

Department of Health and Human Services  
Public Health Service  
National Institutes of Health  
National Cancer Institute

3<sup>rd</sup> Meeting of the NCI-Frederick Advisory Committee (NFAC)  
September 12, 2012

Summary Report

Conference Room 10, C Wing, 6<sup>th</sup> Floor  
Building 31  
Bethesda, Maryland

**National Cancer Institute**  
**3<sup>rd</sup> Meeting of the NCI-Frederick Advisory Committee (NFAC)**  
**September 12, 2012**

**Summary Report**

The NCI-Frederick Advisory Committee (NFAC) convened for its 3<sup>rd</sup> meeting on 12 September 2012, in Conference Room 10, C Wing, 6<sup>th</sup> Floor, Building 31, Bethesda, MD. The meeting was open to the public on Wednesday, 12 September 2012, from 9:00 a.m. to 12:15 p.m., and closed to the public on Wednesday, 12 September 2012, from 12:15 p.m. to 3:00 pm. The NFAC Chairperson, Dr. Zach W. Hall, President Emeritus, Institute for Regenerative Medicine, University of California, San Francisco, CA, presided during both the open and closed sessions.

**NFAC Members**

Dr. Zach W. Hall (Chair)  
\*Dr. James R. Baker (absent)  
Dr. J. Carl Barrett (absent)  
Dr. David Botstein  
\*Dr. Vicki L. Colvin  
Dr. Levi A. Garraway  
Dr. Joe W. Gray  
Dr. Beatrice H. Hahn  
Dr. Monica J. Justice  
Dr. Thomas A. Look (absent)  
Dr. Lawrence J. Marnett  
Dr. Jill P. Mesirov  
Dr. Garry P. Nolan (absent)  
Dr. Kenneth Olden  
Dr. Kenneth J. Pienta  
Dr. Jennifer A. Pietenpol  
Dr. Steven T. Rosen  
\*Dr. Jean Y. J. Wang (absent)  
Dr. Cheryl Willman (absent)

**Ex Officio Members**

Mr. John Czajkowski  
Dr. James H. Doroshow  
Dr. Paulette S. Gray  
Dr. Douglas R. Lowy  
Dr. Alan Rabson (absent)  
Dr. Craig W. Reynolds  
Dr. Margaret A. Tucker  
Dr. Robert H. Wiltrout

**Executive Secretary**

Dr. Thomas M. Vollberg

\* Pending Appointment

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## **I. OPENING REMARKS**

*Dr. Zach W. Hall*

Dr. Zach W. Hall, Chair, called to order the 3<sup>rd</sup> meeting of the NFAC and welcomed the Committee members. After reviewing the charge to the Committee and the mission of the Frederick National Laboratory for Cancer Research (FNLCR), he reminded members of the conflict-of-interest guidelines and confidentiality requirements. Members of the public were welcomed and invited to submit to Dr. Thomas M. Vollberg, Executive Secretary, in writing and within 10 days, any comments regarding items discussed during the meeting.

A motion was made to approve the minutes of the 30 May 2012 NFAC meeting. The motion was seconded, and the Committee unanimously approved the minutes. Dr. Hall informed the Committee that the September 2013 NFAC meeting will be held in Frederick, MD.

## **II. NCI SENIOR LEADERSHIP TEAM: DEFINING THE FUTURE OF FNLCR**

*Dr. Harold Varmus*

Dr. Harold Varmus, Director, NCI, welcomed Committee members, Ex-Officio members, and members of the public attending the meeting. Dr. Varmus noted that since he became NCI Director he has a better understanding of the structure and programs of the FNLCR, and has been impressed by the amount of scientific expertise and opportunities for growth in the Frederick facility. He said that based on what he observed and heard in past NFAC meetings, he felt the name change from NCI-Frederick to the FNLCR better reflected its scope as a national laboratory. The FNLCR is a national laboratory that should have the same impact in the field of cancer research as the Los Alamos National Laboratory, the Fermi Laboratory, or the Lawrence Berkeley National Laboratory have in their respective scientific areas. Dr. Varmus noted several developments at Frederick: a change of leadership within SAIC-Frederick, creation of a contractor-Cooperative Research and Development Agreement (CRADA) policy, and steps to improve how FNLCR's capabilities and resources are communicated to the extramural community. He recognized the Committee's input and advice during previous NFAC meetings that contributed positively to these achievements and the Committee's role in improving visibility of the Frederick operation to the greater scientific community. Progress also has been made in developing a strategic plan for the FNLCR that includes identification of large projects in research areas for which the FNLCR is uniquely qualified. Dr. Varmus thanked the NFAC for making a difference in providing suggestions to the NCI leadership that have made a difference at the FNLCR.

## **III. CANCER NANOTECHNOLOGY —AN OPPORTUNITY FOR NEW THERAPEUTICS AND DIAGNOSTICS**

*Dr. Piotr Grodzinski*

Dr. Piotr Grodzinski, Director, Office of Cancer Nanotechnology Research, Center for Strategic Scientific Initiatives, Office of the Director, NCI, provided context for the Nanotechnology Characterization Laboratory (NCL) of the FNLCR as part of the NCI Alliance for Nanotechnology in Cancer. The use of nanoparticle delivery in cancer therapy, such as for the delivery of chemotherapeutics or small interfering RNA (siRNA), or for nanoparticle-mediated thermal ablation and hyperthermia, is of increasing interest to the NCI and public and private collaborators to improve the public health. Nanoparticles made of organic and inorganic materials are largely the products of individual laboratories in academia and industry. For the purpose of uniform evaluation of these nanomaterials and in-depth understanding of their properties, the scientific community needed a battery of assays by which to characterize all varieties of nanoparticles. The Nanotechnology Characterization Laboratory (NCL) was established with a goal to provide services to academic and industrial investigators where nanoparticles could be characterized uniformly and compared. Strengths of the NCL include the ability to characterize the interactions of nanomaterials with biological systems and to compare data on interactions of different types of nanoparticles, with the ultimate goal of validating nanoparticle agents and tools for their introduction into clinical trials and cancer care.

Dr. Grodzinski spoke on nanomaterials that are finding use in cancer therapy and diagnosis with support of the NCI Nanotechnology Alliance and the NCL. He reviewed the expanding applications of nanoparticles in drug delivery with reduced toxicity profiles, including delivery of drug combinations and imaging agents. He presented a case study of docetaxel-encapsulated poly(lactic-co-glycolic acid) (PLGA) aptamer conjugate used *in vitro* for targeted drug delivery to prostate cancer cells. Results indicated that the conjugate was able to deliver more drug to cells than a non-conjugate. In addition, further *in vivo* studies in tumor-bearing mice found that a targeted conjugate nanoparticle was more effective than non-encapsulated free drug in reducing tumor size. An initial Phase I clinical trial in patients with advanced solid tumors indicated that a docetaxel targeted nanoparticle has a better pharmacological profile as compared to serum-based docetaxel administration, with greater tumor shrinkage at levels lower than the conventional serum-based docetaxel dosages. Early studies also have shown the advantages in the use of nanoparticle constructs for delivering combination therapies.

A current strategy in the NCI Nanotechnology Alliance is to use nanoparticles to deliver established, U.S. Food and Drug Administration (FDA)-approved drugs with enhanced efficacy and lowered toxicity occurring due to nanoparticle encapsulation. A next challenge is to develop drugs that have known efficacy but have not been widely used because of their high toxicity in free form. The promise for the use of this technology is the ability to maintain or increase efficacy while reducing toxicity, especially during the pre-marketing phase of drug development. A joint project of the Nanotechnology Alliance with NCI's Division of Cancer Treatment and Diagnosis (DCTD) is going to review drugs in the NCI portfolio that have a high efficacy/high toxicity profile as candidates for applying this reformulation strategy.

Dr. Grodzinski also explained the use of nanotechnology in developing integrated biobarcode microfluidic chips for *in vitro* diagnostics and monitoring of *in vivo* treatment. An advantage of these chips is that they may be multiplexed for investigating multiple biomolecular signatures at one time and can be used with any bodily fluid of interest. Dr. Grodzinski demonstrated the chips' potential, including the use of chips to measure diverse components from the same sample. Barcode chips have been also modified to monitor secretion of specific proteins from individual cells exposed to different drugs and to assess the effectiveness of therapy.

Dr. Grodzinski illustrated the national scope of the NCI's Nanotechnology Alliance commercial partners and their affiliations with academic research institutions. He illuminated the history of the NCL in providing services to those involved in the Alliance and the wider research community.

Dr. Grodzinski introduced Dr. McNeil for his presentation on the operation of the Nanotechnology Characterization Laboratory.

#### **IV. NANOTECHNOLOGY CHARACTERIZATION LABORATORY—A COMPREHENSIVE RESOURCE FOR PRECLINICAL EVALUATION OF NANOMATERIALS**

*Dr. Scott E. McNeil*

Dr. Scott E. McNeil, Director, NCL, FNLCR, reviewed the Nanotechnology Characterization Laboratory (NCL) concept of operations and its origins in 2004 as an interagency collaboration among NCI, National Institute of Standards and Technology (NIST), and the FDA, with the mission to accelerate the translation of promising nanotechnology cancer drugs and diagnostics. The NCL is within the FNLCR, run for NCI under the contract with SAIC-Frederick, and supports the extramural community by conducting preclinical characterization of nanomaterials. The NCL employs a three-stage assay cascade of physiochemical characterization, *in vitro* experiments and *in vivo* testing for safety and efficacy. The Laboratory collaborates and supports research from academia, private industry, and various federal agencies. One of the most important functions of the NCL is to provide independent validation of results at a time when research

investigations are using ever more intricate and sophisticated materials in a wider range of studies. Significant numbers of Material Transfer Agreements, clinical assays, and animal studies have been accomplished since the NCL was established, and has worked with sponsors in support of Investigational New Drug (IND) and Investigational Device Exemption (IDE) applications with the FDA. The NCL is capable of moving nanomaterials from molecular studies to in vitro and in vivo studies so that they are poised for application in clinical studies, and is positioned to take advantage of complementary capabilities within other critical research areas and activities at the FNLCR. The NCL's purview is to characterize the physical and chemical composition of supplied nanomaterials and to help establish safety and toxicity of the supplied agent. The Laboratory is only involved with production on a limited basis and does not have Good Manufacturing Process (GMP) capabilities.

Dr. McNeil described two characterization case studies to show how the NCL conducts investigations to meet its mission. The first is characterization of a nickel-arsenic (Ni-As) liposome, which initial studies showed it to be extremely toxic. The NCL conducted animal toxicity and safety studies on the Ni-As liposome and found that Ni was a major contributor to the high toxicity. In vivo animal studies confirmed the role of Ni toxicity, resulting in the NCL recommending that the developer pursue an alternative to Ni in the Ni-As liposome. The second characterization case study involved nanoparticle prodrugs, comparing the efficacy and toxicity of a lipid/prodrug self-assembling nanoformulation of docetaxel with Taxotere. Extensive characterization of the nanoparticles was conducted in vitro and in vivo to develop pharmacokinetic profiles. Animal studies, evaluating tumor volumes, animal survival, and percent change in body weight indicated that the nanoformulation was more efficacious than the equi-toxic dose of Taxotere.

The NCL has been in full operation since 2007 and is now able to point to successful studies with nanoparticles that have moved from basic molecular studies into clinical trials. Dr. McNeil said that the NCL has contributed to approval of at least one IND or Investigational Device Exemption (IDE) from the FDA each year. Examples of other successes include BIND-014, a docetaxel-encapsulated PLGA nanoparticle-aptamer conjugate (described earlier by Dr. Grodzinski), which is being tested in an ongoing Phase I safety study in patients with advanced or metastatic cancer, and completion of Phase I trials for a PEGylated colloidal gold nanoparticle-TNF $\alpha$  conjugate, with a Phase II trial in combination with Taxotere beginning this year.

Dr. McNeil described efforts to inform the research community about the NCL through presentations of findings at various research facilities and conferences. In addition, NCL hosted the "NCL Lessons Learned Workshop". The presentations include, in addition to positive findings, results that illustrate what doesn't work. The workshops and presentations are invaluable to investigators in the field and have increased interest in the NCL. NCL has been invited to give traveling versions of the Lessons Learned Workshop at several academic institutions across the country. In addition, NCL investigators and partners are publishing numerous peer-reviewed articles in a wide range of scientific journals.

A future challenge for translational nanomedicine includes meeting the need for large-scale production of nanomaterials for clinical trials. Although NCL does not have the capability at this time for large-scale production, the Laboratory is working with partners and others to test the consistency of the produced materials, assess process design and optimization, validate quality control, and provide assistance for developing methods for in-process testing. In this regard, NCL methods are becoming the de facto standard in the nanomedicine community. Outside the field of oncology, the NCL has had scientific collaborations with the FDA to determine the effects of  $\gamma$ -radiation on nanomaterials and with the National Institute of Environmental Health Sciences (NIEHS) for its U01/U19 Nanotechnology Centers of Excellence. The NCL has matured and now is a leader in the nanotechnology field and is sought out as a model for other countries that are seeking to develop this field.

**In the discussion, the following points were made:**

- Members encouraged the NCL to review the impact of the lack of GMP capability and consider the advantages that attaining standards will bring to large-scale production. Members pointed out that emerging nanotechnologies include a great diversity of nanoparticle formulations. This contributes to the challenges of growing facilities that are capable of GMP production, and will require the maturation of not just one center of GMP capability but instead multiple centers. It was recognized that NCL interactions are primarily with sponsors who originate the nanoparticle concept and not with GMP production facilities. NCL should consider how it may assist the development of quality measures that sponsors may use to obtain adequate production quality from the contract research organizations with whom they contract for GMP capability. Development may require intermediate level production for pilot studies, or intermediate scale-up as a model that informs large scale production methods and quality measurements. NCL, interacting as a consultant to investigators/sponsors in their development of scale-up methods, could assist the growth of multiple, diverse GMP capabilities that address the wide variety of nanoparticle technologies.
- The NCL is a free resource for sponsors, such as those from academia. NCL's engagement by sponsors has come at all stages of development from conceptual to production. It should be left to partners such as pharmaceutical companies to move the nanomaterials into a GMP laboratory for further development.
- The NCL could be the bridge to translation in the field of nanomaterials, but there is a need to address issues of Intellectual Property (IP) rights throughout that process, which is a challenge for the high-risk, innovative projects. The NCL encourages sponsors to develop their IP position prior to working with the NCL. The cost of translational efforts grows exponentially throughout a project, and the NCI Alliance for Nanotechnology program has formed a consortium of 12 members, including industry partners in large pharmaceutical and biotechnology sectors, to address this issue.
- Members acknowledged the NCL's significant accomplishments in providing comprehensive characterization of nanomaterials where this capability did not exist previously.
- NCL animal studies generally show that the use of nanomaterials is beneficial for reducing the toxicities of chemotherapeutics.
- Members recognized that the repurposing of previously effective but highly toxic drugs using nanoparticles that maintain effectiveness but reduce toxicity is an emerging success story for this technology.
- Members requested that speakers to the NFAC be directed to provide explicit information on how their program or project is integrated with the NCI and the FNLCR. This also should include a statement on affiliation of the speaker, components of the program or project conducted by NCI scientists, SAIC-F scientists, or scientists with other affiliations, and the location(s) where the work is being performed.

**V. THE VACCINE PILOT PLANT: USE OF FFRDC FOR URGENT NATIONAL NEED**

*Drs. Richard Schwartz and John R. Gilly*

Dr. Richard Schwartz, Chief, Vaccine Production Program Laboratory (VPPL), Vaccine Research Center, National Institute of Allergy and Infectious Diseases (NIAID), NIH, informed members of ongoing activity at the VPPL in Frederick that is funded through the Federally Funded Research and Development Centers (FFRDC) mechanism. The NIAID Vaccine Research Center (VRC) is involved in the rapid advancement of promising vaccine candidates from the laboratory to the clinic. The scope of the VRC covers

the spectrum of vaccine development from basic and applied virology and immunology, preclinical immunology and animal models, and translation research and development, through clinical trial vaccine testing. The VRC maintains collaborations with other federal agencies and nongovernmental organizations for advanced clinical evaluation. Examples of vaccines researched include gene- and protein-based vaccines and broadly neutralizing monoclonal antibodies (mAbs) for human immunodeficiency virus (HIV), emerging viruses such as Chikungunya, and flaviviruses (Ebola and Marburg) and alphaviruses (V, E, and WEEV) important for biodefense. The VRC also works on seasonal and universal influenza viruses. The VPPL is responsible for translation of ideas and products through development and production for all VRC products, and is designed to concurrently develop two new clinical products within the same timeframe.

Dr. Schwartz addressed the need of the VRC for the Vaccine Clinical Materials Program (VCMP), which is operated by a contractor responsible for GMP production of all VRC clinical products. The contractor also is tasked with the maintenance of ongoing clinical trials. The advantage for use of a FFRDC contractor for these services allows many of the services to be conducted internally instead of having them conducted commercially. Because the time, costs, and technologies needed for vaccine production and GMP, it is more efficient to use a contractor for production and allows the VRC to better meet its mission of rapid development and movement of promising vaccine candidates from the laboratory to the clinic. The use of the VCMP through the FFRDC also is preferred because it manages a contractor-operated pilot plant for the VRC and has GMP capabilities. This mechanism expedites the flow of vaccine candidates from research to the clinic quicker than if these functions were acquired through outside commercial interests.

After the September 2011 terrorist attacks on the United States, the VRC and VCMP expanded their capabilities to include biodefense, which led to expansion of the Vaccine Pilot Plant (VPP) facility to include adequate processing capacity for potential biodefense vaccine candidates. The expansion included increasing the drug production filling capacity and full GMP utilities. Dr. Schwartz reviewed projects in the VPPL and VPP and production of products of the VCMP, including those produced at the VPP or through subcontracts. Successes of VPPL development and VCMP production include the H1N1 vaccine in 2009 and the Chikungunya virus-like particle vaccine.

Dr. John A. Gilly, Director, Vaccine Clinical Materials Program, SAIC-Frederick (SAIC-F), Inc., VRC at Frederick, FNLCR, provided examples of VCMP sourcing for specific needs and listed VRC active subcontracts through the VCMP. The VCMP operates the Vaccine Pilot Plant and has capability and much experience with vaccine production employing pDNA. Also, the VCMP has the ability to issue subcontracts to outside contract research organizations (CROs). Resources accessed through these subcontracts include development of feasibility batches or material for evaluation in early-phase studies, toxicology, animal studies, and GMP production. The NIH and SAIC-F work together to select subcontractors, with SAIC-F VCMP assuming management responsibilities after the selection. An advantage of the subcontracts is to make resources available that might not otherwise be available at the FNLCR or other NIH facilities. An example of the type of project using a subcontractor is for the production of a mAb, where responsibility for production of the antibody is transferred to a subcontractor after development by the VCMP.

Dr. Gilly informed members of the assessment conducted by the VCMP to show the value of in-house project costs to the value of delivered products. The variety of products developed by the VRC is extensive and tracked to determine the efficiency of the program in meeting program needs. A subcontractor's ability to meet VRC deadlines also has been critical for progress and the success of the program. For those subcontractors who could not meet deadlines, the VRC works with them to identify roadblocks and challenges in missed deadlines. Cumulative data from the beginning of the NIAID VRC VCMP in 2006 indicate that among the products are 28 INDs, 54 clinical protocols with 22 drug product types (plus 4 placebo types), and the production and release of 46 drug product lots and 17 placebo lots.

**In the discussion, the following points were made:**

- The VCMP should consider way to serve the broader community. The VCMP currently serves as an informal resource, sharing information, and offers a variety of vector approaches and a wealth of experience.
- The prioritizing of VCMP projects is an ongoing process and is restricted to current capabilities, time, and resources of the VRC.
- Because production of mAbs is a broad platform and there could be an emerging need to quickly produce these in large amounts, the amount of time such production would take under current capabilities at the VRC was discussed. A potential of this program to serve as national resource to assist in responding to an emerging situation was mentioned as something to be considered. Program staff responded that, to produce antibodies quickly at kilogram scale, a stable, defined cell line and an established platform method should be present so that a process will not have to be created anew. It was mentioned the VCMP has experience to draw upon outside resources for vaccine production through subcontracts. In addition, the VCMP also would have access to other excellent resources within SAIC-F to compete and manage such subcontracting needs.

**VI. SAIC-F PARTNERING, ATRF, AND THE OPERATIONAL ENABLEMENT OF LIFE SCIENCES MISSIONS**

*Dr. Atsuo Kuki*

Dr. Atsuo Kuki, Chief Technology Officer, Frederick National Laboratory, SAIC-Frederick, FNLCR, NIH, thanked NFAC members for the opportunity to address the committee and explain SAIC-F partnering, the Advanced Technology Research Facility (ATRF), and the operational enablement of life sciences missions. In the time since the May 2012 NFAC meeting, the SAIC-F has been authorized to enter partnering agreements with the external cancer research community through the contractor-CRADA (cCRADA) mechanism. Additionally, the SAIC-F partners with the extramural community through Technical Services Agreements (TSAs) to perform discrete, fixed-priced services. It is expected that approximately 12 Technical Service Agreements (TSAs) will be completed by the end of this month. Partners are drawn from the breadth of the extramural community, including partners from government, academic, entrepreneurial (SBIR/STTR) and large private sector companies. The pre-approved TSAs will support a wide range of activities, such as reagent assays and integrated *in vivo* services. Examples of the TSAs were provided to show the integration of services that derive from FNLCR support areas, such as the AIDS and Cancer Virus Program (ACVP). In addition, the ATRF is open and operational, and expertise now exists in the FNLCR to enable and support the life sciences missions.

The cCRADA and TSA mechanisms are intended to support a vigorous external research community in areas of interest to the NCI and other NIH Institutes and Centers (ICs). Dr. Kuki reported positive engagement from the SAIC-F scientists in FNL, such as the receipt of three Concept Approval Forms (CAFs) within 8 days of authorization of the cCRADA research pipeline, which then move into formal approval of the CAFs with NCI Lead Program representatives. Each c-CRADA requires full negotiation in a way that is customized to its project. SAIC-F is in discussion with four other potential partners and expects to receive additional CAFs pertaining to these cCRADA opportunities in the near future. Now that the FNLCR is accepting CAFs and the ATRF is functioning, the next priority for SAIC-F will be to begin the process of focusing on the strategic impact of the FNLCR on long-term NCI priorities and further integration of the research programs.

Dr. Kuki shared four examples of integrated multi-laboratory experiments that illustrate the operational enablement of life sciences missions that occurs at FNLCR, such as the NCL nanocharacterization integrated assay cascade and the ACVP's vaccine/therapy non-human primate integrated study. Other

examples of this kind of integration also include imaging and molecular pathway studies within the Laboratory Animal Sciences Program (LASP), and national biospecimen networks such as the Cancer Human Biobank (caHUB). To detail the extent of integration, an example from LASP was illustrated from a DCTD study on small animal imaging to determine dosing uptake of [<sup>89</sup>Zr] - panitumumab in an animal tumor model. Results indicated that tumor uptake directly correlated with *Her-1* expression. The next step for this study is to proceed in plans to investigate this in clinical trials. Another example of integration is the Information Systems Program (ISP) hub for the National Biospecimen Network (NBN), which is intended to provide available biospecimens for studies at the NCI and FNLCR. The integration of functions that is present within the ISP provides a permanent foundation that is useful to support meaningful biospecimen collection. The Genotype-Tissue Expression (GTEx) project already has amassed more than 10,000 normal human tissue specimens of almost all organs and organ systems using a rapid autopsy network. GTEx is operated by NCI's Biorepositories and Biospecimen Research Branch, and SAIC-F conducts histopathology on all samples as part of the Pathology Resource Center. There is a high level of quality control in all biospecimen collection and storage operations. These examples demonstrate integrated cascades of multi-laboratory high-level capabilities that in combination support complex multidisciplinary experimental investigations, and this ability to assemble collections of individual laboratory capabilities is a strength of the FNLCR that enables strategic missions within NCI priorities. Characteristics that are seen in the best FNLCR examples are: multi-technology integrated protocols, relentless emphasis on quality control, a logistical operational focus, familiarity with a range of contractual and regulatory complexity, the building of *de facto* standards and the ability to offer implementation of these to new partners.

**In the discussion, the following points were made:**

- FNLCR's mission of advancing translational medicine and mission as a National Laboratory may present opportunity to integrate with the mission of the National Center for Advancing Translational Sciences (NCATS). NCI's intramural program has a number of existing collaborations and productive interactions with NCATS. Opportunities for catalytic interactions of FNLCR with the NCATS can be anticipated.
- Some members supported a conservative approach in expanding the FNLCR's scope of activities. Another approach may be to focus on those activities that the FNLCR does well and leave other activities to partners or others. NCI and FNLCR leadership recognizes this concern and is providing careful consideration for the types of projects being planned for partnerships. Matrix models have been useful at other national laboratories. Adoption of a matrix approach could be applied to illustrate how demonstration cCRADA projects match with the strategic mission and FNLCR scientific capabilities, and serve as a vision of scientific priority for future cCRADA projects.
- The establishment of the cCRADA and TSA mechanisms should afford the FNLCR opportunities to expand its marketing to the scientific community for specific projects. To create the mantle of a "National Laboratory," it will be important to identify the customers for FNLCR and to publicize the unique capabilities and services of the FNLCR to help outreach to a wider audience than in the past. The FNLCR and SAIC-F leadership is exploring many ways to address and publicize key mission areas and services.

**VII. CLOSED SESSION**

*This portion of the meeting is being closed to the public in accordance with the provisions set forth in section 552b(c)(9)(B) Title 5 U.S.C., and section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix 2).*

Members were instructed to exit the room if they deemed that their participation in the deliberation of any matter before the Committee would be a real conflict or that it would represent the appearance of

a conflict. Members were asked to sign a conflict-of-interest/confidentiality certification to this effect.

The committee met in closed session for the purpose of examining and discussing a Draft FNLCR Strategic Plan. Members absented themselves from the meeting during discussions for which there was potential conflict of interest, real or apparent.

**IX. ADJOURNMENT**

*Dr. Zach W. Hall*

Dr. Hall thanked the Committee members and other invitees for attending. There being no further business, the 3<sup>rd</sup> meeting of the NFAC was adjourned at 2:40 p.m. on Wednesday, September 12, 2012.

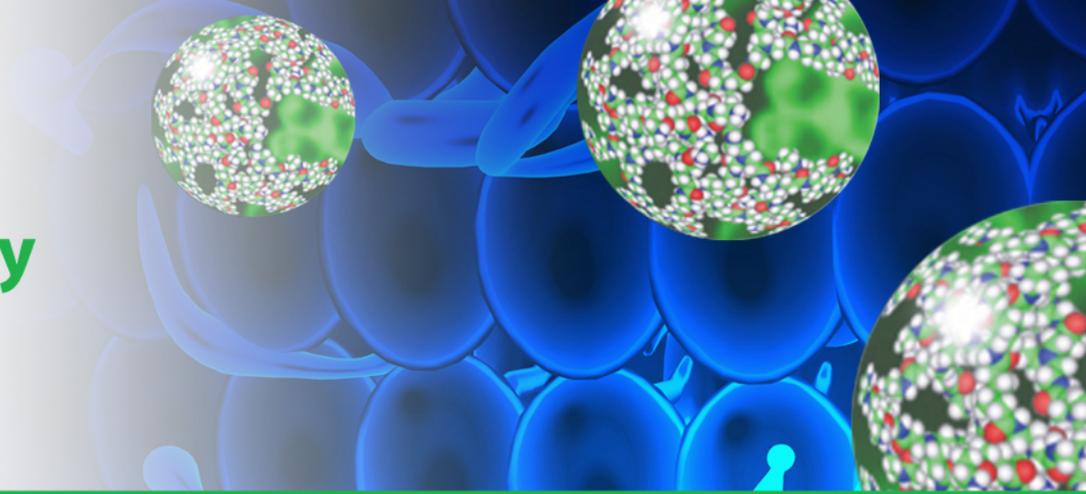
\_\_\_\_\_  
Date

\_\_\_\_\_  
Zach W. Hall, Ph.D., Chair

\_\_\_\_\_  
Date

\_\_\_\_\_  
Thomas M. Vollberg, Ph.D., Executive Secretary

NCI **Alliance** for  
**Nanotechnology**  
in Cancer

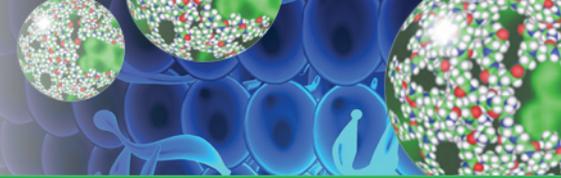


## Cancer Nanotechnology – Opportunity for Novel Therapeutics and Diagnostics

September 12, 2012  
NFAC meeting

Piotr Grodzinski, Ph.D.  
Office of Cancer Nanotechnology Research, NCI

# NCI Alliance for Nanotechnology in Cancer Phase II (start in 2010)



**Centers for Cancer  
Nanotechnology  
Excellence (CCNE)  
U54 Cooperative Agr.**

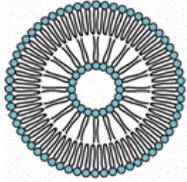
**Cancer Nanotechnology  
Platform Partnerships  
U01 Cooperative Agr.**

**Multi-disciplinary Training  
Awards: K99/R00 and R25**

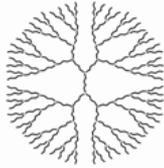
**Nanotechnology  
Characterization Laboratory**

- **Scientific output** – over 500 peer-reviewed journal papers and close to 100 patents and patent submissions published
- **Clinical translation** – over 70 companies in the space of diagnostics and therapy are associated with the program. Majority of them are start-ups.
  - 16 clinical trials are associated with program projects
  - several companies are in pre-IND discussions with FDA
  - formed a consortium to involve large pharma and biotech companies to assist translational process
- **Provocative Questions RFA** – disproportionately large number of awards made to nanotechnology based proposals – total of 7: 6 R01s and 1 R21

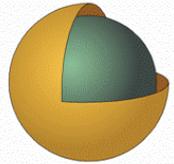
# Different Particles and Different Methods of Making Them



Liposome



Dendrimer



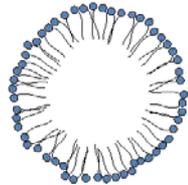
Gold nanoshell



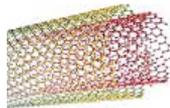
Quantum Dot



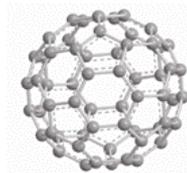
Colloidal gold



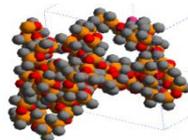
Nanoemulsion



Carbon nanotube



Fullerene



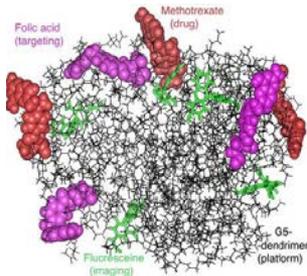
Polymers

**Why we formed NCL? - need for a comprehensive assay kit to evaluate different nanomaterials**

- Covalent organic synthesis
  - Dendrimers, Polymers
- Self-assembly
  - Liposomes, Emulsions, Micelles
- Crystal formation
  - Metal nanoparticles, Quantum dots
- Laser ablation, CVD
  - Fullerenes, carbon nanotubes
- Grinding/milling/fabrication
  - Organic and Inorganic Crystals

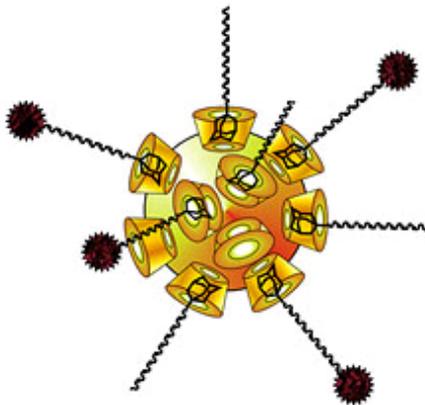
# Nano-therapy Strategies

## Delivery of chemotherapeutics



J. Baker, et al., *Cancer Res.*  
(2005) 65 : 5317

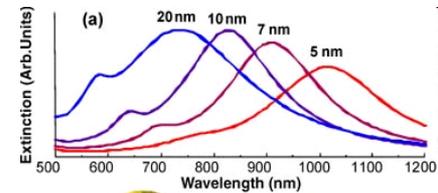
## Delivery of siRNA



M. Davis et al. *Nature* (2010) 464: 1067

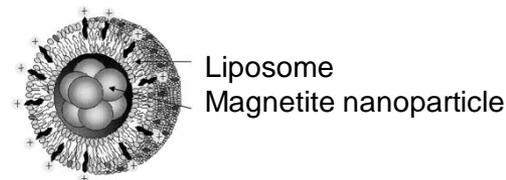
## Hyperthermia

### Photothermal

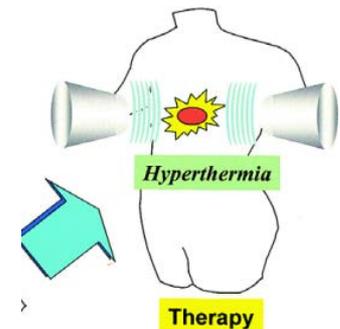


N. Halas, J. West et al,  
*Ann Biomed Eng.*  
(2006) 34: 15

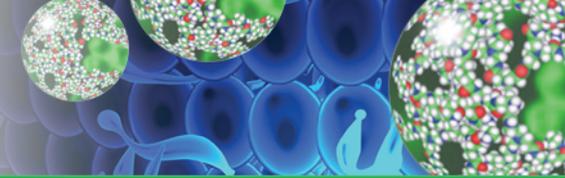
### RF-heated



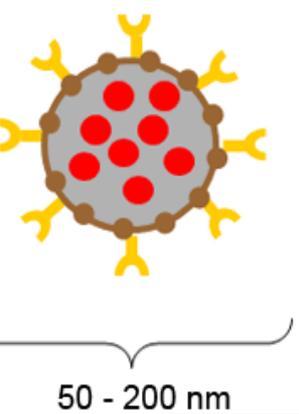
A. Ito et al., *J. of Bioscience and Bioeng.*  
(2005 100: 1)



# Docetaxel-Encapsulated PLGA Nanoparticle-Aptamer Conjugates



## Polymeric platform for drugs or biologics delivery



- Targeting ligand → aptamers (nonimmunogenic, stable in a wide pH range & temperature)
- Surface functionalization → PEG (increased stability)
- Polymer matrix → PLGA (controlled released polymer)
- Therapeutic payload → small molecules, peptides or nucleic acids

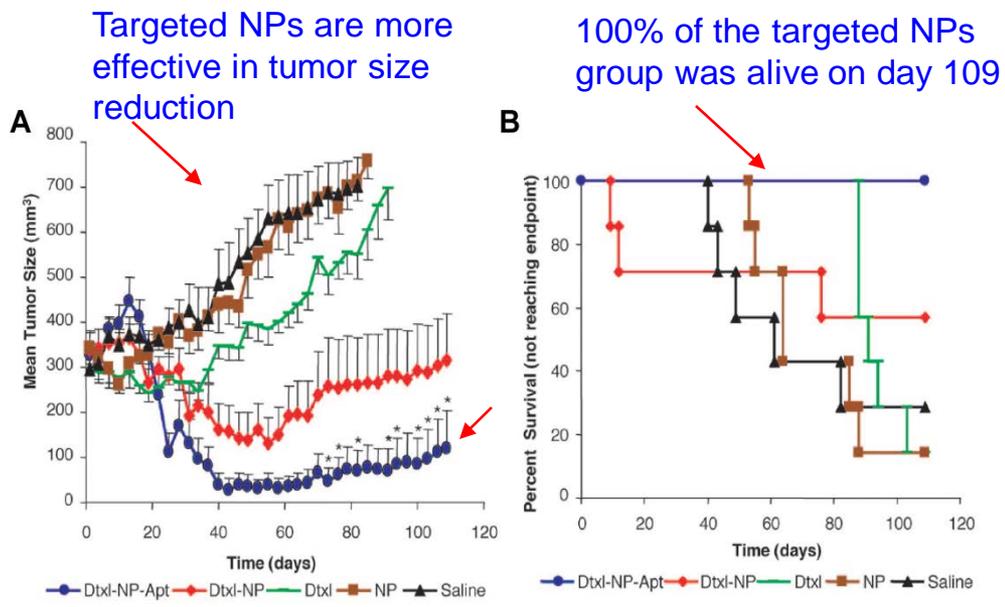
**Advantage:** increased efficacy & reduced toxicity

### Approach:

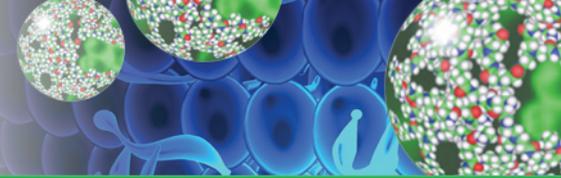
- Docetaxel delivery to prostate cancer
- Aptamer recognizing PSMA on prostate cancer cells (LNCaP cell line)
- The comparative efficacy study of intratumoral injection (40 mg/kg) was evaluated over 109 days

Langer & Farokhzad – MIT – Harvard CCNE

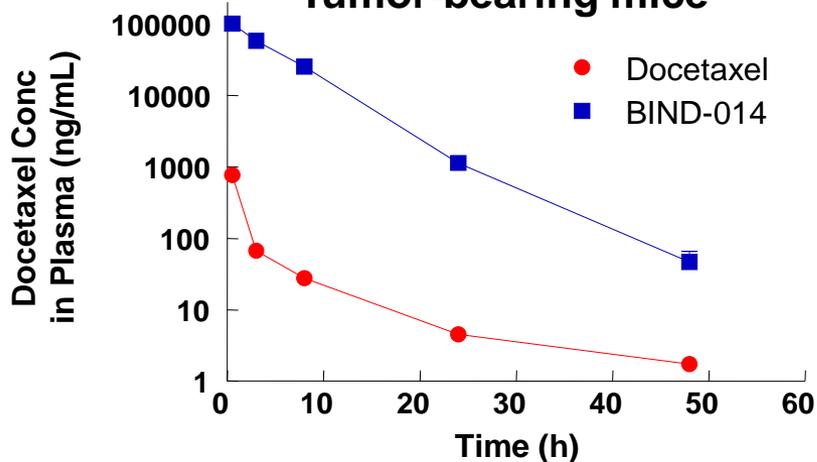
PNAS (2006) 103: 6315  
PNAS (2008) 105: 2586



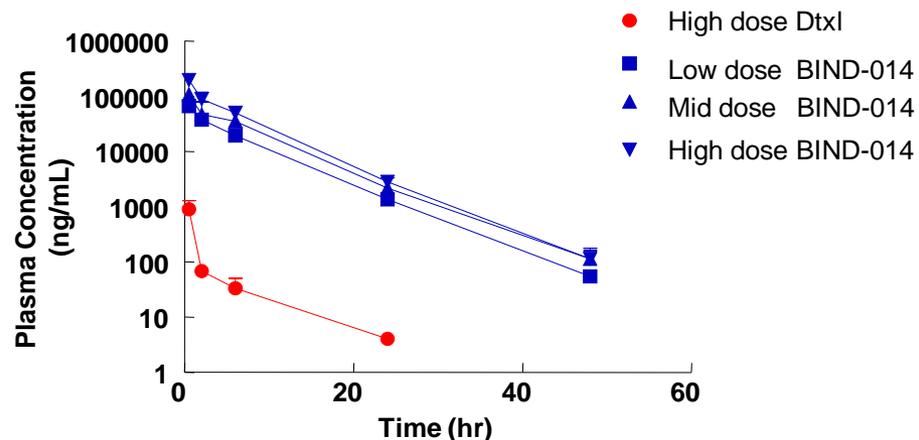
# Comparison of Delivery Profiles for Docetaxel with and without NPs



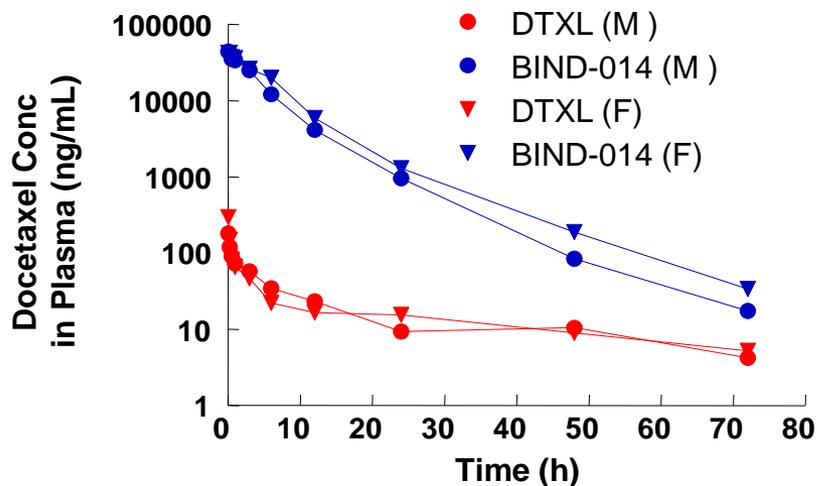
## Tumor-bearing mice



## Rats

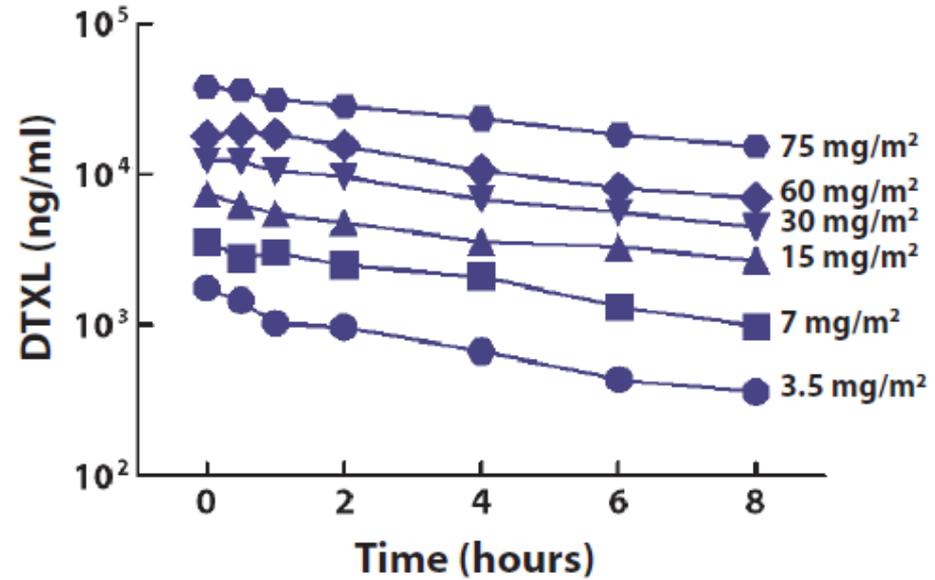
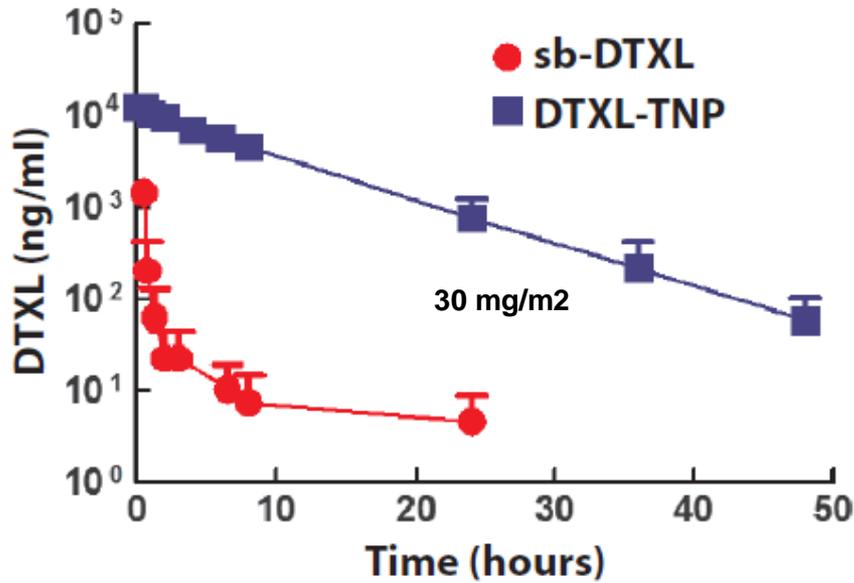
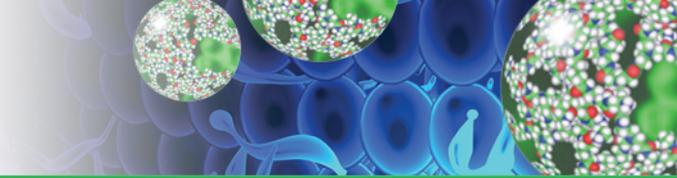


## Non-human primates



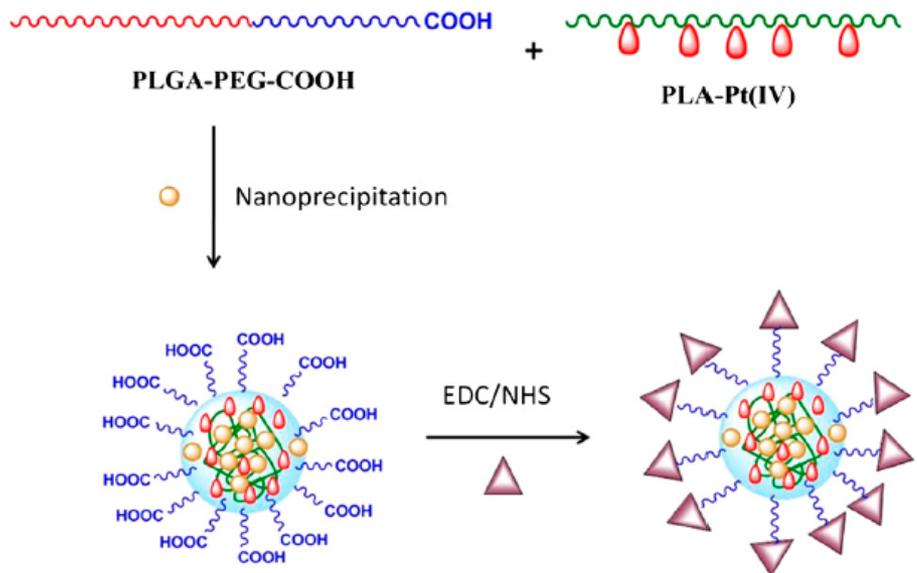
- Long-circulating particles and controlled drug release provide for well-controlled and differentiated PK profile across species
- sb-DTXL elimination from plasma occurs very quickly

# Phase I Clinical Trial – Patient's Data



Hrkach J, Von Hoff D, Langer R et al, Science Transl Medicine (2012) 4:1

# Combination Therapies Using Nanoparticles



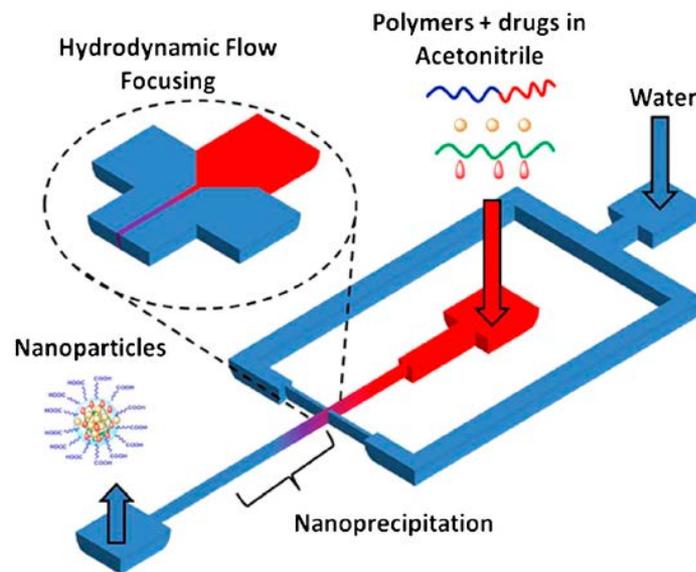
Pt(IV)-monosuccinate (Hydrophilic Drug)    
 Docetaxel (Dtxl) (Hydrophobic Drug)    
 A10-Aptamer (Targeting Ligand)

## Multiple drugs in one NP

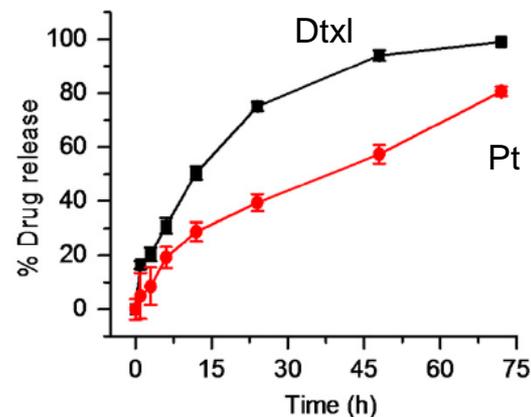
- delivery of a correct ratio of each drug to the target;
- synergistic therapeutic effects;
- ability to control drug exposure temporally

Kolishetti N, Langer R, Farokhzad OC et al., PNAS (2010) 107:17939

A



Microfluidics NP synthesis



In vitro release kinetics in PBS from NPs

## Current

- Using nanoparticles to deliver established chemotherapeutic drugs while enhancing their efficacy
- Existing drugs are readily available and provide a direct, established comparator

## Challenge

- Can we ‘resurrect’ drugs which have high potency, but also high toxicity and failed in free form delivery using nanoparticle-based delivery?

## Action plan

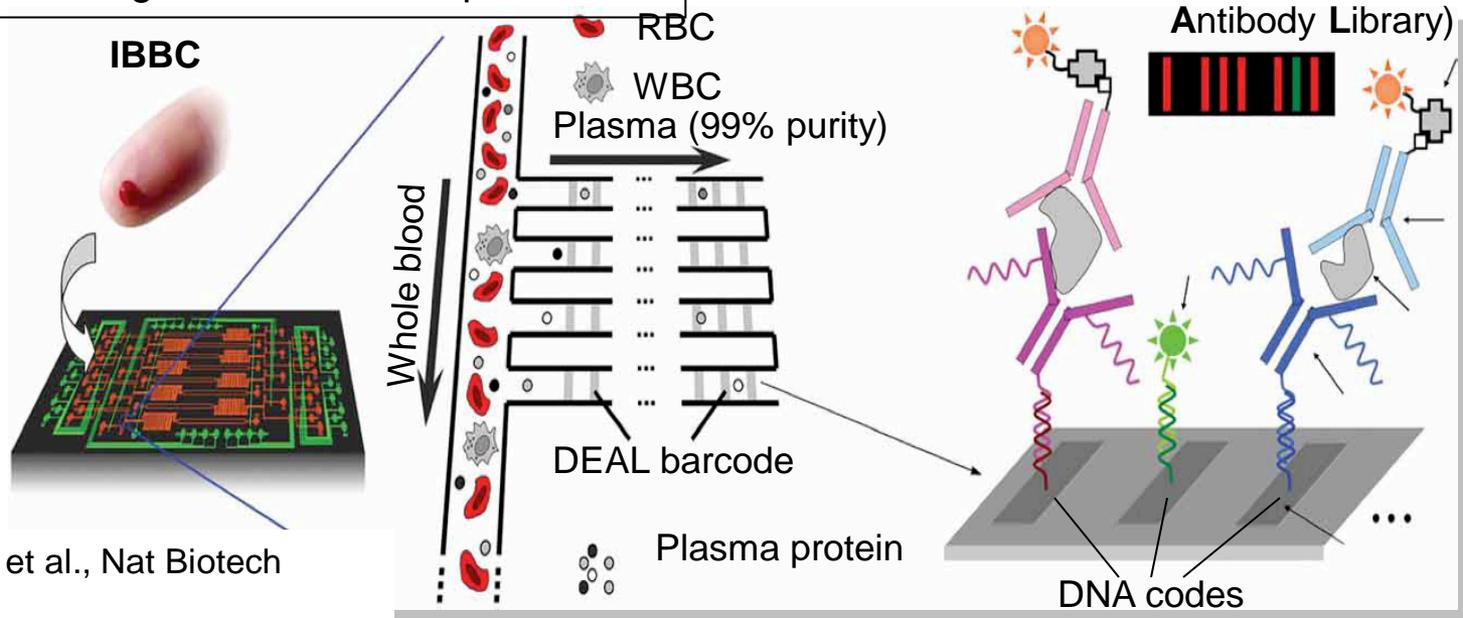
- Proposing a joint development with DCTD to look at few drugs from NCI stockpile.

# Integrated Biobarcode Microfluidic Chip

## *In vitro diagnostics and nanotechnology*

- Modular diagnostics – work with bodily fluids, such as blood, serum, urine, or saliva
- Multiplexing – interrogate several biomolecular signatures at the same time
- Techniques to monitor and capture circulating tumor cells from blood
- Multifunctional capabilities – one platform capable of detecting nucleic acid and protein

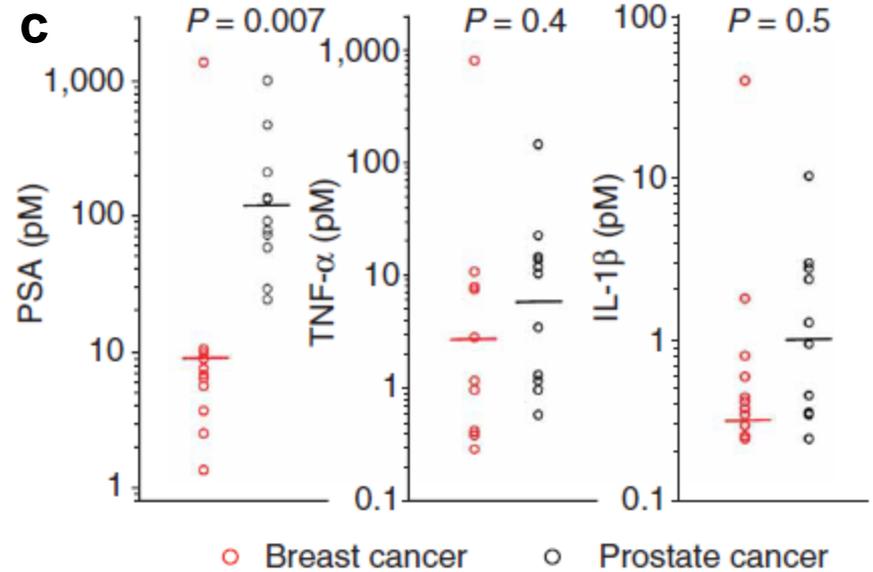
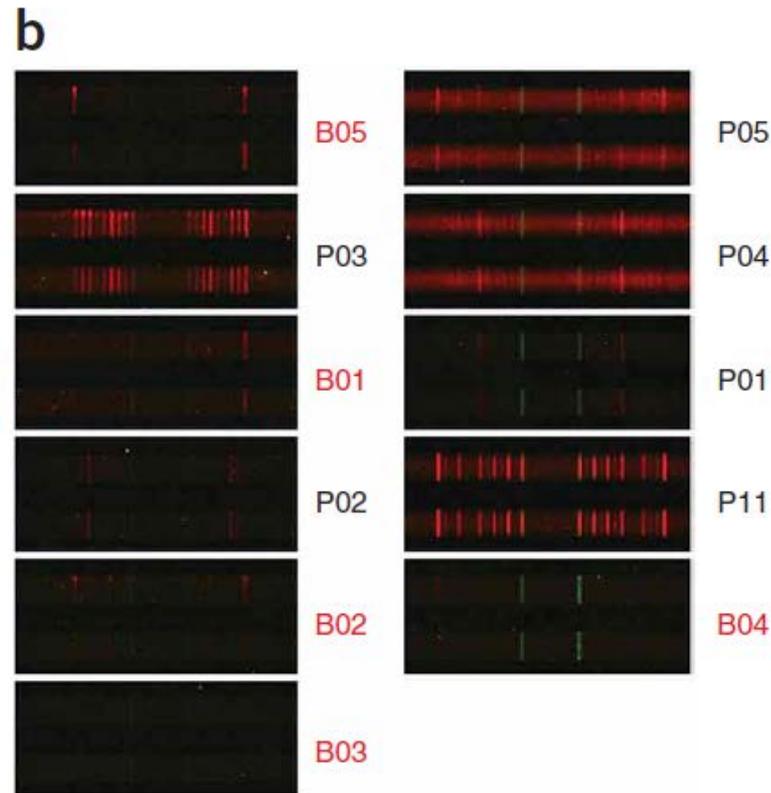
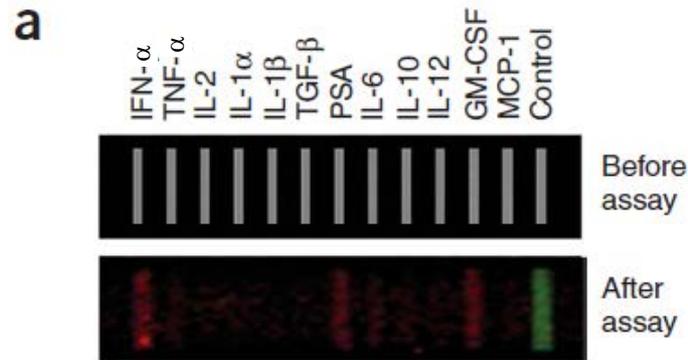
- IBBC - microfluidic device for multiplexed detection of proteins in whole blood sample
- DEAL - single-strain (ss) DNAs bound to antibodies that are labeled with complementary ssDNA oligomers
- Currently tested for molecular and functional analysis of prostate, breast, melanoma, and glioblastoma
- Less than 10 min working time



Fan R, Heath JR et al., Nat Biotech (2008) 26: 1373

Shi Q, Hood L, Mischel PS, Heath JR., Proc Natl Acad Sci U S A (2012) 109:419

# Multiplexed Protein Measurements in Clinical Samples

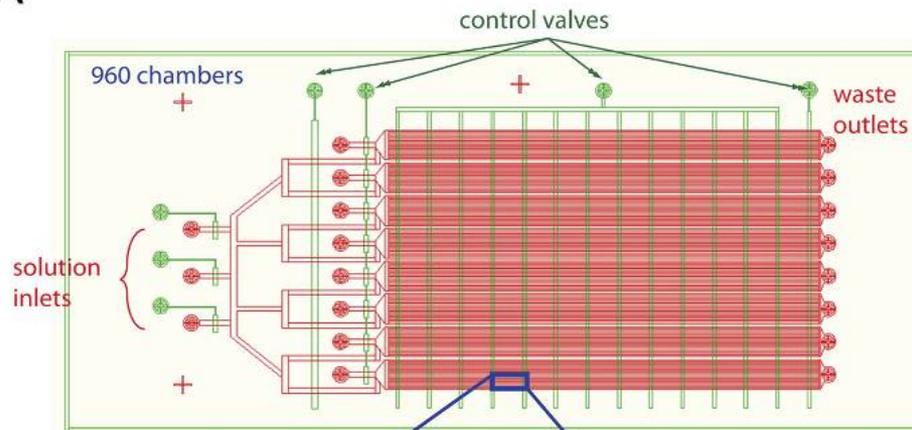


Multiplexed protein measurements of clinical patient sera, (a) Layout of the barcode array used in this study, (b) Representative fluorescence images of barcodes used to measure the cancer marker PSA and 11 cytokines from cancer patient serum samples. B - samples from breast cancer patients; P - samples from prostate cancer patients, (c) Distribution of estimated concentrations of PSA, TNF- $\alpha$  and IL-1 $\beta$  in all serum samples. The horizontal bars mark the mean values.

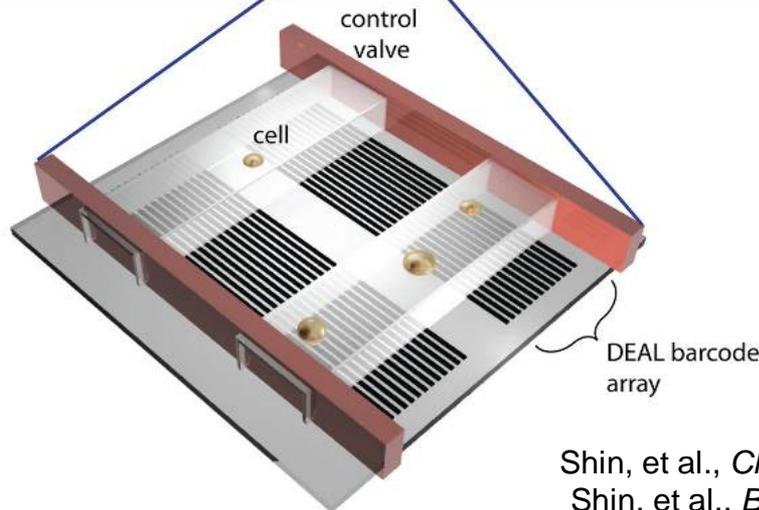
# Single Cell Barcode Chip

Monitor secretion of proteins from individual cells to assess effectiveness of therapies

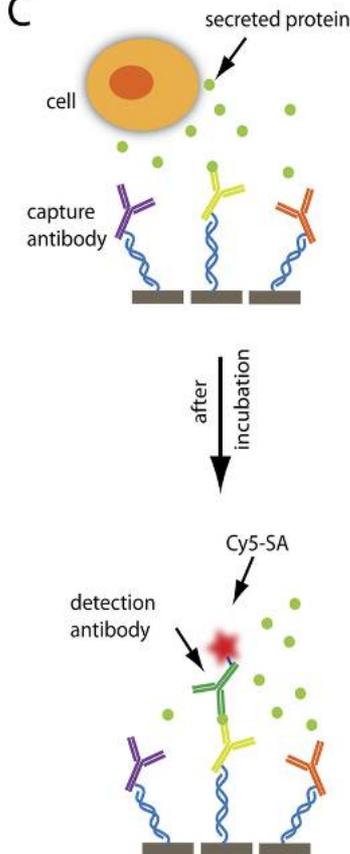
A



B



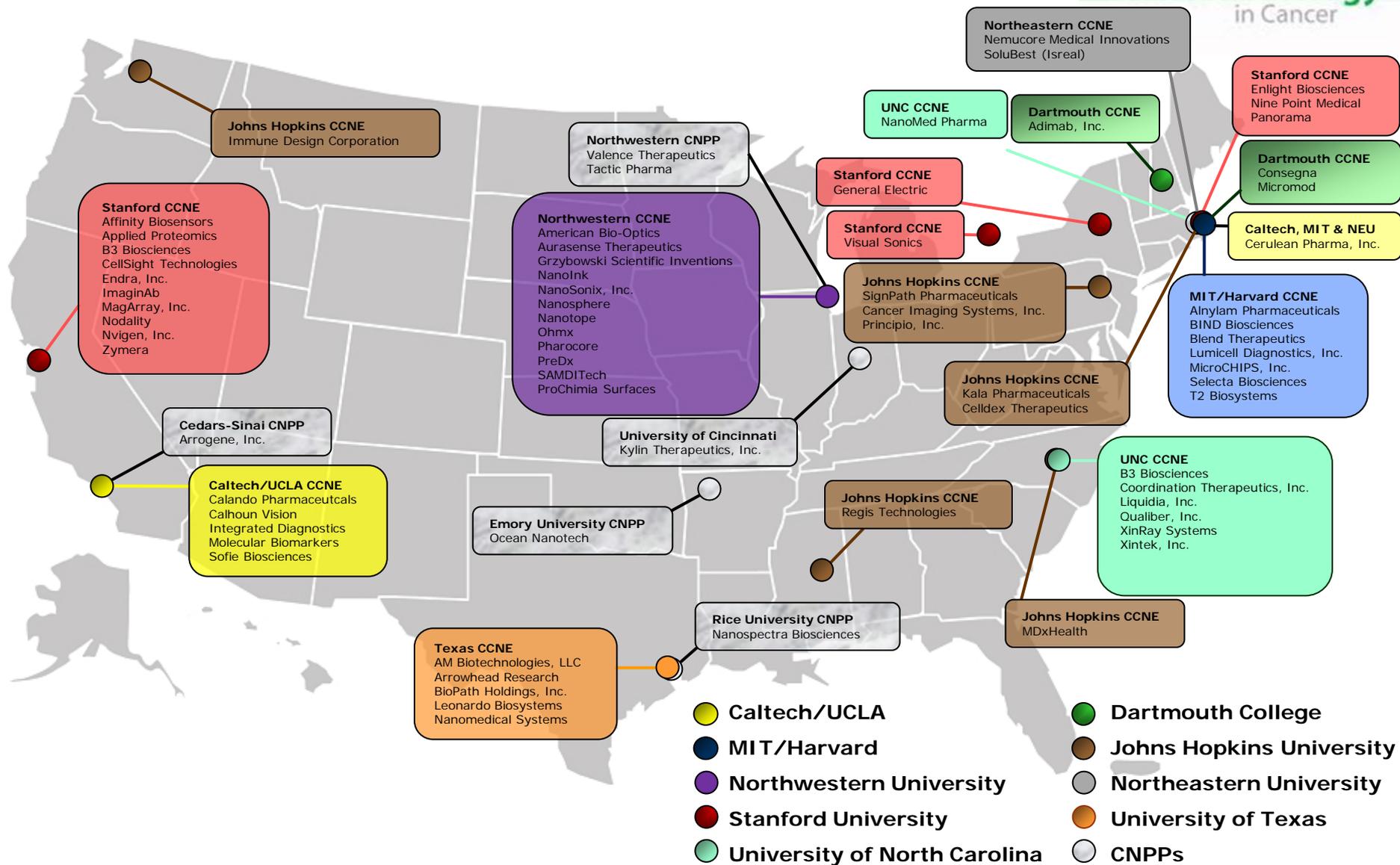
C



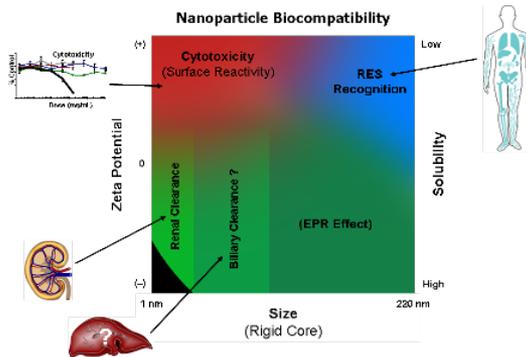
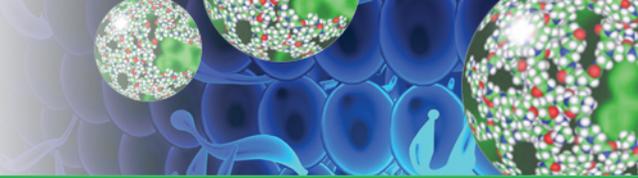
Shin, et al., *ChemPhysChem* 2010 (molecular patterning for these chips)  
Shin, et al., *Biophys J* 2011 (macrophage secretome, information theory)  
Ma, et al., *Nature Medicine*, 2011 (applied to melanoma immunotherapy patients)

# NCI Nanotechnology Alliance Commercial Partners

NCI Alliance for  
**Nanotechnology**  
in Cancer



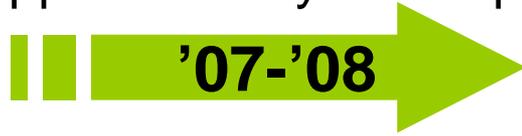
# Nanotechnology Characterization Laboratory: Serving the Community



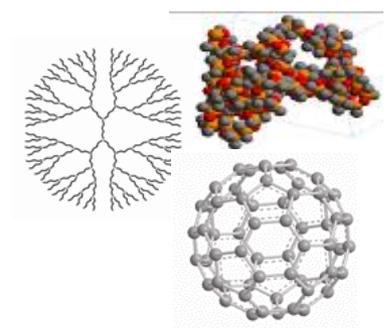
At capacity,  
More mature concepts  
Work with NIEHS



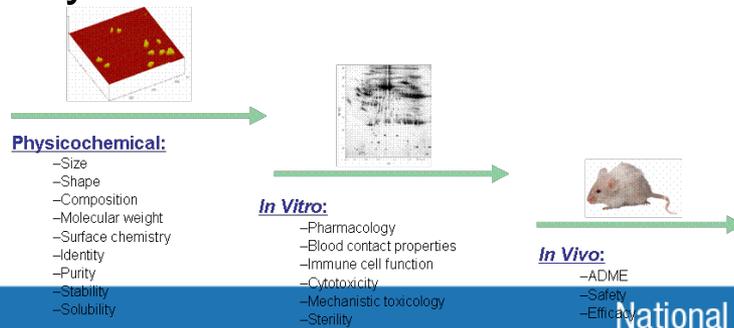
Characterization, SAR studies,  
Support of early development



Receipt of materials



Development of assay cascade



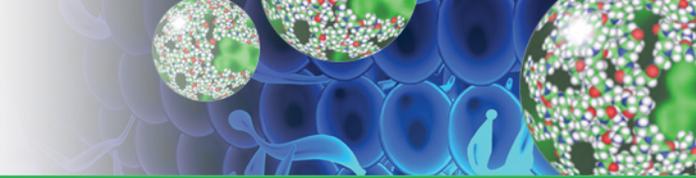
**ANNEX 2**  
NATIONAL CANCER INSTITUTE  
NANOTECHNOLOGY CHARACTERIZATION LABORATORY  
**MATERIAL TRANSFER AGREEMENT**  
The National Cancer Institute (NCI) Nanotechnology Characterization Laboratory (NCL) has been designed to investigate the use of nanoparticulate material for the advancement of cancer research. This Material Transfer Agreement (MTA) permits the exchange of materials and associated information between NCI and the party defined below as "Provider."



Initiation and planning

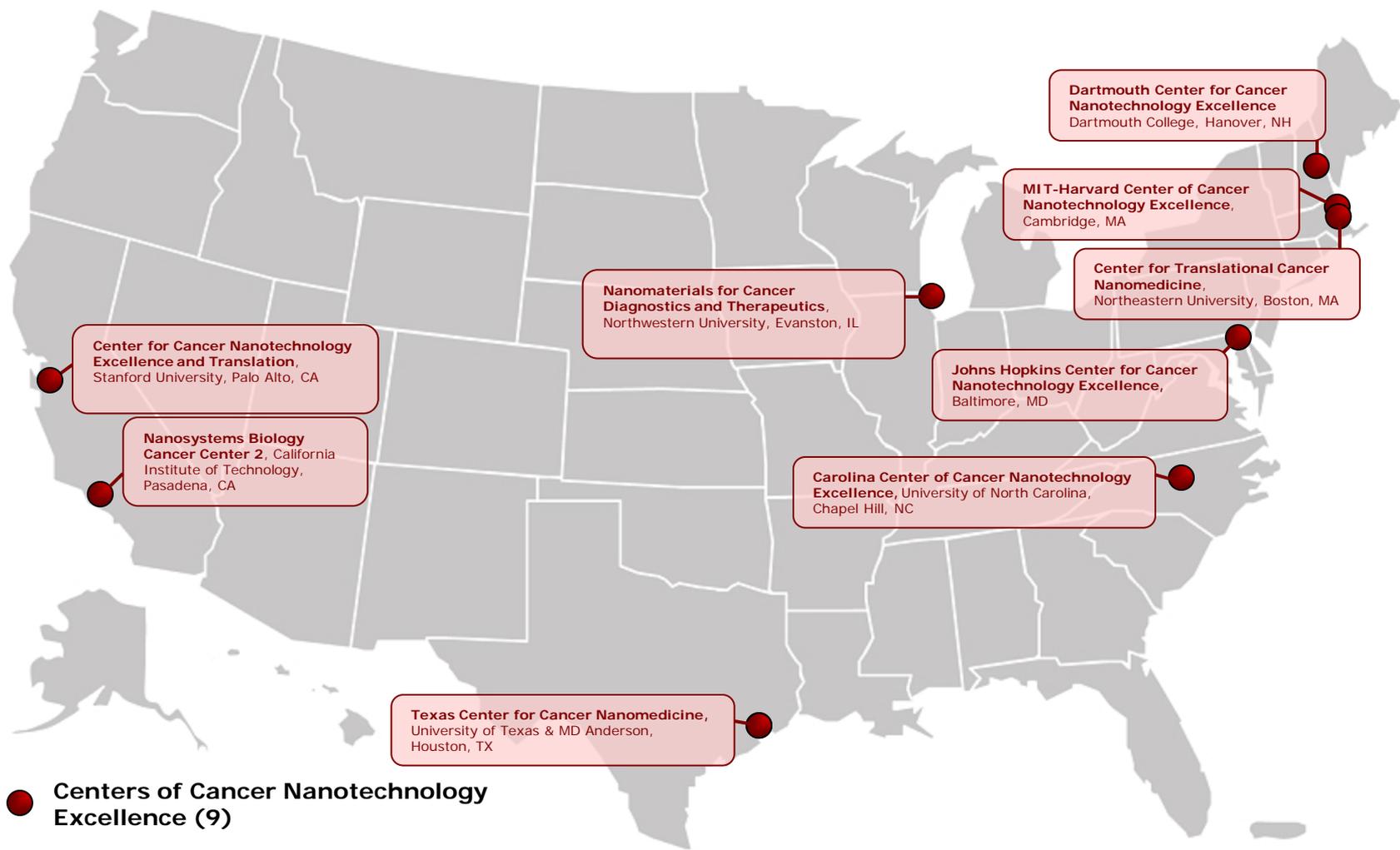
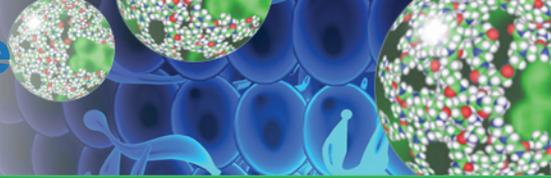


National Cancer Institute



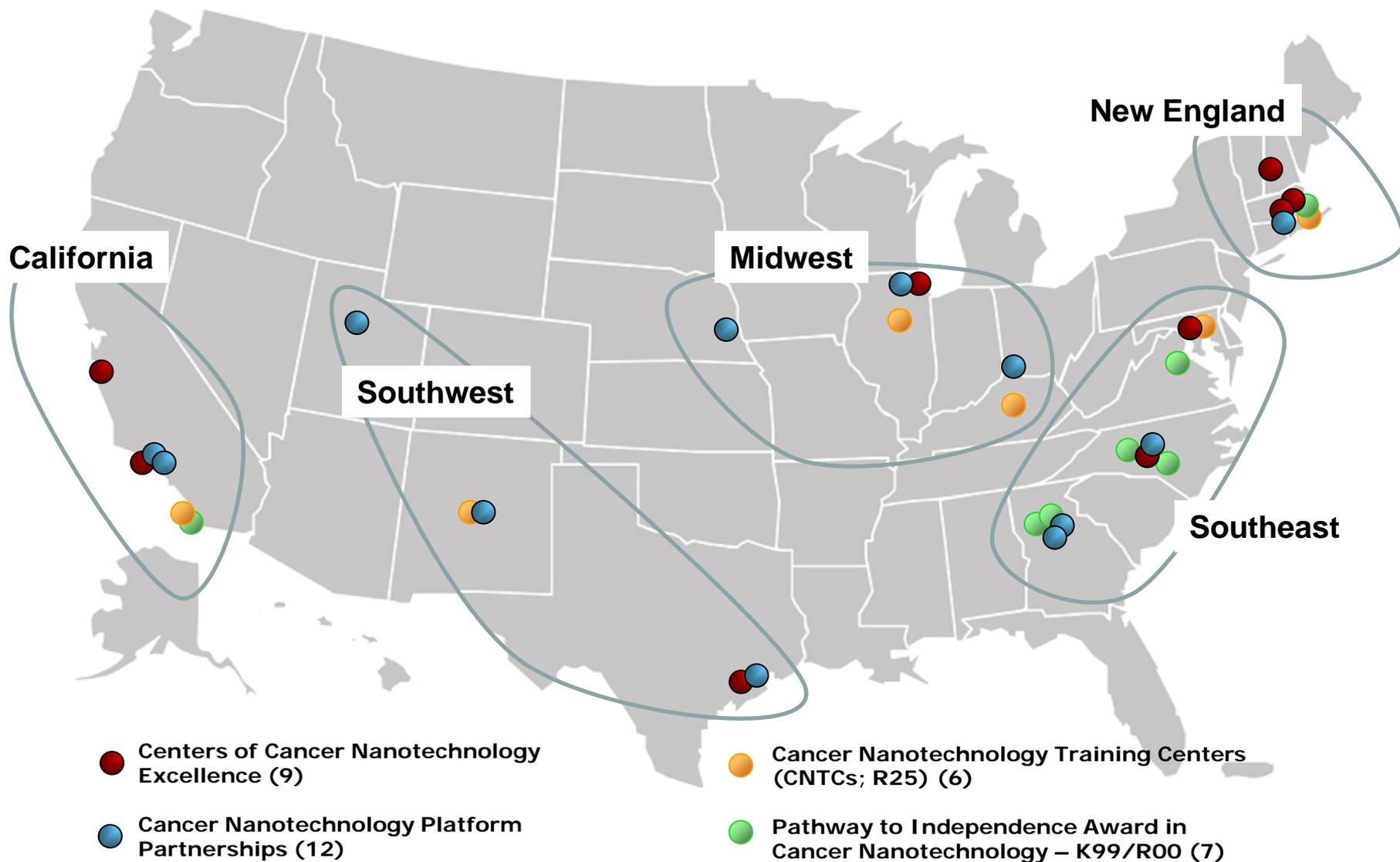
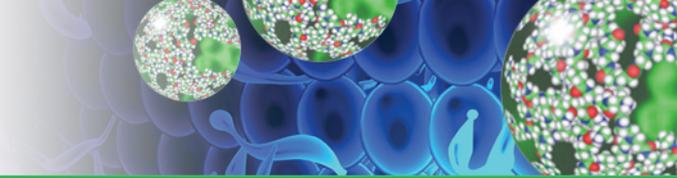
# Supplemental Slides

# Centers of Cancer Nanotechnology Excellence (U54)



● Centers of Cancer Nanotechnology Excellence (9)

# NCI Nanotechnology Alliance Awardees 2010





# Nanotechnology Characterization Laboratory (NCL)

**A Comprehensive Resource  
for Preclinical Evaluation of Nanomaterials**

**Scott E. McNeil  
NCI-Frederick Advisory Committee (NFAC)  
Sept. 12<sup>th</sup>, 2012**

[ncl@mail.nih.gov](mailto:ncl@mail.nih.gov)

**NATIONAL  
CANCER  
INSTITUTE**

**Frederick  
National  
Laboratory**  
for Cancer Research

Advanced Technology Program

**SAIC**

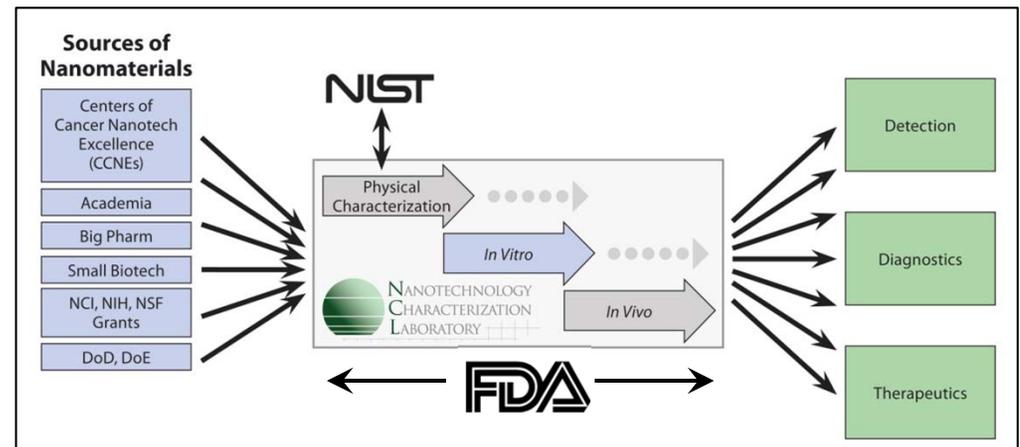
Frederick

Funded by NCI Contract HHSN261200800001E

# NCL Concept of Operations



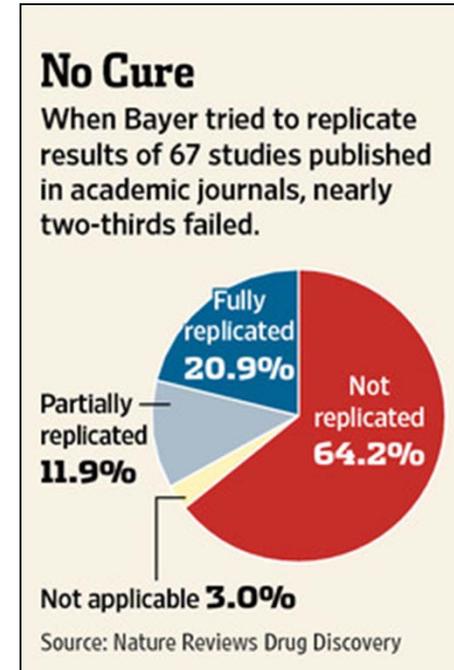
- The NCL was established in 2004 as an interagency collaboration among NCI, NIST, and FDA. The lab's mission is to accelerate the translation of promising nanotech cancer drugs and diagnostics.
- NCL performs preclinical characterization of nanomaterials, including:
  - physicochemical characterization
  - in vitro experiments
  - in vivo testing for safety and efficacy.



**90% of NCL's efforts support the extramural community.**

# Reproducibility

- Success rate of Phase 2 human trials (efficacy trials) down to 18% in 2008-2010.
- Bayer, Pfizer, Amgen, & other Pharma report difficulty replicating published research, “More often than not.”
- Increasing intricacy of experiments and sophisticated materials may exacerbate reproducibility challenges.



G. Naik,  
Scientists'  
Elusive Goal:  
Reproducing  
Study Results,  
Wall Street  
Journal,  
December 2,  
2011

Prinz, Schlange & Asadullah, Believe it or not: how much can we rely on published data on potential drug targets? Nature Reviews Drug Discovery 10, 712, September 2011.

See also: Data Replication & Reproducibility, Special Issue of Science, 2 December 2011, Vol. 334, #6060.

**NCL provides independent validation of results.**

# NCL Extramural Collaborators



# FNL Capabilities

From the Molecular Level, through In Vitro & In Vivo Screening, into Clinics...to the Cure!

NANOTECHNOLOGY CHARACTERIZATION LABORATORY  
Optical Microscopy and

Laboratory  
Immunology

### In Vivo Screening

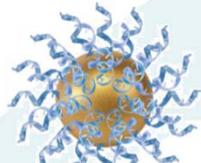
- ADME-Toxicity
- Efficacy
- Pharmacokinetics

### In Vitro Screening

- Blood contact properties
- Toxicity
- Immune cell functions

Protein Expression Lab

Protein Chemistry Lab



Laboratory

Antibody Characterization

### Characterization

- Size
- Composition
- Surface functionality
- Compatibility in biological matrices

Laboratory Technology

Small Animal Imaging Program

### Scale-Up Assistance

- Batch-to-batch consistency
- Process design and optimization
- Quality control
- Developing methods for in-process testing

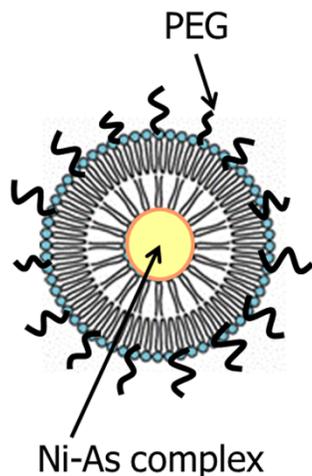


Clinical Support Lab

Analysis of Clinical Samples



# NCL Characterization Case Study: Ni-As Liposomes



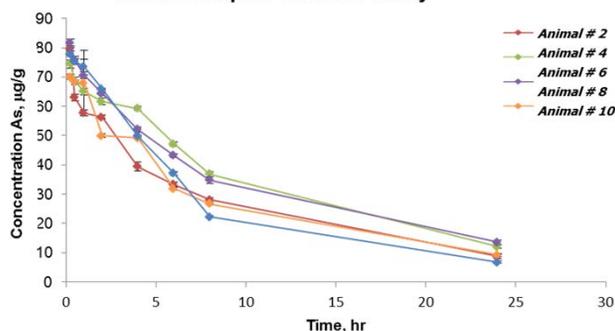
- NCL in vitro studies indicated the control (including the nickel counter ion) liposome was significantly toxic.
- NCL conducted characterization, in vivo tox and efficacy studies to see if this particle was also toxic in animals...

## PCC: Size and Structure

## PCC: ICPMS for Drug Quantitation

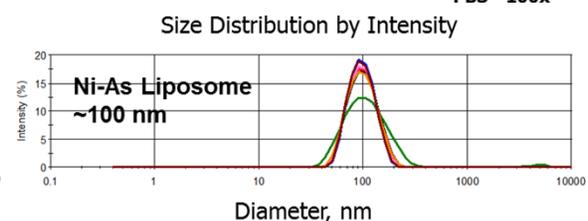
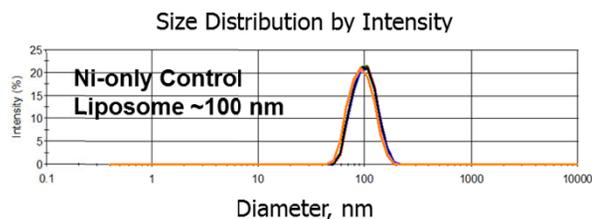


Tissue Samples from PK Study

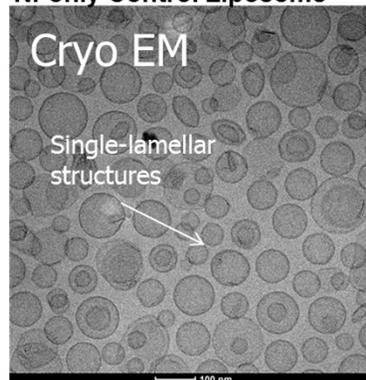


ICP-MS = inductively coupled plasma mass spectrometry; Ni = nickel;  
As = arsenic; PK = pharmacokinetics; PCC = physicochemical characterization

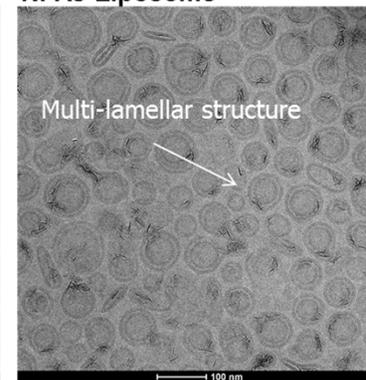
- Water - 10x
- Water - 100x
- 10 mM NaCl - 10x
- 10 mM NaCl - 100x
- PBS - 10x
- PBS - 100x



Ni-only Control Liposome



Ni-As Liposome

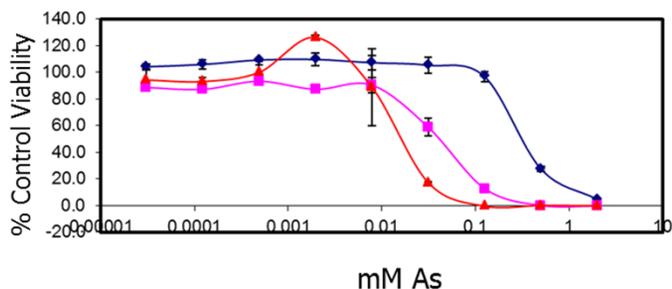


# NCL Characterization Case Study: Ni-As Liposomes

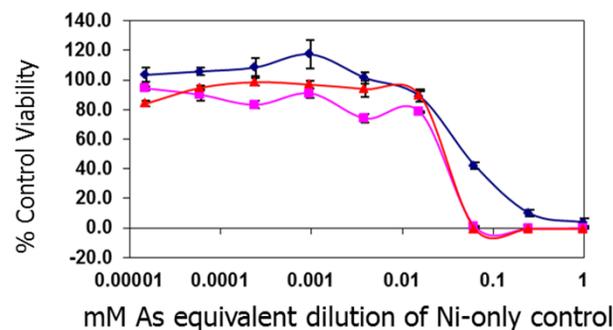
- NCL examined cytotoxicity and immunotoxicity of the formulation and controls in vitro.
- Much of the formulation's cytotoxicity and immunotoxicity was due to Ni rather than As API.

## Cytotoxicity

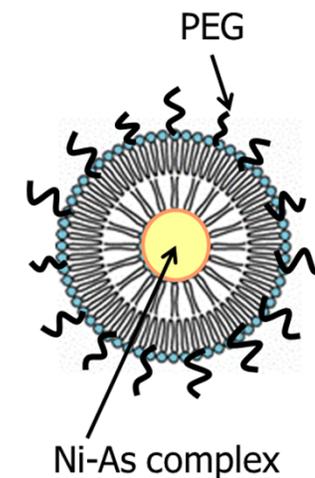
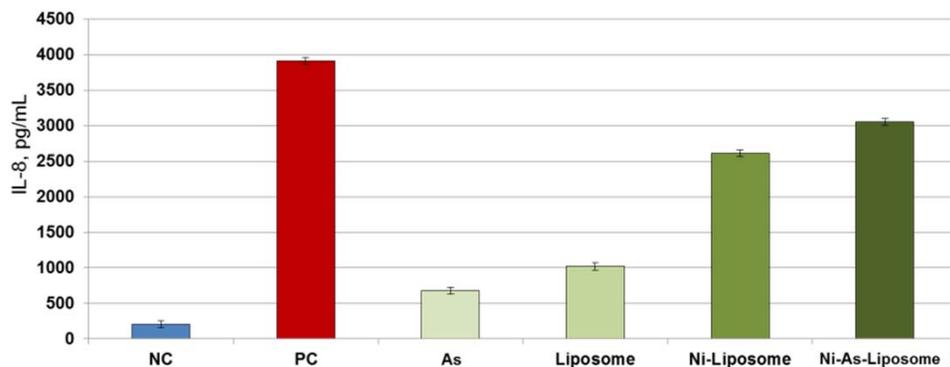
MTT of Ni-As Liposome in LLC-PK1 Cells



MTT of Ni-only Control Liposome LLC-PK1 Cells



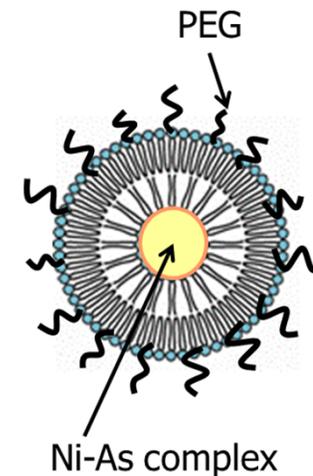
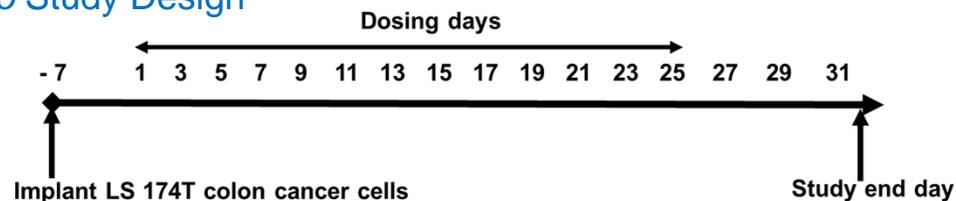
## Immunotoxicity



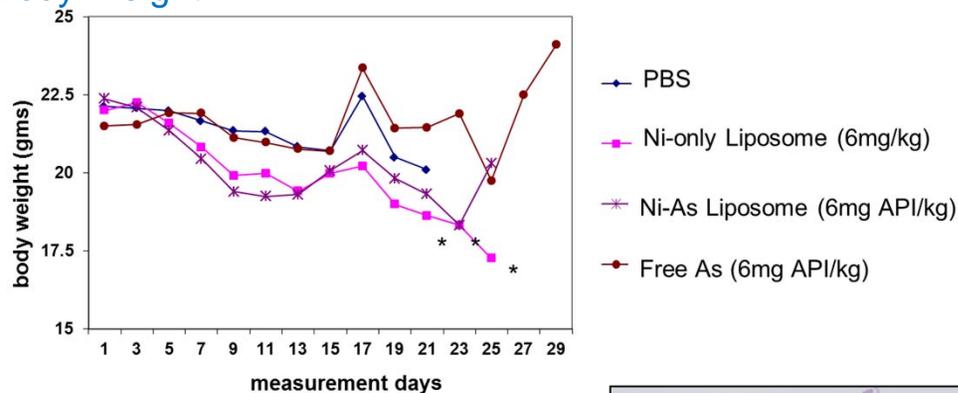
# NCL Characterization Case Study: Ni-As Liposomes

- NCL in vivo study showed the Ni-only liposome caused more body weight loss than the Ni-As liposome.

## In Vivo Study Design

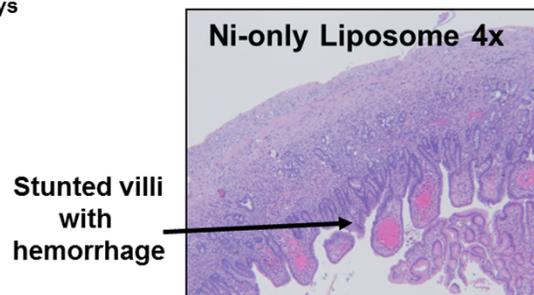


## Animal Body Weight

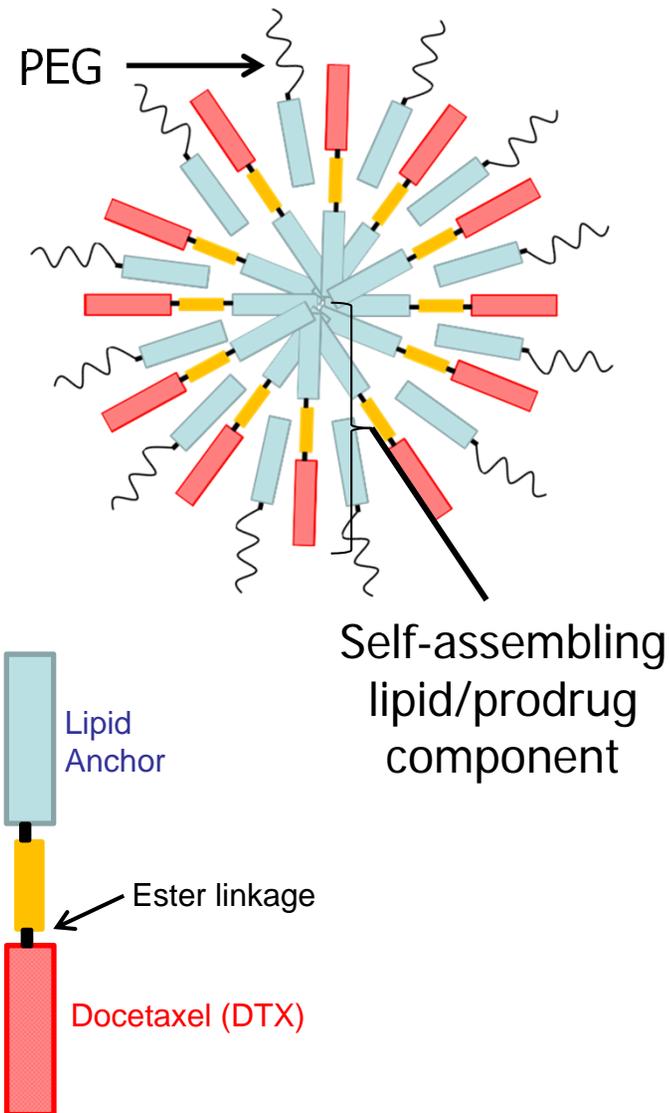


**On NCL's recommendation, developer PI is now pursuing alternatives to Ni.**

Histopathology of inflammation in duodenum

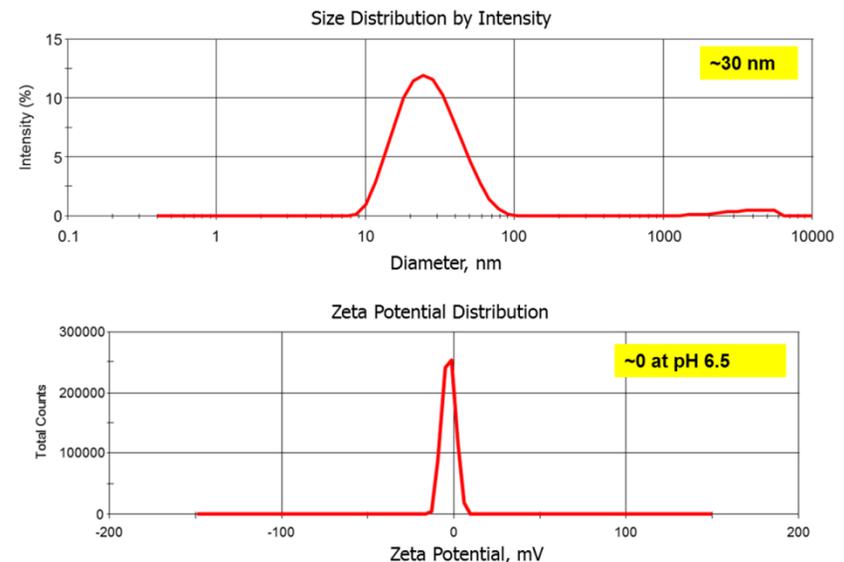


# NCL Characterization Case Study: Nanoparticle Prodrugs



- In theory, nanoparticle will get to tumor, prodrug will be released and DTX (API) cleaved/hydrolyzed.
- NCL characterized samples, measured in vitro plasma hydrolysis rates, in vivo PK, toxicity and efficacy.

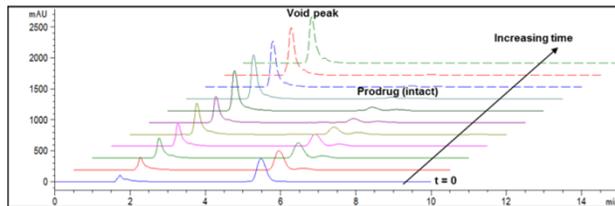
## PCC: Size and Charge



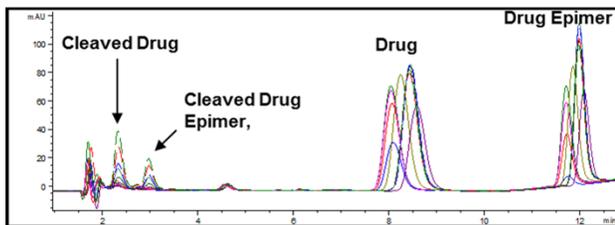
DTX = docetaxel; API = active pharmaceutical ingredient;  
PCC = physicochemical characterization; PK = pharmacokinetics

# NCL Characterization Case Study: Nanoparticle Prodrugs

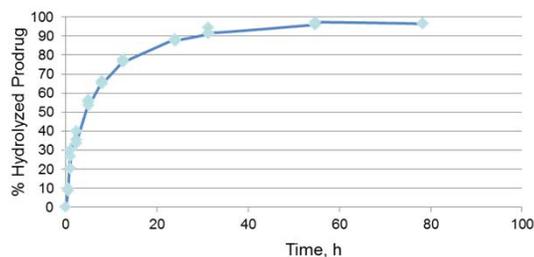
## HPLC



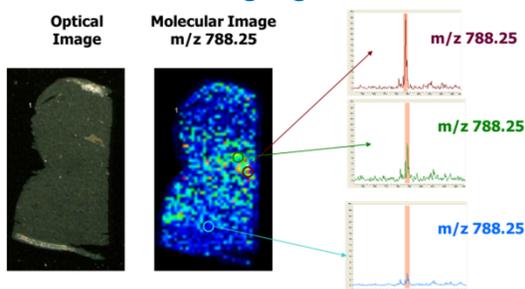
## LC



## In Vitro Prodrug Hydrolysis in Plasma

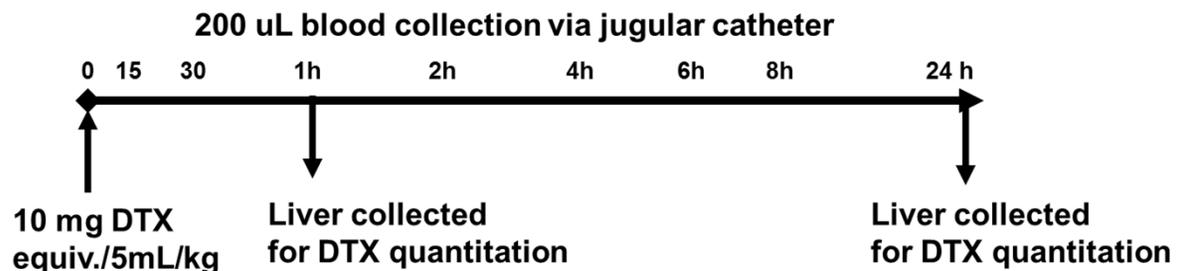
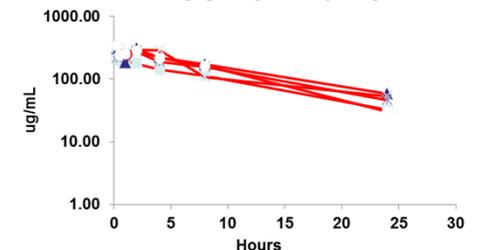


## MALDI Liver Imaging

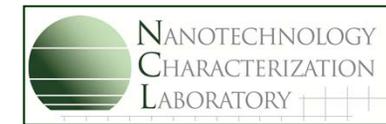


- NCL performed extensive characterization: HPLC to separate components of formulation and plasma. LC to determine cleavage site and drug stability.
- In vivo study to evaluate pharmacokinetics in jugular catheterized 10-wk-old female SD rats. Prodrug concentrations in plasma and liver measured w/ HPLC. MALDI imaging of liver.
- PK suggests distribution into plasma volume only (no tissue distribution). Plasma decay half-life approximately equal to hydrolysis half-life.

## In Vivo Prodrug Plasma Profile

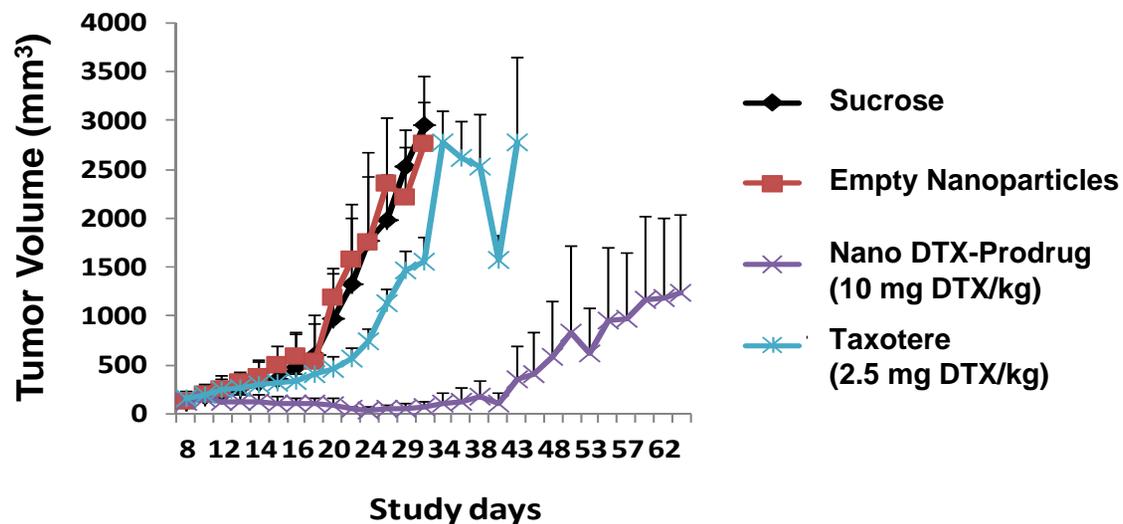


# NCL Characterization Case Study: Nanoparticle Prodrugs

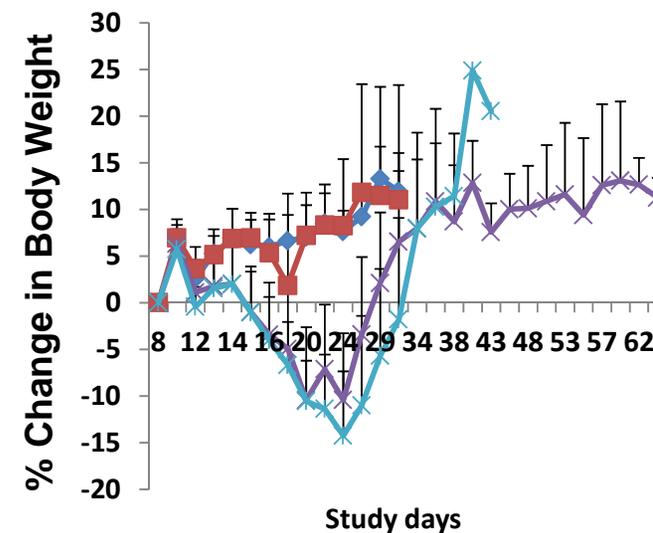


NCI Alliance for  
**Nanotechnology**  
in Cancer

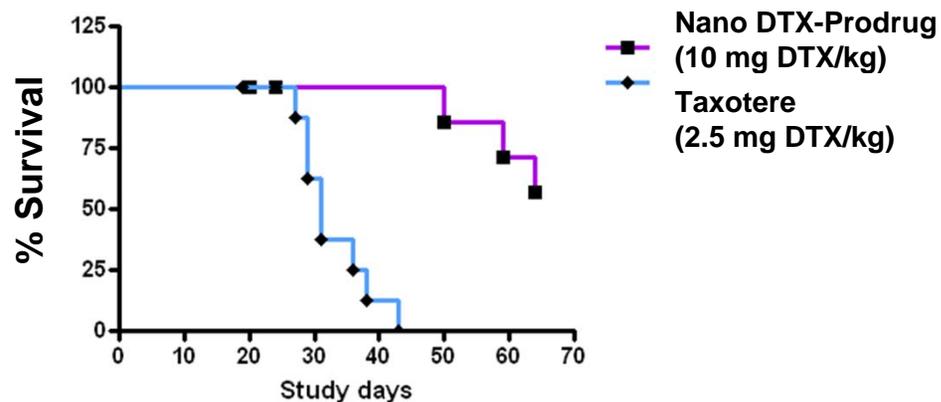
### Tumor Volume



### % Change in Body Weight



### Animal Survival



**More efficacious than an equi-toxic dose of Taxotere.**

# Success Stories: NCL Submissions in Clinics

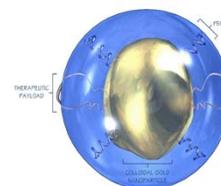


NCI Alliance for  
**Nanotechnology**  
in Cancer



IDE 2008

- Silica-core gold-shell particle for photothermal ablation with NIR irradiation.
- Pilot safety study in head and neck cancers ongoing; efficacy study in lung tumors to start in 2012.



Phase 1  
Complete in 2008

- Aurlmune® PEGylated colloidal gold nanoparticle-TNF $\alpha$  conjugates.
- Phase II study in combination with Taxotere to start in 2012.



AZAYA THERAPEUTICS

IND Dec 2009

- ATI-1123 PEGylated nanoliposomal formulation of docetaxel.
- Phase I safety study in patients with advanced solid tumors complete in 2012.



IND 2011

- BIND-014 docetaxel-encapsulated PLGA nanoparticle-aptamer conjugates.
- Binds PSMA expressed on prostate cancer cells.
- Phase I safety study in patients with advanced or metastatic cancer ongoing.



IND 2010

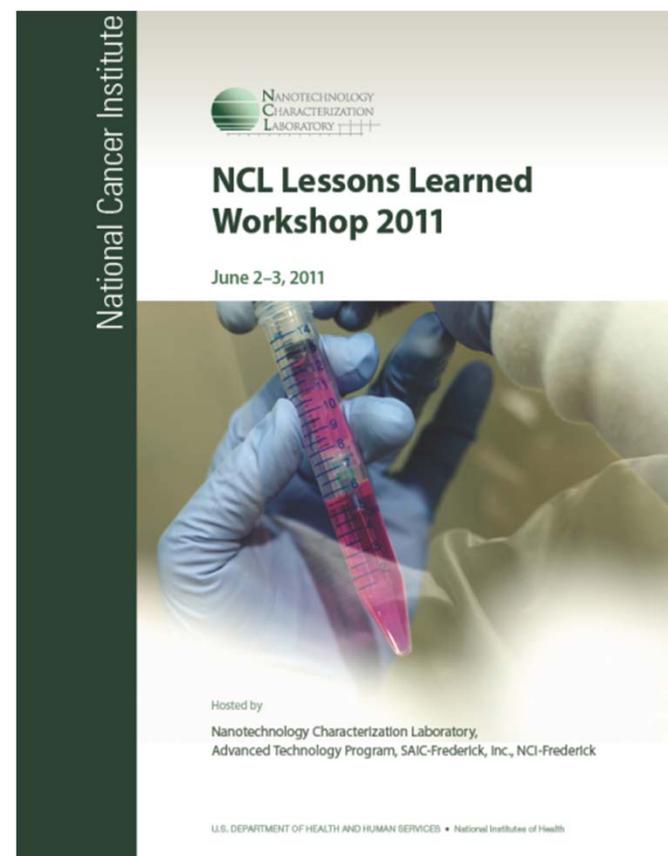
- PNT2258 liposome-encapsulated oligonucleotide for breast and lung cancer.
- Phase I safety study in patients with advanced solid tumors ongoing.

# Getting Results Out to Community



NCI Alliance for  
**Nanotechnology**  
in Cancer

- Lessons Learned Workshop:
  - Draws on NCL's experience with variety of nanomaterials, reagents, preparation methods, etc.
  - Presents negative results, "What doesn't work", not available elsewhere.
  - One-on-one discussions regarding specific nanoparticles/experiments/etc.
  
- NIH, June 2011
- FDA, Oct. 2011
- Carolina CCNE, Dec. 2011.
- Northeastern CCNE, Sept. 2012
- Texas CCNE, Nov. 2012
- Basel, Switzerland planned for 2013
- More as possible...



# Addressing Gaps in Translational Nanomedicine

- Scale up of nanomaterials to large scale production for clinical trials continues to be challenge.
- NCL assists in all aspects, without actually producing large scale batches in-house:
  - Batch-to-batch consistency testing
  - Process design and optimization
  - Quality control
  - Developing methods for in-process testing



**NCL methods continue to become the de facto standard for nanomedicine community.**

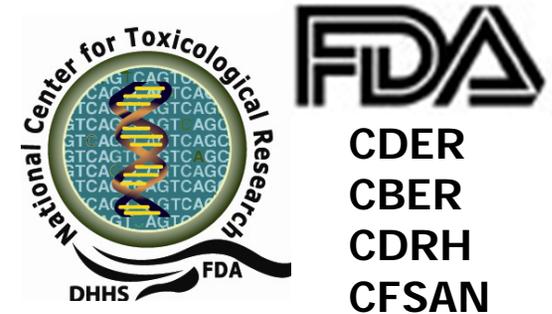
# Nanotech Outside Oncology: NCL Work for Others



- NCL's expertise and resources now support other HHS agencies.

- Scientific Collaborations with FDA

- Dermal penetration of nanomaterials in sunscreens and cosmetics, endotoxin, immune reactions.



- Collaboration with NIEHS for physicochemical characterization to support risk/hazard assessment

- NCL provided key infrastructure support for NIEHS' U01/U19 nanotechnology centers of excellence



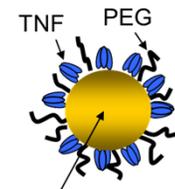
**These collaborations contributed to over \$1M/year in additional funding for NCL/NCI in FY11 & 12.**

# NCL Expertise is in Demand



- European Commission plans to construct “EU version” of NCL.
  - NCL playing an advisory role.
- FDA, EPA, DoD, routinely seeking NCL input on nanotech efforts.
- Approached by Big Pharma for characterization support and for nanotech reformulation of failed drugs.
  - Interest from Sanofi Aventis, J&J, Novartis, many others.

Aurimune®: PEG-coated colloidal gold + TNF- $\alpha$



Colloidal Gold Nanoparticle

IND 2006, Phase II 2012

**The NCL model has been extremely successful.**

**The NCL is now a leader in its field.**

# Acknowledgements



## Nanotechnology Characterization Lab

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Gloryvee Rivera, B.S.

Wendi Custer, B.A.

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Advanced Technology Program



Frederick

Funded by NCI Contracts N01-CO-12400 and HHSN261200800001E 17



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**Vaccine Research Center**

National Institute of Allergy and Infectious Diseases

National Institutes of Health

Department of Health and Human Services

# **The Vaccine Pilot Plant : Use of FFRDC for Urgent National Need**

**Richard M. Schwartz, Ph.D.  
Chief, Vaccine Production Program  
Vaccine Research Center**

**John Gilly, Ph.D.  
Director VCMP  
SAIC**



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**Vaccine Research Center**

National Institute of Allergy and Infectious Diseases

National Institutes of Health

Department of Health and Human Services

# The VRC, VPPL and VCMP

# Vaccine Research Center

---

- VRC mission involves the rapid advancement of promising vaccine candidates from the laboratory to the clinic
  - Basic and applied virology and immunology
  - Pre-clinical immunology – animal models
  - Translational research & development
  - Clinical trial vaccine testing
  - Collaboration with other USG agencies and NGOs for advanced clinical evaluation

# VRC Translational Research Programs

---

## **HIV**

- Gene-based vaccines
- Protein-based vaccines
- Broadly Neutralizing mAb

## **Emerging Diseases**

- Chikungunya vaccine

## **Biodefense**

- Filovirus (Ebola and Marburg) vaccine
- Alphaviruses (V, E and WEEV) vaccine

## **Influenza**

- Seasonal vaccine
- Universal vaccine

# Overview of the Vaccine Production Program Lab (VPPL)

---

- VPPL is responsible for translation of research ideas/products through development and production for all VRC clinical products
- Organization includes resources for:
  - Process (~22 FTE), analytical (~12 FTE) and formulation development (~3 FTE)
  - Project management (~2-3 FTE)
  - Regulatory Affairs (~2 FTE)
- Designed for the concurrent development of 2 new clinical products

# Overview of the Vaccine Clinical Materials Program (VCMP)

---

- Contractor responsible for GMP production of all VRC clinical products
  - Internal production at Vaccine Pilot Plant (VPP)
  - Subcontract production when more effective
- Organization includes resources for:
  - Manufacturing (~40 FTE)
  - QC (~25 FTE)
  - QA (~23 FTE)
  - Management (~9 FTE)
  - Facilities (~19 FTE)
- Staffed for the concurrent production of 2 clinical products and maintenance of on-going trials



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National Institutes of Health

Department of Health and Human Services

# The Need for the VCMP at the VRC

# The VRC's Need for the VCMP

---

- VRC mission involves the rapid advancement of promising vaccine candidates from the laboratory to the clinic
- Necessitates the development of a vaccine production infrastructure that includes the capacity for cGMP production of materials for Phase I/II clinical trials
- Two strategies are possible for obtaining the requisite cGMP capacity:
  - contracting with commercial firms
  - building a government financed manufacturing facility

# Contracting vs Internal Production

---

- Time:
  - Commercial manufacturers typically require up-front commitment of products and processes up to a year in advance; making it difficult, if not impossible, to drive new vaccine candidates forward on accelerated timelines
- Cost:
  - Commercial manufacturers are very expensive (~\$8M for partial VRC01 Phase I clinical material)
- Technology:
  - Technology unique to VRC products is extremely difficult and time intensive to transfer to external manufacturers

# Why the VCMP via the FFRDC at NCI?

---

- Government-controlled GMP production capacity is a critical component for expediting the introduction of vaccine candidates into the clinic.
- Realization that NIAID could not manage a GMP facility based on contracting resources and timeframes required to effectively run a pilot plant
- The FFRDC at NCI-F provided the best mechanism for operation of a contractor-operated pilot plant for the VRC
- Facility Approval Timelines
  - Facility approvals initiated in Jan 2003
  - D&F approved in June 2003
  - Oct 2003 final HHS comments to NIH for award of task to SAIC

# Expansion of the VRC & VCMP Mission

---

- After 9/11 attacks, the mission of the VRC & VCMP expanded from providing clinical lots of HIV vaccines to expeditiously developing, manufacturing and testing vaccines against potential bioterrorism agents.
- To implement this enhanced mission, the scope, and subsequently the size, of the facility expanded to include adequate processing capacity for potential biodefense vaccine candidates.

# The VPP Facility

---

## Facility Scope

- Increased scope for biodefense and emergency\*use
  - From: initial design of 1 small (100L) and 2 medium-scale (400L)
  - To: 2 small, 1 medium and 1 large (2000L) bulk production suites
- Drug product filling capacity up to 30K vials/lot (15K current)
- Multiple locations considered during facility planning
- Meeting with FDA for facility design prior to construction
- Full GMP utilities and Equipment
  - SS bioreactors
  - Disposable media prep and fluid handling equipment utilized



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National Institutes of Health

Department of Health and Human Services

# Current Projects in the VPPL and VCMP

# Projects in the VPPL and VPP

Disease	Product Type							
	pDNA	Adeno	VLP	mAb	rProtein	MVA -Pox	AAV	NP
HIV	X	X, IP		IP	TBD	IP	IP	
Filovirus	X	X, IP				IP		
CHIKV	X		X					
WEVEE	IP		IP					
Universal Influenza	X, IP				IP			IP

X Complete

IP In-progress

# Production of Products by the VCMP

---

- **VCMP has the ability to manufacture products at VPP or via subcontract**
- **Make (VPP) – Buy (Subcontract) Product Decision**
  - Products developed in the VRC research labs utilizing new technology will be developed within the VPPL and produced at VPP (VLP, nanoparticle, rProtein)
  - Products developed in the VRC research labs utilizing platform or collaborator technology may be produced at VPP or via subcontract (pDNA, Ad5, mAb, ChAd3)
  - Products developed in the VRC research labs utilizing commercially available technology will be considered for production via subcontract (large-scale mAb, MVA, AAV, reagent production, CLD & formulation development)

# Production at VPP or Subcontractor

Disease	Product Type Produced at (VPP) or Subcontractor (Sub)							
	pDNA	Adeno	VLP	mAb	rProtein	MVA-Pox	AAV	NP
HIV	VPP	Sub & VPP		Sub & VPP	VPP	Sub	Sub	
Filovirus	VPP	Sub & VPP				Sub		
CHIKV	VPP		VPP					
WEVEE	VPP		VPP					
Universal Influenza	VPP				VPP			VPP



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# **VPPL Development and VCMP Production**

-

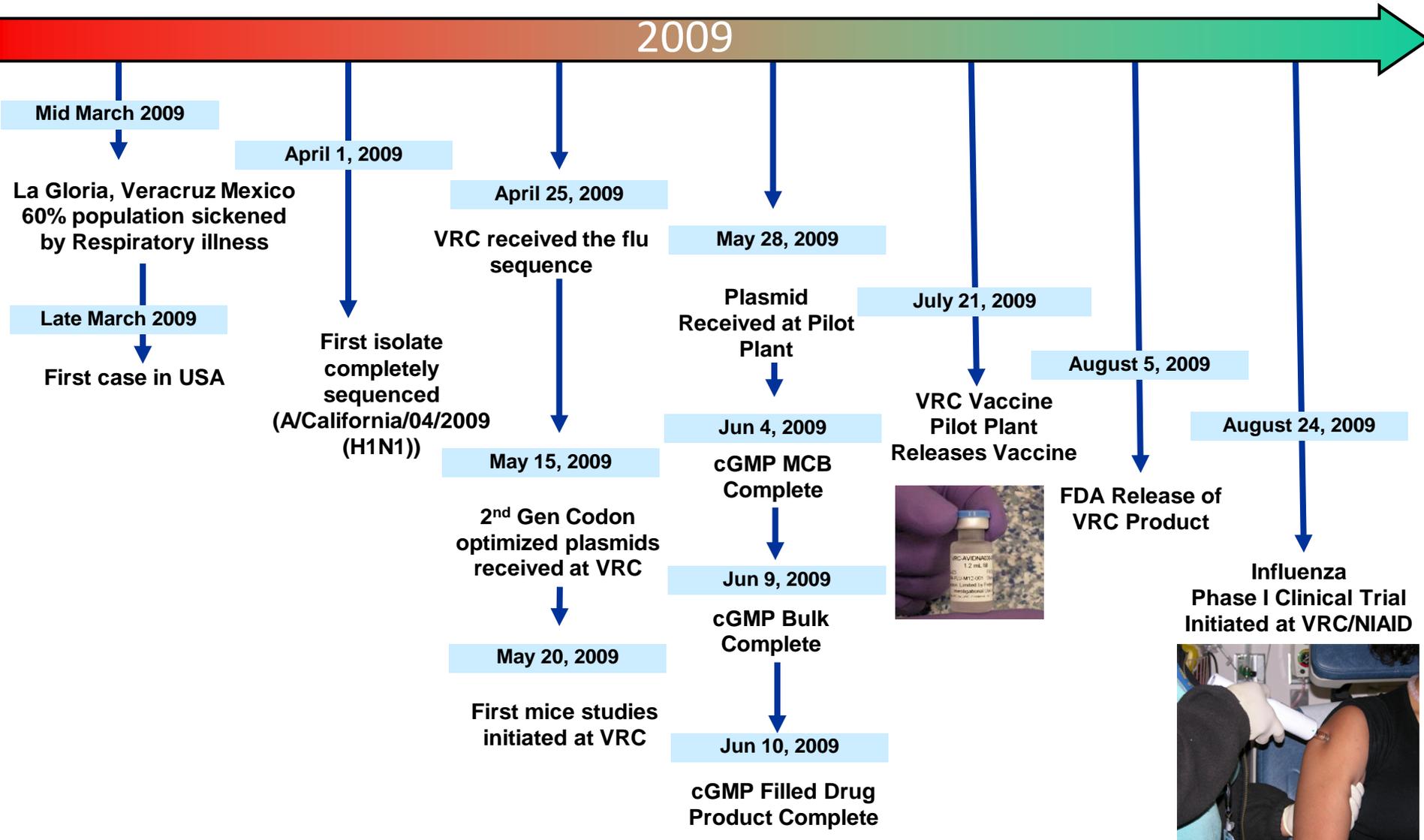
## **Actual Success Stories**

**2009 Pandemic Influenza Vaccine**

**A Chikungunya VLP Vaccine**

# DNA Vaccine Development Timeline - An Example

## Swine-Origin Influenza A (A/California/04/2009 (H1N1))





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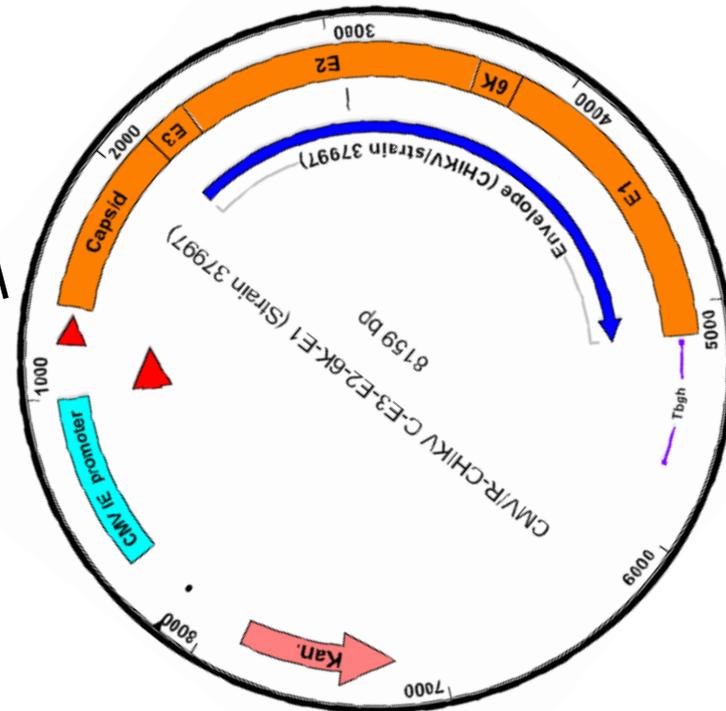
# Chikungunya VLP-Based Vaccine

# CHIKV Genome & Production Plasmid

Chikungunya genome



VLPs constructs: C-Env



# CHIKV cGMP Development and Production

---

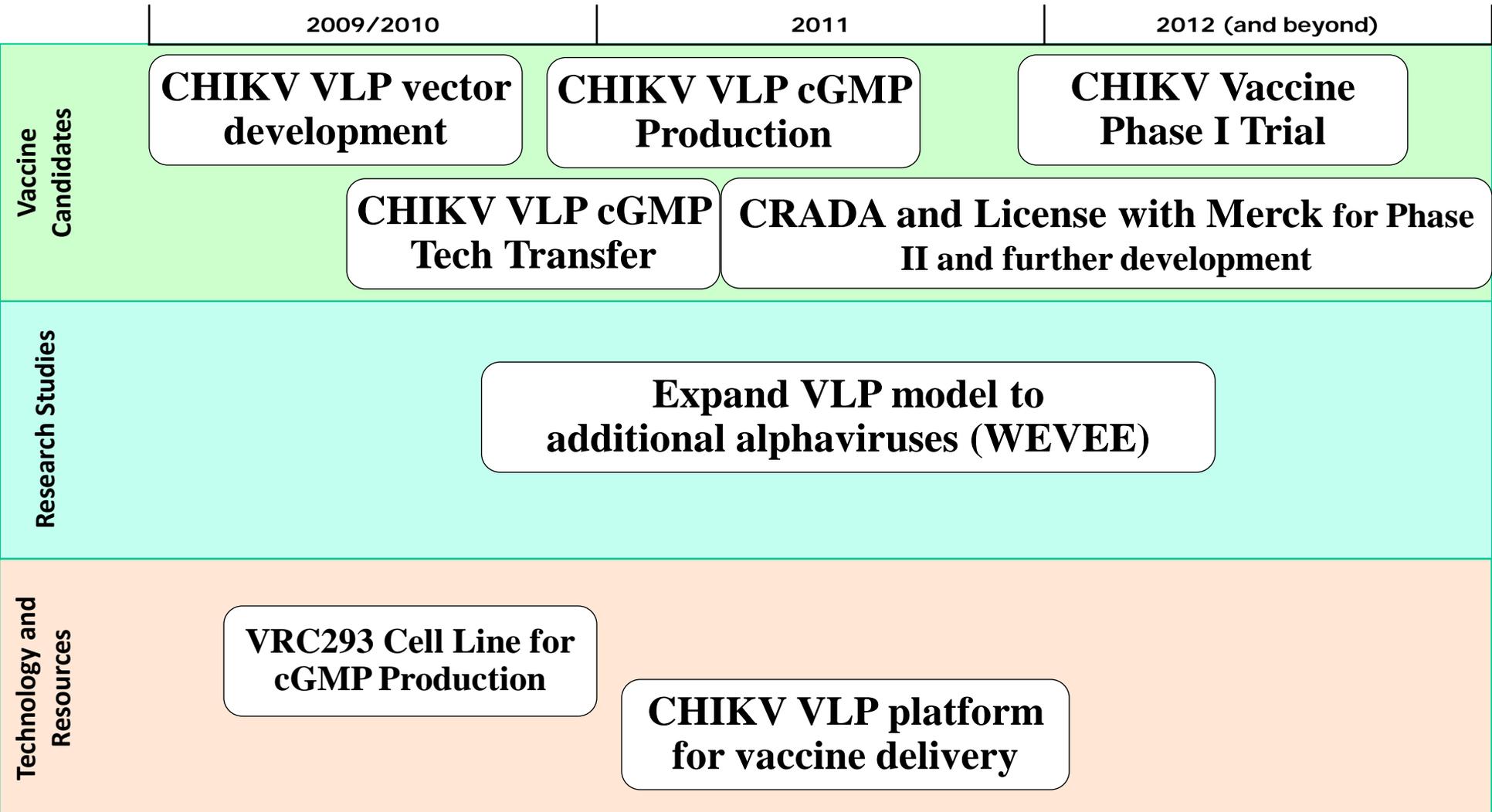
## VPPL Development

- Serum-free HEK-293 cell line
- Upstream process development
- Downstream process development
- Analytical development
- Formulation development (contracted by SAIC-F)

## VPP Manufacturing

- Tech transfer from VPPL to VPP of process and assays
- Bulk manufacturing
- Drug product manufacturing
- Lot release testing
- On-going stability testing

# Chikungunya Virus Vaccine Program





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Department of Health and Human Services

# Examples of VCMP Sourcing for Specific Needs

# VRC Active Subcontracts Through VCMP

<u>Name</u>	<u>Purpose</u>	<u>LTD</u>
Access Bio	Tox/PK Consulting	\$6,000
Bavarian Nordic	CMO (MVA)	\$3,336,000
California Institute of Technology	rAAV Research	\$4,528,530
GenVec	CMO (rAd)	\$5,667,685
Lampire Biological Laboratories, Inc.	Reagent Development	\$101,388
Lonza Sales AG	CMO (bnMAb)	\$8,457,510
Science Applications International Corp	Regulatory	\$238,137
SRI International	Preclinical Tox	\$545,710
TBD - Pending Selection	CMO (rAAV)	\$2,000,000
<b>Grand Total</b>		<b>\$24,880,961</b>

# VRC Active Subcontracts Through VCMP

<u>Name</u>	<u>Purpose</u>	<u>LTD</u>
Beth Israel Deaconess Medical Center	Lab Animal Medicine	\$1,200,000
BioQual	Lab Animal Medicine	\$2,375,362
Dr. Lynn Morris (University of Witswatersrand)	VRC Structural Biology	\$50,000
Duke University Medical Center	Lab Animal Medicine	\$547,332
Full Spectrum Genetics, Inc.	VRC Structural Biology	\$150,000
Kansas State	Lab Animal Medicine	\$115,000
Tulane National Primate Research Center (TNPRC)	Lab Animal Medicine	\$1,061,440
University of Kentucky Research Foundation	Lab Animal Medicine	\$51,782
University of Michigan	Lab Animal Medicine	\$200,000
University of Texas Medical Branch	Lab Animal Medicine	\$418,415
<b>Grand Total</b>		<b>\$6,169,331</b>



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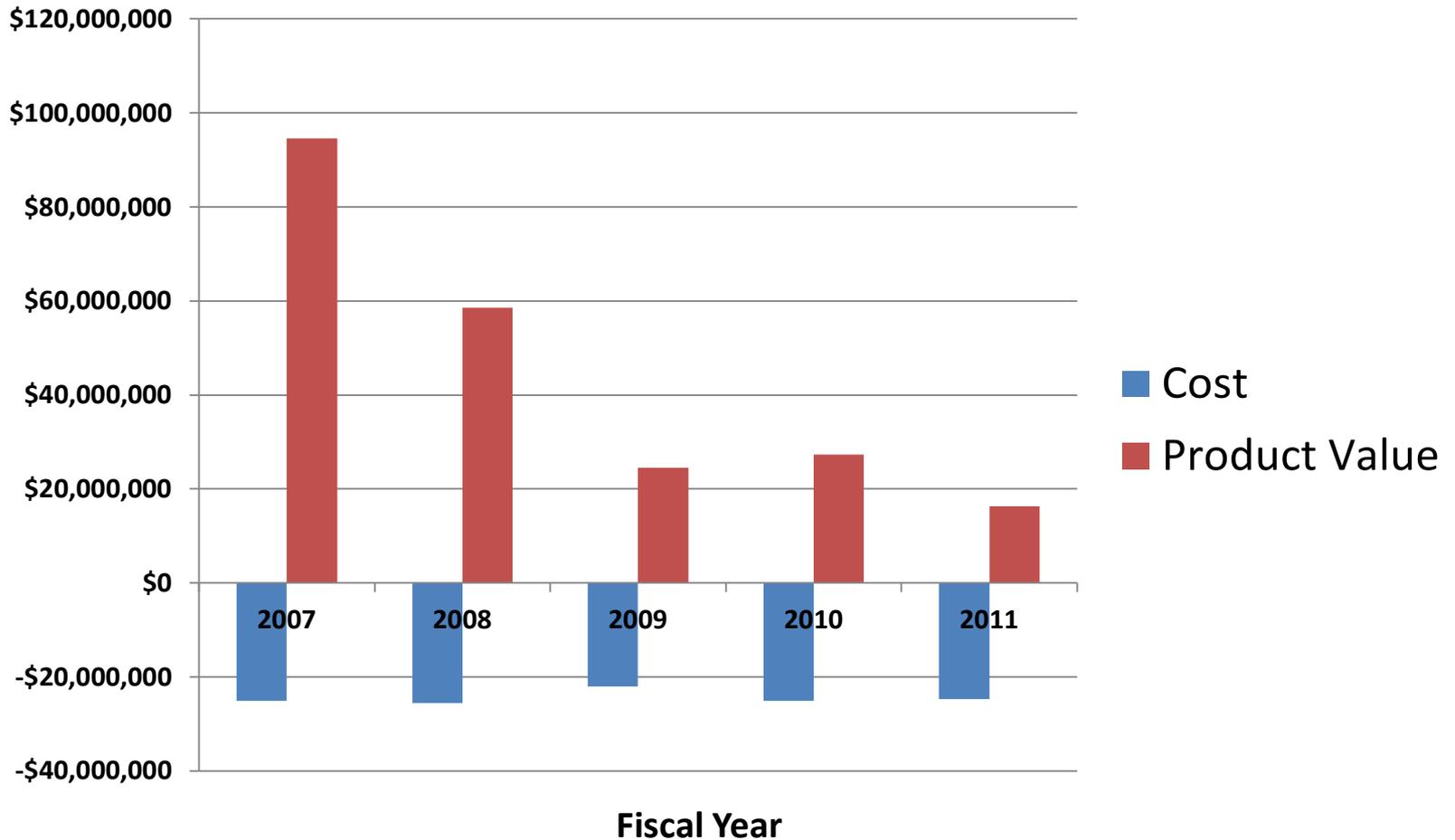
National Institutes of Health

Department of Health and Human Services

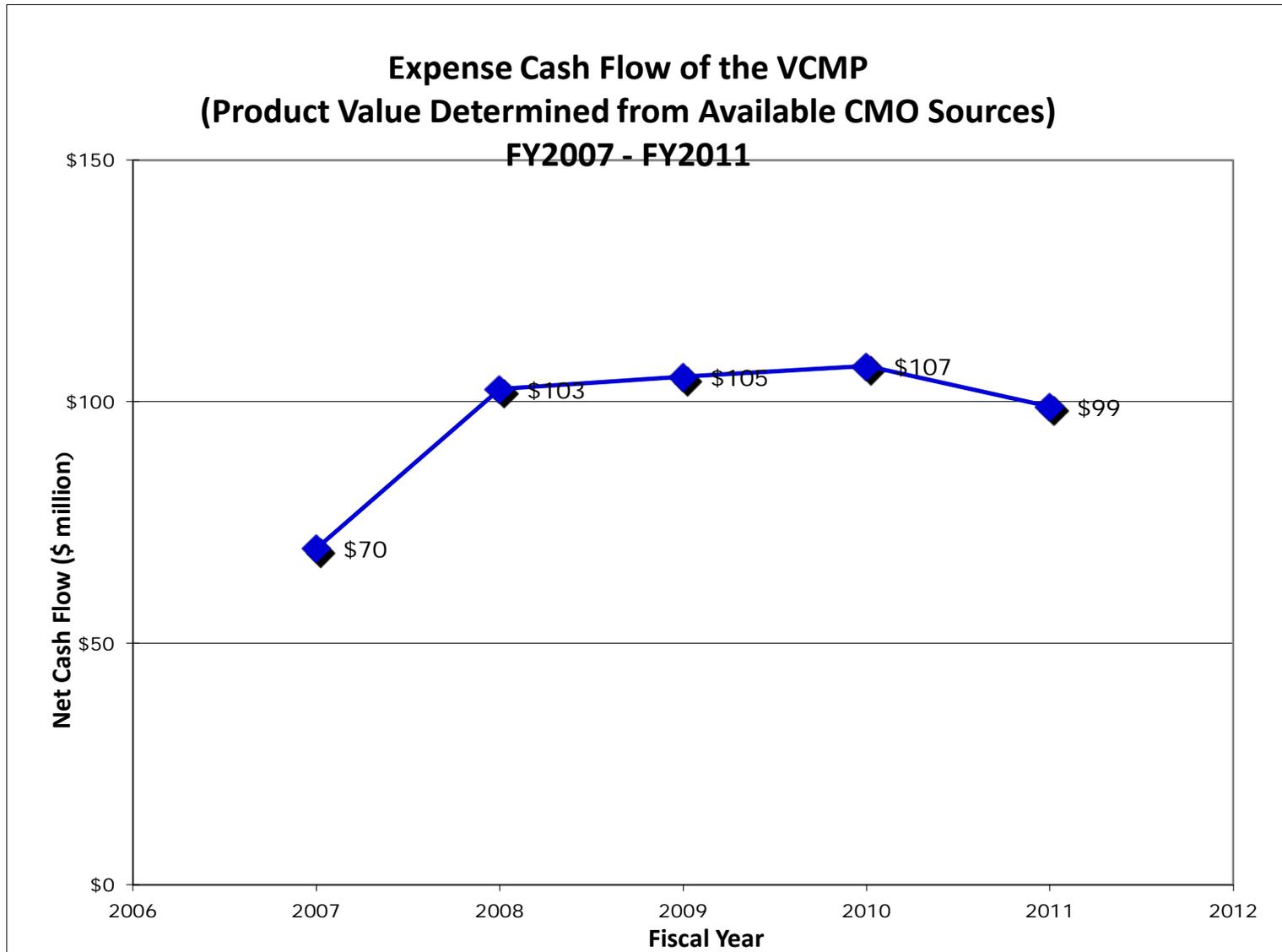
# Tracking In-House Project Costs to the Value of the Delivered Products

# Cost Efficiency of VCMP

VCMP Cost and Output Product Value by Fiscal Year  
2007 - 2011



# Cost Efficiency of VCMP



# Cost Efficiency of VCMP

## Example of Single Year Analysis

<b>FY2011 Products</b>	<b>Bulk (g or L)</b>	<b>Vials</b>	<b>Value</b>
ChikV VLP Tox Lot	16		\$1,153,679
ChikV VLP GMP1	16		\$1,153,679
ChikV VLP GMP2	16		\$1,153,679
ChikV VLP GMP3	16		\$1,153,679
ChikV VLP GMP4	16		\$1,153,679
FluPerth Fill		2665	\$1,037,446
ChikV Fill		782	\$304,421
ChikV Fill		546	\$212,550
ChikV Fill		308	\$119,900
<i>VLP Tech Transfer</i>			<i>\$600,000</i>
HIV mosaic pDNA9663	4.6		\$1,334,000
Flu Perth pDNA 2439 mosaic DNA	24		\$6,960,000
		<b>Total:</b>	<b>\$16,336,713</b>



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# Tracking Responsiveness to Critical VRC Deadlines

# In-House – Outsource Comparison

## VRC01 GMP Production

<u>Key Activity</u>	<u>Original Target</u>	<u>Actual Completion</u>	<u>Difference</u>	<u>Yield (g)</u>	
				<u>Target</u>	<u>Actual</u>
MCB Production*	26-Dec-11	15-Dec-11	-11d		
130L Pilot Bulk #1 (Tox)**	5-Feb-12	15-Dec-11	-52d	188.0	55.2
130L Pilot Bulk #2	14-Jun-12	14-Jun-12	0	188.0	110.6
GMP Documentation	9-Feb-12	14-Jun-12	+130d		
GMP Batch Bulk Production**	12-Mar-12	16-Aug-12	+157d	2,880.0	1,268.0

\* Duration of 18 months from start of cell line development to MCB production

\*\* Pilot #1 process deviations required Pilot #2 to be produced. The GMP batch included significant process deviations resulting in product loss and reprocessing

## 2012-2013 Seasonal Influenza pDNA Trivalent Vaccine Production

<u>Key Activity</u>	<u>Original Target</u>	<u>Actual Completion</u>	<u>Difference</u>
WHO Strain Announcement		23-Feb-12	N/A
Plasmid Construct Avail.	6-Mar-12	30-Jan-12	-28d
B/Wisconsin GMP Bulk	16-Mar-12	2-Mar-12	-10d
A/Victoria GMP Bulk	23-Mar-12	21-Mar-12	-3d
Final Vaccine fill	4-Apr-12	22-Mar-12	-9d
Ship to Clinical Sites	29-May-12	23-May-12	-4d
Protocol Activated/ First enrollment	7-Jun-12	4-Jun-12	-3d



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National Institutes of Health

Department of Health and Human Services

# Summary



# VCMP – Contract Responsibilities

---

## Support to the NIAID Vaccine Research Center (VRC)

The VRC cGMP pilot plant shall be leased and operated by the Contractor with major responsibilities to include, but are not limited to:

- **Support** all aspects of GMP development,
- **Establish and manage** the production, testing, and QA release for Phase I/II products,;
- **Establish** manufacturing processes suitable for eventual manufacture by VRC partners;
- **Comply** with U.S. Food and Drug Administration regulations as is appropriate to meet compliance-level requirements for each product manufactured..
- **Manufacture** Phase I/II clinical lots of candidate vaccines utilizing appropriate cGMP standards;
- **Support** the development activities at the VPPL;
- **Maintain** Quality Systems to support manufacturing of candidate vaccines by other VRC Contractors;
- **Participate** in technology transfer of manufacturing processes as projects are transferred from VPPL to the VCMP
- **Develop and maintain** regulatory Master Files and CMC sections to support all active INDs
- ***Track record for products from the VCMP since 2006:***
  - ***28 INDs.***
  - ***Supporting 54 clinical protocols***
  - ***With 22 drug product types (plus 4 placebo types)***
  - ***Produced and released 46 drug product lots and 17 placebo lots***



## SAIC-F Partnering, ATRF, and the operational enablement of life sciences missions

**Atsuo Kuki**

CTO, SAIC-Frederick

September 12, 2012

**Frederick National Laboratory  
for Cancer Research**

# FNLCR CTO highlights

## *Presentation Outline*



- Access and partnering by external Cancer Research community now **OPEN**:

- Legal and Contractual Alignment from DHHS ✓
- Contract Modification for FNLCR now in place ✓

**cCRADA**  
Authorization  
August 2012

- Access for discrete fixed-price services: TSAs
- R&D Partnering via cCRADAs: the current pipeline
- ATRF: Populated and operational, now building the Innovation Culture
- The **Operational Enablement of Life Sciences Missions**:  
Leading examples of complex multi-lab expts at FNLCR

# Access by the external community:

*Expand value for national cancer research via TSAs*



## National Cancer Research and Development Community

- **Gov't: Federal Agencies, State Universities...**
- **Academic: external investigators, consortia, grant recipients**
- **Entrepreneurial: SBIR/STTR recipients**
- **Private sector R&D: Pharmaceutical and top-tier Biotech industry**

TSA route for getting science done. Oncology & AIDS R&D enabled by FNLCR applied life sciences technology programs :

**Pre-Approved TSAs with fixed pricing, expect ~12** by end of September

- *Integrated in vivo Services for GEMMs (LASP Directorate, Lionel Feigenbaum)*
- *Protein Interaction Analysis; Cancer Biomarkers; ... (ATP Directorate, and BioComputing)*
- *Virologic and Analytical Reagents and Services for HIV, SIV, SHIV (ACVP Directorate, Jeff Lifson)*

# FNLCR Access by the external community

## Technical Service Agreements (TSA)



## Fixed price TSAs (first dozen) to include:

- Complex antigen(s) mass ID for antibody characterization by immunoprecip'n-MALDI-TOF **robotic assay** (ATP, Protein Chemistry Lab)
- Antibody Pairing Assay, Epitope Overlap, **Integrated** SPR protocol (ATP, Protein Chemistry)
- Transgenic Mouse Models by Pronuclear Injection and Cryopreservation of Founder Lines (**Integrated in vivo TSAs** offered by FNL LASP will expand steadily)
- Estrogen Metabolite Biomarkers in biofluids and tissues, LC-MS-MS (ATP, LPAT Analytical)
- >3 from AIDS and Cancer Virus Program at FNL (next slides)



# AIDS and Cancer Virus Program



## Initial 2012 TSA Offerings from the ACVP

### Plasma SIV/SHIV RNA analysis

- Real time qRT-PCR assay, covers all virus isolates in common usage; used in pathogenesis, treatment and prevention/vaccine studies

### HIV-1 p24<sup>CA</sup> antigen capture immunoassay kits \*

\* not intended for analysis of clinical specimens

- Robust time-proven kits specifically engineered to accelerate preclinical research (plates, secondary Ab, detection reagents, **standards**)

## *Additional 2012/13 Planned TSA Offerings from the ACVP*

### SIV/SHIV In Situ Hybridization

- ISH analysis of NHP tissues (LN, gut, other), with virus lineage specific probes, with **quantitative image analysis**; pathogenesis, treatment and vaccine studies

### Single Genome Amplification (SGA) Sequencing

- Limiting dilution PCR sequencing to identify **individual viral variants** in studies of viral transmission, evolution and drug resistance, immune escape

# AIDS and Cancer Virus Program



## Integrated 2012/13 Planned TSA Offerings from the ACVP

### Laser Capture Microdissection (LCM) SGA Sequencing

- Tissue Analysis Core, and Viral Evolution Core, **integrated service**
- LCM to recover selected (virus+) foci from tissue sections, with extraction and Single Genome Amplification sequencing to identify **individual distinct viral variants** in studies of viral transmission, evolution and drug resistance, immune escape

#### Core Labs are the key. ACVP example:

Quantitative Molecular Diagnostics Core, M Piatak, PhD

Biological Products Core, J Bess, Jr, MS

Tissue Analysis Core, J Estes, PhD

Viral Evolution Core, B Keele, PhD



Intramural NCI Programs



External TSA Services



**Unique Integrated Services**

# Partnering with the external community:

## *cCRADA pipeline: submissions for Concept Approval*



### Concept Approval Form (CAF)

- sent to NCI Lead Program to verify Mission alignment, and
- to optimize value as the cCRADA plan takes shape

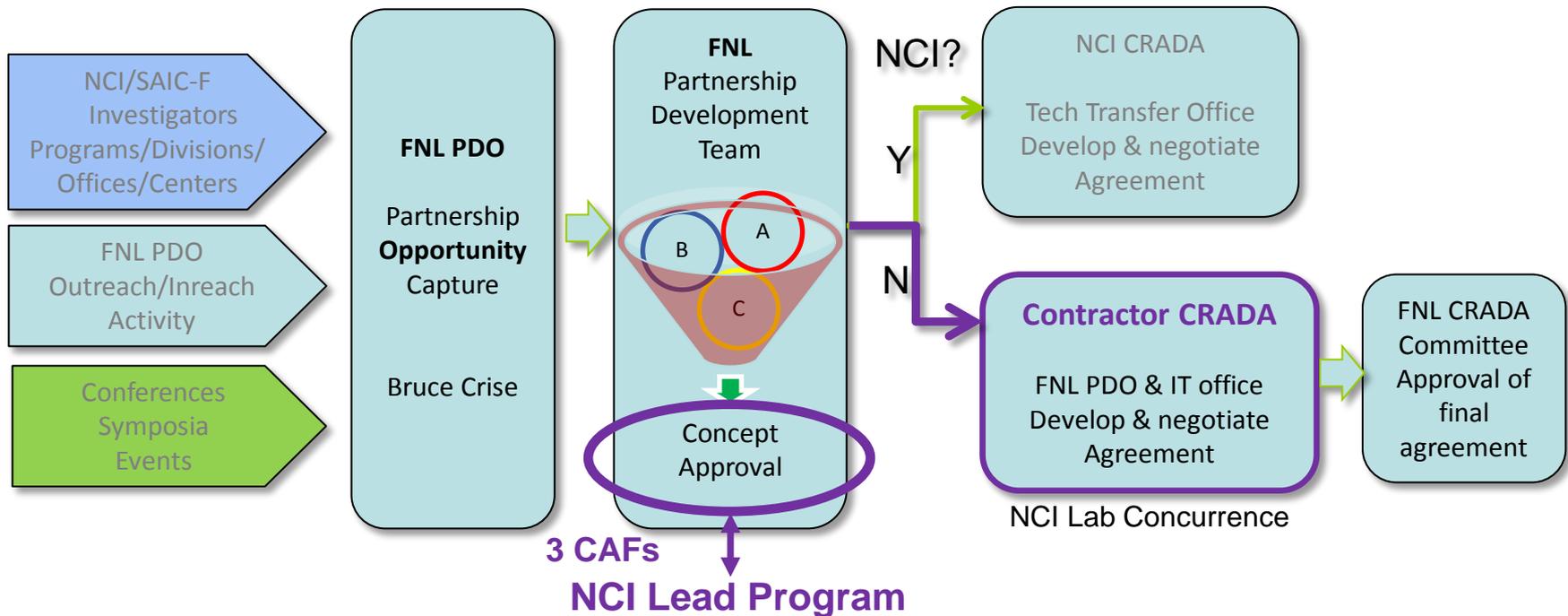
~7  
OPP'Ys

3  
CAFs



by October, expect steady-state of >4 post-CAF

3 CAFs submitted within 8 days of cCRADA authorization



FNL PDO = Frederick National Laboratory Partnership Development office, part of the CTO office

CAF = Concept Approval Form, to verify Mission alignment

Frederick National Laboratory for Cancer Research

# cCRADA pipeline, being vetted

*Breadth of partnership (in preliminary discussion)*



## SAIC-F

Clinical Directorate

ATP / ElecMicroscopy

ATP / Proteomics

ISP / BioComputing

ATP / NCL

ACVP

exploratory

## Partner

Emerging Market Pharma

Industry Consortium

Instrument Maker

Pediatric Comprehensive Cancer Ctr

Pharma / Reformulating Therapeutics

Academic Consortia (NIH funded)

Academic Consortia (Philanthropy funded)

# Partnering Opportunities just a start of Evolution into high impact National Lab



## now:

1. Expanding collaboration from FNL with **Extramural**, **Entrepreneurial**, and **Industrial** partners for Translational Medicine
2. Opening of the new Advanced Technology Research Facility (**ATRF**)
3. Opportunities **span** FNL expertise
  - Molecular, Nanotech, Virologic, Cellular, Tissue, *in vivo*, Imaging, Bioinformatics, Molecular Pathology
  - Clinical support, Biopharmaceutical development, Cancer biomarkers

## ... next

4. Strategic impact on long-term National Cancer priorities:

More than just breadth of Operational capability, the emerging strength in FNL is **Integration across that span**. From here, we will derive

*Top caliber Enablement of Strategic Missions*

# ATRF open. Advanced Technology Program (ATP) labs 70% to 90% operational



## ATP Move to ATRF June 19<sup>th</sup> - present

130 people in 8 Laboratories and ATP Office

48 lab rooms, 4 cold rooms

44 offices, 86 cubicles

5 electron microscopes, 13 mass spec, 60 L fermentor ...

Co-localization of teams into the ATRF is enormously significant.

- Re-invigorating passion for scientific discovery and inspiring previously silo'd tech lab members to seek out **interdisciplinary** approaches
- Nascent spirit of shared purpose and mutual accountability
- Commitment to developing **integrated biology capabilities**

*1<sup>st</sup> ATP-wide innovation event: Lab Tours in Oct and formation of "Trans-ATP Innovation group"*

# FNL emerging strength...

*Integration across Span of Capabilities*



## The Operational Enablement of Life Sciences Missions

*What are some of the key characteristics for success?*

Four leading examples of integrated multi-lab experiments at FNLCR:

1. The **NCL** Nanocharacterization integrated assay cascade
2. The **ACVP** AIDS vaccine/therapy non-human primate integrated study
3. GEMM cascade in **LASP** w/ Imaging, Molecular pathology (e.g. for CAPR)
4. **ISP** integration Hub for national Biospecimen networks (e.g. for caHUB)

# FNL emerging strength...

*Integration across Span of Capabilities*



Operational Enablement of complex multi-lab interdependent cascade expts

1. The Nanocharacterization integrated assay cascade (**NCL, McNeil**)



2. AIDS vaccine non-human primate integrated study (**ACVP, Lifson**)



# FNL emerging strength...

*Integration across Span of Capabilities*

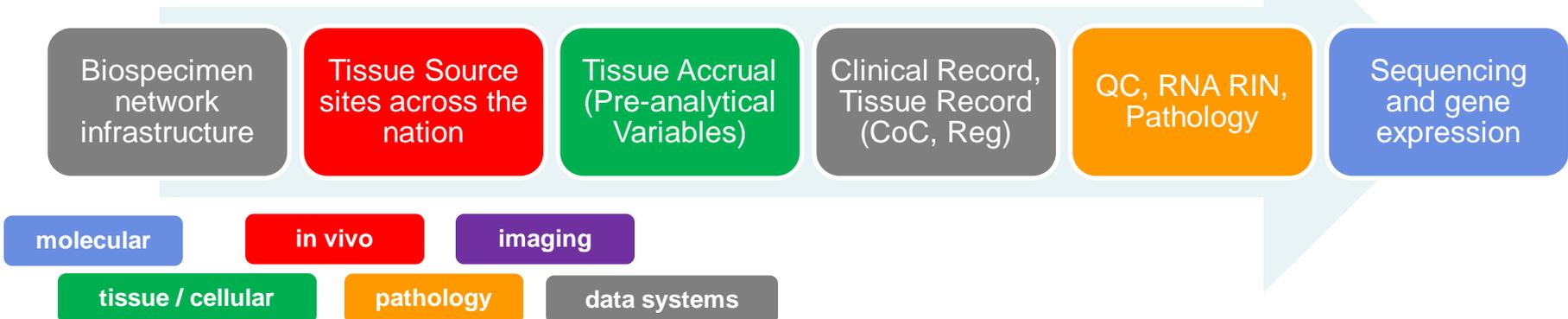


## Operational Enablement of complex multi-lab interdependent cascade expts

### 3. GEMM operation w/ Imaging, Molecular pathology (**LASP**)



### 4. integration Hub for national Biospecimen networks (**ISP**)



### 3. LASP CORE Programs



Laboratory Animal  
Sciences Program,  
L. Feigenbaum

Mouse Model Development

Transgenics  
Gene targeting / mESC

Animal Care

Strain Preservation

Cryopreservation  
Colony expansion



*in-vivo* Imaging

CT/SPECT  
PET  
Biolum/Fluor  
MRI / US

Phenotyping-PHL

NCI-Repository

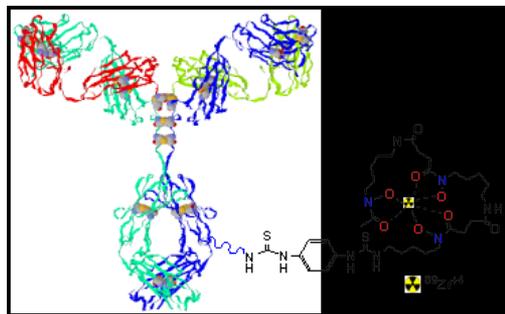
FREDERICK NATIONAL LABORATORY FOR CANCER RESEARCH

# Small Animal Imaging to Inform Dosing

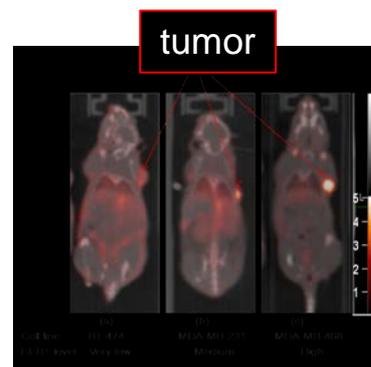
## *Panitumumab: testing targeting in tumor models*



**Integration: (DCTD/NCI):** Radio-labeling and preclinical imaging of [ $^{89}\text{Zr}$ ] - panitumumab in diagnostically relevant low doses to identify determinants of tumor uptake. Next, proceed to clinical trials to be performed at the Molecular Imaging Program, CCR/NCI.



Schematic structure of radio-labeled panitumumab  
Conjugated by Dr. Bhattacharyya (ADRD / SAIC-F)



PET anatomical Imaging performed by LASP / SAIC-F

- **Conclusion:**
  - Tumor Uptake (PET) correlates directly with Her-1 expression (Western)
- **FNL role (broader implications):** Support for intramural programs validate comprehensive Radio-Label and Preclinical Modeling capability
  - transferable to other drugs / targets to inform clinical dosing regimens

Dr.'s Hollingshead & Kaur (NCI: BTB/DTP/DCTD)

L. Feigenbaum



**FNL Capability**

Frederick National Laboratory for Cancer Research

## 4. ISP integration Hub for national Biospecimen networks



N. Roche  
G. Korzeniewski

### Quality: Permanent Foundation for Meaningful Biospecimen Collections

#### *Genotype Tissue Expression (GTEx) project NCI/OBBR*

**GTEx Project to collect normal human tissue in an ambitious 15-30 tissues per case**

- *myocardium, aorta, lung, thyroid, pancreas, peripheral nerve, liver, stomach, brain...*

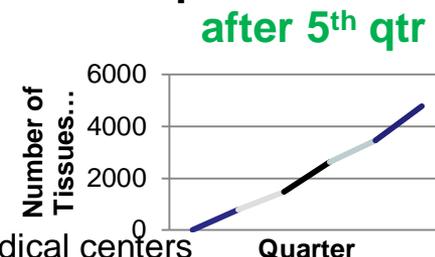
#### Requirements for **Quality** in the specimen collection campaign

- **Pre-analytical Variables**

- *Delay to fixation, time in fixative* “NCI: Biospecimen Preanalytical Variable”
- BPV Phase 2: 900 cases of **ovary, lung, colon and kidney cancers** from four medical centers
- Validation of PAXGENE protocol for GTEx (BMS, Biospecimen Methods Study started in July)

- **Histologic review** (Dr. L Sobin, part of **SAIC-F Pathology Resource Center**)

**Ethical, Legal and Regulatory team:** consent, PII protection and handling of all clinical and research records



#### **Status of Specimen Collection in GTEx**

*June 2011 SAIC-F engaged a rapid autopsy network*

Currently over **10,000 GTEx** specimens have been collected

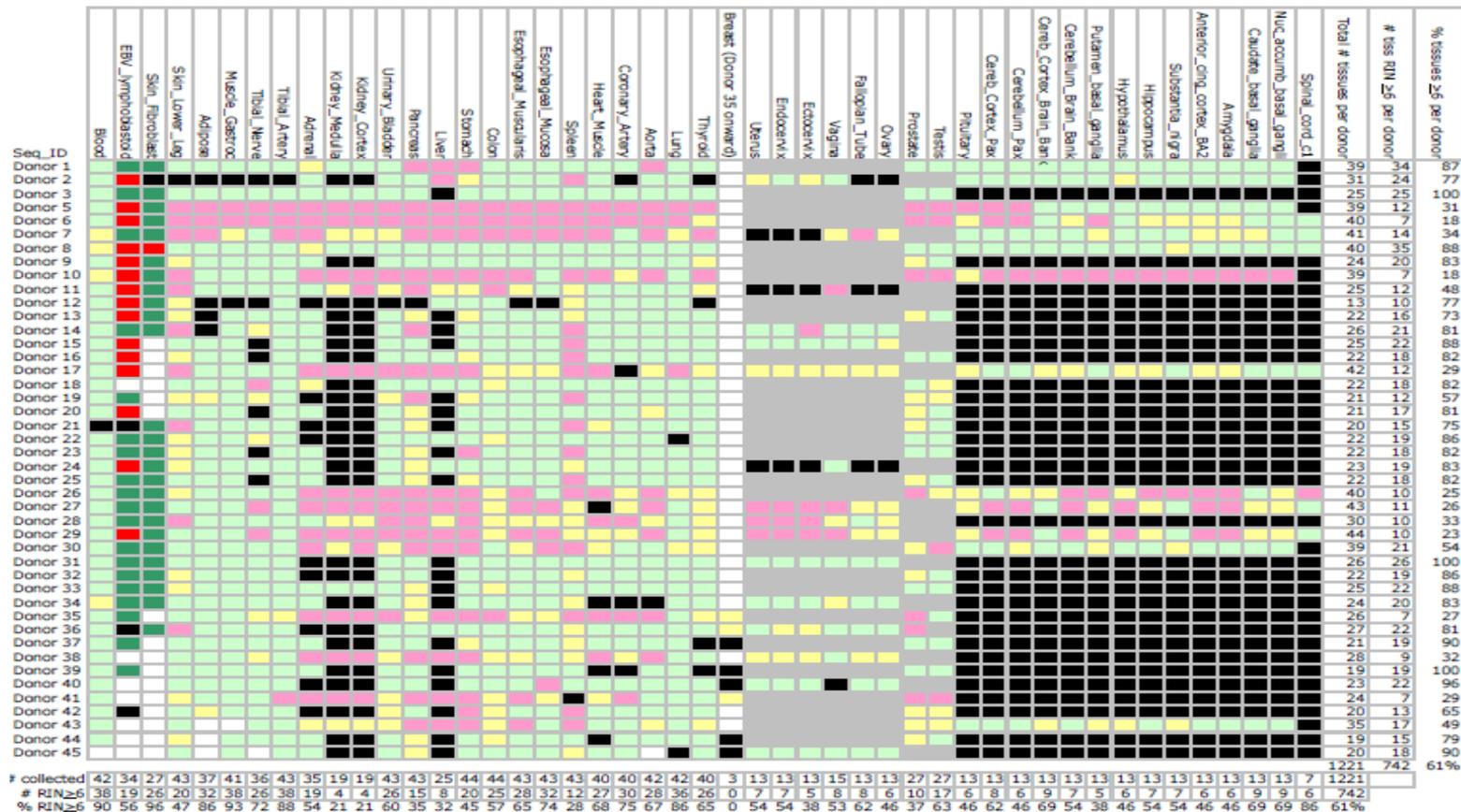
February: **GTEx project will scale** to enable collection of over 750 cases, 32,000 specimens, 300 brains

Validated results enabling SOPs as an **NCI resource for State of the Art specimen collections**

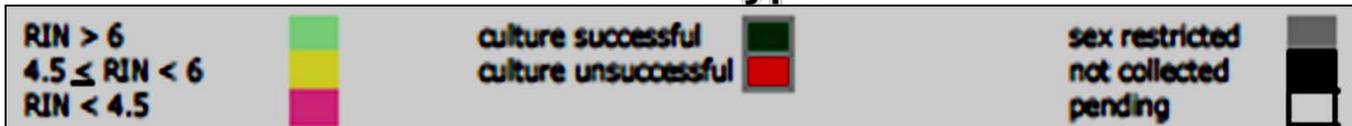
# RIN (RNA quality) values by Histologic Type tracked over thousands of samples in GTEx



Cases



Tissue type



# FNL *enabling and managing* Biospecimens *in the highly variable clinical environment*



caHUB support – multi-program experience in planning, designing, QC, operating *and* scaling biospecimen projects

NIH **GTE**x, NCI **BPV** and **BMS** projects providing

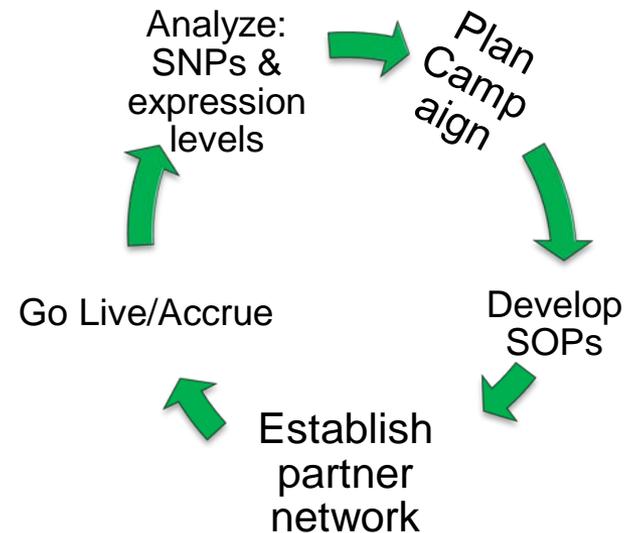
- a rich exchange of lessons learned, best practices and state-of-the-art expertise

The **Pathology Resource Center** under SAIC-F provides

- centralized detailed histologic review of **ALL** tissues collected; ensuring high quality control

Scalable, flexible management by SAIC-F of the

- **Central BioRepository** (Ann Arbor),
- **Central Data Repository** (Frederick)
- **Diverse Biospecimen Source Sites**



**Project Lifecycle continuously applied; Relentless focus on state-of-art QA/QC**

# FNL emerging strength and future

*Integration across Span of Capabilities within and beyond walls of FNLCR*



FNL expertise is most evident as the demonstrated capability to deploy multi-scale technology multi-lab resources into integrated complex (and sometimes nationally networked) cascade expts

1. The Nanocharacterization integrated assay cascade
2. The AIDS vaccine/therapy non-human primate integrated study
3. GEMM cascade w/ Imaging, Molecular pathology
4. ISP integration Hub for national Biospecimen networks

Some characteristics in the best FNL examples to date:

- Multi-technology integrated protocols,
- Relentless emphasis on QC, controls, durable impact
- Logistical operational focus (more industrial than academic)
- Familiarity with a range of contractual and regulatory complexity
- Building *de facto* standards
- Offering implementations of these to new partners

# Summary: FNL is Open



- **TSAs:** OPEN (grow to dozen, then multiple dozens) Selective. Relevant.
- **cCRADA pipeline:** OPEN (expect > 4 steady-state in negotiation post-CAF)
- **ATRF:** OPEN, driving to 100% operational output
- *Emphasis* from CTO vantage (enabling complex missions) :
  - Complex Integrated Functions of high value to National Cancer R&D community



- High quality durable capabilities, clinical and pre-clinical, brought to new partners from the long-term work within FNL directorates, now the newest National Lab
- *de facto* standards, reference quality

***Top caliber Enablement of Strategic Missions within NCI Priorities***

# Additional slides



# AIDS and Cancer Virus Program



ARTICLES

**In Press**

nature  
medicine

## Lymph node T cell responses predict the efficacy of live attenuated SIV vaccines

Yoshinori Fukazawa<sup>1,2,8</sup>, Haesun Park<sup>1,2,8</sup>, Mark J Cameron<sup>3</sup>, Francois Lefebvre<sup>3</sup>, Richard Lum<sup>1,2</sup>, Noel Coombes<sup>1,2</sup>, Eisa Mahyari<sup>1,2</sup>, Shoko Hagen<sup>1,2</sup>, Jin Young Bae<sup>1,2</sup>, Marcelo Delos Reyes III<sup>1,2</sup>, Tonya Swanson<sup>1,2</sup>, Alfred W Legasse<sup>1,2</sup>, Andrew Sylwester<sup>1,2</sup>, Scott G Hansen<sup>1,2</sup>, Andrew T Smith<sup>3</sup>, Petra Stafova<sup>3</sup>, Rebecca Shoemaker<sup>4</sup>, Yuan Li<sup>4</sup>, Kelli Oswald<sup>4</sup>, Michael K Axthelm<sup>1,2</sup>, Adrian McDermott<sup>5</sup>, Guido Ferrari<sup>6</sup>, David C Montefiori<sup>6</sup>, Paul T Edlefsen<sup>7</sup>, Michael Piatak Jr<sup>4</sup>, Jeffrey D Lifson<sup>4</sup>, Rafick P Sékaly<sup>3</sup> & Louis J Picker<sup>1,2</sup>✉

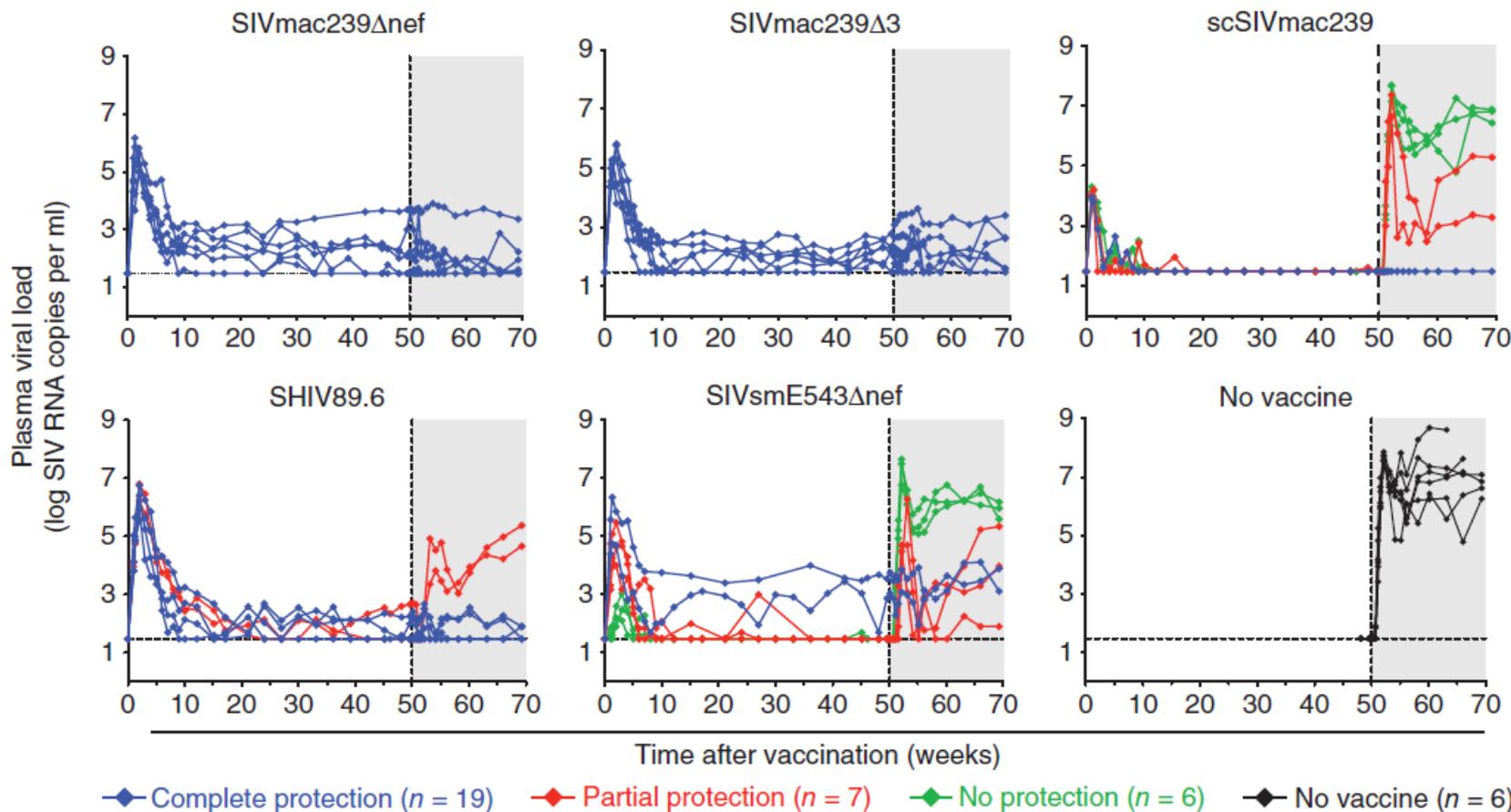
**Persistent low level vaccine immunogen expression from “immune privileged” T<sub>FH</sub> infection by LAV, maintains persistent lymph node T<sub>EM</sub> responses capable of effective early response to and control of WT challenge virus, similar to postulated mechanism of protection by rRh-CMV vectored SIV vaccines**

# AIDS and Cancer Virus Program



Comparative study of 5 different live attenuated SIVs varying in levels of virus expression, persistence and sequence match with challenge virus generated an immune response/protection matrix to evaluate potential immune correlates

nature  
medicine



# AIDS and Cancer Virus Program



**Among cellular and humoral immune responses tested, only LN T cell responses correlated with vaccine protection**

**Table 1** Kruskal-Wallis analysis of the 11 primary immune response predictors compared to the protection categories

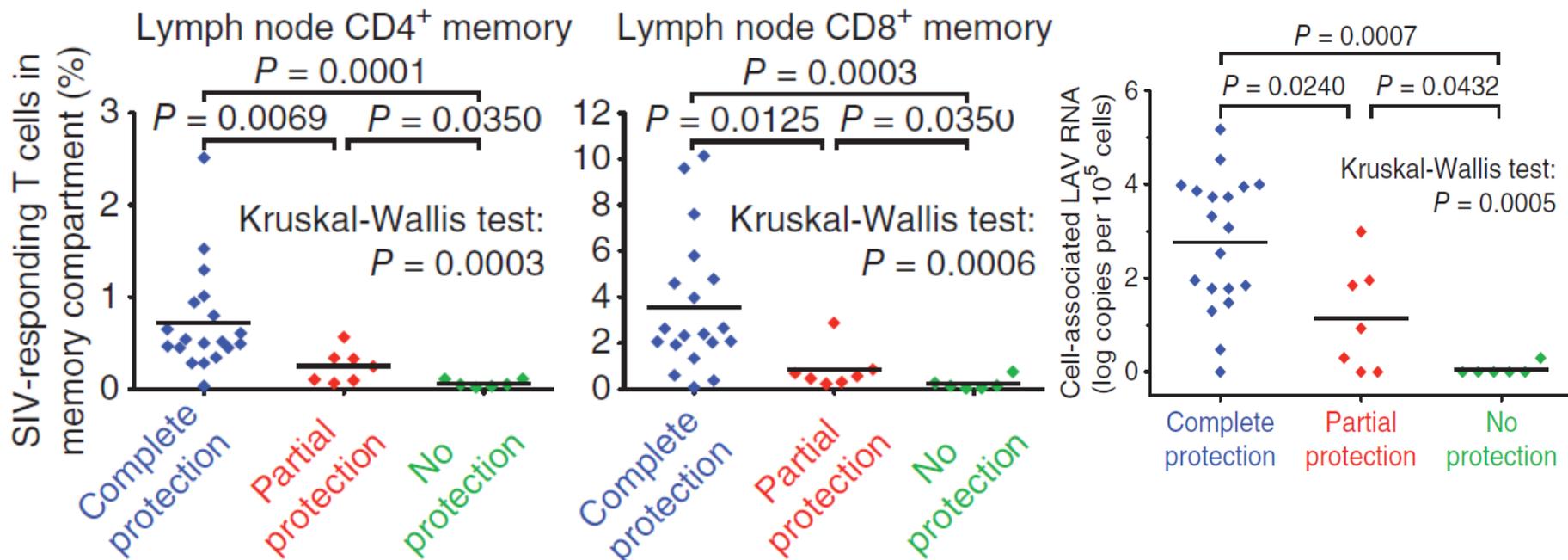
Immune predictors	Unadjusted <i>P</i>	Bonferroni-corrected <i>P</i>
PBMC CD4 <sup>+</sup> T cell response magnitude	0.0672	0.7392
PBMC CD8 <sup>+</sup> T cell response magnitude	0.0195	0.2148
PBMC CD4 <sup>+</sup> T cell response breadth	0.0301	0.3313
PBMC CD8 <sup>+</sup> T cell response breadth	0.1593	1.0000
Lymph node CD4 <sup>+</sup> T cell response magnitude	<b>0.0003</b>	<b>0.0036</b>
Lymph node CD8 <sup>+</sup> T cell response magnitude	<b>0.0006</b>	<b>0.0070</b>
BAL fluid CD4 <sup>+</sup> T cell response magnitude	0.0450	0.4950
BAL fluid CD8 <sup>+</sup> T cell response magnitude	0.0221	0.2426
SIVmac239 neutralizing antibodies	0.1458	1.0000
SIV env-specific antibodies; TCLA SIVmac251 neutralization	0.0079	0.0872
SIV env-specific antibodies; ADCC	0.0073	0.0808

Values in bold are those that reached statistical significance after Bonferroni correction. TCLA, T cell–line adapted; ADCC, antibody-dependent cell-mediated toxicity.

# AIDS and Cancer Virus Program



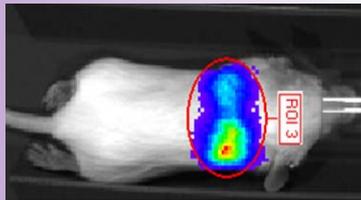
**Persistent expression of LAV RNA in LN (in  $T_{FH}$  cells) is associated with persistent LN SIV-specific  $T_{EM}$  responses; both are correlated with vaccine protection**



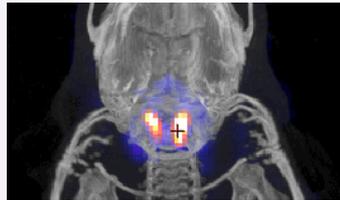
# SAIC-F LASP / Imaging and Histotechnology



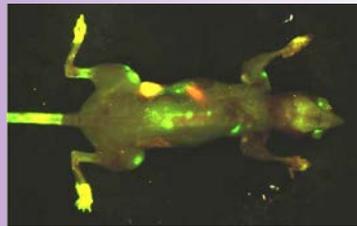
## Small Animal Imaging Program



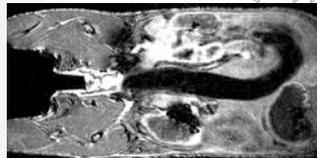
Bioluminescence



CT/SPECT



Fluorescence



MRI



1. Phenotypic analysis of GEM or xenograft models
2. Development of new targets for early phenotypic detection
3. Testing of potential new therapies

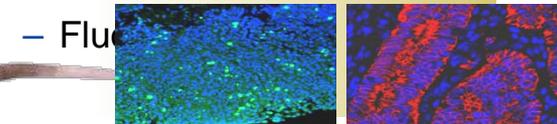
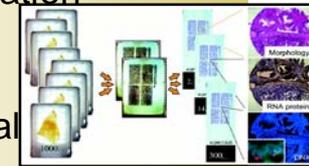
## Pathology and Histotechnology Laboratory

### Histotechnology

- Tissue processing
- Molecular histology assay development
  - Immunohistochemistry
  - *In situ* hybridization
  - etc.

- Image capture/analysis

- Bright field
- Fluorescence



### Veterinary pathology

- Study design
- Protocol development
- Data analysis
- Animal imaging validation

