

Spectrum of Science Conducted at Frederick National Laboratory

Frederick National Laboratory
for Cancer Research

sponsored by the National Cancer Institute



Ethan Dmitrovsky, MD
Laboratory Director
Frederick National Laboratory for Cancer Research
President, Leidos Biomedical 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

- **Review spectrum of scientific work at Frederick National Laboratory.**
- **Discuss operations, how we conduct our work and address scientific and clinical scope of this contract while citing case studies of overcoming challenges.**
- **Emphasize our partnership with the NCI, other Institutes, government agencies and the extramural community.**
- **Answer your questions.**

Spectrum of Our Work

Frederick National Laboratory partners with the NCI, NIAID other Institutes, and government agencies to combat AIDS, cancer and emerging health challenges.



State-of-the art research programs to meet special short and long-term needs of NCI and the cancer research community.



Advanced, next-generation technologies to solve basic and applied problems in the biomedical sciences.

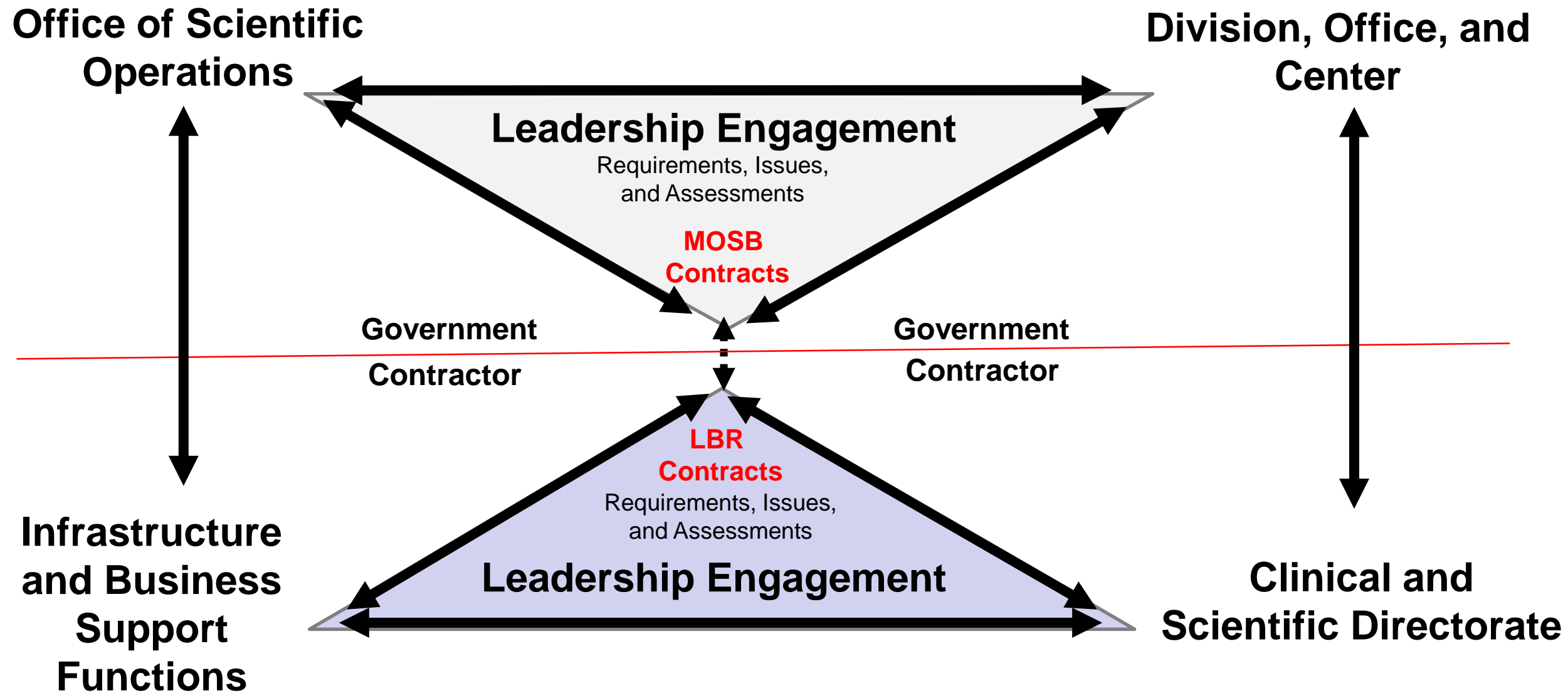


Effective and rapid response to emerging health threats and to changing national priorities in science and technology.



Providing a range of contractual agreement options with flexibility to facilitate the formation of partnerships.

Operational Delivery and the Leidos Biomedical Research Contract



How Frederick National Laboratory Works to Serve the Scientific Community



Severable Work

- **Benefits of services are recurring with annual funded appropriations.**
- **Center for Cancer Research (CCR) is funded as an example of severable work.**
- **FNLCR work is transitioning in the Bridge Contract to Task Orders.**

Non-Severable Work

- **These are distinct multi-year projects for up to 5 years.**
- **To date, 85 Task Orders awarded.**
- **Examples include Ebola and Zika trials and facility refurbishment projects.**
- **Benefits of services are met upon completion of the work.**

FNLCR's executive leadership team held a strategic retreat to align scientific and administrative efforts.

Refurbishment of Scientific Facilities at the NCI Campus at Frederick



NCI Campus at Frederick



Building 538

Building 538 Refurbishment

Renovation brought building to current standards.

Collaboration between NCI, FNLCR, and many subcontractors.

Provides state of the art facility for 10 CCR Principal Investigators, including:

**Macromolecular Crystallography
Structural Biology Laboratory
Chemical Biology Laboratory**

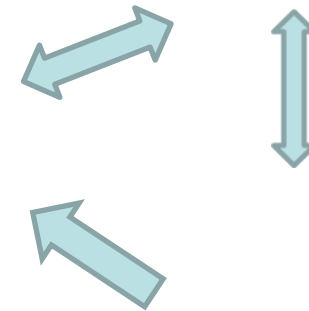
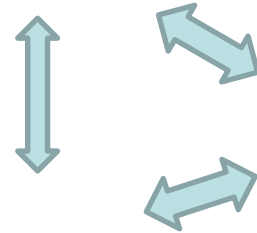
Bidirectional Hub and Spoke Model Serves the Public's Health

Intramural Laboratories
NCI, NIAID and Other Institutes



Extramural NCI-Supported Laboratories, Colleges and Universities

FNLCR – The Hub



Biotechnology Community

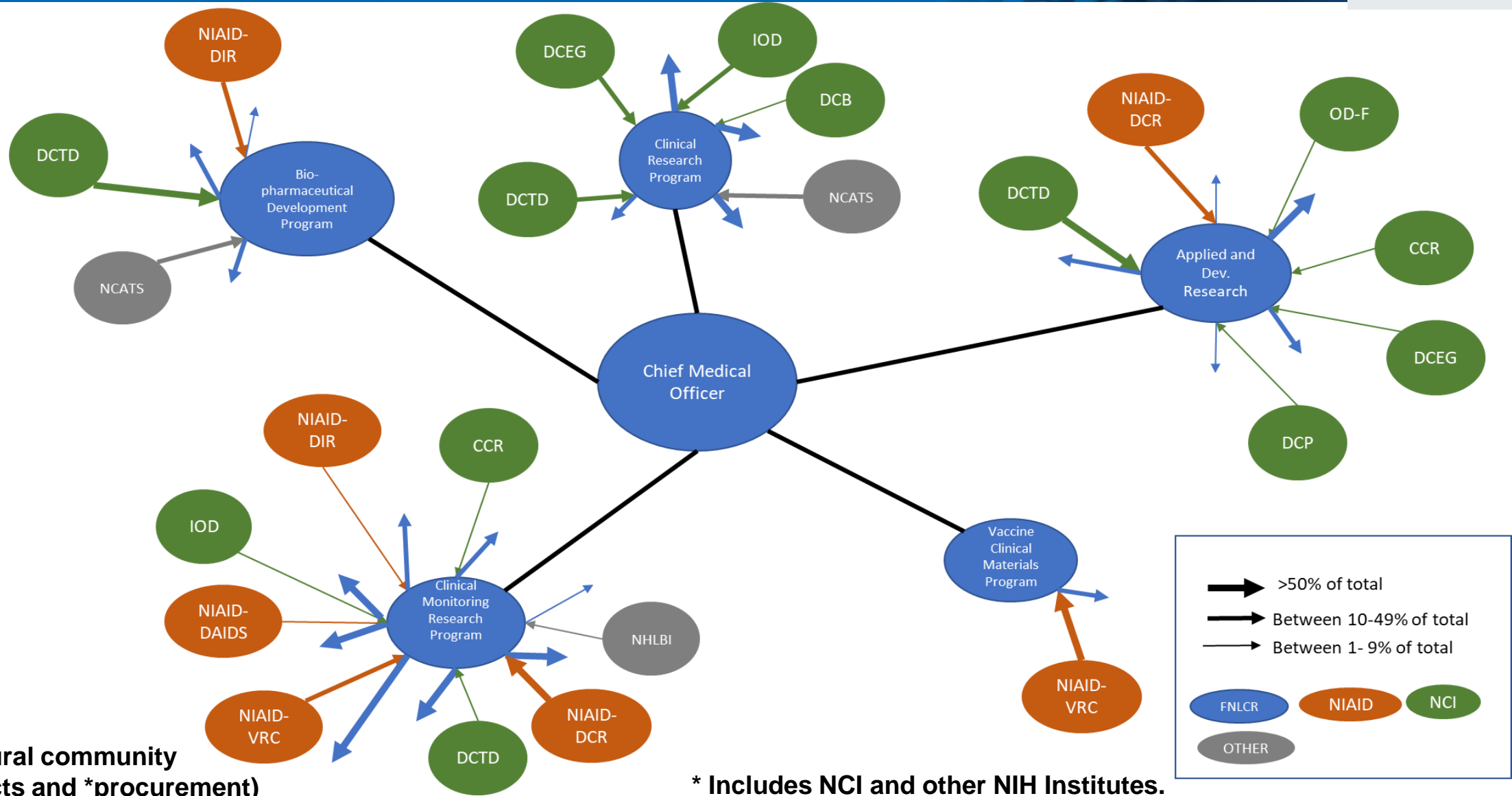


Contract Research

Pharmaceutical Industry



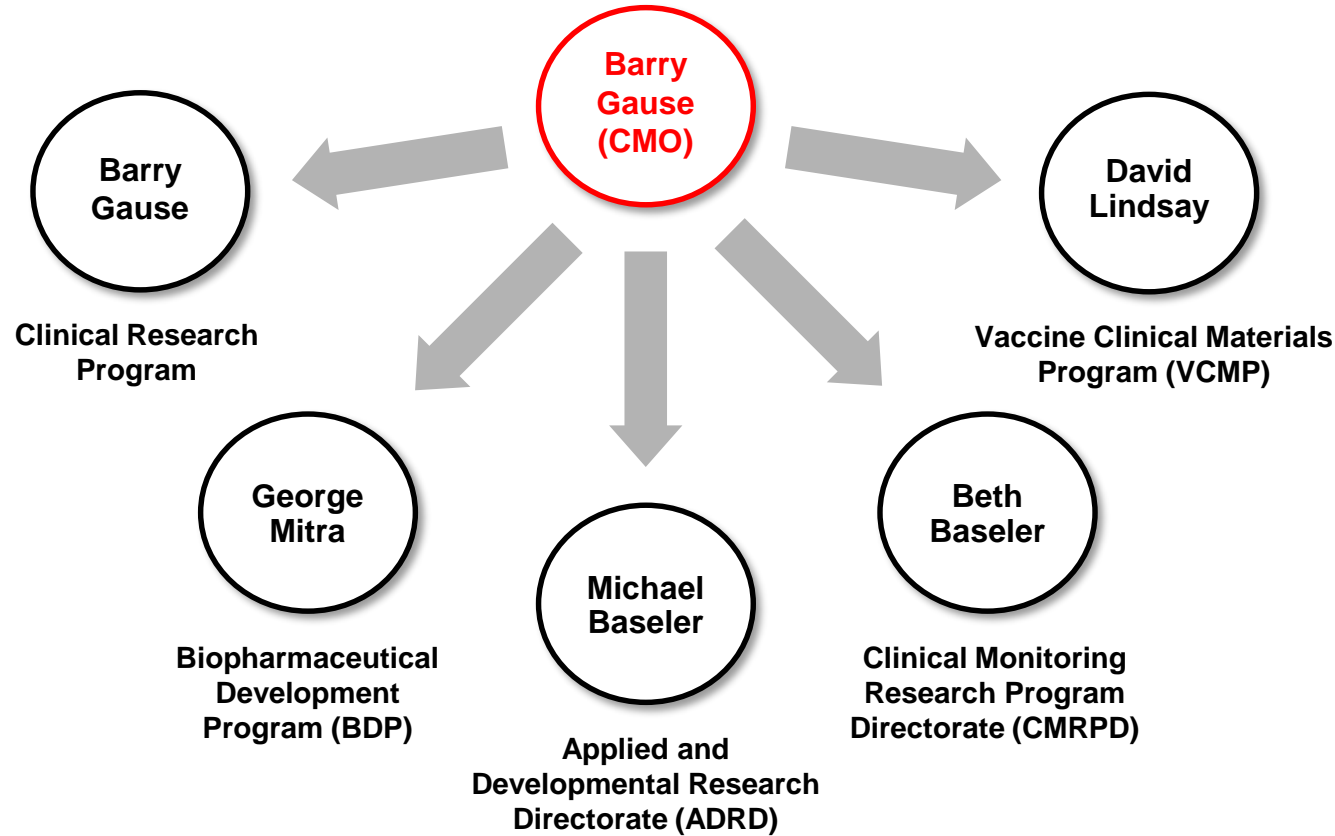
Breadth of Support at Frederick National Laboratory: Chief Medical Officer



**74% to extramural community
(via subcontracts and *procurement)**

*** Includes NCI and other NIH Institutes.**

Clinical Leader: Barry Gause, MD Chief Medical Officer



Examples of Funding Sources

Division of Cancer Treatment and Diagnosis (DCTD)
Center for Cancer Research (CCR)
NIAID Vaccine Research Center (VCR)

Support for NCI CAR-T Cell Trials



Internal Working Group

Stakeholders
Clinical staff
Trial: pediatric AML

Infrastructure

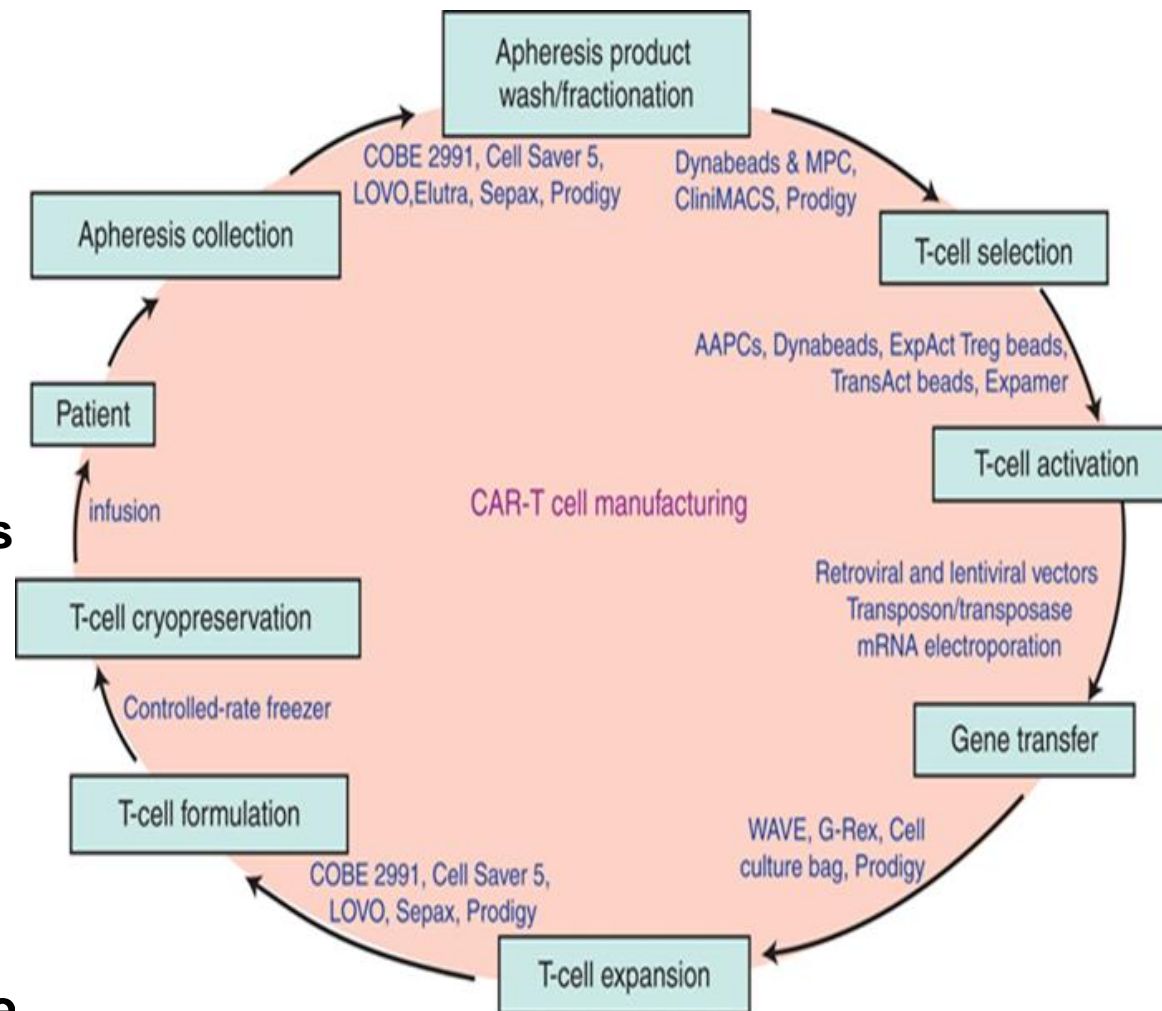
Dry runs
Fresh Leukopacs from healthy donors
Frozen Leukopacs from Hemacare

Phased Approach

- I Clinical Center (summer 2019)
- II CHOP
- III NMDP sites (3-4)

All Sites will have prior experience with CART Cell therapy

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

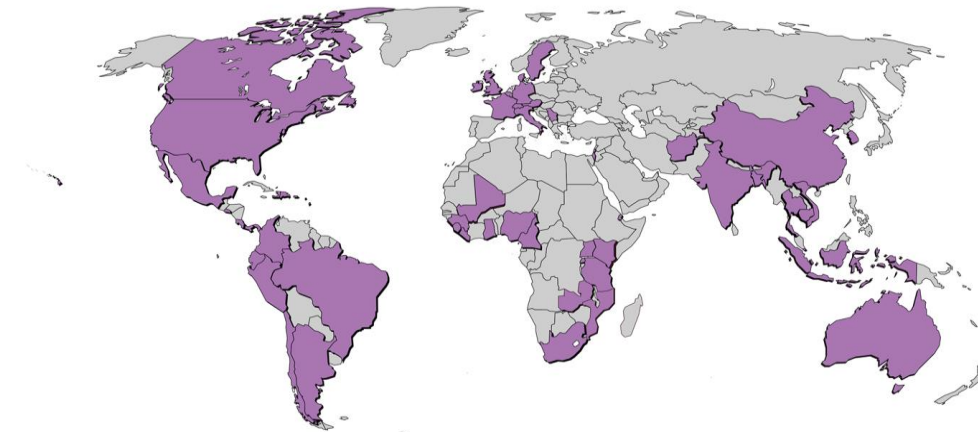


Prodigy

National and International Clinical Trial Support



- **Facilitate efficient and effective support of domestic and international clinical research programs.**
- **Provide laboratory support and comprehensive regulatory, clinical trials management support services.**
- **Support ~400 clinical trials (phase 1-3) in 42 countries.**
- **Trials to combat HPV, Ebola, Zika and other diseases.**



**Beth Baseler and Clinical
Monitoring Research Program
Directorate (CMRPD)**

**Conduct of international clinical trials presents distinct
discovery opportunities and challenges**

Two Ebola Outbreaks in One Year



Simultaneous Outbreaks

**Bikoro
2018**

**April 3: Death
of index case**

**May 7: EVD
confirmation by
qPCR**

**May 8: Official
government
statement**

**July 25: end of the
outbreak**

**Béni
2018**

May

Community Deaths

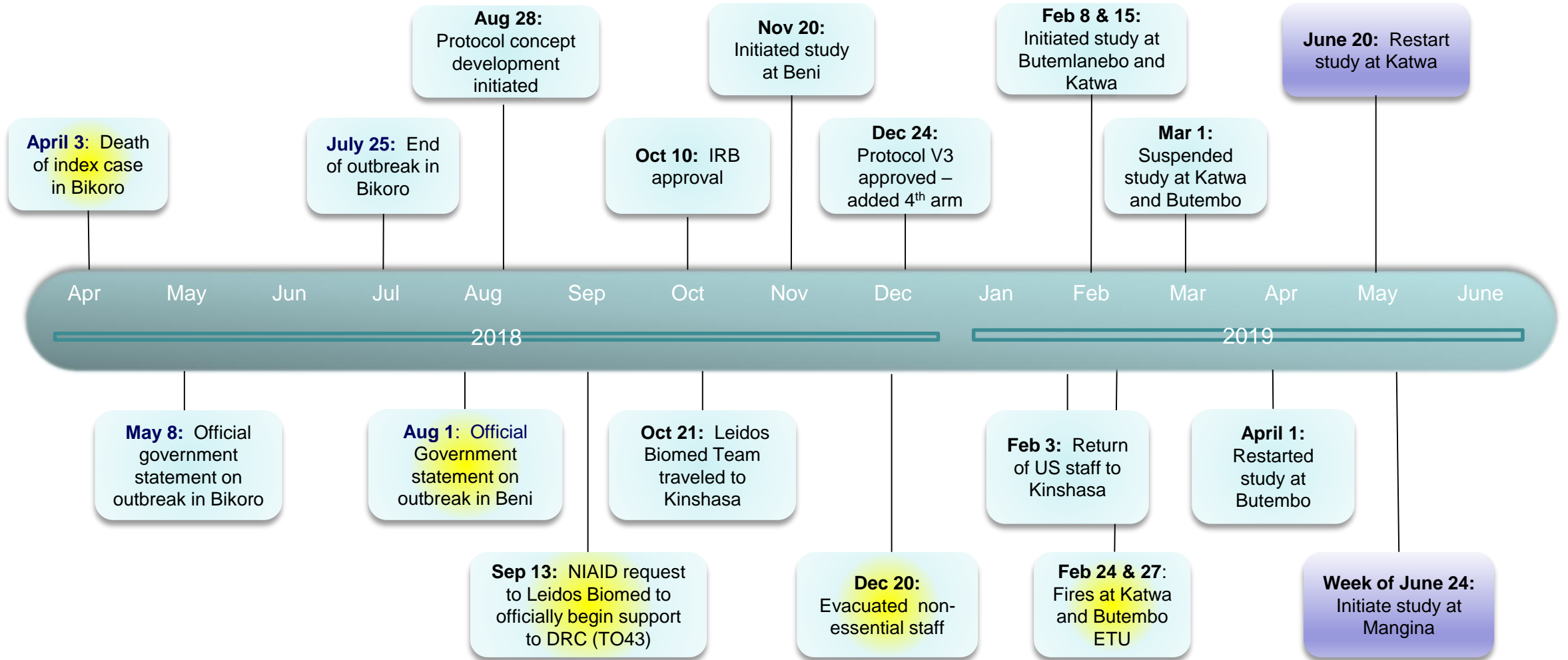
**July 31: EVD
confirmation by qPCR**

**August 1: Official
government
statement**



Accrual to date of 371 of an expected total of 500 evaluable cases (125/arm).

Evolution of the Response to the Ebola Outbreak in The Democratic Republic of the Congo (2018-2019)



Case Study: Rapid Response to Ebola Outbreak in the Democratic Republic of Congo



Ebola Trial MCM RCT Protocol: Multicenter, multi-outbreak, randomized controlled safety and efficacy study of novel therapeutics for Ebola patients.

This is a 1:1:1:1 randomization of enrolled patients to one of three different antibodies (Zmapp, mAb114, or REGN3470-3471-3479) or an anti-viral (GS-5734).

- Ebola outbreak in North Kivu, Democratic Republic of Congo, with 5 million residents already weakened by an armed conflict that spanned many years.**
- There are formidable security challenges with terrorist threats and political instability from the first presidential election since 2001.**
- We were tasked with mounting a medical relief effort to launch this trial. This was done because of our record of a successful Ebola program in Liberia.**
- Based on threat assessments, we urgently removed our team as directed by the Embassy.**
- We worked with NIAID, WHO, UN, DRC, INRB, State Department and Leidos international security experts to redeploy our team with daily and electronic monitoring, electronic and rigorous safety measures.**

International Clinical Trials: Case Study from Zika Trial



Zika 705: Phase 2/2B Randomized trial to evaluate safety and efficacy of a Zika DNA vaccine in healthy adults and adolescents (17 sites: 3 USA, 4 Puerto Rico, and 10 Latin America).

- **Early accrual lagged. (Causes: multiple hurricanes, PI changes, delay in import licenses, track changing patterns of epidemic, variable familiarity with vaccine trials at different sites, and document translation).**
- **Joint VRC-FNLCR working group was formed to rapidly change course.**
- **Streamlined protocol modifications and trained staff at different sites.**
- **Favored accrual to the most effective sites.**
- **Rapid response tailored to needs of each site (clinical, contractual and business operations).**
- **Robust accrual followed (final enrollment of 2,333 subjects).**

There is a standing joint VRC-FNLCR committee to rapidly address concerns.

NIH /NIAID Vaccine Research Center (VCR) Development Cycle



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)

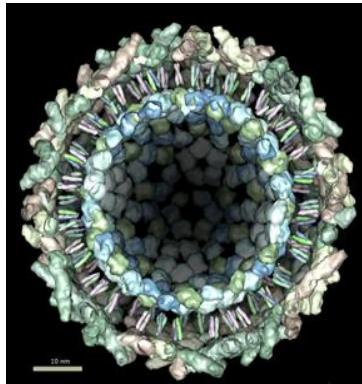
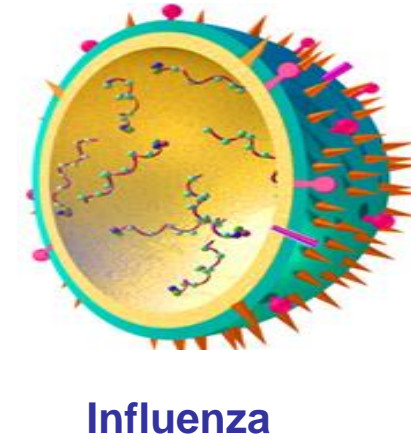
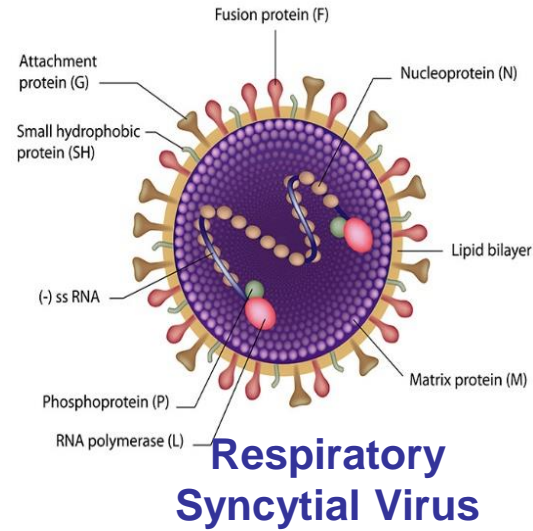
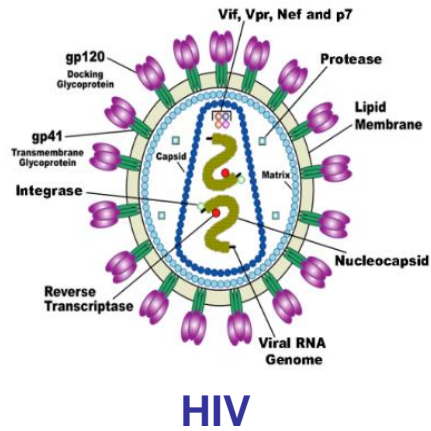


Clinical Trials: US, global

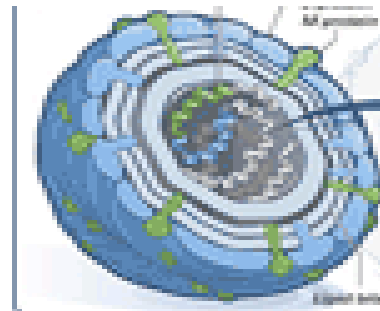


David Lindsay
Pilot Plant

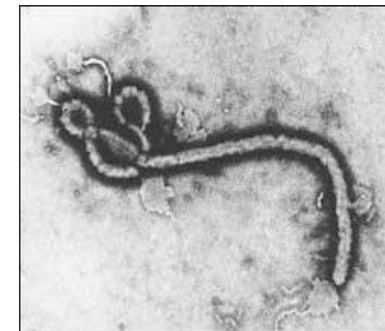
Management of Diverse Projects Related to Vaccine Development and Manufacturing



Chikungunya, Equine Encephalitis Virus

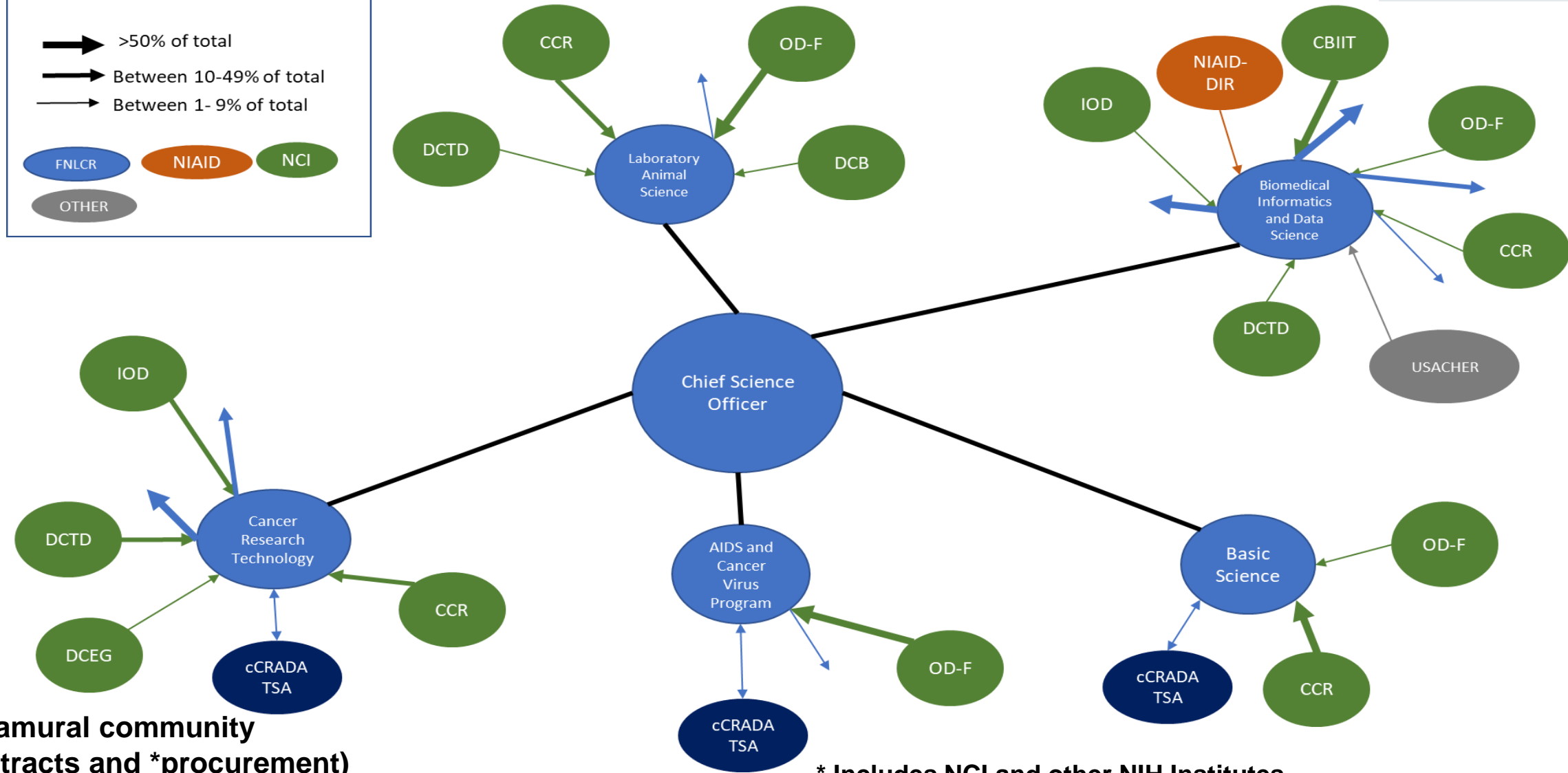
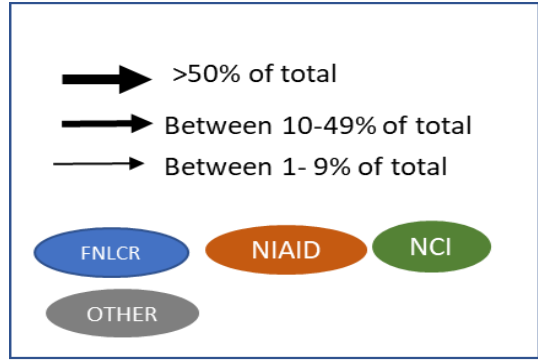


Flavivirus (West Nile, Zika)



Filovirus (Ebola, Marburg)

Breadth of Support at Frederick National Laboratory: Chief Science Officer



**56% to extramural community
(via subcontracts and *procurement)**

* Includes NCI and other NIH Institutes.

Recruitment of Chief Science Officer: Leonard Freedman, PhD

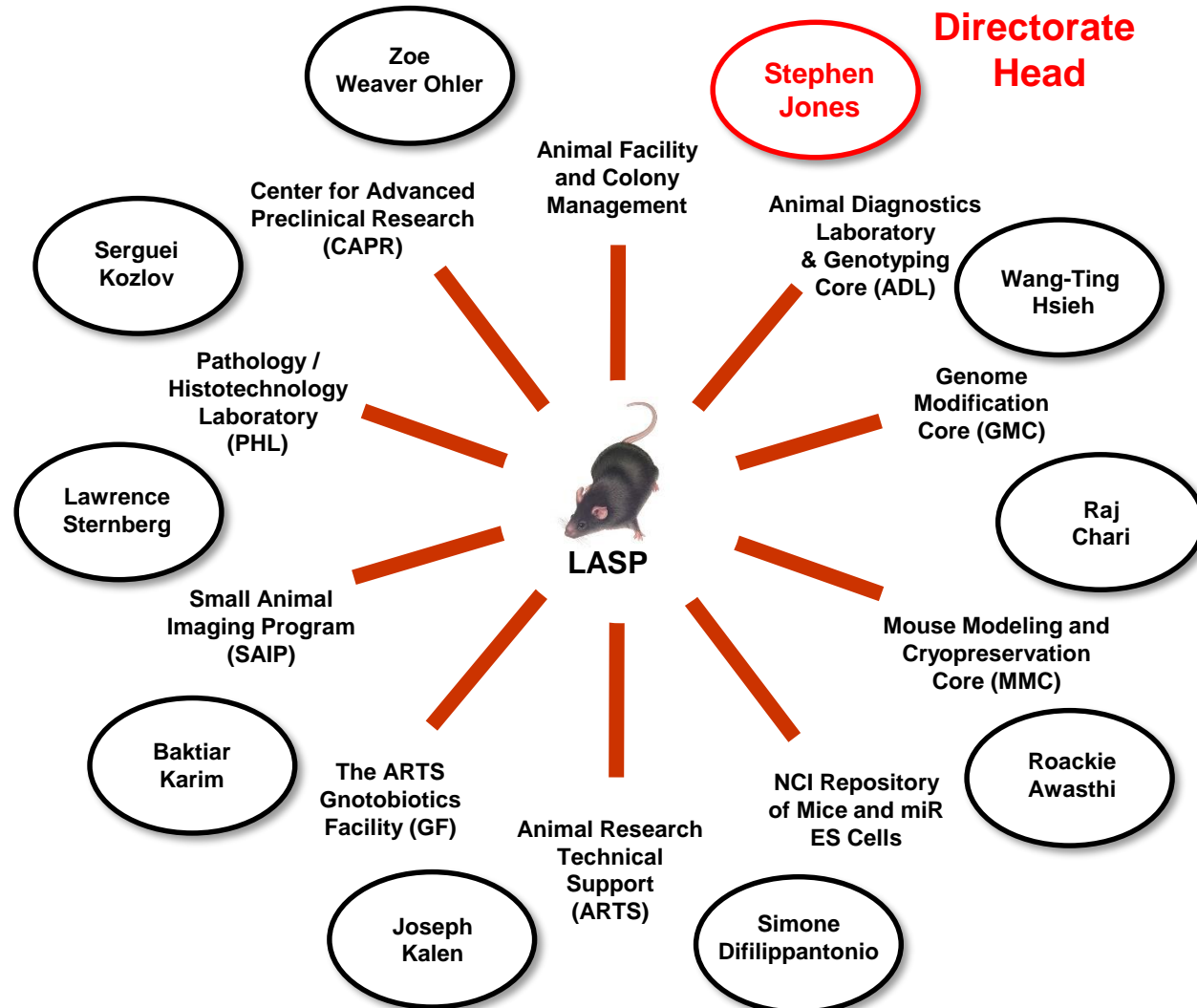


Leonard Freedman, PhD

**Undergraduate degree from Kalamazoo College
Graduate degree from University of Rochester
Trained with Dr. Keith Yamamoto at UCSF
Nuclear receptor signaling expert
Recruited by Dr. Joan Massague to
Memorial Sloan-Kettering Cancer Center
(tenured Member, Professor)
Received NIH MERIT award
Senior Editor of Molecular and Cellular Biology**

**Executive Director at Merck
Vice President at Wyeth
Vice Dean for Research at Jefferson Medical College,
Professor of Biochemistry and Molecular Biology
Founding President, Global Biological Standards Institute**

Laboratory Animal Sciences Program (LASP)



Funding Source
NCI Office of the Director

Supports

NCI Intramural

Center for Cancer Research (CCR)
OD (Animal Health Monitoring)
Division of Cancer Epidemiology and Genetics (DCEG)

NCI Extramural

NCI Division of Cancer Treatment and Diagnosis (DCTD)
Division of Cancer Biology (DCB)
NIAID, NIAMS, FNLCR

Interagency Agreements

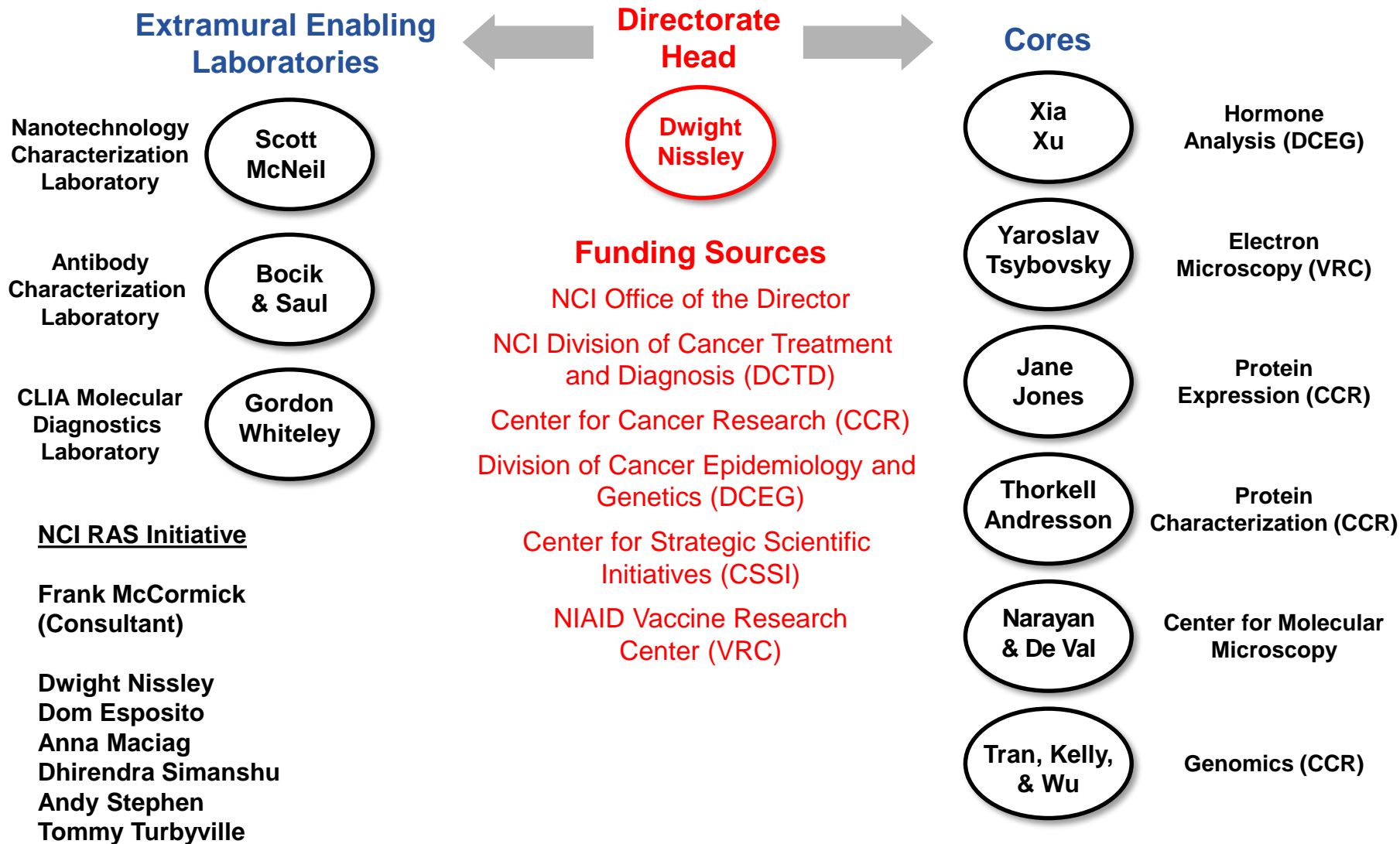
FDA, U.S. Army

cCRADAs

Recent High-Impact Publications

Gril et al., Nat Commun. 9:2705, 2018.
Singh et al., Cell Stem Cell. 23:252, 2018.
Szot et al., J Clin Invest. 128: 2927, 2018.
Yohe et al., Sci Transl Med..10:441, 2018.

Cancer Research Technology Program (CRTP)



C RTP Collaborations and Accomplishments



Extramural

CNIO

Johns Hopkins

Lawrence Livermore

Los Alamos National Laboratory

Lethality Network

MGH

NCI RAS Synthetic Lethality Network

New York Structural Biology Center

Northwestern University

Oak Ridge National Laboratory

Oxford University, UK

UC Berkeley

University of Colorado

University of Florida

University of Illinois

UI-Chicago

University of Maryland

University of Michigan

University of Minnesota

University of New South Wales

University of Turku

University of Wyoming

UNC

UT-Health

Washington University

cCRADAs

The Beatson Institute, Cancer Research UK

Eli Lilly

Sanofi

Theras, Inc

UCSF

Weizmann Institute

Intramural

NCI

NIAID

Major Contributions

- Technology support for NCI Divisions
- Distribution of RAS reference reagents
- Novel compounds and mechanisms for attacking RAS
- Characterization of nanoparticles for drug development
- Reference standard antibodies for extramural community
- User facility for collection of cryo-EM data

Recent High Impact Publications

Arango D, et al, Cell, 2018

Kang Y, et al, Nature, 2018

Venkataraman A, et al, Nat Methods, 2018

Gao Y, et al, Science, 2019

National Cancer Institute National Cryo-EM Facility and Collaborating Institutions



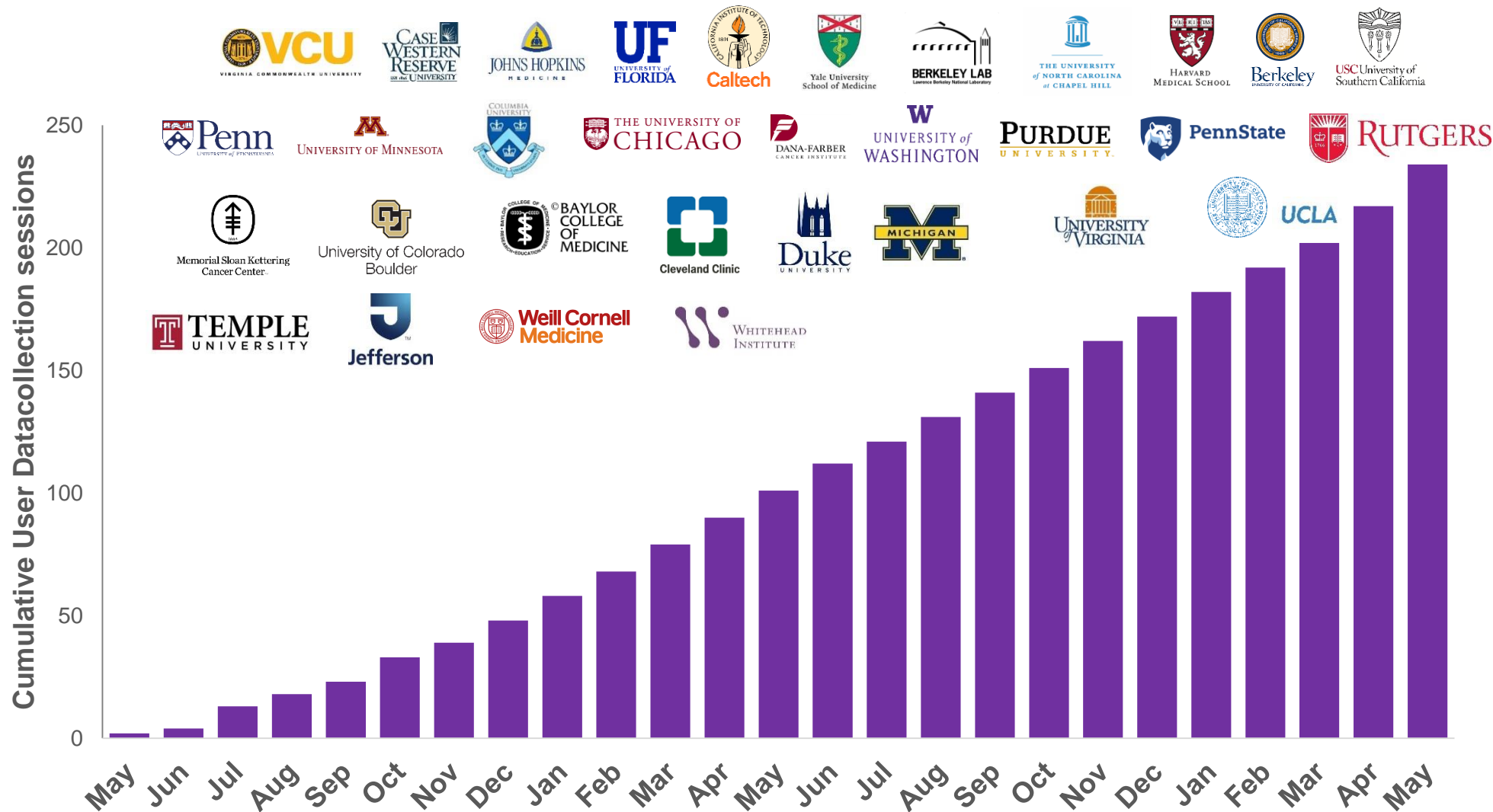
Address gap between need for cryo-EM and access to this instrument.

Opened in May 2017 with one Titan Krios microscope, with second added in Winter 2018.

Addition of third microscope in 2019 if demand grows.

Over 250 cancer-related projects from 32 institutions. Feedback is very positive.

First publications in Nature, Nature Communications, PNAS, Nature Structural and Molecular Biology, and elsewhere.



Leidos Biomedical Research and Hood College Cancer Science Symposium



**Annual meeting: interdisciplinary topics in cancer science and cancer medicine
Hosted by Hood College and inaugural meeting is:
“Imaging Science in Cancer Biology” June 21-23, 2019**

Distinguished Speakers (includes a keynote public lecture)

Organizing Committee

Ethan Dmitrovsky, M.D. (FNLCR)
Andrew Quong, Ph.D. (FNLCR)
Debbie Ricker, Ph.D. (Hood College)
Leonard Freedman, Ph.D. (FNLCR)

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)

Speakers

Cheryl Arrowsmith, PhD, University of Toronto
Ines Chen, PhD, Nature Structural & Molecular Biology
Peter N. Devreotes, PhD, Johns Hopkins University
Joe Gray, PhD, Oregon Health and Science University
Angela Gronenborn, PhD, University of Pittsburgh
Diane Lidke, PhD, University of New Mexico
Doug Lowy, MD, National Cancer Institute
Frank McCormick, PhD, University of California, San Francisco
Wei Min, PhD, Columbia University
Tom Misteli, PhD, National Cancer Institute
David Piwnica-Worms, MD, PhD, University of Texas, MD Anderson
Helen Piwnica-Worms, PhD, University of Texas, MD Anderson
Sriram Subramaniam, PhD, University of British Columbia
Valda Vinson, PhD, AAAS
Hao Wu, PhD, Harvard University

Hood College and Leidos Biomedical Research Imaging Science in Cancer Biology Meeting



Keynote Lecture

Providing the Benefits of Cancer Science to All Americans



Otis Brawley, M.D.

Bloomberg Distinguished Professor

Johns Hopkins University

Department of Oncology, School of Medicine

Department of Epidemiology, Bloomberg School of Public Health

Frederick National Laboratory Director's Distinguished Lecture Series Upcoming Speakers

Frederick
National
Laboratory
for Cancer Research

*sponsored by the
National Cancer Institute*

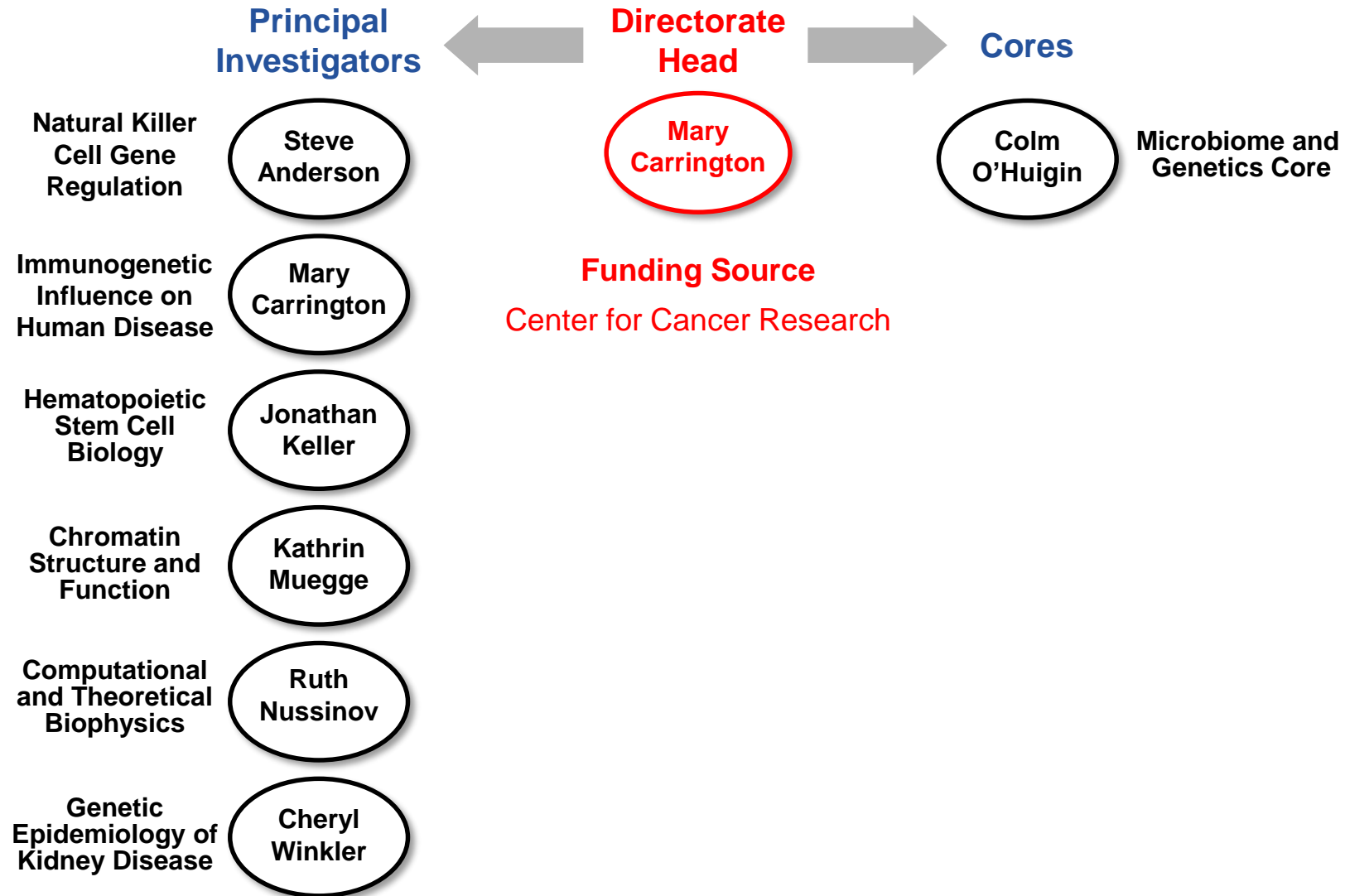


Nancy Speck, Ph.D.
Chair and Professor
Department of Cell and Developmental Biology
Perelman School of Medicine
University of Pennsylvania



Jay Dunlap, Ph.D.
Chair and Professor, Molecular and
Systems Biology
Professor, Biochemistry and Cell Biology
Dartmouth Geisel School of Medicine

Basic Science Program (BSP)



Basic Science Program (BSP) Collaborations



Intramural

NIAID
NIDDK
NCI

Extramural

Harvard

MIT

Oxford Univ.
Cambridge Univ.

Fred Hutchinson

Vanderbilt Univ.

Johns Hopkins

University Kansas

Karolinska Institute

Hebrew Univ.

University of Colorado Denver

Ohio State University

Stanford University

Central South University, China

University of Illinois

University of Maryland

Cleveland Clinic

UCSF

Mount Sinai School of Medicine

cCRADAs

Fred Hutchinson
Univ. of Massachusetts

Major Contributions

- Investigator-initiated research
- Cohort development (disease, therapeutic, vaccine)
- NGS for HLA and KIR
- Procurement for CCR Frederick and BSP

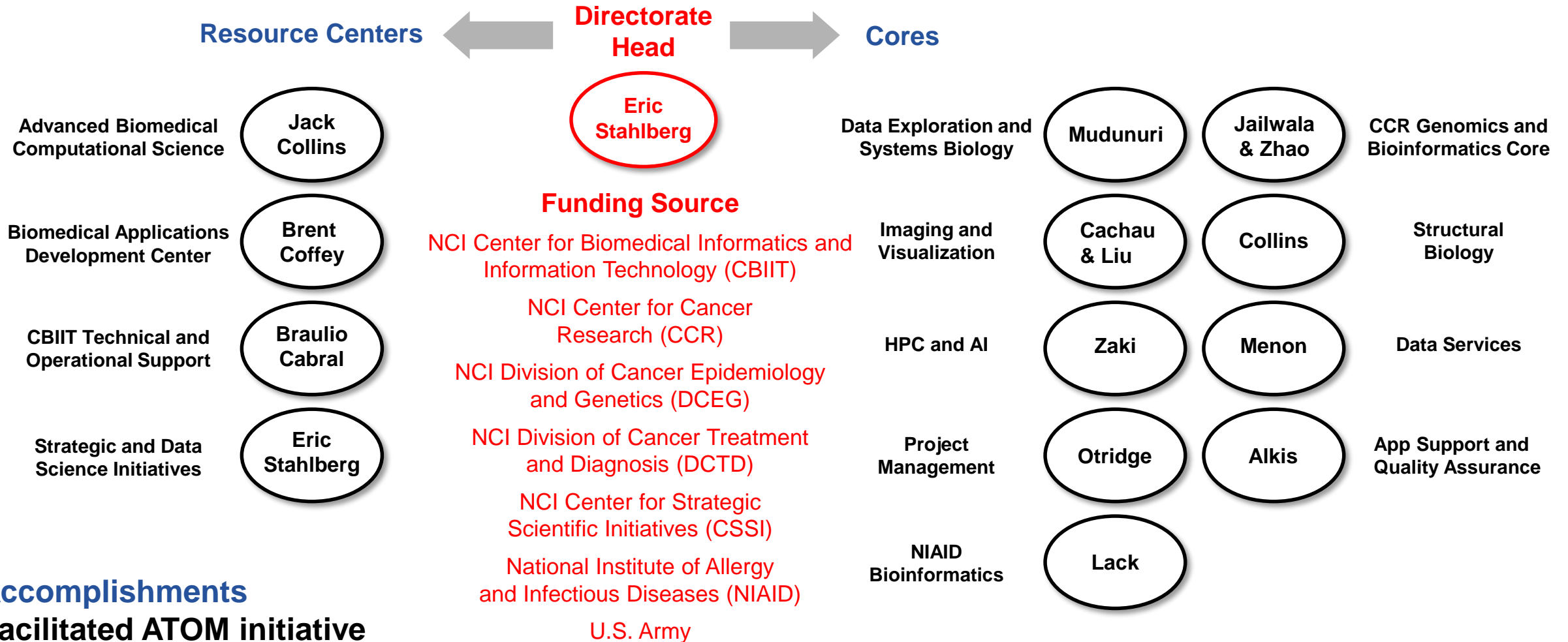
Recent High Impact Publications

Ramsuran V, et al. Science 359: 86, 2018.

Singh SK, et al. Cell Stem Cell 23: 252, 2018.

Maiti A, et al. Nature Communication, 9:2460.2018.

Biomedical Informatics and Data Science



Accomplishments

Facilitated ATOM initiative

Facilitated DOE-NCI JDACS4C advanced computing collaboration.

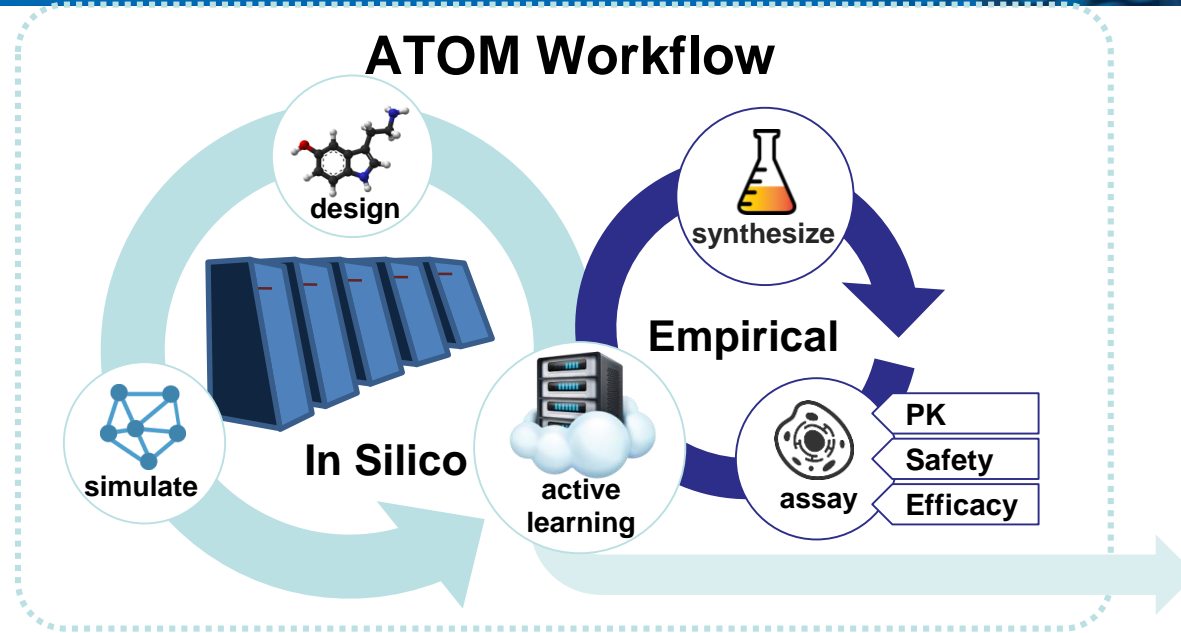
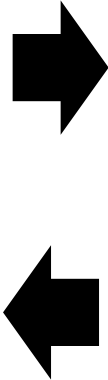
Deep learning models for histopathology image and other analyses.

Accelerated Drug Discovery Concept

Vision of ATOM workflow in practice

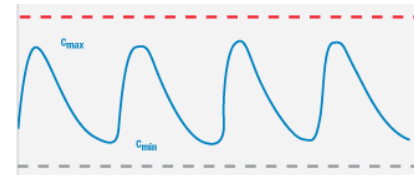
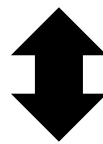


Patient-specific data and samples



Members use workflow for internal drug discovery

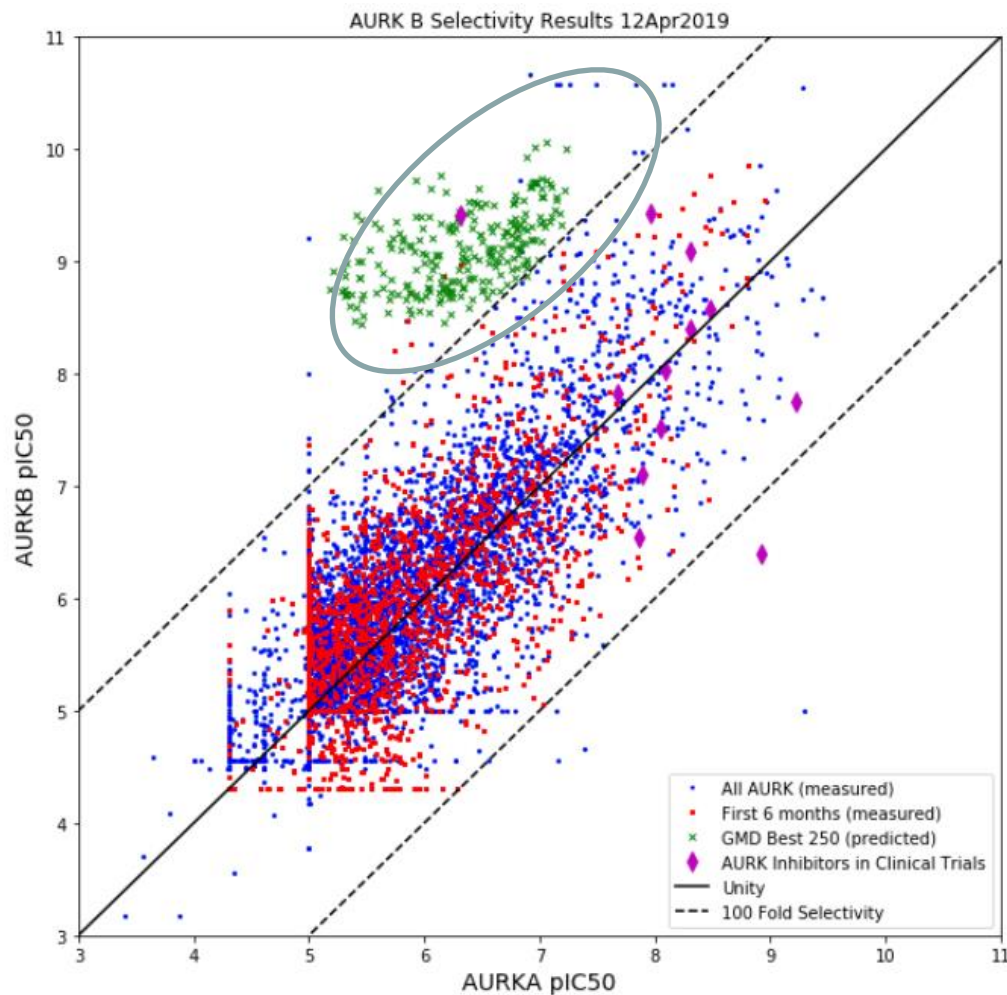
Models of drug behavior in humans



Commercialization by members for patient benefit

ATOM

Initial Pilot Results: New Potent and Selective AURK B Compounds with Favorable Properties



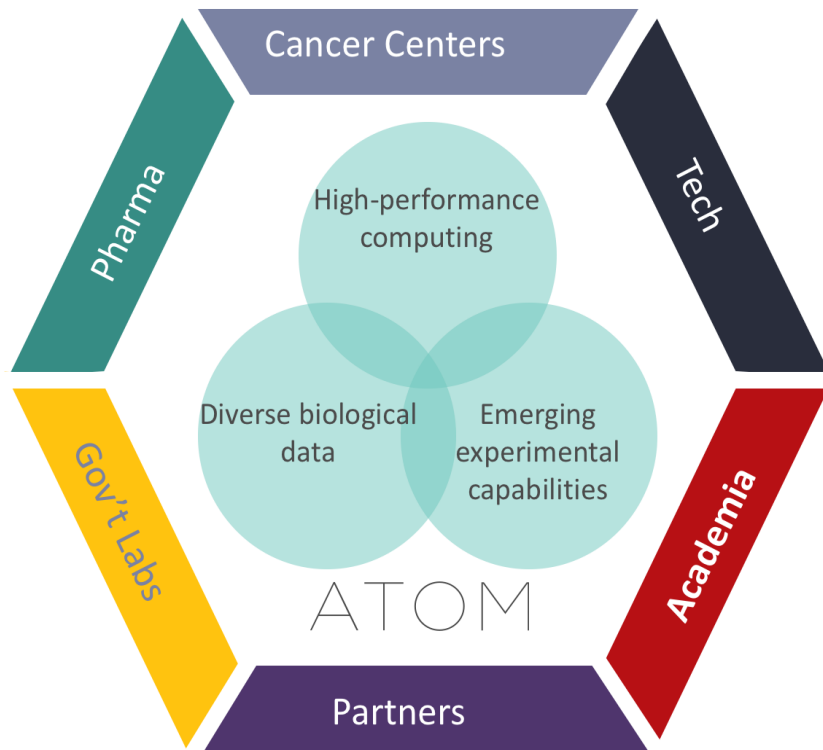
Multi-Parameter Optimization:

AURKB pic50	AURKA pic50	A/B Selectivity (fold)	HERG pic50	BSEP pic50	Solubility	hLM Clint	Solubility	SAS	QED
9.627	5.60	10772	3.260	4.010	6.022	1.819	412.492	2.640	0.437
9.724	5.92	6381	3.202	4.029	4.241	1.338	69.457	2.632	0.460
9.762	6.14	4174	3.197	4.027	4.535	1.322	93.249	2.410	0.367
9.298	5.98	2065	3.198	3.969	5.988	1.455	398.809	2.392	0.627
9.209	5.73	3024	3.200	4.027	7.000	4.371	1096.282	2.498	0.787
9.208	5.81	2477	3.195	4.027	5.413	1.868	224.400	2.397	0.651
9.626	6.18	2784	3.868	3.982	5.447	1.434	232.073	2.332	0.404
9.407	5.41	9984	3.259	4.018	3.704	1.252	40.620	2.784	0.334
9.353	5.75	4028	3.199	4.018	4.470	1.835	87.357	2.339	0.403
9.517	6.45	1160	3.223	3.976	4.353	2.024	77.733	2.222	0.664
9.252	5.79	2922	3.794	3.977	5.207	1.405	182.459	2.441	0.516
9.293	5.61	4851	3.197	3.994	4.006	1.479	54.916	2.627	0.403
9.334	5.56	5926	3.198	4.043	6.552	0.986	700.482	2.818	0.281
9.393	5.93	2911	3.198	4.026	5.343	1.595	209.163	2.624	0.384
9.397	6.05	2247	3.199	4.016	4.017	1.421	55.541	2.640	0.495
9.399	5.97	2682	3.211	3.993	3.554	1.632	34.955	2.255	0.429
9.193	5.96	1720	3.646	3.970	5.044	1.816	155.047	2.472	0.630
9.222	5.30	8342	3.215	4.048	5.936	0.888	378.391	2.628	0.261
9.327	6.25	1205	3.198	4.055	6.356	1.498	575.970	2.380	0.577
9.440	6.39	1116	3.380	3.968	4.635	1.775	103.039	2.361	0.585
9.129	5.88	1775	3.657	4.070	7.134	1.553	1254.501	2.278	0.623
9.338	6.14	1579	3.198	3.967	3.507	1.269	33.360	2.369	0.546
9.516	6.46	1136	3.202	4.067	6.818	0.858	913.920	2.464	0.495
9.278	6.21	1171	3.416	4.069	4.565	1.777	96.042	2.330	0.630
9.090	5.91	1509	3.210	4.052	6.827	0.880	922.242	2.433	0.585
9.365	6.43	869	3.210	4.020	6.059	0.936	427.917	2.686	0.599
9.107	5.53	3788	3.545	3.993	6.339	3.112	565.978	2.501	0.467
9.375	5.45	8340	3.199	4.022	2.663	1.340	14.338	2.754	0.360
9.650	6.05	3951	3.205	3.990	2.503	1.604	12.224	2.426	0.347
8.896	5.64	1821	3.209	4.027	6.561	1.374	707.083	2.181	0.636
9.648	6.48	1482	3.244	4.021	4.026	1.318	56.041	2.577	0.354
9.389	6.28	1284	3.198	4.055	5.250	1.037	190.604	2.754	0.397
9.075	5.98	1235	3.199	4.055	6.027	1.711	414.475	2.527	0.580
9.422	6.35	1179	3.202	4.014	3.214	1.569	24.878	2.503	0.528
9.298	6.27	1063	4.026	4.058	5.720	1.863	304.910	2.474	0.543
9.108	5.80	2028	3.198	4.115	5.448	0.973	232.219	2.608	0.397
8.969	5.60	2333	3.925	3.987	5.674	3.901	291.332	2.224	0.627
9.162	5.70	2884	3.198	4.069	4.387	0.800	80.426	2.520	0.243
9.154	5.87	1907	3.198	4.024	3.459	1.411	31.775	2.319	0.408
9.294	6.41	767	3.253	4.000	4.356	0.939	77.924	2.522	0.500

Validation steps

- Comparison to held out, ground truth data
- Experimentally make and test top compounds

ATOM Technical Progress Snapshot



Data and modeling groundwork

PK and safety data-driven models

Novel hybrid model development

Active learning integrated loop

Knowledge gained will be placed in public domain

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

**Consortium:
Public-Private partnership
GSK, UCSF, FNLCR, and
Lawrence Livermore National Laboratory**

AIDS and Cancer Virus Program (ACVP) Collaborations



Intramural NIAID NCI

Extramural

Boston Children's
Beth Israel
Brigham and Women's
Boston College
CHOP
Emory
Gilead
MD Anderson
Oregon Health
Population Council
Scripps Research Institute
Temple University
UC-Davis
UCSF
University of Melbourne
University of Miami
University of Nebraska
UNC
University of Pennsylvania
UT-Health
University of Wisconsin

cCRADAs

Rockefeller University
UCSF
Gilead
Beth Israel Deaconess

Major Contributions

- Diagnostic tools
- Facilitated HIV testing to secure blood supply
- Non-human primate models
- Innovative therapy
- Disseminated tools and reagents to the community

Recent High Impact Publications

Okoye Aa et al, Nature Medicine, 2018
Marshall VA, et al. PLoS Pathog, 2018
Struwe WB, et al, Cell Rep, 2018

Antiretroviral Therapy Begun Early After Infection Can Clear Initial HIV Infection



Dr. Jeff Lifson

- 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.

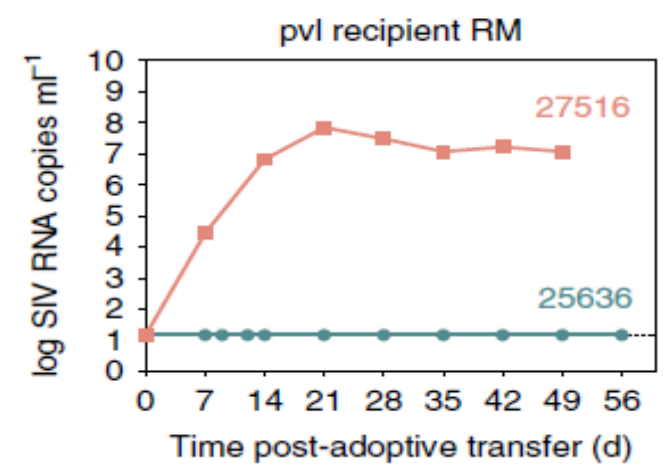
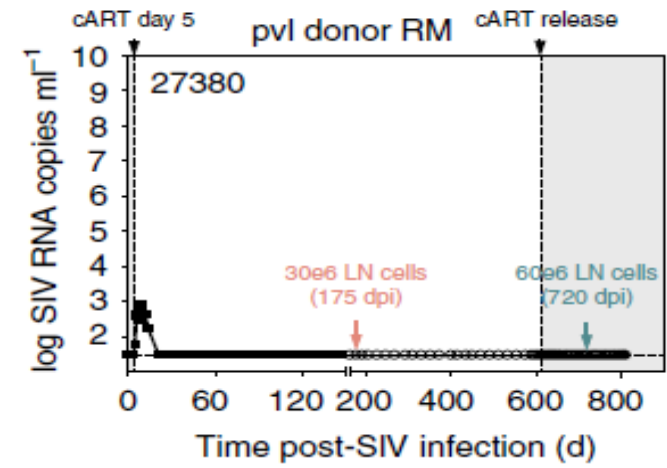
ARTICLES

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nature
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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*}



How We Collaborate with the Extramural Community



Work With Us



OPEN SOLICITATIONS

A range of opportunities are typically available and include research services, facility infrastructure, laboratory supplies, supply chain operations, and support to an onsite occupational health services.



COLLABORATIONS

Our laboratory has a range of contractual agreement options available which offer flexibility to facilitate the formation of partnerships.



VISITING SCHOLARS PROGRAM

We encourage extramural scientists to contact us to explore current available opportunities through our Visiting Scholars Program.



INTELLECTUAL PROPERTY & TECH TRANSFER

The Intellectual Property and Strategic Agreements Office handles patents, copyrights, and several types of collaboration agreements.



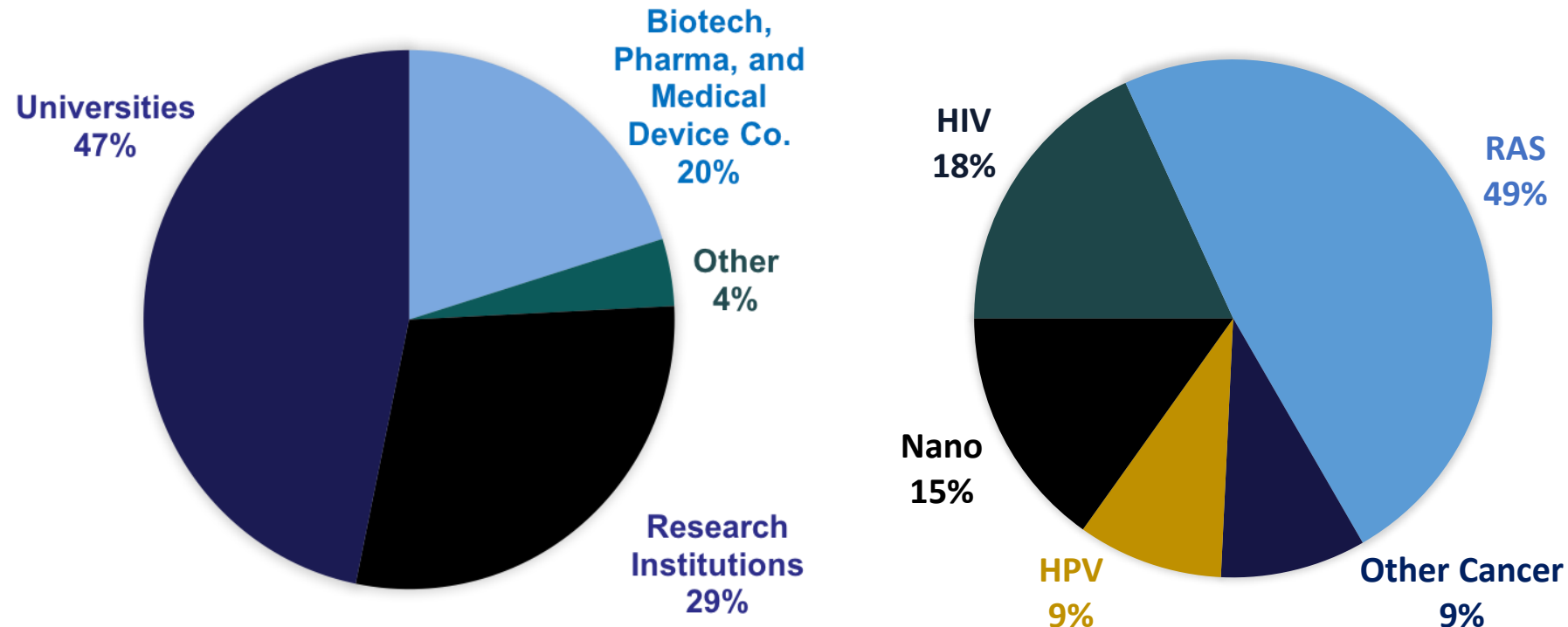
BUSINESS OPPORTUNITIES

Our Acquisitions Directorate supports the national laboratory with high quality products and services to achieve its national mission.

Who Are Our Partners?



- The Frederick National Laboratory has 127 collaborating institutions



- Connect with us at Frederick.Cancer.gov/WorkWithUs

Conclusions



- Reviewed the broad spectrum of scientific work at Frederick National Laboratory for Cancer Research.
- Discussed scope of work, operations and how we perform our work.
- Cited case studies of examples of challenges faced and strategies we used to address them.
- Emphasized our partnership with the NCI, other Institutes, government agencies and the extramural community.