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

52nd Meeting

BOARD OF SCIENTIFIC ADVISORS

Minutes of Meeting

November 5, 2012
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 5, 2012

The Board of Scientific Advisors (BSA), National Cancer Institute (NCI), convened for its 52nd meeting on Monday, 5 November 2012, 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 3:05 p.m. on 5 November for the NCI Director's report; an overview of the Frederick National Laboratory for Cancer Research (FNLCR); a status report on the Provocative Questions Initiative; an update on the large-scale cancer genomics projects: The Cancer Genome Atlas (TCGA) and Therapeutically Applicable Research to Generate Effective Treatments (TARGET); consideration of three requests for applications (RFA) and Cooperative Agreements (Coop. Agr.) reissuance concepts; and, a report on a new U.S. Food and Drug Administration (FDA)−NIH RFA/Coop. Agr. on research relevant to the Family Smoking Prevention and Tobacco Control Act.

BSA Board Members Present:

Dr. Todd R. Golub (Chair)
Dr. Francis Ali-Osman
Dr. Ethan Basch
Dr. Arul M. Chinnaiyan
Dr. Curt I. Civin
Dr. Graham Colditz
Dr. Chi V. Dang
Dr. Robert B. Diasio
Dr. Daniel DiMaio
Dr. Jeffrey A. Drebin
Dr. Brian J. Druker
Dr. Karen M. Emmons
Dr. Betty R. Ferrell
Dr. Kathleen M. Foley
Dr. Stanton L. Gerson
Dr. Joe W. Gray
Dr. Chanita Hughes-Halbert
Dr. Joshua LaBaer
Dr. Theodore S. Lawrence
Dr. Maria E. Martinez
Dr. Luis F. Parada
Dr. Martine F. Roussel (Sherr)
Dr. Kevin M. Shannon
Dr. Mary L. Smith
Dr. Lincoln Stein
Dr. Bruce W. Stillman
Dr. Louise C. Strong
Dr. Gregory L. Verdine
Dr. Cheryl L. Walker
Dr. Irving L. Weissman

Board Members Absent:

Dr. Sangeeta N. Bhatia
Dr. Andrea Califano
Mr. Don Listwin
Dr. Frank M. Torti

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 REMARKS - DR. TODD R. GOLUB

Dr. Todd R. Golub called to order the 52nd regular meeting of the BSA and welcomed current and new members of the Board, NIH and NCI staff, guests, and members of the public. Dr. Golub 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 minutes from the 25 June 2012, 1st Joint Meeting of the BSA and the National Cancer Advisory Board (NCAB), have been approved.

II. REPORT OF THE DIRECTOR, NCI - DR. HAROLD VARMUS

Dr. Harold Varmus, Director, NCI, welcomed members and other attendees. Dr. Varmus expressed sadness at the passing of former congressman, The Honorable Arlen Specter of Pennsylvania. For approximately 20 years, Mr. Specter was the ranking Republican on the U.S. House Appropriations Committee, and through his advocacy was able to provide and maintain notable support for the Nation's cancer research enterprise.

Personnel Actions: Dr. Varmus informed members that the NCI's recruitment for: 1) the Director of the Division of Cancer Epidemiology and Genetics (DCEG) continues, and that Dr. Peggy Tucker continues to serve as Acting Director; and, 2) permanent Directors of the Center for Cancer Genomics (CCG) and the Center for Biological Informatics and Information Technology (CBIIT). Drs. Robert Hoover and Stephen Chanock are serving as Co-Acting Directors of CCG and Dr. George Komatsoulis continues to serve as the Interim Director for CBIIT. BSA members were asked to forward to him names of potential candidates for these positions.

Budget. Dr. Varmus told members that the NCI will be operating under a continuing resolution (CR) until 31 March 2013. He stated that the NCI had started funding non-competitive renewals at 80% of Fiscal Year (FY) 2012 funding and intended to fund new competitive grants at a reduced rate until the budget is approved. It is expected that the NCI will fund approximately the same number of grants in FY 2013 (1,100), as in FY 2012. Members were reminded the NCI must balance funding for applicants with the highest scores with priorities in the programmatic areas, while also ensuring that young investigators continue to be recruited and encouraged.

Legislative: Dr. Varmus described a proposed congressional legislative initiative (Recalcitrant Cancer Research Act of 2012 (H.R. 733, S. 362, S. 3566 / 112th Congress) that addresses "recalcitrant cancers," such as

pancreatic and lung cancers. He noted that 1) this new legislation may require the NCI to conduct specific studies on certain cancers, 2) it has passed the House of Representatives, and, 3) it is currently in the Senate. Dr. Varmus added that the NCI's successful approach to categories of cancer has been toward improving the understanding of the cancer cell of origin, the nature of the cancer, and the genotype. Cancer is not one disease, and even specific cancers, such as pancreatic or lung, have heterogeneity of type.

Recent Travels: In a brief overview of his recent travels, Dr. Varmus told members that he had traveled to Kansas City, KS, to celebrate the opening of a new Cancer Center at the University of Kansas. Internationally, he had traveled to countries interested in cooperating with the new Centers for Global Health. He noted that while in Indonesia, he had met with health scientists and officials to discuss smoking cessation programs, and during his visit to Mexico, he helped launch their new National Cancer Plan.

Workshops. Dr. Varmus informed members of several recent and planned workshops. Specifically, he reported on a: 1) data replication workshop held in September 2012 to address the problem of failing to replicate studies that have been published in high-impact, peer-reviewed journals. He noted that the pressure to publish, especially in high-impact journals, has not always produced the high-quality science that must be expected from the Nation's research enterprise. One suggestion involved using a checklist to raise the standards of published research; 2) workshop focused on the Institute of Medicine's *Toward Precision Medicine* report that reviewed the study of exceptional cancer cases, which are characterized by unusual phenotypes that result in variable responses to drugs. A genotype component also is included in this approach to facilitate the targeting of drugs during treatment. The NCI is working with the pharmaceutical industry to better understand why some patients respond to specific therapies and others do not; and, 3) workshop that resulted from a review of NCI's pancreatic cancer research and identifies new possibilities in assessing risk, developing better methods for pathophysiology, and new therapeutic opportunities. Dr. Varmus noted that Dr. James Doroshow would provide additional details about this last workshop.

Dr. Douglas Lowy, Deputy Director, informed members that: 1) the reorganization of the Community Clinical Oncology Program (CCOPs) and the NCI Community Cancer Centers Program (NCCCP) was proceeding. Dr. Lowy told members that one goal was to bring together groups to increase capacity for cancer care delivery research. After input from NCI Divisions, a new program, the NCI Community Oncology Research Program (NCORP), is being proposed within the Division of Cancer Prevention (DCP) with Dr. Worta McCaskill-Stevens (DCP) selected as Director and Dr. Steven Clauser (Division of Cancer Control and Population Sciences (DCCPS)) as the Associate Director. The proposed program will be presented at a future BSA meeting; and, 2) the President's Cancer Panel (PCP) had held a series of workshops focused on the human papillomavirus (HPV) vaccine, precipitated by the low participation in the vaccine program in the United States. Approximately one in three girls aged 13-17 has been vaccinated, as opposed to much higher rates in other Western countries. The initial two workshops focused on epidemiology, practice standards, and economic impacts, and in April 2013, the final workshop will focus on challenges for global HPV vaccination, including cervical cancer screening. There is general agreement that there is a critical need for additional safety data on HPV vaccines.

Dr. James Doroshow, Deputy Director for Clinical and Translational Research, provided an update on the Pancreatic Cancer Workshop held in mid-October 2012. Dr. Doroshow informed members that the workshop focused on three aspects of pancreatic cancer: risk assessment, cysts on the pancreas that can progress to cancer, and familial pancreatic cancer. Another topic covered in the workshop was therapeutics using small molecules for immunotherapy for pancreatic cancer carcinoma and to develop new agents that target *ras* mutations.

In the discussion, the following points were made:

< The NCI should take a leadership role in influencing attitudes and behavior regarding publication in high-impact journals and emphasizing an investigator's contributions to the research and the rigor of the science.

< Increasing coverage of HPV vaccinations for females and males will have a significant effect on worldwide cancer rates, not just in cervical cancer, but in other cancers as well. Although more than 90 percent of HPV-associated cancers in the developing world are of the cervix, HPV is also associated with oropharyngeal cancer, and may be associated with other cancers.

III. OVERVIEW: THE NEWLY ESTABLISHED FNLCR - DR. DAVID C. HEIMBROOK

In an overview of the Frederick National Laboratory for Cancer Research (FNLCR), Dr. David C. Heimbrook, CEO, SAIC-Frederick (SAIC-F), Inc., told members that the FNLCR has developed partnership activities in support of NCI's extramural programs and the broader extramural community. Dr. Heimbrook indicated that a unique combination of scientific expertise and operational capability supportive of all aspects of applied biology and translational medicine had been utilized. The FNLCR also has the capability to integrate with various government agencies, the extramural community, and industry partners, with a focus on technologies and clinical assays to support those in the research community.

The FNLCR includes the Nanotechnology Characterization Laboratory (NCL), which was established in 2004 as an interagency collaboration among the NCI, FDA, and National Institute of Standards and Technology (NIST). The NCL performs a variety of preclinical characterizations of nanomaterials, including physicochemical characterization, safety and *in vitro* studies, and *in vivo* characterization. Approximately 90 percent of the NCL's efforts support the extramural community, with more than 70 collaborations with a variety of biotechnology companies. One of the most promising areas for the use of nanoparticles/nanomaterials is in repurposing previously approved cancer therapeutics that were discontinued due to high levels of toxicity, such as liposome encapsulated drugs.

Another area that the FNLCR supports is the NCI Experimental Therapeutics (NExT) Program in collaboration with the Division of Cancer Treatment and Diagnosis (DCTD) to create a coordinated cancer therapeutics discovery and development pipeline with the external scientific community. The SAIC-F provides operational and technical support to all phases of the NExT program, including the Molecular Characterization Lab, Clinical Assay Development Program, and the Biopharmaceutical Development Program (BDP). One example of clinical success is the production of the monoclonal antibody ch14.18 with BDP resources. After positive results were reported from a Phase 3 neuroblastoma clinical trial conducted by the Children's Oncology Group, a commercial vendor was found and the drug development process was transferred to them. Similar support is being provided for assay development that is used by the wider research community in clinical trials.

For guiding and monitoring future activities at the FNLCR, the NCI-Frederick Advisory Committee (NFAC) was established, and has met three times in the past 12 months. The NFAC, chaired by Dr. Zachary Hall, President Emeritus, Institute of Regenerative Medicine, University of California, San Francisco, is charged with reviewing the overall research program and making recommendations for the best use of the FNLCR's infrastructure and capabilities. Dr. Heimbrook reviewed the NFAC Cooperative Research and Development Agreement (CRADA) policy that resulted in establishing a contractor-CRADA (cCRADA) mechanism that enables SAIC-F scientists to partner directly with extramural scientists and protects intellectual property rights. Technical Service Agreements (TSAs) that provide access to assays developed by FNLCR have also been developed to increase collaborations with the external research community. Another function of the FNLCR is the Strategic Decision Initiative for the identification and implementation of a "Big Ideas" research approach that is intended to fulfill the "National Laboratory" vision of the NCI for the FNLCR.

Dr. Varmus informed members that the "Big Idea" approach is critical to the future of NCI-supported research through the FNLCR. Three large projects discussed among the NCI leadership include: 1) a megaproject to increase the understanding of treating tumors with *ras* mutations; 2) a target validation effort that envisions comparing the use of genetically altered animals and patient-derived xenographs for preclinical drug testing; and, 3) the building of bioinformatics platforms to integrate clinical and genomic data in an effective manner that meets standards for adequate collection and storage. Other big projects have been suggested and will be considered by the NCI leadership in the future.

In the discussion, the following points were made:

< The NCI sets cancer research priorities for the FNLCR, and the National Institute of Allergy and Infectious Diseases (NIAID) sets priorities for its collaboration.

< The FNLCR maintains informal collaborations with NIH's National Center for Advancing Translational Sciences (NCATS) for drug development, and approximately 85 percent of NCATS is Clinical Translational

Science Awards (CTSA). The NCI is discussing the relationship between NCATS and the NCI-designated Cancer Centers.

< The cCRADA mechanism has been created to allow partners to bring funds to the FNLCR for the use of technologies and resources in kind. A critical component of enticing external groups to participate in the cCRADA mechanism is rapid turnaround time.

IV. STATUS REPORT: PROVOCATIVE QUESTIONS INITITATIVE—DR. ED HARLOW

Dr. Ed Harlow, Special Advisor to the NCI Director, reminded members that the Provocative Questions Initiative (PQI) was established to identify compelling research questions in new or understudied areas and to fund those initiatives likely to move forward various fields of science. Dr. Harlow noted the challenge of developing important research questions, especially in unappreciated and/or understudied research areas.

Dr. Harlow informed members that the BSA approved a three year trial of the PQI. He noted that the first RFA published in 2011 was funded at $22 M for R01s and R21s addressing 24 provocative questions, of which 57 of 738 reviewed applications were funded. The four questions with the smallest number of submissions did not have funded applications. For the 2012 RFA, $30 M has been set aside to fund 24 questions, which includes 7 previous, 8 rewritten, and 9 new questions. The questions were developed through a rigorous process of workshops in the community and online submissions. An NCI Editorial Board composed of intramural and extramural staff was used to refine the 556 submitted questions to 14 new questions, which were then reviewed and combined with the 2011 questions. Dr. Harlow reviewed the questions chosen by the NCI Scientific Program Leaders for the four RFAs in: (1) prevention and risk; (2) mechanisms of tumor development and recurrence; (3) detection, diagnosis, and prognosis; and (4) therapy and outcomes.

Dr. Harlow described possible future directions for the PQI. He noted that increased attention should be provided to the PQI process and development of the RFAs, with improvements in the process for increasing critical thinking on the question subjects. More NCI Division input and involvement are needed to develop other important provocative questions in a variety of research areas. In addition, the PQI website should be maintained as a place to hear from a broad range of researchers.

In the discussion, the following points were made:

< It is expected that awarded applications would continue the research beyond PQI funding, possibly utilizing other funding mechanisms.

< Most of the successful applications were from experienced investigators who expanded their research from their currently funded research area to address PQI questions.

< A member encouraged NCI to bring together groups of researchers within the same topic area (e.g., obesity) who were funded for a PQI. Dr. Varmus suggested that this could be accomplished through Internet chat rooms or via another Web-based platform.

V. UPDATE ON LARGE-SCALE CANCER GENOMICS: TCGA AND TARGET—DR. BARBARA WOLD

Dr. Barbara Wold, Bren Professor of Molecular Biology, California Institute of Technology, Pasadena, CA, provided a brief review and update on large-scale cancer genomics focused on TCGA and TARGET. Genomic signatures are broad, but specific to certain cancers because cancer is predominantly a genomic disease. TCGA and TARGET both focus on discovery science, with TCGA focused on adult cancers from patients with no prior treatment, and TARGET focused on pediatric cancers in selected poor outcome tumors. The Cancer Target and Drug Discovery (CTD^2) program is the drug discovery and pathway function component of NCI's treatment program, with development of DNA-based diagnostics as a parallel research avenue following discovery in TCGA and TARGET. The TCGA program will approach a cost of $1 B when it concludes in 2014, with 40 percent funded through the American Recovery and Reinvestment Act of 2009 (ARRA). TARGET is a smaller program, with total funding of approximately $20 M with 80 percent allocated from ARRA funds. CTD^2 is

expected to have total funding of $60 M when it is completed in 2017.

Dr. Wold reviewed the goals of TCGA and TARGET. She stated that TCGA's uniqueness lies in its compilation of massive amounts of data from all existing platforms for 25 different tumor types into one accessible data center that becomes the starting point for the TCGA pipeline. One rate-limiting aspect for TCGA is collecting high-quality, frozen samples, which is the first step in the pipeline and determines the quality of the data produced. TCGA's goal of securing 500 quality samples for each tumor type has been met for a few tumor types, but progress has slowed on less common tumor types.

Members were told that researchers are encouraged to use TCGA data for their research pre-publication, although TCGA investigators have first publication rights for the data. A comprehensive publication policy has been developed to guide TCGA and outside researchers. The TCGA data center, CGHub, opened in April 2012. Dr. Wold provided examples for the use of data, including new candidate genes for squamous cell lung cancer, illustrations of driver mutation pathways, and heatmap results showing a comparison of somatic copy number alterations between serous-like uterine endometrial, serous ovarian, and basal breast tumors.

Dr. Wold reported on TARGET and the use of whole-genome sequencing in pediatric cancers. Members were told that the focus has been on acute lymphoblastic leukemia (ALL), including relapse; acute myeloid leukemia (AML), including relapse; neuroblastoma (stage 4); osteosarcoma; and Wilms tumor (relapsed patients and anaplasia). TARGET has collected 100−200 cases per tumor type. Using osteosarcoma as an example, Dr. Wold illustrated that clusters of mutations have been found in osteosarcoma samples that may lead to a better understanding of the mechanisms associated with the cancer.

Members were updated on the Formalin Fixed Paraffin Embedded (FFPE) Project to improve sample collection and storage. Dr. Wold also informed members of major genomics opportunities post-TCGA and post-TARGET regarding the pipelines for clinical samples. She noted that genomics will become further embedded in clinical decision making and treatment, but the need continues for a TCGA-like program to inform basic research, especially for improving predictive modeling. Informatics and analysis are rate limiting steps with joint mining of genomics and electronic health records serving as a core challenge for NCI.

In the discussion, the following points were made:

< Members expressed concern that there has not been a discussion of what is needed for biologic validation of genomic data prior to clinical studies.

< Members encouraged the NCI to support viable, frozen cell suspensions, as some genomic studies of chronic myelogenous leukemia (CML) and AML found additional mutations that were not evident using other types of prepared specimens.

< Information on less common types of cancer from external investigators should be integrated into CGHub for sharing with the entire research community.

< The NCI should ensure that TCGA addresses genomic data on pancreatic cancer, which currently is of great interest to the public.

< The NCI should ensure that the data collected by TCGA is preserved in some form after the conclusion of TCGA in 2014 and allow inclusion of new data, possibly as a centralized "Living Cancer Genome Library."

VI. ONGOING AND NEW BUSINESS - DR. TODD R. GOLUB

Mr. John Czajkowski, Deputy Director for Management and Executive Officer, NCI, informed members of the need to formalize the Center for Cancer Training (CCR) within the organizational chart of the NCI Office of the Director. This change will have no impact on CCR's mission, staffing, or organization.

Motion. A motion to designate the CCR as a formal unit within the organizational chart of the NCI was approved unanimously.

VII. RFA/COOPERATIVE AGREEMENT CONCEPTS - PRESENTED BY NCI PROGRAM STAFF

Division of Cancer Treatment and Diagnosis
NCI Early Experimental Therapeutics Network with Phase 1 Emphasis (RFA/Coop. Agr. Reissuance)

Subcommittee Review. Dr. Brian J. Druker, Director, Associate Dean for Oncology, Oregon Health and Science University, expressed the Subcommittee's enthusiastic support for the NCI Early Experimental Therapeutics Network concept reissuance. Dr. Druker said that the Network allows collaborations among institutions with specific expertise on biomarker identification, pharmacokinetics, and genomics to facilitate enrollment of patients for early therapeutic trials. The concept brings many centers together in the Network to assist the movement of early experimental therapeutic agents through the pipeline. The subcommittee supported future expansion of the program to address issues of patient biology, patient variability, drug transporters, metabolism, DNA repair, outcomes, and mandatory collection of both blood and biopsies.

In the discussion, the following points were made:

< NCI program staff informed members that a large, dispersed network was needed because no individual center could accrue enough patients with an appropriate genomic profile to conduct these therapeutic trials.

< To improve understanding how the tumor type and metastatic sites differ, it is expected that every patient will have at least one mandatory biopsy, either at baseline or at the end of the trial.

< A member requested that a more detailed presentation of the Network be given at a future BSA meeting.

The first year cost is estimated at $10 M for 10 UM1 awards, with a total cost of $50 M for 5 years.

Motion. A motion to concur with the DCTD (RFA/Coop. Agr.) re-issuance concept entitled "NCI Early Experimental Therapeutics Network with Phase 1 Emphasis" was approved unanimously.

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Division of Cancer Treatment and Diagnosis
Collaborative Human Tissue Network (CHTN) (RFA/Coop. Agr. Reissuance)

Subcommittee Review. Dr. Arul M. Chinnaiyan, Director, Michigan Center for Translational Pathology, Professor of Urology, University of Michigan Cancer Center, University of Michigan, Ann Arbor, MI, informed members that the Subcommittee strongly supports the program and unanimously recommends the reissuance. Dr. Chinnaiyan stated that the CHTN provides tissue samples for discovery and translational research for the R01 community. It is not technically a repository but collects specimens in a prospective fashion. He noted that the CHTN serves approximately 400 investigators and collects 40,000 samples annually, and has produced 3,000 publications since the inception of the Network in 1987. Feedback from users of this resource rated it as excellent. In addition, the CHTN's standard operating procedures are available on the Network website, and each Network site has a patient advocate and a board-certified oncologist-pathologist to guarantee that specimens are collected according to current guidelines. Turnaround time for providing samples of common and rare cancers was 14 and 40 days, respectively. The cost of a specimen from the Network was approximately $100 for academic researchers and double for commercial interests.

The first year cost is estimated at $5.8 M for 6 U24 awards, with a total cost of $29 M for 5 years.

In the discussion, the following points were made:.

< To provide molecular characterization of samples would ensure that this resource is of maximum value for more researchers, although this also would add substantial costs to the Network.

< A member encouraged the Network to provide viable frozen cell suspensions for rare cancers.

Motion. A motion to concur with the DCTD (RFA/Coop. Agr.) re-issuance concept entitled "Collaborative Human Tissue Network (CHTN)" was approved unanimously.

Division of Cancer Treatment and Diagnosis
The Adult Brain Tumor Consortium (ABTC) (RFA/Coop. Agr. Reissuance)

Dr. Bhupinder S. Mann, Clinical Investigations Branch, DCTD, NCI, provided a brief presentation of the ABTC, which has a research focus on glioblastoma multiforme (GBM). Dr. Mann informed members that research is needed to improve clinical outcomes, including translating accumulating knowledge of tumor biology of GBM into patient-focused clinical applications. The ABTC, formed in 2009 by the North American Brain Tumor Consortium and the New Approaches to Brain Tumor Therapy consortia, has focused on rapidly conducting Phase 1 and Phase 2 studies with an emphasis on pharmacokinetics and pharmacodynamics that incorporate pre- and post-treatment assays with imaging and tissue-based biomarkers. He noted that the ABTC is working cooperatively with Specialized Programs of Research Excellence (SPOREs), program project (P01) investigators, and cooperative groups such as the NCI Clinical Trials Network. Dr. Mann presented a list of ongoing clinical trials to illustrate the breadth of therapies targeting GBM. With current funding, the GBM can accrue approximately 150 patients annually for two Phase 1 and three Phase 2 studies. Dr. Mann described a proof of principle clinical study using microdialysis catheters to determine drug distribution. Members were told that the ABTC external evaluation committee recommended continuing to focus on tumor tissue acquisition and imaging and tissue biomarkers to fully use early drug development capabilities.

Subcommittee Review. Dr. Kathleen M. Foley, Department of Neurologist, Memorial Sloan-Kettering Cancer Center, New York, NY, informed members that the subcommittee was unanimously supportive of reissuance of the ABTC. The Subcommittee recognized the modest but realistic budget and supported the conduct of additional studies in imaging and gene therapy, i.e., if the budget allows.

The first year cost is estimated at $2 M for one cooperative agreement, with a total cost of $10 M for 5 years.

In the discussion, the following points were made:

< Members commented that the ABTC is a unique multi-modality resource and would like to see some expansion in the group. The consortium has a good plan for acquiring tissue and, in the future, should consider collecting blood for pharmacogenetic studies.

< Members recommended that the reissuance RFA include a statement that low accruing sites be dropped from the consortium at set times during the 5 years.

< The ABTC will focus on small proof-of-principle and proof-of-mechanism trials that can be moved to the Cooperative Groups for randomized large trials when the results are positive.

< Members urged the ABTC to include genomic and other data in their projects, similar to the Pediatric Brain Tumor Network, and integrate with other similar projects.

Motion. A motion to concur with the DCTD (RFA/Coop. Agr.) re-issuance concept entitled "Adult Brain Tumor Consortium (ATBC)" was unanimously approved.

Division of Cancer Control and Population Sciences
NIH Competitive Revision Applications for Research Relevant to the Family Smoking Prevention and Tobacco Control Act (P30) (New FDA/NIH RFA/Coop. Agr. Reissuance)
Informational

Dr. Robert T. Croyle, Director, DCCPS, NCI, provided an update on a broad interagency initiative between the NIH and FDA that focuses on tobacco regulatory science. Dr. Croyle stated that the FDA was granted the

authority to regulate tobacco products under the Family Smoking Prevention and Tobacco Control Act on 22 June 2009. The FDA has established the Center for Tobacco Products to oversee efforts to implement the Tobacco Control Act, while the FDA Center for Drug Evaluation and Research (CDER) regulates tobacco cessation products. The Tobacco Control Act has provided opportunities for the NCI through FDA funding of supplement revision grants (P30) for NCI-designated Cancer Centers. Dr. Croyle informed members of the many broad facets of FDA regulatory authority under this legislation, including reporting of ingredients of tobacco products as well as advertising and promotional restrictions. In discussions among the NIH, FDA, and the Centers for Disease Control and Prevention (CDC), decisions were made to have the NIH conduct much of the research on tobacco for the FDA.

Dr. Croyle clarified tobacco responsibilities not regulated by the FDA and accomplishments since the passing of the Tobacco Control Act. He stated that the NIH and FDA created a working group to identify areas of tobacco research that needed immediate attention. These include: 1) setting tobacco product standards to protect the public health; 2) identifying biomarkers for tobacco-associated pathogenesis and disease; and, 3) developing, implementing, and evaluating tobacco product advertising and marketing standards.

Dr. Croyle asked members to inform their institutions and other researchers that funding initiatives for the NIH-FDA Tobacco Control Act and other information are available at http://prevention.nih.gov/tobacco/. He reported that: 1) in FY 2012, approximately 59 percent ($18.6 M) of the $31.5 M provided to the NIH is managed by the NCI; 2) a broad trans NIH PA for unsolicited investigator-initiated proposals for R01, R03, and R21 grants has been issued; and, 3) R01 and U01 competitive revisions as well as P01 and P50 administrative supplements are included in the NIH funding mechanisms. Research priorities for these funding initiatives include: 1) the broad categories of reducing addiction; 2) potential reductions in toxicity and carcinogenicity; 3) adverse health consequences; 4) communications; 5) marketing of tobacco products; and, 6) economics and policies. A new trans-NIH initiative for Tobacco Centers of Regulatory Science for Research (TCORS) program has been issued with $40 M funding for FY 2013.

Members were told that P30 competitive revision supplements are available for the NCI Cancer Centers. The FDA envisions supporting 20 centers at a level of $1 M each for FY 2014. Also, the FDA has published a list of 56 research priorities. Of that number, 10 research priorities have not had much funding activity, such as research on non-cigarette tobacco products, toxicity, and communications activities.

In the discussion, the following points were made:

< Members expressed support for the NIH-FDA initiative and encouraged the NCI to work with Cancer Centers to develop a consistent approach to tobacco control and cessation research.

< NCI staff stated that the FDA is interested in specific product and brand exposure and outcomes data; NCI Cancer Centers were encouraged to collect and analyze these types of data within their current infrastructure for the P30 supplement revisions.

< The NIH is awaiting guidance from the FDA on menthol products, which are disproportionately marketed toward minority communities.

VIII. ADJOURNMENT - DR. TODD R. GOLUB

There being no further business, the 52nd regular meeting of the Board of Scientific Advisors was adjourned at 3:05 p.m. on Monday, 5 November 2012.

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

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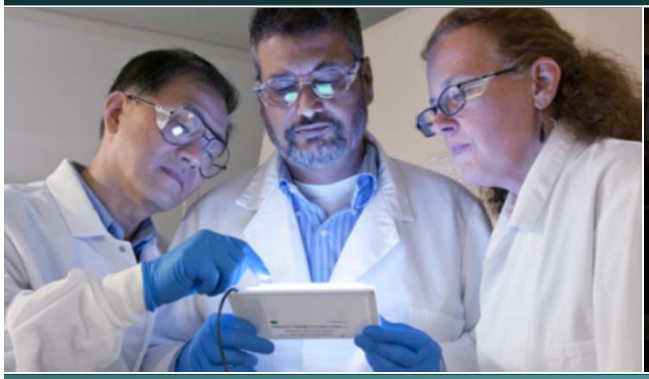
Date Paulette S. Gray, Ph.D.
Executive Secretary, Board of Scientific Advisors

Frederick National Laboratory
for Cancer Research



Frederick National Laboratory for Cancer Research

Presentation to the Board of Scientific Advisors

David C. Heimbrook, Ph.D.

CEO, SAIC-Frederick, Inc.

Nov. 5, 2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES • National Institutes of Health • National Cancer Institute
Frederick National Laboratory is a Federally Funded Research Center, operated by SAIC-Frederick, Inc., for the National Cancer Institute.

Frederick National Laboratory

Presentation Outline

- Our Identity and Mission
- Exemplifying the impact of Frederick National Laboratory programs
- NCI-Frederick Advisory Committee guidance for the future of Frederick National Laboratory

Overview of Frederick National Laboratory for Cancer Research

- **FNLCR is the Federally Funded Research and Development Center**
  - Established in 1972
  - Only FFRDC dedicated to biomedical research
- **Proudly operated by SAIC-Frederick, Inc. on behalf of the National Cancer Institute**
- **Main campus on 70 acres at Ft. Detrick, MD**
  - Co-located with intramural NCI researchers and other NCI activities
  - Additional FNLCR scientists at Bethesda and Rockville sites
- **Mission**: Pursue innovative basic, applied, and translational research leveraging technical expertise, physical infrastructure, and FFRDC status

Defining Characteristics of Frederick National Laboratory for Cancer Research

- **Unique combination** of scientific expertise & operational capability to support all aspects of applied biology and translational medicine
- **Agile :** adapt to changes in NCI priorities
- **Honest Broker :** integrate with government agencies, extramural community, and industry partners
- **Accessible:** technologies and contractor expertise is available to intramural, academic, and industrial biomedical concerns

FNLCR Partnership Development Priorities

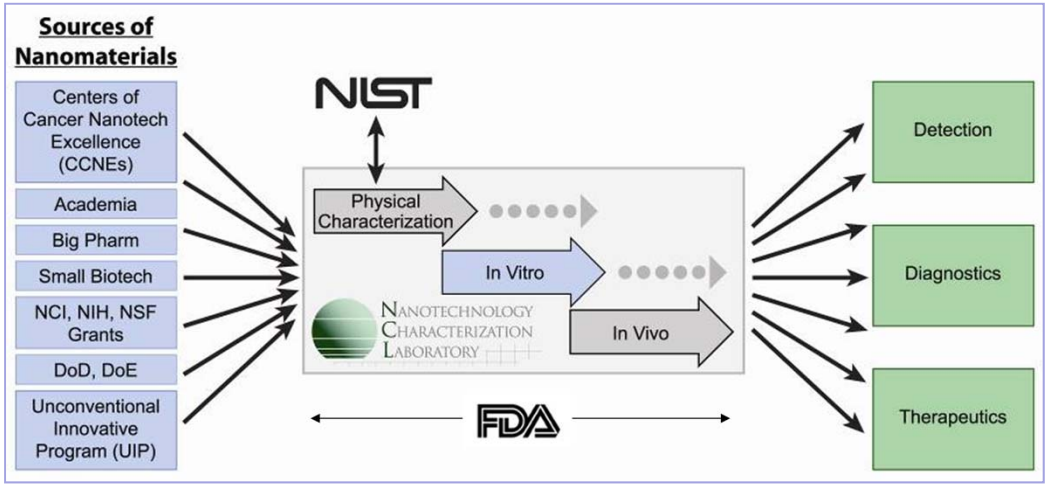
Focus Areas

Supporting the NCI Mission in Cancer and AIDS Research

- **Technology Development and Application**
  - Genomics, Proteomics, Advanced biomedical computing, Biomedical imaging & microscopy, Laboratory animal sciences, Small animal imaging, Clinical Assay technology
- **Accelerate Preclinical Development**
  - Nanotechnology (NCL), Genetically Engineered Mouse Models of cancer (CAPR)
- **Clinical development support**
  - Clinical Assay Development Center, Biopharmaceutical Development Program, Diagnostics and Pharmacodynamics
- **AIDS & Cancer Virus Program**

Nanotechnology Characterization Laboratory (NCL)

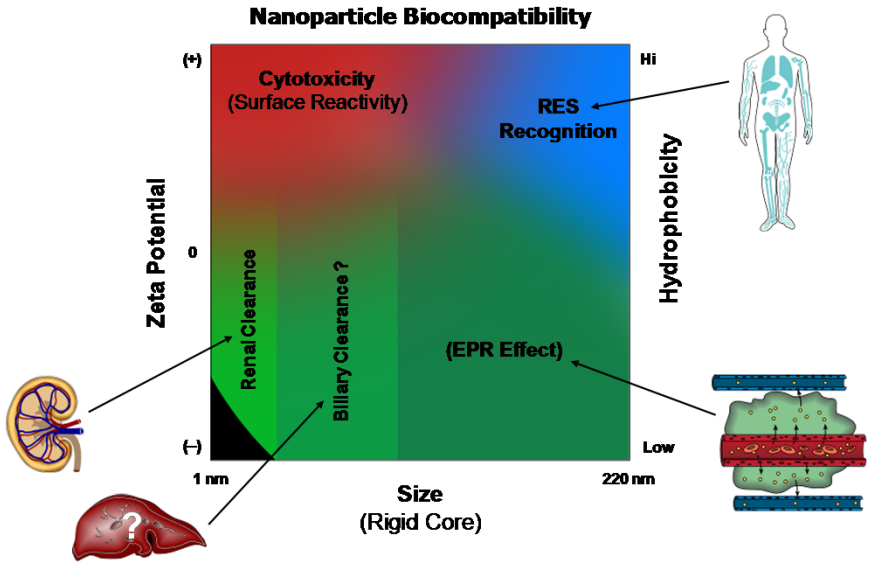
- NCL was established in 2004 as an interagency collaboration among NCI, NIST, and FDA. The lab's mission is to accelerate the translation of promising nanotech cancer drugs and diagnostics
- NCL performs preclinical characterization of nanomaterials, including:
  - physicochemical characterization
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



90% of NCL's efforts support the extramural community

Why NCL Is Needed

- Most nanomaterials come from academic labs focused on materials science
  - Investigators have little experience with oncology, pharmacology, drug development, or regulatory requirements
- Collaboration with NCL allows investigators to take advantage of 'lessons learned':
  - Trends in biocompatibility
  - Gives investigators a heads-up on regulatory requirements



McNeil (2009), *Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology*, 1:264-271.
Nel et al. (2009), *Nature Materials* 8: 543-557.
Cover of *Advanced Drug Delivery Reviews*, June, 2009.

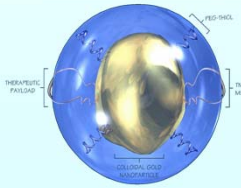
Success Stories:
NCL-aided Submissions to Clinic

AZAYA THERAPEUTICS

IND 2009

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

CYTIMMUNE SCIENCES INC



Phase 1 Completed 2008

- **AuImmune®** : PEGylated colloidal gold nanoparticle-TNFα conjugates
- Phase II study in combination with Taxotere to start in 2012.

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

BIND BIOSCIENCES

IND 2011

Nanospectra

IDE 2008

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

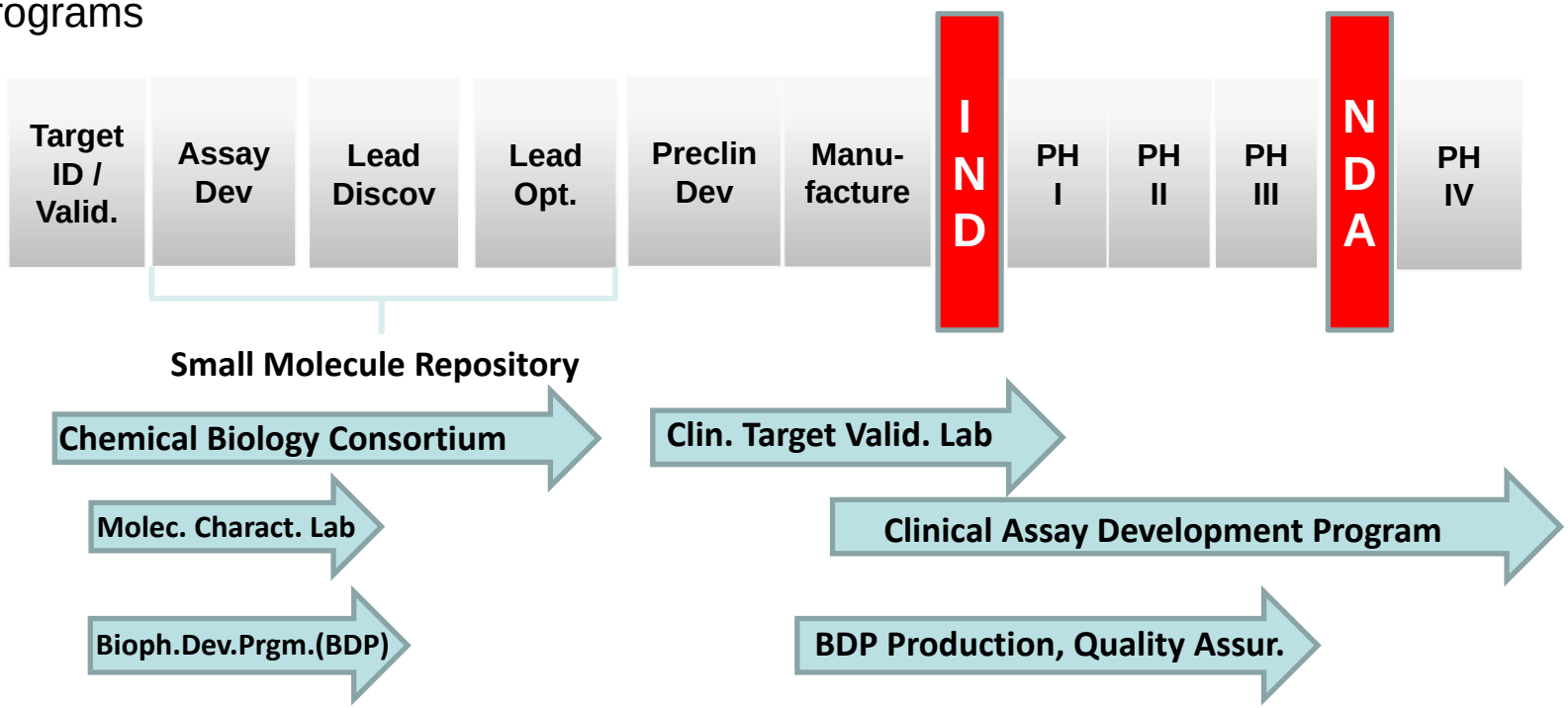
ProNAi

IND 2010

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

The NCI Experimental Therapeutics Program (NExT)

- NExT is led by the Division of Cancer Treatment and Diagnosis to create a coordinated cancer therapeutics discovery and development pipeline with the external scientific community
  - Projects evaluated by extramural Special Emphasis Panel
- SAIC-F provides operational and dedicated technical support to all phases of NExT programs



Supporting Drug Development : Biopharm. Development Program

Sole Source of Monoclonal Antibody ch14.18

Concept : ch14.18 marks neuroblastomas for killing by the immune system by binding to an overexpressed antigen called GD2

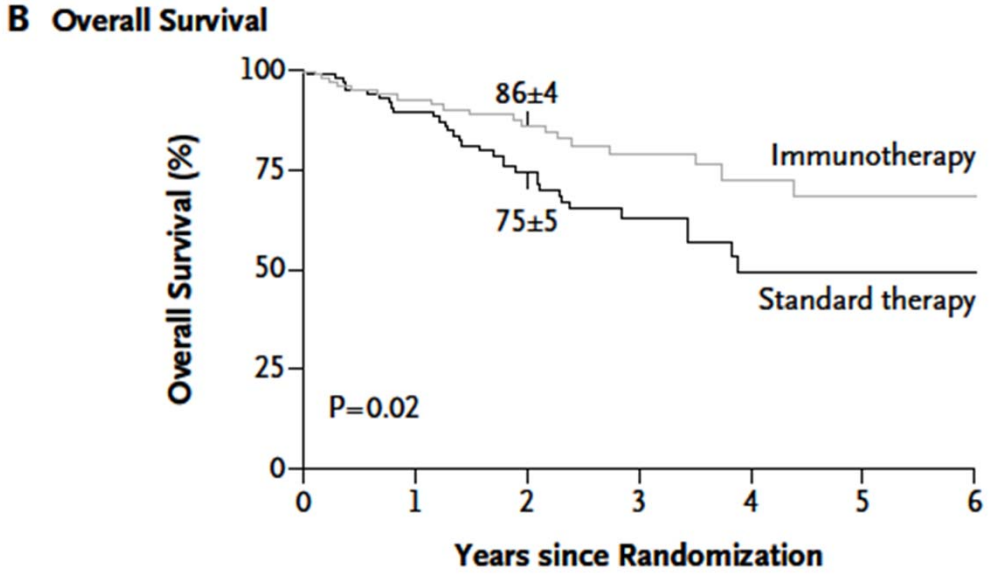
- Due to complexity of process and small market, no commercial vendor would make the antibody

Children's Oncology Group Phase III trial in patients with high-risk neuroblastoma demonstrated clear event-free survival benefit

With the success of the trial, a commercial vendor has been found and our process transferred

The NEW ENGLAND JOURNAL of MEDICINE

363 1324 (2010)



Collaborative Support of AIDS Vaccine Research at FNL

Quantitative Molecular Diagnostics Core

- State of the art capabilities for monitoring virus levels in blood and tissues in NHP models
  - Real-time qPCR/qRT PCR, droplet digital PCR)
- National reference lab
- Critical support of high impact AIDS vaccine studies

LETTER nature doi:10.1038/nature10003

Profound early control of highly pathogenic SIV by an effector memory T-cell vaccine

Scott G. Hansen[1], Julia C. Ford[1], Matthew S. Lewis[1], Abigail B. Ventura[1], Colette M. Hughes[1], Lia Coyne-Johnson[1], Nathan Whizin[1], Kelli Oswald[2], Rebecca Shoemaker[2], Tonya Swanson[1], Alfred W. Legasse[1], Maria J. Chiuchiolo[3], Christopher L. Parks[3], Michael K. Axthelm[1], Jay A. Nelson[1], Michael A. Jarvis[1], Michael Piatak Jr[2], Jeffrey D. Lifson[2] & Louis J. Picker[1]

ARTICLES

nature medicine

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

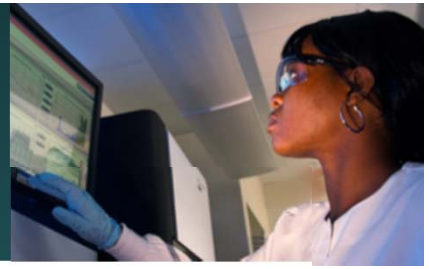
Yoshinori Fukazawa[1,2,8], Haesun Park[1,2,8], Mark J Cameron[3], Francois Lefebvre[3], Richard Lum[1,2], Noel Coombes[1,2], Eisa Mahyari[1,2], Shoko Hagen[1,2], Jin Young Bae[1,2], Marcelo Delos Reyes III[1,2], Tonya Swanson[1,2], Alfred W Legasse[1,2], Andrew Sylwester[1,2], Scott G Hansen[1,2], Andrew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

LETTER nature doi:10.1038/nature11443

Vaccine-induced CD8$^+$ T cells control AIDS virus replication

Philip A. Mudd[1,2], Mauricio A. Martins[3], Adam J. Ericsen[1], Damien C. Tully[4], Karen A. Power[4], Alex T. Bean[1], Shari M. Piaskowski[1], Lijie Duan[5], Aaron Seese[4], Adrianne D. Gladden[4], Kim L. Weisgrau[1], Jessica R. Furlott[1], Young-il Kim[6], Marlon G. Veloso de Santana[7], Eva Rakasz[8], Saverio Capuano III[8], Nancy A. Wilson[1,8], Myrna C. Bonaldo[7], Ricardo Galler[9], David B. Allison[10], Michael Piatak Jr[11], Ashley T. Haase[5], Jeffrey D. Lifson[11], Todd M. Allen[4] & David I. Watkins[3]

NCI-Frederick Advisory Committee
Building for the Future



- **NFAC charge - review the state of research at FNLCR and make recommendations for the best use of its capabilities and infrastructure**
- **15 member committee**

Zachary Hall, Ph.D. Former Director, NINDS Former President; Institute of Regenerative Medicine, UCSF
Emeritus Professor, UCSF

Chair

C. Barrett

D. Botstein

L. Garraway

J. Gray

B. Hahn

M. Justice

T. Look

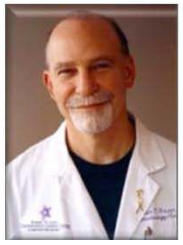
L. Marnett

J. Mesirov

G. Nolan

K. Olden

J. Pietenpol



S. Rosen

C. Willman

Expanding the Partnering Base

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

- **Enables SAIC-Frederick to partner directly with extramural scientists and organizations for access to our science and technology know-how**
- **Use full CRADA authority under CRADA statutes**
  - c-CRADAs for Research, Development, and Testing collaborations
  - “Technical Service Agreement” for tactical evaluation of proprietary partner materials, AIDS testing kits, etc.
- **Intellectual property rights**
  - SAIC-F is the custodian of joint or sole IP emerging from the CRADA
  - Streamlined assignment of exclusive commercialization rights
  - Any royalty streams support FFRDC R&D efforts
- **Processes**
  - Focus on speed
  - Local government review and approval with external input as appropriate

New Partnering Initiatives

Expanding access to FNLCR Resources

- **Cooperative Research and Development Agreements (cCRADA)**
  - Two partnerships received initial concept approval
  - Five additional agreements in development
- **Technical Service Agreement (TSA)**
  - Seven distinct assays approved for external offering
  - Three additional assays submitted for approval, 11 in preparation
  - One agreement signed with UCSF, 4 in progress
- **External-facing FNLCR website operational and evolving**
  - http://frederick.cancer.gov/

FNLCR Strategic Direction Initiatives

- **Identification and Implementation of "Big Ideas"**
  - Fulfill the "National Laboratory" vision
  - Variety of NCI, FNLCR, and external workgroups contributed ideas
    - "Hub-and-spoke" model likely
  - Funding strategies within the existing FNLCR budget under discussion
  - Communication plan under development

- **FNLCR Laboratory Director (NCI)**

Conclusions

- **Frederick National Laboratory for Cancer Research** is a unique resource within the national biomedical research community
- **Program partnerships** facilitate basic and translational research achievements
- **New partnering opportunities** expand the impact of FNLCR science
- **New "big idea" research programs** will strengthen the identity and impact of FNLCR as a National Laboratory

National Cancer Institute

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Provocative Questions Initiative

An update

Ed Harlow

BSA Meeting

November 5, 2012

Provocative Questions Initiative

- Goals are (1) to identify compelling research questions in new or understudied areas and (2) to fund great new science in these areas
- An EXPERIMENT: The BSA has given approval to run a 3 year trial of the RFA.
- We now have two years of question gathering experience: Web-based access for everyone and workshops for direct contact with community
- NCI has run two PQ RFAs: First completed in early summer, second issued with submission deadline in early Dec: 24 PQs/RFA; $22M in new awards for 2011 RFA, $30M committed for 2012 RFA; For both R01s and R21s
- Initiative operationally sits between Investigator-initiated research and traditional RFA

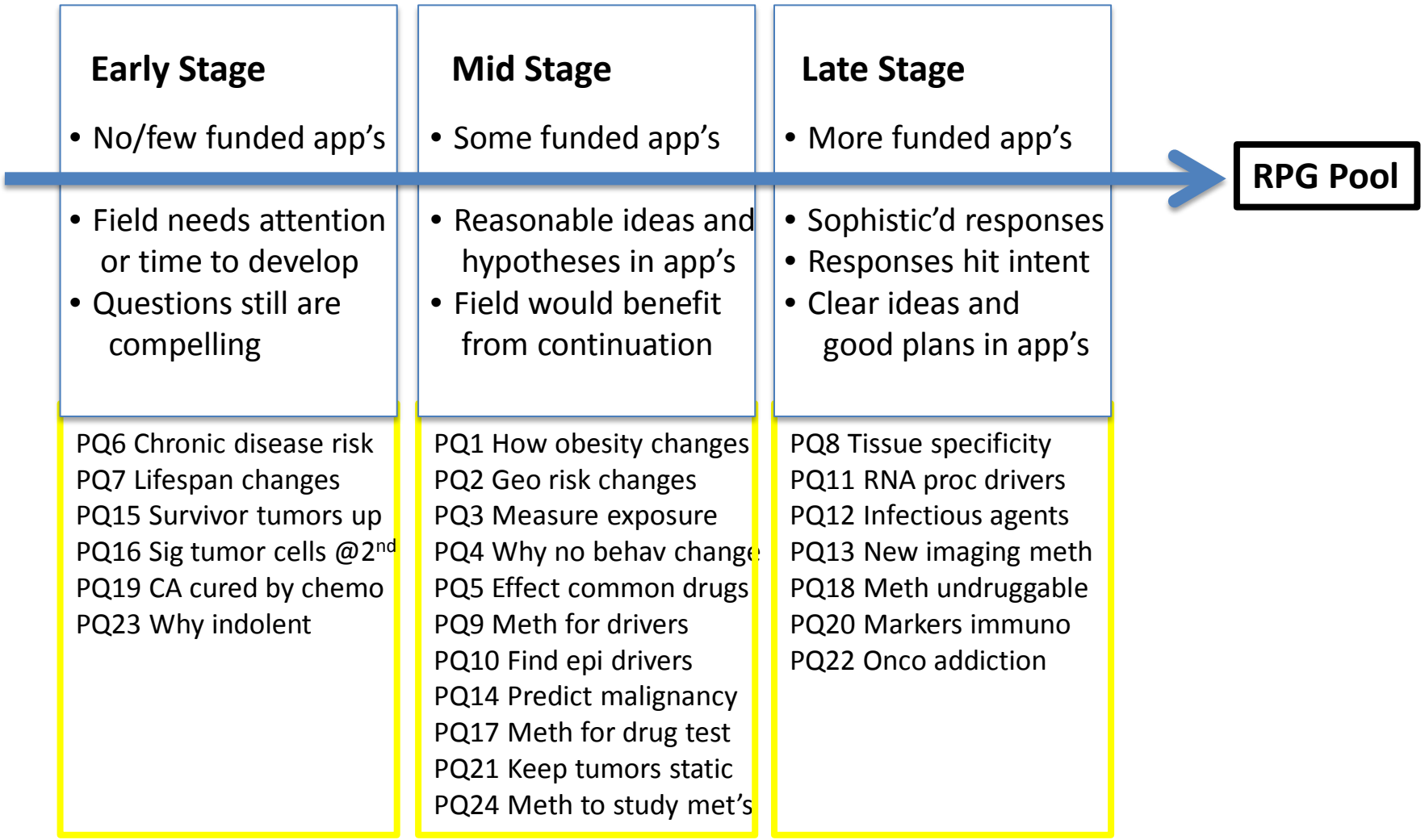
Provocative Questions Initiative: Useful Characteristics

- Power of formulating each project as a research question: *Questions highlight most important nuance of an area*
- Asking the community to nominate questions for consideration: *Community ownership, not NCI*
- Demanding that the questions be on understudied or underappreciated subjects: *New tentacles into hard problems*
- Using a series of community-based workshops to nominate questions: *Community talks, argues*
- Assembling questions from a wide spectrum of our research interests: *No, or few, research areas are ignored*
- Potential counter to conservative thinking and reviewing in tight financial times: *Spreads the focus of research thinking and reviewing*

2011 Provocative Question RFA:
Fun Facts (and some interpretation)

- 738 reviewed applications
- Number of submitted app's per PQ varied from 82 to 7.
- 57 app's were funded, or 7.7% of total submitted.
- The most successful PQs had success rate of ~20%
- Four PQs had no funded applications. PQ15 (Why survivors have higher rate of 2nd tumors), PQ16 (What is significance of tumor cells at 2nd site), PQ19 (Why chemo works sometimes), PQ23 (Why indolent tumors change). PQ15, PQ16, and PQ19 had the 3 fewest submissions of all PQs.
- Maximum number of funded app's/PQ is 6 (PQ1, obesity; PQ18, new methods for undruggable). 5 app's funded for 2 PQs (PQ5, commonly used drugs; PQ12, new infectious agents)
- By my interpretation, 46 of 57 funded applications (81%) were directed to the intent of the PQ.

2011 Provocative Question RFA:
Characterization of Question Success



Work Flow for New PQs for 2012 RFA

- Continued to run workshops in community and at NCI; Continued to collect questions on website

- (All questions from On-line) + (All questions from workshops) = 556, became *The Question Book*

- Editorial Board

  R Ballard-Barbash, S Chanock, E Greenspan, M Hare, P Hartge, T Hecht, K Howcroft, J Lee, C Mackall, L Minasian, T Misteli, S Mitchell, B Spalholz, P Wagner, and J Zwiebel

- 14 New Proposed PQs

2012 PQ RFA

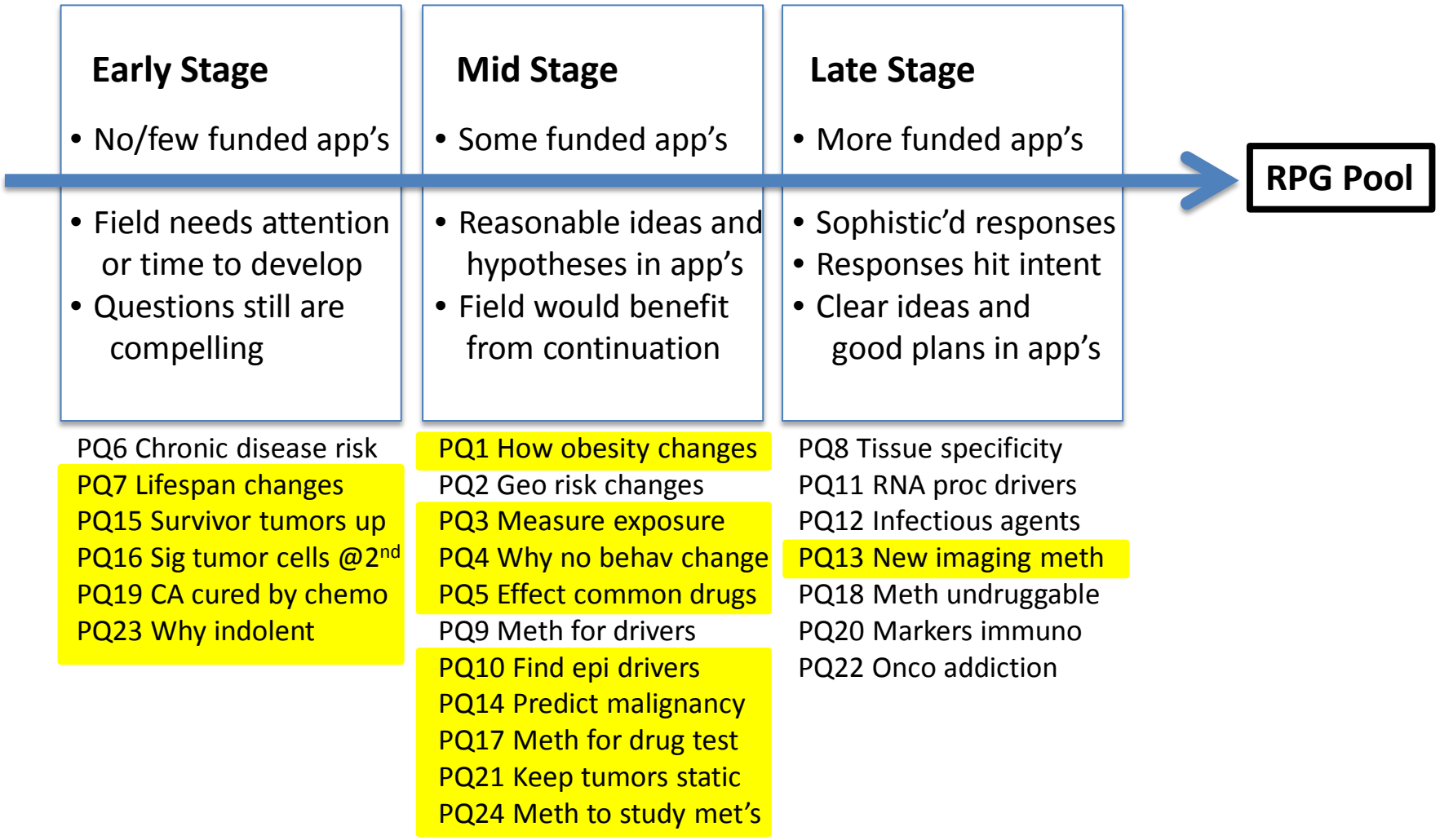
24 PQs for 2011 RFA

14 Potential PQs
From 2012 Collection

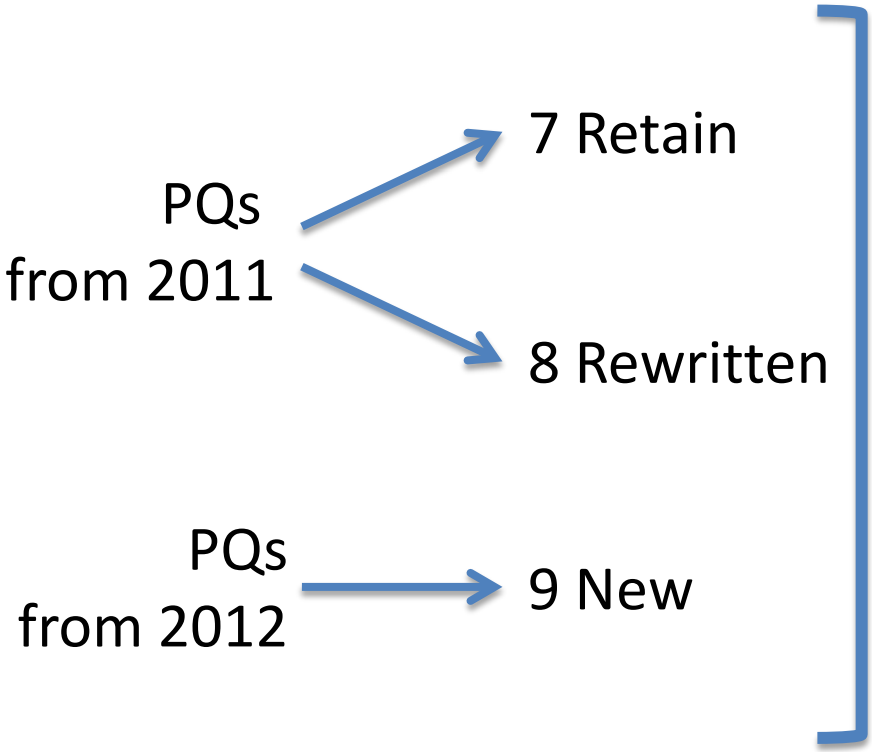
- Ed Board & PQ Program Recommendations
- SPL Decision

24 PQs
2012 RFA

2011 Provocative Question RFA:
15 Subject Areas Saved for 2012 RFA



2012 PQ RFA(s)



RFA 1:
Prevention & Risk
4 PQs 2011
2 PQs 2012

RFA 2:
Mech of Tumor Dev & Recurrence
4 PQs 2011
2 PQs 2012

RFA3:
Detect, Diag, & Prognosis
4 PQs 2011
2 PQs 2012

RFA 4:
Therapy & Outcomes
3 PQs 2011
3 PQs 2012

2012 PQ RFAs

RFA 1: Prevention & Risk

PQ1. (Retain) How does obesity contribute to cancer risk?
PQ3. (Re-written) As modern measurement technologies improve, are there better ways to objectively ascertain exposure to cancer risk?
PQ4. (Re-written) How do cognitive processes such as memory and executive function interact with emotional or habitual processes to influence lifestyle behaviors and decisions, and can we use this knowledge to design strategies to change behaviors that increase cancer risk?
PQ5. (Re-written) What is the molecular mechanism by which a drug (such as aspirin or metformin) that is chronically used for other indications protects against cancer incidence and mortality?
PQ25. (New) How does the level, type, or duration of physical activity influence cancer risk and prognosis?
PQ26. (New) How does susceptibility of exposure to risk factors change during development?

RFA 2: Mech of Tumor Dev & Recur

PQ7. (Re-written) What mechanisms of aging, beyond the accumulation of mutations, promote or protect against cancer development?
PQ10. (Retain) As we improve methods to identify epigenetic changes that occur during tumor development, can we develop approaches to discriminate between “driver” and “passenger” epigenetic events?
PQ15. (Retain) Why do second, independent cancers occur at higher rates in patients who have survived a primary cancer than in a cancer-naïve population?
PQ24. (Retain) Given the difficulty of studying metastasis, can we develop new approaches, such as engineered tissue grafts, to investigate the biology of tumor spread?
PQ27. (New) What molecular and cellular events determine whether the immune response to the earliest stages of malignant transformation leads to immune elimination or tumor promotion?
PQ28. (New) How does the order in which mutations or epigenetic changes occur alter cancer phenotypes or affect the efficacy of targeted therapies?

2012 PQ RFAs

RFA3: Detect, Diag, & Prognosis

PQ13. (Retain) Can tumors be detected when they are two to three orders of magnitude smaller than those currently detected with in vivo imaging modalities?

PQ14. (Retain) Are there definable properties of pre-malignant or other non-invasive lesions that predict the likelihood of progression to metastatic disease?

PQ16. (Re-written) How do we determine the significance of finding cells from a primary tumor at another site and what methods can be developed to make this diagnosis clinically useful?

PQ23. (Retain) Can we determine why some tumors evolve to aggressive malignancy after years of indolence?

PQ29. (New) What molecular events establish tumor dormancy after treatment and what leads to recurrence?

PQ30. (New) How can the physical properties of tumors, such as a cell's electrical, optical or mechanical properties, be used to provide earlier or more reliable cancer detection, diagnosis, prognosis, or monitoring of drug response or tumor recurrence?

RFA 4: Therapy & Outcomes

PQ17. (Re-written) Since current methods to predict the efficacy or toxicity of new drug candidates in humans are often inaccurate, can we develop new methods to test potential therapeutic agents that yield better predictions of response?

PQ19. (Re-written) What molecular properties make some cancers curable with conventional chemotherapy?

PQ21. (Re-written) How does the selective pressure imposed by the use of different types and doses of targeted therapies modify the evolution of drug resistance?

PQ31. (New) What properties of cells in a pre-malignant or pre-invasive field—sometimes described as the result of a cancer field effect—can be used to design treatments for a tumor that has emerged from this field or to block the appearance of future tumors?

PQ32. (New) What mechanisms initiate cachexia in cancer patients, and can we target them to extend lifespan and quality of life for cancer patients?

PQ33. (New) What underlying causal events—e.g., genetic, epigenetic, biologic, behavioral, or environmental—allow certain individuals to survive beyond the expected limits of otherwise highly lethal cancers?

2012 PQ RFAs

- PQ1. (Retain) How does obesity contribute to cancer risk?

- PQ19. (Re-written) What molecular properties make some cancers curable with conventional chemotherapy?

- PQ33. (New) What underlying causal events—e.g., genetic, epigenetic, biologic, behavioral, or environmental—allow certain individuals to survive beyond the expected limits of otherwise highly lethal cancers?

Issues for Consideration

- Increase attention to PQ process and RFA
- Increase critical thinking on question subjects
- Get Divisions more deeply involved
- How hard to push for new PQs?
- PAs or PARs as questions cycle off?
- “Questions” website?

National Cancer Institute

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Provocative Questions
THANKS

Maureen Johnson

Samantha Finstad, Elizabeth Hsu

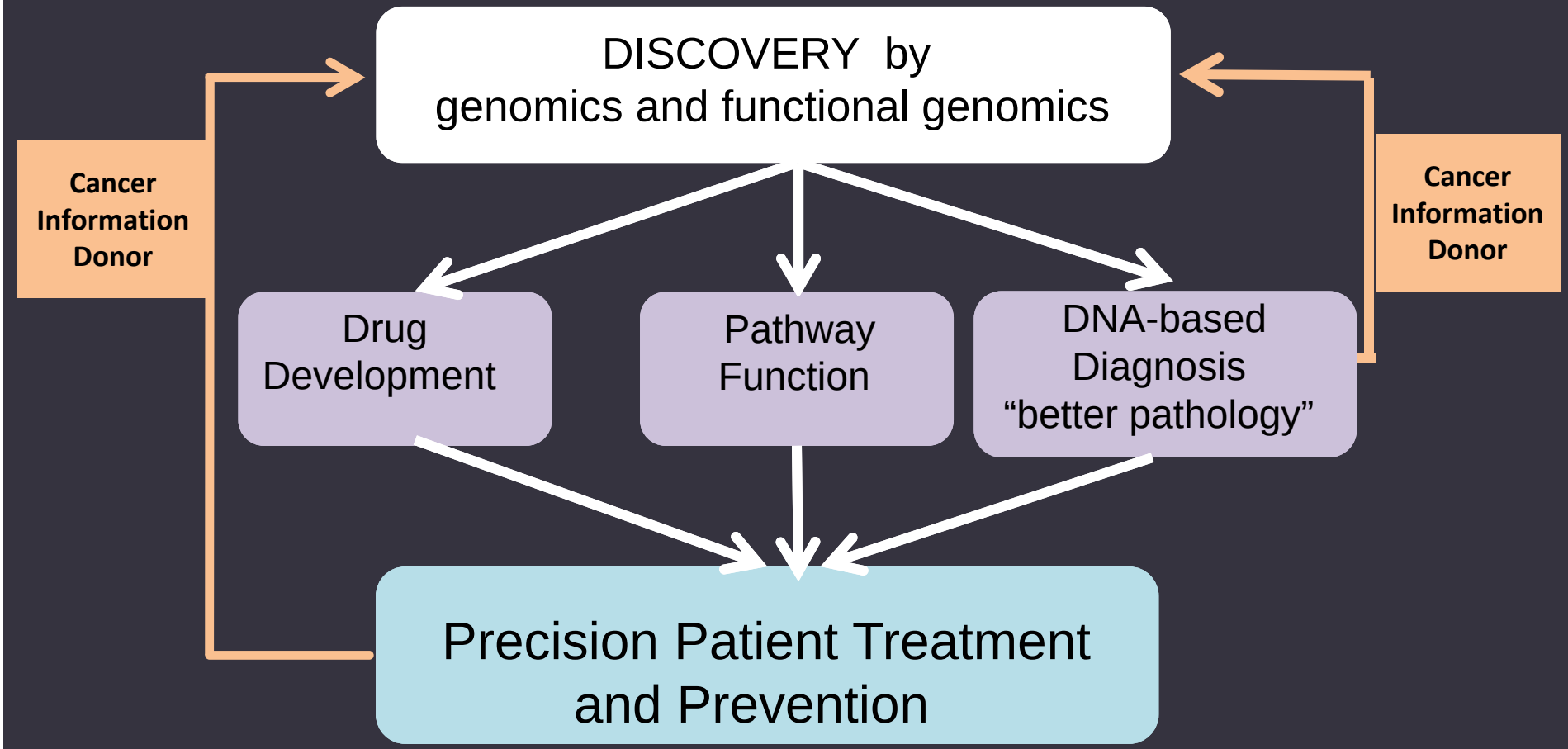
R Ballard-Barbash, S Chanock, E Greenspan, M Hare, P Hartge, T Hecht, K Howcroft, J Lee, C Mackall, L Minasian, T Misteli, S Mitchell, B Spalholz, P Wagner, and J Zwiebel

Jerry Lee, Emily Greenspan, + Program Staff

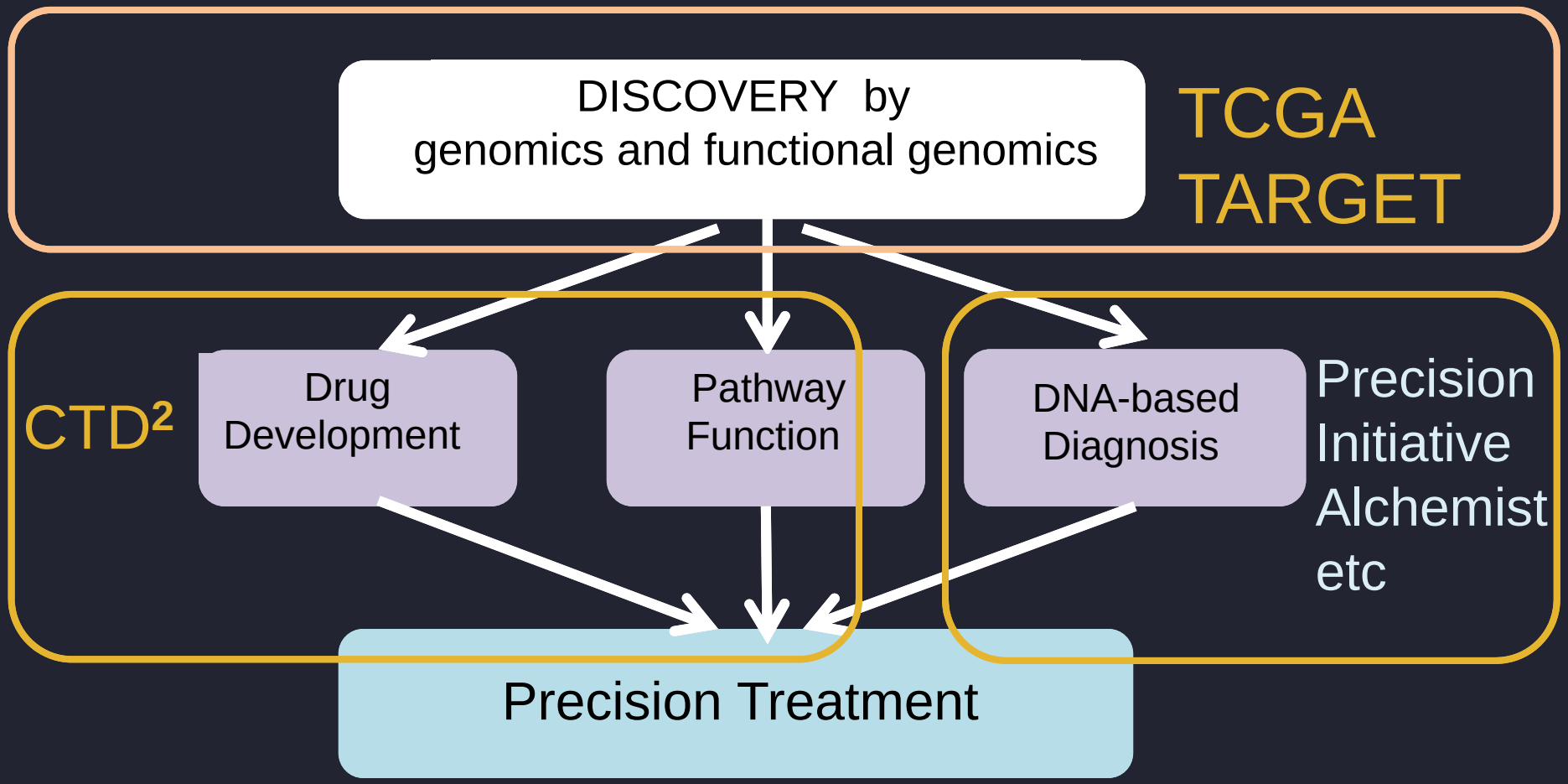
BSA Meeting

November 5, 2012

Large Scale Cancer Genomics at NCI
Present and Future



Where we are...

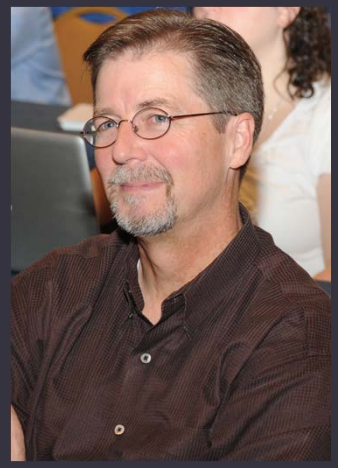

DISCOVERY by
genomics and functional genomics
TCGA
TARGET
CTD²
Drug
Development
Pathway
Function
DNA-based
Diagnosis
Precision
Initiative
Alchemist
etc
Precision Treatment

Kenna Shaw PhD

TCGA = The Cancer Genome Atlas

Adult Cancers

No Prior Treatment



Brad Ozenberger PhD

Daniela Gerhard PhD

TARGET = Therapeutically Applicable Research to Generate Effective Treatments

Pediatric Cancers

Selected poor outcome tumors

CTD^2 = Cancer Target and Drug Discovery

Major Goals of TCGA and TARGET

Discover “driver” genes; learn frequencies

Discover mutation combinations: pathways, networks

Discover RNA expression, methylation, copy number, LOH

Integrate across data types and tumor types

Mine data to suggest treatment - actionable signatures

Trials follow!

Mine data to focus drug development and other treatments

Develop ever-better methods for analysis and make available

Implicit Goals / Questions for TCGA and TARGET

What is the added impact of big “reference data” that are

comprehensive
coherent
high quality
widely accessible

What is the impact of these “Team Science” communities?

Can new TCGA pipeline partner intimately with clinical trials?

With community care?

With RO1 Genomics ?

.....and vice versa?

Major Goals of CTD^2

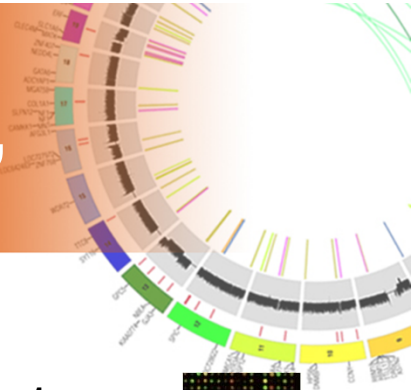
Translate genomic candidates into treatment targets

Develop and use high throughput screens for target validation

Develop and use computational approaches: pathways, drugs

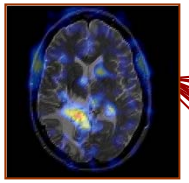
Identify lead drugs

TCGA Design: No Platform Left Behind
Distributed "Team Science"

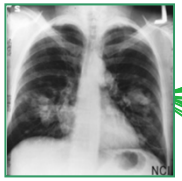


25* forms of cancer

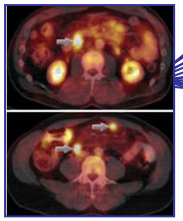
glioblastoma multiforme (brain)



squamous carcinoma (lung)



serous cystadenocarcinoma (ovarian)



Etc. Etc. Etc.

Biospecimen Core Resource with more than 150 Tissue Source Sites

6 Cancer Genomic Characterization Centers

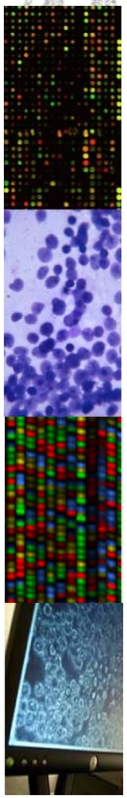
3 Genome Sequencing Centers

7 Genome Data Analysis Centers

Data Coordinating Center

Multiple data types

- Clinical diagnosis
- Treatment history
- Histologic diagnosis
- Pathologic report/images
- Tissue anatomic site
- Surgical history
- Gene expression/RNA sequence
- Chromosomal copy number
- Loss of heterozygosity
- Methylation patterns
- miRNA expression
- DNA sequence
- RPPA (protein)
- Subset for Mass Spec



Robust Pipeline for Comprehensive Genomic Characterization

Tissue Sample

Pathology QC

DNA & RNA Isolation, QC

Sequence
Exomes
Whole genomes

RNA
Copy number
DNA methylation

Data and Results Storage & QC

Integrative computational Analysis

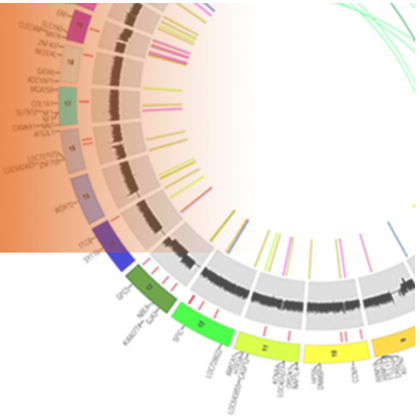
Comprehensive Characterization

High quality frozen samples
costly, rate-limiting

= BCR = GSCs = CGCCs = DCC = GDACs

The Cancer Genome Atlas

TCGA Adult Tumors
Complete 500 primary tumors per type

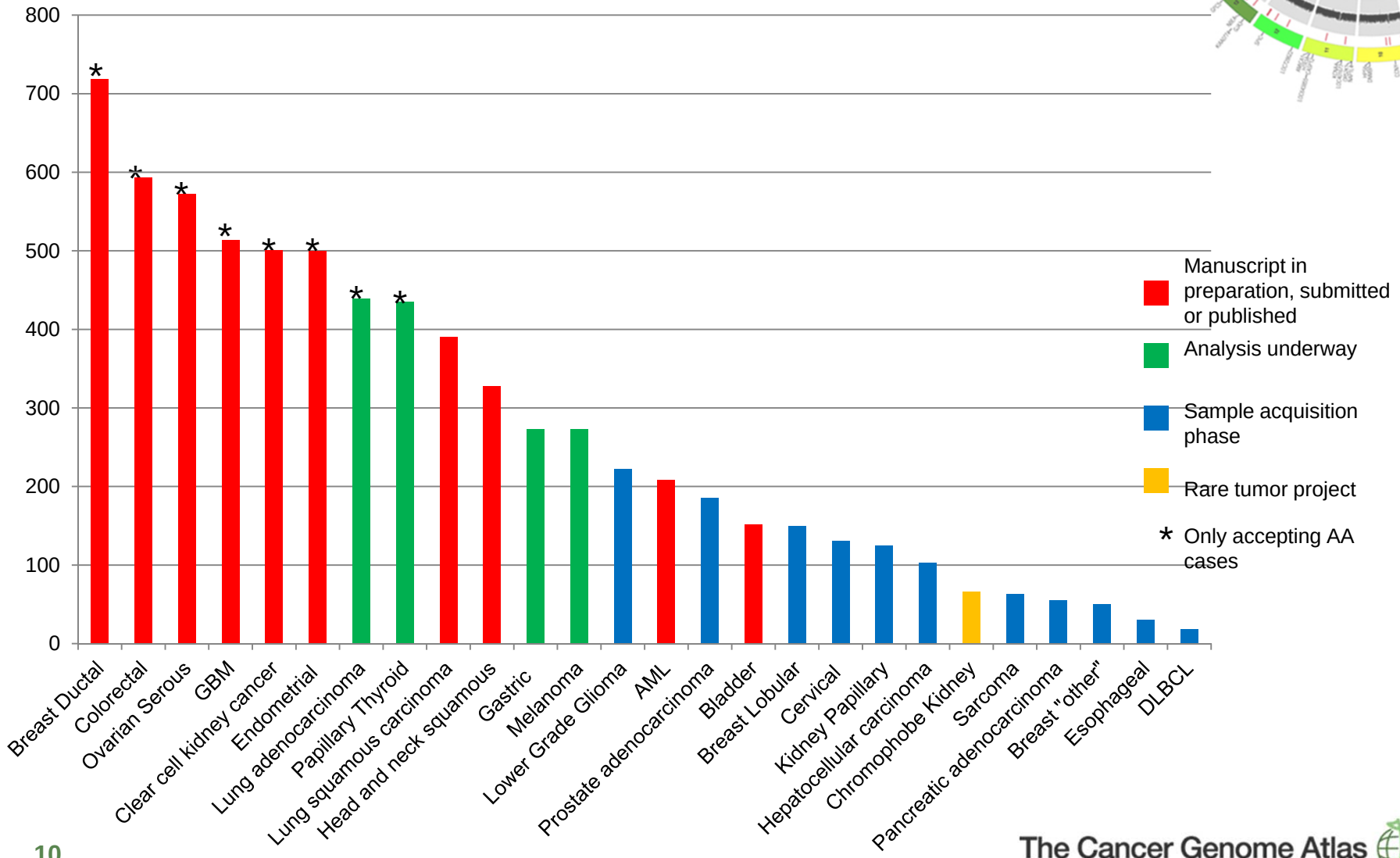


- AML
- Breast Ductal*
- Breast Lobular/Breast Other
- Bladder
- Cervical adeno & squamous
- Colorectal*
- Clear cell kidney*
- Diffuse Large B-cell Lymphoma
- Endometrial carcinoma*
- Esophageal adeno & squamous
- Gastric adenocarcinoma
- Glioblastoma multiforme*
- Head and Neck Squamous
- Hepatocellular
- Lower Grade Glioma
- Lung adeno
- Lung squamous
- Melanoma
- Ovarian serous cystadenocarcinoma*
- Papillary kidney
- Pancreas
- Prostate
- Sarcoma (expanding to 10 subtypes)
- Papillary Thyroid*

**Reached 500 tumor goal*

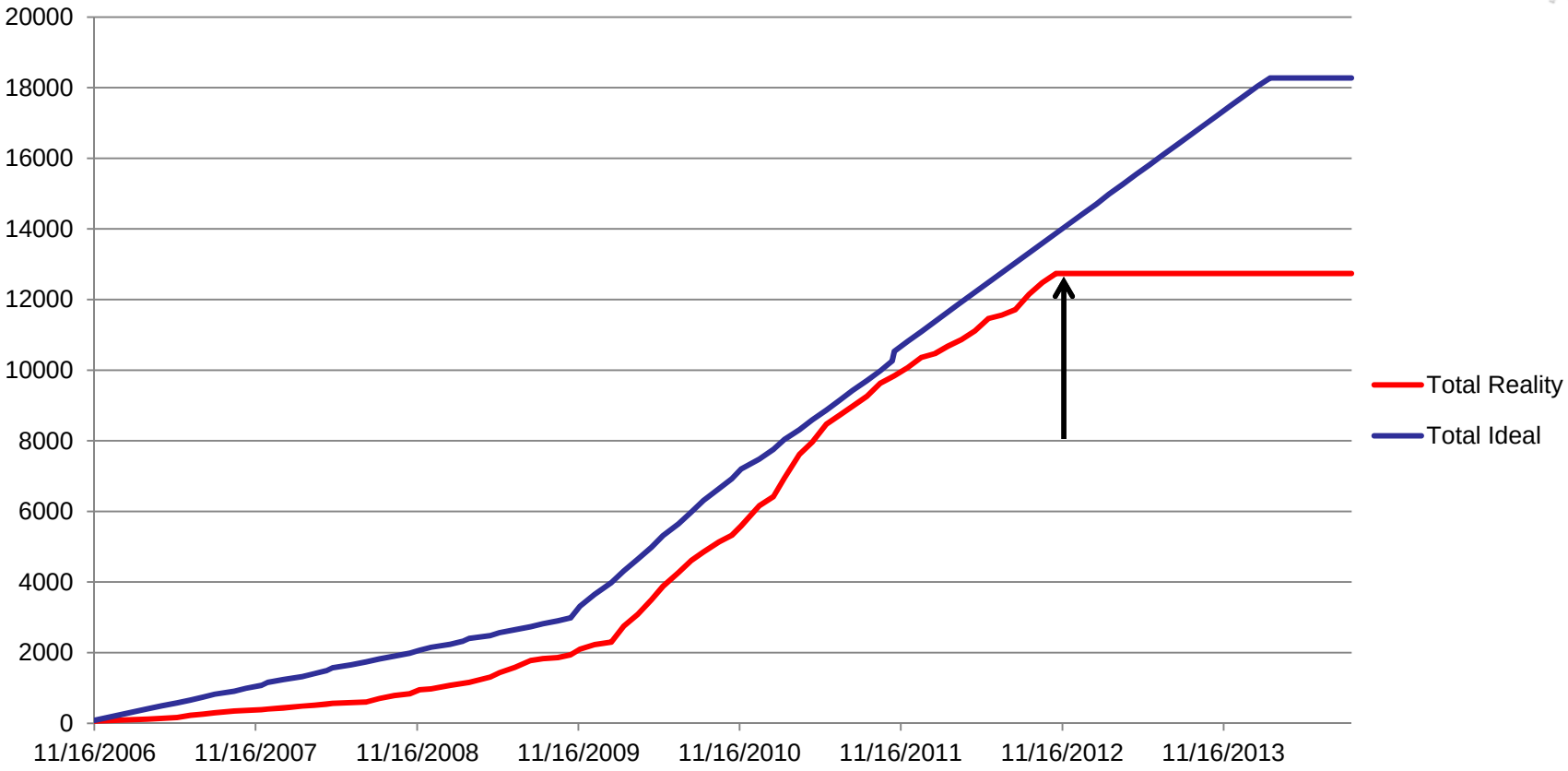
Research papers published or in preparation

TCGA Progress by Tumor Type

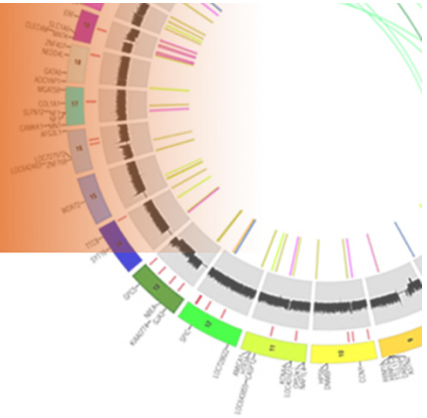


The Cancer Genome Atlas

Accrual challenge is great: Outcome range



New Rare Tumor Project - Launched 2012
50 -100 tumors per type



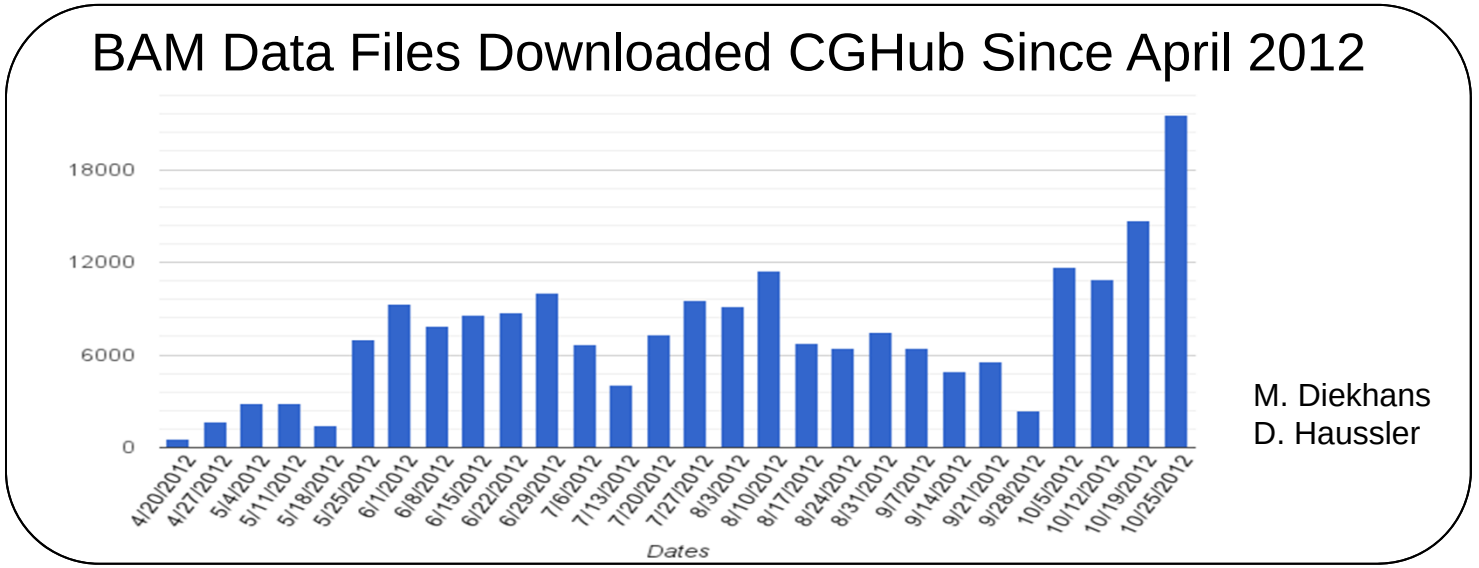
- Adrenocortical Carcinoma*
- Adult ALL (B-cell and T-Cell)
- Anaplastic Thyroid
- Cholangiocarcinoma or Gall Bladder
- Chromophobe kidney*
- High Risk MDS (del 5q- cases)
- Mesothelioma*
- MPNST
- Paraganglioma/Pheochromocytoma
- Testicular Germ Cell
- Uterine Carcinosarcoma*
- Thymoma

*- *Sample Acquisition Ongoing*

Revised Data Access and Publication Policy

- **All data are available pre-publication, but users are asked to allow TCGA a first comprehensive publication**
- **Before TCGA paper, users may publish on *any* tumor type, any time, as long as only one platform is used**
- **After TCGA paper publication, OR 18 months after 100 cases have shipped, any user may use data in any way**
- **Users may use data in grant applications, posters at meetings, etc. all prior to any TCGA paper**
- **For questions – write tcga@mail.nih.gov**

Raw Sequence Downloads from CGHub



M. Diekhans
D. Haussler

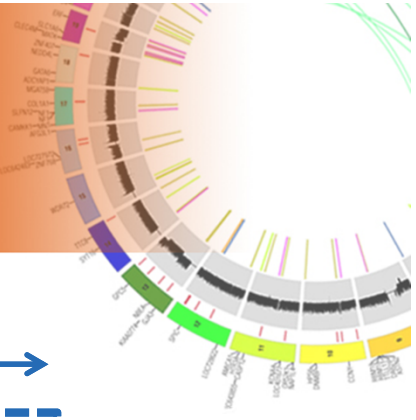
TCGA Data Portal Snapshot: October 2012

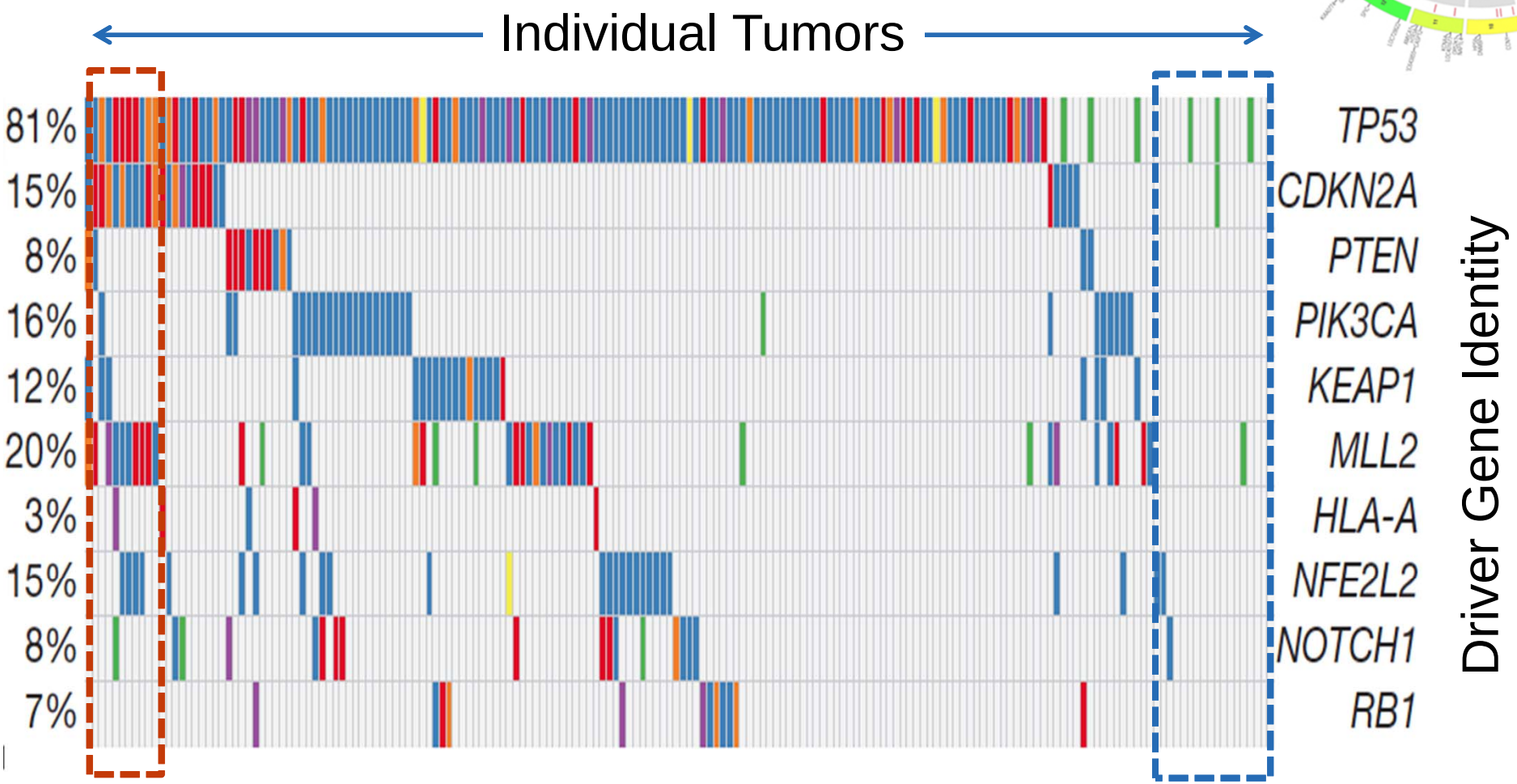
- **>38,000 archive downloads**
- **~350 controlled data; <1% of use is controlled access**
- **Data use "spikes" after publications**

Results: Squamous Cell Lung

"Driver Genes" in diverse combinations

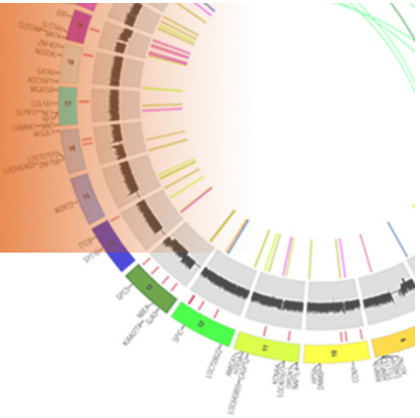
EXOME sequencing





The Cancer Genome Atlas

Results: Squamous Cell Lung



More drivers:
Statistical power issues

10 additional candidates (COSMIC)

> Implications for future study design numbers – how deep is important?

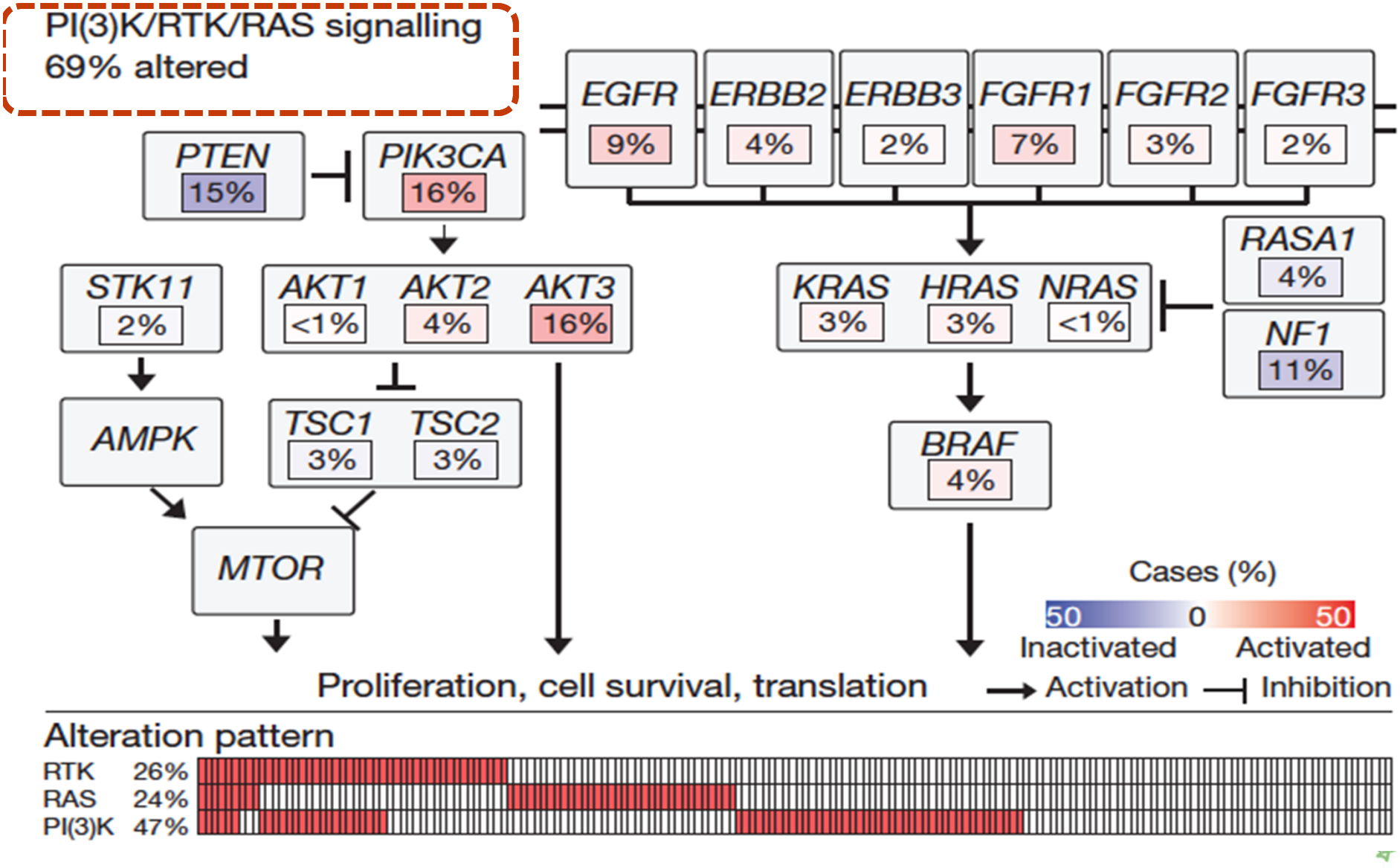
> Meaning of low frequency drivers overall? Meaning in a specific patient?

Must do experiments.....

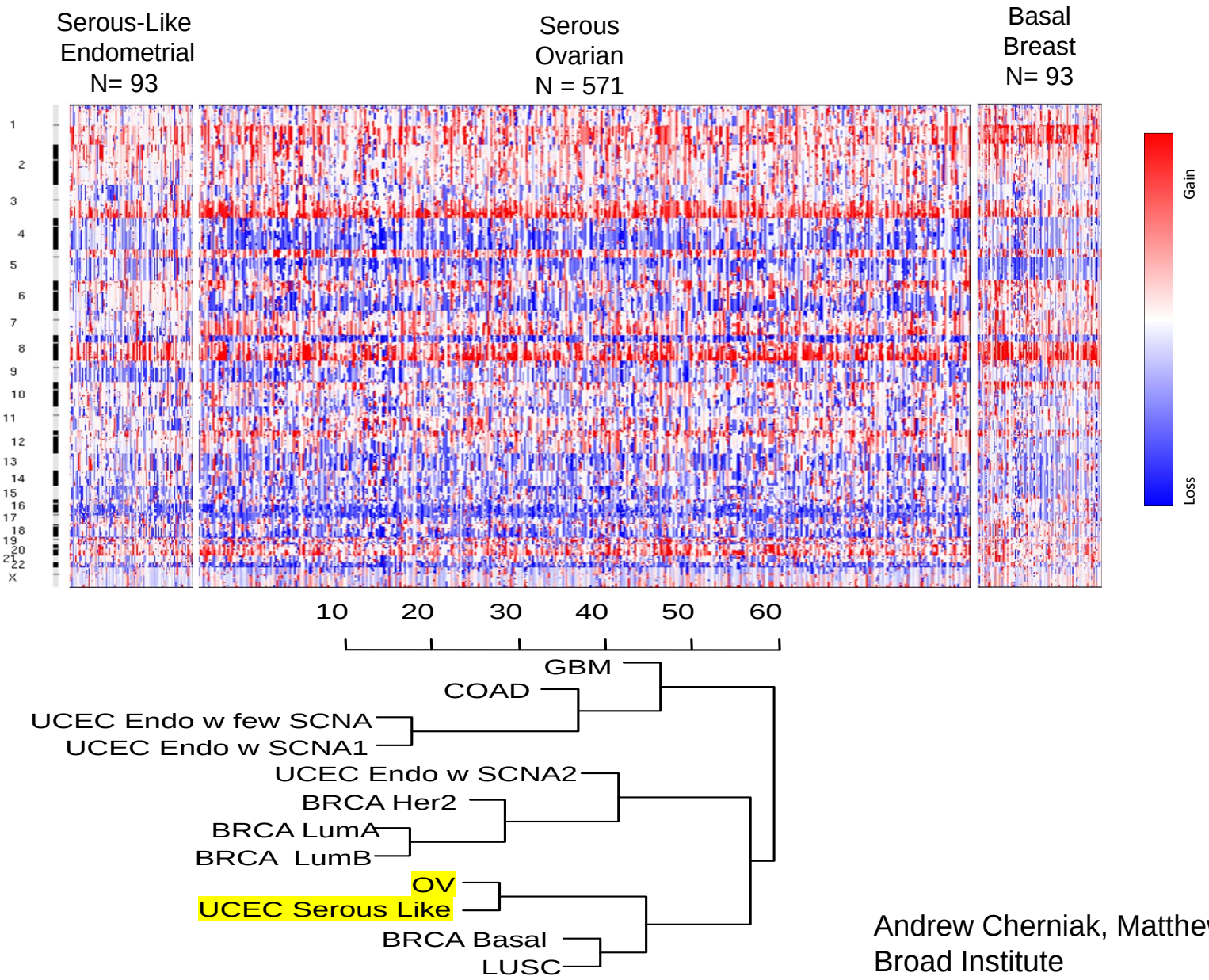
Driver Mutation Pathways

Mutations aggregate in pathways and networks

“Actionable” fraction



Cross-Tumor Integration
Similarities among tumor subsets suggested by Somatic Copy Number data



Andrew Cherniak, Matthew Meyerson
Broad Institute

TCGA reference data mined as starting point for other studies

ARTICLE

doi:10.1038/nature11331

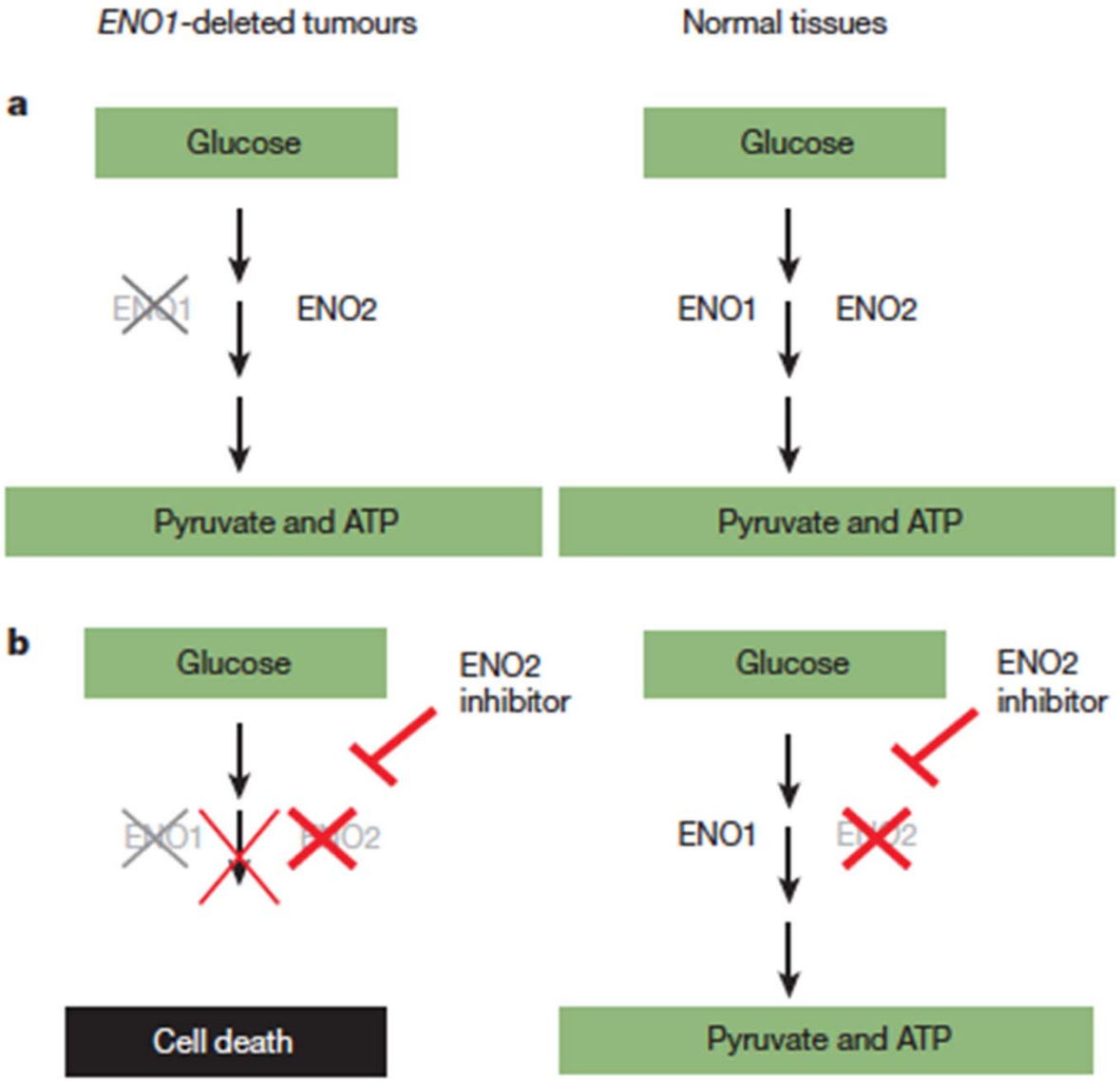
Passenger deletions generate therapeutic vulnerabilities in cancer

Florian L. Muller[1,2,3]*, Simona Colla[1,2,3]*, Elisa Aquilanti[2]*, Veronica E. Manzo[2], Giannicola Genovese[1,2], Jaclyn Lee[2], Daniel Eisenson[2], Rujuta Narurkar[2], Pingna Deng[1,2], Luigi Nezi[1,2], Michelle A. Lee[2,4], Baoli Hu[1,2,5], Jian Hu[1,2,3], Ergun Sahin[2,3], Derrick Ong[1,2,3], Eliot Fletcher-Sananikone[1,2], Dennis Ho[2,3], Lawrence Kwong[1,2], Cameron Brennan[6], Y. Alan Wang[1,2,5], Lynda Chin[1,2,5] & Ronald A. DePinho[2,3,5,7]

Specific (numerically rare) subset of Gliomas display “ride along” deletions of ENO1

This renders them sensitive to ENO2 inhibition

ENO1 “Passenger” deletion creates druggable ENO2 vulnerability – small and specific subset of GBMs



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Pediatric Cancer Genomics

Emphasize tumors with

poor outcomes to current treatment

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

National Cancer Institute

TARGET: Pediatric Cancer Genomics

@ 100-200 cases per tumor type

- Acute lymphoblastic leukemia (ALL), including relapse
- Acute myeloid leukemia (AML), including relapse
- Neuroblastoma (stage 4)
- Osteosarcoma
- Wilms tumor (relapsed patients and anaplasia)

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Summary: TARGET Sequencing completed - August 24, 2012

Disease	WGS Cases (CGI)	Trios (T)	WGS D Cases (Illumina)	WES cases	mRNA-seq
ALL	114	50	2	21 T	12 D
AML	112	52	NA	20 T + 2 D	~100
NBL	10	NA	10	254 D	~35 D
OS	19	NA	12	54 D	54 D
WT	48	NA	NA	28 (T and D)	NA
Total	303*		24	379	

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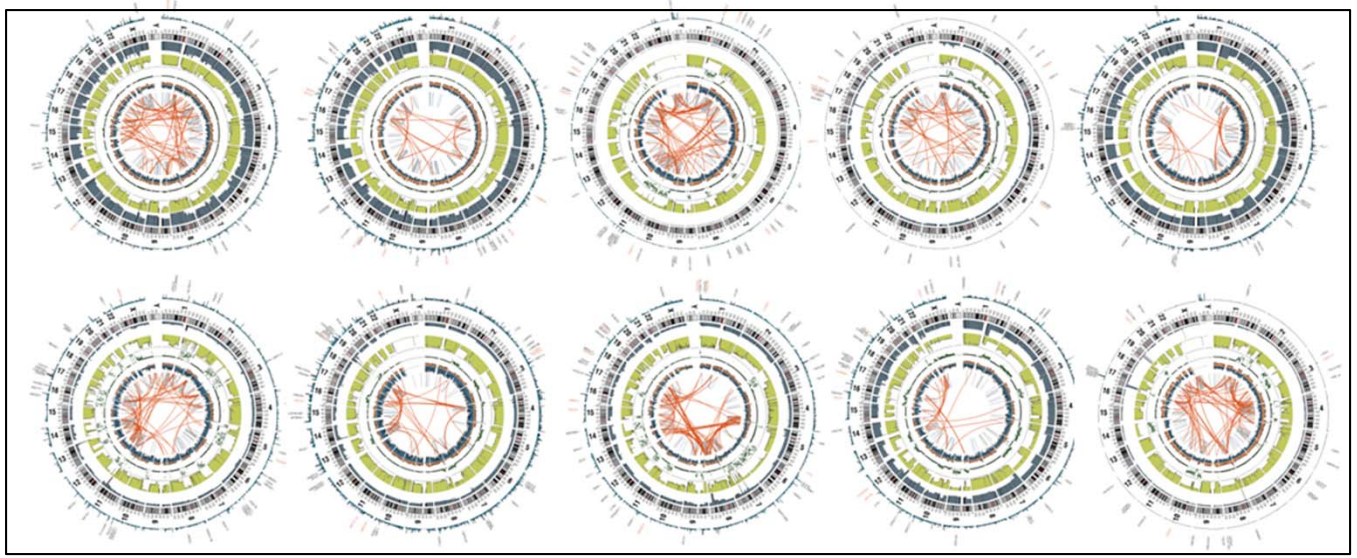
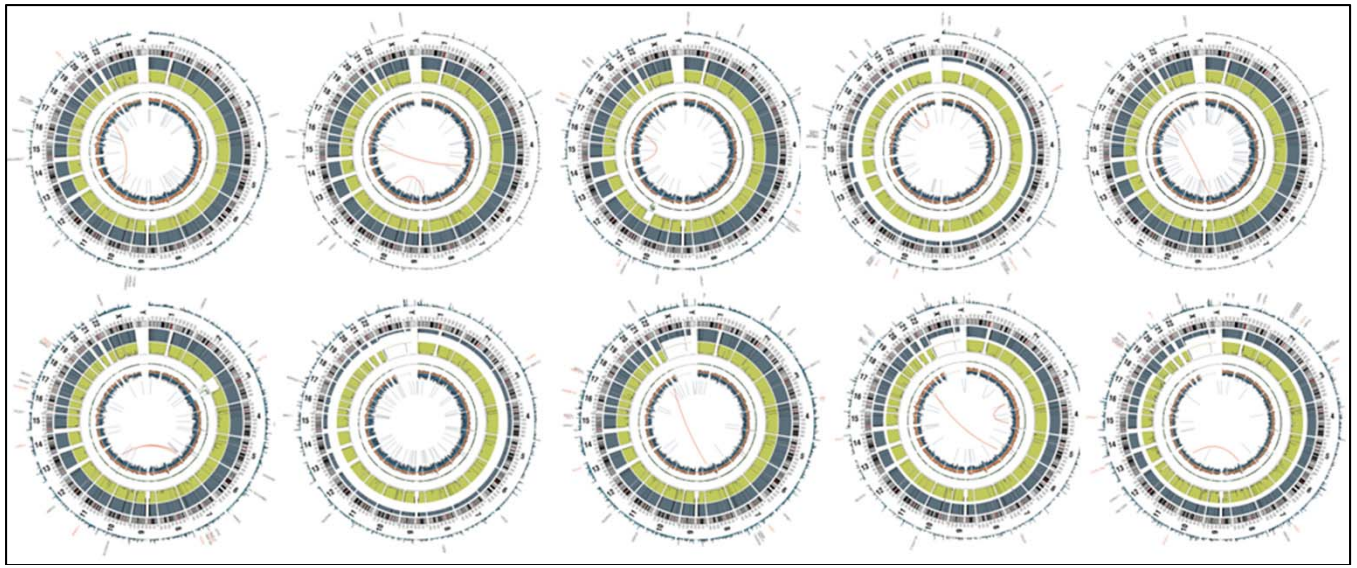
TARGET Whole Genome Sequences show AML “quiet” genome vs Osteosarcoma “agitated” genome

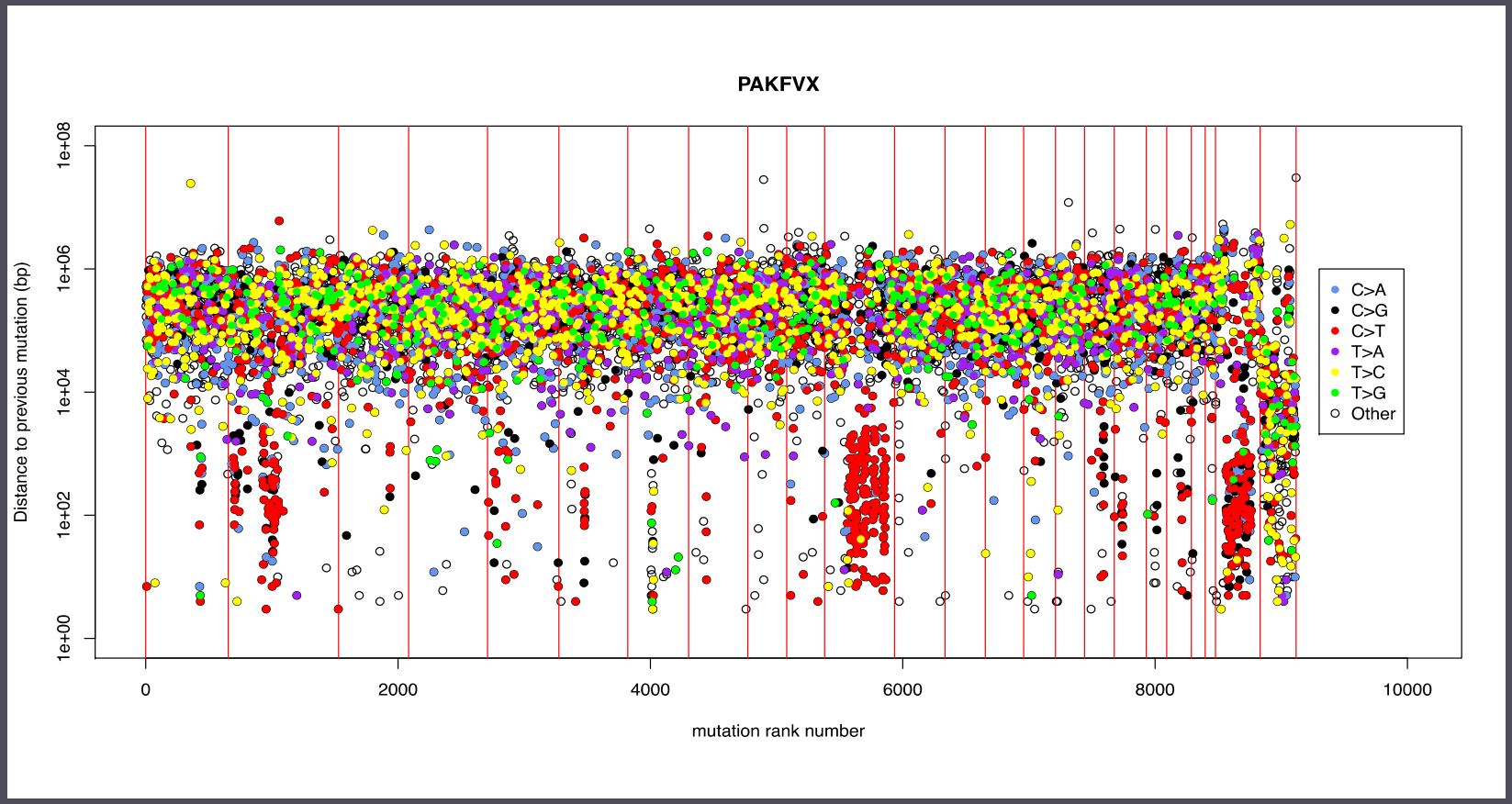


OS



AML

Clusters of mutations close together surround rearrangements – implications for mechanism



Slide adapted from Paul Meltzer, TARGET Osteo Group

CLUSTERS: 17 Osteosarcoma Whole Genomes

•114 TOTAL CLUSTERS (MEDIAN 7; RANGE 1-20)

• 72% SHOW STRAND COORDINATION - NEARLY ALL AT G-C bp

• 4.4% (1538) OF ALL SOMATIC SNV'S ARE IN STRAND COORDINATED CLUSTERS. (MEDIAN 1.9%; RANGE 0.28%-5.6%)

• 71 OVERLAP REFSEQ EXONS

.....In pursuit of mechanistic implications

Slide adapted from Paul Meltzer for TARGET Osteo

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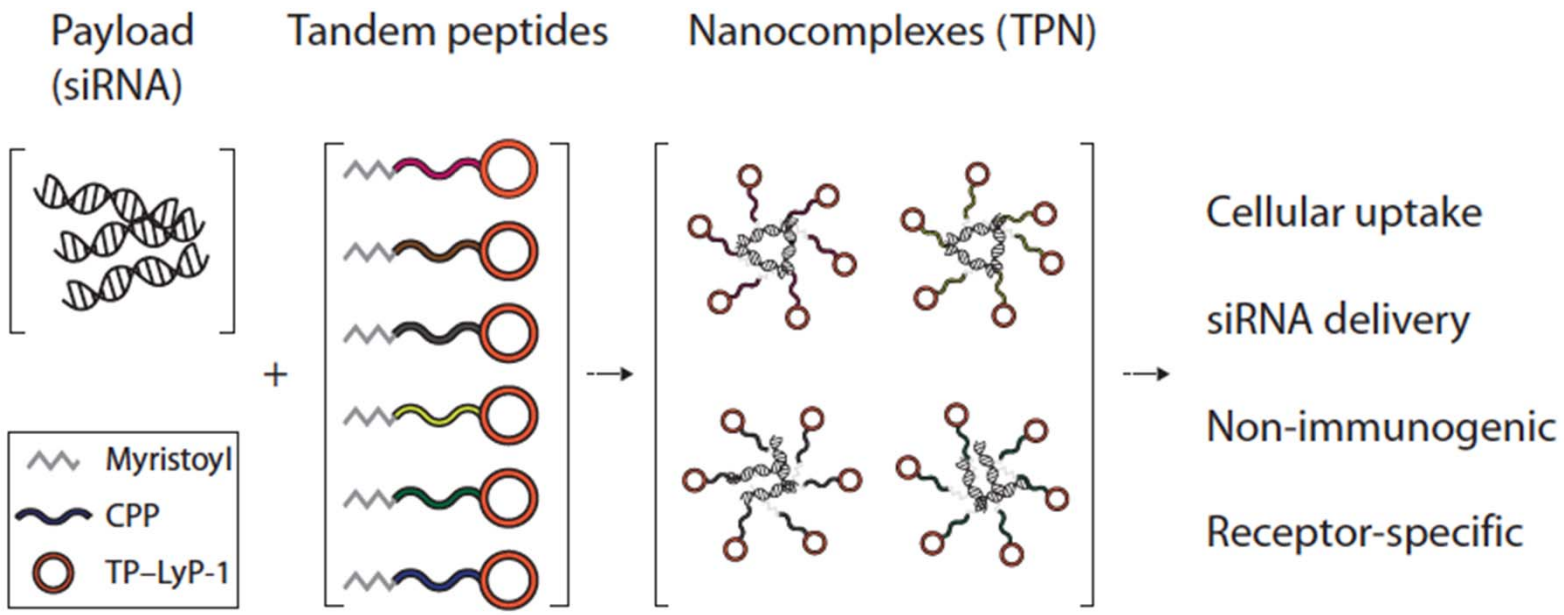
CTD^2 Result: siRNA target gene evaluation ID4 in ovarian tumors



Ren et al Science Translational Med 4, 147, 2012

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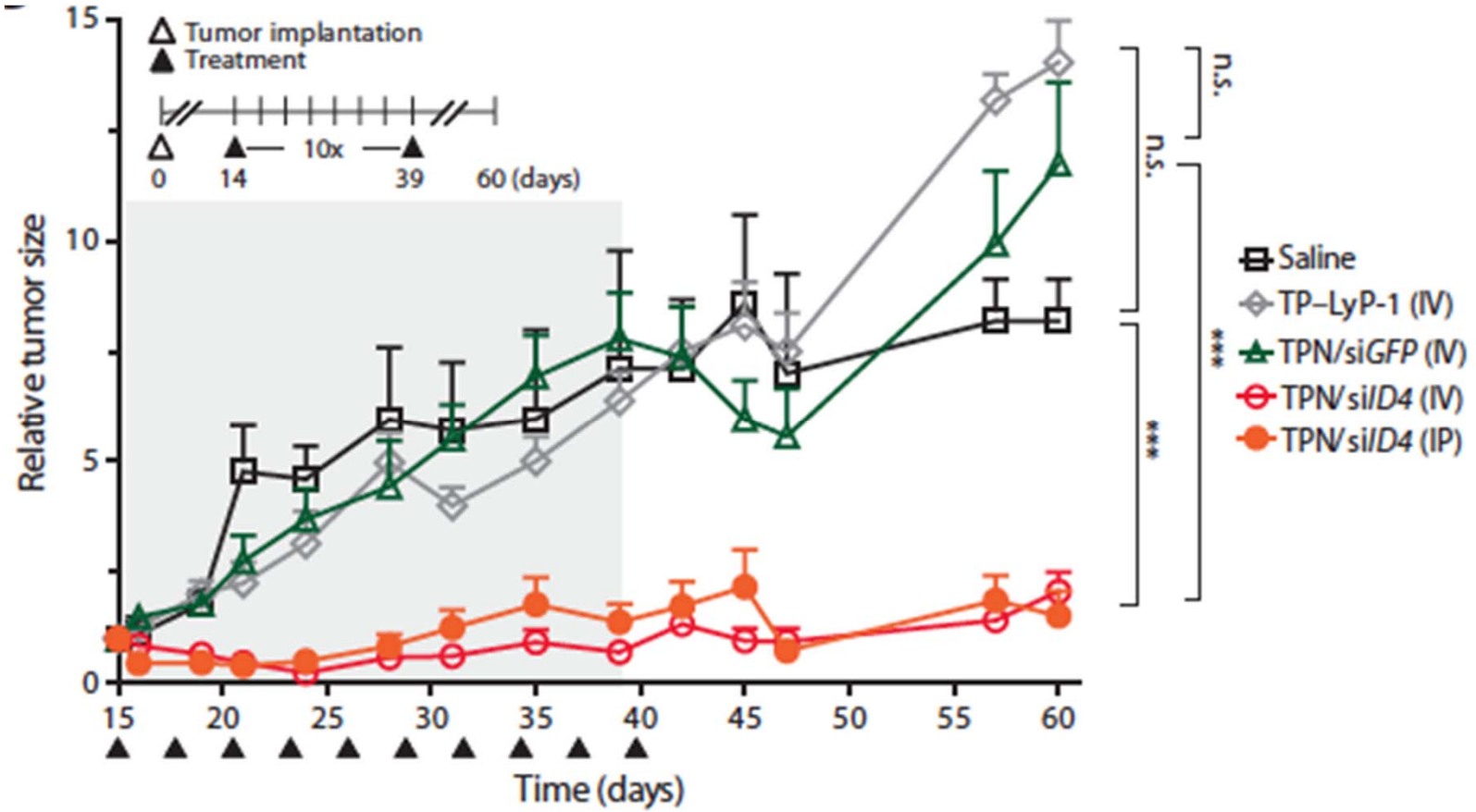
CTD² Result: siRNA target gene evaluation ID4 in ovarian tumors

Human Xenograft test of nanoparticle ID4 siRNA efficacy



Ren et al Science Translational Med 4, 147, 2012

Update FFPE: Formalin Fixed Paraffin Embedded

Critical path to trials and all clinical samples

State of the art

> DNA FFPE ready for many uses

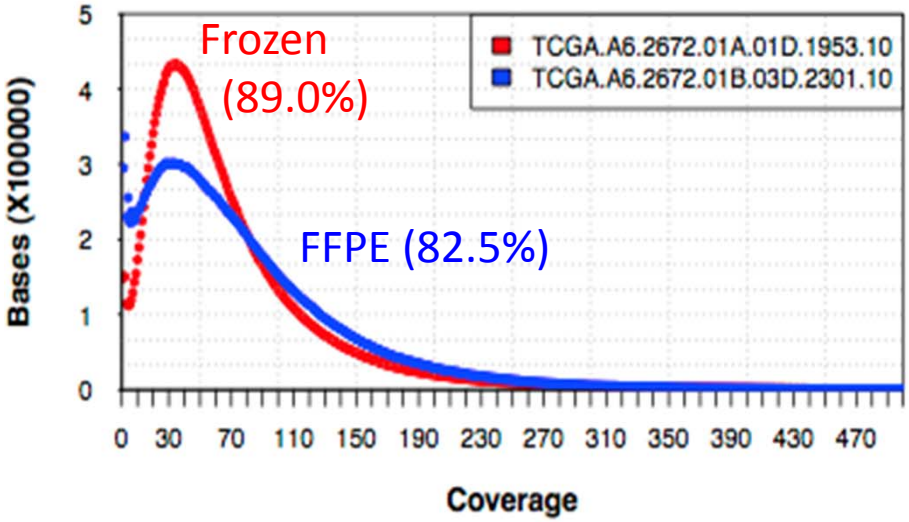
(samples in 5-10 year range; buffered formalin superior)

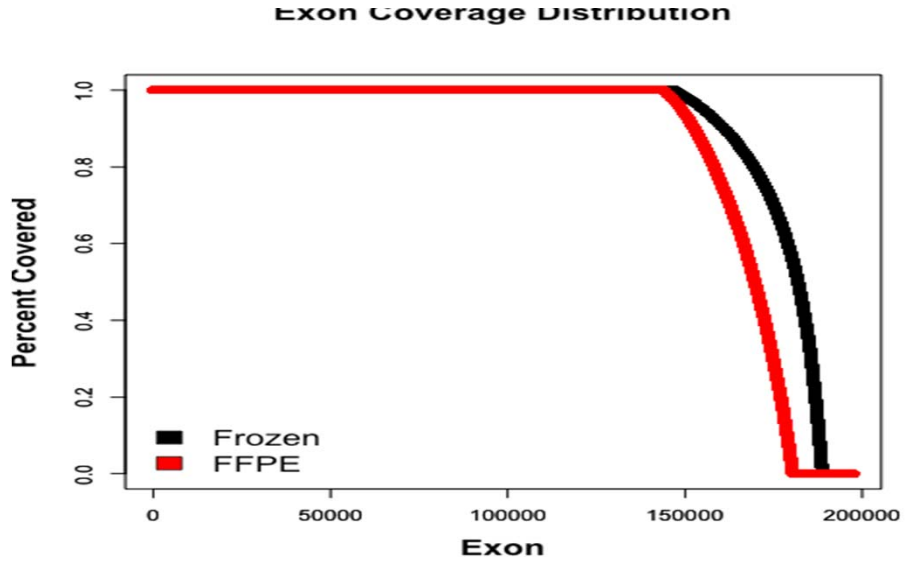
> Becoming strong for RNA alone

> Promising new TCGA protocol for joint DNA/RNA**

**Scott Morris and Erik Zmuda TCGA BCRs

DNA Sequence coverage: Frozen vs. FFPE Exome data

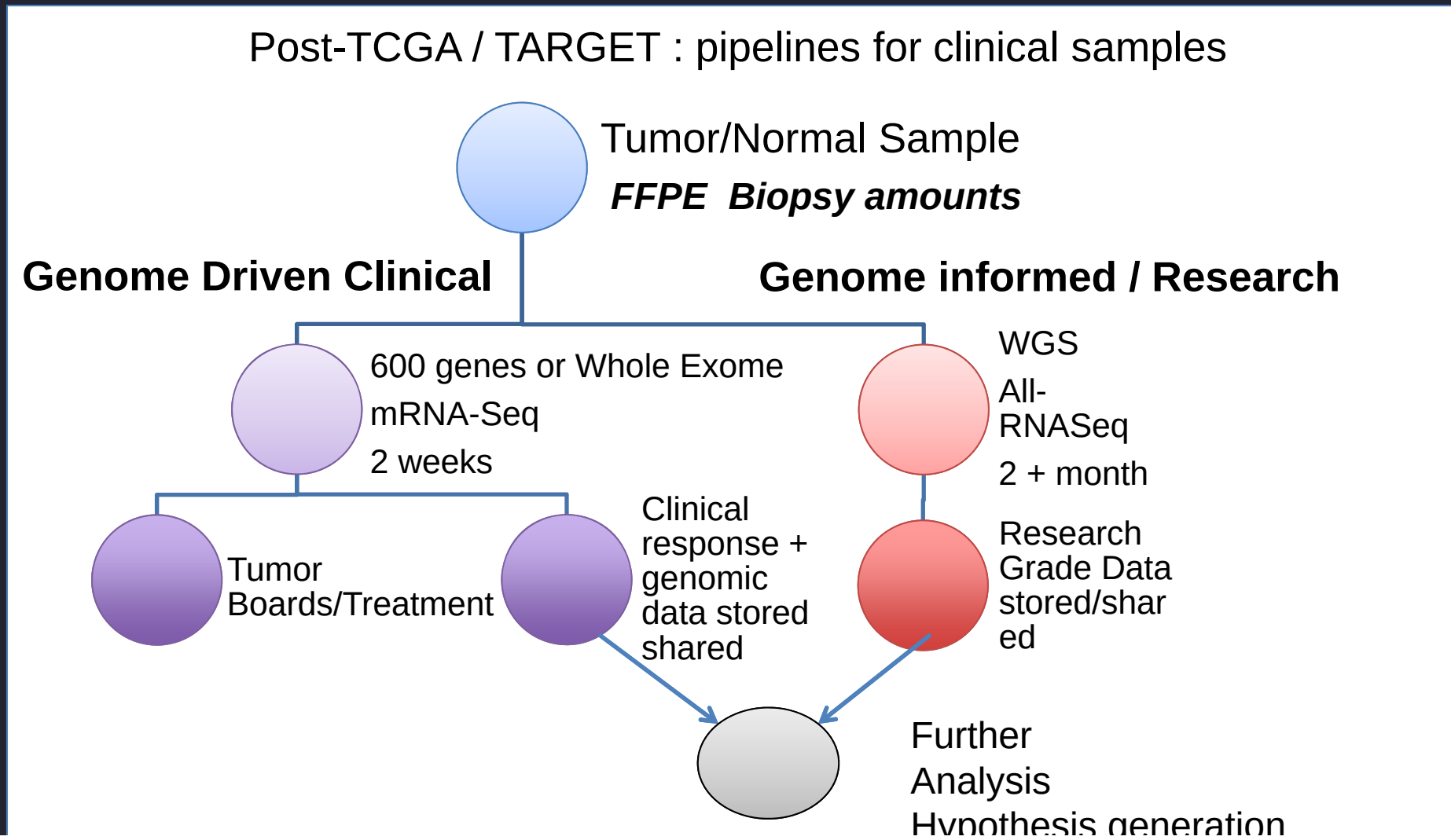




BCR + Baylor TCGA

Major Cancer Genomics Opportunity: Genomics of Progression, Resistance, Metastasis

Path forward - Partner CCG pipelines with new trials: e.g. Alchemist, “Exceptional Cases” .....



Major Cancer Genomics Opportunities 2013 cont...

> Tumor heterogeneity and microenvironment

> Epigenomics broadly defined – Cancer "ENCODE" ?

Provides framework for deep individual projects

> Germline genomics

> Interface with Systems Biology, predictive modeling

Genome Analysis Access and Standards 2013

Whatever problems top your list, you will need

Informatics and Analysis: Toward a Cancer Genome Commons

>Joint mining of genomics data and EHRs

>Data aggregation and access

CGHub is new, working, but will

not scale 10X, 100X, etc

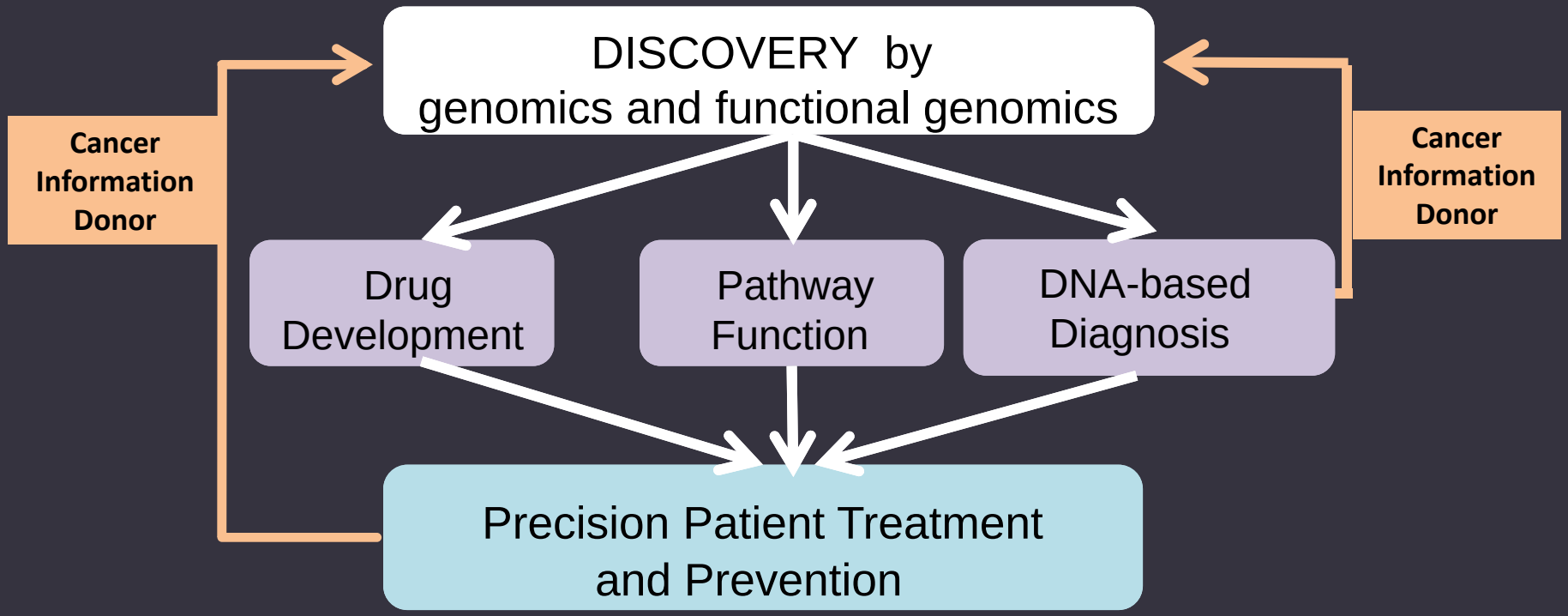
dbGAP will have serious scaling issues

Guidelines and Bake-offs wet and dry

Example = mutation calling series

Future Cancer Genomics at NCI

Make the Cancer Information Donor real: Multiple Steps



1. Partner in trials; answer key questions, fill Library core
2. Pilot RO1 data – a separate Commons Library Branch?
3. Pilot Library branch for true clinical patient donated information

Now Leading CCG

Dr. Louis Staudt

Dr. Stephen Chanock

Joint NCI NHGRI workshop on the future of Cancer Genomics
November 30, 2012

photo: Josh Lewandowski

National Cancer Institute

PRACTICAL ETHICS GUIDANCE FOR BSA MEMBERS

Nancy O'Hanlon
Deputy Ethics Counselor, NCI

National Cancer Institute

GENERAL WAIVER

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

Date: October 25, 2012

TO: Nancy O'Hanlon, Deputy Ethics Counselor, NCI

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

SUBJECT: Conflict of Interest Waiver for Dr. John Doe, Ph.D.

I am writing to request a waiver for Dr. John Doe, a member of the Board of Scientific Advisors (SAB), from the conflict of interest prohibitions of 18 U.S.C. §208(a). Waivers under Section 208(b)(3) may be granted by the appointing official where "the need for the individual's services outweighs the potential for a conflict of interest created by the financial interest involved" and where the individual has made a disclosure of the financial interests at issue. The Office of the General Counsel has determined that you are the appointing official for purposes of Section 208 in accordance with Executive Order 12731 Section 401. Therefore, you have the authority to grant Dr. Doe a waiver under Section 208(b)(3).

Section 208(a) prohibits Federal Executive Branch employees, including Special Government Employees, from participating personally and substantially in particular matters in which any of the following individuals or organizations has a financial interest: (1) the employee; (2) the employee's spouse; (3) the employee's minor child; (4) an organization in which the employee

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RECUSAL

RECUSAL LIST *Updated as of: 10/4/2012*

NAME OF MEMBER: **John Doe, Ph.D.**

ADVISORY COMMITTEE: **Board of Scientific Advisors**

By law, you are prohibited from participating in Board discussions or actions on or relating to any specific party matter involving or affecting any of the following entities:

FINANCIAL INTERESTS:

Name of Entity	Nature of Interest/Relationship	Recusal Expiration Date
Roche	Investment Interest	
American Association for Cancer Research	Board of Directors	
Massachusetts General Hospital / Partners Healthcare	Secondary Employment	
Harvard	Primary Employment	

COVERED RELATIONSHIPS:

Name of Entity	Nature of Interest/Relationship	Recusal Expiration Date
Varian Medical Systems	Scientific Advisory Board	
Cornell University	Spouse's Employment	
University of Texas	Speaking Honorarium	12/31/2012

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Conflict of Interest Provisions

- 18 U.S.C. § 208
  - Criminal Statute
- 5 C.F.R. § 2635.502
  - OGE Regulation

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18 U.S.C. § 208

MAY NOT:

- "personally and substantially participate"
- in a "particular matter"
- in which you have a personal or imputed financial interest
- if the matter will have a "direct and predictable effect" on that interest

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Particular Matters

Two categories of matters:

- Matters involving specific parties
- Matters that do not involve specific parties but focus on the interests of a discrete and identifiable class of persons

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Imputed Interests

- Spouse
- Minor Child
- General partner
- Organization in which one serves as an officer, director, trustee, general partner or employee
- Organization with whom one is negotiating for employment or has an arrangement for future employment

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5 C.F.R. § 2635.502

Appearance Issue

- Should not participate
- In a specific party matter –
  - If the matter will affect the interests of a household member or close relative, OR
  - If you have a covered relationship with a party to the matter (or the party's agent or attorney)

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Covered Relationships

- An entity (other than a prospective employer) with which you have or seek a business, financial or other contractual relationship (e.g. funding sources, award sources)
- The interests of a member of your household or a close relative
- An entity which your parent, spouse or child is seeking to serve as officer, director, trustee, general partner, employee, agent, attorney, consultant or contractor
- Any entity you have served within the last year as officer, director, trustee, general partner, employee, agent, attorney, consultant, contractor or speaker
- Any organization in which you're actively involved

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Interests of Concern

- Employment, agreements
- Service as an officer, director, or trustee
- Business partnerships
- Stocks, bonds, sector funds, options, retirement plans/accounts, debt
- Grant funding
- Consulting
- Paid speaking engagements

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Other Rules

- Gifts – given to influence you as a Board member, or solely because you are a Board member are generally prohibited
- Testimony – need agency permission before testifying as expert for another in matter in which you participated as a Board member
- Charity – can't use title or position, and can't solicit from entity having interests that could be substantially affected by Board activities
- Foreign gifts ≤ $350 or decorations

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Lobbying / Politics

- Appropriated funds cannot be used to "lobby" Congress or encourage others to do so

- The Hatch Act restricts the "political" activities of Board members while you are engaged in the performance of official Government business

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Reissuance of RFA-CA-08-504 Adult Brain Tumor Consortium

Bhupinder S Mann, MBBS
GU, HN and Adult Brain Cancers Therapeutics
Clinical Investigations Branch
CTEP DCTD NCI

William C Timmer, PhD
ABTC Program Director
Clinical Grants and Contracts Branch
CTEP DCTD NCI

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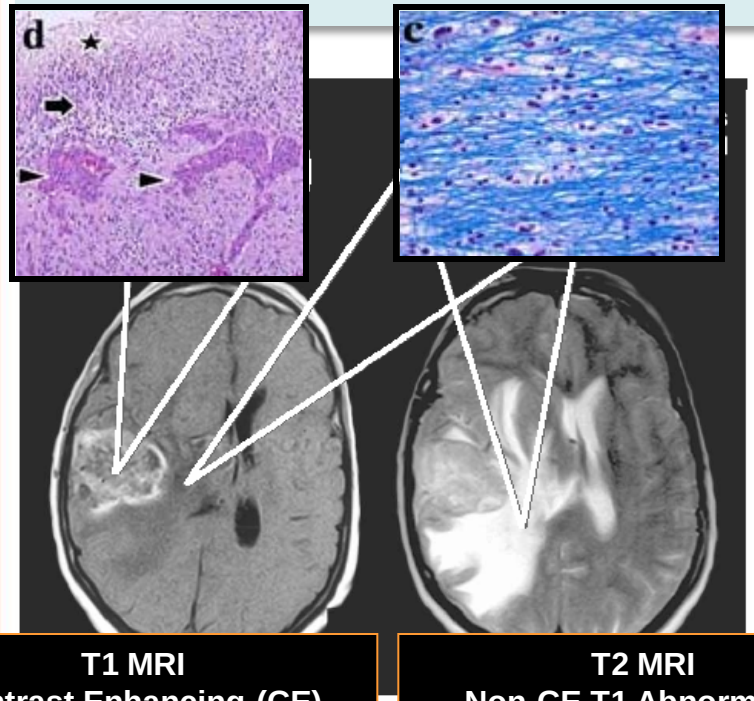
ABTC Focus—Glioblastoma Multiforme

Incidence

- Malignant Brain Tumors: 22,000 annually; 13,000 deaths
- Glioblastoma Multiforme (GBM): 60 – 70%

Current Treatment

- Newly diagnosed: Maximal Resection + RT and Concurrent TMZ + Adjuvant TMZ—Median OS ~ 14 months
- Recurrent: Bevacizumab—Median OS ~ 9 months



T1 MRI
Contrast Enhancing (CE)
Tumor + Non-CE Abnormality

T2 MRI
Non-CE T1 Abnormality
—T2 Hyperintense Infiltration

- Constraints on efficacy of GBM treatments:
  - Infiltrating malignant cells—unable to resect normal brain to get negative margins
  - Radiation tolerance of the normal brain
  - Drug entry across the BBB

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Evolving Understanding of GBM Biology

The Cancer Genome Atlas (TCGA)

- Typical GBM harbors >60 genetic alterations
- Three cellular pathways are affected:
  - Cell proliferation signaling: RTK/PI3K/PTEN
  - Tumor suppressor: p53
  - Tumor suppressor: Rb1
- Gene expression profiling identifies 4 molecular classes:
  - Proneural
  - Neural
  - Classical
  - Mesenchymal

- Opportunity to identify new drug targets
- ~8% of GBM patients participate in clinical trials

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Improving GBM Treatment

Translate accumulating knowledge of ***tumor biology*** into patient focused ***clinical applications***

Need for readily available neuro-oncology expertise for early clinical studies of drugs and other agents likely to be active in GBM—operationally well organized structure, with capacity to adapt new technology rapidly, and incorporate emerging disease biology into early drug development studies

- Obtain *tumor tissue*—before and after (or with and without) drug administration
- Evaluate *drug exposure in tumor* and the *drug effects on the relevant cellular targets*

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ABTC: Operational Since 2009

1999-2008
NABTC (North American Brain Tumor Consortium) and
NABTT (New Approaches to Brain Tumor Therapy)

2009
NABTC and NABTT combined to form
the Adult Brain Tumor Consortium (ABTC)

Co-chair:	Skip Grossman, MD	JHU
Co-chair :	Mike Prados, MD	UCSF
Central Operations Office		JHU
Biostatistics Center		JHU
Pharmacology Center		MGH
Imaging Center		UCSF

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ABTC: Strategy Since Inception 2009

Focus on Early Drug Development

➢Rapidly conduct phase I and II studies with emphasis on PK and PD—*incorporate pre- and post- treatment assays: imaging and tissue based biomarkers*

➢Conduit for new ideas between SPOREs, P01, and Cooperative Groups (NCTN)

•New Agents Committee
•Imaging Committee

•Advisory Committee (Members from Brain SPOREs, US Groups, EORTC)

•Investigational Drugs SC
•Brain Malignancies SC
•Planning Committee for the coming CTPM

ABTC Member Institutions:

Cleveland Clinic
Emory University
Harvard University
Henry Ford Hospital
Johns Hopkins University
Memorial Sloan Kettering CC
Moffitt Cancer Center
University of Alabama
University of California at LA
University of California at SF
University of Pennsylvania
University of Pittsburgh
University of Wisconsin
Wake Forest University

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ABTC Studies: Accruing or Recently Completed

Study	Phase New/Rec	Agent	Comments
0901	II Recurrent	Olaratumab + Ramucirumab	Anti-PDGFRα + Anti-VEGFR2 Monoclonal Antibodies
0902	I and II New	Vorinostat	HDACI Phase II with NCCTG
0903	II Recurrent	Cediranib + Cilengitide	VEGFR2 TKI + Inhibition of endothelial cell migration, survival, tumor cell invasion
0904	II Recurrent	GDC-0449	Hedgehog signaling pathway inhibitor
0906	II Recurrent	RO4929097	γ-secretase inhibitor—inhibits Notch signaling in tumor cells +/- Surgery
1002	I and II Recurrent	RO4929097	+/- Bevacizumab
1101	I Recurrent	Mibefradil	Inhibits Ca entry through Cav3 Ca channel leading to cell cycle arrest + Temozolomide

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ABTC Studies: In Review or Development

Study	Phase New/Rec	Agent	Comments
LOI	II Recurrent	Cabozantinib	C-Met and VEGFR2 Inhibitor
LOI	II Recurrent	Ipilimumab	Anti-CTLA-4 Mo Ab
LOI	I and II New	MK-1775	Wee1 Kinase Inhibitor Phase II with Alliance
LOI	II Recurrent	MK-8776	CHK1 Inhibitor
LOI Solicit	0,I,II Recurrent	MLN0128	TORC1/2 Inh:Cancer cell-tumor microenvironment interaction Phase 0/1 followed by RP2 of bev vs. bev + MLN0128

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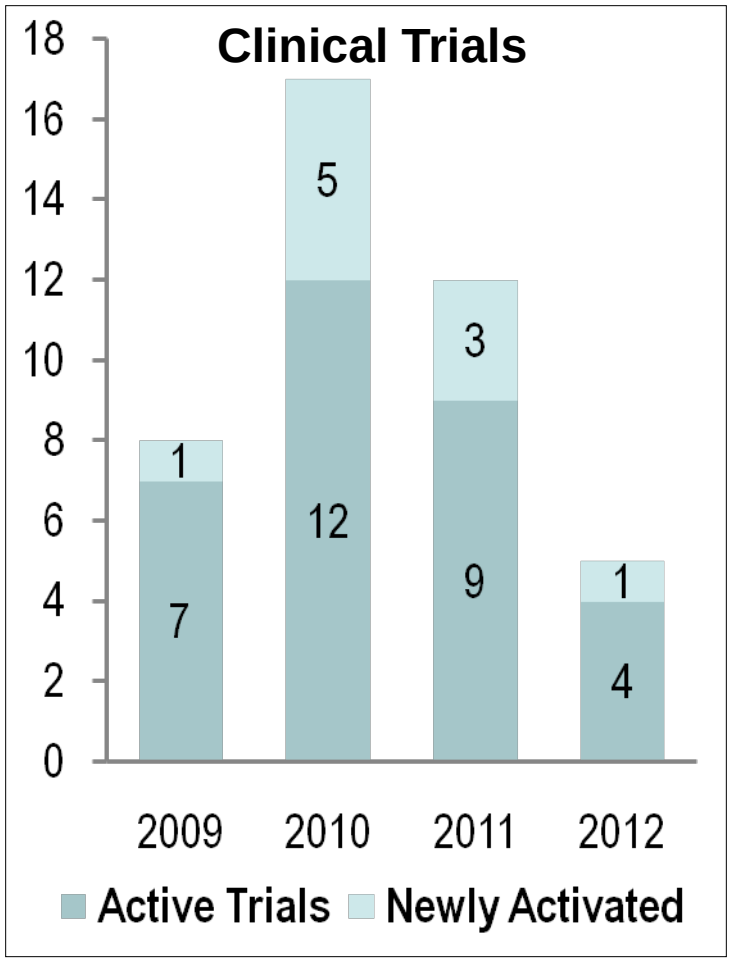
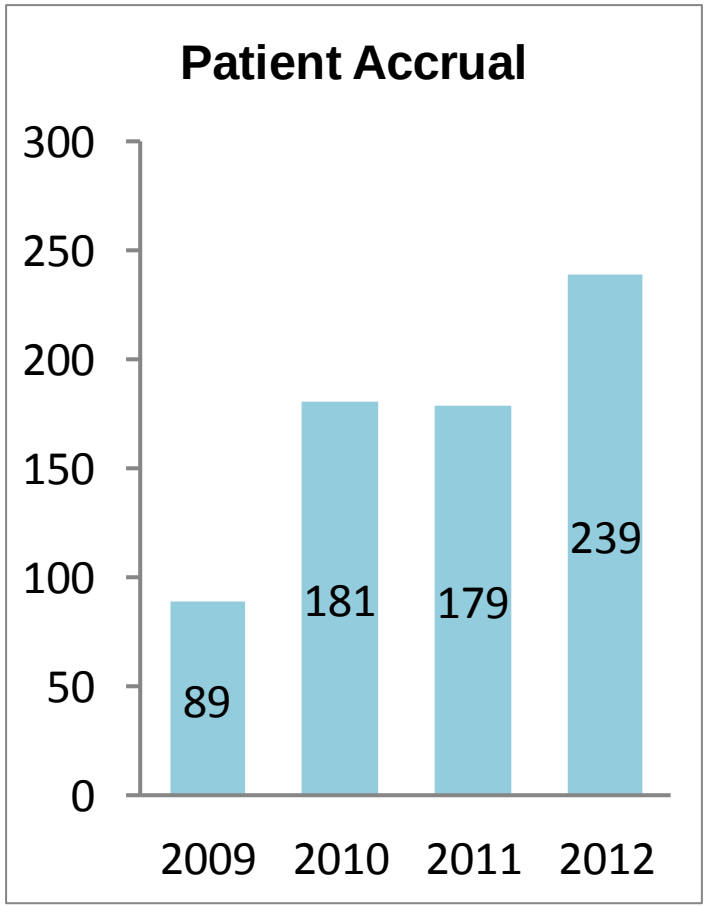
ABTC: Clinical Trials and Accrual





- Current funding can support enrollment of ~150 patients/year
- Two phase I and three phase II studies
- Two additional studies in 2010 due to ARRA funds

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ABTC: Leverage of CTEP-supported Clinical Trials Infrastructure

Adult Brain Tumor Consortium

- is integrated within the CTSU for regulatory and patient enrollment
- utilizes Medidata Rave®
- will have its trials reviewed in the CIRB
- follows OEWG timelines

➢ Thus ABTC is able to do more trials, accrue more patients with less funding

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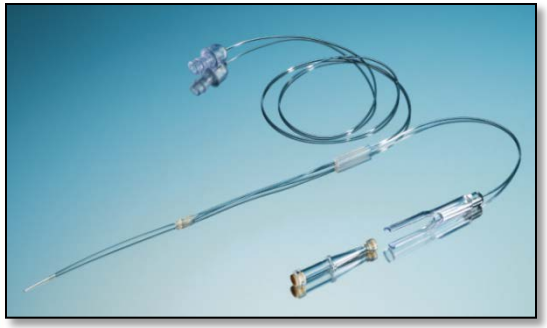
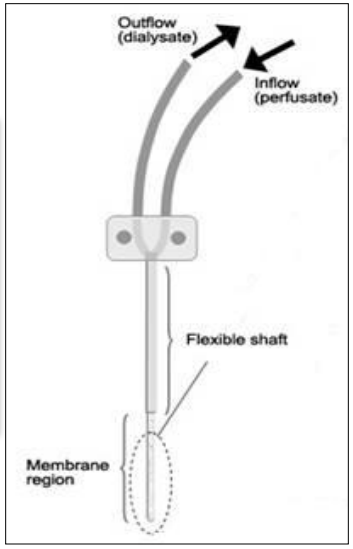
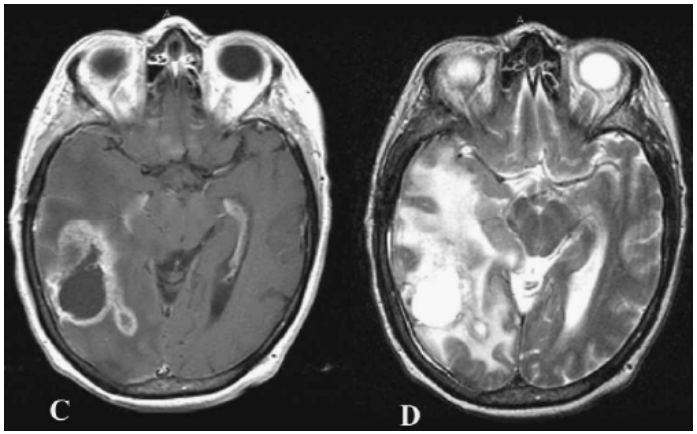
Microdialysis Studies: Drug Entry Across the BBB

Early determination during drug development: Whether the drug crosses BBB and concentrates adequately in malignant tissue?







ABTC investigators are able to conduct MD studies

- **MD catheter in 3 locations: CE tumor, NCE region (T2), and normal brain**
- **Confirm catheter locations, administer drug IV, collect tissue MD samples**
- **Assess drug entry: CE, NCE, and normal brain compared to plasma levels**

- Experience with MTX is published
- Concentration higher in enhancing tumor
- *Proof-of-principal study in gliomas; HDMTX active in PCNSL*

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ABTC 0904: Phase II Study of GDC-0449 (hedgehog signaling inhibitor) in Recurrent GBM

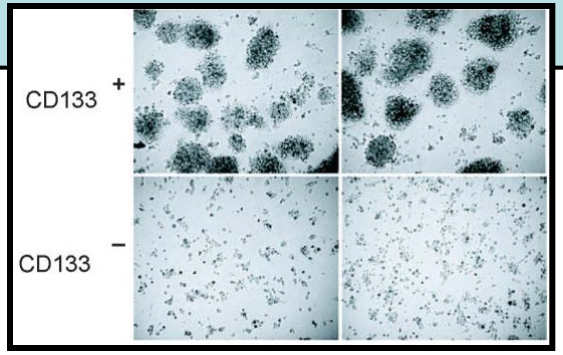
Recurrent GBM
Surgery eligible patients

Arm 1	Arm 2
7days of GDC-0449 Pre-op	No drug pre-op (Control)

Surgery
Tissue for correlative studies

Biomarkers Studies for Drug Effect

- Culture of glioma-derived CD133 + cells by neurosphere assay
- CD133: Neural stem cell surface marker expressed by brain tumor stem cells
- CD133+ cells form neurospheres on cell culture



Clinical Trial Logistics

- Training neurosurgeons in tissue collection
- Coordinating collection and transport of 46 fresh tumor specimens from 8 centers to the central lab at CCCC
  - Tumor mass: 4.5g
  - Time from OR to Lab at CCCC: 20 hrs
  - Viability: 70%

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Feb 2012: ABTC External Evaluation

Summary

- Well organized and developed infrastructure
- Highly qualified group for early translational studies
- Fruitful collaborations with SPORES and groups

Recommendations

- Focus on studies with tumor tissue acquisition and incorporation of imaging & tissue biomarkers to fully use early drug development capabilities
- Further operational improvements:
  - Eliminate low accruing sites
  - Add new members / sites

Impact Score = 2.1

National Cancer Institute

ABTC—Unique Strengths

A core of investigators with expertise in conducting early drug development studies in GBM

- Neuro -surgery, -oncology, -pathology, -imaging expertise
- Central operations to coordinate multiple sites for timely accrual into technically demanding clinical trials
- Manage specialized logistics
  - Training neurosurgeons in viable tumor tissue collection
  - Transport of fresh tumor tissue to a central lab for correlative studies (tumor cell culture)

➢Resources required for early development of GBM treatments are not available under the standard CTEP phase I-II-III drug development programs

➢ABTC functions are distinct from Brain SPOREs: ABTC has the ability to plan and conduct multicenter, early drug development clinical trials

National Cancer Institute

ABTC Funding

Current Award	
$ 2.0 M / year	
Current Expenditures (After administrative reductions)	
Administration (Central office, imaging chair, biostatistics and pathology support)	$ 530,500
PK core	$ 121,000
Capitation	$ 1,100,000
Requested	
$2.0 M / year for 5 years	

ABTC has unique abilities in early drug development: Clinical trials with emphasis on PK and PD; rapidly incorporate tumor biology studies—translational studies required to improve GBM therapy