Frederick National Laboratory
for Cancer Research

FNLCR Operational Update
Progress and Programs

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Laboratory Director & President of Leidos Biomedical Research, Inc.

NFAC Sept 30, 2014

The Frederick National Laboratory is a federally funded research and development center operated by Leidos Biomedical Research,, Inc., for the National Cancer Institute
DEPARTMENT OF HEALTH AND HUMAN SERVICES • National Institutes of Health • National Cancer Institute

History of the Vaccine Clinical Materials Program (VCMP) in Brief

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- **The Vaccine Research Center was created by Executive Order in 1997**
  - *"The VRC is dedicated to translating basic findings into clinically relevant vaccine products. This will require the ability to manufacture candidate vaccines and to evaluate them in Phase I and II clinical studies. The Center will establish the infrastructure to manage regulatory issues and to oversee the good manufacturing practice (GMP) required for vaccine production and human testing"*

    - Dr. T. Fauci, 2001
- **The need for a Pilot Plant to support the mission was identified in 1999**
  - 2003 - The Vaccine Pilot Plant (VPP) plan was approved by the NIH Director
  - 2006 – VPP commenced GMP Manufacturing
- FNLCR operates the VPP on behalf of the National Institute of Allergy and Infectious Disease
  - VCMP Head – Dr. John Gilly
  - NIAID Project Officer – Dr. Richard Schwartz

7116 Geoffery Way
Frederick, MD

Vaccine Pilot Plant Facility
128,000 square feet

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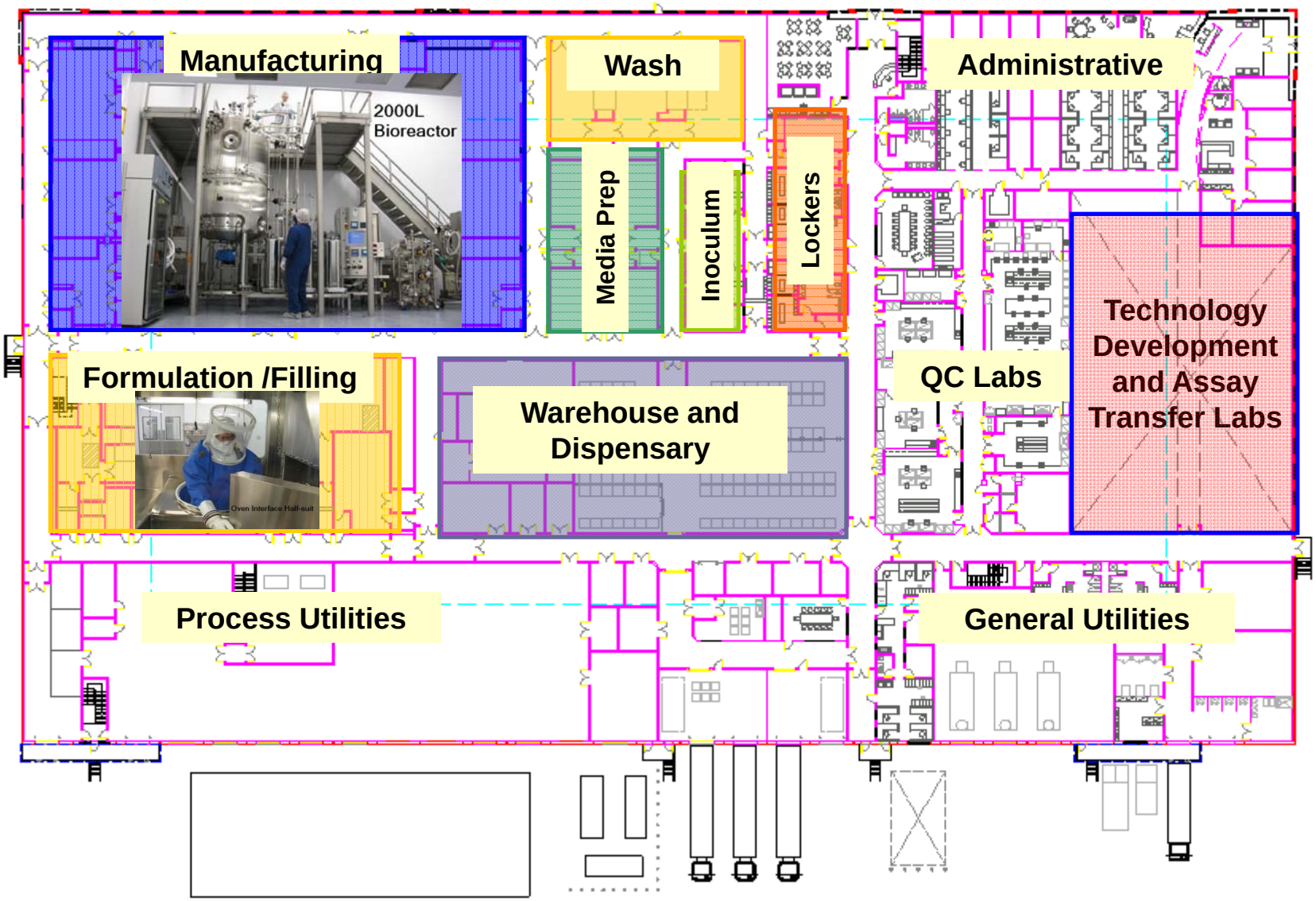

VCMP Platform Technologies

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- **DNA Plasmid Vaccines**
  - Technology development and GMP production at gram scale
- **Adenovirus vector vaccine**
  - Human cell culture technology
- **Virus-Like Particles from Human Cell Culture**
  - Vaccine produced under GMP to support alphavirus disease studies for NIAID/DOD collaboration
  - Chikungunya virus (alphavirus) vaccine produced and released for human study

Safety and tolerability of chikungunya virus-like particle vaccine in healthy adults: a phase 1 dose-escalation trial
- *The Lancet* – 15-Aug-2014

- **2,000L Biotherapeutic Monoclonal Antibody Production**
  - 1 x 2,000L Engineering Run and 6 x 2,000L GMP batches successfully completed (total of 11.4 Kg of GMP monoclonal antibody)

VCMP support for the NIAID's Ebola Vaccine Program

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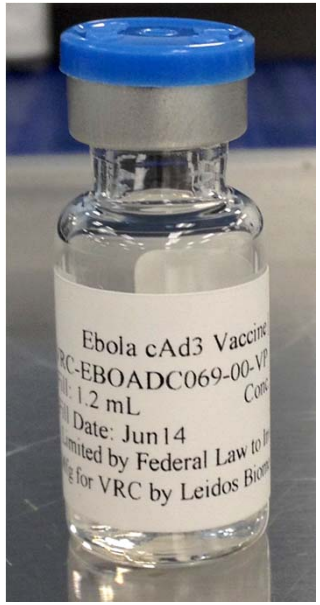
- **The program was initiated by NIAID in 2011 to enable the VCMP to support cGMP vaccine manufacturing, filling, finishing, and regulatory approval**
- **An investigational chimpanzee adenovirus vector vaccine was developed by the VRC in collaboration with Okairos, a European biotech company recently acquired by GSK**
  - Has recently shown promise in primate models (*Nature Med 7 Sept 2014*)
- **FNLCR and the VCMP supports this program by :**
  - Subcontracting the manufacture of the vaccine
  - Conducting the formulation, fill, and finish of the drug product at the VPP
  - Supporting filing of the IND
    - Submitted on a Friday, with "Safe to Proceed" notice from FDA on the following Tuesday
- **First patient in NIH clinical trial in September**



Role of FNLCR in response to a global health threat

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- **VCMP-supported NIAID Ebola vaccine effort is a key part of the international response to the current Ebola epidemic**
  - VCMP provides rapid response capability to enable NIAID's changing priorities

Testing on Experimental Ebola Vaccine to Begin in U.S.
National Institutes of Health to Begin Enrolling Volunteers Next Week in Trial of Ebola Vaccine
- *Wall Street Journal, 28-Aug-2014*

First British volunteer injected with trial Ebola vaccine in Oxford
If vaccine tested on Ruth Atkins and other healthy volunteers is found to work, it will be fast-tracked for use in west Africa
- *The Guardian, 17-Sept-2014*

- **The health threat remains, and we continue to support NIAID's ongoing response to the threat**
  - Additional Support ongoing or under discussion :
    - Development of companion booster vaccine
    - Scale-up of Chimp Adenovirus Ebola vaccines
    - Support for Ebola vaccine clinical trials in Africa

Partnering Update

Expanding access to FNLCR Resources

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- **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, especially 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 August 2012

FNLCR Partnership Pipeline

Approved cCRADAs

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FNLCR	Partner	Subject	Duration	Final Approval
ACVP (Lifson)	University Minn	Anti-Fibrotic Therapy in SIV NHP Model	1 yr	Aug 2013
ACVP (Lifson)	Aaron Diamond AIDS Res Ctr	Development of Models for HIV, Testing in NHPs	5 yrs	Aug 2013
CRTP/PEL (Esposito)	Biogen Idec	Protein scouting and scale-up	3 yrs	Sep 2013
HPV Immuno Lab (Pinto)	Moffitt Cancer Cntr	HPV oral Antibody response in males	6 mths	Jan 2014
CRTP (Stephen)	Northeast. University	K-RAS & Calmodulin 3D Structure	2 yrs	May 2014
CRTP (Wu)	Univ. Maryland, Baltimore	Virus discovery with next-gen seq'ing	1 yr	Aug 2014

Median time from Concept Approval to Signature : 5 months

FNLCR contractor CRADAs in progress

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FNL LEAD	Partner	Subject	Duration
CRTP (Nissley)	**NCI Comprehensive Cancer Center**	RAS Biology, Reagent, & Cell Line Dev. and Validation	3 yrs
ACVP (Lifson)	**Top 10 Pharma**	NHP model of targeting residual virus in individuals on suppressive antiretroviral drug treatment	1 yr
ACVP (Estes)	**Major Research University**	Impact of combination antiretroviral treatment and CD4+ cell depletion on the SIV reservoir in macaques	1 yr
NCL (McNeil)	**Top 10 Pharma**	Characterization of a novel anti-microbial	6 mos
NCL (McNeil)	**Top 20 Pharma**	Nanotech Formulation of a regulatory inhibitor	1 yr
NCL (McNeil)	**Top 10 Pharma**	Nanotech Formulation of a novel Bcl-2/Bcl-Xl inhibitor	1 yr

Other Partnering Agreements
Materials Contractor CRADA

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- Materials cCRADA : New FNL mechanism for transfer of incoming materials that require Intellectual Property considerations
  - Rapid uptake in first two months (Jeff Lifson's CURE research in ACVP)

FNL LEAD	Partner	Subject	Duration	Executed
ACVP (Lifson)	**GSK**	Evaluation of Novel Antiretroviral Drug Regimens in NHP models	1 yr	Jul-14
ACVP (Keele)	**Merck**	Quantification of Viral Reservoirs Contributing to Rebound Viremia Following Interruption of Suppressive Antiviral Therapy	1 yr	Aug-14
ACVP (Estes)	**Top 10 Pharma**	Evaluation of Anti-fibrotic Intervention in Conjunction with Antiretroviral Drug Treatment in SIV infected Primates	1 yr	
ACVP (Ohlen)	**Top 10 Pharma**	Eradication of HIV/SIV Reservoir by Combination of HAART and Adoptive T Cell Immunotherapy	1 yr	

Other Partnering Agreements
Collaboration Agreements

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Collaboration Agreements – no creation of joint intellectual property or transfer of funds

FNL LEAD	Partner	Subject	Duration	Executed
BSP (Winkler)	Instituto Nacional de Ciencias Medicas	Genetic and Environmental Correlates of HIV Transmission	3 yrs	Oct-13
ADRD (NIAID) (Lempiki)	Pacific Biosciences	Improved Bioinformatics for Pathogen Detection	2 yrs	Nov-13
CRTP (Stephen)	Pall Corporation	Monitoring Protein Folding by Intrinsic Fluorescence	1 yr	Feb-14
CRGL (Hutchinson)	Illumina Corporation	Early Access to Universal Forensic Panel	6 mths	Jun-14
CRTP (Stephen)	Albert Einstein	RAS - GAP Co-structures	1 yr	Jul-14
ACVP (Lifson)	Top 10 Pharma & Major Academic Research Intuition	Combination Therapy in HIV/AIDS NHP Model	1 yr	

FNLCR Technical Services

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- **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. Limited collaboration; partner may provide input on experimental design and data analysis

- **FY13 Total Partner Contributions : ~ $ 250,000**
- **FY14 Partner Contributions to date: ~ $ 1,500,000**
- **Technical Services are available from many directorates:**
  - The AIDS and Cancer Virus Program (ACVP) and Laboratory Animal Services Program (LASP) services are most in demand
- **New Technical Services are constantly in development**
  - N = 20 and counting

    http://frederick.cancer.gov/Services/TSA.aspx

National Programs
AIDS and Cancer Virus Program
Nanotechnology Characterization Laboratory

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- **Characteristics of an FNLCR "National Program"**
  - Directed towards a coherent objective
  - Focused on enabling scientific, technical, or medical advances in the broader biomedical community
  - Scientific content fundamentally enabled by teams of FNLCR scientists
  - Highly visible and impactful to the external scientific community
- **Based on this definition, two ongoing efforts preceded RAS as "National Programs"**
  - **AIDS and Cancer Virus Program**
    - FNLCR Lead : Dr. Jeff Lifson
    - NCI sponsor : Dr. Craig Reynolds
  - **Nanotechnology Characterization Laboratory**
    - FNLCR Lead : Dr. Scott McNeil
    - NCI Sponsor : Dr. Piotr Grodzinski

With the support of their sponsors, both programs are poised for strategic expansion

AIDS and Cancer Virus Program

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Mission

Conduct investigator initiated basic and applied research to improve the diagnosis, treatment and prevention of HIV/AIDS and infections with cancer associated viruses, *developing novel research methods, analytical techniques and reagents, proactively making these available to the broader research community*

<u>Distinguishing Features:</u>

- **Small PI headed Research Sections, organized by interest/expertise**
- **Research Support Cores arise from need and *many are unique***
- **Extensive interactions with/support of investigators outside of ACVP (intra- and extramural) by PIs and Cores**
  - ***ACVP as a national resource***

AIDS and Cancer Virus Program

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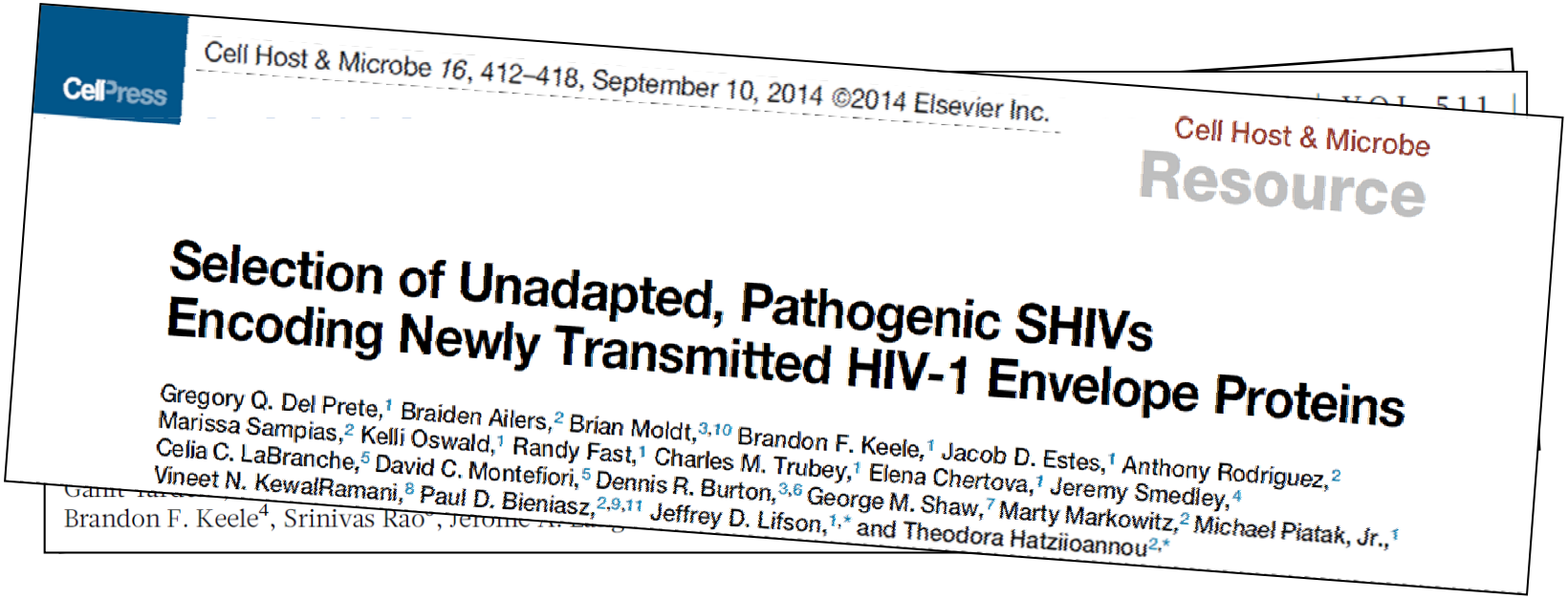
- **Cutting edge science enables high impact publications, creates collaborative demand**
- **Extensive interactions of ACVP scientists with outside collaborators, academic and industry (incl TSAs, cCRADAs)**



CellPress

Cell Host & Microbe *16*, 412–418, September 10, 2014 ©2014 Elsevier Inc.

Cell Host & Microbe

Resource

Selection of Unadapted, Pathogenic SHIVs Encoding Newly Transmitted HIV-1 Envelope Proteins

Gregory Q. Del Prete,[1] Braiden Ailers,[2] Brian Moldt,[3,10] Brandon F. Keele,[1] Jacob D. Estes,[1] Anthony Rodriguez,[2] Marissa Sampias,[2] Kelli Oswald,[1] Randy Fast,[1] Charles M. Trubey,[1] Elena Chertova,[1] Jeremy Smedley,[4] Celia C. LaBranche,[5] David C. Montefiori,[5] Dennis R. Burton,[3,6] George M. Shaw,[7] Marty Markowitz,[2] Michael Piatak, Jr.,[1] Vineet N. KewalRamani,[8] Paul D. Bieniasz,[2,9,11] Jeffrey D. Lifson,[1,*] and Theodora Hatziioannou[2,*]

Brandon F. Keele[4], Srinivas Rao

- **ACVP FY 14 Executed Technical Services Agreements: > $ 1.9 M in committed Partner contributions**

AIDS and Cancer Virus Program: National Laboratory Level Mission and Performance

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Frontiers in AIDS Treatment:

- **Limitations of combination anti-retroviral treatment**
- **Increased emphasis on viral eradication/functional cure:**
  - **Need for more definitive treatment**
  - **Example of Timothy Brown ("the Berlin Patient")**
  - **NIH, industry, and charitable foundation commitment**
- **Critical role for NHP models in this research effort**
- **Established relevant state of the art expertise and unique capabilities in ACVP**

http://www.nytimes.com/2011/11/29/health/new-hope-of-a-cure-for-hiv.html?pagewanted=all&_r=0

LETTER

nature 2013 Oct 3;502(7469):100-4.

Immune clearance of highly pathogenic SIV infection

Scott G. Hansen[1]*, Michael Piatak Jr[2]*, Abigail B. Ventura[1], Colette M. Hughes[1], Roxanne M. Gilbride[1], Julia C. Ford[1], Kelli Oswald[2], Rebecca Shoemaker[2], Yuan Li[2], Matthew S. Lewis[1], Awbrey N. Gilliam[1], Guangwu Xu[1], Nathan Whizin[1], Benjamin J. Burwitz[1], Shannon L. Planer[1], John M. Turner[1], Alfred W. Legasse[1], Michael K. Axthelm[1], Jay A. Nelson[1], Klaus Früh[1], Jonah B. Sacha[1], Jacob D. Estes[2], Brandon F. Keele[2], Paul T. Edlefsen[3], Jeffrey D. Lifson[2] & Louis J. Picker[1]

AIDS and Cancer Virus Program: Enabling the National Program

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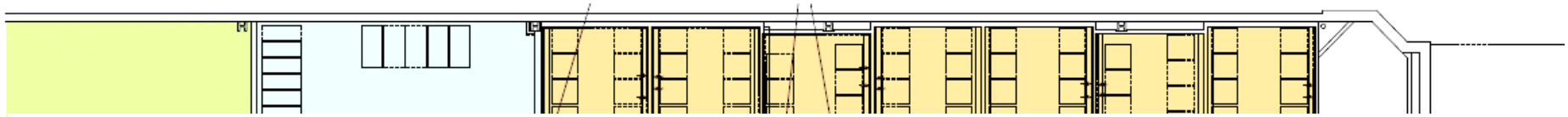
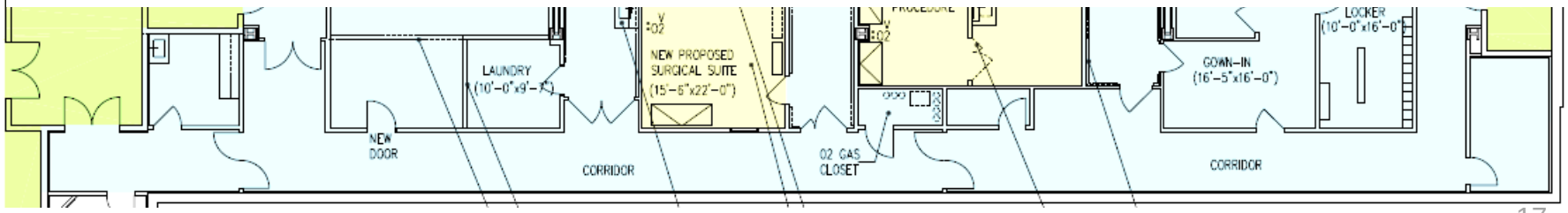


- **Cutting edge science creates collaborative demand (cCRADA)**
- **Current ACVP NHP space is limiting**
- **Opportunity for FNLCR-operated NHP facility in leased off campus space**
- **Meet ACVP needs, allow expansion of cCRADA studies, broadened access to unique ACVP capabilities**
- **Cost effective after initial facility fit out start up costs**



The Nanotechnology Characterization Laboratory's Breadth of Expertise

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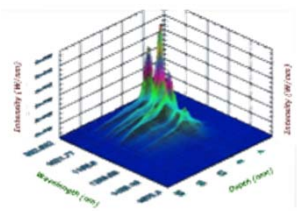
NCL testing is tailored to the platform properties, API, route of administration, and intended therapeutic outcome of the individual nanomedicine.

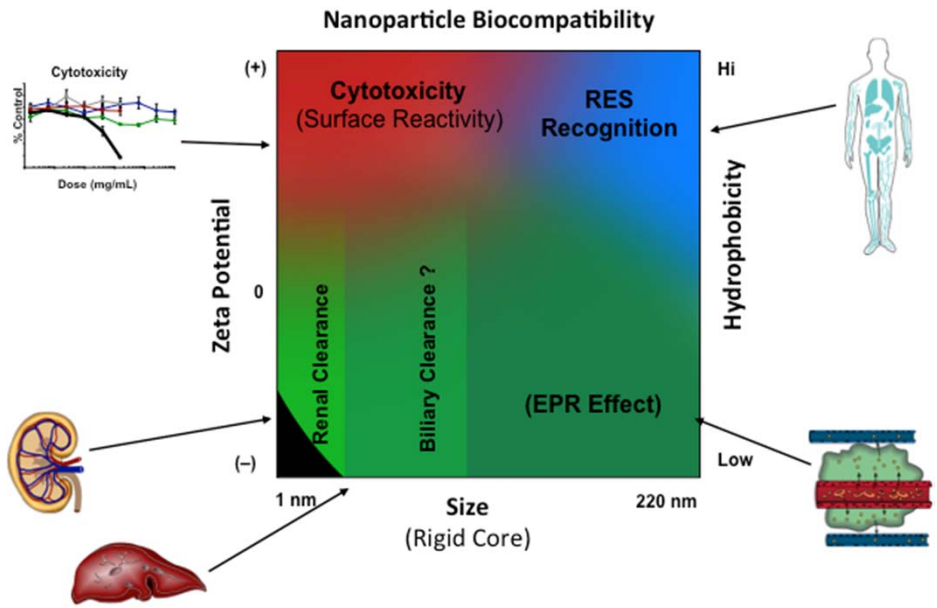
Physicochemical



In vitro

In vivo

NCL fills an unmet need.



NCL testing links physicochemical properties to biological outcomes.

Ten years of providing NCL Assay Cascade testing has given NCL expertise that is unique in the world.

NCL Outcomes

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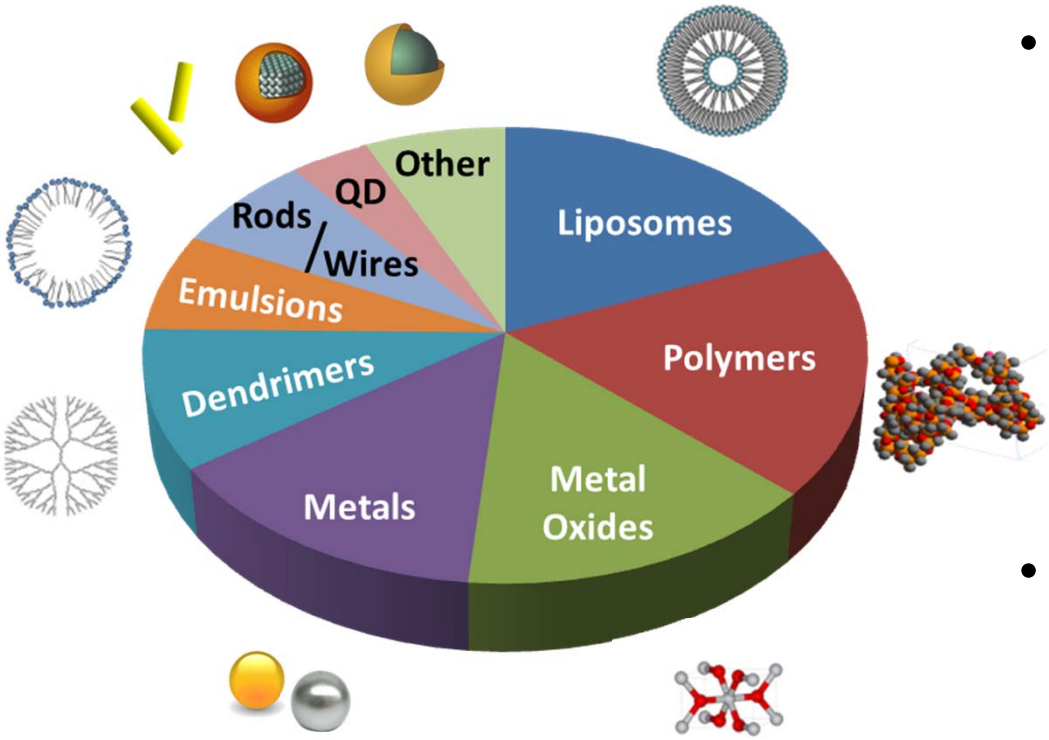

- NCL has characterized more than 300 different nanomaterials and a wide range of platforms.
  - Ten collaborators with products in clinical trials.
  - More than 100 publications
- NCL has an average of 15 active collaborations at any given time and characterizes an average of 75 samples each year.

NCL is the only lab evaluating the wide variety of platforms used in nanomedicine.

NCL Extramural Collaborators

In clinical trials

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PARABON NANOLABS
CuriRx
Massachusetts Institute of Technology
NEMUCORE MEDICAL INNOVATIONS
GE
NANO BIOTIX
PENNSTATE HERSHEY
Milton S. Hershey Medical Center
Nanospectra
LUNA NANOWORKS A Division of Luna Innovations Incorporated
Lombardi COMPREHENSIVE CANCER CENTER at GEORGETOWN UNIVERSITY
SIGNPATH Pharma
Imperial College London
SYNERGENE
Alnis BioSciences, Inc.
UCDAVIS UNIVERSITY OF CALIFORNIA
NORTHWESTERN UNIVERSITY
Celator Pharmaceuticals
Tego BIO SCIENCES
PDS Biotechnology
carigent therapeutics
ALTUS formulation
UCSB
UCLA
CEDARS-SINAI MEDICAL CENTER
Shaare Zedek Medical Center in Jerusalem
Affiliated with the Hebrew University School of Medicine
ATM
SCHOOL OF MEDICINE UT HEALTH SCIENCE CENTER SAN ANTONIO
CYTIMMUNE SCIENCES INC
EMORY
UNIVERSITY OF PITTSBURGH School of Pharmacy THE ART and SCIENCE OF EXCELLENCE
DENDRITECH, INC.
E-GEN
dnt DENDRITIC NANOTECHNOLOGIES, INC
Ensysce biosciences
THE UNIVERSITY of NORTH CAROLINA at CHAPEL HILL
UNIVERSITY of WASHINGTON
Avidimer therapeutics
University at Buffalo The State University of New York
THE STATE UNIVERSITY OF NEW JERSEY RUTGERS
City of Hope
JOHNS HOPKINS MEDICINE
OICR Ontario Institute for Cancer Research
MICHIGAN
evident TECHNOLOGIES
PRINCETON UNIVERSITY
PURDUE UNIVERSITY
Nanoprobes
KEREOS
ProNAi
Mizzou University of Missouri - Columbia
AZAYA THERAPEUTICS
BIND THERAPEUTICS
THE UNIVERSITY OF TEXAS MD Anderson Cancer Center Making Cancer History®
USF UNIVERSITY OF SOUTH FLORIDA
Northeastern University
NanoScan Imaging, LLC
Bexion Pharmaceuticals

Evolving Requests from the Nanomedicine R&D Community

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Access to Instrumentation (e.g. TEM)

How to evaluate batch-to-batch consistency

Standardized assays for size, polydispersity

Physicochemical / Analytical

CMOs/CROs with specific nano expertise, help with outsourcing and tech transfer

Access to in vivo studies required for IND

How to avoid RES / MPS uptake

Nanomedicine vs. Small Molecule Drug PK/PD

Immune Response to Nanoparticles

Targeting & EPR Effect

Biology

Methods to measure encapsulated drug ex vivo

Reformulation of APIs to match nanoparticle capabilities & disease phenotype

Multi-disciplinary

NCL testing of non-oncology nanomedicines

How to establish nanomedicine cGMP

Nanosimilars

Understanding regulatory & IND requirements

Regulatory

International regulatory harmonization

2004 2006 2008 2010 2012 2014

As nanomedicine matures, collaborators request NCL assistance in new and changing areas. NCL has developed new expertise to meet this demand.

NCL as FNL National Program

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NCL Nanotechnology Characterization Laboratory

Continue to Provide Assay Cascade Resource

- Provides "pharmaceutical mentorship" for materials scientists and engineers

Reformulation & cGMP

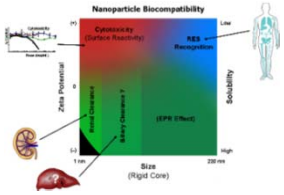
- Collaborations with Pharma, CMOs & industry consortia

Non-oncology Nanomedicines

- Infectious disease, cardiovascular, etc.

Metrology & New Methods

- Working with instrument manufacturers



Basic Research & Grand Challenges

- Immunotox
- Active targeting

Informing Regulatory

- Equivalence testing for nanosimilars
- Addressing FDA's scientific questions
- NBCDs

FDA

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Transnational Collaboration

- EU-NCL

What does success look like?

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Reinforce what already is occurring

- NCL recognized as a hub of the nanomedicine R&D community

Adapt to Maturing Requirements vs. 2004

- NCL's customer base has shifted to include Pharma and larger biotechs in addition to academics & early spin offs

NFAC Support

- Increase visibility, access & impact of nanomedicine in Cancer Centers, among clinicians & oncologists

Different Operating Model

- NCI funding supplemented by other Govt. agencies, cCRADAs with industry, foundations, grants

- Clinical translation of promising nanomedicines to clinics and patients
- Global resource for nanomedicine
- Successful reformulation of APIs, new methods development, informed & harmonized regulatory agencies, new grand challenges in nanomedicine research…

Conclusions

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- **FNLCR support for NIAID's Ebola vaccine efforts** is emerging as a prominent contribution to addressing this international medical challenge

- **Contractor partnering authorities** are being increasingly exploited to enable biomedical researchers in academia and pharma

- **The ACVP and NCL** are poised for expansion and evolution to fulfill their aspiration as "National Programs" within FNLCR