Current Operations and Future Plans

Frederick National Laboratory for Cancer Research

sponsored by the National Cancer Institute

Ethan Dmitrovsky, M.D.

American Cancer Society Professor

President, Leidos Biomedical Research and Laboratory Director, Frederick National Laboratory for Cancer Research

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

Session Objectives

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

· Review our history, achievements, current work and operations.

· Emphasize record of service to the NCI, NIH and extramural scientific community.

· Discuss future plans and answer your questions.

A Notable History

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

1972

Today

~300 Employees
1973

~2,200 Employees
2018

1972
Litton Bionetics, Inc.

1975
FFRDC

1982
Program Resources, Inc.

1990
DynCorp

1995
SAIC

2001
SAIC-Frederick, Inc.
(Renamed Leidos Biomedical Research, Inc. in 2013)

2012
ATRF Opened
National Laboratory Designation

2016
Ft. Detrick Refurbishment

Frederick National Laboratory Serves the Public Interest

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

Frederick National Laboratory is a national resource that combats cancer, AIDS, infectious diseases and emerging challenges to the public's health.

This is done in concert with the National Cancer Institute (NCI), National Institute of Allergy and Infectious Diseases (NIAID), and other Institutes.

(This mission is larger than anyone of us).

Frederick National Laboratory Current Work

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

Types of Research

1. Discovery and translational science.
2. Advanced core facilities are sophisticated scientific platforms supporting interdisciplinary collaborations.
3. Team science led by Frederick National Laboratory (i.e., RAS initiative).
4. Collaborative science in concert with NCI, NIAID, other Institutes and national laboratories.
5. Advanced technology support to the extramural community.

Some Recent Major Achievements

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The RAS Initiative is elucidating RAS biology to enable discovery of agents to combat RAS-driven cancers.

Creation of the Accelerating Therapeutics for Opportunities in Medicine (ATOM) consortium with Lawrence Livermore National Laboratory, GlaxoSmithKline, and UCSF.

Goal : From Target Identification to Clinical Trial in *1 year*

Support of global Zika, Ebola, human papillomavirus and other vaccination efforts.

National Cryo-electron Microscopy User Facility opened and it benefits the extramural community.

Major Achievements in Support of the Extramural Community (Partial List)

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- **BL22/HA22, immunotoxins targeting CD22 for remissions in hairy cell leukemia, commercialization via CRADA.**
- **Ch14.18, mAb targeting GD2, ~50% increase in survival, high risk neuroblastoma in children. Licensed as Unituxin (dinutuximab).**
- **Support Match trial, NExT trial and MoonShot efforts (with DCTD).**
- **PVS-RIPO (Oncolytic Polio Virus) for glioblastoma.**
- **Contributed to development of the HIV-1 kit to secure safety of the nation's blood supply.**
- **Developed and tested vaccines for emerging infectious diseases like Zika and Ebola.**
- **This and other work is done in concert with the NCI, other Institutes and the extramural community.**

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Immune Response Genotypes Determine if Innate Immune Cells Kill or Let Survive HIV Infected Cells

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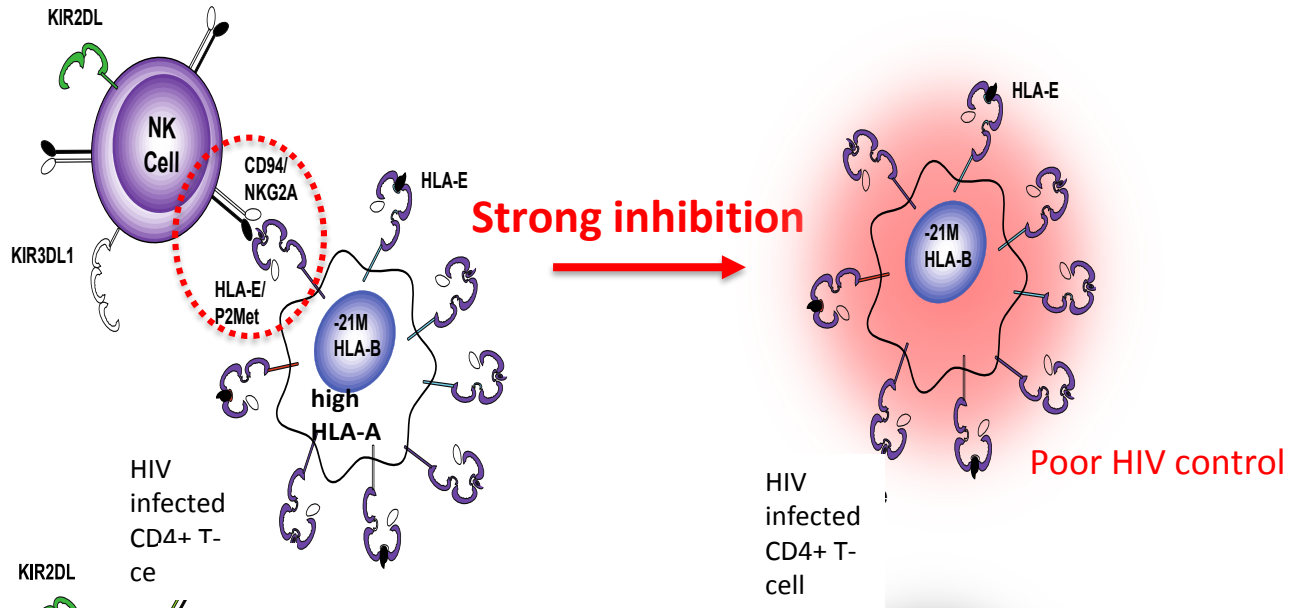
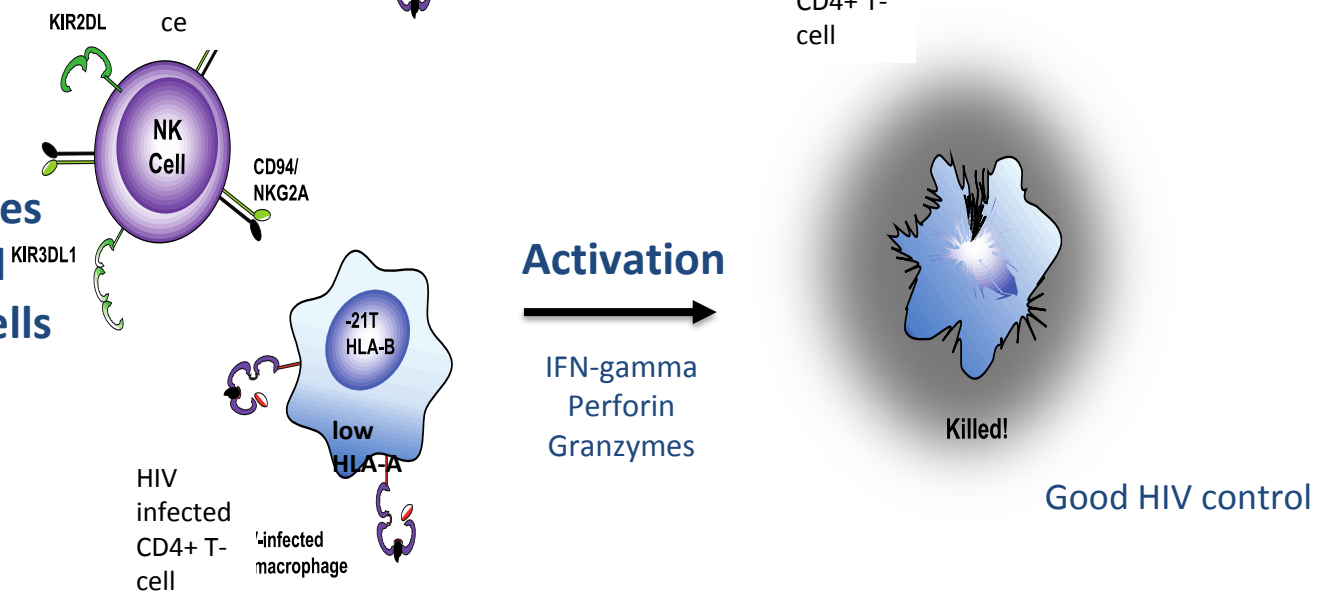
sponsored by the National Cancer Institute

Genotype that causes inhibition of Natural Killer cells

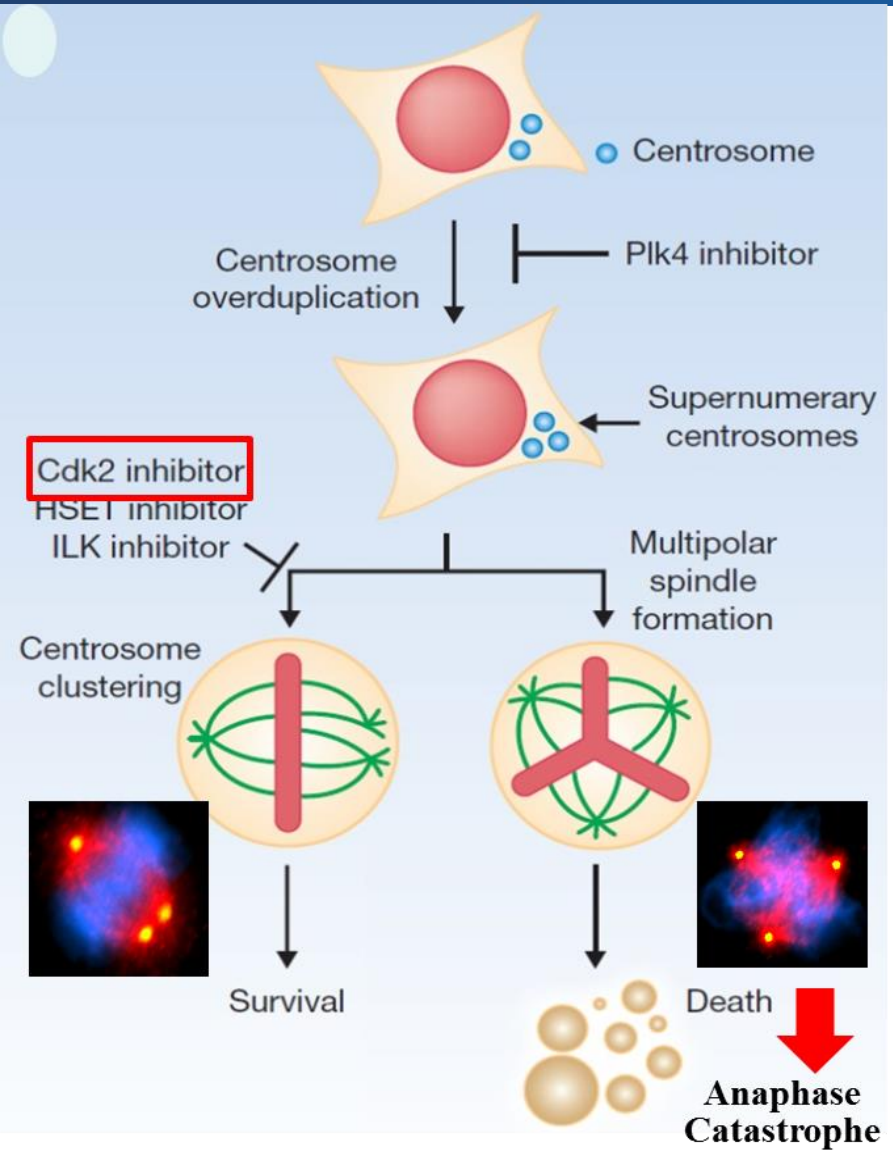


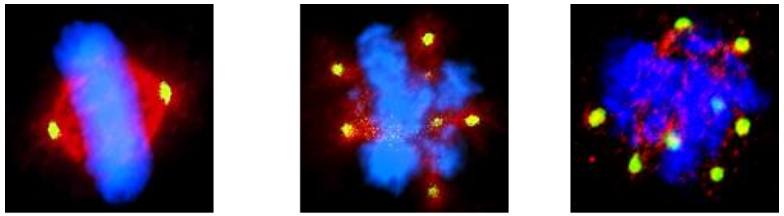
Genotype that enhances killing of HIV infected cells by Natural Killer cells



Ramsuran et al, Science, 2018

Eradicating Aneuploid Cancers by Engaging Anaphase Catastrophe





vehicle

CFI-400945

Galimberti F, et al Clinical Cancer Res, 2010 and 2011
Hu S, et al, Cancer Res., 2016
Hu S et al Mol Caner Ther., 2016
Kawakami M, et al JNCI, 2017
Kawakami M, et al, PNAS, 2018
Kawakami M, et al, Mol Cancer Ther, 2018
Kawakami M, et al, Annual Reviews Pharmacology (in press).

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Laboratory Animal Sciences Program

An Essential Core Capability of Frederick National Laboratory

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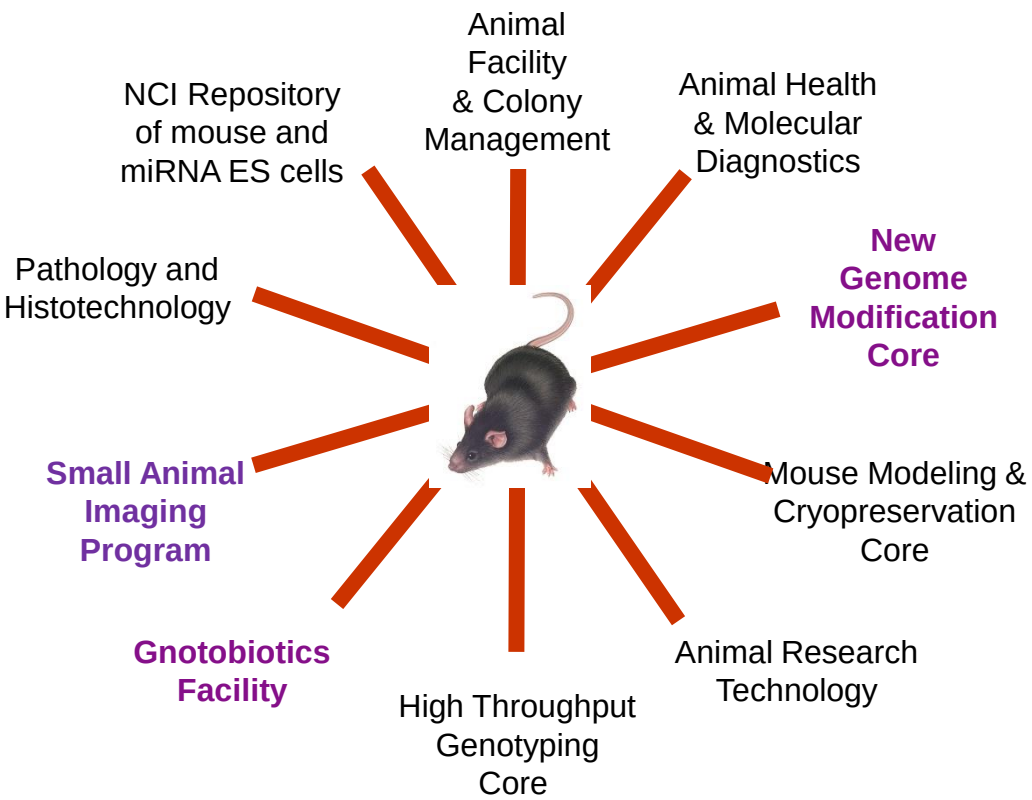
LASP operates the NCI animal facilities and provides routine and specialized husbandry services for Investigators on the Bethesda and Frederick campuses.

- Management of 27 rodent and nonhuman primate research facilities (22 Frederick, 5 Bethesda).
- Maintenance of 133,400 animals occupying 49,228 cages.
- 315 LASP associates (234 Frederick, 81 Bethesda)
- Support of 206 investigators encompassing 551 active animal study protocols.
- Provides support for Frederick and Bethesda ACUC.



LASP staffs and operates many state-of-the-art cores and other facilities to assist NCI Investigators in performing their animal-based cancer and AIDS research.

https://frederick.cancer.gov/science/technology/laboratory-animal-sciences-program

The Nanotechnology Characterization Laboratory at the Frederick National Laboratory

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sponsored by the National Cancer Institute

NCL Nanotechnology Characterization Laboratory

Assay Cascade

- Provides "pharmaceutical mentorship" for materials scientists and engineers

Reformulation

AMGEN
ONYX PHARMACEUTICALS An Amgen subsidiary
AstraZeneca

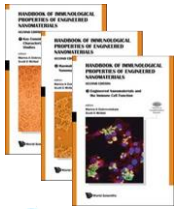
Non-Oncology Nanomaterials

Pfizer

Metrology & New Methods

ISO
USP U.S. Pharmacopeial Convention

Basic Research & Grand Challenges



Informing Regulatory Agencies

i-p-r-f.org International Pharmaceutical Regulators Forum
FDA U.S. FOOD & DRUG ADMINISTRATION
Health Canada
EUROPEAN MEDICINES AGENCY SCIENCE MEDICINES HEALTH

Transnational Collaboration

EUNCL

- EU-NCL fully operational March 2017

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Implementing the RAS Program
Hub, Spoke, and RAS Community Model

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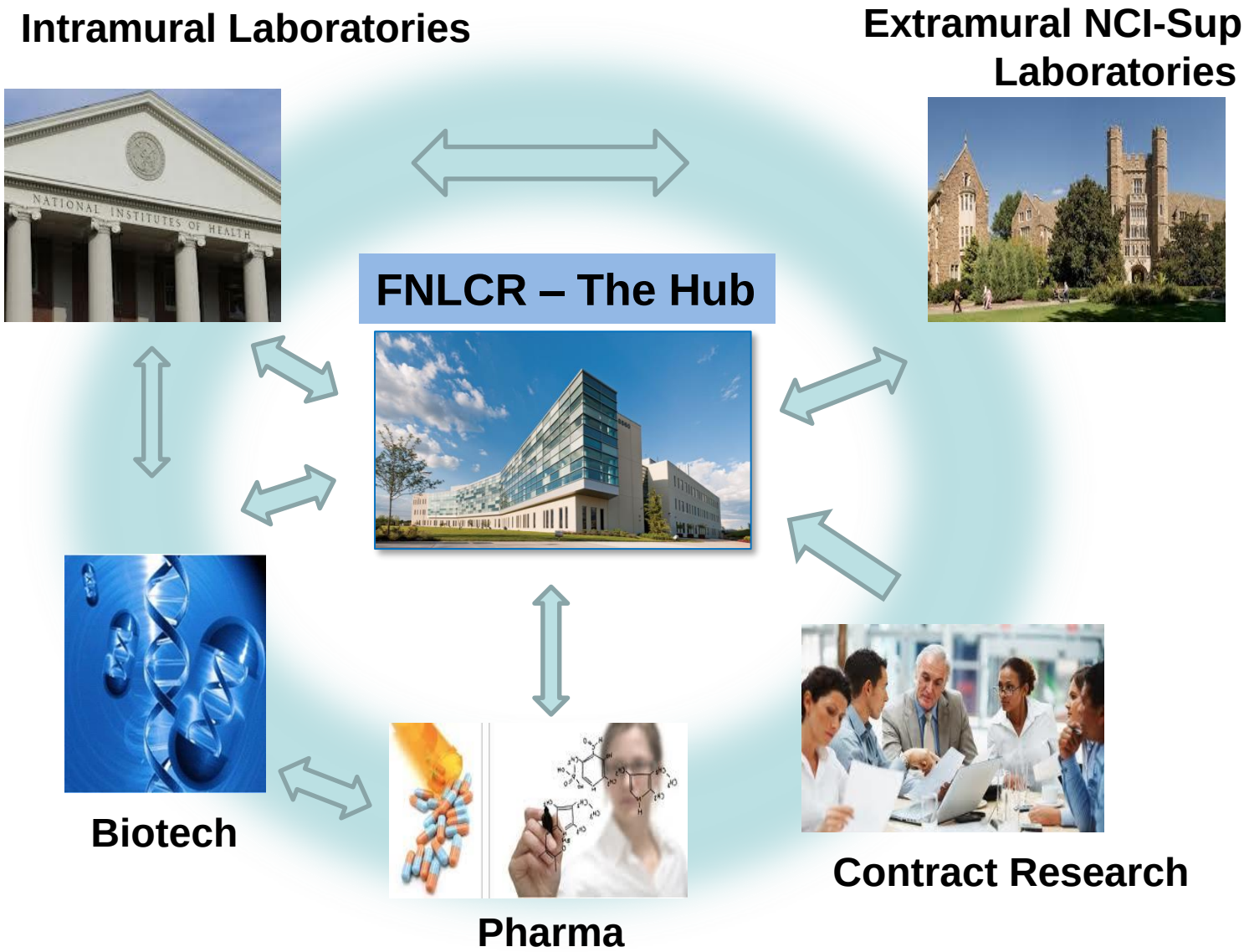

Ras Initiative: Progress

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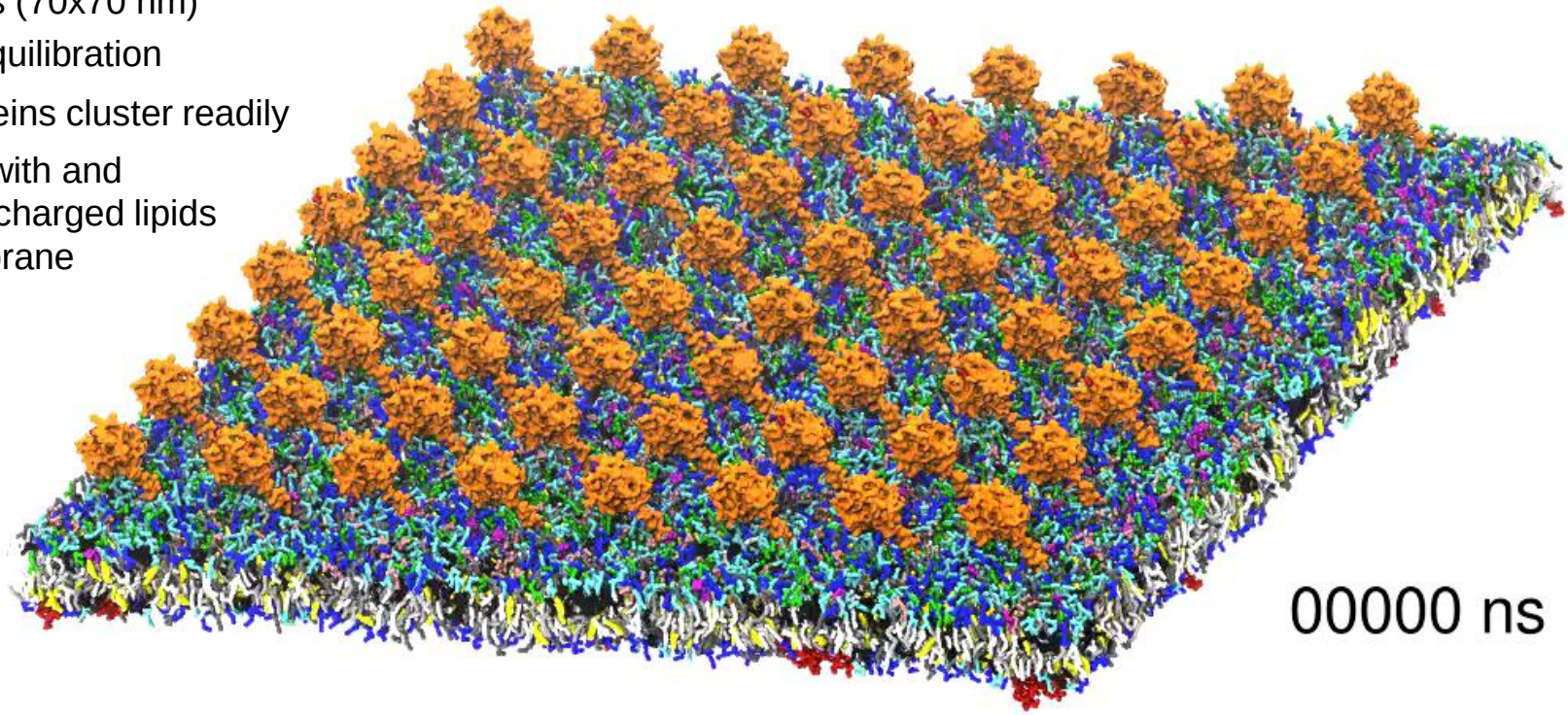
- **RAS initiative continues to focus on two areas:**
  - **Directly targeting *KRAS***
  - **Understanding the biology of *KRAS* in the context of the plasma membrane**
- **Developing a novel class of compounds that specifically target *KRAS*.**
- **Multiple screens to identify leads are ongoing.**
- **Working with Department of Energy to bridge experimental gaps using computation (JDACS4C).**
- **Partnering with the academy, biotech, Pharma and NIH to develop leads and push towards clinic.**

KRAS4b in Plasma Membrane
Simulation

- 20,000 lipids (70x70 nm)
- 40 µs pre-equilibration
- 64 Ras proteins cluster readily
- Associates with and aggregates charged lipids in the membrane



Helgi Ingólfsson, LLNL

ATOM Consortium

Accelerating Therapeutics for Opportunities in Medicine

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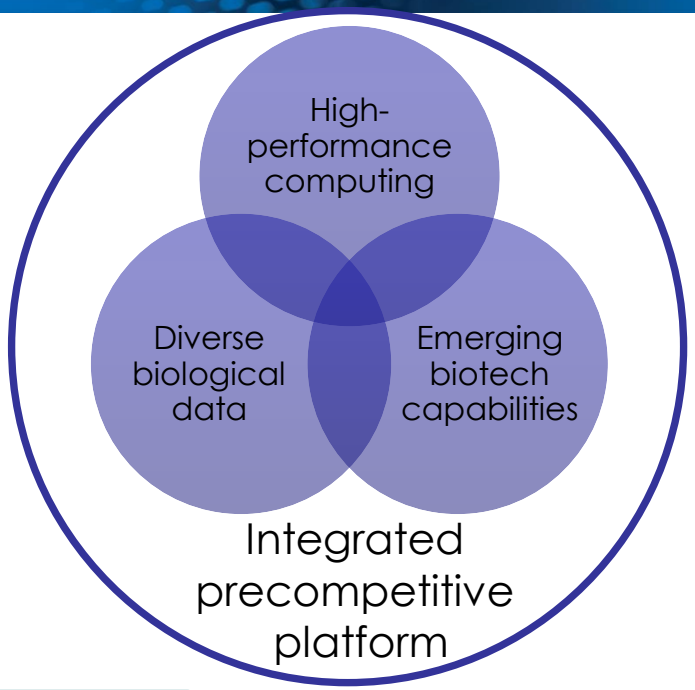
Mission

To accelerate the development of more effective therapies for patients

Vision

A new starting point:
Transform drug discovery from a slow, sequential, and high-failure process into a rapid, integrated, and patient-centric model

How?



3 year goal

Starting from a validated oncology target, deliver a patient-ready cancer therapy in <1 year, a process that currently takes an average of 6 years

ATOM@AACR Outreach Effort

Emails sent to:

515 pharma contacts from FNL and UCSF Strategic Alliances

69 Cancer center directors

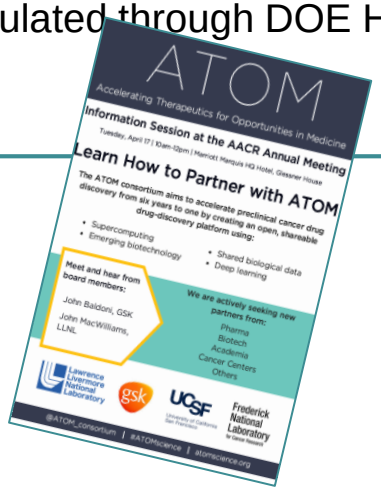
50 NCI academic collaborators

6 national labs directly invited (ANL, ORNL, PNNL, BNL, LANL, and Sandia)

Additional invites circulated through DOE HQ to DOE system-wide users

400

flyers circulated at AACR (NCI booth, ATOM event, and meet the experts meetings)


ATOM
Accelerating Therapeutics for Opportunities in Medicine
Information Session at the AACR Annual Meeting
Tuesday, April 17 | 10am–12pm | Marriott Marquis HQ Hotel, Gleason House
Learn How to Partner with ATOM
The ATOM consortium aims to accelerate preclinical cancer drug discovery from six years to one by creating an open, shareable drug-discovery platform using:
- Supercomputing
- Emerging biotechnology
- Shared biological data
- Deep learning

Meet and hear from board members:
John Baldoni, GSK
John MacWilliams, LLNL

We are actively seeking new partners from:
Pharma
Biotech
Academia
Cancer Centers
Others

Lawrence Livermore National Laboratory
gsk
UCSF
Frederick National Laboratory
@ATOM_consortium | #ATOMscience | atomscience.org

Online presence across multiple websites and platforms:

- FNL website
- ATOM website
- ATOM LinkedIn
- Personal LinkedIn accounts
- FNL, FNL PDO, ATOM, and NCI NCIP Twitter accounts
- FNL Facebook account

Social media activity from FNL and FNL PDO:

20 Twitter posts:

- **11,836** views
- **141** engagements (clicks, retweets, likes)

3 Facebook posts:

- **481** people reached

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Global Support of Vaccine Trials

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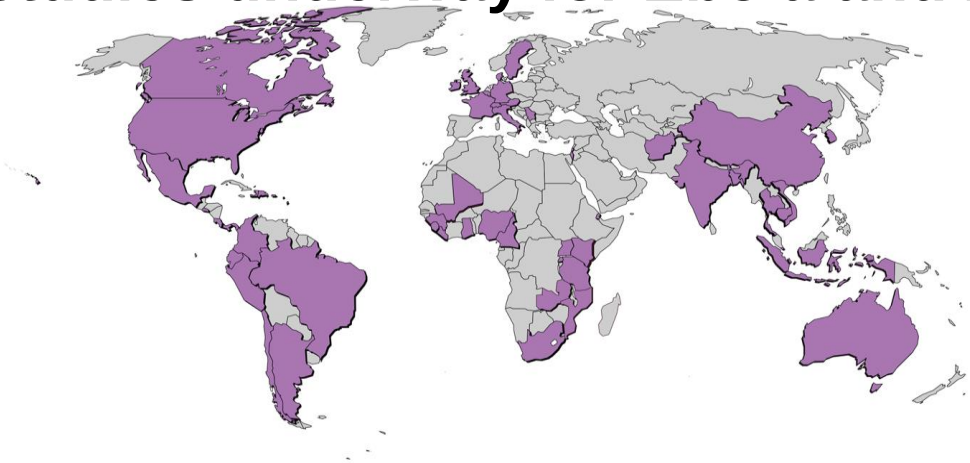
- **Facilitate efficient and effective strategic support of domestic and international clinical research programs.**
- **Provide laboratory support and comprehensive regulatory, clinical trials and project/procurement management support services.**
- **Support ~400 clinical trials (phase 1-3) in 42 countries and Vaccine studies underway for Ebola and Zika.**



HPV Serology Laboratory (Sponsored by NCI and Bill and Melinda Gates Foundation)

Frederick National Laboratory for Cancer Research
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Mission:

A newly established laboratory working in partnership with the HPV scientific community to promote further standardization, harmonization and proficiency of HPV serology assays to assess vaccine immunogenicity in vaccine trials through:

- development of qualified standards, critical reagents (HPV Virus-Like Particles), assays and guidelines that will be made available to the scientific community

Impact:

- **Standardization of critical reagents and assay harmonization**
- **Enable comparisons of data between different vaccines and studies**
- **Accelerate implementation of new vaccines and new vaccine indications**

Operational Status:

- **Launched in January 2017**
- **Ongoing generation of assay secondary standards (sera from 9-valent HPV vaccine recipients) and HPV VLPs (expected date of availability, Summer 2018)**

Partners:

LBR: Ligia Pinto, Troy Kemp
NCI: Doug Lowy, John Schiller, Sean Hanlon
Bill and Melinda Gates Foundation: Peter Dull
CDC: Elizabeth Unger

HPV Serology Lab
Advancing HPV Assay Standardization

Karolinska Institute: Joakim Dillner
Public Health England: Simon Beddows
Biostat Consulting, LLC: Brian Plikaytis
Global Health Network

NIH /NIAID Vaccine Research Center

Development Cycle

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sponsored by the National Cancer Institute

Basic Research–VRC -NIH campus, Bethesda MD

Process development
Analytical development
Formulation dev.

Vaccine Production Program lab (VPPL) Gaithersburg MD

NVITAL Immune Assessment Gaithersburg, MD

Clinical development cycle NIAID / Vaccine Research Center (VRC)

cGMP pilot scale production
Pilot Plant, Frederick MD

- **Design/build: 2003-2004**
- **Commissioned: Dec 2005**
- **In operation 2006**

Clinical Trials: US, global

ZIKV DNA Vaccine Discovery

Frederick National Laboratory for Cancer Research
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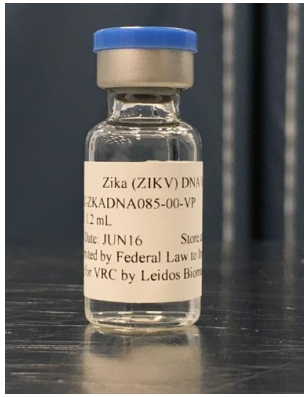
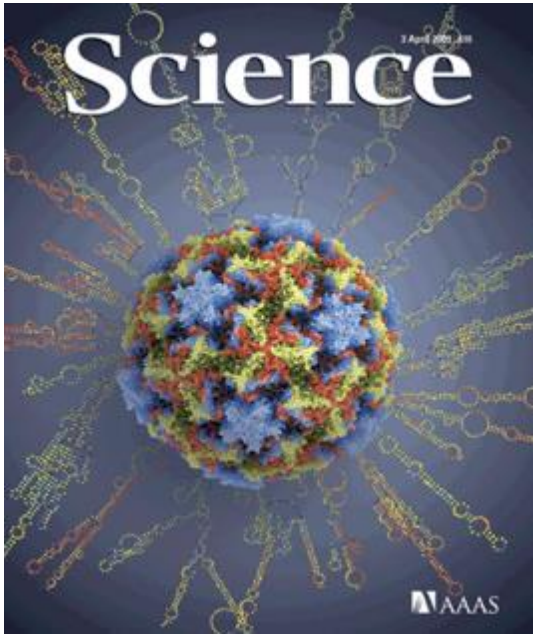
- **Vaccination with DNA expressing the prM and E proteins of ZIKV**
- **Immunogenic in mice and nonhuman primates**
- **Protection against viremia after ZIKV challenge correlated with serum neutralizing activity**



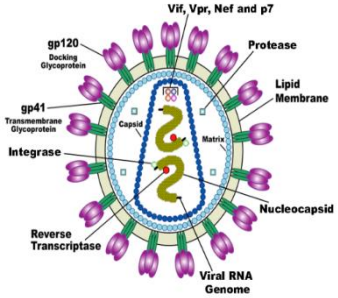


Rapid Development of a DNA Vaccine for Zika Virus

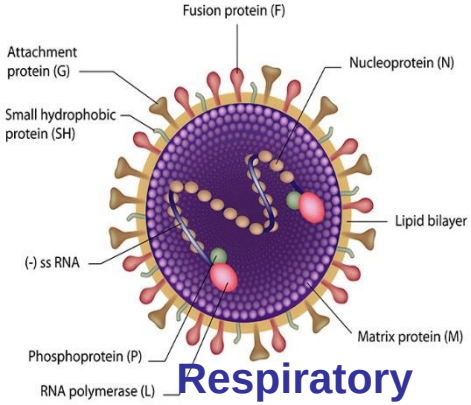
Dowd *et al.*, *Science* 10.1126/science.aai3197 (2016)

Julie Ledgerwood / VRC

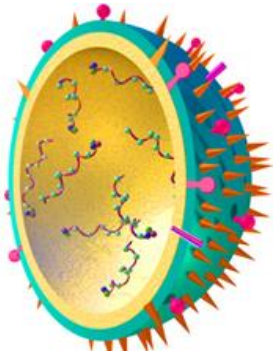
Management of Diverse Projects Related to Vaccine Development and Manufacturing



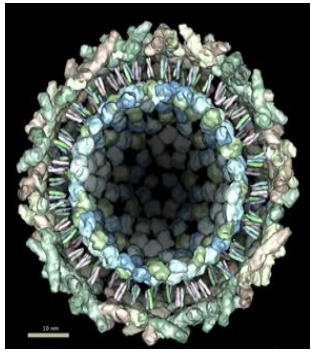
HIV



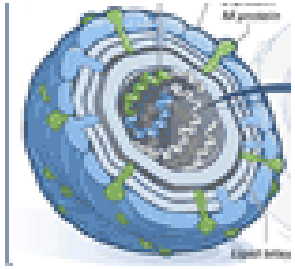
Respiratory Syncytial Virus



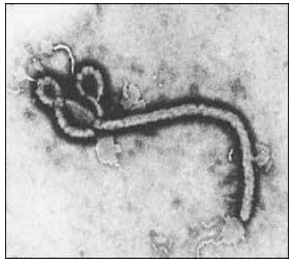
Influenza



Chikungunya, Equine Encephalitis Virus



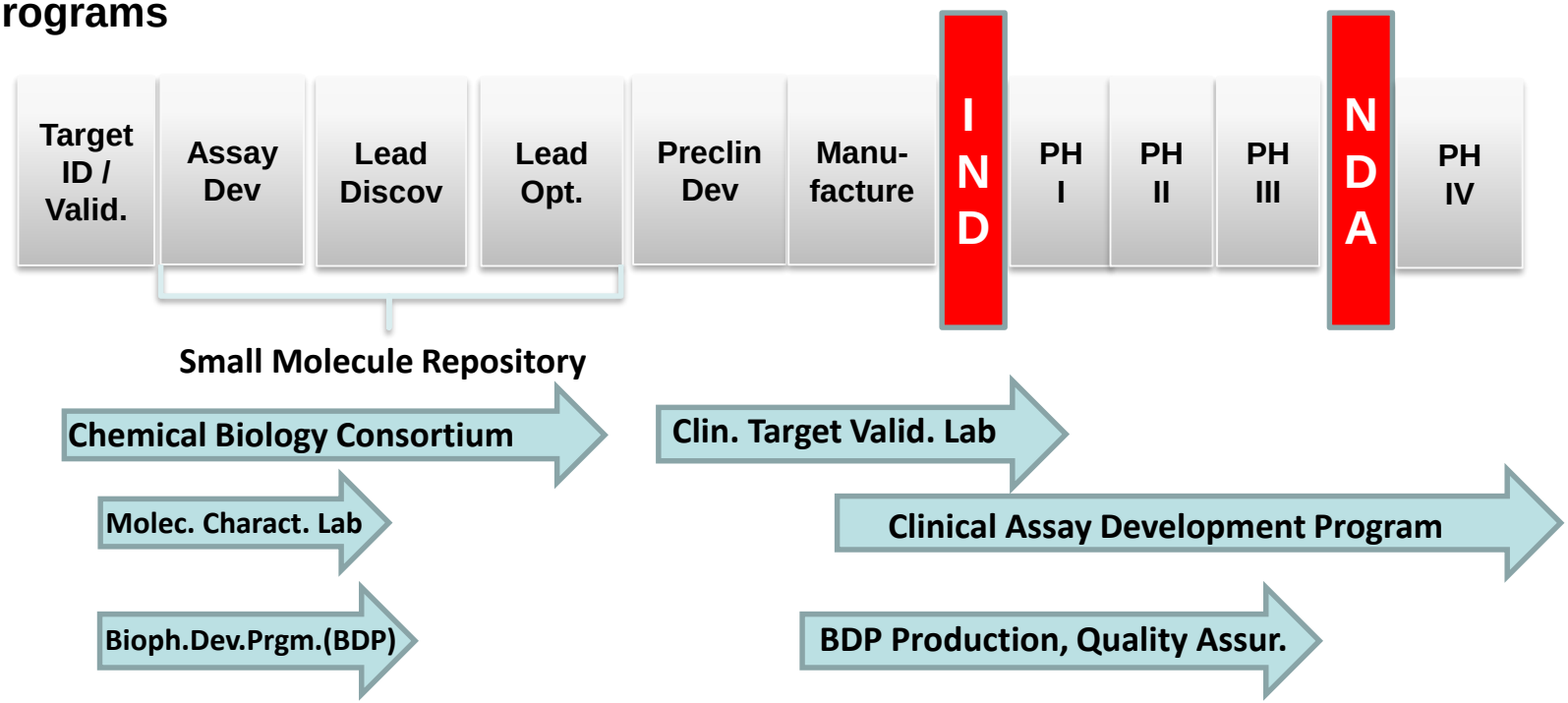
Flavivirus (West Nile, Zika)



Filovirus (Ebola, Marburg)

DCTD : The NCI Experimental Therapeutics Program (NExT)

- **NExT is led by the Division of Cancer Treatment and Diagnosis to create a coordinated cancer therapeutics discovery and development pipeline with the external scientific community**
  - Projects evaluated by extramural Special Emphasis Panel
- **FNLCR provides operational and dedicated technical support to all phases of NExT programs**



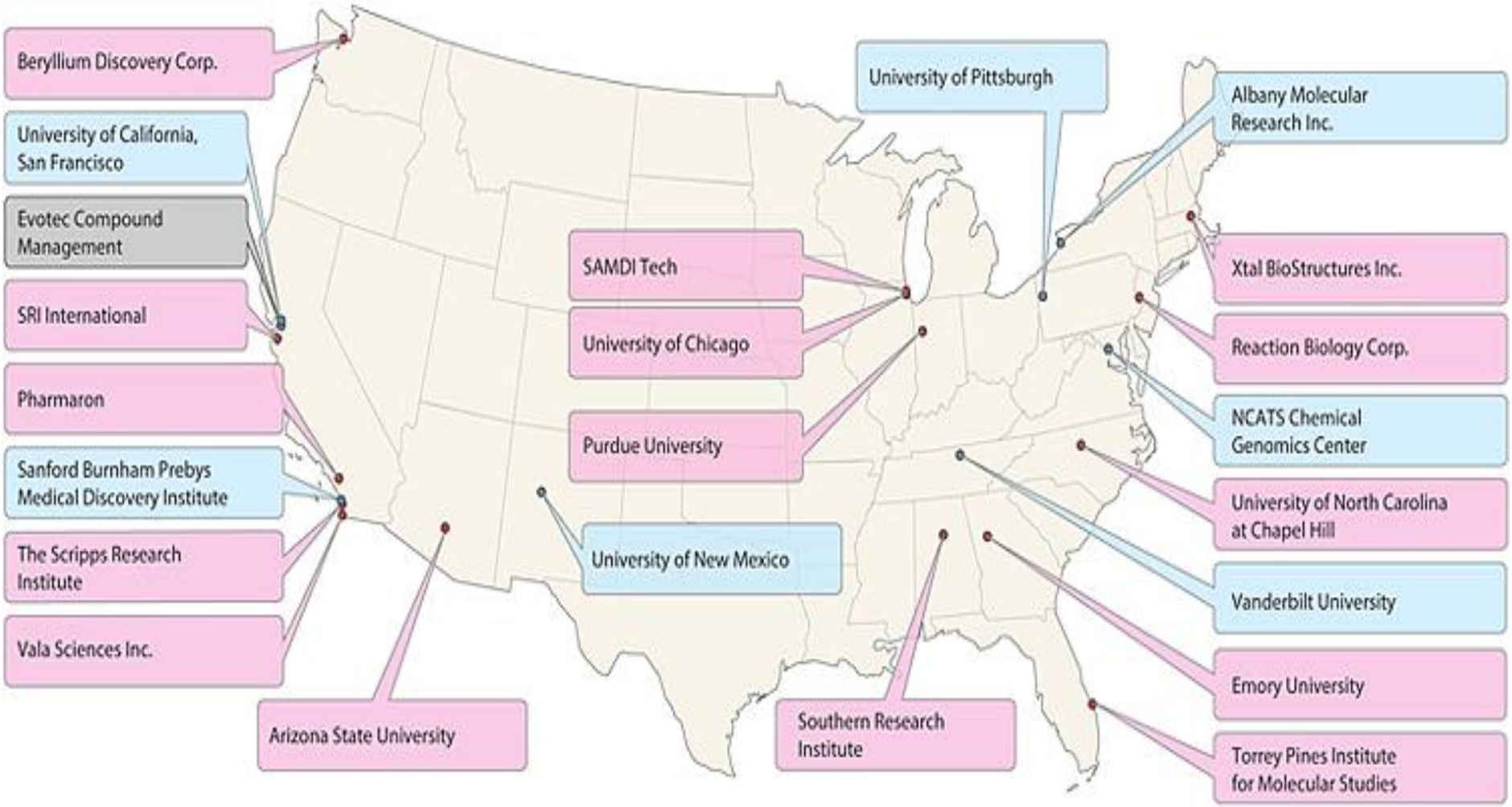
NCI Experimental Therapeutics Program (NExT)
Operationalizing the Chemical Biology Consortium

Frederick National Laboratory is the scientific Project Manager for the Chemical Biology Consortium subcontract portfolio to implement NCI-approved project plans (overseen by NCI Senior Advisory Committee).

- **2008: first Chemical Biology Consortium established (RFP S08-221)**
- **2015: re-competition of the Chemical Biology Consortium (RFP S16-001)**
  - ↪ **7 Dedicated Centers (4 universities, 1 institute, 1 company, NCATS)**
    - **provide scientific leadership of the Chemical Biology Consortium**
    - **contribute to all discovery stages**
  - ↪ **15 Specialized Centers (5 universities, 4 institutes, 6 companies)**
    - **provide uniquely focused technologies at specific discovery stages**
- **$31.3 M in subcontract awards issued by Leidos Biomedical Research**

NCI Experimental Therapeutics Program (NExT)

Operationalizing the Chemical Biology Consortium



The Cancer Moonshot℠ BioBank

- **Establish a national cancer biobank repository containing longitudinally accrued biospecimens from newly diagnosed patients.**
- **To provide high quality biospecimens to serve the scientific needs of investigators.**
  - **Drug resistance and sensitivity**
  - **Response to Immunotherapy – including adverse events**

Phase 1:

Drug resistance	Immunotherapy
Prostate	Prostate
Lung	Lung
Colorectal	Colorectal
AML	
Myeloma	Breast
GI	Brain
Melanoma	Oropharynx
	Salivary Gland
	Ovary

Challenges and Opportunities

- **Patient and physician engagement.**
  - **Focus on enrollment of minorities and underserved by use of NCORP sites.**
- **Collecting longitudinal specimens (especially at progression).**
- **Collecting high quality and quantity of clinical specimens compatible with needs of the research community.**
- **Collecting sufficient patient clinical data.**
- **Building an interactive database serving the biobank as well as patients and their physicians (i.e., collated research and clinical data available for researchers and appropriate access for patients and physicians, i.e., Patient Portal).**
- **Timely sub-contracting.**

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National Cryo-EM Projects Since 2017 Launch

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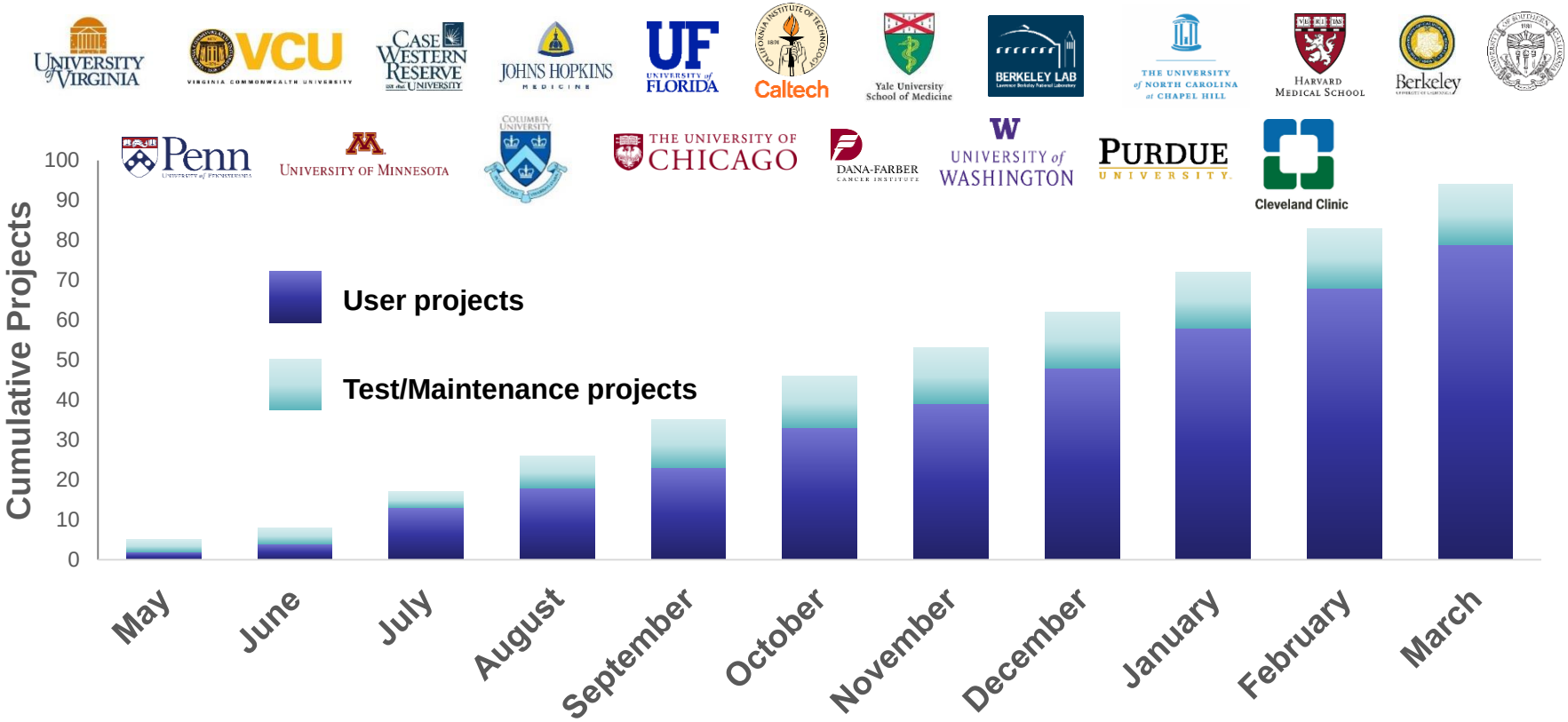

National Cryo-EM Facility (NCEF) in past year had 78 cancer projects from 20 universities and the first publication was in Nature Communication.

Focused Ion Beam Scanning Electron Microscopy (FIB-SEM)

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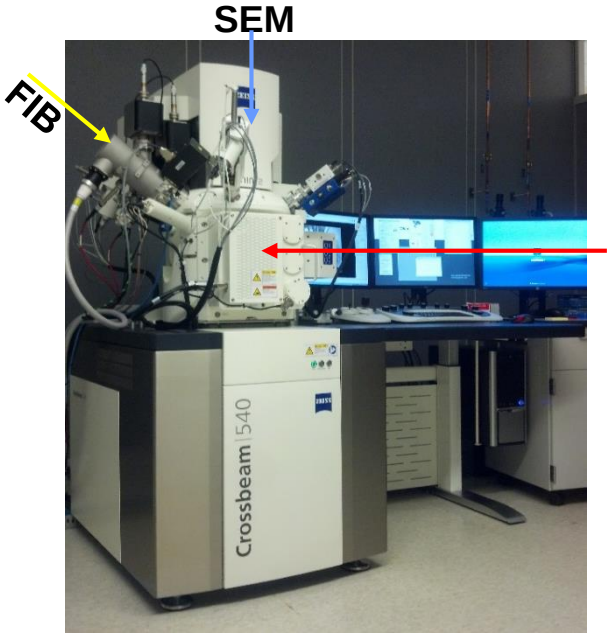
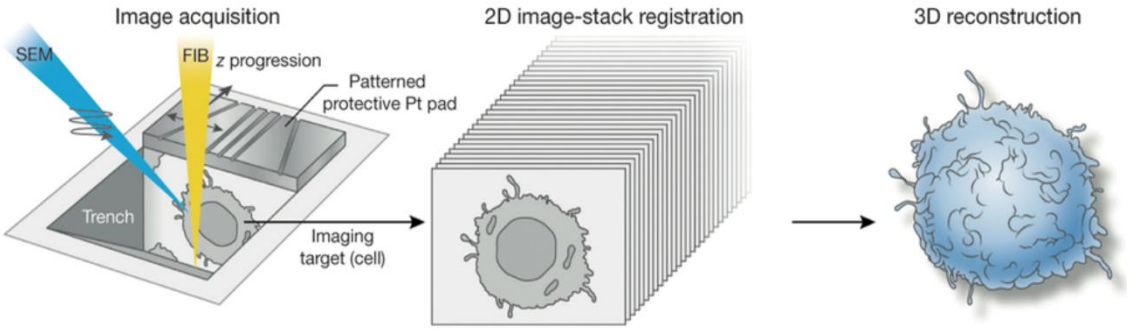
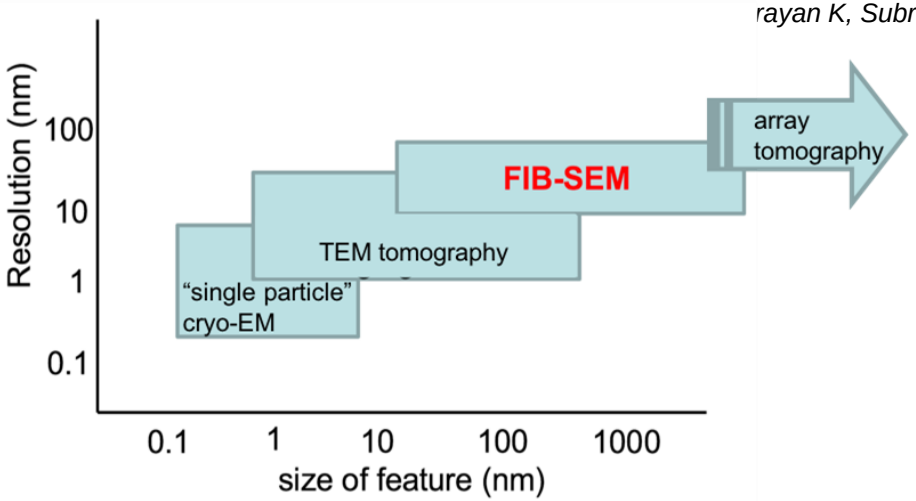


Three dimensional imaging is achieved by iterative cycles of FIB milling and SEM imaging



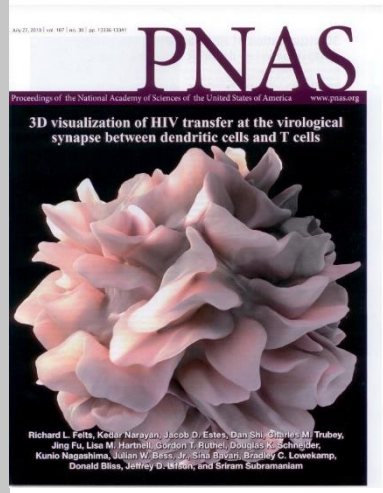
rayan K, Subramaniam S Nat Meth 2015



Imaging Whole Cells in Three Dimension by FIB-SEM

Frederick National Laboratory for Cancer Research

sponsored by the National Cancer Institute



Characterization of the HIV virological synapse

Narayan K, Subramaniam S Nat Meth 2015

Narayan K, Felts RL et al, PNAS 2011

Frederick National Laboratory Initiatives (Partial List)

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1. Launched a listening and learning tour.

2. Held a leadership retreat. We will bring our community together to define our core values.

2. Broadened training opportunities for the next generation (with Georgetown University, Hood College, Mount St Mary University, University of Maryland School of Engineering, Howard University, NCI Mexico and others are welcome).

3. Recreate the Hood College Oncogene Science Conference: "Imaging Science Meets Cancer Biology."

4. Develop a deeper partnership with the NCI, NIAID, other Institutes, national laboratories and the extramural community.

Future Directions

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Our becoming a national laboratory is a source of pride and purpose.

We are working as a community to make this designation our unifying principle.

This will only happen through our scholarship, partnerships and serving the public's interest.

Conclusions

Frederick National Laboratory for Cancer Research
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1. Frederick National Laboratory is a national resource focused primarily on biomedical research.

2. We work with the NCI and other Institutes on problems that are distinct from the academic community, industry and other national laboratories.

3. We are proud of this partnership and work with the NCI/NIH and the extramural community in service of the public's health.

Frederick National Laboratory EcoSystem

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Albany Medical College
Cancer Research UK
Beatson Institute
Children's Hospital Los Angeles
Brown University
Ucla
Columbia University
Boston College
Icahn School of Medicine at Mount Sinai
University of Oxford
Technische Universität München
UT Southwestern Medical Center
Cincinnati Children's
Aaron Diamond AIDS Research Center
Cardiff University Prifysgol Caerdydd
Beth Israel Deaconess Medical Center
UC Davis University of California
GNF
Duke University
CHEO Research Institute
UMass Medical School
Johns Hopkins University
Burnet Institute Medical Research. Practical Action.
cima Centro de Investigación Médica Aplicada Universidad de Navarra
George Mason University
BCM Baylor College of Medicine
Boston Children's Hospital Until every child is well
York University
OHSU
Indiana University School of Medicine
CHOP
Rush
Northeastern University
Temple University
University at Buffalo
University of Pittsburgh
CHU Sainte-Justine Research Center Mother and Child University Hospital Center
Princeton University
cea
University of Cape Town
Saint Louis University Est. 1818
UAB
OMRF
ATM
University of Montana
Harvard
Tulane University
IBIS Instituto de Biomedicina de Sevilla
Population Council Ideas. Evidence. Impact.
Wisconsin University of Wisconsin–Madison
Texas A&M University
Emory University
Penn
Inserm
University of Washington
Brigham Health
Brigham and Women's Hospital
Dartmouth
Ottawa Hospital Research Institute
Institut de recherche de l'Hôpital d'Ottawa
UHN
Deakin University
The Ohio State University
The University of North Carolina at Chapel Hill
UCL
University of Nebraska
Cleveland Clinic Lerner Research Institute
The Rockefeller Foundation
Rutgers
UMDNJ
Partners HealthCare
Helmholtz Zentrum München German Research Center for Environmental Health
The University of Melbourne
The Hebrew University of Jerusalem
Weizmann Institute of Science
The Scripps Research Institute
Northwestern University
Miami
University of Louisville
University of Toronto
The University of Oklahoma Health Sciences Center
UIC University of Illinois at Chicago

Academic

abbvie
PacBio
Sebacia
Pfizer
Gilead
therabiol
AstraZeneca
Eagle Eye
Onyx Pharmaceuticals
Sanofi
Cureport Inspiring Nano Medicine Technology
Pharma Arava
Pall Corporation
Fed Centric Technologies, LLC
Visterra
Theras, Inc.
Daiichi-Sankyo
leidos
Biogen
TOSK
MedImmune
Lilly
Kyras Therapeutics
Inception Sciences
gsk GlaxoSmithKline

Biotechnology

Frederick National Laboratory for Cancer Research

Cancer Centers

University of Nebraska Medical Center
City of Hope
Fred Hutch Cures Start Here
MD Anderson Cancer Center
Koch Institute for Integrative Cancer Research at MIT
Einstein Albert Einstein College of Medicine of Yeshiva University
Moffitt Cancer Center
Mayo Clinic
University of Maryland
UCSF
University of Maryland Baltimore

National Laboratories

U.S. Department of Veterans Affairs
U.S. Food & Drug Administration
Oak Ridge National Laboratory
Argonne National Laboratory
Los Alamos National Laboratory
NIH National Center for Advancing Translational Sciences
Lawrence Livermore National Laboratory
NIST

QUESTIONS?