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

49th Meeting

BOARD OF SCIENTIFIC ADVISORS

Minutes of Meeting

June 20, 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
June 20, 2011

The Board of Scientific Advisors (BSA), National Cancer Institute (NCI), convened for its 49th meeting on Monday, 20 June 2011, at 9:00 a.m. in Conference Room 10, Building 31C, National Institutes of Health (NIH), Bethesda, MD. Dr. Richard L. Schilsky, Professor of Medicine, Section of Hematology and Oncology, Biological Sciences Division, University of Chicago Pritzker School of Medicine, presided as Chair. The meeting was open to the public from 9:00 a.m. until 4:50 p.m. on 20 June for the NCI Director's report; a discussion of perspectives on the BSA; a report on the implementation plan based on the cancer Bioinformatics Grid (caBIG®) Working Group report; establishment of BSA Subcommittees; consideration of Request for Applications (RFA) and Cooperative Agreements (Coop. Agr.) new and reissuance concepts presented by NCI program staff; a report on NCI's support of R21 grants; and a report on the drug scarcity problem.

BSA Board Members Present:

Dr. Richard L. Schilsky (Chair)
Dr. Paul M. Allen
Dr. Christine Ambrosone
Dr. Andrea Califano
Dr. Curt I. Civin
Dr. Robert B. Diasio
Dr. Jeffrey A. Drebin
Dr. Betty R. Ferrell
Dr. Kathleen M. Foley
Dr. Todd R. Golub
Dr. Joe W. Gray
Dr. Mary J. C. Hendrix
Dr. Timothy J. Kinsella
Dr. Joshua LaBaer
Dr. Christopher J. Logothetis
Dr. Maria Martinez
Dr. James L. Omel
Dr. Edith A. Perez
Dr. Stuart L. Schreiber
Dr. Bruce W. Stillman
Dr. Louise C. Strong
Dr. Frank M. Torti
Dr. Jean Y. J. Wang
Dr. Irving L. Weissman

Board Members Absent:

Dr. Michael A. Caligiuri
Dr. Arul M. Chinnaiyan
Dr. Chi V. Dang
Dr. Ronald A. DePinho
Dr. Sanjiv S. Gambhir
Mr. Don Listwin
Dr. Victor J. Strecher
Dr. James K. Willson

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

TABLE OF CONTENTS

I. CALL TO ORDER AND OPENING REMARKS - DR. RICHARD L. SCHILSKY

Dr. Richard L. Schilsky called to order the 49th regular meeting of the BSA and welcomed current and new members of the Board, NIH and NCI staff, guests, and members of the public. Dr. Schilsky reminded Board members of the conflict-of-interest guidelines and confidentiality requirements. Members of the public were invited to submit to Dr. Paulette S. Gray, Director, Division of Extramural Activities (DEA), in writing and within 10 days, comments regarding items discussed during the meeting.

II. CONSIDERATION OF THE 1 MARCH 2011 MEETING MINUTES - DR. RICHARD L. SCHILSKY

Motion: The minutes of the 1 March 2011 meeting were approved unanimously.

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

Dr. Harold Varmus, Director, NCI, welcomed members and provided information about the NCI's fiscal years (FY) 2011 and 2012 budget, as well as specific NCI and NIH activities. Dr. Varmus announced that Drs. James H. Doroshow is the new Deputy Director of Clinical and Translational Research and Jeffrey Abrams and Joseph Tomaszewski are acting co-Directors of the Division of Cancer Treatment and Diagnosis (DCTD). He noted that recruitment for the Director of the Division of Cancer Prevention (DCP) is under way.

Budget: Dr. Varmus informed members that the NCI's FY 2011 budget of $5.059 billion (B) is 1 percent lower than the FY 2010 level. The budget's large commitment base includes: increases in the average size of competing research project grants (RPGs), continued support of several grants originally awarded with American Recovery and Reinvestment Act (ARRA) funds, and construction costs associated with the new Shady Grove facility. Dr. Varmus affirmed NCI's commitment to sustaining its grant portfolio as well as the reorganization of the NCI clinical trials and cooperative groups and continuing scientific discovery through cancer genomics. The NCI is paying noncompeting RPGs at 97 percent, which is approximately 3 percent below the FY 2010 level, and has reduced operating budgets across the Institute. An estimated 1,100 RPGs will be awarded in FY 2011, with special consideration given to young, first-time investigators.

Dr. Varmus informed members that the FY 2012 budget is not likely to increase. The President's Budget (PB) for the NCI currently is 3 percent higher than the FY 2011 level, and the NCI leadership will consider strategies to adapt to a more constrained future at its retreat in mid-July.

NCI Activities: Members were informed that Dr. David Heimbrook, the new chief executive officer of SAIC-Frederick, is working with an advisory group that will oversee and evaluate NCI-Frederick activities. The advisory group will not review individual investigators but will review major programs, evaluate broadly the investments that have been made, and ensure that NCI-Frederick goals are consonant with the general goals of the NCI. Dr. Heimbrook will be invited to address the BSA at a future board meeting.

Members were reminded that the Cooperative Groups are being realigned into four adult groups and one pediatric group, with three centers for tissue storage. The NCI held a successful meeting with the Cooperative Group Leaders and some Cancer Center Directors to open communication channels and ensure that the Cancer Centers play an important role in the oversight of the Cooperative Groups. Dr. Varmus will attend a meeting at Cold Spring Harbor Laboratory, NY, that will discuss the importance of clinical trials and how the Cooperative Groups will adapt to a world of genomics.

Dr. Varmus informed members that Dr. Barbara Wold will serve as the Acting Director of the Center for Cancer Genomics while on sabbatical from her academic position. The NCI will participate in the upcoming International Cancer Genome Consortium meeting in Kyoto, Japan, to discuss collaborative and complementary activities. Dr. Varmus also announced that Dr. Ted Trimble is the Acting Director of the new Center for Global Health (CGH); plans for the CGH will be discussed at the NCI's leadership retreat.

NIH Activities: Dr. Varmus informed members that a portion of NCI's tobacco portfolio will move into the new NIH institute on addiction, and the Division of Cancer Control and Population Sciences (DCCPS) is overseeing the reallocation. The establishment of the National Center for Advancing Translational Sciences (NCATS) is being widely discussed by the biomedical community; the Center will provide a better way to support translational work across the ICs. No new funds will be given to NCATS unless the Cures Acceleration Network (CAN) is authorized in FY 2012. Dr. Varmus, along with Dr. Doroshow, will be discussing the issue of drug shortages with IC Directors, as this problem affects all of NIH.

Interagency Collaborations: The NCI has teamed with the U.S. Food and Drug Administration (FDA), which is announcing new cigarette-labeling requirements. The Institute also is in discussions with the Centers for Medicare and Medicaid Services (CMS), the FDA, and the Centers for Disease Control and Prevention (CDC) regarding cancer care oversight. Dr. Varmus will serve on the FDA-NIH Council.

In the discussion, the following points were made:

< The NCI and FDA have discussed standards for approval of drugs for clinical trials, and the FDA is receptive to considering approval of highly active agents in the context of a genomic profile.

< The ICGC meeting in Kyoto, Japan, should include representatives from pharmaceutical companies that conduct gene sequencing and genomics-based trials.

IV. PERSPECTIVES ON THE BSA - DR. RICHARD L. SCHILSKY

Dr. Schilsky provided a broad critique of the BSA based on his perspective as a Board member since 1999. He reminded members that the BSA's mission is to provide scientific advice on matters concerning scientific program policy, progress, and future direction of the NCI's extramural research programs, in addition to concept review of extramural program initiatives. The Board's advisory role is scientific and does not include deliberation on matters of public policy; the BSA makes recommendations about research priorities and is involved in the evaluation of ongoing programs.

Dr. Schilsky reflected on BSA strengths, which include concept review and program assessment. He noted that the Board provides thoughtful analyses of the concepts and in many instances has dramatically improved the concepts. While the Board performs reasonably well with program assessment, Dr. Schilsky stated that only a segment of NCI's programmatic activities had been presented for review. A suggestion was that the incoming BSA chair work with the NCI leadership to help establish the BSA agenda and ensure sufficient time for discussion of the broad scope of the NCI's activities.

The BSA can improve its role in NCI's strategic scientific planning, participate more actively in priority setting, and better interface with other Advisory Boards, including the Board of Scientific Counselors (BSC) and National Cancer Advisory Board (NCAB). One successful interaction among the Boards was the involvement of BSA members on the NCAB's Working Group "To Create A Strategic Scientific Vision for the National Cancer Program and Review of the NCI." He encouraged a discussion of the Working Group's report at a future BSA meeting.

Members were told that opportunities to improve the BSA's functioning include: greater input into establishing the agenda; receiving a better understanding of context and priorities for new activities, particularly for initiatives that require the development of new infrastructures; and receiving regular progress reports and assessment of strategy and goals for ongoing activities. Dr. Schilsky lauded the NCI leadership for its receptivity to recommendations from the Board regarding particular agenda items. He closed by noting that to be an effective advisory board, the BSA needs to be engaged.

In the discussion, the following points were made:

< Interactions between the Advisory Boards could be enhanced through teleconferences or meetings with the Advisory Board Chairs and NCI leadership, or participation by the Chairs at the NCI's leadership retreats.

< BSA members encouraged a broader overview of the NCI scientific portfolio that would encompass gaps in basic scientific and translational research, as well as training needs. One option is to rotate presentations from NCI Divisions with summaries provided prior to the meeting.

< RFA initiatives should be presented in the context of the relevant scientific portfolio to better understand their value.

< Interim progress reports on BSA approved projects would enable the Board to provide more effective and timely advice throughout the lifespan of the projects.

V. RECOGNITION OF RETIRING MEMBERS - DRS. HAROLD VARMUS AND RICHARD L. SCHILSKY

On behalf of the NCI, Drs. Varmus and Schilsky recognized six retiring BSA members: Drs. Paul M. Allen, Robert L. Kroc Endowed Professor of Pathology, Department of Pathology and Immunology, Washington University School of Medicine; Christopher J. Logothetis, Chairman and Professor, Department of Genitourinary Medical Oncology, The University of Texas, M.D. Anderson Cancer Center; Edith A. Perez, Deputy Director, Mayo Comprehensive Cancer Center, Serene M. and Frances C. Durling Professor of Medicine, Division of Hematology/Oncology, and Chair, Breast Disease Oriented Group, Mayo Clinic; Richard L. Schilsky, Professor of Medicine, Section of Hematology/Oncology, Biological Sciences Division, University of Chicago, Pritzker School of Medicine; Jean Y. Wang, Distinguished Professor of Medicine, University of California, San Diego, School of Medicine, and Associate Director of Basic Research, Moores UCSD Cancer Center; and James K. Willson, Director, Simmons Comprehensive Cancer Center, University of Texas Southwestern Medical Center. Dr. Varmus thanked the retiring members for their contributions and

service on the Board. He expressed particular appreciation to Dr. Schilsky for his service as BSA Chair, 12 years as a member, and overall dedication to the Institute and the Board.

VI. ONGOING AND NEW BUSINESS – Dr. RICHARD L. SCHILSKY

Dr. Schilsky encouraged members to submit potential agenda items for future board meetings. Suggested topics include: an update about the capabilities and successes of the Specialized Program of Research Excellence (SPORE) and its relationship to the Cancer Centers program; a presentation on the NCAB report for NCI's scientific strategic vision; and an overview of grant portfolios and activities supported by each NCI division, office and center.

Establish HIV Malignancy *ad hoc* Subcommittee

Dr. Schilsky presented a proposal to establish a BSA *ad hoc* Subcommittee to advise the Board, the NCI Director, and the Director of the NCI Office of human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) malignancy concerning the most effective use of NCI research resources to advance the NCI's mission with respect to HIV/AIDS and HIV-associated malignancies. He stated that the aim is to prevent, diagnose, and treat these conditions in the United States and throughout the world. The Subcommittee will be comprised of current BSA members, *ad hoc* participants from the scientific community, and a member of the NCAB who serves as a representative on the NIH Office of AIDS Research Advisory Council. A member of this Subcommittee also would serve as a representative on an advisory group to the new Center for Global Health. Dr. Robert Yarchoan will serve as the Executive Secretary.

In the discussion, the following point was made:

< Current trends in AIDS malignancy research include an increased emphasis on non-AIDS defining malignancies, as well as greater attention to the malignancies in Africa and other developing countries. The current NCI AIDS malignancy portfolio reflects changes in the demographics or epidemiology of AIDS and the new Subcommittee will ensure coordination with the Institute's other global health efforts.

Motion. A motion made to establish an HIV Malignancy *ad hoc* Subcommittee was approved unanimously.

Establish caBIG® Oversight a*d hoc* Subcommittee

Dr. Schilsky presented a proposal to establish a BSA *ad hoc* Subcommittee to evaluate the scientific merit of the caBIG® program's ongoing and planned initiatives and to advise the NCI Director and the BSA concerning improvements to the program. Subcommittee membership will include scientists with expertise in bioinformatics, technology, clinical informatics, consumer health, basic research, translational research, bioengineering, and other domains. Mr. John Czajkowski will serve as the Executive Secretary.
In the discussion, the following points were made:

< The NCI-Frederick Advisory Committee will retain oversight of activities at the Frederick campus, including caBIG® activities that occur there.

< This Subcommittee is proposed as an *ad hoc* group but likely will become a standing committee.

Motion. A motion to establish a caBIG® Oversight *ad hoc* Subcommittee was unanimously approved.

VII. IMPLEMENTATION PLAN: CANCER BIOINFORMATICS GRID (caBIG®) WORKING GROUP REPORT - MR. JOHN CZAJKOWSKI

Mr. John Czajkowski, Deputy Director for Management, NCI, presented a summary of the caBIG® Working Group's report and the NCI's plan for implementing its recommendations. Mr. Czajkowski informed members that the Working Group concluded that caBIG® had drifted from its core mission and its supported projects had been unevenly successful. They recommended that the NCI refocus caBIG® toward the development of community-driven standards for data exchange and interoperability, provide support for software tools developed by the academic research community, and establish a community dialogue on interoperability of clinical and research software tools. In response, the NCI is phasing out non-core development projects and adjusting the budget to reflect the new scope. Four core projects, i.e., caTissue, caArray, development of imaging tools, and support for multisite clinical trials, are continuing, with other activities suspended pending review and recommendations from the Working Group.

Members were told that caBIG® will continue to develop community-driven technical standards and interoperability frameworks, foster academic bioinformatics development efforts, and meet community-identified software needs through partnerships with external, open-source development communities. A Scientific Advisory Group (SAG) has been created as a BSA *ad hoc* Subcommittee to foster collaboration with the research community, help set priorities, and provide advice for defining best practices for caBIG®. The SAG will assess the need for software tools, which will be developed through external, open-source community efforts using standards and interoperability specifications provided by caBIG®.

Mr. Czajkowski stated that caBIG®'s role in supporting bioinformatics will include the dissemination, storage, and support of community-developed software, including documentation and assorted metadata; supporting academic groups through its Knowledge Center program; collaboration with NCI scientific divisions to identify current and evolving informatics needs; and development of pre-competitive specifications used to drive academic and commercial software development. He informed members that the program's original funding of $45 million (M) for FY2011, plus ARRA funding of $103 M, has been adjusted to $33 M and $43 M, respectively.

In the discussion, the following points were made:

< The caBIG® Oversight *ad hoc* subcommittee could foster interagency collaborations that address issues important to the broad biological research community, such as promoting computer science research.

< The NCI was encouraged to invite a representative from the National Center for Biotechnology Information (NCBI) to serve as an *ad hoc* member to the SAG.

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

Office of the Director
Research Answers to NCI's Provocative Questions (RFA New)

Dr. Douglas Lowy, Deputy Director, introduced a new concept soliciting research answers to the set of questions assembled by NCI's Provocative Questions project. Dr. Lowy stated that the Provocative Questions project was a community based dialogue to consider and identify important, non-obvious questions in cancer research.

Members were informed that 15 to 20 research questions identified through the Provocative Questions project will be selected for this RFA. A portfolio analysis will be conducted to ensure that selected provocative questions are not already widely supported. The questions fall into many different research areas, including epidemiology, pathogenesis, therapeutics, prevention, and behavior. Proposals should build on specific advances in cancer control; address broad, difficult-to-resolve issues in cancer biology; consider the likelihood of progress within 5 to 10 years; and address ways to overcome obstacles to answering the

question. To encourage participation from investigators new to a field, preliminary data would be unnecessary and the principal investigator's (PI) track record within the field would not be weighed heavily.

The goal of the RFA is to stimulate cancer research in compelling, understudied areas. Dr. Lowy said the initiative is expected to encourage a large number of exciting applications, and to handle the influx, up to three annual reissuances are envisioned. Intermediate success would consist of continuation of funded studies through traditional grants. Long-term success would be having research answers to provocative questions lead to a better understanding of neoplasms and improved cancer risk assessments, treatments, and preventions.

Subcommittee Review. Dr. Stuart Schreiber, Morris Loeb Professor, and Director, Chemical Biology, The Broad Institute of Massachusetts Institute of Technology and Harvard University, expressed the Subcommittee's enthusiasm for the concept, noting that answers to some questions could transform cancer treatment. Dr. Schreiber informed members that the Subcommittee supported the extension of R21 awards to 4 years, observing that 2 years of funding is very restrictive for a grant based on a creative new idea. He noted that this is an opportune time to test new ideas and expand the research portfolio.

The first year cost is estimated at $15 M for 25 R01 and 10 R21 awards, for 4 years and 2 years, respectively.

In the discussion, the following points were made:

< Because many of the provocative questions appear to be transdisciplinary in scope, the grant mechanism needs to accommodate multidisciplinary research teams, such as multi PI applications.

< NCI should consider funding all the grant submissions under the R21 mechanism, with an option for a two year extension based on sufficient progress.

Motion. A motion to concur on the OD's RFA entitled "Research Answers to NCI' Provocative Questions" was approved unanimously for three annual re-issuances with the provision that challenging implementation issues will be addressed.

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Division of Cancer Control and Population Sciences
HMO Cancer Research Network Research Resources (RFA/Coop. Agr. Reissuance)

Dr. Robert Croyle, Director, DCCPS, introduced the concept and the presenter, Dr. Rachel Ballard-Barbash, Associate Director, Applied Research Program, DCCPS. Dr. Ballard-Barbash informed members that there has been a rapid expansion of cancer diagnostic technologies and treatments but a lack of research on treatment interactions and outcomes. Investigators increasingly are seeking access to large clinical populations, especially those with electronic medical records (EMRs) and complete medical histories, to perform pharmaco-epidemiologic studies. The Cancer Research Network (CRN) consists of 14 centers affiliated with health maintenance organizations (HMOs) providing care to 11 million individuals. CRN provides a comparative effectiveness research platform to: 1) examine complex drug interactions, 2) perform long-term outcome studies, and 3) assess treatments for very rare cancers for which it is difficult to conduct clinical trials. Currently, no other NCI or NIH initiatives support research in these areas within a clinical care context. The intent of this concept is to transition the CRN from supporting individual research centers (U19) to a research resources infrastructure (U24) that is more widely available to the cancer research community.

Dr. Ballard-Barbash informed members that an external evaluation committee concluded that the CRN provides a unique data set and has the capacity to serve as a national resource. The network has produced more than 200 publications and has supported training of more than 40 junior investigators; approximately one-half of the associated, collaborative grants awarded during the past 4 years have PIs who are external investigators. The committee recommended that CRN: 1) be supported as a research infrastructure; 2)

develop mechanisms to facilitate increased collaborations with external investigators; and, 3) establish a governance structure to target key areas of scientific excellence, such as, health care delivery research, molecular and genomic technologies, medical decision making, etc.

Dr. Ballard-Barbash stated that the largest component of the proposed research infrastructure is a coordinating center responsible for managing data resources, facilitating research activities, and supporting collaboration across groups. Specific performance criteria for each area of excellence will be evaluated annually; and centers not able to meet those criteria will be dropped. Metrics of success have been developed.

Subcommittee Review. Dr. Christine Ambrosone, Chair of the Department of Cancer Prevention and Control, Roswell Park Cancer Institute, expressed the Subcommittee's support for the reissuance and noted that the CRN is an outstanding resource for epidemiology, etiology, and outcomes research. The evolution of the EMR, along with the dramatic increase in the number of available therapeutic agents and wide deployment of clinical diagnostics, gives the CRN the ability to investigate interactions. The Subcommittee agreed that the concept reissuance addresses many weaknesses of the CRN, such as the limited availability of the data to the broader research community, limited involvement from clinicians, and the lack of well-developed leadership.

The first year cost of one U24 award is estimated at $4 M, with a total cost of $20 M for 5 years.

In the discussion, the following points were made:

< NCI should consider broadening the membership for areas of scientific excellence committees so they have sufficient expertise to propose and prioritize the research studies. The areas of scientific excellence should also include experts from outside the CRN, including clinicians.

< The governance structure will be strengthened and reflect the broader NIH plans for HMO research.

Motion. A motion to concur on the DCCPS's RFA/Coop. Agr. reissuance entitled "HMO Cancer Research Network Research Resources" was approved unanimously.

Office of the Director
SBIR Phase II Bridge Awards to Accelerate the Development of Cancer Therapeutics Imaging Technologies, Interventional Devices, Diagnostics, and Prognostics toward Commercialization (RFA Reissuance)

Dr. Andrew J. Kurtz, Program Director, Small Business Innovative Research (SBIR) Development Center, reminded members that the SBIR program, which supports investigator-initiated projects, is structured in three phases: a Phase I feasibility study for six to twelve months; a two year Phase II project with a commercialization plan; and a Phase II Bridge award that extends promising Phase II projects by encouraging partnerships with third-party investors earlier in the development process. Dr. Kurtz said that the program gives competitive preference and funding priority to applicants who can raise substantial third-party funds, that is, dollar-for-dollar matching. This approach offers the key benefits of incentivizing small companies to market themselves to investors, sharing investment risk between multiple parties, and leveraging dollars with external resources with respect to the commercialization of technology.

The SBIR Program has funded 10 Phase II Bridge awards totaling $27 M, including two in therapeutics, five in imaging, and three in diagnostics; 19 other applications are under consideration. Traditional venture capitalists, strategic partners, and angel investors, investment firms, or individuals have brought nearly $63 M into these projects. The expectation is that the investigator will have acquired the first year of third-party dollars before the award is initiated, with the investment spread across 3 years. The Phase II Bridge awards (FY 2009-2011) will account for approximately 14 percent ($14 M) of the SBIR program's budget

($98 M). Dr. Kurtz informed members that the concept reissuance is for the next 3 years, with two receipt dates expected per year.

Subcommittee Review. Dr. Joshua LaBaer, Virginia G. Piper Chair in Personalized Medicine, and Director, Virginia G. Piper Center for Personalized Diagnostics, The Biodesign Institute, Arizona State University, expressed the Subcommittee's support for the SBIR Phase II Bridge reissuance concept. Dr. LaBaer said that the program is filling an important niche in helping SBIR companies move toward commercialization of technologies. He stated that the Subcommittee also noted that the NCI serves as a model to the NIH in its management of SBIR contracts, both in the quality of leadership and performance.

The first year cost is estimated at $10 M for 5-10 R44 awards, with a total cost of $30 M for 3 years.

Motion. A motion to concur on the OD's RFA reissuance entitled "SBIR Phase II Bridge Awards to Accelerate the Development of Cancer Therapeutics Imaging Technologies, Interventional Devices, Diagnostics, and Prognostics toward Commercialization" was approved unanimously for three re-issuances.

IX. NCI SUPPORT OF R21s - DR. DINAH SINGER

Dr. Dinah Singer, Director, Division of Cancer Biology (DCB), provided a report on NCI's support of the exploratory/developmental (R21) grant mechanism and solicited advice on how NCI should use this mechanism in the future. Dr. Singer informed members that the number of R21 grant applications has increased as R01 grant applications have become more competitive. Because R21 grants are shorter in duration and have smaller budgets, they are perceived to be less competitive than the R01 mechanism. Although the R21 is one of the most common NIH grant mechanisms, it is often misunderstood how NCI uses the mechanism.

Members were informed that the R21 mechanism is designed to support novel, exploratory projects and does not require preliminary data. The grant is limited to $250,000 direct costs over a 2 years period and is not renewable. In contrast, R01 grants are built on an existing body of research, are expected to have preliminary data, and provide up to five years support with no specific budget limit. The R03 grant, which is seldom used by the NCI, is a non-renewable, 2-year grant with a $50,000 per year budget limit; it is designed for feasibility studies, collection of preliminary data, and small, self-contained projects.

The NCI does not participate in the NIH R21 omnibus solicitation and only accepts R21 applications submitted in response to specific program announcements (PAs). Occasionally, NCI has awarded R21 grants with budgets exceeding $275,000 and with durations longer than 2 years. There currently are 59 active NCI PAs for R21s. In 2010, the NCI funded 229 out of 2,060 R21 submissions, reflecting an 11 percent success rate; in contrast, 17 percent of R01 applications submitted the same year were funded. Almost one-half of the awarded R21 applications were in response to only six of the 59 PAs.

Dr. Singer explained that R21 applications are reviewed in Center for Scientific Review (CSR) standing study sections and are interspersed with R01 grants. Analysis of the scores received by grant applications in 2010 showed that R21 grant applications did not score as well, on average, as R01 grant applications. Since 2001, the number of R21 applications submitted has increased by 50 percent; however, their success rate has dropped from 25 to 11 percent. She encouraged members to provide feedback about the NCI's use of the R21 mechanism, including the optimal funding rate, number of receipt dates, continued use of topic-specific announcements, participation in the NIH omnibus PA, or publication of an NCI omnibus PA.

In the discussion, the following points were made:

< It would be instructive to know the number of R01-funded investigators who also held previous R21 grants.

< Members expressed concern about new investigators using the R21 mechanism since the 2-year duration does not provide new researchers with adequate time to establish a laboratory and produce preliminary data for a competitive R01 grant application.

< Members felt there is a real need for a starter grant for new investigators that provides more than two years support.

< The Center for Scientific Review (CSR) currently reviews R21 grants interspersed with R01 grants, unless there are a large number of R21 applications. NCI should consider an omnibus announcement and negotiate for CSR to cluster R21 applications together or to conduct the reviews at NCI.

< NCI R01 and R21 grant application success rate data should be shared with the Board and key stakeholders in the NCI extramural research community.

X. DRUG SCARCITY PROBLEM - DR. JAMES H. DOROSHOW

Dr. Doroshow said that drug scarcity, a problem of increasing magnitude, is pertinent to the treatment of many diseases and to the formulation of adjuvant regimens and other curative agents. He noted that the FDA has developed a drug shortage website that lists oncologic and injectable intravenous drugs, and noted that older generic compounds are particularly at risk. Numerous compounds critical to the practice of general and oncologic medicine, such as propofol, fentanyl patches, and intravenous morphine, are either limited in availability or in danger of becoming so.

Members were told that the drug shortage affects generic drugs, not patented agents, because of 1) consolidation in the generics industry, 2) the limited availability of raw materials in the United States, 3) limited flexibility in the supply chain, regulation, 4) the small number of manufacturers, and 5) budget-driven business decisions. There have been shortages of fluorouracil, leucovorin, and cisplatin for many years, and a manufacturing or supply-chain issue could result in a significant shortage of agents such as gliomycin, cytosine arabinoside, or doxorubicin. The Waxman-Hatch Act has been effective in reducing drug costs for the patient through the availability of generic drugs but does not take into account the cost of disruptions in the manufacturing process. Currently, drug manufacturers are not required to notify the FDA of product discontinuation unless they are the sole producer of a product. The FDA's authority is limited in resolving these problems, which will continue as additional drugs come off patent.

Dr. Doroshow said that several societies met for a summit on this topic in November 2010 and made recommendations focused in three areas: 1) regulation changes; 2) altered raw-material distribution and manufacturing practices; and 3) modified product distribution. An important recommendation is the expansion of FDA authority so that companies are required to provide notification of product withdrawal. Other recommendations addressed an increased awareness of the overseas raw material supplies. These recommendations led to the introduction in Congress of the "Preserving Access to Life Saving Medications Act," which would allow the FDA to learn in advance of an imminent shortage.

The NCI faces a number of issues, including difficulty in interpreting trials that used standard drug regimens with necessary substitutions or additions. This raises the question of whether the NCI should play a role alongside the FDA to alleviate shortages, such as expanding the NCI infrastructure for distributing investigational agents to include generic drugs. Working together closely, the NCI and FDA may be able to formulate long-term solutions.

Short-term options for the NCI to consider include stockpiling vialed or bulk drugs for distribution during shortages. Issues with distributing vialed drugs include drug availability, expiration dates, and differences in state licensing. NCI could also consider acquiring the active pharmaceutical ingredients in bulk and distributing to Cancer Centers or hospitals that can prepare and dispense the drugs. Other issues are: defining the beginning and ending of a shortage; ascertaining whether the initiation of such a process would

lead to long-term dependence on acquired reserves and possibly delay legislative action; drug cost, storage, and distribution; and development of a mechanism for allocation.

In the discussion, the following points were made:

< The scarcity of drugs is foremost an economic problem, rather than a science or regulatory issue.

< A real-time inventory, similar to the infrastructure that was developed during the influenza epidemic, should be considered for identifying availability of drugs across suppliers.

< Expiration dates were noted as a major issue and greatly impacted cost. Members suggested that expiration dates could be extended.

< The NCI should continue to play a major role with the FDA and NIH in forging solutions to drug shortages.

IX. ADJOURNMENT - DR. RICHARD L. SCHILSKY

There being no further business, the 49th regular meeting of the Board of Scientific Advisors was adjourned at 4:50 p.m. on Monday, 20 June 2011.

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Date Richard L. Schilsky, M.D.
Chair, Board of Scientific Advisors

_____ _____

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

Board of Scientific Advisors
Function Statement

Provide scientific advice on a wide variety of matters concerning scientific program policy, progress and future direction of the NCI's extramural research programs, and concept review of extramural program initiatives.

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The Board makes recommendations on research priorities conducted or supported by the Institute. This includes the evaluation of NCI awarded grants, cooperative agreements and contracts and concept review of those activities which it considers meritorious and consistent with the Institute's programs. The advisory role of the Board is scientific and does not include deliberation on matters of public policy.

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Things BSA Does Well

- Concept review
- Program assessment

Things BSA Does Well

- Concept review
- Program assessment…to the extent that programs are presented for review

Things BSA Does Poorly

- Strategic scientific planning
- Priority setting
- Interface with BSC and NCAB

To Create a Strategic Scientific Vision for the National Cancer Program and Review Progress of the National Cancer Institute

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Report of the National Cancer Advisory Board
Ad Hoc Working Group

December 2010

How Can We Do Better?

- Greater input into agenda-setting
- For new activities…need a better understanding of context and priority
- For ongoing activities…need regular progress reports and assessment of strategy and goals
- To be effective we need to be engaged

caBIG® Program Update

Board of Scientific Advisors Meeting

June 20-21, 2011

Outline

- Report of the BSA Ad Hoc Working Group -- recommendations and NCI responses
- caBIG® Next Steps
- caBIG® Budget Adjustments

caBIG® Report and Response

Summary of BSA Working Group Recommendations

- "The caBIG® effort appears diffuse, has drifted from its core mission, and has been unevenly successful."

- Recommended that NCI refocus the program to those aspects broadly recognized as successful and important

Summary of BSA Working Group Recommendations

- Key aspects broadly recognized as successful and important:
  - Development of community-driven standards for data exchange and interoperability
  - Support for the development, maintenance, enhancement, and dissemination of software tools developed by the academic research community
  - Establishment of community dialog on interoperability of clinical and research software tools
  - Moratorium on non-core software development projects
  - Budget should be reviewed and adjusted to reflect recommendations

caBIG® Program Response

- NCI agrees that:
  - caBIG® must be refocused on the core components of 'creation and management of standards for data exchange and support of community-based software tools'
  - Central tenet of program is 'development, maintenance, enhancement, and dissemination of software tools by the academic research community'
  - Newly formed Scientific Advisory Group (SAG) will meet as soon as possible to engage participation of researchers ; first meeting planned for July 2011
  - Must continue exploring strategies to maintain open-source community
  - All non-core development is to be phased out
  - Budget must be scrutinized and adjusted for new scope

caBIG® Next Steps

Next Steps and Priorities

- NCI remains committed to caBIG®, but will refocus the effort and retain key pieces identified as important to the cancer research community
- Key effort will be facilitating community-developed informatics that provide insight in cancer biology and clinical research
- The SAG will foster collaboration with the community, help set priorities, and ensure timely communications
- There is continued support for academic IT efforts, with priorities developed in partnership with NCI Scientific Divisions
- Support is through grants, where appropriate, and dedicated funding as necessary

caBIG® Guiding Principles

- Collaborate more closely with the cancer research community, with oversight by the SAG
- Retain stewardship of the development of community-driven technical standards and interoperability frameworks
- Foster the academic research community's biomedical informatics development efforts through peer-reviewed, investigator-initiated, and high-priority, targeted efforts executed through the NCI Scientific Divisions
- Meet community-identified software development and support needs through partnerships with external open-source development communities

caBIG® Scientific Advisory Group

- Dan Masys, Chair - Vanderbilt University
- Andrea Califano – Columbia University (BSA)
- Jean Wang – UC San Diego
- Joe Gray – University of Oregon (BSA)
- Rebecca Kush – Clinical Data Interchange Standards Consortium
- Gaddy Getz - MIT
- Lynn Vogel – MD Anderson Cancer Center
- Robert Comis - Coalition of Cancer Cooperative Groups
- Paul Fearn – Fred Hutchinson Cancer Center
- Lincoln Stein – University of Ontario
- Brian Athey – University of Michigan
- One additional invitation is pending

caBIG® Community-Generated Tools

- caBIG® will continue to provide support to academic groups through its Knowledge Center program, to provide community support for the tools and infrastructure they provide
- All community tools are open-source, and the software will continue to be made available through NCI web sites (the Support Service Providers program – with 20 SSPs to date – will continue to be available to the community for support of local installation and customization)
- Areas assessed by the SAG as important will have additional development through external open-source community effort
- The caBIG® community will continue to develop and maintain the standards and interoperability specifications necessary to keep the parts working together

Academic Development of Novel Informatics Capabilities

- caBIG® will collaborate with NCI Scientific Divisions to foster efforts addressing current and evolving needs
- Possible projects include:
  - Integration and analysis of multi-dimensional data
  - Storage and distribution of “Big Data”
  - Data visualization and interpretation
  - Natural language processing
  - Analysis of *in vivo* images
  - Development of new approaches for generating evidence
- These examples are subject to review by the SAG

Community-defined Standards and Interoperability

- caBIG® will develop pre-competitive specifications used to drive creation of software by academic and commercial developers
- Possible projects include:
  - Vocabularies/Ontologies
  - Common data elements
  - Information models
  - Interoperability conformance and compliance frameworks
- These examples are subject to review by the SAG

Informatics Capabilities as Part of the Larger Grid

Through the caBIG® program, NCI will:

- Help with long-term dissemination and support of community-developed software by maintaining infrastructure to store software, along with its documentation, and associated metadata

- Support academic institutions by ensuring resources are available for local installation, customization and ongoing extension, through its Knowledge Center Program

- Partner with external open-source development community organizations to provide long-term support for software extension and enhancement outside the NCI mission

Informatics Capabilities as Part of the Larger Grid

- NCI will transfer stewardship of community-developed tools to external, open-source community including:
  - Molecular analysis
  - Management of high-dimensional molecular characterization data
  - Biospecimen management
  - Clinical research tools
  - *In vivo* imaging
  - Multi-center, genetically informed, adaptive clinical trials (caBIG® will maintain standards and test for compliance)

caBIG® Budget Adjustments

NATIONAL CANCER INSTITUTE

caBIG® Budget Adjustments

- Original FY 2011 appropriated budget was $45 million
- ARRA funding from FY 2009/2010 was $103 million
- New scope requires FY 2011 appropriated funding at $33 million
- ARRA funds reduced to $43 million
- Further adjustments of appropriated and ARRA funds are being evaluated
- Funding plans for future years will depend on NCI's budget level

Questions

National Cancer Institute

Provocative Questions RFA

Douglas R. Lowy
Deputy Director, NCI

BSA Meeting
June 20, 2011

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

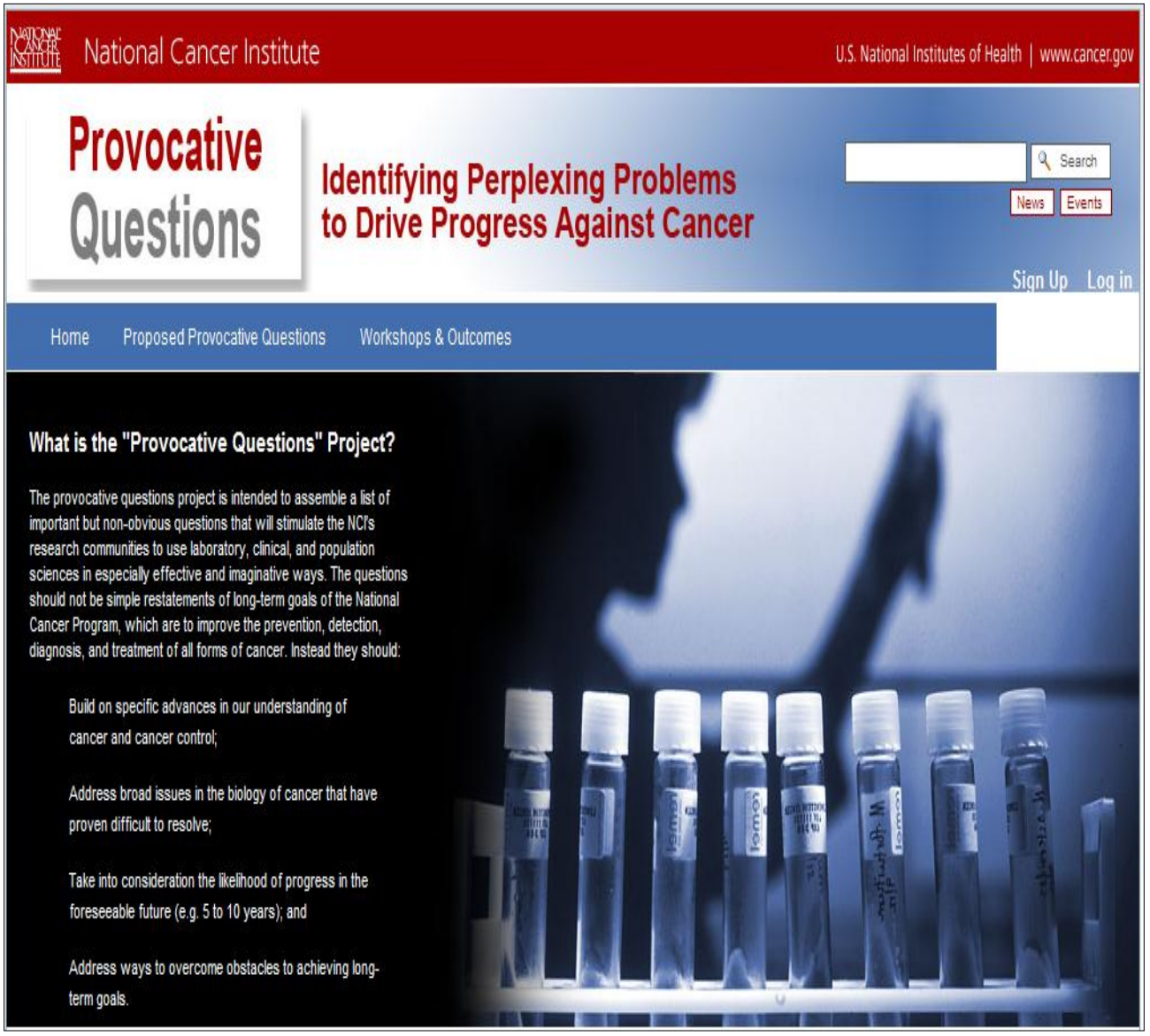
THE PROVOCATIVE QUESTIONS PROJECT

- **Challenge the scientific community to think about and answer important but non-obvious questions that will stimulate NCI's research communities to use laboratory, clinical, and population research in especially effective and imaginative ways.**
  - **The power of a good question: excite the research community**
- **The proposals should:**
  - **Build on specific advances in our understanding of cancer and cancer control**
  - **Address broad issues in the biology of cancer that have proven difficult to resolve**
  - **Take into consideration the likelihood of progress in the foreseeable future (e.g. 5 to 10 years)**
  - **Address ways to overcome obstacles to answering the question**

DEVELOPMENT OF THE PQ'S

- **An interactive, iterative process still in progress**
- **A series of small workshops + website**
- **Four workshops held thus far (Oct, Feb):**
  - **Exploratory**
  - **Clinical and translational sciences**
  - **Behavior, population, epidemiology, and prevention sciences**
  - **Basic sciences**
- **More workshops planned (July, Aug)**
  - **Seattle, San Francisco, Los Angeles, San Diego, Bethesda**

http://provocativequestions.nci.nih.gov/



SELECTION OF PQ'S

- **PQ's developed and selected from meetings and those submitted to website**
  - **Goal for this RFA: 15-20 PQ's**
- **Many types of PQ's: e.g., epidemiology, pathogenesis, prognosis, risk modification, prevention, diagnosis, therapeutics, and behavior**
- **Verify the PQ's are understudied: portfolio analysis by the Office of Science Policy and Analysis (OSPA)**

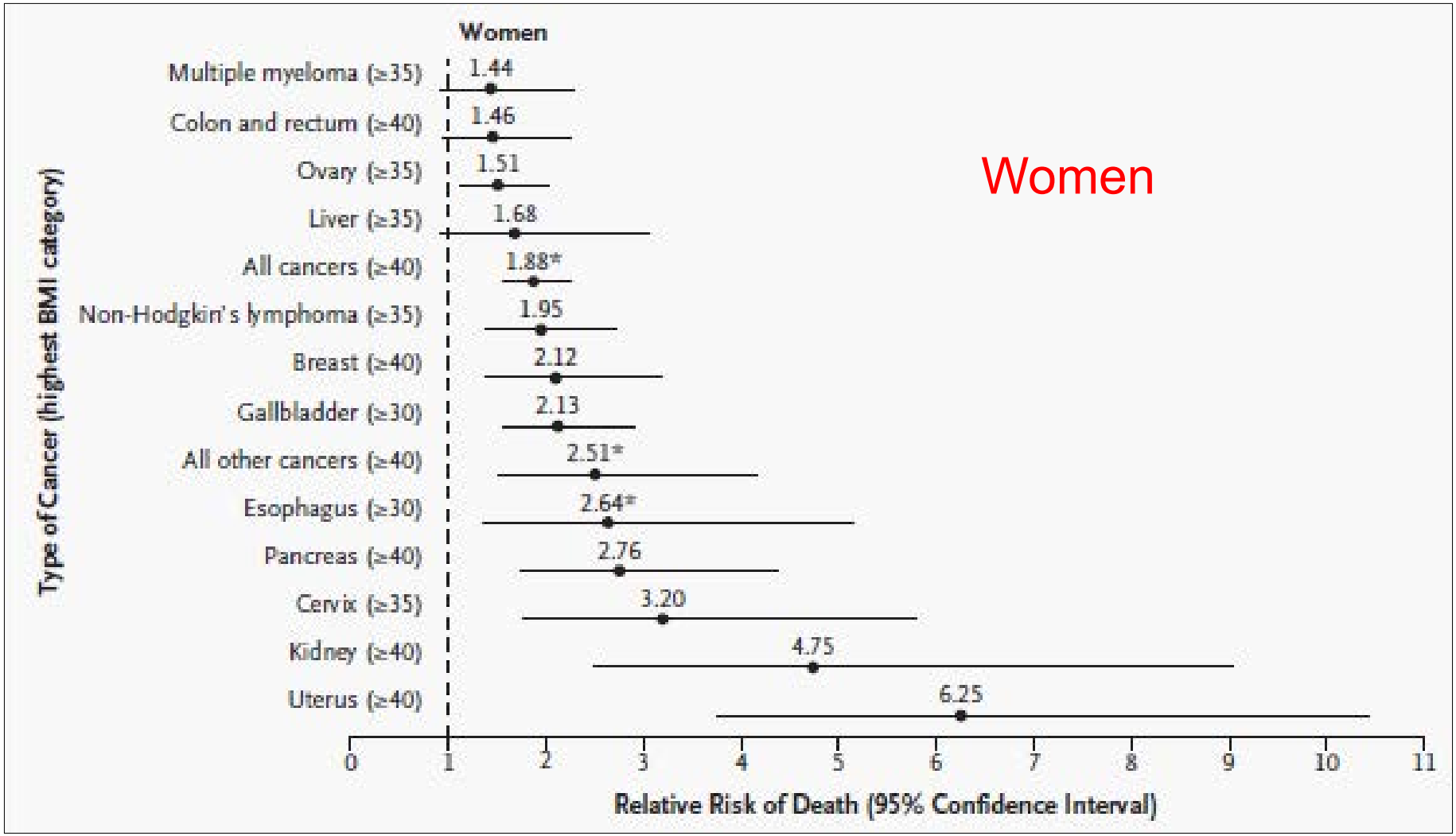
RFA, R21, R01, BUDGET

- **RFA: To highlight research issues that are not well studied**
  - **To move research into these areas quickly and effectively**
- **R21 and R01: Well understood formats**
  - **R21: 2 years funding; R01: 4 years funding**
- **Budget: up to $15 million**
  - **Sufficient to generate community interest and make multiple awards**
  - **Total amount awarded will depend on the number of highly meritorious applications**

REVIEW CRITERIA

- **The 5 standard review criteria (Significance, PI, Innovation, Approach, and Environment)**
- **Applications may come from PI's new to a field**
  - **strength of the applications judged in large part on the power of the *ideas* behind the proposed research**
  - **preliminary data unnecessary**
  - **track record in the field should not be weighed as heavily as in other reviews**

HOW DOES OBESITY CONTRIBUTE TO CANCER RISK?



Women

Calle, EE et al., Overweight, Obesity, and Mortality from Cancer in a Prospectively Studied Cohort of U.S. Adults. N Engl J Med 2003;348:1625-38.

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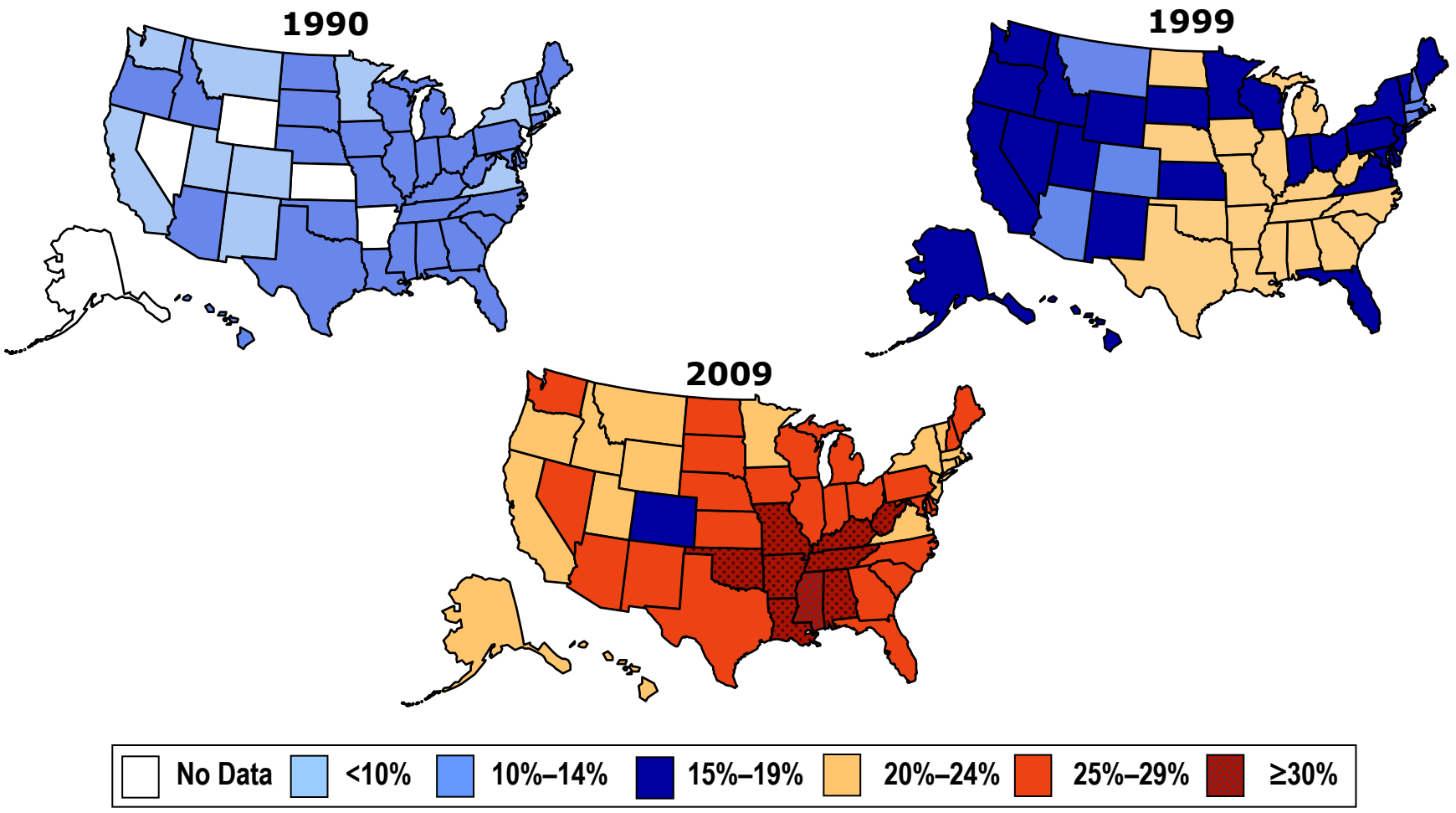
HOW DOES OBESITY CONTRIBUTE TO CANCER RISK?

Obesity Trends (BMI ≥30) Among U.S. Adults



Source: Behavioral Risk Factor Surveillance System, CDC

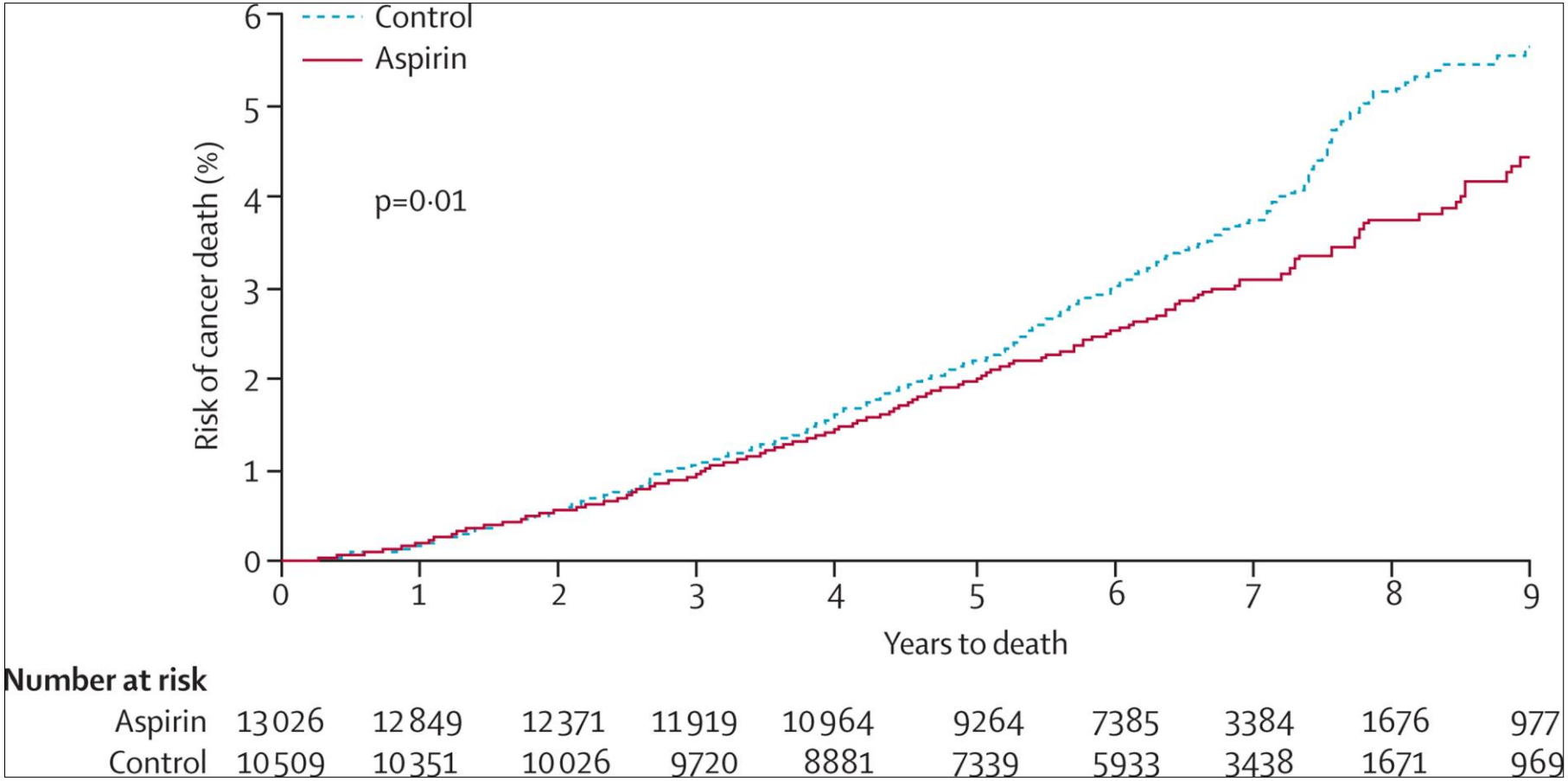
LONG-TERM MORTALITY AFTER GASTRIC BYPASS SURGERY

Distribution of Deaths and Death Rates per 10,000 Person-Years*				
End Point	Matched Subjects			
	Surgery Group (N=7925)		Control Group (N=7925)	
	no.	no./10,000 person-yr	no.	no./10,000 person-yr
All causes of death	213	37.6	321	57.1
Cardiovascular disease	55	9.7	104	18.5
Diabetes	2	0.4	19	3.4
Cancer	31	5.5	73	13.3
Other diseases	62	11.0	89	15.5
All non-disease causes	63	11.1	36	6.4

*Deaths that were caused by disease include all deaths minus those caused by accidents unrelated to drugs, poisonings of undetermined intent, suicides, and other non-disease deaths.

Adams, TD et al., Long-term mortality after gastric bypass surgery. N Engl J Med 2007; 357:753-61.

DO DRUGS THAT ARE COMMONLY AND CHRONICALLY USED FOR OTHER INDICATIONS PREVENT CANCERS AND, IF SO, HOW?



Rothwell et al., Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials. Lancet. 2011 Jan 1;377(9759):31-41. Epub 2010 Dec 6.

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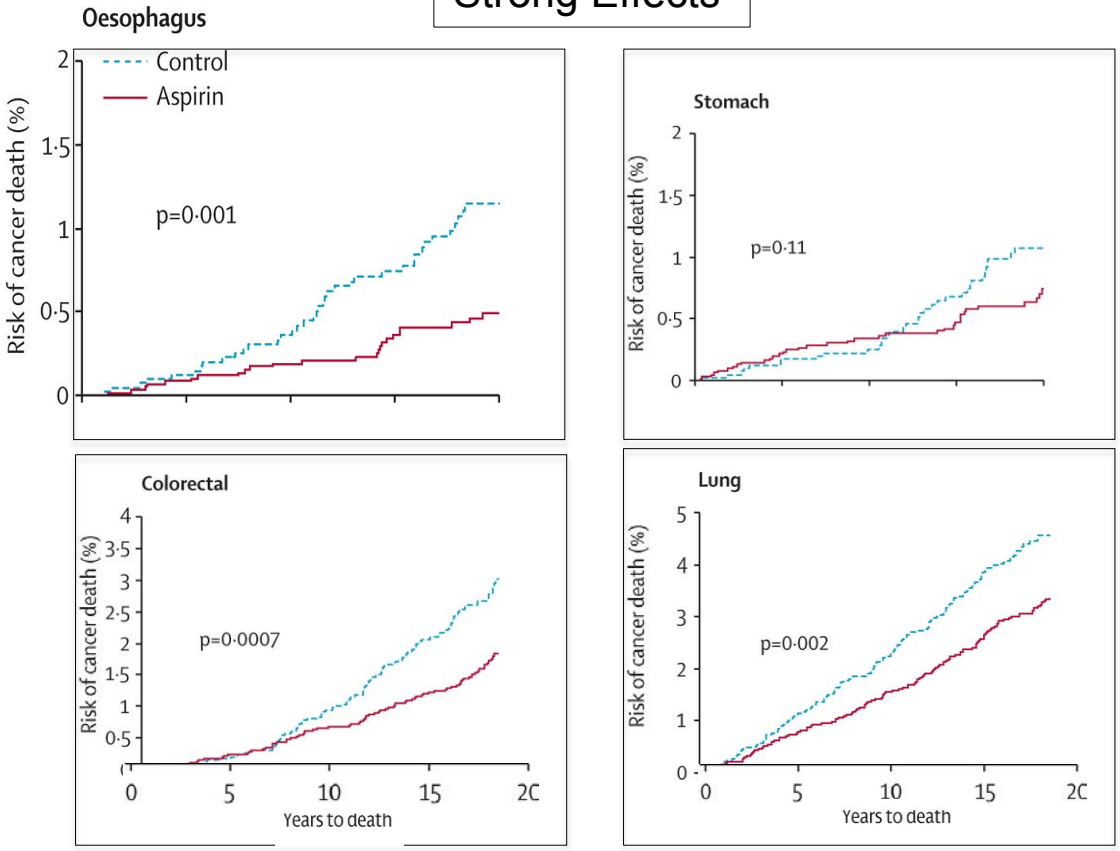
Strong Effects



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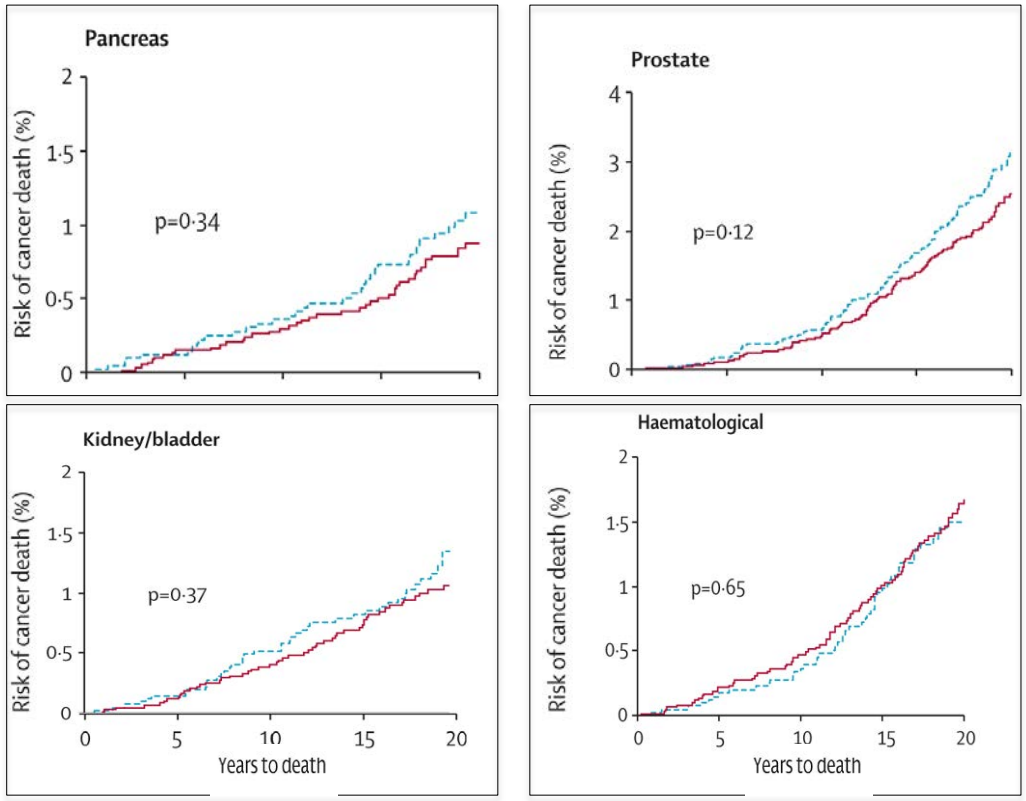
DO DRUGS THAT ARE COMMONLY AND CHRONICALLY USED FOR OTHER INDICATIONS PREVENT CANCERS AND, IF SO, HOW?

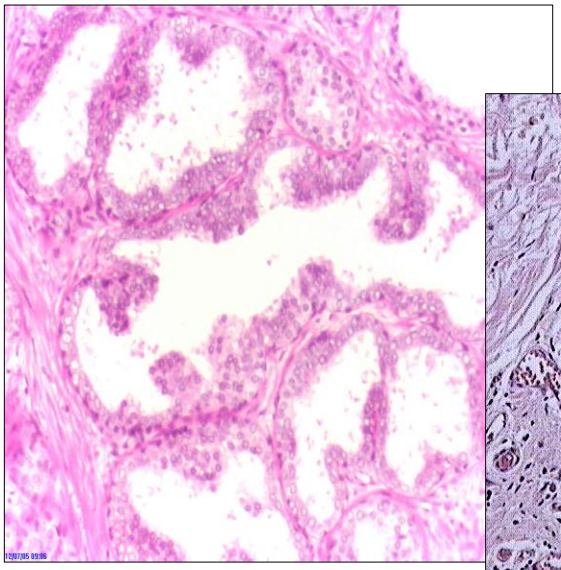
Weak or No Effect



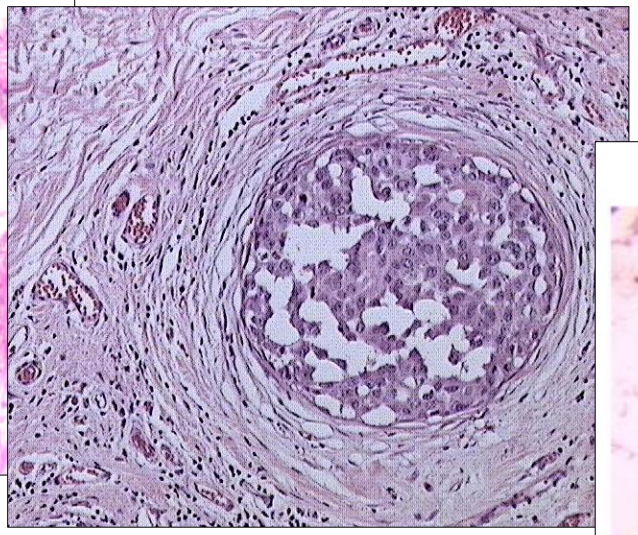
Rothwell et al., Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials. Lancet. 2011 Jan 1;377(9759):31-41. Epub 2010 Dec 6.

WHAT PROPERTIES OF NON-MALIGNANT LESIONS (IN SITU CA'S) PREDICT THE LIKELIHOOD OF INVASIVE DISEASE?

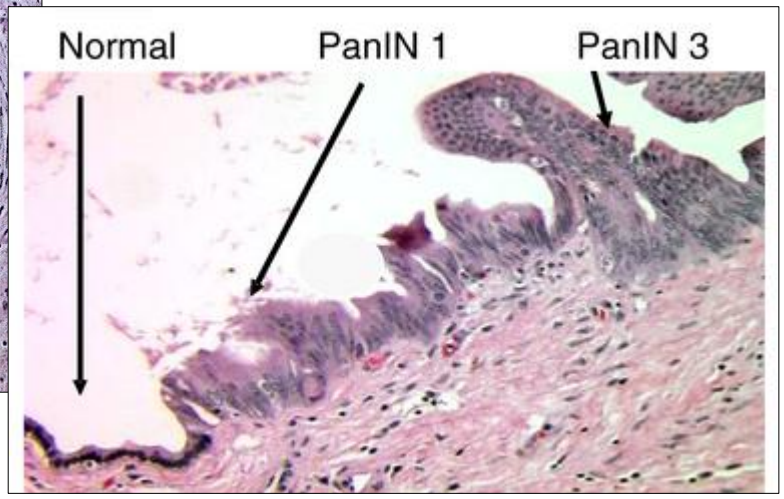
Prostatic Intraepithelial Neoplasia (PIN)



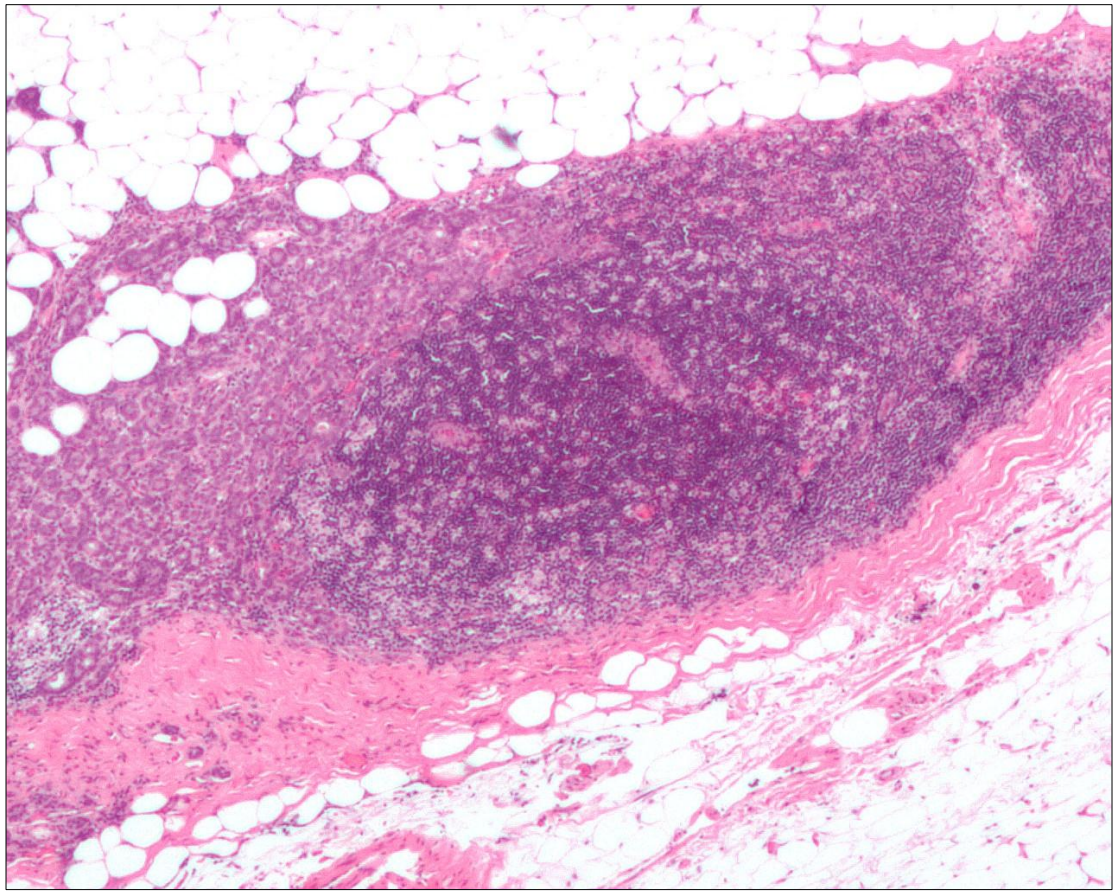
Ductal Carcinoma In Situ (DCIS)



Pancreatic Intraepithelial Neoplasia (PanIN)

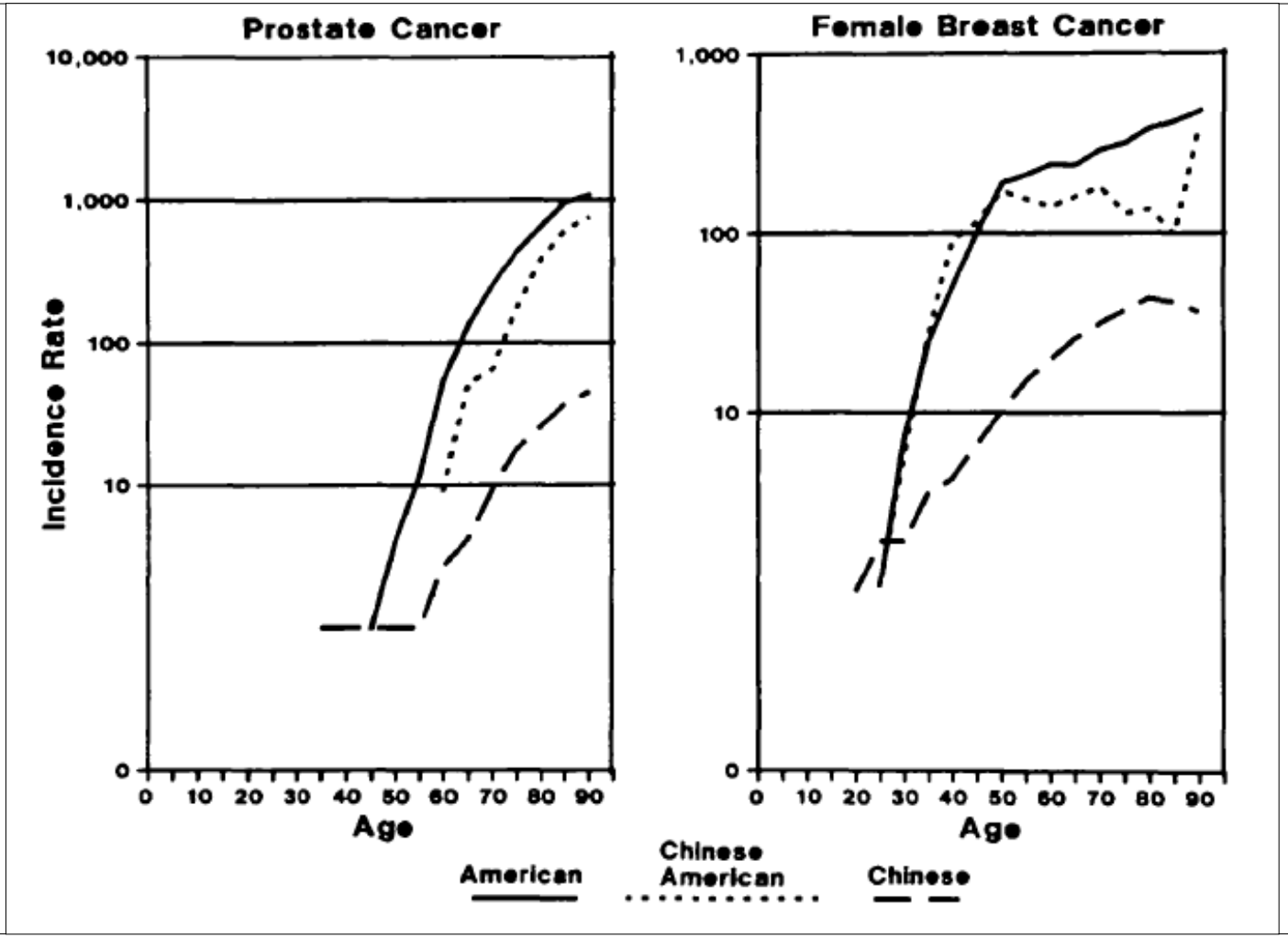


WHAT IS THE CLINICAL SIGNIFICANCE OF FINDING CELLS FROM A PRIMARY TUMOR AT ANOTHER SITE?



Lymph node invaded by ductal breast carcinoma

WHAT ENVIRONMENTAL FACTORS CHANGE THE RISKS OF VARIOUS CANCERS WHEN PEOPLE MOVE FROM ONE GEOGRAPHIC REGION TO ANOTHER?



Yu H., et al. Comparative epidemiology of cancers of the colon, rectum, prostate and breast in Shanghai, China versus the United States. International Journal of Epidemiology 1991, 20: 76-81.

WHY DON'T MORE PEOPLE ALTER BEHAVIORS KNOWN TO INCREASE THE RISK OF CANCERS?

- **The message itself is not designed optimally for impact**
- **The message is not effectively delivered**
- **The interventions to facilitate behavior change are not optimal**

Why are different animals with different sizes and different life spans so different with respect to cancer incidence?

Turtles

Mice

Sharks

Whales….except belugas from the SLE!

WHY ARE SOME DISSEMINATED CANCERS CURED BY CHEMOTHERAPY ALONE?

SUMMARY

- **Stimulate research in compelling, understudied areas**
- **Evaluation of success**
  - **Shorter term:**
    - **A plethora of exciting applications—reissuance**
  - **Intermediate term:**
    - **PI's continue their studies through traditional grant mechanisms**
  - **Longer term**
    - **Answers to the questions**
    - **Better understanding of neoplasms**
    - **Improved risk assessment, prevention, treatment, etc.**

THANKS

Coordination and Portfolio Analysis: Margaret Ames, Lisa Stevens, OSPA staff, Maureen Johnson

Web Designers: Lisa Cole, Clint Malone

RFA Concept: Dinah Singer, Barbara Spalholz, Judy Mietz, Anne Lubenow, Jerry Lee

BSA SUBCOMMITTEE QUESTIONS

"The PQ RFA is an excellent idea but…."

- **Analogous NCI/NIH programs?**
- **Complexity and challenge of the review process**
  - **Getting enough competent reviewers for the two-tiered process?**
  - **"Non-responsive" to RFA: stringent or permissive?**
  - **"Enforcing" the importance of ideas vs. preliminary data?**
    - **Proscribe preliminary data?**
  - **Automatic submission of triaged applications to a regular CSR study section?**

National Cancer Institute

HMO Cancer Research Network (CRN) Research Resource Concept

Rachel Ballard-Barbash, MD, MPH
Martin Brown, PhD (CRN Program Director)

NCI Board of Scientific Advisors
June 20, 2011

National Cancer Institute

Presentation Outline

- Need for National Research Resource
- Unique Qualities of CRN to Serve as National Resource
- Proposed Areas of Scientific Excellence
- Components of New RFA / Budget
- Metrics of Success
- Other NIH HMORN initiatives

National Cancer Institute

Need for National Research Resource within Health Care Delivery Systems

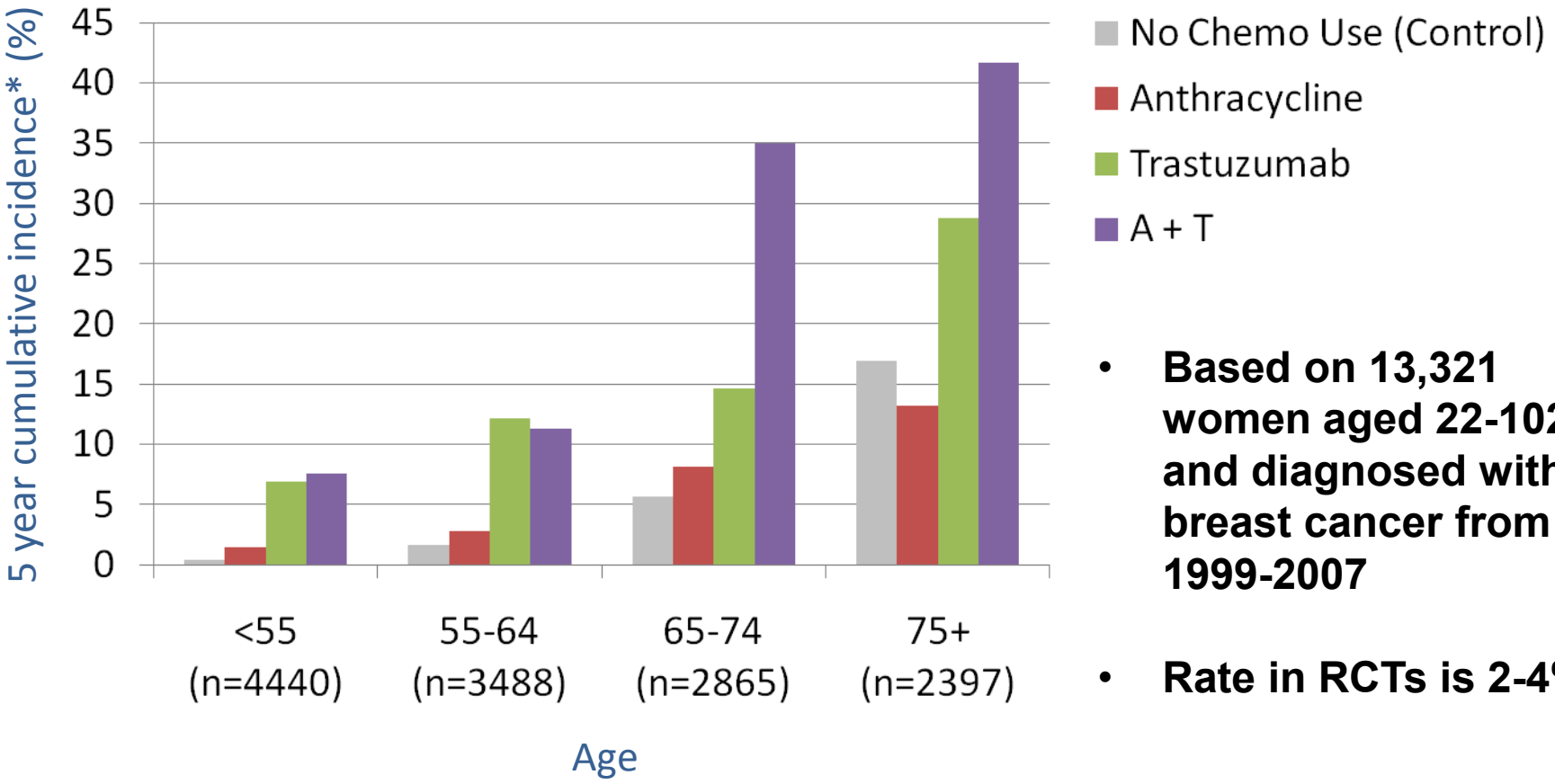
- Rapid expansion in complexity and cost of cancer diagnostic technologies and treatment
  - Lack of research on the interactions among treatments or outcomes of expanded diagnosis
- No other initiative can support diverse multilevel research designs to examine these issues within context of clinical care
- Innovations in EMRs and patient portals have changed landscape of research within the context of care delivery

National Cancer Institute

CRN: Unique Strengths and Opportunities

- Size, scope, and network of research quality data from EHR/VDW
  - Millions of patients with longitudinal clinical care data
- Capacity to evaluate natural experiments that influence cancer care and determine if results from research in controlled settings lead to same outcomes in clinical practice
  - E.g.: Post-market evaluation of drug outcomes or extent of variation in care for recommended therapies
- Provides unique platform for conduct CER as drugs and diagnostic procedures multiple and evolve
  - E.g. Examine drug interactions in complex patients treated with multiple drugs, clinical trials focused on practice questions, and longitudinal studies on health outcomes
- Enables research on how to best provide high quality, targeted care while reducing inefficiencies and cost

Chemotherapy Induced Heart Failure is High in Clinical Practice Compared to RCTs

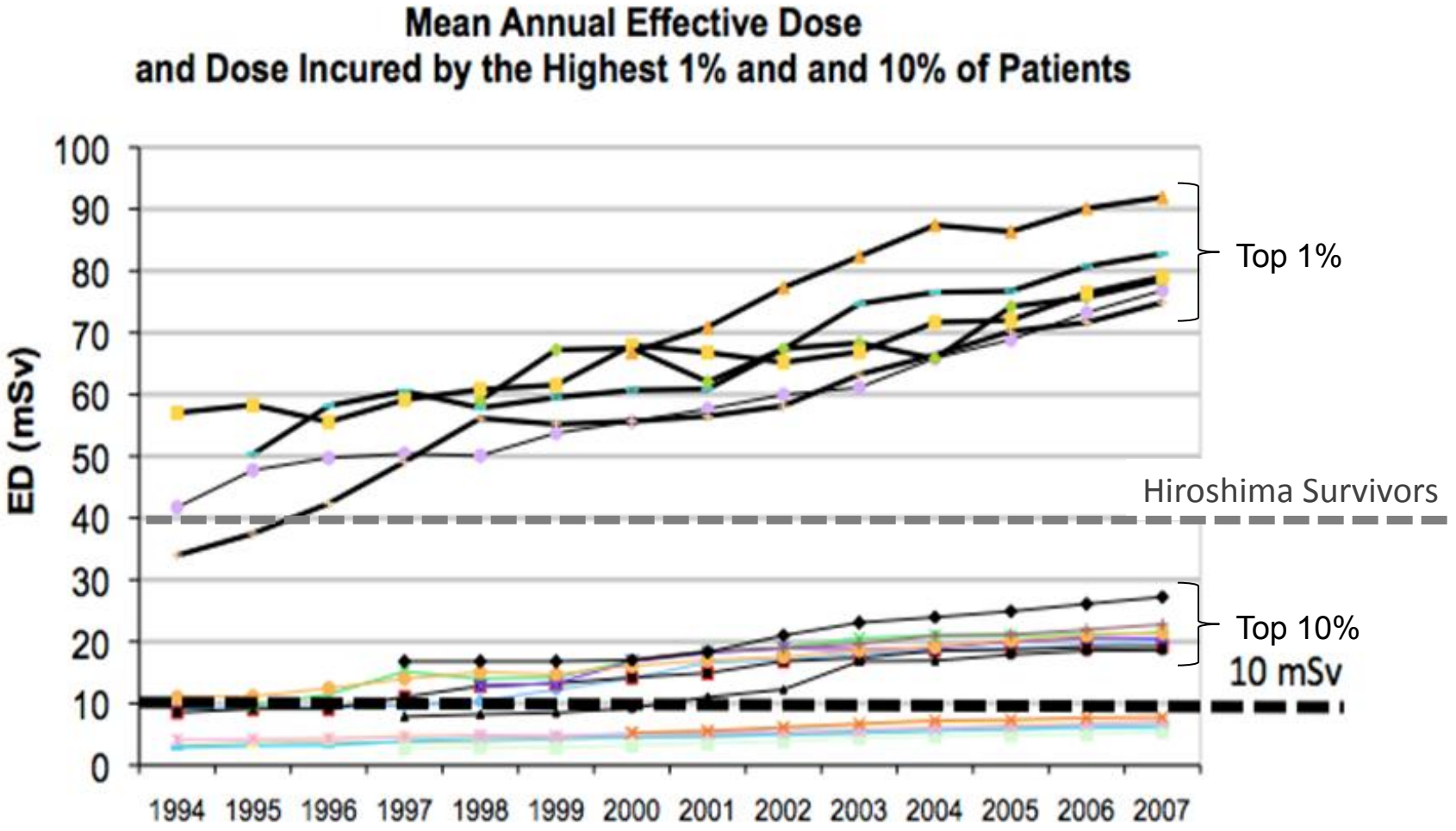


- **Based on 13,321 women aged 22-102 and diagnosed with breast cancer from 1999-2007**
- **Rate in RCTs is 2-4%**

*Adjusted for: health plan, age, Charlson score, summary stage, year of diagnosis, radiation treatment

Bowles EA et al. In preparation for publication

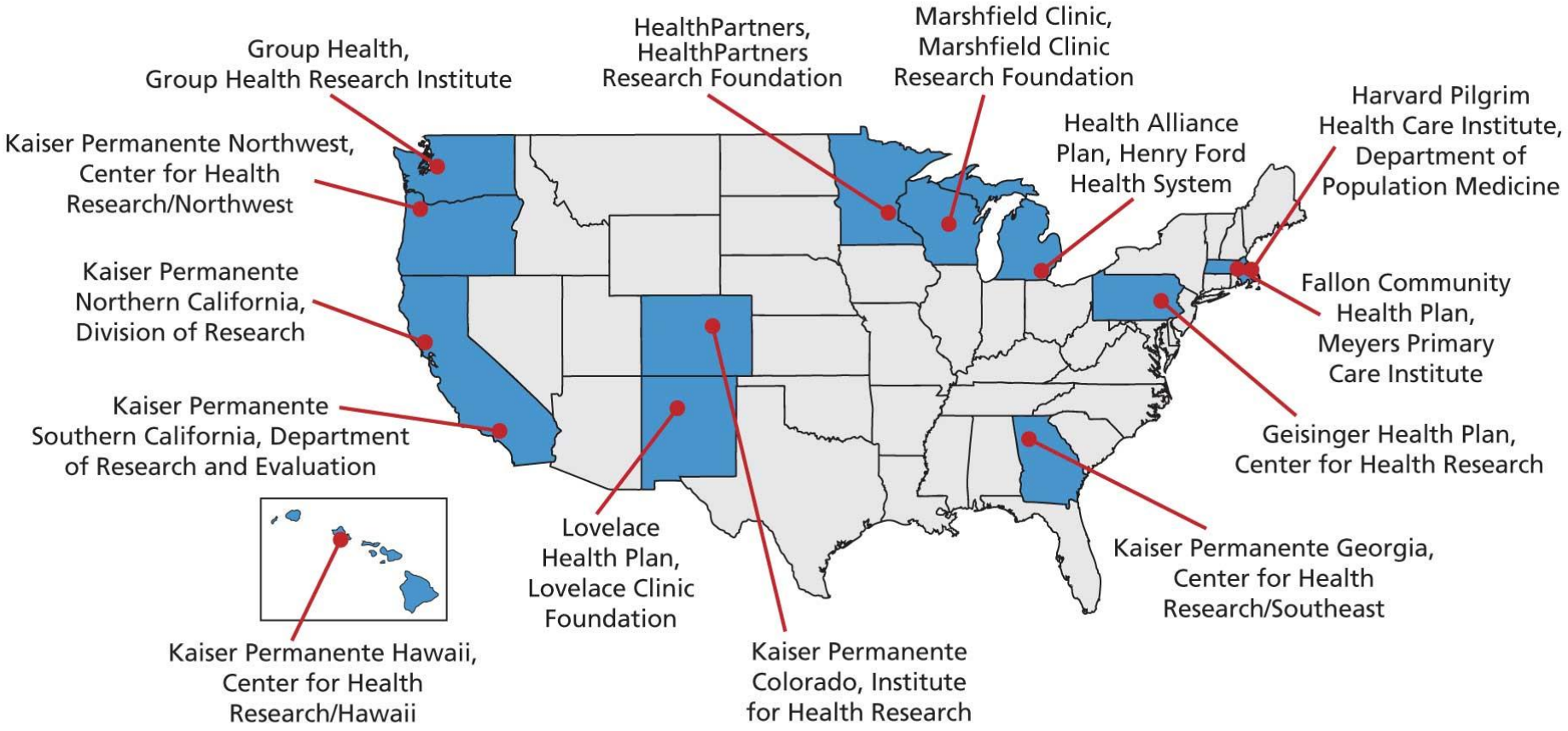
Radiation Exposure has Increased Dramatically: Data from 5 CRN HMOs



For each patient in each year, radiation from all imaging examinations was summed

Smith-Bindman R et al. In preparation for publication

Cancer Research Network Sites



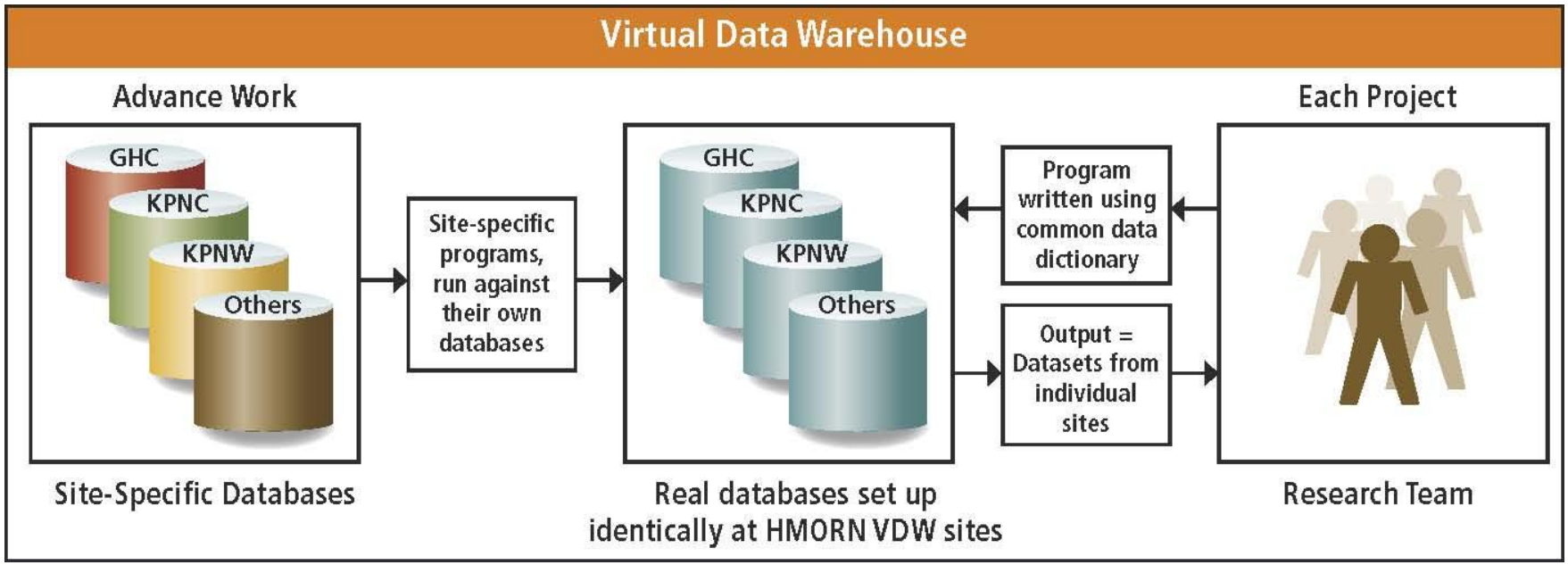
CRN consists of 14 research centers (U19), affiliated with HMOs that provide care for 11 million individuals

National Cancer Institute

Nature of CRN Data

- Patient-specific clinical care data documented in context of regular practice are transformed into standardized, high quality data that can be used for cancer research
- Retention rate for cancer survivors is nearly 85% at five years post-diagnosis
- Longitudinal clinical care data are unique to the CRN
- CRN is well suited for studies of cancer quality of care, survivorship, and long-term outcomes
- Can address issues in patients with rare cancer or complex medical conditions that cannot be well studied with existing clinical trial systems

Virtual Data Warehouse (VDW)

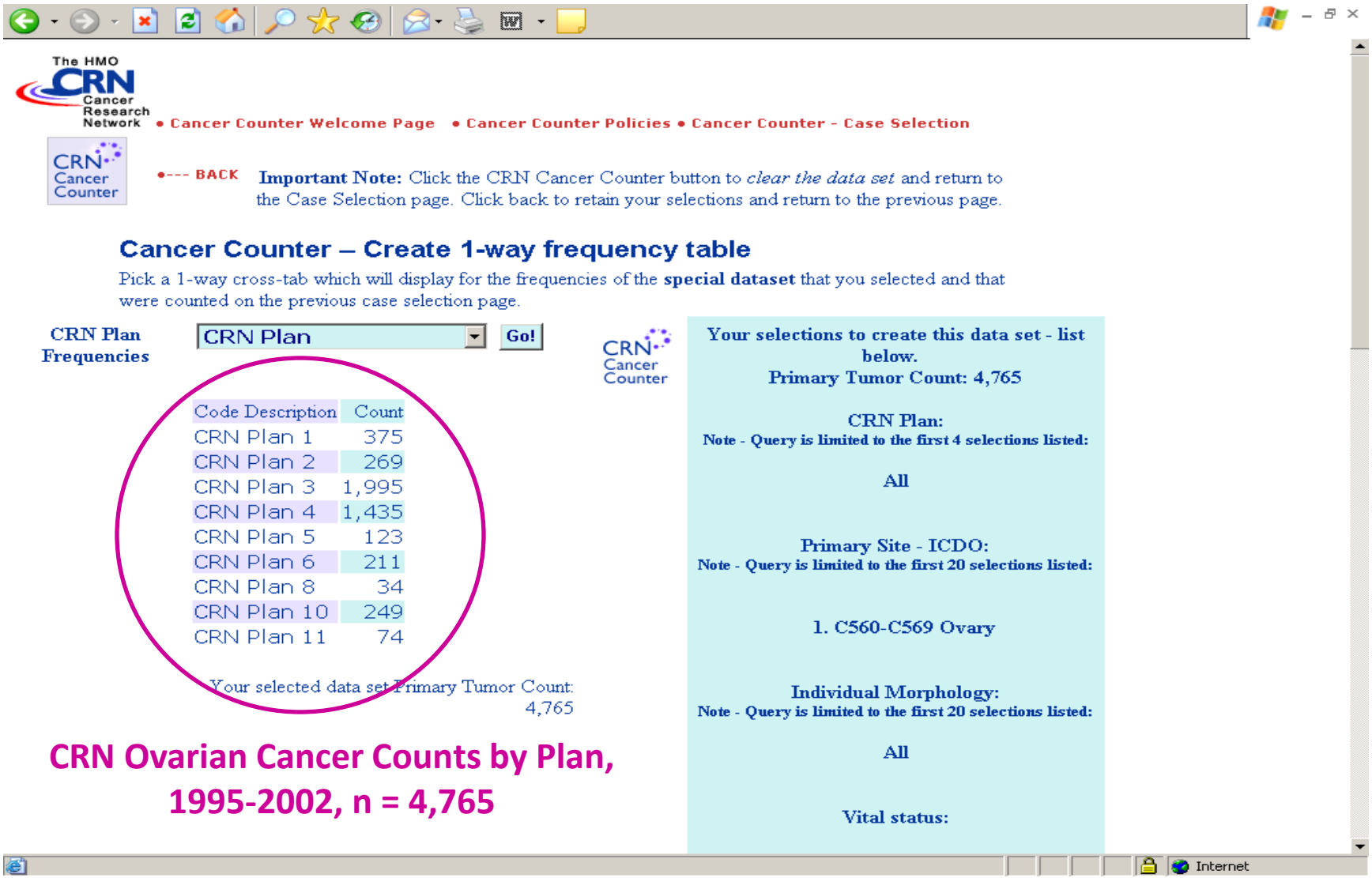


- ~11,000,000 total enrollees
- ~100,000 incident cancers/year
- ~69,000,000 Rx fills/year
- 505 clinic sites
- 8 affiliations with cancer centers

The VDW is populated by automated data from the following sources:

- Tumor registry
- Enrollment
- Demographics
- Geocoding
- Utilization
- Laboratory
- Pharmacy
- Chemotherapy
- Radiology
- Pathology

Cancer Counter Enables Rapid Assessment of Power for Specific Research Questions



The HMO CRN Cancer Research Network • Cancer Counter Welcome Page • Cancer Counter Policies • Cancer Counter - Case Selection

CRN Cancer Counter •--- BACK **Important Note:** Click the CRN Cancer Counter button to *clear the data set* and return to the Case Selection page. Click back to retain your selections and return to the previous page.

Cancer Counter – Create 1-way frequency table

Pick a 1-way cross-tab which will display for the frequencies of the **special dataset** that you selected and that were counted on the previous case selection page.

CRN Plan Frequencies CRN Plan Go!

Code Description	Count
CRN Plan 1	375
CRN Plan 2	269
CRN Plan 3	1,995
CRN Plan 4	1,435
CRN Plan 5	123
CRN Plan 6	211
CRN Plan 8	34
CRN Plan 10	249
CRN Plan 11	74

Your selected data set Primary Tumor Count: 4,765

CRN Cancer Counter

Your selections to create this data set - list below.
Primary Tumor Count: 4,765

CRN Plan:
Note - Query is limited to the first 4 selections listed:

All

Primary Site - ICDO:
Note - Query is limited to the first 20 selections listed:

1. C560-C569 Ovary

Individual Morphology:
Note - Query is limited to the first 20 selections listed:

All

Vital status:

Internet

CRN Ovarian Cancer Counts by Plan, 1995-2002, n = 4,765

National Cancer Institute

Recommendations from External Evaluation

D. Ransohoff, K. Kerlikowske, D. Schrag, T. Tosteson

"CRN provides unique data and has capacity to serve as a national resource that should be preserved and strengthened"

- Support infrastructure and collaboration rather than specific scientific projects
- Develop and maximize mechanisms and interfaces to facilitate collaboration of external researchers with CRN
- Formulate strongest scientific questions by cultivating expertise from CRN and external investigators
- Develop governance structure to target areas of scientific excellence

Key Areas of Scientific Excellence

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

Extramural Research Community

Health Care Delivery Research

Molecular & Genomic Technologies

CRN Sites

Medical Decision Making

Risk Stratification

Emerging Tech

Cancer Survivorship

Extramural Research Community

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

National Cancer Institute

Key Areas of Scientific Excellence

- Use of **molecular and genomic technologies** in community practice
  - Which patient groups experience improved outcomes from treated tailored on clinical characteristics and molecular ? (i.e. Do colorectal cancer patients receive KRAS /BRAF testing, and does it alter care and improve outcomes?)

- **Health care delivery research**, including multi-level systems and comparative effectiveness research of cancer services
  - Can EMR-based outreach be combined with pharmacy data to identify women non-adherent to adjuvant hormonal treatment (i.e., tamoxifen, raloxifene) and interventions be developed to improve treatment adherence and outcomes?

National Cancer Institute

Key Areas of Scientific Excellence

- Quantification of **risk stratification** though large-scale epidemiologic studies that utilize data on molecular, biologic, behavioral, lifestyle, pharmacologic, radiologic, and other risk (and protective) factors
  - What is the long-term cancer risk/benefit associated with common drugs, such as NSAIDS or statins, or cumulative radiation exposure from common imaging studies?

- Increased understanding of **medical decision making**, and development / evaluation of tools to enhance physician-patient cancer communication and improve care quality
  - Can physician and patient web portals, informed by data from EMRs, improve continuity of care for cancer patients to enhance treatment decision making and increase adherence to guideline-consistent care?

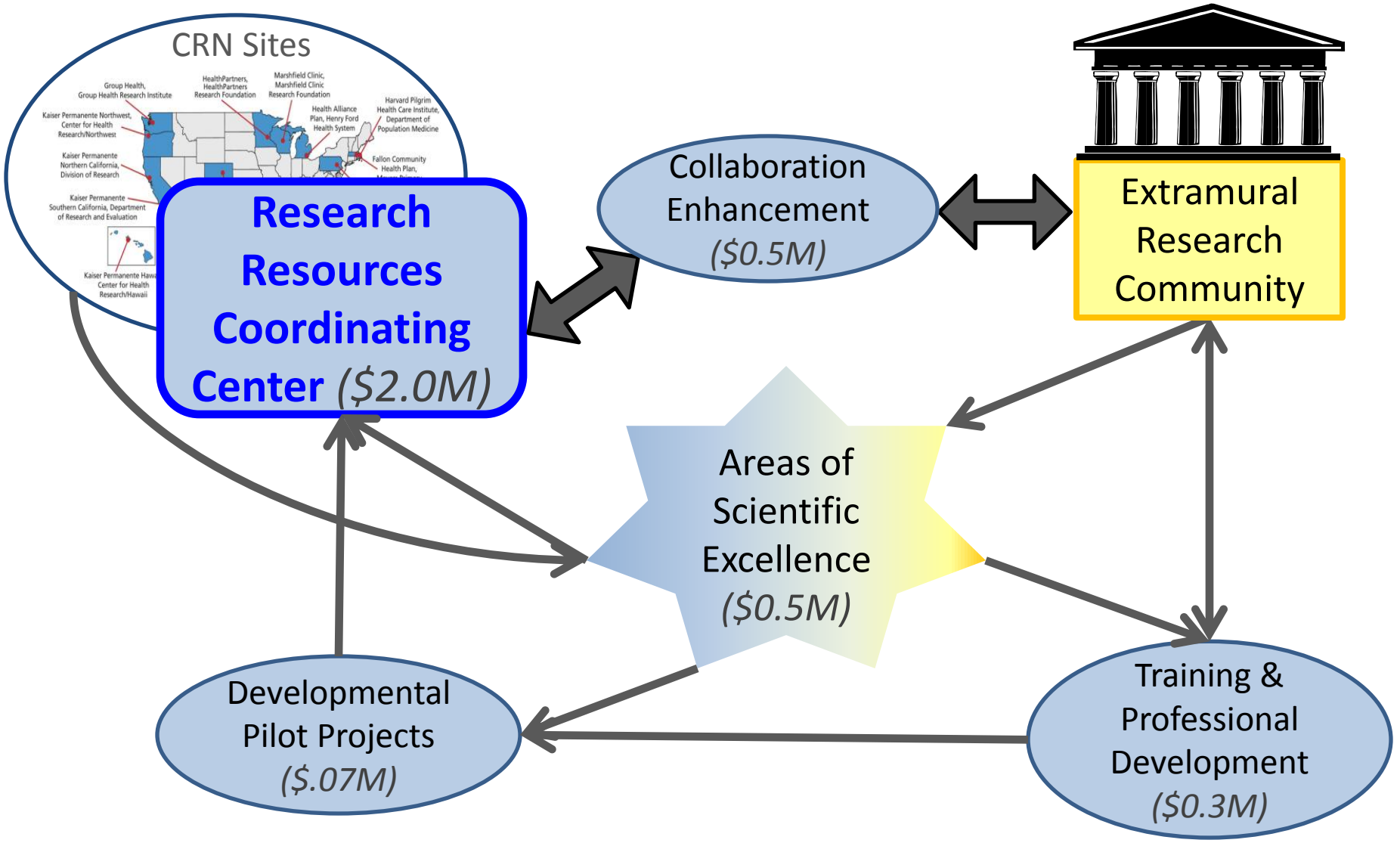
National Cancer Institute

Key Areas of Scientific Excellence

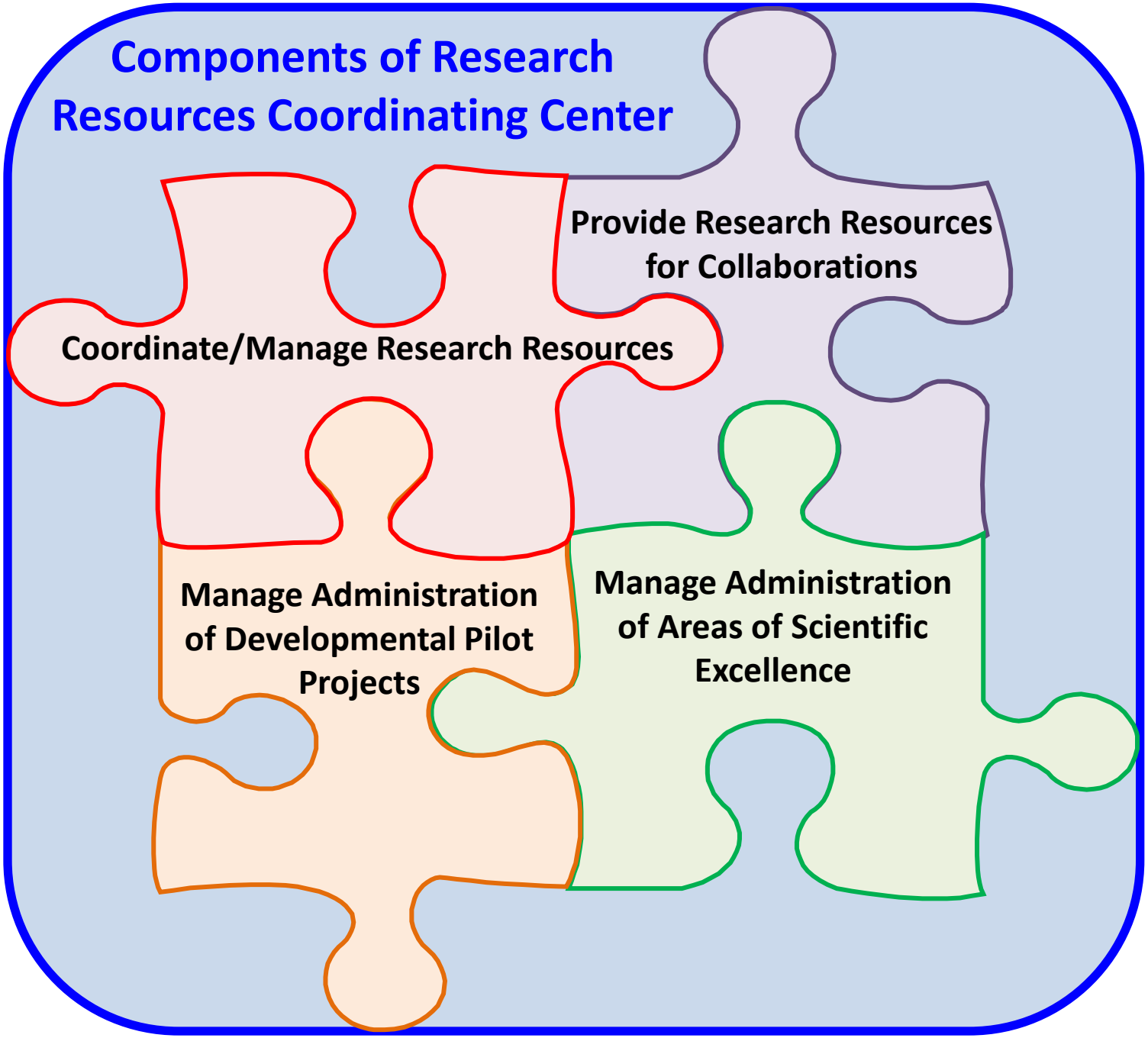
- **Cancer survivorship**, including long-term consequences of cancer treatment, surveillance, supportive care, care coordination, recurrence, quality of life, and family burden
  - Which breast cancer patients treated with anthracyclines and/or trastuzumab are at greater risk of cardiotoxicity than similar patients treated with no chemotherapy?

- Validation, dissemination, and implementation research on **emerging technologies** including risk prediction, diagnostic and prognostic, and informatics / communications technologies
  - Is it possible to determine clinical and molecular markers that reliably predict low risk of breast cancer recurrence in women diagnosed with ductal carcinoma in situ?

Components of New Research Resource RFA



Total budget = $4.0M per year for 5 years


Components of Research Resources Coordinating Center
Provide Research Resources for Collaborations
Coordinate/Manage Research Resources
Manage Administration of Developmental Pilot Projects
Manage Administration of Areas of Scientific Excellence

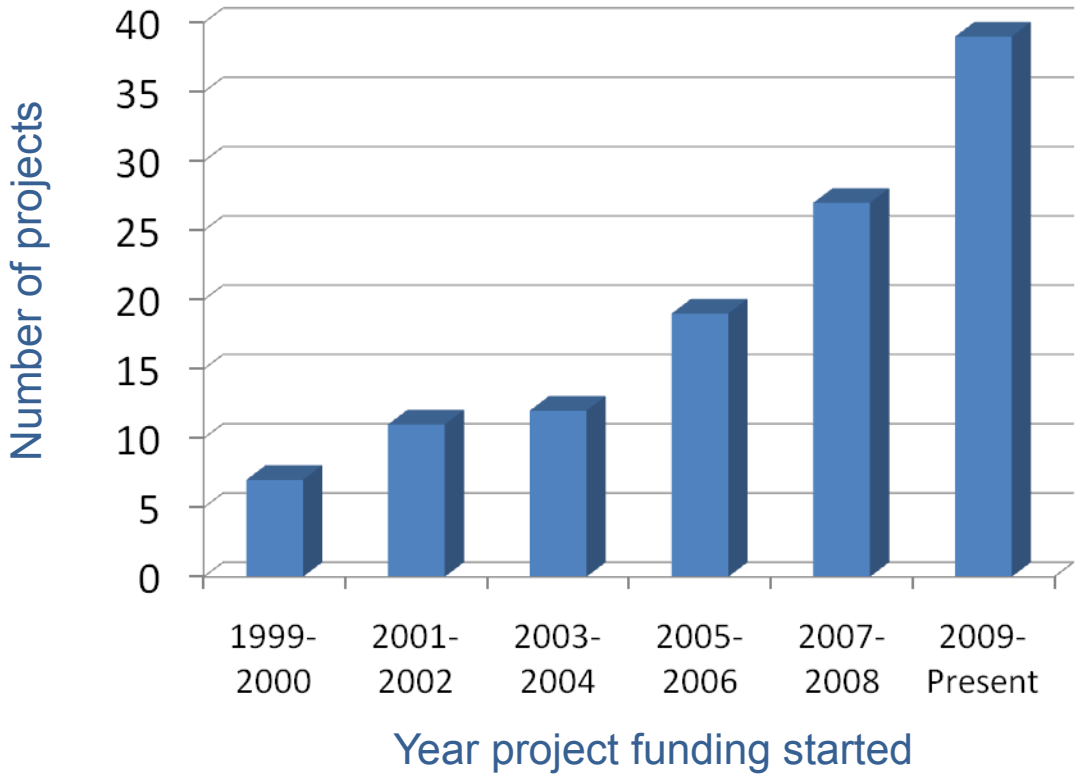
National Cancer Institute

CRN Has Demonstrated Capacity to Serve as a National Resource

- Increased use of the HMORN for national research
  - Recognized by AHRQ, FDA, NIH OD, and other NIH institutes
- Successful competition for competitive funding
  - Increase in number of funded grants using CRN as a resource since 2006
  - 50% of these collaborative grants awarded to PIs outside the CRN
- Growth in rate of scientific publications
  - At least 210 publications in peer-reviewed scientific journals; over 100 published in last 4 years
- Professional development of junior investigators
  - Over 40 investigators have interfaced with the CRN in their training; CRN Scholars Program was implemented in 2007

National Cancer Institute

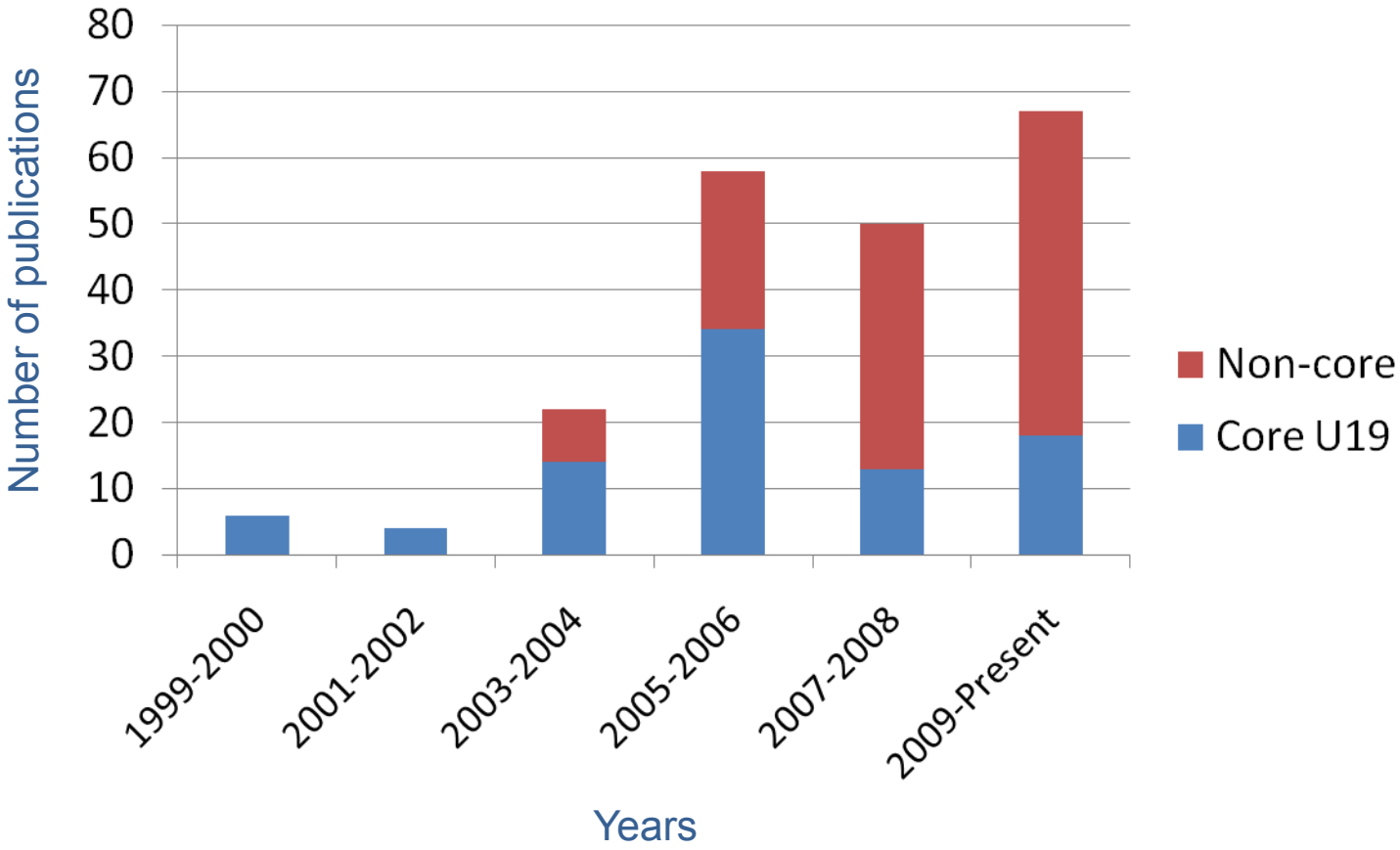
Growth in Funded* Research Projects Using the CRN, 1999-Present



*Includes NCI-funded grants and contracts as well as projects funded by AHRQ, CDC, DoD, ACS, IOM, and NHGRI that used the CRN; http://crn.cancer.gov/projects/projects.php

National Cancer Institute

Growth in CRN Publication Rate, 1999-Present



National Cancer Institute

What Will Be Lost if CRN U24 RFA is Not Funded?

- Cancer-directed resource within community practice for CER and other PCORI-related research
- Potential for rapidly evaluating the effects of new cancer discoveries within clinical practice
- Further enhancement and development of VDW with data elements in cancer domains
  - Examples: chemotherapy agents; radiation; prognostic biomarkers; biospecimen linkage; recurrence; adverse events; screening; risk factors; co-morbidities
- Proactive facilitation of ongoing engagement with Cancer Centers and cooperative groups
- Engagement of external researchers in developing cancer specific areas of scientific excellence and related collaborative research

National Cancer Institute

Issues Addressed with Change to U24

- Develop focused and limited set of areas of scientific excellence with membership from CRN sites that can contribute substantively . Incorporate extramural researchers as key members of these teams.
  - **Issue: Lack of focused scientific agenda, especially in cancer treatment related research**
- Mandate specific performance criteria in RFA that will be evaluated annually; failure to meet requirements will result in improvement plans, adjustments to funding, and other relevant actions.
  - **Issue: Variable capacity across sites to engage in meaningful research**
- Formalize relationships between CRN oncologists, other CRN researchers, and NCI cooperative groups; enhance existing relationships between CRN sites and cancer centers; increase visibility of CRN to the entire extramural research community
  - **Issue: Limited targeted engagement of external investigators with expertise in cancer**

National Cancer Institute

Issues Addressed with Change to U24

- Provide dedicated resources to “navigate” inception and development of new collaborative research projects with external collaborators.
  - **Issue: Less than optimal process for conceptualizing and implementing collaborative research projects**

- Engage more cancer expertise and more closely monitor CRN site and project performance. Based on maturation of infrastructure, increased recent grant funding, and engagement of more clinical experts, the increase in research publications is expected to continue and improve further.
  - **Issue: Less than optimal utilization of the CRN resource in terms of timely scientific publication and dissemination of research results into practice and policy**

National Cancer Institute

More Rapid Engagement of Extramural Investigators

- Trans-NCI Program Announcement
  - Approach for highlighting unique areas of scientific excellence and key questions within those areas
- Competitive funding mechanism
  - Could bring specialized expertise and technical resources into collaboration with CRN
  - Enhance more timely and efficient examination of selected research priorities
  - Supplement existing NCI initiatives, such as cancer centers, cooperative groups and other grant mechanisms

National Cancer Institute

Metrics of Success

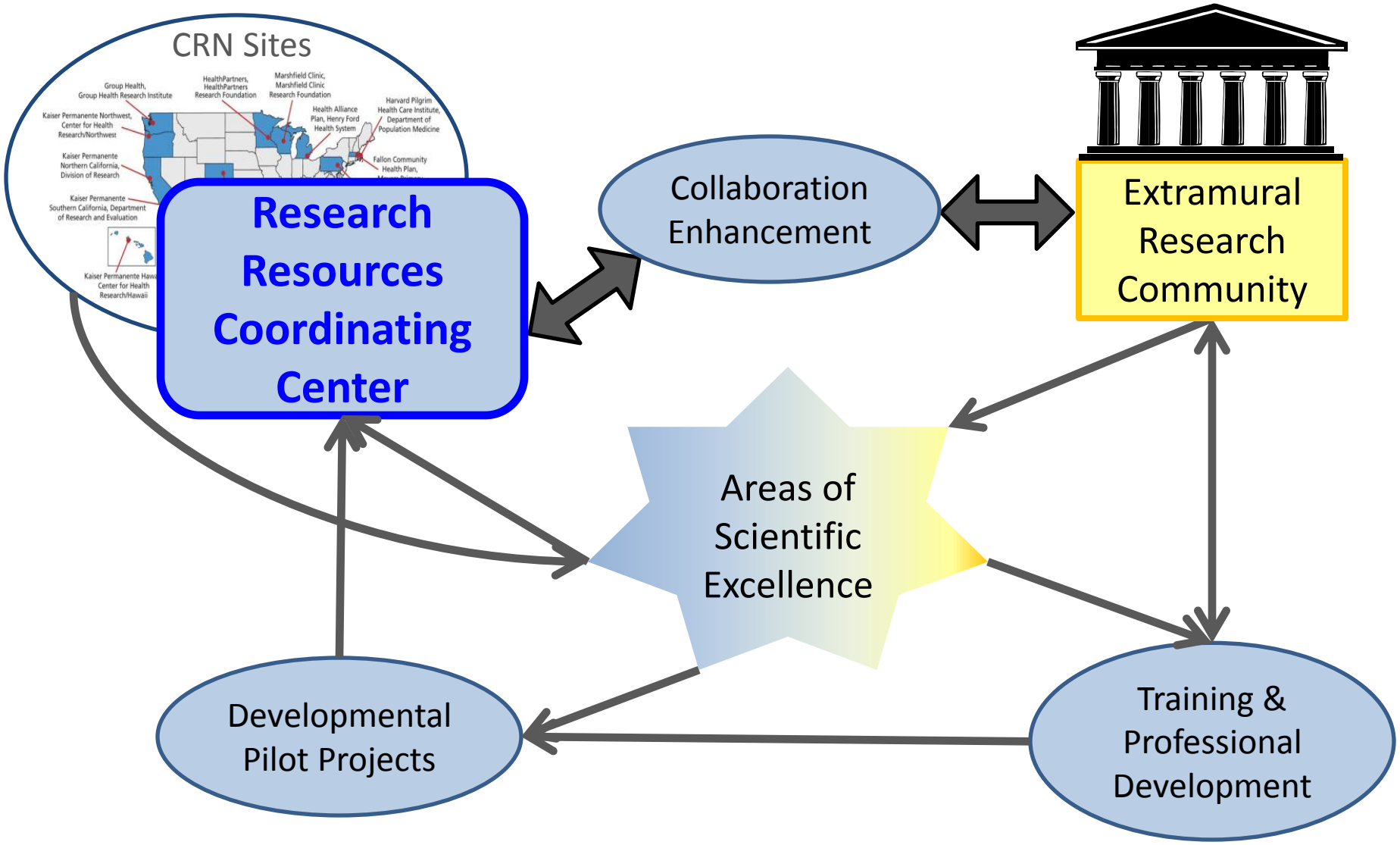
- Use of CRN as a “real world” population test-bed for cancer care innovations
- Research capacity
  - Durable, robust, validated resource that can be re-used for multiple projects across multiple domains
  - Ability to rapidly establish retrospective cohorts and prospective accrual to multi-level intervention studies or pragmatic trials
- Success in developing focused scientific areas of excellence
- Increased scientific research productivity (e.g. grant funded research projects) with outcomes disseminated into practice
- Others: Collaborative success; Develop future research leaders

National Cancer Institute

Other NIH HMORN Initiatives

- HMO Research Network Collaboratory (NIH Common Fund)
  - Will not address diseases covered by other larger NIH ICs (cancer, heart disease)
  - Designed to address research questions for less common diseases (smaller NIH institutes) or research needs common to many diseases
- Larger disease specific IC efforts are continuing
  - Cardiovascular Research Network (NHLBI)
  - Mental Health Data Resource (NIMH)
- Synergy and coordination with NCI initiatives and other initiatives across HHS

Components of New Research Resource RFA



SBIR Phase IIB Bridge Award

RFA Concept Review (Reissuance)

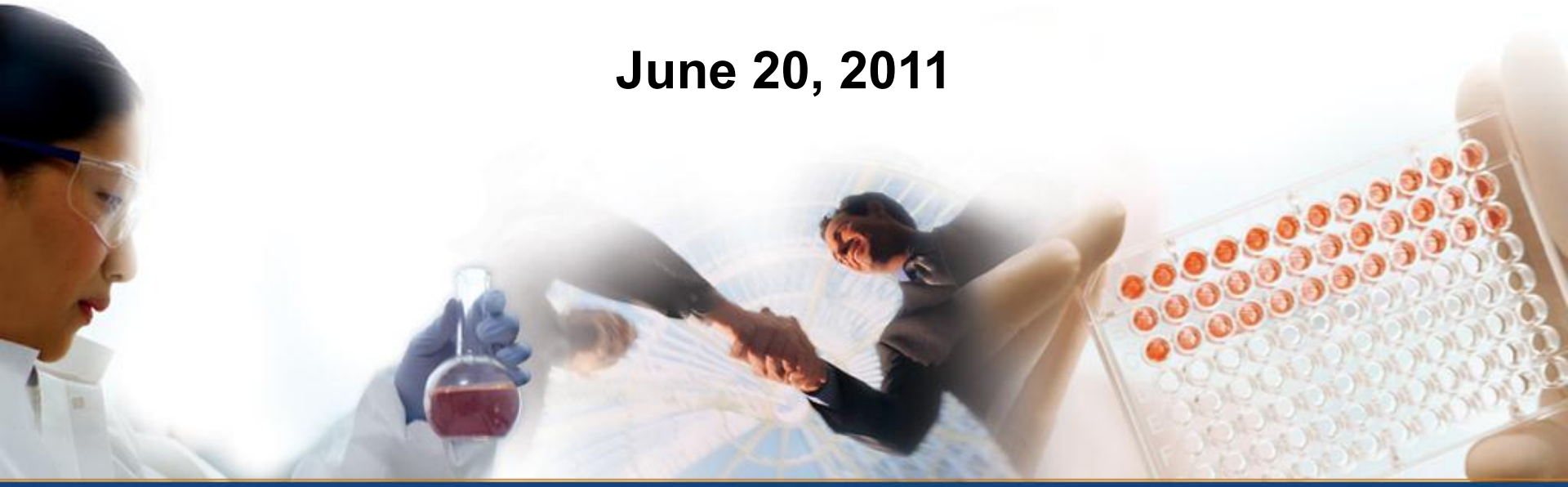
Presented to

NCI Board of Scientific Advisors

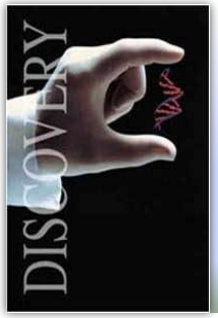
Presented by

Andrew J. Kurtz, PhD

June 20, 2011

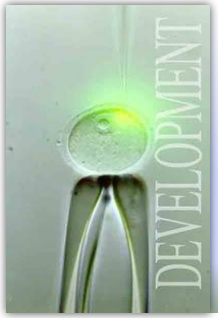


SBIR & STTR: Three-Phases



PHASE I – R41, R43

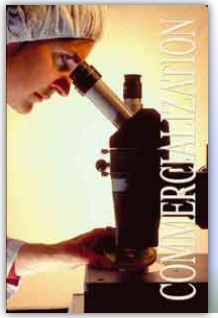
- **Feasibility Study**
- **$150K and 6-month (SBIR) ***
- ***or* 12-month (STTR) Award**



PHASE II – R42, R44

- **Full Research/R&D**
- **$1M and 2-year Award (SBIR & STTR) ***
- **Commercialization plan required**

Phase IIB Bridge Award



PHASE III

- **Commercialization Stage**
- **Use of non-SBIR/STTR Funds**

* Note: Actual funding levels may differ by topic.

SBIR Phase IIB Bridge Award

Competing Renewal Program for SBIR Phase II Awards

- **Provides additional NIH funding to extend promising projects**
- **Helps selected projects/companies cross the "Valley of Death" by:**
  - Incentivizing partnerships with third-party investors & strategic partners
  - Facilitating third-party investments earlier in the development process

How do we accomplish these goals?

- **Program gives competitive preference and funding priority to applicants that can raise substantial third-party funds (i.e., ≥ 1:1 match)**
  - Affords NIH the opportunity to leverage millions in external resources
  - Provides valuable input from third-party investors in several ways:
    1. Rigorous commercialization due diligence prior to award
    2. Commercialization guidance during the award
    3. Additional financing beyond the Bridge Award project period

Original RFA (FY09)

SBIR & STTR

Technical Scope: Cancer Therapies & Imaging Technologies

- Original concept developed in collaboration with staff from NCI's Division of Cancer Treatment and Diagnosis (DCTD)
- Focus on areas requiring substantial capital for clinical validation & FDA approval
- Opportunity to impact >50% of the Phase II projects in NCI's SBIR portfolio

Mechanism & Budgets

- Uses the SBIR Phase II (R44) competing renewal mechanism
- ➢ **Provides up to $1 M per year for up to 3 years ($3 M total)**

Eligibility

- Current Phase II awards & and those ending within the last 2 years
- Cancer-related Phase II projects funded by other NIH institutes
  (must conform to the technical scope specified in the RFA)

Original RFA (FY09)

- **Special Review Criteria**
  - Balanced consideration of technical and commercial merits
  - Emphasis on IP and regulatory strategy
  - Complete disclosure of applicant's SBIR commercialization history
  - ➢ **Fundraising plan***
- **Preferred 3rd-party Matching Funds**
  - Cash, liquid assets, convertible debt
- **Sources of Funds**
  - Another company, venture capital firm, individual "angel" investor, foundation, university, state or local government, or any combination

**** Applications with strong fundraising plans are rewarded with higher scores***

Part I Overview Information

Department of Health and Human Services

Participating Organizations
National Institutes of Health (NIH), (http://www.nih.gov)

Components of Participating Organizations
National Cancer Institute (NCI), (http://www.cancer.gov)

Title: SBIR Phase II Bridge Awards to Accelerate the Development of New Cancer Therapies and Cancer Imaging Technologies Toward Commercialization (SBIR [R44])

Announcement Type
New

Request For Applications (RFA) Number: RFA-CA-08-021

NOTICE: Applications submitted in response to this Funding Opportunity Announcement (FOA) for Federal assistance must be submitted electronically through Grants.gov (http://www.grants.gov) using the SF424 Research and Related (R&R) forms and the SF424 (R&R) Application Guide.

APPLICATIONS MAY NOT BE SUBMITTED IN PAPER FORMAT.

This FOA must be read in conjunction with the application guidelines included with this announcement in Grants.gov/Apply for Grants (hereafter called Grants.gov/Apply).

A registration process is necessary before submission and applicants are highly encouraged to start the process at least four (4) weeks prior to the grant submission date. See Section IV.

Apply for Grant Electronically

For Assistance downloading this or any Grants.gov application package, please contact Grants.gov Customer Support at http://grants.gov/CustomerSupport

Catalog of Federal Domestic Assistance Number(s)
93.394, 93.395

Key Dates
Release/Posted Date: May 14, 2008

Technical Scope Expanded in FY10

SBIR & STTR

Cancer Therapeutics (FY09)

- Small molecule anticancer agents
- Anticancer biologics, including therapeutic vaccines
- Multifunctional canc[illegible]otechnology
- Anticancer drug de[illegible]

Opportunity to impact >75% of the Phase II projects in NCI's SBIR portfolio

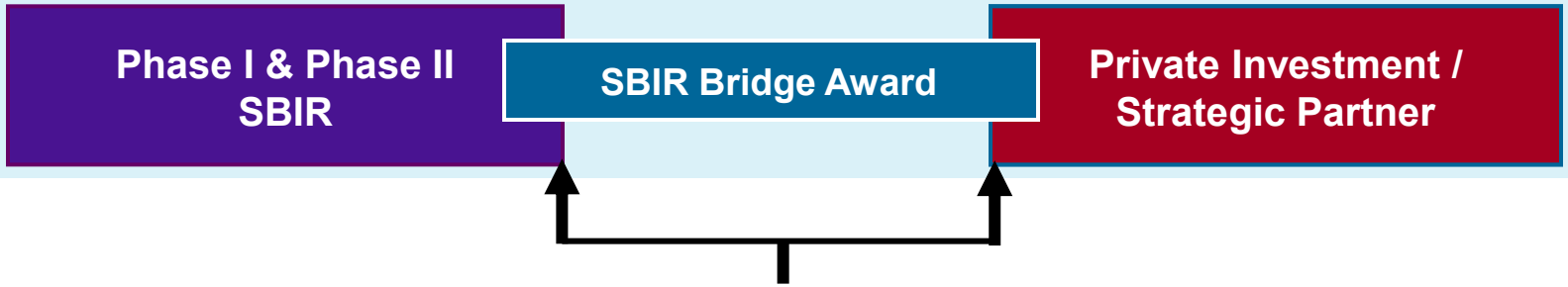
Cancer Imaging Techn[illegible] & *In Vivo* Diagnostics (FY09)

- Medical devices for[illegible]age-guided interventions
- Radiation therapy d[illegible]niques
- Imaging agents, inc[illegible]uticals
- Devices and techno[illegible]ostics

→ *In Vitro* and *Ex Vivo* Cancer Diagnostics and Prognostics (New in FY10)

- Molecular diagnostics and prognostics, including in vitro diagnostic multivariate index assays (IVDMIA)
- Image analysis tools for diagnosis
- Spectroscopic techniques for *in vivo* and *ex vivo* tissue analysis

EXAMPLE: Drug Development



The "Valley of Death" is the problem

SBIR Bridge Award addresses the problem by bridging the "Valley of Death"

EXAMPLE: Drug Development

SBIR Bridge Award allows NCI to share investment risk by incentivizing Private Investors to evaluate projects and commit funds much earlier

Valley of Death:
Moving Target & Technology Specific

Applicants must provide a concise "Statement of Need". This statement is expected to provide answers to the questions listed below:

- What is the perceived "Valley of Death" for the product/technology?
- Why is additional government funding critically needed to accelerate the development of the product or technology toward commercialization?
- What activities are being proposed that would not otherwise be possible through independent third-party investments OR would be significantly delayed without additional NIH support?
- To what extent would a possible award advance the product or technology far enough to attract sufficient, independent third-party financing and/or strategic partnerships to carry out full commercialization?

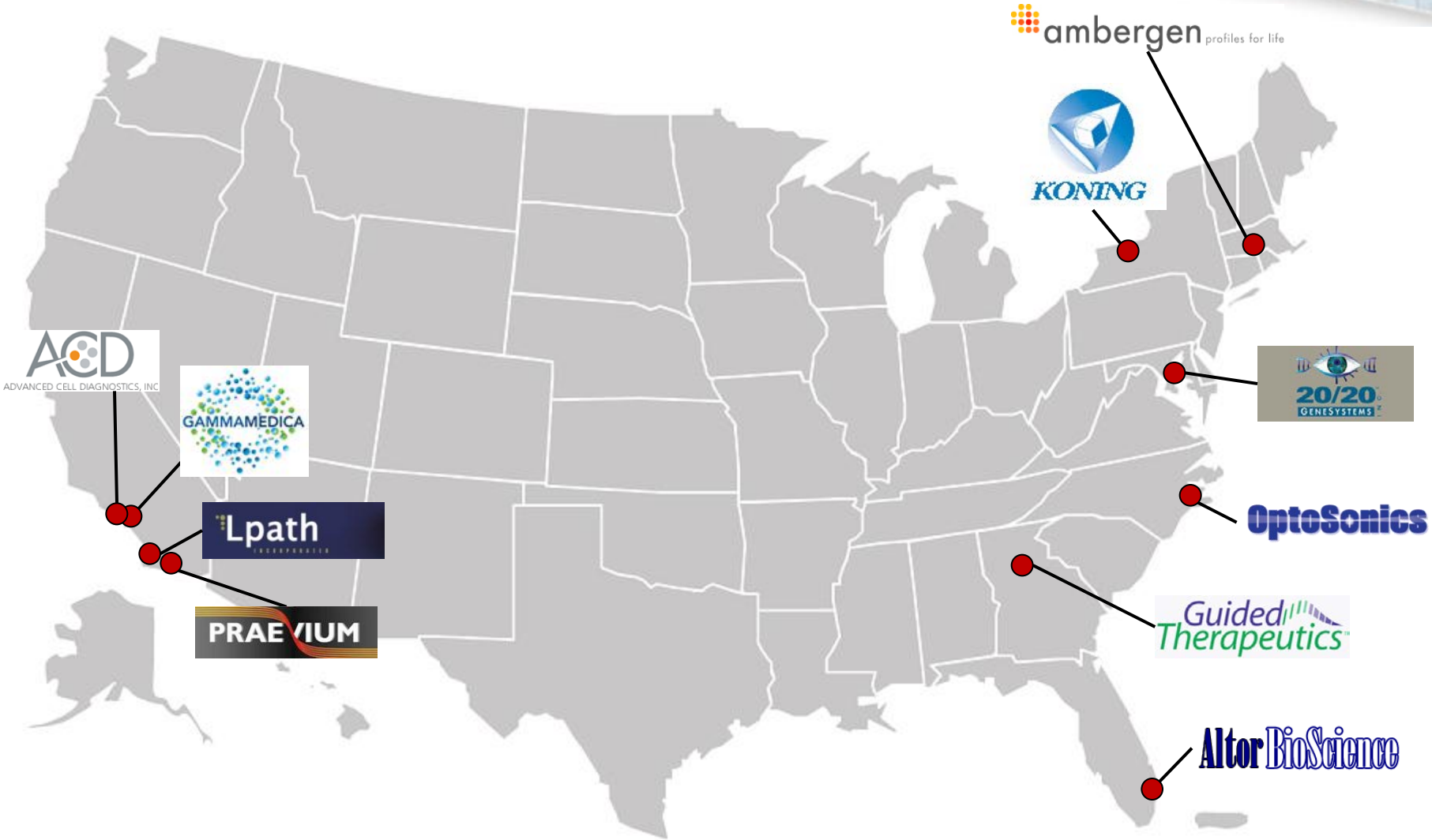
Applications by Receipt Date

		Applications Received					
RFA #	FY	Date	Therapeutics	Imaging	Diagnostics/ Prognostics	Total	Funded
CA08-021	2009	Sep 2008	11	12	0	23	→ 2
		Feb 2009	9	10	0	19	→ 4
CA10-009	2010	Mar 2010	8	10	8	26	→ 4
CA11-002	2011	Apr 2011	5	7	7	19	*Pending review*

Program recommends reissuing the RFA each year for the next three years, with two receipt dates per year

Ten Bridge Awards: FY09/FY10

SBIR & STTR



Ten Bridge Awards: FY09/FY10

SBIR & STTR

FY	Company	Technology/Product	Award Size
2009	**Lpath Therapeutics**	Humanized monoclonal antibody for treatment of prostate cancer	$3,000,000
2009	**Optosonics**	Photoacoustic CT for preclinical molecular imaging	$2,997,247
2009	**Guided Therapeutics**	Fluorescence/reflectance spectroscopy for detection of cervical cancer	$2,517,125
2009	**Koning Corporation**	High-performance breast CT as diagnostic adjunct to mammography	$2,986,453
2009	**Gamma Medica-Ideas**	Molecular imaging to detect metabolic activity of breast lesions	$3,000,000
2009	**Altor BioScience**	Tumor-targeted immunotherapy for treatment of p53-positive cancers	$2,969,291
2010	**20/20 GeneSystems**	mTOR companion diagnostic assay	$2,750,000
2010	**Advanced Cell Diagnostics**	*In situ* RNA detection assay for analyzing circulating tumor cells	$2,996,450
2010	**Ambergen**	Expression-based prognostic assay for recurrence of colorectal cancer	$2,998,830
2010	**Praevium Research**	High-performance imaging engine for optical coherence tomography	$1,180,420
		Total	**$27,395,816**

↓

2 therapeutics

5 imaging technologies

3 diagnostics

Third-Party Investment

Cumulative for Ten Bridge Awards (FY09/FY10)

SBIR & STTR

SANDERLING VENTURES

PSILOS

Sansar Capital Management LLC

MERCK SERONO

enlight biosciences

CAPITAL RESOURCE PARTNERS

THORLABS

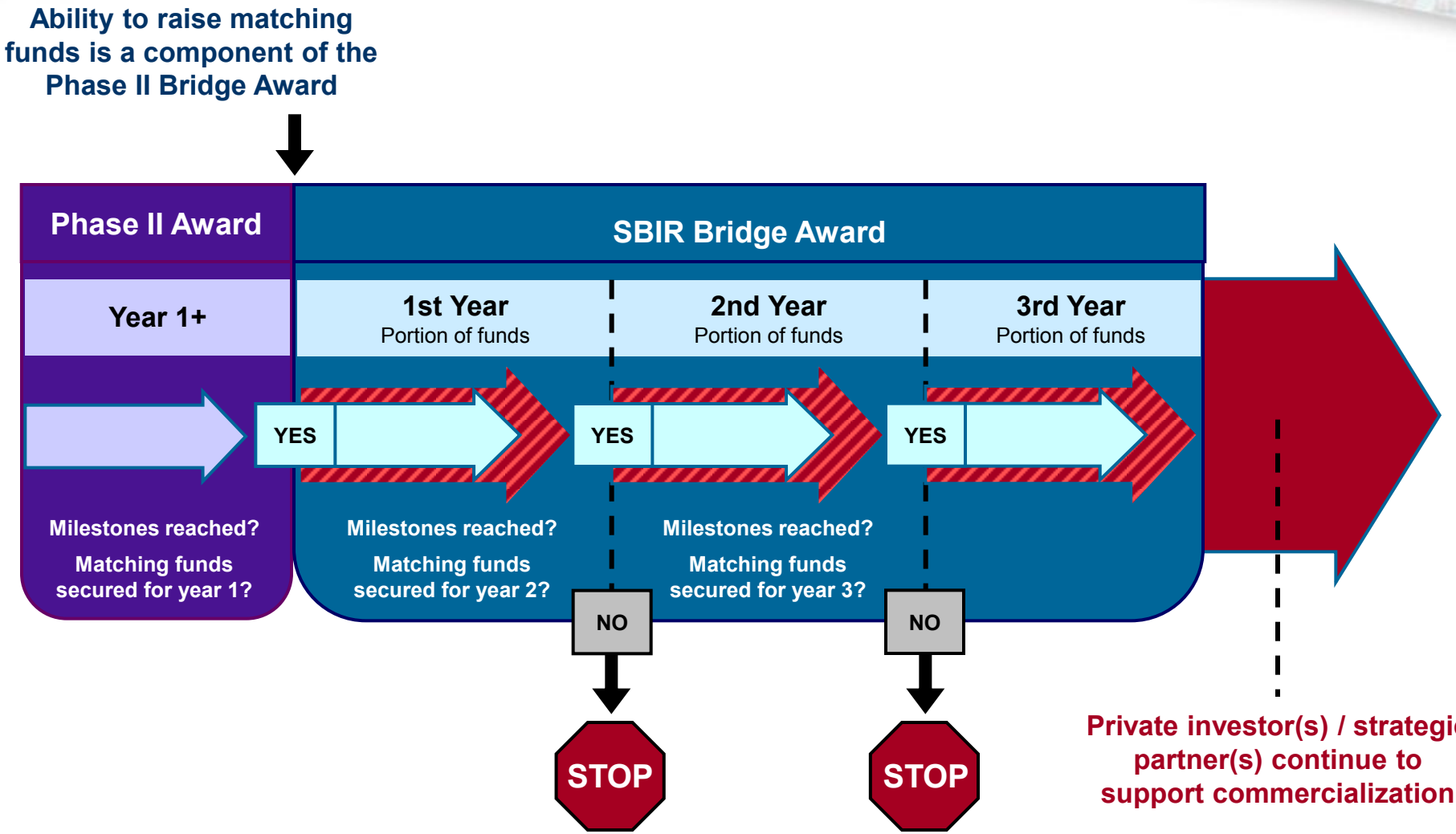
MORNINGSIDE

Alere™

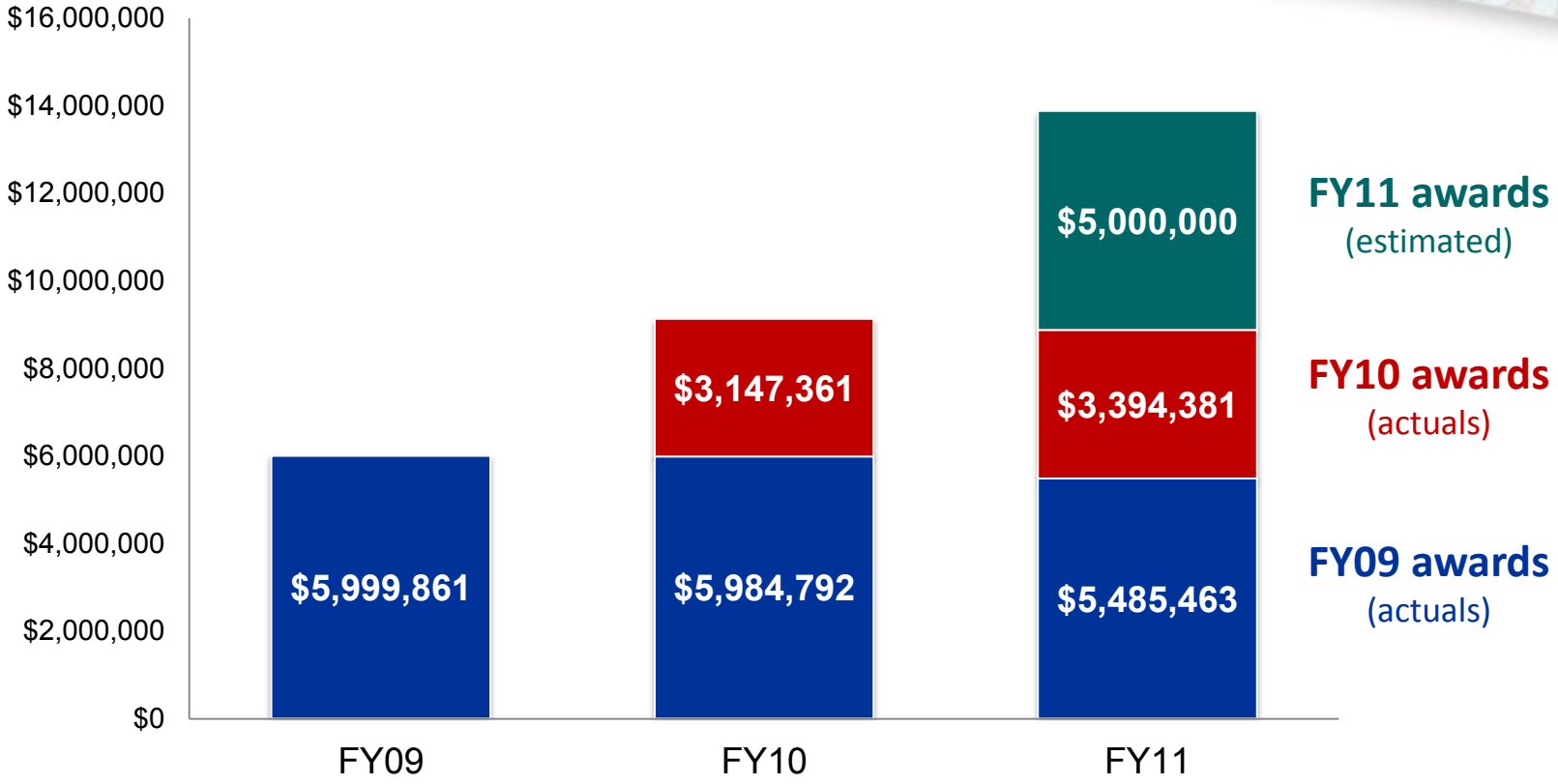
Traditional VC	$21,500,000	34%
Strategic Partners	$24,200,000	38%
Other Investment Firms	$5,500,000	9%
Individuals & Others	$11,750,000	19%

Investor Total	**$62,950,000**
NCI Total	**$27,395,816**
Leverage	**> 2 to 1**

Milestone-Based Awards



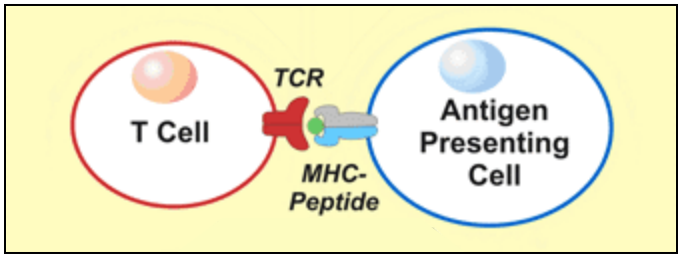
Bridge Award (Pilot Phase)



NCI SBIR set-aside	**$97.1 M**	**$98.8 M**	**~ $98 M**
Bridge funding	**$6.0 M**	**$9.1 M**	**~ $14 M**
% of total SBIR	6.2 %	9.2 %	~ 14 %
	(actuals)	(actuals)	(estimated)

Altor Bioscience, Inc.
(Miramar, FL)

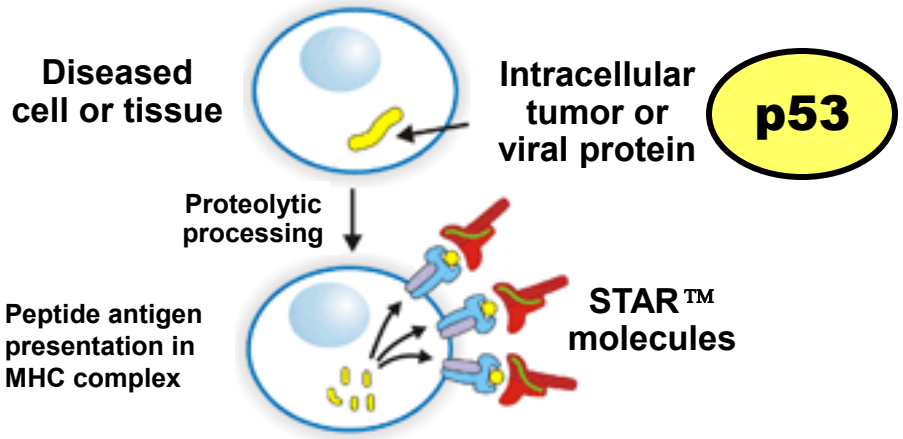
SBIR & STTR



Major histocompatibility complex (MHC)

T-cell receptor (TCR)

STAR ™ ≡ Soluble T-cell Antigen Receptor



STAR ™ molecules target disease-specific antigens

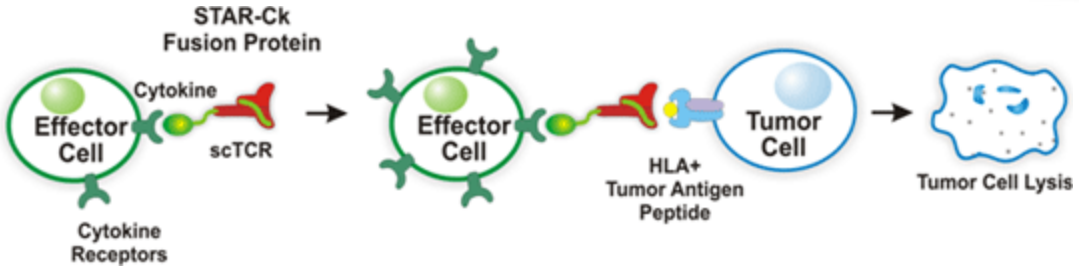
Drug ≡  **IL-2**

(ALT-801)

Altor Bioscience, Inc.
(Miramar, FL)

SBIR & STTR

ALT-801



SBIR Phase I & Phase II

- Inhibits growth or causes regression of primary tumors derived from human p53-positive/HLA-A2.1 cancer cells in several xenograft models
- Exhibits significantly better antitumor activity than recombinant human IL-2 alone
- ALT-801 was advanced as a clinical candidate and evaluated in a Phase I clinical study **(ClinicalTrials.gov: NCT01029873)**
  - Treatment of 26 patients with progressive metastatic p53-positive malignancies
  - Primary endpoints: Safety, MTD, pharmacokinetics
  - Secondary endpoints: Immunogenicity and antitumor response

➢ ***ALT-801 exhibited favorable safety and PK profiles at the MTD level***

Altor Bioscience, Inc.
(Miramar, FL)

SBIR & STTR

$3.0 million Phase II Bridge Award

- Further assessment of the anti-tumor activities of ALT-801 for advanced/metastatic melanoma, renal cell carcinoma, head and neck adenocarcinoma, and prostate cancer
- Cisplatin regimen has been developed to replace the ALT-801 monotherapy regimen for a Phase Ib/II study in patients with metastatic melanoma
  (ClinicalTrials.gov: NCT01029873)
  - Eight clinical sites in the U.S. have been initiated and are screening patients for enrollment in this study
  - Results of the dose escalation phase will be used to establish ALT-801 plus cisplatin treatment regimens in Phase II clinical studies for other indications

---

SANDERLING VENTURES

Third-Party Investment: $8,000,000

- In July 2008, Altor signed a term sheet to raise a total of $8.0M in a financing round led by Sanderling Ventures
- Bridge fundraising is complete, and additional funds have been raised beyond the original commitment

Enlight Biosciences Structure

SBIR & STTR

- Guide Enlight focus areas
- Create "wish list"
- Invest in portfolio companies

PureTech Ventures

Enlight Biosciences

Endra

Newco 2

Etc.

NCI: $3M

OptoSonics

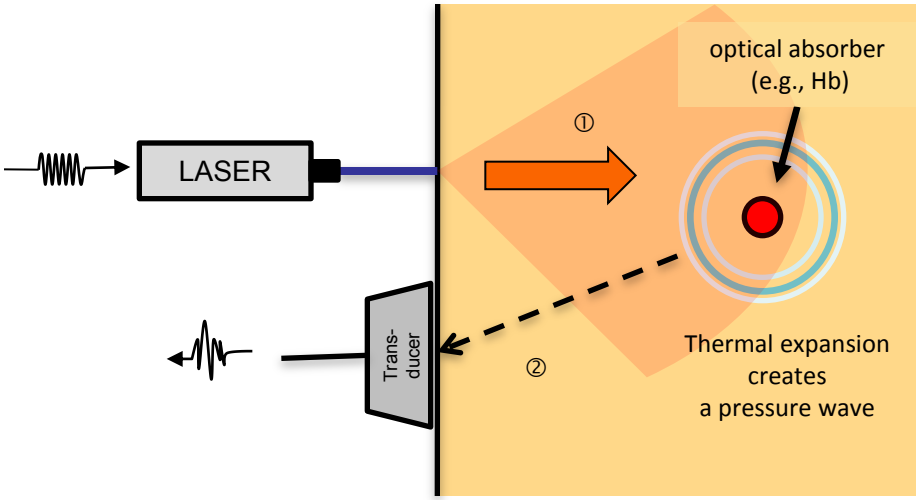
Endra: $3M

Photoacoustic CT for preclinical imaging

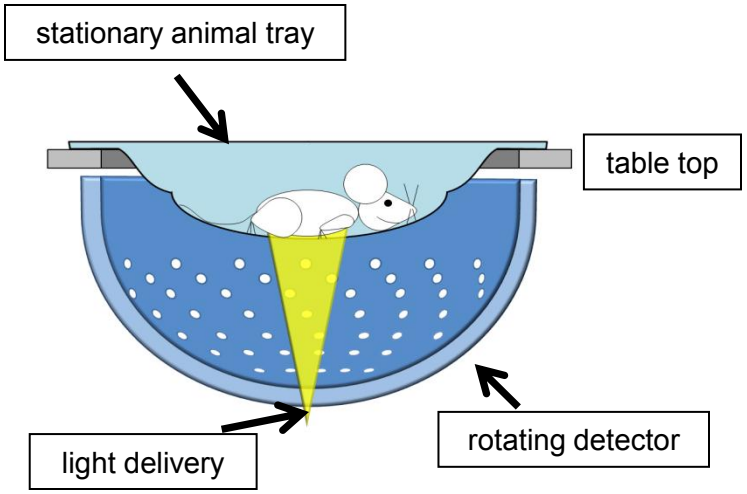
SBIR & STTR

Goal: Develop a 3-D optical imaging technique with increased depth and resolution relative to current optical techniques

How it works: acoustic waves are generated when short pulses of light are absorbed by tissue



Nexus 128: uses a tunable laser and 128 acoustic receivers to produce multi-spectral images, in less than 1 minute



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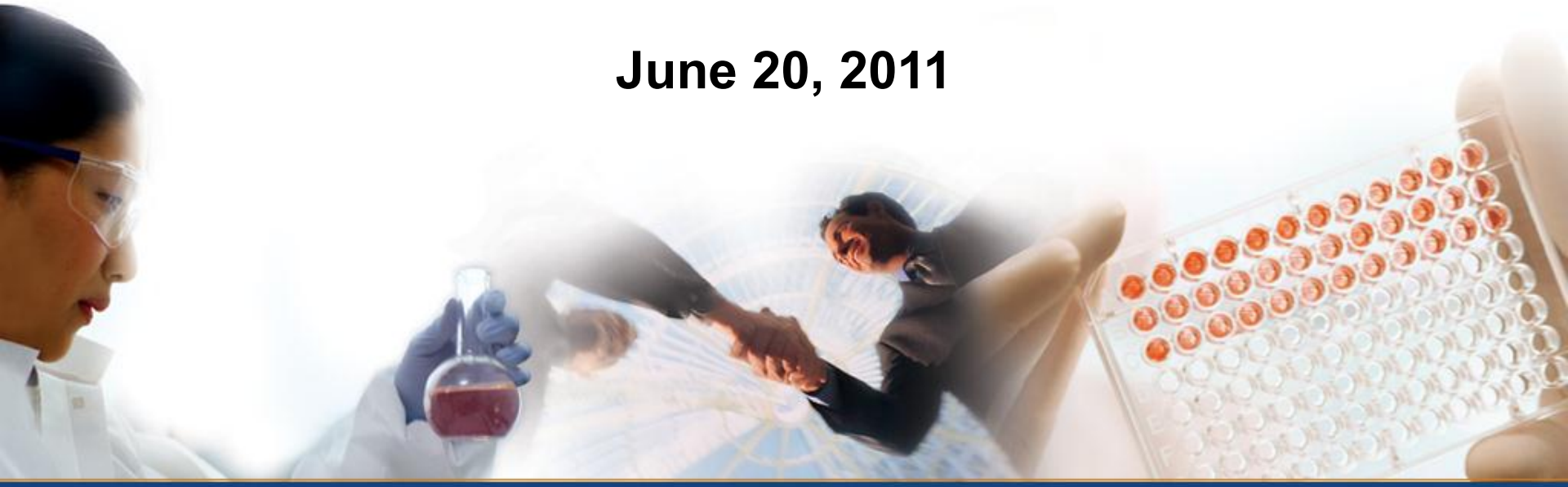


Program Evaluation, Looking Ahead

SBIR & STTR

Summary
Applications Received Feb 2009

Peer Review Rank	Score	Grant Number	PI
1	148	2R44CA110149-03	Bambot
2	154	1R44CA143716-01	Wagenaar
3	159	2R44CA097550-05A1	Wong
4	171	2R44CA103236-05A1	Ning
5	223	2R44CA091392-06A1	Sarvazyan
6	240	2R44CA140389-04A1	Burdette
7	249	2R44CA109850-08A1	Spaulding
8	258	2R44CA115205-04	Mattern
9	258	2R44CA101573-04A1	McNichols
10	261	9R44CA095930-06A1	Monticello
11	294	9R44CA119502-04A1	Stefansic
12	305	2R44CA110227-06A1	Kleerekoper
13	319	2R44CA089959-05	Oraevsky.
14	321	2R44CA096025-06A1	Fakhrai
15	Unscored	2R44CA085097-06	Conway
16	Unscored	2R44CA094566-04A1	Morgan
17	Unscored	2R44CA096409-04	Hansen

Funded

Not funded

Long-term, how do the outcomes for funded Bridge Award projects/ companies compare to those that missed the cut?

NCI's Support of R21's

Dinah Singer, Ph.D.
Director
Division of Cancer Biology

How Should NCI Use the R21 Grant Mechanism?

- What is the NIH definition of an R21 grant? How does it differ from an RO1 or RO3?
- How is NCI currently using the R21 grant mechanism?
- What is NCI's current level of support of R21 grants?
- What should be NCI's policies on R21 grants?

What is the NIH Definition of an R21 Grant? How Does It Differ from an RO1 or RO3?

Mechanism	Research	Support Level	Duration	Restrictions
R21	Exploratory/devel-opmental research projects	Up to $275K DC Total	2 years	Not renewable
R01	Discrete, specified research project	No specific dollar limit	3-5 years	Advance permission for $500K DC/yr or more
R03	Feasibility studies, collection of preliminary data, small self-contained projects	Up to $50,000DC per year	2 years	Not renewable

How Do NIH Institutes Solicit R21 Grant Applications?

- **NIH R21 Parent Announcement (Omnibus) PA-10-069**
  - **Participating NIH Institutes and Centers:**

    NCCAM, NEI, NHGRI, NHLBI, NIA, NIAAA, NIAID, NIAMS, NIBIB, NICHD, NIDA, NIDCD, NIDCR, NIDDK, NIEHS, NIMH, NINDS, NINR, and NLM
  - **Investigator Initiated**

- **Institute Specific Program Announcement**
  - **NIH Institutes and Centers that accept R21 applications only in response to their specific funding opportunity announcements:**

    FIC, NCI, NCMHD, NCRR and NIGMS
  - **Institute targeted area**

How is NCI currently using the R21 grant mechanism?

- NCI does not accept unsolicited R21 grant applications
- NCI only accepts R21 grant applications that respond to specific NCI participating Funding Opportunity Announcements (PA's, PAR's, or RFA's)
- Some R21 grants' budgets and duration exceed the NIH definition; some have supported pilot or feasibility studies.
- NCI currently has 59 R21 Funding Opportunities Announcements
  - 34 are NCI initiated
  - 25 are NCI participating

Current NCI Support of R21 Grants

Mechanism	# of Applications Submitted 2010 (2011)	# Awarded (2010)	Total Funded (2010)
R21	**2060** (2519)	**229**	**592**
R01	**4874** (4952)	**850**	**3998**

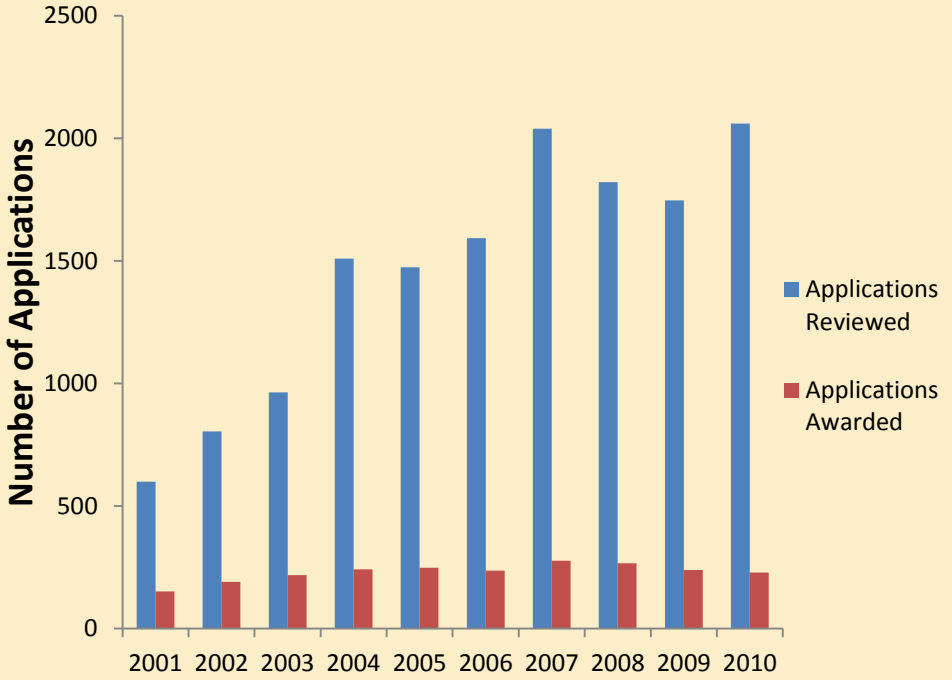
Six PA's Receive Nearly Half of All R21 Grant Applications

1. **PA08-268 -** Exploratory Studies In Cancer Detection, Diagnosis, And Prognosis (R21) **(260 Applications**)
2. **PAR08-025** - Quick-trials For Novel Cancer Therapies And Prevention: Exploratory Grants (R21) **(160 Applications**)
3. **PA08-165** - Stem Cells And Cancer (R21) **(158 Applications**)
4. **PA08-208** - Pilot Studies In Pancreatic Cancer (R21) **(140 Applications**)
5. **PA08-053** - Nanoscience And Nanotechnology In Biology And Medicine (R21) **(114 Applications**)
6. **PA09-130** - Exploratory Grants For Behavioral Research In Cancer Control (R21) **(113 Applications**)

Success Rate of NCI R21 Applications in 2010

PA	# of applications submitted	% receiving score	# receiving 10% or better
PA08-267 - Exploratory Studies In Cancer Detection, Diagnosis, And Prognosis	260	49%	7%
PA08-165 - Stem Cells And Cancer	158	46%	6%
PA08-208 - Pilot Studies In Pancreatic Cancer	140	51%	9%
PA08-053 - Nanoscience And Nanotechnology In Biology And Medicine	114	56%	5%
PA09-130 - Exploratory Grants For Behavioral Research In Cancer Control	113	59%	4%
PAR08-025 - Quick-trials For Novel Cancer Therapies And Prevention: Exploratory Grants	160	52%	4%
	AVERAGES	52%	5.8%
Research Project Grants (R01's)	4874	57%	10%

Success Rates of NCI R21 Applications from 2001-2010

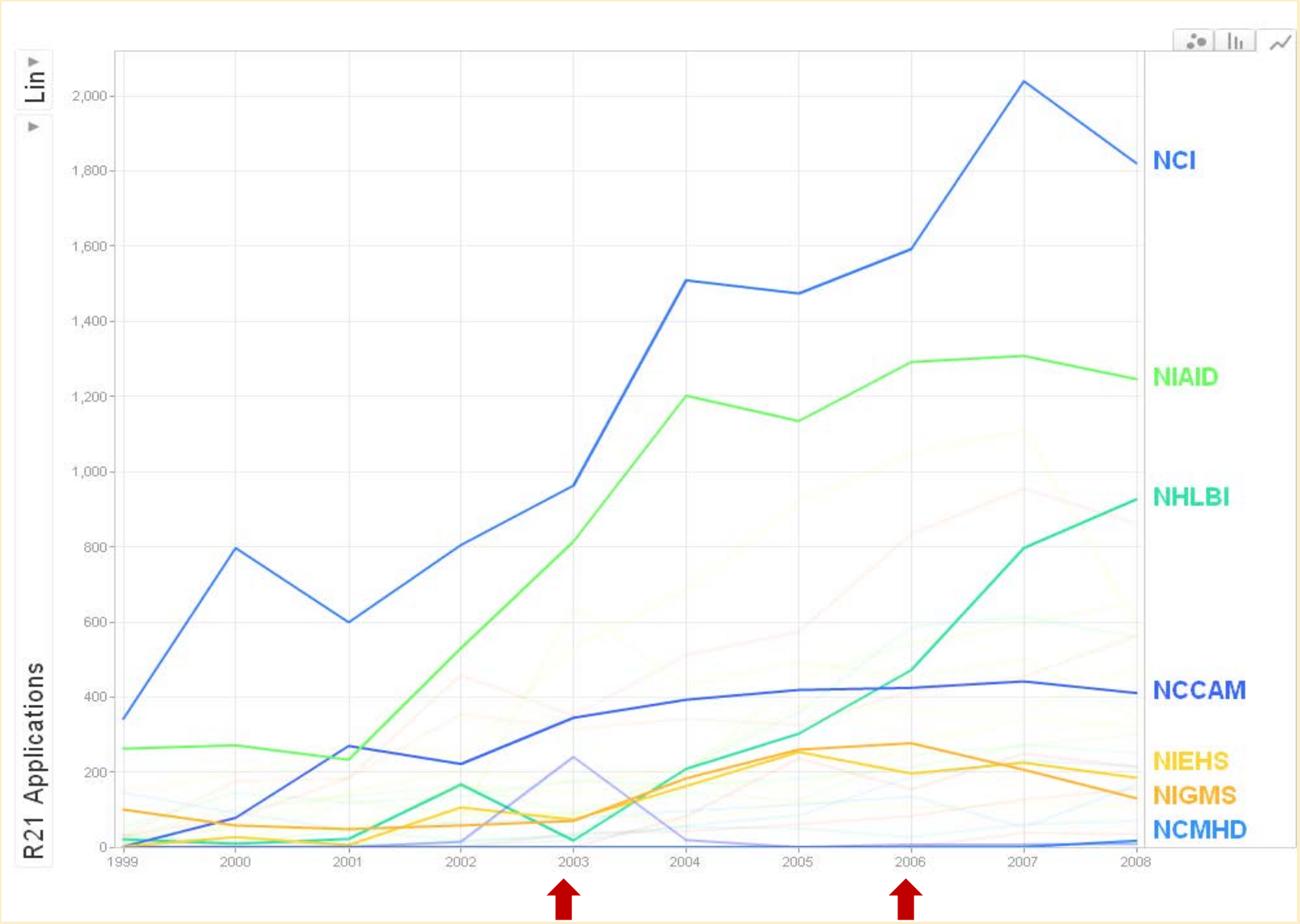


Fiscal Year	Number of Applications Submitted	Number of Applications Awarded	Success Rate[2]	Total Funding[3]
2001	599	152	**25.4%**	$29,016,372
2002	804	191	23.8%	$33,801,636
2003	963	219	22.7%	$42,755,154
2004	1509	242	16.0%	$42,069,312
2005	1474	249	16.9%	$43,252,146
2006	1592	237	14.9%	$43,664,296
2007	2039	277	13.6%	$51,891,571
2008	1821	267	14.7%	$56,443,487
2009	1747	239	13.7%	$50,145,321
2010	2060	229	**11.1%**	$48,159,879

Questions for BSA

- How should NCI use the R21 grant mechanism?
  - NCI specified research areas
  - Investigator initiated research areas
  - Both
- How should NCI solicit R21 grant applications?
  - Continue to issue topic-specific PA's
    - Limit number issued
    - Limit receipt dates
  - Issue an NCI Omnibus PA
  - Participate in the NIH Omnibus PA

R21's Applications Across the NIH



NCI issued R21 Funding Opportunities

Announcement Number	Related Announc.	Issuing Organization	Release Date	Opening Date (SF424 Only)	Expiration Date	Activity Code(s)	Title
PAR-11-216	See Related	NCI	05/24/2011	06/27/2011	03/14/2014	R21	Early Phase Clinical Trials in Imaging and Image-Guided Interventions (R21)
PA-11-159	See Related	NCI	03/17/2011	05/16/2011	05/08/2014	R21	Biomarkers of Infection-Associated Cancers (R21)
PA-11-161	See Related	NCI	03/17/2011	05/16/2011	05/08/2014	R21	Enhancing Tumoricidal Activity of Natural Killer (NK) Cells by Dietary Components for Cancer Prevention (R21)
PA-11-163	See Related	NCI	03/17/2011	05/16/2011	05/08/2014	R21	The Effect of Racial and Ethnic Discrimination/Bias on Health Care Delivery (R21)
PA-11-074	See Related	NCI	12/09/2010	01/16/2011	01/08/2014	R21	Mitochondria in Cancer Epidemiology, Detection, Diagnosis and Prognosis (R21)
PA-10-291	See Related	NCI	09/29/2010	12/07/2010	09/08/2013	R21	Research on Malignancies in the Context of HIV/AIDS (R21)
PA-10-088	See Related	NCI	03/17/2010	05/16/2010	05/08/2013	R21	Exploratory Cancer Prevention Studies Involving Molecular Targets for Bioactive Food Components (R21)
PA-10-053	See Related	NCI	12/10/2009	01/16/2010	01/08/2013	R21	School Nutrition and Physical Activity Policies, Obesogenic Behaviors and Weight Outcomes (R21)
PA-10-032	See Related	NCI	11/24/2009	01/16/2010	01/08/2013	R21	Epigenetic Approaches in Cancer Epidemiology (R21)
PA-10-026	See Related	NCI	11/16/2009	01/16/2010	01/08/2013	R21	Development, Application, and Evaluation of Prediction Models for Cancer Risk and Prognosis (R21)
PA-10-028	See Related	NCI	11/16/2009	01/16/2010	01/08/2013	R21	Obesity Policy Research: Evaluation and Measures (R21)
PA-09-238	See Related	NCI	07/22/2009	09/16/2009	09/08/2012	R21	Exfoliated Cells and Circulating DNA in Cancer Detection and Diagnosis (R21)
PAR-09-225	See Related	NCI	07/17/2009	09/16/2009	09/08/2012	R21	Improving Diet and Physical Activity Assessment (R21)
PA-09-235	See Related	NCI	07/15/2009	09/16/2009	09/08/2012	R21	Diet, Epigenetic Events, and Cancer Prevention (R21)
PAR-09-162	See Related	NCI	06/11/2009	09/23/2009	11/24/2011	R21	Exploratory Grant Award to Promote Workforce Diversity in Basic Cancer Research (R21)
PA-09-198	See Related	NCI	06/01/2009	09/16/2009	09/08/2012	R21	Biomarkers for Early Detection of Hematopoietic Malignancies (R21)
PA-09-200	See Related	NCI	06/01/2009	09/16/2009	09/08/2012	R21	Identifying Non-coding RNA Targets for Cancer Early Detection and Prevention (R21)
PA-09-167	See Related	NCI	04/17/2009	05/18/2009	05/08/2012	R21	Developmental Projects in Complementary Approaches to Cancer Care and Treatment (R21)
PAR-09-160	See Related	NCI	04/16/2009	05/23/2009	11/24/2011	R21	Exploratory/Developmental Grants Program for Basic Cancer Research in Cancer Health Disparities (R21)
PA-09-158	See Related	NCI	04/14/2009	05/16/2009	05/08/2012	R21	Developmental Research in Cancer Prognosis and Prediction (R21)
PA-09-149	See Related	NCI	04/08/2009	05/16/2009	05/08/2012	R21	Studies of Energy Balance and Cancer in Humans (R21)
PA-09-144	See Related	NCI	04/03/2009	05/16/2009	05/08/2012	R21	Cancer Surveillance Using Health Claims-based Data System (R21)
PA-09-130	See Related	NCI	03/13/2009	05/16/2009	05/08/2012	R21	Exploratory Grants for Behavioral Research in Cancer Control (R21)
PA-09-047	See Related	NCI	02/19/2009	05/16/2009	05/08/2012	R21	Testing Tobacco Products Promoted to Reduce Harm (R21)
PA-09-024	See Related	NCI	11/06/2008	01/16/2009	01/08/2012	R21	Erythropoiesis Stimulating Agents and Tumor Progression (R21)
PA-09-005	See Related	NCI	10/06/2008	01/16/2009	01/08/2012	R21	Understanding the Effects of Emerging Cellular, Molecular, and Genomic Technologies on Cancer Health Care Delivery (R21)
PA-08-267	See Related	NCI	09/23/2008	01/16/2009	09/08/2012	R21	Exploratory Studies in Cancer Detection, Diagnosis, and Prognosis (R21)
PA-08-244	See Related	NCI	08/19/2008	09/16/2008	09/08/2011	R21	Etiology, Prevention, and Treatment of Hepatocellular Carcinoma(R21)
PA-08-240	See Related	NCI	08/14/2008	09/16/2008	09/08/2011	R21	Impact of Health Communication Strategies on Dietary Behaviors (R21)
PA-08-221	See Related	NCI	07/30/2008	09/16/2008	09/08/2011	R21	Investigational Nutrigenetic Studies for Cancer Prevention (R21)
PA-08-208	See Related	NCI	07/18/2008	09/16/2008	09/08/2011	R21	Pilot studies in Pancreatic Cancer (R21)
PA-08-211	See Related	NCI	07/18/2008	09/16/2008	09/08/2011	R21	Diet-Induced Changes in Inflammation as Determinants of Colon Cancer (R21)
PA-08-193	See Related	NCI	07/03/2008	09/16/2008	09/08/2011	R21	Geographic and Contextual Influences on Energy Balance-Related Health Behaviors (R21)
PA-08-077	See Related	NCI	01/17/2008	01/17/2008	11/06/2011	R21	Research on the Economics of Diet, Activity and Energy Balance (R21)

National Cancer Institute

Cancer Drug Shortages: A Critical Problem

NCI Board of Scientific Advisors Meeting

James H. Doroshow, M.D.

June 20, 2011

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Cancer Institute

Cancer Drug Shortages: An Undeniable Problem

WALL STREET JOURNAL APRIL 14, 2011

By JENNIFER CORBETT DOOREN

A shortage of a key leukemia drug that started last year has worsened, causing many major cancer centers such as the Johns Hopkins Hospital to start rationing the drug and others to turn away patients from community hospitals that have run out of the medication.

The Washington Post 04/19/2011

Without this drug, leukemia patients won't be cured

Hagop M. Kantarjian, MD

In the United States this year, about 10,000 people will receive a diagnosis of acute myeloid leukemia (AML). Since mid-December, the most effective drug to treat this fatal disease has been in dangerously short supply. The chemotherapy medication cytarabine was first approved by the Food and Drug Administration in 1969. For four decades, it has been the backbone of AML treatment. A doctor at a large center in Nebraska wrote, "We are completely out after the end of the week and no cytarabine in sight. It is like we live in a Third World country!“ "Sorry, we're out of stock" is simply not acceptable.

CHICAGO, June 7 (Reuters) - Cancer medicines desperately needed by sick children and adults are in short supply, undermining the ability of U.S. doctors to administer treatments, top oncologists warned this week. Generic chemotherapy drugs are in particularly tight supply at the nation's hospitals, including mainstay cancer treatments such as cisplatin, doxorubicin, cytarabine and leucovorin.

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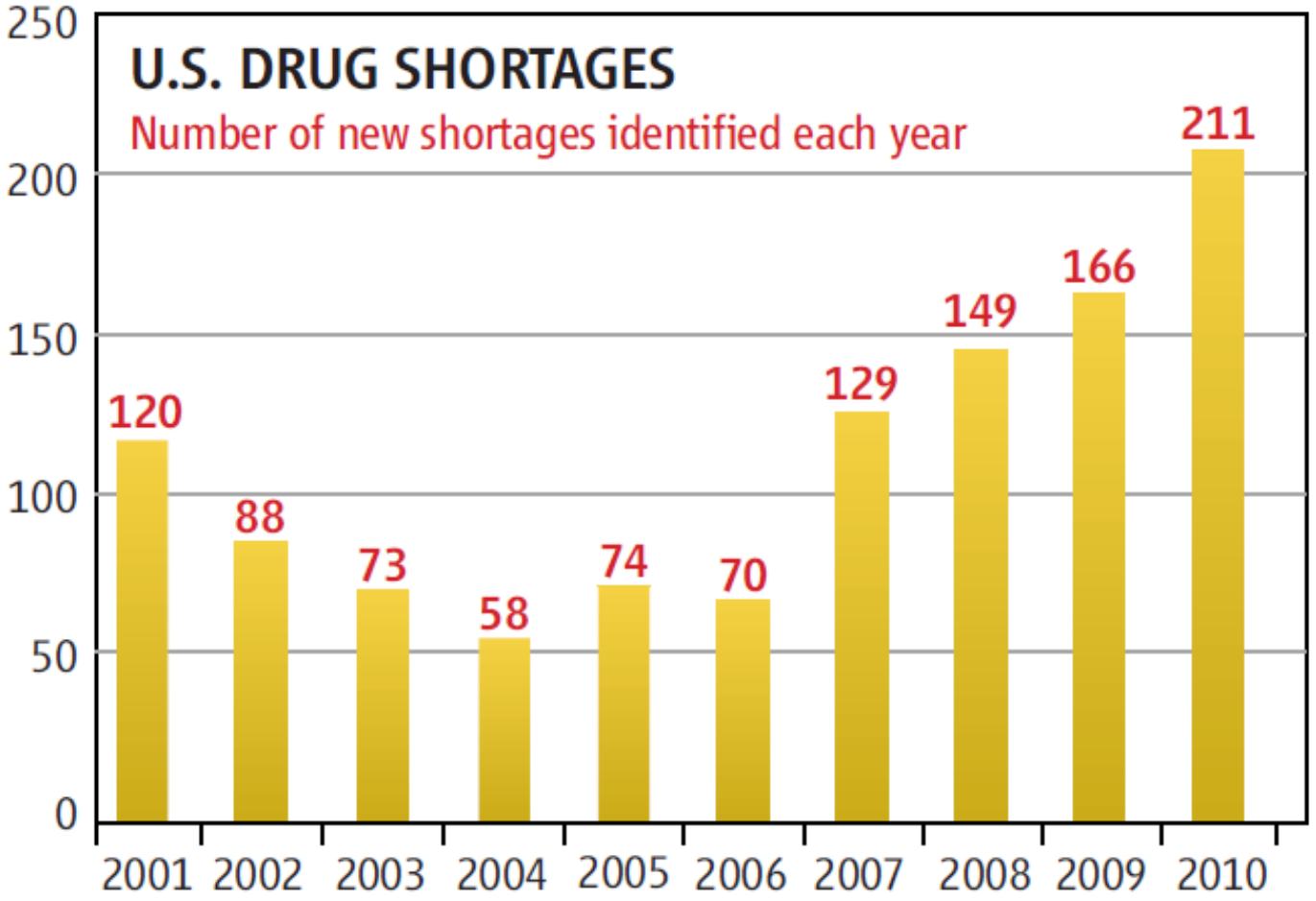
Drug Shortages: An Increasing Problem



Science 332: 523, 2011

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FDA Drug Shortage Website
June 17, 2011

200 Line Items: Not Just Oncologic Agents

67 Total Unique Compounds

10 oral
3 topical
54 injectable (80%)

10 Unique injectable antineoplastic agents
--up to 35 total 'at risk'

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FDA Drug Shortage Website (Sample Drugs) June 17, 2011

Acetylcysteine Inhalation	Doxorubicin lyophilized powder	Neupro (rotigotine transdermal)
Amikacin Injection	Erythromycin lactobionate inj	Norepinephrine Bitartrate Inj
Ammonium Chloride Inj	Etoposide solution for inj	Oxsoralen (methoxsalen) topical
Ammonium molybdate inj	Fentanyl Transdermal System	Oxsoralen-Ultra (methoxsalen) caps
Ammonul (phenylacetate/benzoate)	Foscarnet Sodium Injection	Pentosan Polysulfate sodium caps
Amphetamine Mixed Salts, ER Caps	Fosphenytoin Sodium Inj	Phenylephrine HCl Injection
Aquasol A, 50,000 units/mL	Furosemide Injection	Potassium Phosphate
Arginine 10% injection	Haloperidol Decanoate Injection	Procainamide HCL Injection
Avalide (irbesartan&HCTZ)Tabs	Intravenous Fat Emulsion	Propofol Injection
Bleomycin Injection	Leucovorin Ca Lyophilized Powder	Sodium Chloride 23.4% and 14.6%
Calcitriol 1 mcg/mL Inj	Levorphanol 2mg Tablets	Sodium Phosphate Injection
Calcium Chloride Inj	Lorazepam Injection	Succinylcholine injection
Calcium Gluconate	Magnesium Sulfate Injection	Sulfamethoxazole/trimethoprim inj
Cisplatin injection	Methylphenidate Transdermal	Tamiflu Oral Suspension 12mg/ml
Cleviprex 0.5 mg/mL	Metoclopramide injection	Thiotepa for Injection
Cytarabine Injection	Mexiletine Capsules	Thyroid (desiccated) tablets
Daunorubicin HCl inj	Mustargen (mechlorethamine) inj	Thyrolar Tablets
Desmopressin Inj	Multi-Vitamin Infusion	Tromethamine
Dexamethasone Inj	Nalbuphine Injection	Vasopressin Injection
Digoxin Injection	NeoProfen (ibuprofen lysine) Inj	Vecuronium Injection
Diltiazem Injection	Neostigmine methylsulfate inj	Vincristine Sulfate Injection

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Relative Costs: Tail Wags the Dog

$125 billion total cost of cancer treatment in 2010

$20 billion sales of non-generic anticancer drugs in 2010

$0.4 billion generic injectable sales in 2010 (N=34 drugs)

Generic Injectable Drugs Only 2% of non-Generic Sales

But 100% of Shortage Items

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Reasons for Shortages 2010

- **Consolidation in the generics industry**
  - ✓ As agent "ages" number of producers declines; no alternative drugs especially for sterile injectables
- **Raw materials availability**
  - ✓ Production of active pharmaceutical ingredients now overwhelmingly off-shore (>80% China or India); explains ~ 10% of injectable shortages
- **Supply chain**
  - ✓ Fewer suppliers with tighter inventories ("just in time" production) means less flexibility in system
  - ✓ Difficult to significantly ramp up production (if only two or three manufacturers) ~ 20%
- **Manufacturing and Regulatory**
  - ✓ Smallest number of manufacturers for sterile injectable products; complex processes
  - ✓ Same production lines for multiple products; quality recalls ~ 45% of shortages
  - ✓ Cost of filing Abbreviated NDAs and Supplemental NDAs; USP standards--changes
- **Business decisions**
  - ✓ Relatively low margins
  - ✓ Costs of changes in GMP production—factory shutdowns ~ 5%

Modified from E.R. Fox, PharmD.

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Reasons for Shortages 2010 (contd.)

- Waxman-Hatch Act of 1984 created current generic drug system
  - ✓ Highly effective at lowering drug costs via competitive market
  - ✓ Unintended consequences:
    - ➢ To lower cost of business, supply chain very tight
    - ➢ No requirement to buffer even minor disruptions
- Expectation that situation will get worse
- What can/should the FDA do?
  - ✓ If a manufacturing shortage, FDA can use regulatory discretion to mitigate risk to patients—encourage ramp up, expedite regulatory requirements for approval of increased manufacturing capacity, and in rare cases can allow temporary importation (propofol)
  - ✓ BUT, FDA cannot force manufacturer's to produce a product, and currently, cannot force a manufacturer to report plans to discontinue production unless they are a sole source
  - ✓ FDA does not make or distribute drugs—even though the public thinks they do

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Drug Shortage Summit
November 5, 2010

American Society of Anesthesiologists

ASCO® American Society of Clinical Oncology
Making a world of difference in cancer care

American Society of Health-System Pharmacists®

ISMP INSTITUTE FOR SAFE MEDICATION PRACTICES

✓ Regulatory changes: Expand FDA authority to require manufacturer notification of withdrawals; require confidential notification of FDA when a single manufacturing source; require manufacturing redundancies as part of FDA approval process

✓ Raw materials sourcing and manufacturing: Establish communication channels to improve notification of anticipated shortages to FDA

✓ Distribution factors: Improve distribution interactions and procurement amongst group purchasing organizations

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Remedies Under Consideration

June 1, 2011 (AP) — US Senators Amy Klobuchar, (D) Minnesota, and Robert Casey, (D) Pennsylvania, have introduced the: "Preserving Access to Life-Saving Medications Act." Under the bill, drug makers would have to immediately notify the FDA when a shortage of raw materials or other problem would likely cause a shortage. The FDA would then be allowed to work with other domestic and international manufacturers to maintain an uninterrupted supply.

- Helpful in the long run; defines a new problem more expeditiously
- Does not make drugs available when there is an acute shortage
- Similarly, communication recommendations from the Summit do not alleviate current, severe shortages

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Generic Drug Shortage Hinders NCI Clinical Research Programs

- **NCI sponsors clinical research studies that include these generic drugs as part of comparator groups and as add-ons with investigational drugs**

- **Investigators in these research studies report:**

  - ✓ **Inability to enroll new patients when drug supply not assured**
  - ✓ **Patients on-study receiving alternate drugs when supply not available**
  - ✓ **Concern about interpretation of results when drug substitutions occur**

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Is There a Role for the NCI to Work with FDA to Alleviate Cancer Drug Shortages?

- NCI has more than 50 years of experience in making and distributing drugs

- The NCI infrastructure for new drug development could be leveraged to provide short-term supplies for individual drugs as shortages emerge

- NCI staff can work with together with FDA-HHS and professional societies to formulate **long-term solutions** in the **private sector** – for **all** therapeutic categories

- NCI action could stimulate leadership in other diseases

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Short-term Options to Consider

- NCI could acquire and distribute finished drug products
  - ✓ Primary difficulty—vials not available for purchase during shortage; does not expand total available supply; could exacerbate acute shortage
  - ✓ Expiration dates of finished products mandates continuous updating
  - ✓ State-by-state licensing for distribution of finished drug products
  - ✓ Most expensive option and requires longer time to build reserve
- NCI could acquire and distribute bulk drug supplies
  - ✓ The active pharmaceutical ingredients (API) could be acquired for storage by NCI, and distributed during period of shortage
  - ✓ In general, most active ingredients are not in short supply even when the finished drug supply is in a severe shortage
  - ✓ Cancer Centers, hospitals, and other organizations can prepare and dispense final drug solutions for patients as established in the USP compounding monographs
  - ✓ Requires considerable advance planning re: supply chain, risks of using compounded drug
- FDA might take role of defining beginning/end of shortage and assisting NCI in selecting drugs to be acquired

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Potential Consequences

Positive	Negative
• Alleviate short-term (~ 3-4 month) shortages of injectable generic anticancer agents; immediate clinical benefit	• Long-term dependence on NCI reserves might delay legislative action
• Guarantee availability of iv generics used in NCI-supported clinical trials	• Cost of drugs, drug storage, drug distribution, and mechanisms for setting up appropriate system for allocation
• Provide time for regulatory and/or legislative actions to facilitate market-based solutions	• Potential risks of using compounded rather than vialed agents
• Enhance NCI/NIH interactions with FDA	• If use API, availability limited to sites with compounding pharmacies

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"No Sign of Abating"

Dr. Richard Schilsky, cancer specialist at the University of Chicago and a past ASCO president, said the shortages have been going on for about nine months with no sign of abating. "When you talk to the drug companies, they say there are manufacturing problems or they are taking plants offline then it takes a while to get them back up," he said. "They point the finger at the FDA, saying the FDA is under-resourced and they can't get plants inspected to allow resumption of drug production. "The drug suppliers are in the middle of this as well," he said.