

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

50th Meeting

BOARD OF SCIENTIFIC ADVISORS

Minutes of Meeting

**November 7, 2011
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, 2011

The Board of Scientific Advisors (BSA), National Cancer Institute (NCI), convened for its 50th meeting on Monday, 7 November 2011, 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 3:10 p.m. on 7 November for the NCI Director's report; a status report from the caBIG[®] Oversight *ad Hoc* Subcommittee; an update on the Chernobyl tissue bank; consideration of request for applications (RFA) and Cooperative Agreements (Coop. Agr.) new and reissuance concepts presented by NCI program staff; and an overview of the NCI Center for Global Health.

BSA Board Members Present:

Dr. Todd R. Golub (Chair)
Dr. Francis Ali-Osman
Dr. Christine B. Ambrosone
Dr. Andrea Califano
Dr. Michael A. Caligiuri
Dr. Arul M. Chinnaiyan
Dr. Curt I. Civin
Dr. Robert B. Diasio
Dr. Jeffrey A. Drebin
Dr. Karen M. Emmons
Dr. Betty R. Ferrell
Dr. Stanton L. Gerson
Dr. Joe W. Gray
Dr. Mary J. C. Hendrix
Dr. Timothy J. Kinsella
Dr. Joshua LaBaer
Dr. Theodore S. Lawrence
Dr. James L. Omel
Dr. Lincoln Stein

Dr. Victor J. Strecher
Dr. Louise C. Strong
Dr. Frank M. Torti
Dr. Irving L. Weissman

Board Members Absent:

Dr. Sangeeta N. Bhatia
Dr. Chi V. Dang
Dr. Ronald A. DePinho
Dr. Brian J. Druker
Dr. Kathleen M. Foley
Dr. Sanjiv S. Gambhir
Mr. Don Listwin
Dr. Maria E. Martinez
Dr. Luis F. Parada
Dr. Stuart L. Schreiber
Dr. Bruce W. Stillman
Dr. Gregory L. Verdine

Others present: Members of NCI's Senior 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 50th regular meeting of the BSA and welcomed current and new members of the Board, NIH and NCI staff, guests, and members of the public. Board members were reminded 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.

II. CONSIDERATION OF THE 20 JUNE 2011 MEETING MINUTES—DR. TODD R. GOLUB

Motion: The minutes of the 20 June 2011 meeting were approved unanimously.

III. REPORT OF THE DIRECTOR, NCI—DRS. HAROLD VARMUS, DOUGLAS LOWY, AND JAMES DOROSHOW

Dr. Harold Varmus, Director, NCI, welcomed members and provided information about the Institute's budget for the current and upcoming fiscal years (FY) as well as other NCI news.

Budget. Dr. Varmus informed members that the NCI's budget for FY 2011 (\$5.059 billion [B]) was 1 percent below the FY 2010 level. Despite a large commitment base, the NCI remains committed to maintaining the numbers of grants awarded, supporting genomics activities, and refining the clinical trials system. Members were reminded that NCI programs recently experienced across-the-board reductions and that approximately 1,100 new research program grants (RPGs) at a 14th percentile success rate were awarded, which is similar to the NIH's overall success rate.

Dr. Varmus told members that the NIH is operating under a continuing resolution (CR), and its FY 2012 budget is expected to differ from the FY 2011 level by -1 to +3 percent; budget proposals are under discussion in both the Senate and House. He noted that the NCI has adopted a conservative approach by paying non-competitive renewal RPGs at 90 percent and new and competing awards at 80 percent until the budget is finalized. Funding has been made at the 7th percentile, with consideration for additional grants that scored in a lower percentile. At the July 2011 NCI senior leadership retreat, a consensus was reached to not continue reductions across the Institute but rather identify programs that could be decreased or stopped. BSA member Dr. Chi V. Dang, Professor of Medicine, Division of Hematology-

Oncology, Department of Medicine, and Director, Abramson Cancer Center, and Director, Abramson Family Cancer Research Institute, Perlman School of Medicine, University of Pennsylvania, attended the retreat as the Board's representative.

Members were told that the NIH is preparing the FY 2013 budget for submission to the Office of Management and Budget (OMB). Each Institute and Center (IC) is submitting ideas for three new initiatives to the NIH Office of the Director; the NCI's ideas cover cancer drug development, genomics, and prevention. Dr. Varmus also informed members that the NCI has begun to prepare its bypass budget proposal for FY 2013, which will feature six cancers not covered in last year's report.

NCI Activities. Dr. Varmus informed members that: 1) in response to the 24 questions posted as part of the Provocative Questions Initiative RFA, more than 700 letters of intent (LOIs) had been received. Members were told that he and Dr. Edward Harlow were writing an article on this exercise, which will provide a new means for setting priorities by involving the cancer research community; 2) the issue of drug shortages has become a widespread topic with the release by President Obama of an Executive Order that: (a) strengthens notification requirements to the U.S. Food and Drug Administration (FDA); (b) expedites FDA review of production facilities; and (c) charges the U.S. Department of Justice to look at the generic drug market. Some legislation on the issue is pending, and several reports have been released regarding the FDA's management of the problem and an analysis of the market forces. Discussions about various approaches to the shortage continue within the Department of Health and Human Services (HHS), including incentives and penalties; 3) as a follow up to the discussion of the R21 award mechanism at the previous BSA meeting, the NCI is preparing an Omnibus announcement for the R21 award that will eliminate the multiple R21 initiatives; and 4) an advisory committee to the NCI-Frederick operations has been established. The committee requested the development of a website that lists all NCI-Frederick services available to extramural investigators and supported the development of a contractor Cooperative Research and Development Agreement (CRADA).

International Cancer Research Activities. Dr. Varmus reported on a September meeting of leaders from cancer research and funding organizations from 15 to 18 countries to discuss common issue, including tobacco control and product packaging, genomics, improving the care of patients in poor countries, establishing research bases in low- and middle-income countries, prevention policies in different countries, and training, among other topics; proceedings from the meeting are being prepared. Dr. Varmus also described his recent trip to East Africa, where he participated in the groundbreaking of a new cancer research hospital in Kampala, Uganda, and visited Rwanda. The NCI has provided longstanding support of cancer research in Uganda with Burkitt's lymphoma being of particular research interest given the disease's association with the Epstein-Barr virus (EBV) and malaria. A collaborative opportunity exists to understand the disease better with new genomics technologies and development of EBV vaccines. Rwanda has a strong commitment to health with a universal child early vaccination program, including a human papillomavirus (HPV) vaccine initiative. Dr. Varmus observed that both Uganda and Rwanda will benefit from the use of mobile health tools and information exchanges through electronic devices to improve pathology, agent selection, and other aspects of cancer care.

BSA Role. Dr. Varmus reviewed a number of topics in which the BSA could engage, such as: 1) the NCI's overall genomics efforts, including the Cancer Genome Atlas (TCGA) and biological clinical issues that emerge from the findings of TCGA; 2) new approaches to combining molecular biology and genomic information and biomedical tools to improve diagnosis and classification of cancer as described in the report *Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease*; 3) biomarker issues; and 4) team science.

NIH Interactions with Industry. Members were told that the NIH is interested in forming closer ties with industry regarding target validation or discovery and validation of antibodies and immune strategies as well as specifying potential targets for therapeutics. This involves sharing information and collaborating in the pre-competitive space with the aim of a deeper understanding of phenotype and genotype through modern molecular biology. The cancer community has a significant role, particularly with the improved understanding of genotype gained from the Genome-Wide Association Study (GWAS)

and high-throughput sequencing studies. Drs. Varmus and James Doroshow, Deputy Director for Clinical and Translational Research, will plan a steering committee that will include Dr. Golub and representation from other advisory groups as well as stakeholders from the private and nonprofit sectors. Plans are to hold a workshop to determine the extent to which data aggregation in an open site for collaborative research might help accelerate the efforts to find better ways to prevent and treat cancer.

Trans-Institutional Clinical Genomic Efforts. Dr. Doroshow informed members that he attended a strategic retreat in Toronto at the Ontario Institute for Cancer Research, where discussion topics included clinical genomics efforts and how tissues are handled (fixed/not) and curated, genomic information managed and aggregated, and how information could best inform the design and implementation of clinical trials. The premise was to discuss how institutions could improve and share their efforts and knowledge in the context of clinical information for the greater cancer community.

In the discussion, the following points were made:

- < The NCI should consider opportunities to extend pain management and palliative care efforts in countries that are advancing cancer care to reduce the burden of cancer.
- < The California Institute of Regenerative Medicine (CIRM) provides an example of a mechanism that encourages collaboration in the clinical trial process through formation of disease teams from academia and small companies.
- < A major obstacle to team science is recognition in the tenure system. Members encouraged the NCI to provide leadership regarding the level of credit given in publications, such as a white paper or article.
- < Members supported greater interaction between the NCI and industry as many pharmaceutical companies have begun outsourcing a significant amount of their research portfolios to academia.
- < The physics community may provide a model of how to incentivize funding agencies around the world, including obtaining support for sophisticated ideas and sustaining the field.

IV. STATUS REPORT: caBIG[®] OVERSIGHT *AD HOC* SUBCOMMITTEE—DR. DANIEL MASYS

Dr. Daniel Masys, Professor and Chair of the Department of Biomedical Informatics, Vanderbilt University, presented an update on the progress of the cancer Biomedical Information Grid (caBIG[®]) oversight committee. Dr. Masys reminded members that a March 2011 report from the caBIG[®] Working Group concluded that support for clinical informatics tools is mission critical for NCI; however, the overall impact of caBIG[®] was not commensurate with the level of investment in that program. The Working Group identified the lack of independent scientific oversight as a significant problem and recommended the establishment of the BSA caBIG[®] Oversight *ad Hoc* Subcommittee. Subcommittee membership was established in June 2011 and is divided into three subgroups: Bioinformatics and Basic Cancer Research, Clinical and Translational Informatics, and Informatics Infrastructure.

Dr. Masys reported that the Subcommittee has developed a set of project review criteria addressing specific findings from the caBIG[®] Working Group report that will be widely published. The ten review criteria for projects include: a defined basic, translational, or clinical need; predetermined evaluation metrics; the ability to enable data sharing; the flexibility and generalizability to anticipate change; deliverable in time frame and budget proposed; potential breadth of implementation across organizations, a plan for long-term maintenance of the tool and fiscal sustainability; completion of a stakeholder assessment; and the products having enough market value to gain adoption without incentives.

Members were informed that the NCI will monitor ongoing caBIG[®] projects as well as provide project-specific summaries to the Subcommittee for its review. Reviews will follow the procedures of current

NIH study sections, using impact scores to evaluate projects. The impact scores represent the likelihood that the project will make a sustained, powerful impact on the field. Dr. Masys said that impact scores and narrative assessments from project reviews will be reported to the full BSA.

In the discussion, the following points were made:

- < In addition to focusing on specific projects, the Subcommittee is encouraged to collaborate with caBIG[®] leadership to formulate a strategic vision for the overall goals.
- < Subcommittee activities will include identifying emerging challenges, such as clinical genomics, and providing concept-level guidance for addressing those challenges.

V. UPDATE: THE CHERNOBYL TISSUE BANK—DR. RIHAB YASSIN

Dr. Rihab Yassin, Program Director, Cancer Cell Biology Branch, Division of Cancer Biology, presented a brief overview of the Chernobyl Tissue Bank (CTB). Dr. Yassin stated that the CTB was established in 1998 in response to evidence of increased pediatric thyroid cancer rates in the aftermath of the Chernobyl nuclear plant accident. The CTB collects thyroid carcinomas and adenomas from patients from Russia and Ukraine who were 19 years old or younger at the time of the accident. Clinical and pathological data were collected on 3,861 total cases with 2,794 confirmed thyroid cancers by the study's own pathology panel.

Dr. Yassin told members that the CTB is a collaborative, international organization supported by the NCI, the European Commission, and the Sasakawa Foundation of Japan and is managed by a coordinating center at the Imperial College London. The CTB has a complex governance structure led by the Steering Committee, which is composed of representatives from the sponsoring organizations as well as directors of the institutes in Chernobyl countries. CTB tumor tissue sections and extracted deoxyribonucleic acid (DNA) or ribonucleic acid (RNA) can be accessed by investigators through an application on their website. Applications are reviewed by the CTB Advisory Board and are ranked by scientific merit.

Members were informed that the CTB has the largest collection of thyroid tumors in the world. It allows for the exchange of results generated with limited tissue samples and serves as a model for global collaboration on cancer biology. The incidence of sporadic thyroid cancer is rising in the United States and throughout the world. Dr. Yassin noted that the type of sporadic thyroid cancer on the rise, papillary thyroid cancer, is the same type that is observed in the Chernobyl cases.

In the discussion, the following points were made:

- < The Institutional Review Boards (IRBs) of some foreign institutions are stricter than in the United States; for some types of genetic studies, participants would have to be re-consented.
- < There is a dosimetry working group that estimates the radiation exposure of the participants based on the locations of their residences at the time of the accident. No radiation signature has been identified with these thyroid cancers.
- < Aside from effects on workers who cleaned the plant, to date the only scientifically established late health effect of the Chernobyl nuclear accident is thyroid cancer.

VI. RFA/COOPERATIVE AGREEMENT CONCEPTS—PRESENTED BY NCI PROGRAM STAFF

**Division of Cancer Treatment and Diagnosis
A Data Resource for Blood and Marrow Transplants (RFA/Coop. Agr. Reissuance)**

Subcommittee Review. Dr. Curt I. Civin, Director, Center for Stem Cell Biology & Regenerative Medicine, Professor of Pediatrics & Physiology, Associate Dean for Research, University of Maryland

School of Medicine, expressed the Subcommittee's enthusiasm for the reissuance concept. Dr. Civin noted that the Data Resource for Blood and Marrow Transplants funds outcomes research on blood and marrow transplant patients in North America and in collaboration with European and other international organizations. This resource has been visionary in terms of health outcomes research as all blood and marrow transplants are subject to outcomes analysis. He informed members that the Subcommittee approved of the approach, commended outstanding leadership, and noted the impressive number of high-impact publications that have changed the worldwide practice in the blood and marrow transplant field.

The first year cost for one award is estimated at \$2.35 M, with a total cost of \$11.75 M for 5 years.

Motion. A motion to concur on the Division of Cancer Treatment and Diagnosis' (DCTD) Request for Applications (RFA)/Cooperative Agreement (Coop. Agr.) reissuance entitled "A Data Resource for Blood and Marrow Transplants" was approved unanimously.

Office of the Director Innovative Molecular Analysis Technologies Program (RFA Reissuance)

Dr. Tony Dickherber, Program Manager, Innovative Molecular Analysis Technologies (IMAT), Center for Strategic Scientific Initiatives (CSSI), presented a proposal on the request for re-issuance of the IMAT concept. Dr. Dickherber said that a substantial portion of the NCI's technology-driven, investigator-initiated research is funded through the IMAT program. It has a proven record of success and continues to receive a large volume of applications. The program is transdivisional, investigator initiated, and emphasizes the development and testing of high-risk/high-impact, multidisciplinary cancer-relevant technologies. It uses the R21 and R33 grant mechanisms, which are focused on exploratory and early phases of technology development.

Members were told that the IMAT program has supported the early development for a range of technologies that are now commercialized and widely used, including GeneChip[®] arrays, Quantum Dots, and RNALater[®]. IMAT supported the development of the Microfluidic Genetic Analysis platform for sequence detection from whole blood in less than 30 minutes, which was awarded the 2008 Innovation of the Year Award from the Association for Laboratory Automation. The Raindance[®] Microfluidic RDT-1000, a system that isolates nanoliter volumes of solution allowing for the analysis of single cells or single molecules, is in the late stages of development. The NanoTrap[®] Biomarker Discovery Platform uses hydrogel nanoparticles to capture and preserve low-abundance proteins from complex solution and is licensed by Shimadzu Scientific.

Dr. Dickherber informed members that technologies developed through the IMAT program are also being adopted by the research community and include: a platform of integrated genomics approaches to identify and validate cancer targets, developed at the Dana-Farber Cancer Center; and mass spectrometry probes used to measure the concentrations of structurally defined intercellular metabolites, developed at Princeton University. The current IMAT portfolio has 98 active projects developing a diverse range of tools. A large portion of the portfolio is devoted to the development of high-throughput platforms for proteomics, genetics, and epigenetics.

Subcommittee Review. Dr. Joe W. Gray, Gordon Moore Endowed Chair; Chair, Department of Biomedical Engineering; and Director, Center for Spatial Systems Biomedicine; Oregon Health and Science University, expressed the Subcommittee's support for the reissuance, noting that technology advances are currently driving a large segment of biological research. Dr. Gray noted that IMAT is one of the few programs at the NIH devoted to funding technology development, and the project has been incredibly productive, innovative, and high risk. The diversity of enabling technologies developed and their commercial translation has been impressive. Dr. Gray added that the Subcommittee supported approximately a 50 percent increase in the IMAT budget.

The first year cost of 29 R21 and 12 R33 awards is estimated at \$10 M, with a total cost of \$22-27 M for 3 years.

In the discussion, the following point was made:

< NCI should consider methods to inform the research community of newly developed IMAT technologies.

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

**Division of Cancer Treatment and Diagnosis
Pediatric Phase I/Pilot Consortium (RFA/Coop. Agr. Reissuance)**

Dr. Malcolm A. Smith, Associate Branch Chief, Cancer Therapy Evaluation Program (CTEP), explained that pediatric Phase I clinical trials are conducted differently than adult clinical trials. Due to the smaller numbers of patients, multi-institutional studies are generally required and substantial infrastructure must be in place to support the trials. Ethical issues limit allowable risks to children participating in research studies and impact how they are designed. Because of limited interest at pharmaceutical companies for conducting pediatric clinical trials, the NCI plays a critical role in supporting the teams of investigators.

The pediatric Phase I clinical trials resource has been supported by the NCI since 1992. Approximately 20 percent of childhood cancers do not have treatments that are sufficiently effective. Current studies of the Phase I/Pilot Consortium include Phase I trials of the Janus kinase (JAK) inhibitor ruxolitinib for acute lymphoblastic leukemia and the anaplastic lymphoma receptor tyrosine kinase (ALK) inhibitor crizotinib for neuroblastoma, anaplastic large cell lymphoma, and other cancers with ALK mutations. The consortium also develops pharmacokinetic datasets for agents in pediatric evaluation since the pharmacokinetics and adverse effects of an agent may be different in children. The consortium's Phase I clinical trials and pharmacodynamic and pharmacokinetic evaluations serve as the basis of subsequent trials performed by the Children's Oncology Group (COG).

Dr. Smith told members that the scope of the clinical trials performed by the Phase I/Pilot Consortium are quite different from those of the COG. The two groups are integrated in appropriate ways, however. They share meetings, a clinical data management system, and protocol development resources; there is no duplicative infrastructure. If the Phase I/Pilot Consortium were merged into the COG, there is a risk that the pediatric Phase I trials and their needs would be de-emphasized because of the high priority of Phase II and III trials. The Phase I/Pilot Consortium has a strong record of accomplishment and is the premier organization for conducting pediatric clinical trials on anticancer agents.

Subcommittee Review. Dr. Civin expressed the Subcommittee's strong support for the RFA reissuance. The Subcommittee asked about the inclusion of biospecimens in the program's pharmacodynamic/pharmacokinetic strategy. Peripheral blood lymphocytes and serum are currently used to measure pharmacodynamic effects in a pediatric Phase I setting.

The first year cost is estimated at \$3.47 M for one U01 award, with a total cost of \$18.05 M for 5 years.

In the discussion, the following point was made:

< The Phase I/Pilot Consortium has the flexibility to include additional institutions, if needed.

Motion. A motion to concur on the DCTD's RFA/Coop. Agr. reissuance entitled "Pediatric Phase I/Pilot Consortium" was approved unanimously.

NCI National Clinical Trials Network (RFA/Coop. Agr. New)

Dr. Jeff Abrams, Acting Director for Clinical Research, DCTD, introduced the concept and the presenter, Dr. Margaret Mooney, Chief, Clinical Investigations Branch, CTEP. Dr. Mooney provided an overview of the NCI's clinical trials program, which includes 3,100 institutions, 14,000 investigators, and approximately 25,000 patients enrolled on treatment trials annually in the United States. She informed

members that the NCI Clinical Trials Network (NCTN) conducts research on important clinical questions that are not priorities for industry, including combinations of novel agents developed by different sponsors, multi-modality regimens, and therapies for pediatric cancers and rare cancers. During the past six years, the program has supported more than 30 practice-changing trials and over 10 FDA indications for new oncology agents. Dr. Mooney reminded members that the NCI clinical trials system underwent an extensive review and revision and developed new consensus goals to: improve the efficiency of the trial system; incorporate innovative science and trial design; improve trial prioritization selection, and completion; and encourage participation of patients and physicians. Participating groups voluntarily merged from nine adult groups to four adult groups. These and other efforts have resulted in new, aggressive targets to reduce the timeframe about 50 percent for Phase II and Phase III trials among other improvements.

Dr. Mooney informed members that the NCTN RFA concept provides a new organizational structure that consolidates the infrastructure into one pediatric group and up to four adult groups. In addition, the system will better provide opportunities to integrate new agents into trials and evaluate them in molecularly-defined subsets. Dr. Mooney described the six components proposed for the new national network, their review criteria, budget, and tentative timeline for implementation: (1) group operations centers; (2) group statistical and data management centers; (3) collaboration with Canadian clinical trials network; (4) integrated translational science awards; (5) radiation therapy and imaging core services; and (6) lead academic participating sites. All NCTN components will be reviewed at the same time with new review criteria emphasizing integration and collaboration for overall scientific achievement and operational efficiency.

Subcommittee Review. Dr. Michael A. Caligiuri, Chief Executive Officer and Director, The Comprehensive Cancer Center, Ohio State University, expressed the Subcommittee's support for the concept and acknowledged NCI staff's responsiveness to the Subcommittee's concerns. The Subcommittee supported the new emphasis on accruals from all groups, uniform peer reviewed evaluations of applications, focus on late Phase II and early Phase III trials, and the use of the U10 mechanism for individual institutions placing more accountability on the investigators and individual institutions for therapeutic and correlative science trials. The Subcommittee also appreciated the: inclusion of imaging and radiation oncology research; incentives for improved interactions with comprehensive Cancer Centers; increased reimbursement per subject through reduction in accrual rates; and, use of biospecimen repositories, biomarkers, and the imaging cores.

The first year cost is estimated at \$178.24 M for 43-58 U10 and U24 awards, with a total cost of \$879.22 M for 5 years.

In the discussion, the following points were made:

- < The NCTN should incorporate nurse researchers and other professionals with interest in quality of life (QOL), and expand QOL assessment beyond function measures.
- < The NCI was encouraged to include support for the collection of blood specimens as part of the enhanced reimbursement.
- < Cancer prevention and control components will be supported through the Community Clinical Oncology Program (CCOP) in coordination with NCTN on research goals and activities.
- < Staff affirmed NCI's commitment to involve patient advocates.
- < The NCI is refining its informed consent template to allow genomic study of prospective tissue collections.
- < Members requested that the data generated in the trials and clinical metadata be made publicly available at the time of publication. The NCI requires data sharing but acknowledges that contingencies based on licensing by industry partners need to be addressed.

- < Inclusion of a more specific role of genomics in clinical trials to ensure that data are well integrated should be incorporated into the RFAs.
- < NCI staff confirmed that the program includes a diverse patient population, particularly in pediatric oncology as well as in rare tumors in the United States and sufficient African American and Asian participation.
- < The NCI should identify how the NCTN structure can improve and simplify the IRB process. NCI staff noted that accreditation work is underway to establish central IRBs for adult and pediatric studies.

Motion. A motion to concur on the DCTD's RFA/Coop. Agr. reissuance entitled "NCI National Clinical Trials Network" was approved unanimously. The Board also expressed strong enthusiasm for making patient-level data publically available and revising the patient informed consent form to allow use of patient data in genomic studies.

VII. OVERVIEW: NCI CENTER FOR GLOBAL HEALTH—DR. TED TRIMBLE

Dr. Ted Trimble, Director, Center for Global Health (CGH), presented an overview of NCI's commitment to global health and cancer control. Dr. Trimble reminded members that the global burden of cancer has increased significantly rising to 7.6 million in 2008 worldwide. The NCI has a long history of global collaborations that include the International Cancer Genome Consortium (ICCC), International Epidemiology Consortia (IEC), the International Cancer Screening Network (ICSN), and the International Tobacco Control Policy Evaluation Consortium (ITCPEC). Specific cancer research projects and activities span the globe, from China to Costa Rica, and encompass prevention and treatment of many cancers, such as liver, gastric, cervical, and lung cancers, as well as human papilloma virus (HPV) biology and prophylactic vaccines.

Dr. Trimble described the NCI's new management plan with the CGH subsuming the activities of the current Office of International Affairs (OIA), the NCI-Liaison Office in Brussels, the International Network for Cancer Treatment and Research (INCTR), Office of Latin American Cancer Program Development (OLACPD), and Office of China Cancer Programs (OCCP). The OIA oversees the NCI's involvement in the Middle East Cancer Consortium, All-Ireland National Cancer Institute Cancer Consortium, International Union for Cancer Control (IUCC), Breast Global Health Initiative (BGHI), and the African Organization for Research and Training in Cancer (AORTC). The OLACPD has worked with the: American Society of Hematology (ASH) on cytogenetic standardization for certain hematologic malignancies; American Society of Clinical Oncology (ASCO) on clinical trials training workshops; and e Susan G. Komen Foundation on cervical cancer. In addition, OLACPD is involved in developing a cancer research network with the United States, Mexico, Brazil, Chile, Uruguay, and Argentina, with a pilot study in molecular profiling of stage 2 and 3 breast cancer in Latin American women. Dr. Trimble said that the OCCP has been involved with the NIH-China National Natural Science Foundation Collaborative Biomedical Research Program as well as joint workshops on nanotechnology, biomarkers, cancer prevention and screening, bioinformatics, biorepository standards, and environmental pollution and cancer. In addition, several NCI-designated Cancer Centers are active in Africa, including in Uganda, Malawi, Nigeria, Ghana, and Kenya.

The NCI CGH is tasked with coordinating global cancer research across the NCI and its divisions and centers. Dr. Trimble described the CGH's partnerships with NIH institutes and centers including The John E. Fogarty Center, National Institute of Allergy and Infectious Diseases (NIAID), National Heart, Lung, and Blood Institute (NHLBI), and National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) in tobacco and human immunodeficiency virus (HIV) research as well as other programs. Dr. Trimble informed members that the CGH also will take the forefront in NCI's global partnerships with: the Centers for Disease Control and Prevention (CDC), FDA, U.S. President's Emergency Plan for AIDS Relief (PEPFAR), Red Ribbon/Pink Ribbon, and U.S. Agency for International Development (USAID); international organizations, including the World Health

Organization (WHO), the International Agency for Research on Cancer (IARC), and the International Atomic Energy Agency (IAEA); professional societies, nongovernmental organizations, and the pharmaceutical and biotechnology industries. Other roles for the CGH include partnership with other national governments, multilateral government collaborations, and with university global health programs and NCI-designated cancer centers.

Dr. Trimble concluded his presentation with a broad look at NCI's work in global cancer research, which spans the cancer continuum, prevention, diagnosis, treatment, and survivorship, as well as palliative care. Topics include cancer biology, epidemiology, molecular genetics, proteomics, and pharmacogenomics, as well as communications and behavioral health sciences.

In the discussion, the following points were made:

- < The NCI's scope is broad but also will address specific scientific problems, such as the EBV vaccine, methods to control tobacco, and epidemiologic study of human migratory effects on cancer incidence.
- < Many opportunities exist in underdeveloped countries to incorporate palliative care in the NCI's global cancer research studies and collaborative efforts.
- < Members were invited to participate with the National Cancer Advisory Board (NCAB) in a workshop regarding NCI's global health activities.

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

Dr. Golub asked members for comments regarding accessing the BSA members-only website and potential topics for future Board meetings.

In the discussion, the following point was made:

- < Members indicated that the BSA members-only website was easy to use and that all materials were accessible.

IX. ADJOURNMENT—DR. TODD R. GOLUB

There being no further business, the 50th regular meeting of the Board of Scientific Advisors was adjourned at 3:10 p.m. on Monday, 7 November 2011.

Date
Chair, Board of Scientific Advisors

Todd R. Golub, M.D.

Date

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

Status Report:
Cancer Biomedical Informatics Grid (caBIG[®])
Oversight ad hoc Subcommittee

Board of Scientific Advisors
November 7, 2011

March 2011 Report Conclusions

- Support for clinical informatics tools and algorithmic advances is mission-critical for NCI
- Strong community support for original caBIG[®] vision and goals
- caBIG[®] successes offset by several serious problems
- Overall impact not commensurate with level of investment

Conclusions, cont'd

- Main problems with caBIG[®] approach
 - Cart-before-the-horse grand vision
 - Technology-centric approach to data sharing
 - Unfocused expansion
 - One-size-fits-all approach
 - Unsustainable business model for both NCI and users
 - Lack of independent scientific oversight

Immediate Tactical Recommendations

1. **Institute an immediate moratorium on all ongoing internal and commercial contractor-based software development projects** while initiating a mitigation plan to lessen the impact of this moratorium on the cancer research community.
2. **Institute a one-year moratorium on new projects, contracts and subcontracts by caBIG[®].**
3. **Provide a one-year extension on current caBIG[®]-supported academic efforts** for development, dissemination, and maintenance of new and existing community-developed software tools

Immediate Tactical Recommendations

4. **Establish an independent oversight committee,** representing academic, industrial, and government (NCI, NIH) perspectives to review planned initiatives for scientific merit and to recommend effective transition options for current users of caBIG[®] tools.
5. **Conduct a thorough audit of all aspects of the caBIG[®] budget and expenditures.**

caBIG Budget Adjustments

Annual Budget

	FY 2008	FY 2009	FY 2010	FY 2011
caBIG Program	\$52,328,321	\$55,388,488	\$47,222,391	\$33,287,546

ARRA Funding

(adjusted based on BSA report)

Budgeted	Reduction	Adjusted Budget	Expended
\$103,000,000	\$60,699,878	\$42,300,121	\$41,587,373

caBIG oversight committee progress

- Committee membership established
June 2011
- First meeting (in person) July 25, 2011
Chicago
- Subsequent monthly phone meetings to:
 - Develop operating procedures
 - Create working groups

caBIG Oversight ad hoc Subcommittee Group Roster

Daniel Masys, M.D., University of Washington (Chair)

Brian Athey, Ph.D., University of Michigan

Andrea Califano, Ph.D.*, Columbia University

Robert Comis, M.D., Coalition of Cancer Cooperative Groups

Paul Fern, M.B.A., Univ. Washington/Fred Hutchinson Cancer Ctr

Gad Getz, Ph.D., Broad Institute

Joe Gray, Ph.D.*, Oregon Health Sciences University

Rebecca Kush, Ph.D., Clinical Data Interchange Standards Consortium

Lincoln Stein, M.D., Ph.D.*, Ontario Institute for Cancer Research

Lynn Vogel, Ph.D., MD Anderson

Jean Y. Wang, Ph.D., University of California, San Diego
Cancer Center

Executive Secretaries: John Czajkowski, M.P.A. and Paulette Gray, Ph.D.

Committee Management Officer: Ms. Claire L. Harris

* BSA Member

Working Groups

- **Bioinformatics and Basic Cancer Research**
 - projects and activities that support, promote and accelerate basic “wet bench” cancer research, as well as bioinformatics analytical methods and tools for in silico research aimed at molecular biology, cells, tissues, and systems biology.
- **Clinical and Translational Informatics**
 - projects and activities that support cancer-related clinical and translational research, including tissue banking and translation to community practice.
- **Informatics Infrastructure**
 - infrastructure that crosses application domains, such as terminology and vocabulary systems, and knowledge representation standards.

caBIG project review criteria (10)

1. Does the activity, application or resource meet a well-articulated and attainable need of basic, translational or clinical researchers or cancer health care (ie., is there a „driving biological or clinical project“ and are the intended users members of the project team)?
2. How will success or failure be evaluated? Analogous to stopping rules for clinical protocols, what will be the stopping rules for ending the project if it either fails to meet its technical objectives or fails to be adopted even if technically successful?

caBIG project review criteria (10)

3. Will the activity, resource, or application, if successful, make some objectively measurable incremental progress toward the overall caBIG® vision of interoperability of data and systems? Will it enable data sharing and make use of and/or enhance open international standards for research? Will it follow the development principles of caBIG®?
4. Is the activity, resource or application designed to anticipate change in a rapidly expanding knowledge base of science and practice? Flexibility and generalizability are important characteristics for longevity in an era of agile science.

caBIG project review criteria (10)

5. Is the intended deliverable of the project achievable in the time frame and budget proposed?
6. Will the output of the project be broadly implementable by organizations of varying size and sophistication?
Will it be used broadly by organizations and institutions outside of NCI/Cancer Centers (e.g. other NIH centers or academic research organizations)?

caBIG project review criteria (10)

7. Is there a documented plan for long term maintenance, enhancement and fiscal sustainability of the activity, application or resource and its user base?
8. What is the user base and has there been a stakeholder assessment to assure that the activity, application or resource will indeed meet a currently unmet need or a reasonably anticipated future need?

caBIG project review criteria (10)

9. Is the project generalizable and likely to create value or address broad needs across the community of cancer centers and investigators? Or would this activity, resource or application be perceived as a “pet project” of an “in” group?
10. Does the activity, resource or application have enough market value to gain adoption without incentives, or if financial or policy incentives are required, are they justified?

Oversight subcommittee review process and output

- NCI provides
 - Overall tracking grid of ongoing caBIG projects
 - Structured project-specific summary sheets for subcommittee review (template created)
- Workgroup review process uses study section scoring (impact score 1-9), with full subcommittee discussion of split scores
- Subcommittee reports scoring and assessment to BSA

Questions?

**Update:
The Chernobyl Tissue Bank**

**Rihab Yassin, Ph.D.
Division of Cancer Biology**

**BSA Presentation
November 07, 2011**

The Chernobyl Tissue Bank (CTB)

- **Thyroid cancer specimen bank from Chernobyl-affected patients**
- **Initiated in the aftermath of the Chernobyl nuclear plant accident**
- **International collaborative response to emerging evidence of increases in pediatric thyroid cancer**

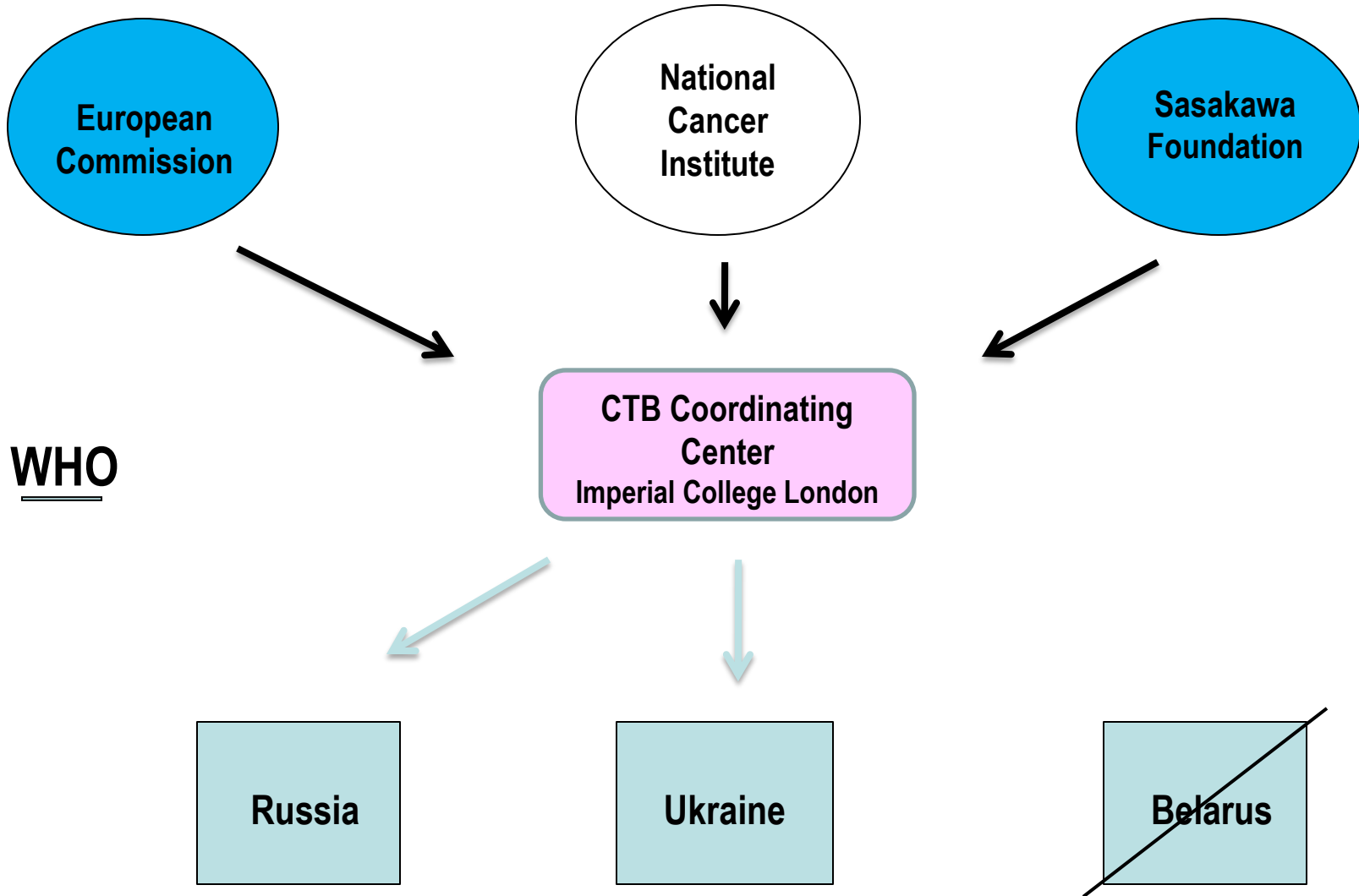
The Chernobyl Tissue Bank

<u>Number of Cases</u>				
<u>Age at Exposure</u>	<u>Belarus</u>	<u>Russian Fed.</u>	<u>Ukraine</u>	<u>Total</u>
0 – 14yrs	1711	349	1762	3822
15 – 17yrs	<u>299</u>	<u>134</u>	<u>582</u>	<u>1015</u>
Total	2010	483	2344	4837

The Chernobyl Tissue Bank

- **Collects thyroid carcinomas/cellular adenomas from the contaminated oblasts**
 - Russia and Ukraine
 - Patients 19 years/younger at the time of the accident
 - Operated on/after October 1, 1998
 - 3861 total cases; 2794 confirmed cancers
- **Also collects clinical/pathological data**
 - Pathology for all CTB cases is reviewed by a renowned Pathology Panel

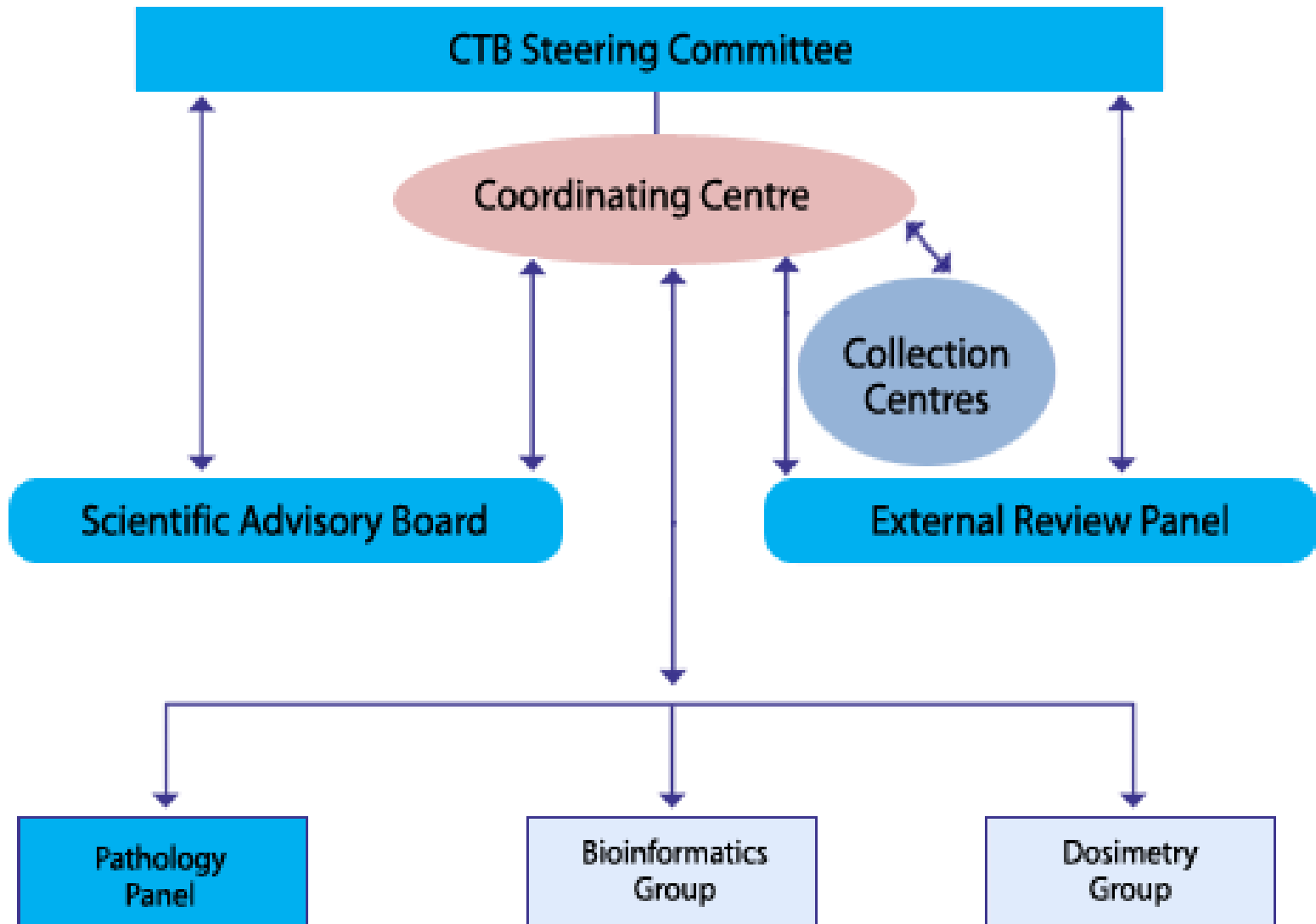
Organizational Structure of the CTB



WHO

The Chernobyl Tissue Bank Governance

(<http://www.chernobyltissuebank.com/index.html>)



Access to CTB Biomaterials

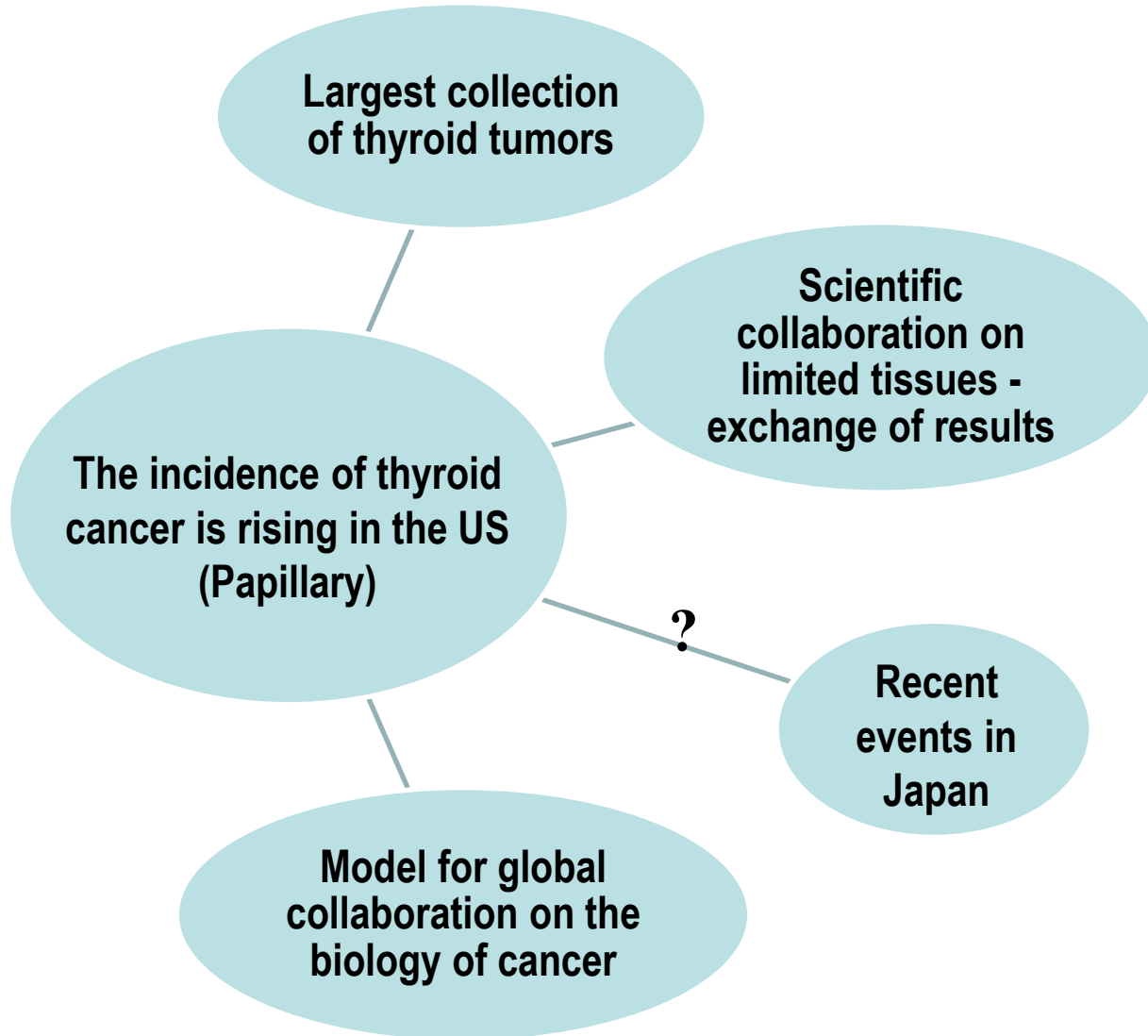
- **Applications reviewed by the CTB External Review Panel**
 - Ranking based on scientific merit
 - Concurrence by the CTB Scientific Advisory Board

- **Does not supply thyroid tissue, only tissue sections and extracted bioanalytes**
 - Preserves valuable specimens for future research
 - Enables broad assessments of the tumors

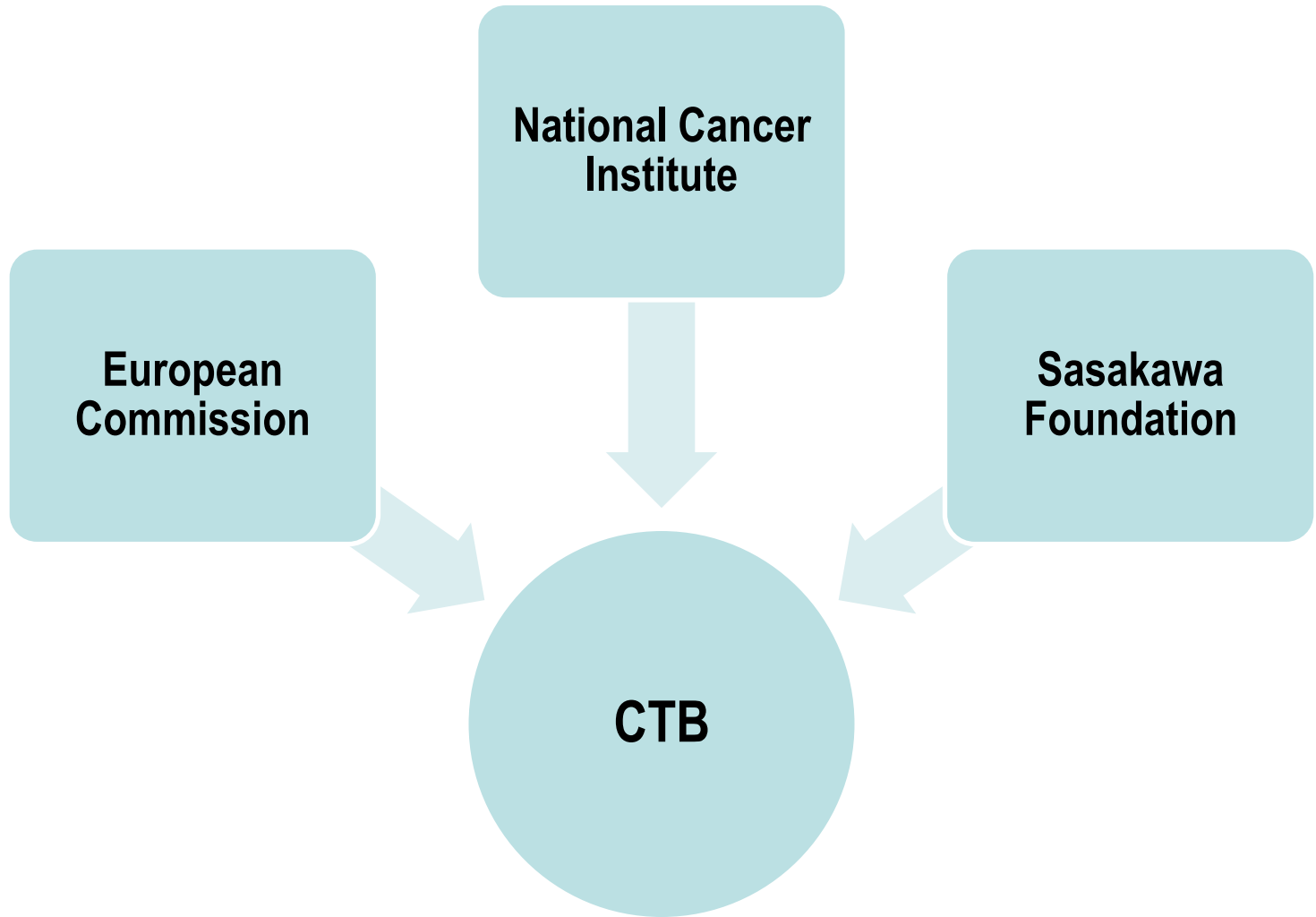
Biomaterials Released to Approved Projects

<u>Type of Sample</u>	<u>Aliquots Released</u>	<u>Released 09/08-present</u>
RNA	2397	726
DNA	1627	818
DNA from Blood	451	305
FFPE Sections	6300	722

CTB Significant Attributes



CTB Collaborative Funding



The Chernobyl Tissue Bank

Questions?

Request for Reissuance
of the



INNOVATIVE MOLECULAR
ANALYSIS TECHNOLOGIES

Request for Applications

Tony Dickherber

Office of Biorepositories and Biospecimen Research,
Center for Strategic Scientific Initiatives
Office of the Director

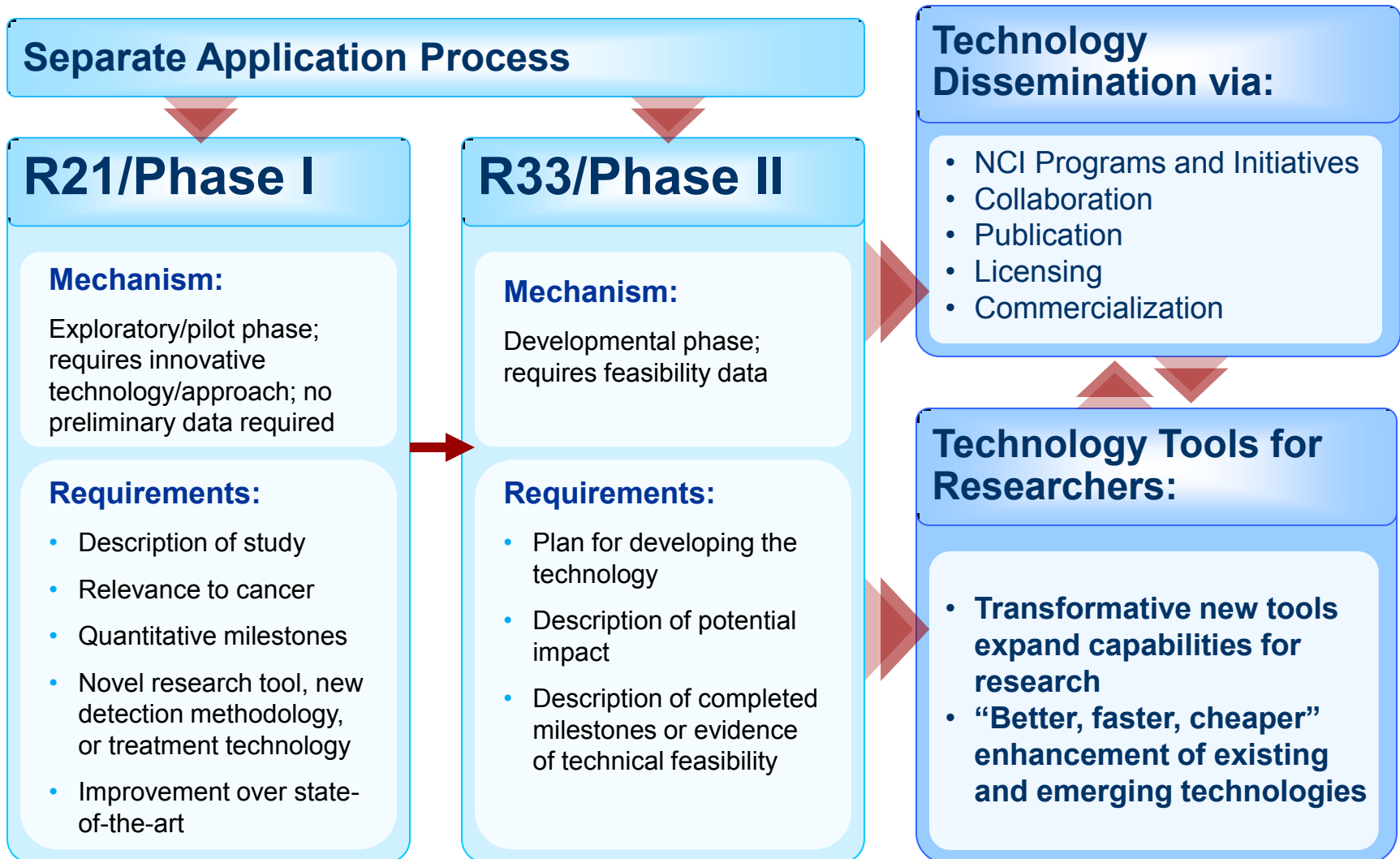
*National Cancer Institute
National Institutes of Health*

Reasons for RFA Reissuance

1. Substantial portion of NCI's technology-driven investigator-initiated research portfolio
2. Proven success record, enabled by a unique mechanism of NCI review
3. Continue to receive a large number of applications

- Utilizes **100% investigator-initiated** R21 and R33 Research Project Grants
- Emphasis on supporting development, testing, and validation of **high-risk/high-impact** multidisciplinary, cancer-relevant technologies
- **Trans-divisional**, cooperative initiative focused on technological innovation with specific exclusions to minimize overlap or duplication with other programs/initiatives [DCTD, DCB, DCCPS, DCP]

Technology Development Structure



Past IMAT credits ...

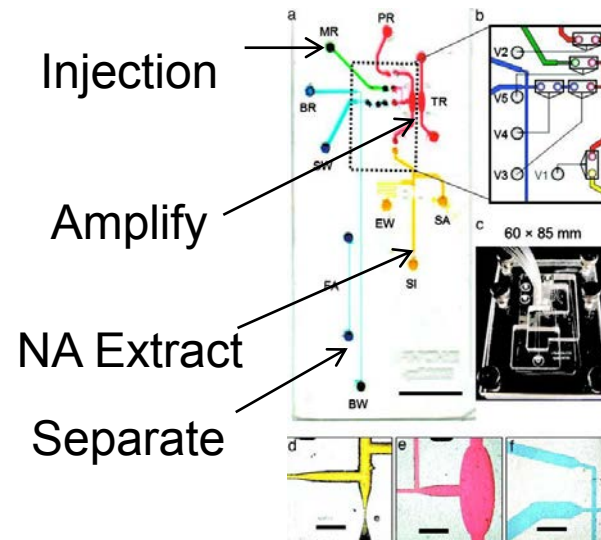
- **ICAT** by Applied Biosystems [2001]
- **Mudpit**, licensed by the Scripps Research Institute [2001]
- **Rolling Circle Amplification**, available from Amersham Biosciences (now GE Healthcare), [2002]
- Affymetrix **GeneChip**[®] and **CustomSeq**[®] arrays [2002]
- Illumina Bead technology (**BeadChip**, **Beadstation**, and **Sentrix BeadArray**) [2004]
- **Quantum Dots**, purchased by Invitrogen [2005]
- **MELT**[®] & **RNA Later**[®] by Ambion [2005 and 2008, respectively]

Microfluidic Genetic Analysis

- Provides target-sequence detection from whole blood in less than 30 minutes
- >25 published articles utilizing this and several awarded patents
- 2008 Innovation of the Year Award, *Association for Laboratory Automation*,
- Licensed by both Lockheed Martin and ZyGEM [2009]



PI: James Landers, PhD
Professor, Dept of Chemistry
University of Virginia

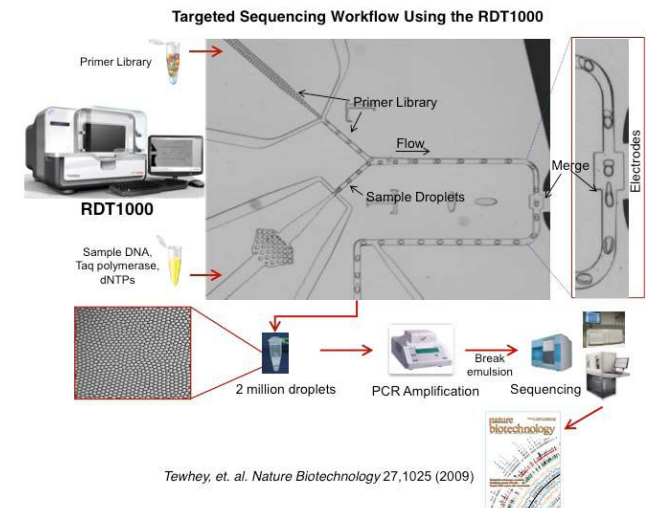
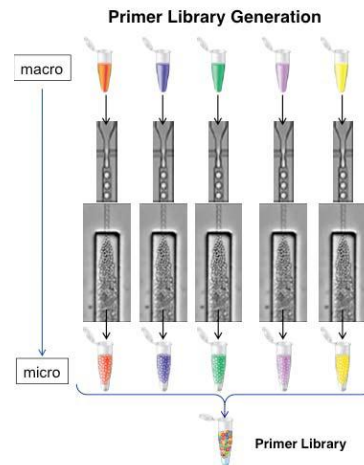


Raindance® Microfluidic RDT-1000

- Platform for isolating nanoliter volumes of solution using oil droplets at rate of 10 million/hour at varying size. Allows isolation of target analytes for single-cell analysis, high-throughput sequencing, etc
- Runner-up for 2009 Innovation of the Year, *Association for Laboratory Automation*
- Commercialized by Raindance® (2009). Currently collaborating with Ambry Genetics on ADMESeq™

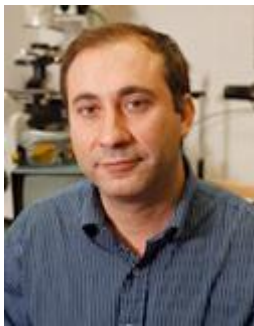


PI: Darren Link, PhD
Co-founder and VP of R&D
Raindance Technologies

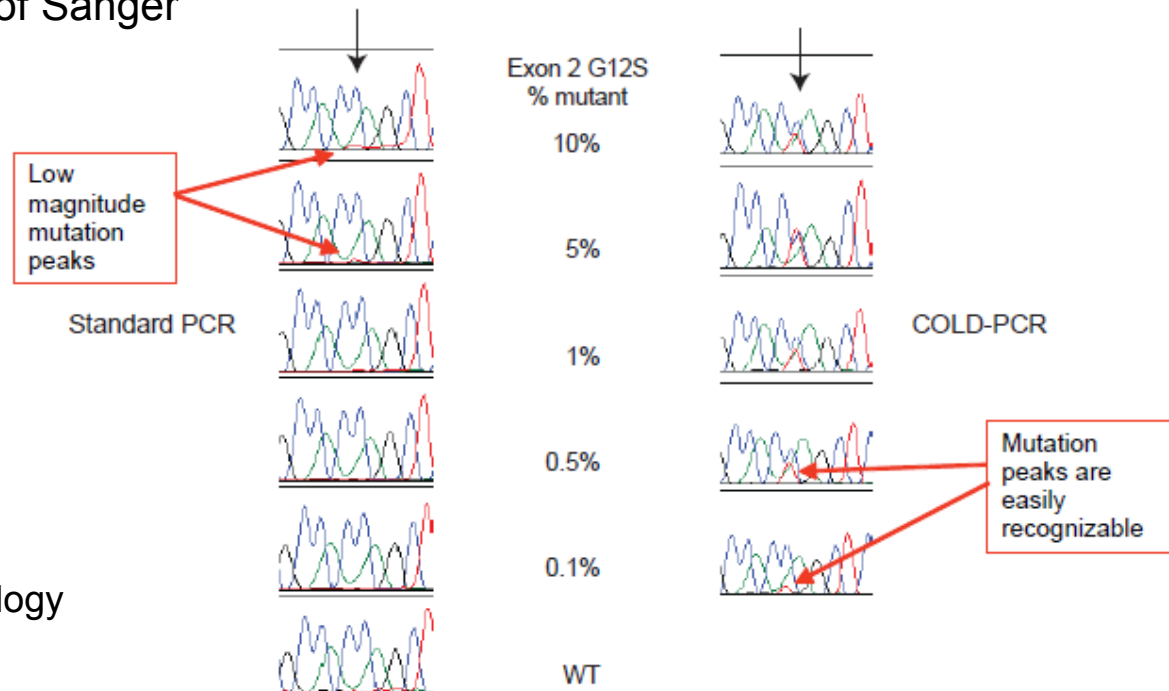




- Rare mutation detection methodology to preferentially amplify mutated DNA via low temperature denaturation during PCR
 - Better than 1 mutant in 1,000 WT copies sensitivity
- Licensed exclusively by Transgenomic [2009] and used in Surveyor suite of Sanger sequencing products



PI: Mike Makrigiorgos, PhD
Associate Professor, Radiation Oncology
Dana-Farber/Harvard Cancer Center

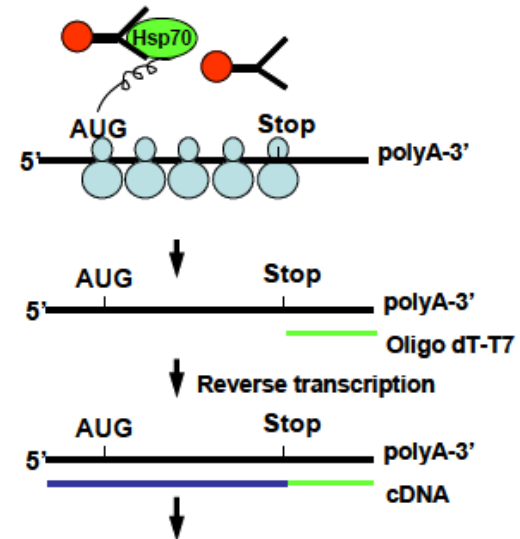


TrIP-Chip Technology

- Affinity capture beads that bind translationally-active mRNA only for high-throughput expression profiling
 - Enables investigation of translational control with limited sample quantities
- Licensed by OceanRidge Biosciences [2010]



PI: Jingfang Ju, PhD
Associate Professor of Pathology
Stony Brook University Medical Center

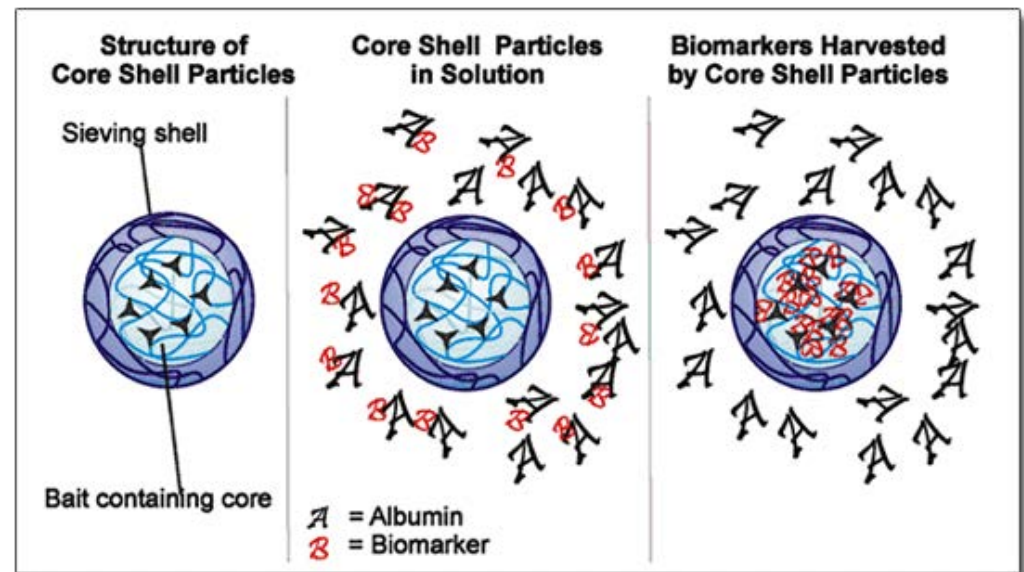


Gene Expression analysis (Microarray, qPCR and Sequencing)

- 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

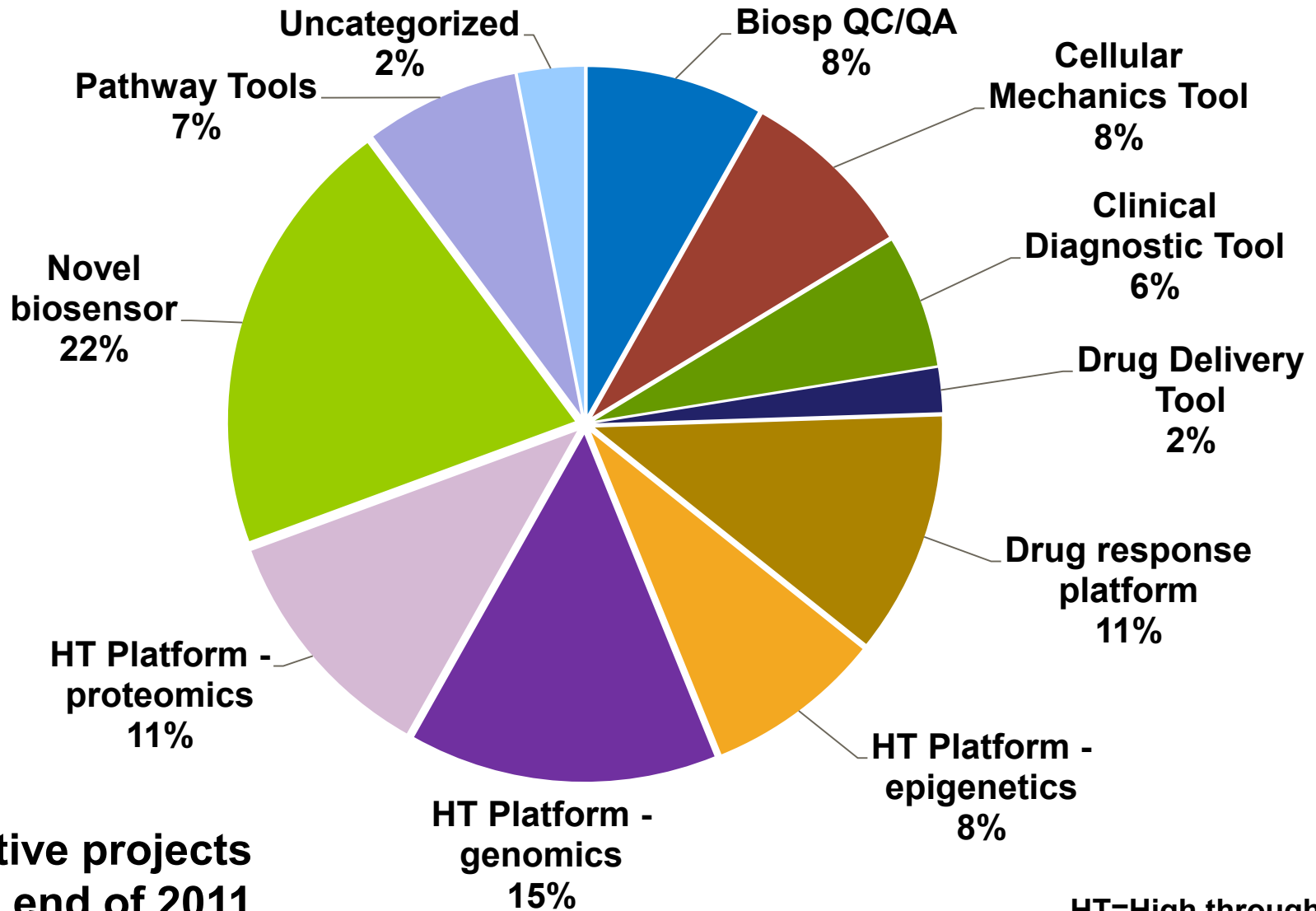


PI: Lance Liotta, MD, PhD
Co-Director, Center for Applied
Proteomics and Molecular Medicine
George Mason University



- Integrated genomic approaches to ID and validate cancer targets
 - William Hahn, Dana Farber Cancer Center (R33)
- MS-probing metabolic dynamics
 - Joshua Rabinowitz, Princeton University (R21)

Diversity of the current IMAT portfolio



**98 active projects
at the end of 2011**

HT=High throughput

RFA Reissuance Requested for

Early-Stage Innovative Technology Development for Cancer Research [R21]	\$5,000,000 (est. 25 new awards)
Advanced-Stage Development, Application and Validation of Transformative Emerging Technologies for Cancer Research [R33]	\$3,500,000 (est. 10 new awards)
Innovative Technologies for Cancer Biospecimen Sciences [R21]	\$800,000 (est. 4 new awards)
Applied Emerging Technologies for Cancer Biospecimen Sciences [R33]	\$700,000 (est. 2 new awards)

- Program presses biology to the forefront of science
 - 3-year R21 is a positive development
 - Suggest a 50% increase in the budget
-

Thank You

IMAT “Staff”

Officer	DOC	Position	Contact
Compton, Carolyn	NCI/OD/CSSI	Acting Director	comptcar@mail.nih.gov
Dickherber, Tony	NCI/OD/CSSI	Program Analyst	dickherberaj@mail.nih.gov
DeClue, Jeffrey	NCI/DEA/SRLB	Scientific Review Officer	decluej@mail.nih.gov
Divi, Rao	NCI/DCCPS	Program Director	divir@mail.nih.gov
Knowlton, J. Randy	NCI/DCB	Program Director	knowltoj@mail.nih.gov
Rasooly, Avraham	NCI/OD/CRCHD	Program Director	rasooly@nih.gov
Sorbara, Lynn	NCI/DCP	Program Director	lynns@mail.nih.gov
Tricoli, James	NCI/DCTD	Program Director	tricolij@mail.nih.gov
Wagner, Paul	NCI/DCP	Program Director	wagnerp@mail.nih.gov

Extra Slides

Program Mission:

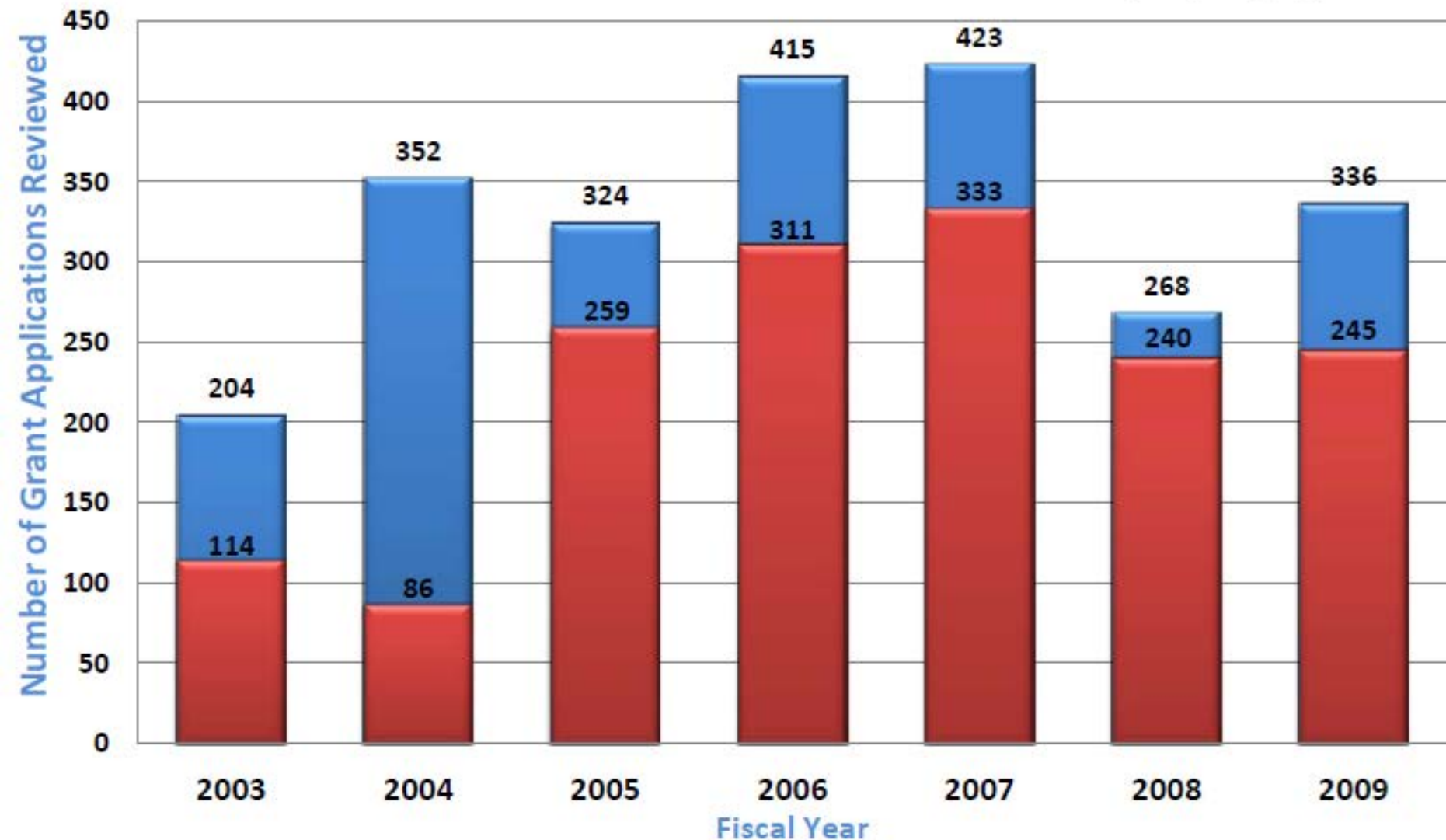
To support the development, maturation, and dissemination of novel and potentially transformative next-generation technologies through an approach of balanced but targeted innovation in support of clinical, laboratory, or epidemiological research on cancer.

Program Goals:

- To focus innovative technology development on cancer
- To solicit highly innovative technology development projects from the scientific and medical communities
- To accelerate the maturation of meritorious technologies from feasibility to development
- To support the development of a diverse, qualified workforce to accomplish the above goals and mission

**All Technology Initiatives
Applications Reviewed by NCI/DEA
FY03-09**

Technology Applications
IMAT(R21/R33) Applications



Withdrawn applications not included. All data obtained from NCI DEA Annual Reports.

Internal Evaluation [eSPA]

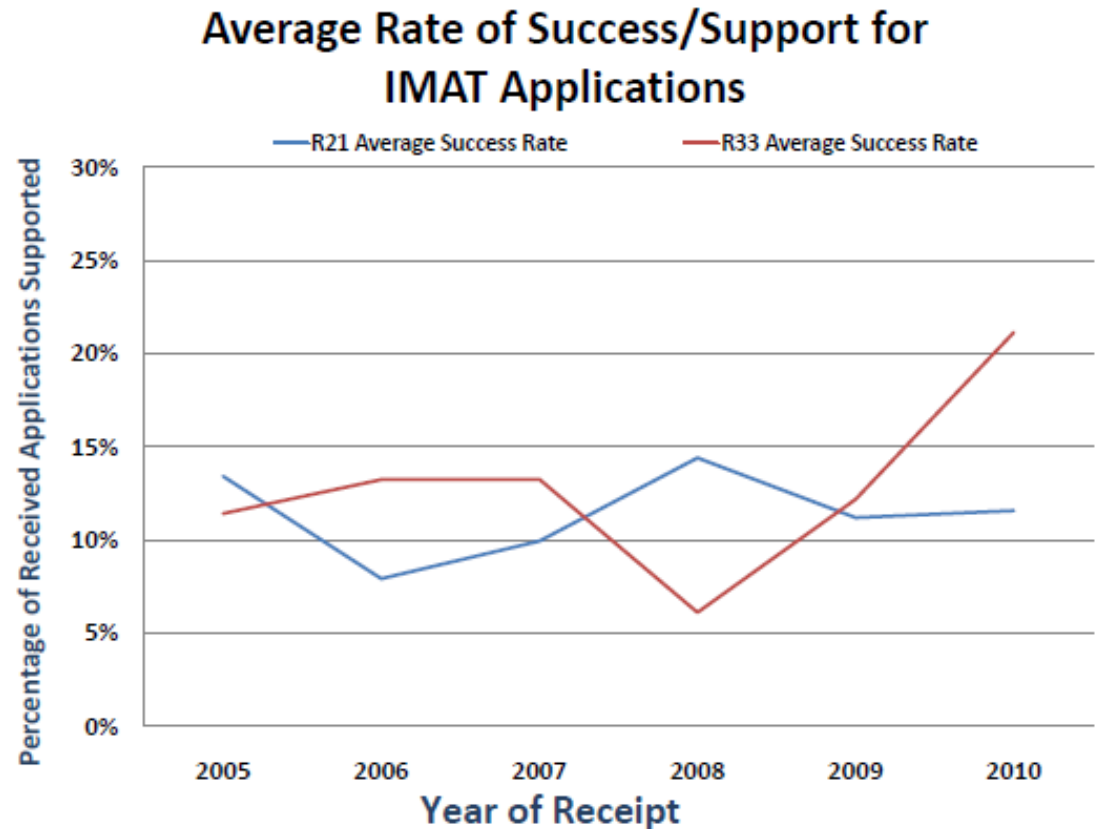
- 46 FOAs from FY99 – FY10 (multiple receipt dates for many of these)
 - Not counting 41 awards pending for FY11

	# Projects	Average Priority Score (old)	Average Priority Score (new)	Average Success Rate	# Publications	Average # of publications per project	Average journal impact factor	Average times cited w/o self
IMAT R21	172	160	24.2	11%	307	1.8	4	10
IMAT R33	171	162	24.2	12%	1,124	7.5	6	37
Total	343	161	24.2		1,431	4.1	5	31

- Top 10% of all R21's account for over 50% of all R21 publications
- Top 15% of all R33's account for 50% of all R33 publications.

Motivation for reissuance request

Year of Receipt	Ave Score of Supported R21's	Ave Score of Supported R33's
2005	154.2	160.6
2006	162.3	153.2
2007	154.8	146.1
2008	156.8	157.7
2009	24.2	24.2
2010	22.9	22.7



- IMAT has become a well-known, highly-competitive source for supporting innovative technology ideas, with the benefit that these ideas are directed towards cancer researchers
- The technology development investment of the NCI is small, and IMAT has traditionally represented a significant component of this overall investment

Detailed Historical Record

RFA's CA05-CA10	Mechanism	Success Rates by Receipt Year and Solicitation							
		CA05	CA06	CA07	CA08	CA09	CA10	Overall	
Biospecimens	R21	12.1%	12.5%	13.2%	19.2%	12.9%	11.1%	13.4%	
	R33	14.3%	28.6%	0.0%	0.0%	14.3%	22.2%	13.3%	
EMAT	R21	9.9%	9.6%	3.1%	4.5%	13.7%	16.9%	7.2%	
	R33	13.5%	11.1%	11.1%	26.2%	11.8%	20.9%	16.0%	
IMAT	R21	16.7%	6.3%	11.7%	12.4%	10.0%	9.0%	10.8%	
	R33	7.7%	12.9%	19.4%				14.0%	
		Average Scores for Supported Grants by Receipt Year and Solicitation							
		CA05	CA06	CA07	CA08	CA09	CA10	Overall (Old Scale)	Overall (New Scale)
Biospecimens	R21	151.50	174.50	164.29	154.20	27.50	28.00	160.08	27.71
	R33	165.00	161.00	NA	NA	32.00	25.50	163.20	27.67
EMAT	R21	161.63	160.50	152.67	157.67	23.57	23.36	153.92	23.44
	R33	153.40	135.00	140.83	157.27	22.25	22.11	151.47	22.15
IMAT	R21	151.94	157.44	156.45	157.25	23.50	21.67	156.73	22.55
	R33	164.00	150.50	143.57				143.57	

Detailed Historical Record

RFA's CA05-CA10	Mechanism	Success Rates by Receipt Year and Solicitation						
		CA05	CA06	CA07	CA08	CA09	CA10	Overall
Biospecimens	R21	12.1%	12.5%	13.2%	19.2%	12.9%	11.1%	13.4%
	R33	14.3%	28.6%	0.0%	0.0%	14.3%	22.2%	13.3%
EMAT	R21	9.9%	9.6%	3.1%	4.5%	13.7%	16.9%	7.2%
	R33	13.5%	11.1%	11.1%	26.2%	11.8%	20.9%	16.0%
IMAT	R21	16.7%	6.3%	11.7%	12.4%	10.0%	9.0%	10.8%
	R33	7.7%	12.9%	19.4%				14.0%
		Number of Applications Received by Receipt Year and Solicitation						
	Mechanism	CA05	CA06	CA07	CA08	CA09	CA10	Total
Biospecimens	R21	33	32	53	26	31	27	202
	R33	7	7	8	7	7	9	45
EMAT	R21	81	94	293	67	51	65	651
	R33	37	27	54	42	34	43	237
IMAT	R21	102	144	247	129	140	167	929
	R33	26	31	36				

Pediatric Phase I / Pilot Consortium

Malcolm A. Smith, MD, PhD

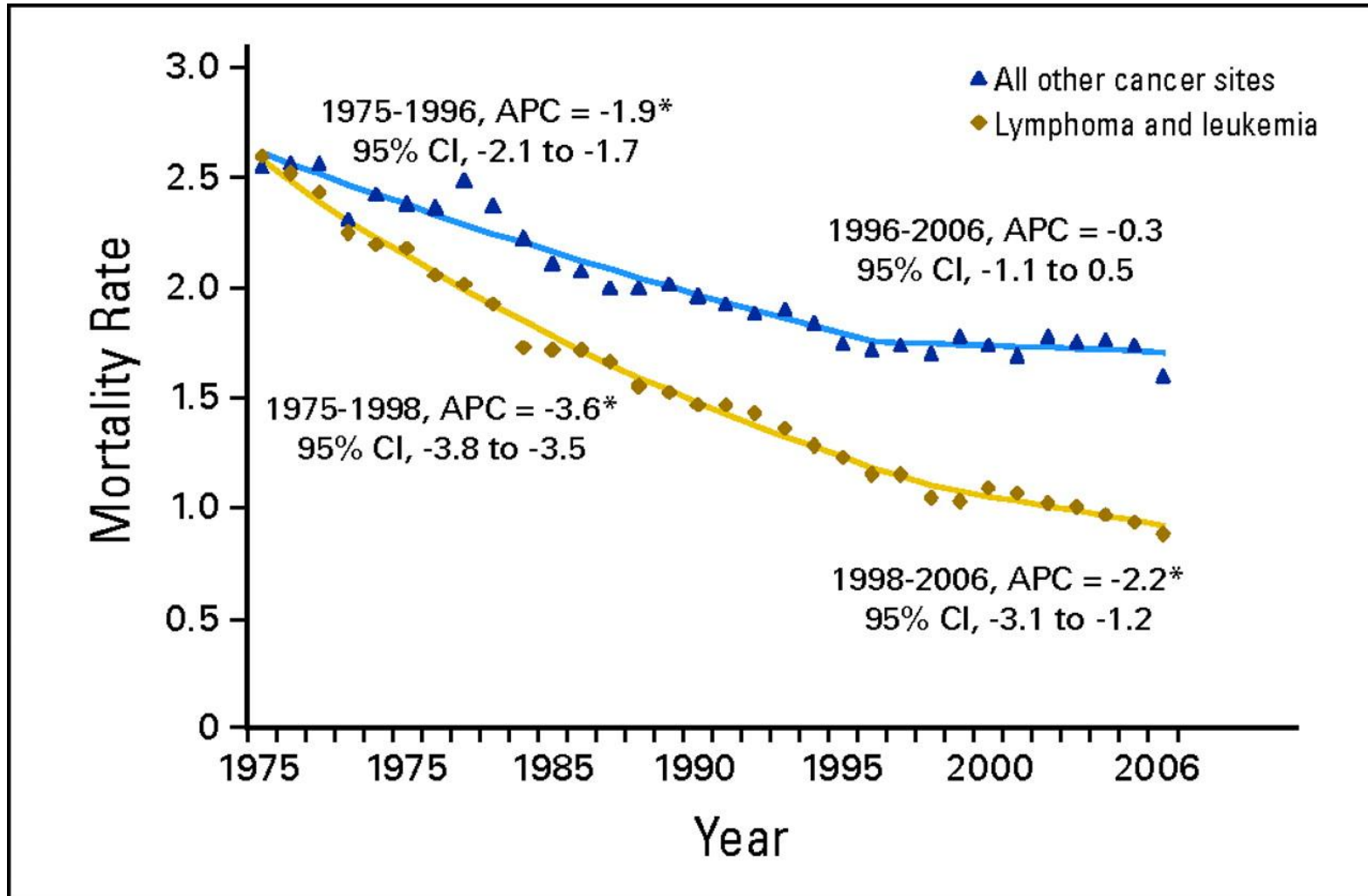
Cancer Therapy Evaluation Program

November 2011

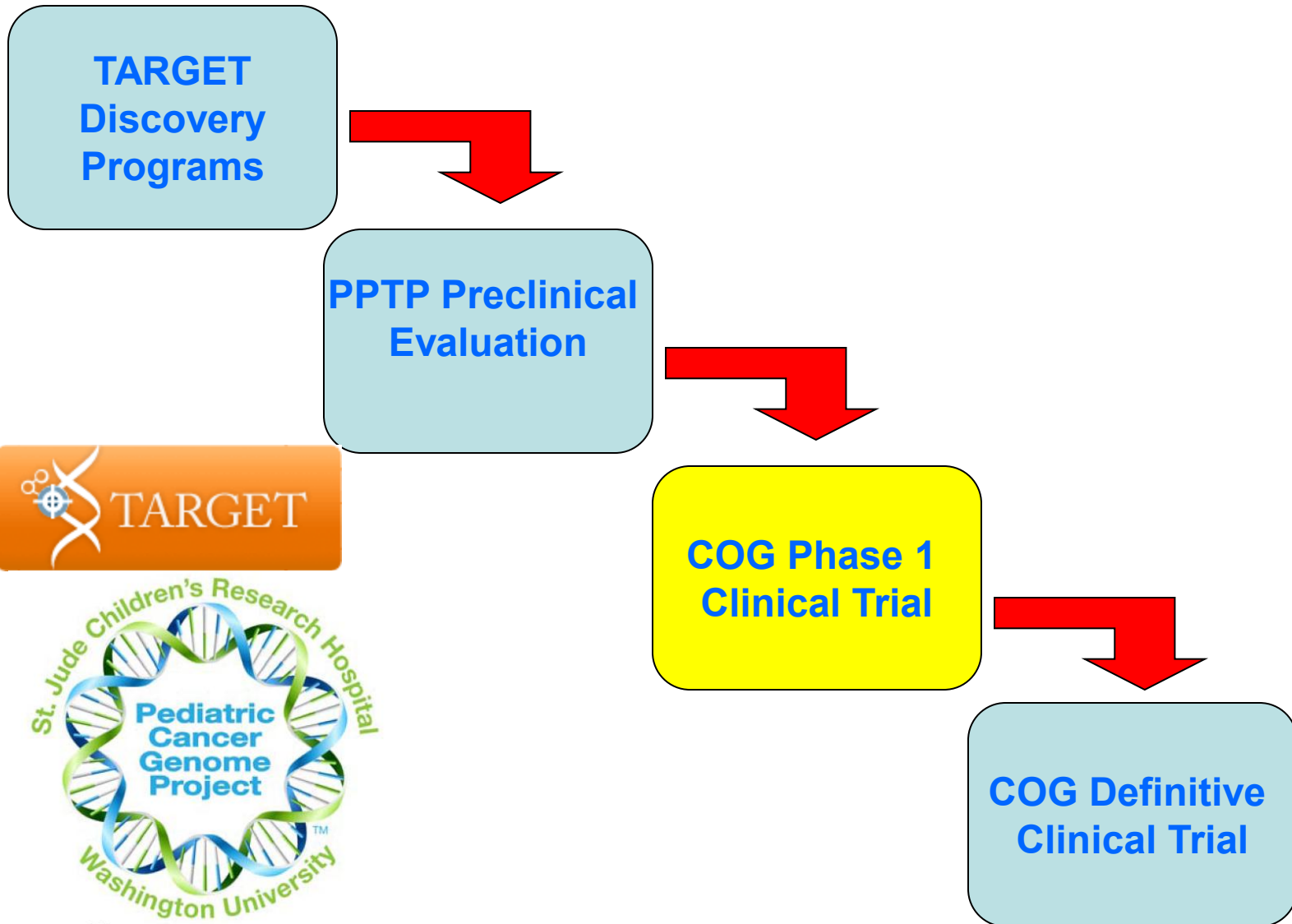
Pediatric Phase I / Pilot Consortium – Children Are Different

- Multi-institutional studies required:
 - Substantial infrastructure required for site training, for study monitoring, and for implementing PK/PD/Imaging studies
- Ethical issues limit risks to children participating in correlative research studies
 - Direct impact on type of PD studies that can be performed
- Pharmaceutical interest is limited →
 - Limited non-NIH funding stream for pediatric drug development
 - NCI plays unique role in supporting teams of experienced investigators to safely & efficiently conduct multi-institutional “first-in children” studies

US childhood mortality trends for lymphoma and leukemia, and all other cancer sites combined



Strategy for Discovering Effective New Treatments for Children with Cancer



COG Phase 1/Pilot Consortium

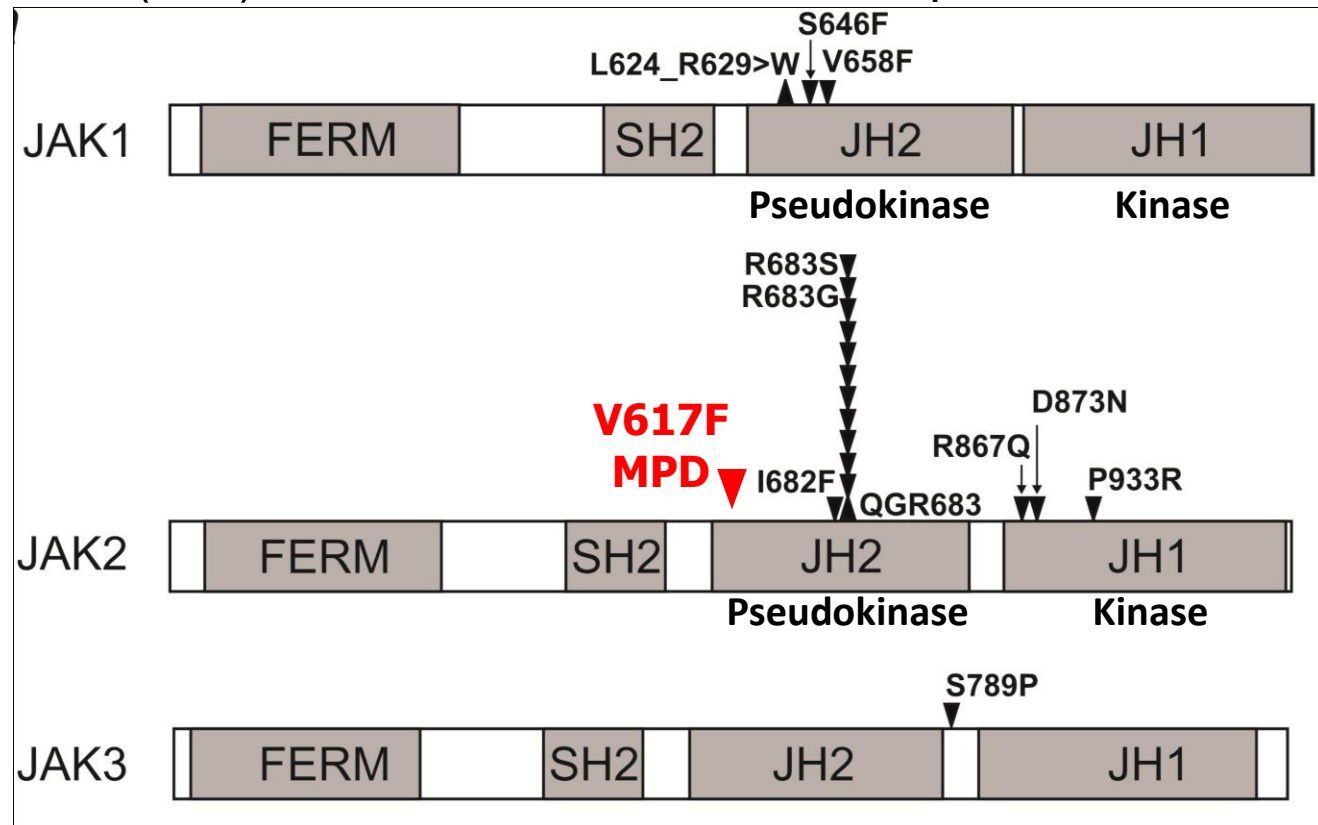
- History of NCI support:
 - Pediatric phase 1 clinical trials resource supported by NCI since 1992
 - COG Phase 1 Consortium supported since 2002
 - NCI continues providing primary support for pediatric phase 1 trials in children with cancer in North America
- Ongoing need:
 - Approximately 20% of children for whom current treatments not sufficiently effective. Continued need for NCI support of an experienced team of investigators to conduct first-in-children studies for new anticancer agents with novel mechanisms of action and molecular targets

Consortium Contributions

- Phase 1 evaluations of targeted agents building on genomic and preclinical discoveries:
 - ALK inhibitor crizotinib phase 1 study focusing on patients with neuroblastoma and ALCL and other tumors with ALK mutations.
 - JAK inhibitor ruxolitinib (INCB018424) phase 1 study following up on discovery of JAK mutations in high-risk B-precursor ALL.
 - Aurora A kinase inhibitor MLN8237 phase 1 study following up on PPTP findings of high activity for MLN8237 against ALL and neuroblastoma preclinical models.
 - NTX-010 (Seneca Valley Virus, SVV-001) oncolytic virus phase 1 study focusing on patients with neuroendocrine tumors
- COG Phase 1 Consortium conducts phase 1 studies with intensive monitoring and PK / PD evaluations
- COG builds on Consortium phase 1 studies by developing phase 2 and subsequently phase 3 clinical trials using dose/schedule/PK data generated by the Consortium.

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

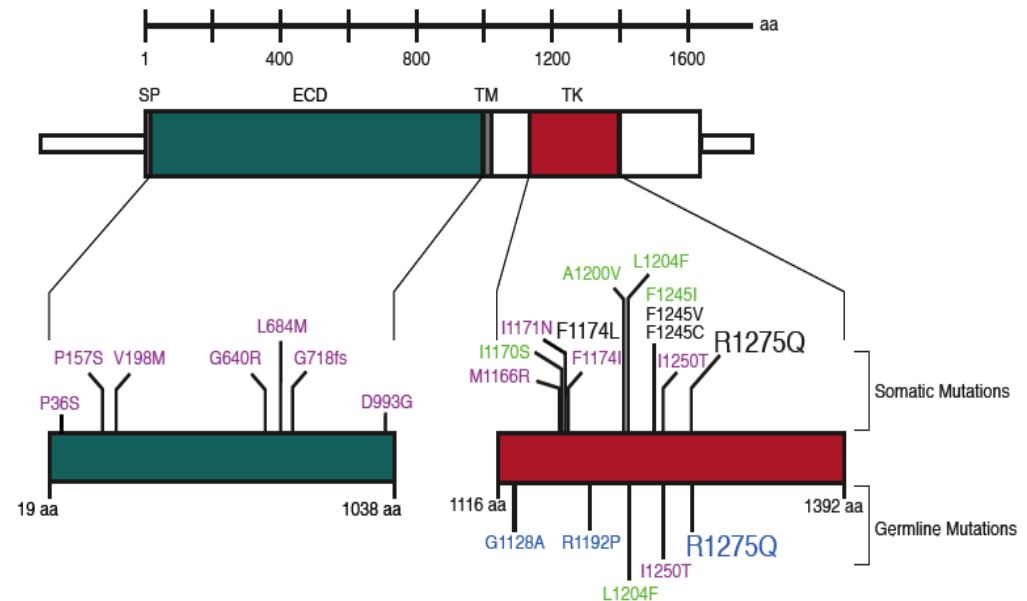
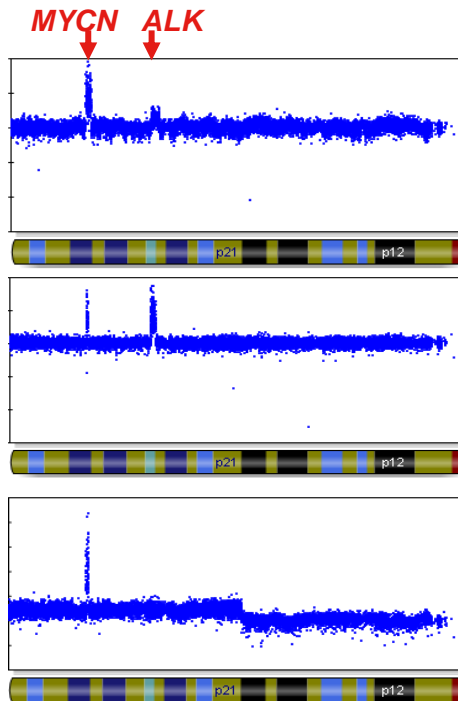


Clinical Translation by COG Phase 1 Consortium

- Phase 1 trial of JAK inhibitor ruxolitinib (INCB18424) in Sept 2010 in collaboration with Incyte.
- Ruxolitinib in development for adults with myelofibrosis (MF):
 - JAK2 mutations common for this condition
 - NDA filed in June 2011
- Eventual COG plan for combining JAK inhibitor for JAK-mutant ALL in same way that imatinib has been added to standard chemotherapy for BCR-ABL ALL.

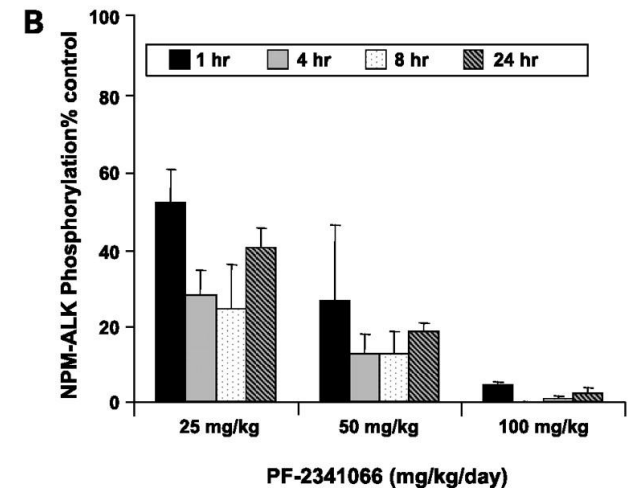
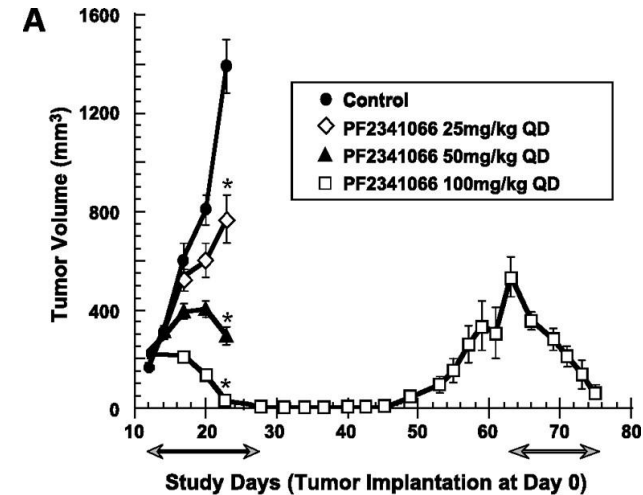
ALK is an Oncogenic Kinase in Neuroblastoma

- Co-discovery of ALK as the familial neuroblastoma gene (Mosse, Nature 2008) and frequent somatic amplification and mutation (TARGET)
 - Amplification: 31/599 (5.2%)
 - Focal gain: 102/599 (17.0%)
 - Mutations in kinase domain: 43/552 (7.2%)
 - Mutations in extracellular domain: Present, frequency still be defined



ALK-mutated (translocated) tumors are highly sensitive to ALK inhibitors

- PF-02341066 in the Karpas299 xenograft model (NPM-ALK ALCL).
- 1st cycle of treatment initiated on day 11 through day 23 (except the 100 mg/kg group, which was treated through day 28).
- A 2nd cycle of treatment initiated on day 62 - 76 for the 100 mg/kg/d group after tumor regrowth.
- COG Phase 1 Consortium initiated phase 1 trial of ALK inhibitor crizotinib (PF-02341066) Sept 2009.



Consortium Contributions

- Phase 1 evaluations of targeted agents building on genomic and preclinical discoveries:
 - ALK inhibitor crizotinib phase 1 study focusing on patients with neuroblastoma and ALCL and other tumors with ALK mutations.
 - JAK inhibitor ruxolitinib (INCB018424) phase 1 study following up on discovery of JAK mutations in high-risk B-precursor ALL.
 - Aurora A kinase inhibitor MLN8237 phase 1 study following up on PPTP findings of high activity for MLN8237 against ALL and neuroblastoma preclinical models.
 - NTX-010 (Seneca Valley Virus, SVV-001) oncolytic virus phase 1 study focusing on patients with neuroendocrine tumors
- COG Phase 1 Consortium conducts phase 1 studies with intensive monitoring and PK / PD evaluations
- COG builds on Consortium phase 1 studies by developing phase 2 and subsequently phase 3 clinical trials using dose/schedule/PK data generated by the Consortium.

Further Clinical Evaluations of Agents Recently Studied by COG Phase 1 Consortium

Trial	Agent(s)	Current status
ADVL0319	Lenalidomide	Phase 2 CNS trial in children with recurrent low-grade gliomas
ADVL0413	Sorafenib	Frontline for FLT3 positive AML
ADVL0414	VOIT	Frontline COG pilot study for high risk rhabdomyosarcoma
ADVL0416	SAHA + Cis RA	Frontline PBTC trial for infants with CNS embryonal tumors
ADVL0419	Valproic acid	Frontline Texas-Oklahoma Pediatric Neuro-Oncology trial in BSG and unresectable HGG
ADVL0515	CBDCA + VBL	Under consideration by CNS tumor committee
ADVL0516	Dasatinib	Frontline COG trial for children/young adults with Philadelphia chromosome positive ALL
ADVL0517	Ispinesib	No further development; CTEP withdrew IND
ADVL0612	Sunitinib	Phase 2 COG trial for children with recurrent CNS tumors
ADVL0712	IMC-A12	Phase 2 COG trial for children with sarcomas and other solid tumors and frontline study for metastatic rhabdomyosarcoma
ADVL0714	VEGF Trap	No further pediatric development due to toxicity and PK profile
ADVL0812	MLN8237	Phase 2 COG trial in refractory/recurrent solid tumors including neuroblastoma and ALL

Would making the Phase 1 Consortium part of COG be a more efficient use of resources?

- The Consortium is integrated with COG in appropriate ways:
 - Clinical data management system
 - Protocol development resources
 - Shared meetings
 - Thus, no duplicative infrastructure
- Scope of clinical trials for the Consortium is very different from those of COG:
 - Intensity of monitoring and data reporting
 - Numbers of patients per trial and numbers of participating institutions
 - Emphasis on PK, PD, and imaging endpoints
 - If COG were to take responsibility for phase 1 trials, it would need to replicate the Consortium's capabilities in these areas
- There would be little or no budgetary savings from incorporating the Consortium into COG assuming that the same scope of work was maintained

What is gained by having the Phase 1 Consortium distinct from COG?

- Focused NCI and peer review to ensure that the Consortium has the following:
 - Strong scientific leadership,
 - Data collection and management procedures that meet the high standards for granularity, accuracy, and timeliness required for phase 1 trials,
 - Appropriate integration of PK and PD
 - High productivity in developing and completing clinical trials
- Phase 1 studies would represent a small percentage of COG accrual if Consortium were merged into COG:
 - Risk that phase 1 trials would be de-emphasized because of the higher priority for COG of larger phase 2 and 3 trials

Budget Considerations

- Flat Budget relative to FY10:
 - Direct cost in Year 1 of \$3 million
 - Total cost in Year 1 of \$3.47 million
- Apportioning of funds:
 - Scientific Leadership (~10%)
 - Protocol Development & Regulatory (15%-20%)
 - Statistics and Data Management (~10%)
 - Imaging (15%-20%)
 - Pharmacokinetic/Biology Support (~5%)
 - Travel (4%)
 - Basic Member Institution Site Support (~40%)

Conclusions

- COG Phase 1 / Pilot Consortium is premier organization for conduct of “first in children” clinical trials for anticancer agents
- Record of accomplishment:
 - Protocols activated and completed
 - Patients enrolled
 - Publications and presentations
 - Contributions to COG PK studies
 - Mentoring junior faculty
 - Integrating new imaging methods into pediatric phase 1 trials
- Consortium is needed so that children can benefit from advances in cancer biology and drug development in coming years.

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Acting Director for Clinical Research, DCTD
Associate Director, CTEP

Meg Mooney, MD
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on behalf of the

Division of Cancer Treatment & Diagnosis:

*Biometric Research Branch, Cancer Diagnosis Program,
Cancer Imaging Program, Cancer Therapy Evaluation Program, and
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Division of Cancer Prevention:

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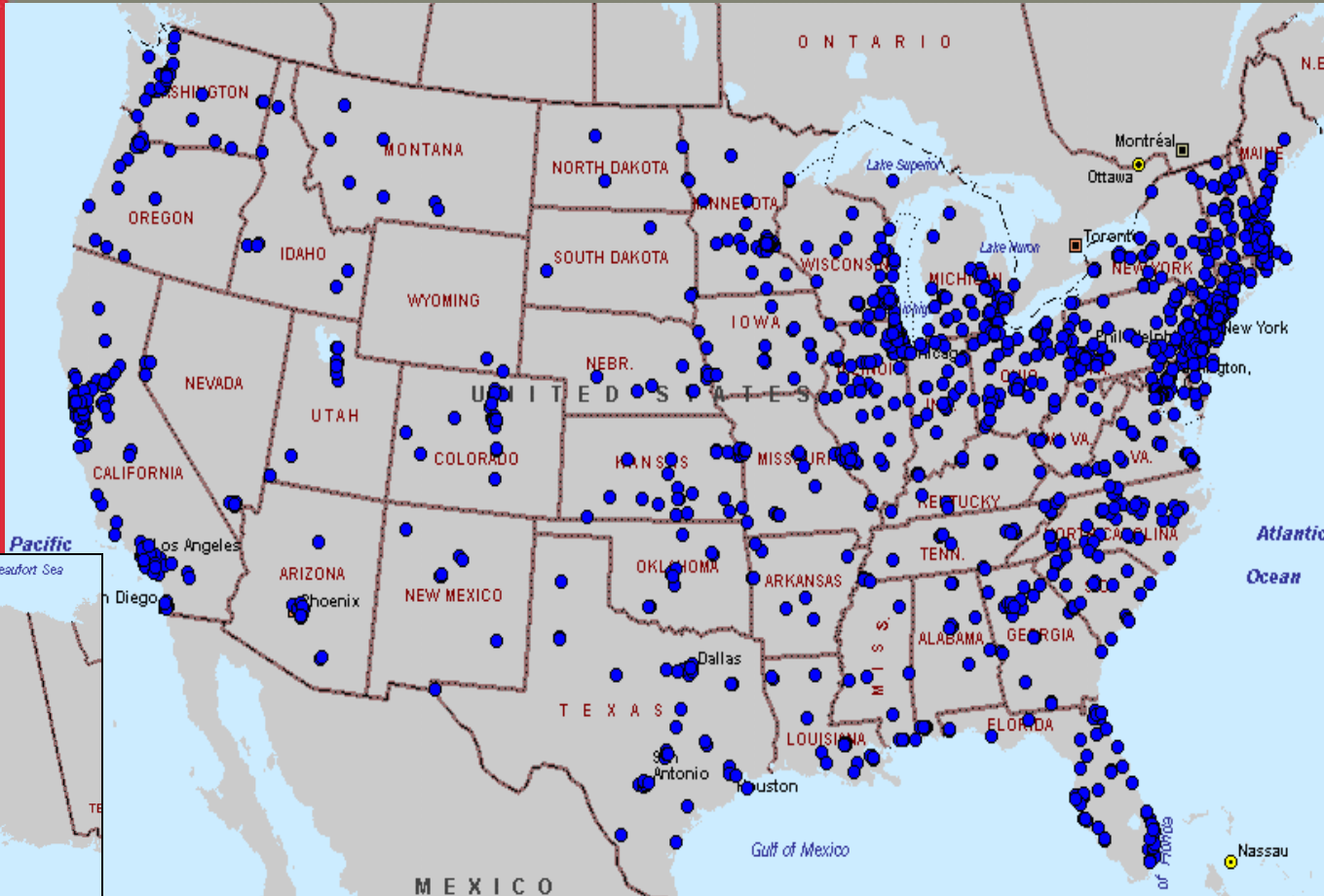
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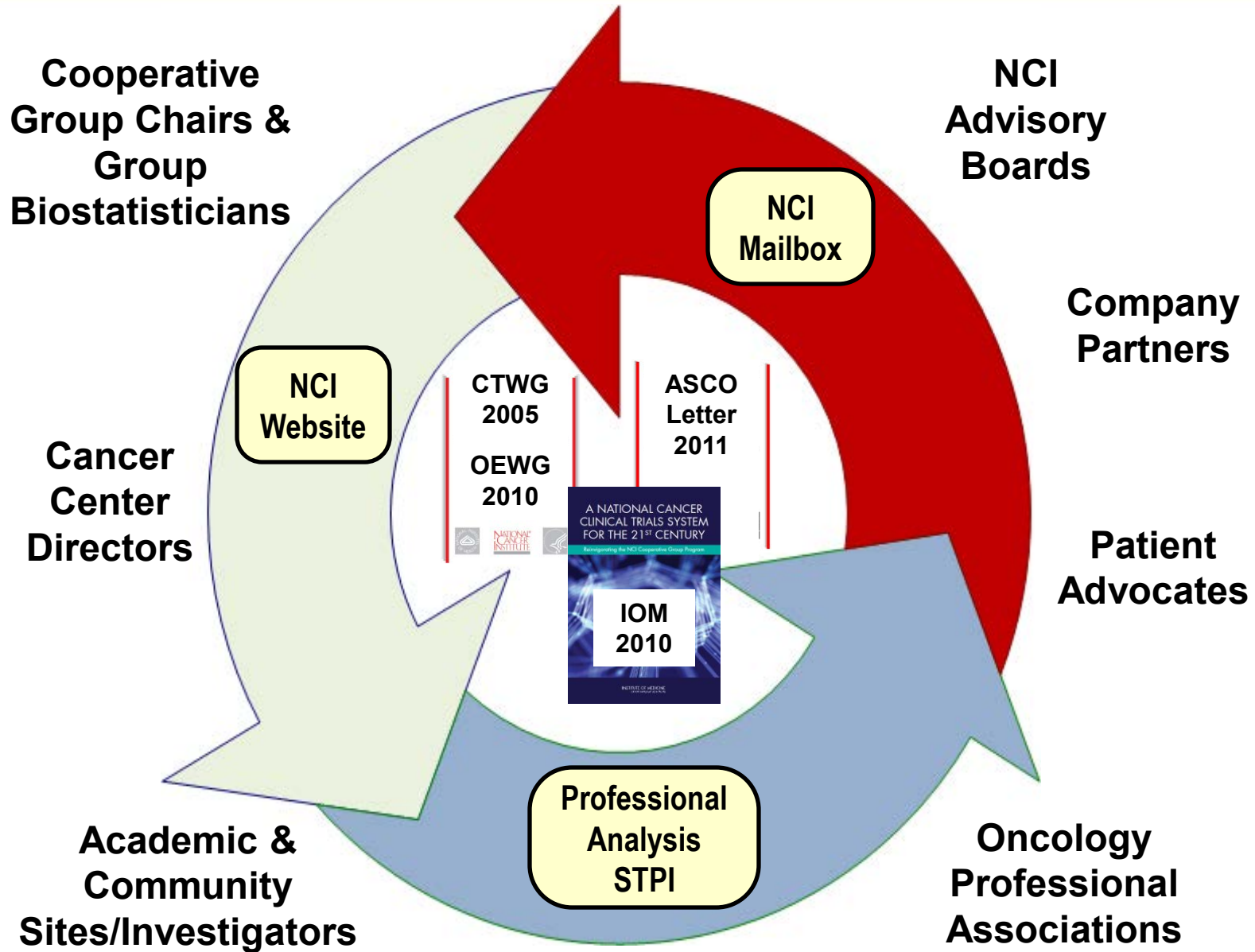
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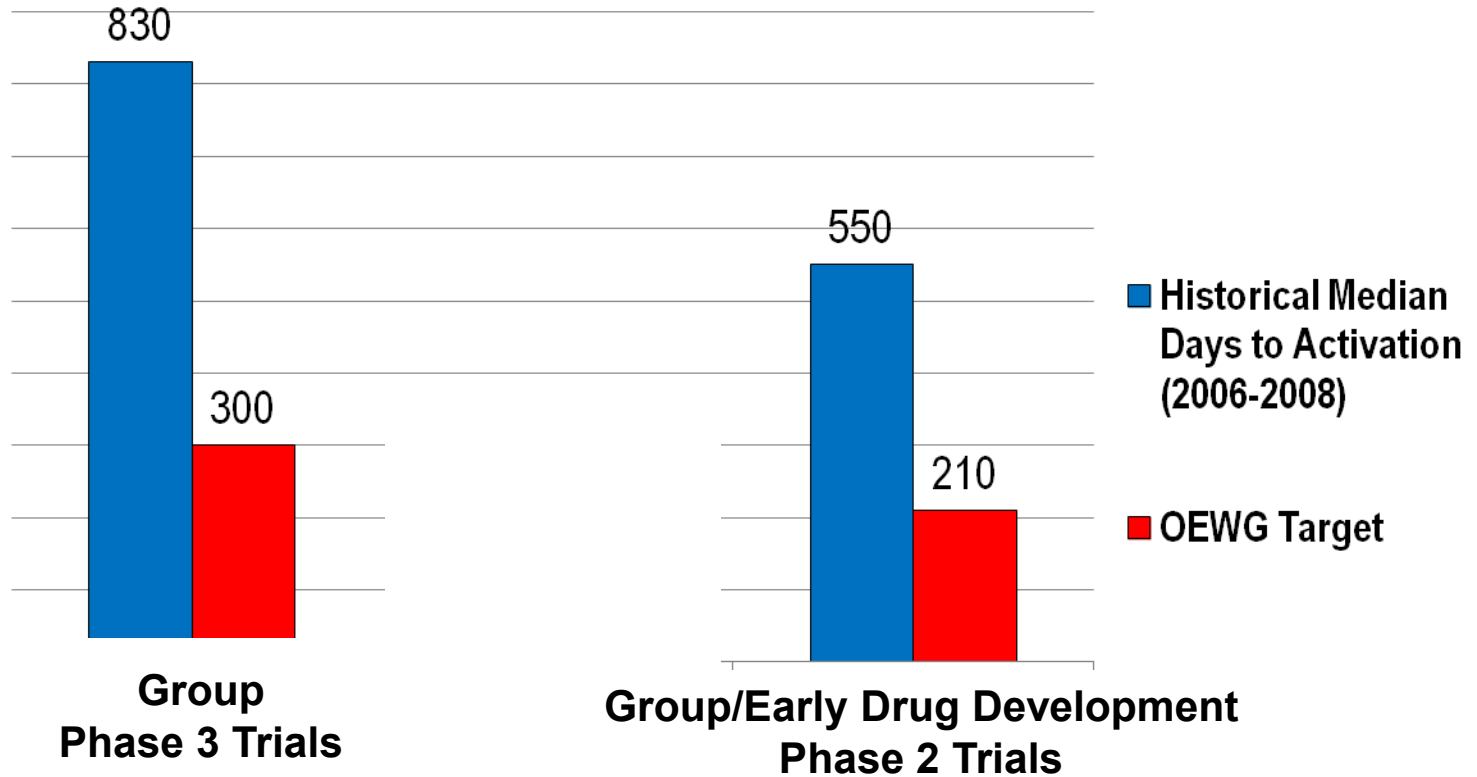
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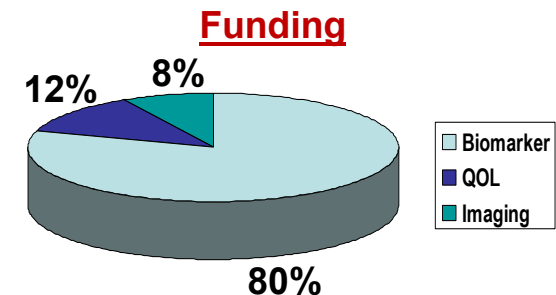
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Disease-Specific Steering Committees : Prioritizing Clinical Trials

Steering Committee	Year Established	Co-Chairs as of 10-7-2011 Disease-Specific Steering Committees (SCs)
GI	2006	Dan Haller, MD & Joel Tepper, MD (Incoming Co-Chair Neal Meropol, MD)
Gyne	2006	David M. Gershenson, MD, Gillian Thomas, MD, & Michael Birrer, MD
Head & Neck	2007	David Adelstein, MD, David Brizel, MD, & David Schuller, MD
GU	2008	Eric Klein, MD, George Wilding, MD*, & Anthony Zietman, MD
Breast	2008	Charles Geyer, MD & Nancy Davidson, MD*
Thoracic	2008	David Harpole, MD, William Sause, MD, & Mark Socinski, MD
Leukemia	2009	Wendy Stock, MD & Jerry Radich, MD
Lymphoma	2009	Oliver Press, MD & Julie Vose, MD
Myeloma	2009	Morie Gertz, MD & Nikhil Munshi, MD
Brain	2010	Ian Pollack, MD & Al Yung, MD
Pediatrics (Heme & Solid Tumors)	2011	David Poplack, MD & Robert Arceci, MD, PhD (Hematology) Mark Bernstein, MD & Katherine Matthay, MD (Solid Tumors)

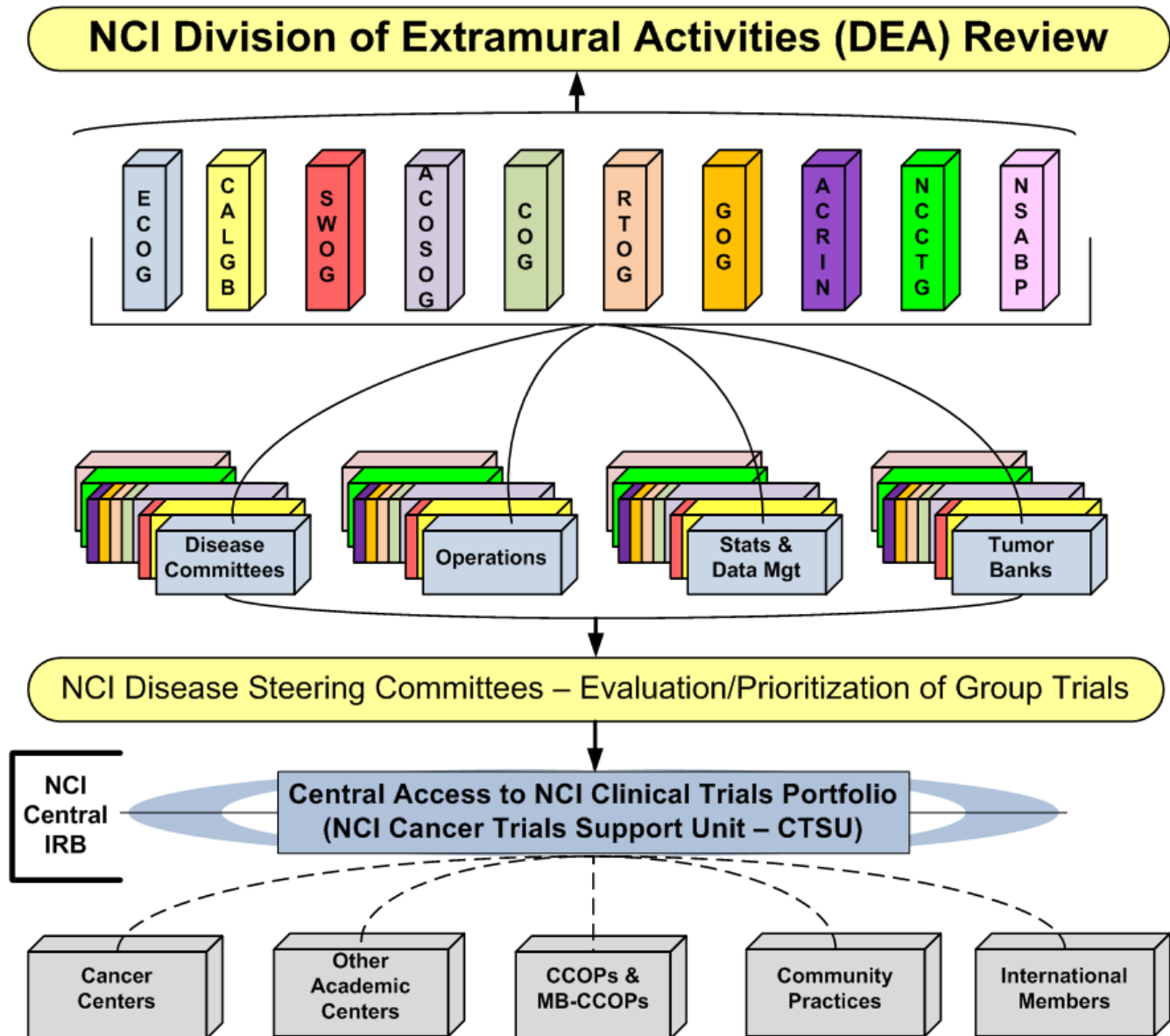
*Cancer Center Directors

Over 170 Concepts evaluated since inception of SCs

Related Steering Committees as of 10-7-2011: (Non-disease Focus)

- **Investigational Drug Steering Committee**
 - Co-Chairs: Pat LoRusso, DO, & Dan Sullivan, MD
- **Clinical Imaging Steering Committee**
 - Co-Chairs: Steven Larson, MD & Etta Pisano, MD
- **Symptom Management & Health-Related Quality of Life Steering Committee**
 - Co-Chairs: Deborah Bruner, RN, PhD & Michael J. Fisch, MD, MPH
- **Patient Advocate Steering Committee**
 - Co-Chairs: Regina Vidaver & Nancy Roach

Structure of Program: As of January 2011

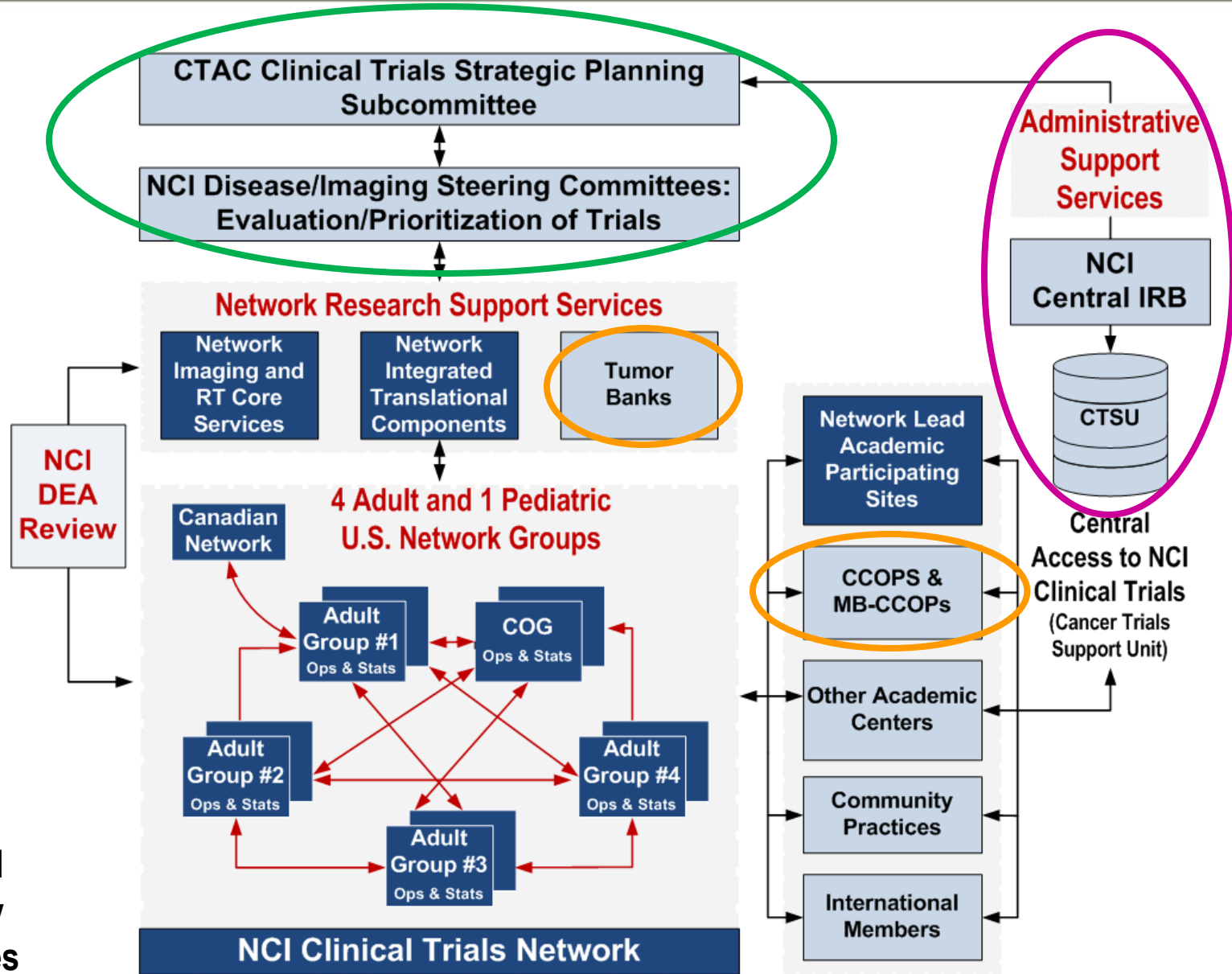


Next Steps in Transforming the System

- **New RFA for an Integrated National Clinical Trials Network**
- **Consolidated Organizational Structure with Funding for 1 Pediatric Group and up to 4 Adult Groups**
- **Review Criteria with Emphasis on Integration & Collaboration for Overall Scientific Achievement and Operational Efficiency**
- **Funding Model with Increased Per-Case Reimbursement for “High-Performance” Academic & Community Sites**
- **Competitive Integrated Translational Science Awards**
- **Revitalize Cancer Center Role in the Network (U10 awards)**

Introducing A New Organizational Structure

NCI Clinical Trials Network



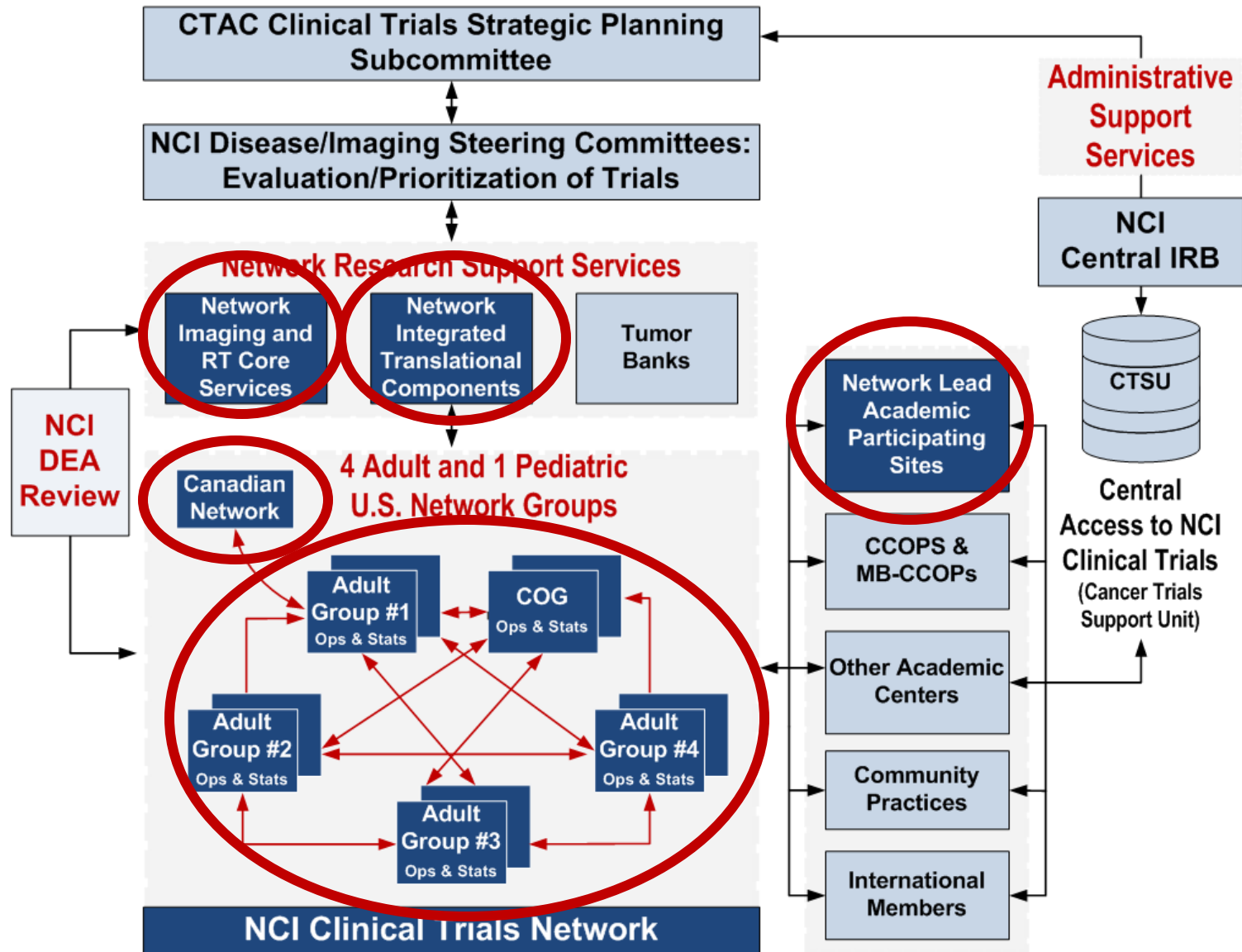
Other NCI Grant Programs
 Dark blue boxes signify NCI DEAR reviewed grant-funded components under Extramural RFA Advisory Committees

Rationale for Transforming Current Program: How Will Consolidated Network System Help?

- **Consolidate infrastructure to gain efficiencies (e.g., IT, Regulatory, Administrative, Tissue Resource Management)**
- **Consolidate Imaging & RT core services to benefit entire Network**
- **Integrate new components into trials to provide value-added research questions (e.g., advanced imaging, translational science)**
- **Integrate new agents into trials**
 - **Ex:** Erlotinib, crizotinib, & ipilimumab are being integrated into trials in earlier stages of lung cancer & melanoma treatment requiring screening large populations & combining the agents optimally with surgery, RT, and immunotherapy
- **Evaluate new agents in molecularly-defined disease subsets**
 - **Ex:** Even for common diseases such as breast cancer, # of molecularly-defined patient subsets is increasing & there is a need for trial prioritization evaluating multiple new agents with standard regimens across subsets to avoid duplication & optimize accrual

Introducing A New Organizational Structure

NCI Clinical Trials Network



Network Component Description

Group Operations Ctrs & Group Stats Ctrs

- **Provide scientific strategy & goals across broad range of diseases**
- **Responsible for Network Group administration including**
 - Study conception, protocol development, and accrual to trials
 - Adherence to “Operational Efficiency” timelines
 - Audits and QA/QC of protocol therapy
 - Coordinating biospecimen collection from patients on trials
 - Compliance with FDA, OHRP, NCI/NIH regulations
- **Statistical leadership for effective design & trial conduct**
- **Monitors data quality for primary analysis & correlative science**
- **Supports data mgt & analyses for studies outside the Network Groups as appropriate (e.g., Steering Committee-approved studies)**

Network Components Review Criteria

Group Operations & Statistical Centers

- **Reconfigure NCI/NIH external peer-review of System**
 - **Emphasis on incentives for a national system with trials open to all qualified sites & sites able to credit any Group to which they belong**
 - **Review of all Network Groups/components at same time (specific review panels for particular Network components)**
 - **Scientific evaluation will shift to evaluating Group role in national network, overall scientific strategy, innovation and quality (~50%)**
 - **Review criteria for operational efficiency & collaborative management of Network (~50%)**
 - ✓ **Coordination with other Network Groups, NCI programs, NCI investigators outside Groups (e.g., CCOPs, MB-CCOPs, Tumor Banks, Cancer Centers, SPORES, N01s/U01s, P01s, etc.)**

Network Description & Review Criteria

Lead Academic Participating Sites

- **Description**
 - Multiple-PI grants for academic institutions with demonstrated scientific leadership in ≥ 1 adult Network Groups, substantial accrual, & excellent data quality (“high-performance” sites)
 - Targeted at NCI Comprehensive and Clinical Cancer Centers and other leading academic centers
- **Review Criteria**
 - Meets accrual threshold set from trials across entire Network
 - Expertise & leadership role in Group(s)
 - Data quality
 - Contributions to translational science within Group trials
 - Scientific collaborations across Cancer Center/Institution & Network

Network Description & Review Criteria

Integrated Translational Science Awards

- **Description**
 - Multiple-PI grants to support prominent researchers for their expertise and efforts in incorporating molecular studies into Network trials & enabling acquisition of preliminary data for further research
 - Laboratory-based researchers will also facilitate hand-off of early phase clinical trial findings into later phase, definitive trials
- **Review Criteria**
 - Peer-review of quality of scientific approach & plans for integration of translational science into clinical trials
 - Leverages independently funded laboratory resources with Group clinical specimens & data to benefit Group research aims
 - Research area likely to benefit trial efforts across Network

Network Description & Review Criteria

Core Services & Canadian Partner Network

- **RT and Imaging Core Services**
 - Provides scientific leadership for incorporating appropriate QA & image data management for research trials involving RT & imaging
 - Review Criteria for scientific leadership & expertise as Network-wide resource, integrated IT platforms for capturing and storing images, & efficient procedures for accessing site data for RT & image-related trial questions
- **Canadian Collaborating Trials Network**
 - NCI Program has had long history of collaboration with Canadian sites and non-profit Canadian clinical trial organizations
 - Review Criteria for ability to provide appropriate regulatory oversight for US Networks trials conducted in Canada, irrespective of which Group leads trial and to be full partners in accruing patients to US Network trials

Overview of RFA: Cooperative Agreement FOAs and Estimated # Grants

Network Component	Mechanism (Duration)	Est. Max. # Grants	Frequency New Application Accepted?	Multiple PI Option?
Group Operations Centers	U10 (5 Yrs)	5	Every 5 Years	Yes
Group Statistical & Data Mgt Centers	U10 (5 Yrs)	5	Every 5 Years	Yes
Canadian Collaborating Network	U10 (5 Yrs)	1	Every 5 Years	Yes
Integrated Translational Science Awards	U10 (5 Yrs)	1 to 5	Every 5 Years	Yes
RT and Imaging Core Services	U24 (5 Yrs)	1 to 2	Every 5 Years	Yes
Lead Academic Participating Sites	U10 (5 Yrs)	30 to 40	Any Year	Yes

Principles of Network Funding Plan

- **All external reviews of the NCI clinical trials system emphasized need to provide increased research reimbursement to ensure continued participation of sites in the public program**
- **Base “per-case” reimbursement for patient enrollment in the program has remained fixed at \$2,000 per patient in treatment trials for over a decade**
 - **2006 estimate for average per patient cost in industry trials was \$4,700 for phase 3 & \$8,450 for phase 2 Trials (& some industry trials at \geq \$15,000)**
 - **Survey in 2009 of Group sites found that of those planning to limit participation in the program (32% of respondents), 75% cited inadequate reimbursement for the decline in their level of participation**
- **“High-Performance” sites incur additional infrastructure costs due to the number of patients they accrue & additional funding is especially needed to compensate these sites for their large patient follow-up burden - (propose additional \$2,000 /pt for these sites for total of ~\$4,000/pt)**

Budget History for Components of NCI National Clinical Trials Network

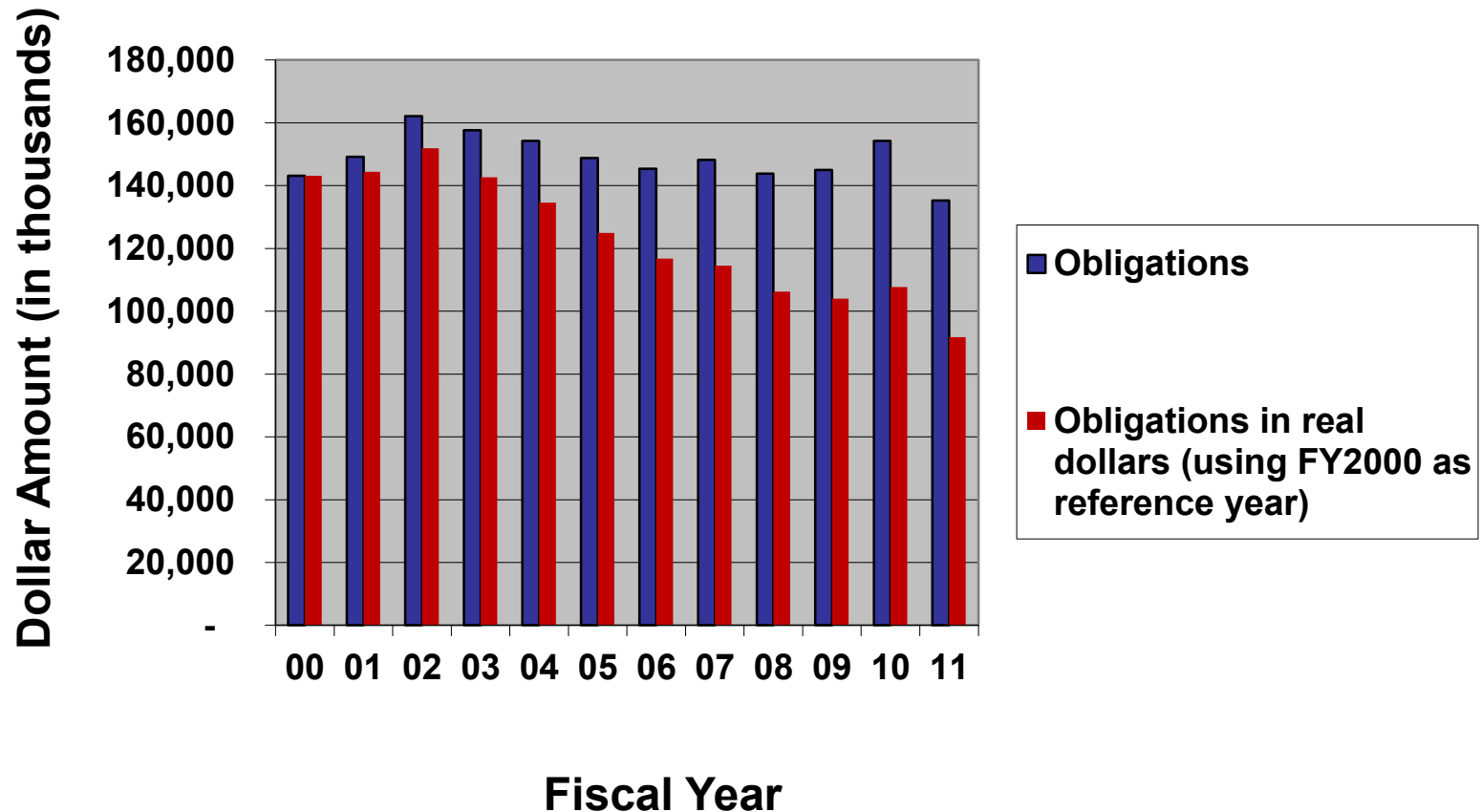
Base Divisional Set-Aside for Network/Group Program *	FY2006	FY2007	FY2008	FY2009	FY2010	FY2011 (Estimated)	Grand Total (Over 6 Yrs)	% Grand Total
Group Operations & Statistical Centers (including Capitation for Majority of Accrual)	\$128,833,204	\$126,516,480	\$126,141,046	\$126,380,185	\$127,127,666	\$120,304,563	\$755,303,144	78.7%
Participating Site U10s	\$ 12,532,773	\$11,375,647	\$11,074,808	\$11,241,179	\$11,823,333	\$10,839,407	\$ 68,887,147	7.2%
Core Services for Imaging & RT (RPC, QARC)	\$ 4,185,608	\$4,302,227	\$ 4,271,987	\$ 4,224,437	\$ 4,307,091	\$ 4,131,527	\$25,422,877	2.6%
Subtotal	\$145,551,585	\$142,194,354	\$141,487,841	\$141,845,801	\$143,258,090	\$135,275,496 **	\$849,613,167	
Estimated CTSU Capitation	\$ 4,000,000	\$ 3,779,781	\$ 4,289,927	\$ 5,162,362	\$ 5,174,165	\$ 5,040,000	\$ 27,446,235	2.9%
Subtotal	\$ 149,551,585	\$145,974,135	\$145,777,768	\$147,008,163	\$148,432,255	\$140,315,496	\$877,059,402	
ACRIN	\$7,002,444	\$15,442,054	\$13,129,762	\$13,509,478	\$12,816,778	\$10,612,813	\$ 72,513,329	7.6%
ATC	\$1,644,551	\$ 1,749,999	\$ 1,716,026	\$ 1,716,026	\$1,716,030	\$ 1,716,026	\$ 10,258,658	1.1%
Grand Total	\$158,198,580	\$163,166,188	\$160,623,556	\$162,233,667	\$162,965,063	\$152,644,335	\$959,831,389	100.0%

* Does not include ARRA funding and special "one-time" supplements (e.g., transition supplements) or funding provided by other NCI/NIH Programs for Special Initiatives (e.g., complexity funding)

** Base funding was decreased by FY2011 general budget cuts

Trials Program Funding 2000 to 2011: Real \$

Cooperative Group Obligations 2000-2011 Deflated Using BRDPI



5-Year Annual Funding Request for NCI Clinical Trials Network

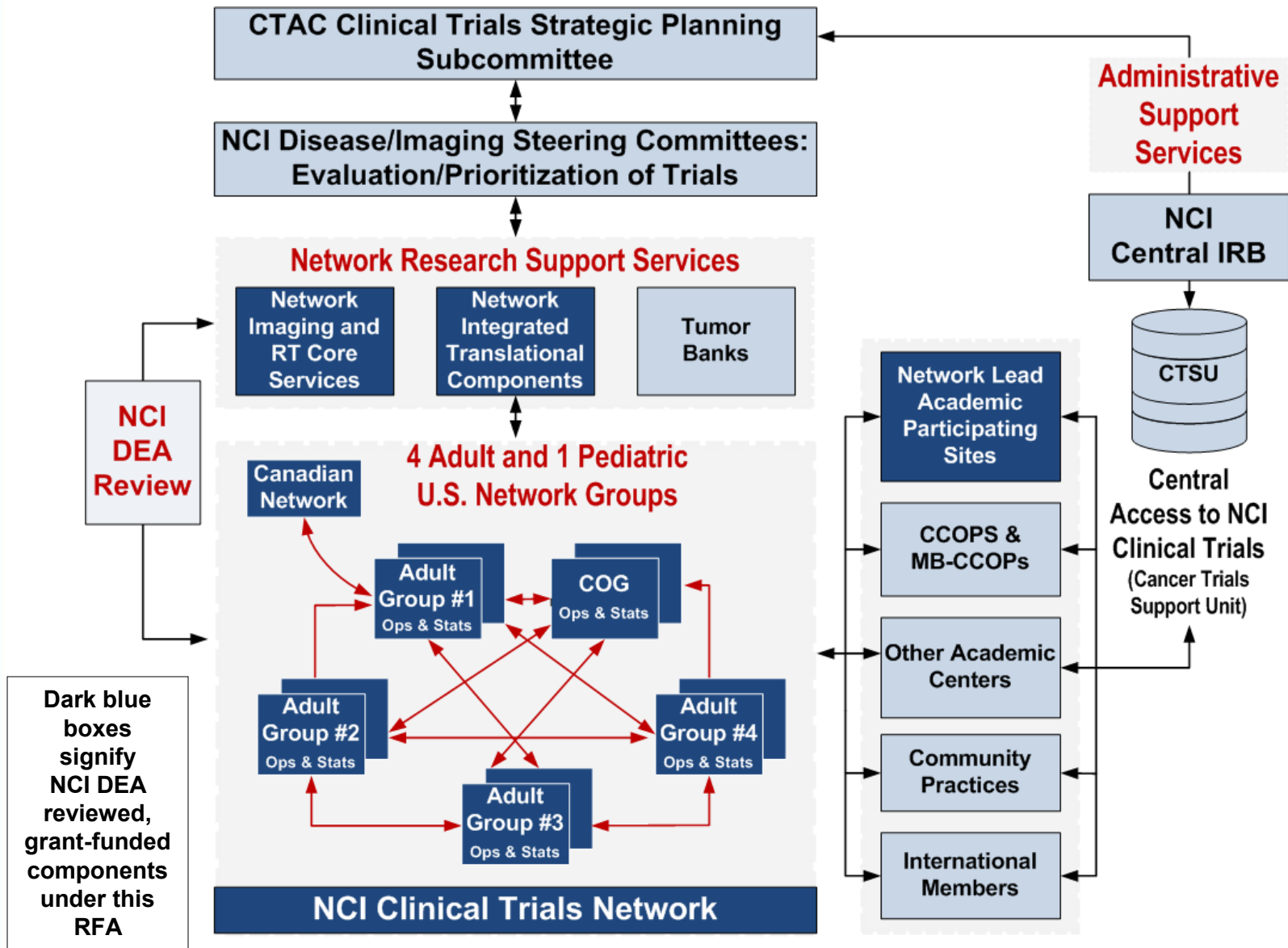
Category for Base Division Set-Aside for Network Program	Annual Total Cost for FY14 to FY18 Based on 20% Reduction in Accrual Compared to Average Accrual Over Last 6 Years (Approx. 20,000 Treatment Trial Enrollments)
Funding Based on FY2011 Levels: Group Operations & Statistical Centers (includes Capitation), Lead Academic Participating Sites, and Core Services	\$ 152,644,335
Funding Request Based on New Funding Model & BIQSFP:	
Increase Capitation to "High-Performance" DCTD-funded Sites	\$ 11,520,000
Increase Capitation to "High-Performance" DCP-funded CCOPs & MB-CCOPs	\$ 10,080,000
Increase Funding for Integral and Integrated Markers (BIQSPF)	\$ 4,000,000
Subtotal:	\$ 25,600,000
Grand Total:	\$ 178,244,335 *

* The 5-Year Total Cost Funding Request for FY2014 to FY2018 for the NCTN is \$891,221,675

Strategic Planning for the New NCTN Program

- **Treatment trial accrual has been dominated by Breast and GI Cancer trials, especially large adjuvant trials, over past decade**
- **The new funding model will require Network organizations and Steering Committees to monitor the balance of trials prioritized for development and help develop a strategic consensus about the diseases in which to encourage more trials as scientific opportunities arise**
- **New review criteria should facilitate more trials in disease areas which have been typically underrepresented, relative to their incidence, and portfolio balance will be monitored closely by CTAC's NCTN Strategic Planning Subcommittee to ensure that scientific opportunities in less common tumors are not missed**

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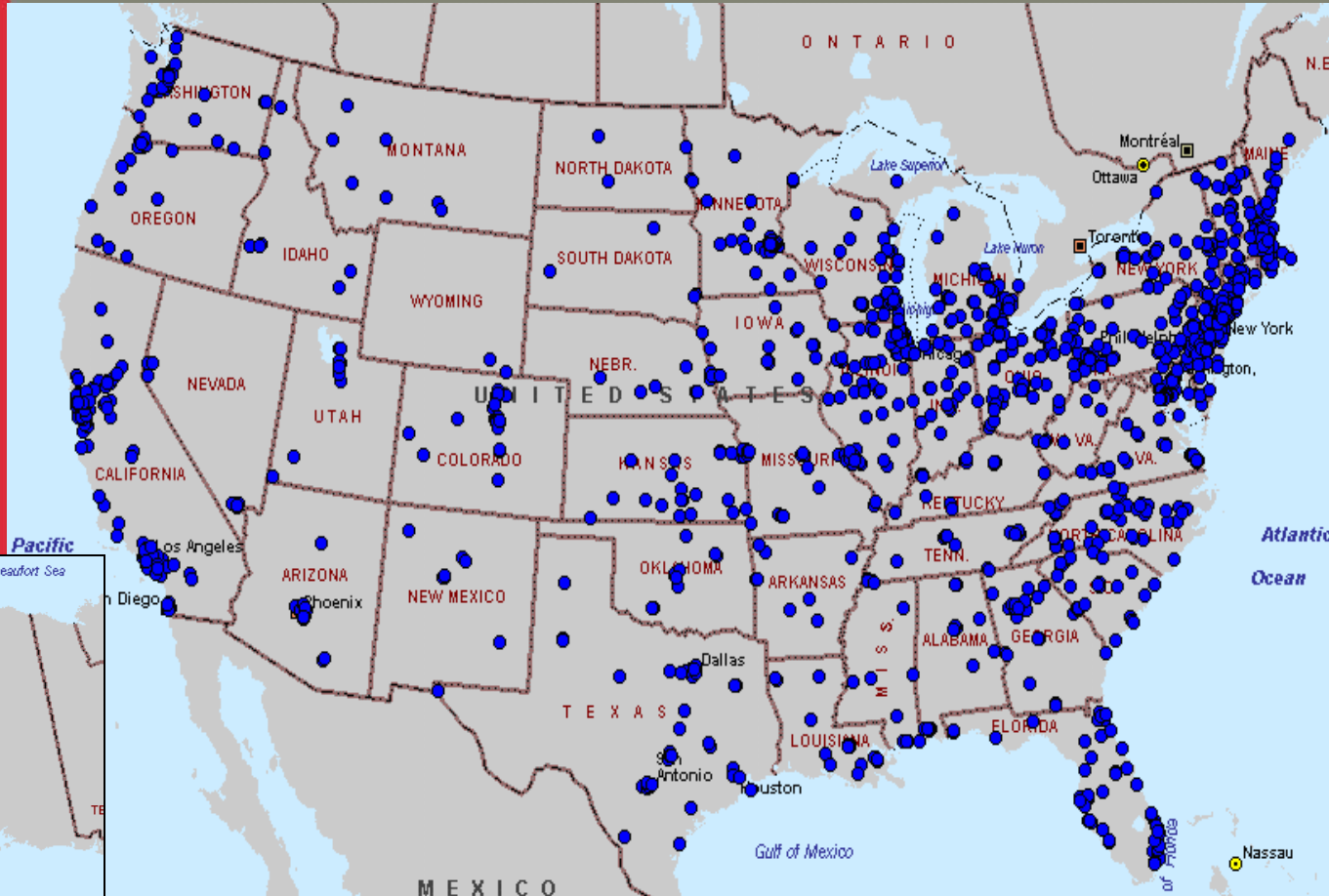
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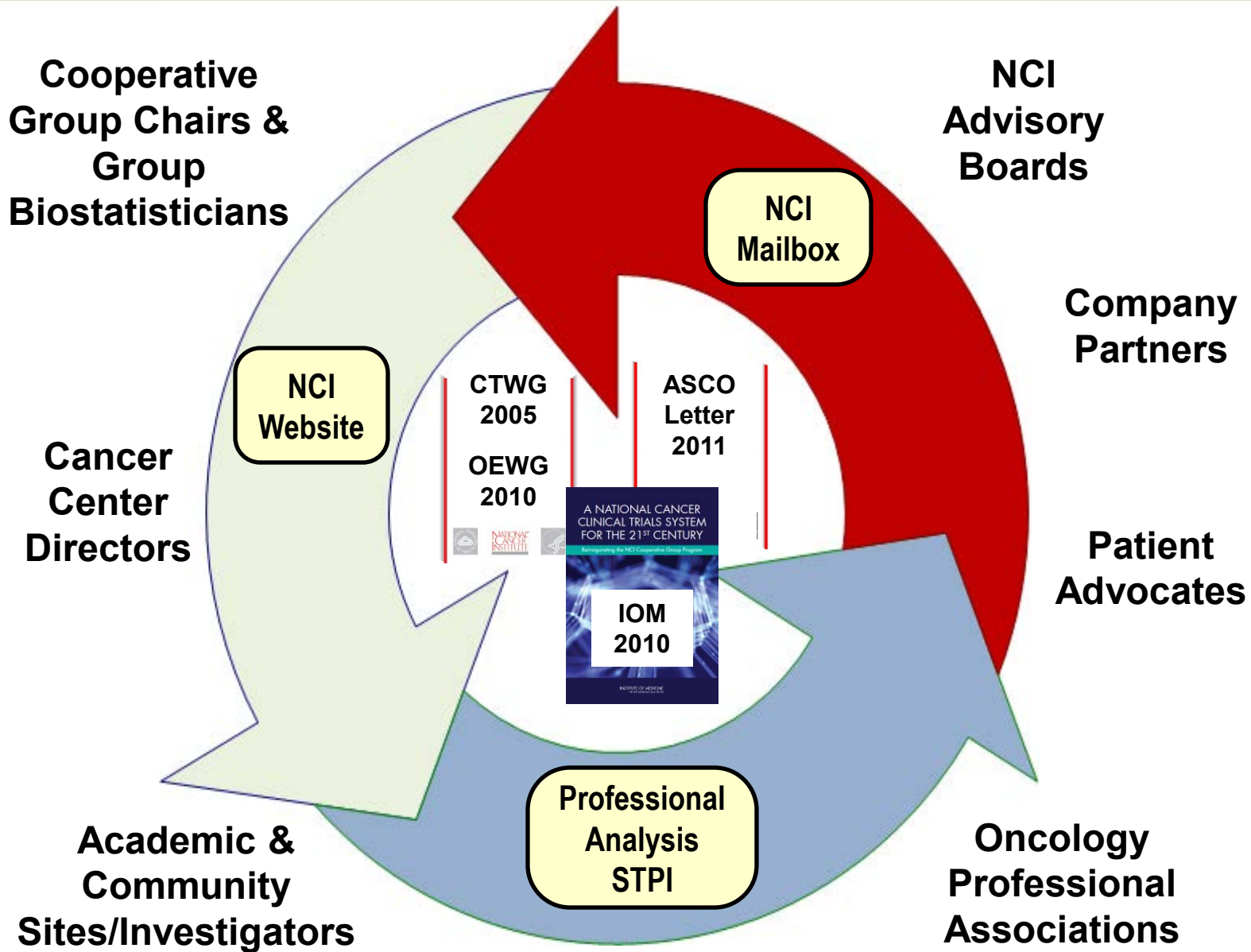
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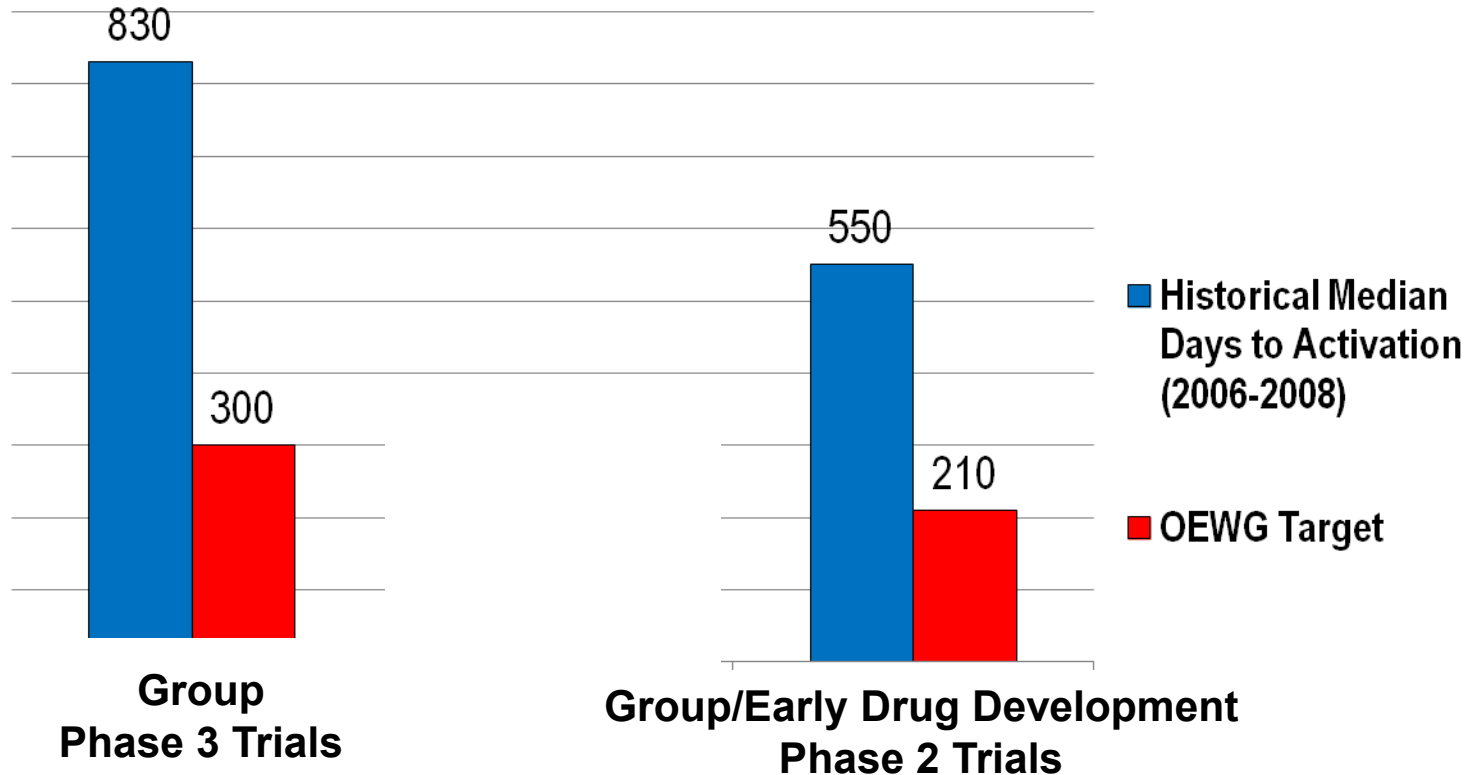
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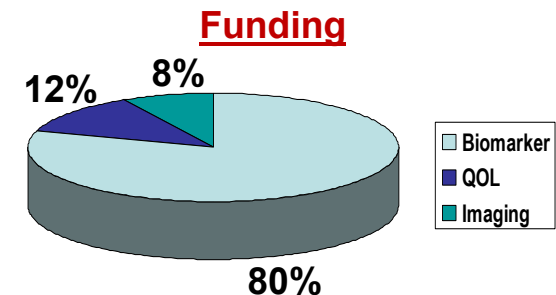
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- **COG: AAML0531:** Evaluation of Bortezomib and Sorafenib for patients with de novo AML & FLT3 ITD (high allelic ratio)
- **RTOG-1010:** Evaluating the Addition of Trastuzumab to Trimodality Treatment of HER2 Overexpressing Esophageal Adenocarcinoma
- **S1007:** Standard Adjuvant Endocrine Therapy +/- Chemotherapy in Patients with 1-3 Positive Nodes, Hormone-responsive and HER2-negative Breast Cancer According to Gene Profile/Recurrence Score



Disease-Specific Steering Committees : Prioritizing Clinical Trials

Steering Committee	Year Established	Co-Chairs as of 10-7-2011 Disease-Specific Steering Committees (SCs)
GI	2006	Dan Haller, MD & Joel Tepper, MD (Incoming Co-Chair Neal Meropol, MD)
Gyne	2006	David M. Gershenson, MD, Gillian Thomas, MD, & Michael Birrer, MD
Head & Neck	2007	David Adelstein, MD, David Brizel, MD, & David Schuller, MD
GU	2008	Eric Klein, MD, George Wilding, MD*, & Anthony Zietman, MD
Breast	2008	Charles Geyer, MD & Nancy Davidson, MD*
Thoracic	2008	David Harpole, MD, William Sause, MD, & Mark Socinski, MD
Leukemia	2009	Wendy Stock, MD & Jerry Radich, MD
Lymphoma	2009	Oliver Press, MD & Julie Vose, MD
Myeloma	2009	Morie Gertz, MD & Nikhil Munshi, MD
Brain	2010	Ian Pollack, MD & Al Yung, MD
Pediatrics (Heme & Solid Tumors)	2011	David Poplack, MD & Robert Arceci, MD, PhD (Hematology) Mark Bernstein, MD & Katherine Matthay, MD (Solid Tumors)

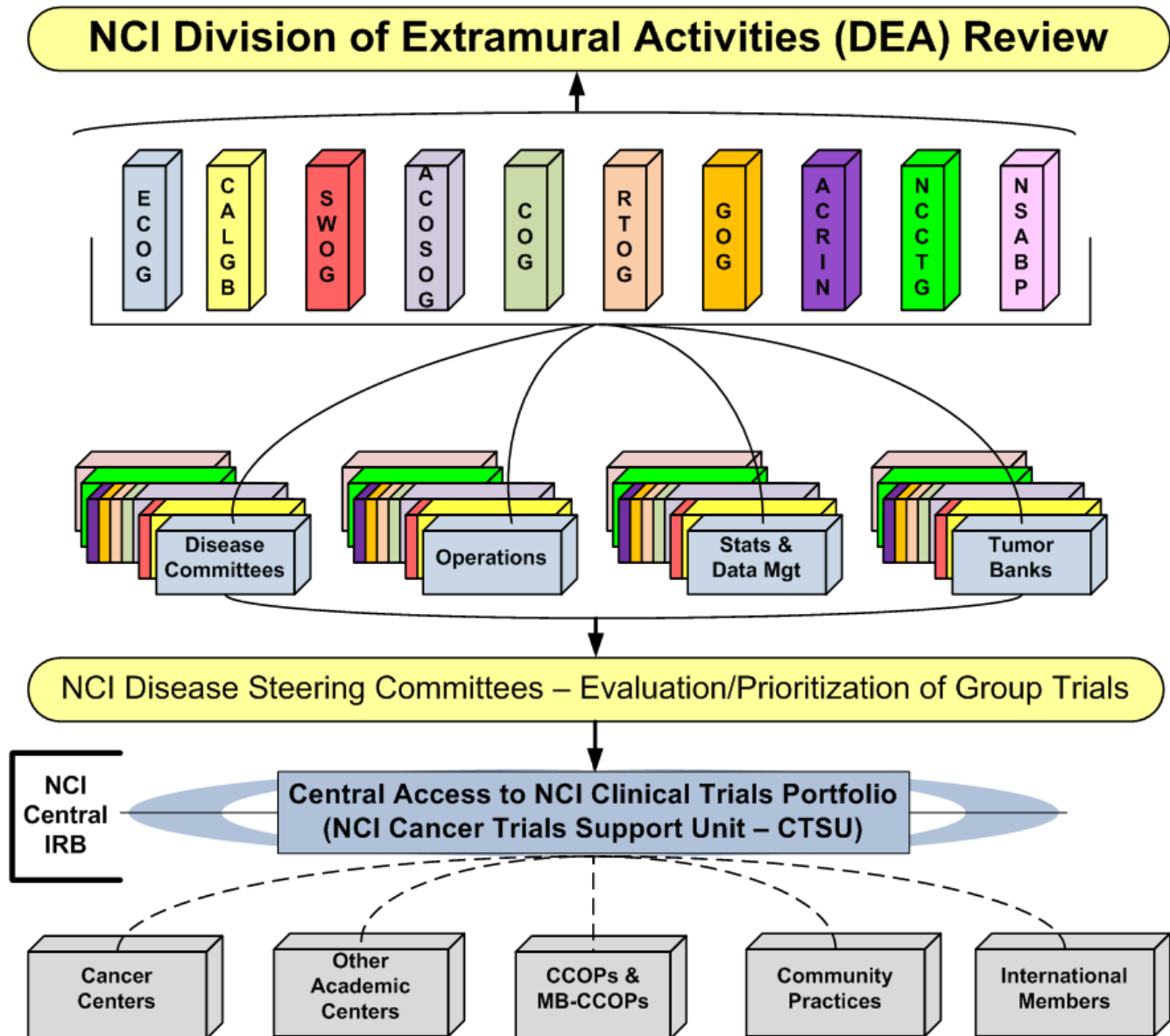
*Cancer Center Directors

Over 170 Concepts evaluated since inception of SCs

Related Steering Committees as of 10-7-2011: (Non-disease Focus)

- **Investigational Drug Steering Committee**
 - Co-Chairs: Pat LoRusso, DO, & Dan Sullivan, MD
- **Clinical Imaging Steering Committee**
 - Co-Chairs: Steven Larson, MD & Etta Pisano, MD
- **Symptom Management & Health-Related Quality of Life Steering Committee**
 - Co-Chairs: Deborah Bruner, RN, PhD & Michael J. Fisch, MD, MPH
- **Patient Advocate Steering Committee**
 - Co-Chairs: Regina Vidaver & Nancy Roach

Structure of Program: As of January 2011

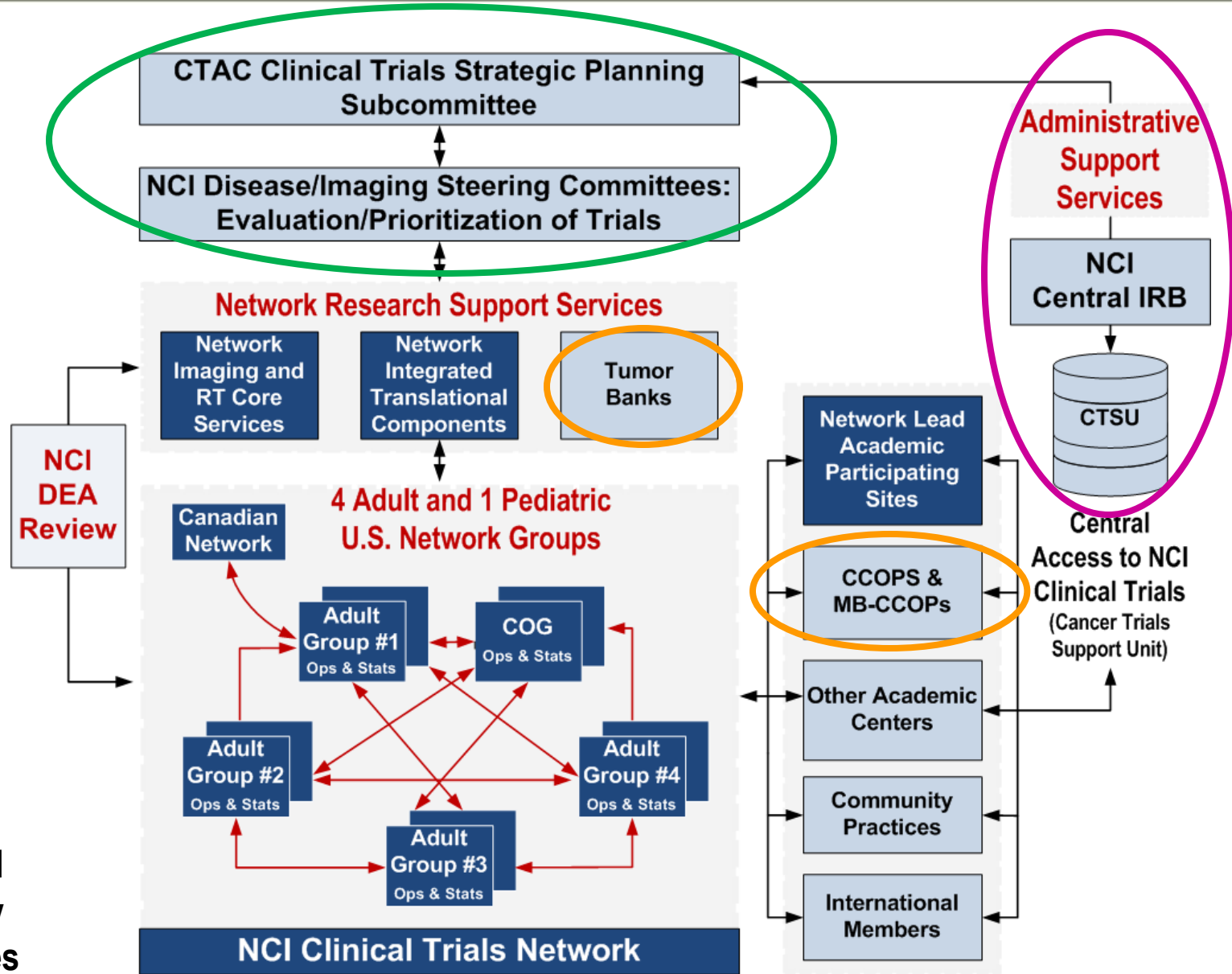


Next Steps in Transforming the System

- **New RFA for an Integrated National Clinical Trials Network**
- **Consolidated Organizational Structure with Funding for 1 Pediatric Group and up to 4 Adult Groups**
- **Review Criteria with Emphasis on Integration & Collaboration for Overall Scientific Achievement and Operational Efficiency**
- **Funding Model with Increased Per-Case Reimbursement for “High-Performance” Academic & Community Sites**
- **Competitive Integrated Translational Science Awards**
- **Revitalize Cancer Center Role in the Network (U10 awards)**

Introducing A New Organizational Structure

NCI Clinical Trials Network



Other NCI Grant Programs
 Dark blue boxes signify NCI DEAR reviewed grant-funded components under Extramural RFA Advisory Committees

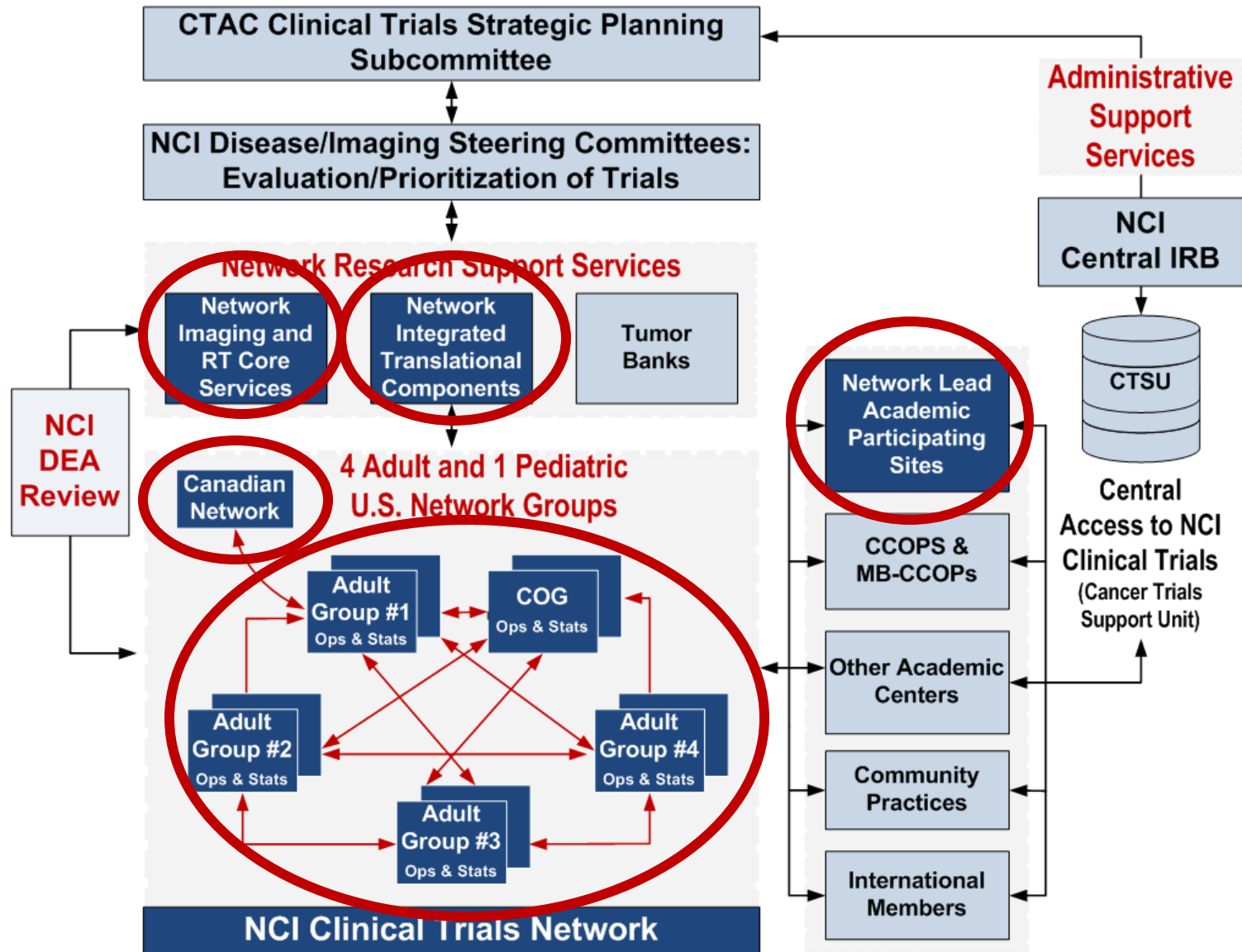
Rationale for Transforming Current Program:

How Will Consolidated Network System Help?

- **Consolidate infrastructure to gain efficiencies (e.g., IT, Regulatory, Administrative, Tissue Resource Management)**
- **Consolidate Imaging & RT core services to benefit entire Network**
- **Integrate new components into trials to provide value-added research questions (e.g., advanced imaging, translational science)**
- **Integrate new agents into trials**
 - **Ex:** Erlotinib, crizotinib, & ipilimumab are being integrated into trials in earlier stages of lung cancer & melanoma treatment requiring screening large populations & combining the agents optimally with surgery, RT, and immunotherapy
- **Evaluate new agents in molecularly-defined disease subsets**
 - **Ex:** Even for common diseases such as breast cancer, # of molecularly-defined patient subsets is increasing & there is a need for trial prioritization evaluating multiple new agents with standard regimens across subsets to avoid duplication & optimize accrual

Introducing A New Organizational Structure

NCI Clinical Trials Network



Network Component Description

Group Operations Ctrs & Group Stats Ctrs

- **Provide scientific strategy & goals across broad range of diseases**
- **Responsible for Network Group administration including**
 - Study conception, protocol development, and accrual to trials
 - Adherence to “Operational Efficiency” timelines
 - Audits and QA/QC of protocol therapy
 - Coordinating biospecimen collection from patients on trials
 - Compliance with FDA, OHRP, NCI/NIH regulations
- **Statistical leadership for effective design & trial conduct**
- **Monitors data quality for primary analysis & correlative science**
- **Supports data mgt & analyses for studies outside the Network Groups as appropriate (e.g., Steering Committee-approved studies)**

Network Components Review Criteria

Group Operations & Statistical Centers

- **Reconfigure NCI/NIH external peer-review of System**
 - **Emphasis on incentives for a national system with trials open to all qualified sites & sites able to credit any Group to which they belong**
 - **Review of all Network Groups/components at same time (specific review panels for particular Network components)**
 - **Scientific evaluation will shift to evaluating Group role in national network, overall scientific strategy, innovation and quality (~50%)**
 - **Review criteria for operational efficiency & collaborative management of Network (~50%)**
 - ✓ **Coordination with other Network Groups, NCI programs, NCI investigators outside Groups (e.g., CCOPs, MB-CCOPs, Tumor Banks, Cancer Centers, SPORES, N01s/U01s, P01s, etc.)**

Network Description & Review Criteria

Lead Academic Participating Sites

- **Description**
 - Multiple-PI grants for academic institutions with demonstrated scientific leadership in ≥ 1 adult Network Groups, substantial accrual, & excellent data quality (“high-performance” sites)
 - Targeted at NCI Comprehensive and Clinical Cancer Centers and other leading academic centers
- **Review Criteria**
 - Meets accrual threshold set from trials across entire Network
 - Expertise & leadership role in Group(s)
 - Data quality
 - Contributions to translational science within Group trials
 - Scientific collaborations across Cancer Center/Institution & Network

Network Description & Review Criteria

Integrated Translational Science Awards

- **Description**
 - Multiple-PI grants to support prominent researchers for their expertise and efforts in incorporating molecular studies into Network trials & enabling acquisition of preliminary data for further research
 - Laboratory-based researchers will also facilitate hand-off of early phase clinical trial findings into later phase, definitive trials
- **Review Criteria**
 - Peer-review of quality of scientific approach & plans for integration of translational science into clinical trials
 - Leverages independently funded laboratory resources with Group clinical specimens & data to benefit Group research aims
 - Research area likely to benefit trial efforts across Network

Network Description & Review Criteria

Core Services & Canadian Partner Network

- **RT and Imaging Core Services**
 - Provides scientific leadership for incorporating appropriate QA & image data management for research trials involving RT & imaging
 - Review Criteria for scientific leadership & expertise as Network-wide resource, integrated IT platforms for capturing and storing images, & efficient procedures for accessing site data for RT & image-related trial questions
- **Canadian Collaborating Trials Network**
 - NCI Program has had long history of collaboration with Canadian sites and non-profit Canadian clinical trial organizations
 - Review Criteria for ability to provide appropriate regulatory oversight for US Networks trials conducted in Canada, irrespective of which Group leads trial and to be full partners in accruing patients to US Network trials

Overview of RFA: Cooperative Agreement FOAs and Estimated # Grants

Network Component	Mechanism (Duration)	Est. Max. # Grants	Frequency New Application Accepted?	Multiple PI Option?
Group Operations Centers	U10 (5 Yrs)	5	Every 5 Years	Yes
Group Statistical & Data Mgt Centers	U10 (5 Yrs)	5	Every 5 Years	Yes
Canadian Collaborating Network	U10 (5 Yrs)	1	Every 5 Years	Yes
Integrated Translational Science Awards	U10 (5 Yrs)	1 to 5	Every 5 Years	Yes
RT and Imaging Core Services	U24 (5 Yrs)	1 to 2	Every 5 Years	Yes
Lead Academic Participating Sites	U10 (5 Yrs)	30 to 40	Any Year	Yes

Principles of Network Funding Plan

- **All external reviews of the NCI clinical trials system emphasized need to provide increased research reimbursement to ensure continued participation of sites in the public program**
- **Base “per-case” reimbursement for patient enrollment in the program has remained fixed at \$2,000 per patient in treatment trials for over a decade**
 - **2006 estimate for average per patient cost in industry trials was \$4,700 for phase 3 & \$8,450 for phase 2 Trials (& some industry trials at \geq \$15,000)**
 - **Survey in 2009 of Group sites found that of those planning to limit participation in the program (32% of respondents), 75% cited inadequate reimbursement for the decline in their level of participation**
- **“High-Performance” sites incur additional infrastructure costs due to the number of patients they accrue & additional funding is especially needed to compensate these sites for their large patient follow-up burden - (propose additional \$2,000 /pt for these sites for total of ~\$4,000/pt)**

Budget History for Components of NCI Clinical Trials Network

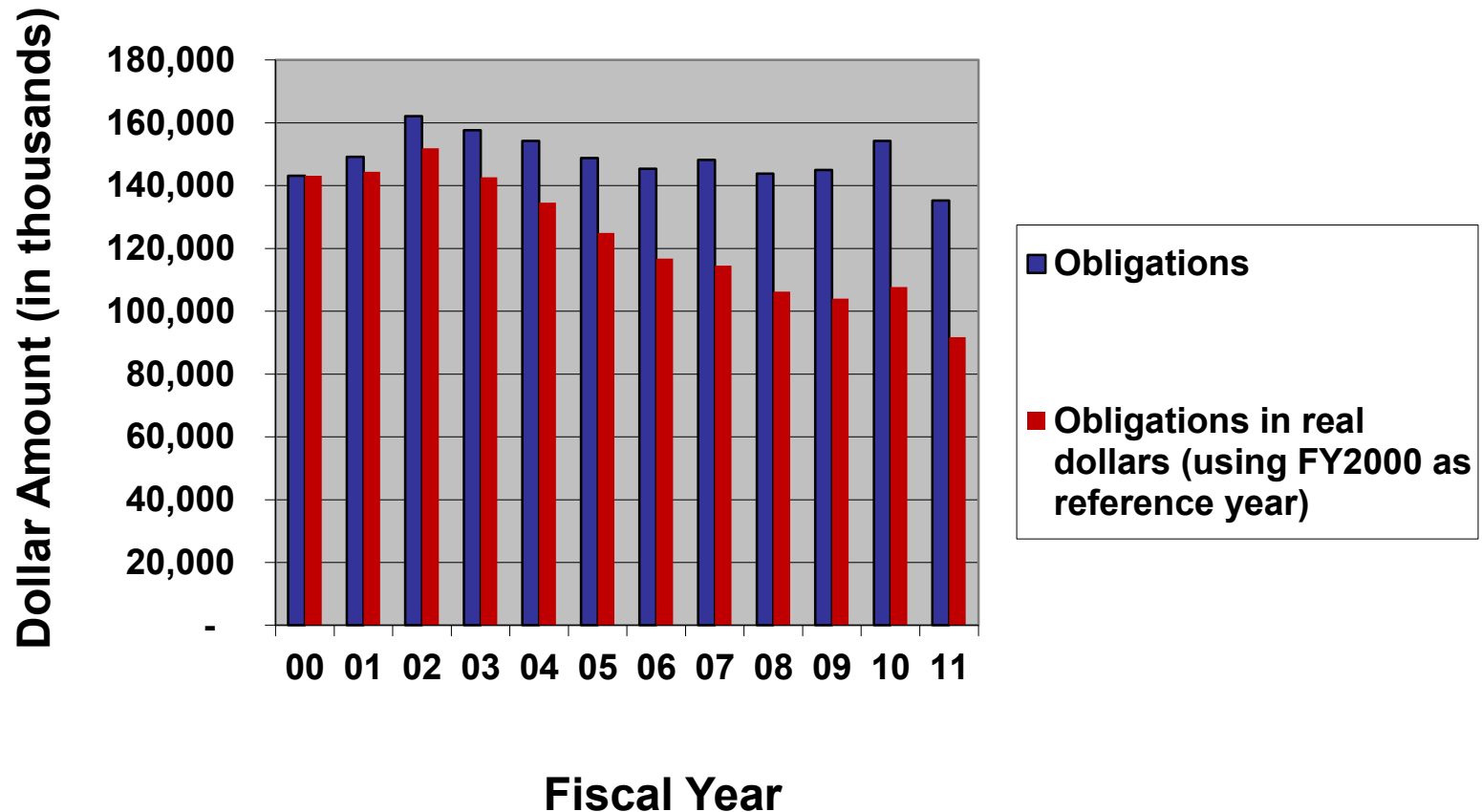
Base Divisional Set-Aside for Network/Group Program *	FY2006	FY2007	FY2008	FY2009	FY2010	FY2011 (Estimated)	Grand Total (Over 6 Yrs)	% Grand Total
Group Operations & Statistical Centers (including Capitation for Majority of Accrual)	\$128,833,204	\$126,516,480	\$126,141,046	\$126,380,185	\$127,127,666	\$120,304,563	\$755,303,144	78.7%
Participating Site U10s	\$ 12,532,773	\$11,375,647	\$11,074,808	\$11,241,179	\$11,823,333	\$10,839,407	\$ 68,887,147	7.2%
Core Services for Imaging & RT (RPC, QARC)	\$ 4,185,608	\$4,302,227	\$ 4,271,987	\$ 4,224,437	\$ 4,307,091	\$ 4,131,527	\$25,422,877	2.6%
Subtotal	\$145,551,585	\$142,194,354	\$141,487,841	\$141,845,801	\$143,258,090	\$135,275,496 **	\$849,613,167	
Estimated CTSU Capitation	\$ 4,000,000	\$ 3,779,781	\$ 4,289,927	\$ 5,162,362	\$ 5,174,165	\$ 5,040,000	\$ 27,446,235	2.9%
Subtotal	\$ 149,551,585	\$145,974,135	\$145,777,768	\$147,008,163	\$148,432,255	\$140,315,496	\$877,059,402	
ACRIN	\$7,002,444	\$15,442,054	\$13,129,762	\$13,509,478	\$12,816,778	\$10,612,813	\$ 72,513,329	7.6%
ATC	\$1,644,551	\$ 1,749,999	\$ 1,716,026	\$ 1,716,026	\$1,716,030	\$ 1,716,026	\$ 10,258,658	1.1%
Grand Total	\$158,198,580	\$163,166,188	\$160,623,556	\$162,233,667	\$162,965,063	\$152,644,335	\$959,831,389	100.0%

* Does not include ARRA funding and special "one-time" supplements (e.g., transition supplements) or funding provided by other NCI/NIH Programs for Special Initiatives (e.g., complexity funding)

** Base funding was decreased by FY2011 general budget cuts

Trials Program Funding 2000 to 2011: Real \$

Cooperative Group Obligations 2000-2011 Deflated Using BRDPI



5-Year Annual Funding Request for NCI Clinical Trials Network

Category for Base Division Set-Aside for Network Program	Annual Total Cost for FY14 to FY18 Based on 20% Reduction in Accrual Compared to Average Accrual Over Last 6 Years (Approx. 20,000 Treatment Trial Enrollments)
Funding Based on FY2011 Levels: Group Operations & Statistical Centers (includes Capitation), Lead Academic Participating Sites, and Core Services	\$ 152,644,335
Funding Request Based on New Funding Model & BIQSFP:	
Increase Capitation to "High-Performance" DCTD-funded Sites	\$ 11,520,000
Increase Capitation to "High-Performance" DCP-funded CCOPs & MB-CCOPs	\$ 10,080,000
Increase Funding for Integral and Integrated Markers (BIQSPF)	\$ 4,000,000
Subtotal:	\$ 25,600,000
Grand Total:	\$ 178,244,335 *

* The 5-Year Total Cost Funding Request for FY2014 to FY2018 for the NCTN is \$891,221,675

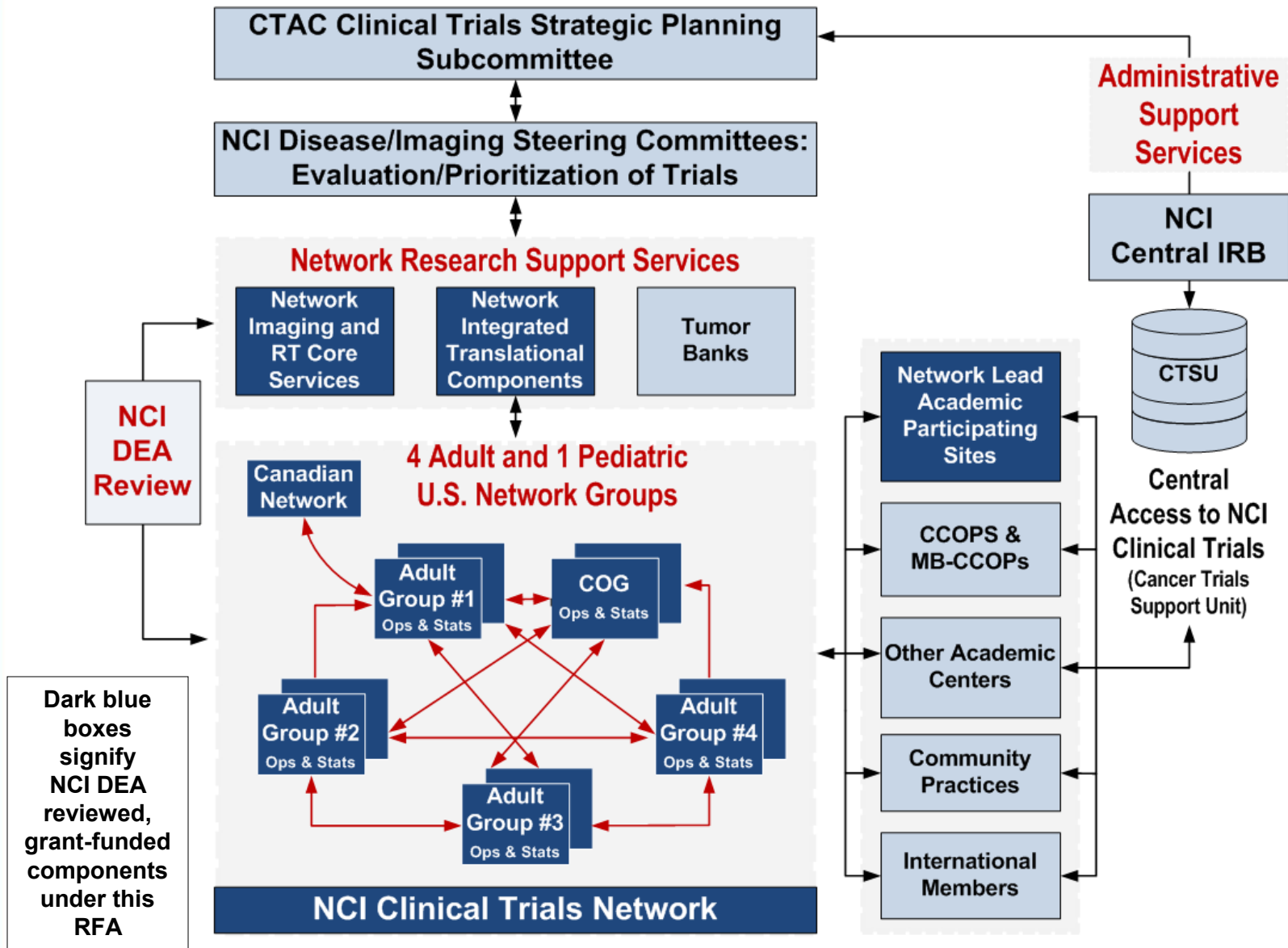
Strategic Planning for the New NCTN Program

- **Treatment trial accrual has been dominated by Breast and GI Cancer trials, especially large adjuvant trials, over past decade**
- **The new funding model will require Network organizations and Steering Committees to monitor the balance of trials prioritized for development and help develop a strategic consensus about the diseases in which to encourage more trials as scientific opportunities arise**
- **New review criteria should facilitate more trials in disease areas which have been typically underrepresented, relative to their incidence, and portfolio balance will be monitored closely by CTAC's NCTN Strategic Planning Subcommittee to ensure that scientific opportunities in less common tumors are not missed**

Tentative Timeline for Potential Implementation

BSA Concept Review	Nov 2011
NCI DEA & NIH Review FOA/Guidelines	Nov 2011 – July 2012
New FOA Released/Published	July 2012
Receipt Competing Applications	Winter 2012 [Nov 2012- Feb 2013]
Review Competing Applications	Summer 2012 [May 2013 - Aug 2013]
NCAB Review	Dec 2013
Rollout of Awards in FY2014	March 2014

Introducing A New Organizational Structure NCI Clinical Trials Network



NCI's commitment to global health and global cancer control

Edward L. Trimble, MD, MPH

Center for Global Health

Global burden of cancer

Year	Number of cancer deaths	% in developing world
2002	6.2 million	55%
2008	7.6 million	64%
2030	13.2 million	69%

Potentially modifiable risk factors for cancer

- Tobacco (17% of cancers)
- Chronic infections (17% of cancers)
 - Liver cancer (Hepatitis B and C), cervical and head & neck cancer (human papillomavirus), stomach cancer (Helicobacter pylori), Kaposi's sarcoma, nasopharyngeal carcinoma, Burkitt's lymphoma, etc
- Obesity: diet and exercise
- Alcohol intake
- (Increasing age)

Some NCI Global Collaborations

- International Cancer Genome Consortium
 - The Cancer Genome Atlas Project
- International epidemiology consortia
- International Cancer Screening Network
- International Tobacco Control Policy Evaluation Consortium

Some DCEG international projects

- China: Biliary tract cancer (Shanghai), liver cancer (Jiangsu); nutritional supplements for cancer prevention (Henan), gastric cancer & treatment of H.pylori infections (Shandong), cervical cancer screening (Shanxi), lung cancer among tin miners (Yunnan), benzene exposure in factory workers
- Costa Rica: epidemiology of HPV infection, screening and management of preinvasive cervical neoplasia, phase III trials of prophylactic HPV vaccines

CCR: HPV biology and prophylactic HPV vaccines



Existing NCI International Offices

- Office of International Affairs
- Office of Latin American Cancer Program Development
- NCI Liaison Office-Brussels
- Office of China Cancer Program Development
- International Network for Cancer Treatment and Research

Office of International Affairs

- Middle East Cancer Consortium (since 1996)
 - Cyprus, Egypt, Israel, Jordan, Palestinian Authority, & Turkey
 - Major projects: cancer registries, palliative care
- All-Ireland National Cancer Institute Cancer Consortium (since 1999)
 - Republic of Ireland, Northern Ireland, US
 - Major projects: prevention, clinical trials, registries, epi, health economics, palliative care

Office of International Affairs

- International Union for Cancer Control
 - Travelling fellowships
- Breast Global Health Initiative
 - Founded by Fred Hutchinson and Susan Komen for the Cure to develop and implement guidelines for low- and middle-income countries
- African Organization for Research and Treatment of Cancer
 - Meetings and small grants program

Office of Latin American Cancer Program Development

- **NCI-ASH| US-Mexico Cytogenetics Standardization Project**
- **NCI-ASCO| International Clinical Trials Training Workshop (Latin America)**
- **Trans-NCI Collaboration with Latin American Cancer Epidemiology (LACE)**
- **Trans-NCI Gallbladder Project Planning Meeting**
- **Trans-NCI Collaboration | Workshop for Cervical Cancer Prevention**
- **Susan G. Komen for the Cure®**

United States-Latin America Cancer Research Network (US-LA CRN):

A bi-lateral agreement (LOI) among governments was signed in September 2009 where all governments “intend to enhance and expand cooperative efforts in the field of public health, medicine, science and cancer research”.

Connecting at the government, institution, and investigator levels

Provide a framework to encourage bilateral cooperation in addressing issues and problems of importance in the fields of public health, medicine, science and cancer research



Pilot Study

Molecular Profiling of Stage II and III Breast Cancer in Latin American Women Receiving Standard of Care Treatment (MPBC)

Primary Objective

To characterize the distribution of invasive breast cancer stage II and III molecular profiles in Latin American women

Office of China Cancer Programs

- NIH-China National Natural Science Foundation Collaborative Biomedical Research Program
- Joint workshops:
 - Nanotechnology (2008, 2010), Bioinformatics (2010), Environmental pollution and cancer (2010), Biorepository standards (2011)
 - Biomarkers (2012), Building the evidence base for cancer prevention and screening (2012)

Some NCI-designated Cancer Centers active in Africa

- Fred Hutchinson Cancer Research Center: Uganda
- University of North Carolina: Malawi
- University of Maryland: Nigeria
- University of Michigan: Ghana
- Indiana University: Kenya

Roles for NCI Center for Global Health

- Coordination of global cancer research across NCI
- Partnership with other NCI divisions, centers, and offices in global cancer research
 - Development of new initiatives, facilitation of research
- Partnership with other NIH ICs in global health research
 - Fogarty, NIAID, NHBLI, NIDDK, etc

Current NCI-Fogarty partnerships

- International Tobacco and Health Research and Capacity Building Program
- HIV Research Training Program
- International Research Collaboration Award
- Global Research Initiative Program

Potential Fogarty Programs

- Chronic, NCDs and Disorders Across the Lifespan (D43)
- International Research Ethics Education and Curriculum Development
- Ecology and Evolution of Infectious Diseases
- Framework Innovations
- Medical Education Partnership Initiative
- Extramural Research Associates Development

Roles for NCI and NCI Center for Global Health

- Partnership with other DHHS and federal agencies
 - CDC, FDA, OHPR, PEPFAR, Red Ribbon/ Pink Ribbon, US AID, etc
- Partnership with WHO, International Agency for Research on Cancer, International Atomic Energy Agency, regional and country WHO offices

Roles for NCI and NCI Center for Global Health

- Partnerships with professional societies
 - ASCO, AACR, ASTRO, ACOS, Oncology Nursing Society, etc
- Partnership with NGOs
 - American Cancer Society, International Union for Cancer Control, Susan Komen for the Cure, Lance Armstrong Foundation, etc
- Partnership with pharma and biotechnology industries

Roles for NCI and NCI Center for Global Health

- Partnerships with other national governments (ministries of health, national cancer institutes, etc)
- Multilateral governmental partnerships
 - EC, Latin American Cancer Research Network, Organization for Economic Collaboration and Development, etc
- Partnerships with university global health programs and NCI-designated cancer centers

Scope of global cancer research

- Across cancer continuum
- Cancer biology, epidemiology, molecular genetics, genomics, proteomics, gene-environment interaction, pharmacogenomics, etc
- Cancer registration, prevention, screening, early diagnosis, imaging, treatment, symptom management, survivorship, palliative care, etc
- Cancer communications, behavior, health system organization, effectiveness, quality, implementation science, etc

Vision for NCI and NCI Center for Global Health

- Varmus HV & Trimble EL. Integrating cancer control into global health. Science Translational Medicine 2011;3:1-3
- For more information:
- <http://www.cancer.gov/aboutnci/globalhealth>
- Email: tt6m@nih.gov