NCI Director's Update

Norman E. Sharpless, M.D.

3rd Virtual Meeting of the Frederick National Laboratory Advisory Committee

May 21, 2020

@NCIDirector
@TheNCI

NIH NATIONAL CANCER INSTITUTE

Operating Status: NCI at Frederick and FNLCR

- As of Friday, May 15, telework for all eligible staff is **extended until further notice.**
- Supports continued physical distancing to reduce the risk of COVID-19 infection for everyone
- Only mission-critical activities should be conducted in person.

Path to Full Return and the New Normal

"You don't make the timeline. The virus makes the timeline." - Dr. Anthony Fauci

	Current State & Baseline for Planning	GROUP A Onsite Specific Work	GROUP B Increasing Onsite Specific Work	GROUP C Integration of Teleworkers	GROUP D Full Return
INDICATORS	Developing agency plan; increased need for patient care	Data supports moving forward	At least 3 weeks & data supports moving forward	At least 3 weeks & data supports moving forward	At least 3 weeks & data supports moving forward
PRINCIPLES	**Assess Environmental State and Prep IC Workforce Plans**	**Work that Cannot be Completed Remotely**	**Work that is Difficult to Complete Remotely**	**Integration of Teleworkers**	**Full Return to Workspace**
STAFFING	Current State: IRP exceptions, employees supporting increasing CC patient census	Staff whose work must be done onsite (i.e. campus support, intramural research)	Staff whose work is best done onsite and Tier 3 staff on weather/safety leave	Staff who can successfully telework but are willing and able to return on site	All staff
HEALTH & SAFETY	Current State	Targets for staffing; Physical distancing (6ft); All meetings remote and mission critical travel	Targets for staffing; Physical distancing (6ft); All meetings remote and mission critical travel	TBD	TBD
TIMELINE	Present	Earliest - June	Earliest - July	TBD	TBD

People with Cancer & Cancer Survivors

- Vulnerable to poor outcomes from COVID infection
- Cancer care delivery interruptions due to the pandemic

Research Expertise & Capacity

- Decades of leadership in virology
- Intramural and extramural research infrastructure
- Collaborations and convening power

Moral Obligation

- Duty to contribute to address a global public health crisis

COVID-19 Serology

Cancer Currents: An NCI Cancer Research Blog

NCI Part of Federal Effort to Evaluate Antibody Tests for Novel Coronavirus

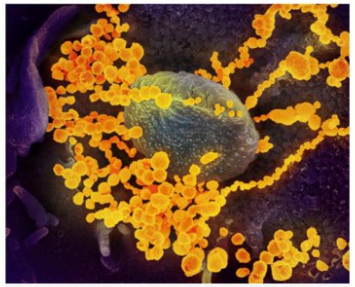
Subscribe

May 5, 2020, by NCI Staff

As part of a collaboration with the Food and Drug Administration (FDA) and several other government agencies and academic medical centers, NCI is evaluating commercially available antibody tests for SARS-CoV-2, the novel coronavirus that causes COVID-19.

NCI has already assessed several of the tests and has provided the findings to FDA.

While "cancer research and cancer care remain job number one at NCI," said NCI Director Norman Sharpless, M.D., "NCI has unique research capabilities and capacities. So, to help in this public health crisis, we believe, is a moral obligation."

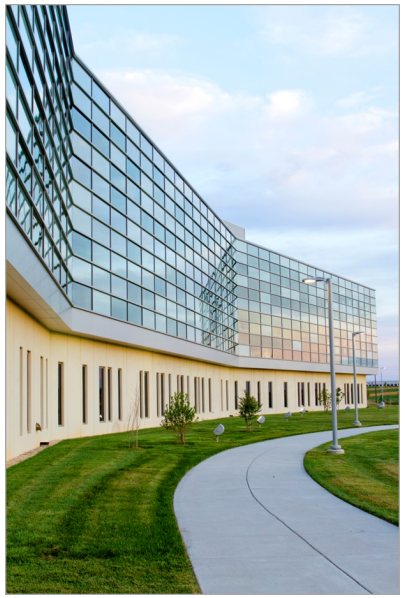


SARS-CoV-2 (gold), the virus that causes COVID-19, emerging from the surface of cells cultured in the lab.
Credit: National Institute of Allergy and Infectious Diseases

FDA

Coronavirus (COVID-19) Update: Serological Test Validation and Education Efforts

Insight into FDA's Revised Policy on Antibody Tests: Prioritizing Access and Accuracy

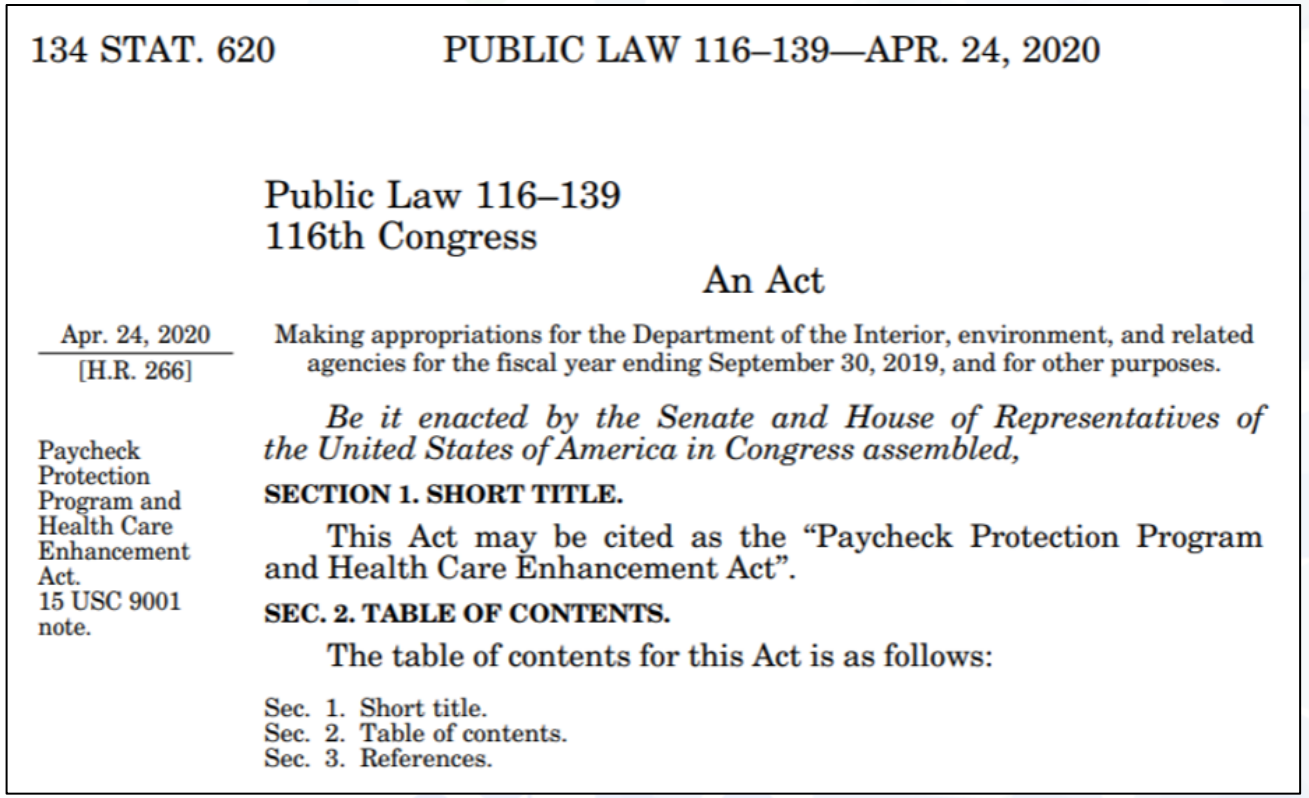


Frederick National Laboratory for Cancer Research
sponsored by the National Cancer Institute

The Frederick National Laboratory for Cancer Research and COVID-19 serology testing

Supplemental funding from Congress

- Enacted April 24th
- $306M for NCI to **develop**, **validate**, **improve**, and **implement** serological testing and associated technologies
- COVID-19 focused and *distinct* from annual appropriation



134 STAT. 620 PUBLIC LAW 116–139—APR. 24, 2020

Public Law 116–139
116th Congress

An Act

Apr. 24, 2020
[H.R. 266]

Making appropriations for the Department of the Interior, environment, and related agencies for the fiscal year ending September 30, 2019, and for other purposes.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

Paycheck Protection Program and Health Care Enhancement Act.
15 USC 9001 note.

SECTION 1. SHORT TITLE.

This Act may be cited as the "Paycheck Protection Program and Health Care Enhancement Act".

SEC. 2. TABLE OF CONTENTS.

The table of contents for this Act is as follows:

Sec. 1. Short title.
Sec. 2. Table of contents.
Sec. 3. References.

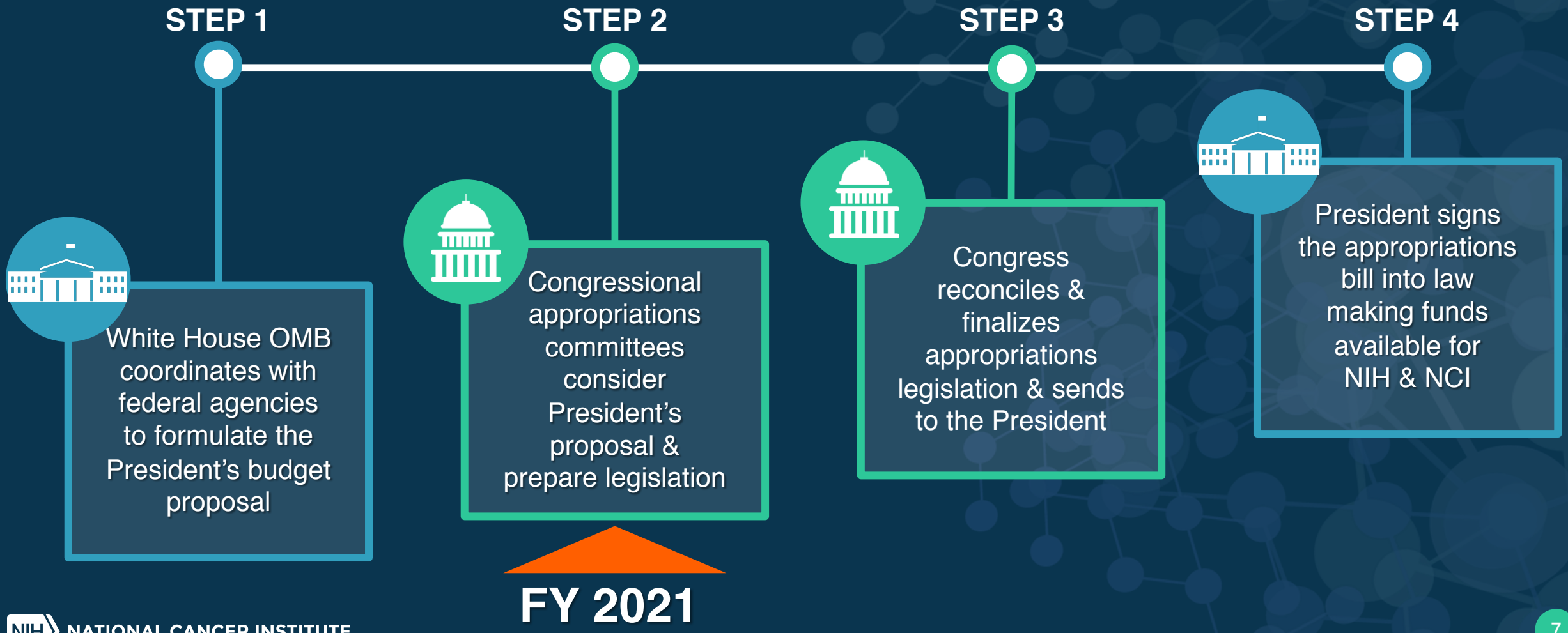
Develop, validate, improve, and implement serological testing and associated technologies

Serology and Immunology Capacity Building

Clinical Serological Sciences

Foundational Serological Sciences

Appropriations Outlook



Leadership Update

Philip E. Castle, Ph.D.
Director, Division of Cancer Prevention

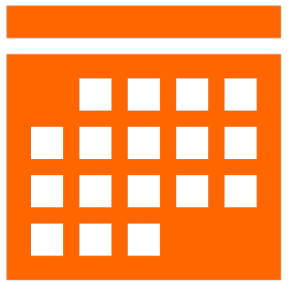
Childhood Cancer Data Initiative (CCDI) Update

- BSA Working Group met on March 27. Participants' discussion centered on an overarching question:

  What is the most critical scientific question that the group should focus on and how does it relate to data sharing?

- Working Group Report to be presented during the next Joint Board Meeting (June 2020)

Cell-based Therapy and Vector Production
Biopharmaceutical Development Program



Accepting applications starting Summer 2020

Will evaluate potential viral production projects proposed by the extramural community

- Development proposals
- Clinical proposals

Cell therapy products

Miltenyi CliniMACS/Prodigy systems

Vector products

- Lentivirus, Retrovirus, CRISPR/Cas9

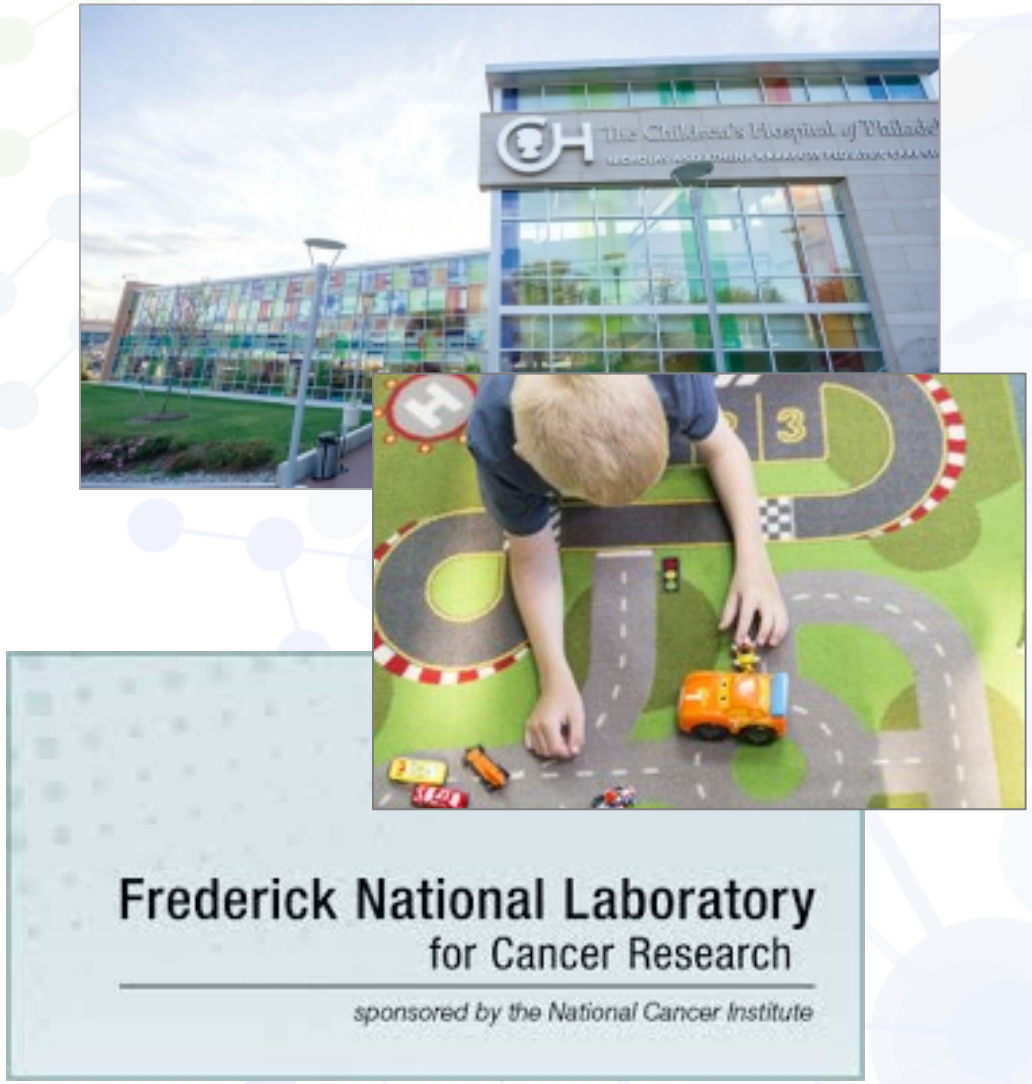
CD33 CAR T Trial

Study of Anti-CD33 Chimeric Antigen Receptor-Expressing T Cells (CD33CART) in Children and Young Adults With Relapsed/Refractory Acute Myeloid Leukemia

ClinicalTrials.gov Identifier: NCT03971799

Principal Investigators:

- Nirali Shah, MD, MHSc, NCI
- Richard Aplenc, MD, PhD, Children's Hospital of Philadelphia



Important advance for Kaposi Sarcoma

FDA grants accelerated approval to pomalidomide for Kaposi sarcoma

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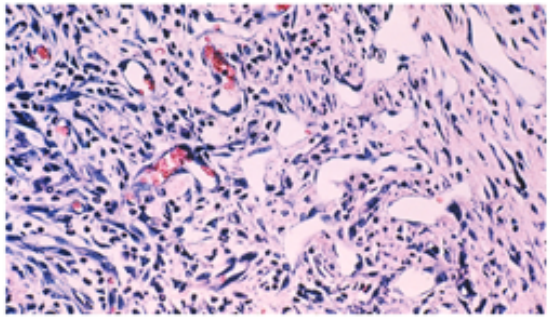
On May 14, 2020, the Food and Drug Administration expanded the indication of pomalidomide (POMALYST, Celgene Corporation) to include treating adult patients with AIDS-related Kaposi sarcoma after failure of highly active antiretroviral therapy and Kaposi sarcoma in adult patients who are HIV-negative.

"Pomalyst has shown positive results in Kaposi sarcoma patients, regardless of their HIV status," said Dr. Yarchoan. "Also, it provides a therapy that is taken orally and works by a different mechanism of action than the cytotoxic chemotherapy drugs generally used to treat Kaposi sarcoma."

NIH NATIONAL CANCER INSTITUTE
Center for Cancer Research

FDA approves pomalidomide for AIDS-related Kaposi sarcoma



Kaposi sarcoma
Photo courtesy of NCI Visuals Online

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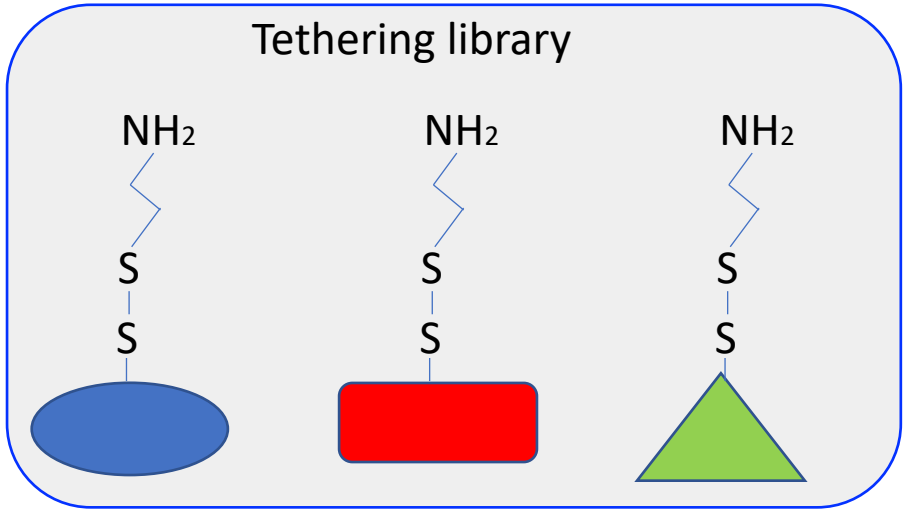
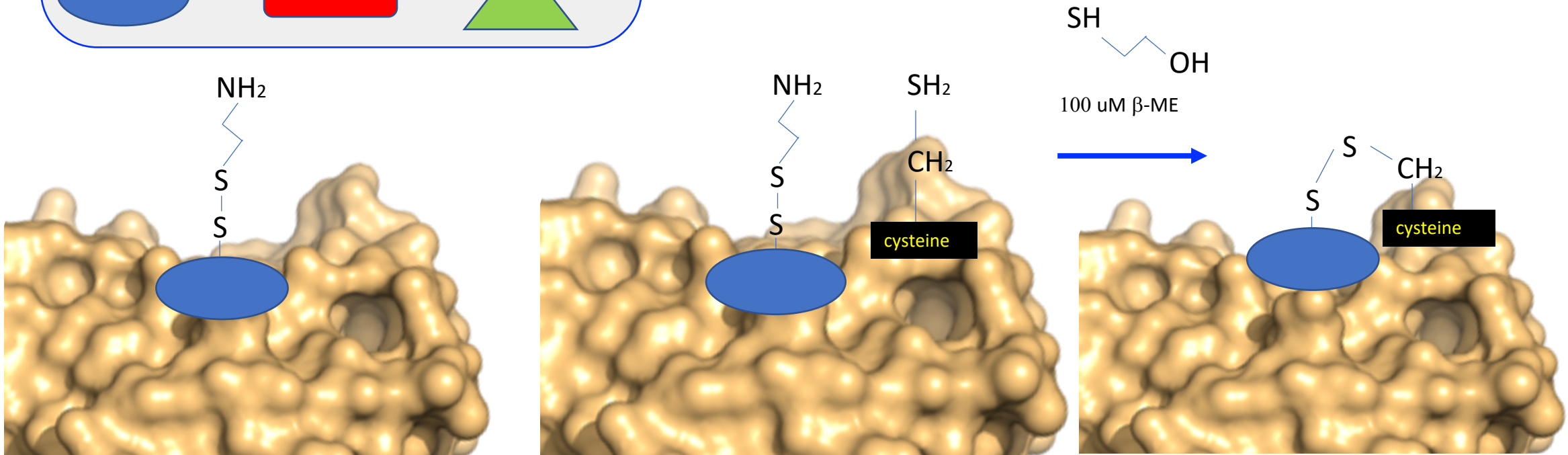
Kaposi sarcoma is a rare form of cancer that usually presents as skin lesions but can also develop in several other areas of the body including the lungs, lymph nodes and digestive system. The disease occurs at a rate of about 6 cases per million people each year in the United States, and mostly affects people who are immunocompromised.

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



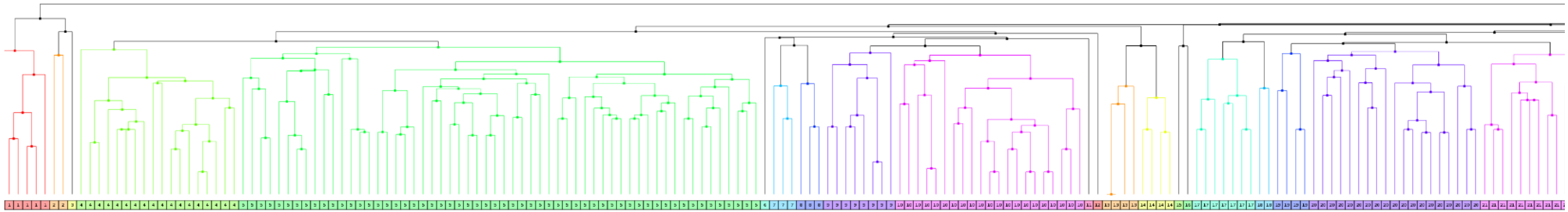
FNL Disulfide tethering library

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

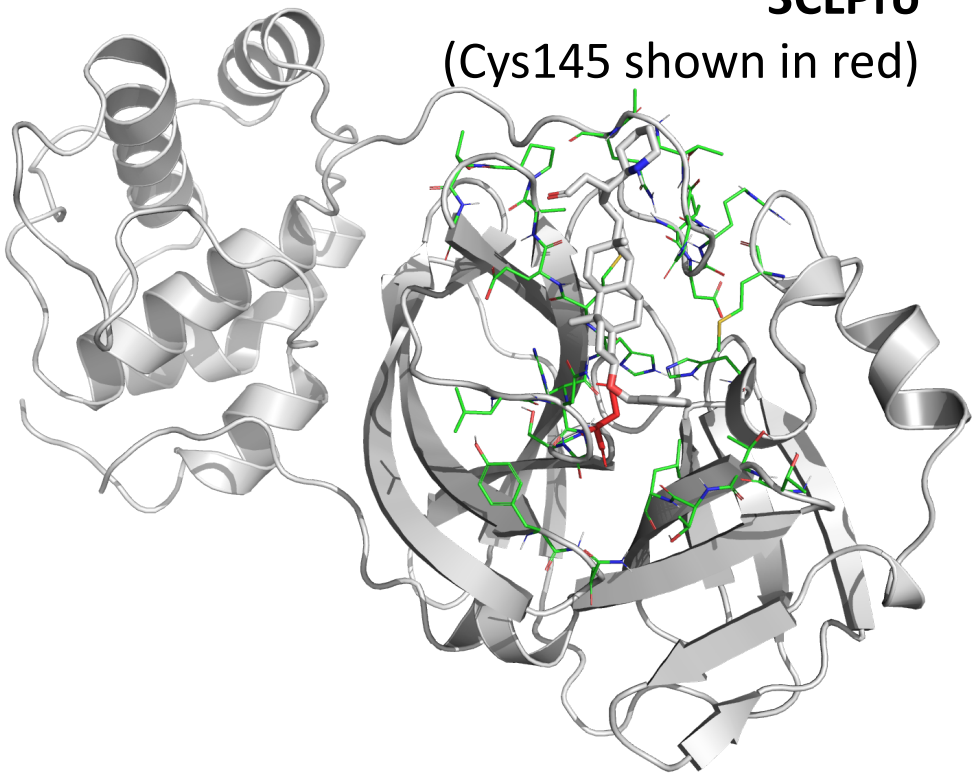
- Good fragment-like properties (MW <300, ClogP ≤ 3, $_n$(H-bond donors/acceptors) ≤3 etc.)
- Minimal overly complex molecules
- Exclusion of compounds with unnecessary stereochemistry (e.g. racemizable groups)
- Exclusion of PAINS / reactive groups



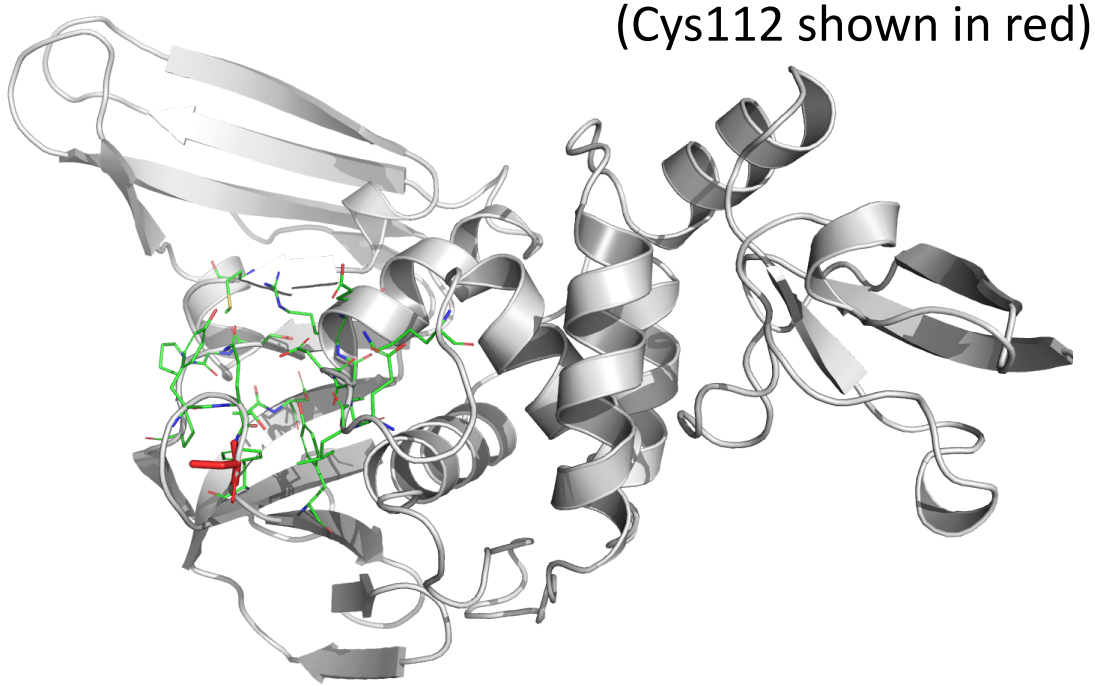
Hierarchical clustering example (different clusters represented by color)

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

3CLPro
(Cys145 shown in red)



PLPro
(Cys112 shown in red)



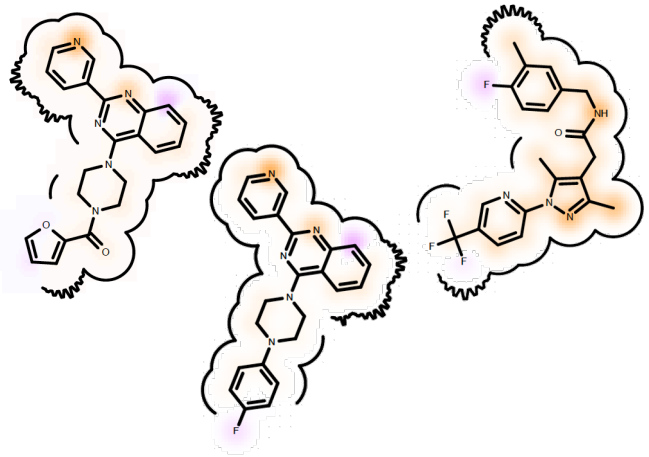
- Both proteins have at least 10 exposed cysteine residues that can be targeted for covalent inhibition
- Covalent inhibitors can have better antiviral activity
- AI-methods provide rapid “leads” that can test for inhibition across both targets

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

ANL (AI Approaches)

Docking @ Scale across supercomputing facilities

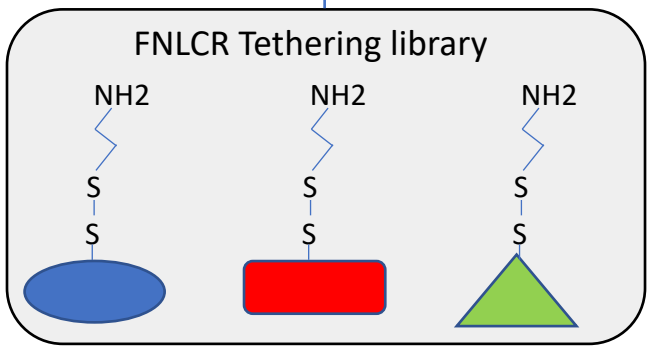
AI-based consensus ranking/ scoring



University of Chicago

Lead refinement / medchem / biochemical experiments

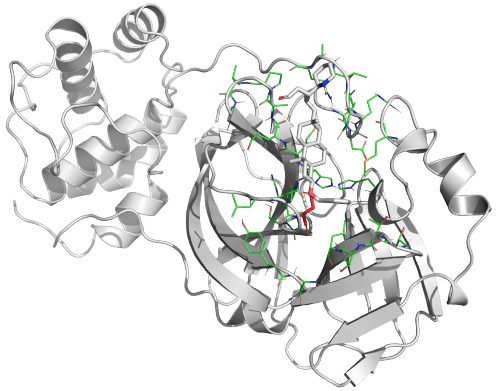
Screening against 3CLPro and PLPro



ANL (Crystallography)

Hits that can be co-crystallized / crystal soaks

Leads are deposited in the public domain (websites)



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Discussion