Current Operations and Future Plans

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Session Objectives

∙ 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

1972

~300 Employees

1973

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

Today

~2,200 Employees

2018

Ft. Detrick
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

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

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)

- 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

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

Genotype that causes inhibition of Natural Killer cells

Strong inhibition

Ramsuran et al, Science, 2018
Eradicating Aneuploid Cancers by Engaging Anaphase Catastrophe

- Hu S et al. Mol Cancer Ther., 2016
- Kawakami M, et al. JNCI, 2017
- Kawakami M, et al. PNAS, 2018
- Kawakami M, et al. Mol Cancer Ther, 2018
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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.

The Nanotechnology Characterization Laboratory at the Frederick National Laboratory

Assay Cascade
- Provides “pharmaceutical mentorship” for materials scientists and engineers

Reformulation

Non-Oncology Nanomaterials

Metrology & New Methods

Basic Research & Grand Challenges

Informing Regulatory Agencies

Transnational Collaboration
- EU-NCL fully operational March 2017
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Implementing the RAS Program
*Hub, Spoke, and RAS Community Model*

- **The Hub**
- Extramural NCI-Supported Laboratories
- Intramural Laboratories
- Biotech
- Pharma
- Contract Research

*FNLCR*
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 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
To accelerate the development of more effective therapies for patients.

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

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

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

400 flyers circulated at AACR (NCI booth, ATOM event, and meet the experts meetings)
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Global Support of Vaccine Trials

- 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)

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
Karolinska Institute: Joakim Dillner
Public Health England: Simon Beddows
Biostat Consulting, LLC: Brian Plikaytis
Global Health Network
**NIH /NIAID Vaccine Research Center**

*Development Cycle*

**Basic Research**
- VRC - NIH campus, Bethesda MD

**Process development**
- Analytical development
- Formulation dev.

**Clinical development cycle**
- NIAID / Vaccine Research Center (VRC)

**NVITAL Immune Assessment**
- Gaithersburg, MD

**Clinical Trials**
- US, global

**cGMP pilot scale production**
- Pilot Plant, Frederick MD
  - Design/build: 2003-2004
  - Commissioned: Dec 2005
  - In operation 2006
ZIKV DNA Vaccine Discovery

- 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

![Diagram showing the phases of NExT Program]

- Target ID / Valid.
- Assay Dev
- Lead Discov
- Preclin Dev
- Manufacture
- IND
- PH I
- PH II
- PH III
- NDA
- PH IV

Small Molecule Repository

Chemical Biology Consortium

Molec. Charact. Lab

Bioph. Dev. Prgm. (BDP)

Clin. Target Valid. Lab

Clinical Assay Development Program

BDP Production, Quality Assur.
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.
  
  o Drug resistance and sensitivity
  
  o Response to Immunotherapy – including adverse events

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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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Cumulative Projects

User projects

Test/Maintenance projects

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)

Three dimensional imaging is achieved by iterative cycles of FIB milling and SEM imaging.
Imaging Whole Cells in Three Dimension by FIB-SEM

Narayan K, Subramaniam S Nat Meth 2015

Characterization of the HIV virological synapse

Narayan K, Felts RL et al, PNAS 2011
Frederick National Laboratory Initiatives
(Partial List)

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).


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

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.
QUESTIONS?