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

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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)

Frederick National Laboratory for Cancer Research

Need to get this done… use the **National Lab**

We build dozens of TSA – Specialized FNLCR Approved Services

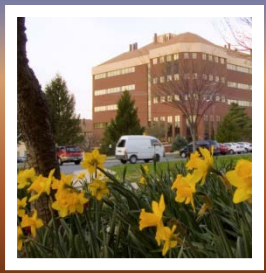
Investigator notifies our FNL PDO

Scientific Program: Defined Work Scope for FNL Lab

Execute Technical Services Agreement with external group

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^{CA} 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)

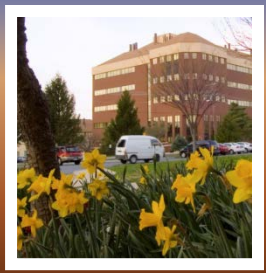
Additional 2012/13 Planned TSA Offerings from the ACVP

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

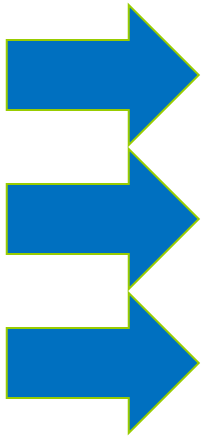
Core Labs are the key. ACVP example:

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:

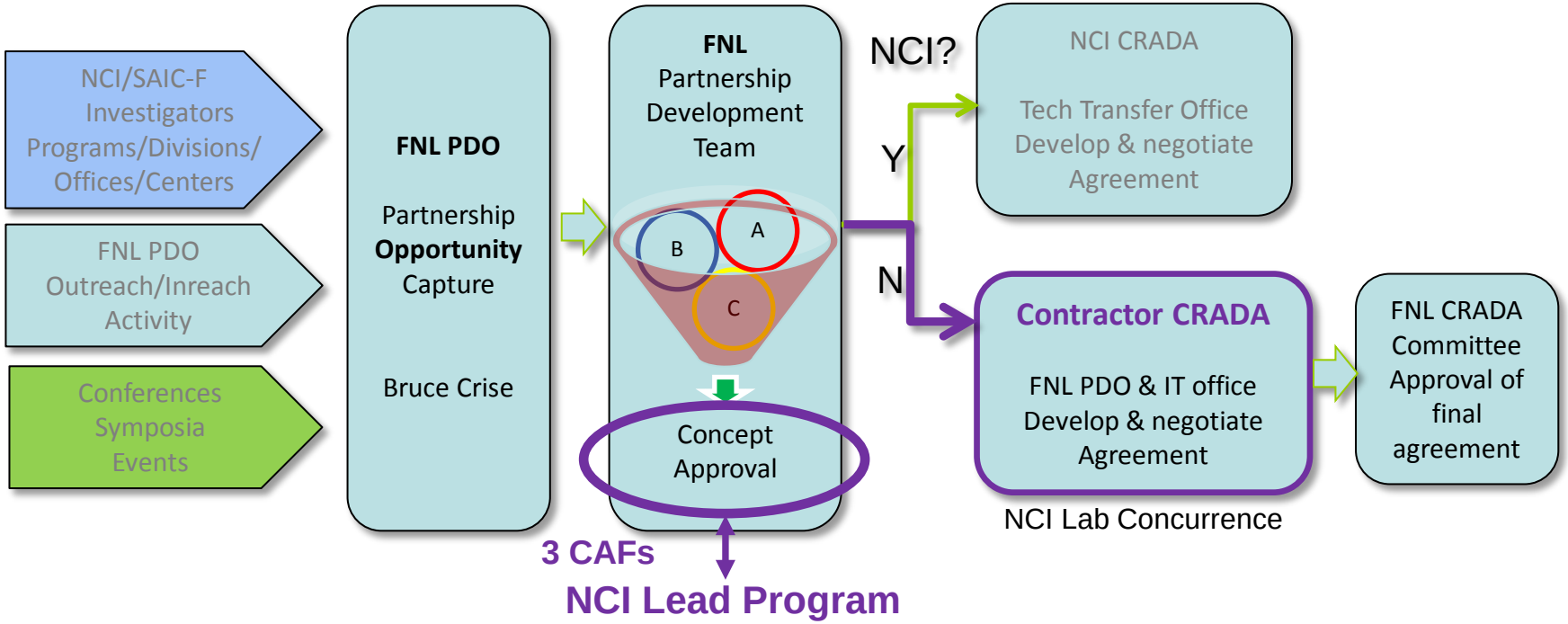
cCRADA pipeline: submissions for Concept Approval

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

cCRADA pipeline, being vetted

Breadth of partnership (in preliminary discussion)

SAIC-F	Partner
Clinical Directorate	Emerging Market Pharma
ATP / ElecMicroscopy	Industry Consortium
ATP / Proteomics	Instrument Maker
ISP / BioComputing	Pediatric Comprehensive Cancer Ctr
ATP / NCL	Pharma / Reformulating Therapeutics
ACVP	Academic Consortia (NIH funded)
exploratory	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 19th - 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

1st 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**)

Nano-particle EM → Cytotox → Plasma, Tissue surface chem → in vivo Tox → in vivo distribution → imaging

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

Virologic genomics → Disease progression NHP → T-cell immune system dynamics → Molecular pathology → Quantitative imaging → Viral lineage and genetic variation

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**)

Transgene Design & Prep → Micro-inject into egg pronucleus → GEMM → Genotypic characteriz'n founders → Experimental therapy → Imaging & Pathology

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

Biospecimen network infrastructure → Tissue Source sites across the nation → Tissue Accrual (Pre-analytical Variables) → Clinical Record, Tissue Record (CoC, Reg) → QC, RNA RIN, Pathology → Sequencing and gene expression

molecular | in vivo | imaging | tissue / cellular | pathology | data systems

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

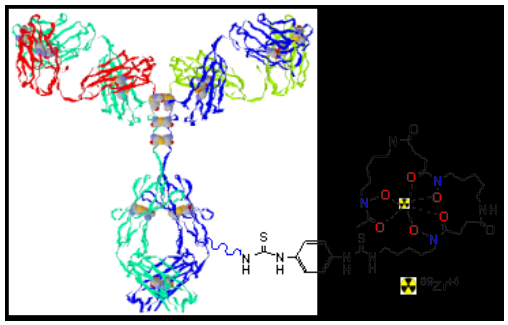
Phenotyping-PHL

NCI-Repository

Small Animal Imaging to Inform Dosing

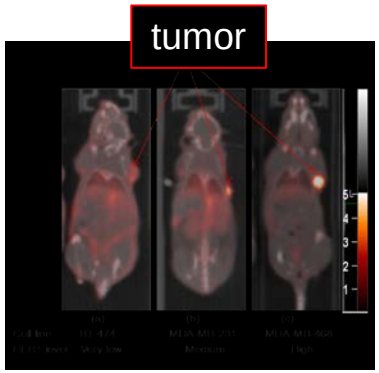
Panitumumab: testing targeting in tumor models

Integration: (DCTD/NCI): Radio-labeling and preclinical imaging of [^{89}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)**

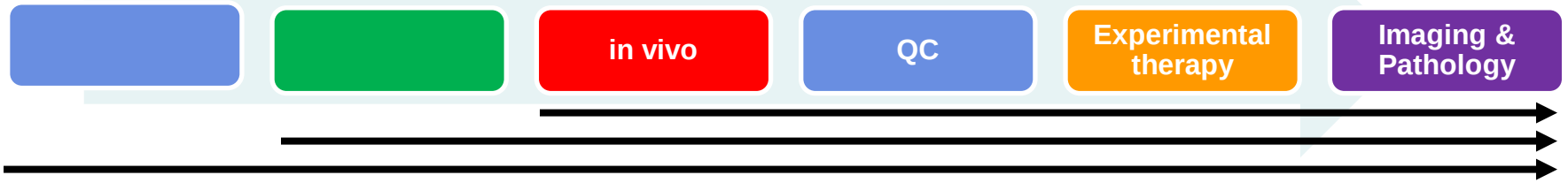


PET anatomical Imaging performed by **LASP / SAIC-F**

- **Conclusion**: Dr.'s Hollingshead & Kaur (NCI: BTB/DTP/DCTD)
  - *Tumor Uptake (PET) correlates directly with Her-1 expression (Western)*
- **FNL role (broader implications)**: **L. Feigenbaum**

Support for intramural programs validate comprehensive Radio-Label and Preclinical Modeling capability

- transferable to other drugs / targets to inform clinical dosing regiments



FNL Capability

4. ISP integration Hub for national Biospecimen networks

Quality: Permanent Foundation for Meaningful Biospecimen Collections

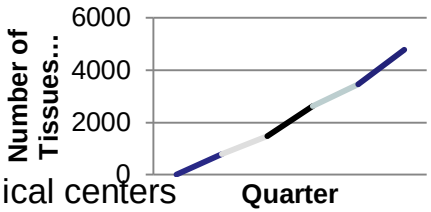
N. Roche
G. Korzeniewski

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…*

after 5th qtr



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*

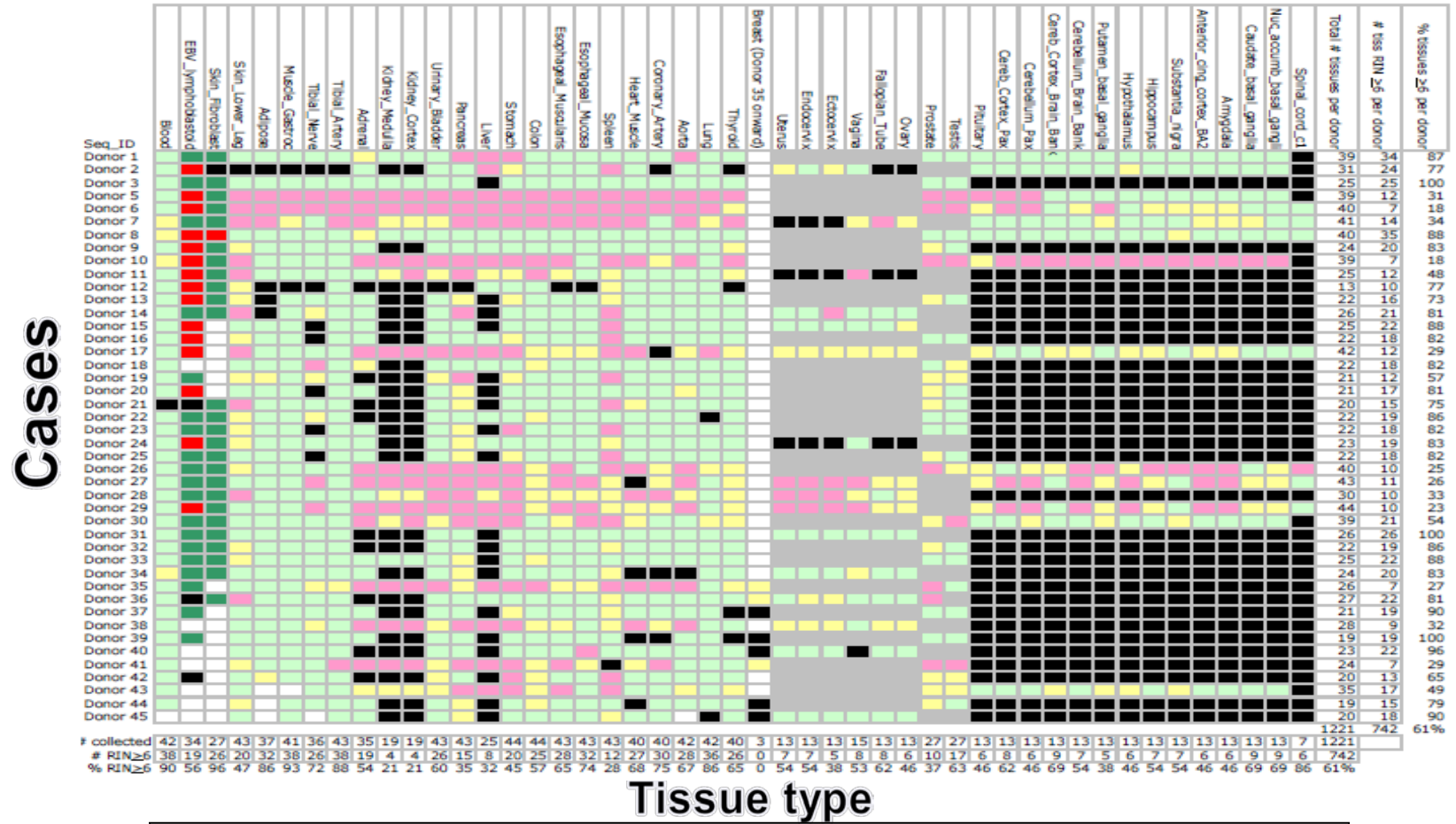
Currently over **10,000 GTEx** specimens have been collected

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



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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 **GTEx**, NCI **BPV** and **BMS** projects providing

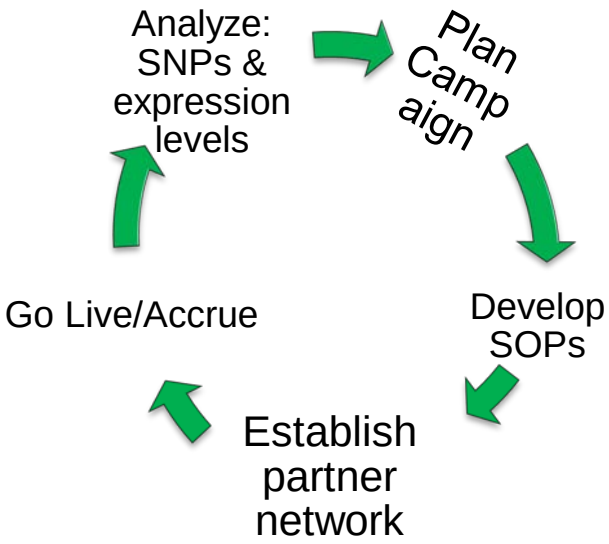
- **a rich exchange of lessons learned, best practices and state-of-the-art expertise**

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

nature medicine

In Press

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

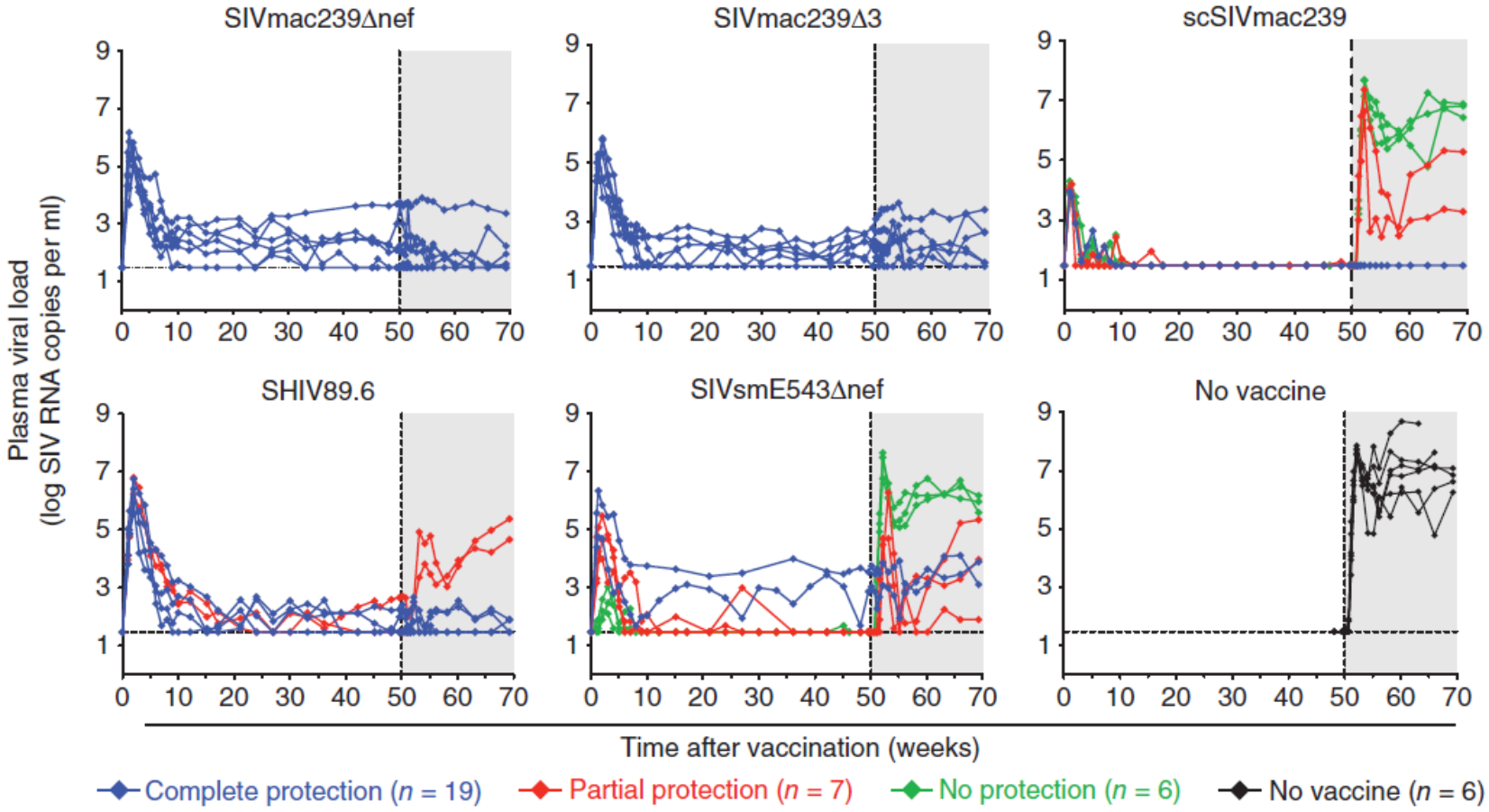
Yoshinori Fukazawa[1,2,8], Haesun Park[1,2,8], Mark J Cameron[3], Francois Lefebvre[3], Richard Lum[1,2], Noel Coombes[1,2], Eisa Mahyari[1,2], Shoko Hagen[1,2], Jin Young Bae[1,2], Marcelo Delos Reyes III[1,2], Tonya Swanson[1,2], Alfred W Legasse[1,2], Andrew Sylwester[1,2], Scott G Hansen[1,2], Andrew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

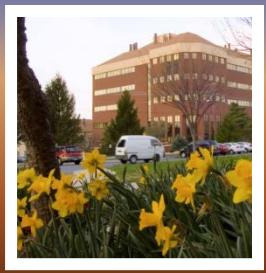
Persistent low level vaccine immunogen expression from "immune privileged" T_{FH} infection by LAV, maintains persistent lymph node T_{EM} responses capable of effective early response to and control of WT challenge virus, similar to postulated mechanism of protection by rRh-CMV vectored SIV vaccines

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

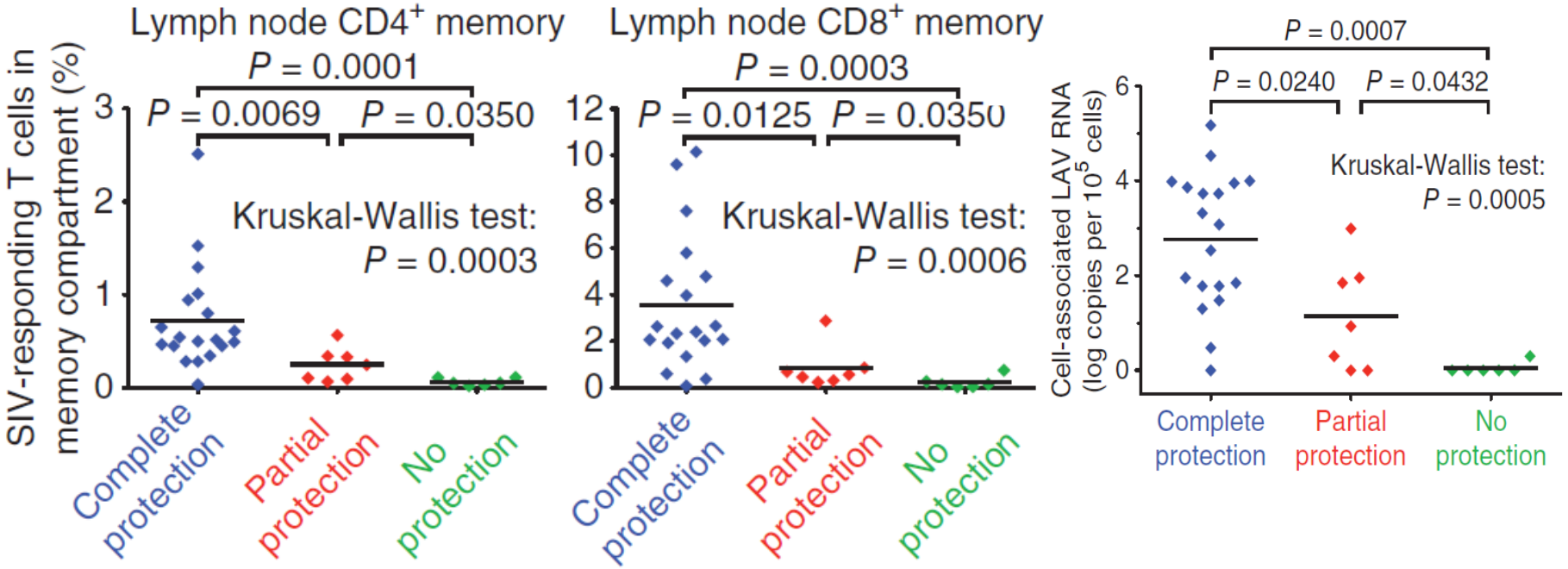
Table 1 Kruskal-Wallis analysis of the 11 primary immune response predictors compared to the protection categories

Immune predictors	Unadjusted *P*	Bonferroni-corrected *P*
PBMC $CD4^+$ T cell response magnitude	0.0672	0.7392
PBMC $CD8^+$ T cell response magnitude	0.0195	0.2148
PBMC $CD4^+$ T cell response breadth	0.0301	0.3313
PBMC $CD8^+$ T cell response breadth	0.1593	1.0000
Lymph node $CD4^+$ T cell response magnitude	**0.0003**	**0.0036**
Lymph node $CD8^+$ T cell response magnitude	**0.0006**	**0.0070**
BAL fluid $CD4^+$ T cell response magnitude	0.0450	0.4950
BAL fluid $CD8^+$ 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.

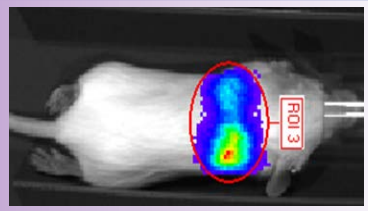
AIDS and Cancer Virus Program

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

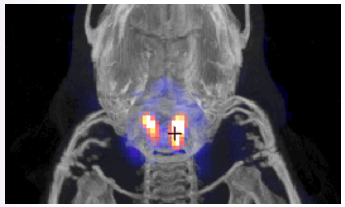


SAIC-F LASP / Imaging and Histotechnology

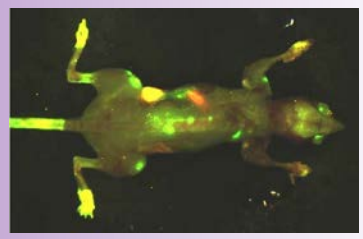
Small Animal Imaging Program



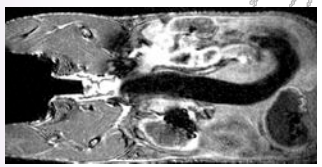
Bioluminescence



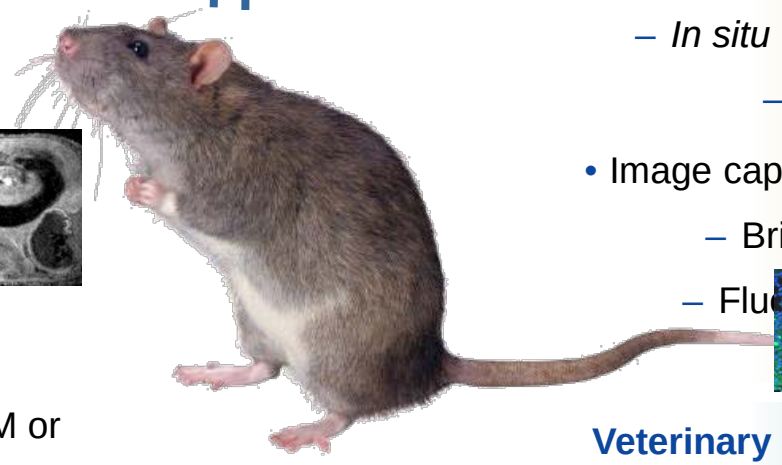
CT/SPECT



Fluorescence



MRI

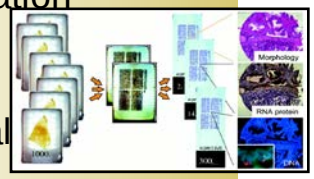


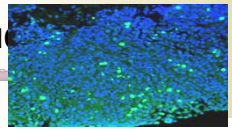
1. Phenotypic analysis of GEM or xenograft models
2. Development of new targets for early phenotypic detection
3. Testing of potential new therapies

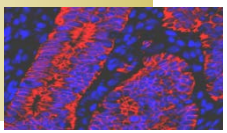
Pathology and Histotechnology Laboratory

Histotechnology

- Tissue processing
- Molecular histology assay development
  - Immunohistochemistry
  - *In situ* hybridization
  - etc.
- Image capture/anal
  - Bright field
  - Flu







Veterinary pathology

- Study design
- Protocol develop
- Data analysis
- Animal imaging val