

Frederick National Laboratory Current Work and Future Directions

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

- **Discuss our current and future work.**
- **Emphasize our partnership with the NCI, other Institutes, the extramural community and those patients who we serve.**
- **Answer your questions.**

Frederick National Laboratory Serves the Public Interest

Frederick National Laboratory is a national resource that combats cancer, AIDS, infectious diseases and emerging challenges to the public's health. We tackle problems that others do not.

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

This mission is larger than anyone of us.

We serve in areas not readily addressed by others.

Bidirectional Hub and Spoke Model of Serving the Public's Health

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Intramural Laboratories



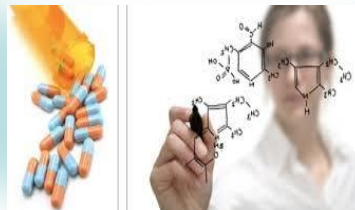
Extramural NCI-Supported Laboratories



FNLCR – The Hub



Biotech



Pharma



Contract Research

How We Do Our Work

FY18 Awarded Task Orders



Dr. Kathy Terlesky, FNLCR

Sponsor	Total Awarded	Titles of the Major Initiatives (FY15-FY18)
National Cancer Institute		
CCG	3	Human Cancer Models Initiative, Refractory Cancers Biospecimens, HIV+ Tumor Characterization
CSSI	3	Lung Cancer Multiple Reaction Monitoring Assay, Multi-omics Analyses (CPTAC), Antibody Production and Characterization
OD	3	Replacement of the Animal Facility Colony, BIQSFP Precision Medicine Study, Bioequivalency Studies
DCP	1	Medicinal Chemistry Support for Chemopreventive Agent Development
DCTD	18	Monitor Circulating Tumor Nucleic Acid, MATCH, Epstein-Barr Virus-like Particles, Refractory Cancers Biospecimen Acquisition, Multi-omics Analyses for CPTAC, BIQSFP Precision Medicine
Facilities Refurbishment	14	Building Refurbishments to Buildings 433, 469, 538, 539, 560, and 1066, plus misc. infrastructure improvements
Moonshot		
CCG	1	MasterLymph
DCEG	1	Accelerated Control of Cervical Cancer
CBIIT	2	Cancer Data Ecosystem, Data Commons
DCB	1	Human Tumor Atlas Pilot
DCTD	2	Retrospective Tumor Characterization, Biobank and Repositories
CGH	1	Development of Human Cancer Models Initiative Catalog
National Institute of Allergy and Infectious Disease (NIAID)		
NIAID	30	Advance Universal Flu Vaccine, Ebolavirus Vaccines in W. Africa, HIV Clinical Research in West Africa, Zika Virus & other Emerging Infectious Diseases
Other NIH Institutes		
NIH (NCATS)	1	CMC Support for NCATS Gene Therapy for AADC Deficiency; Pompe Disease; DMD; Fuch Dystrophy

New Leaders at Frederick National Laboratory for Cancer Research

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Beth Baseler
Clinical Monitoring
Research Program Directorate



Eric Stahlberg, PhD
Biomedical Informatics and
Data Science Directorate



Leonard Freedman, PhD
Chief Science Officer

Focus on the Frederick National Laboratory Community



FNLCR Leadership Team held a retreat. An outcome was an initiative to define core values to shape our identity as a national laboratory.

Dr. David Lindsay and Christopher March lead this effort that brought together colleagues from every part of FNLCR.

We will be rolling out the Workstride Program at FNLCR. This benefits program created by Johns Hopkins Cancer Center supports employees and their families and caregivers who are dealing with cancer.

Support is also provided to the employees' supervisors so they can learn how best to assist colleagues with a cancer diagnosis in the workplace.

- Provides web-based tools and support of a nurse navigator.**
- Maintains confidentiality and savings for FNLCR and our employees.**
- We thank David Frick and Christopher March in HR and our medical carriers who provide this service at no cost to FNL employees.**

Outreach to the Community

Listening and learning tour.

Executive leadership team held.

Reached out to local, national and international centers to establish collaborations.

Discussed Frederick National Laboratory at Frederick Rotary Club, University of Maryland Cancer Center, Georgetown University Lombardi Cancer Center, Lawrence Livermore Laboratory, National Academy of Medicine and Engineering, American Academy of Arts and Sciences, and elsewhere.

Recreated the popular NCI-Hood cancer meeting.

Launched the Frederick National Laboratory Director's Distinguished Lecture Series.

New MOUs for Frederick National Laboratory

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**Hood College
Mount St. Mary's University**

**President
Chapdelaine, Hood**



Georgetown University
President DeGioia, Dr. Dimolitsas
Dr. Weiner, Dr. Quong and
Dr. Heimbrook

**President Trainor,
Mount St. Mary's**



**Howard University, iCURE,
NCI-Mexico, and CREST**
Provost Wutoh, Howard University, Dr.
Springfield, NCI, Dr. Herrera, NCI-Mexico,
Dr. Horn, Frederick CREST



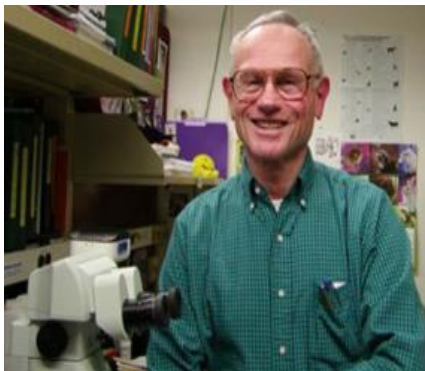
**Colleagues: Shannon Jackson, Beverly Hayes,
Richard Pendleton, Dr. Popov, Dr. Haywood,
Dr. Pannucci, Monica Slate, Dr. Quong,
Dr. Komschlies, and Lisa Coleman**



Frederick National Laboratory Director's Distinguished Lecture Series

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Dr. Michael Sporn
Dartmouth



Dr. Ned Sharpless
National Cancer Institute



Dr. Doug Lowy
National Cancer Institute



Dr. James Allison
MD Anderson Cancer Center



Dr. Helen Piwnicka-Worms
MD Anderson Cancer Center

Frederick National Laboratory and Hood College Cancer Science Symposium

- Annual meeting emphasizing interdisciplinary topics in cancer biology and oncology
- Hosted by Hood College and inaugural meeting is: “Imaging in Cancer Biology” June 21-23, 2019
- Organizing Committee
 - Ethan Dmitrovsky, M.D. (FNLCR)
 - Andrew Quong, Ph.D. (FNLCR)
 - Debbie Ricker, Ph.D. (Hood College)
- Advisory Committee
 - Sriram Subramanian, Ph.D. (UBC)
 - Frank McCormick, Ph.D. (UCSF)
 - Sara Hook, Ph.D. (NCI)
 - Valda Vinson, Ph.D. (Science)
 - Ines Chen, Ph.D. (Nature)
 - Jean-Charles Soria, M.D., Ph.D. (Medimmune)

Frederick National Laboratory (What We Do)

Types of Research

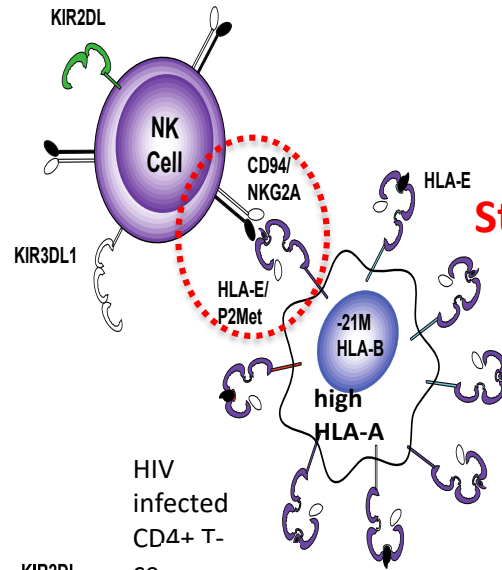
- 1. Discovery science.**
- 2. Advanced core facility support.**
- 3. Collaborative science in concert with NCI, NIAID, other Institutes.**
- 4. Team science led by FNLCR (ie, RAS initiative).**
- 5. Advanced technology support to extramural community.**

Immune Response Genotypes Determine Survival of HIV Infected Cells

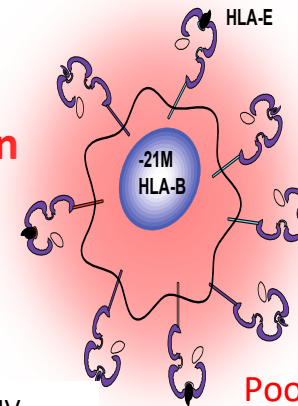


Dr. Tom Misteli, NCI
Dr. Mary Carrington, FNLCR

Genotype that causes inhibition of Natural Killer cells



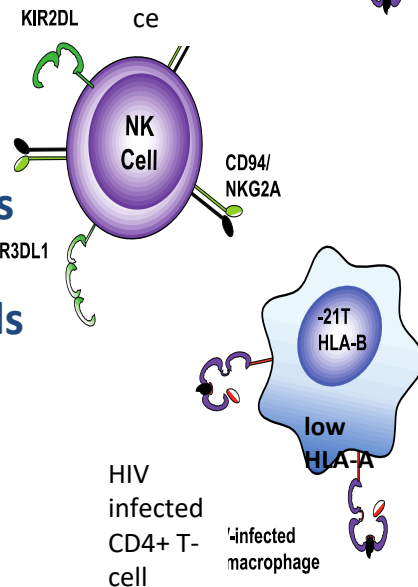
Strong inhibition



Poor HIV control

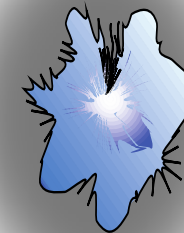
HIV infected CD4+ T-cell

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



Activation

IFN-gamma
Perforin
Granzymes



Killed!

Good HIV control

**Ramsuran et al,
Science, 2018**

Antiretroviral Therapy Begun Early After Infection Can Clear Initial HIV Infection



Dr. Jeff Lifson, FNLCR

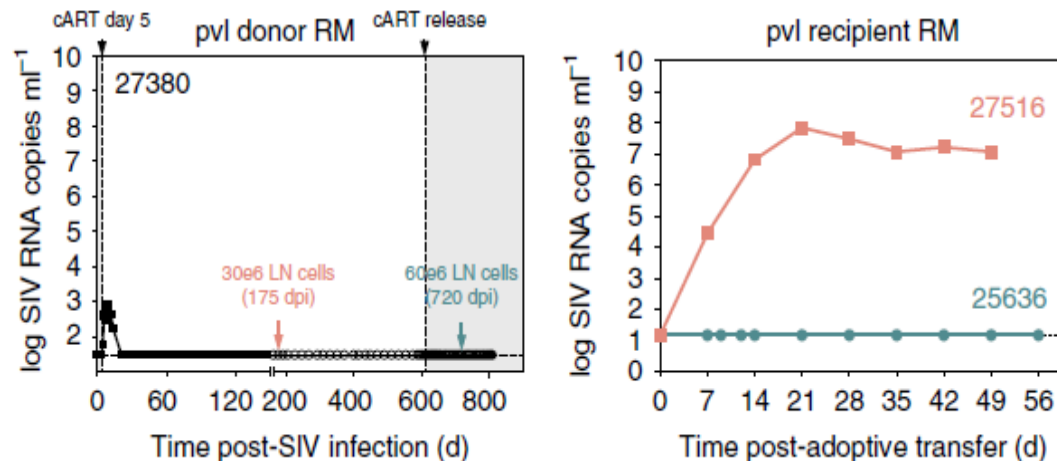
- Antiretroviral drug therapy initiated at different times post-SIV infection of rhesus macaques
- Outcome depended on timing of treatment initiation
- Early treatment for ~ 2 years → eventual decline or clearance of infection without recurrence after stopping treatment begun within 5 days of initial infection.
- The window of opportunity to prevent full systemic AIDS virus infection may be longer than once thought with implications for treatment and prevention.

ARTICLES
NATURE MEDICINE | VOL 24 | SEPTEMBER 2018 | 1430-1440 |

**nature
medicine**

Early antiretroviral therapy limits SIV reservoir establishment to delay or prevent post-treatment viral rebound

Afam A. Okoye¹, Scott G. Hansen¹, Mukta Vaidya¹, Yoshinori Fukazawa¹, Haesun Park¹, Derick M. Duell¹, Richard Lum¹, Colette M. Hughes¹, Abigail B. Ventura¹, Emily Ainslie¹, Julia C. Ford¹, David Morrow¹, Roxanne M. Gilbride¹, Alfred W. Legasse¹, Joseph Hesselgesser², Romas Geleziunas², Yuan Li³, Kelli Oswald³, Rebecca Shoemaker³, Randy Fast³, William J. Bosche³, Bhavesh R. Borate⁴, Paul T. Edlefsen⁴, Michael K. Axthelm¹, Louis J. Picker^{1*} and Jeffrey D. Lifson^{3*}



Laboratory Animal Sciences Program

An Essential Core Capability of Frederick National Laboratory

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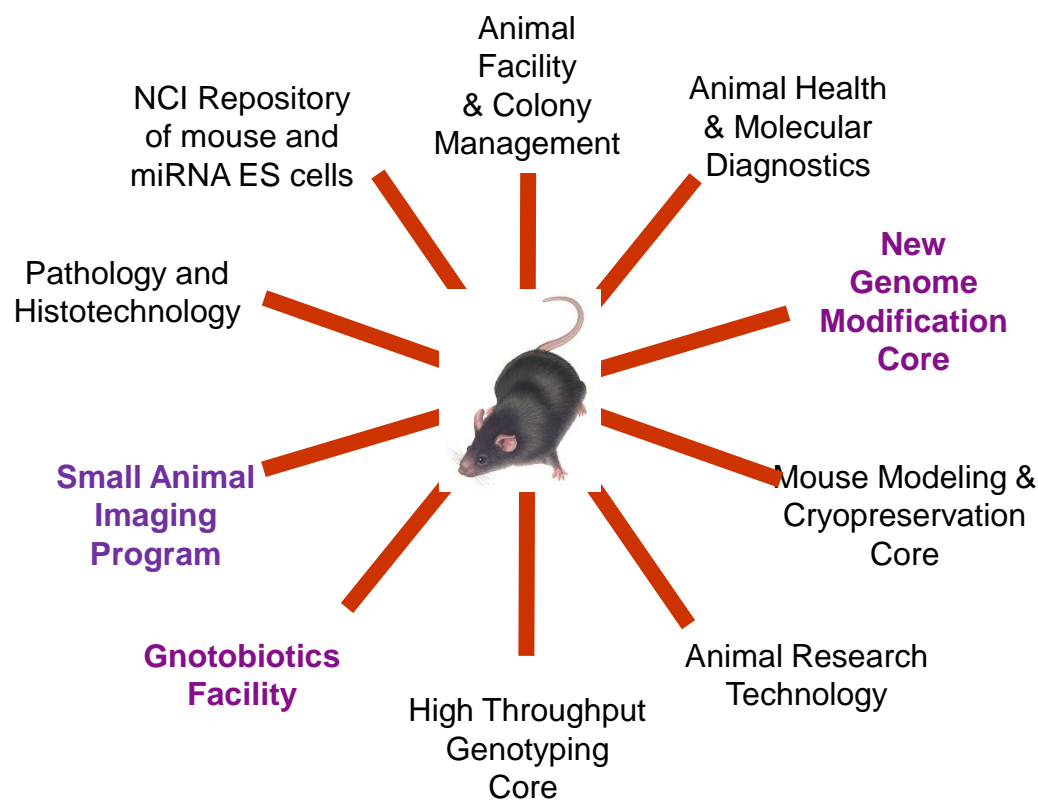
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LASP operates the NCI animal facilities and provides routine and specialized husbandry services for Investigators on the Bethesda and Frederick campuses.

- 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>



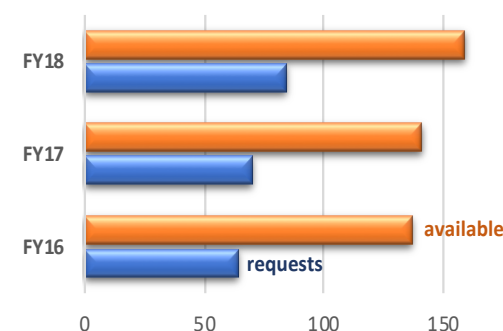
Laboratory Animal Sciences Program

Recent Advances

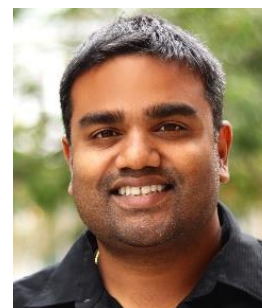
The NCI Mouse Repository is supported by the Division of Cancer Biology (DCB). Accepts submitted GEMs from the cancer community based on rigorous criteria (unique, not commercially available, and value). The Repository expands strains, cryopreserves, archives, and ships frozen germplasm to the community. **Available strains and shipment requests increased 15-20% since FY16.**



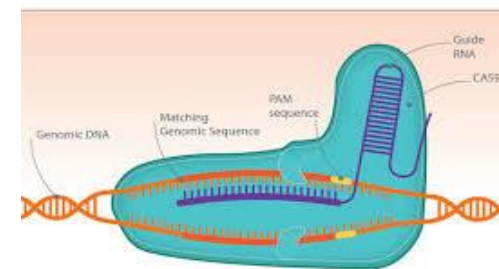
Dr. Stephen Jones



The Genome Modification Core (GMC) is supported by the Center for Cancer Research (CCR). Provides expert advice on design and use of CRISPRs, TALENs, and other nucleases. **Since inception only 10 months ago**, the GMC served 44 CCR Investigators and completed 77 projects.



Dr. Raj Chari



The Gnotobiotics Facility (GF) is funded by the Center for Cancer Research (CCR) and Office of Scientific Operations (OSO) to support research on the role of the microbiota in inflammation and anti-tumor response. Services include the rederivation, breeding, and conduct of experiments on germ-free (axenic) and gnotobiotic (defined microbiome) mice. **GF doubled in size and usage over the past year.**



Dr. Simone Difilippantonio



NIH /NIAID Vaccine Research Center Development Cycle



Dr. David Lindsay, FNLCR

Basic Research—VRC -NIH campus, Bethesda MD



Process development
Analytical
development
Formulation dev.

Vaccine Production
Program lab (VPPL)
Gaithersburg MD

Clinical development cycle
NIAID / Vaccine Research Center
(VRC)



NVITAL Immune
Assessment
Gaithersburg, MD



Clinical Trials: US, global



Public and Private Sector Leaders

Drug Discovery, High Performance Computing, Big Data Expertise

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Joint Research Committee



Jim
Brase
CTO | Co-Lead
LLNL



Stacie
Calad-Thomson
COO | Co-Lead
GSK



Tom
Rush
CSO | Co-Lead
GSK



Michelle
Arkin
UCSF



Amy
Gryshuk
LLNL



Dwight
Nissley
FNLCR

Governing Board



John
Baldoni
GSK



John MacWilliams
LLNL



Alan
Ashworth
UCSF



Ethan
Dmitrovsky
FNLCR



Patricia Falcone
LLNL



Jason
Paragas
LLNL

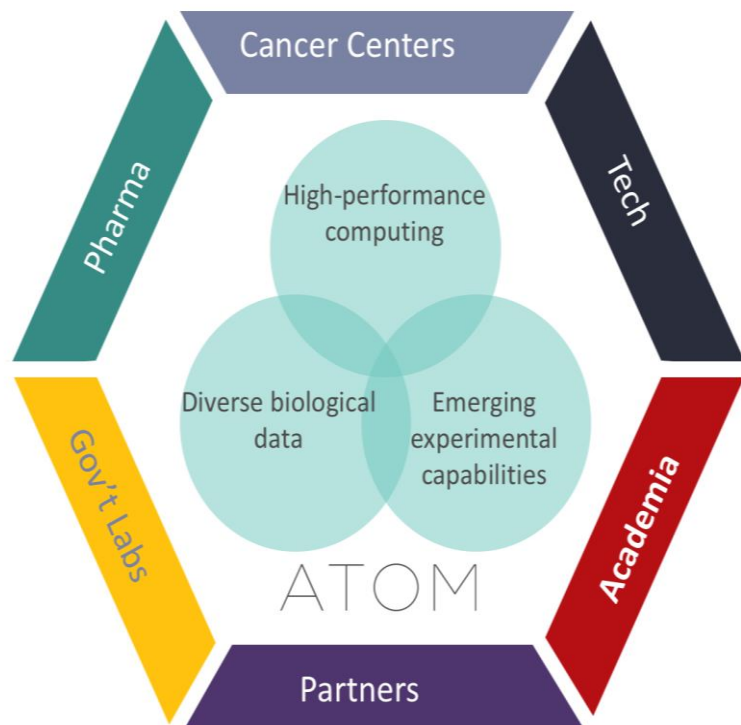


Barry
Selick
UCSF



Eric
Stahlberg
FNLCR

ATOM Technical Progress Snapshot



Data and modeling groundwork

PK and safety data-driven models

Novel hybrid model development

Active learning integrated loop

**Accelerating Therapeutics
for Opportunities in
Medicine (ATOM)**

Support NCI Car-T Cell Trials



Dr. James Doroshow, NCI
Dr. Barry Gause, FNLCR
Dr. George Mitra, FNLCR

Internal Working Group

Stakeholders

Clinical staff

External Review Panel

Dry runs

Fresh Leukopacs from Healthy donors

Frozen Leukopacs from Hemacare

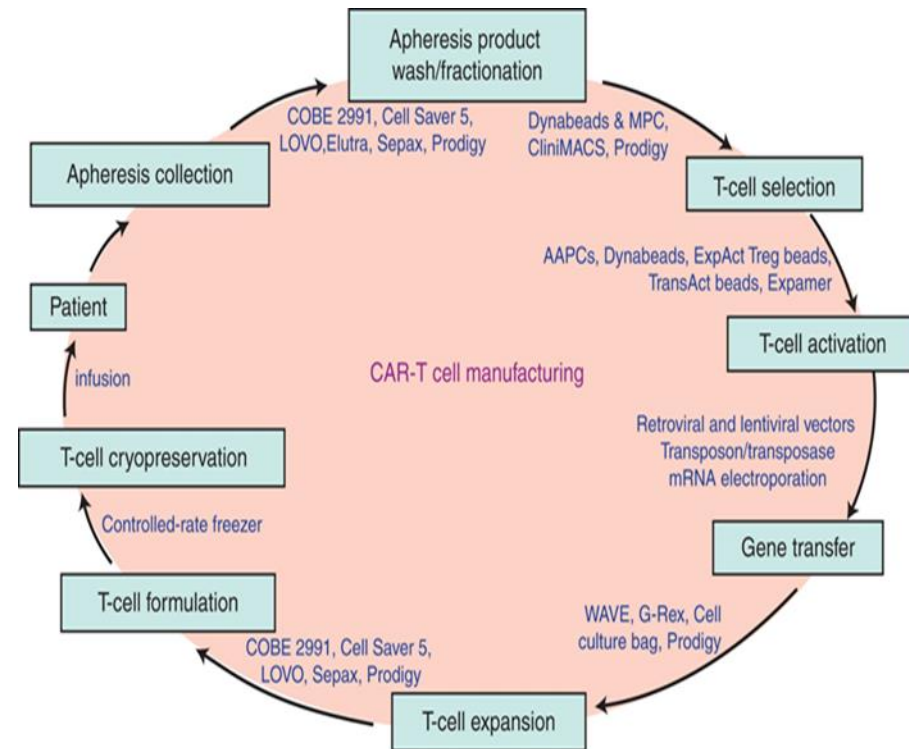
Phased Approach

I - Clinical Center

II - CHOP

III - NMDP sites (3-4)

All Sites will have prior experience
with CART Cell Therapy



Prodigy

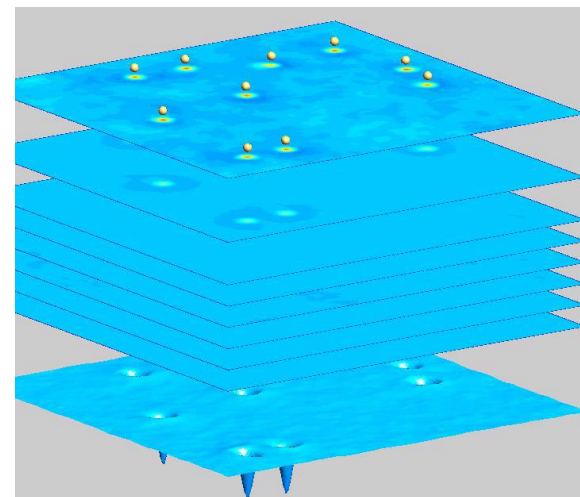
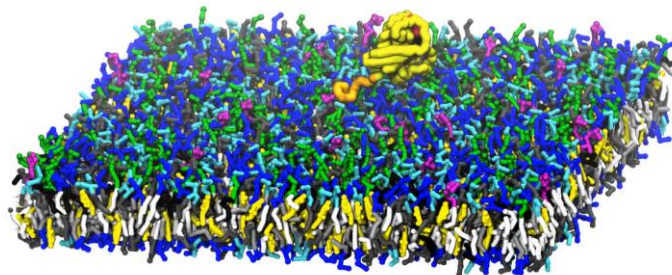
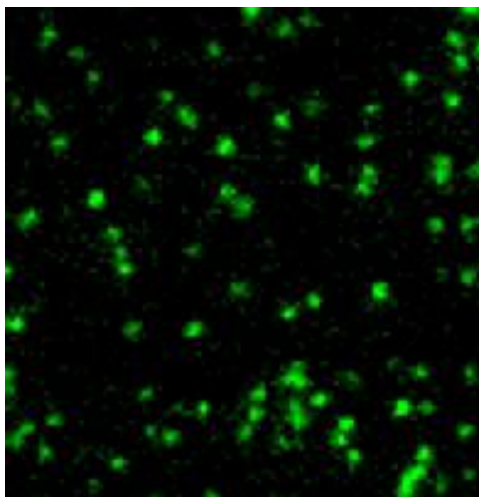
Ras Initiative: Progress

- **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 biotech, Pharma and NIH to develop leads and push towards clinic.**

Computational Science to Elucidate RAS-Membrane Biology

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Dr. Dwight Nissley
FNLCR



Dr. Fred Streitz
LLNL and DOE



Frederick National Laboratory brings cancer research to space by having a payload on the International Space Station to form enhanced Ras crystals for x-ray diffraction studies.

National Cryo-EM Overview and Team

- Mission is to address gap between need for cryo-EM and access to this expensive instrument.
- Opened in May 2017 with one Titan Krios microscope, with second in Winter 2018.
- Addition of third microscope in 2019 if demand grows.
- Over 145 cancer-related projects from 26 institutions across US have been completed; feedback is very positive.
- First publications appeared in *Nature*, *Nature Communications*, *PNAS*, *Nature Structural and Molecular Biology*, and elsewhere.

National Cryo-EM Facility (NCEF) Personnel



Ethan Dmitrovsky
Lab Director, FNLCR



Dwight Nissley
Director, CRTP, FNLCR



Ulrich Baxa
Senior Microscopist,
NCEF

Sriram Subramaniam
FNLCR Cryo-EM
Program Advisor

(Founding Director, NCEF)



Thomas Edwards
Microscopist, NCEF



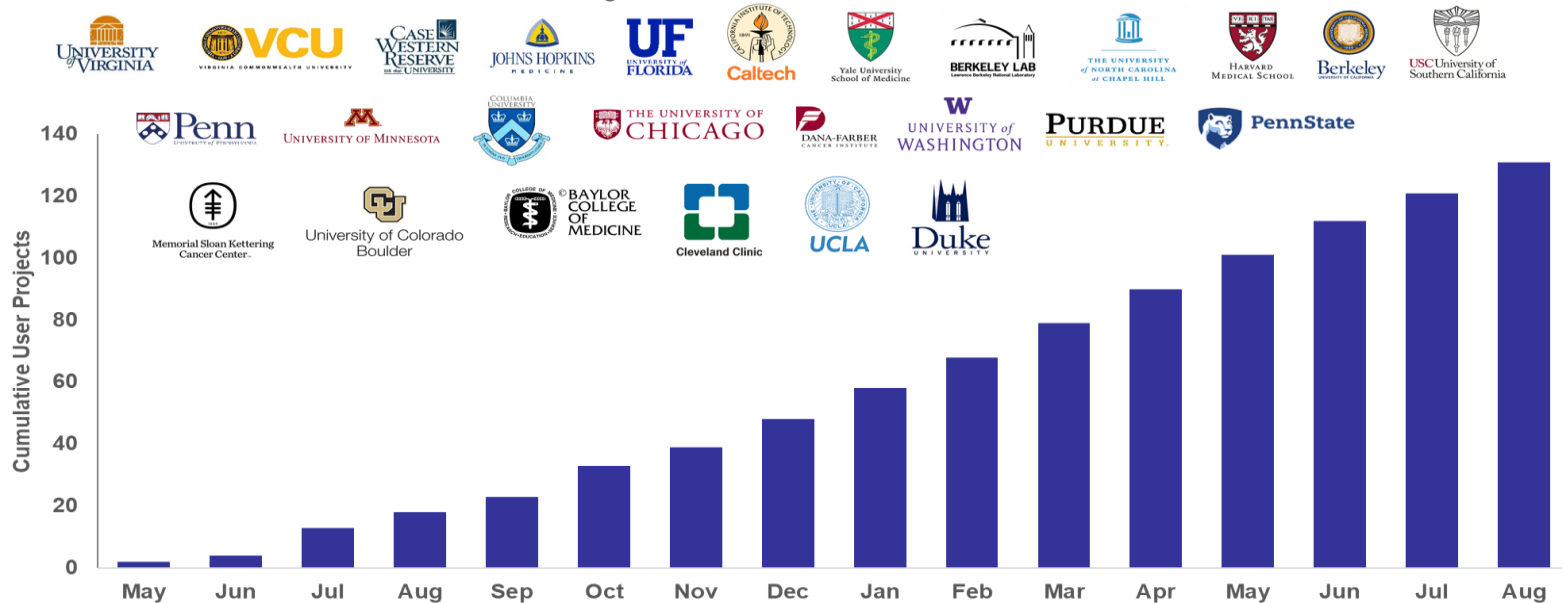
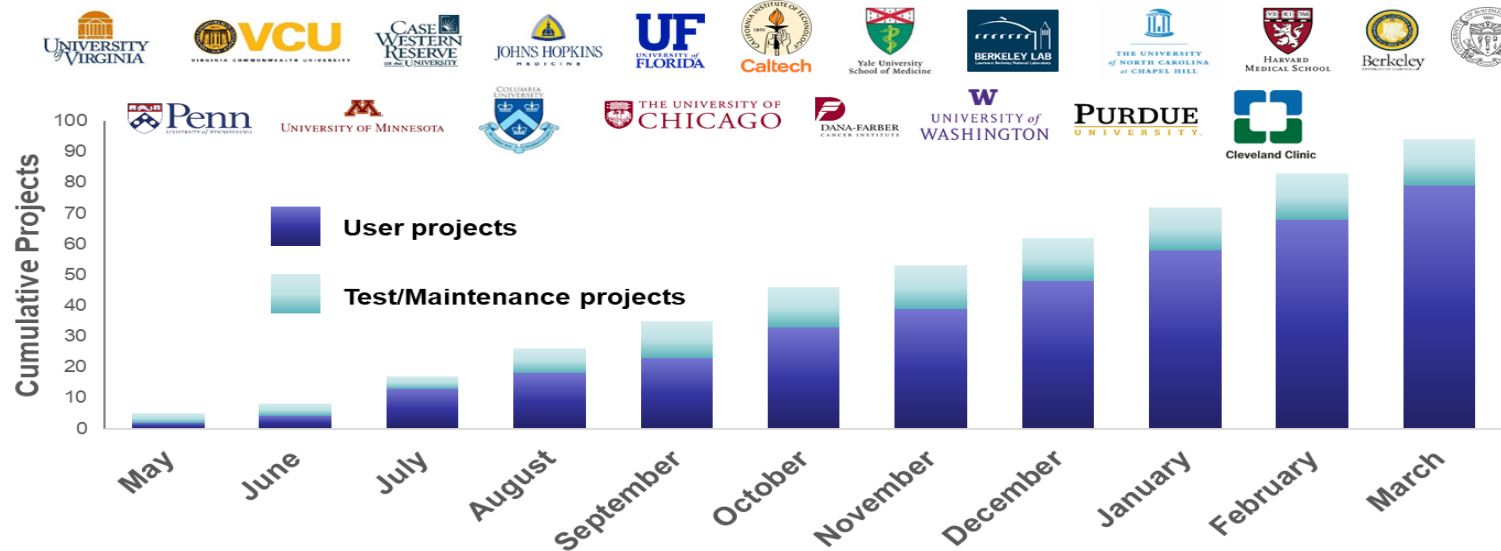
Helen Wang
Project Manager, NCEF



Matt Hutchison
IT Support, NCEF



National Cryo-Electron Microscopy Projects Since 2017 Launch



Conclusions

- 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



**Frederick
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Laboratory**
for Cancer Research



National Laboratories

