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

2nd Meeting of the NCI-Frederick Advisory Committee (NFAC)
May 30, 2012

Summary Report

Conference Room 10, C Wing, 6th Floor
Building 31
Bethesda, Maryland

National Cancer Institute
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Summary Report

The NCI-Frederick Advisory Committee (NFAC) convened for its 2nd meeting on 30 May 2012, in Conference Room 10, C Wing, 6th Floor, Building 31, Bethesda, MD. The meeting was open to the public on Wednesday, 30 May 2012, from 9:00 a.m. to 11:25 a.m., and closed to the public on Wednesday, 30 May 2012, from 11:25 a.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. J. Carl Barrett
Dr. David Botstein
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
Dr. Kenneth Olden (absent)
Dr. Jennifer A. Pietenpol
Dr. Steven T. Rosen
Dr. Cheryl Willman

***Ex Officio* Members**
Mr. John Czajkowski
Dr. James H. Doroshow
Dr. Joseph F. Fraumeni, Jr. (absent)
Dr. Paulette S. Gray
Dr. Douglas R. Lowy
Dr. Alan Rabson (absent)
Dr. Craig W. Reynolds
Dr. Robert H. Wiltrout

Executive Secretary
Dr. Thomas M. Vollberg

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I. OPENING REMARKS

Drs. Zach W. Hall and Harold Varmus

Dr. Zach W. Hall, Chair, called to order the 2nd meeting of the NFAC and welcomed the Committee members. 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.

Dr. Harold Varmus, Director, NCI, welcomed and expressed appreciation to members for their service on this advisory committee. Dr. Varmus reminded members that the NFAC was established following questions expressed by the National Cancer Advisory Board (NCAB) for clarity about Frederick's activities, and that the forthcoming Strategic Plan for the Frederick National Laboratory for Cancer Research (FNLCR) is a further response to those concerns. In addition, the renaming of the NCI-Frederick enterprise to distinguish and define its current and potential operations and collaborative activities, as well as the new leadership at SAIC-Frederick, reflects positive changes for the organization. Dr. Varmus said that senior NCI leadership is involved with the preparation of the Strategic Plan, but clarity is needed concerning responsibility for the report and its intended audience. He noted that the FNLCR provides a remarkable opportunity for cancer research. The Strategic Plan should help integrate the National Laboratory with other NCI endeavors by enhancing collaborative activities, clarifying NCI and Contractor operations, making best use of its resources, and inviting the extramural community to work in collaboration with FNLCR's scientists.

II. UPDATE ON PARTNERSHIP EFFORTS AT THE FREDERICK NATIONAL LABORATORY FOR CANCER RESEARCH (FNLCR)

Dr. David C. Heimbrook

Dr. David C. Heimbrook, Chief Executive Officer (CEO), SAIC-Frederick, provided an update report on partnership efforts at the FNLCR. Dr. Heimbrook informed members that the highest priority for new partnerships will be with high-profile partners seeking co-location at the FNLCR for scientific collaborations that provide substantive and durable benefit to the AIDS and cancer research community. The FNLCR offers several types of partnerships. One way to prioritize partnership is on the basis of their alignment to the NCI mission and their potential impact. General partnerships provide high specific value to the partner and general value to a broader cancer research community. High-impact partnerships are aligned with the NCI's long-term strategic goals but may lack broad partner recognition. High-profile partnerships support scientific goals and convey prestige to the NCI. The co-location of partner scientists at FNLCR facilities would boost the value of a partnership by enhancing collaborative interactions with FNLCR staff.

Partnership activities span the entire FNLCR and are not restricted to the Advanced Technology Program or the Advanced Technology Research Facility (ATRF). Focus areas include major FNLCR programs, such as preclinical development acceleration activities (the Nanotechnology Characterization Laboratory [NCL] and the Genetically Engineered Mouse Models of Cancer [CAPR]); the AIDS Cancer Virus Program; the Laboratory Animal Sciences Program; the Small Animal Imaging Program; and clinical development support programs (the Clinical Assay Development Center and the Biopharmaceutical Development Program). Other priority areas are genomics, proteomics, advanced biomedical computing, biomedical imaging, and microscopy.

Dr. Heimbrook said that processes for review, approval, and management of FNLCR contractor partnering opportunities have been established. Partnering mechanisms include the Technical Service Agreement (TSA) and the Contractor-Cooperative Research and Development Agreement (Contractor-CRADA) as well as standard NIH mechanisms. The TSA and Contractor-CRADA contract vehicles are accessed through SAIC-Frederick and should be available to all researchers who are external to the NIH. The TSA provides pre-approved services, such as for a reagent assay, and primarily is used for material transfer studies. The Contractor-CRADA requires completion of a Concept Approval Form for review by the FNLCR

Partnership Development Team and approval from the NCI. Use of this mechanism includes some initial funds from the partner, with additional future monies provided based on milestones tied to the stages of work completed.

The partnership development process for TSAs includes a posting of available services on the FNLCR website through the Partnership Development Office (PDO), development of the scientific program joint work statement, and execution of the TSA. The process by which other CRADAs are reviewed and prioritized include dissemination of the available services through the PDO, concept approval by the FNLCR Partnership Development team, and approval as either an NCI- or Contractor-CRADA, the latter which requires additional CRADA Committee's approval of the final agreement. Expected timelines are 2 weeks for the TSA and fewer months for the Contractor-CRADA than for an NCI-CRADA. Dr. Heimbrook described several "virtual" partnership project requests from different customers utilizing various mechanisms. Refinements made in the partnership development process based on these experiences include modifications to cost estimate and report forms; in addition, clarifications will be provided for conceptual approval, and projects' strategic fit with the program mission will be ascertained.

Outreach activities have identified a number of potential partnering opportunities that will make personnel, services, facilities, expertise, material, and equipment accessible to both parties. Partnership opportunities encompass pharmaceutical, biotechnology, and information technology companies; nonprofit research institutions; and academia. Projects include: lung cancer, genetically engineered mouse model novel kinase inhibitors; metabolomics discovery center; bioinformatics cloud computing workflows; human papilloma virus (HPV) vaccine studies; and 3-dimensional electron microscopy tomography. One example is FNLCR's potential partnership with Agilent Technologies to identify metabolite biomarkers of cancers and perform extraction methodology by using a unique mouse model of ovarian cancer that combines mass spectrometry and nuclear magnetic resonance (NMR). This collaboration is strengthened through Agilent's hardware and software capabilities, NCI's cancer models, and FNLCR's metabolomics expertise.

The Contractor-CRADA is in the approval process, and refinements to the external website are underway. Templates and forms have been completed, the management process has been mapped, and training has been completed for FNLCR programs and laboratories. In addition, SAIC-Frederick has recruited a Chief Technical Officer, Dr. Atsuo Kuki, who will join SAIC-Frederick in July 2012, and a ribbon-cutting ceremony for the ATRF occurred in May 2012, with scientists moving to the facility in June.

In the discussion, the following points were made:

- CRADA agreements should clearly describe each partner's rights to intellectual property (IP) that might emerge from cooperative work.

- The scientific review of proposals for contractor-CRADAs is an internal FNLCR activity without input of external scientists. The process should balance scientific rigor with the desire for timeliness of review.

- Members expressed concern that the shorter timeframe for the Contractor-CRADA may result in disincentives for NCI CRADAs. The value of collaboration with the NCI provides an incentive to investigators; the NCI will diligently review the NCI CRADA process for ways to accelerate it.

- Partners have been found through a variety of ways, including through active searching by the NCI, SAIC-Frederick, or the partnering organization. The FNLCR should consider direct engagement with potential partners, including cancer centers, key academic centers, the American Cancer Society, and the Leukemia & Lymphoma Society®, to distill best ideas for development.

- Members expressed approval for the revised website.

- The strategic plan should provide direction for FNLCR partnerships and delineate the scientific foci that form priority for selecting partnerships, particularly the FNLCR's unique capabilities as a leader in advanced technology. The plan also should weigh the advantages of possible models for FNLCR, such as: (1) long-term projects that are difficult to implement through standard mechanisms; and (2) high-technology, multidisciplinary projects that cannot be conducted by one academic laboratory.

- The FNLCR would facilitate optimal partnerships by providing examples of real or imagined partnerships that illustrate types of partnerships that could benefit from the scientific focal areas or unique mission capabilities (e.g., use of the Advanced Technology Research Facility, biologics manufacturing facility to advance drugs and develop assays, mouse models, multidisciplinary capabilities, etc.).

III. FNLCR VISITING SCHOLARS PROGRAM (VSP)

Dr. David C. Heimbrook

Dr. Heimbrook described the FNLCR's Visiting Scholars Program (VSP), one component of FNLCR's training efforts to advance cancer research, diagnostics, and drug development through state-of the-art science and technology; encourage extramural access to the FNLCR; and facilitate research collaborations. Opportunities for visitors range from formal programs to non-program mechanisms, and they include high school students through mid-career investigators; there are on average 500 annual visitors through the Government programs and fewer than 100 through the Contractor; however, only a fraction of the visitors have been mid-career and established investigators.

The NCI and SAIC-Frederick recently established a VSP to systematically identify senior researchers who can both learn and contribute to the FNLCR mission. The VSP provides a cohesive programmatic approach to attract and engage visiting researchers, particularly more advanced researchers who bring special knowledge about areas of interest. The Program allows FNLCR leadership to define cross-functional opportunities to proactively recruit scientists and provides a greater breadth in funding mechanisms for training.

With seed funding support from the Office of Scientific Operations, the laboratories at FNLCR identified opportunities to be shared with the external scientific community, and initial proposal topics were published in early April 2012. The topics encompassed four areas: (1) affinity reagents against proteins that are differentially expressed in cancer cells; (2) proteomics, particularly applying mass spectrometry to quantitatively measure cancer-associated proteins in tissues and fluid samples using a cost-effective, multiplexed assay; (3) virus genomics, with a focus on new sequencing strategies for cancer-causing viruses, especially HPV and Kaposi's sarcoma herpesvirus (KSHV); and (4) advanced preclinical research that uses genetically engineered mouse models to accelerate biomarker discovery and predict the utility. NCI's and FNLCR's Offices of Communication have advertised the VSP program through web pages, brochures, social media outlets, and blast e-mails to NIH contacts and other interested groups. Responses to the proposal have come from 11 countries and have included more than 2,700 visitors to VSP web pages; 45 e-inquiries, and 20 expressions of interest. Dr. Heimbrook acknowledged the quality of proposals received, with examples of a visit and seminar planned for a senior scientist from Pacific Northwest Laboratories, another Federally Funded Research and Development Center (FFRDC), with experience on biomarker discovery and development wanting to work at the FNLCR on proteomics and affinity reagents; and proposed novel models for cost-sharing between FNLCR and other academic agencies. Some candidates have been referred to other programs as appropriate.

The proposals will be evaluated, and the FNLCR sponsoring laboratory will make final decisions; the goal is to achieve a 45-day turnaround time from completion of initial vetting to the final decision. Future steps for the VSP are to expand participation and opportunities for senior visiting scholars, improving

advertising outreach, and developing the metrics to assess the impact. Dr. Heimbrook encouraged members to spread the word to attract potential sponsors, eminent scholars and candidate research and technology development partners.

In the discussion, the following points were made:

- To better target the intended audience, the promotional materials about the VSP should clarify the unique capabilities (e.g., databases, sample repositories) that the FNLCR offers.

- The FNLCR's Strategic Plan should provide overarching principles that build and promote the FNLCR's capabilities as the "leading edge of technology," provide direction for FNLCR VSP and partnerships, engage the community through long-term consensus building to ensure that customer needs are addressed, and ensure that only critical projects are supported. The Strategic Plan also must consider the FNLCR as an integrated part of the NCI, with a mission partly defined by NCI's Divisions, Offices, and Centers.

- NCI-supported cores in institutions throughout the United States currently collaborate with individual FNLCR investigators and laboratories, but there is an opportunity to develop relationships at a strategic level.

IV. CLINICAL ASSAY DEVELOPMENT, VALIDATION, AND TRAINING

Drs. James H. Doroshow and Ralph E. Parchment

Dr. James H. Doroshow, Deputy Director for Clinical and Translational Research, NCI, NIH stated that the NCI Division of Cancer Treatment and Diagnosis (DCTD) is reevaluating its design of early-phase trials because of recent, high-profile, late-stage development failures of agents that lacked proof-of-mechanism. In this new approach, early clinical trials, designed to show proof-of-mechanism—that is, drug action on the intended tumor target—will be conducted. The DCTD has tasked the FNLCR with developing high-quality pharmacodynamic (PD) assays for use in these early, proof-of-mechanism trials. Dr. Doroshow introduced Dr. Ralph E. Parchment, Director, Laboratory of Human Toxicology and Pharmacology, FNLCR, who described the pharmacodynamics assay development support that the FNLCR provides to DCTD-sponsored early clinical trials.

Dr. Parchment explained that the FNLCR's PD assay support system is comprised of three parts: PD assay development, validation, and fit-for-purpose demonstration; PD analysis of clinical specimens; and "at-a-distance" assay quality assurance/quality control (QA/QC). Measurement variability, biological variability, and drug effectiveness all affect the ability to demonstrate successful target modulation. At the FNLCR, standard operating procedures (SOPs) for sample handling, which affect measurement variability, are considered carefully because they can be key fit-for-purpose issues, as shown by the effect of temperature on the stability of MET oncoprotein. In certain cases, such as that of Hif-1α, assay conditions that minimize the influence of specimen processing can be developed because the processes that degrade it are well understood.

Proof-of-mechanism for an agent can be evaluated at both the primary (target) and secondary (pathway) levels. For example, the effects of indenoisoquinolines, which are topoisomerase inhibitors, have been measured by immunoassay of total topoisomerase 1 (TOP1-IA). Indenoisoquinolines also result in accumulation of DNA double-strand breaks, quantifiable by an immunofluorescence assay for a particular histone, γH2Ax. Unpublished results from preclinical assays showed a dose-response effect of the new indenoisoquinoline NSC 724998 on total TOP1-IA. In addition, unpublished data from early clinical trials demonstrated that NSC 724998 treatment reduced tumor TOP1-IA in some patients. These studies evaluated effects at a single time point. The varying response over time to the topoisomerase inhibitor Topotecan, exhibited in mouse xenografts and non-tumor bearing mice, suggests that timing is an important factor when evaluating response during PD assay development.

Repeated sampling to determine treatment response over time can be evaluated more easily by using circulating tumor cells (CTCs) instead of biopsy tissue. This requires adapting PD assays to CTCs, as was done successfully for the γH2Ax assay, which was validated in cancer cell lines and blood samples from patients undergoing chemotherapy. In alliance with industry, the FNLCR is developing a universal CTC analysis device to improve CTC analytical capabilities. The alpha prototype of this instrument, developed in partnership with ApoCell, Inc., overcomes some of the limitations of existing cell marker-based systems, being capable of isolating CTCs from multiple malignancies and nonclinical models. The alpha prototype will be delivered in August 2012, and initial clinical trial support is expected by May 2013.

The FNLCR's mission includes transfer of PD assays and training other user groups to perform PD assays. The FNLCR offers onsite, laboratory-based training courses, which have been attended by academic researchers, NIH intramural researchers, and industry representatives. Also, the FNLCR supplies quality-controlled key reagents; and posts up-to-date SOPs. In addition, results and lessons-learned are shared by the various outside laboratories.

The selection of molecular targets for assay development is guided by the priorities of the NCI experimental therapeutics (NeXT) program, the NCAB's PD Functional Working Group, and *ad hoc* consultation with experts. The FNLCR's PD assay development portfolio emphasizes multiplexing of analytes for processes and pathways that are targeted.

In the discussion, the following points were made:

- To date, cell-type sorting has been a challenging problem for existing technologies, such as flow cytometry. Preliminary results indicate that the universal CTC analysis device is able to separate CTCs, which are found in blood when a tumor is present, from blood cells using differences in biophysical characteristics, although the nature of these differences are not well understood; the device should be validated against established technologies.

- Differences in pharmacokinetics and delivery make the translation of animal model-based drug development to human use challenging. To address this important issue, the FNLCR replicates existing clinical protocols as much as possible, and investigators work closely with FNLCR pharmacologists including involvement of a formulations laboratory. The FNLCR should make the expertise of its formulations group widely available to the extramural research community.

- The FNLCR's PD assay development program exemplifies its unique ability to apply resources to solve difficult problems in unconventional areas. The wide range of expertise of its personnel and its use of contract-based funding mechanisms allow it to assemble interdisciplinary teams easily and rapidly. In addition, the preclinical modeling facility is an invaluable resource, providing optimal conditions for method validation. The laboratory's internal QA program also is exceptional.

- To date, the FNLCR has trained 38 users in academia and pharmaceutical companies to conduct PD assays developed by the program. The FNLCR also conducts PD assays to support researchers who choose not to undergo training.

- The FNLCR's PD assay development program exemplifies the unique ability of the FNLCR to bring an interdisciplinary approach to a complex research problem in a rapid timeframe. This type of study that involves assembling complex arrays of interdisciplinary expertise is one model by which the FNLCR resources can be used effectively. Another future direction in which to utilize the unique resources of the FNLCR may be to identify and develop a single, transformative application, that otherwise, for any number of reasons, would not be available to the research community.

V. CLOSED SESSION

Dr. Zach W. Hall

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 2nd meeting of the NFAC was adjourned at 3:00 p.m. on Wednesday, May 30, 2012.

_____ _____

Date Zach W. Hall, Ph.D., Chair

_____ _____

Date Thomas M. Vollberg, Ph.D., Executive Secretary

Partnership Development Update to NCI Frederick Advisory Committee

David Heimbrook, CEO, SAIC-Frederick

May 30, 2012

Frederick National Laboratory
for Cancer Research

FNLCR Partnership Development
Presentation Outline

- Priorities
- Processes
- Key Partnering Opportunities
- Status Update : Partnership Development tools
- Discussion

FNLCR Partnership Development Priorities

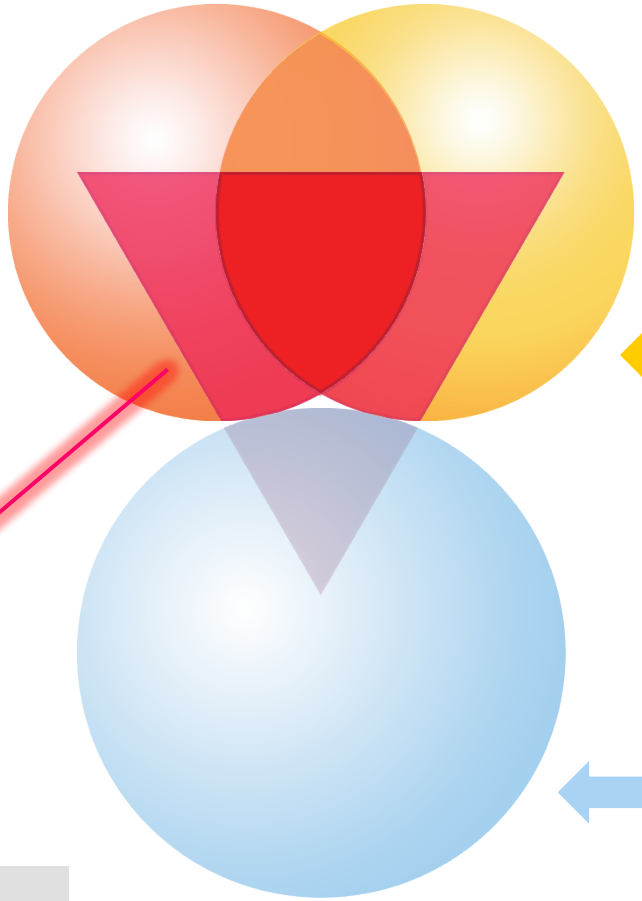
Types of Partnerships

High Profile Partnerships convey prestige to the NCI and its partnering efforts based on both the partner's name recognition and the goal

Example: big pharma evaluations of development-stage therapeutics in our preclinical models; technology development with major equipment manufacturer

High Impact Partnerships are closely aligned with specific strategic, scientific, or operational goals of the NCI, but may lack broad partner name recognition

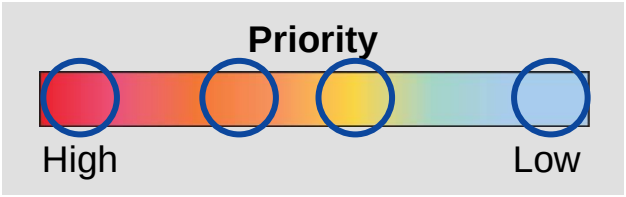
Example: SBIR / STTR recipients, award grantees, etc.



Co-location of scientists at FNLCR boosts value of all partnerships

General Partnerships are aligned with broader NCI / government goals, but provide less reciprocal value

Example: collaborations which offset infrastructure costs; simple service agreements



FNLCR Partnership Development Priorities

Focus Areas

Partnering focus in Oncology & AIDS through applied technology programs of the FNLCR:

- Technology Development and Application
  - Genomics, proteomics, Advanced biomedical computing, Biomedical imaging & microscopy, Laboratory animal sciences program, Small animal imaging program
- Preclinical development acceleration
  - Nanotechnology (NCL), Genetically Engineered Mouse Models of cancer (CAPR)
- Clinical development support
  - Clinical Assay Development Center, Biopharmaceutical Development Program
- AIDS Cancer Vaccine Program

Not restricted to Advanced Technology Program or the ATRF

Frederick National Laboratory for Cancer Research

Partnering Mechanisms Internal Reference Sheet

For general information use only

Acronym	Type of Agreement	Who can execute?		Can both participate?	Can NCI or FFRDC receive $$?	IP Promise	Which type of customer can engage?
		NCI/TTC	FFRDC/OTS				
CDA	Confidential Disclosure Agreement	yes	yes	yes	no	no	all
MTA	Material Transfer Agreement	yes	yes	yes	no	no	1,2,3,5
CTA	Clinical Trial Agreement	yes	no	yes	no	no	all
CA	Collaboration Agreement	yes	yes	yes	no	no	all
	Beta Testing Agreement	yes	yes	yes	no	no	all
TSA	Technical Services Agreement	no	yes	no	yes (FFRDC)	no	2,3,4,5
c-CRADA	Contractor CRADA	no	yes	no	yes (FFRDC)	yes	2,3,4,5
NCI CRADA	Cooperative R&D Agreement	yes	no	yes	yes	yes	3,4,5
-u-CRADA	-- Umbrella CRADA	yes	no	no	yes	yes	3,4,5
	-- Clinical Trial CRADA	yes	no	yes	yes	yes	all
-m-CRADA	-- Materials CRADA	yes	no	no	yes	yes	3,4,5
IAA or IAG	Interagency Agreement	yes	no	no	yes	n/a	2

Yellow indicates new offering

Types of Customers

1 NIH Researcher (includes NCI)
2 Other Federal researcher (i.e., CDC, DHS, USAMRIID)
3 Academic researcher (may be a grant recipient)
4 Researcher employed by a commercial entity
5 Non-Federal government funded researcher, i.e., state university

All can use TSA and c-CRADA

FNLCR Partnership Development Processes

Contractor agreements

Technical Service Agreement (TSA)

- Pre-approved services (under final review May 2012)
- Requires
  - Cost Estimate
  - Signed Agreement by the Outside Party and SAIC-Frederick CEO
  - Receipt of Funds Prior to Beginning Work

c-Cooperative Research and Development Agreement (c-CRADA)

- Requires
  - Completion of a Concept Approval Form for review by the FNL Partnership Development Team
  - Approval by the NCI Program
  - Approval by the NCI Management Operations and Support Branch (MOSB)
  - Receipt of Funds (Milestone Payment) Prior to Beginning Work

FNLCR Partnership Development Processes

Opportunity Capture, Concept Approval, Agreements

Various customer gateways

Time Target

FNLCR Website TSA - Approved Services

FNL PDO Notification

Scientific Program Joint Work Statement

Execute Technical Services Agreement

2 weeks

NCI/SAIC-F Investigators Programs/Divisions/ Offices/Centers

FNL PDO Outreach/Inreach Activity

Conferences Symposia Events

FNL PDO

Partnership Opportunity Capture

FNL Partnership Development Team

A

B

C

Conceptual Approval

NCI?

Y

N

NCI CRADA

Tech Transfer Office Develop & negotiate Agreement

Contractor CRADA

FNL PDO Develop & negotiate Agreement

NCI Lab Concurrence

FNL CRADA Committee Approval of final agreement

Months

Fewer months

FNL PDO = Frederick National Laboratory Partnership Development office

TSA = Technical Services Agreement (Contractor M-CRADA)

FNLCR Partnership Development Processes

Test Exercises

NCI "customers" submitted virtual partnership project requests:

- TSA request ; SIV qPCR/RT-PCR assays in AIDS Cancer Vaccine Program (ACVP)
- Therapeutic agent testing in Nanotechnology Characterization Laboratory (NCL)
- Contractor CRADA : Transgenic mouse development platform development with Laboratory Animal Sciences Program (LASP)
- Contractor CRADA : Evaluation of HDAC inhibitors for HIV (ACVP)
- Contractor CRADA : Develop therapeutic delivery system using virus-like particles (PEL)

Lessons learned and "tune-ups" in progress:

- TSA: Goal of 10 business day process turnaround; achieved 17 days
  - Cost estimate forms have been streamlined; report formats tuned-up
- CRADA (LASP): Process through FNL Partnership Development Team went smoothly; clarifications needed for conceptual approval; PDO to engage program sooner
- NCL: Projects declined due to poor strategic fit with program mission

FNLCR Partnership Development Opportunities

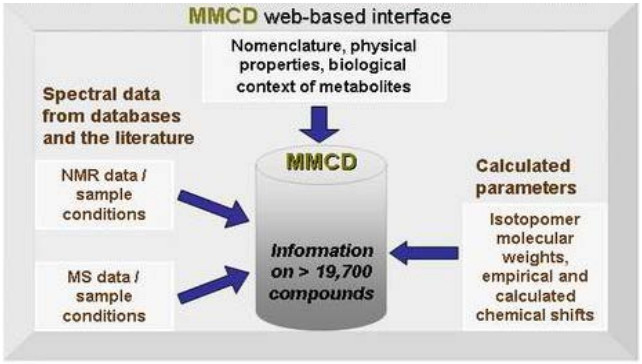
Sample Market Segments and Scenarios

Partner	Segment	FNLCR Lab/Program Alignment	Project/Mechanism
CLOVIS ONCOLOGY	Pharma	Center for Advanced Preclinical Research Cancer therapeutics development	Lung cancer GEM model novel kinase inhibitors NCI CRADA
Agilent Technologies	Biotech	Laboratory of Proteomics & Analytical Technologies (LPAT) Technology development	Develop Metabolomics Discovery Center/ Potential Contr. CRADA
Microsoft	Information Technology	Advanced Biomedical Computing Center Technology development	Bioinformatics cloud computing workflows/ Potential Contr. CRADA
FRED HUTCHINSON CANCER RESEARCH CENTER A LIFE OF SCIENCE	Non-profit Research Inst.	HPV Immunology Laboratory Assay development and validation	HPV vaccine studies/ NCI CRADA or Ctr CRADA
	Academia	Electron Microscopy Laboratory Advanced imaging techniques & assays	3-D EM tomography Potential Contr. TSAs

Scientific partnerships benefit FNLCR laboratories and partnering organizations by making personnel, services, facilities, expertise, material, and equipment accessible to both partners.

Agilent: HP / HI / Co-location Opportunity

Metabolomics Discovery Lab



- Agilent and FNLCR will develop a combined MS/NMR center to identify metabolite biomarkers of cancers
- Initial studies will utilize a unique mouse model of ovarian cancer in which tumor development is tightly controlled
- Metabolomic data will be combined with genomic and proteomic data from same mouse models to distinguish disease-related changes from background variation
- Discoveries made using the mouse model will be validated in both mouse and human diseases

Successful outcomes are strengthened through the hardware and software capabilities afforded through Agilent Technologies, cancer models available within the NCI, and metabolomics expertise at the FNLCR

Contractor CRADA Management Status

- ✓ CRADA and TSA template agreement documents finalized
- ✓ CRADA Concept Approval Forms finalized
- ✓ Management process mapped
- ✓ Management process training completed for ATP, LASP, ACVP laboratories/programs
- ✓ External FNLCR Website (TSA services)—usability/functionality testing complete

Items in final stages of completion

- Approved list of TSA services (May 2012)
- Pilot CRADA scenario test runs
- Deviated FAR clauses review and approval (TBD)
- Contract Modification (TBD)

FNLCR Website: Functionality Testing Completed

View of Services Landing Page

NATIONAL CANCER INSTITUTE

For Our Staff

Frederick National Laboratory
for Cancer Research

Enter search term

Home | Research | Business | Products & Services | Careers & Training | About Us

Home: Products and Services

Products and Services

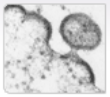
The Frederick National Laboratory for Cancer Research translates basic research findings into new technologies and treatments for patients with cancer and AIDS.

Animal Sciences

Providing cutting-edge animal services through highly developed expertise and technologies.

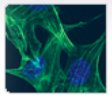
Nucleic Acid Technologies

Developing the tools and assays to define the molecular signatures of cancer and HIV/AIDS.



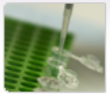
HIV/SIV

The AIDS and Cancer Virus Program is an integrated, multidisciplinary program that pursues basic and applied studies.



Imaging/Microscopy

Providing a broad range of training and support, including image acquisition and quantitative analysis.



Pre-clinical & Clinical Assays

The Frederick National Lab has expertise covering a broad spectrum of testing and clinical trial support.

Biopharmaceuticals

Product Development, GMP Manufacturing Resources and Preclinical Reagent Repository

Proteins & Proteomics

Protein expression, detection, and characterization technologies that define complex interactions leading to cancer.

Tumor Repository

Transplantable in vivo-derived tumors and in vitro-established tumor cell lines from various species.

Still need help?

For general questions, please e-mail our Project Officers at ncifoso@nih.gov or call 301-846-1108.

FNLCR Partnership Development

Recruiting New Leadership

Chief Technical Officer, SAIC-Frederick

- Atsuo Kuki, Ph.D. will join SAIC-Frederick July 9
  - BS Chemistry (Yale); PhD Biophysics (Stanford)
  - Joined Chemistry faculty at Cornell, followed by 15 years drug discovery experience in Biotech and Pharma in Chemistry and Discovery Technologies

- Recruiting and candidate evaluation assisted by interviews with local NCI leadership and external search committee

FNLCR Partnership Development

Advanced Technology Research Facility

Ceremonial Ribbon Cutting on May 21, 2012

- Concurrent with Frederick County Chamber of Commerce Centennial celebration
- 700 state and local business leaders, politicians, and dignitaries

Substantive completion mid-June

Scientist moves begin immediately thereafter

FNL Partnership Development

Conclusions

- Top priority for new partnerships will be with high-profile partners seeking co-location at FNL for scientific collaborations providing substantive and durable benefit to the AIDS and cancer research community
- Management processes for review, approval, and management of FNL contractor partnering opportunities have been established
  - Require real-world validation
- Sustained outreach activities have identified a number of potential opportunities
  - No deals signed yet
- Elements of Contractor CRADA authority still await government approval

Questions & Comments?

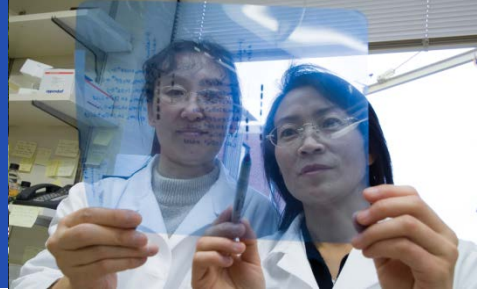
Training and Partnering:
Visiting Scholars Program

David C. Heimbrook, Ph.D.
CEO, SAIC-Frederick, Inc.

May 30, 2012

Frederick National Laboratory
for Cancer Research

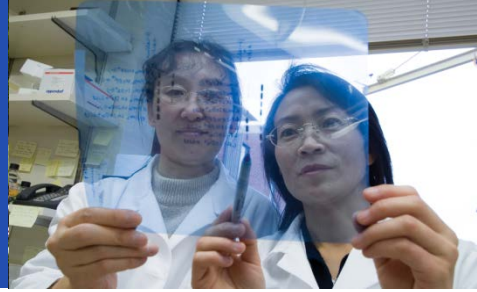
Frederick National Laboratory Endeavors to…



- Maximize impact on cancer research, diagnostics and drug discovery/development through state-of-the-art science and technology;
- Encourage extramural access to the intellectual capital and facilities of the only federal national laboratory in the United States devoted exclusively to biomedical research
- Facilitate research collaborations and enhance professional training to accelerate progress

Our training efforts contribute to all three objectives

Broad Array of Visiting Scientist Opportunities at FNLCR



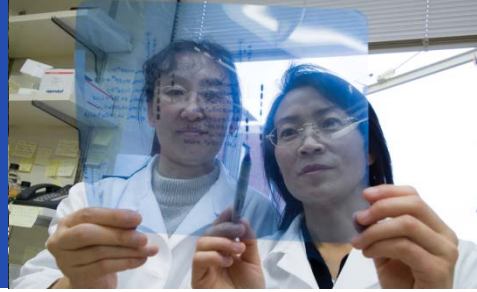
	Objective	Relevant Programs		Non-Program Mechanisms		Average # per year at FNLCR	
		Gov	Contr	Gov	Contr	Gov	Contr
HS Students	Training	2	-	-	-	50	-
Undergrad Students	Training	4	-	-	-	100	-
Post-Baccalaureate Students	Training	4	-	-	YES	21	0
Graduate Students	Training	4	-	-	YES	11	6
Postdocs	Training; Contributes Skilled Labor	4	**VSP**	YES	YES	293	31
Mid-Career and Established Investigator	Full R&D collaboration; Exchange of skills and ideas; Some training	-	**VSP**	YES	YES	70	12

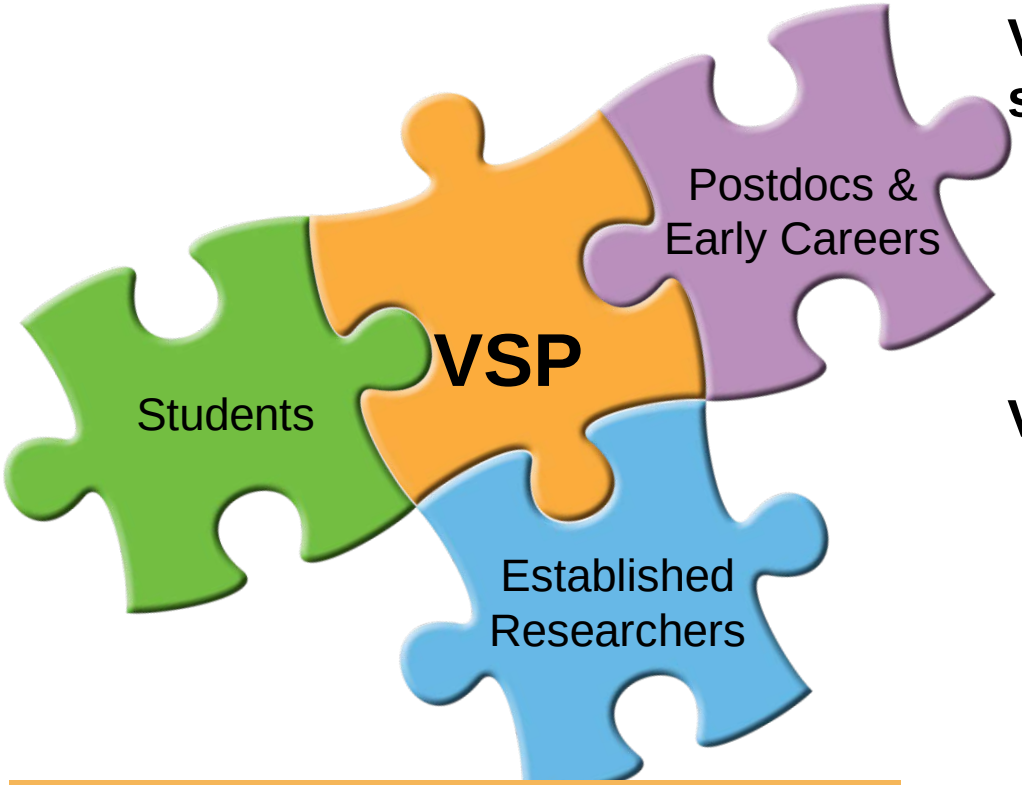
Training mission – Students at all levels

Senior visitors are generally identified by PI and focus on a single research program

Visiting Scholar Program (VSP) is an FNLCR-Level Program to systematically identify senior researchers who will both learn and contribute to the FNLCR mission, across programs, agencies, and affiliations

The Visiting Scholar Program Adds Value





Programmatic approach provides cohesiveness and coordination for attracting and engaging visiting researchers

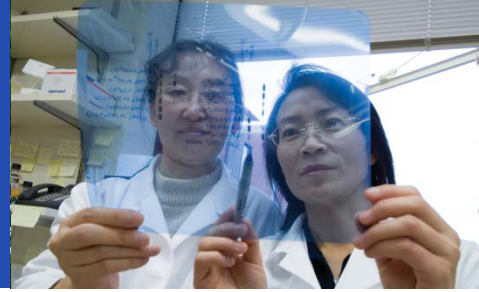
VSP Integrates multiple visiting scientist approaches at FNL level

- Common outreach to leverage government and contractor programs

VSP adds new functionality

- Define specific opportunities to recruit for
- Seek more advanced researchers with reciprocity in training and learning
- Greater breadth in funding mechanisms

Visiting Scholar Program Kick-start with Sponsor-defined Opportunities



Affinity Reagents

Developing a portfolio of novel approaches to **generate affinity reagents against proteins differentially expressed in cancer cells**.

Proteomics

Developing a cost-attractive, multiplexed assay that is easily accessible to physicians and **uses mass spectrometry to quantitatively measure cancer-associated proteins** in tissue or fluid clinical samples.

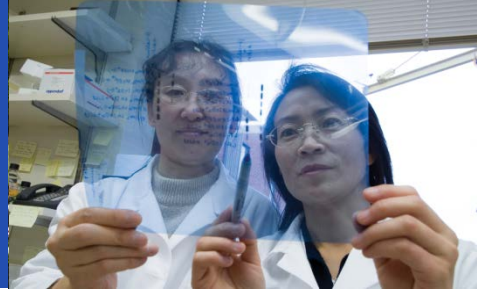
Virus Genomics

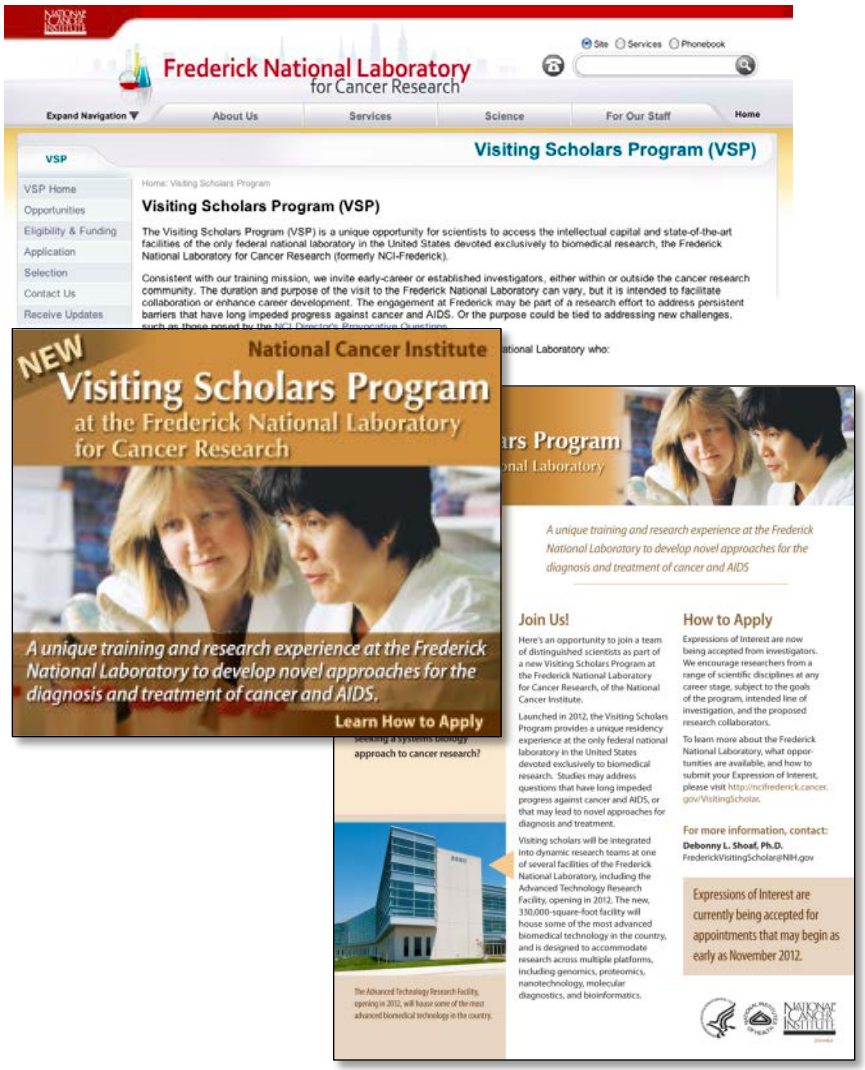
Apply state-of–the-art sequencing and analysis capabilities and develop **new analysis strategies for cancer-causing viruses**. Focus on human papilloma viruses (HPV) and Kaposi's sarcoma herpesvirus (KSHV).

Advanced Preclinical Research

Visiting Scholars will work with NCI Center for Advanced Preclinical Research (CAPR) researchers to address challenges in the use of **Genetically Engineered Mouse Models (GEMMs) to accelerate biomarker/molecular discovery, and improve utility in predicting therapeutic outcomes**.

Advertising the VSP

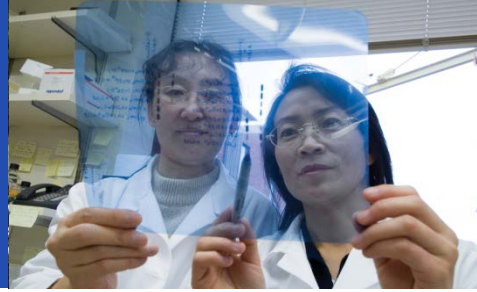




FNL Office of Communications & NIH Office of Communications and Education (OCE)

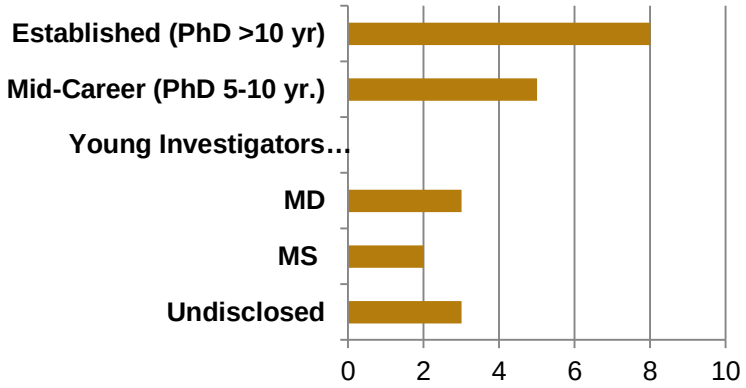
- VSP Web Pages
- Brochures
- Social Media
- Banner Ads and Newsletters in ***Nature, Biotechniques, Genomeweb***
- Email to select NIH contacts, 8 interest groups, 19 NCI DOCs, 11 external societies, institutes, organizations

Broad Response to Initial Proposals: Success Indicators



International Interest

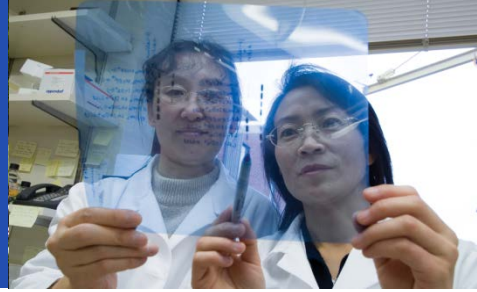
US, Argentina, Brazil, Canada, China, India, Kenya, Korea, Sweden, Turkey, United Arab Emirates



In ~45 days (Apr 1 – May 16):

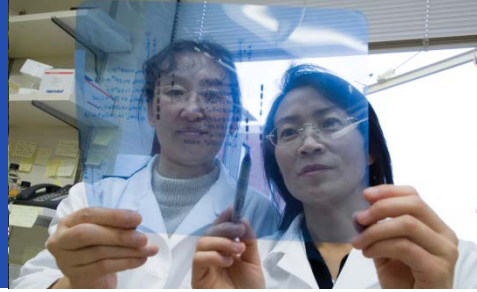
- 2,719 Visitors to VSP web pages
- 45 inquiries to Visiting Scholar e-mail box
- 20 Expressions of Interest submitted
- Mostly mid-career & established researchers
- Range of resource requested $0 to $100k
- Duration 2 days to 2 years

Response to Initial Proposals
Notable opportunities



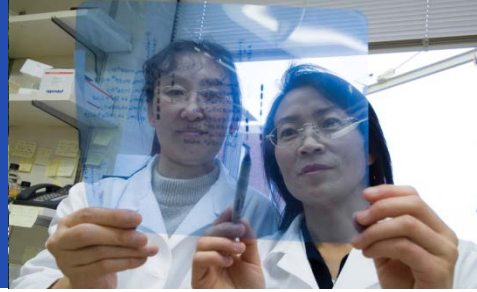
- Senior scientist from Pacific Northwest Laboratories (FFRDC) with experience on biomarker discovery and development wishes to explore a “sabbatical” at FNLCR to work on Proteomics and Affinity Reagents proposals
  - Visit and seminar planned
- Novel models for cost-sharing between FNLCR and other academic and government agencies proposed
- References to other visiting scientist programs provided to some candidates, as appropriate

Next Steps for the Visiting Scientist Program



- Complete evaluations of existing proposals and establish first Visiting Scientist scholars at Frederick National Lab
  - "Sponsor" lab (funding source) makes final decision
  - Goal – 45 day turnaround time from completion of initial vetting to final decision
- Expand participation & opportunities within FNLCR programs (FY 2013 and beyond)
  - Expand breadth of investigator-sponsored proposals
  - Optimize outreach and advertising based on 2012 results
- Develop metrics to assess impact of Visiting Scholars

What We Ask of You



- **Engage!** Help us spread the word to attract potential sponsors, eminent scholars and candidate research & technology development partners
- Suggest ways to improve the VSP

Contact:

Debonny Shoaf, Ph.D.

FrederickVisitingScholar@NIH.gov

Phone: 301-378-0225

- *or visit our website* : http://web.ncifcrf.gov/VisitingScholar

Clinical Assay Development, Validation & Training

Pharmacodynamic Assay Support of DCTD-Sponsored Early Clinical Trials

May 30, 2012

NCI Program Lead - James H Doroshow, MD
Division of Cancer Treatment & Diagnosis

FNLCR Lead - Ralph E Parchment, PhD
Director, Laboratory of Human Toxicology & Pharmacology
SAIC-Frederick

Should Early Phase Trials Be Designed to Generate Evidence Supporting Proof-of-Mechanism?

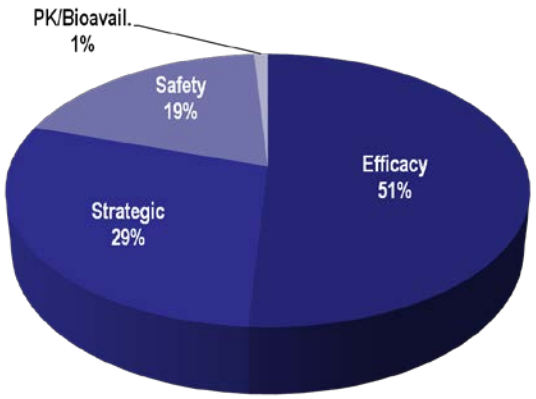
- **Background:** Recent cancer small molecule development has been characterized by both high profile successes (crizotinib; vemurafenib) and failures (BSI-201). Successes were rapid and resulted from molecular stratification; failure associated with lack of P-of-M.

- **Feasibility:** Should we only develop agents that can be brought to the clinic under conditions that demonstrate P-of-M? Should resources be refocused around this paradigm with a consequent decrease in the number of trials performed and drugs evaluated?

- **Implications for success:** Fewer costly, late stage development failures; improved understanding of actual mechanism of action or resistance in the clinic; improved rationale for the selection of combination therapies for development.

Should Early Phase Trials Be Designed to Generate Evidence Supporting Proof-of-Mechanism?

- **Demonstrate drug action on intended tumor target (proof of mechanism) in a human malignancy early in development**
  - evaluate hypotheses surrounding mechanism of action *per se*
  - evidence of target modulation in the clinic assists decision to move agent forward, or not . . .
  - evaluate relationship of drug schedule and systemic exposure to target effects
  - examine relevance of marker chosen to represent target modulation
  - prior to expectation of efficacy



Overall Phase II Success Rate 18% (2008-2009)

Nature Rev. Drug Discov. 10: 1, 2011

- **NOT predictive of clinical benefit**
  - only later stage (larger) trials can define relevance of target modulation to tumor growth inhibition
  - only consequent changes in cell biology (and perhaps biochemistry) would be expected to predict clinical benefit

Clin. Cancer Res. 14: 3658-3663, 2008

Modern Drug Development Needs PoM/PoC-Based Trials

DCTD tasked FNLCR/SAIC-F to provide pharmacodynamic (PD) assay support

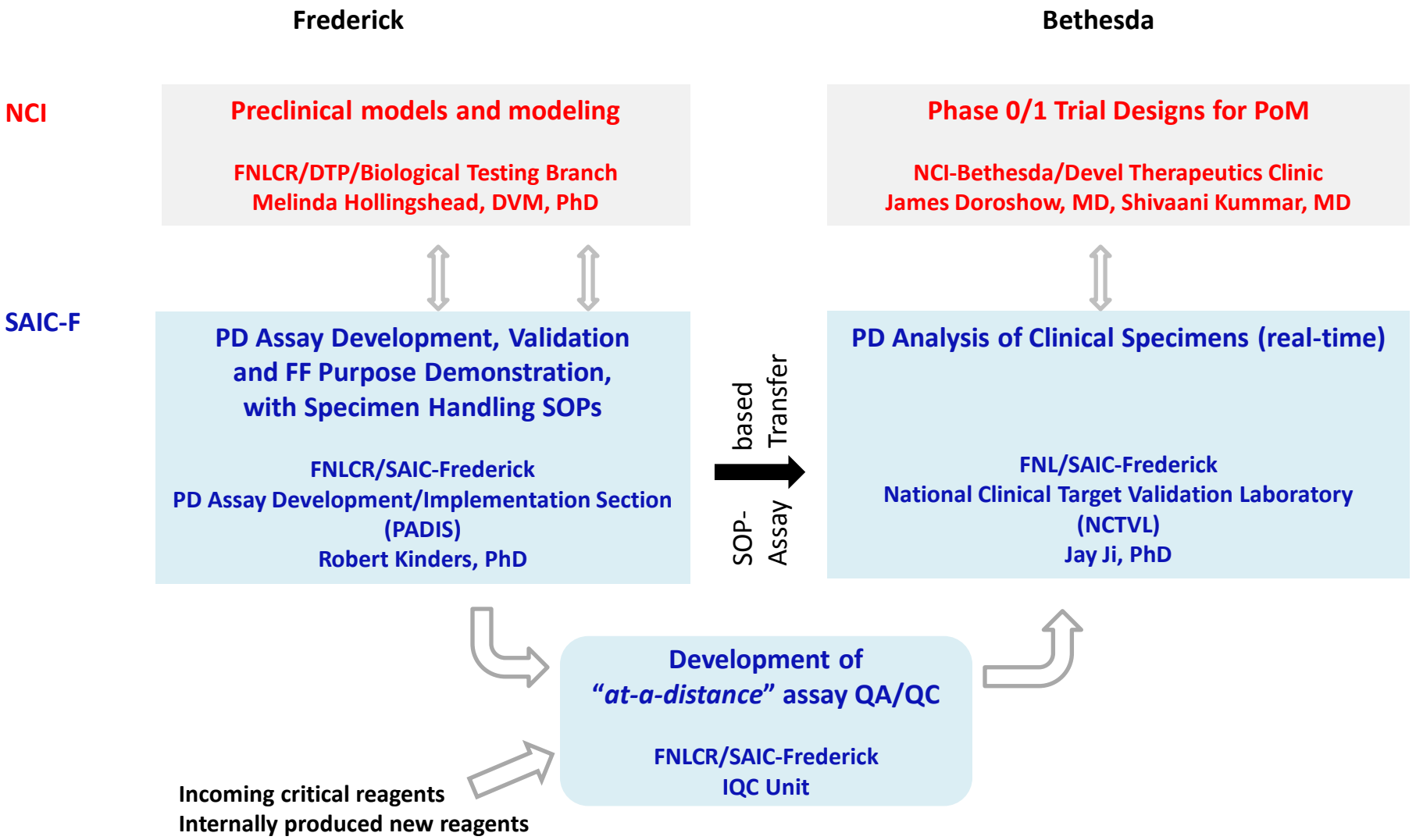
- PD assay development lab (PADIS) - develop, validate and prove assay fitness-for-purpose
- Clinical PD lab (NCTVL) – real time PD analysis of internal and CTEP trial specimens
- Long-term, open access to clinically proven assays, while maintaining assay quality

Portfolio of PD assays for high value molecular responses, based on expert input

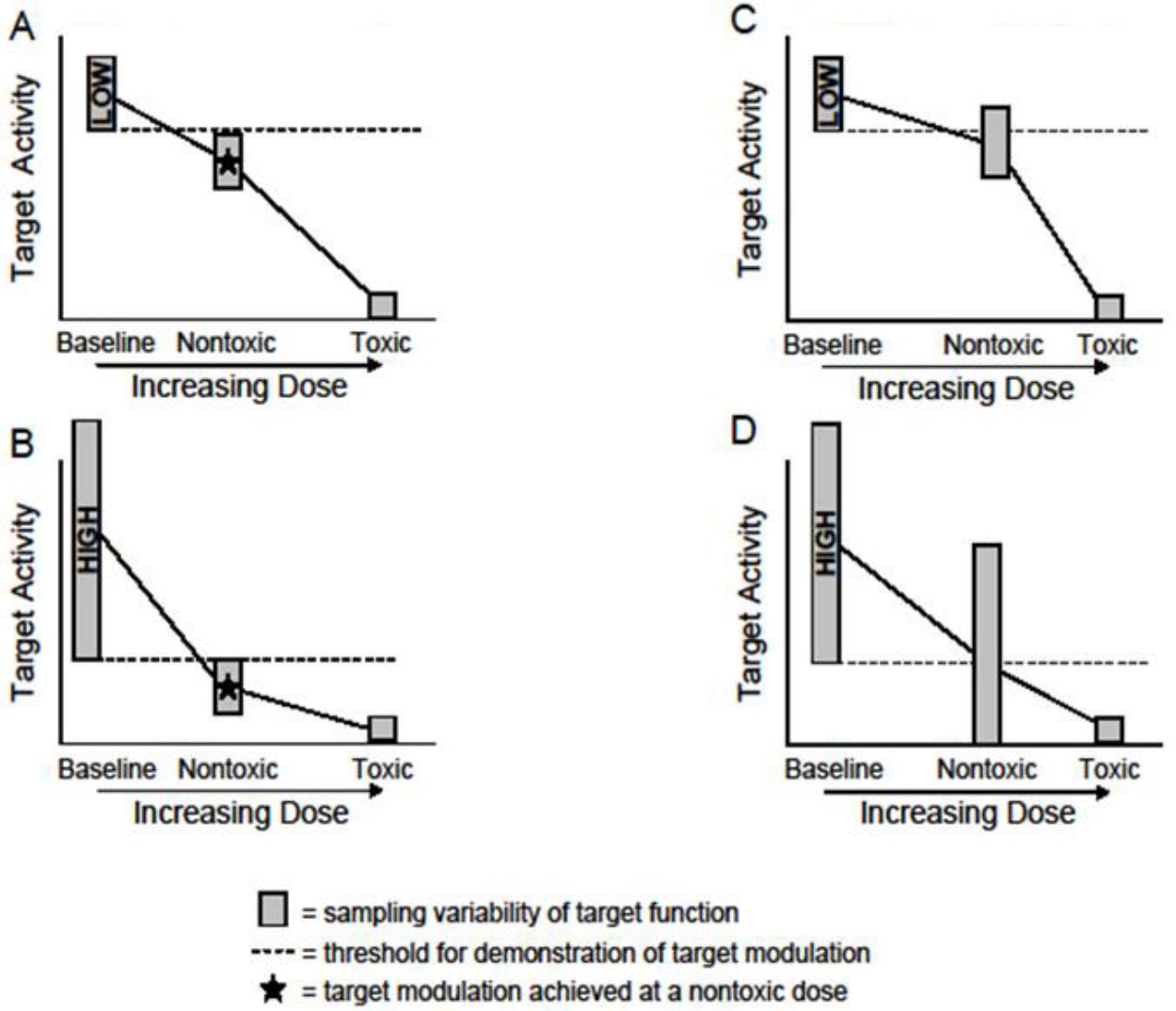
Developmental Therapeutics Clinic to explore trial designs incorporating tumor PD

Mandatory target assessment during CTEP Phase 1 trials (“no assay, no trial”)

Integrated PD Assay Support of the DCTD Program



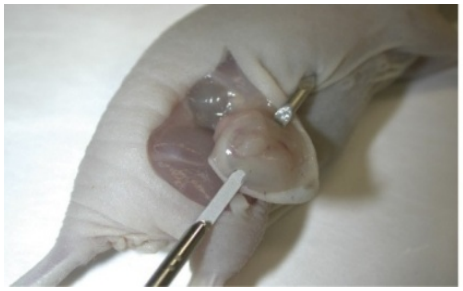
Both Target Variability and Drug Drive PD Success

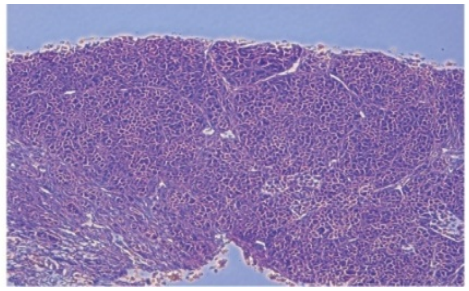


Clin. Cancer Res. 14: 3658-3663, 2008

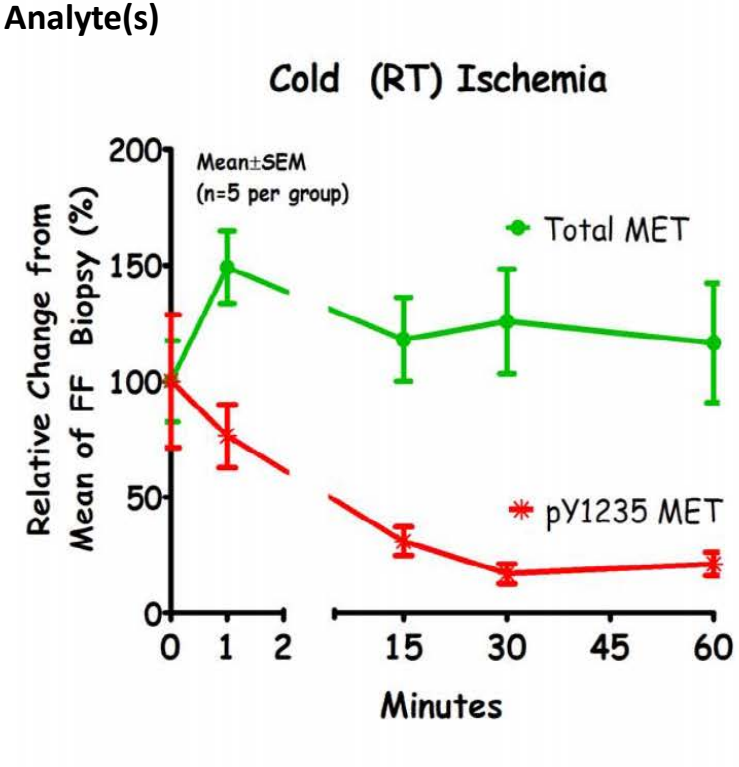
Specimen Handling SOPs – a Key Fit-for-Purpose Issue

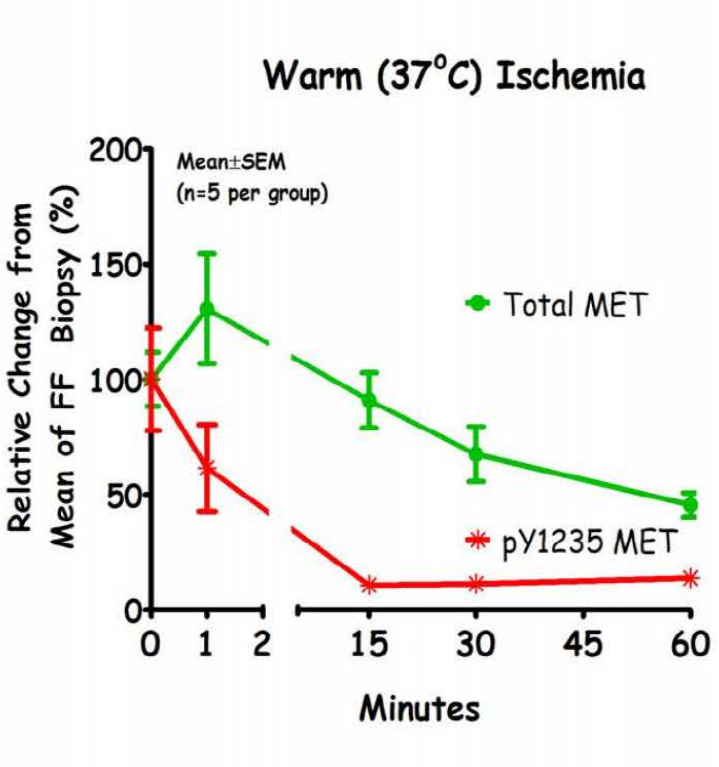
Develop with Clinically-Relevant Samples





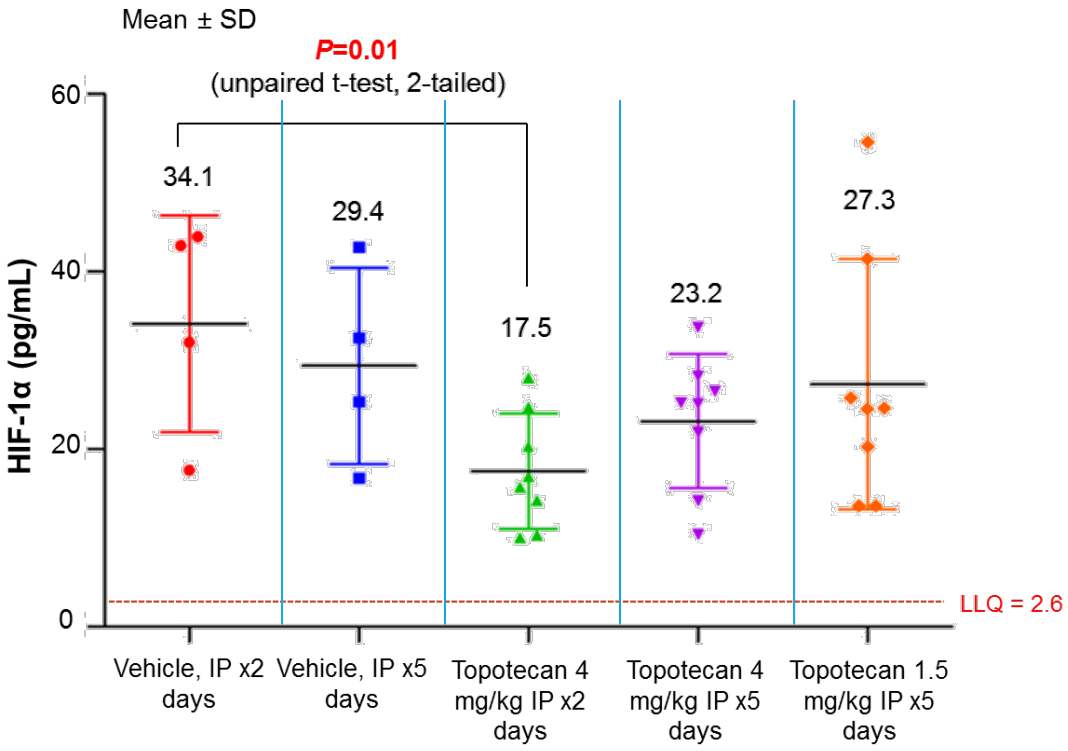
Stabilize the Analyte(s)

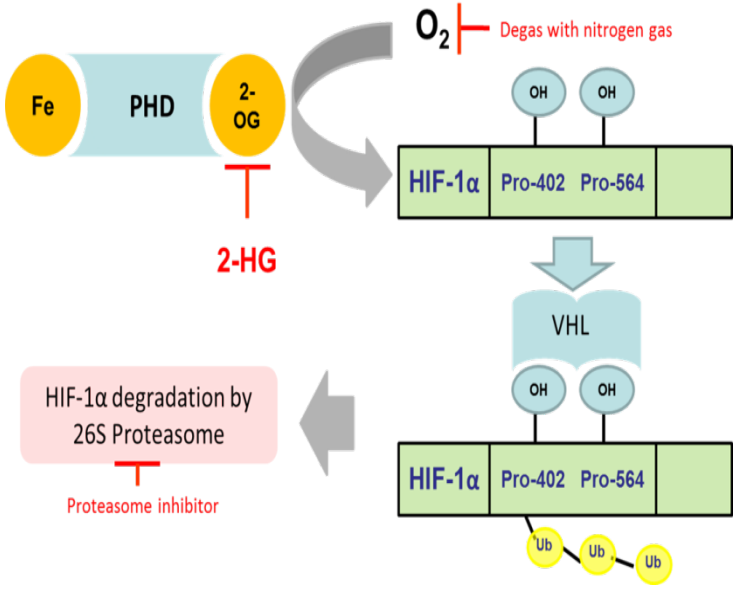




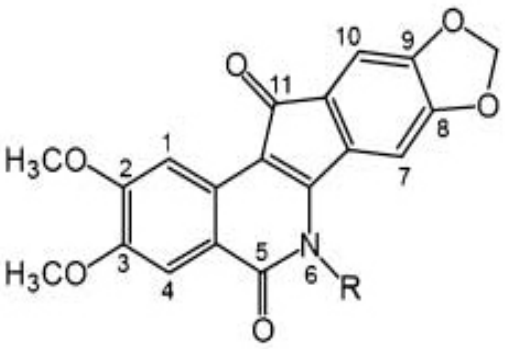
Minimize the Influence of Specimen Processing - Key for Immunoassay of Hif-1α (Hif1α-IA)

Stabilize the Analyte(s)





Development of Indenoisoquinolines with Clinical PD Assays



R =

—CH_3	**NSC 314622**
—$(CH_2)_3$—NH—$(CH_2)_2OH$	**NSC 706744 (MJ-III-65)**
—$(CH_2)_3$—N⟨ ⟩N	**NSC 725776**
—$(CH_2)_3$—N⟨ ⟩O	**NSC 724998**

Unique, non-camptothecin Topo I inhibitors

- chemically stable
- low cross-resistance with camptothecin analogs (irinotecan; topotecan)
- not substrates for ABCG2 efflux pump
- prolonged stability of complex
- unique patterns of DNA cleavage
- produce dose- and time-dependent DNA double strand breaks → γH2Ax

Discovery/Development Path

- discovered by Yves Pommier (NCI intramural program)
- developed by DCTD
- FIH Randomized NCI Phase I trial of NSC 724998 vs 725776

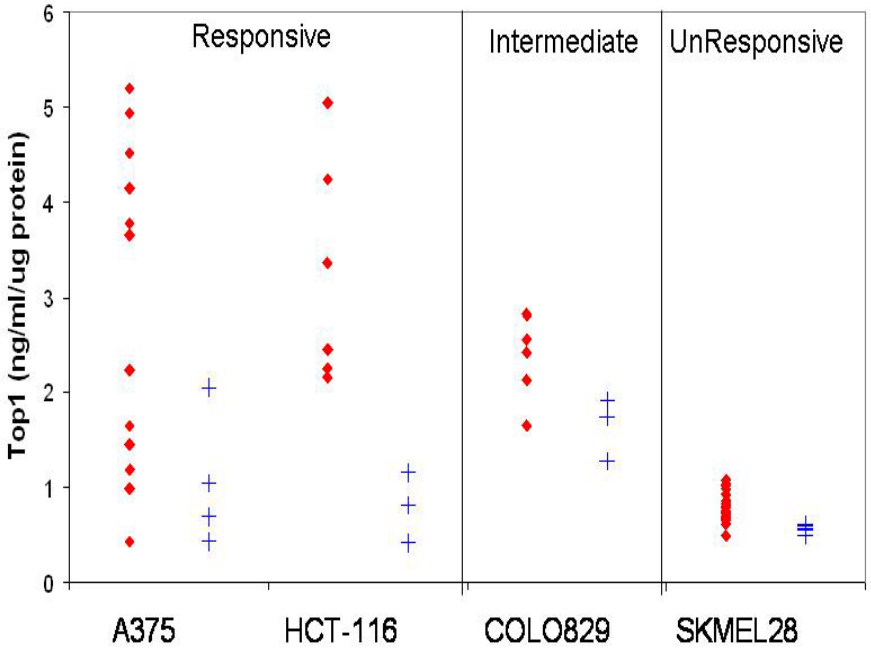
Develop comprehensive PD package for proof of mechanism evaluation PRIOR to FIH studies:

1º level PD: TOP1-immunoassay (new)
2º level PD: γH2Ax-qIFA
2º level PD: γH2Ax-CTC

Immunoassay for total Topoisomerase 1 (TOP1-IA) - Preclinical

Effect of Topotecan on TOP1 Levels in Xenograft Bx Specimens

4h Topotecan (15 mg/kg) vs Vehicle Control

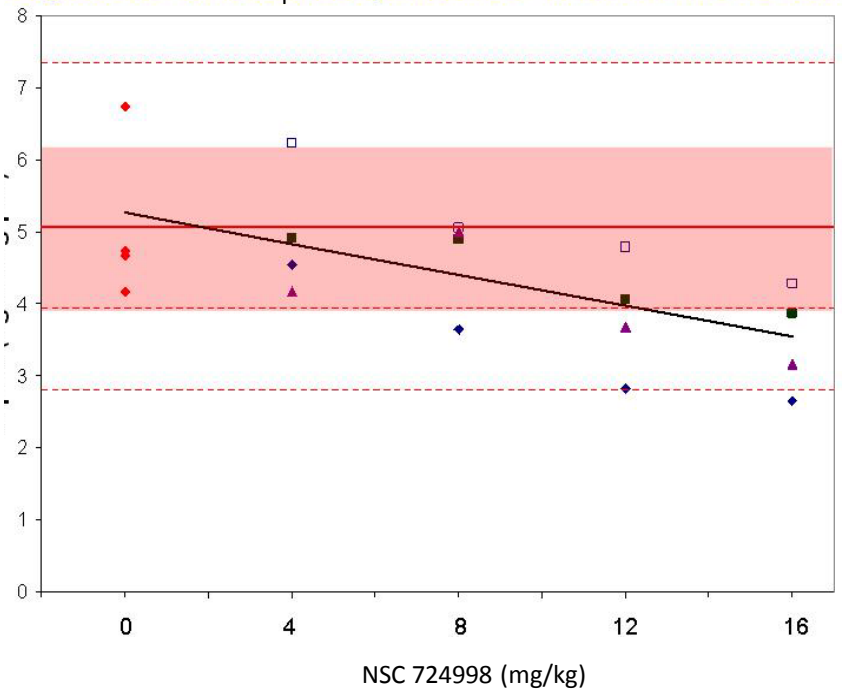


Effect of NSC 724998 on TOP1 Levels in A375 Xenografts

Vehicle Range:
Solid red line = Avg

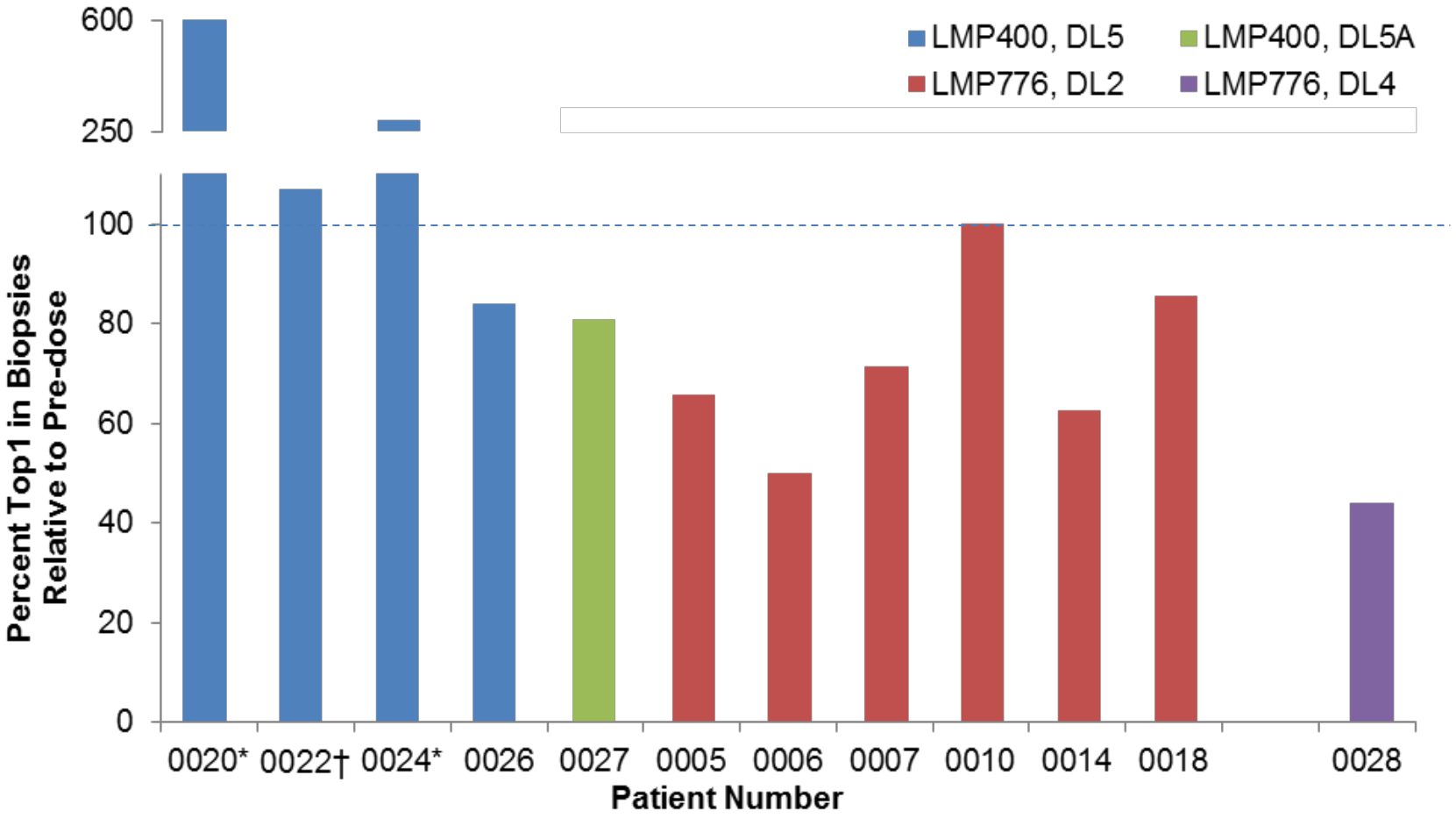
Dashed red line = Avg ± 1 and 2 SD

Black line = Dose Response of indeno NSC 724998



PlosOne, submitted

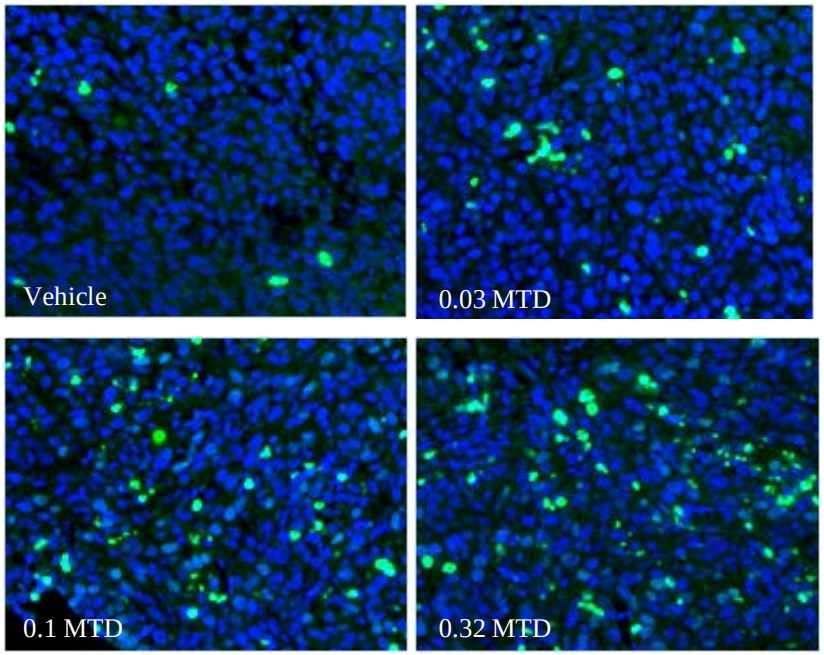
Immunoassay for total Topoisomerase 1 (TOP1-IA) - Clinical



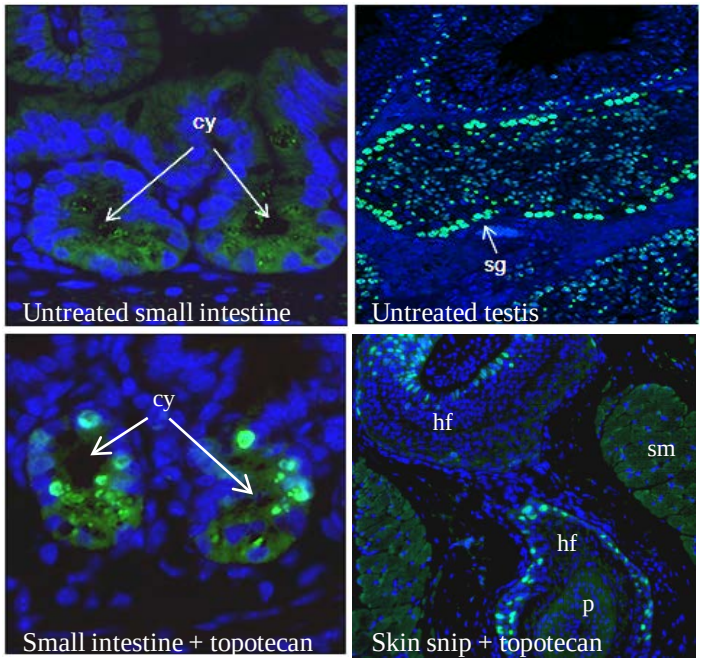
Unpublished, ASCO 2012

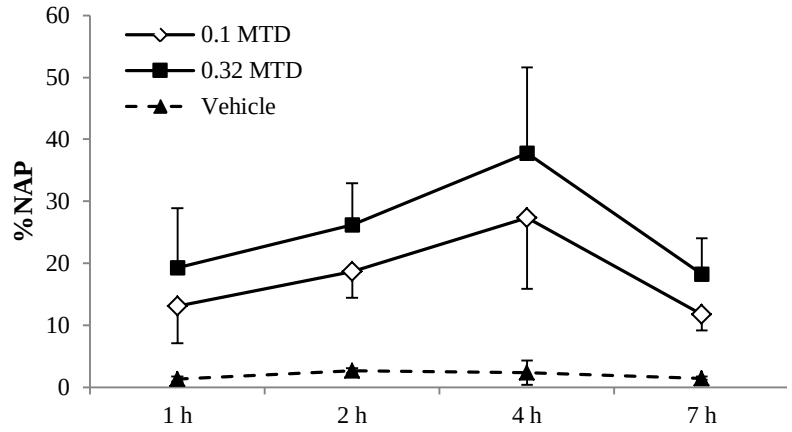
Quantitative Immunofluorescence Assay for γH2Ax (γH2Ax-qIFA)

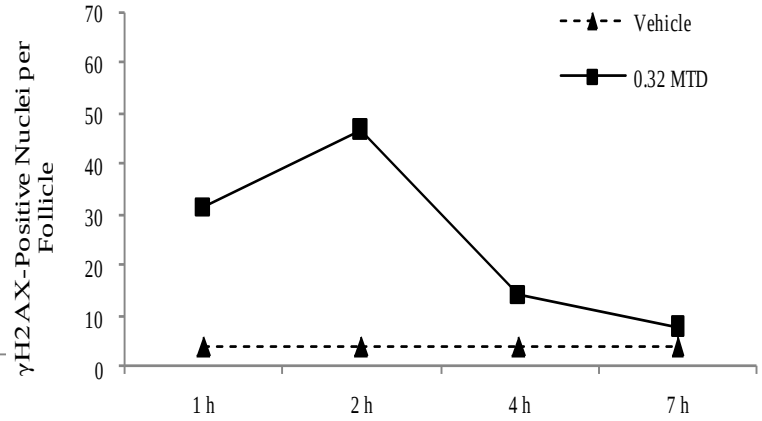
Topotecan-Treated Mice; A375 Xenografts



Topotecan-Treated Non-Tumor Bearing Mice

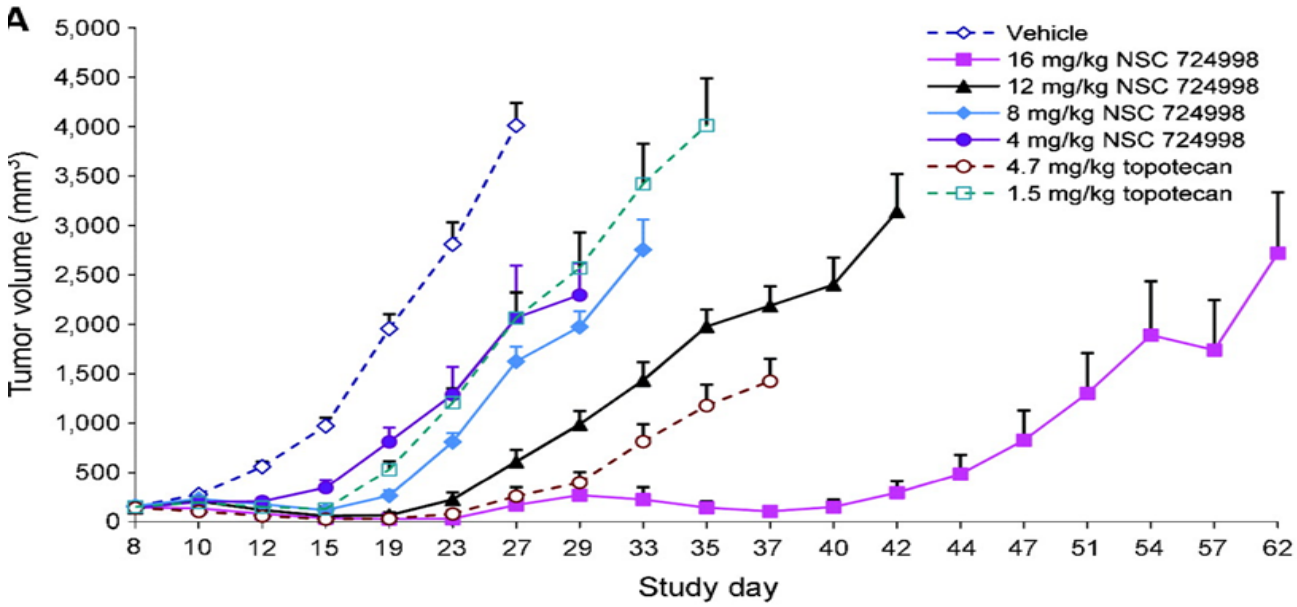


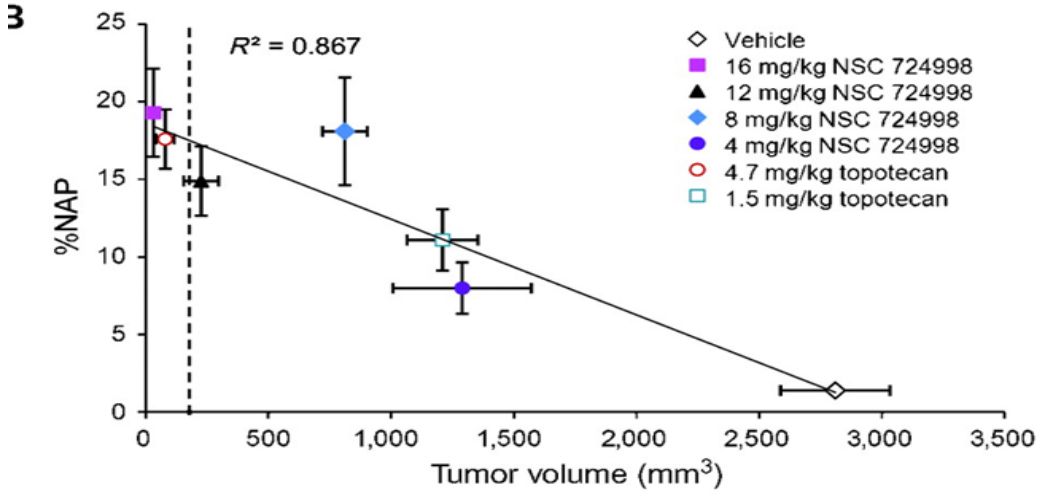




Clin. Cancer Res 16: 5447-57, 2010

Quantitative Immunofluorescence Assay for γH2Ax (γH2Ax-qIFA)





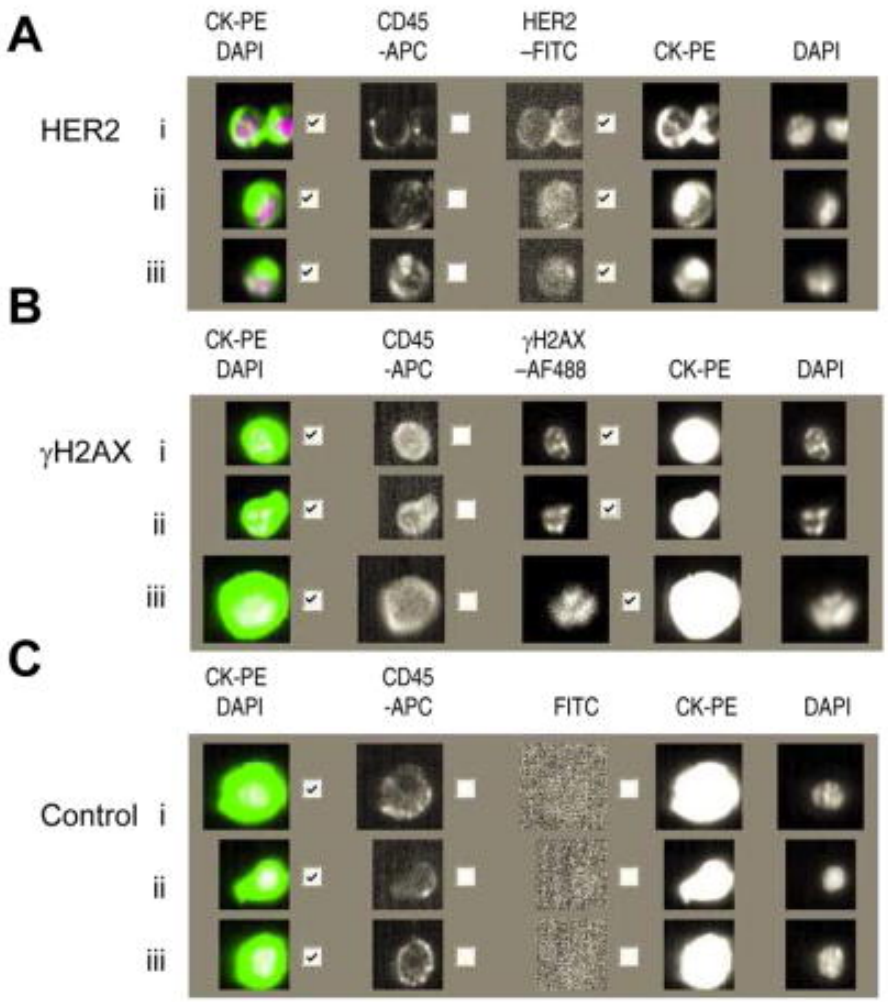
in vitro tolerance of TOP1 inhibitors by human and murine hematopoietic stem cells (CFU-GM)

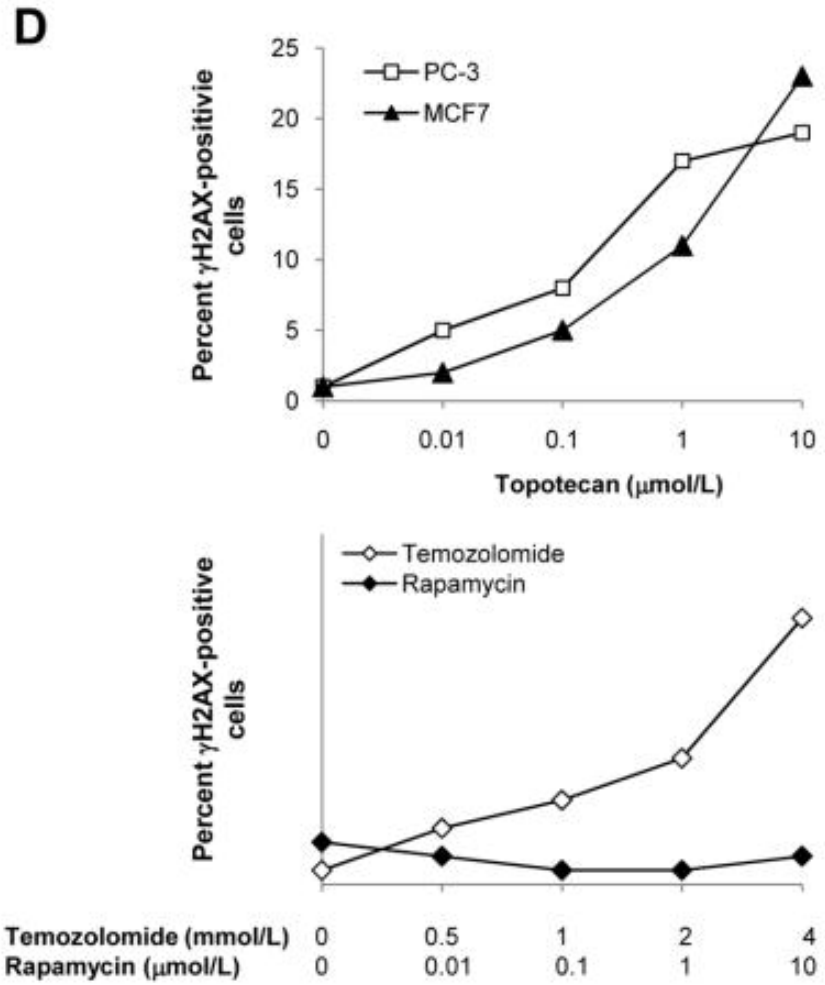
Investigational Agent	Mouse IC90 (nM) μ ± SD (range)	Human IC90 (nM) μ ± SD (range)
Topotecan Hydrochloride (Hycamtin)	120 ± 50 (64 - 160)	5.9 ± 5.1 (1.7 - 15)
NSC 724998	29 ± 12 (18 - 41)	27 ± 14 (7.1 - 45)
NSC 725776	26 ± 12 (12 – 35)	6.6 ± 2.6 (4.1 – 10)
Direct comparison study conducted on 3 mouse, 6 human marrow specimens		

Clin. Cancer Res. 16: 5447-57, 2010

Unpublished

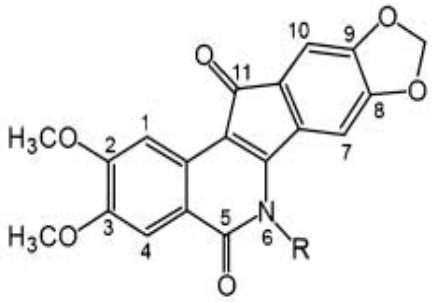
Adapting the γH2Ax Assay to Circulating Tumor Cells (γH2Ax-CTC)



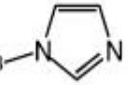
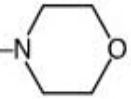


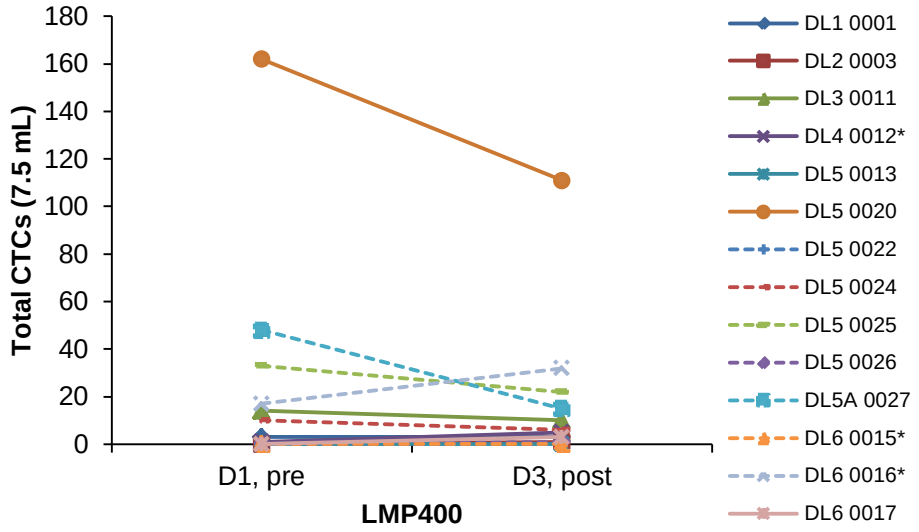
Clin Cancer Res 16: 1073-1084, 2010

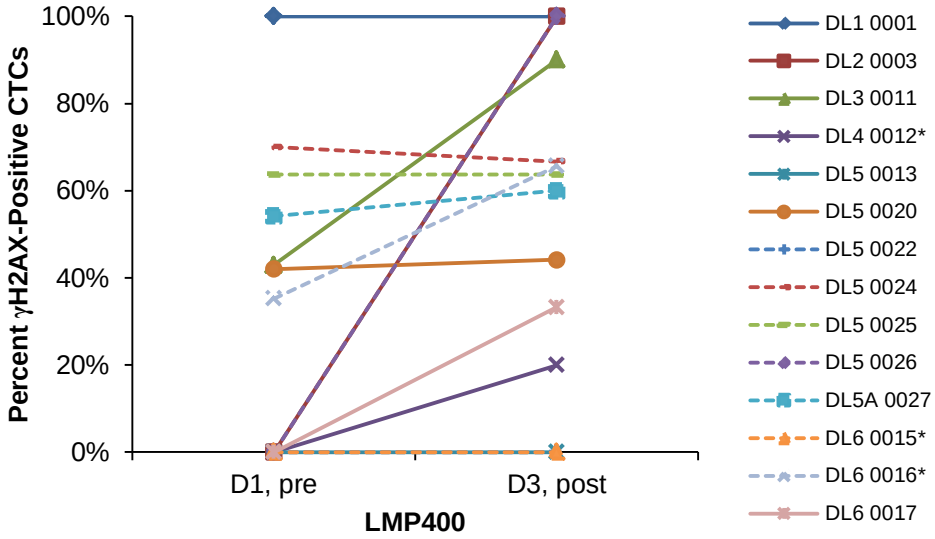
CTC γH2Ax Response to Indenoisoquinolines



R =

—CH_3	**NSC 314622**
—$(CH_2)_3$—NH—$(CH_2)_2OH$	**NSC 706744 (MJ-III-65)**
—$(CH_2)_3$— 	**NSC 725776**
—$(CH_2)_3$— 	**NSC 724998**





Pushing CTC Technology toward Universal Analysis

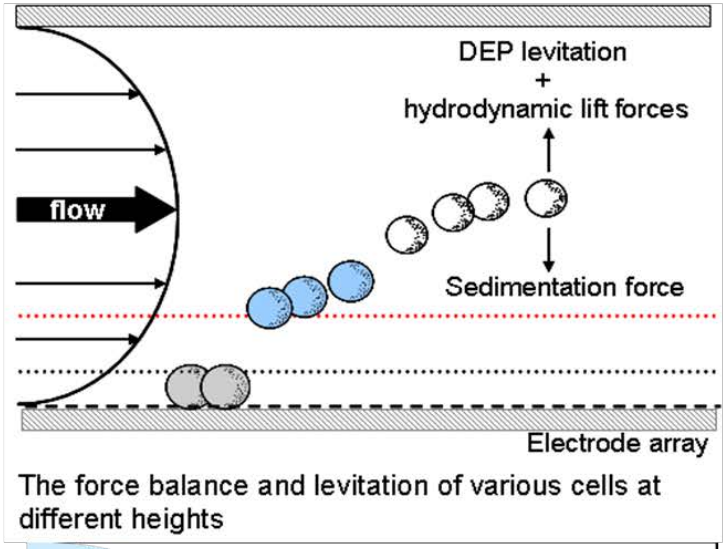
DESIGN FEATURES from SAIC-F to Meet Expected Needs in CTC Analysis

- Cell surface antigen-independent separation of CTCs from blood (EpCAM-neg CTCs)
- Capable of evaluating carcinomas, sarcomas and lymphomas
- Clinically validated with small volume samples (0.1 – 1.0 cc)
- Interfaces directly with down-stream molecular analyses – both PD and Dx
- Capable of evaluating non-clinical cancer models

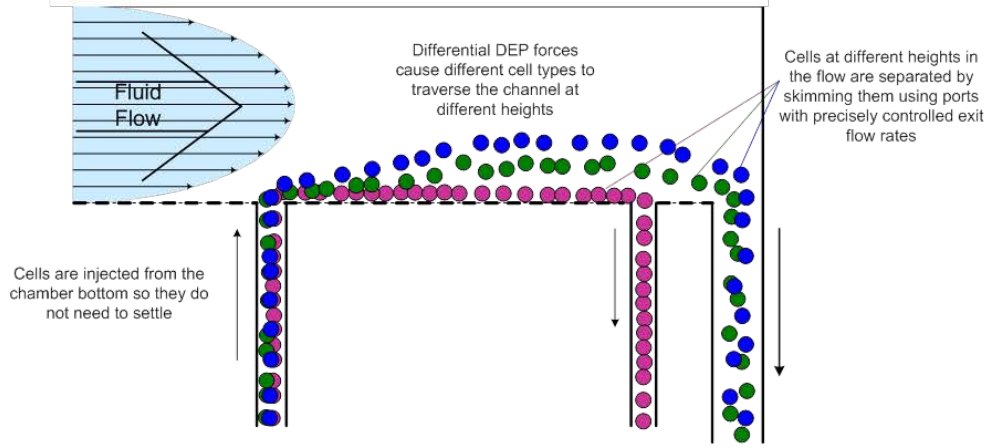
These Design Features were incorporated into a SAIC-F RFP to develop instrumentation that moves past limitations of the Veridex Cell Search and other marker-based systems

Selection of ApoCell, Inc to Deliver a Universal CTC Device

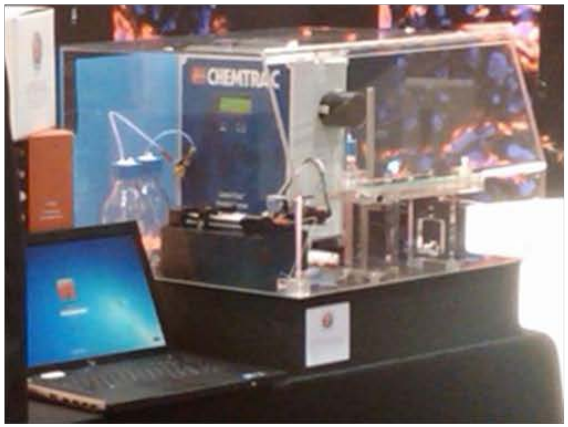
Dielectrophoretic Field-Flow Fractionation (DEP-FFF)



The force balance and levitation of various cells at different heights



- DEP-FFF utilizes balance of physical forces in a laminar flow chamber to isolate CTCs from blood cells
- Throughput is high compared to other systems; 1 ml of blood can be processed in <30 minutes



APOCELL
molecular profiling & diagnostics

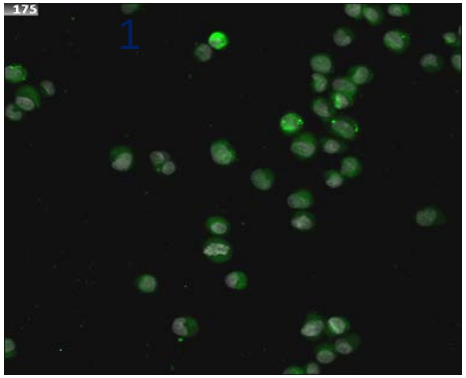
Universal CTC Isolation Technology with PD Evaluation

ApoStream prototype isolated viable EpCAM negative tumor cells:
spiked human ovarian carcinoma and canine osteosarcoma cell lines

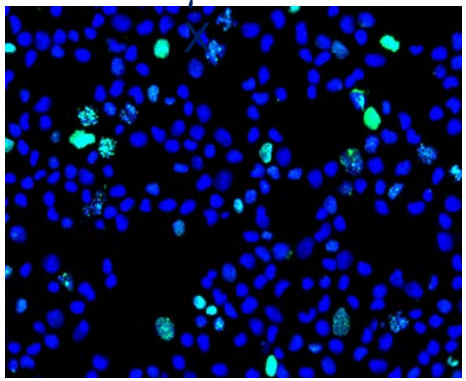
	Recovery	Viability	Enrichment
preoptimization	%	%	Fold
	33+/-1.3	>95	1326
IGROV-1 (EpCam Neg)	83+/-6.0	>95	1446
BW.KOSA (Canine)	78.5+/-0.5	>95	4440
IGROV-1 cells (EpCAM neg) spiked into human PBMCs			
.KOSA cells spiked into dog blood			

PD response (γH2AX) of a canine OS cell line to indenoisoquinoline ex vivo:

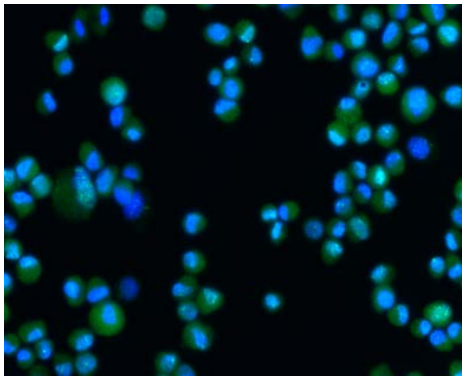
Fibronectin-



γH2A

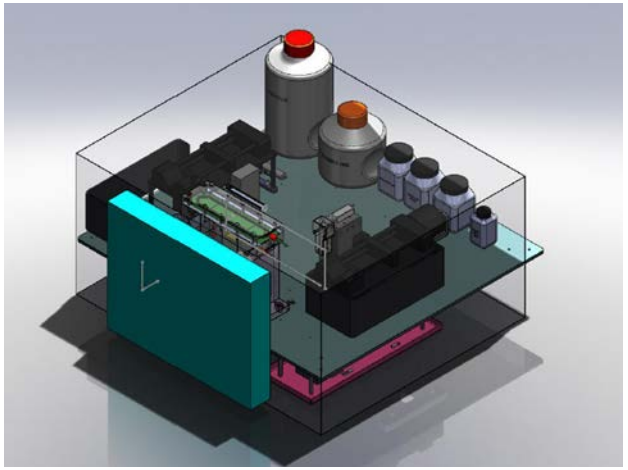


EGFR



Alpha Prototype Delivery and Use at the FNLCR

- Fit-for-Purpose demonstration using blood specimens from a canine clinical trial of the indenoisoquinolines
  - Ongoing
  - Uses Breadboard Prototype
  - Dog Lymphoma phenotyping
  - Use γH2Ax as the PD marker

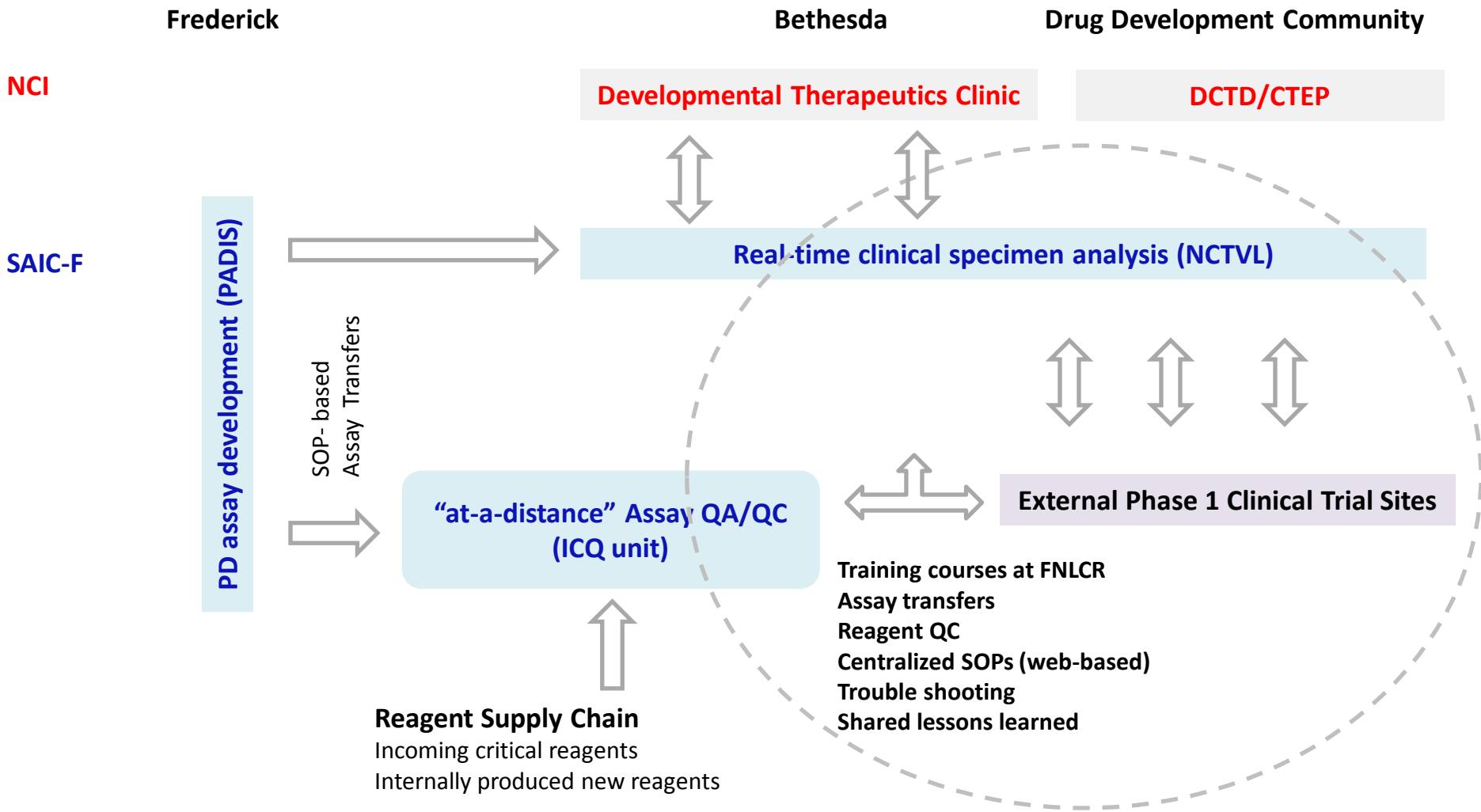


- Alpha prototype delivery:
  - ApoCell in August 2012
  - FNLCR/PADIS in October 2012

- SOP-based Methods Transfer
  - December 2012

- Initiate clinical trial support
  - March-May 2013

Creating User Groups for Validated, Proven PD Assay



Quality Assurance/Quality Control at a Distance - Shared Clinical PD Assays with Robust Performance

A) Onsite, laboratory-based training classes at the FNLCR

PD Assay Certification Courses at FNLCR					
Assay	# of classes	# of attendees	universities & research institutions	NIH programs	pharma/ Biotech/CRO
PAR-IA	9	29	16	9	4
γH2Ax-qIFA	5	18	9	7	2
γH2Ax-CTC	3	8	5	1	2
TOP1-IA	preparation/scheduling				

as of May 2012

B) Quality controlled supply chain for key reagents

- Assays faced with using R&D grade, rather than Dx grade, reagents and suppliers
- Custom orders of reagents/subcontracts to specifications (Epitomics, Argonne Natl Lab)
- Acceptance criteria applied to incoming batches before distribution to clinical labs
  - ❖ batches both of PcAb and MoAb have been rejected (fate of these in the community is unknown)

C) Web accessible current SOPs, training dates, and forms to request key reagents

http://dctd.cancer.gov/ResearchResources/ResearchResources-biomarkers.htm

D) Assay "User Groups"

- Centralized change control of SOPs
- Assay troubleshooting results shared with all assay sites
- Recalls of key reagent batches are possible via a distribution tracking system

Selection of Molecular Targets in Early Assay Development

	Selection of Targets	Scientific Foundation	Feasibility
NCI	NExT Special Emphasis Panel prioritized drug discovery and development projects • Includes early clinical trials		
	PD Functional Working Group of the Therapeutic Subcomm, NCAB	PD FWG	
SAIC-F		ad hoc experts and consults weekly PD program/assay meetings	

PD assay development lab

PD Assay Development Portfolio – Emphasis on Multiplex

	PD POM (MOA)	Pathway Consequences	Cell Stasis/Loss (POC)
Concept (scientific foundation)	pGSK3α/β-IA‡‡ Mer Kinase-IA‡‡	**Energy Control-IA‡‡** AXIN, β-CATNN, PKA, LKB1, AMPK, PKCβ, AKT2, ULK1, GYS1, PDH-A1, PDP-1, BIM1 **DDR2-qIFAx** pATR and FANCD2/--/--/--/-- (DAPI) *BRCA1, ATM, XRCC1, DNA-PK, XPA	Cell Cycle Status Necrosis-qIFA Hydropic Degeneration-qIFA Caspase-independent Death-qIFA Oncosis-qIFA
Feasibility	JAK/pSTAT3-qIFA‡‡ pATR-qIFA	**Rx2-qIFA4** Rx1-qIFA3 + vim/ker (DAPI) **Signal Transduction-IA‡‡** PIK3CA, pS^{473}Akt, Akt isoforms, pT^{308}Akt (covered by SBIR), mTORC1/2, pS6K, p4EBP1, PTEN, pERK	Autophagy-IA LC3-II-qIFA
Development and Validation (PADIS)	ccTOP1-IA pMET-IA ver 2.0 (denaturing) pY^{1235}/ pY^{1356}MET-IA cIAP-qIFA‡‡ HSP70 RT-qPCR‡‡	**Glycolysis-IA‡‡** HK2, pPDHE1α, PKM2, LDH-A **DDR1-qIFA4** **HR/BER/NHEJ/NER/MMR** pNBS1, RAD51/--/--/ERCC1/γH2Ax (DAPI) **Angiogenesis** ESM1, CD68, CD31, CD163 GSTπ or RASSF1-CTC	**EMT1-qIFA4** β-CATN, E/N-Cad, Vim or Ker (DAPI) **Apoptosis (intrinsic)-IA** Dimerized BAX-Bcl-2, BAX-BAX, BAK-BAX, BAK-BAK, Bak-Bcl-2, SMAC-SMAC Total pS^{99}BAD, cleaved-Lamin-B, BAD, BAX, BAK, BIM, 17/19 Kd neoantigen cCasp-3, Mcl-1, Bcl-xl, survivin
SOP-based Transfer (PADIS→IQC, NCTVL)	pMET-IA pY^{1235}/ pY^{1356}MET-IA	**Rx1-qIFA3** γH2A/cCasp-3/Ki67 (DAPI) HIF1α-IA	

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