DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE

54th Meeting

BOARD OF SCIENTIFIC ADVISORS

Minutes of Meeting

November 7, 2013
Building 31C, Conference Room 10
Bethesda, Maryland

DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE

BOARD OF SCIENTIFIC ADVISORS

MINUTES OF MEETING
November 7, 2013

The Board of Scientific Advisors (BSA), National Cancer Institute (NCI), convened for its 54th meeting on Thursday, 7 November 2013, at 9:00 a.m. in Conference Room 10, Building 31C, National Institutes of Health (NIH), Bethesda, MD. Dr. Todd R. Golub, Director, Cancer Program, The Broad Institute of Massachusetts Institute of Technology and Harvard University, presided as Chair. The meeting was open to the public from 9:00 a.m. until 4:30 p.m. on 7 November for the NCI Director's report; consideration of requests for application (RFAs) and Cooperative Agreements (Coop. Agr.) for the Biospecimen Banks to support NCI-Clinical Trials Network (NCTN), Using Social Media to Understand and Address Substance Use and Addiction, Innovative Molecular Analysis Technologies (IMAT), Pediatric Preclinical Testing Program (PPTP), a request for proposal (RFP), and Molecular Characterization of Screen-Detected Lesions; a status report on the Physical Sciences-Oncology Centers (PS-OC) Program; and a report on Metabolic Reprogramming to Improve Immunotherapy.

BSA Board Members Present:

Dr. Todd R. Golub (Chair)
Dr. Francis Ali-Osman
Dr. Dafna Bar-Sagi
Dr. Ethan M. Basch
Dr. Curt I. Civin
Dr. Daniel C. DiMaio
Dr. Jeffrey A. Drebin
Dr. Karen M. Emmons
Dr. Betty Ferrell
Dr. Stanton L. Gerson
Dr. Joe W. Gray
Dr. Chanita Hughes-Halbert
Dr. Joshua LaBaer
Dr. Theodore S. Lawrence
Dr. Maria E. Martinez
Dr. Kevin M. Shannon
Dr. Lincoln Stein
Dr. Bruce W. Stillman
Dr. Cheryl L. Walker
Dr. Irving L. Weissman

Board Members Absent:

Dr. Kenneth C. Anderson
Dr. Sangeeta N. Bhatia
Dr. Andrea Califano
Dr. Arul M. Chinnaiyan
Dr. Graham Colditz
Dr. Chi V. Dang
Dr. Robert B. Diasio
Dr. Brian J. Druker
Dr. Kathleen M. Foley
Mr. Don Listwin
Dr. Luis F. Parada
Dr. Martine F. Roussel (Sherr)
Dr. Mary L. Smith
Dr. Louise C. Strong
Dr. Frank M. Torti
Dr. Gregory L. Verdine

Others present: Members of NCI's Scientific Program Leaders (SPL), NCI staff, members of the extramural community, and press representatives.

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I. CALL TO ORDER AND OPENING REMARKSCDR. TODD R. GOLUB

Dr. Todd R. Golub called to order the 54th regular meeting of the BSA and welcomed current members of the Board, NIH and NCI staff, guests, and members of the public. Dr. Golub also welcomed new members of the Board, Kenneth C. Anderson, Kraft Family Professor of Medicine, Harvard Medical School, and Director, Lebow Institute for Myeloma Therapeutics, Dana-Farber Cancer Institute; and Dafna Bar-Sagi, Vice Dean for Science, Senior Vice President, and Chief Scientific Officer, Langone Medical Center, New York University (NYU) School of Medicine. He reminded Board members of the conflict-of-interest guidelines and confidentiality requirements. Members of the public were invited to submit to Dr. Paulette S. Gray, Director, Division of Extramural Activities (DEA), in writing and within 10 days, comments regarding items discussed during the meeting. Dr. Golub noted that the official minutes from the 24–25 June 2013 joint BSA and National Cancer Advisory Board (NCAB) meeting were approved electronically and were in the Board book.

II. REPORT OF THE DIRECTOR, NCICDR. HAROLD VARMUS

Dr. Harold Varmus, Director, NCI, welcomed members, commented on the shutdown, and provided information about the Institute's budget and legislative news for the current and upcoming fiscal year (FY) as well as NCI news. Members were informed that Dr. Warren Kibbe is the new Director of the Center for Biomedical Informatics and Information Technology (CBIIT) and expressed appreciation to Dr. George Komatsoulis for serving as CBIIT's Acting Director.

Effect of the Government Shutdown. Dr. Varmus reflected on the disruption to the NCI's work because of the government shutdown. He recognized the hardship experienced by all NCI staff, including newly arrived postdoctoral investigators, and expressed appreciation to those who were required to work, and acknowledged the efforts of NCI Intramural Research Program (IRP) leaders during the shutdown. Dr. Varmus also thanked staff involved in the budget and grant-making systems, who ensured that there were

no significant delays in the reviewing, processing, and awarding of grants impacted by the shutdown. He noted that a meeting about the Center for Cancer Genomics (CCG) was rescheduled for early December 2013, and plans to proceed with the Outstanding Investigator Award program have been delayed.

Budget. Members were reminded that the NCI is operating under a continuing resolution (CR) through 15 January 2014 with a 3-month budget based on FY 2013 levels. The NCI is in the process of awarding grants, with noncompeting awards (Type 5) paid at the 90 percent level. The Institute experienced a 6 percent budget decrease in FY 2013, including 5.1 percent reduction from sequestration plus taps from the Department of Health and Human Services (HHS) to help fund the insurance exchanges. By making reductions in other NCI activities, NCI was able to fund a similar number of awards as in FY2012.

Members were informed that modest but persistent declines in individual investigator (R01) applications, particularly from early stage and new investigators, resulted in small declines in the number of R01 awards in FY 2013. There was a increase in the number of exploratory 2-year R21 submissions and awards although the success rates remain lower than R01s. The program project (P01) applications experienced better success rates. Dr. Varmus referred members to the NCI website for further details.

Recent Activities. Dr. Varmus described a pilot project planned by the NCI using several RFAs to evaluate a new biosketch in grant submissions that highlights the investigator's five most important contributions to science rather than an emphasis on a bibliography. He noted that the Howard Hughes Medical Institute and other organizations already use a similar approach.

Dr. Varmus referred members to a recent article and editorial in *The Economist* concerning issues in replicating data. A group is proposing to reproduce work conducted by NIH scientists published in approximately 50 papers during the past 3 years; it is unclear how work that took several years and cost hundreds of thousands of dollars will be replicated over a short term with very small amounts of money and without necessary skills. The NIH is considering ways to improve how studies are conducted, including by examining the existing culture of science and underlying conditions that encourage scientists to publish prematurely with inadequate attention to detail. The NCI has established checklists to help improve the likelihood of replicability, including guidelines for conducting "-omic" studies.

Members were told that the report on pancreatic ductal adenocarcinoma research in response to the Recalcitrant Cancer Act is being completed, and that another report on small cell lung cancer is being prepared. In addition, the NCI is participating in discussions with the Centers for Medicare and Medicaid Services (CMS) regarding the appropriate coverage for follow up tests for lung cancer following the National Lung Screening Trial (NLST) results and the U.S. Preventive Services Task Force's draft report on helical computed tomography (CT) scanning for lung cancer. Discussions with CMS also include interest in developing diagnostics that depend on genomics and other molecular technologies in cancer diagnosis and lead to a more precise choice of therapies.

Dr. Varmus informed members that the President's Cancer Panel Report on human papilloma virus (HPV) vaccination will be published shortly. The presentation of the David E. Barnes Global Health Lecture by Mr. Bill Gates, co-Chair and Trustee of the Bill and Melinda Gates Foundation, was rescheduled to December 2013, to accommodate the government shutdown; Mr. Gates has expressed an interest in developing a wider range of interactions with the NIH, including NCI. Other news included a recent International Cancer Genome Consortium gathering in Toronto, Canada, and the new Global Alliance, which is planning a meeting for March 2014. In addition, the consortium of leaders of international funding agencies for cancer will meet in Paris, France, in January 2014. Dr. Varmus distributed to members a recent profile of himself and NCI objectives that highlight the Institute's vision for world health during this time of fiscal constraint.

RAS Project. Dr. Douglas Lowy, Deputy Director, provided an update about the Ras project. An *ad hoc* oversight committee chaired by NCI-Frederick Advisory Committee member Dr. Levi Garroway,

Associate Professor, Department of Medicine, Harvard Medical School, and Assistant Professor of Medicine, Medical Oncology Services, Dana-Farber Cancer Institute, has been established. In addition, Dr. Frank McCormick, Director, Comprehensive Cancer Center and Cancer Research Institute, University of California San Francisco School of Medicine, is leading efforts to engage the Ras community through a February 2014 workshop, and a website with both static and dynamic components. Dr. Varmus reminded members the project is structured as a hub-and-spoke model; he added that the Frederick National Laboratory for Cancer Research (FNLCR, the hub) is productive and making reagents for Ras activities, and that outreach is underway to engage the research community and other stakeholders (the spokes).

In the discussion, the following points were made:

< Members encouraged the NCI to engage with the Gates Foundation in areas involving cancer and infections, including malaria, Burkitt's lymphoma, and the Epstein-Barr virus (EBV).

< The issue of study replication presents challenges, including questions of how much data cannot be replicated. Dr. Varmus responded that industry has made efforts to determine how many findings of interest have been replicated but is reluctant to share the identity of the papers.

< PubMed conducted a pilot project that allowed online comments on published papers. NIH is now considering allowing all scientists to provide comments on publications.

< The NCI should provide input to CMS' Coverage with Evidence Development Program as well as gain greater access for NCI investigators to CMS datasets.

< Members noted the Ras project's current emphasis on Kirsten A and B (KRAS) mutations and encouraged the NCI to address other types of Ras mutations and neurofibromin 1 (NF1). NCI leadership stated that discussions about the Project's expansion are underway.

III. RFA/COOPERATIVE AGREEMENT CONCEPTS—NCI PROGRAM STAFF

Division of Cancer Treatment and Diagnosis (DCTD)

Biospecimen Banks to Support NCI-Clinical Trials Network (NCTN) (RFA/Coop. Agr. New)

Dr. Irina A. Lubensky, Chief, Pathology Investigation and Resources Branch, Cancer Diagnosis Program, DCTD, described a concept to provide a NCI Clinical Trials Network (NCTN) biospecimen resource for validation studies of predictive and prognostic markers, assay development and validation, and discovery. Members were reminded that the NCI Cooperative Groups recently consolidated from nine groups into four adult and one pediatric NCTN groups. Biospecimen banks have been an integral part of the Cooperative Groups and and provide researchers with well-annotated specimens and clinical data from the Phase III and large Phase II clinical trials. Specimen collection and distribution (2008–2012) among the Cooperative Groups and the extramural community has included solid tumor, serum, and leukemia specimens, resulting in 744 publications. Examples of the Program's scientific impact include: high-dose daunorubicin selectively benefits acute myeloid leukemia (AML) patients with specific mutations; the *OncotypeDx*™ test improved risk stratification in stage II and III colon cancer; and human papilloma virus (HPV) associated oropharyngeal cancers are a clinical entity distinct from smoking-related head and neck cancers.

Members were informed that the concept will help consolidate and reorganize the NCTN banking network, support banking infrastructure for collection and storage of specimens, and provide a system for cataloging and retrieving specimens and associated data. A centralized specimen application process and

review by a Central Correlative Science Review Committee will streamline access to biospecimens. In addition, the NCTN Biospecimen information technology (IT) Navigator system, a central inventory database of specimens available for research, will provide an integrated search engine to support extramural researchers.

Subcommittee Review. Dr. Francis Ali-Osman, Margaret Harris and David Silverman Distinguished Professor of Neuro-Oncology Research, and Associate Director for Translational Research, Duke University School of Medicine, Duke University Medical Center, expressed the Subcommittee's support for the concept. Dr. Ali-Osman stated that the Subcommittee encouraged the NCI to consider formal oversight to ensure that specimens are made available to the broader scientific community. Stringent guidelines should delineate prioritization for access to tissue samples, and the five banks should coordinate their expertise in standard operating procedures. Benefits of this resource include the potential correlative research questions that could be considered. The Subcommittee also supported the addition of the informatics pathway through the Navigator system, and suggested that the expected use of early phase tissue samples should be more clearly defined.

In the discussion, the following points were made:

< Members discussed alternative banking models, such as a multi-site distribution system or an approach to better support molecular characterization of specimens.

< Members encouraged consideration of the biospecimen bank as a clinical resource for the broader cancer research community rather than a narrower focus on clinical data elements for a specific clinical trial.

< Stored specimens should also include dissociated whole tumor samples as viable frozen cell suspensions.

< NCI program staff clarified that informed consent forms will include use for future research questions that could include genomics investigations.

< The centralized Correlative Science Review Committee for the NCTN will include broad representation drawn from the Cooperative Groups as well as other experts and the extramural community to ensure that the NCTN bank is used as a national resource.

< The NCI should incorporate a "Users Committee" to ensure that complaints about availability, access, and quality are addressed. In addition, the program's evaluation metrics should indicate the extent of community use of the specimen and data.

The first year cost is estimated at $11.75 M for 5 U24 awards, with a total cost of $58.75 M for 5 years.

Motion. A motion to concur with the Division of Cancer Treatment and Diagnosis's (DCTD) request for application/cooperative agreement (RFA/Coop. Agr.) concept entitled "Biospecimen Banks to Support NCI-Clinical Trials Network (NCTN)" was approved unanimously with staff's agreement to establishment of a "Users Committee" and development of success metrics for annual evaluation of the program.

Division of Cancer Control and Population Sciences (DCCPS)

Using Social Media to Understand and Address Substance Use and Addiction (RFA New)

Dr. Wen-ying Sylvia Chou, Health Communication and Informatics Research Branch, Division of Cancer Control and Population Sciences (DCCPS), described a trans-NIH concept to advance research in

substance use and addiction in partnership with the Collaborative Research on Addiction at NIH (CRAN), including the National Institute on Drug Abuse (NIDA) and National Institute on Alcohol Abuse and Alcoholism (NIAAA). The communication landscape has shifted dramatically with the rapid growth of mobile and Web technologies and proliferation of user-generated content. In response to these changes, health stakeholders (e.g., the Institute of Medicine [IOM], Healthy People 2020) have called on the NIH for new communication approaches that use social media to better engage patients and alleviate disease burden. The President's Cancer Panel has identified "Emerging Media and Cancer Prevention" as its FY 2013–2014 topic. An article in *Nature* showed how investigators are conducting observational and intervention research on health behavior using online interactions.

Members were informed that this concept investigates the impact of social media on alcohol, tobacco, and other drug use, abuse, and addiction through observational studies and interventions that take advantage of newer research methods, such as natural language processing, social network analysis, and data visualization techniques. The objectives are to mine social media content to understand risk factors and real-time substance use patterns and consequences for alcohol, tobacco, and other drug use, as well as the utility of social media for health promotion and industry marketing of tobacco and alcohol. Additional aims include: defining the effect of social media engagement on behavior change; understanding the influence of social media on alcohol, tobacco, and other drug use (e.g., identification, prevention, treatment); and identifying intervention characteristics that contribute to the diffusion and adoption of addiction and substance use control programs. Members were told that the concept calls for multi-disciplinary expertise and streamlined and innovative research designs.

Subcommittee Review. Dr. Joshua LaBaer, Chair, The Directorate, Biodesign Institute, and Director, Virginia G. Piper Center for Personalized Diagnostics, Arizona State University, expressed the Subcommittee's strong enthusiasm for this timely concept, reflecting on the pervasiveness and continued rapid growth of social media as a venue both to impart messages and learn from others. The Subcommittee noted that lessons likely could be garnered from the commercial marketing industry, the rapid pace of technological changes will require nimbleness, and the ability to reach racial and ethnically diverse populations should be emphasized.

In the discussion, the following points were made:

< The NIH should make a concerted effort to study informed consent, de-identification, and other ethical issues carefully before launching this program and during the application review process.

< Concerns were raised about potential misuse of research published algorithms, such as detection of people with alcohol, tobacco, and other drug dependencies.

< Members noted the increased interest in informatics and methodological issues involved in aggregating and analyzing unstructured data from social media sources to better elucidate health behaviors and the early detection of disease outbreaks.

The first year cost for the NCI is estimated at $200,000 (and $5 M for the Collaborative Research on Addiction at NIH [CRAN]) for 10 R01 and R21 awards, with a total cost of $15 M for the CRAN for up to 3 years.

Motion. A motion to concur with the Division of Cancer Control and Population Sciences' (DCCPS (RFA/Coop. Agr. entitled "Using Social Media To Understand and Address Substance Use and Addiction" was approved unanimously.

Office of the Director

Innovative Molecular Analysis Technologies Program (RFA/Coop. Agr. Reissue)

Dr. Anthony Dickherber, Center for Strategic Scientific Initiatives, introduced the concept for the reissuance of four RFA solicitations for the Innovative Molecular Analysis Technologies (IMAT) Program. Dr. Dickherber informed members that the focus is on early-stage development of high-risk and high-impact molecular and cellular analysis technologies to advance cancer research and clinical care. Program accomplishments include support for significant technologies across many platforms, including proteomics, genomics, epigenomics, clinical diagnostics, sample preparation, and drug screening or delivery.

IMAT provides a unique solicitation within the NCI that is not being met by other funding mechanisms across the NIH for early-stage technology development support. Solicitations continue to receive a substantial number of high-scoring applications, and the Program has achieved a significant record of success as verified though several outcome evaluations. Success rates for applications have been approximately 10 percent over the life of the program since 2005. Dr. Dickherber stated that the reissuance request supports the development and validation of innovative (R21) and emerging (R33) technologies for (1) molecular and cellular analysis for cancer research and (2) cancer-relevant biospecimen sciences. The RFA mechanism provides several advantages, including assurance of NCI interest in technology development and control over responsiveness and review.

Subcommittee Review. Dr. Joe W. Gray, Gordon Moore Endowed Chair, Department of Biomedical Engineering, Knight Cancer Institute, Oregon Health and Science University, expressed the Subcommittee's support for the concept reissuance, noting that this program supports a special type of cancer research that would not be well treated by standard peer review study sections. Dr. Gray informed members that the Subcommittee suggested that the program could be extended NIH-wide to support technologies addressing other diseases, and appreciated that there are no restrictions regarding international or other applicants.

In the discussion, the following point was made:

< Technologies that only have an impact on cancer research or cancer care are supported.

The first year cost is estimated at $10.5 M for 32 to 40 R21 and R33 awards, with a total cost of $25–35 M for 3 years.

Motion. A motion to concur with the reissuance of the Office of the Director's (OD) RFA concept entitled "Innovative Molecular Analysis Technologies Program (IMAT)" was approved unanimously.

Division of Cancer Treatment and Diagnosis

Pediatric Preclinical Testing Program (RFP Reissue)

Dr. Malcom A. Smith, Associate Branch Chief for Pediatric Oncology, Cancer Therapy Evaluation Program (CTEP), stated that the NCI's Pediatric Preclinical Testing Program (PPTP), which includes six testing sites and collaborations with more than 50 companies. Dr. Smith noted that Significant challenges associated with pediatric oncology drug development include low priority for pharmaceutical companies, a limited patient population for conducting clinical trials, and prioritization of the numerous candidate agents entering the clinic. Since 2005, the program has executed more than 80 material transfer agreements (MTAs) and issued more than 50 publications. Five agents are in clinical evaluation, three are in development, and four are pending development for treatment of acute lymphoblastic leukemia (ALL), including those subtypes that are highest risk and most difficult to treat. PPTP protocols ensure reliability of results, addressing the systematic problem of the inability of industry and clinical trials to validate discovery results. PPTP mouse pharmacokinetic testing combined with murine xenograft models greatly

improves assessments of clinical activity as compared with *in vitro* data. PPTP preclinical testing also allows single-agent assessment, which is virtually precluded by pediatric clinical trial treatment paradigms. Dr. Smith shared several examples of PPTP results, including informing Phase I and 2 trials for development of selumetinib for low grade astrocytomas (LGAs) in children; an ongoing pediatric Phase I trial of BMN 673 plus low-dose PARP (Poly ADP ribose polymerase) inhibitor temozolomide (TMZ) for Ewing's sarcoma; and promising results for the MDM2 (murine double minute 2) inhibitor RG7112 in infant ALL.

Members were told that the reissuance concept enhances the PPTP's capabilities for evaluating more central nervous system (CNS) tumors; increases efficiency and economy by more selective testing based on molecular characterization data; increases focus on combination testing; and evaluates pediatric-specific agents. Dr. Smith informed members that a RFP or contract mechanism was selected to facilitate systematic testing using a standard protocol, ensure rapid data dissemination, maintain tight timelines, and screen as many agents as possible. The reissuance is proposed as an open competition. The RFP could require applicants to show that they have performed due diligence for model selection, and an annual review of the sites will be performed by an external advisory committee.

Subcommittee Review. Dr. Kevin M. Shannon, Roma and Marvin Auerback Distinguished Professor in Molecular Oncology, University of California, San Francisco, expressed the Subcommittee's support for the concept and acknowledged NCI staff's responsiveness to the Subcommittee's concerns. The Subcommittee agreed that the structure facilitated efficient and timely evaluation of therapeutics, and appreciated the extensive publication of positive and negative results, and progress to Phase I trials of some of the agents tested. They asked about the selection criteria for sites, the criteria for cell line inclusion, and the justification for performing expensive *in vivo* testing for agents with existing animal and adult data. Recommendations included mining deeper genomic information about tumor cell lines via whole exome or genome sequencing, as well as expanding to diseases beyond ALL, testing more combinations, and expanding to chemotherapy-radiation combination therapies. Concerns were expressed about the limited number of sites and the limited scope of methodological innovation within the existing structure.

In the discussion, the following points were made:

< Members asked about xenografts specific to adolescent and young adult cancers. NCI staff responded that sarcomas are the most prevalent cancers in adolescents and young adults, and these are well-represented in the panel, as is Ph-like ALL.

< Members recommended integrating the Program with the patient-derived mouse xenografts (PDX) repository and genetically engineered mice (GEM) activities that are ongoing at the FNLCR.

< Pharmocodynamic testing to validate that the target has been reached, particularly in cases of negative activity, is performed.

< Genomic data on models will be required under the new contract, and results will be publically available on the program's website.

The first year cost is estimated at $2.7 M for 1 RFP award, with a total cost of $13.5 M for 5 years.

Motion. A motion to concur with the reissuance of the DCTD's request for proposal (RFP) concept entitled "Pediatric Preclinical Testing Program" was approved with 16 yeas, 1 nay, and no abstentions.

Division of Cancer Prevention (DCP) and Division of Cancer Biology (DCB)

Molecular Characterization of Screen-Detected Lesions (RFA/Coop. Agr. New)

Dr. Barry Kramer, Director, DCP, presented a new concept on the molecular characterization of screen-detected lesions to phenotypically distinguish between and predict lesions that likely are life threatening versus those that are indolent and not requiring immediate treatment. The heterogeneity of cancer progression and the association of cancer with the aging process have led to overtreatment of very slowly developing and nonprogressive cancers that would not have been diagnosed in the absence of screening programs. The best known example is prostate cancer screening in the United States, with an estimated more than 1.3 million men overdiagnosed since 1975, virtually all of whom elected for major treatment. There is evidence of overdiagnosis of other diseases, including melanoma where screening in the Medicare population had no effect on mortality, and breast cancer, where the screening mammography has led to a dramatic increase in the detection of early stage disease with no increase in the detection of metastatic disease in U.S. women.

To address this important issue, the NCI proposes to examine key biological questions: the molecular characteristics that defines indolent versus progressor legions; the lineage relationships among indolent, interval, and malignant lesions; the selective forces that shape the evolution of a cancer during its progression to becoming invasive; and the role of the tissue microenvironment in modulating or determining outcomes or progression rates. Members were informed that the concept will undertake a comprehensive characterization of tumor cell and microenvironment components of screen-detected early lesions and missed interval cancers. Data from cross-sectional studies have demonstrated that the microenvironment has a role in tumor progression and that chromosomal instability, microsatellite instability, genome-wide aneuploidy, and loss or gain of whole chromosome or chromosome arms in the tumor or its microenvironment can accelerate progression. Types of studies can include: molecular and cellular comparison with features of aggressive interval cancers; single-cell analyses of tumor heterogeneity within lesions; novel mouse models, organoid cultures, or patient-derived xenografts; systems approaches and modeling; and sequential imaging with molecular approaches to elucidate any dynamic changes.

A Consortium of Molecular Characterization of Screen-Detected Lesions is proposed that will work with the NCI early detection and screening programs, molecular/cellular characterization laboratories, and the Coordination and Data Management Group (CDMG). A consortium brings the advantages of uniform data collection, protocols and analyses; common data elements; reproducibility of data collection; creation of a national resource; and central management of the Institutional Review Board (IRB), material transfer agreements, and protocols. Applications will need to include a collaborative arrangement with existing biospecimen networks or consortia, demonstrate the ability to procure appropriate specimens, and be willing to share samples across the consortium on cross-laboratory discovery and verification.

Subcommittee Review. Dr. LaBaer told members that the subcommittee supported the concept and remarked that knowing the history of the cancers to be studied will help overcome the problem of overtreatment. He noted that the Subcommittee encouraged the NCI to help investigators obtain tumor samples, ensure that grantees propose predictive tests and follow good practices, and consider focusing on fewer than four tumor types to ensure successful deep characterization of several rather than a more cursory characterization of all four. The concept should clearly distinguish between screening and interval cancers.

In the discussion, the following points were made:

< Prospective approaches include excising the whole lesion and its surrounding microenvironment to record tumor heterogeneity and glean biological insights.

< Members suggested that collaborations be established with investigators in Europe, where it is more prevalent to follow tumors without progression rather than treat them.

< Members encouraged the NCI to incorporate a rapid autopsy model for viable frozen cell suspensions to better identify preneoplastic lesions and clonal progression in additional tissues.

The first year cost is estimated at $5 M ($1.6 M from Breast Cancer Stamp Act Fund) for 6 U01/U24 awards, with a total cost of $25 M for 5 years.

Motion. A motion to concur with the Division of Cancer Prevention (DCP) and Division of Cancer Biology's (DCB) RFA/Coop. Agr. entitled "Molecular Characterization of Screen-Detected Lesions" was approved unanimously.

IV. ONGOING AND NEW BUSINESS—DR. TODD R. GOLUB

Dr. Golub said that a report of the a*d hoc* Subcommittee on Human Immuno-deficiency Virus (HIV) and Acquired Immune Deficiency Syndrome (AIDS) Malignancy was provided at the 2nd Joint Meeting of the BSA and National Cancer Advisory Board (NCAB) in June 2013, and he referred members to the summary in the Board books.

Motion. A motion made to accept the BSA a*d hoc* Subcommittee on Human Immunodeficiency Virus (HIV) and Acquired Immune Deficiency Syndrome (AIDS) Malignancies was approved unanimously.

V. STATUS REPORT: PHYSICAL SCIENCES-ONCOLOGY CENTERS (PS-OC) PROGRAM—DR. LARRY A. NAGAHARA

Dr. Larry A. Nagahara introduced the PS-OC Program, which promotes interactions between physical scientists and cancer biologists to find new ways of understanding and treating cancer. The PS-OC Program implemented a Center/Network approach to accelerate adoption of concepts and advanced tools from the physical sciences by creating teams of physical scientists and cancer researchers, providing training and career development opportunities, and sponsoring investigator-initiated pilot projects. The Program is comprised of 12 Centers, each co-directed by a physical scientist and a cancer biologist, with more than 700 investigators and 600 trainees from more than 100 domestic and foreign institutions participating in the PS-OC Network.

Dr. Nagahara noted that one project supported by the PS-OC Program is based on a physics theory that describes the complex behavior that arises from long-range interactions among weakly interacting parts which was applied to understand the development of resistance to drug therapies in cancer patients. Another project supported to determine the strong association of multiple distinct factors with increased risk and/or poor outcomes in cancer, researchers compared the rapid transformation of interacting as opposed to solitary ras-transformed mammary acini to a malignant phenotype. Currently, a clinical investigation of the biophysical properties of a collagen as a risk factor for developing "silent" breast cancers in African-American women is being conducted.

Members were informed that the number of transdisciplinary publications were dramatically increased since investigators began receiving PS-OC Program funding. Similarly, increased interactions in the Network occurred. To facilitate communication among physical scientists and cancer biologists, cell lines

were shared among PS-OC Program participants, leading to an ongoing "Living Project" that is coordinating biophysical examination of identical cell lines. The Network has supported almost 500 trainees and has steadily added to its portfolio of pilot projects.

At the end of FY 2014, the NCI proposes to reissue the PS-OC Program as a competing new program announcement (PAR) to solicit the best new ideas, focusing on two themes: spatial-temporal organization and information transfer in cancer, and the physical dynamics of cancer. To determine the best way to transition to the PAR mechanism, the Program examined other PAR programs, considered Program evaluations, and incorporated information from the PS-OC Program's Implementation Team aspects of the Program. The U54 specialized center is the preferred mechanism to fund two to three projects per center, the education/training program, and pilot projects. Plans include two receipt dates per year, except for FY2014 having one receipt date.

In the discussion, the following points were made:

< Members expressed concern that the proposed funding mechanism does not allow investigators who are not affiliated with the centers to apply for support independently. An R01 mechanism could be added to the Program.

< Members noted that the examples of projects funded by the Program were limited to application of mechanical concepts and indicated that the scope of interactions with physical scientists should be broadened. NCI staff clarified that the scope is broader than was portrayed by the few examples presented.

VI. METABOLIC REPROGRAMMING TO IMPROVE IMMUNOTHERAPY—DR. DINAH SINGER

Dr. Dinah Singer, Director, DCB, introduced a concept on tumor immunometabolism that provides a better understanding of metabolic processes that support robust anti-tumor immune responses *in vivo*, as well as effects on immune effector functions in the tumor microenvironment, to improve cancer immunotherapy. Dr. Singer explained that cancer cells proliferate by switching from oxidative phosphorylation to aerobic glycolysis and thus generate biosynthetic intermediates necessary to support rapid growth. Little work has been done to demonstrate how these changes impact immune components of the tumor, specifically T cells. Immunological studies of the metabolism of T cells elucidate the metabolic events that occur as T cells transition from a naïve resting state to an active state. Resting T cells rely on oxidative phosphorylation, but in response to activation, they switch to aerobic glycolysis and undergo rapid proliferation and differentiation. Changes in the tumor microenvironment may affect the recruitment of T cells and their ability to switch to aerobic glycolysis and become activated. The metabolic microenvironment of the tumor may cause the immunosuppression that is associated with tumor growth. The mechanisms by which metabolic changes in the tumor affect the immune system interacting with it remain unknown, but elucidation of these mechanisms could lead to new cancer therapies aimed at reprogramming metabolism to alter T cell activity, and thus enhance immunotherapy.

The NCI supported a workshop in 2012 on the effects of tumor metabolism on T cell activity, which identified two research areas: (1) reprogramming the anti-tumor immune cells to improve immunotherapy; and (2) targeting cancer cell metabolism to inhibit growth without compromising anti-tumor immunity. To advance collaboration in tumor immunometabolism, the NCI is releasing a PAR that will support cross-disciplinary supplements, or revision applications, to existing NCI-funded grants with at least two years remaining on the grant. Examples of potential collaborations include a cancer biologist working with a tumor immunologist and a systems biologist to develop computational models of metabolic interactions, or a tumor immunologist working with a cancer biologist and an *in vivo* imager to

study the homing of T cells. Dr. Singer noted that the intent of the PAR is to gain a better understanding of the metabolic interactions between T cells (resting versus active) and tumor metabolism.

In the discussion, the following points were made:

< Grant supplements could include projects investigating the effects of diet, exercise, and nutrition on metabolism. Studies of tumor neo-angiogens, however, are covered through other NCI programs.

< The NCI was encouraged to consider the innate immune system as well as the effect of manipulators on immune system elements. In addition, members suggested that experiments be conducted in parallel with *in vivo* mouse studies to follow cell lineages.

< In response to a query about the rationale to promote collaborations using supplements versus new interdisciplinary grants, Dr. Singer clarified that the grant supplements are intended to seed collaborations, which may grow into multi-principal investigator R01 grants.

VII. ADJOURNMENT—DR. TODD R. GOLUB

There being no further business, the 54th regular meeting of the Board of Scientific Advisors was adjourned at 3:43 p.m. on Thursday, 7 November 2013.

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Date Todd R. Golub, M.D.
Chair, Board of Scientific Advisors

_____ _____

Date Paulette S. Gray, Ph.D.
Executive Secretary, Board of Scientific Advisors

National Cancer Institute

Request for Application (RFA)

U24 Cooperative Agreement for Biospecimen Banks to Support NCI Clinical Trials Network (NCTN)

Irina A. Lubensky, M.D.

Chief, Pathology Investigation & Resources Branch

Cancer Diagnosis Program

Division of Cancer Treatment & Diagnosis

BSA Meeting, November 7, 2013

National Cancer Institute

NCTN Biospecimens

- **Biospecimens are collected on NCTN Trial protocols (U10 grants) and used for integral and integrated marker studies/assays (prognosis/prediction)**

- **Specimens that remain in excess after clinical trial requirements have been met become "legacy" specimens and are distributed to investigators following a defined NCTN access process and approval of the study by expert review**

- **NCTN Biospecimens**
  - **Validation studies of predictive/prognostic markers**
  - **Assay development/validation**
  - **Discovery**

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Cooperative Group Banks (CGB) History

- Current 9 Cooperative Group Banks:
  ACOSOG, CALGB, NCCTG, NSABP, RTOG, GOG, ECOG, SWOG, COG
- Banks are an integral part of the NCTN (supported by U10 grants)
- Unique resource: collect, store and provide researchers with well-annotated specimens and clinical data from phase III and large phase II NCI Cooperative Group Clinical trials
- NCI Cooperative Group Banking RFA (Cancer Diagnosis Program):
  9 U24 Cooperative Agreement Grants (9/2005-3/31/2010)
  9 U24 grant supplements (4/1/2010-3/31/2012)
  9 U24 Cooperative Agreement Grants (4/1/2012-3/31/2015)
  Supplements for common IT Navigator development (9/2012-present)
- Present U24 CA RFA supports a harmonized NCTN banking network for reorganized 4 Adult and 1 Pediatric NCTN Groups:
  ALLIANCE, NRG, ECOG-ACRIN, SWOG, COG

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Specimen Activities in 9 Cooperative Group Banks (2008-2012)

Solid Tumor Specimens Collected	**400,866**
Solid Tumor Specimens Distributed	**277,063**
Serum Specimens Collected	**129,148**
Serum Specimens Distributed	**45,823**
Intra/Inter Group Investigators Supported	**418**
External Investigators Supported	**93**
Leukemia Specimens Collected	**93,805**
Leukemia Specimens Distributed	**37,501**
Intra/Inter Group Investigators Supported	**109**
External Investigators Supported	**54**

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Scientific Impact (2008-2012)

- High-dose daunorubicin selectively benefits AML patients with mutations in DNMT3A, NPM1 or MLL translocations (Patel JP, *et al*., *NEJM*; 2012)
- *OncotypeDx*™ test improved risk stratification in stage II & III colon cancer (O'Connell MJ, *et al*., *J Clin Oncol;* 2010)
- Relative paucity of recurrent somatic mutations in pediatric neuroblastomas challenges current therapeutic strategies that rely on frequently altered oncogenic drivers (Pugh TJ, *et al*., *Nature Genet,* 2013)
- HPV associated oropharyngeal cancers are a different clinical entity compared to smoking related head and neck cancers (Ang KK, *et al*., *NEJM,* 2010; & Fakhry C, *et al*., *JNCI,* 2008)
- Identification of new recurrent mutations, such as ID3, in Burkitt's & DLBCL opens possibility of better clinical trial design in patients with targetable mutations (Love C, *et al*., *Nature Genet*., 2012)

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U24 Banking RFA Goals

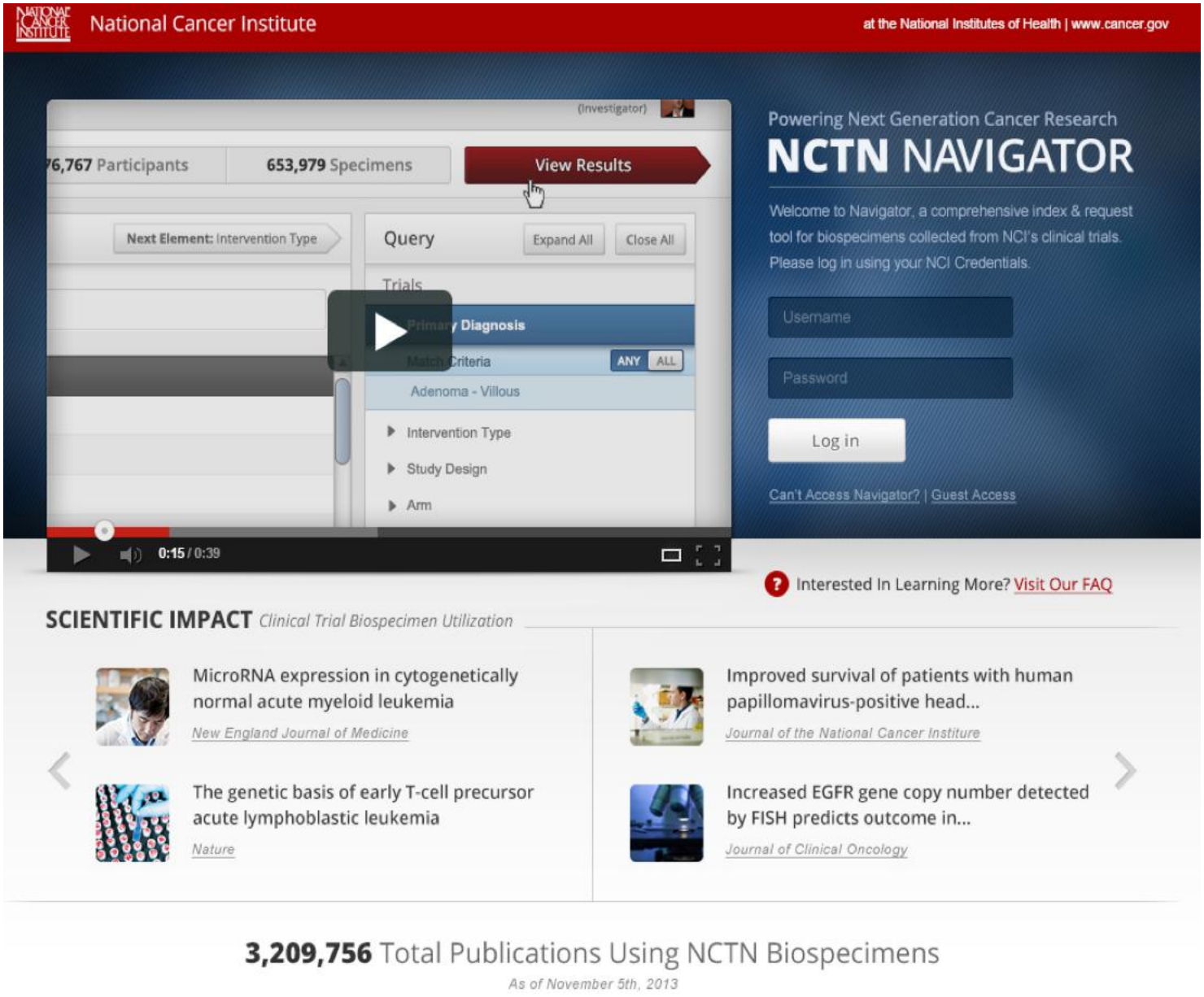
- Consolidate current CGBs into a harmonized NCTN biospecimen banking network for 4 Adult and 1 Pediatric NCTN Groups
- Support banking infrastructure for prospective collection and storage of specimens on ongoing and new NCI trials
- Build a system for cataloging and retrieving of "legacy specimens" and specimen-associated data
- Support NCTN Biospecimen IT Navigator system, a central inventory database of specimens available for research with an integrated search engine to access specimens for the research community
- Support a bank to collect, store, and distribute biospecimens from early phase trials performed by CTEP's Experimental Therapeutics-Clinical Trials Network (ET-CTN)
- Streamline access to biospecimens:
  - Create a centralized Front Door specimen application process to support access to the NCTN Banks (CDP)
  - Create Central Correlative Science Review Committee to review NCTN biospecimen proposals (CTEP)

NCTN IT-Navigator Goals

1. Consolidate inventory of biospecimens

2. Connect biospecimens and clinical data

3. Provide biospecimen access to research community



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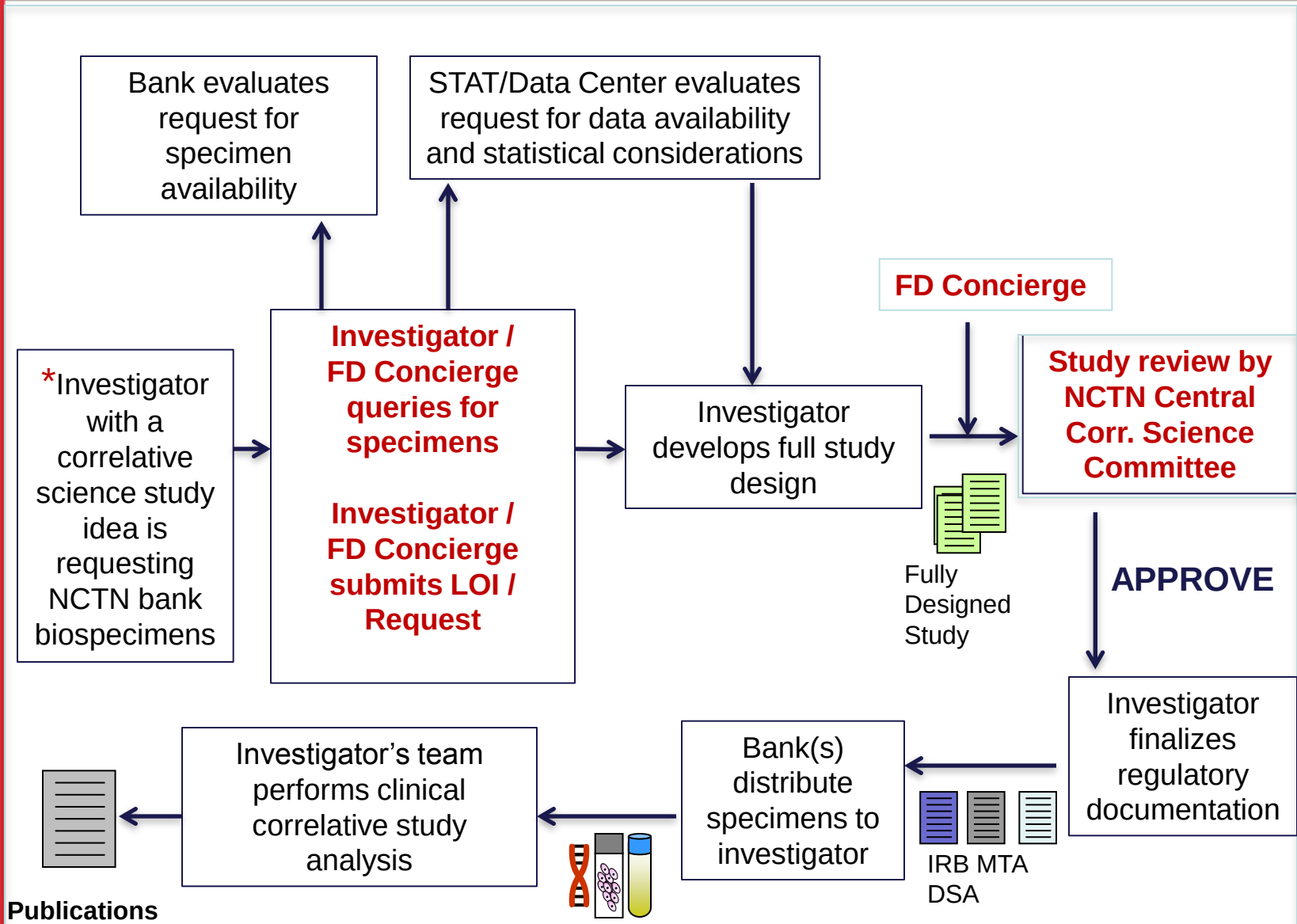
'Front Door (FD)' NCTN Biospecimen Request Process



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New U24 Banking RFA

- Consolidated NCTN biospecimen banking network
- One U24 banking grant for each new NCTN Group (5 awards)
- Grant PIs - specialists in biospecimen banking
- ALL solid tumor & leukemia banking infrastructure & operations with common SOPs
- NCTN Biospecimen IT Navigator: common inventory; specimen-data link; access for researchers; monitoring
- Centralized Front Door process: access to “legacy” specimens; application tracking, timekeeping
- One bank to collect, store & distribute biospecimens from ET-CTN trials

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U24 Banking RFA Budget

- **Portfolio analysis: no similar resource at the NCI**

- **5 awards to support 5 NCTN Biospecimen Banks**

- **Total cost for 5 banks per year: $11.75M**
  - **Banking Operations/Infrastructure: $9.68M**
  - **Banking IT + IT Navigator Maintenance: $1.32M**
  - **Banking Early Phase Clinical Trial Specimens: $0.75M**
    (restricted funds)

- **Total cost for 5 banks over 5 years: $58.75M**

Using Social Media to Understand and Address Substance Use and Addiction

Trans-NIH RFA Concept presentation to NCI Board of Scientific Advisors

Wen-ying Sylvia Chou, PhD, MPH
Health Communication and Informatics Research Branch

November 7, 2013

Partnership with Collaborative Research on Addiction at NIH (CRAN)

- A trans-NIH Initiative to advance research in substance use and addiction
- IC contributions to CRAN
  - 70% NIDA
  - 25% NIAAA
  - 4% NCI
  - 1% the rest of NIH
- This NCI-led RFA was:
  - Approved by CRAN in June 2013, with a set-aside fund of **$5M for FY14**
  - Approved by NIDA and NIAAA leadership
  - Approved by NCI's SPL in September 2013

Overview

- Background & rationale
- RFA purpose and scope
- RFA approach

What is social media?

- **User-generated content as part of social interaction through web technologies (including mobile)**
- Transparency and accessibility of interactions
- Examples: Facebook, YouTube, Twitter, CaringBridge, Patientslikeme, online support groups and discussion forums

Changes in communication landscape

- Rapid growth of mobile and Web 2.0 technologies
  - US Internet penetration >80% [1]
  - Social media use >72% among Internet users [2]
- Changing communication ecology
  - Proliferation of user-generated content blurs boundaries between communicators and public [3,4]
- Distilling hype from reality: opportunities for health behavioral research[4]

1.Fox S. 2013. Pew Internet Health.

2. Chou WS et al. 2009. Social media use in the US: Implications for Health Communication. *JMIR*.

3. Centola D. Social Media and the Science of Health Behavior. *Circulation*.

4.Chou WS et al. 2013. Web 2.0 for health communication: Reviewing the current evidence. *AJPH*.

Who uses social networking sites

% of internet users within each group who use social networking sites

	All internet users (n=1,895)	**72%**
a	Men (n=874)	70
b	Women (n=1,021)	74
	Race/ethnicity	
a	White, Non-Hispanic (n=1,331)	70
b	Black, Non-Hispanic (n=207)	75
c	Hispanic (n=196)	80[a]
	Age	
a	18-29 (n=395)	89[bcd]
b	30-49 (n=542)	78[cd]
c	50-64 (n=553)	60[d]
d	65+ (n=356)	43
	Education level	
a	No high school diploma (n=99)	67
b	High school grad (n=473)	72
c	Some College (n=517)	73
d	College + (n=790)	72
	Annual household income	
a	Less than $30,000/yr (n=417)	75
b	$30,000-$49,999 (n=320)	72
c	$50,000-$74,999 (n=279)	74
d	$75,000+ (n=559)	71
	Urbanity	
a	Urban (n=649)	74
b	Suburban (n=893)	71
c	Rural (n=351)	69

Hispanics significantly more likely to use social media

Tripled since 2009

Source: Pew Internet and American Life Project, 2013.

Changes in communication landscape

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Stakeholder Recommendations

- **IOM reports** and **Healthy People 2020**[1, 2, 3] call upon the NIH to support the development of new communication approaches leveraging social media to facilitate patient engagement and alleviate disease burden
- "**Emerging media and cancer prevention**" identified as 2013-14 focus of the President's Cancer Panel (Dr. Rimer's presentation to Joint NCAB/BSA Meeting, June 23)

1. For the Public's Health: Investing in a Healthier Future. 2012. The National Academies Press
2. Promoting Health Literacy to Encourage Prevention and Wellness: Workshop Summary. 2011. The National Academies Press.
3. U.S. Department of Health and Human Services. Office of Disease Prevention and Health Promotion. Healthy People 2020. Health Communication and Health Information Technology. Washington, DC. Available at http://www.healthypeople.gov/2020/default.aspx

Social media interactions reveal public attitudes, perceptions and knowledge about health

Communication surveillance opportunities

The New York Times

Research

Social Media Join Toolkit for Hunters of Disease

By BRONWYN GARRITY
Published: June 13, 2011

"Social media — Facebook, Google, Twitter, location-based services like Foursquare and more — are changing the way epidemiologists discover and track the spread of disease…"

The New York Times

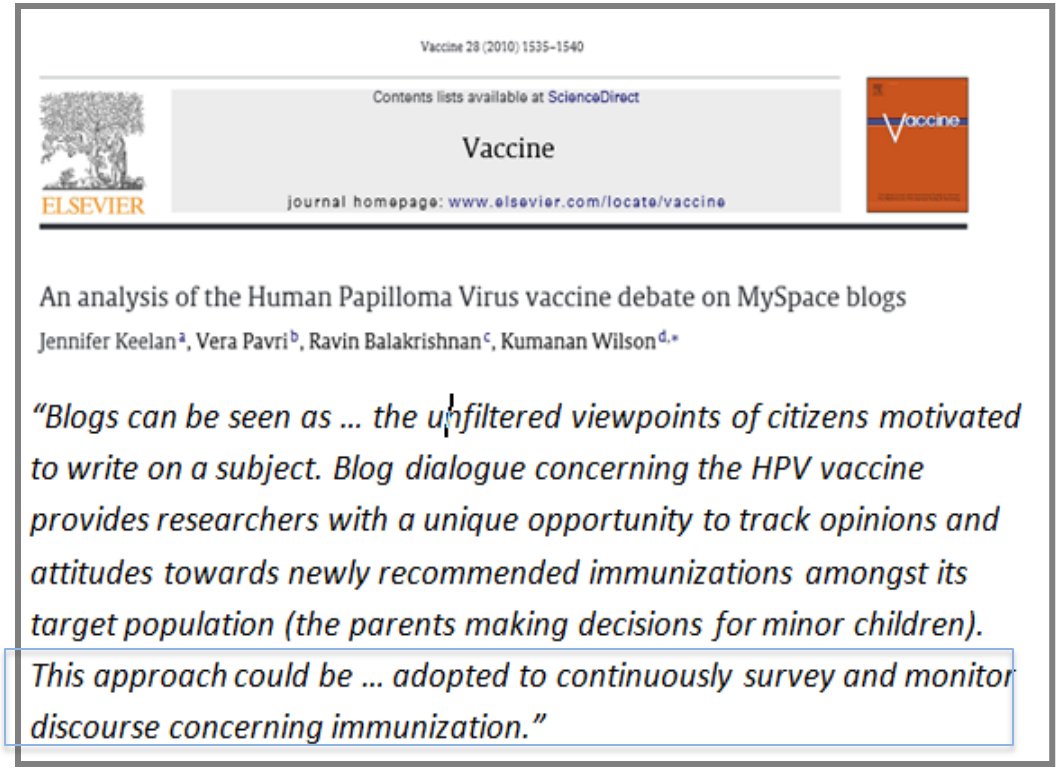
SundayReview

There's a Fly in My Tweets

By HENRY KAUTZ
Published: June 21, 2013

"…a small but growing number of research groups have initiated similar efforts to ***leverage the torrent of online information for social good.****"*

"…. The millions of people posting to sites like Twitter and Facebook can be viewed as a vast organic sensor network, providing a real-time stream of data about the social, biological and physical worlds."



Vaccine 28 (2010) 1535–1540

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

ELSEVIER

An analysis of the Human Papilloma Virus vaccine debate on MySpace blogs

Jennifer Keelan[a], Vera Pavri[b], Ravin Balakrishnan[c], Kumanan Wilson[d,*]

"Blogs can be seen as … the unfiltered viewpoints of citizens motivated to write on a subject. Blog dialogue concerning the HPV vaccine provides researchers with a unique opportunity to track opinions and attitudes towards newly recommended immunizations amongst its target population (the parents making decisions for minor children). This approach could be … adopted to continuously survey and monitor discourse concerning immunization."

Observational and intervention research using online interactions

nature International weekly journal of science

A 61-million-person experiment in social influence and political mobilization

Robert M. Bond[1], Christopher J. Fariss[1], Jason J. Jones[2], Adam D. I. Kramer[3], Cameron Marlow[3], Jaime E. Settle[1] & James H. Fowler[1,4]

"…online messages might influence… offline behaviors…the growing availability of cheap and large-scale online social network data means that these experiments can be easily conducted in the field…it will be important to use these methods to identify which real world behaviors are amenable to online interventions."

2136 Circulation May 28, 2013

Social Media as a Tool in Medicine

Social Media and the Science of Health Behavior

Damon Centola, PhD

Table 2. Comparison of Methods for Studying Social Influences on Health Behaviors

	Traditional Observational Data	Laboratory Experiment	Digital Observational Data	Internet Experiment
Scale	✓	X	✓	✓
Measurement	X	✓	✓	✓
Structural control	X	✓	X	✓
Replication	X	✓	X	✓
Behavioral fidelity	✓	X	✓	✓

Purpose of the RFA

Investigate the impact of social media (SM) on 'alcohol, tobacco, and other drug' (ATOD) use, abuse and addiction;

2 complementary approaches:

- **Observational studies** using SM as data/surveillance tool to understand risk factors, attitudes, and behaviors associated with ATOD use
- **Interventions** to test reach, engagement, and behavioral and health impact of SM on ATOD screening, prevention, and treatment

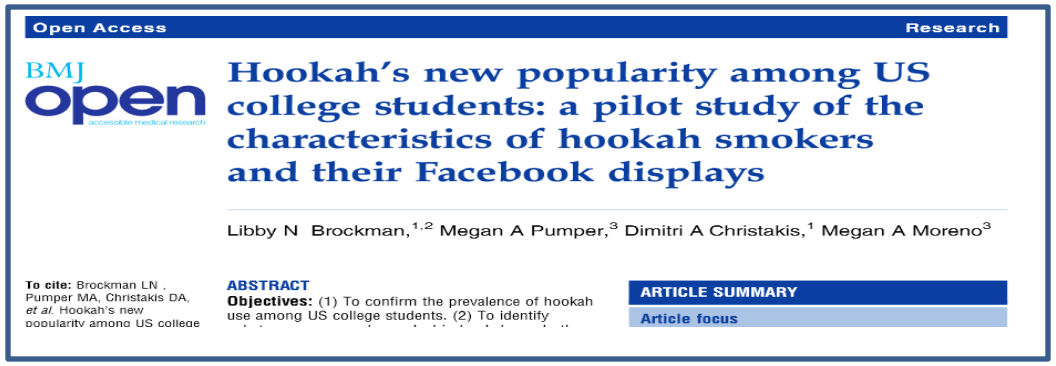
New and nimble research methods

- Natural Language Processing (NLP) for content analysis
  - E.g., sentiment analysis
- Social network analysis
- Data visualization techniques
  - E.g., spatial and temporal analyses
- Natural experiments and observational trials
- Private sector partnership
  - Expertise in measures and methods
  - Use of commercially available data mining techniques (e.g., Google Trends; Mechanical Turk)
- Fields traditionally outside of cancer:
  - E.g., Computer science, systems engineering, computational linguistics, behavioral economics, social marketing

Key objectives (1)

- Mine SM content to understand:
  - Risk factors associated with ATOD use
  - Real-time substance use patterns, consequences, triggering social contexts, and peer-to-peer interactions about ATOD use
  - Use and utility of SM for health promotion
  - Use and utility of SM for tobacco/alcohol marketing by industries
- Describe SM use patterns across populations
  - Age, SES, geographic location, network, health & ATOD use
- Test hypotheses on the effect of SM engagement on multiple levels of behavior change

Example:



Open Access Research

BMJ open accessible medical research

Hookah's new popularity among US college students: a pilot study of the characteristics of hookah smokers and their Facebook displays

Libby N Brockman,[1,2] Megan A Pumper,[3] Dimitri A Christakis,[1] Megan A Moreno[3]

To cite: Brockman LN , Pumper MA, Christakis DA, *et al*. Hookah's new popularity among US college

ABSTRACT

Objectives: (1) To confirm the prevalence of hookah use among US college students. (2) To identify

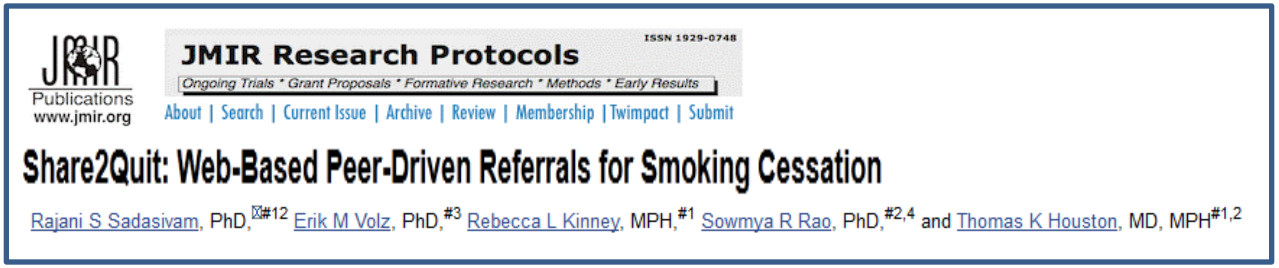
ARTICLE SUMMARY

Article focus

Key objectives (2)

- Ascertain feasibility and effectiveness of SM for ATOD use identification, prevention, service delivery and treatment
  - Theory-based, dynamic interventions
    - Mobile-based, peer-driven programs
  - Use of SM to overcome barriers to substance abuse treatment (e.g., stigma, cost, and lack of physical access to treatment)
- Identify intervention characteristics that contribute to the diffusion and adoption of addiction and substance use control programs

Example:



FOA approach

- Mechanism of Support
  - NIH R21s and R01s (up to 3-year; with cap on $)
- Additional requirements
  - Multi-disciplinary expertise
  - Streamlined and nimble research design
- RFA
  - Creation of Special Emphasis Panel led by NCI
  - One-time receipt date in FY 2014
  - Anticipated number of awards: 8-10

Thank you!

NATIONAL CANCER INSTITUTE

INNOVATIVE MOLECULAR ANALYSIS TECHNOLOGIES

Request for reissuance of four Request for Application (RFA) solicitations

November 2013

IMAT Program Overview

- ***Technology-focused***. Projects lacking a sufficient focus on early-stage technology development are administratively withdrawn

- Emphasis on supporting development and validation of ***high-risk/high-impact*** molecular and cellular analysis technologies ***to advance cancer research and clinical care***

- ***100% Investigator initiated*** *r*esearch project grants, utilizing the R21 and R33 award mechanisms for phase-1 and phase-2 levels of support

- ***Trans-divisional***, cooperative initiative focused on technological innovation with specific inclusions to minimize overlap or duplication with other programs/initiatives

IMAT FOA & Evaluation History

IMAT PAR Released
- 1 R21/R33
- 1 R41/R42
- 1 R43/R44

IMAT PAR Renewed
- 2 R21/R33
- 1 R41/R42
- 1 R43/R44

IMAT PAR Renewed
- 2 R21/R33
- 2 R41/R42
- 2 R43/R44

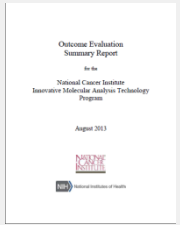
IMAT RFAs Approved
- 3 R21/R33
- 2 R41/R42
- 2 R43/R44

RFAs Renewed
- 3 R21 (3 yr awards)
- 3 R33
- 2 R41/R42
- 2 R43/R44

Full Program Evaluation

Evaluative Update

RFAs Renewed
- 2 R21 (3 yr awards)
- 2 R33

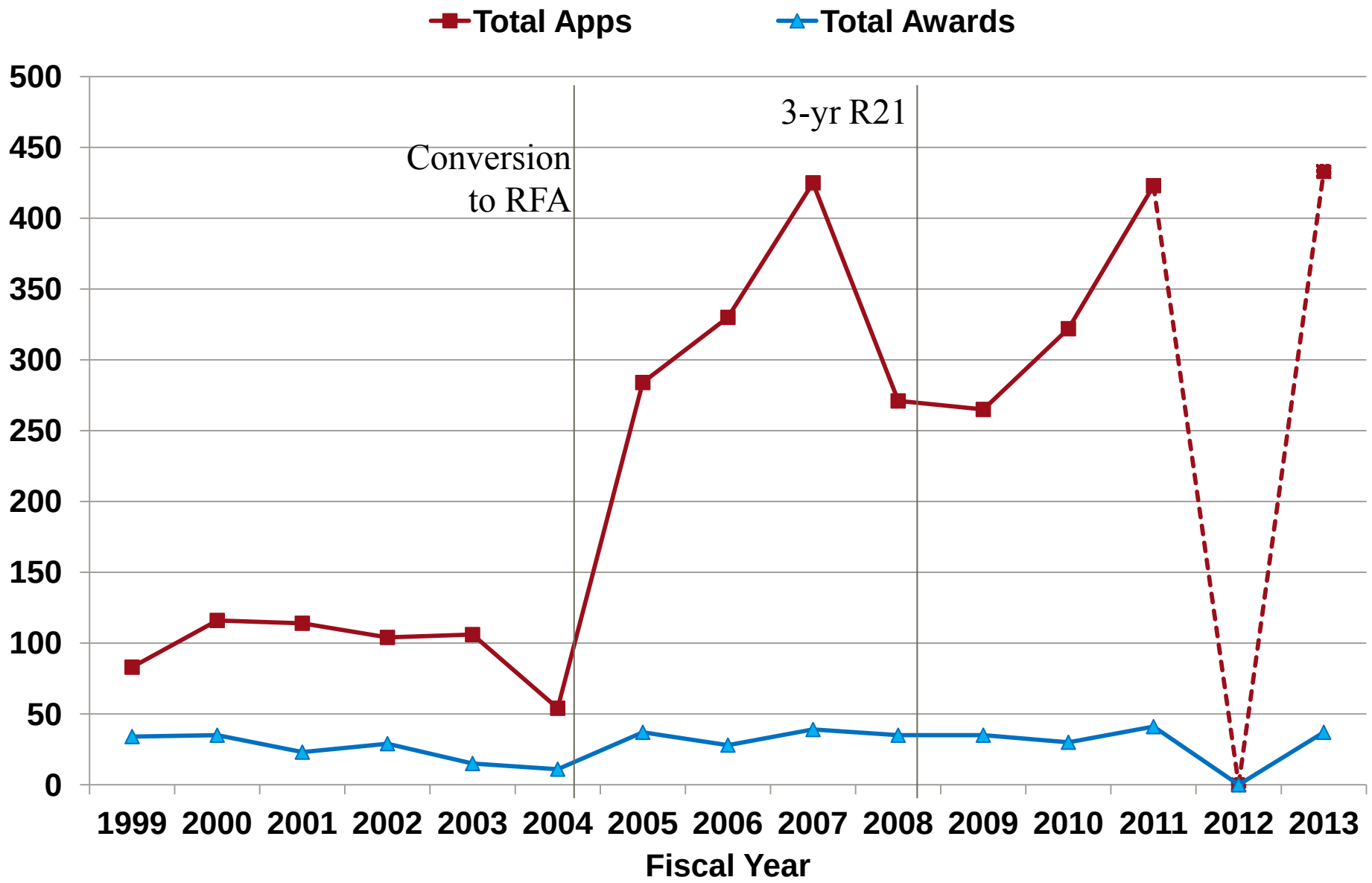


Targeted Evaluation

Ongoing Evaluation

1998 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013

IMAT Application & Award History



Graph is inclusive of all R21 and R33 applications and awards only

Sampling of successful IMAT Technologies

Proteomics

- Dynamic Range Enhancement Applied to Mass Spec (**DREAMS**) (Smith CA081654)
- **Gateway** ORF Cloning Tool (Vidal CA081658)
- Multi-Dimensional Protein Identification Technology (**MuDPIT**) (Yates CA081665)
- Isotope-Coded Affinity Tags (**ICAT**) (Aebersold CA084698)
- **Synchrotron Footprinting** (Chance CA084713)
- Nanowire field effect transistors (**NWFETs**) (Lieber CA091357)
- Deuterium exchange Mass Spec (**DXMS**), (Woods CA099835)
- Nucleic Acid Programmable Protein Array (**NAPPA**) (LaBaer, CA099191)

Genomics

- **Digital Optical Chemistry** (Garner CA081656)
- **Rolling Circle Amplification** (Lizardi CA081671)
- Representational Oligonucleotide Microarray Analysis(**ROMA**) (Wigler CA081674)
- Multi-photon Intravital Imaging (**MPIVI**) (Condeelis CA089829)
- **Recombomice** (Engelward CA084740)
- Pyrophosphorolysis Activated Polymerization (**PAP**) (Sommer CA094334)
- **Pair-end Sequencing** to screen structural rearrangements (Collins CA103068)
- **Digital Transcriptome Subraction** (Moore CA120726)
- **Zinc Finger Nucleases** for targeted double-strand breaks (Porteus CA120681)
- **COLD-PCR** (Makrigiorgos, CA138280)

Epigenomics

- Differential Methylation Hybridization (**DMH**) (Huang CA084701)
- Chromatin Immunoprecipitation with next gen Sequencing (**ChIP-Seq**) (Ren CA105829)

Clinical Diagnostics

- Paramagnetic chemical exchange saturation transfer (**ParaCEST**) (Sherry CA084697)
- **Near IR Probes** for *in vivo* diagnostics (Tung CA088365)
- MicroSOL IEF (Invitrogen as **Zoom IEF Fractionator**) (Speicher CA0943600)
- Microfluidic Genetic Analysis (**MGA**) chip (Landers CA16115)
- **Oncomap** (Garraway CA126674)

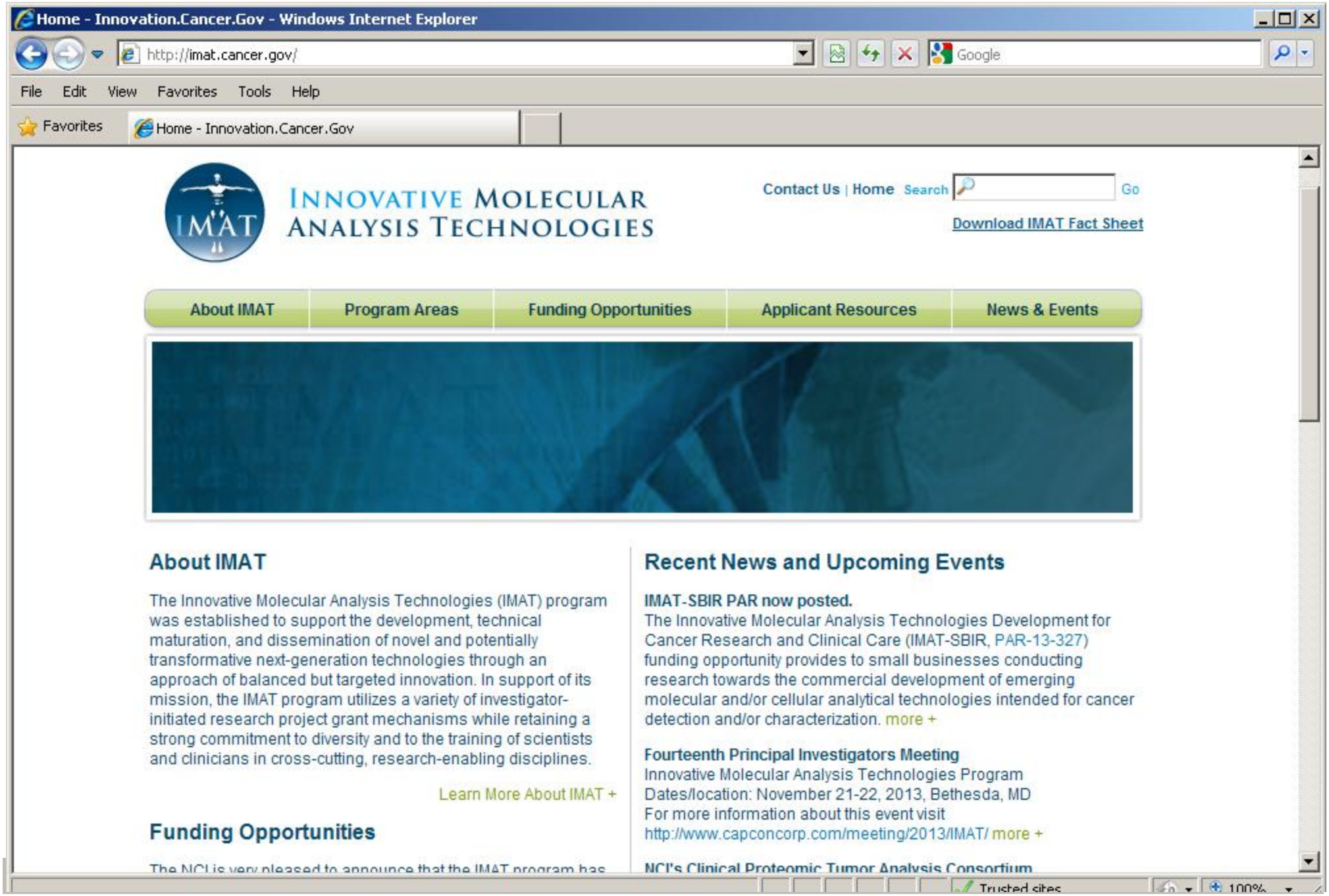
Sample preparation

- **Magnetic Cell Sorting**, now available from Ikotech (Chalmers CA081662)
- Dielectrophoresis Field Flow Fractionation (**DEP-FFF**) available as ApoStream™ system from ApoCell (Gascoyne CA088364)
- Cryopreservation followed by culturing of CML cells (Sims CA105514)
- **RainDance** Oil Droplet Microfluidics (Link CA125693)
- **NanoVelcro** (Tseng CA151159)

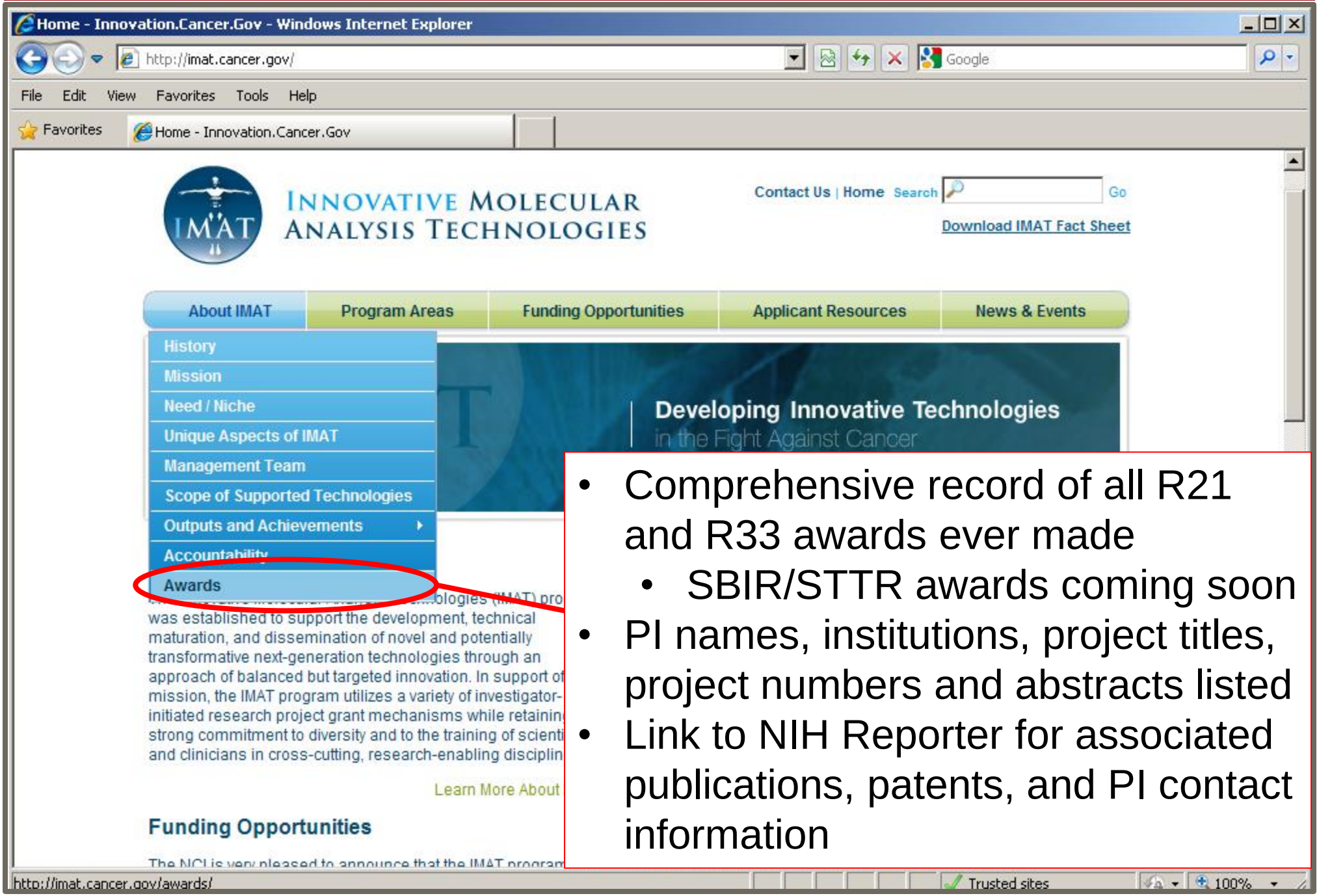
Drug Screening or Delivery

- One Bead One Compound (**OBOC**) (Lam CA086364)
- Genetically modified T-cells for acute lymphoblastic leukemia treatment (Cooper CA116127)

http://innovation.cancer.gov



http://innovation.cancer.gov



- Comprehensive record of all R21 and R33 awards ever made
  - SBIR/STTR awards coming soon
- PI names, institutions, project titles, project numbers and abstracts listed
- Link to NIH Reporter for associated publications, patents, and PI contact information

Motivation for Request for Reissuance

1. IMAT program continues to account for the majority of NCI's support for investigator-initiated technology development, addressing an area unmet by other FOAs

2. IMAT solicitations continue to receive a substantial number of high-scoring applications

3. A significant record of success, as verified by multiple external program outcome evaluations

Recent Outcome Evaluation

- An evaluation is required for any reissuance of an RFA program at NCI
- 2013 outcome evaluation focuses on recent successes only
- Evaluation Objectives
  1. Are submissions to and awards from the IMAT program unique within the NCI portfolio?
  2. Does the program work to support technology development appropriately?
  3. Does the program support technologies useful to the cancer research community?

Translation of IMAT technologies into hypothesis driven research

- 60 applications submitted to NIH leveraging IMAT-supported technology for hypothesis-driven research (32 to NCI directly, and 51 with focus on advancing cancer research)
  - 24 R01 applications (10 submitted to NCI), with 22 focused on cancer research
    - 6 successful (3 to NCI)
  - 75% of all applications drew specific enthusiasm from primary reviewers for the IMAT-supported technology component

Reissuance Request

Request to reissue 4 RFAs

1. Early-Stage Innovative Molecular Analysis Technology Development for Cancer Research (**IMT R21**)
2. Advanced Development and Validation of Emerging Molecular Analysis Technologies for Cancer Research (**EMT R33**)
3. Early-Stage Innovative Technologies for Cancer Biospecimen Sciences (**BSP R21**)
4. Advanced Development and Validation of Emerging Technologies for Cancer Biospecimen Sciences (**BSP R33**)

Table. History of applications and awards for each FOA

RFA Series	IMT R21 Apps	IMT R21 Awards	EMT R33 Apps	EMT R33 Awards	BSP R21 Apps	BSP R21 Awards	BSP R33 Apps	BSP R33 Awards
CA05	102	17	36	5	33	4	6	1
CA06	144	9	27	3	32	4	2	0
CA07	248	29	57	6	65	8	13	1
CA08	125	16	42	3	24	5	7	0
CA09	174	14	34	4	33	4	8	1
CA10	223	16	51	9	30	3	10	2
CA12	276	19	100	11	44	3	13	3
Total	**1478**	**120**	**428**	**41**	**288**	**31**	**77**	**8**

Advantages of the RFA Mechanism

- Assurance of NCI interest in technology development
  - Designed to address a specific need that other NCI initiatives are not currently meeting
  - Investigators at every stage of their career, but especially young investigators, do not consider the NIH and NCI as interested in supporting technology development

- Control over responsiveness and review
  - Administrative responsiveness determination, controlling the locus of review, and ability to work with DEA Scientific Review Officers seen as critical to managing the program
  - Without the RFA mechanism, use of these elements are at the discretion of NIH/CSR

IMAT Core Program Team

Officer	DOC	Contact
Chuaqui, Rodrigo	DCTD	chuaquir@mail.nih.gov
Dickherber, Tony	OD/CSSI	dickherberaj@mail.nih.gov
Divi, Rao	DCCPS	divir@mail.nih.gov
Knowlton, J. Randy	DCB	knowltoj@mail.nih.gov
Ossandon, Miguel	DCTD	ossandom@mail.nih.gov
Rahbar, Amir	SBIR DC	rahbaram@mail.nih.gov
Sorbara, Lynn	DCP	lynns@mail.nih.gov
Wagner, Paul	DCP	wagnerp@mail.nih.gov

Summary of Reissuance Request

- Innovative and emerging molecular & cellular analysis technology development for cancer research
  1. IMT R21: $5M set aside to support approximately 20 new R21 grants per year
  2. EMT R33: $4M set aside to support approximately 12 new R33 grants per year

- Innovative and emerging technologies for cancer-relevant biospecimen sciences
  3. BSP R21: $0.8M to support approximately 3 new R21 grants per year
  4. BSP R33: $0.7M to support approximately 2 new R33 grants per year

QUESTIONS?

Extra Slides

Extended IMAT Network

DCB

Structural Biology & Molecular Applications Branch

- **Randy Knowlton**
- Jerry Li
- Jennifer Couch (Chief)

DCCPS

Epidemiology & Genetics Research Program – Methods & Technologies Branch

- **Rao Divi**
- Mukesh Verma (Chief)

DCP

Cancer Biomarkers Program

- **Paul Wagner**
- **Lynn Sorbara**
- Karl Krueger
- Jacob Kagan
- Christos Patriotis
- Sudhir Srivastava (Director)

CSSI

- **Tony Dickherber**
- Jerry Lee

SBIR DC

- **Amir Rahbar**
- Andy Kurtz (Team Lead)

DCTD

Cancer Diagnosis Program

Diagnostic Biomarkers & Technology Branch

- **Miguel Ossandon**
- Brian Sorg
- Tawnya McKee
- Jim Tricoli (Chief)

Pathology Investigation and Resources Branch

- **Rodrigo Chuaqui**
- Ani Ganguly
- Irina Lubensky (Chief)

Diagnostics Evaluation Branch

- Kim Jessup(Chief)

Biorepositories & Biospecimen Research Branch

- Lokesh Agrawal
- Helen Moore (Acting Chief)

BSA Subcommittee Questions

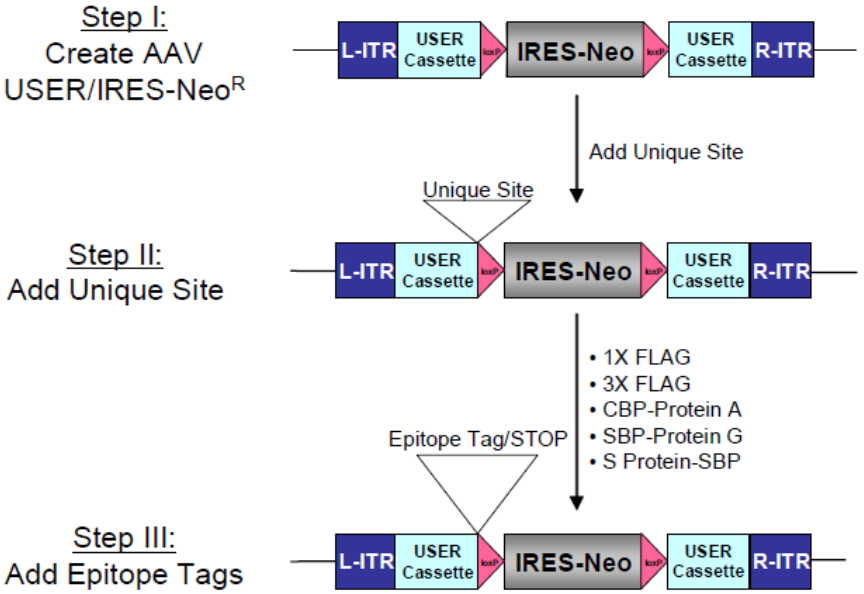
1. From a historical perspective, what has this program accomplished in terms of technological advances?
2. How has this initiative advanced cancer research?
3. Would the newly developed technologies have occurred without this initiative?
4. Other than publications and patents, what evaluation measures/criteria are being used to determine success?
5. What were the specific accomplishments during the last 5 years?
6. Provide a list of issued patents – include the inventors, title, abstract, and issue date.
7. Why are you using the RFA/Cooperative Agreement mechanism to continue this initiative?
8. Could the same outcomes occur if this was a SBIR and/or STTR supported initiative?

Endogenous Epitope Tagging (EET)

- Process for adding epitope tags to endogenous human genes in human cells and use these for generating endogenous interactomes via immunoprecipitation followed by mass spec
  - Subplants need to create new polyclonal antibodies in less time
  - Recently awarded R01 (w/ perfect score) to explore differential mechanistic and phenotypic activity of cdk4 and cdk6 in GBM using EET

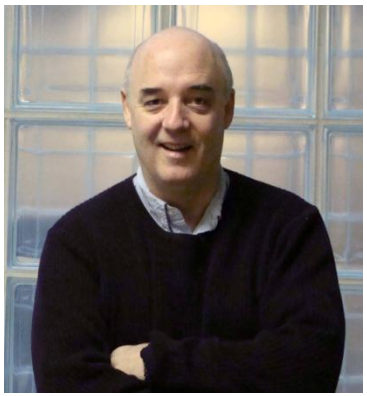
PI: Todd Waldman, MD, PhD
Professor, Molecular Oncology
Georgetown University

Georgetown | Lombardi
COMPREHENSIVE CANCER CENTER

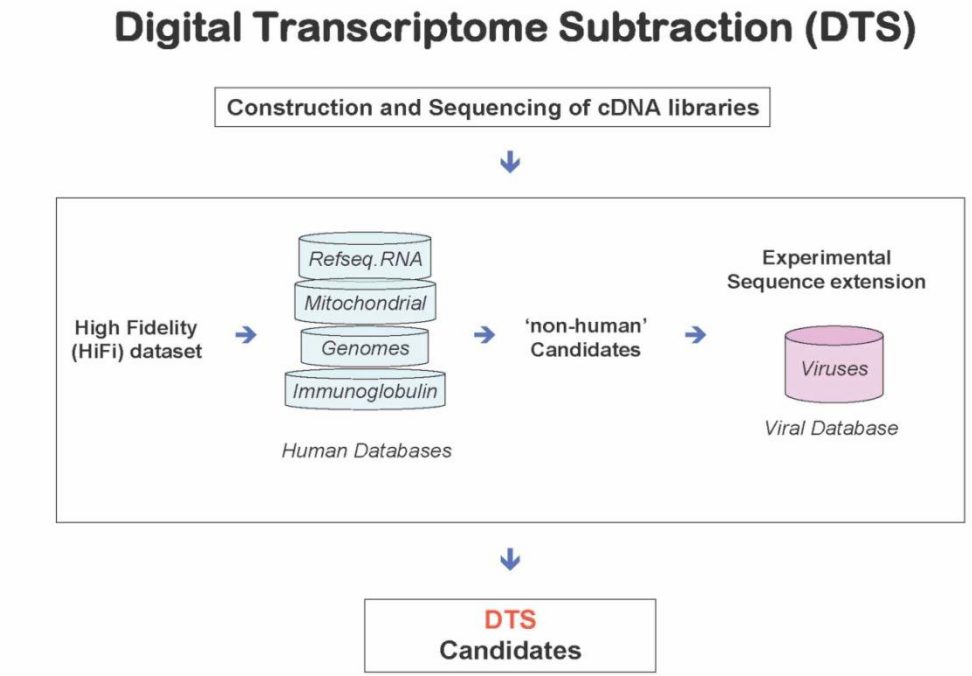


Digital Transcriptome Subtraction

- Viral screening protocol leveraging NGS
  - Discovered Merkel cell polyomavirus as part of the funded project, the 7th known human cancer virus (Shuda *et al*, PNAS 2008; Feng *et al* Science 2008)
- Predominantly informatics-based technique for isolating non-human sequences from NGS data by subtracting known human sequences (GenBank)



PI: Patrick Moore, MD, MPH
Director, Cancer Virology Program
UPCI Professor, Molecular Genetics & Biochem
University of Pittsburgh, Pittsburgh



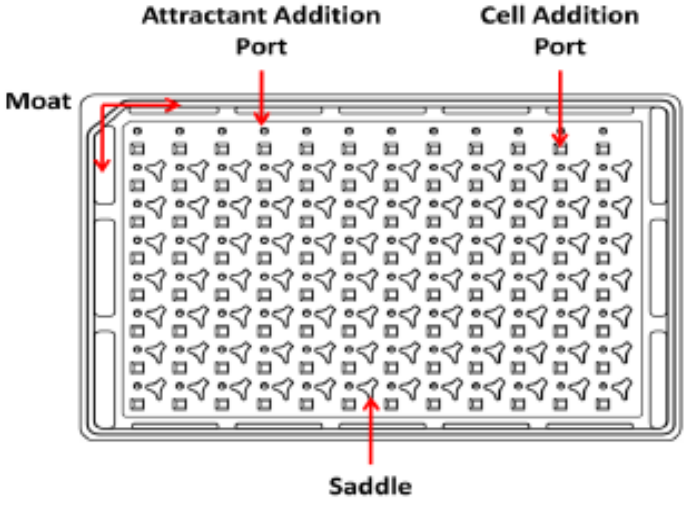
Feng et al. J Virol. 2007;81:11332-40

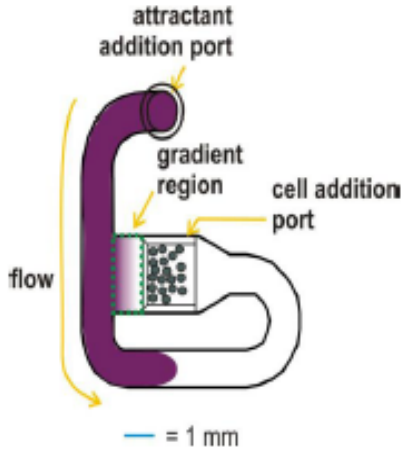
Image from http://www.tumorvirology.pitt.edu/

Iuvo™ Platform

- Microchannel cell-based assay for chemotaxis-based isolation and culturing of tumor cells for high-content analysis
  - Advantages are that platform enables standardized, automated cell sorting with quantification and high-content screening at low cost
- Commercialized by Bellbrook Labs [2008] and exclusively licensed by Thermo Fisher Scientific [2012] for use with their Cellulomics instruments

PI: David Beebe, PhD
Professor of Bioengineering
University of Wisconsin-Madison

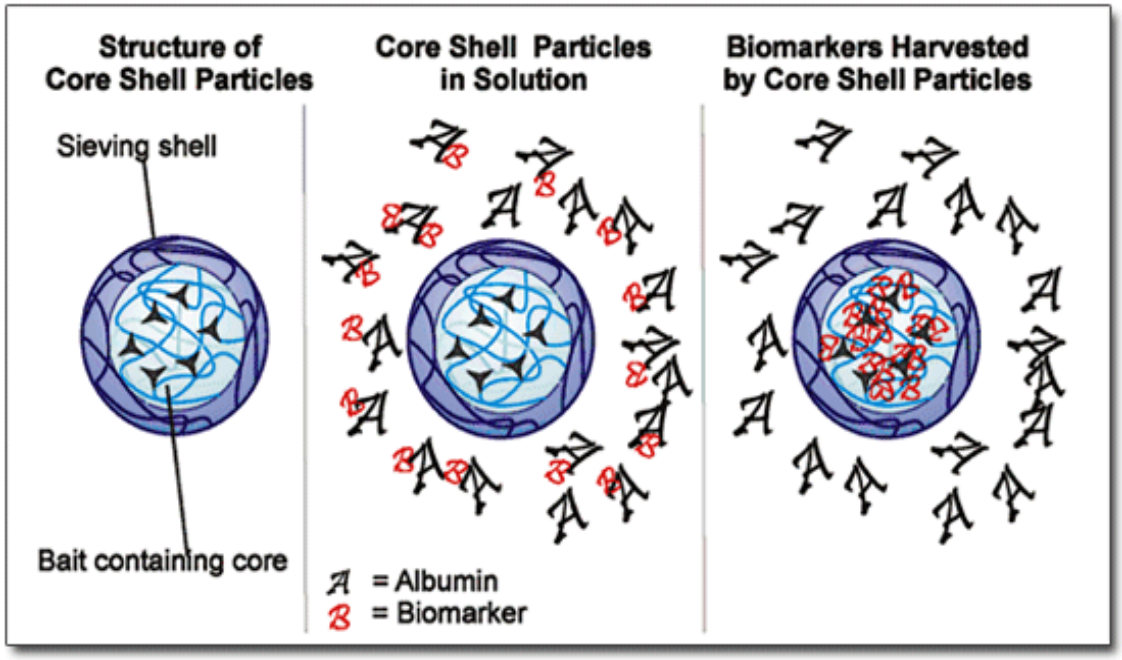




NanoTrap® Biomarker Discovery Platform

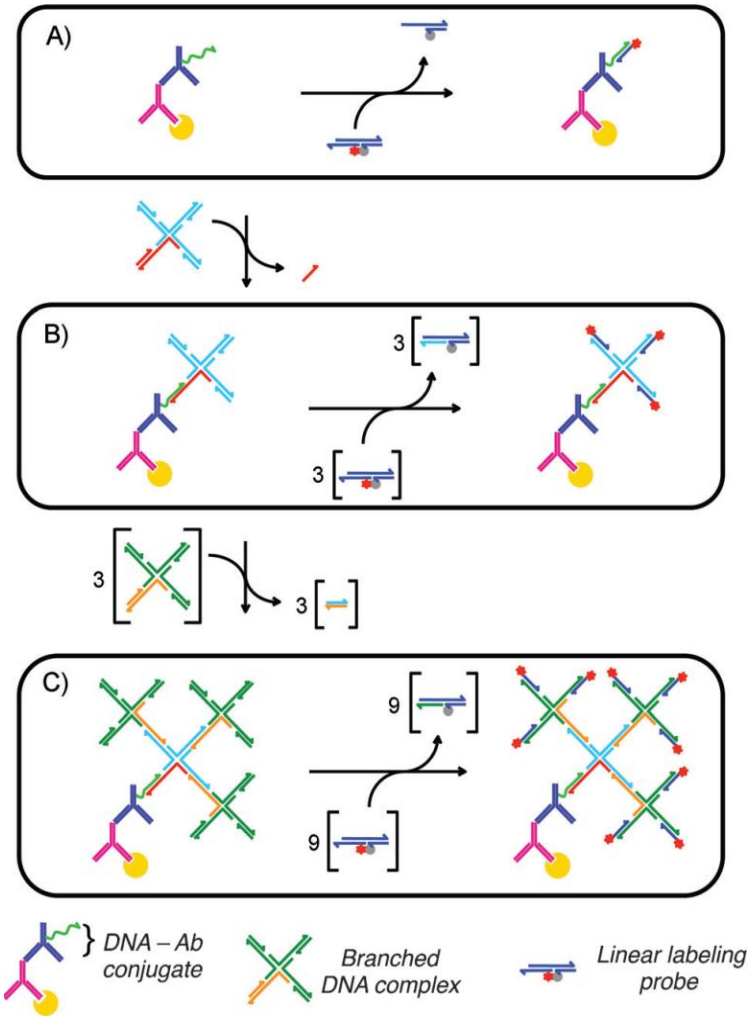
- Porous core shell hydrogel nanoparticles with affinity via “bait chemistry” and size exclusion for selection of biomolecular target
- Allows for immediate preservation and conservation of low-abundance target biomarkers in complex solutions, including whole blood
- Licensed by Shimadzu Scientific [2010] and made available in partnership with Ceres Nanosciences and Nonlinear Dynamics

PI: Lance Liotta, MD, PhD
Co-Director, Center for Applied Proteomics and Molecular Medicine
George Mason University



DNA-Catalyzed Molecular Biomarker Imaging Amplification (DC-MBIA)

- Dynamic DNA based programmable imaging probes
  - Highly multiplexed and reiterative immuno-fluorescence imaging capability for *in situ* studies
- Enzyme-free, isothermal, programmable, and regenerative system uses no harsh chemicals
- Multiplex imaging with 10-min to label and 10-min to erase



Diehl *et al*, ChemBioChem 2012, 13, 2722-8

PI: Michael Diehl, PhD
Asst. Professor of Bioeng/Chemistry
Rice University

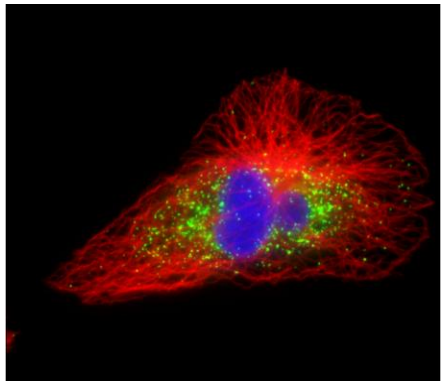
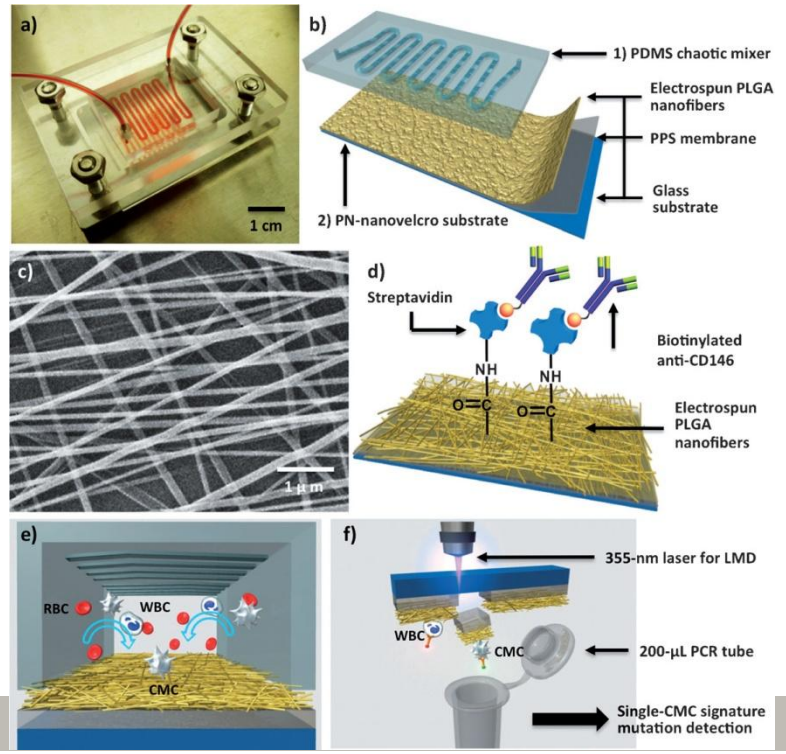


Image from http://diehllab.rice.edu

NanoVelcro: Circulating Tumor Cell Capture

- PLGA nanofibers to form NanoVelcro for high-purity isolation of circulating tumor cells from blood.
- Herringbone structures provide “chaotic mixing” to improve interaction frequency with substrate
  - Cells remain viable for laser capture microdissection and exome sequencing
- Applying platform to study therapeutic efficacy

PI: Hsian-Rong Tseng, PhD
Ass Prof Molecular & Medical Pharmacology, UCLA

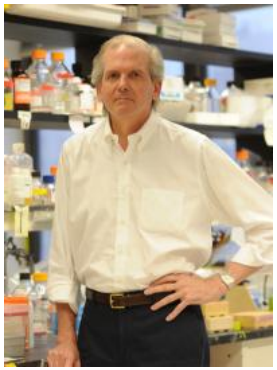


Hou *et al*, Angw Chem 2012, 52(12)

Methyl-MAPS

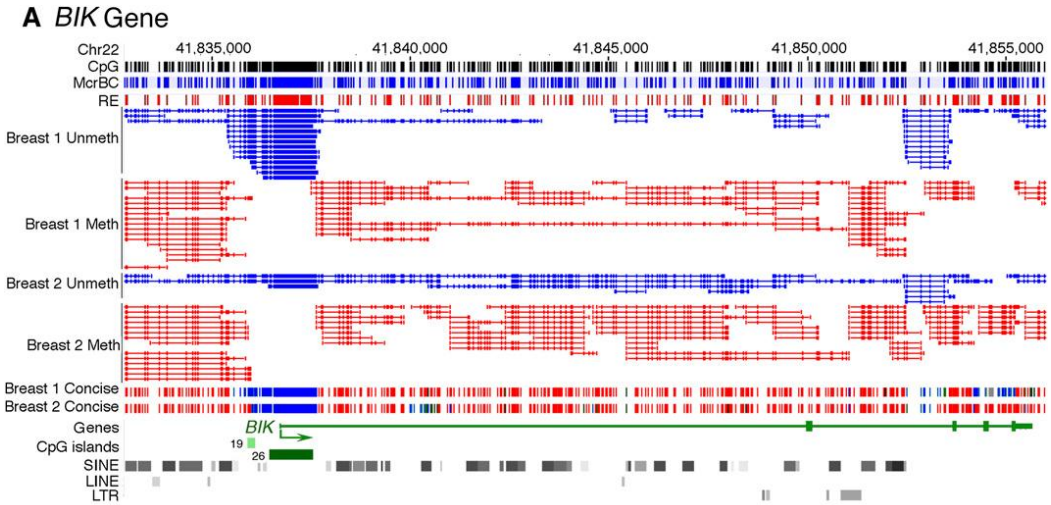
- Methylation MApping by Pair-end Sequencing (Methyl-MAPS) is novel methylation detection technique that allows fractionation of the whole genome into methylated and unmethylated pools, combined with ultra high-throughput sequencing.

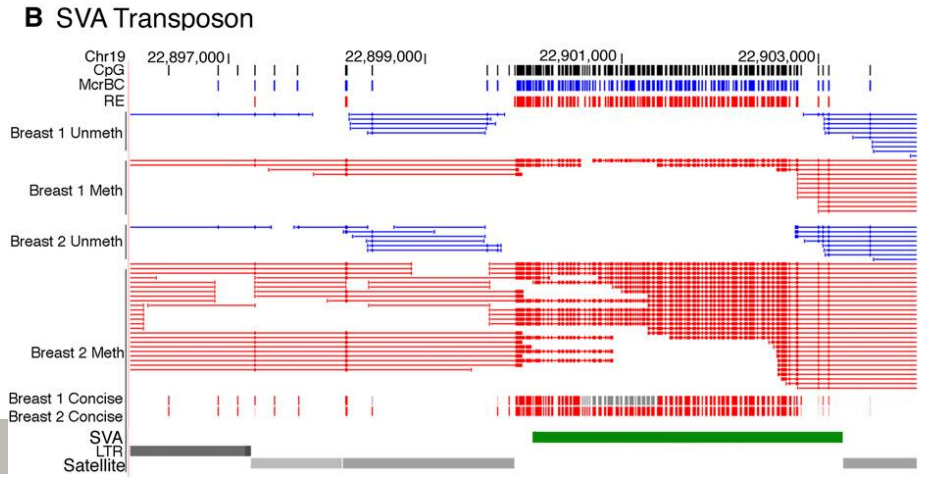
- Awarded new PQ-R01 to investigate methylation patterns and their role in tumorigenesis



PI: Timothy Bestor, PhD
Professor, Dept of Chemistry
Columbia University

Columbia University Medical Center
Department of Genetics & Development





RNA QC Models: SNAQ & STAR-Seq

- Developed a broad array of internal standard materials and mixtures available to the public for RNA analysis.
  - Standardized Nucleic Acid Quantification (SNAQ) and Standardized RNA-Seq (StaR-Seq) are RNA quality assessment/quality control protocols and materials, licensed by Accugenomics as internal standards for array of molecular diagnostic assays.
- Work is highlighted by Nature Methods Technology Report (May 2013)

AccuGenomics

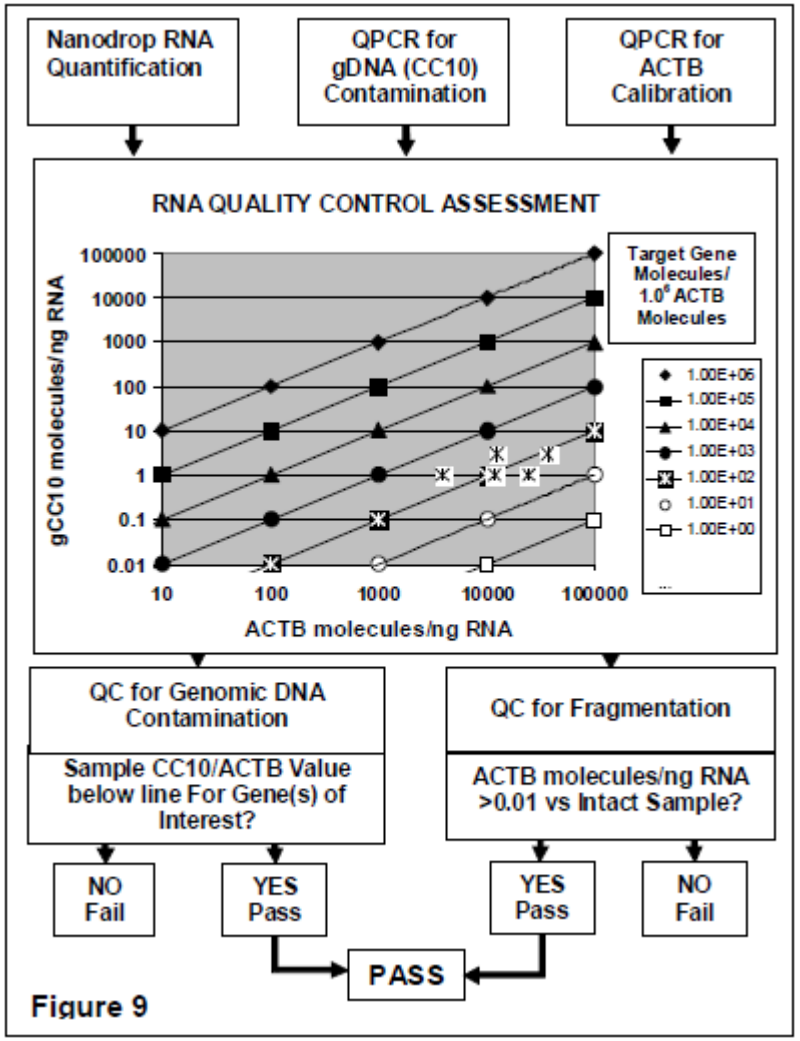


Figure 9

PI: James Willey, MD
Professor of Medicine & Pathology
University of Toledo

Outcome Summary of IMAT FY2010 Awards

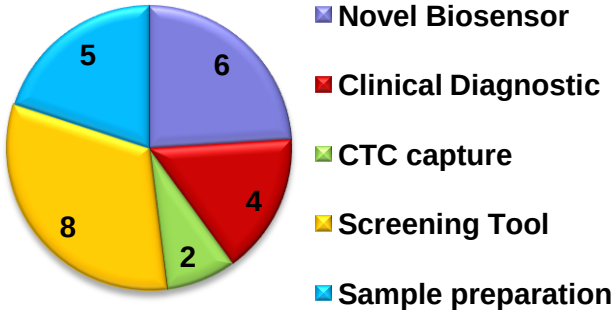
Concept → Proof of Principle → Development → Testing & Validation → Scale Up → Dissemination

Technology Development Pipeline

280 R21 Applications
→25 Awards

R21

19 projects completed milestones (as of June 2013)



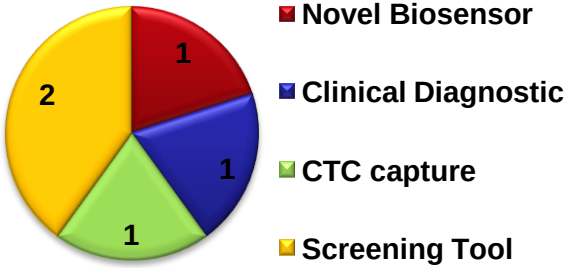
- 53 new NIH applications (11 awarded, 8 pending) indicate use of technology (27 submitted to NCI)
  - 10 applications for IMAT R33 (+1 for IMAT R21), with 2 awarded and 3 pending
- 32 patent applications submitted (3 awarded)
  - Several licensures in progress
- 114 publications in refereed journals
  - Upper quartile cited by ~28 on average (max 57)

42 R33 Applications
→5 Awards

R33

- 7 new NIH applications (1 awarded, 2 pending) indicate use of technology (5 submitted to NCI)
- 5 patent applications submitted (1 awarded)
  - 2 licensed (Cytomag, LLC, NewCo), and others in process
- 14 publications in refereed journals

3 completed all aims with evidence of success (as of June 2013)



Cancer Technology RFI responses

- 16 responses
  - 5 group responses, the rest individuals
- 38 suggestions
  - 23 suggestions within the scope of IMAT
    - 2 suggestions for which we have no active projects (targeted immunotherapies)
  - 15 suggestions out of scope
    - Therapeutic efficacy
    - Bioinformatics
    - *In vivo* imaging tools

Applications Submitted

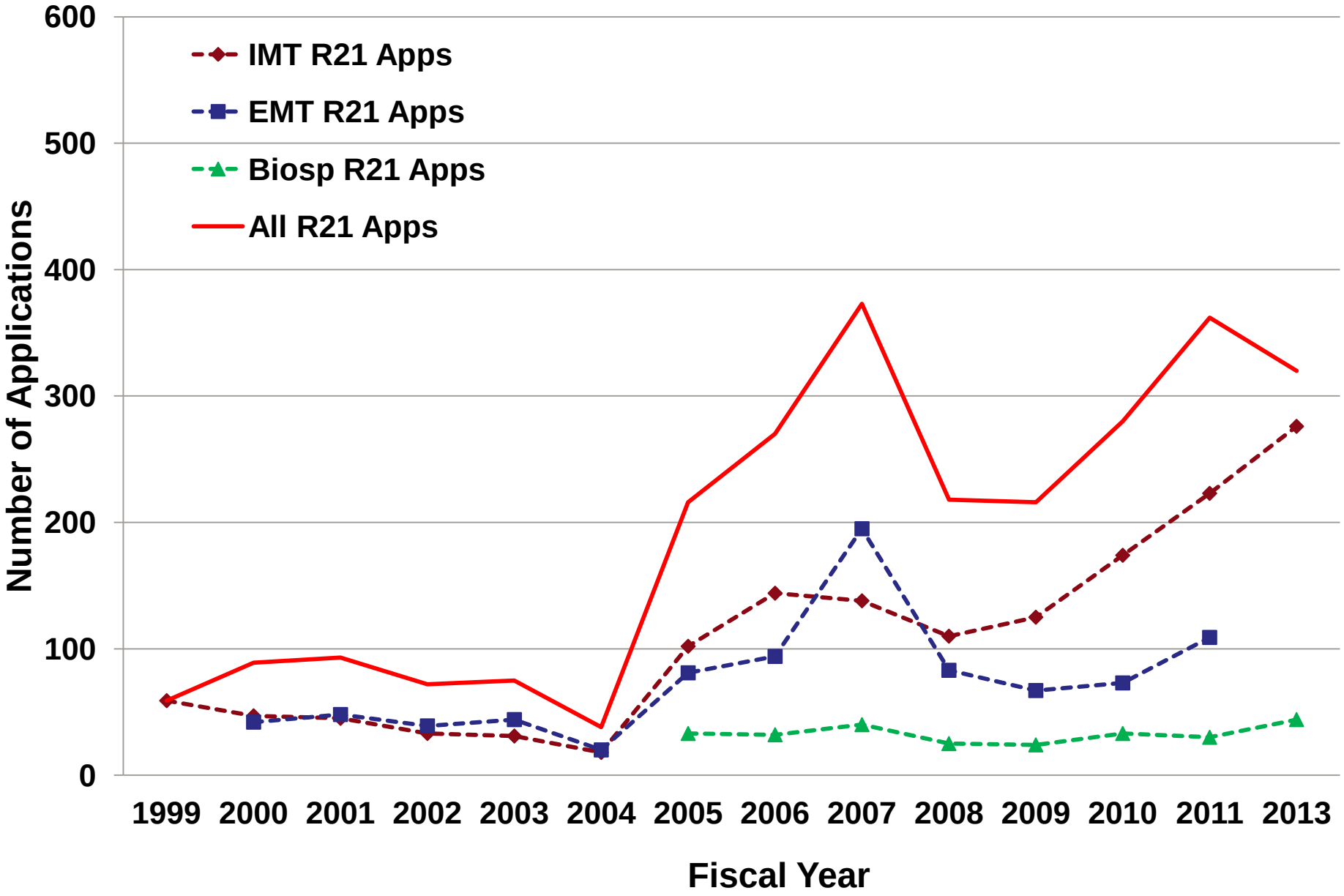
	FOA series	R21 Base Award: PAR98	PAR99	PAR01	CA05	CA06	CA07	CA08	CA09	CA10	CA12	Total	All R33 Apps Rec'd	% of R33 Apps Received
R33 Apps w/ base R21 awd	PAR98	0										0	24	0%
	PAR99	4	0									4	48	8%
	PAR01	6	4	1								11	79	14%
	CA05	2	4	2								8	68	12%
	CA06	1	0	3	1							5	60	8%
	CA07	1	7	7	5	1						21	105	20%
	CA08	0	0	0	0	5	3					8	49	16%
	CA09	0	0	1	2	1	5	0				9	42	21%
	CA10	0	0	1	0	2	5	6	1			15	61	25%
	CA12	0	0	2	2	0	2	5	9	2		22	112	20%
	CA13*	0	1	3	1	0	2	2	6	4	0	19	94	20%
	Total # Apps	14	16	20	11	9	17	13	16	6	0	122	742	16%
	# Resub's	3	2	5	5	3	4	4	4	1	0	31		4%
	Total # R21 awds made per FOA	25	44	38	29	21	60	32	25	30	22			
	% of R21 awds from base FOA seeking trans'n	**44%**	**32%**	**39%**	**21%**	**29%**	**22%**	**28%**	**48%**	**17%**	0%			

Awards Granted

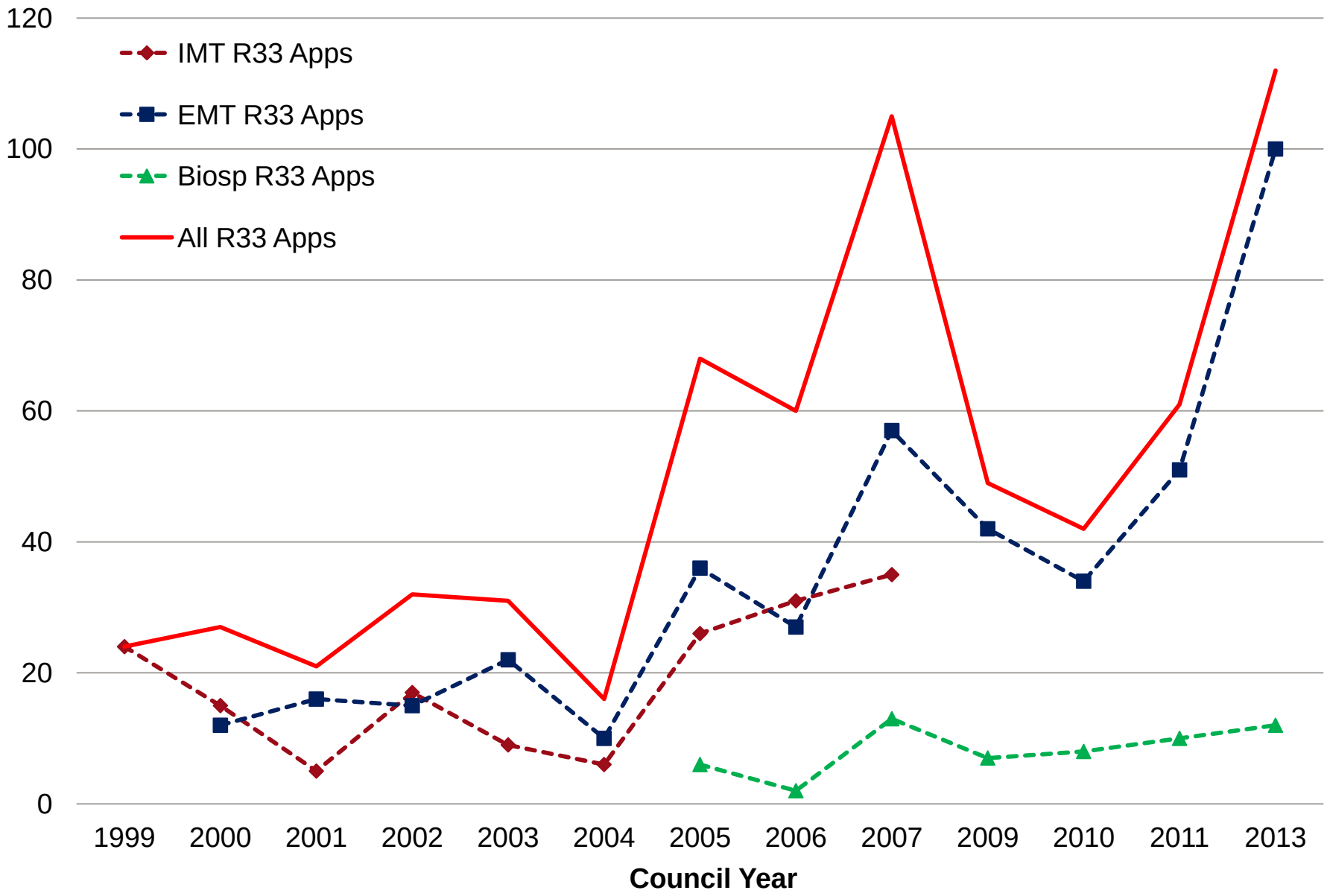
	FOA series	R21 Base Award: PAR98	PAR99	PAR01	CA05	CA06	CA07	CA08	CA09	CA10	CA12	Total	success rate per R33 FOA	**All R33 Awds**	% of R33 Awards Given
Successful R21 -> R33 Transition	PAR98	0										0		9	
	PAR99	1	0									1	25%	14	7%
	PAR01	1	0	1								2	18%	17	12%
	CA05	0	2	0								2	25%	8	25%
	CA06	1	0	0	0							1	20%	7	14%
	CA07	1	0	1	2	0						4	19%	14	29%
	CA08	0	0	0	0	1	1					2	25%	3	67%
	CA09	0	0	0	1	0	0	0				1	11%	5	20%
	CA10	0	0	0	0	1	2	2	1			6	40%	11	55%
	CA12	0	0	0	1	0	0	2	1	0		4	18%	14	29%
	CA13*	0	0	0	0	0	0	0	1	0	0	1*	5%*	5*	
	Total	4	2	2	4	2	3	4	3	0	0	24			
	Success Rate per attempt for base R21 FOA	**29%**	**13%**	**11%**	**36%**	**22%**	**19%**	**33%**	**19%**	0%					

*1 of 3 rounds accounted for. 11 applications still pending review

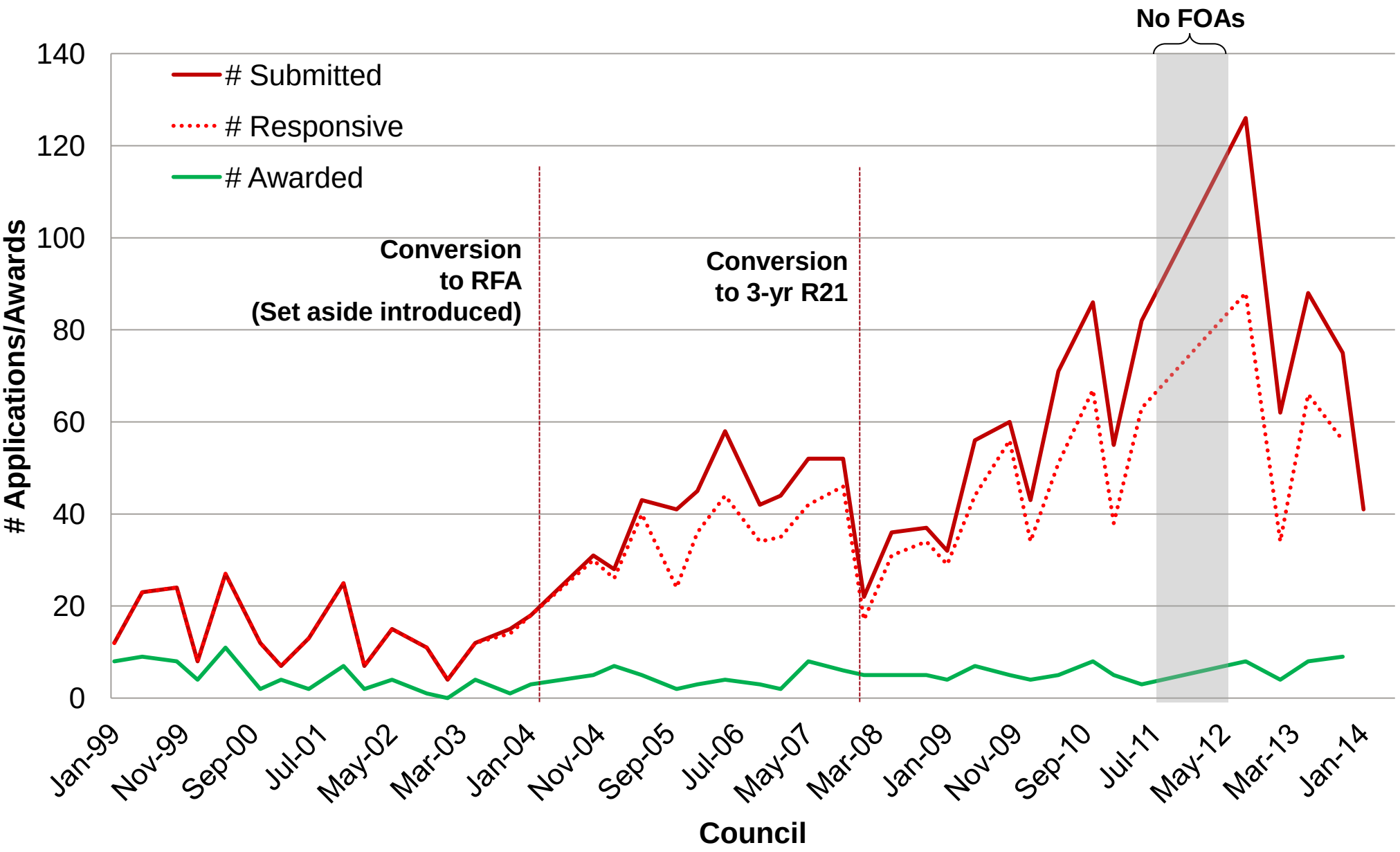
IMAT R21 Application History



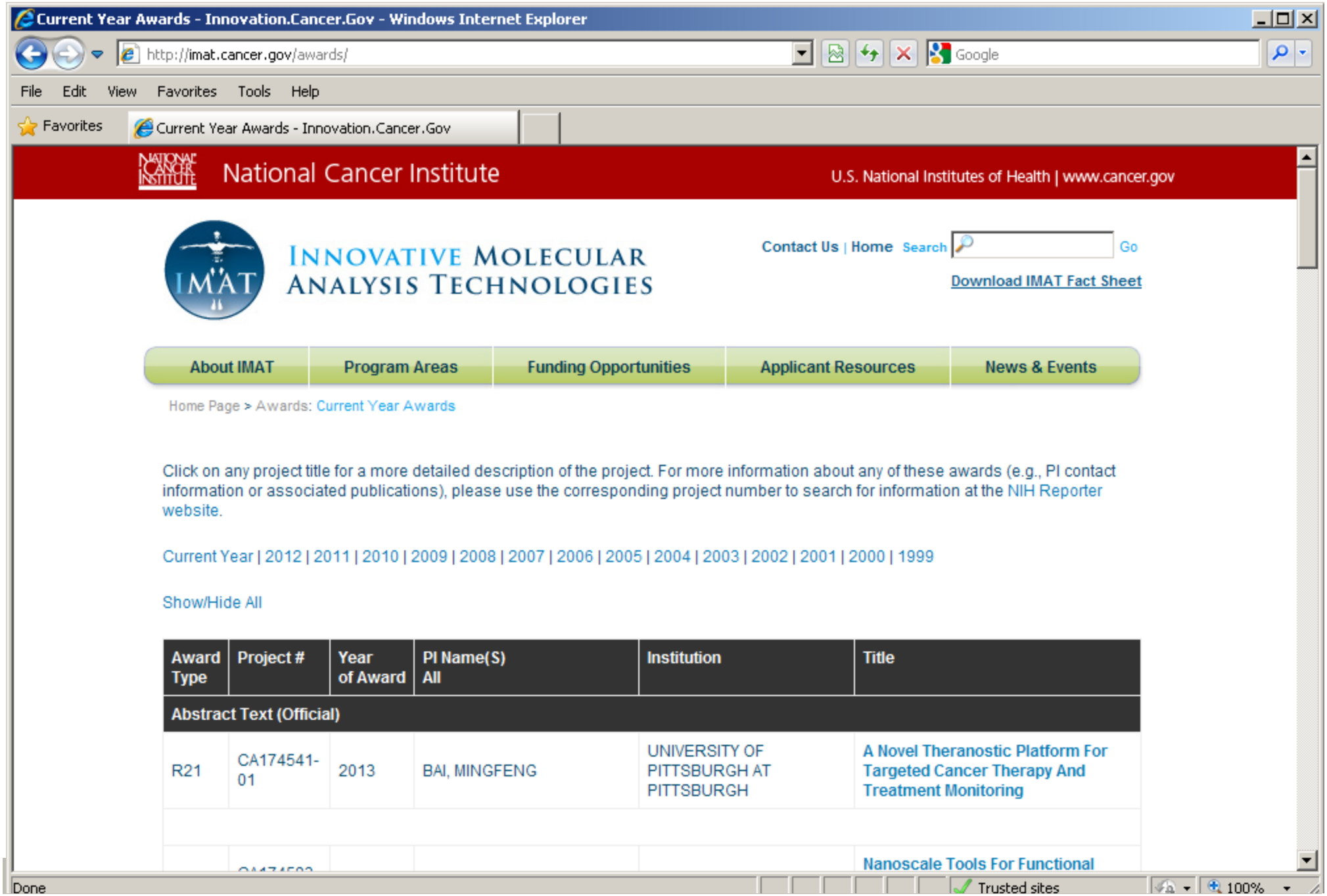
IMAT R33 Application History



IMT R21 Applications Submitted/Awarded per round of receipt



http://innovation.cancer.gov



Noteworthy IMAT SBIR Platforms

- **GeneChip® CustomSeq®** resequencing arrays from Affymetrix (Oliner CA081949)
- **BeadArray** gene expression assay system from Illumina (Chee CA081952)
- **BeadChip** arrays, **BeadLab** and **BeadStation** enabling NGS from Illumina (Chee CA083398)
- **PI 3K inhibitor screening** platform from Echelon Biosciences (now Aeterna Zentaris) (Drees CA81835)
- **ActivePipettes** used in Rainmaker microarray dispenser from Engineering Arts (Wiktor CA083390)
- **TRIO** multspectral diagnostic imaging from CRi, now Perkin Elmer (Levenson CA088684)
- Functionalization of **Quantum Dots** from Quantum Dot Corporation (Bruchez (CA088391)
- Mass Spec ImmunoAssays (**MSIA**) from Intrinsic Bioprobes (Nedelkov CA099117)
- **Light Activation System** from Syntrix, now SuperNova Life Sciences (Zebala CA099333)
- **PhosphScan®** kits from Cell Signaling Technology, Inc (Rush CA101106)
- **ONIX** microfluidic perfusion cell toxicity screening system by CELLASIC Corp (Lee CA120619)

FY2013 Award Summary

- IMT R21 [CA12-002/CA13-001]
  - 225 applications submitted, 156 reviewed
  - 21 awards
    - Overall Success Rate = 9%
- EMT R33 [CA12-003/CA13-002]
  - 98 applications submitted, 82 reviewed
  - 12 awards
    - Overall Success Rate = 12%
- Biosp R21 & R33 [CA12-004&5/CA13-003&4]
  - 53 applications submitted, 49 reviewed
  - 4 awards
    - Overall Success Rate = 8%
- 1st year Total Costs = $10.1M

Q1: Uniqueness of Applications

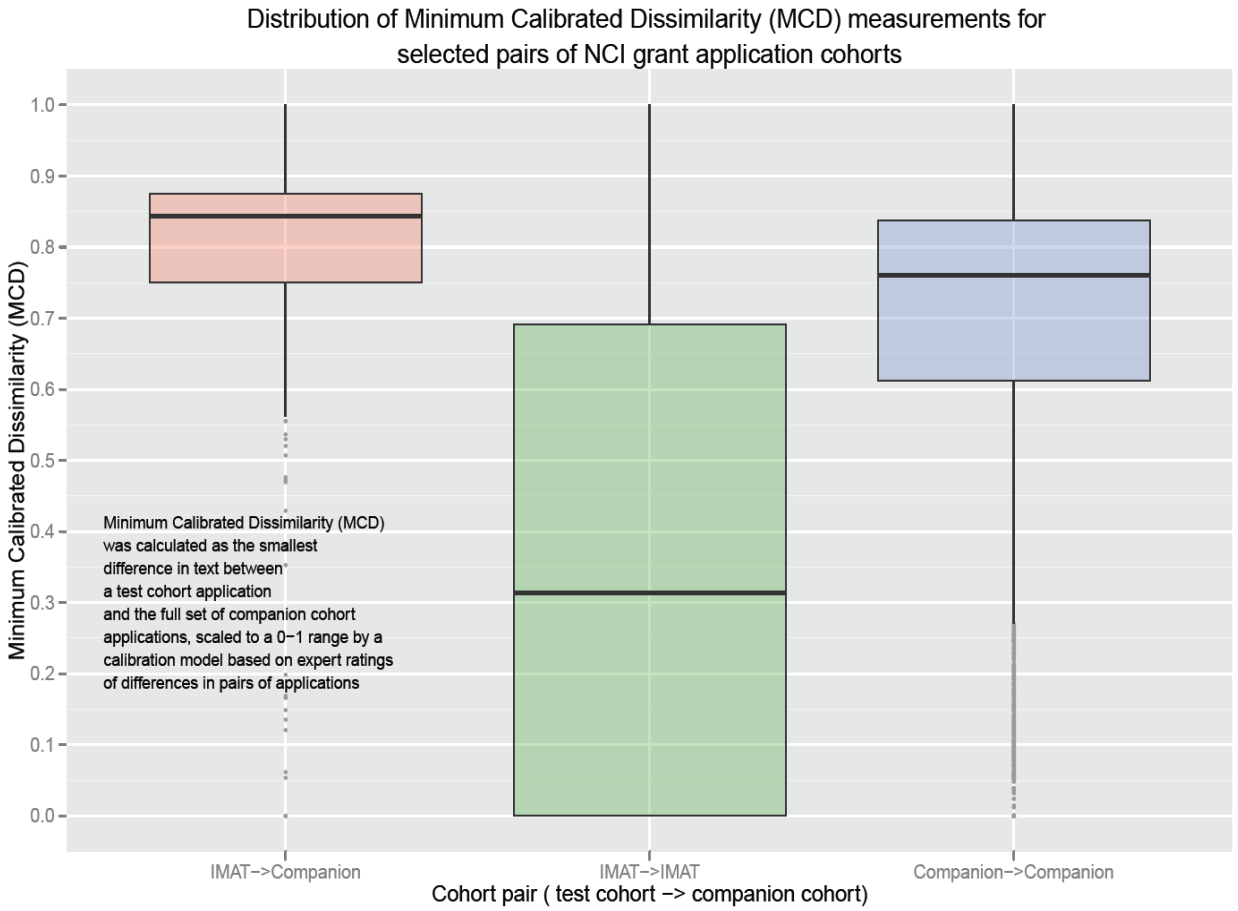
- **Scope**: CA12-00X submissions alone as most recent record with evidence
  - 432 applications [320 R21, 112 R33]
  - 316 responsive [222 R21, 94 R33]
  - 36 awards [22 R21, 14 R33]

- **Metrics**
  - Text mining of IMAT applications in comparison to other relevant NCI & NIH applications
  - Breakdown of non-cancer research applicants
  - Interviews with investigators

Q1: Unique applications for NCI

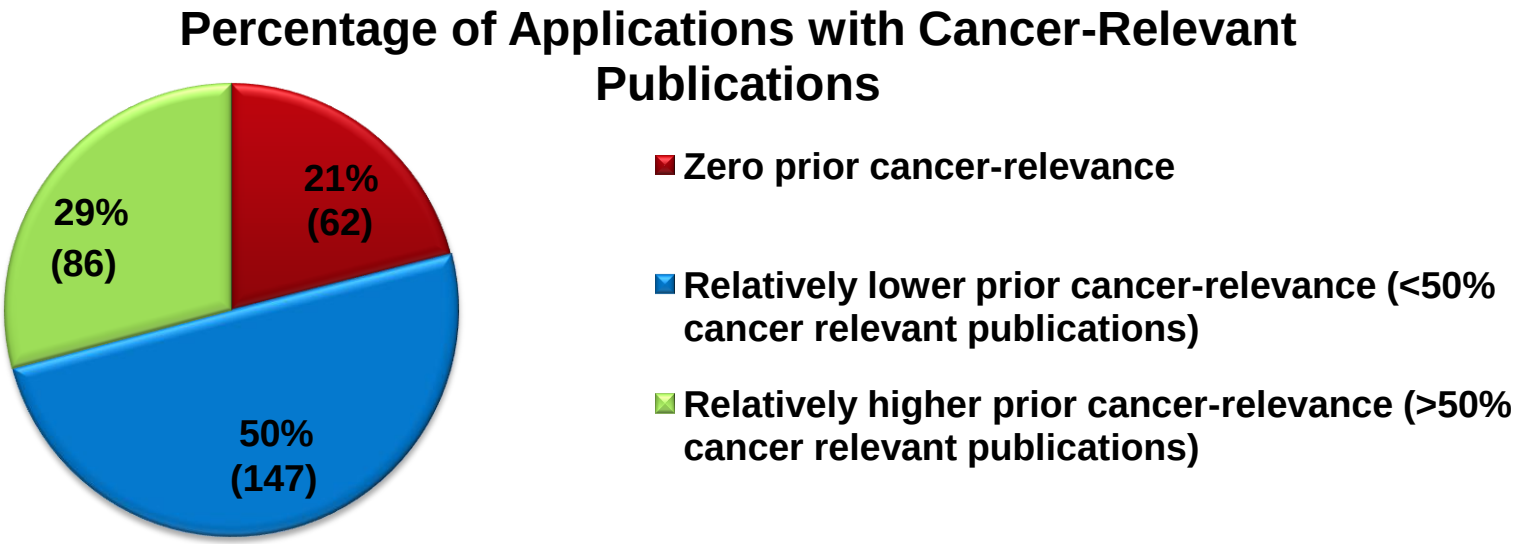
- Experience of program directors across the NCI confirms uniqueness of IMAT applications
- Experience of applicants confirms uniqueness of IMAT applications

- Text screening comparison analysis shows statistically significant difference between IMAT and other biotechnology and bioengineering applications to NCI



Q1: Unique applications for NCI

- Drawing applicants with non-traditional cancer research backgrounds
  - 21% of applicants (62) had no publication history in the last 5 years indicating cancer relevant research. 3 of the 35 awards (9%) made these rounds went to this group.
  - 50% of applicants (147) had less than half of their publications in the last 5 years indicating cancer-relevant research. 20 of the 35 awards (57%) made these rounds went to this group.



Q2: Effectiveness for Tech Dev

- **Scope**: Awards to CA09 [25 R21 and 5 R33 awards]

- **Metrics**:
  - Milestones met for R21
  - Responsiveness record
  - Patents submitted/awarded
  - Peer-reviewed publications
  - Transition from R21→R33

Q3: Usefulness of technologies supported

- **Scope**: Awards to CA09 [25 R21 and 5 R33 awards]

- **Metrics:**
  - Bibliometrics
  - Subsequent applications for NIH supported research (with and without the PI)
  - Commercialization activity (licensing, patent awards)

Example Projects for FY10 Award Categories

- **Novel Biosensor technologies**
  - Mitochodrial potential chips (MiP-Chips) (Burke, R21)
  - 3D nanocavity array (Chiles, R21)
  - Dynamic DNA: erasable molecular imaging probes (Diehl, R21)
  - FRET-based intracellular redox probes (Kenis, R33)
- **Screening Tools**
  - Targeted Genomic Circularization Sequencing (TGC-Seq) (Ji, R21)
  - Global PTK profiling microarrays (Turk, R21)
  - Capillary isotachophoresis (CITP) for isolation of low abundance protein (Lee, R21)
  - Methyl-MAPS (Mapping Analysis by Pair-End Sequencing) (Bestor, R33)
- **Clinical Diagnostics**
  - Application of Spatial Light Interference Microscopy (SLIM) to remote label-free blood smear-based Dx (Popescu, R21)
  - Metallic Phosphate/Apoferritin Nanoparticle Array (MPNA) hand-held immunosensor (Liu, R21)
- **Sample preparation**
  - Endogenous Epitope Tagging (Waldman, R21)
  - Methods for extracting DNA suitable for NGS from small FFPE samples (Barrett, R21)
  - STARSEQ & SNAQ: RNA quality assessment standards (Willey, R21)

Q2(&3): Successful development of technology

- Publication record indicates useful contributions to the field across all award types
- Citations by cancer-focused research papers indicate early indicator of interest and potentially uptake

	2-yr R21 (15 projects)	3-yr R21 (10 projects)	R33 (5 projects)	Total (30 projects)
All Publications*	**53**	**43**	**12**	**116**
Average Publications per Project (Max)	**3.5 (17)**	**4.3 (14)**	**2.4 (5)**	**3.6 (17)**
Average Total # of Citations per Project (Max)	**28 (123)**	**40 (216)**	**9 (24)**	**29 (216)**
Average Cancer-Relevant Citing Publications (Max)	**4 (21)**	**3 (11)**	**1 (5)**	**3 (21)**
Average Prestige Ratio (Max)	**29% (69%)**	**40% (77%)**	**18% (50%)**	**31% (77%)**
Median Impact Factor Quartile (Min)	**1 (1)**	**1 (1)**	**2 (1)**	**1 (1)**

*These publications are indexed in Web of Science with citation data available.

Q3:Evidence of Utility – Commercialization

- 37 US patent applications directly resulting (+32 international)
- 4 patents granted (applications filed before IMAT award)
- 6 licensing agreements in place or in negotiation on unique platforms
- 1 commercially available platform (Oris Pro™ migration kit from Platypus Technologies)

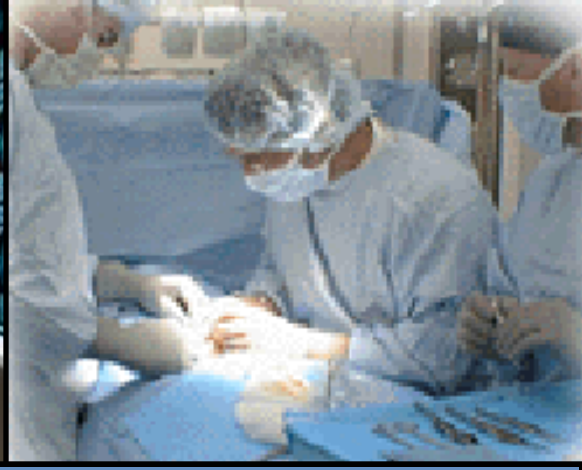
Method to Identify Application/Award	Provisional Patent Application	Patent Application	Patent Award	Licensure
Acknowledgement of IMAT Grant Number in Patent Record	0	1	0	0
Match by Technology Short Name and Investigator Name	0	31	2	0
PI Reporting	4	45	2	6
Distinct Total	**3**	**37**	**4**	**6**

Original RFA Evaluation Criteria

In order to properly monitor the effectiveness of the NCI Innovative Molecular Analysis Technologies (IMAT) program, and maximize its utility for the broad cancer continuum of researchers, clinicians and ultimately patients, it is important to engage in on-going evaluation of the IMAT portfolio and assess progress on the intended mission and goals of the program. Upon approval for reissuance of IMAT solicitations in 2011, the following list of evaluation criteria were approved by both NCI leadership and the NCI Board of Scientific Advisors:

- the number of publications that cite a specific IMAT award number;
- the number of patent applications submitted to the USPTO that cite a specific IMAT award number in one of four government interest fields;
- the number of patent applications granted or approved by the USPTO based on patent applications that cite a specific IMAT award number in one of four government interest fields;
- the number of IMAT-funded technologies now used in other NCI and NIH strategic initiatives; and
- a series of follow-up case studies on previously funded technology development projects and platforms, including their current use by and utility to the extramural scientific and clinical communities.

National Cancer Institute



Pediatric Preclinical Testing Program (PPTP)

November 2013

Malcolm A. Smith, MD, PhD
Cancer Therapy Evaluation Program
National Cancer Institute, U.S.A.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

National Cancer Institute

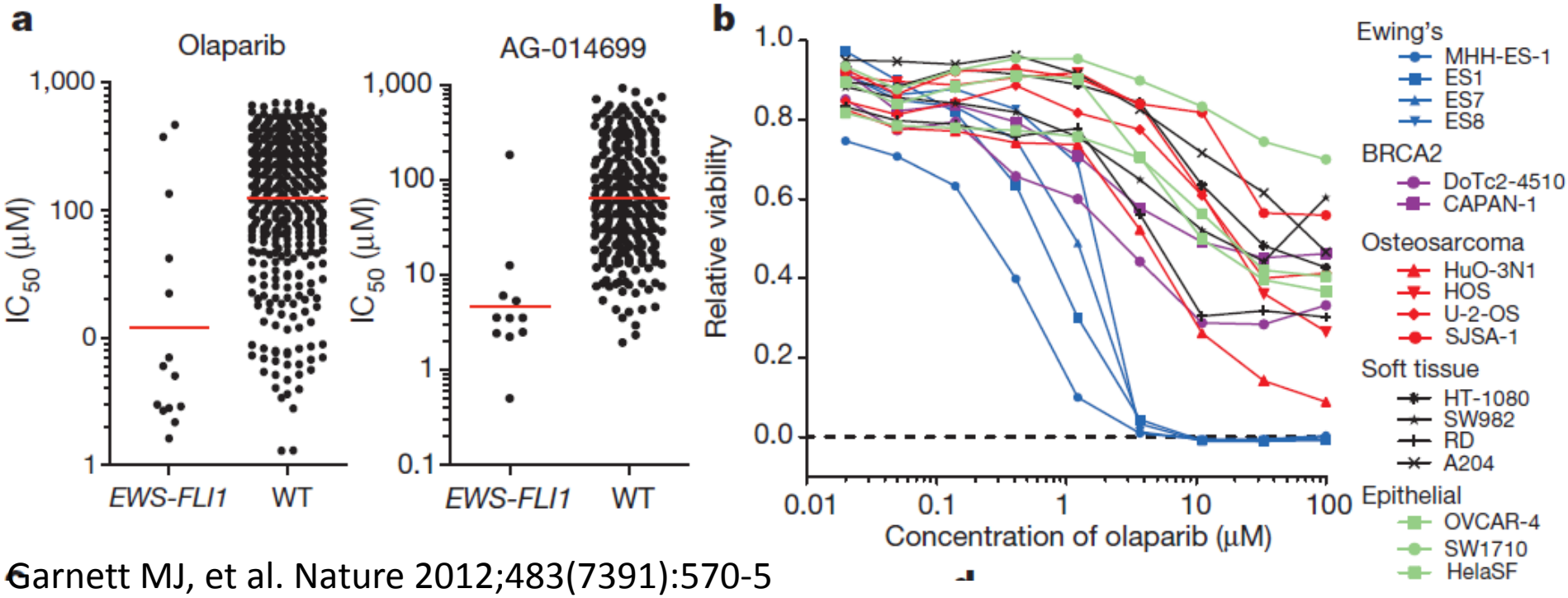
Pediatric Oncology Drug Development

- Pediatric drug development is challenging
  - Limited pharmaceutical company interest
  - Limited number of clinical trials that can be conducted
  - Many anticancer agents entering pipeline
  - Critical need for effective prioritization
- Role of the PPTP
  - Provide evidence to support the presence or absence of a **therapeutic window** for specific agents against selected diseases

Example of Difficulty of Assessing Therapeutic Window: Ewing sarcoma cell lines are sensitive to PARP inhibition

A. EWS-FLI1-translocation-positive cell lines show lower IC_{50} values to olaparib and AG-014699 compared to non-EWS-FLI1 cell lines.

B. Dose–response curves to olaparib after 6 days of constant drug exposure. Cell lines are classified according to tissue subtype.



Garnett MJ, et al. Nature 2012;483(7391):570-5

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In Vivo Testing

- Allows assessment of anticancer activity in relationship to systemic exposures that animals tolerate
- Pediatric preclinical testing has an advantage over adult cancer testing in that tolerable human systemic exposures are often known by the time testing occurs

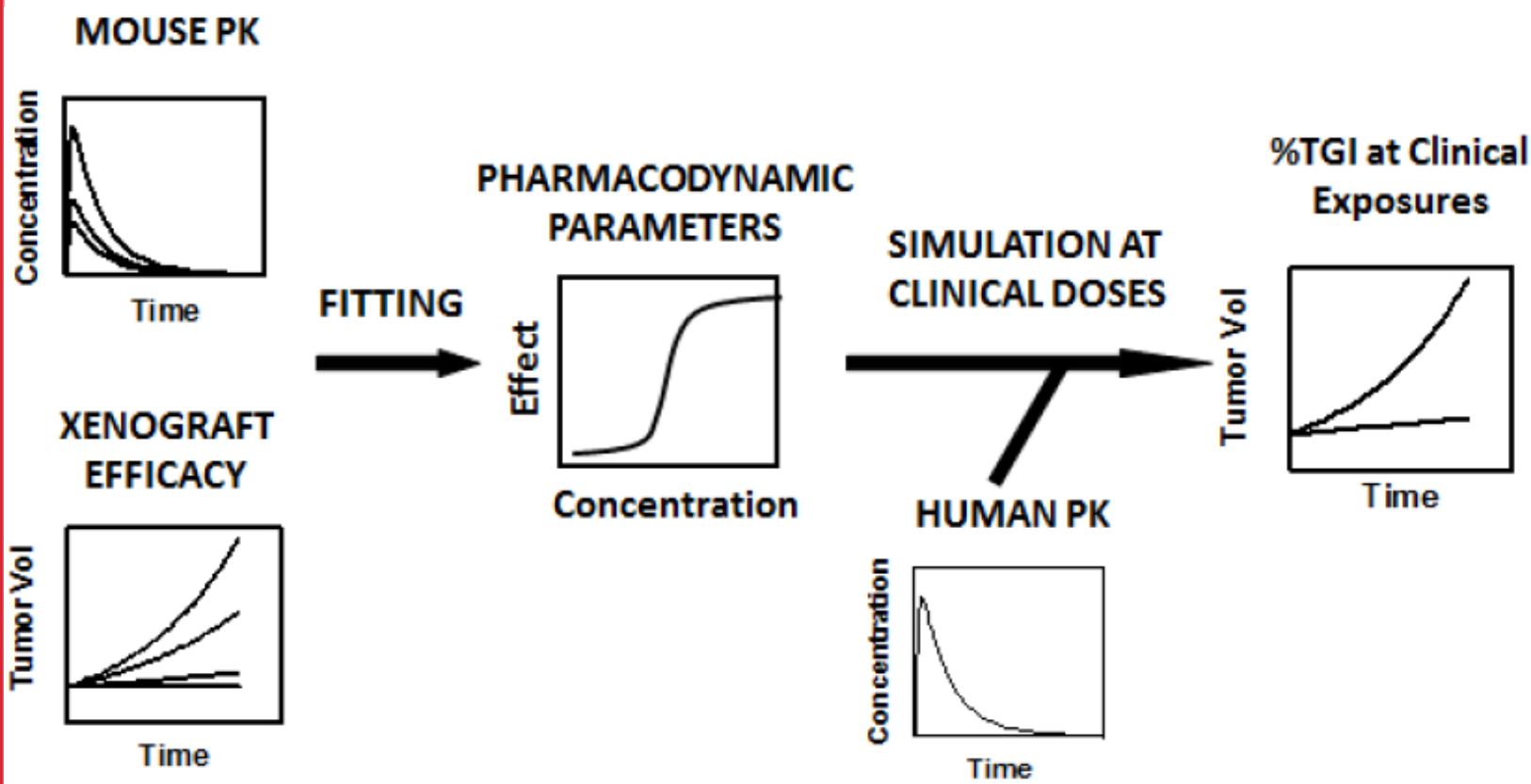
National Cancer Institute

Clinical Cancer Research

Anti-tumor activity of targeted and cytotoxic agents in murine subcutaneous tumor models correlates with clinical response

Harvey Wong, Edna F. Choo, Bruno Alicke, et al.

Clin Cancer Res Published OnlineFirst May 30, 2012.



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The Critical Need for Incorporating Pharmacokinetics into Preclinical Testing

- "A significant correlation (r = 0.91, P = 0.0008) was observed between simulated xenograft/allograft TGI driven by human pharmacokinetics and clinical response but not when TGI observed at maximum tolerated doses in mice was correlated with clinical response (r = 0.36, P = 0.34)."
  - Wong H, et al. Antitumor activity of targeted and cytotoxic agents in murine subcutaneous tumor models correlates with clinical response. Clin Cancer Res 2012:18(14):3846-3855.
- Recent PPTP examples of incorporation of PK include PR-104 and eribulin.

National Cancer Institute

Raise standards for preclinical cancer research

C. **Glenn Begley** and **Lee M. Ellis** propose how methods, publications and incentives must change if patients are to benefit.

29 MARCH 2012 | VOL 483 | NATURE | 531

- 53 'landmark' studies in hematology and oncology for which independent validation attempted.
  - Scientific findings confirmed in **only 6 (11%) cases**.
  - Some non-reproducible preclinical papers spawned an entire field, with 100s of secondary publications.
  - Some of the research triggered a series of clinical studies.

- Conclusion: The inability of industry and clinical trials to validate results from the majority of publications on potential therapeutic targets suggests a general, systemic problem.

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PPTP Steps to Ensure Reliability of Results

- Standard testing protocols
- Blinded testing
- Standard analytic metrics for defining activity
  - Tumor regression (objective response)
  - Time to event
- Multiple models for each histotype studied
- Molecular characterization of models to confirm identify and biological similarity to clinical specimens
- Presentation/publication of all testing results

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Pediatric Preclinical Testing Program

- Research contract with Dr. Peter Houghton as Principle Investigator and with 6 testing sites.
- Primary focus on in vivo testing with standard panels of 4-8 xenograft lines per histotype
- Initiated testing in 2005
- More than 50 companies with which PPTP has established collaborations
- More than 80 executed MTAs
- More than 50 publications of testing results

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Molecular/Biological Characterization

- Majority of models are patient derived xenografts not subjected to in vitro culture
- Gene expression profiles (cDNA & Affymetrix arrays and Illumina arrays)
- SNP analysis using Affymetrix GeneChip Human Mapping array
- Tissue arrays for immunohistochemical testing
- Data available through PPTP web site
- Sequencing of cell lines and xenografts in 2013 through collaboration with Office of Cancer Genomics

Agents Transitioned (or to be transitioned) to the Clinic

- In clinical evaluation:
  - Alisertib (MLN8237)
  - NTX-010
  - Selumetinib
  - Rapalog plus standard chemotherapy
  - IGF-1R antibodies
- In development:
  - Eribulin
  - BMN 673 plus temozolomide
  - Glembatumumab vedotin
- Future/Pending development:
  - SAR3419
  - MDM2 inhibitor
  - Bcl2 inhibitor
  - Lorvotuzumab mertansine (IMGN901)

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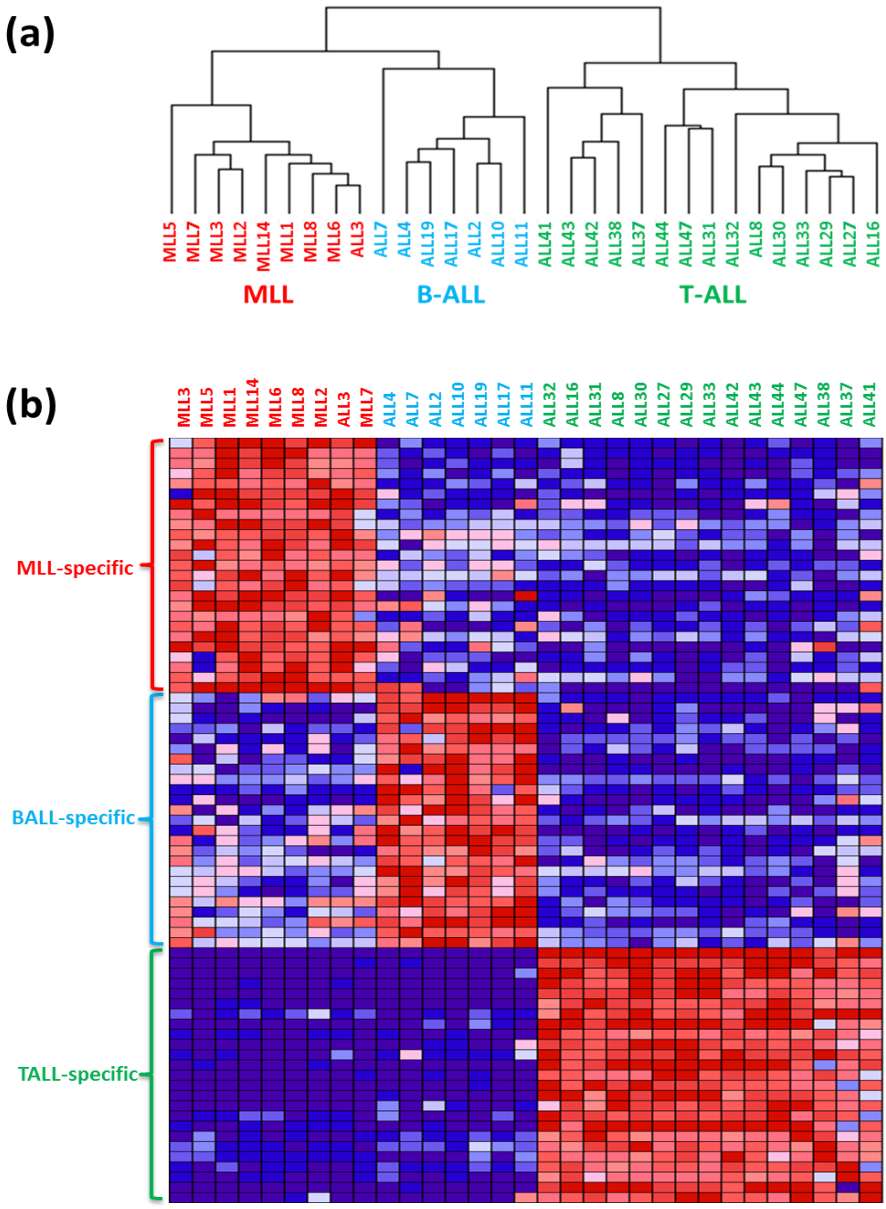
Acute Lymphoblastic Leukemia Panel

- Standard panel of 8 lines:
  - Bcr-Abl ALL (1)
  - T-cell ALL (2)
  - MLL ALL (1)
  - B-precursor ALL (4)
- Expanded panels
  - MLL
  - JAK-mutated ALL / Ph-like ALL
  - T-cell (including ETP)



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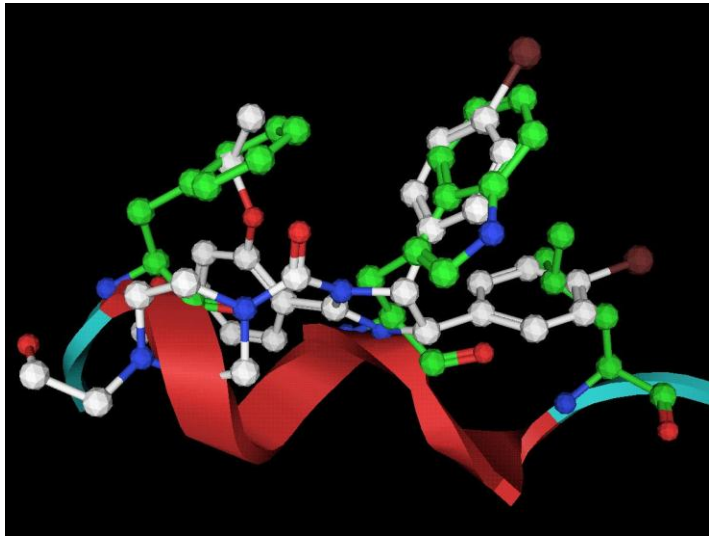
MDM2 Inhibitor RG7112

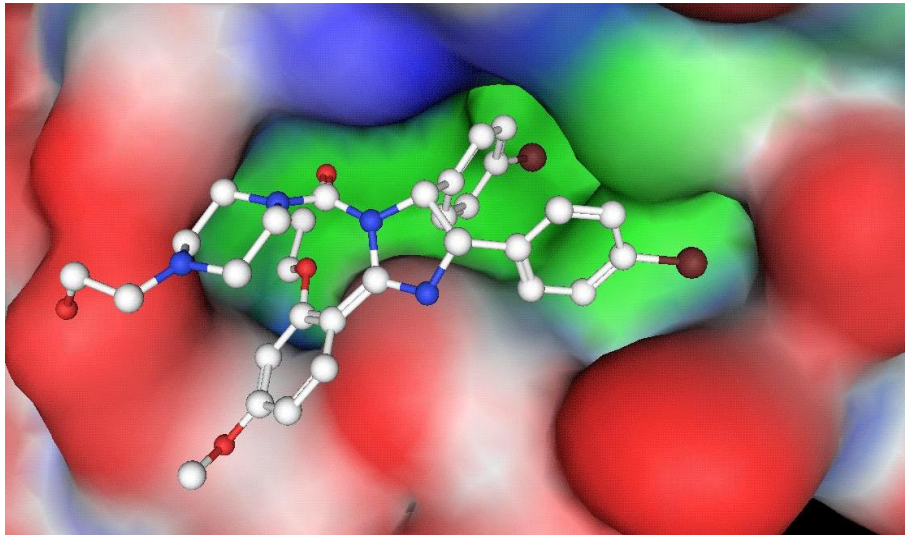
National Cancer Institute

HDM2 Antagonists Bind to the p53-Binding Site on HDM2

- Overlay of Nutlin-2 with HDM2 binding residues of p53



- Derived from crystal structure Of HDM2 – Nutlin-2 complex



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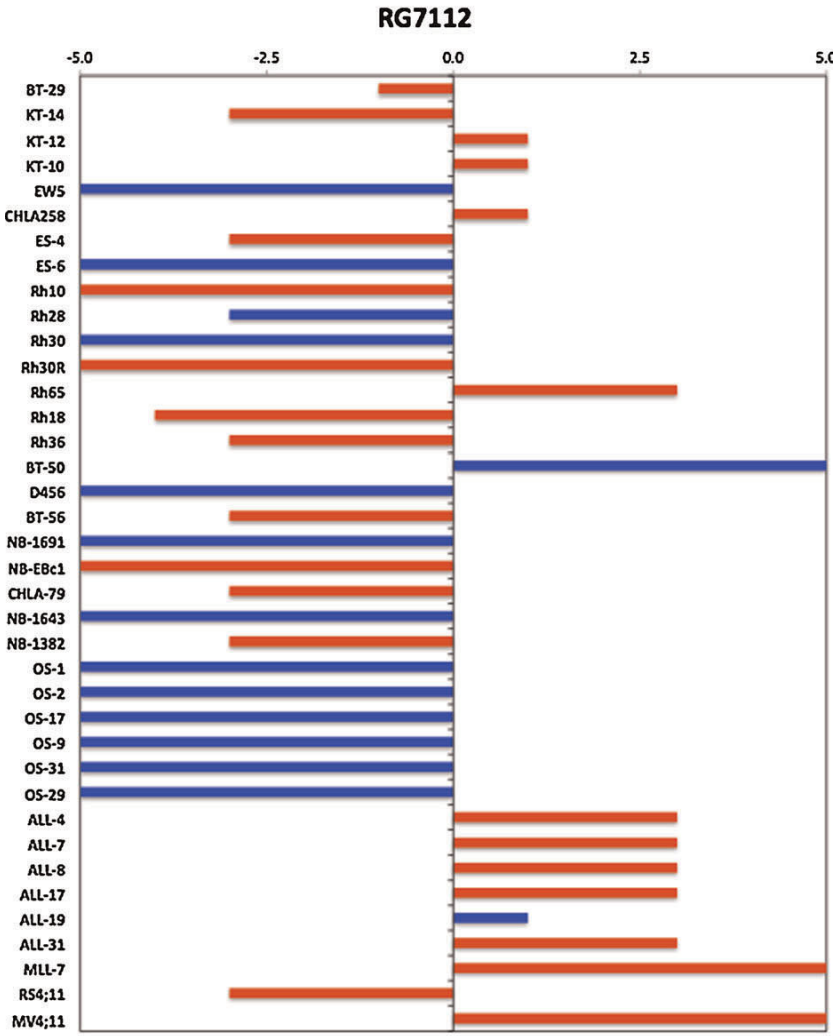
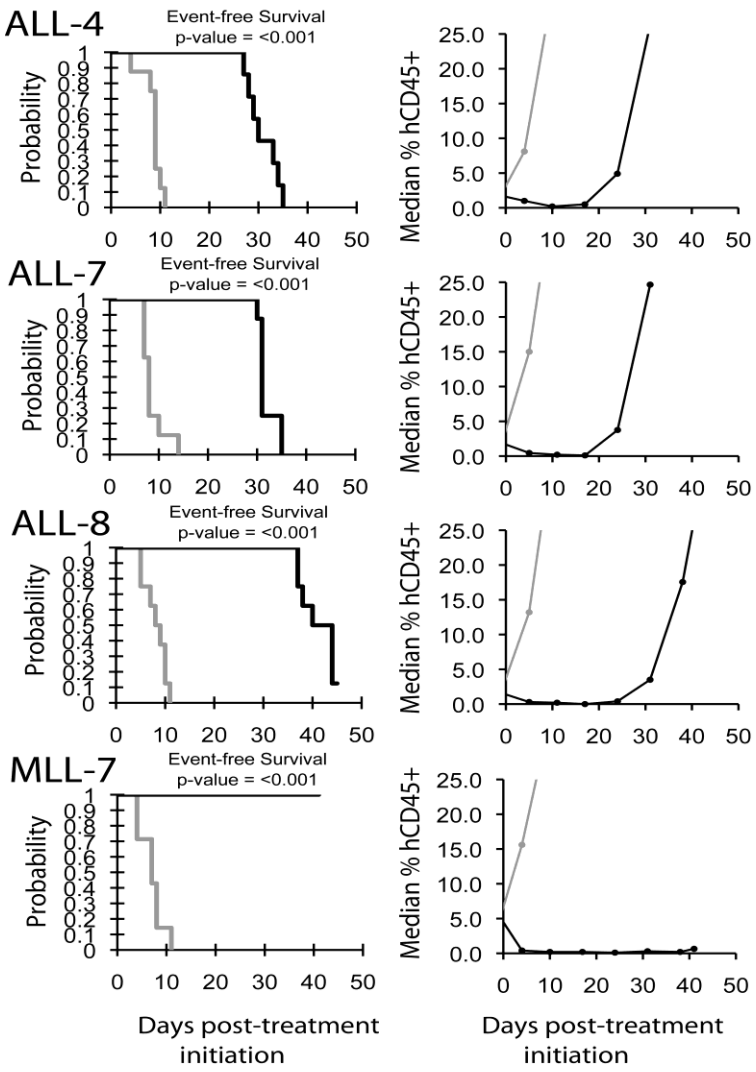
RG7112 ALL Activity

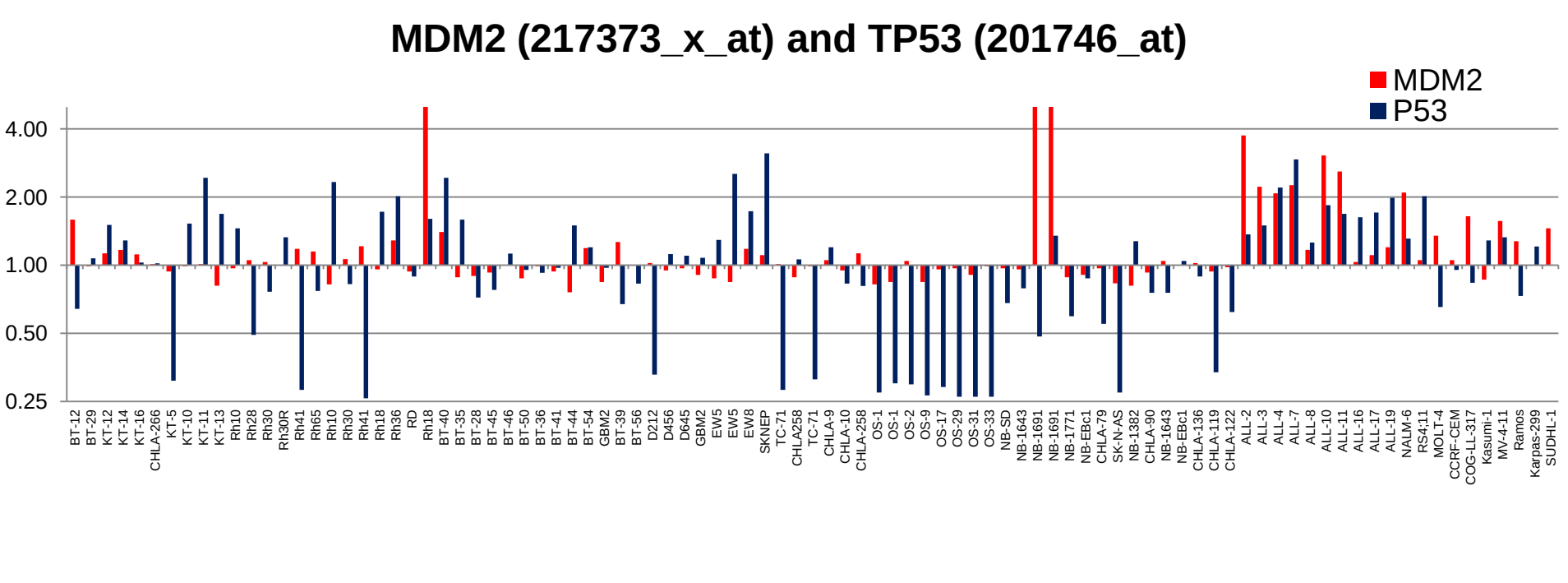




- 100 mg/kg daily for 14 days followed by 4 weeks of observation

Carol H, et al. Pediatr Blood Cancer 2013:60(4):633-641.

MDM2 and P53 Expression



- The osteosarcoma xenografts were p53 WT, but had very low p53 expression and low MDM2 expression. They did not respond to RG7112. *in vivo*.
- The ALL xenografts expressed the highest levels of p53 and MDM2 among the PPTP panels and showed the most consistent *in vivo* responses to RG7112.
- Two PPTP xenografts have MDM2 amplification, Rh18 and NB-1691, and both showed high MDM2 expression. Neither responded to RG7112.

Carol H, et al. Pediatr Blood Cancer 2013:60(4):633-641.

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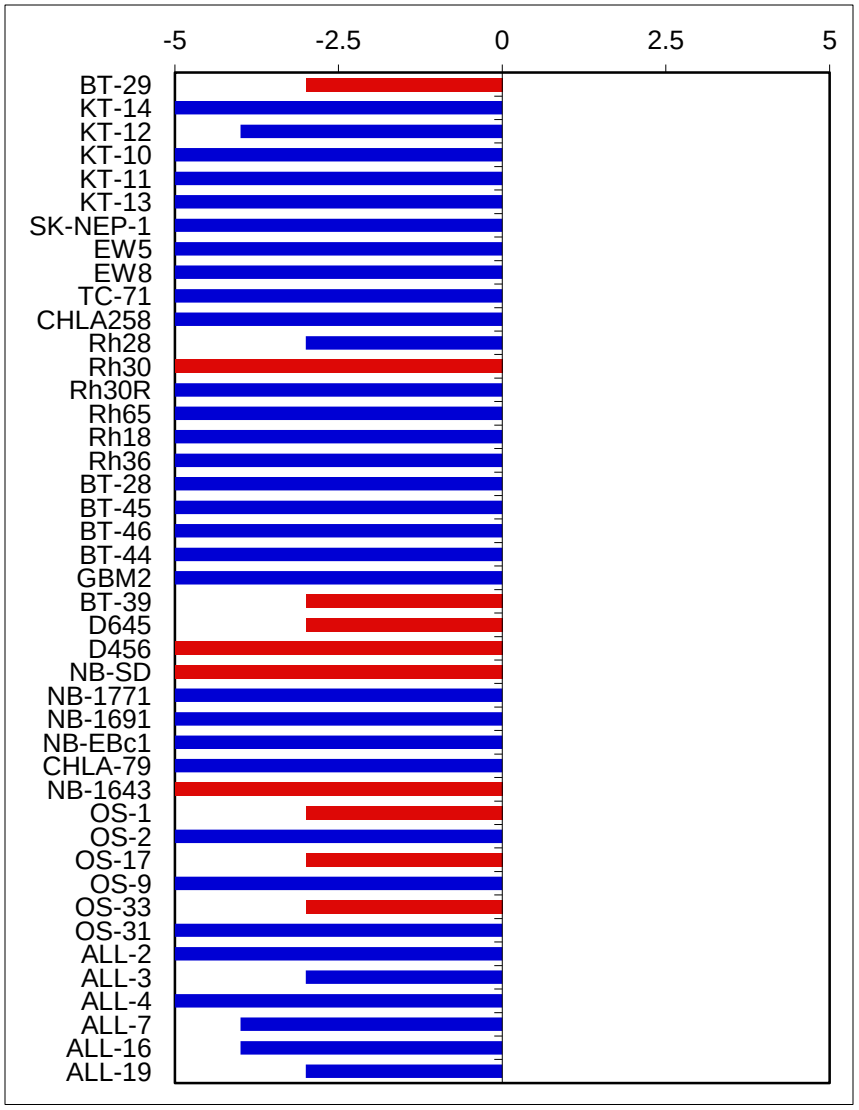
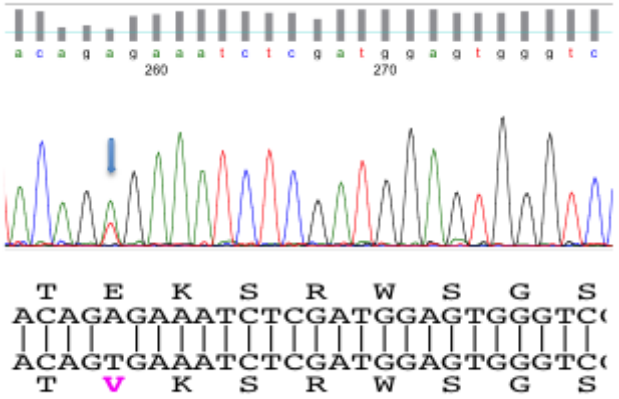
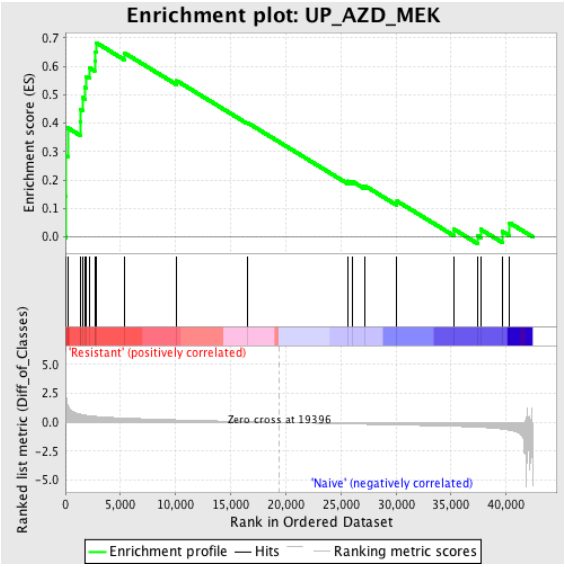
Selumetinib – MEK Inhibitor

The MEK inhibitor selumetinib (AZD-6244) has limited activity in the PPTP screen

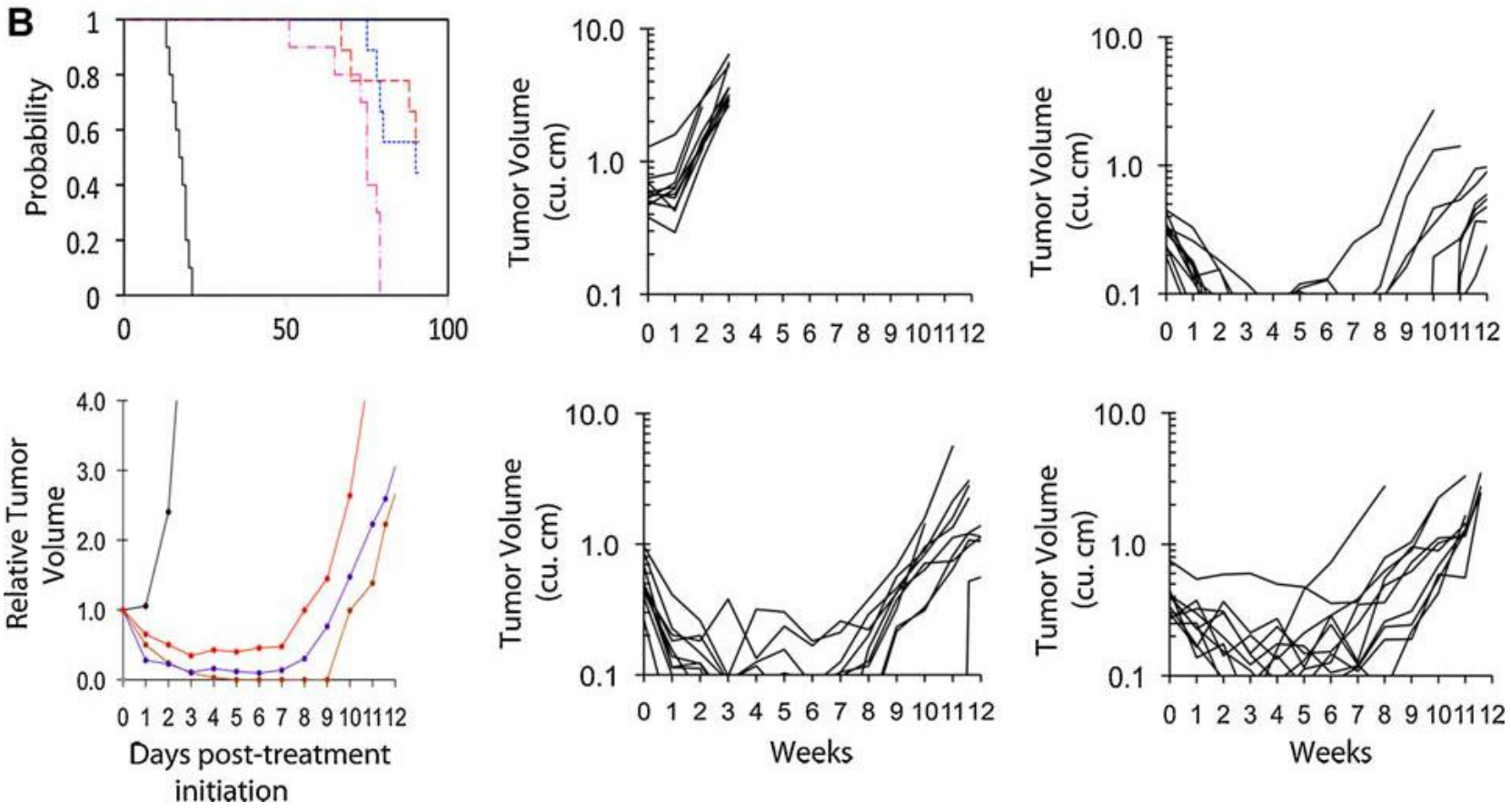






Kolb EA, et al. Pediatr Blood Cancer. 2010;55(4):668-77

Selumetinib (AZD6244) against a low-grade astrocytoma xenograft (BT-40) with the BRAF V600E mutation



Kolb EA, et al. Pediatr Blood Cancer. 2010;55(4):668-77

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Pediatric Development of Selumetinib

- Pediatric development of selumetinib influenced by PPTP results.
- Phase 1 study by Pediatric Brain Tumor Consortium (PBTC) restricted to children with refractory low grade astrocytomas (LGAs).
- Phase 2 expansion proceeding focusing on patients with BRAF-mutated LGA.
- Phase 1 results to be presented as “late breaking” abstract at Society for Neuro-Oncology Meeting.

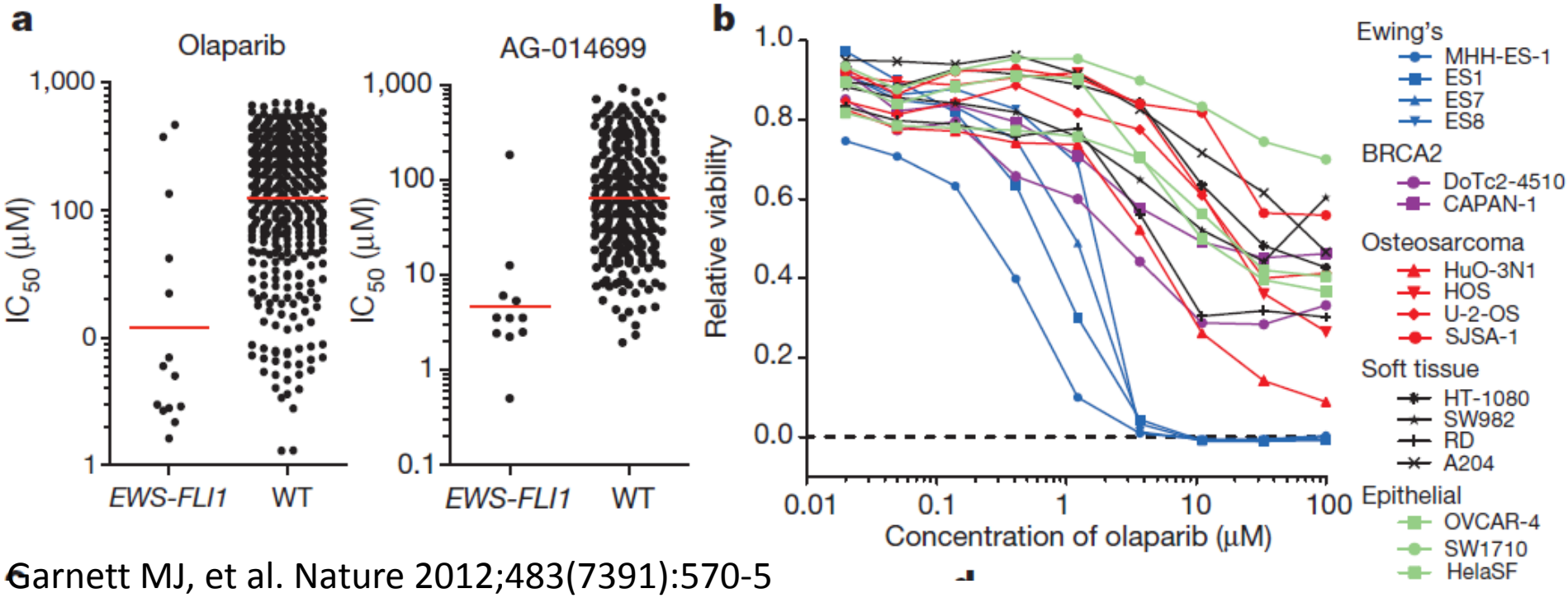
National Cancer Institute

BMN 673 plus temozolomide

Ewing sarcoma cell lines are sensitive to PARP inhibition

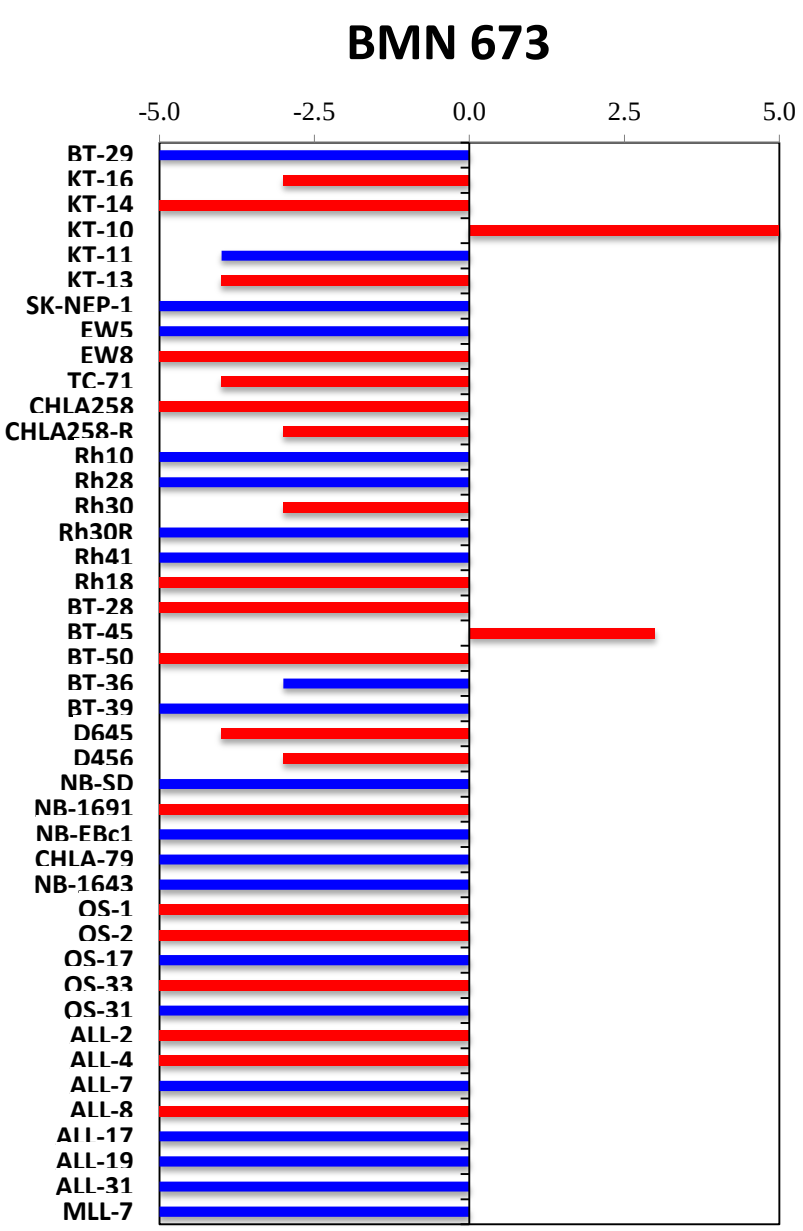
A. EWS-FLI1-translocation-positive cell lines show lower IC_{50} values to olaparib and AG-014699 compared to non-EWS-FLI1 cell lines.

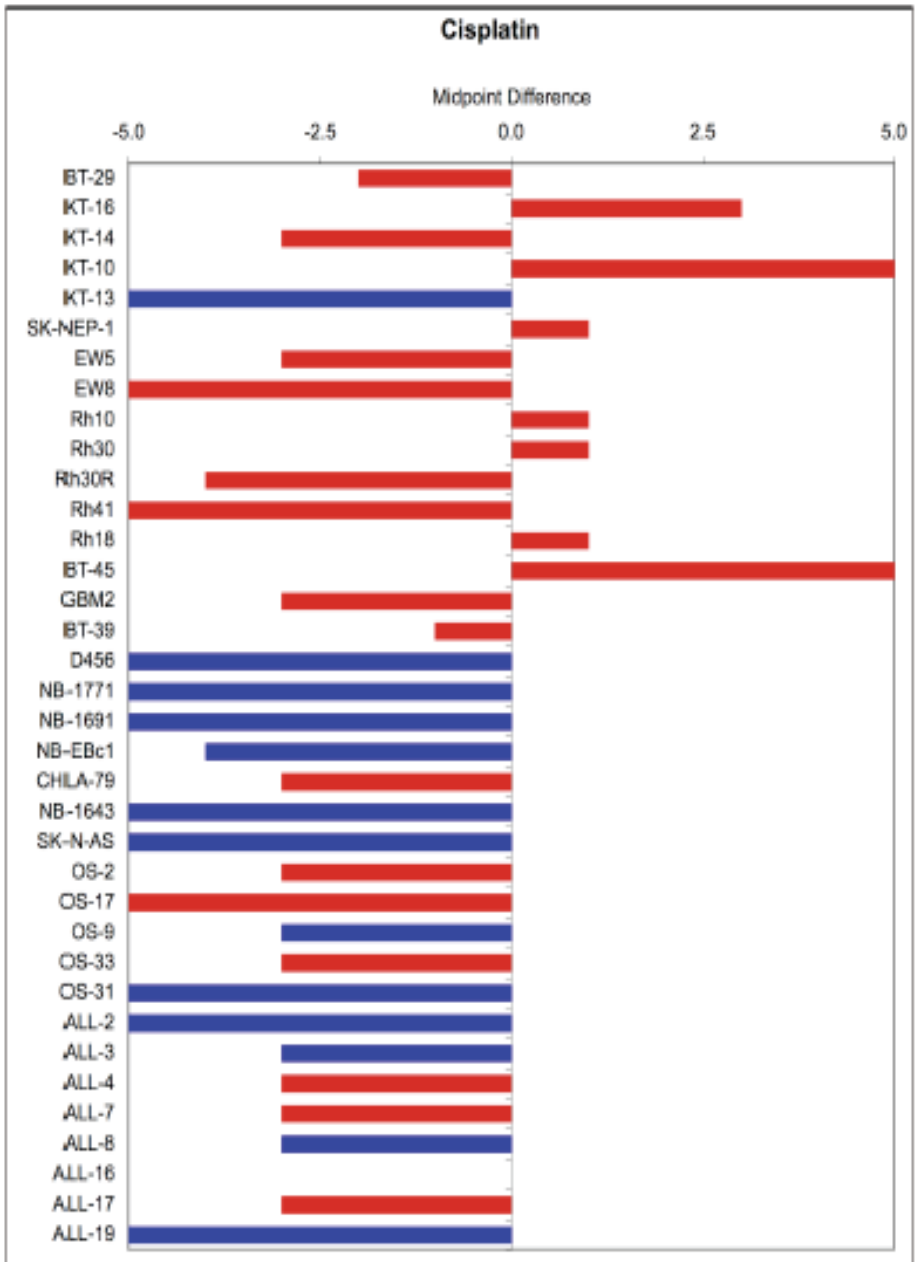
B. Dose–response curves to olaparib after 6 days of constant drug exposure. Cell lines are classified according to tissue subtype.



Garnett MJ, et al. Nature 2012;483(7391):570-5

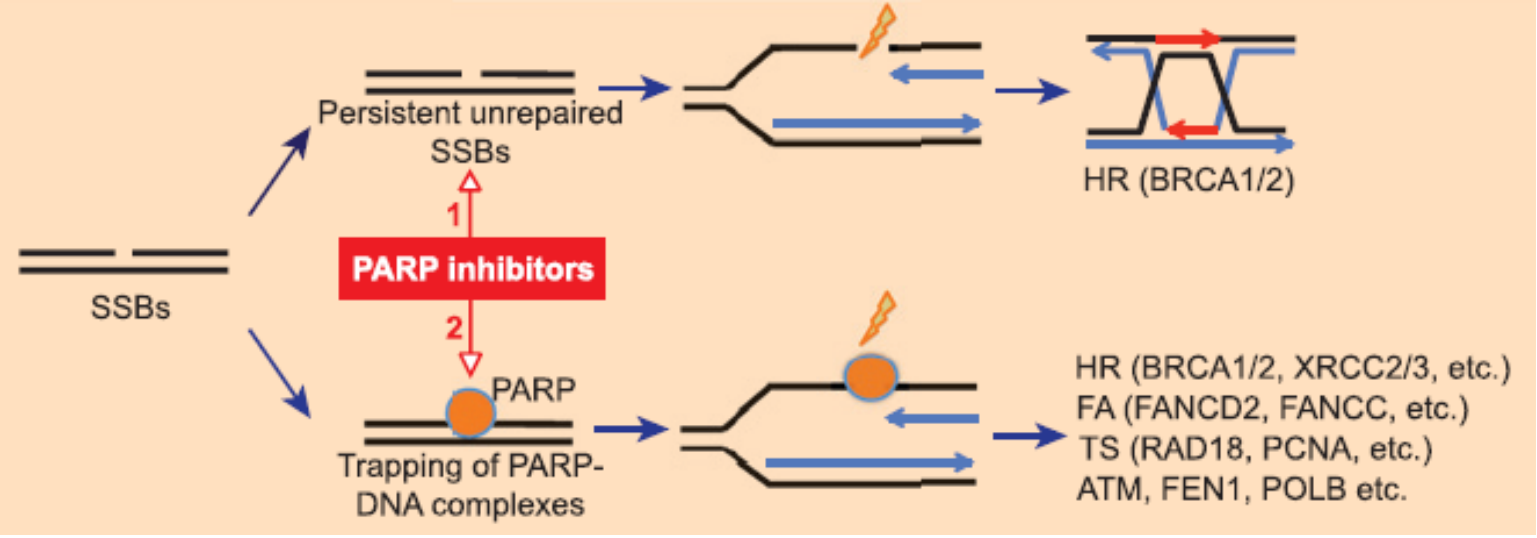
Cisplatin and BMN 673 Single Agent in Vivo Activity





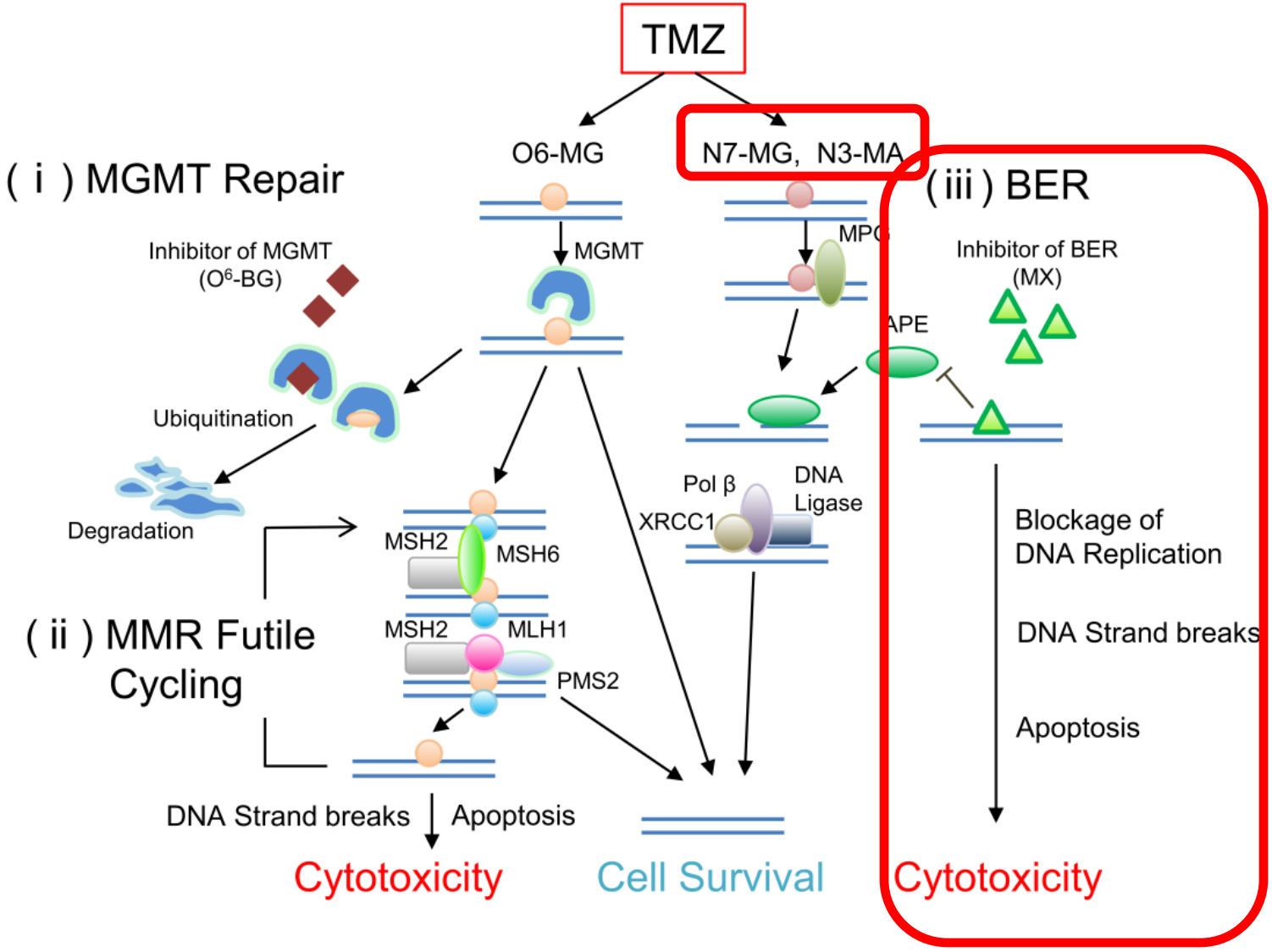
Dual Cytotoxic Mechanisms of PARP Inhibitors

- Catalytic inhibition (upper pathway) interferes with the repair of SSBs, leading to replication fork damage that requires HR repair.
- Trapping of PARP–DNA complexes also leads to replication fork damage but uses additional repair pathways including Fanconi pathway (FA), template switching (TS), ATM, FEN1 (replicative flap endonuclease), and polymerase β.



Murai J, et al. Cancer Research. 2012;72(21):5588-99

PARP Inhibitors Converting TMZ-Induced N7-MG and N3-MA into Lethal Lesions



Kohsaka and Tanaka (2013) http://dx.doi.org/10.5772/54353

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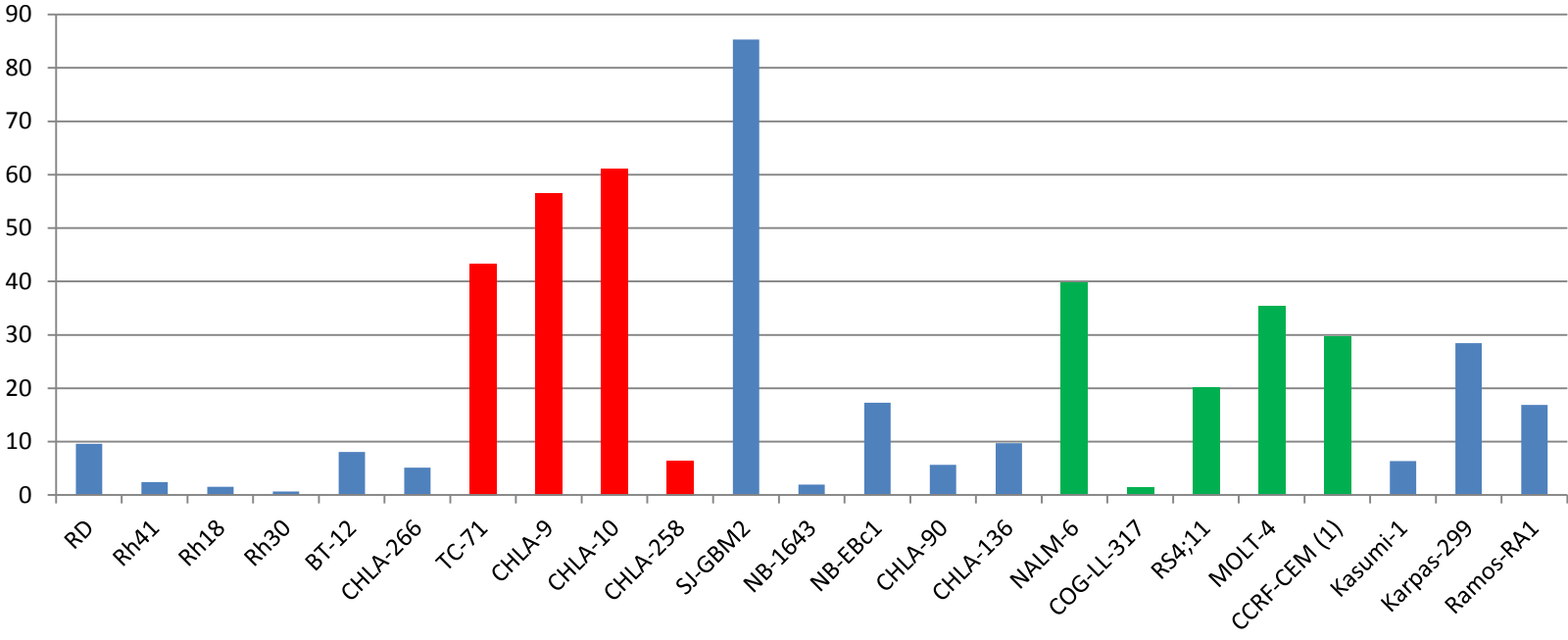
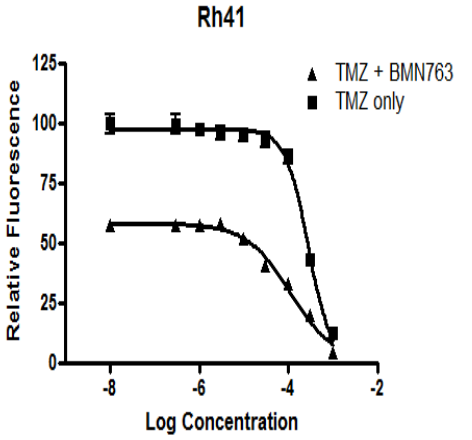
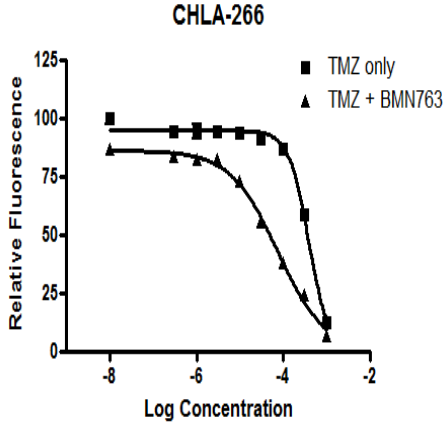
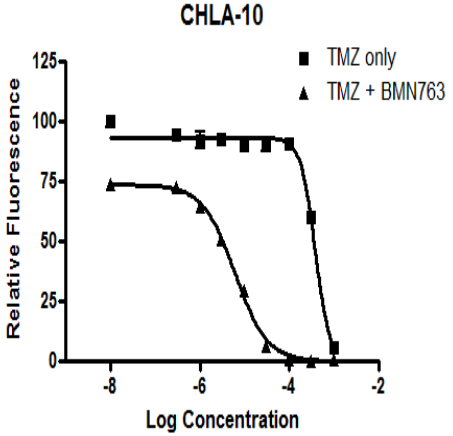
Fold Potentiation of TMZ IC_{50} Values by BMN 673 (10 nM)









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Legend for TMZ + BMZ673 Combination Studies (Dose/Schedules)

- **0904 Only**: Temozolomide (TMZ) at 30 mg/kg/dose daily x 5 days
- **1206 Only**: BMN 673 at 0.25 mg/kg/dose BID x 5 days
- **Combo A (High-dose TMZ)**: TMZ at 30 mg/kg/dose daily x 5 days plus BMN 673 at 0.1 mg/kg/dose BID x 5 days
- **Combo B (High-dose BMN 673)**: TMZ at 12 mg/kg/dose daily x 5 days plus BMN 673 at 0.25 mg/kg/dose BID x 5 days

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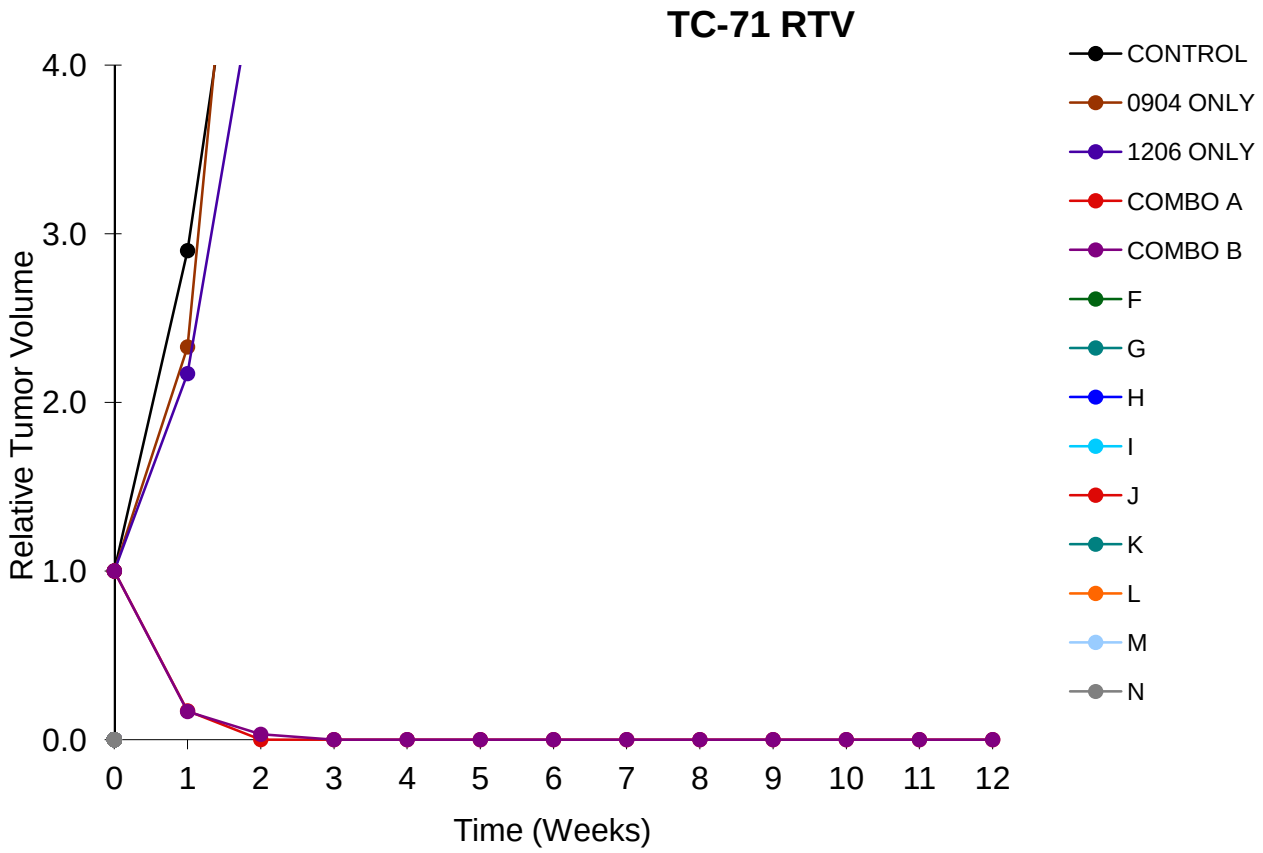
TC-71 (Ewing Sarcoma): Response to BMN 673 and Temozolomide



- Pediatric phase 1 trial of BMN 673 plus low dose temozolomide in development.

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Agents with Limited Tumor-Regressing Activity against Pediatric Preclinical Models

- Notch pathway inhibitors (GSI)
- Hsp90 inhibitors
- Ibrutinib for B-precursor ALL
- MEK inhibitors (excepting LGA)
- AKT inhibitors
- TOR kinase inhibitors
- Bcl-2 inhibitors (solid tumors)
- Arsenic trioxide (Ewing sarcoma)
- Cytarabine (Ewing sarcoma)

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Contract (RFP) vs Cooperative Agreement (RFA)?

- The RFP mechanism initially selected because the objective of the PPTP:
  - to systematically perform testing of selected agents using a standard testing protocol and
  - to quickly make these data available to the childhood cancer research community.
- Given this objective, a contract mechanism was felt to be appropriate and most conducive to maintaining the tight timelines required for a large in vivo testing program testing up to 10 agents per year.

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Individually Competing Each Tumor Testing Site?

- The advantage of this approach is enhanced competition.
- The challenge is that the program requires a considerable degree of central coordination (e.g., agent distribution, information distribution, data analysis, preparation of reports, etc.).
- Need to consider mechanism for supporting both coordination activity and competition of individual sites.

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Future Plans

- Enhancing capabilities for evaluating CNS tumors
- Increasing efficiency and economy:
  - More selective testing based on molecular characterization
  - Consolidation of non-CNS solid tumor testing sites
- Enhancing options for output of data for bioinformatic analysis for non-PPTP researchers
- Increased focus on combination testing
- Evaluating pediatric specific agents

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PPTP Funding History

Funding History Obligation by Year	
FY2010	$2,938,868
FY2011	$2,791,925
FY2012	$2,700,000
FY2013	$2,700,000
FY2014	$ TBD

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Conclusion

- PPTP is unique resource
- PPTP activities not replicated within industry or academia
- PPTP results enhance efficiency of childhood cancer clinical research:
  - Limiting lines of nonproductive research
  - Focusing attention on promising areas
- More than ever reliable and robust preclinical data are needed given the broad range of potential therapeutic agents and the increasing challenges associated with clinical development of agents for children with cancer

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Back-up Slides

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Increasing Competition in Site Selection

- Are best sites / best models being employed for testing for each disease panel??
- Overall contract is an open competition
- Requirement for applicant to describe selection process for subcontracts and include:
  - Solicitation for subcontract sites
  - Criteria for selection of sites
  - Review and selection process
- Annual review of sites by External Advisory Committee and NCI with option for requiring change in testing sites

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Preclinical-Clinical Comparisons

- Dasatinib is only active in vivo at standard doses against a BCR-ABL ALL xenograft.
- Gamma-secretase inhibitors that block Notch pathway signaling are ineffective against solid tumor models as well as against T-ALL xenografts with Notch1 mutations.
- Standard agents such as vincristine, cyclophosphamide, and topotecan show patterns of activity that are consistent with their major clinical patterns of activity.
- Monoclonal antibodies to IGF-1R induce regressions as single agents against a minority of Ewing sarcoma xenografts.
- The MEK inhibitor selumetinib is effective against BRAF-mutated low-grade astrocytoma.
- The addition of rapamycin to standard chemotherapy agents (a vinca alkaloid and cyclophosphamide) is more effective than chemotherapy alone for rhabdomyosarcoma.

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PPTP Combination Testing

- Therapeutic enhancement: combination significantly better than either single agent used at their MTD
- mTOR inhibitor plus standard cytotoxic agents.
  - Therapeutic enhancement commonly observed for cyclophosphamide (CPM) and vincristine
  - Able to give each at their single agent MTDs with rapamycin
- PPTP results led to COG ARST0921 randomized phase 2 clinical trial for children with relapsed RMS in 1st relapse.
  - Vinorelbine/CPM plus either temsirolimus or bevacizumab

Published Online First on January 6, 2010 as 10.1158/1535-7163.MCT-09-0952

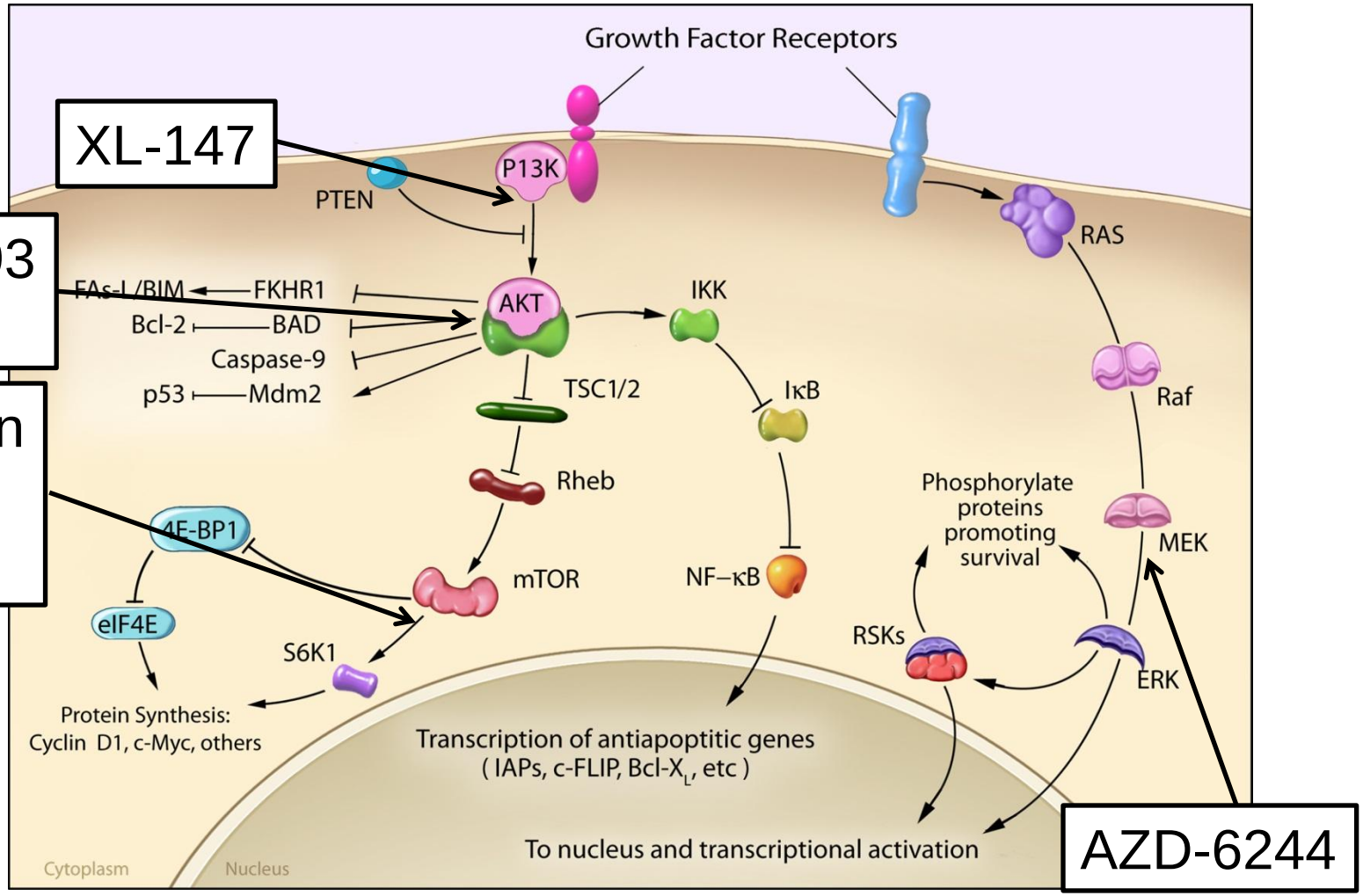
Molecular Cancer Therapeutics

Research Article

Stage 2 Combination Testing of Rapamycin with Cytotoxic Agents by the Pediatric Preclinical Testing Program

Peter J. Houghton[1], Christopher L. Morton[2], Richard Gorlick[3], Richard B. Lock[4], Hernan Carol[4], C. Patrick Reynolds[5], Min H. Kang[5], John M. Maris[6], Stephen T. Keir[7], E. Anders Kolb[8], Jianrong Wu[2], Amy W. Wozniak[2], Catherine A. Billups[2], Larry Rubinstein[9], and Malcolm A. Smith[10]

Inhibitors of the PI3K and MAPK Pathways



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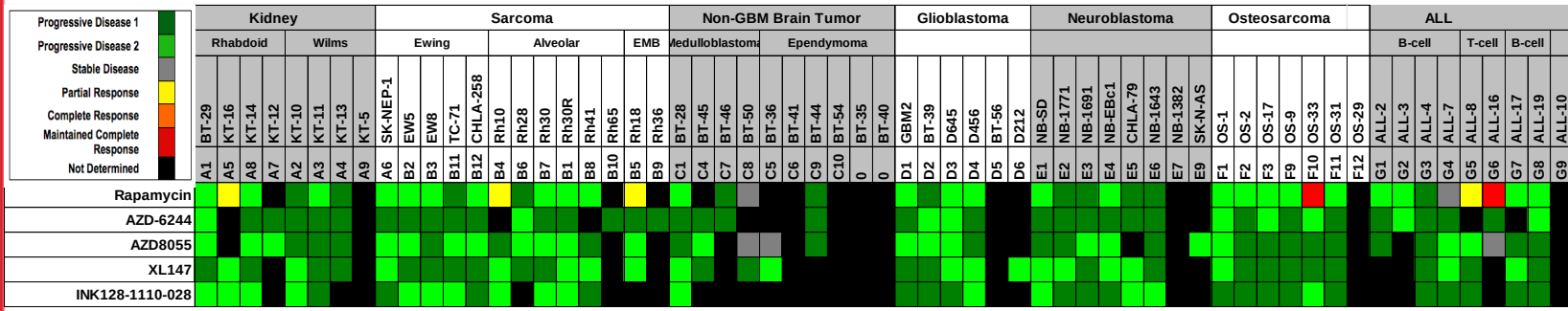
PI3K and MAPK Pathway Inhibitors

- Activating mutations in PI3K and MAPK pathways are common for some adult cancers.
- Most pediatric cancers examined to date do not have mutations in these pathways (exceptions are notable).
- The available data suggest that kinase inhibitors targeting the PI3K pathway and MAPK pathway have limited ability to induce tumor regressions for the biological subtypes represented by the PPTP in vivo models.



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Eribulin (novel tublin-binding agent)

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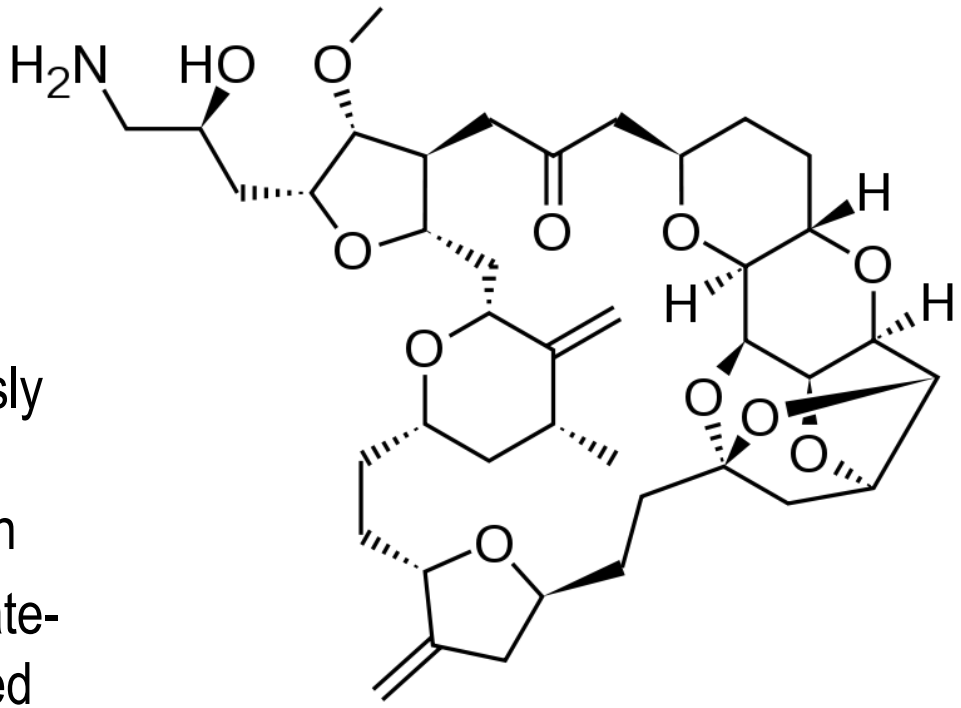
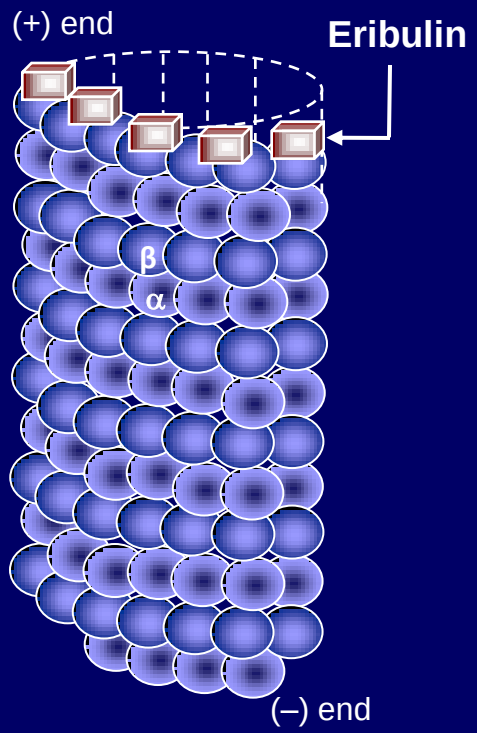
Eribulin Mesylate

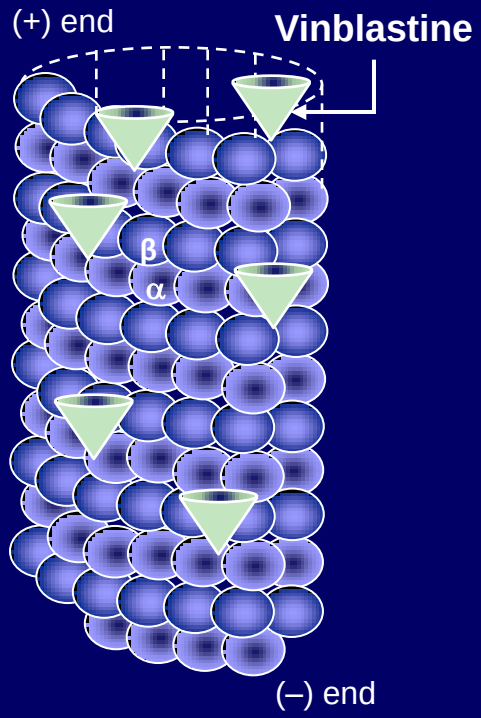
- Synthetic analogue of halichondrin B
- Microtubule inhibitor with a binding site different from current agents
- Administered intravenously without reconstitution as a 2 - 5–minute infusion
- Approved in the US for late-line treatment of advanced breast cancer

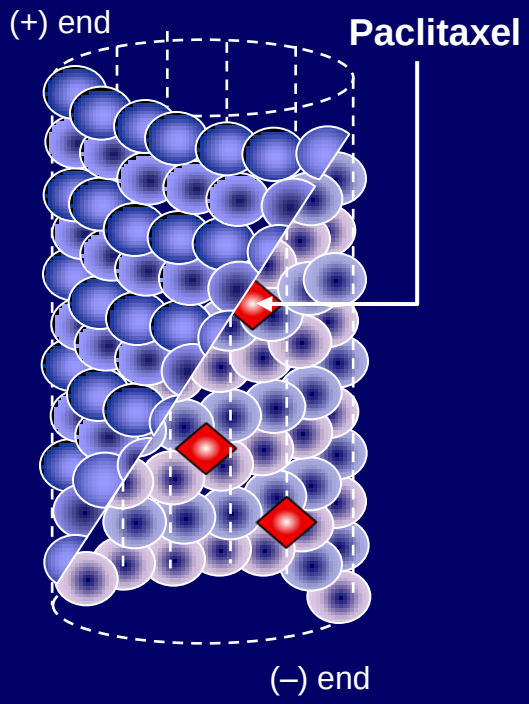


Eribulin Binding Site Differs From Other Microtubule Inhibitors

- Eribulin binds to (+) ends
- Vinblastine binds to (+) ends and along sides
- Paclitaxel and docetaxel bind to β subunits at inside surface







Eribulin is active against drug-resistant cells that harbor β-tubulin mutations associated with taxane resistance.

Modified from Jordan MA and Wilson L. *Nat Rev Cancer*. 2004;4:253-65.

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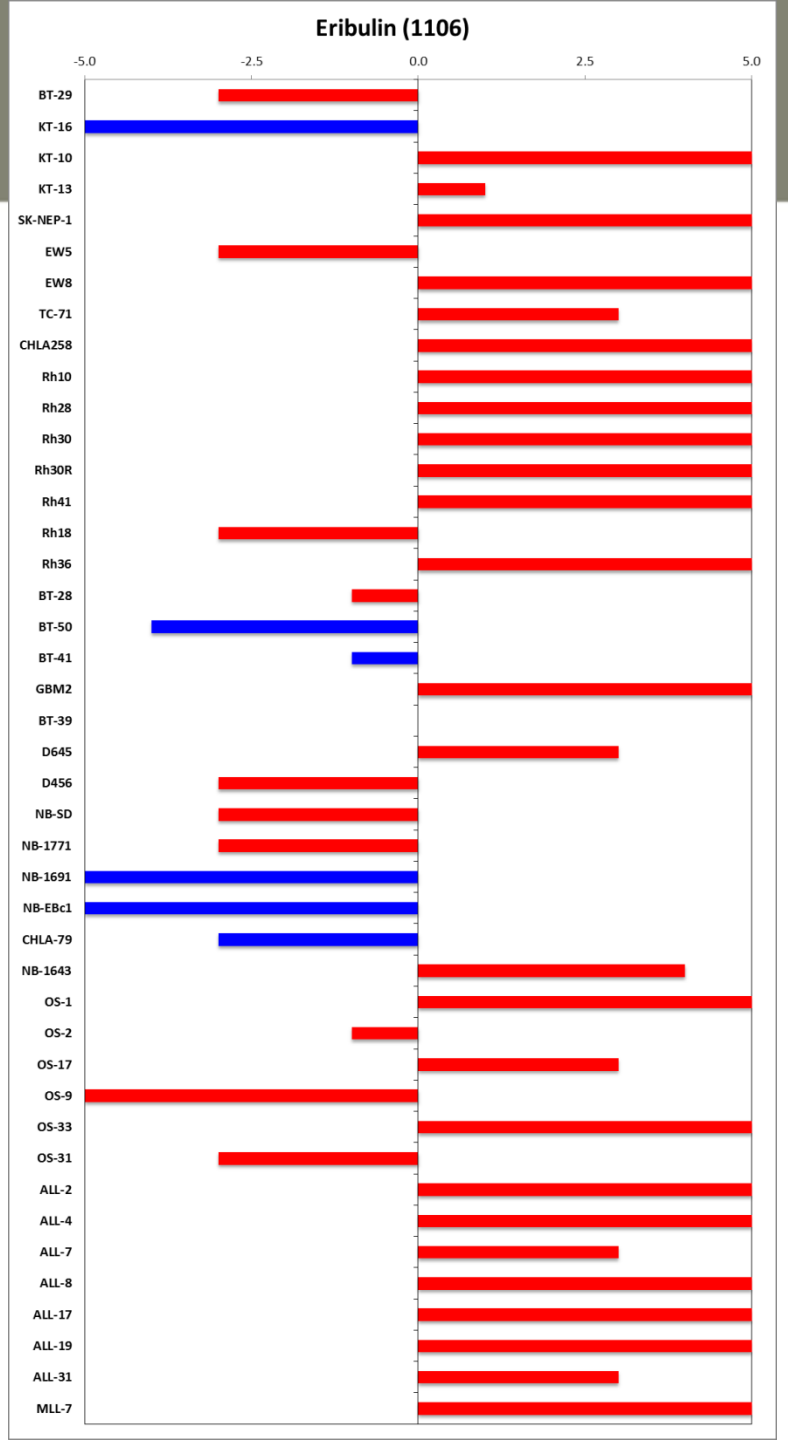
Eribulin in Vivo Activity

- 24 of 30 (80%) solid tumor models evaluable for the EFS T/C activity metric demonstrated EFS T/C > 2.0, with 7 lines showing intermediate activity and 17 showing high activity.

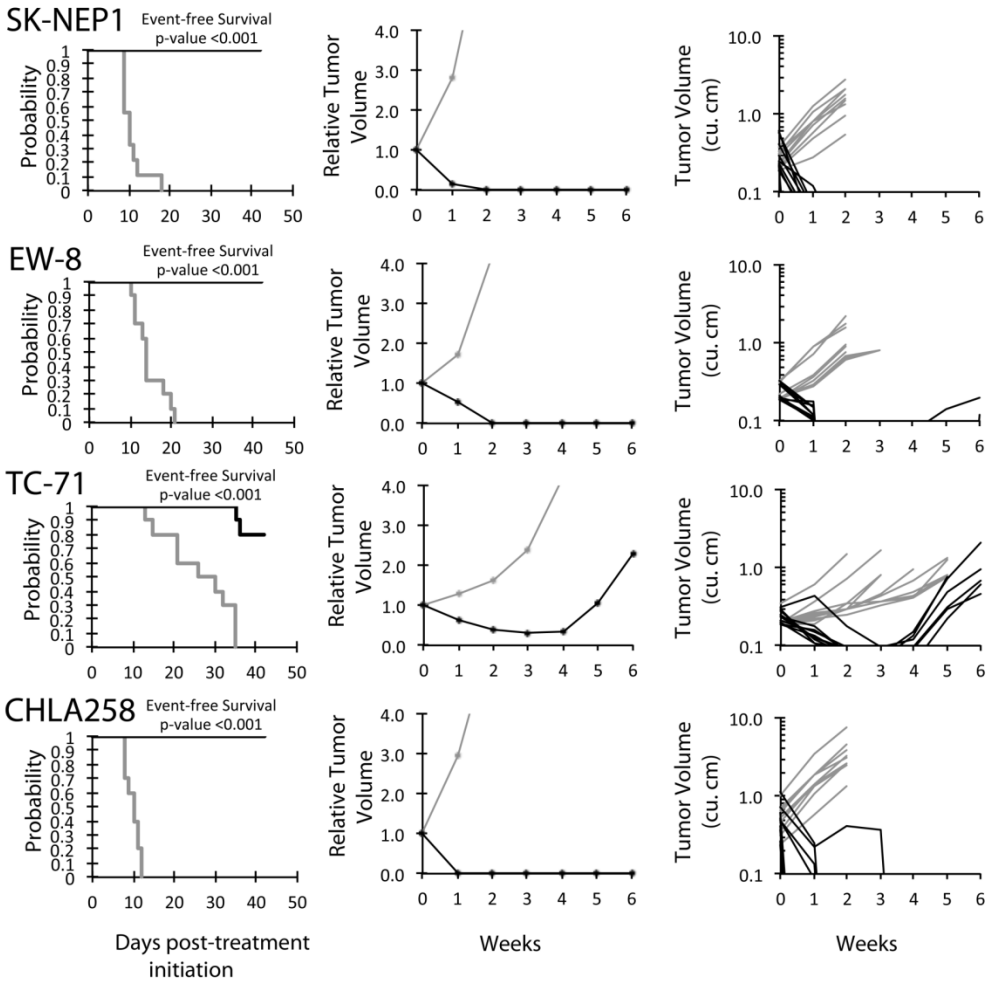
- CR/MCRs:
  - 4 of 5 evaluable Ewing xenografts,
  - 6 of 7 RMS xenografts,
  - 2 of 4 glioblastoma xenografts, and
  - 3 of 6 evaluable osteosarcoma xenografts.
  - 8 of 8 ALL



Kolb EA, et al. Pediatr Blood Cancer 2013

National Cancer Institute

Examples of Eribulin Activity Against Ewing Sarcoma Xenografts



- Used 1 mg/kg Q4D x 3 schedule

Kolb EA, et al. Pediatr Blood Cancer 2013

National Cancer Institute

Mouse versus Human Systemic Exposures

- Comparison of mouse PK (1 mg/kg IP) and human PK (1.4 mg/m^2 IV)

- Mouse

Dose (mg/kg)	Route	Tissue	Cmax (ng/mL)	Cmax/D (ng/mL/D)	tmax (h)	t1/2 (h)	AUC0-t (ng·h/mL)	AUC0-inf (ng·h/mL)	AUC0-inf/D (ng·h/mL/D)
1	i.p.	plasma	1032.354	1032.354	0.167	3.76	651.627	657.629	657.629

- Human

Study	N	AUC (ng*hr/ml)
Goel (1)	9	856
Devriese (2)	9	971
Devriese (3)	11	757
Devriese (4)	6	600
Mukohara (5)	6	673
Weighted average	41	790

Kolb EA, et al. Pediatr Blood Cancer 2013

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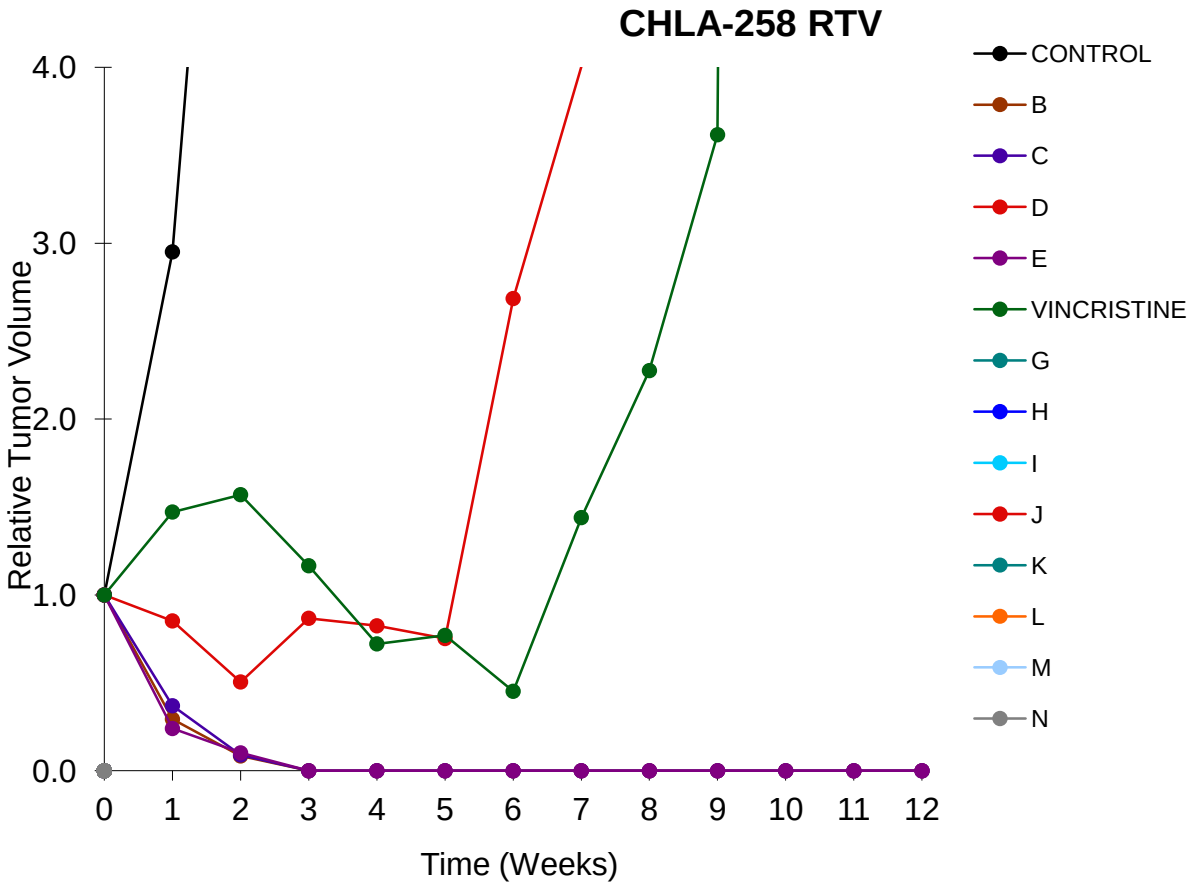
Eribulin Dose-Response



- **B** = 1 mg/kg q7d X 3 **C** = 0.5 mg/kg q7d X 3
- **D** = 0.25 mg/kg q7d X 3 **E** = 1 mg/kg q7d X 2
- **Vincristine** = 1 mg/kg weekly x 6

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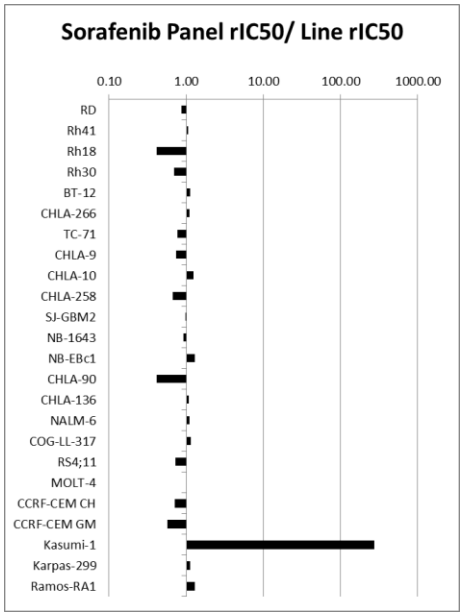
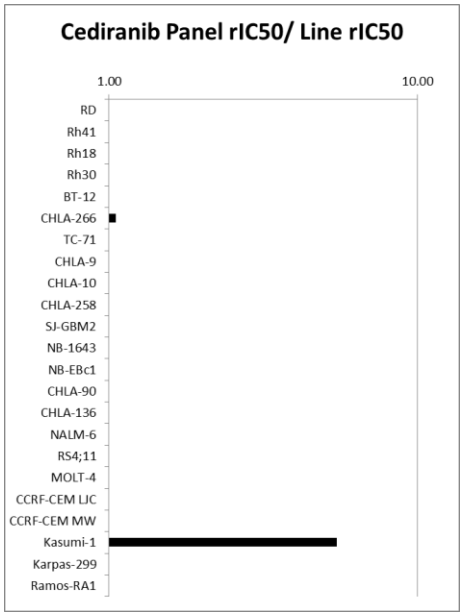
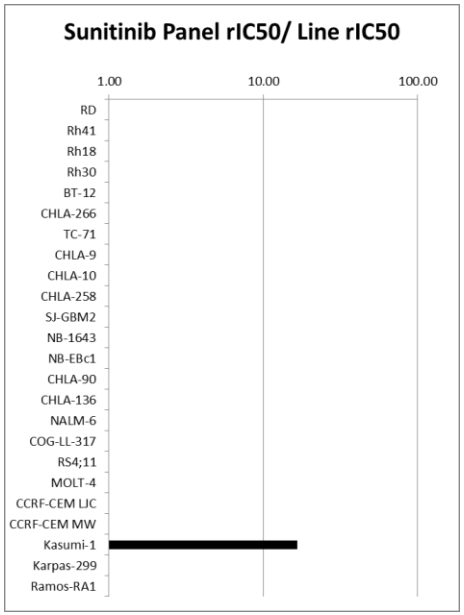
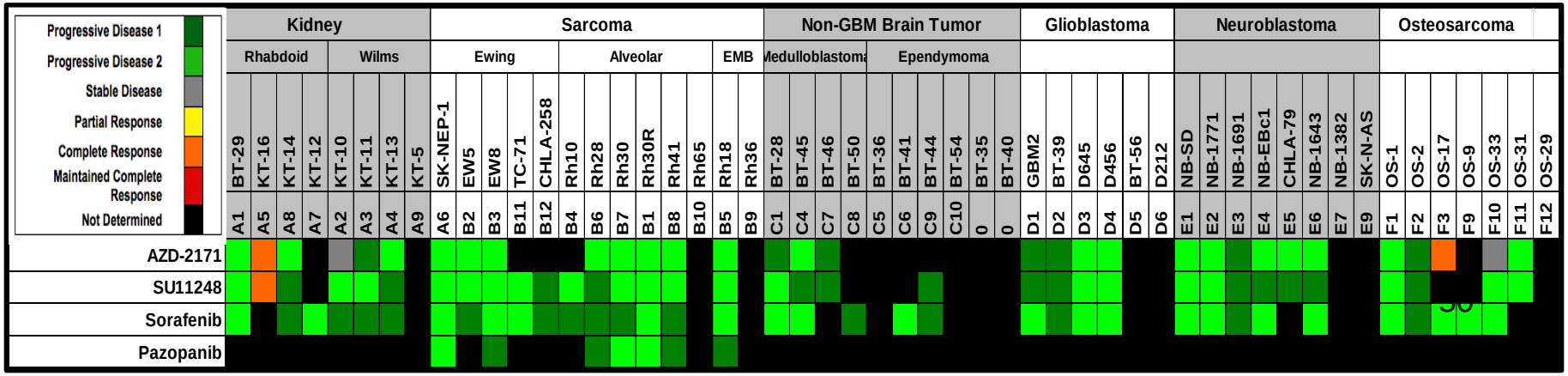
VEGFR2-Targeted Agents

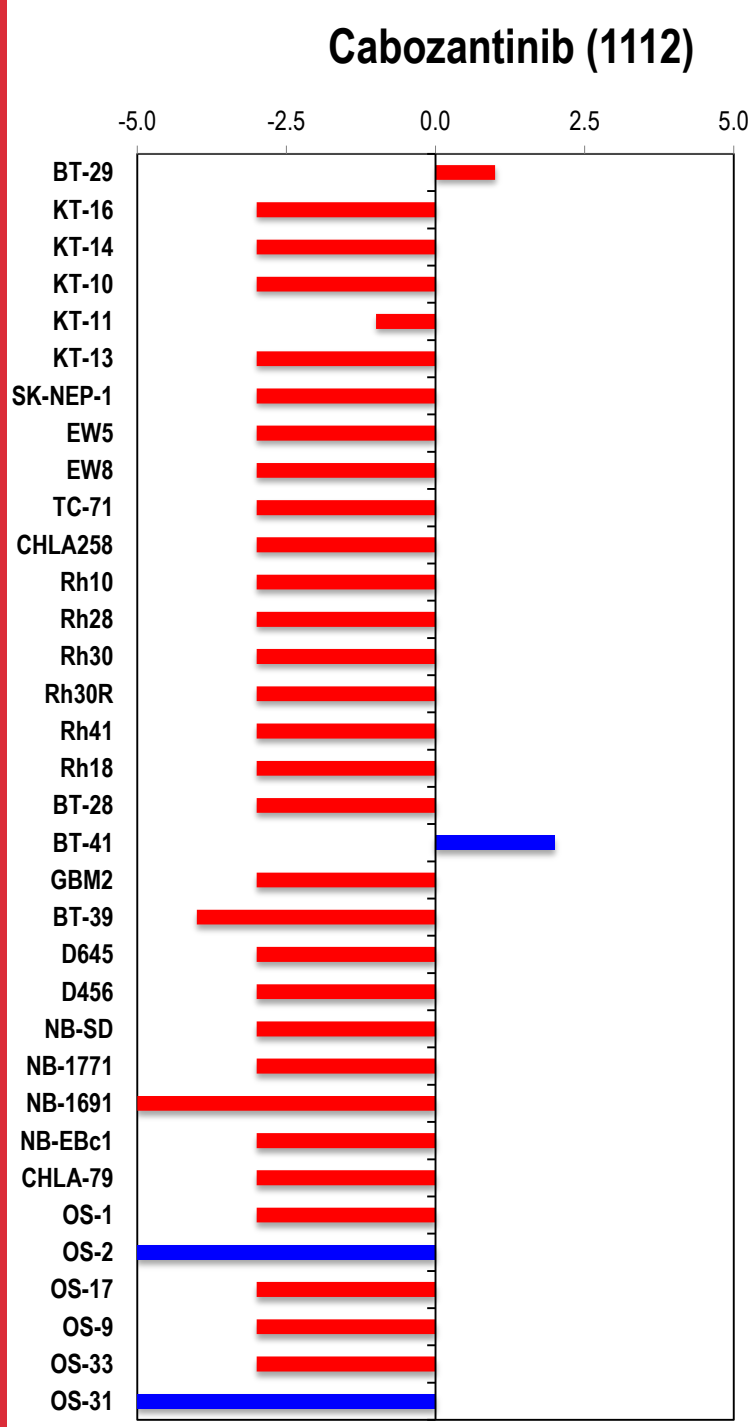
VEGFR2 Inhibitors: In Vitro & in Vivo



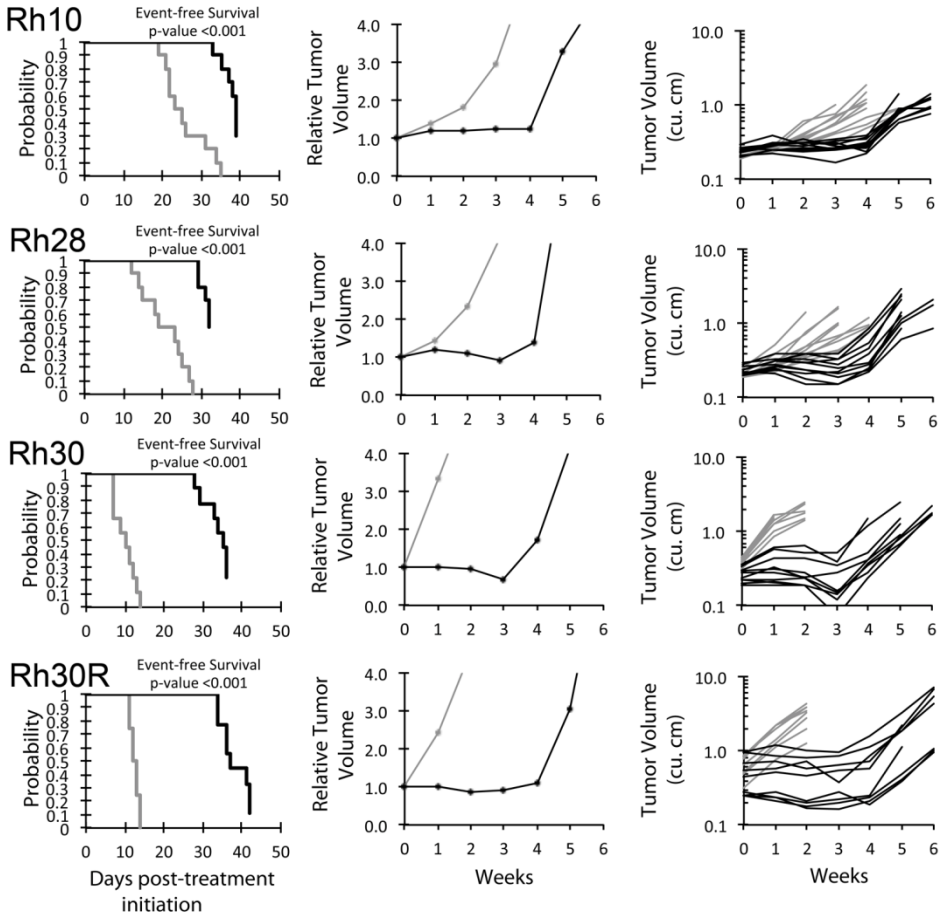








Cabozantinib in Vivo Results



Dose/Schedule: 30 mg/kg x 21 days

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Notch Pathway Inhibitors

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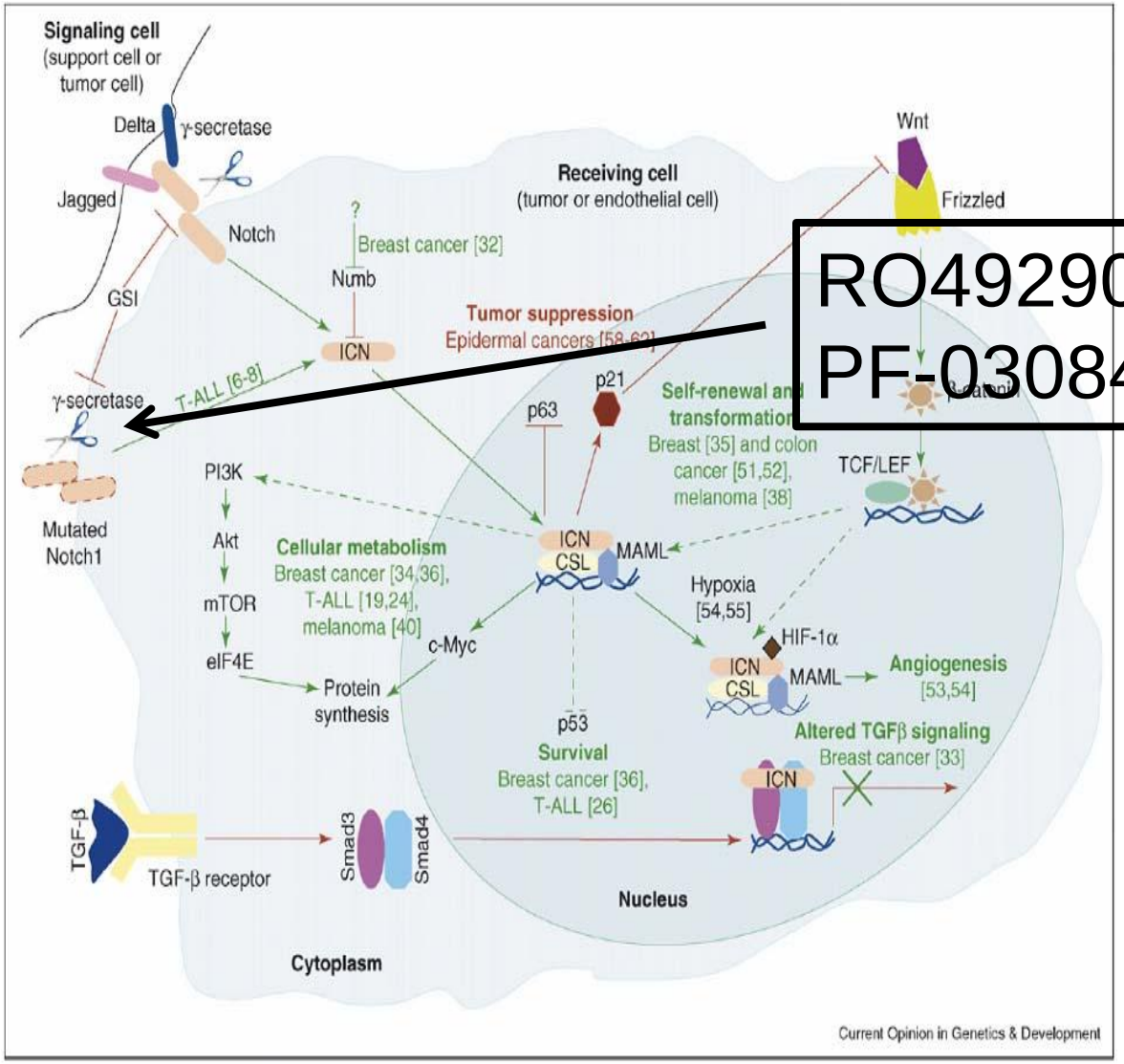
Notch Pathway Activation and T-cell ALL



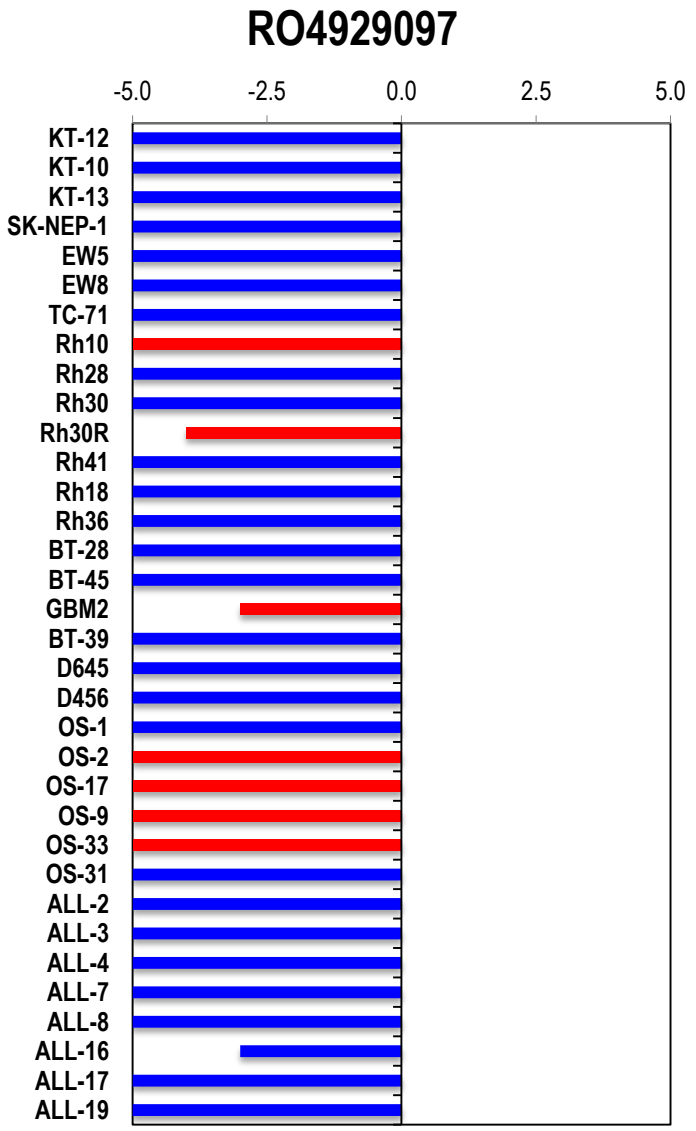
RO4929097
PF-03084014

Monideepa R, Pear WS, Aster JC. Current Opinion in Genetics & Development 2007, 17:52–59.

National Cancer Institute

Limited in Vivo Activity for Notch Inhibitors

- Lack of in vivo activity against PPTP xenografts for the gamma-secretase inhibitor (GSI).
- Tested second GSI (PF-03084014) and observed little activity against multiple T-cell ALL xenografts with Notch1 mutations.



Kolb EA, et al. Pediatr Blood Cancer 2012:58(5):815-818.

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Antibody-Drug Conjugates

National Cancer Institute

CD56 Expression on NCI Pediatric Tumor Xenografts

Tumor Line	N	IHC Score: 3+ - 3 Homo	3 Hetero	2-3 Hetero or Homo	< 2 Hetero	0
Brain	9	4	0	3	1	1
Kidney*	4	3	0	1	0	0
Neuroblastoma	7	5	1	1	0	0
Osteosarcoma	4	0	2	1	1	0
Rhabdomyosarcoma	7	5	0	2	0	0
Totals	**31**	**17**	**3**	**8**	**2**	**1**

*3 of 3 Wilms tumor xenografts 3-3+ homogeneous staining

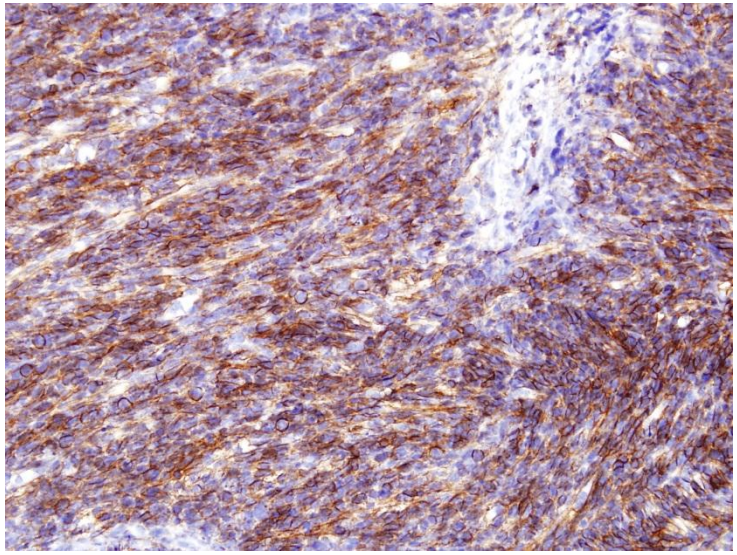
Houghton PJ, et al. Mol Cancer Ther 2011:10(11 Suppl):Abstr #C105

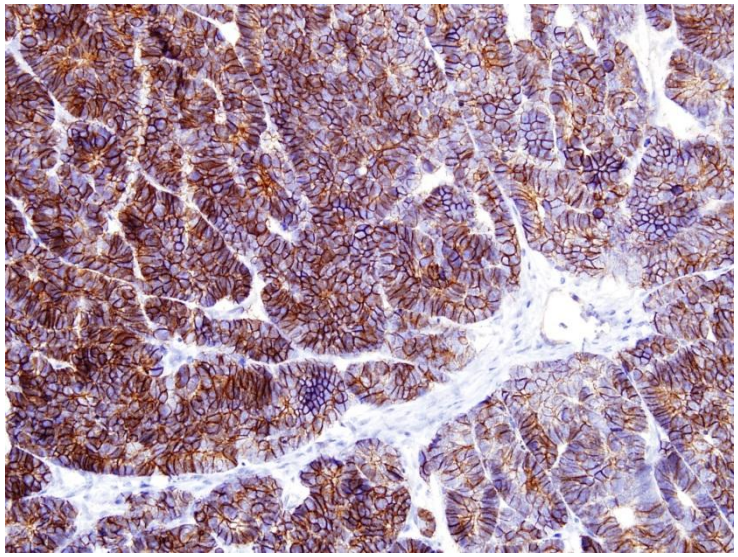
National Cancer Institute

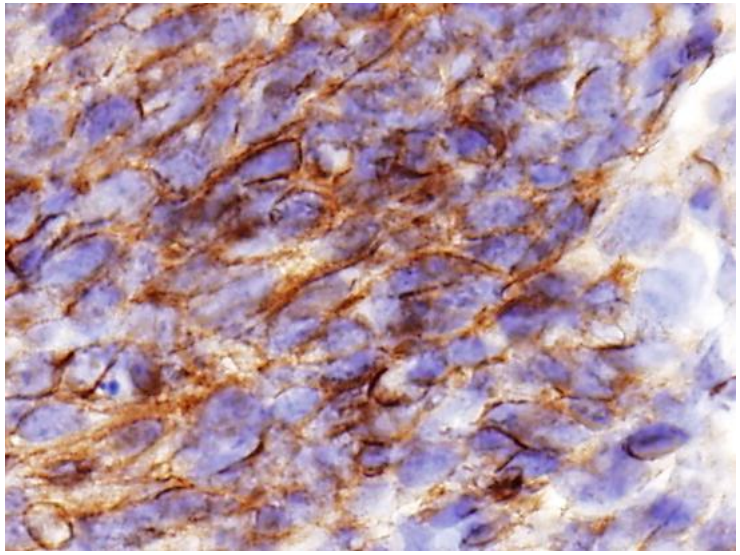
CD56: Homogeneous Staining Pattern

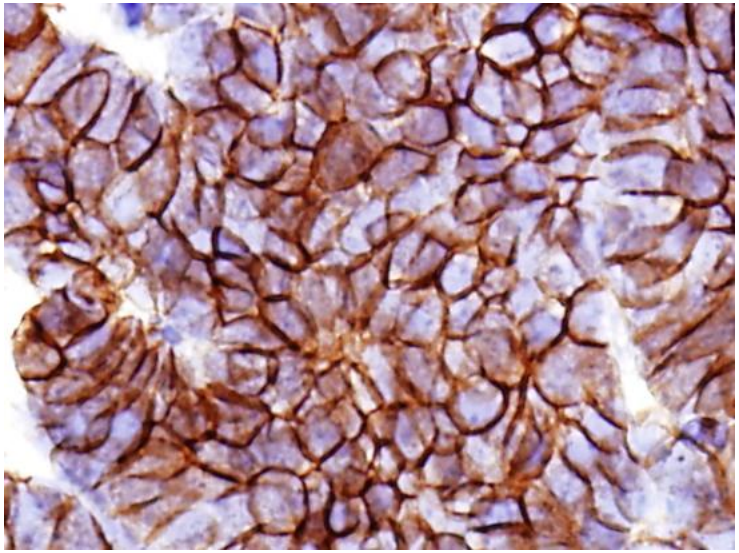
- KT-5

KT-10









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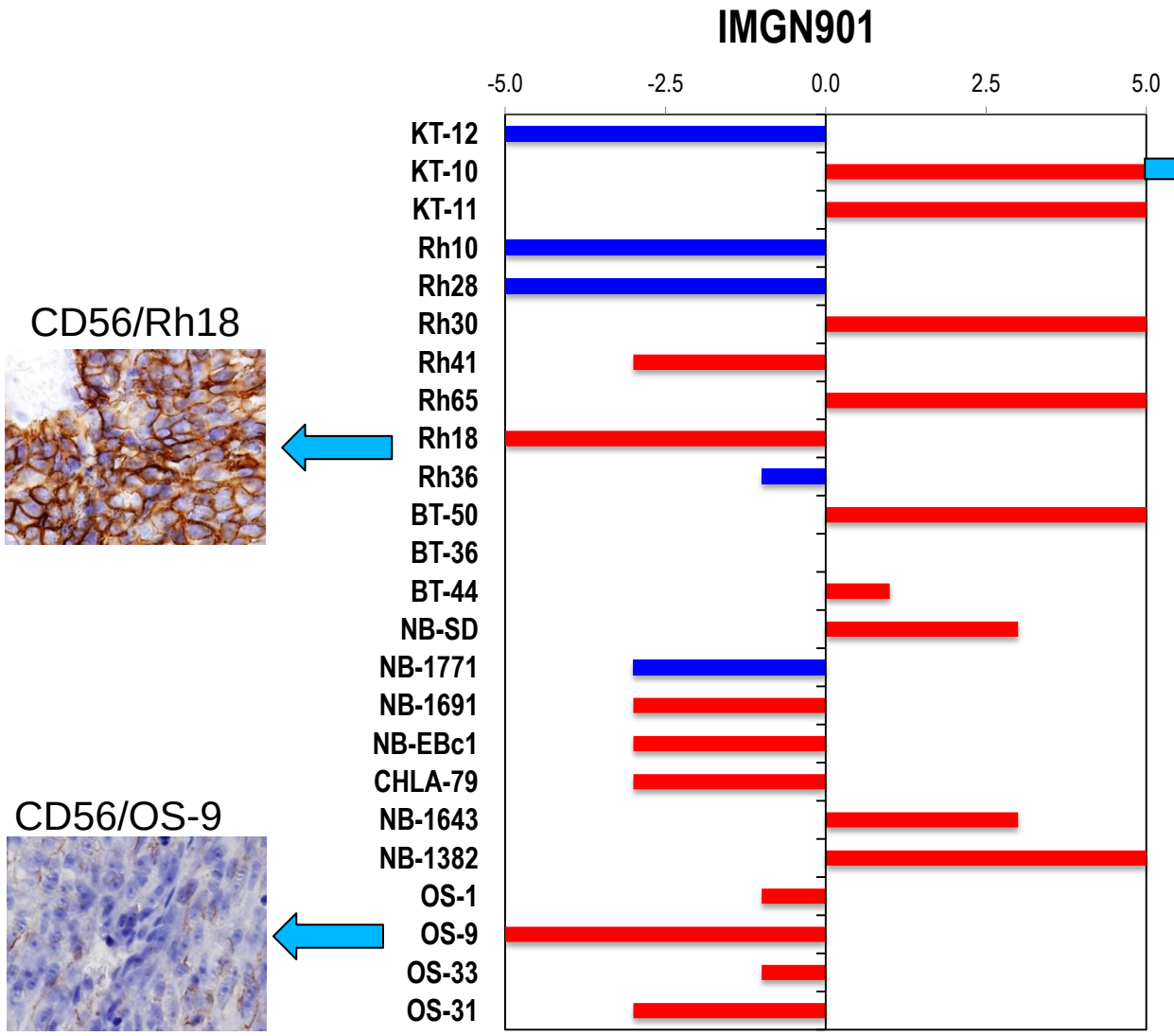
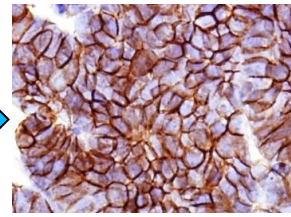
IMGN901 Response and CD56 Expression



CD56/KT-10



CD56/Rh18

CD56/OS-9

- Each of the 9 xenografts achieving an objective response showed homogeneous staining by IHC for CD56 with expression levels of 2-3, 3 or 3+.

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Antibody-Drug Conjugates

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GPNMB as a Cancer Therapy Target

- Over-expressed in a number of cancer types
  - Melanoma, breast cancer, NSCLC, lymphoma
- Overexpression correlated with poor prognosis in breast cancer
  - High tumor expression of GPNMB specifically correlated to poor prognosis in TNBC
- Membrane expression accessible to antibody therapy, efficiently internalized for antibody-drug-conjugate approaches
- Glembatumumab vedotin is ADC targeting GPNMB expressing cancers under development by Celldex

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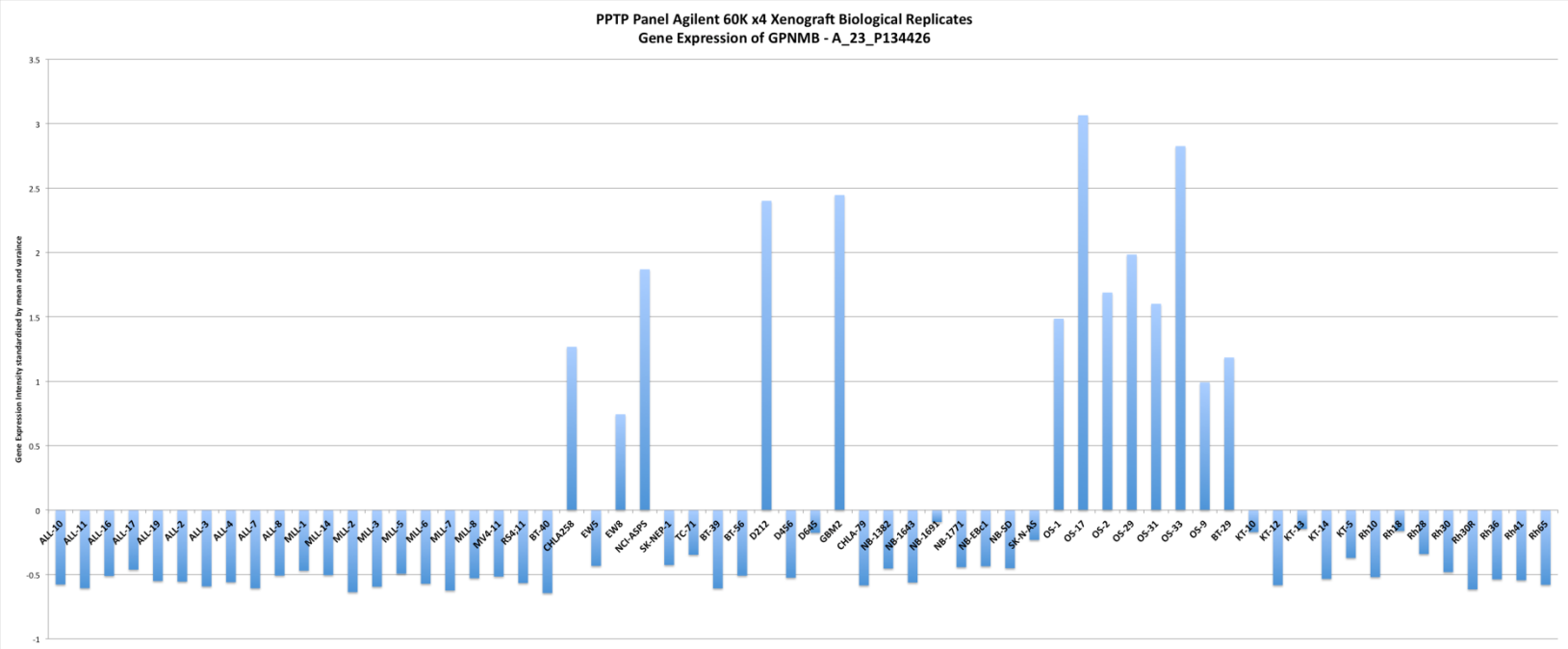
GPNMB Expression



Line	IHC Results % tumor	IHC Results Intensity	% Stroma Results	Stroma Intensity	Tumor component - Epithelial
OS-1	5	2+	N/A	N/A	>99%
OS-2	40	2+	N/A	N/A	>99%
OS-9	30	1+	1%	3+	90%
OS-17	80	2-3+	0%	0	80%
OS-29	60	2+	5%	1+	90%
OS-31	0	0	1%	3+	95%
OS-33	5	2+	N/A	N/A	>99%

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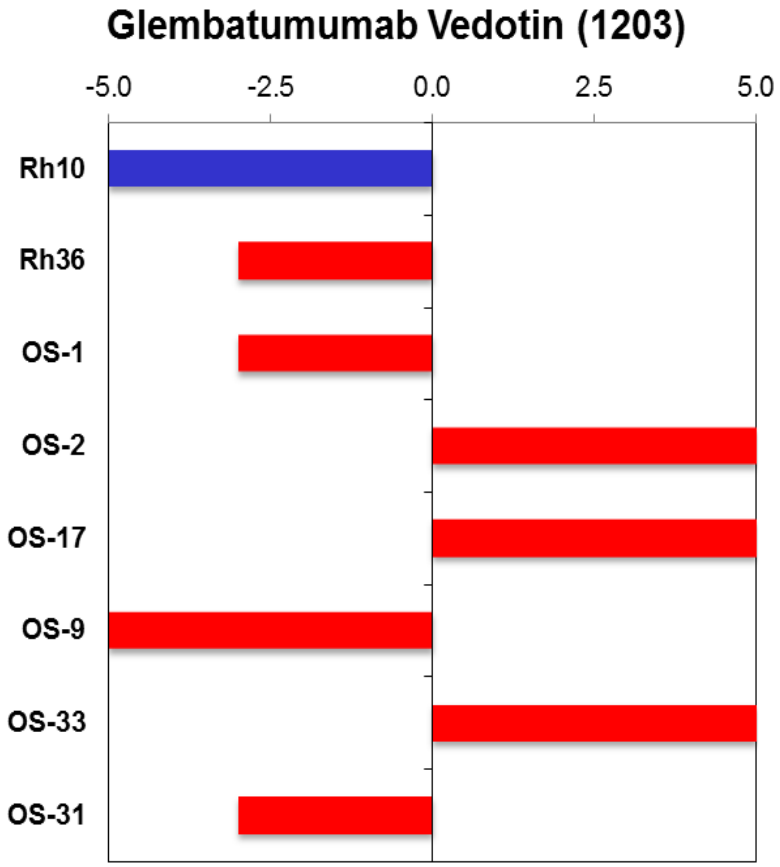
Glembatumumab Vedotin

- An antibody-auristatin conjugate that targets cells expressing GPNMB.
- Glembatumumab vedotin induces remissions in GPNMB-expressing osteosarcoma, but not in rhabdomyosarcoma.
- Pediatric clinical trial being planned for patients with osteosarcoma.



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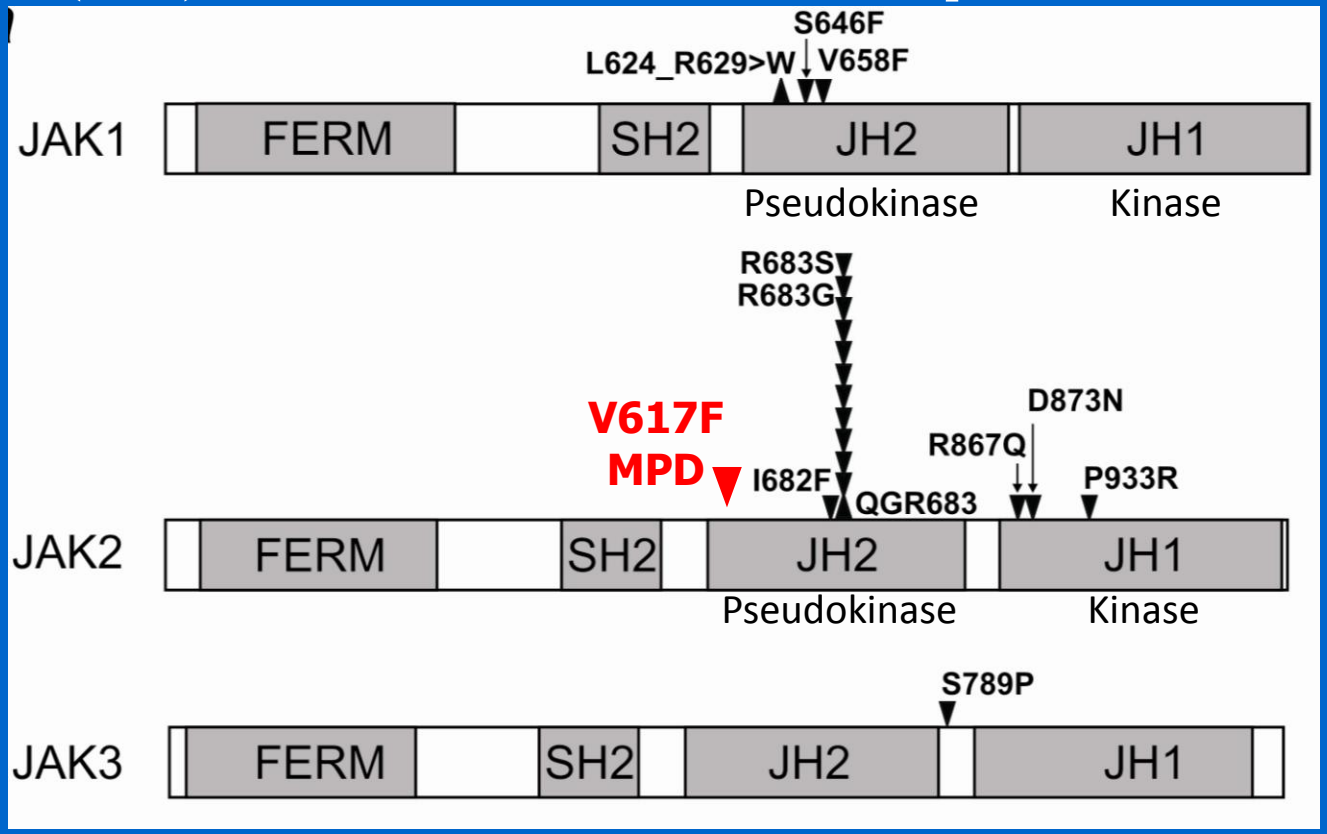
JAK Inhibitors

JAK mutations in "BCR-ABL1-like" ALL

- JAK2 (n=16): 10 R683G; 3 non-R683G pseudokinase domain; 3 kinase domain
- JAK1 (n=3): 3 pseudokinase domain
- JAK3 (n=1): uncertain functional consequences



Mullighan CG, et al. PNAS 2009:106(23):9414-9418

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Testing JAK-STAT Pathway Inhibitors for ALL

- Pick ALL models with relevant mutations from xenografts established by direct transplantation into NOD-SCID mice

ALL-10 (JAK1 V658)	**TARGET-047 (JAK2 R683)**
TARGET-144 (JAK1 L624)	**TARGET-020 (JAK2 R867)**
TARGET-038 (JAK2 I682)	**TARGET-174 (JAK2 P933)**

- Evaluate role of different mutations in effecting response to therapy
- Illustrates the emerging “standard of care” for evaluating molecularly targeted agents

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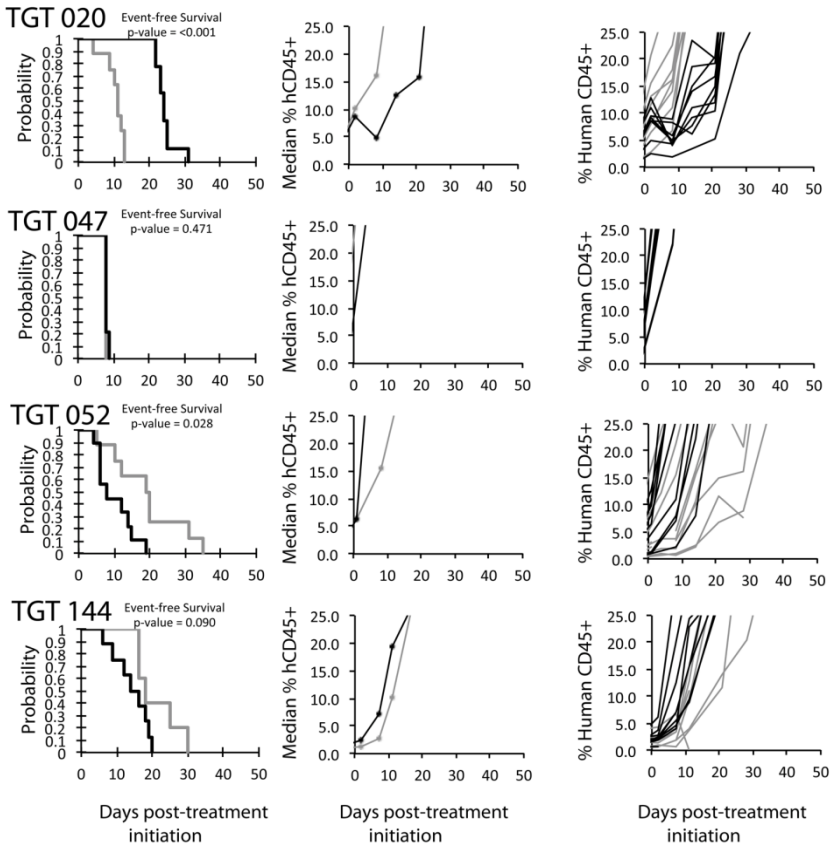
Going against the Paradigm: Limited activity of JAK inhibitor against JAK-mutated ALL xenografts

- AZD1480 evaluated against 6 ALL xenografts with JAK1 or JAK2 mutations
- No objective responses (CR or PR) observed
- Similar results observed for ruxolitinib by different research team.
- Similar to lack of effect of JAK inhibitors on MPN malignant clone.
- JAK-translocations potentially different in their response to JAK inhibitors.



Carol, et al. AACR 2012

National Cancer Institute

Criteria for Agents for PPTP Evaluation

- The agent should generally be one for which clinical testing in children is considered a potential priority, with testing able to begin within 12 to 24 months. Satisfactorily addressing this criterion will generally imply an active development plan for the agent for adult cancers and a willingness to consider pediatric evaluations of the agent.
- The agent should have plausible relevance to the treatment of childhood cancers, based on current understanding of the mechanism of action of the agent and current understanding of the biology of childhood cancers.
- Agents with molecular targets or mechanisms of action that have not been previously addressed by the PPTP will be prioritized higher than agents whose molecular targets have previously been addressed by the PPTP.
- Sufficient quantity of agent available for testing.

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Sensitivity, Specificity, and Prevalence

- Assume 10% prevalence of true actives
- Negative test results are likely to be true
- Increasing sensitivity & specificity leads to increased probability of success for positive result.
- False positives remain relatively common even with reasonably reliable testing program.

	Sensitivity	Specificity	PPV	NPV
Scenario 1	50%	50%	10%	90%
Scenario 2	90%	20%	11%	95%
Scenario 3	80%	80%	31%	97%
Scenario 4	90%	90%	50%	99%

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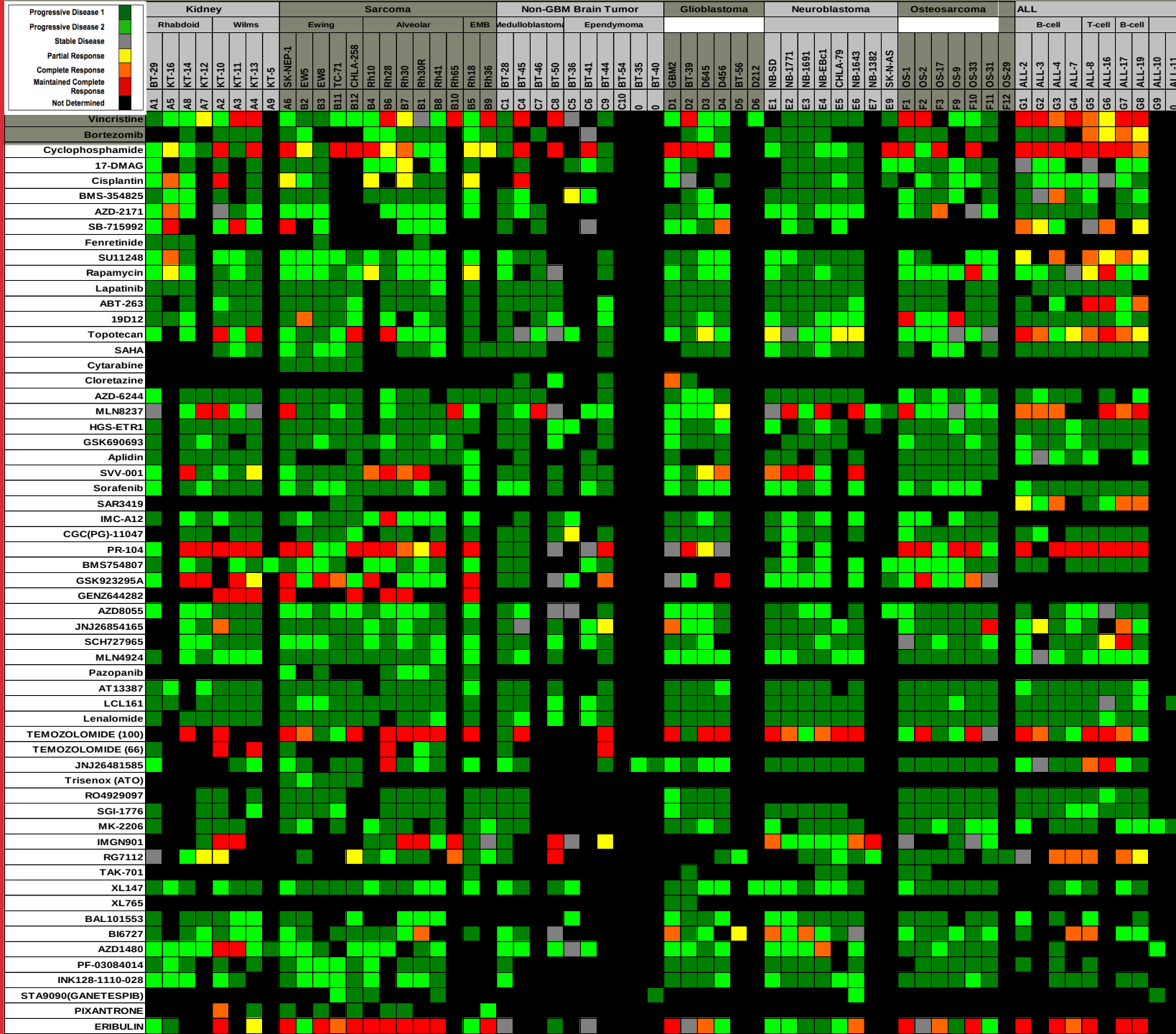
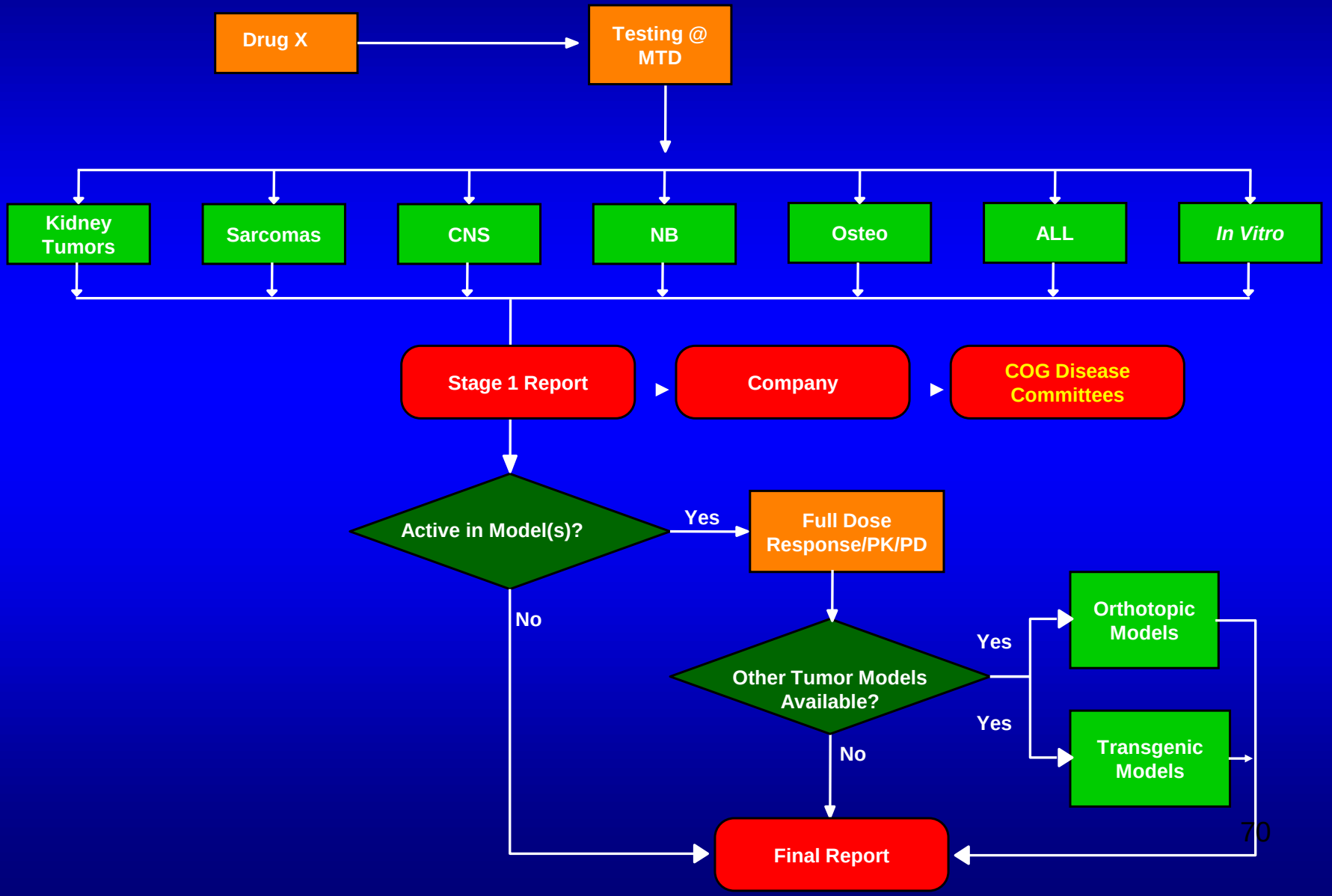


Two-Stage Process for Drug Evaluation



National Cancer Institute

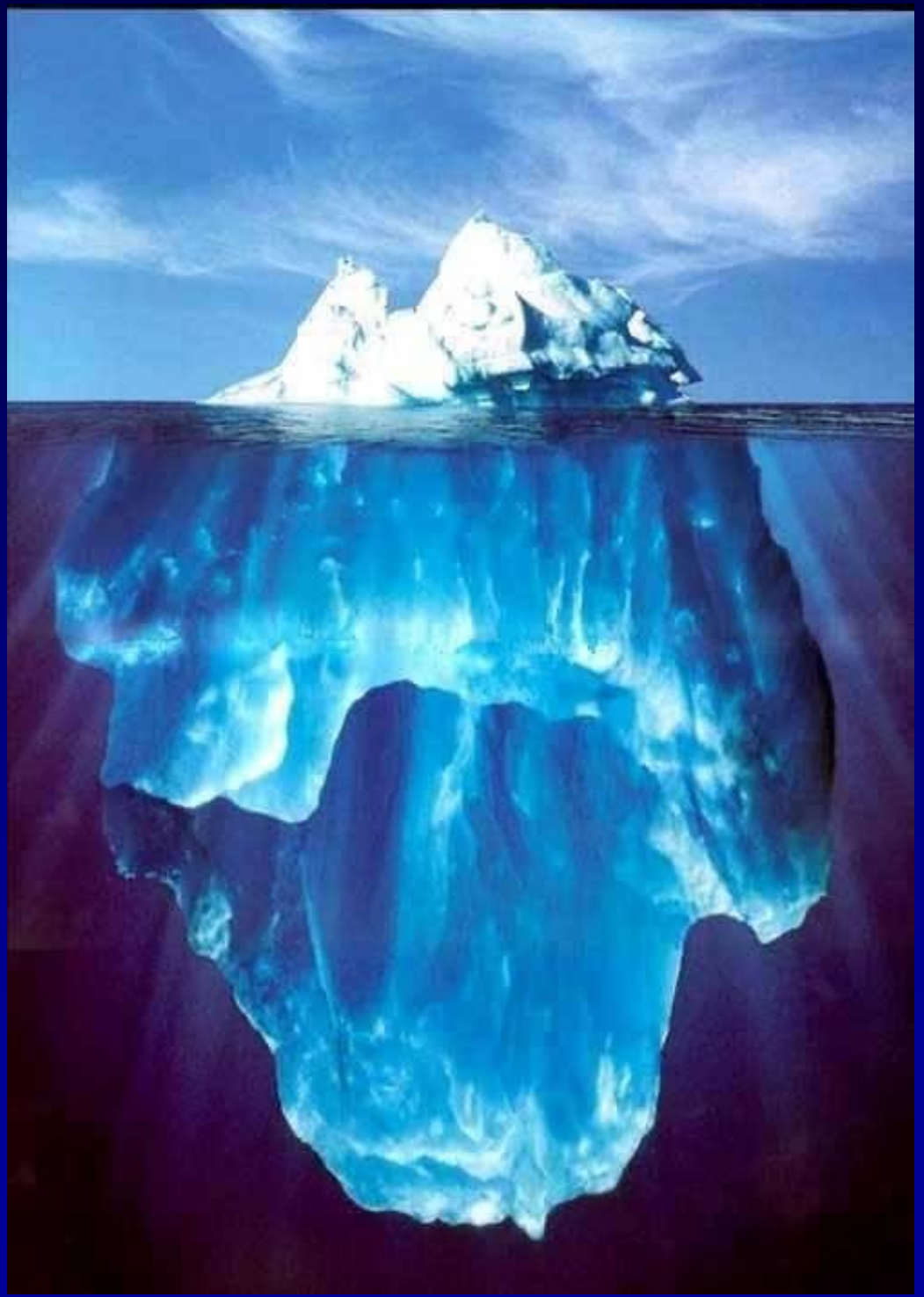
Molecular Characterization of Screen-Detected Lesions

NCI Board of Scientific Advisors
November 2013

Barry Kramer (Division of Cancer Prevention)
Dinah Singer (Division of Cancer Biology)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health



Current Challenges with Screening and Early Detection

- **Phenotypically distinguishing between lesions that are likely to progress and those that are indolent and require no immediate treatment**
- **Predicting whether lesions that are detected by sensitive screening tests are indolent (hence, not requiring immediate treatment) or progressive and potentially life-threatening**

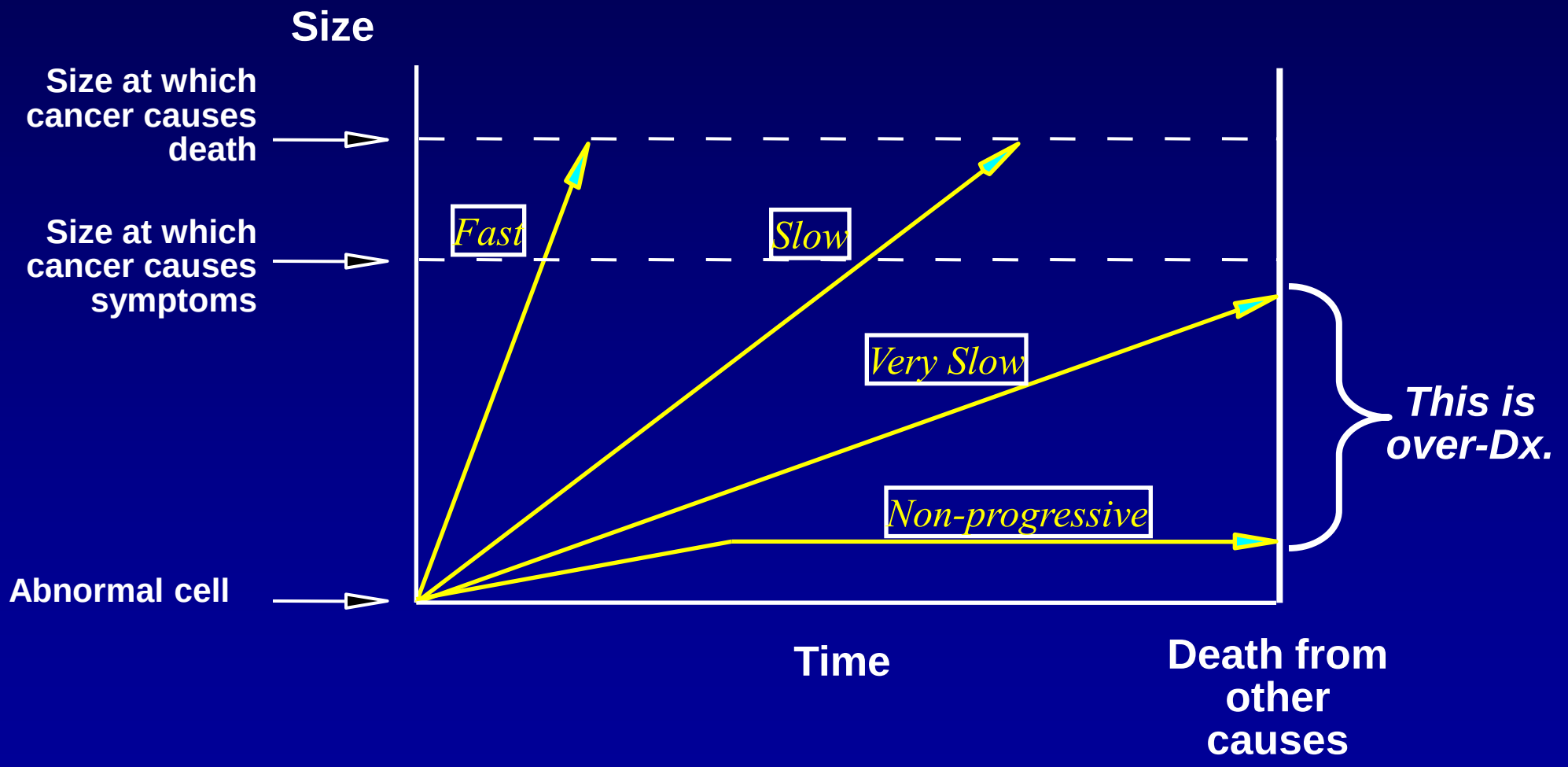
Increase in cancer incidence (particularly early stages), but no change in mortality indicates overdiagnosis

Requirements for Overdiagnosis

- Existence of a silent disease reservoir
- Activities leading to its detection (particularly screening)

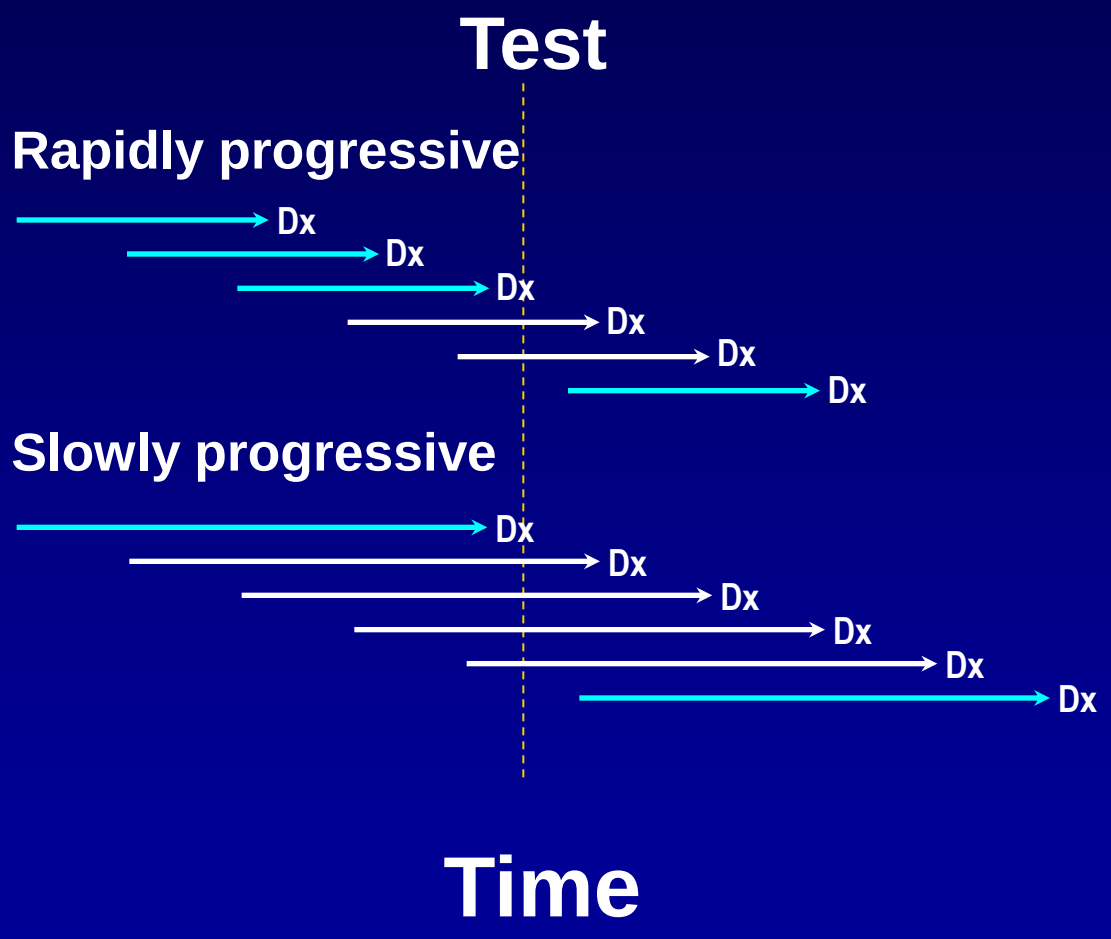
From G. Welch and W. Black, JNCI 2010

The Heterogeneity of Cancer Progression

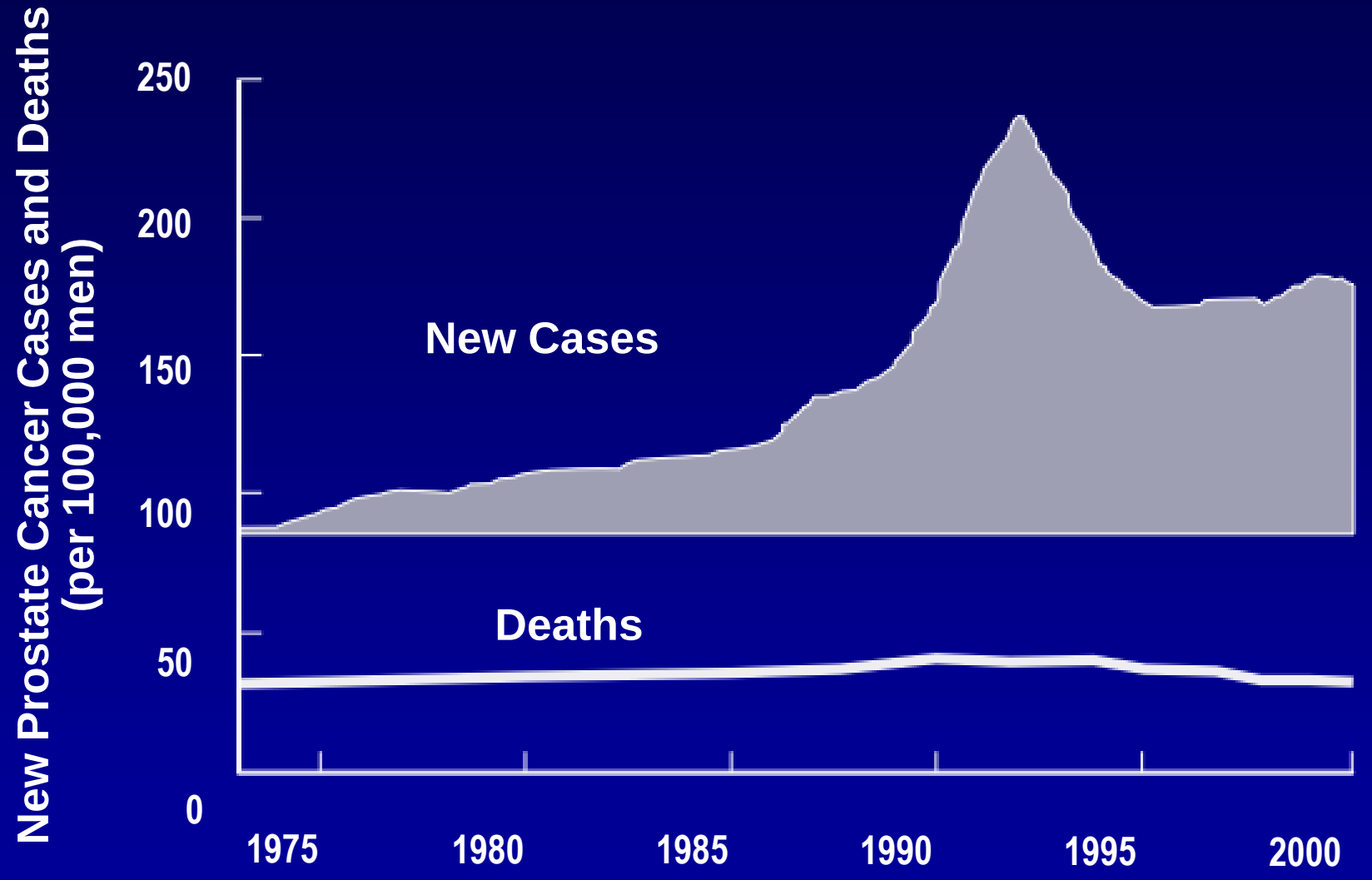


(Courtesy of H. Gilbert Welch, Dartmouth)

Length Biased Sampling



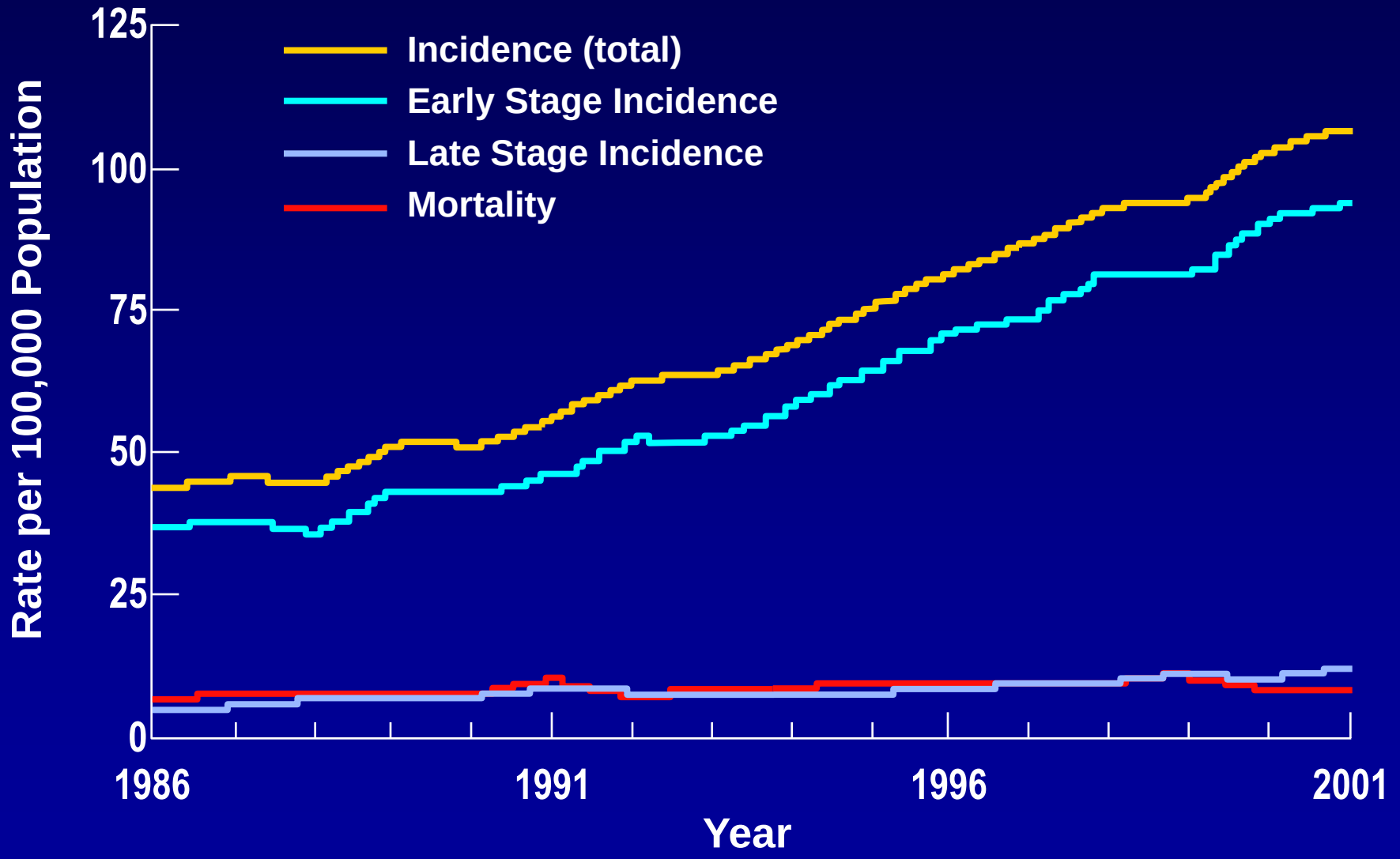
U.S. Prostate Cancer Incidence vs. Mortality Over-Diagnosis



From . Welch, *"Should I Be Tested for Cancer?"*, 2004

NCI Division of Cancer Prevention

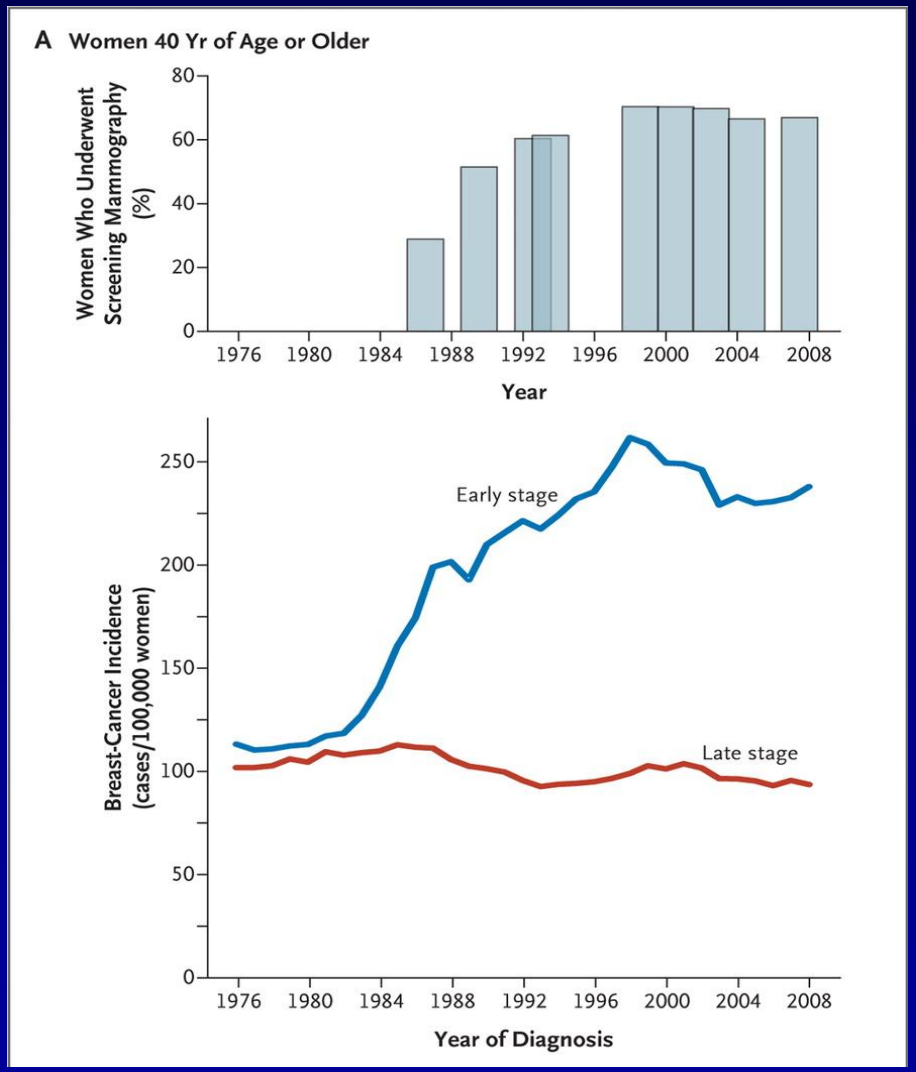
Evidence of Melanoma Overdiagnosis in the Medicare Population



G. Welch, *BMJ*, 2005

NCI Division of Cancer Prevention

Use of Screening Mammography and Incidence of Stage-Specific Breast Cancer in the U.S., 1976–2008



The NEW ENGLAND JOURNAL of MEDICINE

Bleyer A, Welch HG. N Engl J Med 2012;367:1998-2005.

NCI Division of Cancer Prevention

Key Biological Questions

- What molecular/cellular characteristics (genetic, epigenetic, cell physiology, signaling profile, metabolism, microenvironment, and immune reaction) define indolent versus progressor lesions that are detected by screening tests?
- Are there lineage relationships among indolent, interval, and malignant lesions?
- What kind of selective forces shape the evolution of a cancer during its progression to become invasive?
- What role does the tissue microenvironment play in modulating or determining the biological behavior of the screen-detected lesions?

DCP Workshop on Molecularly Defined Natural History of Cancer

- A two-day Think-Tank meeting was held on March 8-9, 2012 in Bethesda, MD to discuss the overdiagnosis issue

- The conclusion: it is critical to determine the molecular and cellular characteristics of both the lesion itself and its microenvironment that predict lesion's behavior.

Microenvironment and Tumor Progression

- Role of microenvironment in tumor progression is being demonstrated.
- Chromosomal instability, microsatellite instability, genome-wide aneupoloidy, loss or gain of whole chromosome or chromosome arms may accelerate progression.
- However, these studies are cross-sectional and do not address the dynamics of evolving lesions, especially in the context of screening.

Constitution of Tumor Microenvironment

Physiological Parameters [glycolytic pathway, hypoxia, ***acidic tumor microenvironment*** (acidic pH), etc.]

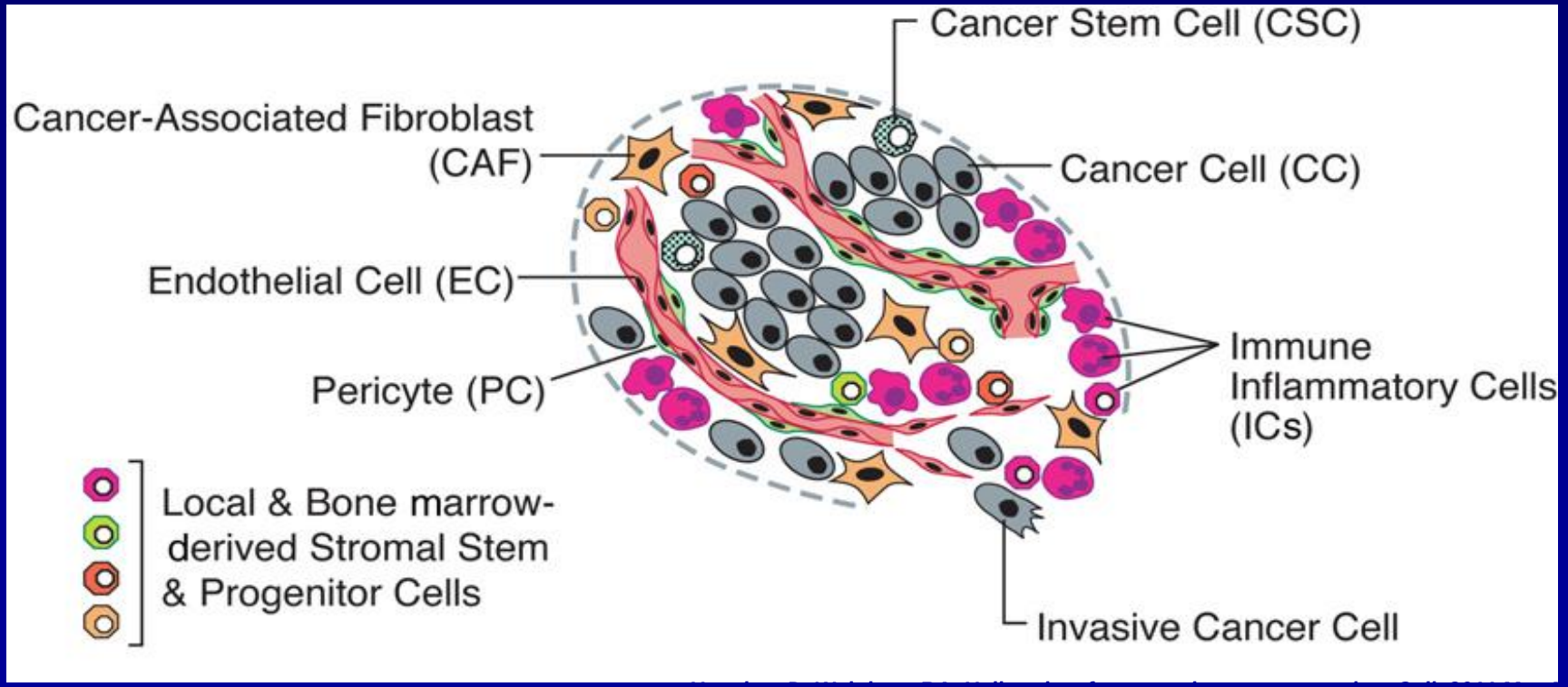
Malignant Cells (cancer cell, cancer stem cell, etc)

Vasculature and Stroma (endothelial progenitor cell, pericyte, bone marrow derived cell, etc)

Immune Response Cells (macrophages, mast cells, tumor-infiltrating lymphocytes, etc)

Extracellular Matrix (fibronectin, collagen, integrins, MMP, tetraspanins, etc)

Secreted Proteins (chemokines, growth factors, etc), including gradients



NCI Division of Cancer Prevention

Goal of This Initiative

To support a consortium of multidisciplinary research programs that undertake a comprehensive characterization of tumor cell and microenvironment components of screening-detected early lesions and missed interval cancers

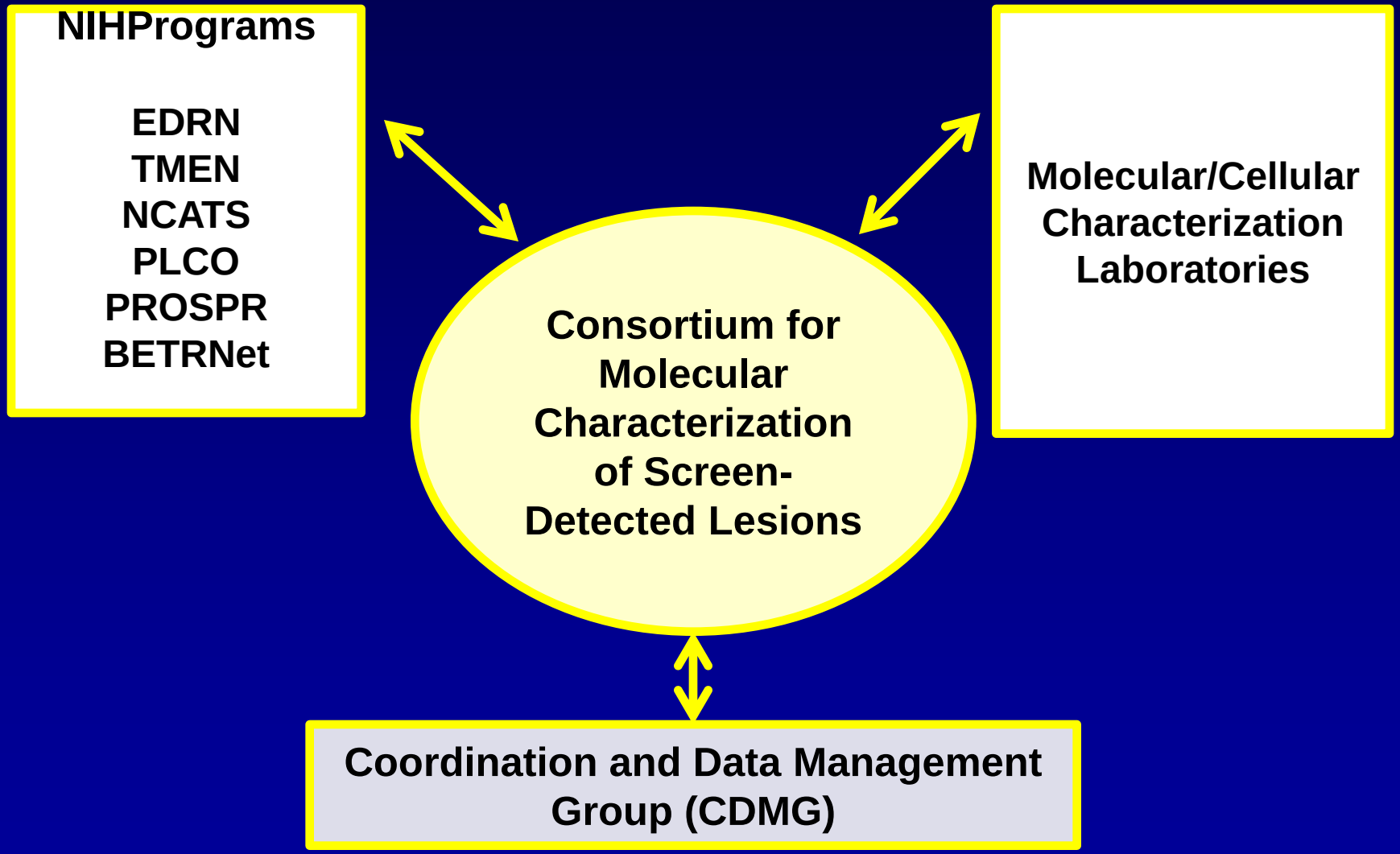
Types of Studies That Can be Undertaken (1)

- Molecular & cellular comparisons to determine whether a subset of screen-detected lesions shares features with aggressive interval cancers (missed by screening) that are likely to have progressing phenotypes
- Single cell analyses of tumor heterogeneity within lesions
- Phenotyping cellular components of lesions, including the tumor cells and surrounding microenvironment

Types of Studies That Can be Undertaken (2)

- Establishing novel mouse models, organoid cultures or patient derived xenografts from screening-detected lesions that maintain the original tumor architecture
- Systems approaches and modeling using experimental data (genomics, epigenomics, proteomics, imaging etc.) to define “disease dynamics”
- Sequential imaging together with molecular approaches to elucidate dynamic changes occurring during progressive disease

Organization Structure of the Consortium



Why Consortium?

- Uniform data collection, protocols, analyses
- Common Data Elements (CDEs) for serial sample collection and clinical annotation
- Reproducibility of data collection including verification and auditing
- Creation of a national resource for valuable samples of screen-detected and of interval cancers for future use
- Central management of IRB, material transfer agreements, and protocols

Portfolio Analysis

- Portfolio analysis yields a few funded grants in progression and microenvironment; however these studies are preliminary and not generalizable because the lack of appropriate annotation, e.g., screen- or symptom-detected lesions
- Keywords: indolent cancer and progression (3)
- Therefore, portfolio analysis fully supports the need for an early diagnosis initiative

Funding Mechanism and Budget

- Cooperative Agreement U01/U24 $5 M/yr of which $1.6 M supported by Breast Cancer Stamp Act Funds; Total Five Year $25 M
  - Breakdown: $4.5 M for U01 and $500 K for U24 per year;
  - Five-Year Total Cost: $25 M
- Allows NCI staff involvement in providing direction, cross talk, dissemination of information and assistance in meeting the programmatic goals
- Facilitates development of resources for biospecimens, reagent generation and dissemination of research tools and biologics
- NCI-DEA organized Special Emphasis Panel to review the application

Application Requirements

Applications will be required to:

- Include collaborative arrangement with existing or ongoing biospecimen networks or consortia as a partner on the application
- Clearly demonstrate the ability to procure appropriate specimens for the proposed study
- Be willing to share samples across the Consortium on cross-laboratory discovery and verification

Above requirements will be made part of the Notice of Grants Award (NGA)

Existing Resources

- Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO)
- National Lung Screening Trial (NLST)
- Clinical and Translational Science Awards (CTSA)
- Canary-EDRN Prostate Active Surveillance Study (PASS) Cohort
- Specialized Programs of Research Excellence (SPOREs)
- DOD Specimen Banks (case-control specimens on prostate, breast, colon)
- VA Hospitals (archived specimens)
- Various Academic Autopsy Collections (Nebraska, Cornell, Johns Hopkins, etc.)

Number of Cases by Specimens Available for Selected Cancers in PLCO[1]

	Serum (pre-Dx)	Plasma (pre-Dx)	Red Cells (pre-Dx)	Buffy Coat	Whole Blood	Buccal Cells/ DNA[2]	Tumor Tissue
Prostate	3924	3870	4018	3270	3106	2131	1058
Screen-detected	1448	1399	1466	1170	1053	NA	496
Interval	123	121	123	90	88	NA	41
Others[3]	2353	2350	2429	2010	1965	NA	521
Lung	1570	1202	1589	1060	1051	870	436
Screen-detected	268	82	262	197	159	NA	97
Interval	141	57	138	84	94	NA	17
Others[3]	1161	1063	1189	779	798	NA	322
Breast (F)[4]	1984	1930	1972	1803	1583	1687	807
Melanoma[4]	636	625	645	619	505	494	NA[5]
Pancreas[4]	357	348	345	262	217	24	NA[5]

Note:

1. **Data as of January 31, 2013.**
2. **Buccal cells were collected from control arm only.**
3. **Others: Never screened and post-screening cases (and control arm for tumor tissue).**
4. **Detection mode for breast cancer, melanoma and pancreatic cancers is unknown.**
5. **Tumor tissue samples are not available for melanoma and pancreatic cancers.**

NLST Specimens and Screen Detected/Interval Cases

		# of Cases	% of Cases with Tumor Tissue Available[1]	% of Cases with Serum, Urine and Sputum Available[1]
Screen detected	CT Arm	649	65%	20%
	CXR Arm	279	56%	20%
Interval	CT Arm	44	26%	20%
	CXR Arm	137	24%	20%
Others[2]	CT Arm	367	21%	20%
	CXR Arm	525	13%	20%
Total lung cancers	CT Arm	1060	44%	20%
	CXR Arm	941	25%	20%

Note:
1. Approximate percentages.
2. Never screened and post-screening cases.

Available PCPT Biospecimens by Arm and Detection Mode

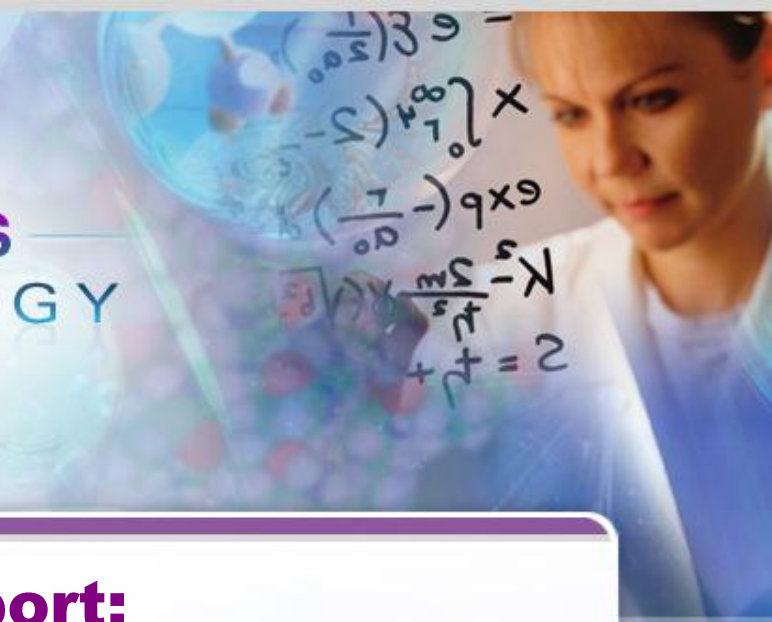
Arm	Detection mode	# of prostate cancer cases[1]	% of Cases with pre-Dx serum available[2]	% of Cases with WBC/DNA available[2]	# of cases with prostatectomy tissue available[3]
Finasteride	For cause[4]	435	~95%	~60%	149
	End of study biopsy	368	~95%	~60%	73
	All	803	~95%	~60%	222
Placebo	For cause[4]	571	~95%	~60%	186
	End of study biopsy	576	~95%	~60%	120
	All	1147	~95%	~60%	306

Notes:

1. Data from: Thompson et al., N Engl J Med. 2003 Jul 17;349(3):215-24. The influence of finasteride on the development of prostate cancer.
2. Estimated percentage of cases with specimens available.
3. Data from: Lucia et al., J Natl Cancer Inst. 2007 Sep 19;99(18):1375-83. Finasteride and high-grade prostate cancer in the Prostate Cancer Prevention Trial.
4. Number of cases in whom a biopsy was performed for a cause either during the study or at the end of study and cases who underwent another procedure such as transurethral resection of the prostate during the trial.

National Cancer Institute

PHYSICAL SCIENCES in ONCOLOGY



Status Report: Physical Sciences-Oncology Centers (PS-OC) Program

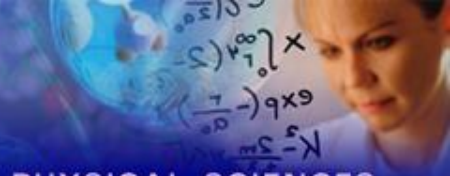
Larry A. Nagahara

Board of Scientific Advisors, November 7, 2013

Physical Sciences-Oncology Centers (PS-OC) Program: Premise

- Physical scientists have a history of contributing to cancer research (notably with advanced tools); however, they have faired less well in receiving grants where concepts from these disciplines are applied.
  - ***Advanced Tools: Proton Beam Therapy, MRI/PET/CT Imaging***
  - ***Concepts: Graph/Network Theory; Bayes' Theorem***
- Nascent concepts/ideas often take many years to establish and still more years to become "mainstream".
- Jerome Cornfield and team brought the concept of Bayesian methods, used more commonly by the information (encryption) community a decade earlier (1940's), to answer the following question:
  - **What's the probability that someone would develop lung cancer, given that he/she was/is a smoker?**
  - JNCI 1951, JNCI 1959, Surgeon General 1964

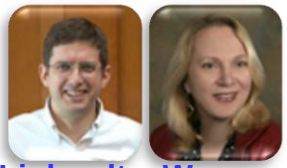
Physical Sciences-Oncology Centers (PS-OC) Program: Premise



- Center/Network approach implemented for the PS-OC Program to **accelerate the adoption ("learning curve") of concepts and advanced tools from the physical sciences** that can be shared more readily with other investigators in the center/network and beyond.
- Increases cross-section for impact (*e.g.,* new insights) by **conjoining teams of physical scientists and cancer researchers** that are focused on relevant questions and systems in cancer.
- Training/career development is a key component for **generating early adopters** of these concepts/tools.
- **Investigator-initiated center pilots/trans-network pilots** to further accelerate adoption and enhance integration between the two fields.

PS-OC Network (circa 2013): Physical scientists & cancer researchers integrated at the start

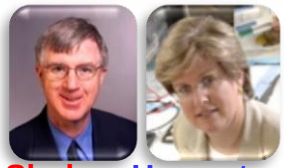
PHYSICAL SCIENCES in ONCOLOGY


Liphardt Weaver

Stanford


O'Halloran Licht

Northwestern


Shuler Hempstead

Cornell


Manalis Jacks

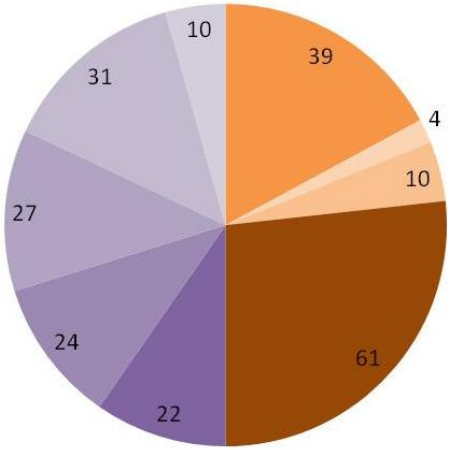
MIT


Hillis Agus

USC


Michor Holland

DFCI



Scripps

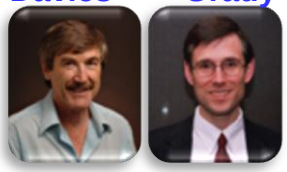
Kuhn Bethel

Princeton

Austin Tlsty

ASU

Davies Grady

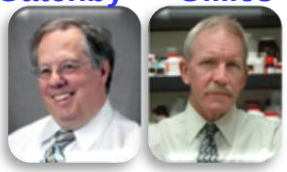


TMHRI

Ferrari Curley

Moffitt

Gatenby Gillies



Johns Hopkins

Wirtz Semenza

PI + SI

12 "Virtual" Centers

Over 110 Institutions:

- 83 Domestic
- 32 Foreign

corresponding to:

- 700+ investigators, collaborators, & advisors
- 600+ trainees (post-docs, graduate, & undergraduate)

participating in the PS-OC Network

NATIONAL CANCER INSTITUTE

Cancer Problem: Many cancer patients develop resistance to therapy

What are the fundamental bases of rapid development of resistance?

Traditional View:

External stress + Microenvironment =

⇨ Selection of the fittest

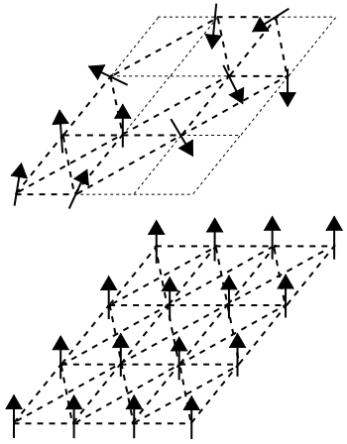
⇨ Development of resistance

Additional Physical Science Perspective:

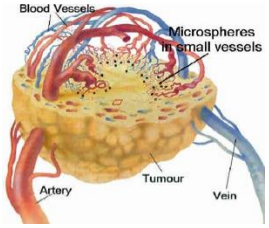
Spin glass model helps understand long-range interactions amongst weakly interacting parts.

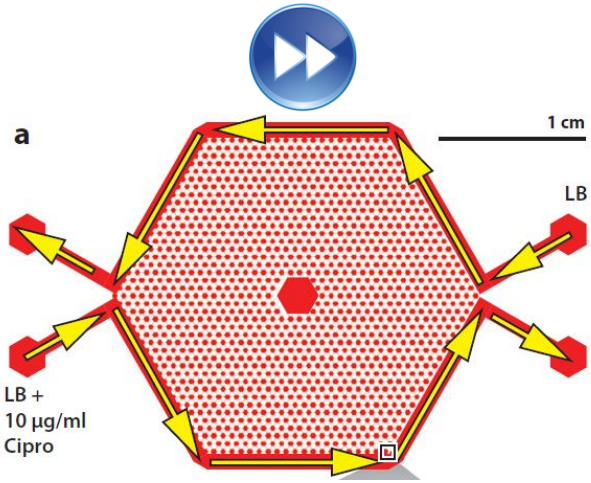
Spatially heterogeneous "micro-habitats" are critical to accelerated cell resistance.

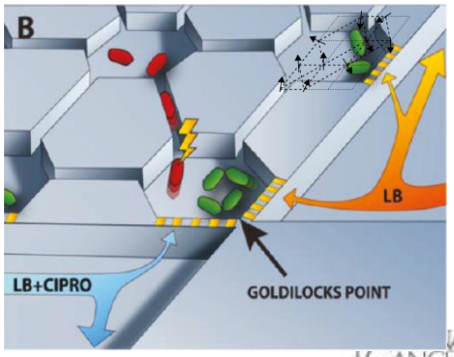
(Robert Austin, Princeton PS-OC) – Physics theory of spin glass is a general way to understand complex behavior which arises when weakly interacting agents exhibit "frustrations" – conflicting (multiple) choices/commands. Likewise, cancer cells have conflicting commands given to them by neighbors and are reflective of the phenotypic and genotypic complexity observed.



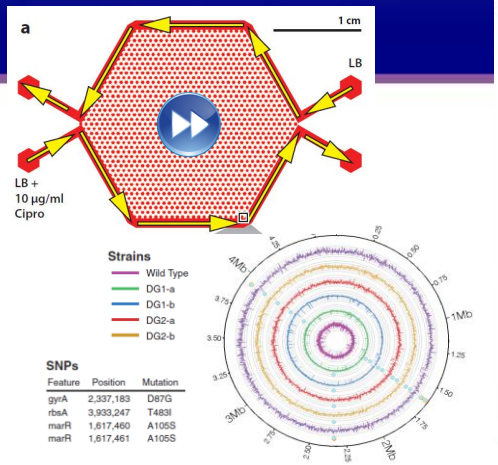
Spin Glass Analogy

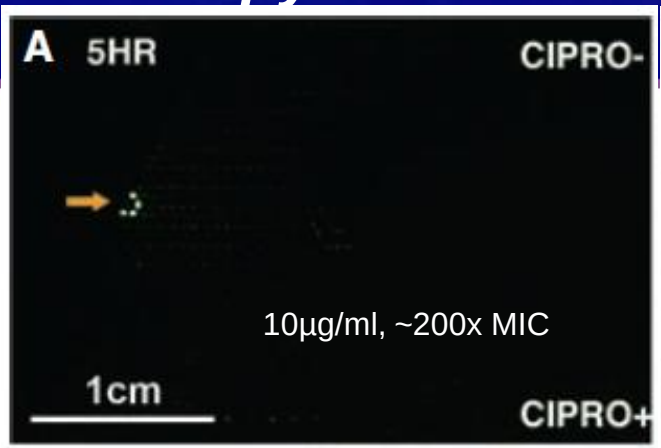


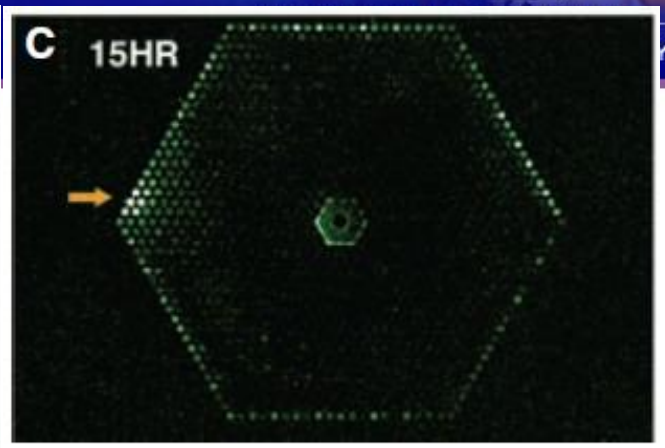




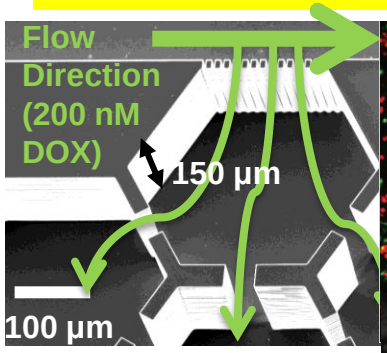
Cancer Problem: Many cancer patients develop resistance to therapy

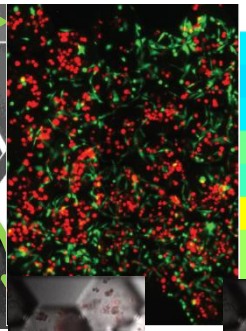


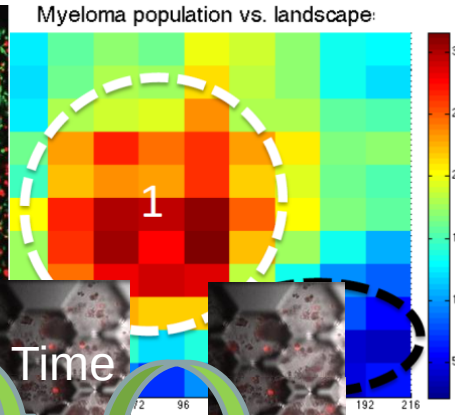


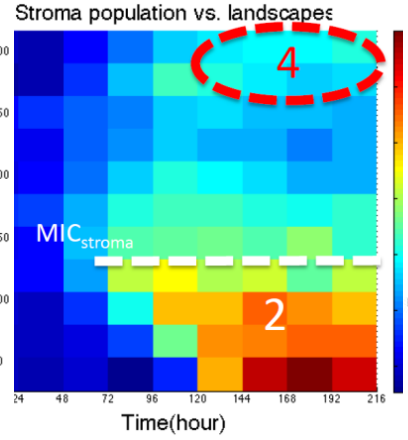


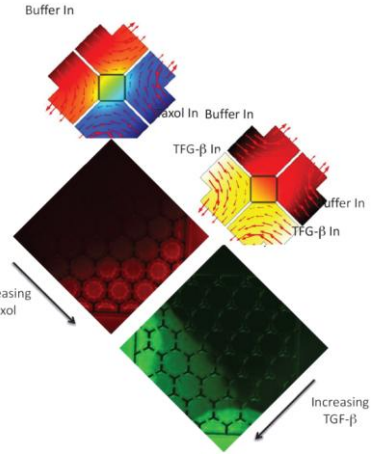
***Princeton's "Spin Glass" Model + "Fast-Forward" Tool: Intra-Center Project & Trans-Network Pilot* (Moffitt PS-OC) *Evolution of resistance in multiple myeloma in the microhabitat with drug gradients*.**











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Cancer Problem: Distinct parameters (genetic, anatomical, physical) are strongly associated with increased risk/poor outcomes

Why do so many different factors all matter so much to outcome?

Traditional View:

Certain genetic , physical, anatomical properties are known risk/outcome parameters for certain types of cancers.

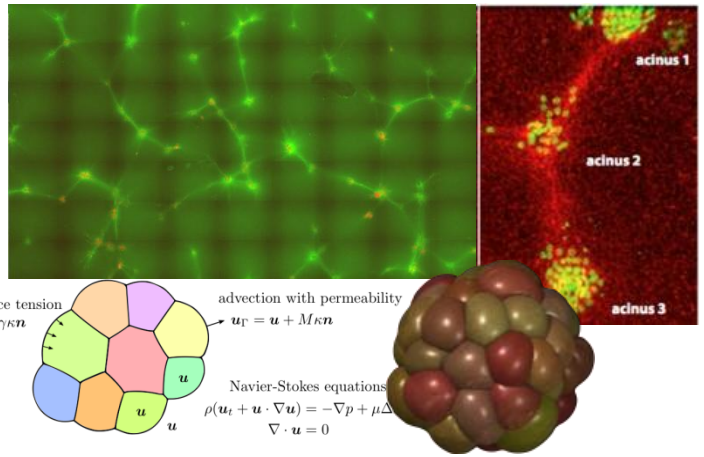
Loose association with each other.

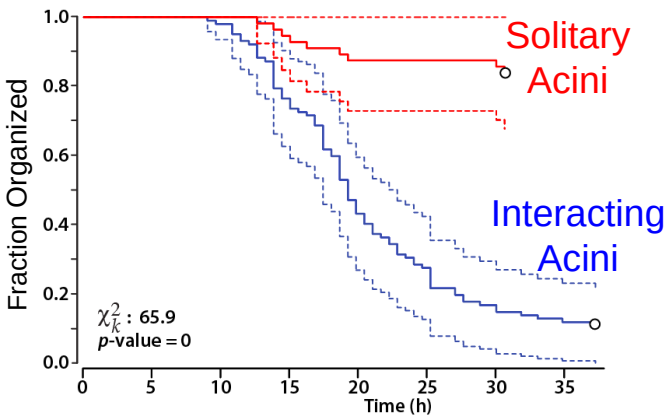
Additional Physical Science Perspective:

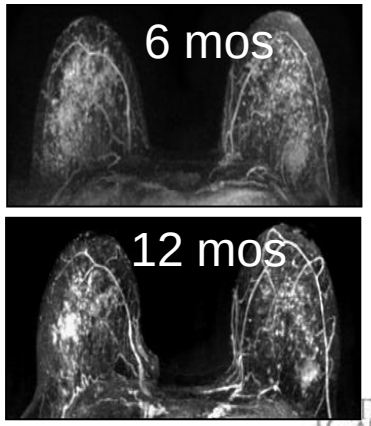
Groups of acini interact cooperatively to transition to an invasive phenotype.

This invasive phenotype may be controlled by tensile stress.

(Jan Liphardt, Stanford PS-OC) – Physicists, cancer researchers, and mathematicians used Ras-transformed mammary acini to investigate the physical interactions and **mechanical cooperativity** over long distances that indicate the transition/progression to a malignant phenotype is a **collective phenomenon**. **Invented first principles multiphysics algorithm** for 3D cell-tissue mechanics computational model. Currently, conducting a pilot project on the biophysical properties of a collagen a risk factors for developing 'silent' breast cancers







Pilot project: biophysical factor of 'silent' cancer in AA women.

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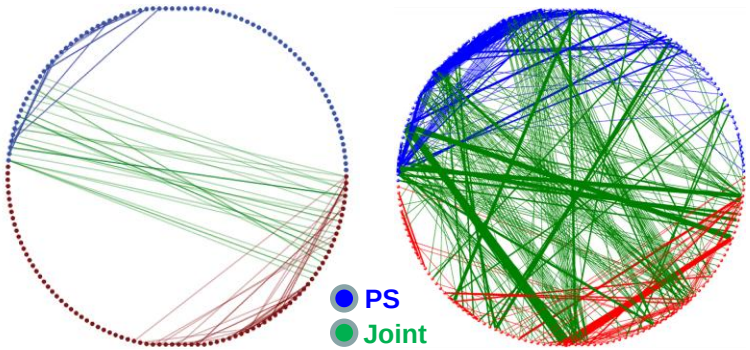
Collaborative and Scientific Output

PS-OC Program FY'09 – present:

PHYSICAL SCIENCES in ONCOLOGY

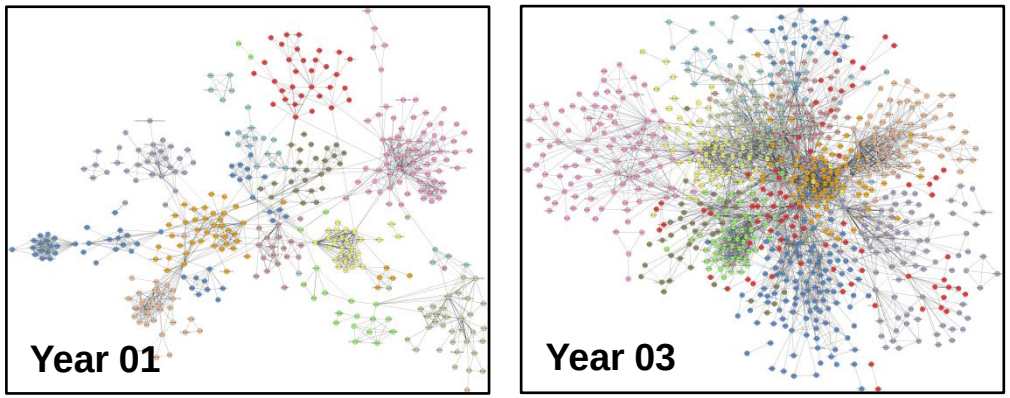
Increase in Transdisciplinary Authorship Compared to Pre-Award Years



Pre-Award 2006-2008

PS-OC Years 2010-2012

More Than 2-Fold Increase in Interactions* Resulting in a Further Integrated Network



* Interactions (reported by investigators in progress report): joint publication, on-going collaboration (exchange material, students, etc.)

- ***Advanced Tools:** Xiaolin Nan & Frank McCormick (UCB PS-OC): Super resolution imaging reveals dimerization-dependent Ras/Raf signaling – PNAS (2013) (doi:10.1073/pnas.1318188110)*
- ***Concepts:** Alexander van Oudenaarden, Hans Clevers, & Tyler Jacks (MIT PS-OC): Apply the concept of control theory and statistical physics to predict optimality in intestinal crypt development – Cell 148, 608 (2012)*

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Lessons from the Phage Treaty

How do I culture better interactions between physical scientists and cancer researchers…

- **"helped many physicists make the transition to biology"**
- **They encouraged other investigators in the field to concentrate on seven bacteriophages ... That way, experimental results from different laboratories could be compared.**

(Standarization)

calteches.library.caltech.edu/584/02/
Ann. Rev. Genet 1982. 16:501-05

Collective Insights of Physical Science Parameters: "Living Project"

PHYSICAL SCIENCES in ONCOLOGY

SCIENTIFIC REPORTS | 3 : 1449 | DOI: 10.1038/srep01449

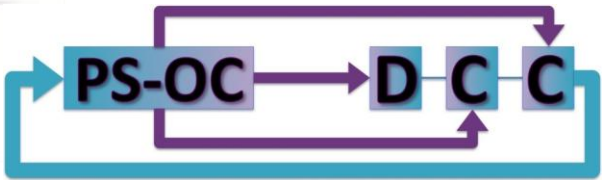
A physical sciences network characterization of non-tumorigenic and metastatic cells

The Physical Sciences - Oncology Centers Network*

- First large-scale, comprehensive, biophysical examination of identical cells
  - 17 Institutions
  - 20 Labs
  - 24 Techniques/approaches
- Combined analysis through Data Jamboree

- Continued as a "Living Project" through repository and database
- Raw data (published/ unpublished) for additional analysis
- Request for additional characterization (data upload required post-publication)

PS-OC Network Bioresource Core Facility



http://opso.cancer.gov/data/

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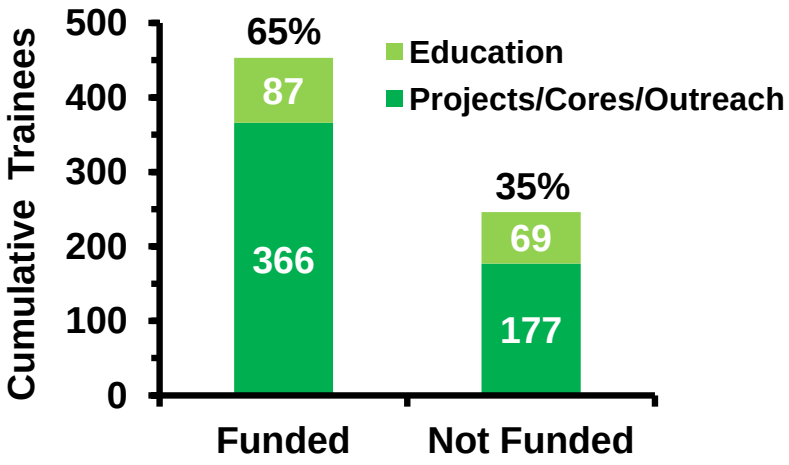
Training & Pilot Projects Output

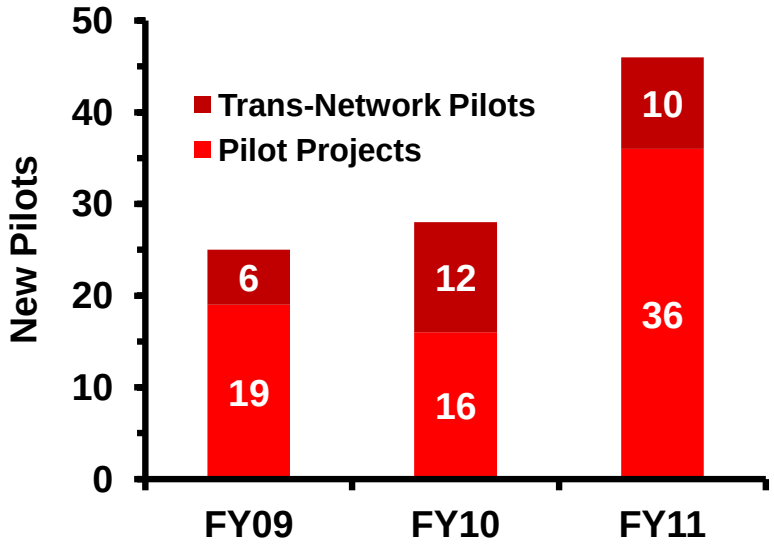
Various Components Provide Flexibility to Investigators

Network Supported ~ 450 Trainees and a Range of Training Opportunities



- Training is a key component for **generating early adopters** of these concepts.

Network Added ~100 Exploratory Studies



- **Investigator-initiated center pilots/trans-network pilots** to accelerate adoption and enhance integration between the two fields

Physical Sciences-Oncology Centers (PS-OC) Program PAR Request

OPSO staff discussions with:

- ❖ Other PAR programs w/ network
  - ❑ NIOSH Agriculture Disease Centers (U54) – PO: Allen Robinson
  - ❑ Quantitative Imaging Network (QIN: U01) – PO: Larry Clarke/Robert Nordstrom
  - ❑ Specialized Programs of Research Excellence (SPORE: P50) – PO: Toby Hecht
- ❖ Program Evaluations
- ❖ PS-OC Implementation Team

Issuances of PS-OC Program (PAR)

- **2 Themes (suggested):**
  - **The Physical Dynamics of Cancer**
  - **Spatial Organization and Cancer**
- **Competition under Type 1**
- **U54 mechanism up to $1.5M (DC)/year – center (5 years max.)**
  - **2-3 Projects/Center**
  - **Education/Training Unit**
  - **Pilot/Trans-Network Projects**
- **Two receipt dates per year for 3 years, except FY'14 having only one receipt date**

PS-OC PAR Suggested Thematic Areas

PHYSICAL SCIENCES in ONCOLOGY

Based on:

1) **Inputs from scientific workshops (75% external to PS-OC Program);**
2) **Scientific advances from program;**
3) **Portfolio analysis of NCI portfolio;**
4) **NCI program leaders**

The Physical Dynamics of Cancer

- ***Overview:*** ***Physical properties such as bioelectric signals, transport phenomena, mechanical cues, and thermal fluctuations*** may regulate (+/-) the initiation and progression of cancer.
- ***Relevant Physical Science Approaches:*** Precision measurements on single-cells and bulk samples, high-dimensional analysis, computational physics

Spatio-Temporal Organization and Information Transfer in Cancer

- ***Overview:*** ***Organization of structures across all length scales (e.g., subcellular, cell, tissue, organ) and time scales*** is required for maintaining the transfer of information that is critical for controlled growth.
- ***Relevant Physical Science Approaches:*** Advanced imaging and measurements, tissue mimetic and engineering, computational physics

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PS-OC PAR Implementation Team

NCI DOC Members

- CCT: Jonathan Wiest
- CRCHD: Alison Lin
- DCB: Dan Gallahan
- DCCPS: Mukesh Verma
- DCP: Nada Vydelingum
- DCTD: John (Kim) Jessup
- OPSO: Sean Hanlon

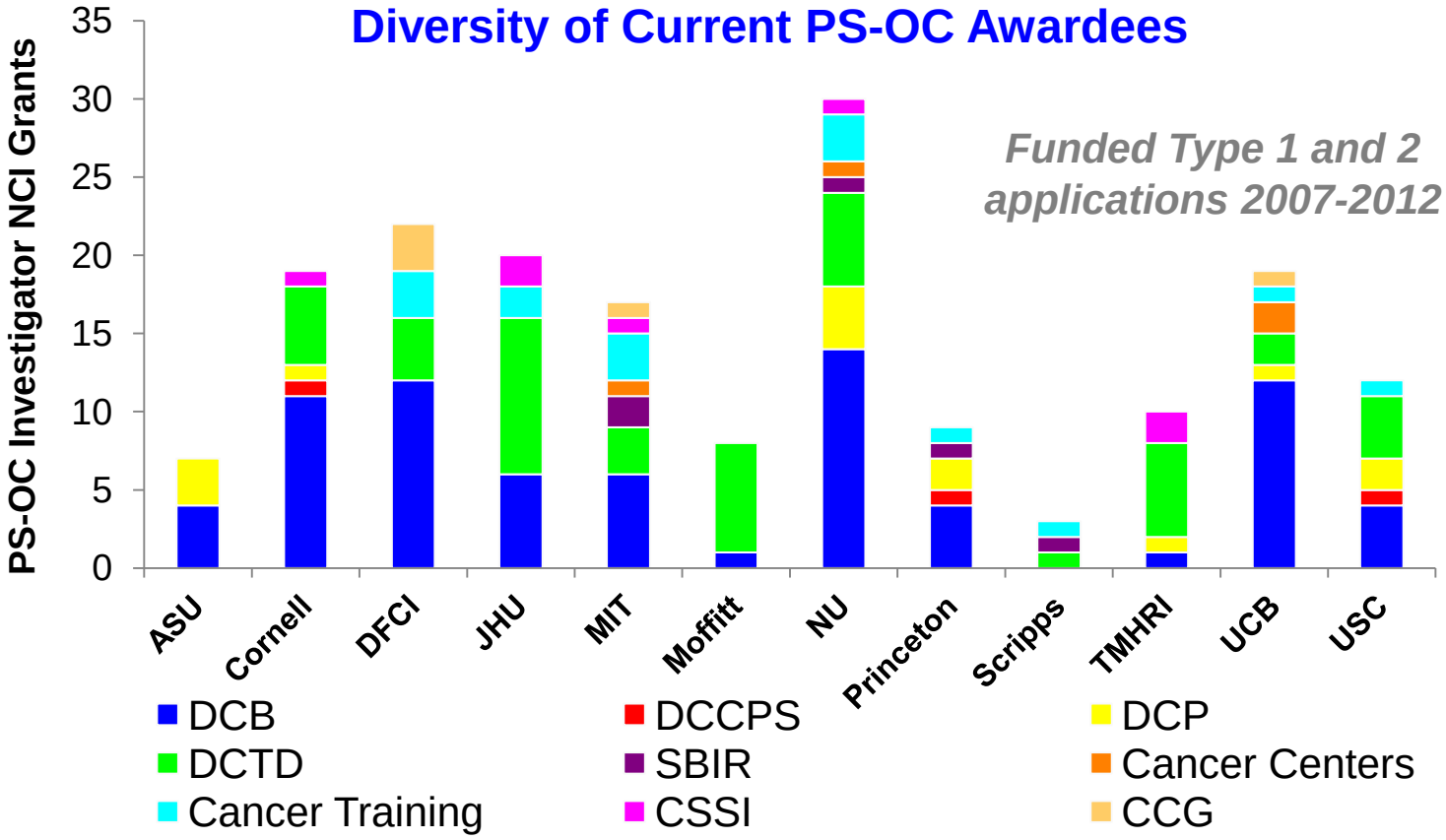
Extensive role of the Implementation Team:

- Provide programmatic suggestions and insights in preparing the PAR
- Assist in pre-application, application, post-review, and pre-award activities;
- Communicate and gather PS-OC-relevant information to your DOC's program staff in a timely fashion, as appropriate;
- Identification of a suitable DOC program official (PO) and/or project scientist (PS).

Diversification of Potential Applicants

PHYSICAL SCIENCES in ONCOLOGY

- Letter on Intent (LOI) to be due 6-8 weeks before application is due
- In case a DOC would like to hold the grant, ample time is allotted to obtain DOC approval with their respective director.



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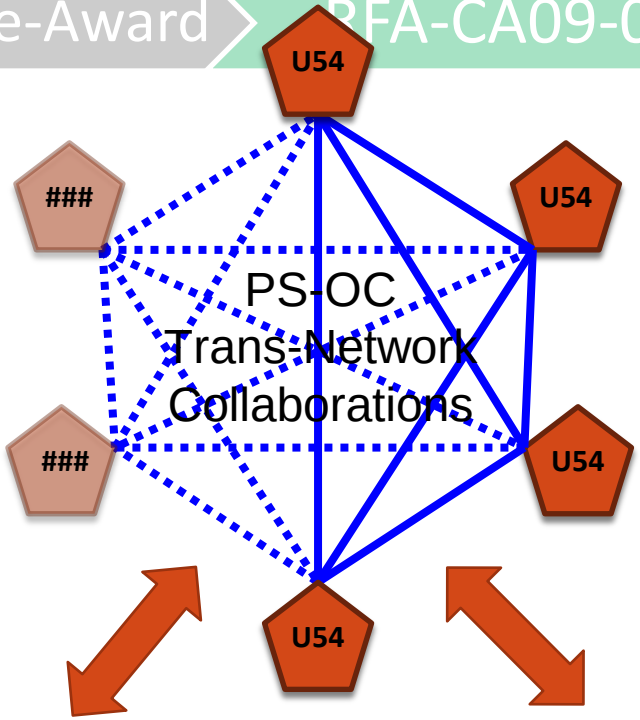
Proposed PS-OC PAR Program FY'14-FY'16:

Organization and Process

PHYSICAL SCIENCES in ONCOLOGY

FY09 ★**FY14** **FY16**

Pre-Award | RFA-CA09-009 | **PS-OC Network PAR** | Future



NCI Staff

CCT CRCHD DCB

DCCPS DCP DCTD

OPSO ··· (project scientists)

Scientific Focus Group

Outstanding (physician)scientists to help advise/guide the program.

Issuances of PS-OC Program (PAR)

- 2 Themes (suggested):
  - The Physical Dynamics of Cancer
  - Spatial Organization and Cancer
- Competitive Direct [illegible]
- U54 Mechanism up to $1.5M (DC)/year – center (5 years max.)
  - 2-3 Projects/Center
  - Education/Training Unit
  - Pilot/Trans-Network Projects
- Two receipt dates per year for 3 years, except FY'14 having only one receipt date

"Bring the physics, not just the physicist, to biology"…oncology

OPSO Team

PHYSICAL SCIENCES in ONCOLOGY

Mariam Eljanne, PhD
Project Manager

Michael G. Espey, PhD
Project Manager

Jonathan Franca-Koh, PhD
Project Manager

Sean E. Hanlon, PhD
Project Manager

Nastaran Z. Kuhn, PhD
Project Manager

Nicole M. Moore, ScD
Project Manager

Teresa K. Schuessler, MS
Health Communications Fellow

Katrina I. Theisz, MS
Operations Coordinator

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Thanks!
Questions?

Backup Slides

NCI-OPSO/NSF-ENG & MPS Joint Collaborations:

PHYSICAL SCIENCES in ONCOLOGY

Physical and LIfe Sciences Early Research (PLIER) Awards

Physical and Engineering Sciences in Oncology (PESO)

PROGRAM ANNOUNCEMENT
NSF 12-514

National Science Foundation

Directorate for Engineering **(ENG)**
- Division of Civil, Mechanical and Manufacturing Innovation
- Division of Electrical, Communications and Cyber Systems
- Division of Chemical, Bioengineering, Environmental, and Transport Systems

Directorate for Mathematical & Physical Sciences **(MPS)**
- Division of Materials Research

National Cancer Institute

	Leverage Funding	*Total Funds*
2011: 6 Awards	*~3:1*	*$2.6 M*
2012: 6 Awards	*>3:1*	*$3.2 M*

NSF-MPS Workshops

November 1-2 2010

Physics of Cancer Metastasis

November 13-14 2012

Theoretical Foundations of Drug and Immune Resistance in Cancer

November 5-6 2013

Physical Principles of Human Cancer Imaging

Cancer Problem: RAS-RAF-MAPK pathway is abnormally activated many cancers

PHYSICAL SCIENCES in ONCOLOGY

How does the spatial organization of signaling pathways modulate function?

Traditional View:

Immunoprecipitation and crystalography experiments suggest a role for multimerization of RAF in activation of the pathway

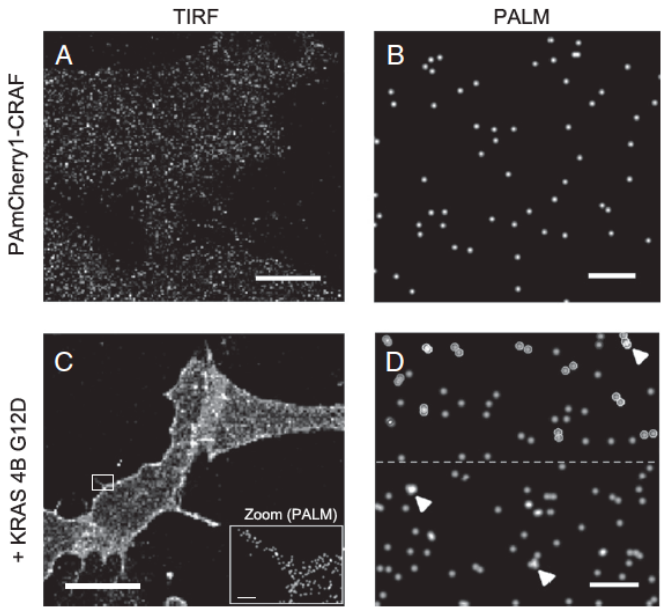
The degree and location of multimerization are currently unknown.

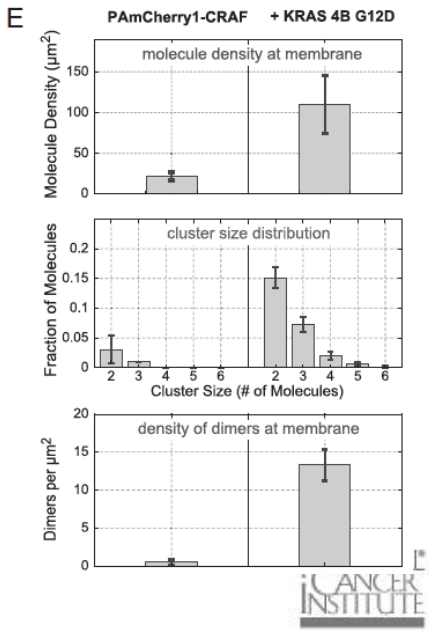
Additional Physical Science Perspective:

PALM and spatial analysis techniques allow high precision spatial and stoichiometric analysis of single molecules in intact cells.

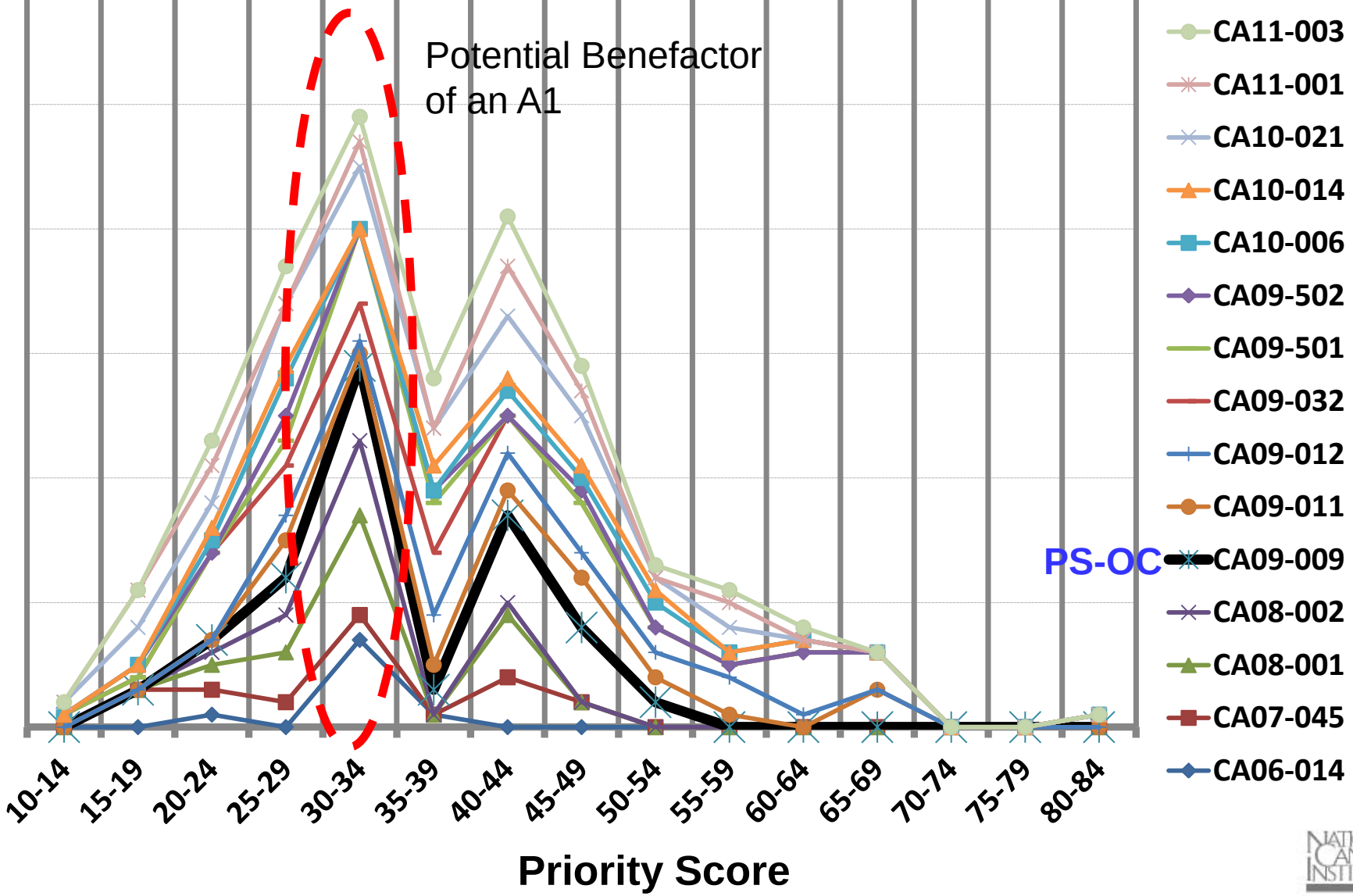
Show that CRAF forms dimers and multimers at the cell surface under activating conditions.

Xiaolin Nan/Steve Chu and Frank McCormick Stanford PS-OC – Photoactivated localization microscopy (PALM) combined with computer simulations and spatial analysis techniques allows high precision protein localization and stoichiometric analysis through directly visualization of CRAF multimers under activating conditions.





Bimodal Distribution: U54 Mechanisms



APHELION – A Study by the World Technology Evaluation Center (WTEC)

- **APHELION**: Assessment of Physical Sciences and Engineering Advances in Life Sciences and Oncology
- **Goal**: To determine the status and trends of research and development whereby physical sciences and engineering principles are being applied to cancer research, oncology, and other biomedical research areas in leading laboratories and organizations via an on-site peer review process in Europe and Asia.

http://www.wtec.org/aphelion

APHELION - Distinguished Panelists and Advisors

PHYSICAL SCIENCES in ONCOLOGY

Expert panel

- Chair: Paul Janmey, UPenn
- Dan Fletcher, UCB
- Sharon Gerecht, JHU
- Parag Mallick, Stanford
- Owen McCarty, OHSU
- Lance Munn, Harvard
- Cindy Reinhart-King, Cornell

Advisors

- Tito Fojo, NCI
- Denis Wirtz, JHU


Paul

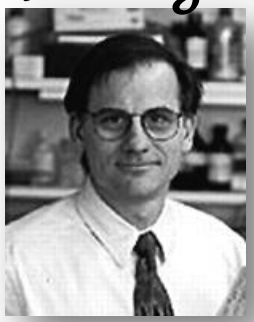

Dan


Sharon


Parag


Owen


Lance


Cindy


Denis

APHELION

http://www.wtec.org/aphelion

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APHELION Europe Sites (25) Visited

http://wtec.org/aphelion/index.php

PHYSICAL SCIENCES in ONCOLOGY

FRANCE
- Institute Curie, Paris
- University of Paris Diderot

GERMANY
- Dresden Technical University
- Gottingen University
- Max Planck Institute (Dresden, Gottingen)
- Technical University of Munich
- University of Heidelberg
- University of Leipzig
- University of Rostock

ISRAEL
- Technion University
- Weizmann Institute

ITALY
- European Institute of Oncology
- University of Milan
- University of Padua

SWEDEN
- The Karolinksa Institute
- The Royal Institute of Technology
- Uppsala University

The NETHERLANDS
- Hubrecht Institute, Utrecht
- Radboud University Nijmegen
- The University of Leiden

SPAIN
- University of Barcelona
- University of Basque Country

SWITZERLAND
- Ecole Polytechnique Federal de Lausanne (EPFL)
- University of Basel

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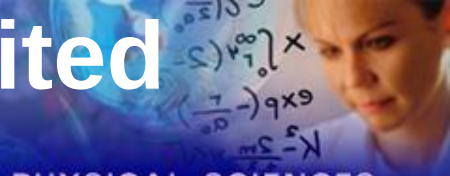
APHELION Asia Sites (20) Visited

http://wtec.org/aphelion/index.php



CHINA

- East China University of Science and Technology
- Beijing Tumor Hospital
- Beijing University Medical Center
- Center for Theoretical Biology, Peking University
- Department of Biomedical Engineering, Peking University
- Institute of Physics, CAS

HONG KONG

- Centre for Cancer Research, University of Hong Kong
- Center for Quantitative Systems, Hong Kong Baptist University
- Institute for Computational and Theoretical Studies

JAPAN

- Center for Developmental Biology, RIKEN
- Center for iPS Cell Research and Application, Kyoto University
- Immunology Frontier Research Center, Osaka University
- Laboratory for Cellular Systems Modeling, RIKEN Yokohama
- Laboratory of Bioimaging and Cell Signaling, Kyoto University

SINGAPORE

- Cancer Science Institute, NUS
- Centre for BioImaging Sciences, NUS
- Institute of Molecular Biology, A*Star
- Mechanobiology Institute, NUS
- Nanyang Technological University

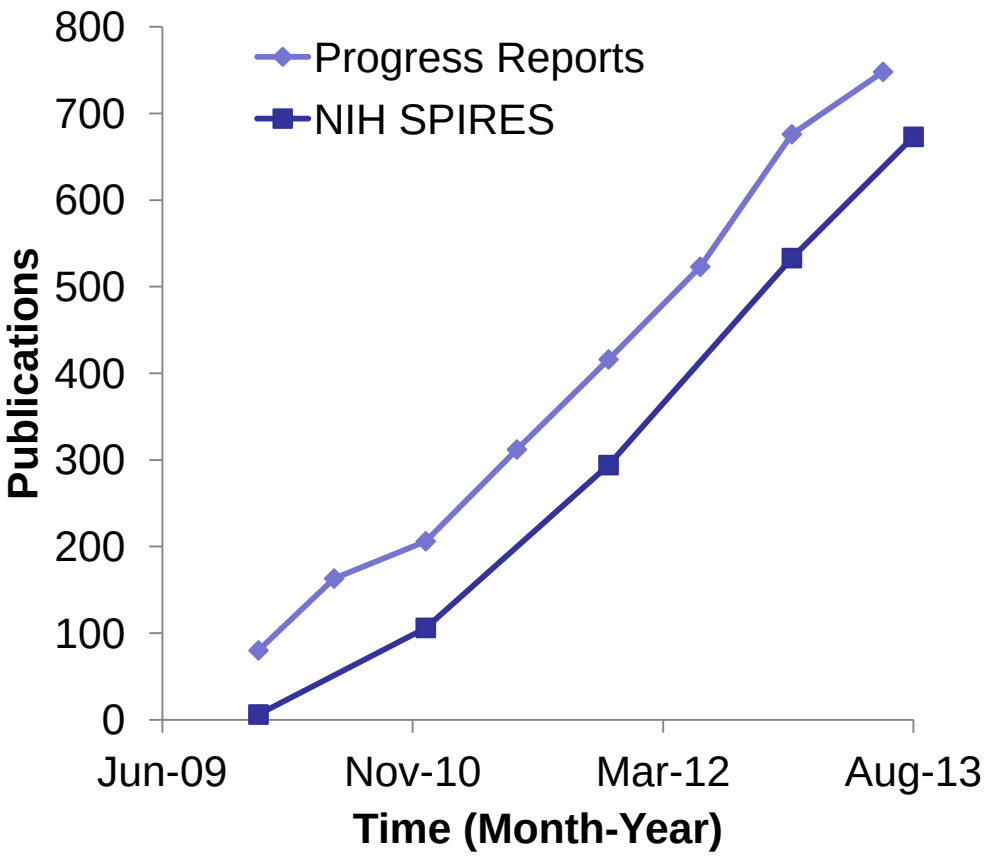
TAIWAN

- Institute of Biological Chemistry, Academia Sinica

Publication Statistics

June 2013

PHYSICAL SCIENCES in ONCOLOGY



Total # of Pubs……..748
Average Impact Factor…….. 9.31
Average first year citations……...6.21
Number of Journals…….. 273

Most Frequent Journals

Journal	# of Pubs	Journal Impact Factor
PNAS	39	9.66
PLoS One	38	4.20
Cancer Research	25	7.90
Physical Biology	24	2.60
Blood	17	10.18
Cell	16	32.33
Nature	16	35.90
Biophysical journal	11	3.86
Nucleic Acids Research	11	7.96
Biomaterials	10	7.45
Nature Biotechnology	10	26.24
Frontiers in Oncology	10	0.00

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Collaborative and Scientific Output

PS-OC Program FY'09 – present:

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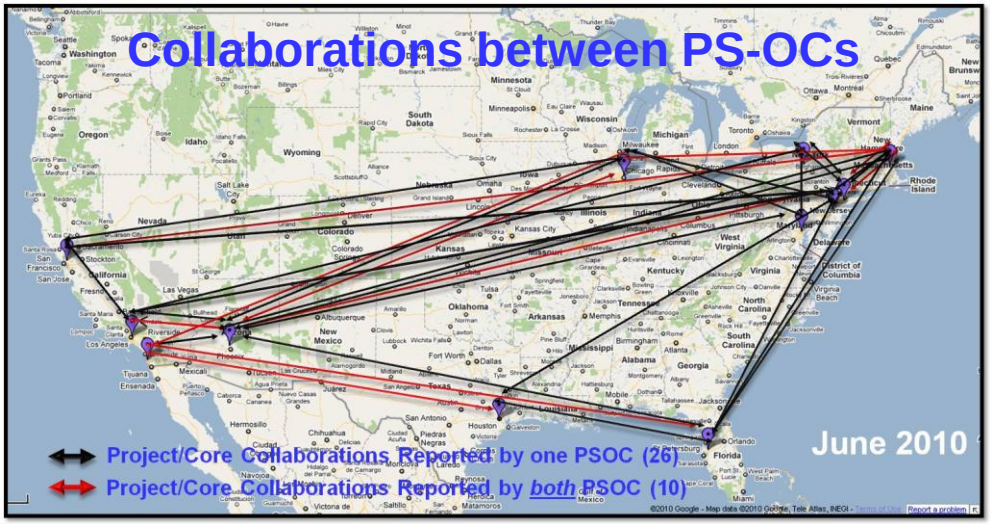
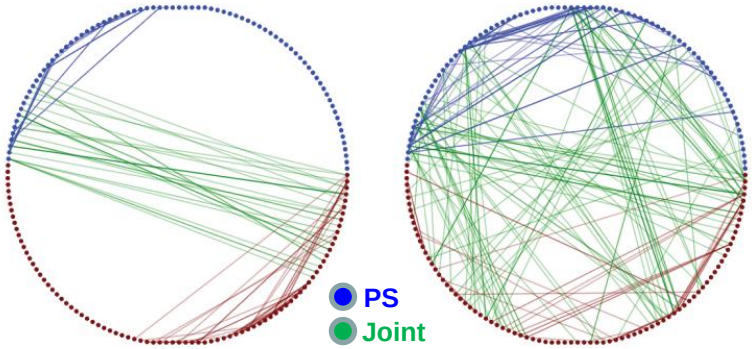
interdisciplinary iTRAQR
TEAM REPORTING, ANALYSIS, AND QUERY RESOURCE



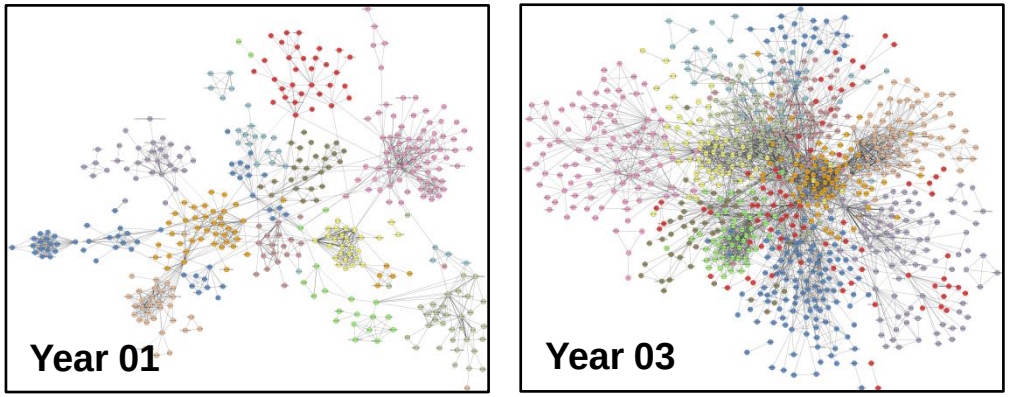
Increase in Transdisciplinary Authorship Compared to Pre-Award Years



Pre-Award 2006-2008

PS-OC Years 2010-2012

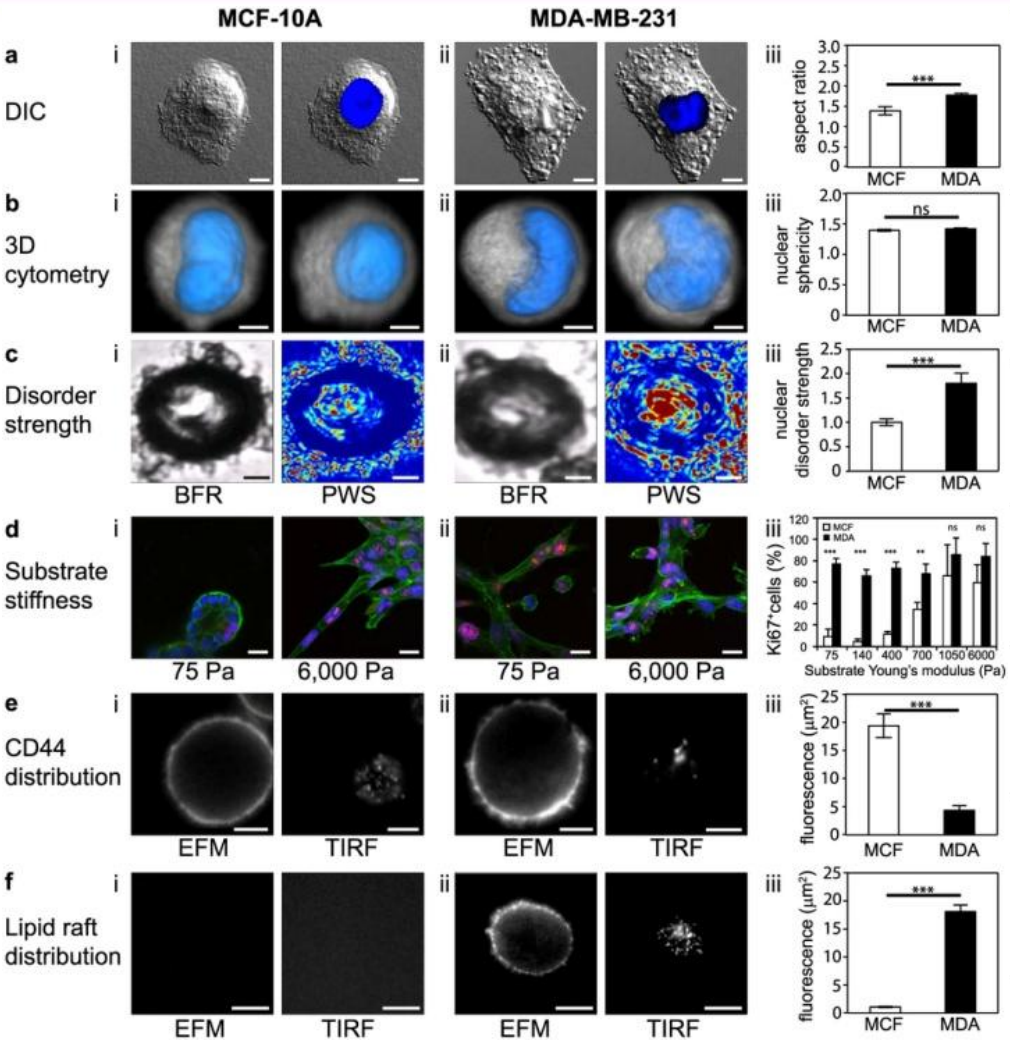
More Than 2-Fold Increase in Interactions* Resulting in a Further Integrated Network

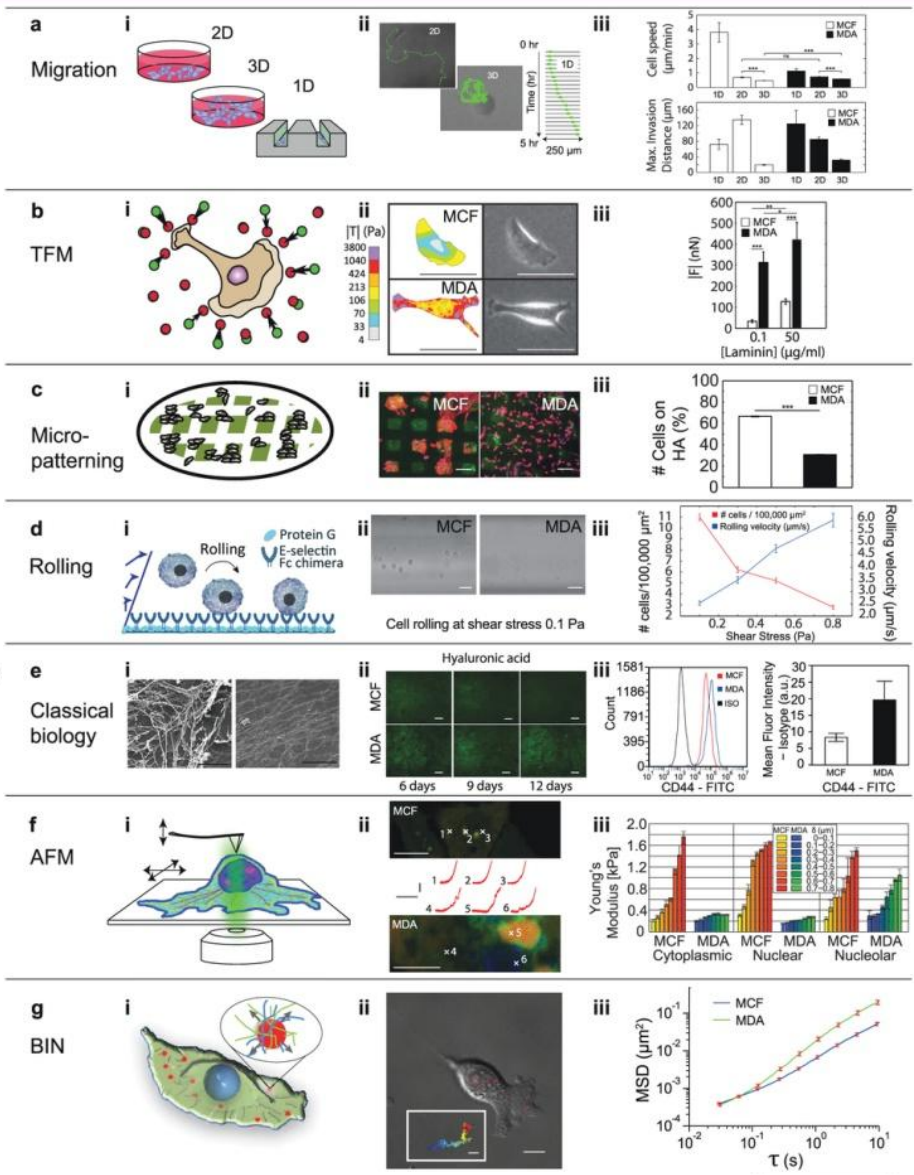


* Interactions (reported by investigators in progress report): joint publication, on-going collaboration (exchange material, students, etc.)

Collective Insights of Physical Science Parameters: "Living Project"

PHYSICAL SCIENCES in ONCOLOGY





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Metabolic Reprogramming to Improve Immunotherapy

Kevin Howcroft
Cancer Immunotherapy and Hematology Branch
Division of Cancer Biology

Dinah Singer
Division of Cancer Biology

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

National Cancer Institute

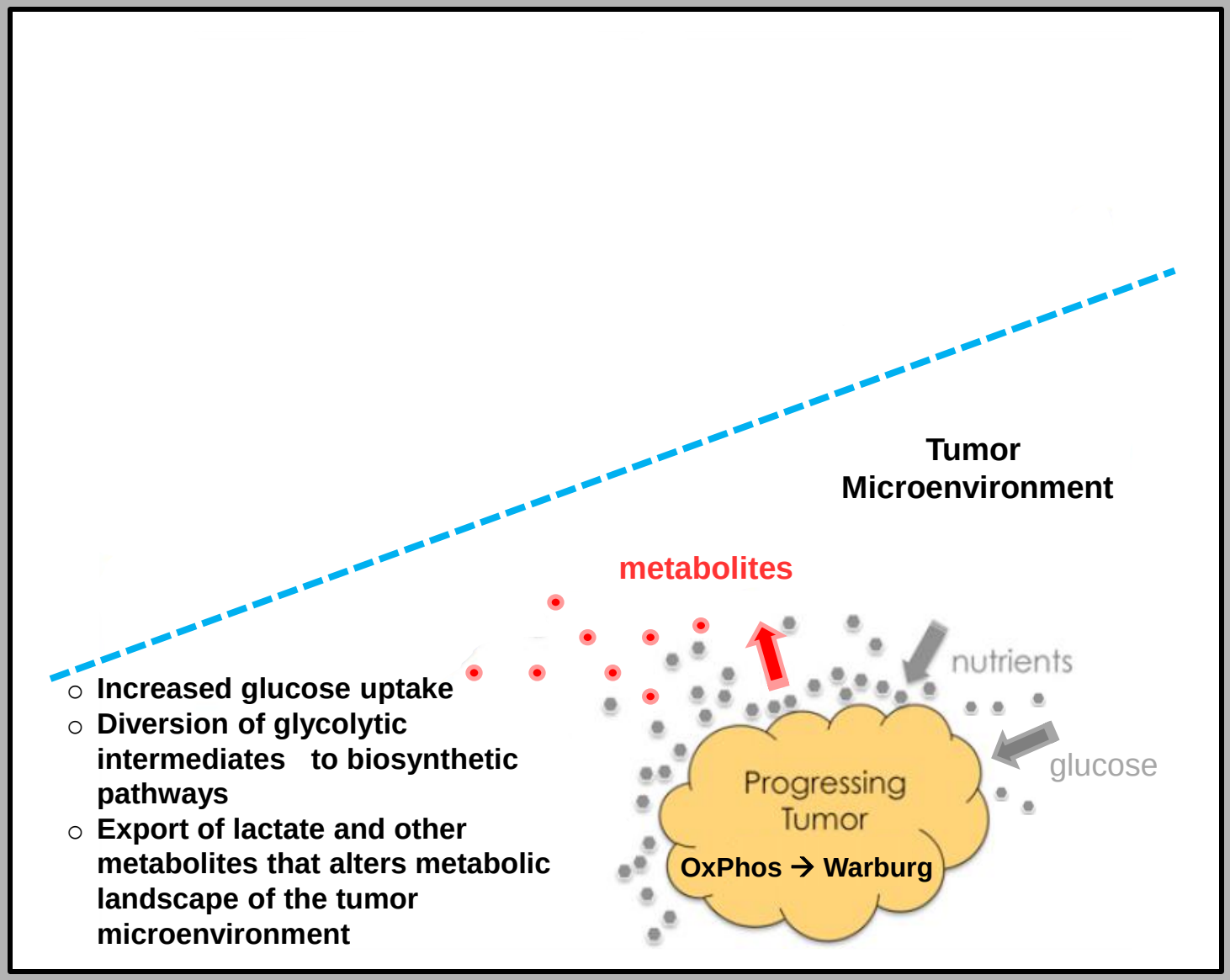
Metabolic Reprogramming to Improve Immunotherapy

The overall goals of this concept are to:

- **generate a mechanistic understanding of the metabolic processes that support robust anti-tumor immune responses *in vivo***
- **determine how the metabolic landscape of the tumor microenvironment affects immune effector functions**
- **use this information to manipulate (or reprogram) the metabolic pathways used by the tumor, the effectors of the immune response, or both to improve cancer immunotherapy**

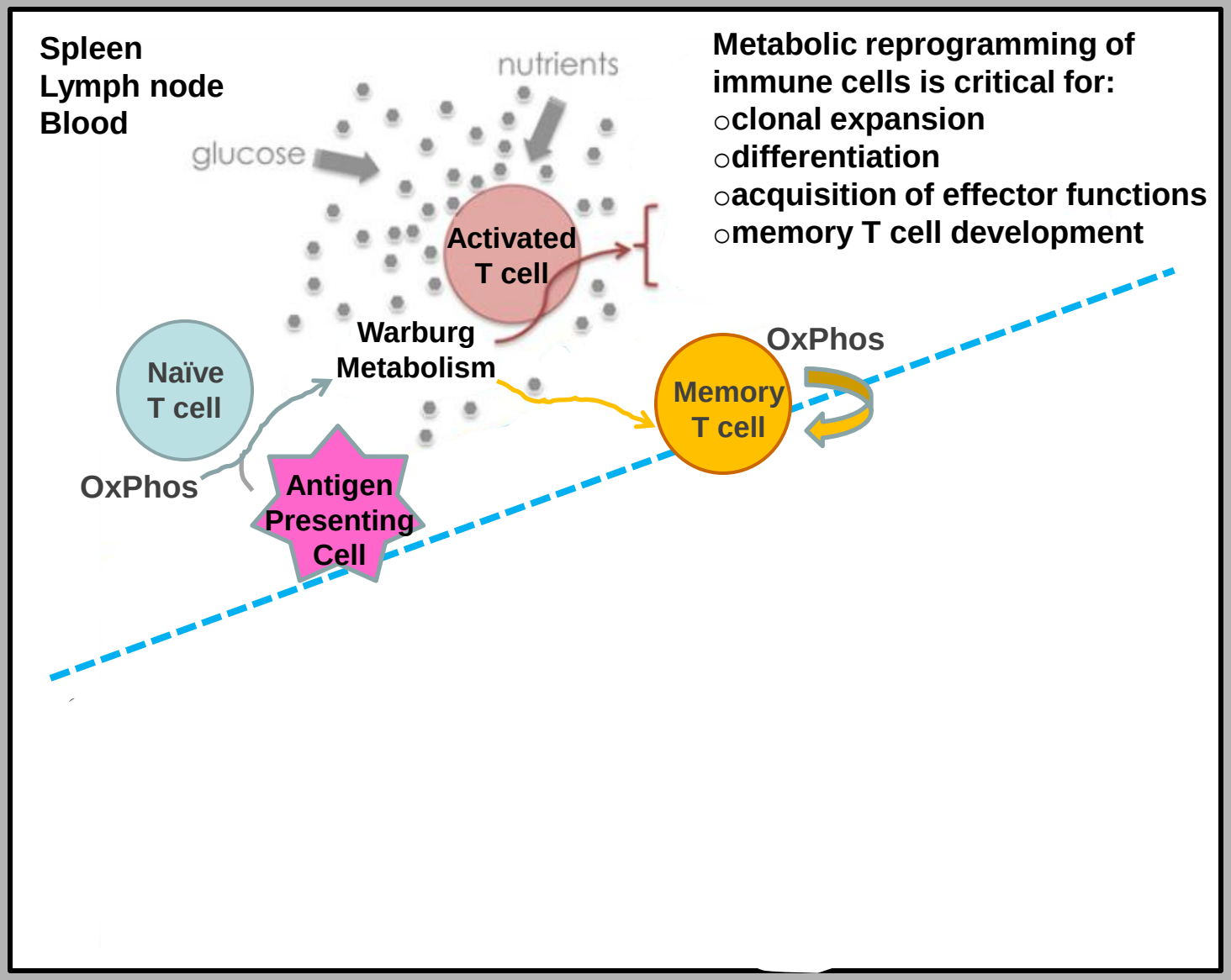
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Cancer Cells Reprogram Metabolism to Support Growth and Survival



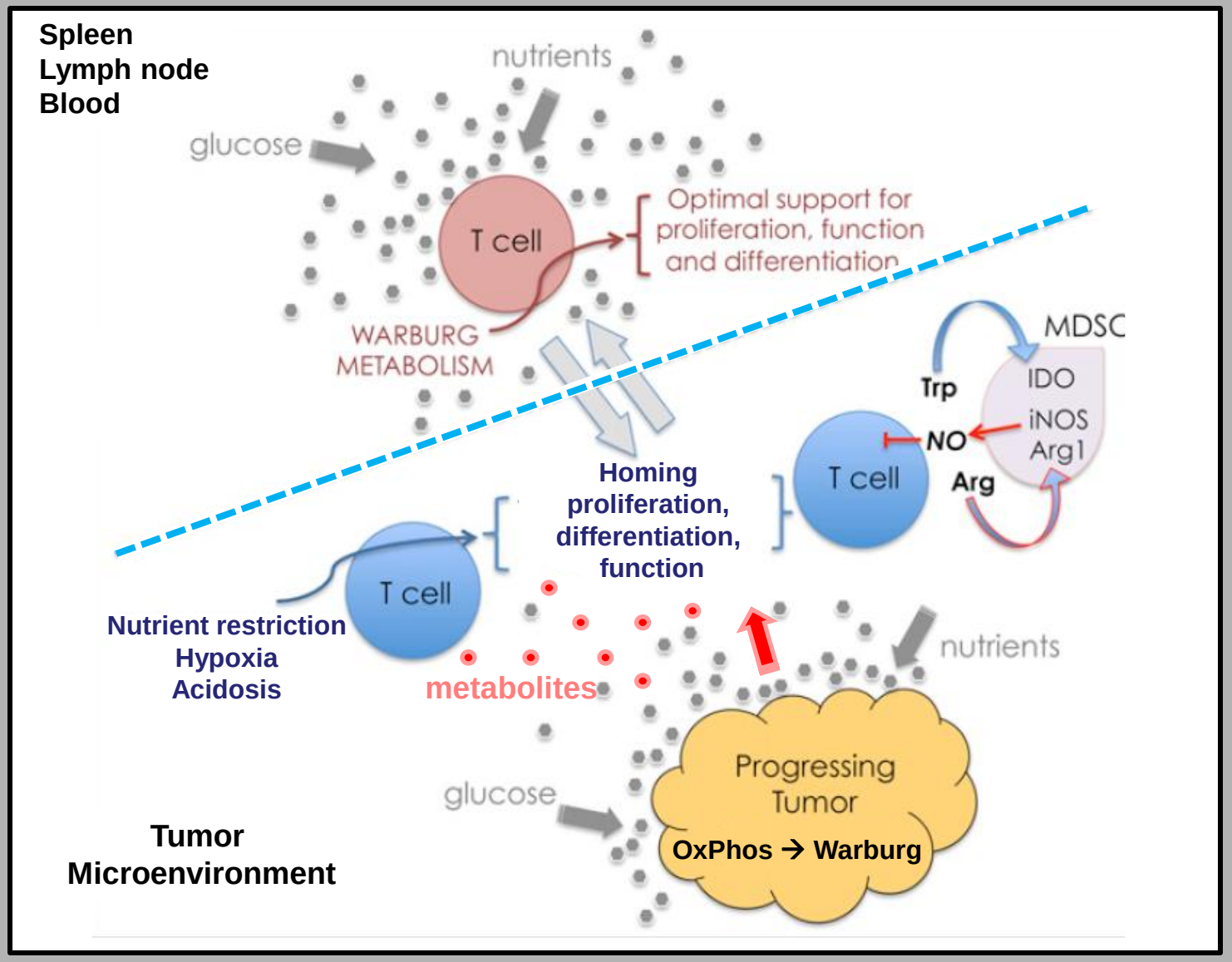
Adapted from Pearce, EL. 2013. Immunity 378: 633-643,

Activated Immune Cells Undergo Metabolic Reprogramming



Adapted from Pearce, EL. 2013. Immunity 378: 633-643,

Tumor Metabolic Landscapes can Regulate Anti-Tumor Immune Function



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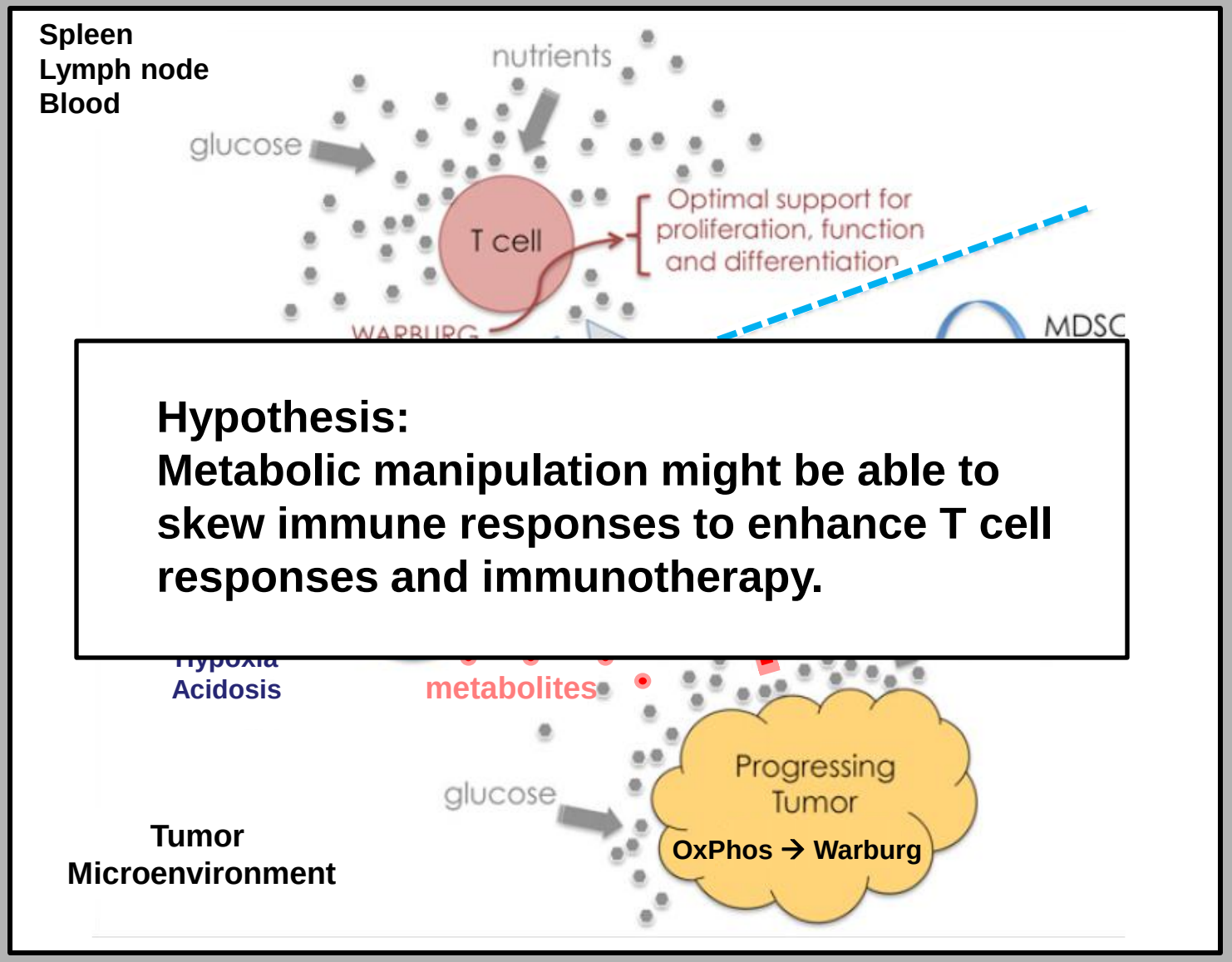
Tumor Metabolic Landscapes can Regulate Anti-Tumor Immune Function



Adapted from Pearce, EL. 2013. Immunity 378: 633-643,

Address Knowledge Gap and Path Forward

Overarching Directions for Future Studies:

a) **Approaches to reprogram the metabolism of anti-tumor immune cells (either *ex vivo* or *in vivo*) to improve immunotherapy (homing, effector function, and/or persistence)**

b) Approaches to target cancer cell metabolism to impair cancer cell survival without compromising anti-tumor immunity.

Path Forward:

- **Catalyze collaborations between tumor immunologists, cancer biologists, computational modelers and tool/technology specialists aimed at developing innovative approaches to utilize metabolic reprogramming to improve cancer immunotherapy.**

Specific Challenges

Examples :

- **How do the metabolic environments in normal tissues, immune tissues, and tumors affect immune cell development and/or effector function?**
- **How do specific metabolites affect various immune states such as activation, anergy, development of long-lived memory cells versus short-lived effector cells, and homing to their proper niche?**
- **Do metabolites act as signaling molecules in transcription that effect cellular differentiation?**

Implementation Plan

Goal: Encourage new collaborations focused on tumor immunometabolism

Mechanism:

- **Supplement existing NCI funded grants to support collaborative research projects through revision applications (formerly called competing supplements).**

Funding Opportunity:

- **PAR with no budget set-aside.**
- **Standard Receipt Dates; beginning March, 2014.**
- **Active in FY15 - FY18.**

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Examples of Collaborations

- A cancer biologist with an existing NCI RO1 focused on cancer cell metabolism could form a collaboration with a tumor immunologist and a systems biologist to develop computational models of metabolic interactions
- A tumor immunologist with an existing NCI RO1 focused on metabolic events associated with activated T cells could form a collaboration with a cancer biologist studying metabolism and with an in vivo imager to study homing.

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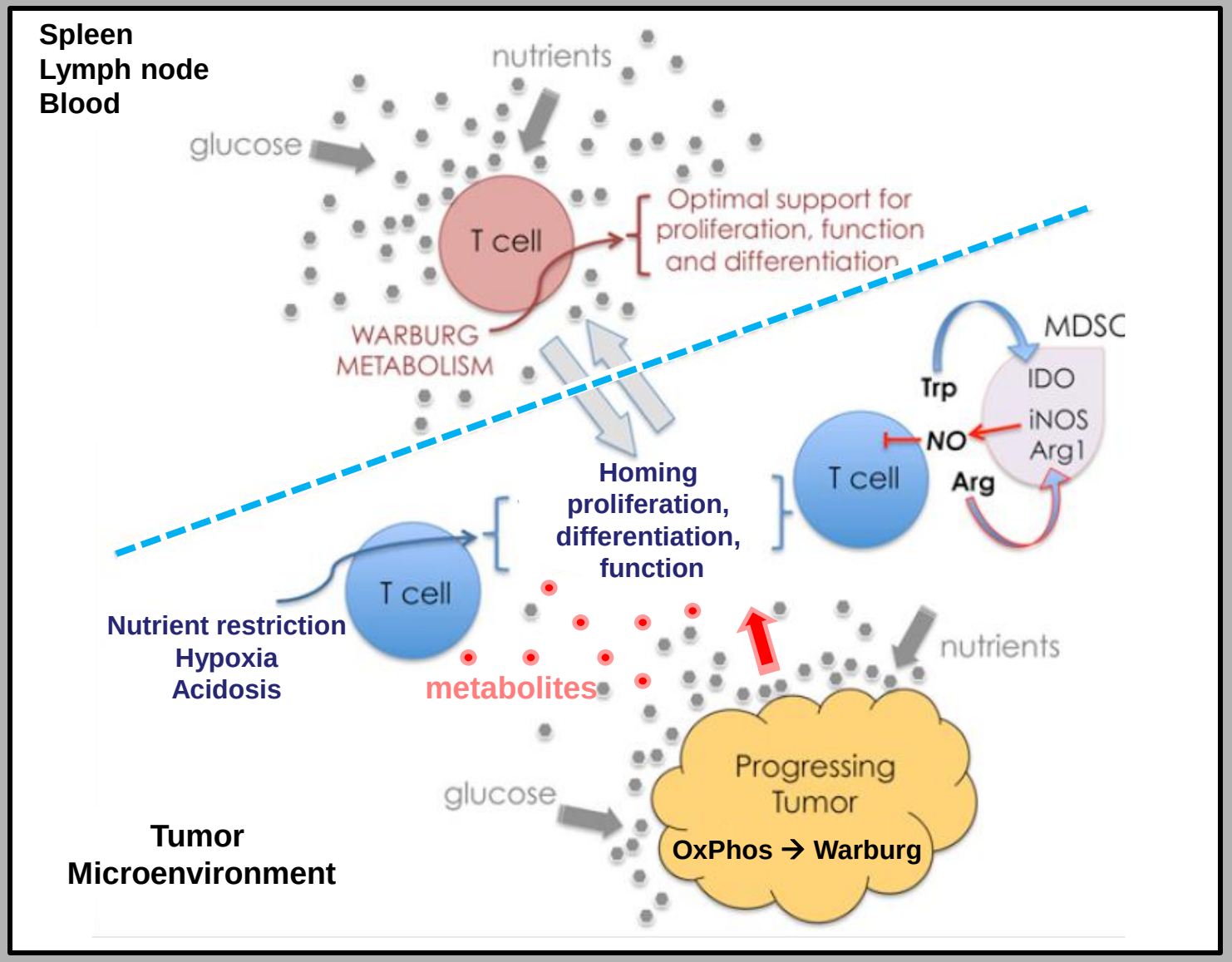
Collaboration Criteria

- Must propose cross-disciplinary research involving cancer biologists and immunologists aimed at complementary areas of metabolic research and, if justified, a metabolomics, computational tools, or imaging component.
- May support up to three collaborating groups, including the PI of the parent grant
- Must be complementary to the parent grant
- Must have a minimum of two years remaining on the parent grant at the time of award

Tumor Metabolic Landscapes can Regulate Anti-Tumor Immune Function



Questions?

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Portfolio Analysis

Searching the NIH Reporter for applications that cross reference the terms immunotherapy, metabolism, and cancer netted only five applications that would minimally meet the outlines of this FOA - only one R21 specifically included metabolic reprogramming of immune cell populations to improve immunotherapy.

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NCI/DCB Activities to Promote Research Collaborations (APRC) 1998-2010

- **The APRC program supported new interdisciplinary collaborations to bridge disparate fields and expand the pool of scientists working in cancer research.**
- **The APRC provided administrative supplements to support 2-3 collaborating units (from complementary fields) focused on achieving specific research objectives by pooling their respective expertise and efforts.**
- **Funding decisions were made rapidly, allowing collaborations to initiate quickly.**
- **The annual allocation to DCB for the program was $1-1.5M. Over the years, it funded 437 collaborations, with a peak in 2004 of 85 consortia.**
- **An independent evaluation after the conclusion of the APRC assessed its success. Among the conclusions: " Most impressive, the majority of the investigators thought that they could not have accomplished their work without APRC funding."**