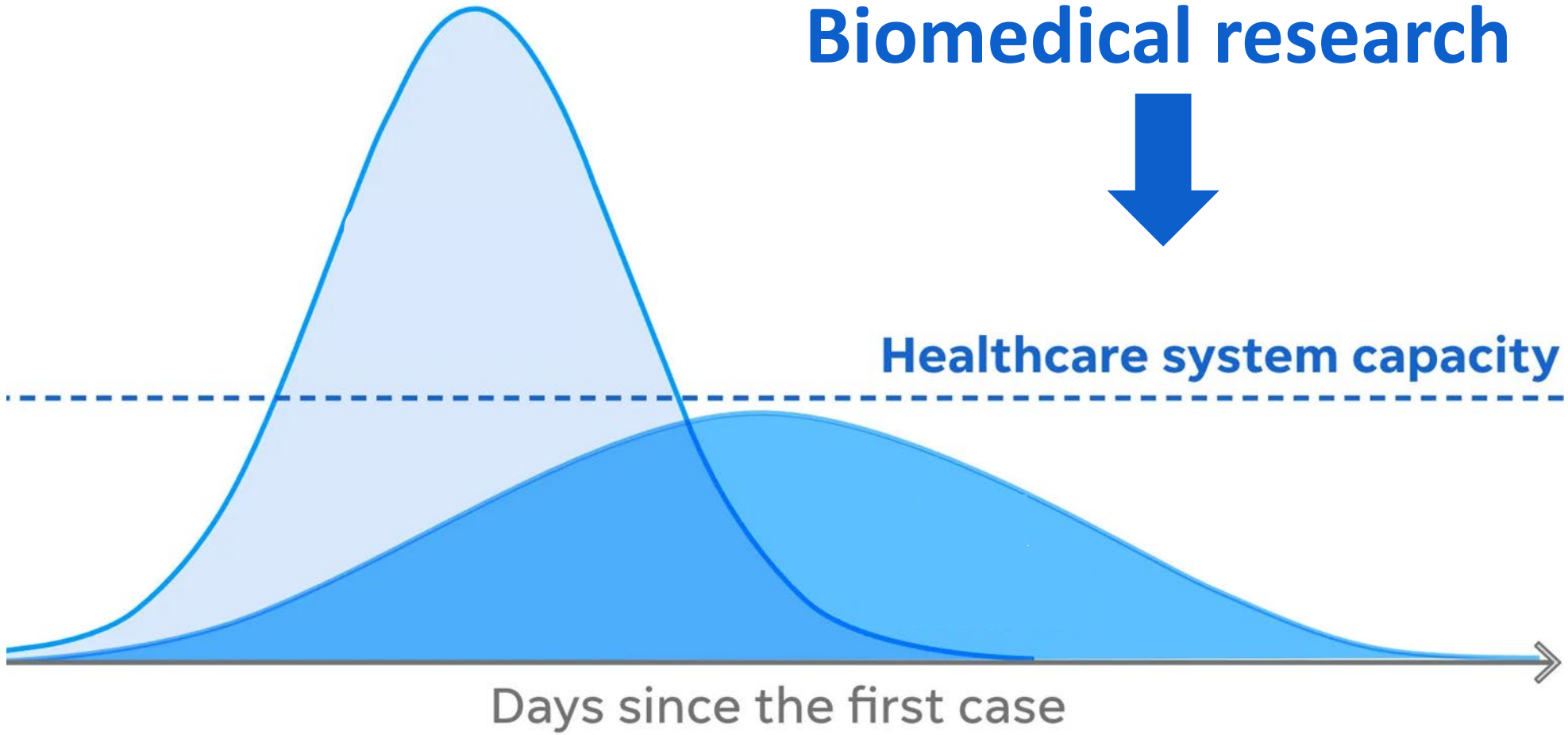
The overall goal of global research on SARS-CoV-2: From mountain to molehill



Discussion