FNLCR Update
Progress and Programs
David Heimbrook, Ph.D.
Laboratory Director & President of Leidos Biomedical Research, Inc.

FNLAC May 8, 2017
Overview of Frederick National Laboratory for Cancer Research

FNLCR is the only Federally Funded Research and Development Center (FFRDC) dedicated exclusively to biomedical research

- Proudly operated in the public interest by Leidos Biomedical Research, Inc (formerly SAIC-Frederick) on behalf of the National Cancer Institute

Main campus located on 70 acres at Ft. Detrick, MD

- Leidos Biomed employees co-located with NCI researchers and other contractors on the NCI Campus at Frederick
- Additional Leidos Biomed scientists at Bethesda, Rockville and other sites

Mission

Provide a unique national resource for the development of new technologies and the translation of basic science discoveries into novel agents for the prevention, diagnosis and treatment of cancer and AIDS.
The FFRDC provides the NCI unique technical and response capabilities, including:

- **Flexibility** – due to the broad charter and use of contractor staff
- **Rapid Response** – new or cutting edge projects can be accomplished more expeditiously.
- **Increased Efficiency** – due to:
  - familiarity with the Government’s needs and access to Government expertise and resources beyond what is common in a normal contract; *and*
  - technical expertise aligned with Government’s mission
- **The FFRDC designation requires FNLCR to meet the NCI’s rapidly changing needs that cannot be achieved *as effectively* by other NCI components or through other government mechanisms.**
Leidos Biomedical Research
Organizational Chart

Leidos Biomedical Research, Inc.*
Dr. David Heimbrook
President

Environment, Health,
and Safety Directorate
Ms. Terri Bray
Directorate Head

Technology and Research Group
Dr. David Heimbrook
Chief Science Officer, Interim

Clinical Group
Dr. Barry Gause
Chief Medical Officer

Scientific Programs

Clinical Research
Program Directorate
Dr. Barry Gause
Directorate Head

Biopharmaceutical Development
Program Directorate
Dr. George Mitra
Directorate Head

Vaccine Clinical Materials
Program Directorate
Dr. David Lindsay
Directorate Head

Data Science and
Information Technology Program
Dr. David Heimbrook
Directorate Head, Interim

Applied and Developmental
Research Directorate
Dr. Michael Basei
Directorate Head

Cancer Research
Technology Directorate
Dr. Dwight Nisly
Directorate Head

AIDS and Cancer Virus
Program Directorate
Dr. Jeff Lifson
Directorate Head

Basic Science
Program Directorate
Dr. Mary Carrington
Directorate Head

Laboratory Animal Sciences
Program Directorate
Dr. Stephen Jones
Directorate Head

Operations and Financial Group
Dr. Kathy Teresisky
Chief Operating Officer

Business Enterprise Systems
Directorate
Mr. Brett Smith
Directorate Head

Contracts and
Acquisitions Directorate
Ms. Beverly Hayes
Directorate Head

Human Resources
Directorate
Mr. Chris March
Directorate Head

Facilities Maintenance
and Engineering Directorate
Dr. Dante Tedaldi
Directorate Head

Financial Management
Directorate
Mr. Tim Boyle
Directorate Head

* Leidos Biomedical Research, Inc., operates the
Frederick National Laboratory for Cancer Research
sponsored by the National Cancer Institute
FNLCR Total: $669M

NCI, $489M, 73%

Non-NCI, $180M, 27%
NCI Total: $489M

- DCTD: $121M (25%)
- DCEG: $24M (5%)
- IOD: $61M (12%)
- OD-F: $162M (33%)
- CBIIT: $30M (6%)
- CCR: $85M (18%)
- Other: $6M (1%)

CBIIT – Center for Biomedical Informatics and Information Technology
CCR – Center for Cancer Research
DCEG – Div. of Cancer Epidemiology and Genetics
DCTD – Div. of Cancer Treatment and Diagnosis
IOD – Immediate Office of the Director
OD-F – Office of the Director - Frederick
Other – DCB – Division of Cancer Biology,
DCCPS – Division of Cancer Control and Population Sciences,
DCP – Division of Cancer Prevention
• **Continued growth in support of NIAID**
  – Zika vaccine manufacture and clinical trial support

• **Renewal of the RAS Initiative** (FNLAC – 2016)
• **Direct Partnering authorities** (FNLAC - 2012)
• **Nanotechnology Characterization Laboratory 2.0** (FNLAC - 2015)
• **Laboratory-Directed Exploratory Research** (FNLAC - 2015)
NIH / NIAID Vaccine Research Center

Development cycle

Basic Research – VRC - NIH campus, Bethesda MD

Clinical development cycle
NIAID / Vaccine Research Center (VRC)

NVITAL Immune Assessment
Gaithersburg, MD

Process development
Analytical development
Formulation dev.

Vaccine Production Program lab (VPPL)
Gaithersburg MD

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

- 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
VCMP Zika Manufacturing, Testing & Release

- Plasmid was received on 15 April 2016
  - Drug Substance (DS) Manufacture
    - Completed on 27 May 2016
  - Drug Product (DP) Manufacture
    - Completed on 15 Jun 2016 : 664 vials
    - QC testing completed 28 June
      - Sterility testing completed mid-July
- Target release met: 21 July 2016

Phase 1 - First vaccination 02 Aug 2016
Ongoing ZIKA pDNA clinical supply activities (Candidate 2)

- Completed testing and release of 7000+ vial lot DP completed March 23, 2017
  - 1.5 ml fill configuration in 3 ml vials
  - Released May 2017

- Executing contingency bulk drug substance manufacture, testing and release (tentative fill slot into vialed DP in Q2 2017)
- Produce additional PBS placebo vials
- Continue stability testing on all DS and DP batches produced at the pilot plant over the course of clinical trials per approved protocol
Clinical Monitoring Research Program
Support for NIAID Zika DNA Vaccine Trials

A Phase 2/2b, Randomized Trial to Evaluate the Safety and Immunogenicity of a Zika Virus DNA Vaccine
Healthy Volunteers Ages 15-35

20 sites in the US, Caribbean, Central and South America

<table>
<thead>
<tr>
<th>VRC 705 Phase 2b</th>
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<tbody>
<tr>
<td><strong>Part A</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group</th>
<th>n=</th>
<th>Total Dose</th>
<th>Number of Injections</th>
<th>Number of Limbs</th>
<th>Day 0</th>
<th>Week 4</th>
<th>Week 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30</td>
<td>4 mg</td>
<td>2</td>
<td>2 limbs (both arms)</td>
<td>DNA</td>
<td>DNA</td>
<td>DNA</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
<td>4 mg</td>
<td>4</td>
<td>4 limbs (arms and legs)</td>
<td>DNA</td>
<td>DNA</td>
<td>DNA</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>8 mg</td>
<td>4</td>
<td>4 limbs (arms and legs)</td>
<td>DNA</td>
<td>DNA</td>
<td>DNA</td>
</tr>
<tr>
<td>Total</td>
<td>90</td>
<td></td>
<td></td>
<td></td>
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</table>

Part B proceeds if Phase 1 and Part A results promising

<table>
<thead>
<tr>
<th>Part B</th>
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</table>

(To begin accrual following analysis of preliminary data from Part A)

<table>
<thead>
<tr>
<th>Group</th>
<th>n=</th>
<th>Total Dose</th>
<th>Number of Injections</th>
<th>Number of Limbs</th>
<th>Day 0</th>
<th>Week 4</th>
<th>Week 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>1200</td>
<td>TBD</td>
<td>TBD</td>
<td>TBD</td>
<td>DNA</td>
<td>DNA</td>
<td>DNA</td>
</tr>
<tr>
<td>5</td>
<td>1200</td>
<td>N/A</td>
<td>TBD</td>
<td>TBD</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
</tr>
<tr>
<td>Total</td>
<td>2400</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

Blinded evaluation of case rates to increase sample size as needed

Protocol Chairs: Julie Ledgerwood and Grace Chen
IND Sponsor: VRC/NIAID

Julie Ledgerwood / VRC
CMRP : Support to the Division of Clinical Research, NIAID

Launch and conduct a portfolio of clinical research studies to better understand Zika virus (ZIKV) and to improve outcomes for patients afflicted with ZIKV

- Established new sites in Tapachula, Chiapas
  - Central lab in Mexico City
- Developed natural history study (Zik01)
  - Febrile Rash Cohort
- Zika vs. Dengue vs. Chikungunya
  - Guillain-Barre Cohort
  - Asymptomatic household members Cohort
- Began June 2016
- First enrollment October 2016
RAS Initiative
Follow-up to FNLAC Feedback

Immediate follow up to FNLAC guidance (Nov 2016):

- Emphasis on partnerships that give the RAS Initiative significant influence on inhibitor development priorities
- Develop in house medicinal chemistry capability
- Develop *in silico* screening capabilities
- Develop models for RAS activation of effectors

RAS Initiative Post-renewal strategy will be presented in detail following discussions with the expanded RAS *ad hoc* working group
Partnering Update
Expanding access to FNLCR Resources

• Contractor Cooperative Research and Development Agreements (cCRADA)
  – Research collaboration involving intellectual and material contributions by FNLCR scientists and external partner(s), with no participation in the joint work statement by government personnel
  – Useful for projects of significant scope and duration, specifically translational research and technology development, with defined resource commitments and future intellectual property (IP) considerations
  – Can include co-location and additional staffing
  – Commonly used by DOE FFRDCs, and designed to foster strategic technology-based partnering

Contractor partnering authorities approved in 2012
Total of **28** cCRADAs executed from FY13 to FY17
  - Approval times: 1-12 months
  - Median time from Concept Approval to Signature: 6 months

Total Partner Contribution: $6.8 million

*Employee Invention Reports (EIR)s (to date): 6*

*Patent applications resulting from cCRADAs (to date): 2*

*Also completed: 3 materials cCRADA's and 2 collaboration agreements*
<table>
<thead>
<tr>
<th>FNLCR</th>
<th>Partner</th>
<th>Subject</th>
<th>Duration</th>
<th>Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRTP (Nissley)</td>
<td>Eli Lilly</td>
<td>Identification of KRAS allele-specific complexes</td>
<td>2 yrs</td>
<td>Oct 2016</td>
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<tr>
<td>BSP (Matsuo)</td>
<td>Univ. of Mass</td>
<td>Dissecting APOBEC3’s for HIB-1 restriction</td>
<td>5 yrs</td>
<td>Dec 2016</td>
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<tr>
<td>CRTP (Holderfield)</td>
<td>Novartis</td>
<td>Identify anti-RAF-dimerization compounds</td>
<td>1 yr</td>
<td>Dec 2016</td>
</tr>
<tr>
<td>ADRD (Pinto)</td>
<td>Moffitt Cancer Center</td>
<td>Evaluation of HPV-specific antibody and B cell response</td>
<td>2 yrs</td>
<td>Dec 2016</td>
</tr>
<tr>
<td>ACVP (Estes)</td>
<td>Boston Children’s Hospital</td>
<td>Characterization of FDCs as a reservoir for HIV</td>
<td>1 yr</td>
<td>Mar 2017</td>
</tr>
<tr>
<td>CRTP (Nissley)</td>
<td>TheRas</td>
<td>Dev. and characterization of KRAS targeting compounds.</td>
<td>2 yrs</td>
<td>Mar 2017</td>
</tr>
<tr>
<td>CRTP (Holderfield)</td>
<td>Beatson Institute</td>
<td>Developing Kras/Raf effector binding assay</td>
<td>2 yrs</td>
<td>Mar 2017</td>
</tr>
</tbody>
</table>

Median time from Concept Approval to Signature: 7 months
## FNLCR contractor CRADAs in progress

<table>
<thead>
<tr>
<th>FNL LEAD</th>
<th>Partner</th>
<th>Subject</th>
<th>Duration</th>
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</thead>
<tbody>
<tr>
<td>BSP (Carrington)</td>
<td>Cancer Center</td>
<td>The role of HLA-A expression levels in defining permissible HLA mismatches in hematopoietic stem cell and cord blood transplantation</td>
<td>2 yrs</td>
</tr>
<tr>
<td>ADRD (Pinto)</td>
<td>Foundation + Institute</td>
<td>A dose Reduction Immunobridging and Safety Study of two HPV vaccines in Tanzanian girls</td>
<td>6 yrs</td>
</tr>
<tr>
<td>CRTP (Stephen)</td>
<td>Research Institute</td>
<td>Identification of small molecules that bind or modulate KRAS4b using in silico docking.</td>
<td>2 yrs</td>
</tr>
<tr>
<td>CRTP-NCL (McNeil)</td>
<td>Major Corp</td>
<td>Characterization and Formulation of Nanomaterials</td>
<td>4-5 yrs</td>
</tr>
</tbody>
</table>
Technical Service Agreement (TSA)

Streamlined agreement executed under CRADA statute allowing FNLCR labs to provide well-defined and validated research services to the scientific community. Pre-approved services are authorized for provision by Contracting Office.

- FY16 Total Partner Contributions: ~ $ 2.1 million
- FY17 Partner Contributions to date: ~ $ 1.3 million
- Partner Contributions to date: ~ $ 6.7 million

Over 200 agreements and 85 partners to date

23 Technical Services are available from many directorates:

- The AIDS and Cancer Virus Program (ACVP) and Laboratory Animal Services Program (LASP) services are most requested

New Technical Services are constantly in development

http://frederick.cancer.gov/Services/TSA.aspx
Nanotechnology Characterization Lab

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

Reformulation
- Collaborations with Pharma, CMOs & industry consortia

Non-Oncology Nanomaterials
- Other indications, EHS, etc.

Metrology & New Methods
- Working with instrument manufacturers; keeping pace with the growing complexity of nanotech

Basic Research & Grand Challenges
- Immunotoxicology; active targeting

Informing Regulatory Agencies
- Addressing FDA’s scientific questions
- Equivalence testing for nanosimilars

Transnational Collaboration
- EU-NCL

NCL 2.0 presented 2015
Implementation of NCL 2.0

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
NCL is a partner in the establishment of a multi-national NCL-like entity in Europe

- Advised the set up of the EU-NCL, a consortia of 8 labs across 7 countries. **Expands much-needed access to nanomaterial characterization for developers.**
- Provided intensive training at FNLCR for members of EU-NCL Core Expert Team.
- Afforded EU-NCL assay qualification by comparing characterization data for ONIVYDE (irinotecan liposome injection, for advanced pancreatic cancer).
- Tested EU-NCL with “bugged” samples
  - The “bugs” were selected to reflect issues common with samples in early development that would not be present in commercial samples.

**EU-NCL fully operational March 2017**
Innovation: Lab-Directed Exploratory Research (LDER) fund at FNLCR

Emulating a Cornerstone of DOE FFRDC Success

- Virtually all significant new projects at the DOE FFRDCs visited started with Lab-Directed R and D, funded by a DOE Lab-specific “tax” on all funding
  - Varying levels of government involvement in project approval in different Labs

- Emulating FFRDC Best Practice: LDER Fund Objectives
  - Enhance the innovation, creativity, originality, and quality of its research activities
  - Facilitate collaborations within FNLCR
  - Engage local universities to encourage collaboration and strategic interactions
  - Enable demonstration of exploratory “proof of concept” projects which will lead to durable funding through contract or grant mechanisms

- The Laboratory Director of FNLCR is responsible for the overall execution and management performance of the LDER program

Status: NCI committed up to $1 Million to this effort for FY 2016
(renewed for FY2017)
## Laboratory Directed Exploratory Research Funded Projects

### FY2016

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Title</th>
<th>Program</th>
<th>FY16 Budget</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ligia Pinto</td>
<td>Oral Immune Profiles in HPV-Related Oral Cancers</td>
<td>Applied and Developmental Research</td>
<td>$176,039</td>
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<tr>
<td>Xiaolin Wu</td>
<td>Genomic analysis of NCF1 and its pseudogenes in p47phox CGD</td>
<td>Cancer Research and Technology Program</td>
<td>$108,000</td>
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<tr>
<td>Stephen Lockett</td>
<td>Modeling Cell Heterogeneity Dynamics in Tumors in Response to Drugs</td>
<td>Cancer Research and Technology Program</td>
<td>$23,657</td>
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<tr>
<td>Zoe Weaver Ohler</td>
<td>Identification of EGFR tyrosine kinase inhibitor drug resistance and development of models to improve therapeutic efficacy</td>
<td>Laboratory Animal Sciences Program</td>
<td>$106,145</td>
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<tr>
<td>Mary Carrington</td>
<td>KIR/HLA interaction: influence on risk of nasopharyngeal carcinoma (NPC) in China</td>
<td>Basic Sciences Program</td>
<td>$70,000</td>
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</table>

### New FY2017

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Title</th>
<th>Program</th>
<th>FY17 Budget</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stephen Adler</td>
<td>The Development of a Micro-Dose Calibrator</td>
<td>Clinical Research Program</td>
<td>$21,656</td>
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<tr>
<td>Eckart Bindewald</td>
<td>Targeting KRAS-Expressing Cancers with Conditional RNA Activation</td>
<td>Basic Science Program</td>
<td>$94,884</td>
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<tr>
<td>Tommy Turbyville</td>
<td>3D Micro-printed Tissue and High Content Imaging as a Predictive Model for Evaluating Targeted Drug Therapies</td>
<td>Cancer Research and Technology Program</td>
<td>$29,578</td>
</tr>
<tr>
<td>Nazzarena Labo</td>
<td>Development of a Multiplexed Isotype Specific Serological Assay for Kaposi’s Sarcoma Herpesvirus (KSHV)</td>
<td>AIDS and Cancer Virus Program</td>
<td>$87,378</td>
</tr>
</tbody>
</table>
2017 Awards to FNLCR Staff

• Dr. Claudia Haywood – 2017 “Excellence in Technology Transfer” from the Federal Laboratory Consortium for Technology Transfer
  – With a team from NIAID for a cooperative effort to hasten the delivery of a safe and effective Ebola vaccine during the 2014 outbreak in West Africa

• Dr. Eric Stahlberg – selected as one of FCW’s 2017 Federal 100
  – For his “vision…leadership,… and determination…” leading to the DOE / NCI collaboration to apply High-Performance Computing capabilities to daunting challenges in Cancer Research
Thank you for your attention

Questions?