

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

1st Regular Meeting of the NCI-Frederick Advisory Committee (NFAC)
January 25, 2012

Summary Report

Executive Boardroom
NCI-Frederick Conference Center, Fort Detrick
Frederick, Maryland

National Cancer Institute
1st Regular Meeting of the NCI-Frederick Advisory Committee (NFAC)
January 25, 2012

Summary Report

The NCI-Frederick Advisory Committee (NFAC) convened for its 1st regular meeting on 25 January 2012, in the Executive Boardroom, NCI-Frederick Conference Center, Fort Detrick, Frederick, MD. Dr. Zach W. Hall, President Emeritus, Institute for Regenerative Medicine, University of California, San Francisco, CA, presided during the meeting. The meeting was open to the public 25 January 2012 from 10:30 a.m. to 3:56 p.m.

NFAC Members

Dr. Zach W. Hall (Chair)
Dr. J. Carl Barrett
Dr. David Botstein
Dr. Levi A. Garraway
Dr. Joe W. Gray (absent)
Dr. Beatrice H. Hahn
Dr. Monica J. Justice
Dr. Thomas A. Look
Dr. Lawrence J. Marnett
Dr. Jill P. Mesirov
Dr. Garry P. Nolan (absent)
Dr. Kenneth Olden
Dr. Jennifer A. Pietenpol
Dr. Steven T. Rosen* (absent)
Dr. Cheryl Willman

Ex Officio Members

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

Executive Secretary

Dr. Thomas M. Vollberg

* pending appointment

Table of Contents

I.	Opening Remarks—Drs. Zach W. Hall and Harold Varmus	1
II.	Division of Cancer Epidemiology and Genetics (DCEG) Core Genotyping Facility— Dr. Stephen Chanock	1
III.	Overview of NCI-Frederick Support to NIAID—Dr. H. Clifford Lane.....	3
IV.	Working Lunch/Open Discussion—Dr. Zach W. Hall	4
V.	The Life Cycle of Programs at the NCI-Frederick—Drs. Craig W. Reynolds, Piotr Grodzinski, James Doroshow, and Robert H. Wilttrout.....	5
VI.	Building Public/Private Partnerships—Dr. David C. Heimbrook.....	7
	External Website Overview—Ms. Julie Hartman	9
VII.	AIDS and Cancer Virus Program (ACVP)—Dr. Jeff Lifson	9
VIII.	Discussion and Next Steps—Dr. Zach W. Hall	11
IX.	Adjournment—Dr. Zach W. Hall	12

I. OPENING REMARKS

Drs. Zach W. Hall and Harold Varmus

Dr. Zach W. Hall, Chair, called to order the 1st regular meeting of the NFAC and welcomed the Committee members. He reminded Committee members of the conflict-of-interest guidelines and confidentiality requirements and thanked staff who arranged the Committee's tour of the NCI-Frederick facilities.

Dr. Harold Varmus, Director, welcomed and expressed appreciation to members for their willingness to advise about the NCI-Frederick enterprise, which is the sole Federally Funded Research and Development Center (FFRDC) laboratory housed within the Department of Health and Human Services (HHS). Dr. Varmus said that the NCI-Frederick enterprise provides an opportunity to reduce barriers between the intramural and extramural research communities, particularly with contract help from Dr. David Heimbrook, CEO of SAIC-Frederick.

Dr. Varmus reviewed suggestions that were stated during NFAC's orientation meeting, including the development of a strategic plan for NCI-Frederick. He encouraged members to consider how NCI-Frederick is uniquely qualified to advance NCI's mission, including its work in cancer cells and genetics and clinical applications, as well as to review the list of NCI-Frederick's activities that will be posted online. The NCI leadership retreat, which included several extramural participants, discussed whether there are activities that can be conducted only at NCI-Frederick. Other important considerations are how the NCI-Frederick laboratories can better serve the extramural community, including the Cancer Centers, and the need for more effective branding and identification similar to that of other national laboratories with a strong contract basis. Dr. Varmus referred to the Howard Hughes Medical Institute's Janelia Farm as an example of a facility that provides unique biomedical services.

II. DIVISION OF CANCER EPIDEMIOLOGY AND GENETICS (DCEG) CORE GENOTYPING FACILITY

Dr. Stephen Chanock

Dr. Stephen Chanock, Chief, Laboratory of Translational Genomics, and Director, Core Genotyping Facility (CGF), Division of Cancer Epidemiology and Genetics (DCEG), presented the CGF as a dedicated facility that has evolved into a successful program. Located at the Advanced Technology Center in Gaithersburg, MD, and affiliated with the FFRDC operated by SAIC-Frederick, the CGF was established by the NCI approximately a decade ago. Its mission is to conduct high-quality molecular epidemiology studies and provide educational opportunities in genetic analysis through courses and seminars. The emphasis of molecular epidemiology studies is on germline contributions to risk and gene-environment interactions, with a recent transition to germline/somatic interactions and interactions of somatic alterations with environmental risk factors. Milestones of the CGF have progressed from 2001 to the present from candidate SNP functional data to population-based whole-genome sequencing. It has evolved into a successful, highly productive program. The CGF has adequate laboratory space (4,618 ft²) optimized for genomics workflows, as well as dry-lab offices (1,615 ft²), on-site storage data (105 ft²), and additional cryogenic storage (145 ft²).

Dr. Chanock described the CGF core operations, which go beyond sequencing to collaboration and innovation. This is an aspect of the CGF that takes it beyond its original designation as a facility for sequencing. The advantages of affiliating the CGF with the NCI-Frederick are: the opportunities for close collaboration between NCI investigators and SAIC-Frederick experts; close monitoring by the NCI to ensure that milestones are met; and the opportunity to drive scientific challenges within the partnership. The CGF has a nimble organizational structure that allows resources and scientists to be quickly shifted to areas of need. The ability of the CGF to stay ahead of the science of epidemiology and genetics is illustrated by the more than 550 publications produced from CGF initiatives, many in high-impact journals. The breadth of these publications shows that the CGF has been able to adapt to changing technologies, analytic tools,

and other factors that are required to stay in the lead in this important field. Review of CGF operations is ongoing and includes those from every level of operation to guarantee critical review of projects. Dr. Chanock described the review processes, including a Genotyping Review Committee and a Laboratory Information Management System (LIMS) to track all laboratory processes, store genomic and related laboratory data, and provide web-based access to data throughout CGF laboratory processes. Quality-control measures are built into each step of the operation's organization. The use of open-source codes facilitates cooperation with the wider scientific community and assists in developing outside partnerships.

Dr. Chanock reviewed the data information technology infrastructure available to the CGF and noted the challenges in collecting and storing large amounts of data over the long term, particularly handling the results of genome-wide association studies (GWAS) and new generation sequencing. Currently, approximately 80,000 GWAS SNP scans have been conducted and are stored within the CGF data center for analyses. These data allow researchers to look across many cancers and factors, such as body mass index and smoking, to find gene/disease associations, as well as gene variations to allow identification of subgroups and risk of disease. Recent results from these data include the identification of large scale mosaic aneuploidy in approximately one to two percent of the older population in the 57,000 genomes scanned in blood and buccal swabs.

The CGF has faced administrative challenges in the past few years, the most recent being during a 2007 reorganization in which it was placed in the ATP during which time a series of diversions and restrictions were imposed. By 2009, the CGF was placed back under the SAIC Research Administration, where it now resides. Another recent challenge was a sample handling bottleneck resulting from quality control issues that caused production delays at DNA Extraction and Sample Handling Laboratory (DESL); this was corrected in 2011, when the stand-alone service laboratory DESL, was integrated into the CGF.

The current focus of activities for the CGF includes redirecting the role of GWAS for less common diseases with limited biospecimens; completing the understanding of the contribution of common variants to cancer risk; and using denser arrays for less common variations. In addition, exome and whole-genome sequencing will be conducted for the Family and Special Population Analysis, with follow-up in families and unrelated participants. Challenges include the complete transition from GWAS to sequencing for the investigation of germ-line susceptibility, further integration of environmental exposures, and optimal storage, processing, and mining of whole-genome sequence data.

In the discussion, the following points were made:

- Integration of the sequencing and data centers is unique to the CGF and allows the scientists generating the data and those analyzing the data to work collaboratively.
- The term “core facility” may be misapplied to the CGF at this point, and because of integration of CGF programs, it may be reasonable to consider a change in designation to more accurately designate its functions.
- There is a need to expand data collection capacity in the next six months to take advantage of data collection from emerging technologies.
- Members encouraged the NCI to consider capturing information on environmental exposures to determine connections between exposure history and somatic mutations.
- One of the main challenges is data sharing with the extramural genomic community, which CGF/DCEG does by placing published GWAS on the database of Genotypes and Phenotypes (dbGaP). There is a need to expand this effort and to develop guidelines that address how to allow access to sequencing data, what users need access, how users intend to apply the data, and how to obtain consent for use of the data.

- The use of cohorts should be catalogued, and a list of cohorts established within the NCI should be prepared.
- Building on the growing interests in epigenetic markers, the CGF should generate data for markers of exposure over the course of a lifetime.

III. OVERVIEW OF NCI-FREDERICK SUPPORT TO NIAID

Dr. H. Clifford Lane

Dr. H. Clifford Lane, Deputy Director for Clinical Research and Special Projects, National Institute of Allergy and Infectious Diseases (NIAID), told members that NCI-Frederick is a critical component of NIAID's clinical research efforts, and many NIAID divisions benefit from the wide array of support activities of NCI-Frederick. NCI-Frederick supports the NIAID mandate to maintain a robust basic and applied research portfolio in microbiology, infectious diseases, and immunology, and to respond rapidly to new and emerging disease threats. An advantage provided by NCI-Frederick is its ability to hire personnel with proven expertise quickly. Dr. Lane said that the consistency, flexibility, and rapid response time have been key factors in NIAID's selection of NCI-Frederick for specific activities. NIAID's intramural projects supported by NCI-Frederick are subject to normal review mechanisms.

NCI-Frederick provides the NIAID with clinical research infrastructure assistance and has been instrumental in improving clinical protocol development. NIAID intramural investigators were surveyed to rate barriers to efficient clinical research, and focus groups determined that the clinical research support services provided to investigators were inadequate to meet the complex demands of clinical research. In response to this need, NCI-Frederick and the NIAID developed a Protocol Development Program (PDP) to navigate the multitude of requirements and generate protocols as quickly as possible. NCI-Frederick also supported NIAID's clinical research investigating IL-15, which is an important cytokine in oncology and infectious disease due to its potent induction of T-cell expansion and differentiation. NCI-Frederick produced a large quantity of clinical-grade IL-15, which is being used in intramural and extramural studies. Notably, in one such study performed at NCI-Frederick, peripheral T-cell levels increased 100-fold in healthy primates given injections of IL-15.

Dr. Lane said that NCI-Frederick also has provided support for NIAID Special Projects, which are critical and urgent research needs identified by the NIAID Director. The H1N1 pandemic occurred in 2009, creating a crucial need for prospective cohort data. Following the Centers for Disease Control and Prevention's (CDC) request for assistance, the NIAID solicited support from NCI-Frederick, and within 2 months a protocol was written and the first patients were enrolled in a multinational study to monitor influenza incidence in real time. The NIAID also identified the biomarker D-dimer as a strong predictor of negative outcome from influenza, facilitated in part by the robust biospecimen repository housed at NCI-Frederick.

NIAID Special Projects often involve international governments. The Mexican government requested that the NIAID perform an observational and therapy trial, which is being supported by NCI-Frederick, in response to an outbreak of H1N1. NCI-Frederick also is providing laboratory support to monitor the incidence of influenza-like illness in Mexico over time. In the Phidisa Special Project, South African leadership requested that research be conducted to confirm the cause of illness in the military and justify treatments. NCI-Frederick performed a study to investigate different treatment regimes in a large South African cohort. The results from this study proved the effectiveness of standard therapies to the South African government. NCI-Frederick also is supporting the DC Partnership for AIDS Progress to evaluate observational data to inform clinical practices.

In the discussion, the following points were made:

- NCI-Frederick provides added value to NIH Institutes and Centers (ICs) through its ability to streamline approval processes for intramural protocols. Metrics to measure the success of NCI-Frederick are being collected; preliminary results suggest a dramatic decrease in investigator frustration since the implementation of the PDP.
- Working with the NCI-F FFRDC contractor (currently SAIC-Frederick) increases efficiency through mechanisms that vary by project. The FFRDC flexibility facilitates the hiring of additional people or redeployment of a large workforce, as needed to respond to meet urgent requests. The cost is offset somewhat by the contractor's flexibility and rapid response capabilities. A decision to utilize the FFRDC to accomplish a goal follows a determination that the project cannot be accomplished effectively through other mechanisms.
- NCI-Frederick positively influences the culture of the closely integrated intramural NCI program, particularly in terms of innovation.
- NCI-Frederick provides significant help in organizing clinical trials for the NIAID and NCI intramural research program and is particularly well suited for creative opportunities to their clinical programs.
- The NCI-Frederick FFRDC includes special capabilities, such as the Nanotechnology Characterization Laboratory, that are sought out and utilized to support projects from intramural programs of other NIH ICs and other government agencies.
- The non-human primates (NHPs) referenced by Dr. Lane are not housed at NCI-Frederick, but the studies are performed under a contract managed by NCI-Frederick.

IV. WORKING LUNCH/OPEN DISCUSSION

Dr. Hall led a discussion about a revised name for the NCI-Frederick enterprise. He noted the current issues of low visibility for the NCI-Frederick enterprise and confusion about its activities among the general community. Dr. Hall said that the key words to discuss are: national laboratory, Frederick, and cancer. Two suggested names focus on the location in which the activity occurs: 1) Frederick National Laboratory for Cancer Research, 2) Frederick National Cancer Laboratories.

In the discussion, the following points were made:

- Members noted that the NCI brand brings political and national benefits but might not adequately distinguish between NCI-Frederick activities and other NCI programs. Members supported the inclusion of "cancer" in the title but cautioned that this may convey a narrow focus and discourage use by other NIH ICs. Consensus existed for use of "Cancer" in the name.
- Members debated the use of "national laboratory" versus "NCI" in the name. The term "National" will enhance the perception of NCI-Frederick as a national resource. However, because many facilities named "National Laboratory" are Department of Energy (DoE) FFRDCs use of "National Laboratory" could cause confusion if NCI or cancer is not included in the name.
- Members discussed that "Frederick" is already accepted as a short-hand identifier for the NCI-Frederick FFRDC and supported inclusion of the location name "Frederick" as the initial word of the name.

V. THE LIFE CYCLE OF PROGRAMS AT THE NCI-FREDERICK

Drs. Craig W. Reynolds, Piotr Grodzinski, James Doroshow, and Robert H. Wiltrout

Overview. Dr. Craig W. Reynolds, Associate Director, provided an overview of how new programs begin in NCI-Frederick. He informed members that NCI Divisions, Offices, and Centers develop the concepts, obtain input from NCI-Frederick staff, and provide funding for the programs. The NCI-Frederick project and contracting officers receive requests to initiate new programs through an electronic request system called “Yellow Tasks.” They consider whether the requested task would be completed most effectively through the FFRDC or a grant or contract mechanism, as well as the project scope and proposed costs. Specifically, they consider whether the project could serve as a national resource, requires very close collaboration with the contractor, and depends on a long-term relationship with contract employees to ensure flexible and rapid response capabilities. If the project meets these parameters, the NCI project and contracting officers and the contractor then discuss the project structure and their respective roles in implementation and overview. It is the contractor’s responsibility to perform the task and manage any outsourced activities.

Dr. Reynolds said that the NCI Divisions, Offices, and Centers monitor the dedicated research programs that they sponsor. The NCI-Frederick Office of Scientific Operations monitors shared-service programs, including the Advanced Technology Program (ATP), AIDS and Cancer Virus Program (ACVP), and Laboratory Animal Sciences Program (LASP). Dr. Reynolds said that the shared-service programs are reviewed; either annually (select parts of the LASP), on a 3-year cycle (ATP), or on a 4-year cycle (ACVP). Reviews are conducted by outside experts (LASP), a combination of outside experts and NCI/NIH principal investigators (ATP), or the NCI Board of Scientific Counselors (ACVP). The ATP review covers core services and their unique value to the NCI as well as administrative costs, personnel, and technology development. Dr. Reynolds next introduced the speakers who described several dedicated research programs at NCI-Frederick: Drs. Piotr Grodzinski, Director, Office of Cancer Nanotechnology Research, Center for Strategic Scientific Initiatives, Office of the Director; James Doroshow, Deputy Director for Clinical and Translational Research; and Robert H. Wiltrout, Director, Center for Cancer Research (CCR).

Nanotechnology Characterization Laboratory (NCL): Foundation, Operation, Scientific Output, and Peer Review. Dr. Grodzinski said that the NCL has become a highly respected national resource for the evaluation of nanomaterials to be used in new diagnostics and therapeutics. Established in 2004 as an interagency collaboration among the NCI, National Institute of Standards and Technology (NIST), and U.S. Food and Drug Administration (FDA) in response to the needs of the emerging nanotechnology field, NCL’s budget is located within the Alliance for Nanotechnology in Cancer program. The NCL performs preclinical characterization of nanomaterials, such as physiochemical characterization, *in vitro* experiments, and *in vivo* testing in animal studies for safety and efficacy; 90 percent of its efforts support the extramural community. It also develops standard formats as well as materials and data to share with the community.

During the past seven years, the NCL has characterized more than 250 candidate nanotechnology formulations, some of which are being used in clinical trials. The laboratory conducts approximately 20 animal studies and releases 10 publications each year. It collaborates with other government agencies, such as providing support for National Institute of Environmental Health Sciences (NIEHS) center grants on nanotechnology health implications research, including the characterization and safety review of nanomaterials. In addition, the NCL has worked with NIST to develop reference materials and with ASTM International and the International Organization for Standardization (ISO) to develop standards for nanomaterial characterization.

The NCL has examined various parameters of materials in specific studies to help develop design guidelines for nanoparticles for therapeutic application. Dr. Grodzinski showed the collective results charting the dependence between particle size, charge, hydrophobicity, and operation in different modes of biocompatibility, and then stated that this information can be predictive for developing nanoparticles with

characteristics that are most appropriate for the delivery and release in particular circumstances, such as the uptake and passage of a nanomaterial from the blood stream through the endoplasmic reticulum. In addition, a joint study with the FDA examined the dermal penetration of TiO₂, which is used in sunblock lotions, to determine if it can pass into the bloodstream. Transmission electron microscopy (TEM) and energy dispersive X-ray (EDX) technologies were used to scan for the presence of TiO₂ but showed no penetration beyond the stratum corneum (the upper part of the skin) and no elevated titanium levels in the lymph nodes or liver. In another study, the NCL examined gold nanoshells, which is a material composed of gold and silica that is used for localized hyperthermia. The nanoshells are heated locally through microabsorption of the appropriate wave length to improve circulation times. The NCL evaluated two sets of material that came from the same laboratory but were behaving differently: the first batch had more toxic effects on the animals, whereas the second batch was largely benign. Extensive characterization showed identical physicochemical characterization but differences in protein binding that were determined to be based on variation in the polyethylene glycol (PEG) coating. Based on this finding, the NCL developed a “lot release” PEG gel assay.

Dr. Grodzinski said that NCL oversight is provided by a Scientific Oversight Committee, which conducts annual reviews of the program. Additional input is obtained from external experts in nanotechnology as well as other extramural investigators. Trends and advances in NCL characterization are shared with the research community through an annual two-day workshop at the NIH and shorter seminars at the FDA and universities. Extramural applications for projects undergo careful review; approximately one-half of the 40 projects submitted to the NCL in 2011 were accepted. Dr. Grodzinski noted that the NCL supports the extramural community as an independent and objective resource and it will be a key player in establishing relationships with industry within the future ATRF.

Life Cycle of an Investigational Biologic and Biologics Production at NCI-Frederick.

Dr. Doroshov described the scope, evolving priorities, and future of investigational biologics and biologics production at NCI-Frederick. The NCI Experimental Therapeutics (NExT) program supports therapeutic and diagnostic discovery and development, with nearly all NExT-supported biologics activities conducted at NCI-Frederick. Immunotherapeutics, including gene vectors and antibodies, comprise 40 percent of the NExT portfolio. Most NExT applications are received from academia and small pharmaceutical companies, and funding is highly selective, with only four to five applications reaching the higher tier out of the approximately 30 to 35 submitted per funding cycle. The number of projects funded dropped from 30, as of four years ago, to the current level of fourteen as a result of ongoing prioritization efforts by a working group composed of academics and members of industry.

The prioritization process is based on scientific merit, feasibility, relevance to NCI mission, novelty and clinical need. For biologics, the focus is on the needs of the immunotherapy community for agents to supply clinical trials. Examples of the changing priorities of the biologics portfolio based on evaluations by the working group include: the closure of the CMV vaccine because of development problems that could not be overcome, and placing a high priority project for interleukin (IL)-7 on hold because of rekindled commercial interest in production of the cytokine.

Oversight of the NCI-Frederick Biologics Facility occurs through both internal and external review. These reviews include daily interactions between the NCI and SAIC-Frederick staff and leadership, monthly budget and project reports, and annual budget assessments, which in FY 2011 identified budgetary issues as well as the need to reduce the number of agents in development and focus on producing sufficient quantities for clinical trials. A subsequent external review of the Biopharmaceutical Development Program (BDP) concluded that staffing should be decreased, projects costs should be reduced by outsourcing project development and funding only those projects that require NCI manufacturing, and space requirements should be re-evaluated.

Mechanisms for CCR Program Change at NCI-Frederick. Dr. Wiltout summarized the history and current use of the review process as a mechanism for program change at NCI-Frederick. The CCR

program research is distributed primarily between the Bethesda and Frederick campuses, with the CCR providing 20 percent of NCI-Frederick's funding. NCI-Frederick research quality is ensured by multiple review mechanisms, including *ad hoc* external review by the National Cancer Advisory Board (NCAB) and NCI Divisions, extramural BSC review, and intramural and extramural core services review. The Bishop-Calabresi report in 1998 was the product of an NCAB *ad hoc* review and resulted in the reorganization and realignment of the components of the NCI-Frederick research program into intramural and extramural divisions (the Division of Basic Sciences [DBS] and Division of Clinical Sciences [DCS], respectively). In 2001, DBS activities in Frederick and Bethesda as well as the DCS (Division of Clinical Sciences) were reorganized and brought together in the CCR.

The BSC process, a quadrennial retrospective and prospective review by extramural scientists, drives high-quality, cost-effective research and encourages high-risk approaches at the CCR. The BSC evaluates programs and individual PIs, providing recommendations that the science directors use to guide reconfigurations of resources and staffing. Past staffing changes allowed hiring in tenure track positions that increased the gender diversity of staffing at the CCR and NCI-Frederick. In addition, BSC recommendations led to the creation of new laboratories and branches at NCI-Frederick, including the sequencing and bioinformatics cores, as well as several closings.

Program changes allow NCI-Frederick to capitalize on research strengths and advance new initiatives. New directions in scientific research include the Cancer Inflammation Program (CIP), formed in 2005 and led by Dr. Giorgio Trinchieri, which has fostered close collaborations within the CCR and benefited from NCI-Frederick's expertise in mouse models. The Center for Advanced Preclinical Research (CAPR), formed in 2008 as a national resource for early-stage, preclinical testing of candidate drugs, has accelerated screening and development of cancer drugs and biomarkers. Dr. Wiltout observed that business plans for five potential extramural partnerships with CAPR have been drafted, fulfilling expectations that CAPR will be a national resource funded largely through extramural outreach.

In the discussion, the following points were made:

- In terms of support to the biomedical research and public health communities outside the NCI, NCI-Frederick provides services to the Departments of Defense, Energy, and Homeland Security and other federal agencies through the ATP and to other NIH and extramural investigators through the ACVP.
- The LASP program and Charles River facility are distinct in their provision of animals for the intramural and extramural communities, respectively. The Charles River laboratory was an integrated part of NCI-Frederick at one time but is now separate.
- Synergies among NCI-Frederick laboratories are possible that will provide a national resource and avoid resource duplication in advancing cancer research. For instance, opportunity for synergism between the NCL, NExT and CAPR exists in the integration of mouse models into evaluations of antibodies, nanotherapeutics and nanotechnology devices. Partnerships with nanotechnology manufacturers could facilitate production, storage, and availability of needed nanomaterials.
- The CAPR provides some murine model support for the extramural community. Members encouraged the NCI to provide online a list of the genetically engineered mouse models (GEMM) being deployed at NCI-Frederick.

VI. BUILDING PUBLIC/PRIVATE PARTNERSHIPS

Dr. David C. Heimbrook

Dr. Heimbrook described the Advanced Technology Partnerships Initiative (ATPI), which aims to accelerate translational research and development in cancer and AIDS. The NCI established the ATPI

concept in 2007 to promote technological, biological, diagnostic, and other partnerships between the public and private sectors. Mechanisms used to facilitate collaborations include: the material transfer agreement (MTA), β -testing agreement, collaboration agreement, cooperative research and development agreement (CRADA), “umbrella” (multiple laboratory) CRADA, and clinical trial CRADA. Through December 2011, the ATPI formed 110 partnerships, mostly with biotechnology firms, including 68 MTAs, 28 collaboration agreements, six β -testing agreements, seven NCI CRADAs, and one NCI umbrella CRADA.

Examples of successful collaborations include an interagency agreement with the NIEHS to provide physicochemical characterization for nanomaterial risk and hazard assessment studies; through this partnership, the NCL provides key infrastructure support for NIEHS’ nanotechnology centers of excellence and is characterizing 12 nanomaterials (e.g., cerium dioxide, nanosilver, and carbon nanotubes) per year. In addition, Sporian[®] Microsystems, Inc., the FDA, and SAIC-Frederick worked together in a collaboration agreement to provide a proof-of-concept HIV detection assay for testing in remote regions.

Dr. Heimbrook reminded members that CRADAs are relied on to make government facilities, intellectual property (IP), and expertise available to collaborating partners to advance the development of scientific and technological knowledge and products. In addition, the Materials CRADA (M-CRADA) involves the transfer of proprietary material to the NIH laboratory where minimal collaboration is intended. He said that SAIC-Frederick scientists currently can enter into external CRADAs only through existing NCI agreements under scope, timing, and IP parameters set by NIH policy.

SAIC-Frederick’s CRADA partnerships currently include: the feasibility evaluation of General Electric’s proprietary nanoparticle diagnostic imaging agents; and cancer modeling and mechanism of action studies with Amplimmune through an umbrella CRADA to advance AMP-224 and AMP-110 into the clinical setting. Dr. Heimbrook noted as a result of this collaboration, Amplimmune tested product candidates in otherwise inaccessible infectious disease models as well as novel therapeutic combinations; the company also refined its understanding of the AMP-224 mechanism and has co-submitted several manuscripts for publication.

Dr. Heimbrook pointed out that FFRDCs are permitted to have their own CRADA programs, called the “Contractor-CRADA.” Whereas the Department of Energy’s FFRDCs utilize the Contractor-CRADA frequently to expand access to their technology and expertise, SAIC-Frederick does not have an independent CRADA program. He reviewed the contractual changes needed to enable the Contractor-CRADA for SAIC-Frederick, including modification of the DEC Amendment, work flow proposals and draft CRADA templates. These changes are currently in Government review. Under the Contractor-CRADA, support for ongoing government programs will remain the priority; full CRADA authority will be provided to SAIC-Frederick, including M-CRADAs and other collaborations; IP rights will be clearly defined, with royalty streams supporting the FFRDC research and development efforts; and processes will be put in place that emphasize speed and incorporate local government review. The Contractor-CRADA expands extramural and commercial access to NCI-Frederick science and expertise, facilitates cost recovery, and supports the October 28, 2011, Presidential Memorandum on accelerating technology transfer and commercialization of federal research. Dr. Heimbrook also reviewed potential partnerships under discussion, such as work with the U.S. Forest Service on nanocrystalline cellulose as an alternative nanomaterial to carbon nanotubes, and the timeline for outreach efforts.

In the discussion, the following points were made:

- Dr. Hall reported for the record a resolution which passed during the orientation and introductory session for the NCI-Frederick Advisory Committee on August 31, 2011. Presentations included information on CRADAs and the use of “Contractor-CRADAs” at other FFRDCs. Those present on August 31st felt strongly about providing an indication of support for availability of the Contractor-CRADA. A resolution, “By resolution, strong endorsement is given for the importance and

potential usefulness of the Contractor-Cooperative Research and Development Agreement (Contractor-CRADA).”, was proposed and was passed unanimously.

- The Contractor-CRADA would cover NCI-Frederick activities that do not involve the NCI employees; any involvement by the government requires a government CRADA. Review and approval procedures for acceptance of new projects are being developed. The NCI is involved in the review and approval process to establish that new projects meet the mission and represent excess work capacity
- Members expressed unanimous support for the Contractor-CRADA and requested further details at a future meeting about the processes for scientific oversight, ensuring the fit of new programs within the NCI-Frederick portfolio, and other appropriate aspects to demonstrate how the CRADA program will operate.
- The extramural partner or another independent resource will provide funding for projects conducted through the Contractor-CRADA. Federal grant funds might be used in certain circumstances to cover the costs of requested services under a Contractor-CRADA arrangement; leadership in the NCI and SAIC-Frederick will provide clarification about this issue in the future.
- SAIC-Frederick is considering a technology transfer mechanism and business development office to help manage intellectual property (IP) rights and revenue streams; any royalty revenue from IP rights of SAIC-Frederick that result from these arrangements will be directed back to the FFRDC.

External Website Overview

Ms. Julie Hartman

Ms. Julie Hartman, Education Program Specialist, Office of Scientific Operations, Office of the Director, NCI-Frederick, provided a brief overview of the draft external website that presents the NCI-Frederick as a national resource. The website describes products, services, and collaboration opportunities available to extramural investigators. It includes multiple entry points to doing business with NCI-Frederick, including technology transfer, partnership and collaboration, and working with NCI-Frederick, as well as specific products and services. The Office of Communications will conduct a user’s test, and the website will be made publically accessible following the establishment of the Contractor-CRADA. Dr. Hall said that several NFAC members have agreed to serve on a committee to provide final review of the website.

In the discussion, the following points were made:

- The website should provide a clear explanation of NCI-Frederick and present the broad scope of NCI-Frederick activities without overemphasis of translational work. The home page should describe the mission, provide quick links to NCI-Frederick scientists and programs, and meet the intended audience’s needs.
- Members should send additional comments to Ms. Hartmann.

VII. AIDS AND CANCER VIRUS PROGRAM

Dr. Jeffrey D. Lifson

Dr. Jeffrey D. Lifson, Senior Principal Scientist and Director, AIDS and Cancer Virus Program (ACVP), provided an overview of the ACVP, which conducts multidisciplinary research in basic and applied virology to improve the diagnosis, treatment, and prevention of HIV/AIDS and infections with cancer-associated viruses. The ACVP is comprised of seven research sections and eight research support

cores that provide unique reagents and other research materials and provide a variety of specialized analytical capabilities to the research community. Through highly interactive, complementary, and extensive collaborative relationships with other NCI, NIH, and extramural investigators, the ACVP achieves synergistic research advances.

Dr. Lifson described several research projects illustrating the success of the ACVP in advancing the field of viral research and facilitating extramural studies. One ongoing study investigates the mechanism of mucosal transmission of HIV by studying simian immunodeficiency virus (SIV) in macaques to determine the kinetics of viral infection and the route of viral progression. A series of synonymous point mutations was introduced into infectious molecular clones of SIVmac239, allowing sequence-based tracking of distinct variants. The viruses were mixed equally and introduced into macaques through atraumatic vaginal challenge. Comprehensive tissue analysis monitored the viral load and defined the genetic composition of the virus present in different tissues over time. One macaque was found to contain as many as five SIVmac239 variants in vaginal and endocervix mucosal tissues within 5 days after inoculation, but showed no evidence of blood infection. The virus was found in the draining lymph nodes, and some distant lymph nodes, suggesting that the initial spread is lymphatic rather than hematogenous.

Another ACVP study in collaboration with Dr. Louis Picker, Oregon National Primate Research Center, examined the protective efficacy of effector T-cell inductive responses. Common “prime-boost” vaccines induce central memory immune responses, but the response time is too protracted for viruses such as HIV, which have high variation and replication kinetics. Investigators generated an immune response with pre-deployed effector T-cells by using recombinant rhesus CMV vectors, which produce broad and persistent T-cell responses. Control animals showed high levels of plasma viral load. Prime-boost treated animals showed a modest and transient decrease in peak viremia. Remarkably, after transient viremia, one-half of the animals inoculated with CMV vectors became and remained aviremic over time, even after *in vivo* depletion of CD8 T cells by monoclonal antibody treatment, suggesting a progressive clearance of virus. Ultrasensitive nested and quantitative PCR amplification techniques to detect SIV RNA demonstrated only extraordinarily low levels. These studies have exciting implications for future prophylactic and therapeutic vaccine modalities.

The ACVP is proactive in developing novel research methods, analytical techniques, and reagents, and then providing materials, protocols, and support to the broader research community. Between 40 and 80 percent of certain resources developed internally are distributed to support the extramural research community. Dr. Lifson said that improved implementation of the M-CRADA and Contractor-CRADA mechanisms to expand and facilitate support will assist other investigators and promote research progress.

In the discussion, the following points were made:

- The ACVP limits its use of non-human primate (NHP) subjects to studies for which there are no other effective ways to address important research questions. NHP work for the ACVP is conducted at the NCI NHP facility on the Bethesda campus or at collaborating institutions.
- Principal investigators and core service activities within the ACVP are reviewed every four years for their innovation, quality of work, and service provided to the community, using the same Site Visit Review mechanism employed for NCI Principal Investigators.
- Dr. Lifson said that his interest in coming to NCI-Frederick was based on collaborative opportunities and infrastructure not necessarily available to other intramural researchers and that his career would otherwise likely have been in academia.
- Although many in the extramural community are interested in using reagents developed by NCI intramural investigators, such as human papillomavirus (HPV) vaccines, there has not been a mechanism by which to conduct assays except through NCI-Frederick; the Contractor-CRADA

offers a fee-for-service mechanism that will fill this need. In addition, a benefit of the ACVP and other NCI-Frederick programs is that a single laboratory can conduct the same assay in support of other research laboratories and in a way that provides efficiency and consistent results.

- Future research in central memory versus effector memory responses will be important to better understand the mechanism of sustained aviremia induced by effector T-cells. In addition, the effector T-cell project provides exciting proof-of-concept, but research is at an early stage and clinical development has not begun.

VIII. DISCUSSION AND NEXT STEPS

Dr. Zach W. Hall

Dr. Hall led a discussion about other business and future steps.

In the discussion, the following points were made:

- Members reached consensus to adjust the frequency and length of committee meetings to accommodate schedules and hold more in-depth discussions.
- NCI-Frederick should develop a publicity and marketing campaign regarding the Contractor-CRADA once it is approved and make preparations to handle a potential surge of interest from the extramural community.
- Future presentations to the NFAC about NCI-Frederick programs should include contextual information about how the program fits scientifically and fiscally within the NCI and Divisions, Offices, and Centers.
- NCI-Frederick should consider programs to allow distinguished scientists, extramural investigators, junior faculty, and technical staff = to visit and learn about NCI-Frederick's advanced technologies and capabilities through sabbatical periods and similar arrangements. NCI-Frederick leadership should keep the NFAC updated about its progress in establishing such programs.

RESOLUTION:

By resolution, the NFAC will meet in May 2012 and September 2012 for one day each and thenceforth twice a year for 1.5 days each.

- A motion to accept the resolution for the NFAC meeting schedule was approved unanimously.

IX. ADJOURNMENT

Dr. Zach W. Hall

Dr. Hall thanked the Committee members and other invitees for attending. There being no further business, the 1st regular meeting of the NFAC was adjourned at 3:56 p.m. on Wednesday, January 25, 2012.

Date

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

Date

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

DCEG Core Genotyping Facility

Stephen Chanock, M.D.

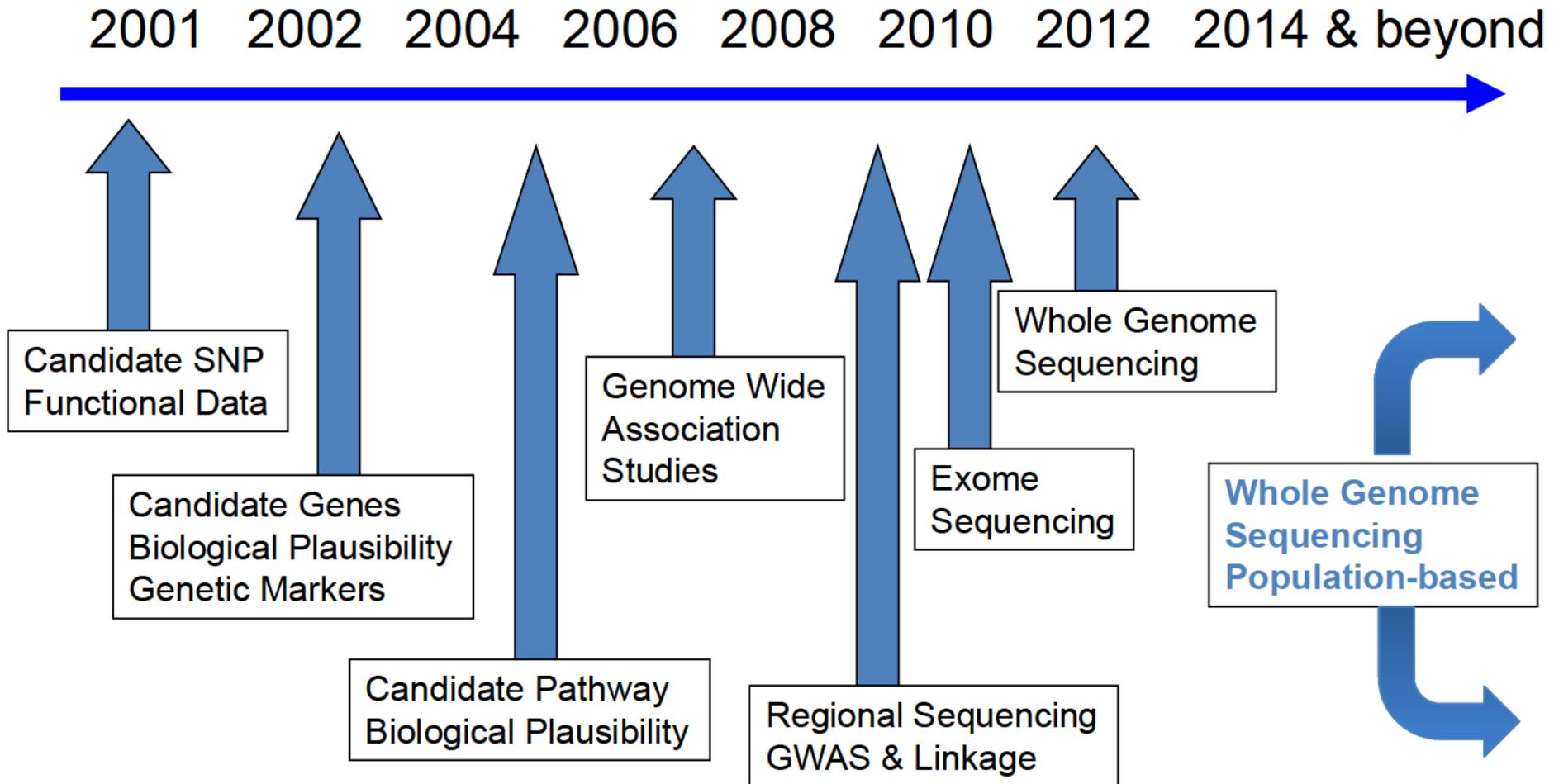
**Chief, Laboratory of Translational Genomics
Director, Core Genotyping Facility**

January 25, 2012

Mission of Core Genotyping Facility (CGF)

- Conduct of high quality molecular epidemiology studies
 - Emphasis on:
 - Germline contribution to risk
 - Gene-environment interactions
 - Transition to:
 - Germline/somatic interactions
 - Interaction of somatic alterations with environmental risk factors
- Education
 - Genetics analysis courses & seminars

Milestones at the Core Genotyping Facility



NATIONAL CANCER INSTITUTE
Division of Cancer Epidemiology and Genetics

Office of the Director
Joseph F. Fraumeni, Jr., M.D.
Director

Administrative Resource Center
Donna Siegle
Director, Office of Administrative Services,
DCEG

**Office of Communications
& Special Initiatives**
Catherine B. McClave, M.S.
Chief

Office of Education
Jackie A. Lavigne, Ph.D., M.P.H.
Chief

**Office of Division
Operations & Analysis**
Marianne K. Henderson, M.S.
Chief

**Epidemiology and
Biostatistics Program**
Robert N. Hoover, M.D., Sc.D.
Director

**Human Genetics
Program**
Margaret A. Tucker, M.D.
Director

Biostatistics Branch
Nilanjan Chatterjee, Ph.D.
Chief

**Hormonal & Reproductive
Epidemiology Branch**
Louise A. Brinton, Ph.D.
Chief

**Genetic
Epidemiology Branch**
Neil E. Caporaso, M.D.
Chief

**Clinical
Genetics Branch**
Mark H. Greene, M.D.
Chief

**Infections & Immuno-
Epidemiology Branch**
Allan Hildesheim, Ph.D.
Chief

**Nutritional
Epidemiology Branch**
Vacant

**NCI Core Genotyping
Facility**
Stephen J. Chanock, M.D.
Director

**Laboratory of
Translational Genomics**
Stephen J. Chanock, M.D.
Chief

**Occupational &
Environmental
Epidemiology Branch**
Debra T. Silverman, Sc.D.
Chief

**Radiation
Epidemiology Branch**
Martha S. Linet, M.D.
Chief

Office of Director of SAIC

Dedicated Support

Core Genotyping Facility (CGF) DNA
Extraction & Sample Handling (DESL)

Basic Research Program

Dedicated Support

Laboratory of Translational Genomics
Genetic Epidemiology Branch Laboratory

**DCEG Activities at the
Frederick Federal Research
and Development Center
(SAIC-F)**

Applied & Development Directories (ADD)

Dedicated Support

Repository Methods
Immunological Monitoring

Shared Services

Bioprocessing & Transformations
Repository Support

Advanced Technology Program

Shared Services

Lab of Molecular Technology
Laboratory of Proteomics & Analytical Technology
(LPAT Hormone Unit – dedicated to DCEG)

CGF Facilities Footprint

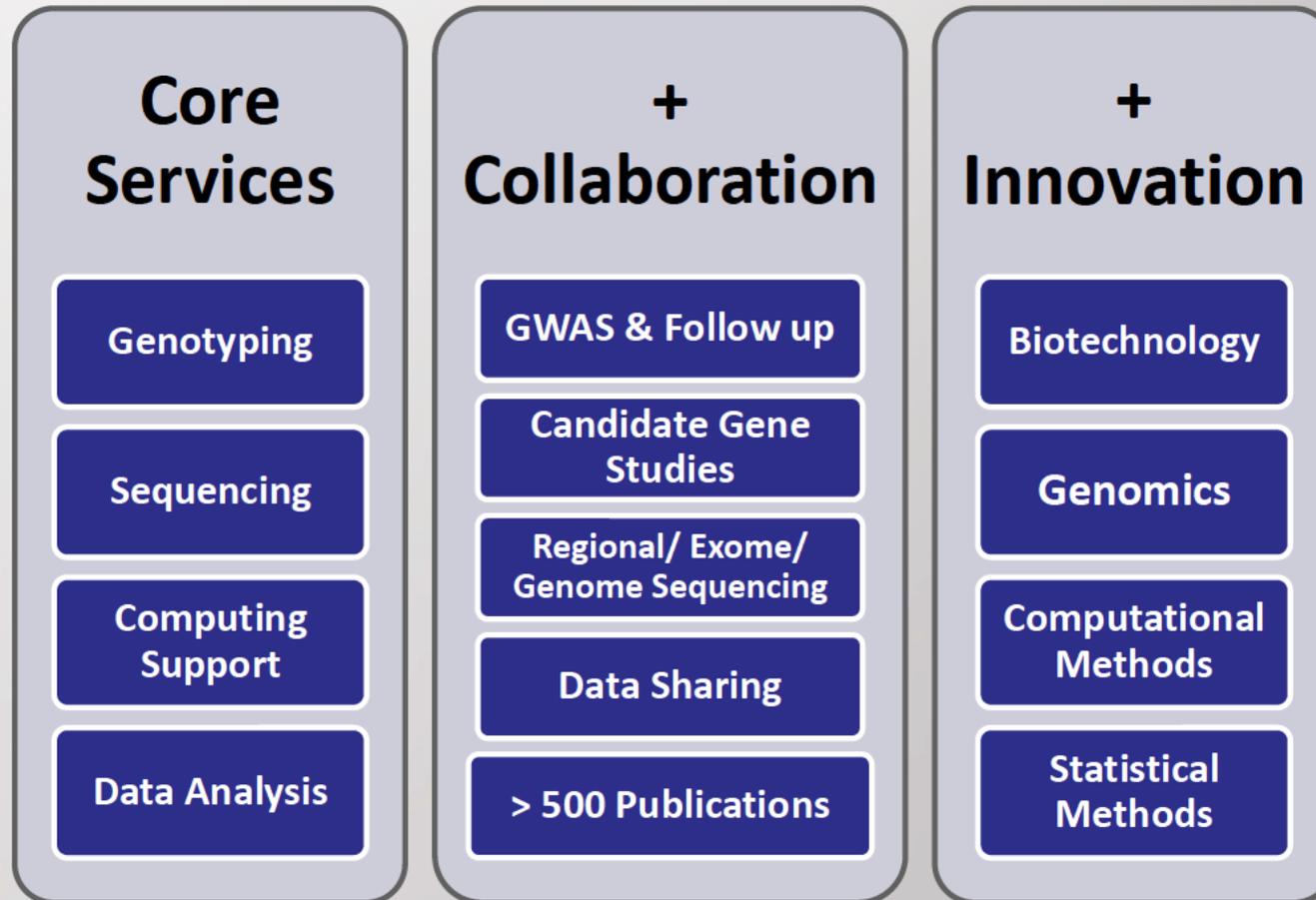
Advanced Technology Center: Gaithersburg



The Core Genotyping Facility

Dedicated DCEG Facility

What's in a name? Core Plus Plus





Meredith Yeager
Scientific Director

Amy Hutchinson
Operations &
Administration



DESL

Open
Production
Laboratory

- LIMS
- Genotyping
- Sequencing
- QA/QC
- Technology Transfer*

Joe Boland
Research &
Development



Kevin Jacobs
Bioinformatics &
Analysis



Investigation of Alternatives

- DCEG Conducted Molecular Epidemiology Pilot Study 2001-2003
 - 5 Companies asked to produce defined data sets
 - Common issues
 - Slow
 - Costly
 - Poor performance with QC
- Periodic reassessment of contract work
 - Loss of scientific ownership
 - Variability in deliverables

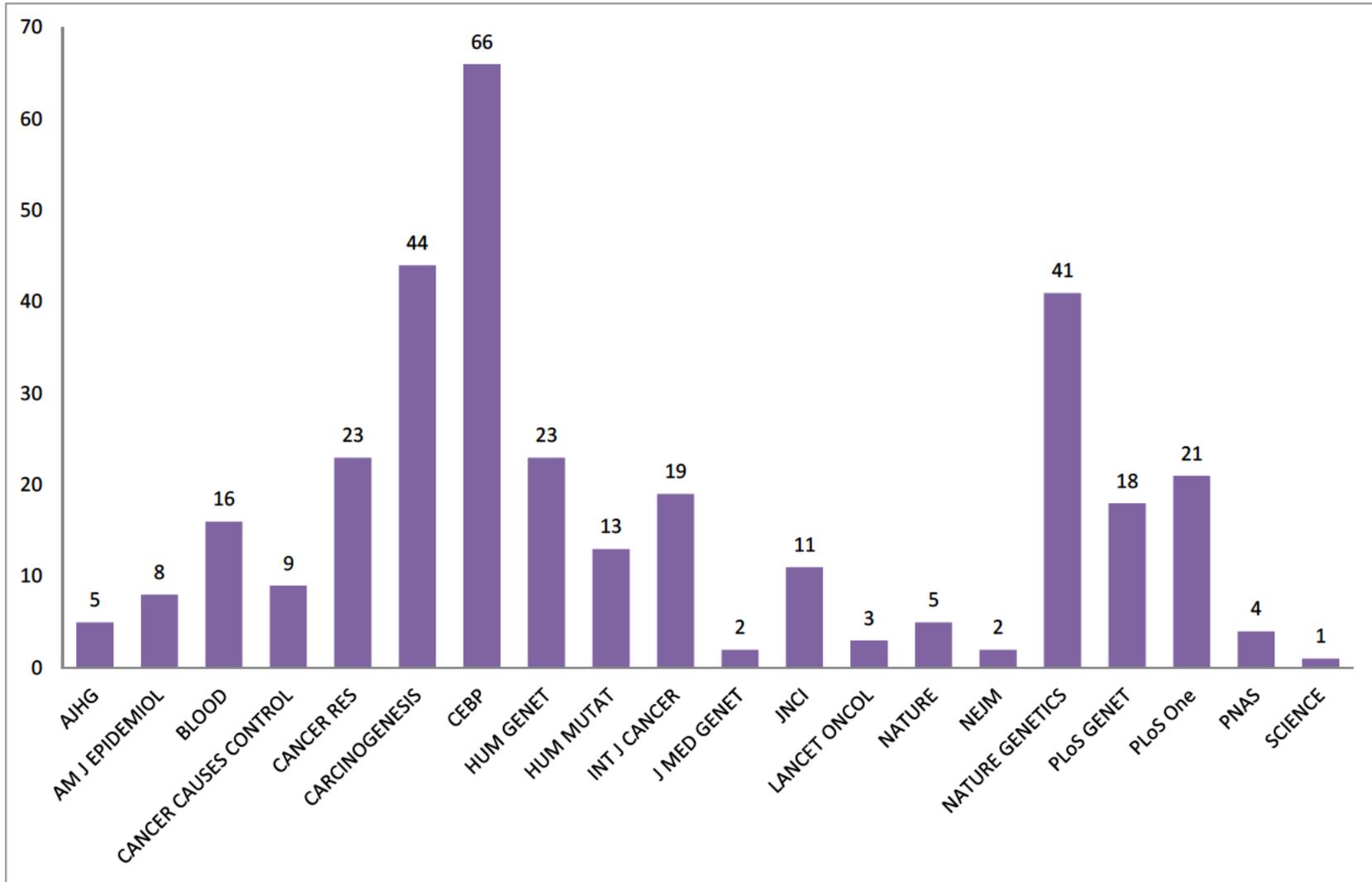
Value of creating CGF within FFRDC

- Close collaboration between NCI investigators and SAIC-F experts
- NCI can monitor every step and assess capacity to meet milestones
- Opportunity to drive scientific challenges in partnership
 - *Bridging Epidemiology and Genetics*

Nimble Personnel Structure

- Reorganization began with 9 SAIC FTEs
 - Reorganization and expansion 2002-2006
 - CGEMS funding for 5 additional analysts
- Current FTEs: 42
 - Shift from wet to dry positions in last 3 years
- Establish expertise for genetic analysis
 - Avoid “blackbox/blackhole” of contract
- Embed NCI oversight within SAIC work flow
 - Daily- no..... hourly discussions

536 CGF Publications for 2002-2011



Review of DCEG Projects for CGF

- Proposals discussed and approved by Branch Chiefs prior to submission
- Varies by scope & cost
 - Senior Leadership for Genomics Committee (SLGC) provides concept review for
 - GWAS chips
 - Sequencing of Exome/Whole Genome
 - Genotype Review Committee (GRC)
 - All projects greater than \$25,000

Senior Leadership for Genomics Committee (SLGC)

Mission

Review & Approval of

GWAS chips

Exome/WGS

Determines priority for

Illumina Infinium

Data Sharing and Access

Issues

Membership

J Fraumeni

P Tucker

R Hoover

P Hartge

S Chanock

M Henderson

Monthly Meetings with Minutes

Genotyping Review Committee (GRC)

Mission

Critique of Science

Statistical Review

Approval letter required
to proceed to CGF
queue

Minutes

Chair can approve small
projects & revisions

Membership

Chair:

P Tucker, Director, HGP

PIs from each Branch

rotate every 2 years

S Chanock

K Pitt

CGF Review Processes

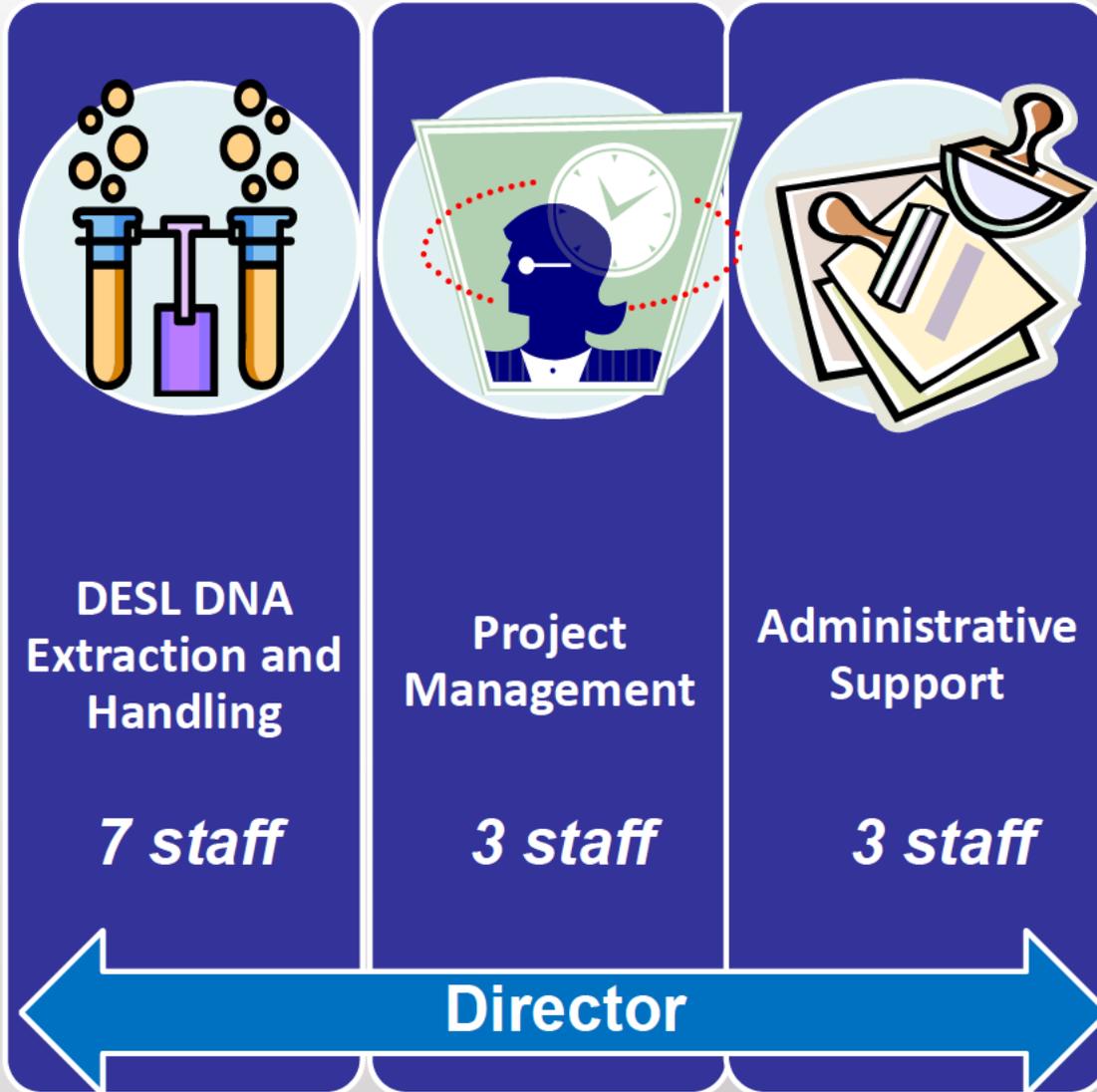
- Weekly conference
- Monthly SLGC meeting
- Quarterly SAIC report
- Biannual review of budget by OD DCEG
- Quadrennial Site Visit
 - May 2012 for CGF

Dedicated Facility Support

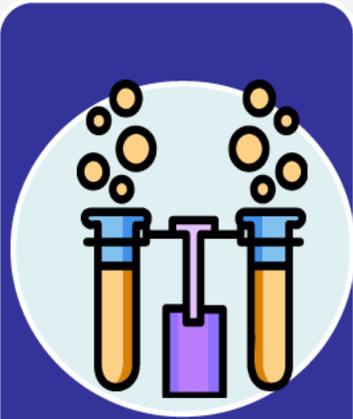
- DCEG directly supports
 - Personnel
 - Equipment
 - Maintenance
- Each project competes for DCEG resources

Operations

Research & Development

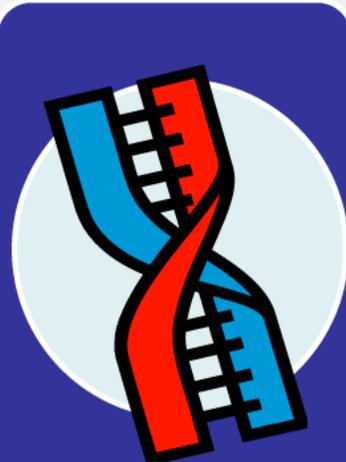


Production Laboratory



Production
Genotyping

6 staff



Production
Sequencing

3 staff



Quality
Assurance &
Control

3 staff



LIMS

4 staff



Technology
Transfer



Critical CGF Laboratory Team



Quality
Assurance &
Control

3 staff

- Review technology performance metrics
- Generate and update:
 - SOPs
 - Staff training
- Equipment maintenance
- Follow-up on laboratory problems
- Cost savings measures



CGF Bioinformatics & Scientific Operations

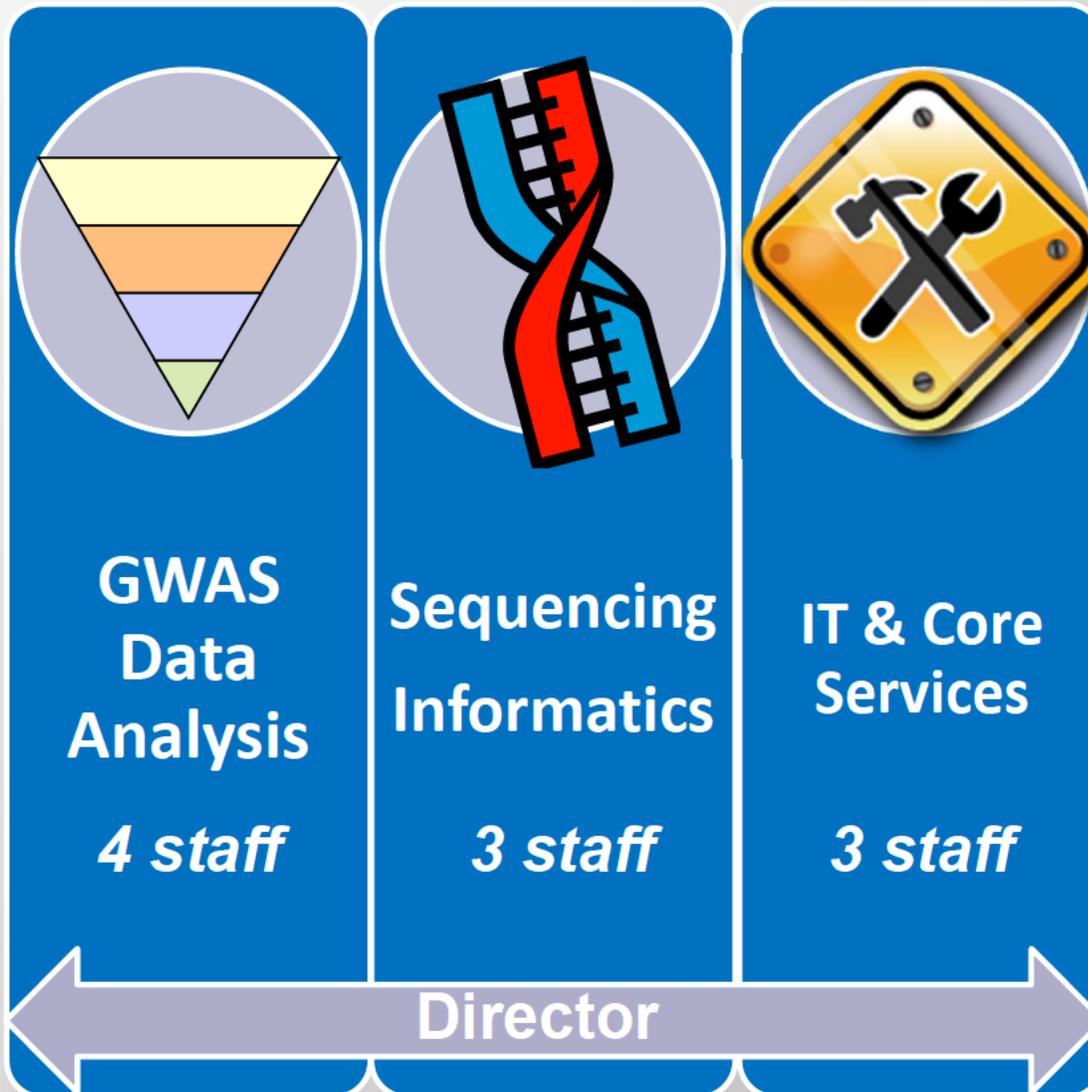


- Maintains Commercial LIMS
 - LabVantage 2004
- Customize content for CGF workflow
- Oversees archiving of data
 - Virtual lab note books only
- Oversee security/permissions

- Maintains websites
 - Public CGF
 - <http://cgf.nci.nih.gov/>
 - VariantGPS (replaces SNP500)
 - <http://variantgps.nci.nih.gov>

Bioinformatics & Analysis Version 3.0

Science and informatics at warp speed



Open Source Tools

- GLU software: <http://code.google.com/p/glu-genetics>
- Genotype data
 - SNP array data management
 - Quality control, population structure, & association analysis
- Next-generation sequencing (NGS)
 - Infrastructure to produce and manage alignments
 - Parse and manipulate variants
 - Conversions to/from VCF, GFF, PLINK, BEAGLE, Germline, GLU
 - Annotation of known/novel, function, frequency
 - Efficient *in silico* exome/regional pull-down
 - Visualization tools: Coverage, ploidy, CNV, SV, allelic ratio

Onsite CGF IT Infrastructure



IT & Core
Services

3 staff

- High-performance computing clusters
 - Over 640 CPU cores, >2 TB RAM
 - Supporting CGF
 - + DCEG (LTG, BB, REB, GEB)
 - + CCR/SAIC-F Sequencing Facility
- Laboratory instrument support
 - Integrated high performance computing
- Large-scale data storage subsystems
 - Over 300 TB tier 1 storage
- Local and wide-area networking
- Battery and generator backup of computing and HVAC
- Systems administration and security
 - Interface with CBIIT and CIT

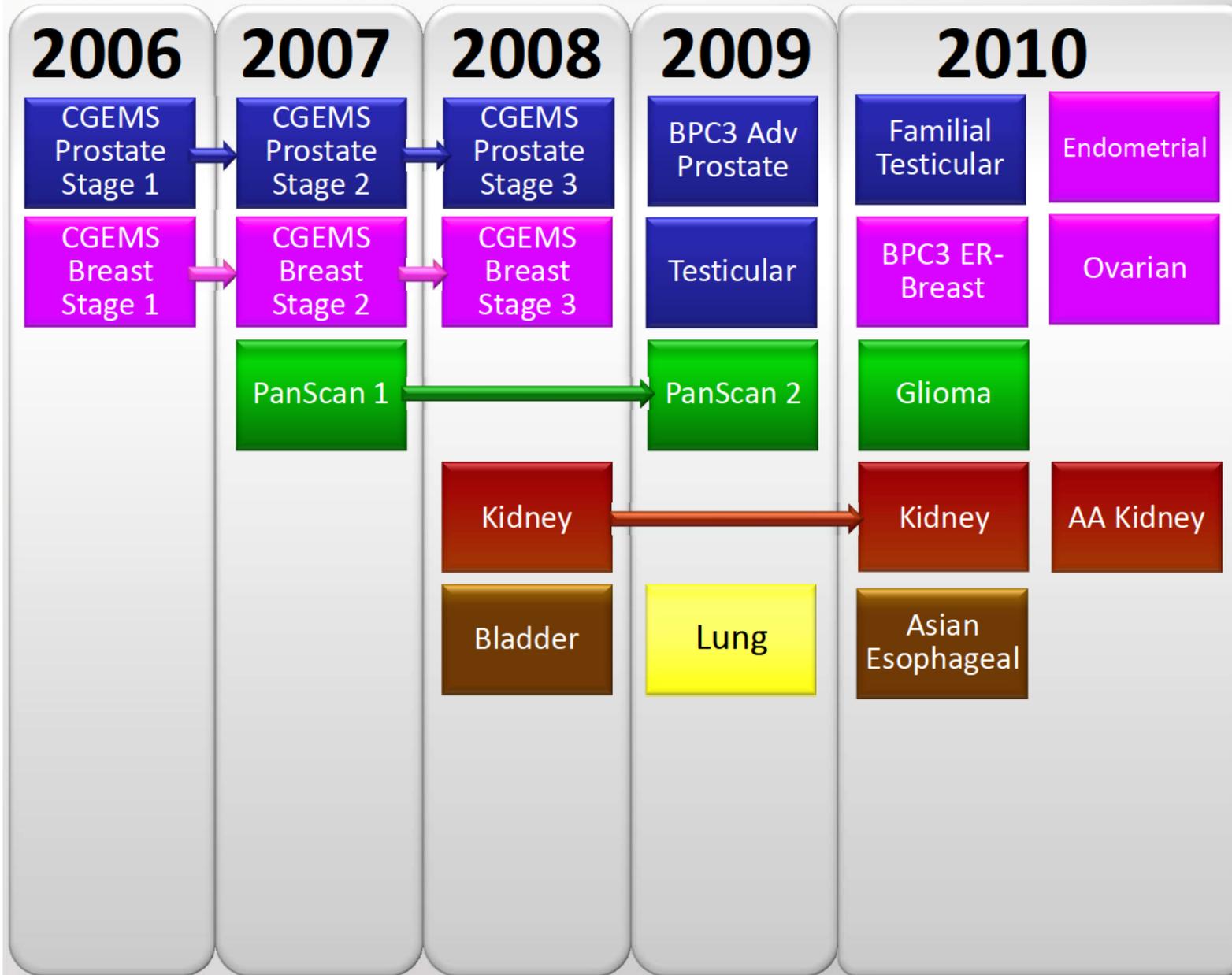


CGF Data Output since 2002

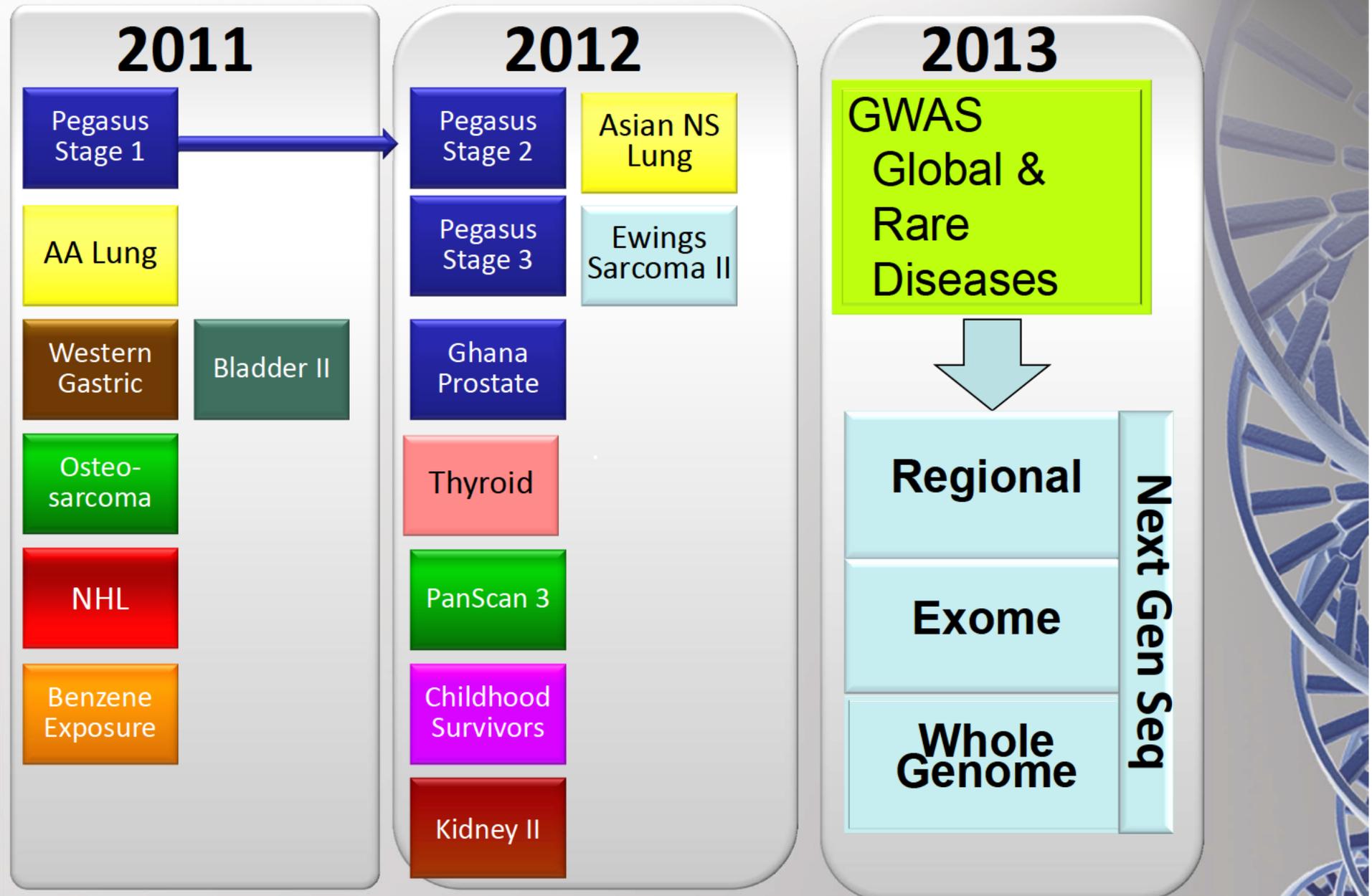
Analyzed & Delivered Data

SNP/CNV Genotypes:	76 x 10 ¹²
Regional Sequences:	100 Gbps
High-coverage exomes:	231, 2 Tbps aligned sequence, 200x avg coverage for Illumina HiSeq + Nimblegen 10-12x for Roche/454
Whole-genomes:	78, 15 Tbps aligned sequence, 60x avg coverage, Complete Genomics

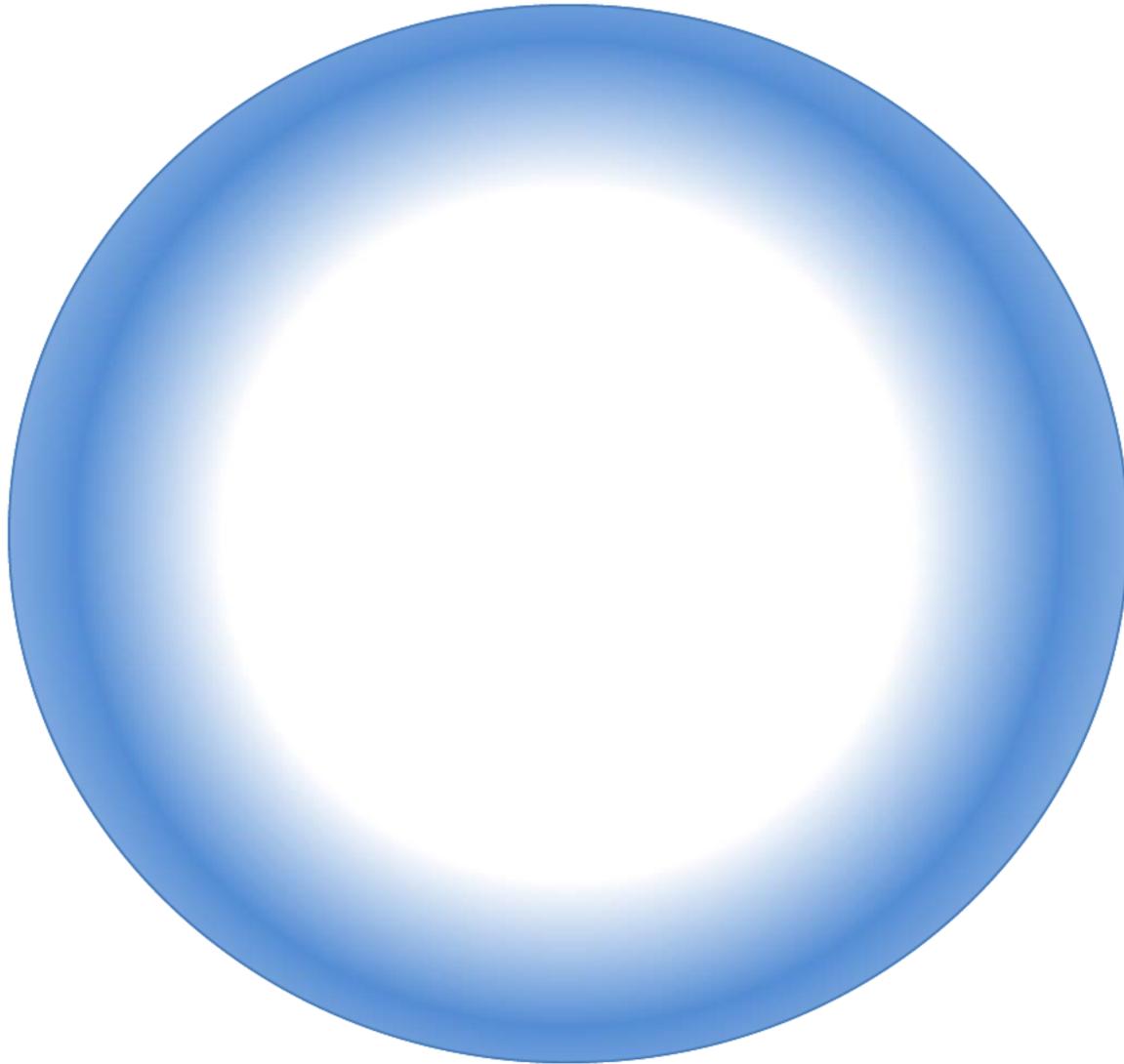
GWAS Timeline



GWAS->Sequencing Timeline



DCEG Total GWAS Set (TGS)



Resource based on DCEG 'TGS'

Zhaoming Wang, Kevin B Jacobs
Meredith Yeager, Amy Hutchinson
Joshua Sampson, Nilanjan Chatterjee,
Demetrius Albanes, Sonja I Berndt
Charles C Chung, W Ryan Diver
Susan M Gapstur, Lauren R Teras
Christopher A Haiman, Brian E Henderson,
Daniel Stram, Xiang Deng, Ann W Hsing,
Jarmo Virtamo, Michael A Eberle,
Jennifer L Stone, Mark P Purdue,
Phil Taylor, Margaret Tucker,
Stephen J Chanock

© 2012 Nature America, Inc. All rights reserved.

Improved imputation of common and uncommon SNPs with a new reference set

Statistical imputation of genotype data is an important statistical technique that uses patterns of linkage disequilibrium observed in a reference set of haplotypes to computationally predict genetic variants in silico¹. Currently, the most popular reference sets are the publicly available International HapMap² and 1000 Genomes data sets³. Although these resources are valuable for imputing a sizeable fraction of common SNPs, they may not be optimal for imputing data for the next generation of genome-wide association studies (GWAS) and SNP arrays, which explore a fraction of uncommon variants.

We have built a new resource for the imputation of SNPs for existing and future GWAS, known as the Division of Cancer Epidemiology and Genetics (DCEG) Reference Set. The data set has genotypes for cancer-free individuals, including 728 of European ancestry from three large prospectively sampled studies⁴⁻⁶, 98 African-American individuals from the Prostate, Lung, Colon and Ovary Cancer Screening Trial (PLCO), 74 Chinese individuals from a clinical trial in Shanxi, China (SHNX)⁷ and 349 individuals from the HapMap Project (Table 1). The final harmonized data set includes 2.8 million autosomal polymorphic SNPs for 1,249 individuals after rigorous quality control metrics were applied (see Supplementary Methods and Supplementary Tables 1 and 2).

We compared the imputation performance of the DCEG Reference Set to that of the International HapMap and 1000 Genomes reference sets, which are available from the IMPUTE2 website (see URLs). We assessed imputation accuracy by taking directly genotyped SNP data from the DCEG Reference Set and masking subsets to simulate data from two low-cost commercial genotyping arrays commonly used in GWAS studies (Illumina Human Hap660 and Human OmniExpress). Probabilistic genotypes were imputed using both IMPUTE2 (ref. 8) and BEAGLE⁹ software and compared with the masked genotyped SNPs. Accuracy was measured using the squared Pearson correlation coefficient (R^2) under an allelic dosage model (see Supplementary Methods). Using the new reference set, we observed higher imputation accuracy than that achieved with the

combination of 1000 Genomes and HapMap data across a spectrum of minor allele frequencies (MAFs) (Fig. 1). Accuracy in individuals of European ancestry imputed from Hap660 or OmniExpress arrays, measured by the proportion of variants imputed with $R^2 > 0.8$, improved by 34%, 23% and 12% for variants with MAFs of 3%, 5% and 10%, respectively. We estimated the difference in power to detect associations in GWAS designs between an imputed data set and one composed of directly genotyped SNPs with the DCEG Reference Set by adapting a model developed by Park et al.¹⁰. When using Hap660 data for imputation, we observed detection rates of 92.9% when imputing with the DCEG Reference Set and 84.7% with the 1000 Genomes and HapMap reference sets relative to the detection rate attained with directly genotyped SNPs; for OmniExpress data, we observed detection rates of 93.9% and 86.2% for these reference sets, respectively.

Because imputation accuracy depends on the similarity of haplotypes between

reference and study populations, we examined an extreme scenario in which we used a reference population from Finland (Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, ATBC) to impute genotypes using OmniExpress data from a US population of European ancestry (PLCO) (Supplementary Fig. 1). For common SNPs, there was minimal loss of imputation accuracy when using the reference population from Finland relative to the US-based Cancer Prevention Study II (CPSII) or a combined population of HapMap individuals from Utah of Northern and Western European ancestry (CEU) and from northern Italy (Toscani in Italy, TSI). This result suggests that, for common variants, a reference set of sufficient size can adequately predict common SNPs when there is a discrepancy in population ancestry, provided that comparable haplotypes are sufficiently represented. This observation should enable investigators to proceed more confidently with imputation without additional genotyping in related but not identical populations.

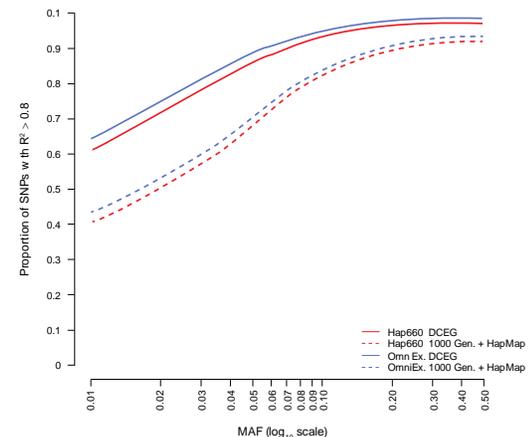
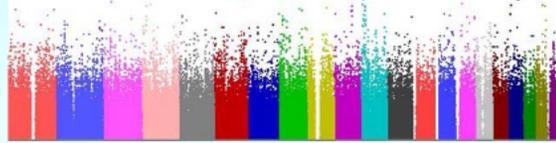


Figure 1 Imputation accuracy for individuals of European ancestry with the DCEG Reference Set and publicly available reference sets. The proportion of SNPs with allelic dosage $R^2 > 0.8$ by MAF is shown on the log scale to emphasize differences at smaller values. Red lines show imputation of Hap660 data, and blue lines show imputation of OmniExpress data. Solid lines, imputation using the DCEG Reference Set; dashed lines, imputation using the 1000 Genomes plus HapMap 3 reference sets.

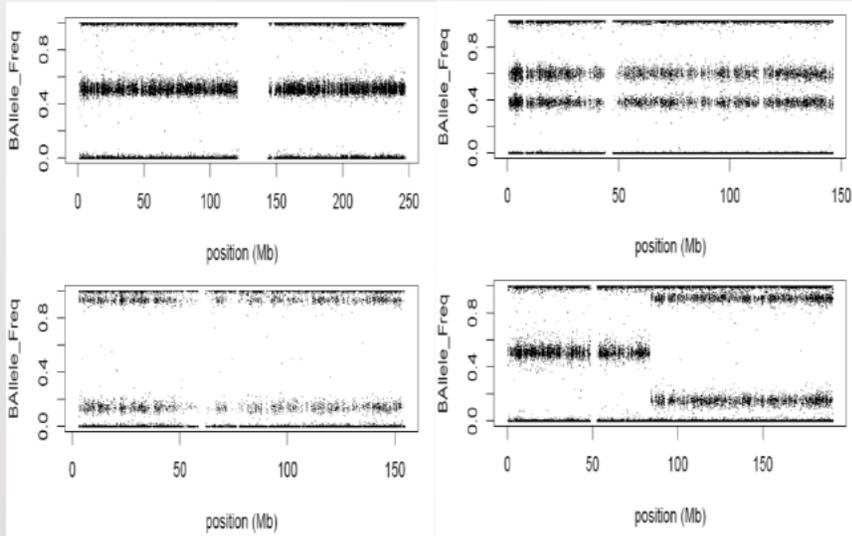
Unanticipated Directions



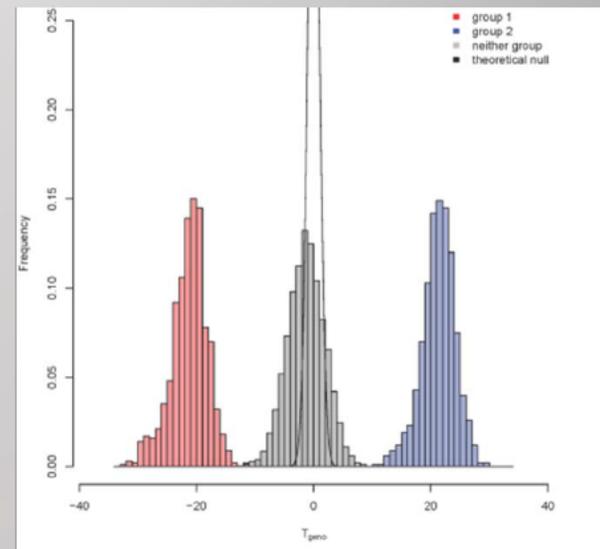
Genome-wide
association studies

Large chromosomal abnormalities,
structural variation, aneuploidy in
Germ-line DNA

Privacy & Confidentiality
GWAS membership

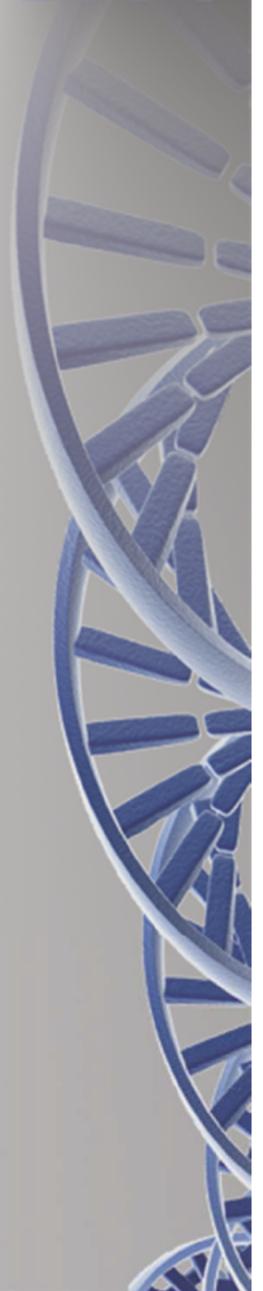
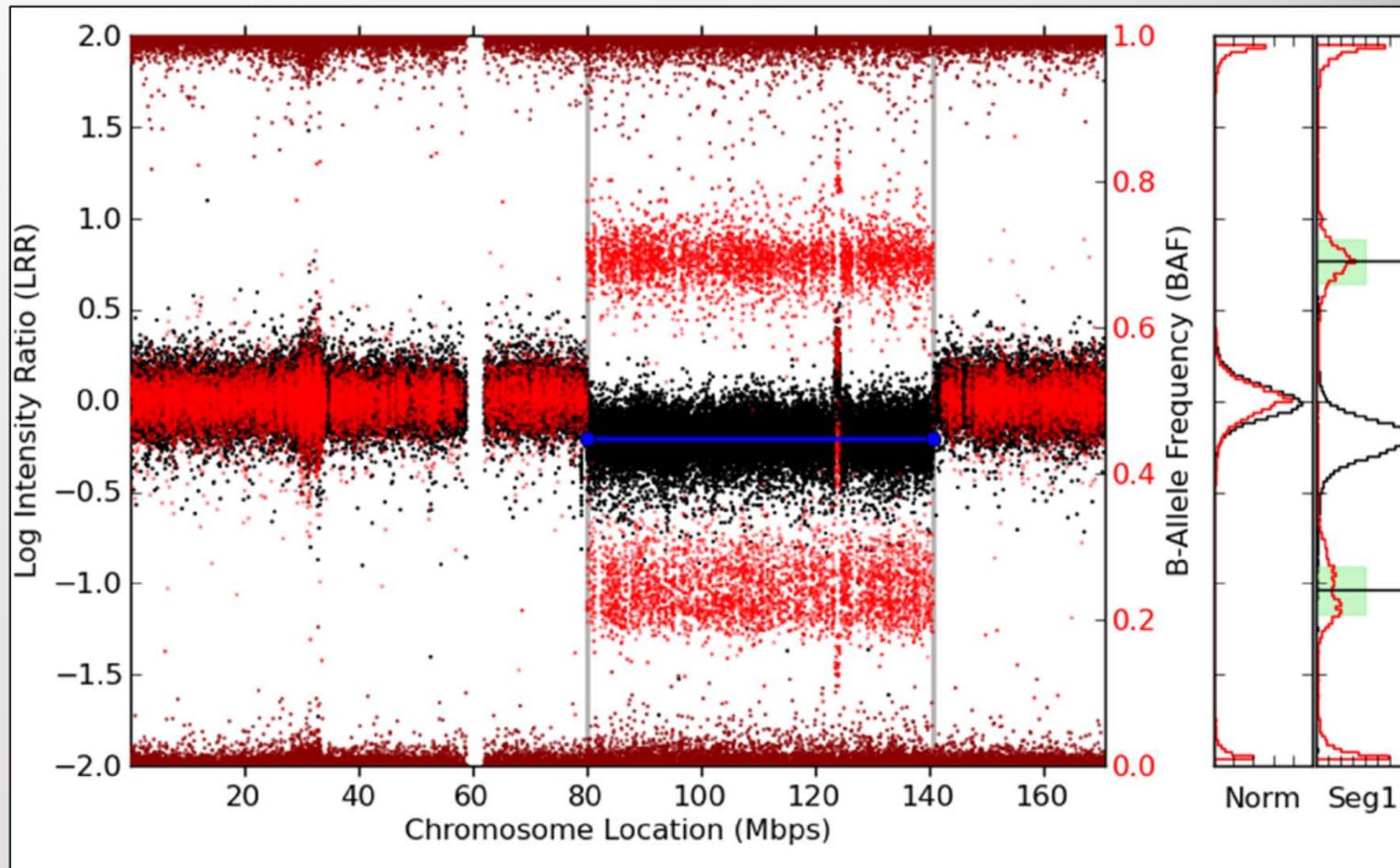


Rodriguez-Santiago AJHG 2010



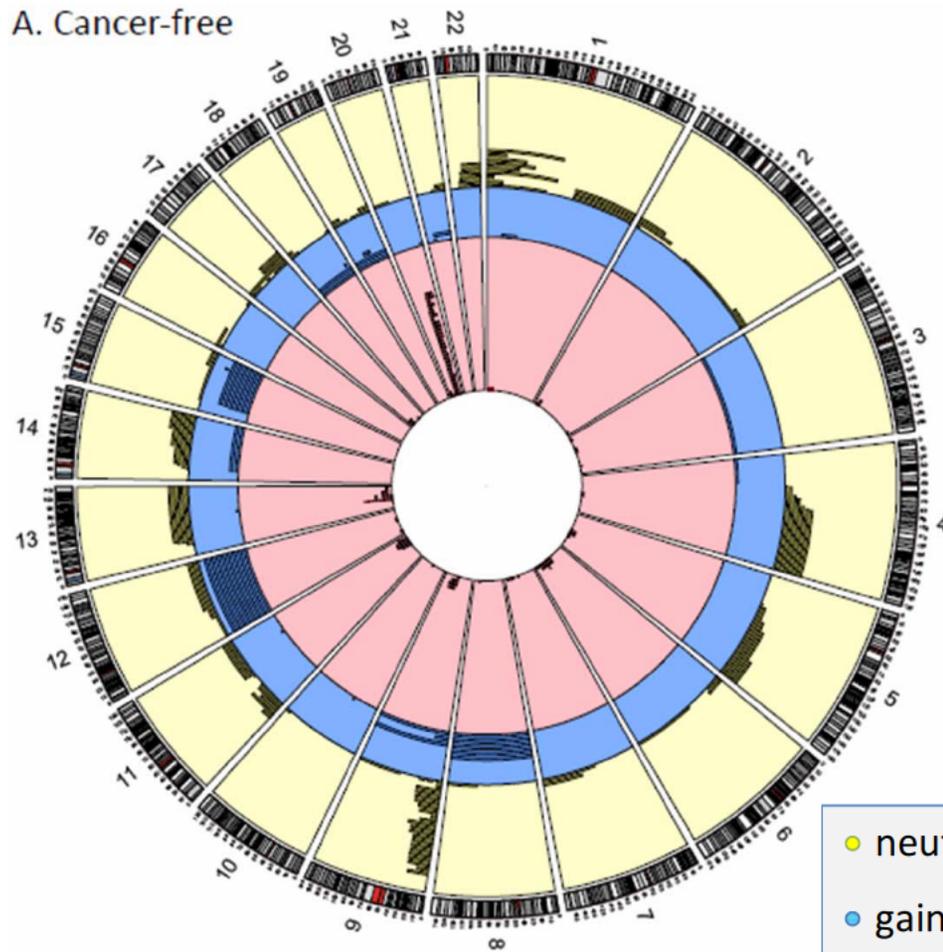
Jacobs Nature Genetics 2009

Mosaic Deletion

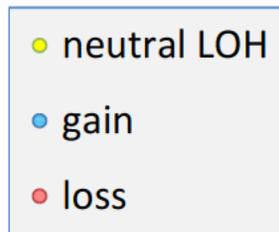
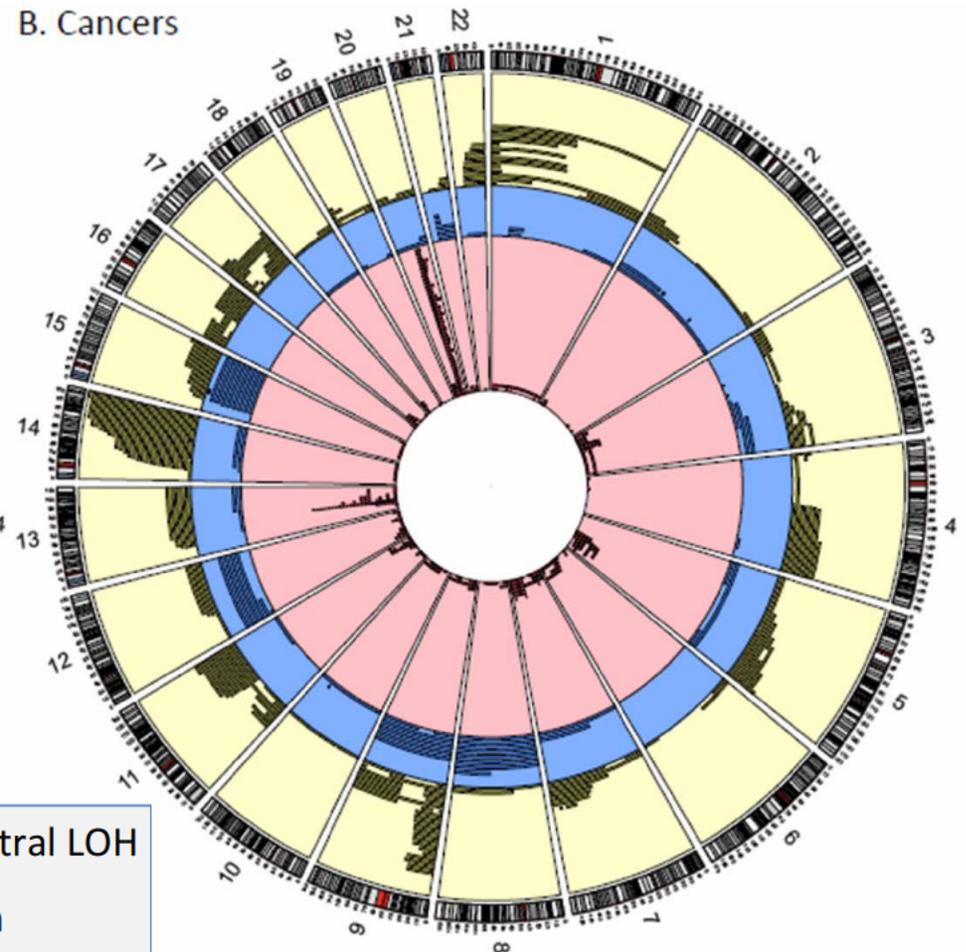


Circos Plot of large mosaic events (> 2 Mb) in 57,583 individuals

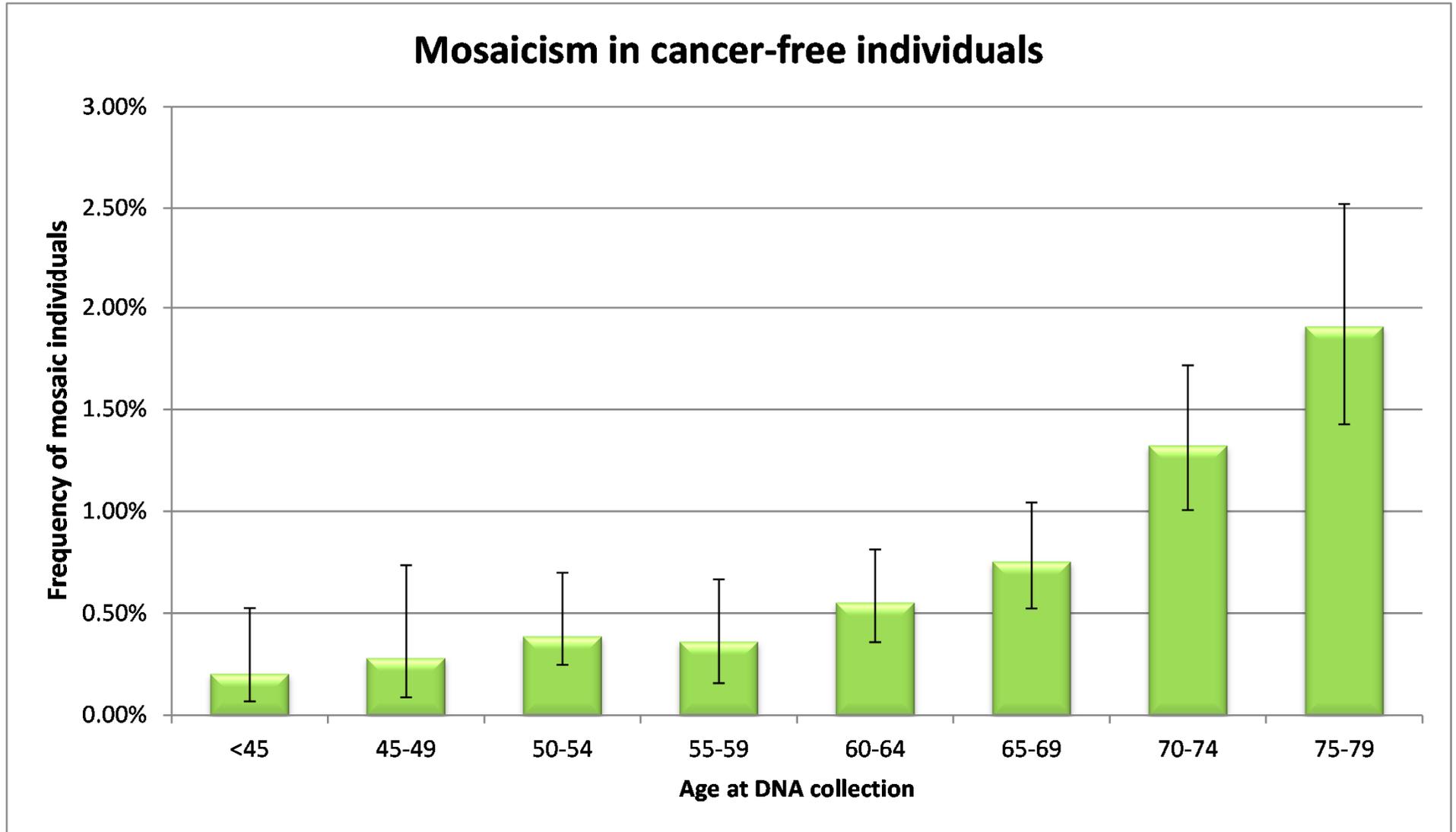
A. Cancer-free



B. Cancers



Age at DNA Collection is the Strongest Predictor of Genetic Mosaicism



CGF & Data Sharing



- Posted first public GWAS datasets for breast & prostate cancer
 - Aggregate data removed in 2008 in response to NIH policy change
- Led development of standards for GWAS posting with dbGaP
- Contributed all DCEG GWAS datasets to dbGaP
- CGF was instrumental in addressing privacy issues with GWAS and other high-dimensional aggregate genomics data

LETTERS

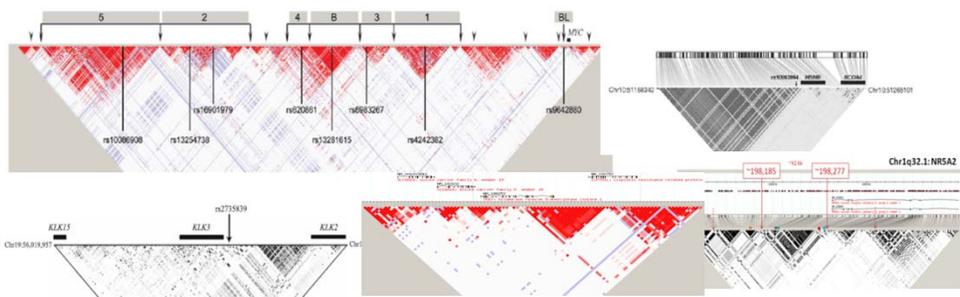
nature
genetics

A new statistic and its power to infer membership
in a genome-wide association study using genotype
frequencies

Kevin B Jacobs¹⁻³, Meredith Yeager^{1,2}, Sholom Wacholder², David Craig⁴, Peter Kraft⁵, David J Hunter⁵,
Justin Paschal⁶, Teri A Manolio⁷, Margaret Tucker², Robert N Hoover², Gilles D Thomas²,
Stephen J Chanock^{2,8} & Nilanjan Chatterjee^{2,8}

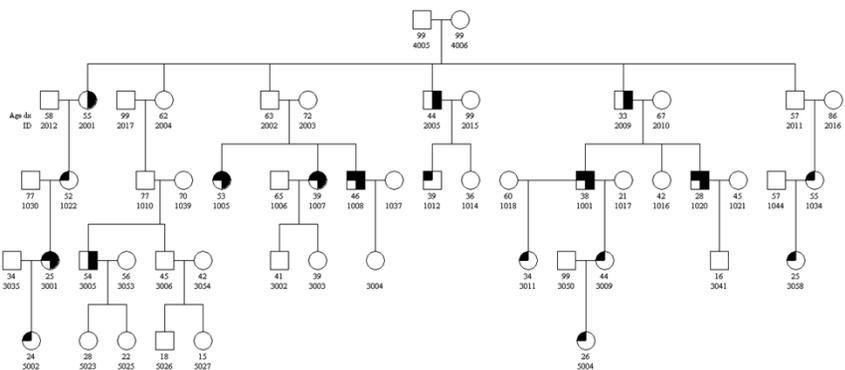
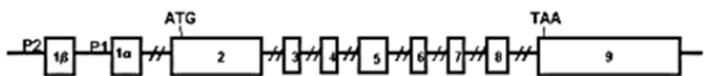
erved.

Regional GWAS and linkage follow-up



Candidate gene/exon

Sequencing



Whole exome



Whole genome

NGS Capabilities

Roche 454 GS FLX (2)

- Installed 2008
- Chosen for:
 - Read length
 - Multiplexing capability
- Current Output:
 - Multiplexing up to 264 samples
 - Average of 350-400bp/read



~~Illumina HiScan SQ~~

- ~~Installed August 2010~~



Illumina HiSeq 2000

- Installed April 2011
- Chosen for:
 - Throughput sufficient for exome/whole genome sequencing
- Current Output:
 - 300 Gbps/week (16 exomes)
 - 76-100 bp PE reads
- Expanded sequencing applications
 - CHiPseq
 - RNAseq

Life Technology/Ion Torrent PGM

- First Installed Jan 2011
- 6 machines as of Jan 2012
- Chosen for:
 - Cost
 - Reliability
 - Flexibility



Bumps along the way....

2007: Movement into ATP-SAIC

- Expectation of better alignment with program resources

2009: Movement out

- ATP Leadership sought to interrupt close collaboration and direct towards other business opportunities
- Placed under SAIC Research Administration OD

Recent Bump

- Sample handling bottleneck
 - CGF processes used for setting up DNA Extraction & Sample Handling Lab (DESL) in 2006
 - Increased demands stressed DESL
 - Stand alone service lab was realigned with CGF in 2011 due to
 - Quality Control Issues
 - Production Delays

Current Focus of Activities

Role of GWAS for:

1. Less common diseases w/ limited biospecimens
2. Complete our understanding of the contribution of common variant to cancer risk
 - Overall and population specific
3. Denser arrays for less common variation

Family & Special Population Analysis

- Exome & whole-genome sequencing
- Follow-up in families and unrelated subjects

Challenges Ahead

- Transition from GWAS to sequencing for investigation of germ-line susceptibility
- Further integration of environmental exposures
- Optimal storage, processing, and mining of whole-genome sequence data

Critical Mass

Analytical and Bioinformatic Expertise

- Close collaboration from inception to publication
 - Studies
 - Methodology
- Software development & dissemination
- Systematic data sharing
- Integrative analysis across studies & data types

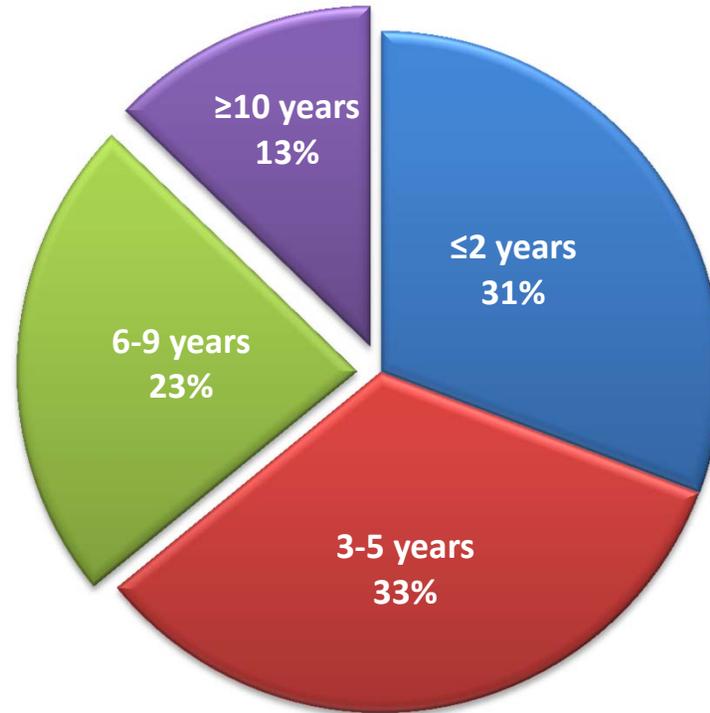
Success of DCEG Core Genotyping Facility

- DCEG's decades of investment in epidemiology & genetics
 - Close collaborations between DCEG & FFRDC (CGF) epidemiologists, biostatisticians, geneticists, bioinformaticians and laboratory experts
- Dedicated facility framework

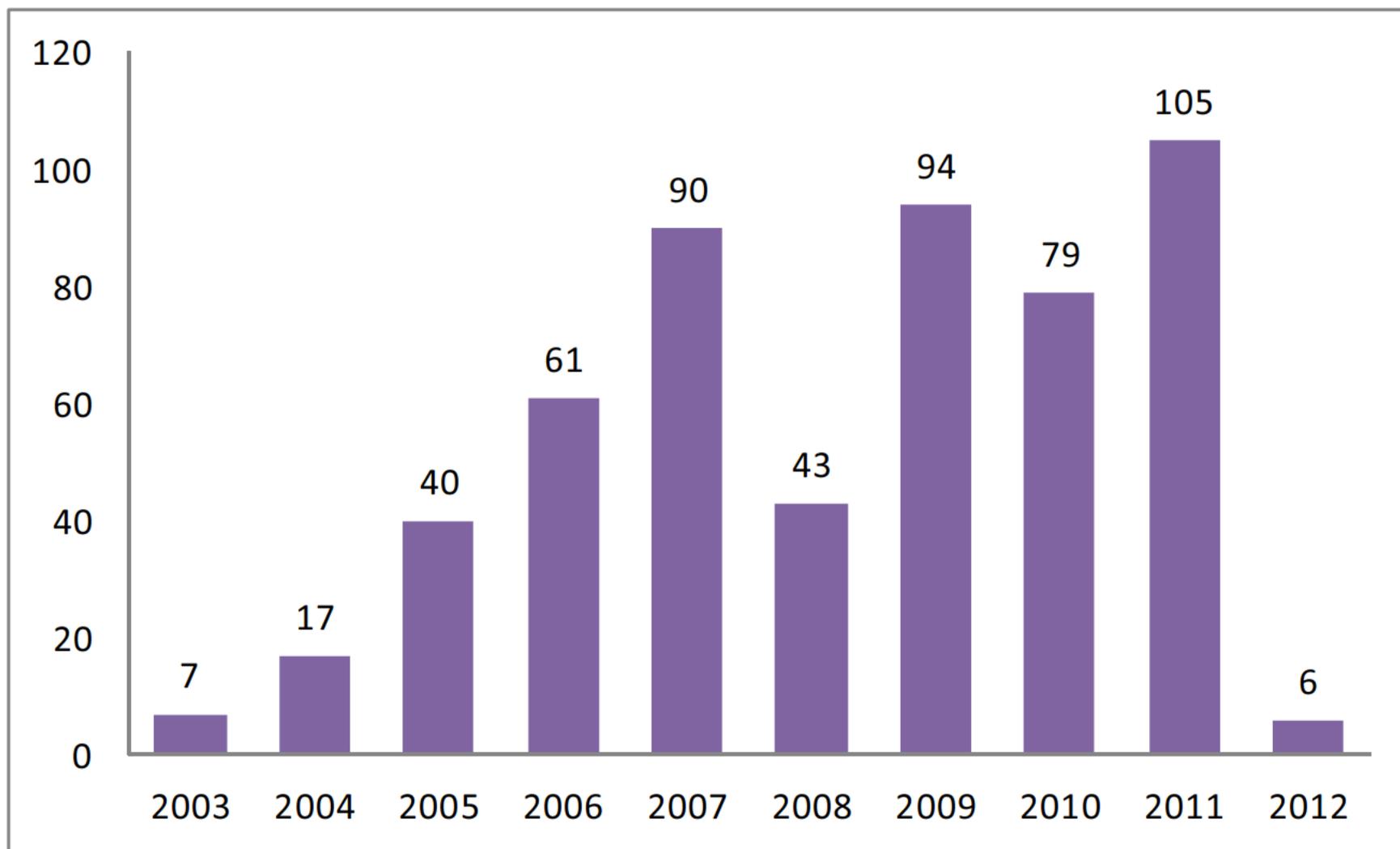
Possible Questions

Stability of CGF Staff

Years of Employment at CGF



Number of CGF-coauthored publications per year



Technology Assessment

- Collaboration with Academic and Commercial Laboratories
 - Early Access
 - Rapid Evaluation of Emerging Technologies
 - 15 Projects
 - Assist in DCEG PIs in Application & Study Design
 - Translation to Production Capacity
 - Prevent Waste of Biospecimens and Resources

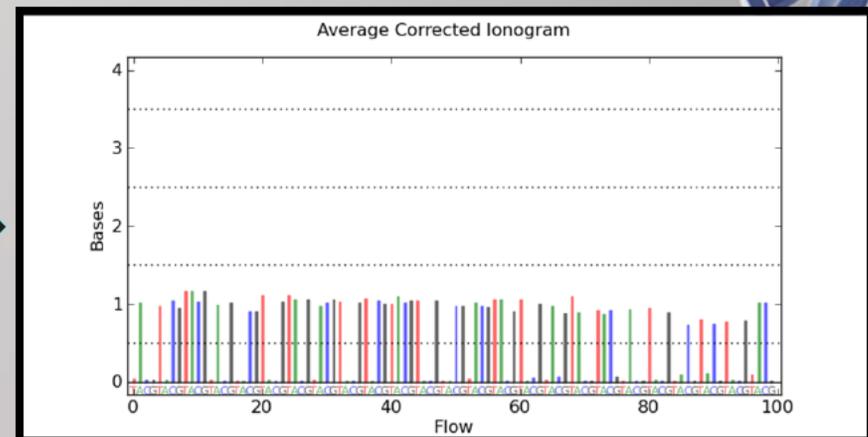
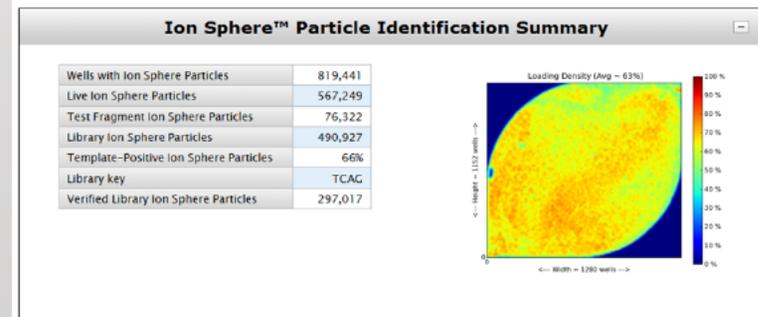
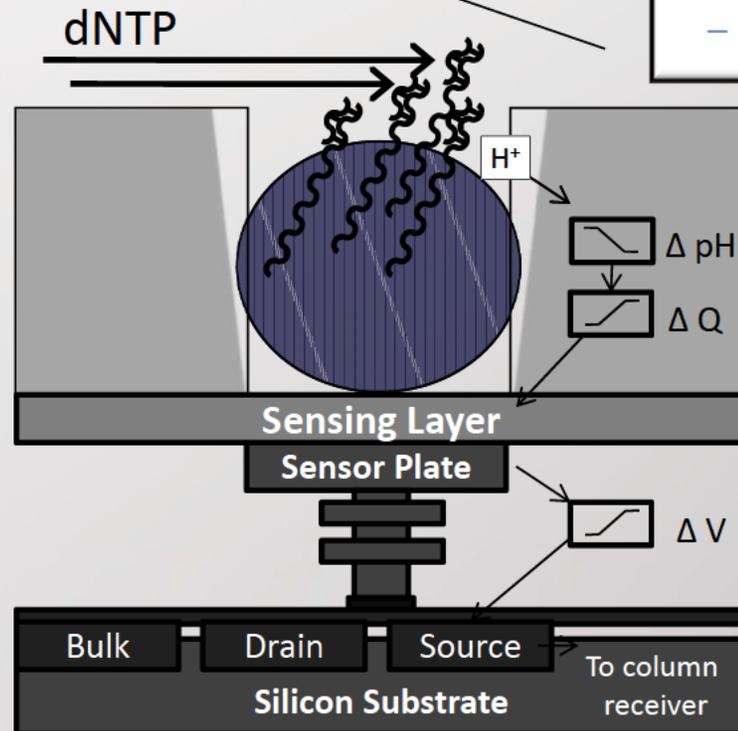
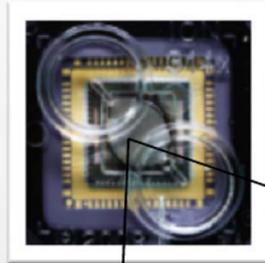
R & D Projects @ CGF

- WGA Kits
- Fluidigm
 - Biomark
 - Access Array
- Illumina β testing
 - Infinium/Omni
 - Methylation
- Exome Capture
- Raindance
- Ion Torrent
- ABI
 - SNaPshot, SNPlex
 - DME Panels
- EPOCH
- Sequenom* (1st gen)
- 454- Exome
- Affymetrix*
- Illumina-HiScan

Ion Torrent Technology

DNA → Ions → Sequence

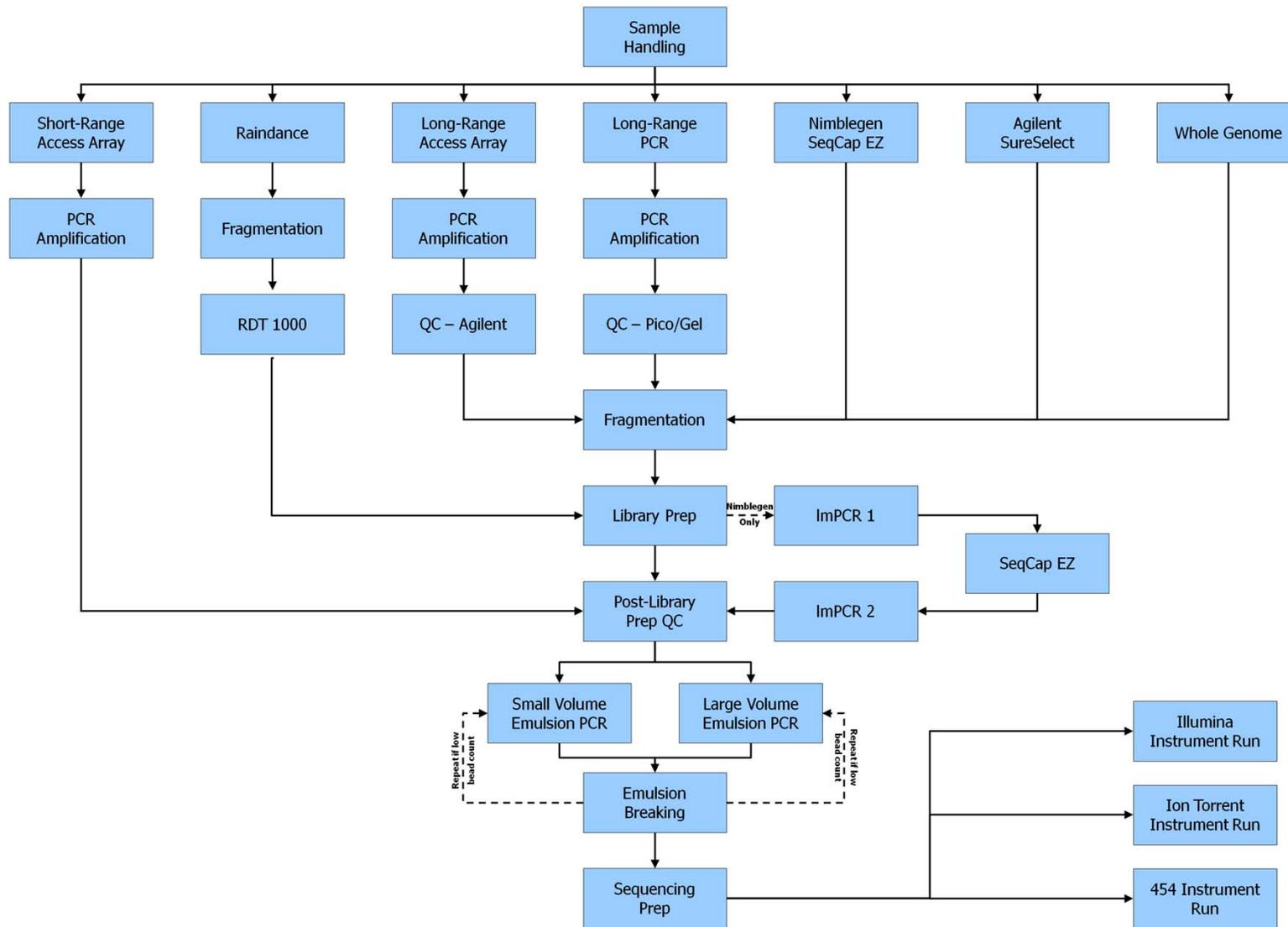
- Nucleotides flow sequentially over Ion semiconductor chip
- One sensor per well per sequencing reaction
- Direct detection of natural DNA extension
- Millions of sequencing reactions per chip
- Fast cycle time, real time detection



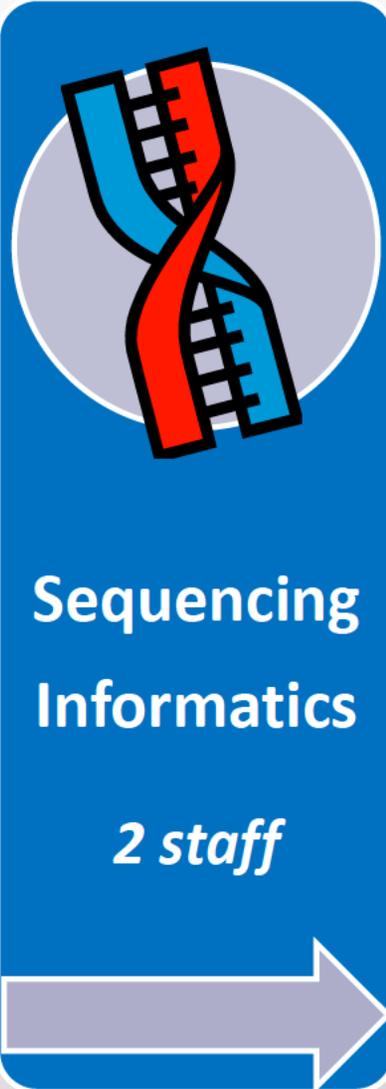
Ion Torrent Investment: 'Small Job Shop'

- Confirmation of exome and targeted variant sequencing
- Reduced cost
- Rapid turnaround: 2 week total @ 12-18 chips/day
- Custom activities
 1. Large amplicon / highly-multiplex sample studies
 2. RNAseq studies
 - a. whole transcriptome
 - b. small RNA
 3. Fixed or custom amplicon panels for preclinical sample and tumor profiling
 4. FFPE sample sequencing
 5. Rapid exome sequencing and supplementation
 6. Methyseq (RainDance and/or Ion reagents)

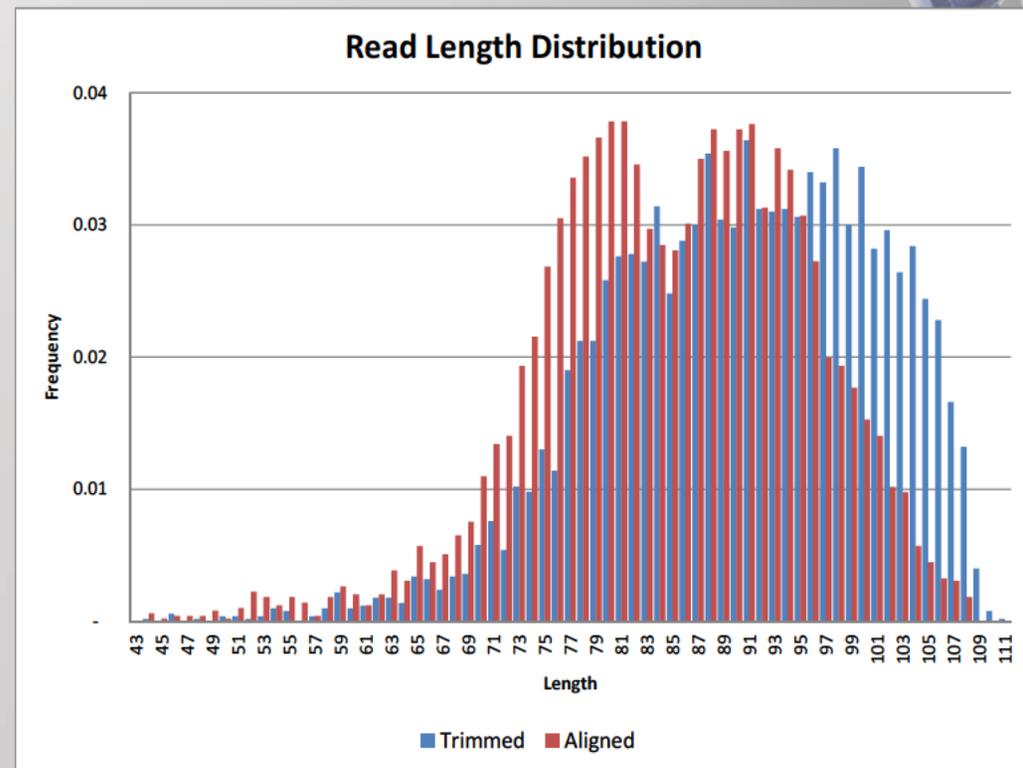
CGF Sequencing Workflows



CGF Bioinformatics & Scientific Operations

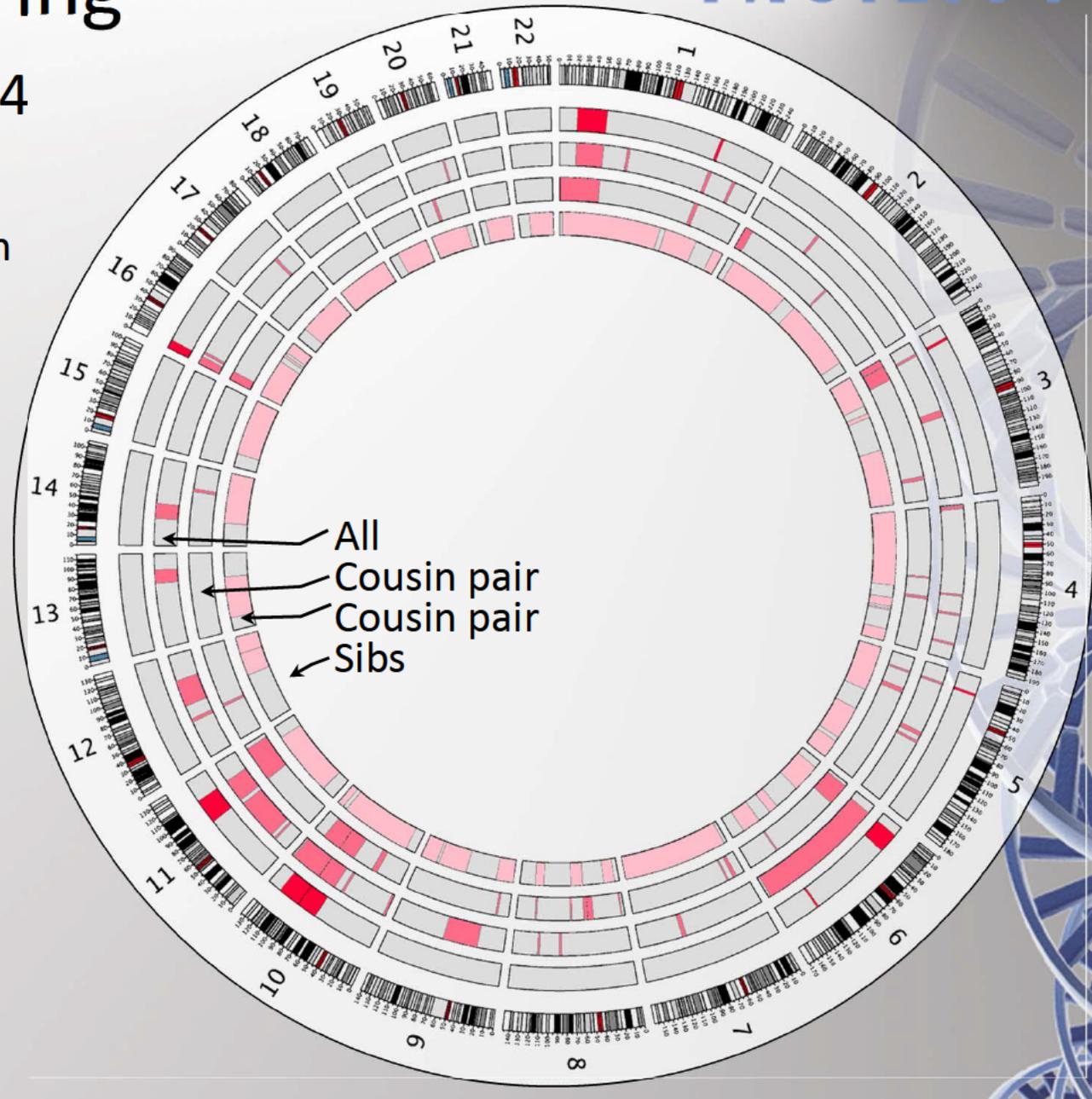


- Sequencing Data Analysis
- Working on development of standard analysis pipeline
- Feedback metrics and reports to the laboratory



IBD Sharing

- Based on 3,277,154 autosomal SNPs
 - Biallelic, polymorphic, in dbSNP, Mendelian consistent
- Methods
 - Phasing: BEAGLE
 - IBD sharing: Germline
 - Plot: Circos



DCEG GWAS Available on dbGaP

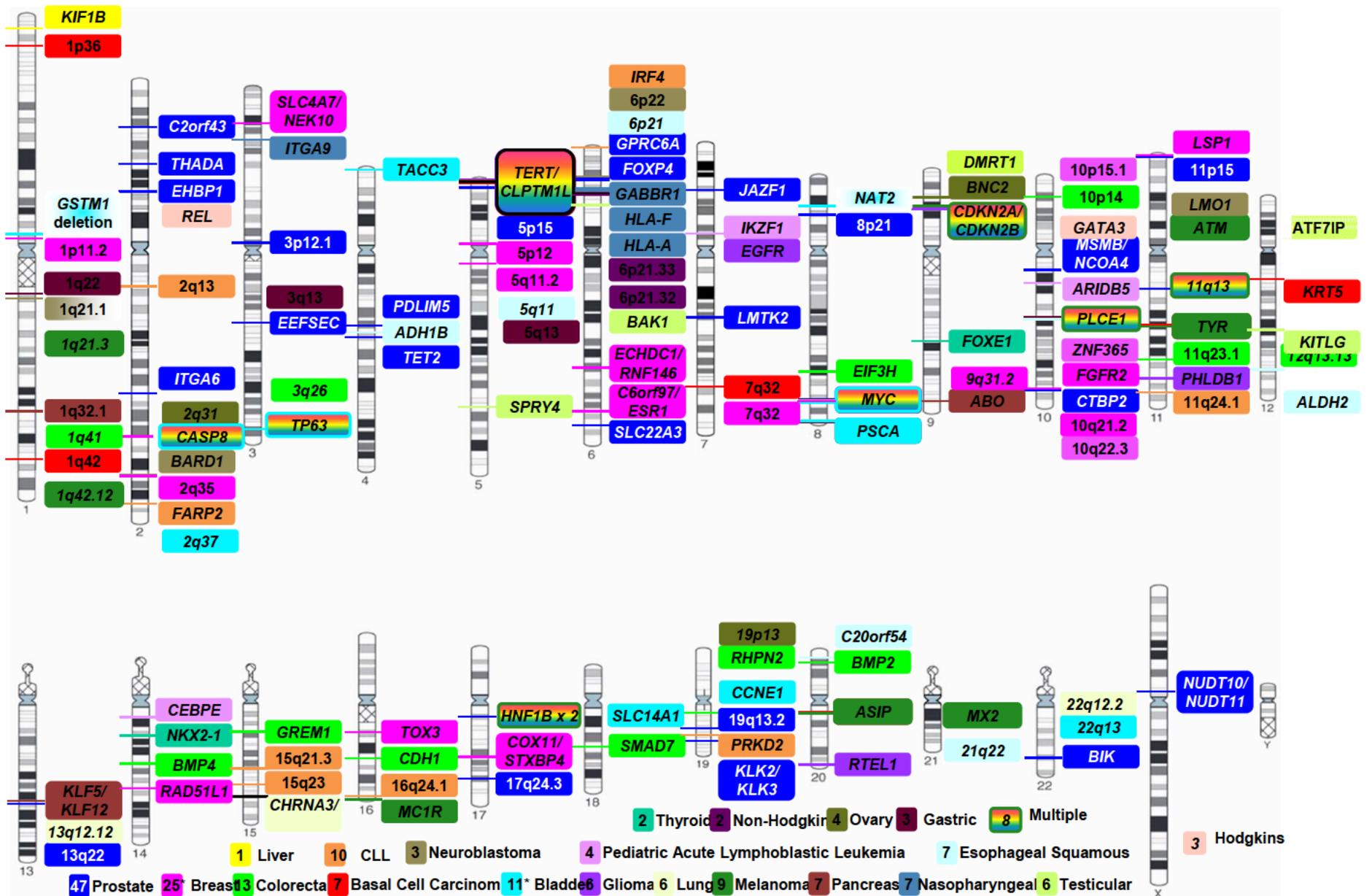
Shift from caBIG to dbGaP in 2009



GWAS Site	# Approved
Breast*	134
Prostate*	92
Pancreas	88
Lung	118
Bladder	16
Renal	15
UGI (China)	12
Imputation	7

**Previously on CGEMS Site with > 100 for each*

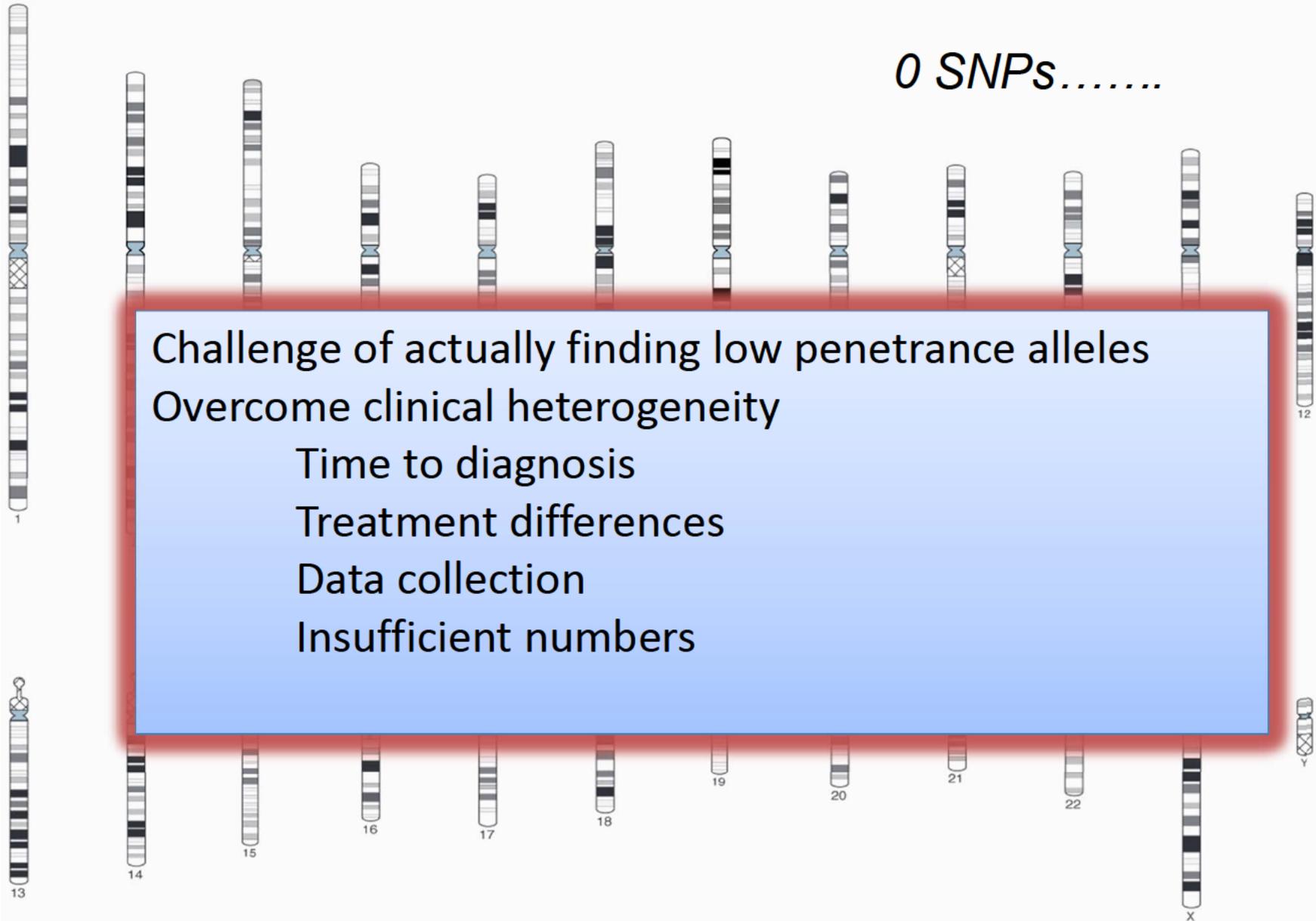
5 years of cancer GWAS – 216 signals for 24 cancer types



CANCER GWAS Hits for SURVIVAL or OUTCOME

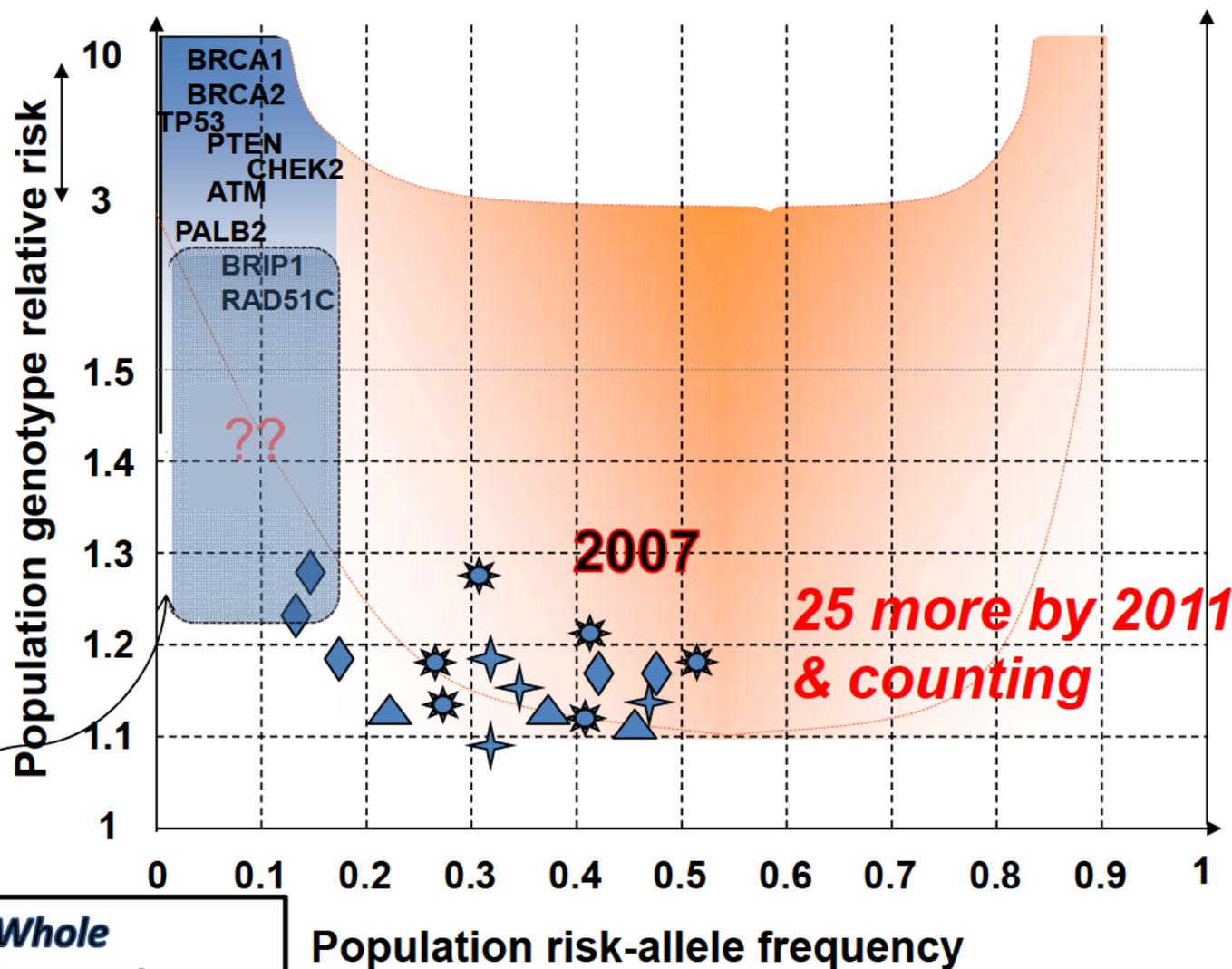
0 SNPs.....

Challenge of actually finding low penetrance alleles
Overcome clinical heterogeneity
Time to diagnosis
Treatment differences
Data collection
Insufficient numbers



Genetic Predisposition to Breast Cancer European Population

1990



**Exome & Whole
Genome Sequencing**

★ BCAC
 ✦ CGEMS/BCAC
 ◆ WTCCC
 ▲ Other

Theoretical Limits of Risk Prediction

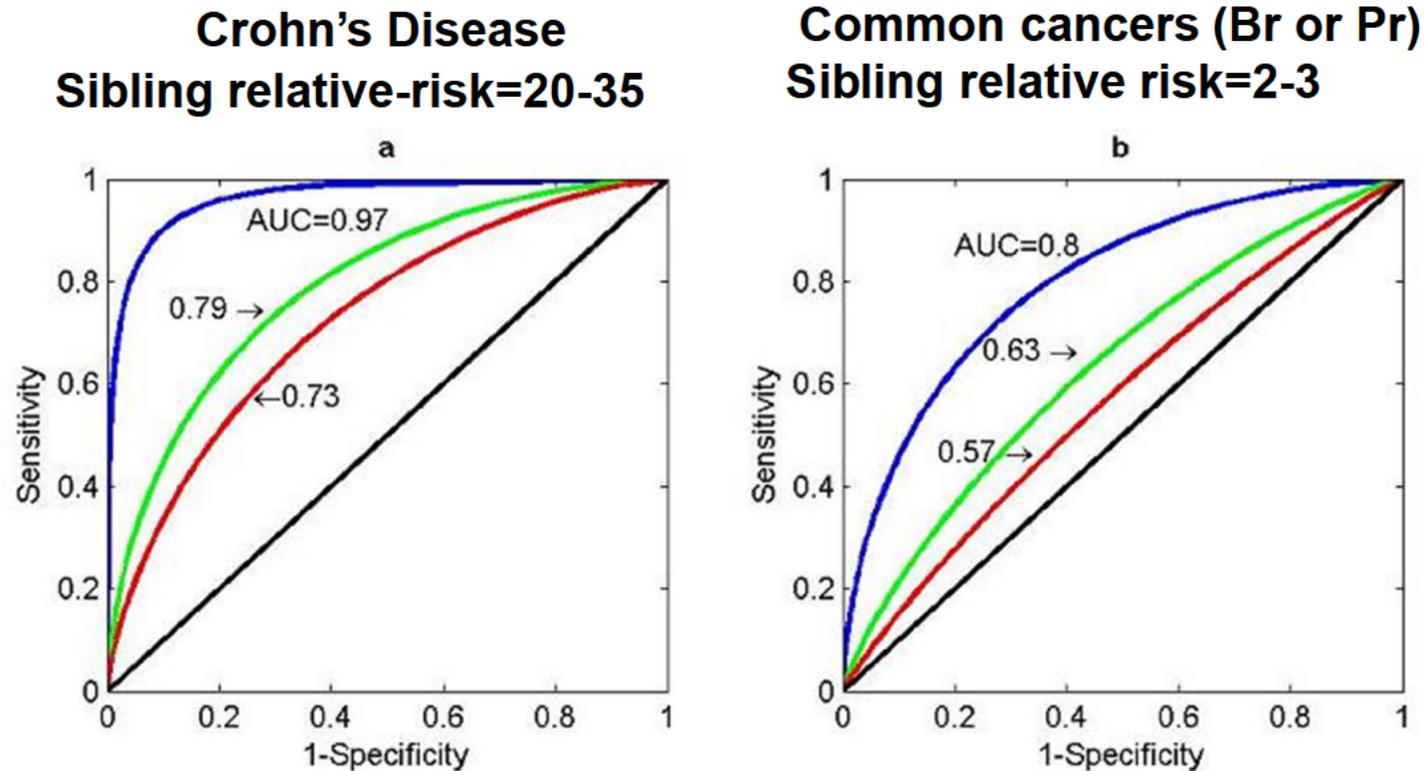


Figure 2 Receiver operator characteristics (ROC) curves for genetics risk models.

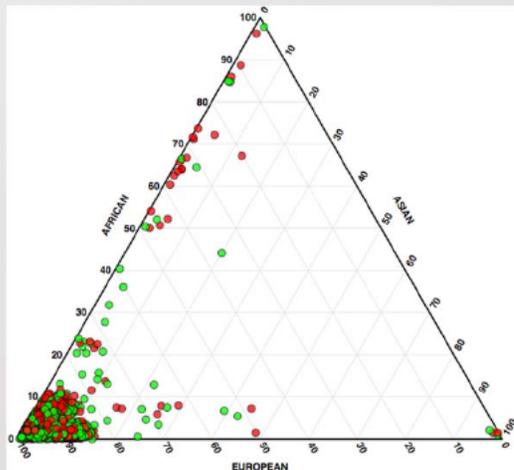
- Random
- Using known loci
- Using all estimated loci
- Ideal (if we could explain all heritability)

Quality Control

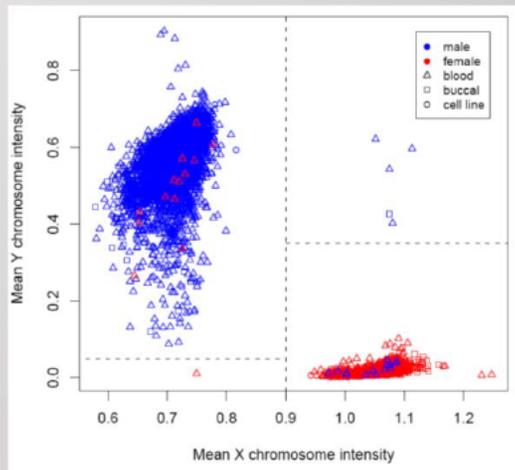


Genome-wide association studies

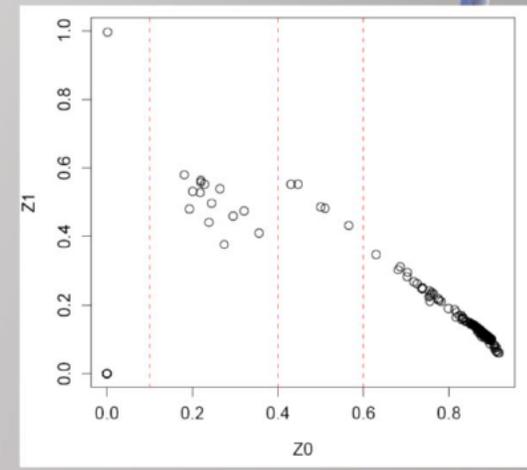
Population genetics and ancestry



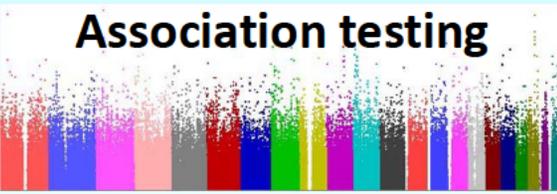
Sex verification



Relationship testing



Association testing



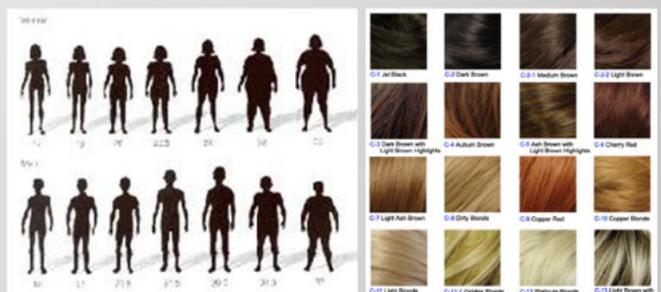
Genome-wide
association studies

Behavioral traits



Tobacco,
Caffeine,
Alcohol

Biometrics



Height, Weight, BMI,
Menarche/Menopause
Hair and eye color

Nutrient levels

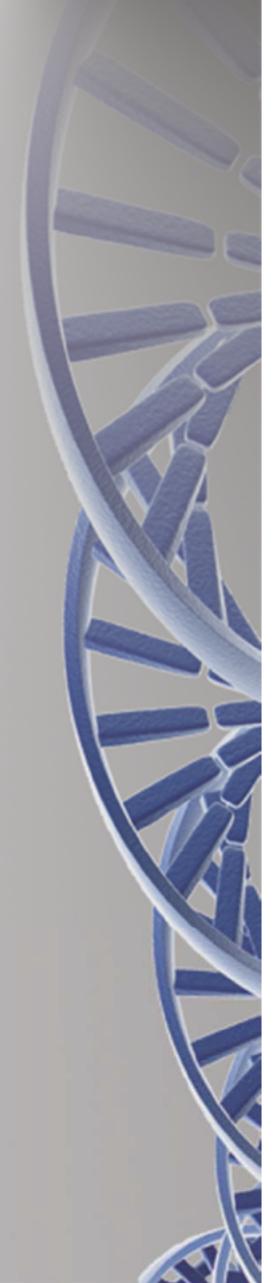
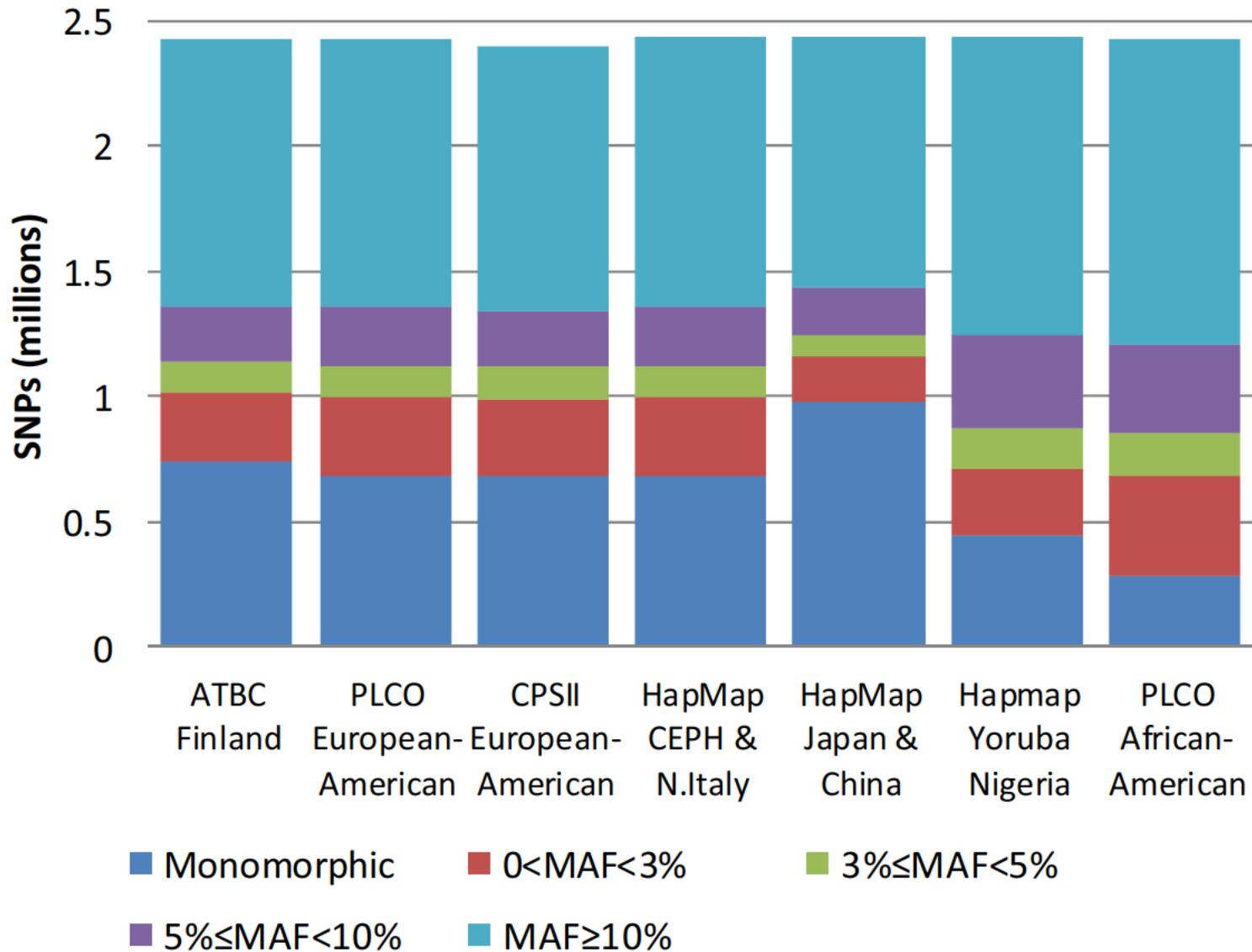


Vitamins D, B₁₂
Carotene, etc.

...and much more!

DCEG & International Consortia (e.g., GIANT, SUNLIGHT)

Omni2.5 allele frequency distribution



Rare Variants Create Synthetic Genome-Wide Associations

Samuel P. Dickson^{1,2}, Kai Wang³, Ian Krantz^{3,4,5}, Hakon Hakonarson^{3,4,5}, David B. Goldstein^{1*}

1 Institute for Genome Sciences and Policy, Center for Human Genome Variation, Duke University, Durham, North Carolina, United States of America, **2** Bioinformatics Research Center, North Carolina State University, Raleigh, North Carolina, United States of America, **3** Center for Applied Genomics, Children's Hospital of Pennsylvania, Philadelphia, Pennsylvania, United States of America, **4** Division of Human Genetics, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, United States of America, **5** Department of Pediatrics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania, United States of America

Really?

Rapid communication 231

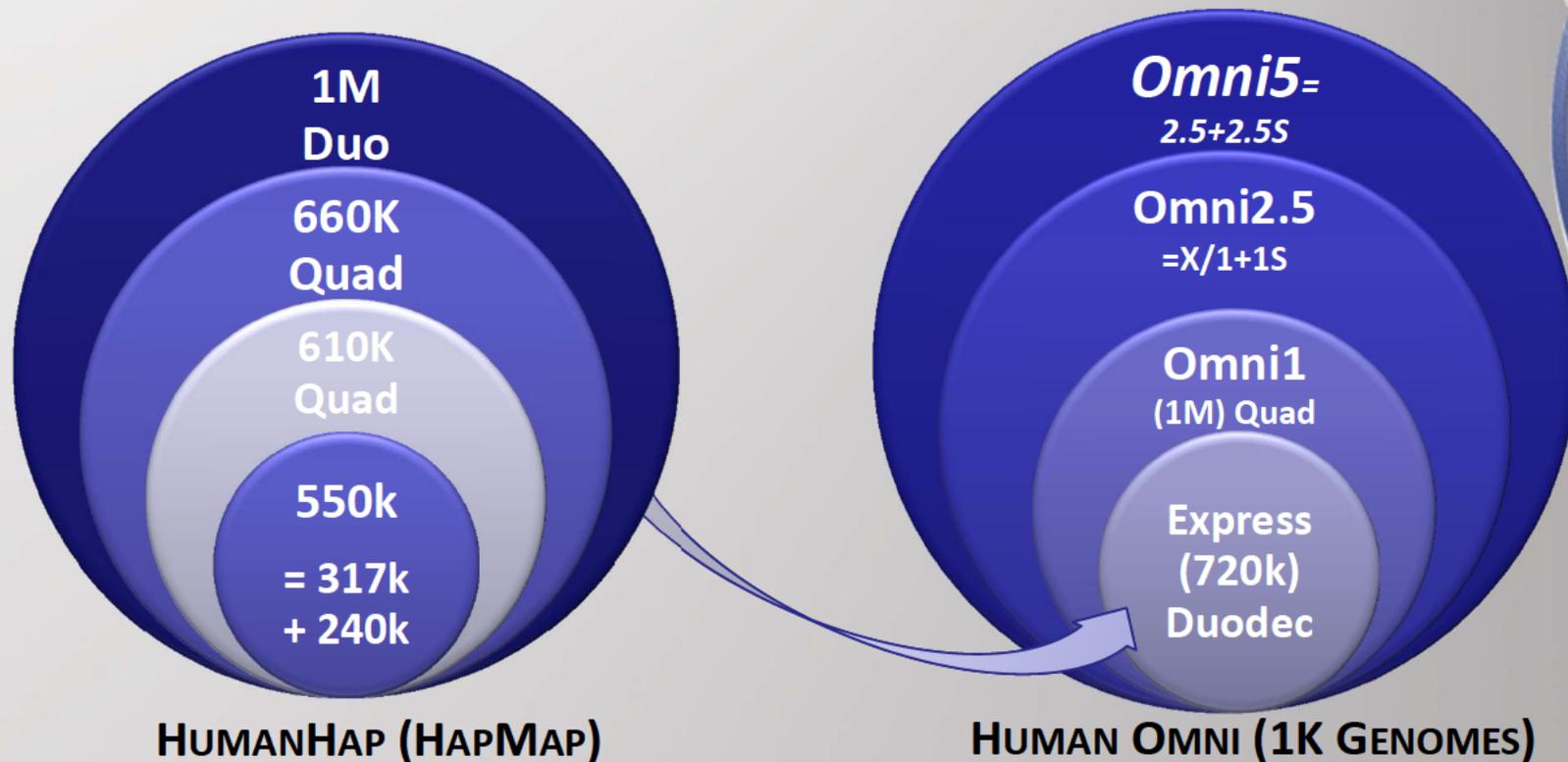
A single nucleotide polymorphism tags variation in the arylamine *N*-acetyltransferase 2 phenotype in populations of European background

Montserrat García-Closas^{a,l}, David W. Hein^d, Debra Silverman^a, Núria Malats^k, Meredith Yeager^{a,b}, Kevin Jacobs^{a,b}, Mark A. Doll^d, Jonine D. Figueroa^a, Dalsu Baris^a, Molly Schwenn^e, Manolis Kogevinas^{g,h,i,m}, Alison Johnson^f, Nilanjan Chatterjee^a, Lee E. Moore^a, Timothy Moeller^c, Francisco X. Real^{l,j}, Stephen Chanock^{a,b} and Nathaniel Rothman^a

Pharmacogenet
Genomics. 2011
Apr;21(4):231-6.

Illumina GWAS Capacity

- Current capacity is ~432 Infinium arrays/week
 - 1,728 samples/week for quad arrays (660k, Omni1, Omni5)
 - 3,456 samples/week for octo arrays (Omni1S, 2.5, 2.5S)
 - 5,184 samples/week for duodec arrays (iSelect/OmniX)

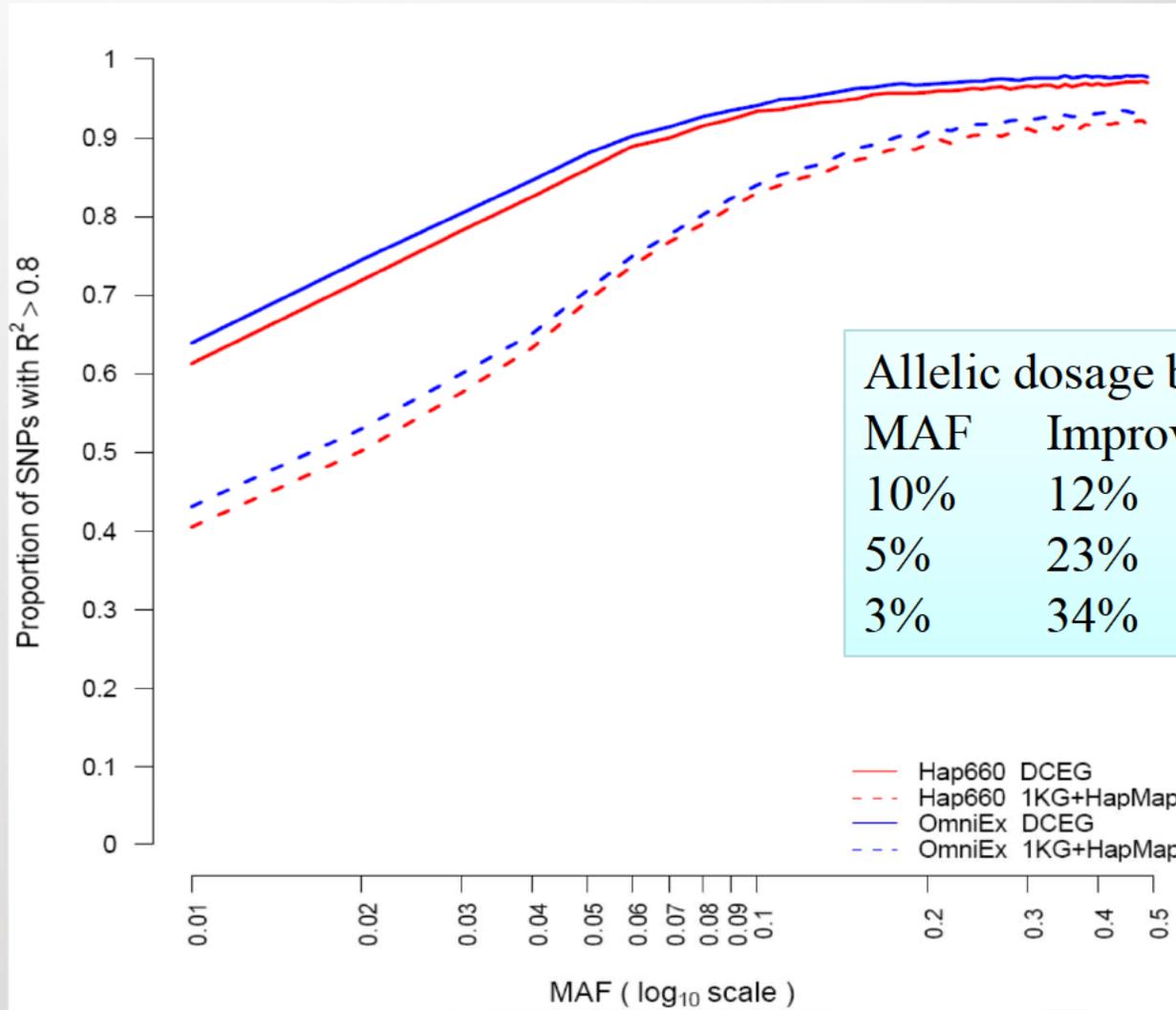


Samples included in Build 1 of DCEG Imputation Reference Set

Group	Populations				Illumina Array			
	European American	African American	African	Asian	Hap660	Hap1	Omni1	Omni2.5
ATBC	246					✓	✓	✓
CPSII	227					✓	✓	✓
PLCO	255					✓	✓	✓
PLCO		98				✓		✓
SHNX				74	✓			✓
HapMap								
CEU	116							✓
CHB				44				✓
JPT				44				✓
TSI	86							✓
YRI			59					✓
Total	930	98	59	162				

Available in dbGaP in October 2011

Imputation accuracy for European-American data
with DCEG and public reference set

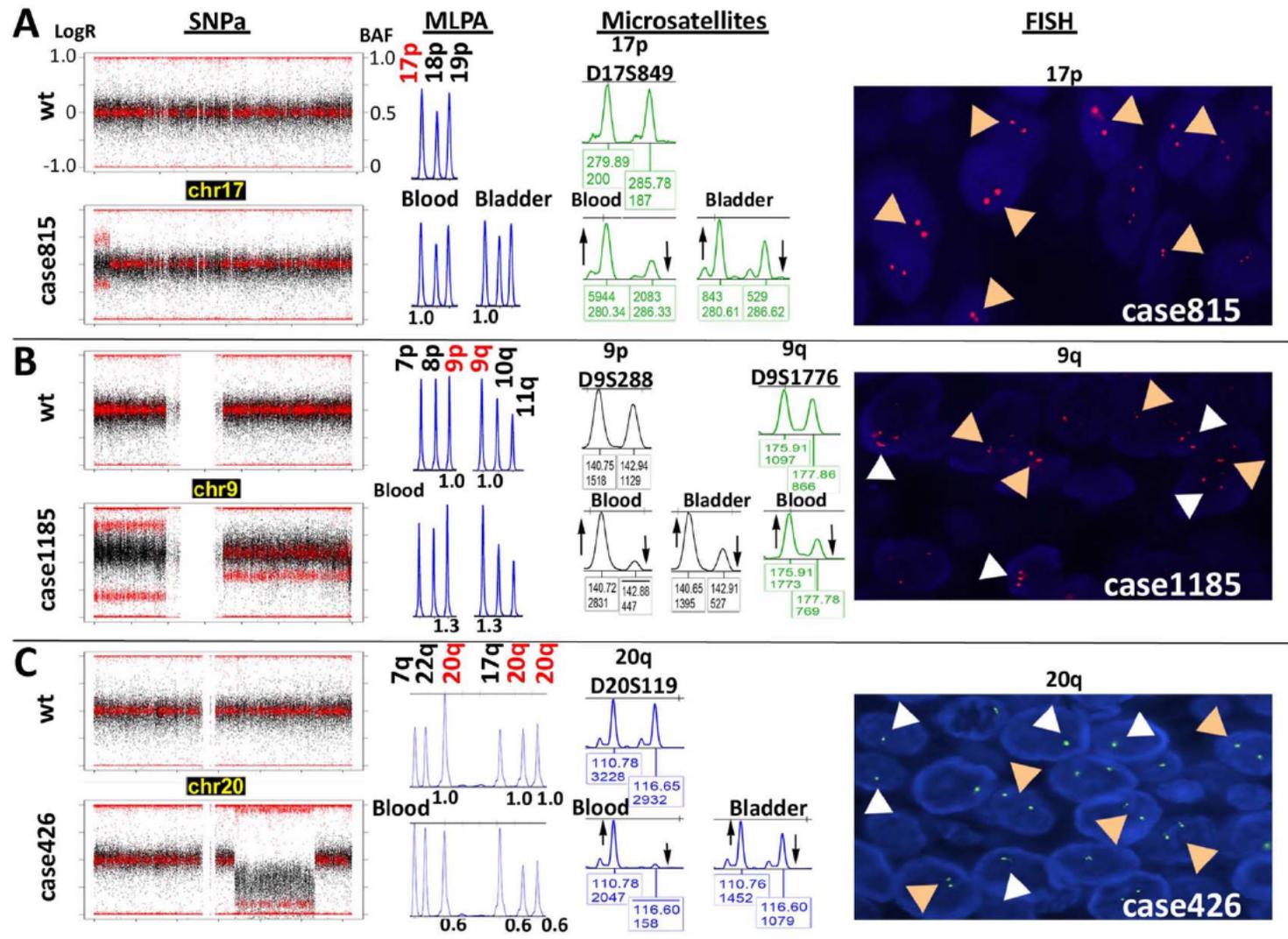


Allelic dosage based $R^2 > 0.8$

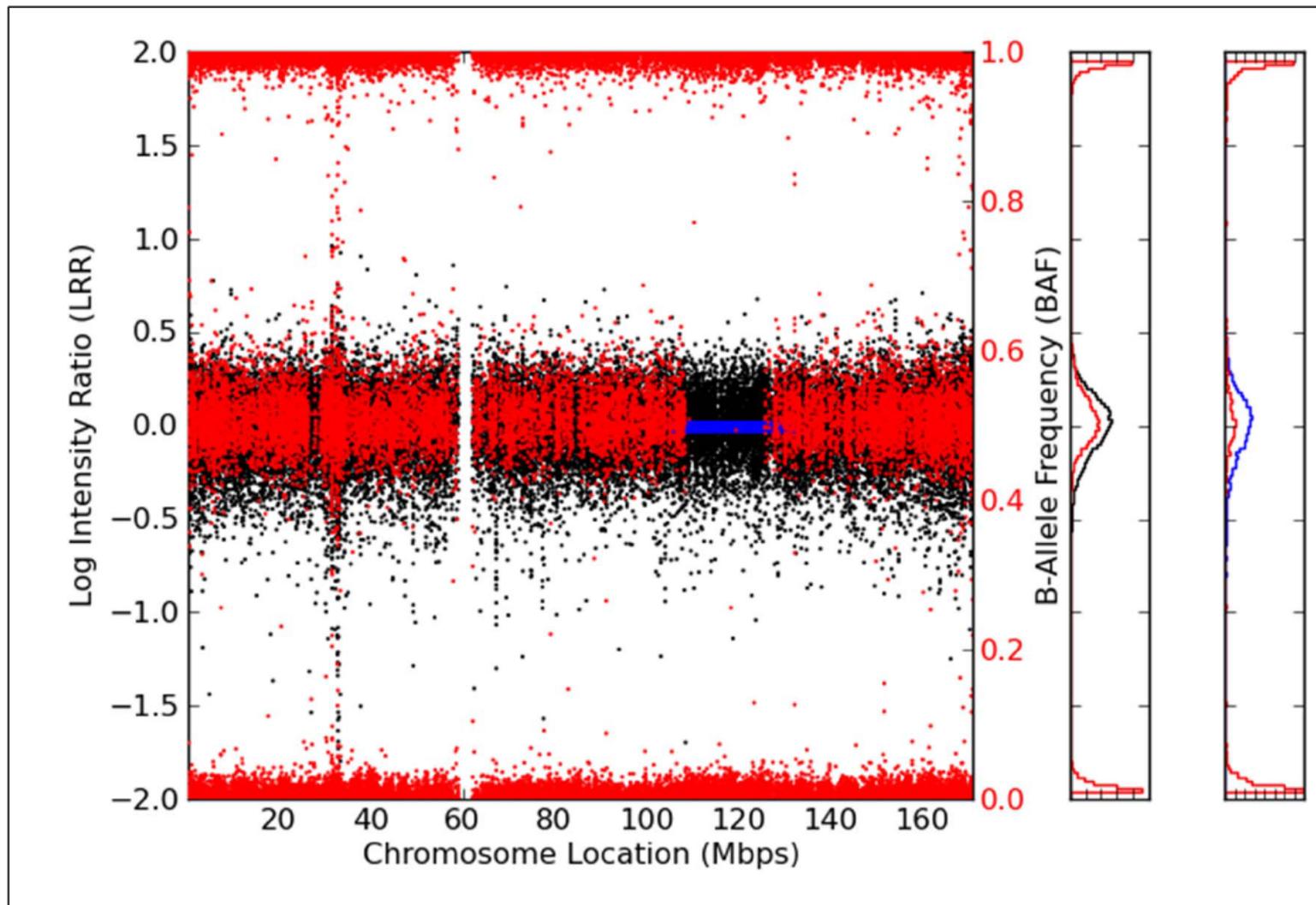
MAF	Improvement
10%	12%
5%	23%
3%	34%

3 sets of 60 samples using IMPUTE2 (Confirmed with BEAGLE)
R2 (pearson) for correlation

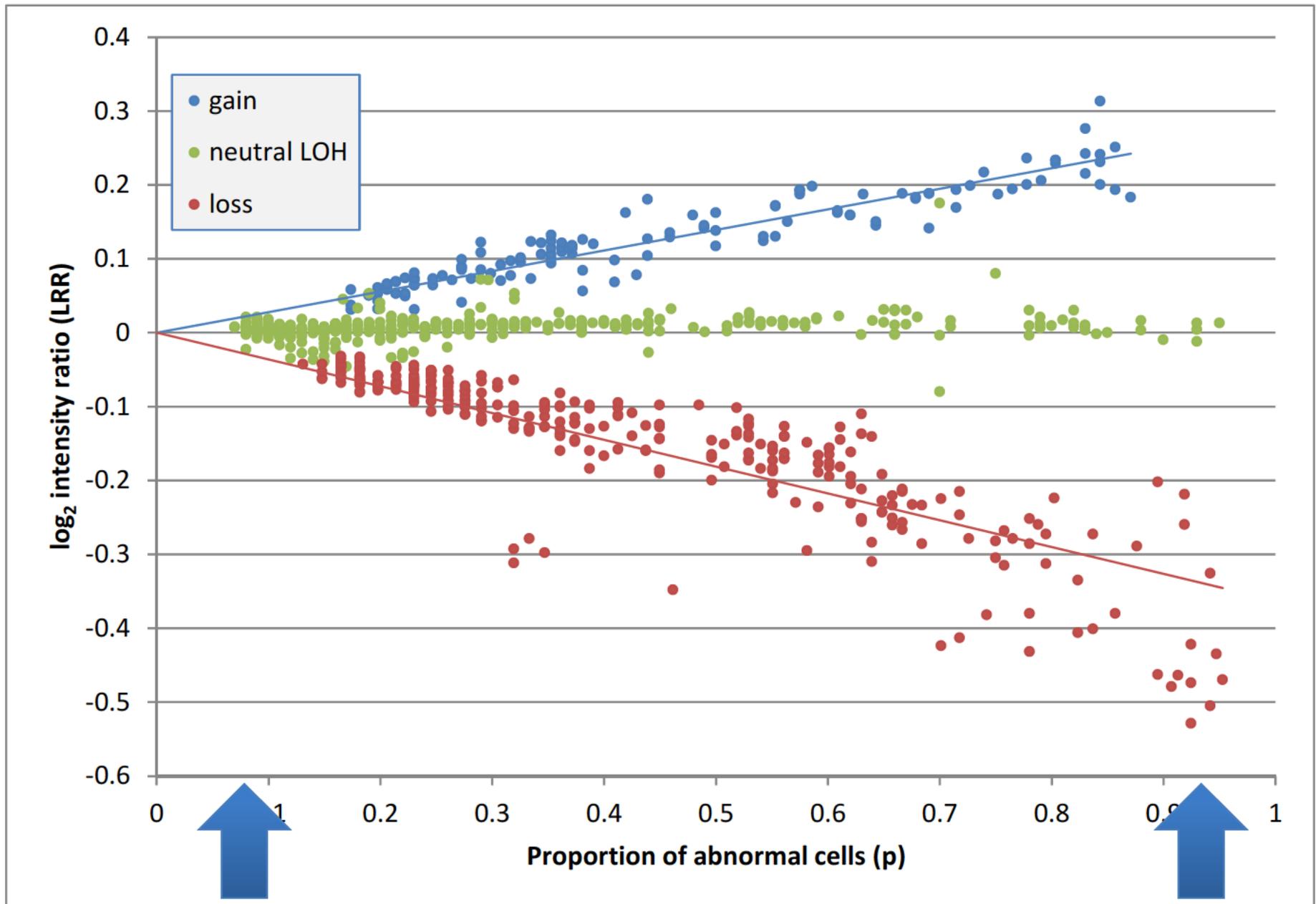
Validation for 42 events: 100% Validation



Segment inherited identical by descent (probably not *de novo* LOH)



Genetic Mosaic Events



Frequency of mosaic events by type & location

		Mosaic Chromosome Count					Mosaic Chromosome Frequency (%)				
Event Location		gain	loss	cnloh	mixed	Total	gain	loss	cnloh	mixed	Total
chromosome		62	11	42	5	120	9.7	1.7	6.6	0.8	18.7
telomeric P		11	13	114	1	139	1.7	2.0	17.8	0.2	21.7
telomeric Q		9	10	149	0	168	1.4	1.6	23.2	0.0	26.2
interstitial		14	185	2	1	202	2.2	28.9	0.3	0.2	31.5
span centromere		1	1	2	0	4	0.2	0.2	0.3	0.0	0.6
complex		0	3	0	5	8	0.0	0.5	0.0	0.8	1.2
	Total	97	223	309	12	641	15.1	34.8	48.2	1.9	

Adjusted Analysis of Association Between Genetic Mosaicism and Cancer in 49 studies

	All Cancer Cases			Likely Untreated			Possibly Treated		
	OR	95% CI	P value	OR	95% CI	P value	OR	95% CI	P Value
Non-heme Cancers	1.27	1.05-1.52	0.012	1.45	1.18-1.80	5.4E-04	1.03	0.81-1.30	0.804

Preliminary evidence for
Lung & kidney cancer

Early Detection of Hematological Cancers as Genetic Mosaicism

	Mosaic Counts			Non-Mosaic Counts			Mosaic Frequency (%)		
	Possibly			Possibly			Possibly		
	Untreated	Treated	Total	Untreated	Treated	Total	Untreated	Treated	Overall
hematologic cancer	9	9	18	34	62	96	20.93	12.68	15.79
leukemia	9	8	17	34	11	45	20.93	42.11	27.42
lymphocytic	5	4	9	14	5	19	26.32	44.44	32.14
myeloid	3	4	7	16	5	21	15.79	44.44	25.00
other/nos	1	0	1	4	1	5	20.00	0.00	16.67
lymphoma	0	1	1	0	42	42		2.33	2.33
multiple myeloma	0	0	0	0	9	9		0.00	0.00

- For untreated leukemia vs. cancer-free controls
 - DNA collected at least one year prior to diagnosis
 - OR=35.4 (14.7-76.6 95% CI), $p=3.8 \times 10^{-11}$
- DNA was obtained >5 years prior to diagnosis for 6 mosaic individuals, with the longest interval being 14 years

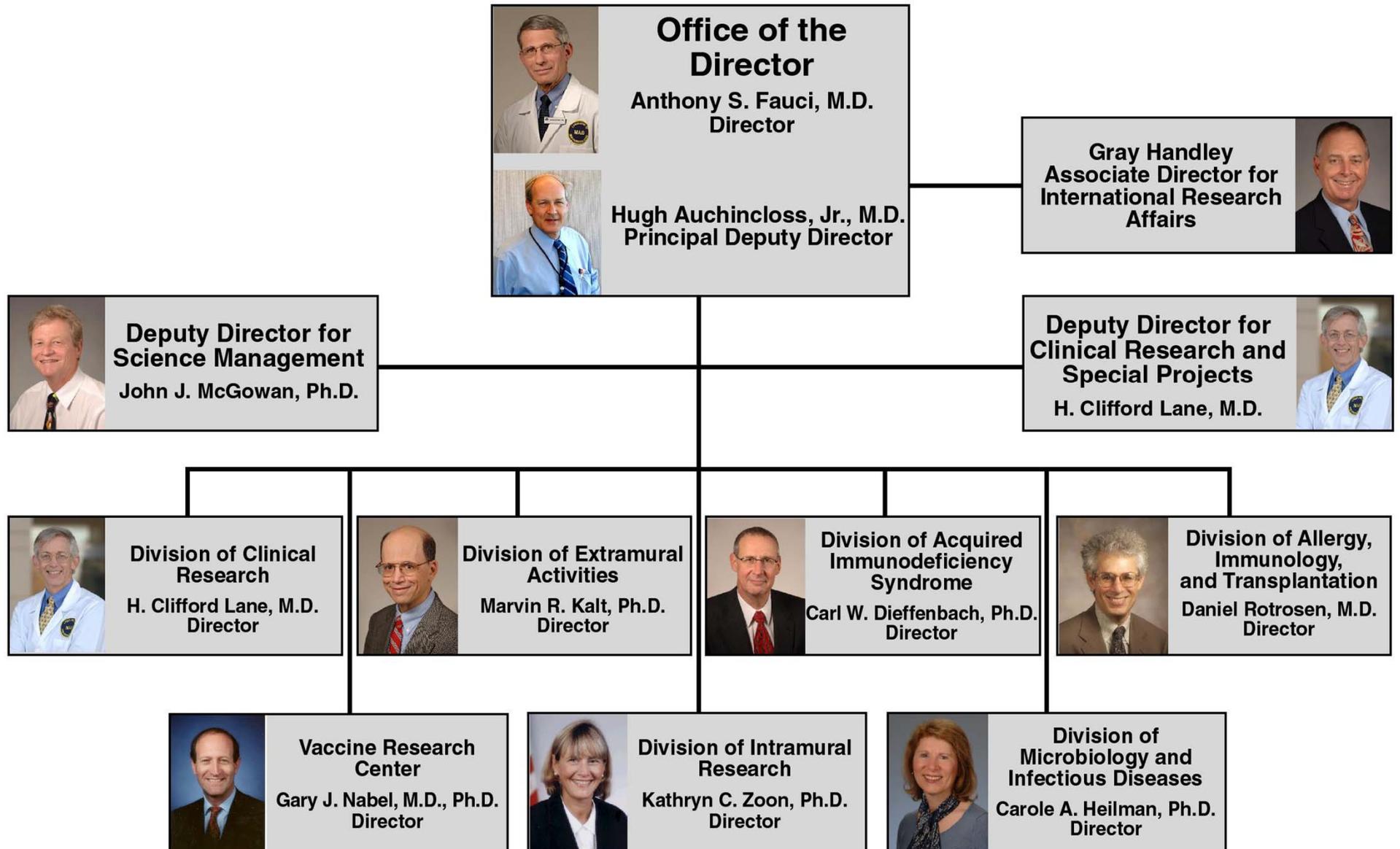
Overview of NCI- Frederick support to NIAID

H. Clifford Lane, MD

**Deputy Director for Clinical Research and Special Projects
National Institute of Allergy and Infectious Diseases
January 25, 2012**



NIAID Organizational Structure



National Institutes of Health

Budget Comparison by Institute/Center

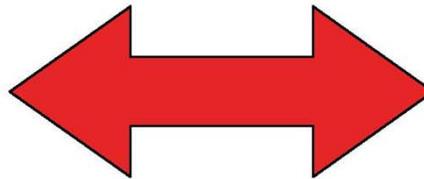
(Dollars in Thousands)

IC	FY 2011 Enacted	FY 2012 Enacted	Percent Change
NCI	\$ 5,058,577	\$ 5,072,183	0.3%
NIAID	4,478,668	4,490,711	0.3
NHLBI	3,069,723	3,079,021	0.3
NHGRI	511,497	512,873	0.3
NCRR	1,257,754	-	-100.0
NCATS	-	575,366	-
NIGMS	2,033,782	2,430,036	19.5
Other ICs	12,913,127	13,037,334	1.0
Subtotal	\$29,323,128	\$29,197,524	-0.4%
OD	1,166,963	1,459,117	25.0
B & F	49,900	125,344	151.2
Total	\$30,539,991	\$30,781,985	0.8%

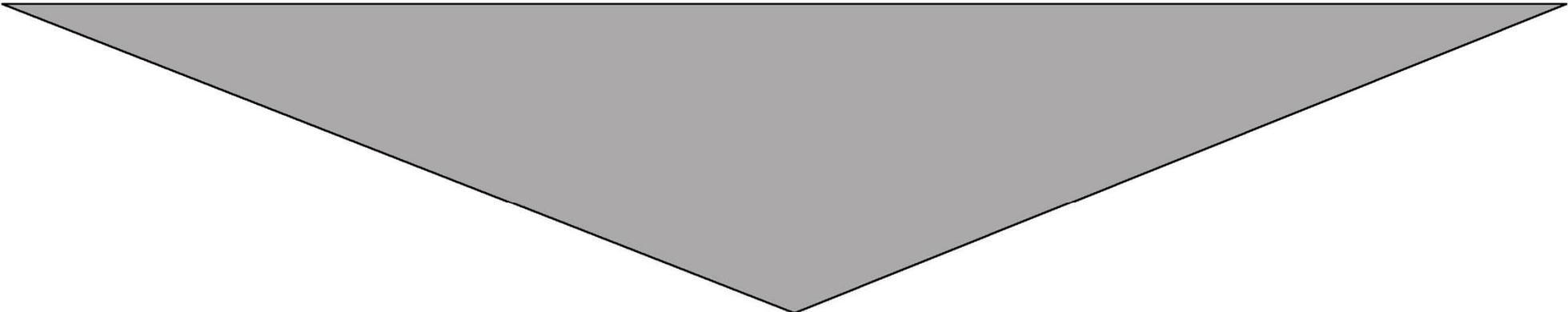
FY 2011 excludes the \$297.3M passed through to the Global Fund to allow comparison with FY 2012

NIAID Research: A Dual Mandate

Maintain and “grow” a robust basic and applied research portfolio in microbiology, infectious diseases, immunology and immune-mediated diseases



Respond rapidly to new and emerging disease threats



New/Improved Interventions

The Frederick Post

A real friend is someone who takes a winter vacation on a sun-drenched beach and *doesn't* send a card.

—Farmers' Almanac

RALEIGH QUAKER, JR.
P. O. BOX 115
BRUNSWICK MD 21715
APR 3 78

res Frederick, Maryland 21701

Saturday, March 18, 1978

4 Sections

Press Run Today | Post News 18,325 | Total 31,750

15¢

Detrick labs to house gene manipulation work

By ROLLIE ATKINSON
Staff Writer

Once a tiny airfield in the 1930s, and then the home of the U.S. Army Chemical Corps' massive effort into biological warfare research from 1943-1972, Frederick's Fort Detrick is now destined to become the home of the nation's major containment laboratory for genetic manipulation research.

In between, the complex of highly specialized scientific research facilities has been used for basic cancer research and continuing investigations into infectious diseases and development of new medical protection for the nation's armed forces. It remains the home of the Frederick Cancer Research Center and the U.S. Army Medical Research Institute of Infectious Diseases.

Friday, officials of the National In-

stitutes of Health (NIH) announced the launching of controversial recombinant DNA experiments at Fort Detrick in renovated germ warfare labs.

The international scientific community continues to express interest in Fort Detrick — the home of the first attempts in biocontainment procedures and the testing ground for much of today's knowledge into biosafety and work with hazardous organisms and substances.

When NASA sought expertise in developing a containment facility to receive and study its "moon rocks" — it borrowed designs and practices developed through the years of Detrick's experience with germ warfare.

The national Communicable Disease Center in Atlanta, Ga. also looked to Fort Detrick's experience and personnel in devising new laboratories to contain

studies with dangerous disease organisms.

And, when NIH sought a location for elaborate and expensive maximum containment facilities they logically turned again to Fort Detrick, with its former germ warfare labs standing idle.

Now, with \$250,000 worth of renovation and new equipment, Frederick will gain new notoriety as the home of the nation's major effort into controversial

gene-splicing experiments.

That new notoriety may not always be positive.

Friday, for the first time since Vietnam War days, protesters bearing placards reading "Who should play God?" and "Do the ends always justify the means?" stood vigil at Fort Detrick outside a large press briefing near build-

(Continued On Page A-6)

Are DNA hazards overrated?

By ROLLIE ATKINSON
Staff Writer

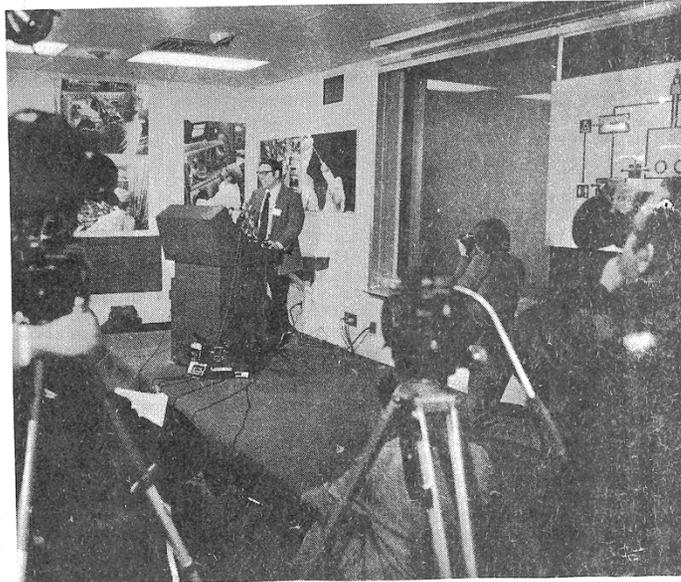
Dr. Malcolm Martin, who will direct the risk assessment experiments here into recombinant DNA techniques, believes, as many other scientists now do, that the precautionary measures, public controversy and elaborate and expensive safety facilities of gene-splicing may all be "exaggerated."

But, there was a time, a short three years ago, when many scientists like Dr. Martin issued public warnings on the potential hazards of recombinant DNA work.

A group of prominent scientists led a successful move to ban certain recombinant DNA tests with known pathogens and human cells and instigated the formation of National Institutes of Health (NIH) safety guidelines on the research.

Now, however, some of those same scientists regret sounding the alarm which also created wider spread public protests and debate, such as a small demonstration by local people Friday at Fort Detrick.

"You will never be able to answer all the possible risk scenarios involved in recombinant work," Dr. Martin admitted.



Scientists and pickets

Members of the international press filled a meeting room at Fort Detrick Friday morning to hear presentations on the recombinant DNA experiments to be conducted there. Shown here speaking before still and television cameras is Dr. Bernard Talbot, special assistant for Intramural Affairs. While



the meeting progressed smoothly indoors, demonstrators from the People's Business Commission and Western Maryland Clergy and Laity Concerned remained present but peaceful outside. For more photos see page A-3. (Photos by C. Kurt Holter)

Are DNA hazards underrated?

By ROLLIE ATKINSON
Staff Writer

A member of a silent vigil opposing the opening of a local recombinant DNA lab at Fort Detrick stepped forward Friday during a press briefing to challenge "the spending of taxpayer's money for the federal government to experiment with the creation of new life forms."

Jeremy Rifkin, author of *Who Should Play God*, a critical book on the subject of recombinant DNA and genetic engineering, encountered National Institutes of Health (NIH) officials by saying: "You are right, this is an historical moment for all of us. Our government is about to embark into the Brave New World of manipulating the genes of life. We should be asking why do this type of research at all."

Outside, near the recently-renovated maximum containment gene-splicing laboratory, a group of local citizens, clergy and other members of Rifkin's Peoples Business Commission stood in silence with signs reading, "Who should play God?" and "Do the ends always justify the means?"

Asked if the protest was in any way connected to former germ warfare research at Fort Detrick, one protester

NIAID / NCI Frederick Timeline

- **1978 – Recombinant DNA experiments in Bldg. 550**
- **1985 – Immunologic monitoring of patients with AIDS in Bldg. 560; later moved to Bldg. 469**
- **1986 – Mike Baseler hired**
- **1994 – Virologic monitoring of patients with AIDS in Bldg. 550**
- **2005 – Vaccine Pilot Plant**

Support Provided by NCI-Frederick to NIAID

- **Clinical Research Infrastructure**
- **Support to “Special Projects”**

Clinical Research Infrastructure Support Provided by NCI-Frederick

- **MDs, Nurses,
Pharmacists**
- **Protocol
Development**
- **IND Management**
- **Clinical Research
Monitoring**
- **Laboratory Support**
 - **Monitoring**
 - **Biomarker analysis**
 - **Repository**
 - **Biopharmaceuticals**
 - **Vaccine Production**
 - **Education**

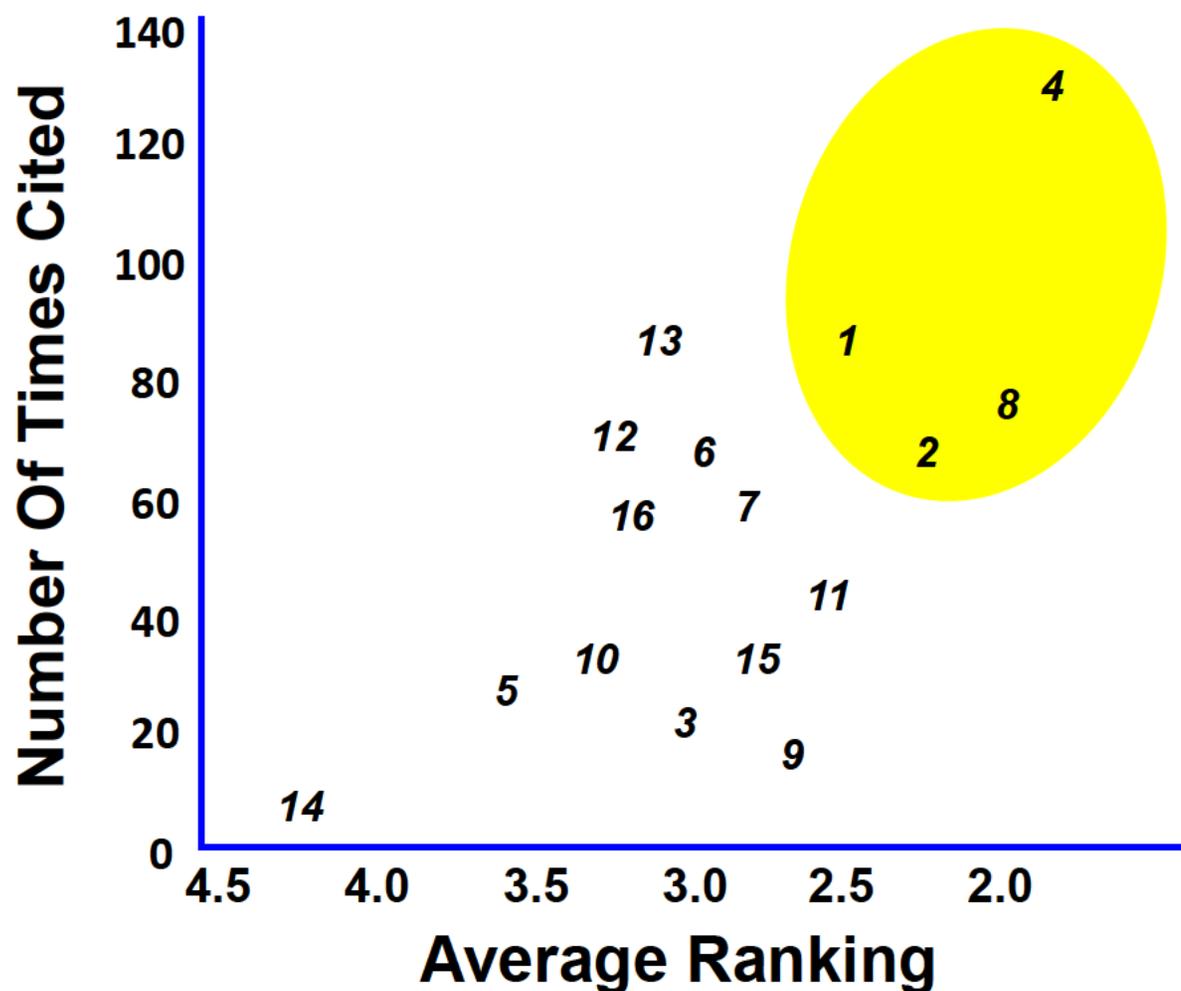
Clinical Research Infrastructure Support Provided by NCI-Frederick

- MDs, Nurses,
Pharmacists
- **Protocol
Development**
- IND Management
- Clinical Research
Monitoring
- Laboratory Support
 - Monitoring
 - Biomarker analysis
 - Repository
 - Biopharmaceuticals
 - Vaccine Production
- Education

Barriers to Clinical Research Project (2007)

- **Identify key policies, practices. Regulations, and legislation governing NIH-sponsored human subject clinical research that limit the effectiveness and efficiency of clinical research**
- **Make recommendations to facilitate and improve effectiveness and efficiency of clinical research**

Initial Targeted Barriers- Based on Frequency and Ranking

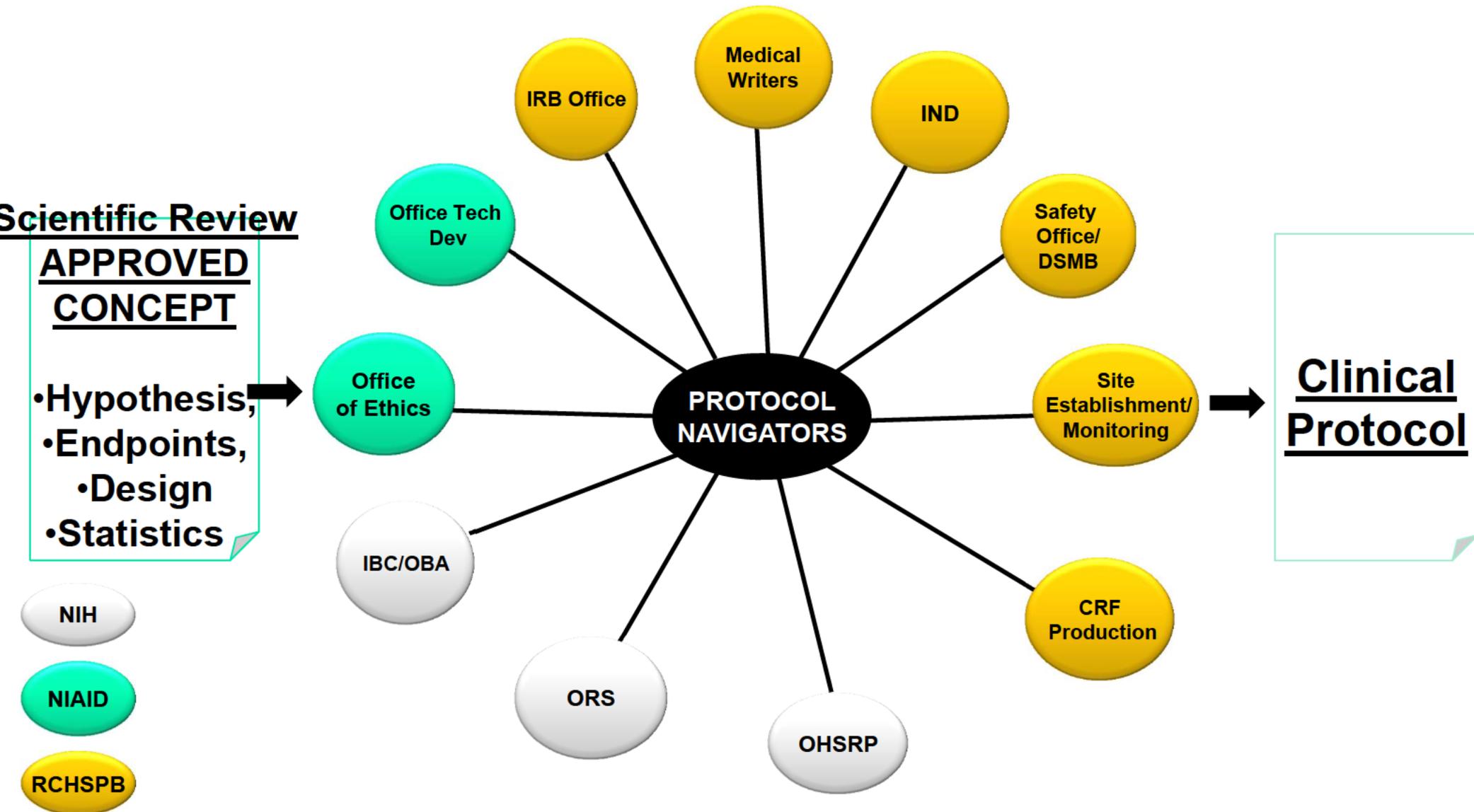


BARRIER	
1	Scientific Review / Approval Protocols
2	Interaction – Industry / Tech Transfer
3	Bio-Safety Committee Review
4	IRB & Ethical Issues
5	Site Registration / Approval
6	Informed Consent & Documentation
7	Conflict Of Interest
8	Adequacy Of Resources
9	Conflicts – U.S. / Local Requirements
10	Adverse Event reporting
11	FDA / OHRP Interactions
12	Protocol Monitoring & Compliance
13	Management Of Samples
14	Research-related Injury
15	Work In International Settings
16	Collaborations

Survey of Intramural Investigators: Results and Response

- **Identified that Clinical Research Support Services were inadequate to meet the increasingly complex demands of clinical research.**
- **In response to this need, NIAID moved forward to develop a Protocol Navigation/Protocol Development Program.**

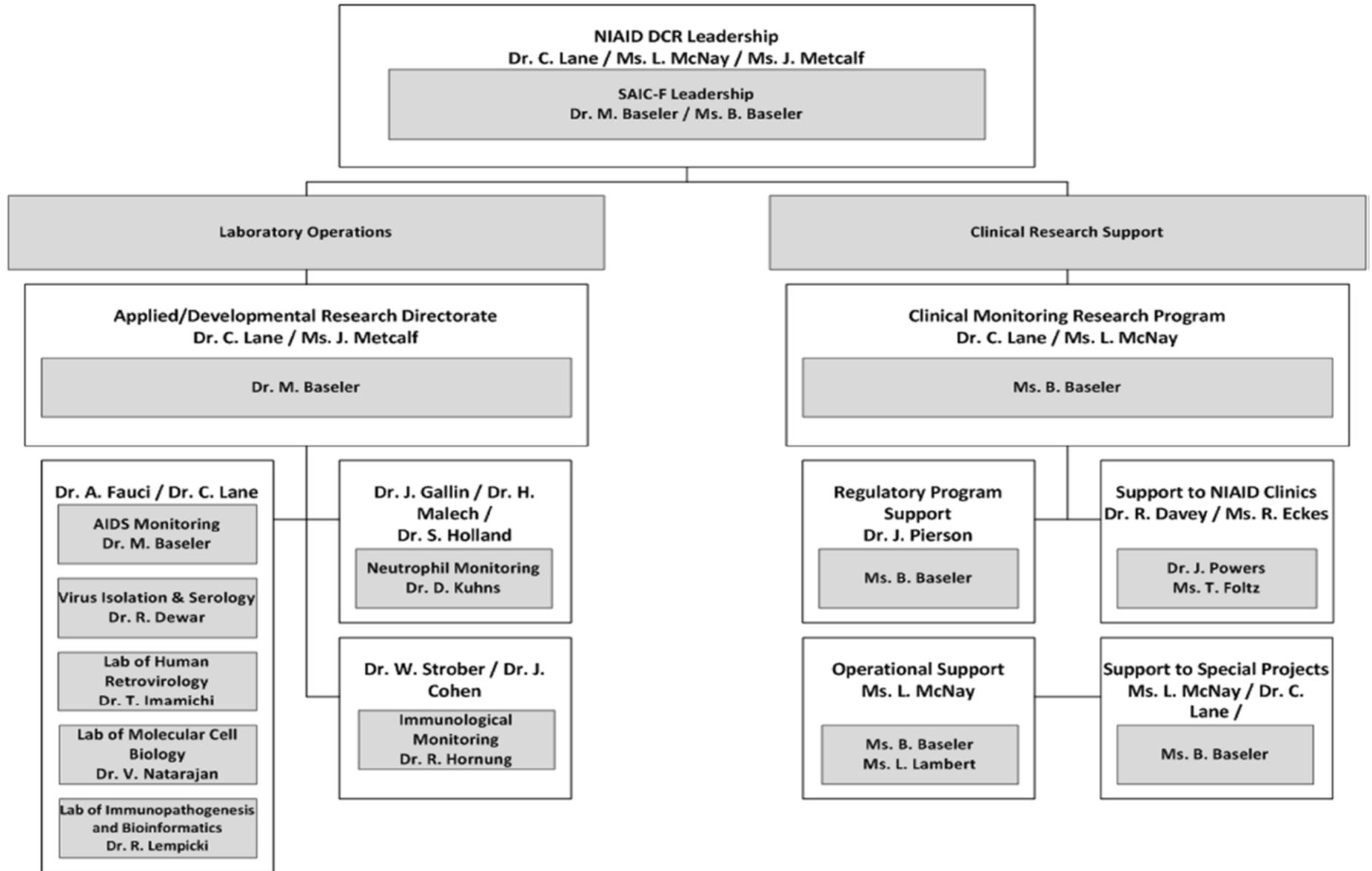
The Protocol Navigator Interface



Factors Leading to Choice of NCI-Frederick for a Given Task

- **Need for an ongoing, close working relationship**
- **Recurrent similar tasks, minimize need for training new staff**
- **Rapid response**
- **Complement other awards**

NCI-Frederick Support to NIAID Clinical Research and Special Projects



Clinical Research Infrastructure Support Provided by NCI-Frederick

- MDs, Nurses,
Pharmacists
- Protocol
Development
- IND Management
- Clinical Research
Monitoring

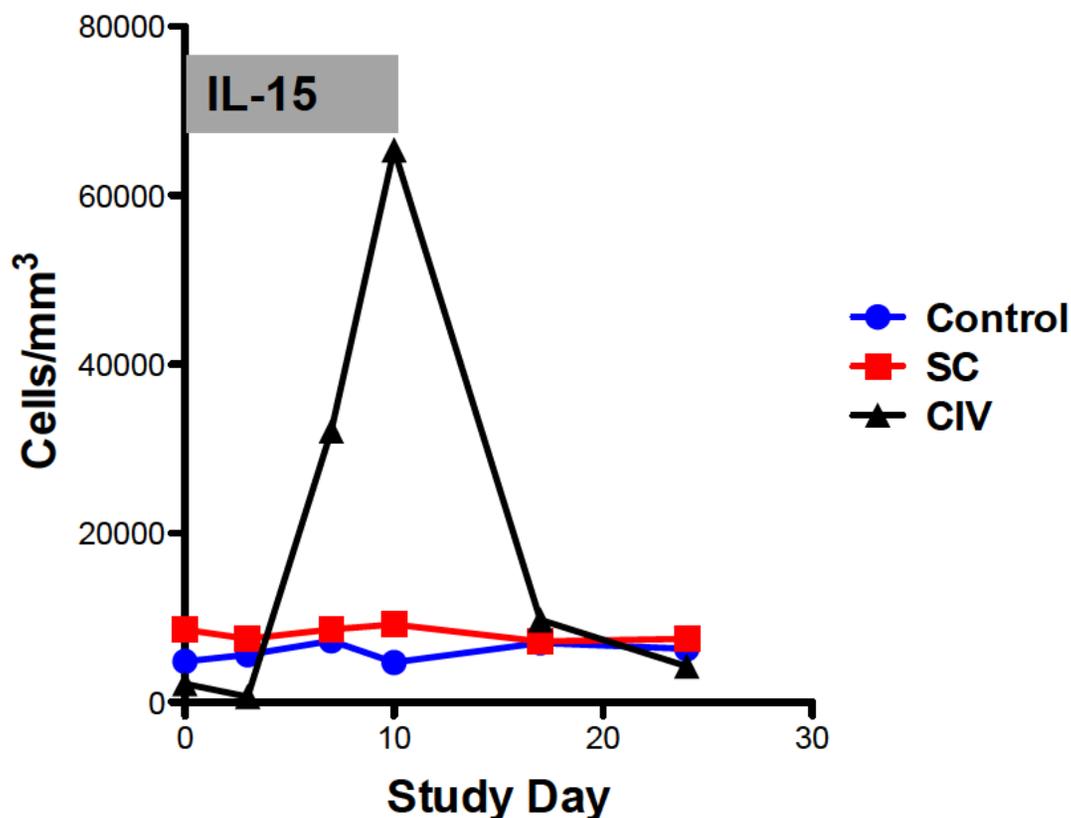
- **Laboratory Support**
 - Monitoring
 - Biomarker analysis
 - Repository
 - **Biopharmaceuticals**
 - Vaccine Production
- Education

Development of IL-15 as a Potential Treatment for HIV/AIDS

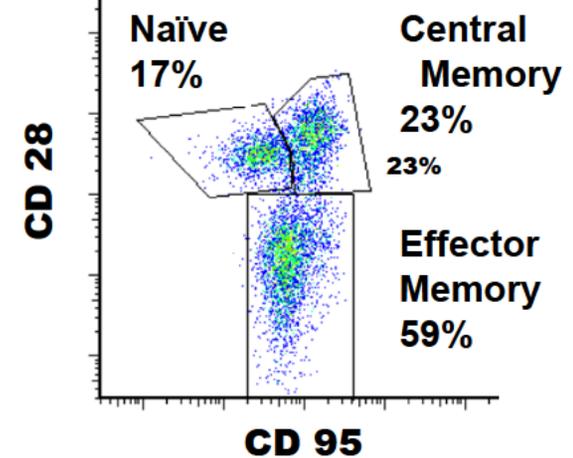
- **Common gamma-chain using cytokine with potent effects on CD8+ T cells**
- **Studied by Tom Waldmann for many years but no commercial development**
- **Working together with Tom and NCI-Frederick, clinical grade IL-15 has been produced and is in clinical trials**

100-Fold Increase in Effector CD8+ T Cells in Non-Human Primates Treated with a 10-Day Continuous IV Infusion of IL-15

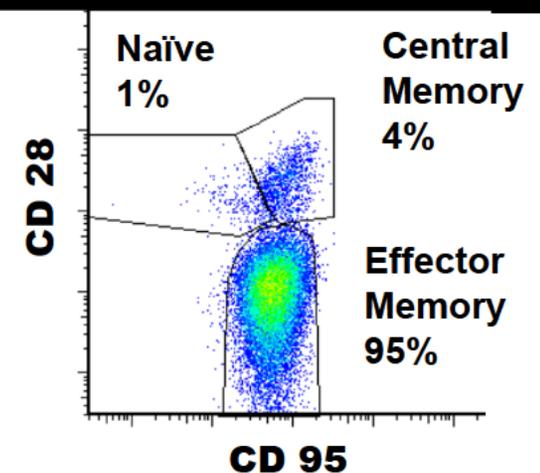
Total CD8 T Lymphocyte Counts



Day 0



Day 10



Support Provided by NCI-Frederick to NIAID

- Clinical Research Infrastructure
- **Support to “Special Projects”**

Characteristics of NIAID Special Projects

- **Identified by NIAID Director**
 - **High priority**
 - **Urgent and compelling**
 - **No other mechanism could easily meet the need**
 - **Often involve other governments**

Current Special Projects in NIAID

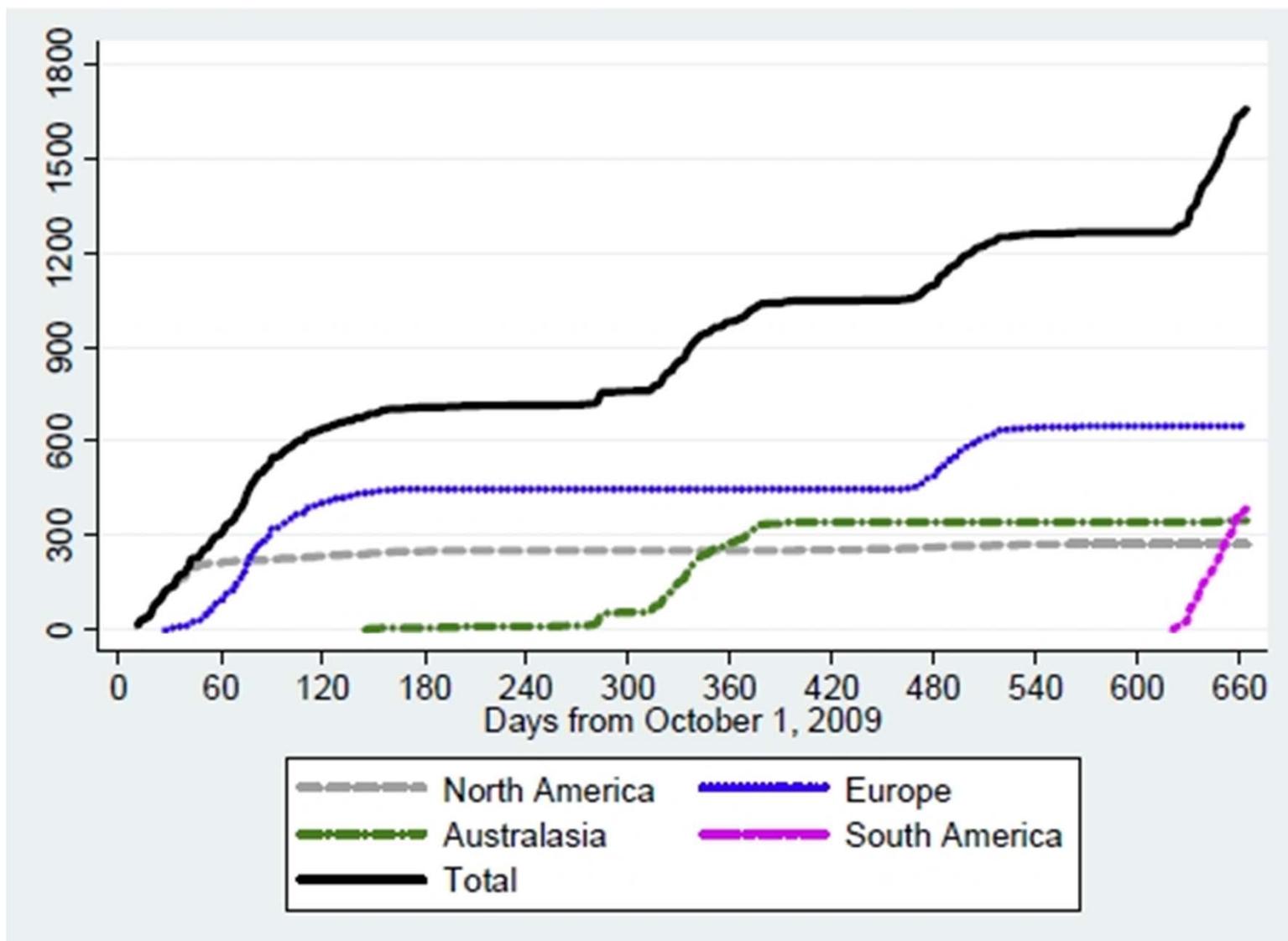
- **Influenza**
 - **Observational cohort studies**
 - **Interventional studies**
- **Project Phidisa (US-South Africa)**
- **DC Partnership for HIV/AIDS**
- **US DoD ID Clinical Research Program**

One Never Knows Where the Next Influenza Pandemic Will Arise



INSIGHT- Observational Cohort Study FLU 002

Cumulative enrollment over time by geographic region.



D-dimer and Risk of Bad Outcome in FLU 002 and FLU 003

D-dimer Tertile*	Odds Ratio (CI)		
	FLU 002	FLU 003 General Ward	FLU 003 ICU
1 (lowest)	1.0	1.0	1.0
2	1.9 (0.6-6.1)	3.3 (0.8-12.9)	4.9 (0.9-25.7)
3 (highest)	4.2 (1.3-13.8)	6.8 (1.9-24.9)	22.0 (3.1-157.3)

*Univariate model; tertiles computed separately for each cohort

Special Project: La Red- Mexico



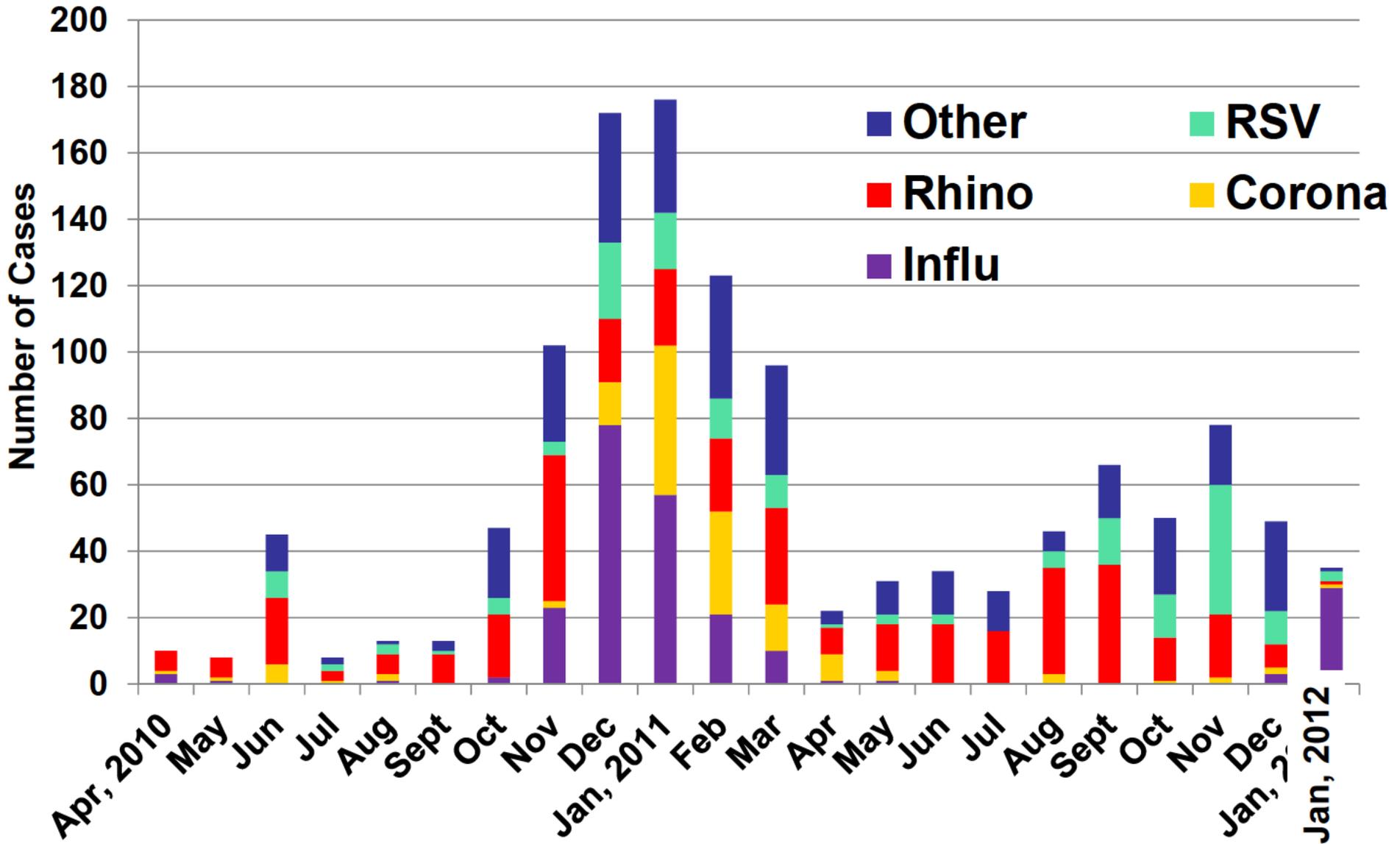
**Signing of the Letter of Intent with the Mexico Minister of Health
2009**

La Red- Mexico Emerging Infectious Diseases Clinical Research Network

- LOI between NIAID and MoH of Mexico in 2009
- 5 clinical sites in Mexico City
- Observational Study of Influenza-like illness in Mexico
- Influenza Combination Therapy Trial



ILI002 – Enrollment as of Jan 10, 2012. n=1,776



Special Project: Phidisa

■ Partnership between South African National Defense Force, NIH, US DoD, and US State Department

■ Goals

- Provide treatment to HIV-positive SANDF members and their dependents in the context of clinical research
- Answer research questions relevant to S. Africa
- Build research capacity within the South African Military Health Service (SAMHS)

■ Over 6000 volunteers enrolled as of December, 2011



Signing of Formal Agreements between US and RSA by US Embassy and South African Officials



Amb. Frasier and Minister Lakota
April 26, 2005

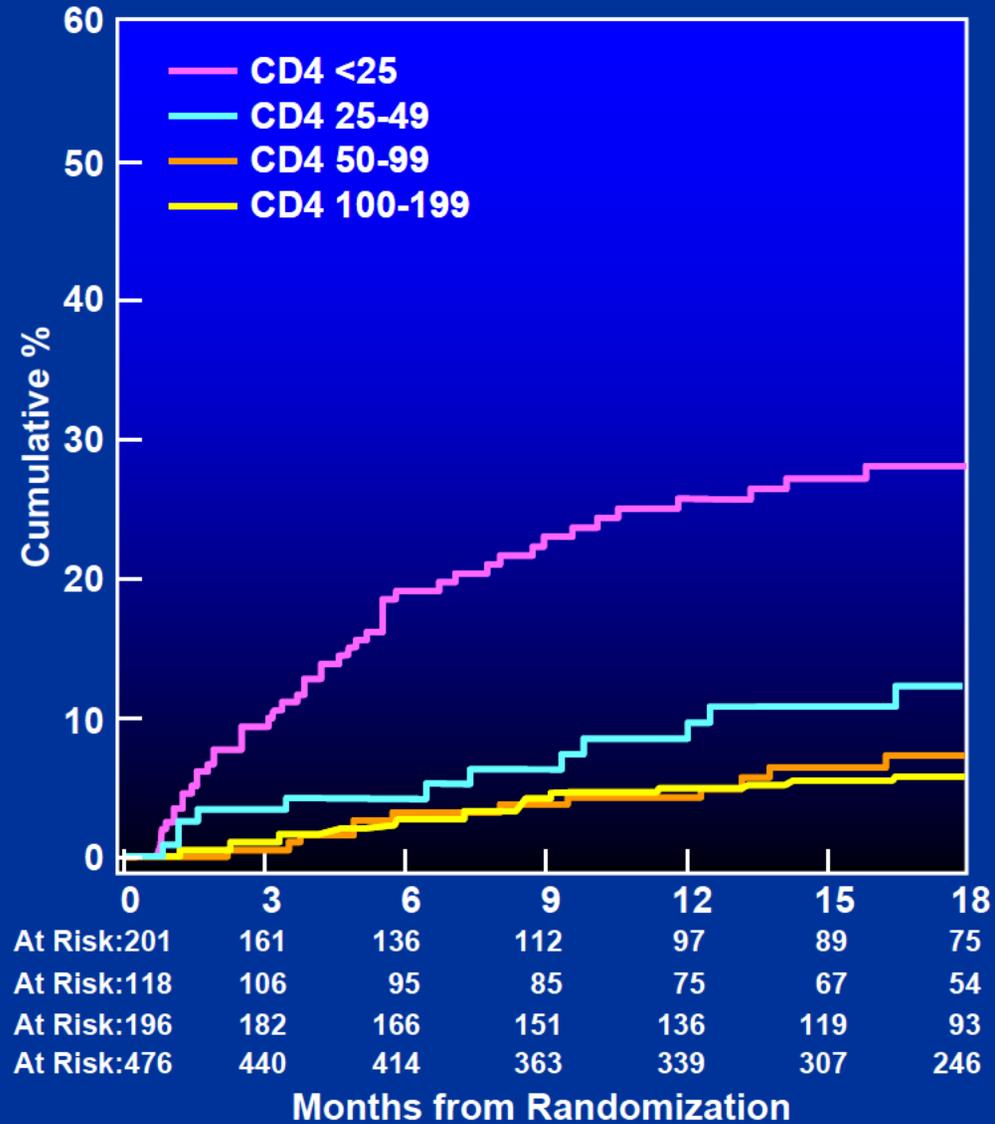
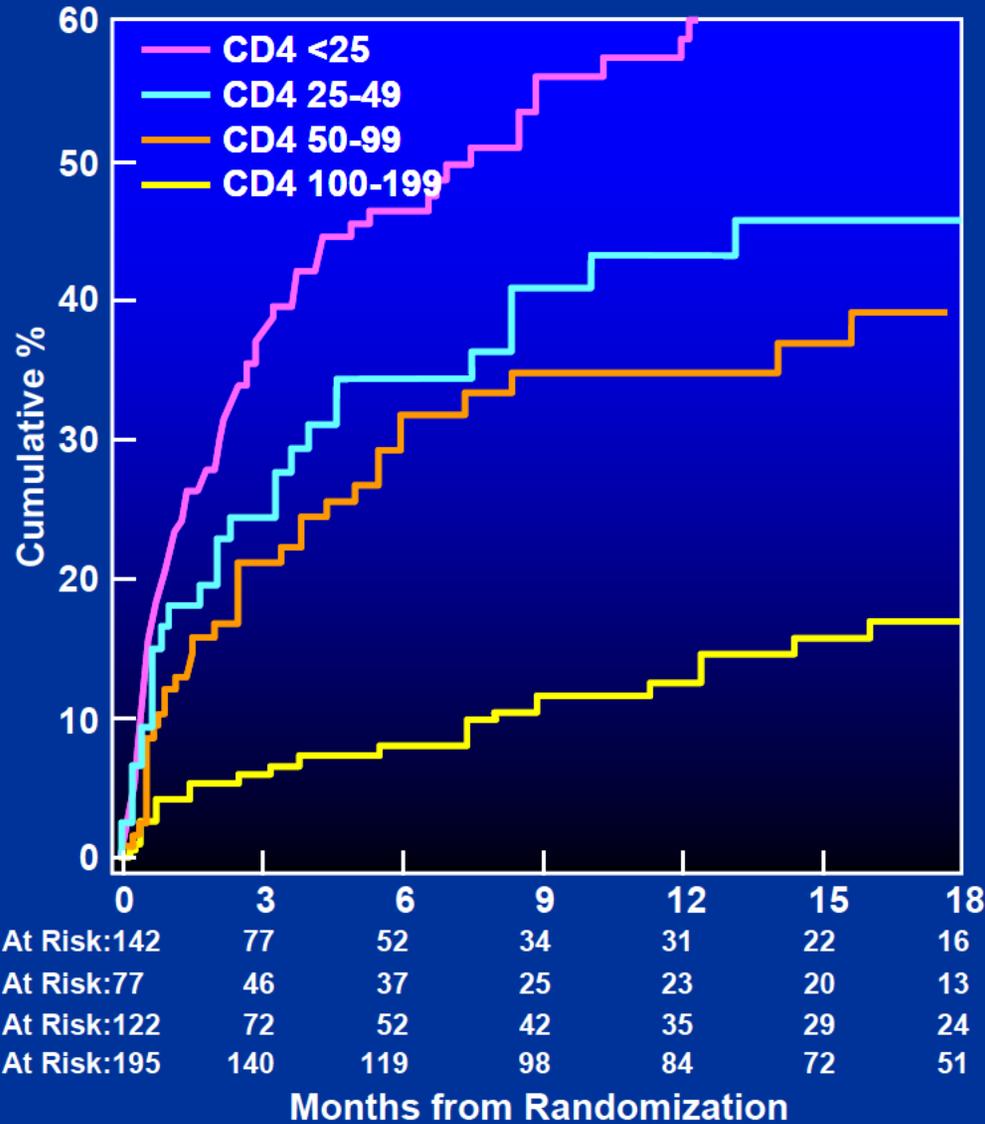


DCM La Lime and MG Motumi
October 5, 2010



Comparison of Outcomes in Untreated vs. Treated Pts.

K-M Estimates of Mortality Rates Over Follow-up by CD4; $p < 0.0001$



Special Project- DC PFAP

Launch of D.C. Partnership for HIV/AIDS Progress, Jan. 12, 2010



Photos: V. Aiyer/Executive Office of the D.C. Mayor (L); J. Marquardt (R)



Carl Dieffenbach, PhD
Director, Division of AIDS
National Institute of Allergy and
Infectious Diseases



Henry Masur, MD
Chief
Critical Care Medicine
Department
NIH-Clinical Center



Gregory Pappas, MD, PhD
Senior Deputy Director for HIV/AIDS,
Hepatitis, STD, and TB Administration,
Department of Health
District of Columbia

The mission of DC PFAP Sub specialty Clinics is to reduce the burden of HIV in DC by developing an innovative community-based clinical research program that will inform health care strategies and impact the AIDS epidemic and create a model for other urban areas and globally.

DCPFAP Steering Committee

NIAID Review of Projects Supported by NCI- Frederick

- **Board of Scientific Counselors for Projects led by Intramural Investigators**
- **For Special Projects there are Two Levels of Review**
 - **NIAID Research Initiative Committee**
 - **Project-Specific External Scientific Advisory Committees**

Summary

- **NCI-Frederick is a critical component of the NIAID clinical research effort**
- **This is especially true for the support of intramural investigators and “Special Projects”**
- **Consistency, flexibility and rapid response time are key factors in choosing NCI-Frederick for select activities within the NIAID portfolio**

Overview – The Life Cycle of Programs at the NCI-Frederick

NCI-Frederick Advisory Committee
January 25, 2012

U.S. DEPARTMENT
OF HEALTH AND
HUMAN SERVICES

National Institutes
of Health



Initiation of New Programs at NCI-Frederick

- Ideas for new research programs come from the NCI Divisions, Offices, and Centers (DOCs).
- As appropriate, advice and input on concepts for new programs are obtained by the DOCs.
- The DOCs are responsible for funding each new program.
- New program concepts are often discussed with NCI-Frederick staff (both government and contractor) to help sort out the implementation details - but the final statement of work (SOW) for the new program is the responsibility of the DOCs.
- New projects are brought to the NCI-Frederick through an electronic request system called Yellow Tasks.

Initiation of New Programs (cont.)

- Requests to initiate new programs (Yellow Tasks) are sent to the NCI-Frederick Project Officer (PO) and Contracting Officer (CO) to determine;
 - Is the effort within the scope or special competency of the FFRDC?
 - Does capacity exist to carry out the effort?
 - Is the work considered inherently governmental?
 - Does funding exist for the project?
 - Are the costs proposed reasonable, allowable and allocable?
 - Can the work be accomplished most effectively as a grant, contract, or through the FFRDC?

Initiation of New Programs (cont.)

- Following approval of the Yellow Task by the NCI PO and CO the proposed programs are brought to the OTS contractor who will determine how to proceed with the effort
 - To facilitate complicated or large programs the contractor may develop a project team composed of both government and contractor staff.
 - The contractor/project team may recommend to perform the effort in-house (NCI-Frederick) or choose to outsource the requirement.
 - If the effort is outsourced the contractor would openly solicit and evaluate all proposals following commercial best practices which generally follow the spirit and intent of the normal NIH/NCI procurement processes found in the NIH Policy Manual.
 - The final source selection is made by the contractor but the process and final selection may be reviewed and concurred to by the NCI CO and PO.

Monitoring of Programs at the NCI-Frederick

- The monitoring of dedicated research programs at the NCI-Frederick is the responsibility of the sponsoring NCI DOCs.
- The appropriate source of advice and frequency of monitoring of dedicated research programs is determined by the DOCs.
- The monitoring of shared-service programs at the NCI-Frederick is the responsibility of the NCI-Frederick Office of Scientific Operations (OSO).
 - Advanced Technology Program (ATP)
 - AIDS and Cancer Virus Program (ACVP)
 - Laboratory Animal Sciences Program (LASP)

Monitoring of Shared-service Programs

- Advanced Technology Program (ATP)
 - Since 1998 complete review of all laboratories every 3 years
 - Review committees are composed of NCI/NIH users (PIs) and outside experts (50/50)
 - Reviews cover administration cost, personnel, core services, technology development, and value added to NCI
- AIDS and Cancer Virus Program (ACVP)
 - Review of both the PI research effort and core service laboratories every 3 years - conducted by the NCI Board of Scientific Counselors (BSC)
- Laboratory Animal Sciences Program (LASP)
 - Annual review of selected parts of the program done by contracted outside experts

Monitoring of Dedicated Programs

- Dr. Grodzinski - Office of Nanotechnology Research (OCNR), CSSI; Nanotechnology Characterization Laboratory (NCL)
- Dr. Doroshov - Division of Cancer Treatment and Diagnosis (DCTD)
- Dr. Wiltrout - Center for Cancer Research (CCR)

Nanotechnology Characterization Laboratory: *Foundation, Operation, Scientific Output, and Peer Review*

Piotr Grodzinski, Ph.D.

January 25, 2012



Advanced Technology Program



<http://ncl.cancer.gov>

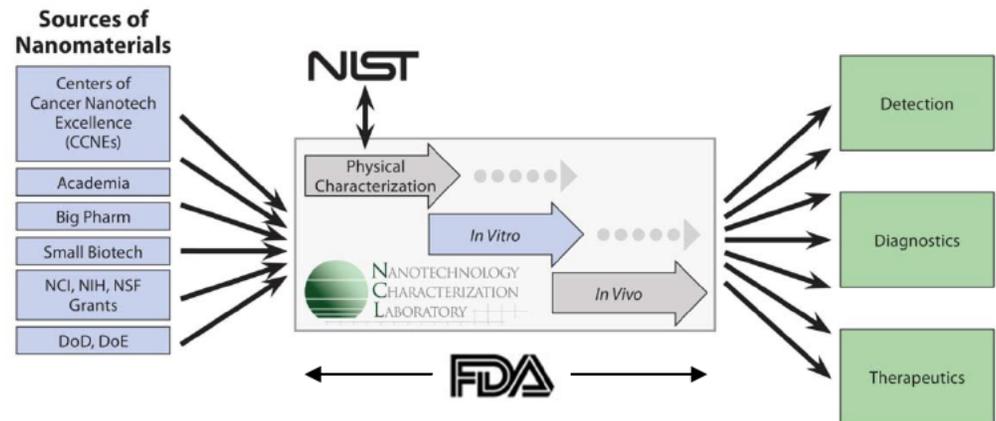


Frederick

NCL – Background



- The NCL is a resource for in-depth characterization of nanomaterials to be used in new diagnostics and therapeutics. The data produced by the NCL facilitates translation of promising nanotech formulations to the clinic.
- The NCL was established in 2004 as an interagency collaboration among NCI, NIST, and FDA. Its budgets were included in Funding Plans (2005, 2010) of the Alliance for Nanotechnology
- Scott McNeil heads the laboratory.
- NCL performs preclinical characterization of nanomaterials, including:
 - physicochemical characterization
 - *in vitro* experiments
 - *in vivo* testing for safety and efficacy.



90% of NCL's efforts support the extramural community.

NCL – Why It Was Established?



- NCL was established in response to an NCI survey of investigators working in cancer nanotechnology. The PIs identified areas requiring additional support:
 - Standard assays for nanomaterials characterization
 - Hub for the data on different nanomaterials
 - Development of reference materials
 - Interdisciplinary expertise
- NCL is perceived as an objective entity, does not ‘compete’ with academic or industrial researchers
- Collaboration with NCL allows PIs to take advantage of “lessons learned” – sharing data on:
 - Trends in biocompatibility
 - Performance of different nanomaterials
 - Conduit to FDA strategies towards nanotechnology.

Accomplishments

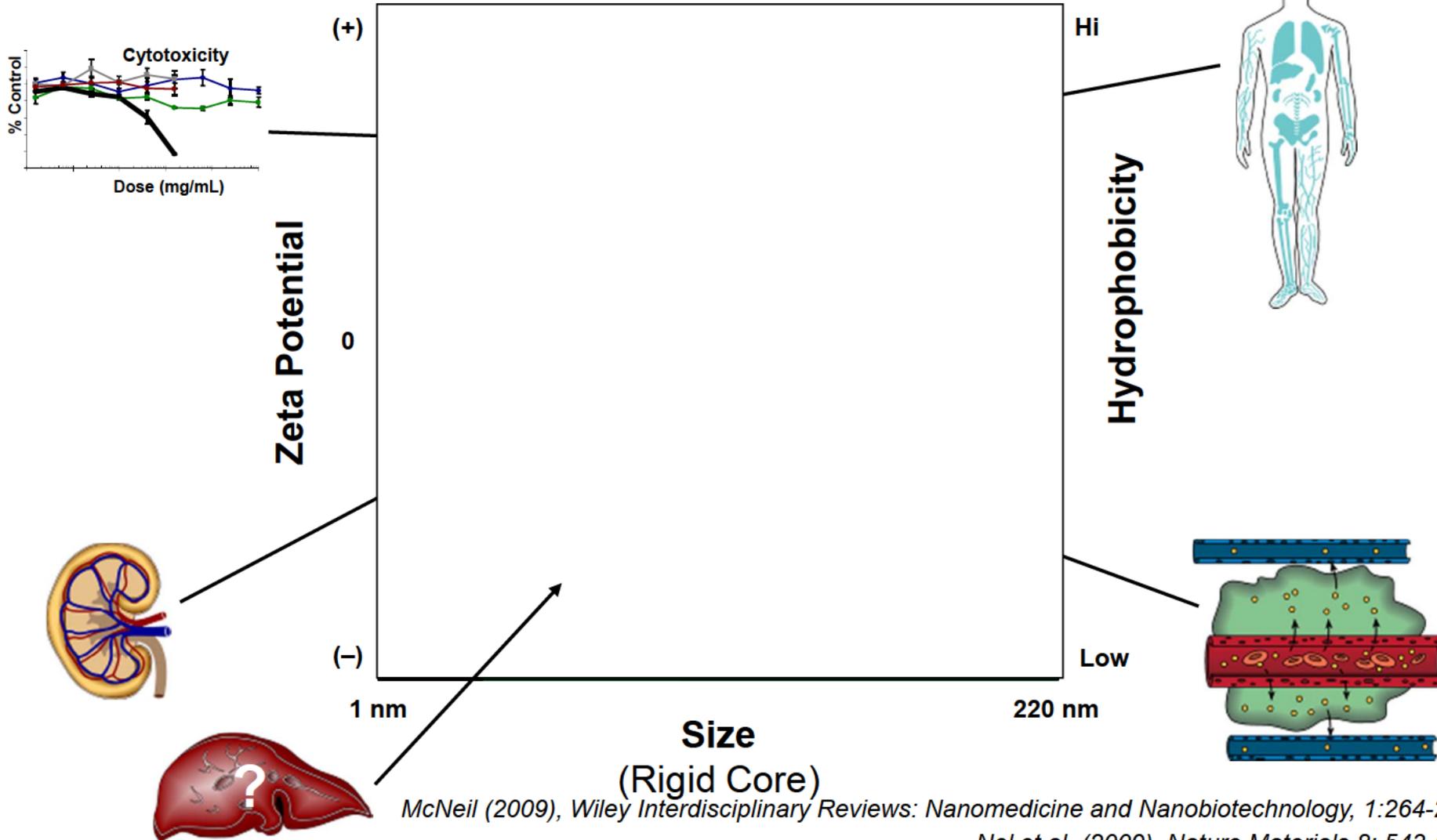


- NCL has characterized more than 250 candidate nanotech formulations, 5 of which are in clinical trials, many more in pre-IND stages.
- Each year of operations:
 - ~20 animal studies
 - ~10 publications
 - over 900 pages of data for collaborators in reports
 - ~10 new materials transfer agreements (MTAs)
- NCL collaborates and supports other institutes and agencies:
 - provides support for NIEHS center grants on 'nanotechnology health implications research'
 - Collaborates on database developments; caNanoLab (NCI), nano-registry with NIBIB and NIEHS;
- Standards development and interlaboratory studies with ASTM & ISO. Reference material development with NIST.



Nanoparticle Biocompatibility

Nanoparticle Biocompatibility

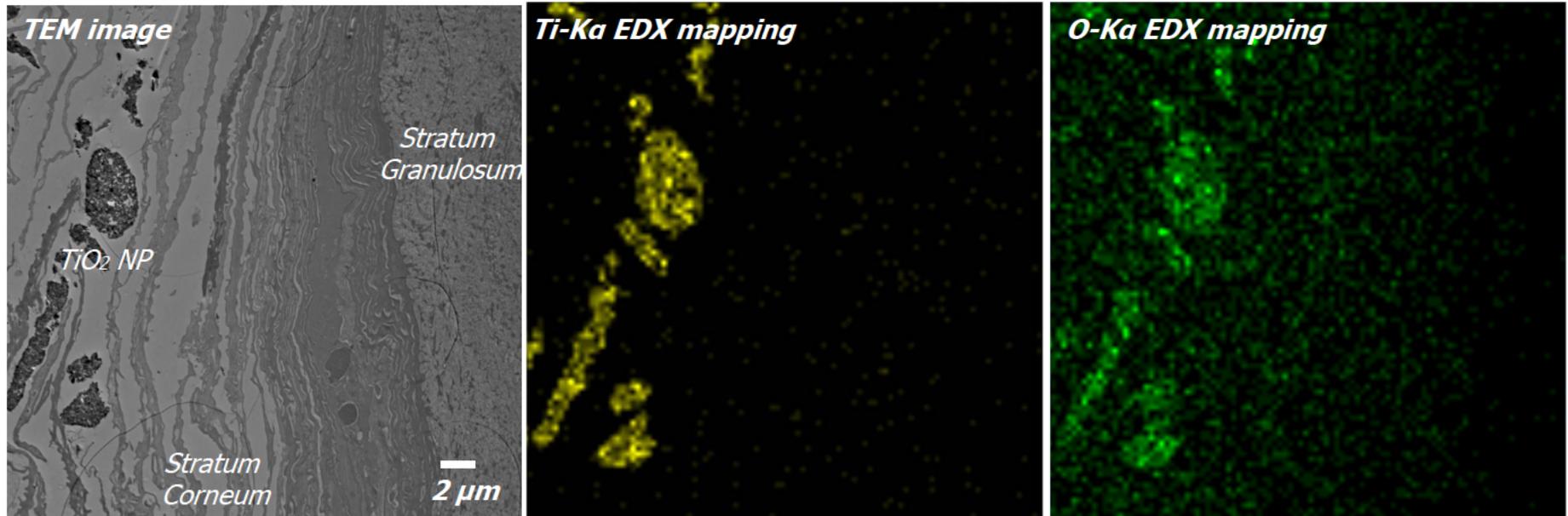


McNeil (2009), *Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology*, 1:264-271.

Nel et al. (2009), *Nature Materials* 8: 543-557.

Cover of *Advanced Drug Delivery Reviews*, June, 2009.

Dermal Penetration of TiO_2 In Sunscreen Formulations



Studies on minipigs skin using:

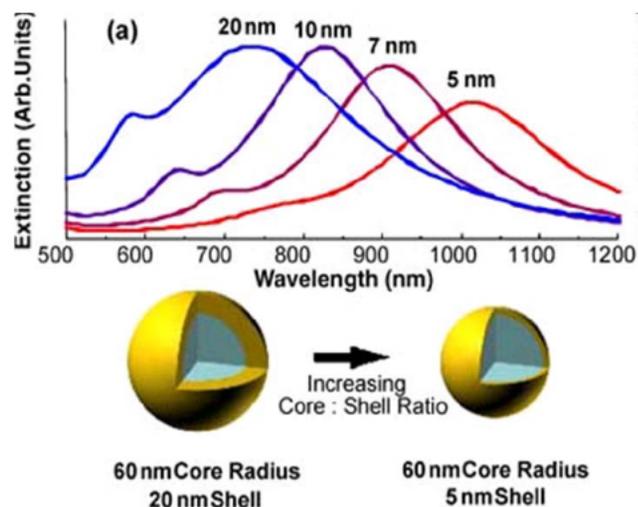
- Transmission Electron Microscopy (TEM)
- Energy Dispersive X-ray (EDX)
- No penetration beyond stratum corneum
- No elevated titanium levels in lymph nodes and liver

TiO₂ Particles were detected only in stratum corneum

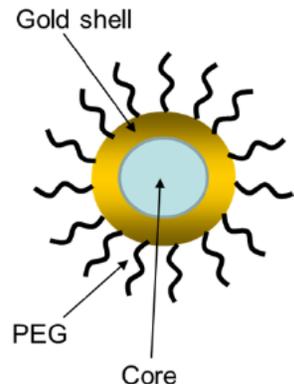
Patri, A. et. al. J. Appl. Tox. (2009) 29, 662-672.

Sadrieh, N. et. al. Toxicol. Sci. (2010) 115, 156-166.

Studies of Gold Nanoshells



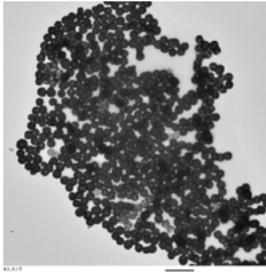
- Evaluation of two different batches of gold nanoshells, the first batch was ~6 months older than the 2nd;
- In tox studies, 1st batch caused extensive toxicity, 2nd batch was largely benign.



Batch 1 : Extensive pigmentation in liver, spleen, lungs, ovaries, muzzles, granulomous lesions in lungs.

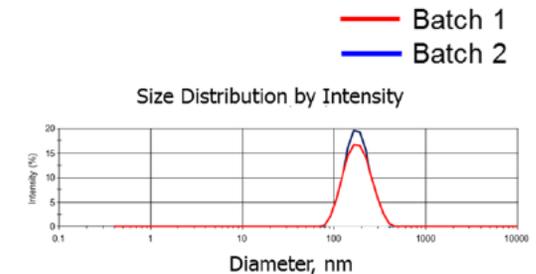
Batch 2: Few, statistically insignificant, mild lung lesions

Mechanism of Toxicity – Gold Nanoshells

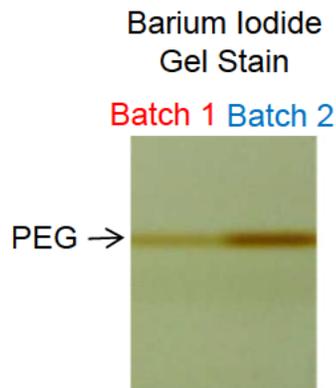
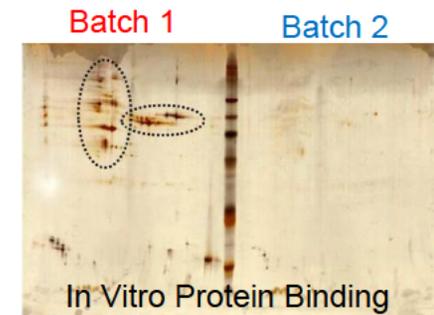


Batch 1 and Batch 2 appeared identical by TEM.

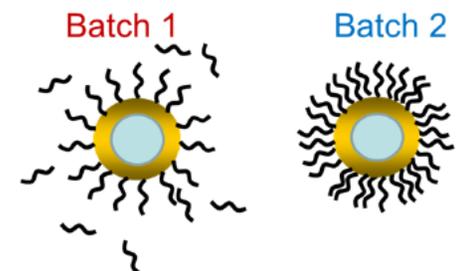
- NCL performed extensive characterization: the two batches seemed identical by physicochemical characterization.



- NCL *in vitro* characterization revealed a difference in protein binding. Batch 1 binds more protein than batch 2.



- NCL determined the difference in protein binding was due to a difference in PEG coating – the PEG was dissociating over time. NCL developed a “lot release” PEG gel assay.



Less PEG → Distribution to the Lung and other organs

NCL – Oversight and Peer Review



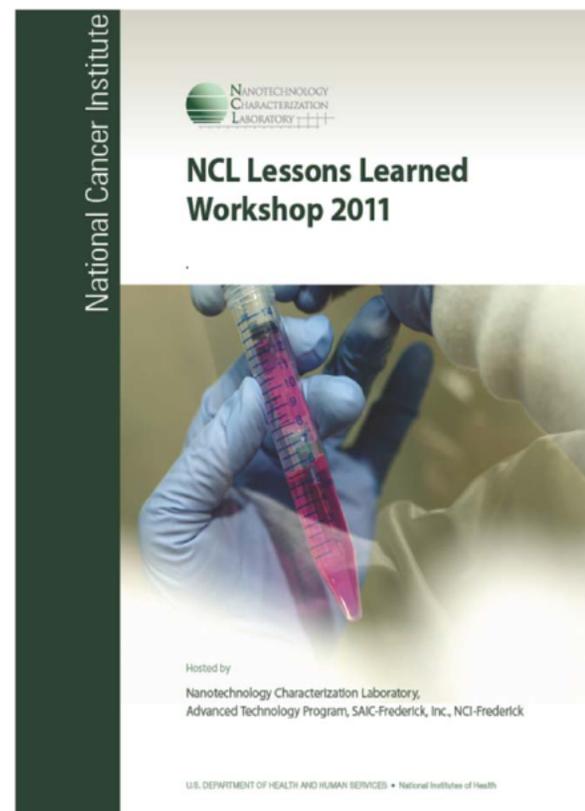
- Scientific Oversight Committee (SOC) made up of scientists from NCI, NIST, FDA and EPA provides oversight to the laboratory's operation;
 - SOC meets annually in Frederick to review the laboratory's progress and discuss future directions.
- Extramural inputs from nanotechnology leaders and consultants: e.g., Andre Nel, UCLA; Martin Philbert, U. Michigan; Günter Oberdörster, Rochester U.;
- Input from CCNEs, extramural investigators from academia, industry, and government.

Lessons Learned Workshop



NCI Alliance for
Nanotechnology
in Cancer

- NCL communicates the “lessons learned” from NCL characterization to the research community:
 - Annual 2-day workshop at NIH
 - Shorter 1-day seminars at FDA and universities.



Review of Incoming Projects



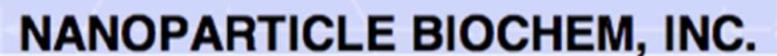
- NCL receives applications every quarter from extramural community – academia, industry, and government;
- Committee reviews applications based on:
 - **Demonstrated efficacy *in vitro* and/or in animal models**
 - Advantages over existing cancer therapies or diagnostics
 - Existing characterization data
 - Inherent toxicity or environmental concerns
 - Proposed path to clinical trials
- In 2010-2011, NCL received 42 white paper applications. More than half were accepted. Rejected applications either didn't show an advantage over existing formulations or were self-limiting (for example lack of stable process to produce material).

Summary



- NCL has become highly respected national resource for evaluation of nanomaterials to be used in new diagnostics and therapeutics;
- It supports extramural community as an independent and objective resource;
- NCL will be a key player in establishing relationships with industry within future ATRF;
- Several NIH institutes and other agencies approached NCL to collaborate and learn about its operational model.

NCL Extramural Collaborators



Life Cycle of an Investigational Biologic & Biologics Production at NCI-Frederick

James H. Doroshow, M.D.
Deputy Director for Clinical & Translational Research
National Cancer Institute

NCI-Frederick Advisory Committee

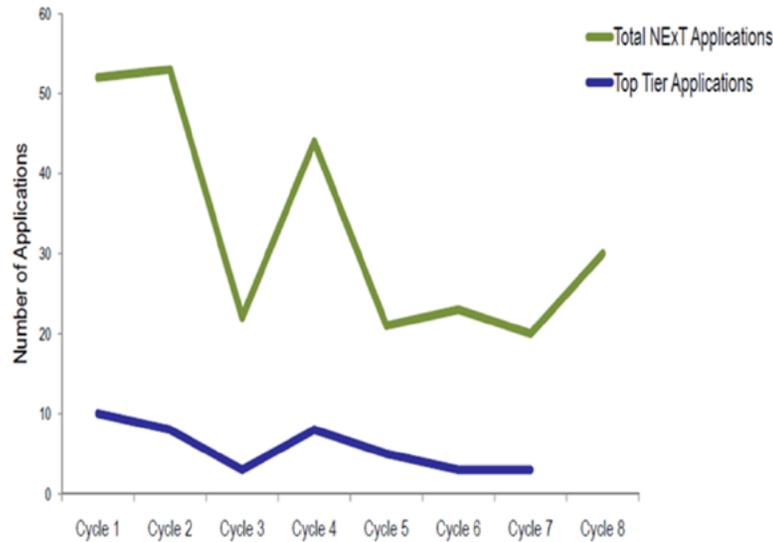
Frederick, MD
January 25, 2012

Therapeutic/Diagnostic Discovery & Development Support Provided by NExT

- Medicinal chemistry, HTS, lead optimization (F)
- Enhanced chemical synthesis of small molecules and peptides (F)
- Scale-up production of small molecules (N), biologicals (F), imaging agents (N)
- Isolation and purification of naturally occurring substances (F)
- Development of early stage, clinical pharmacodynamic assays (F)
- Exploratory toxicology studies and pharmacokinetic evaluation (N)
- PK/efficacy/ADME studies (bioanalytical method development) (N)
- Development of suitable formulations (N)
- Range-finding initial toxicology and IND-directed toxicology (N)
- Product development planning and advice in IND preparation (N)
- **Later-stage preclinical development of monoclonal antibodies, recombinant proteins, therapeutic vaccines, and gene therapy agents (F)**
- Manufacture of drug supplies (N)
- Analytical methods development for bulk material; formulation (N)
- CLIA-grade clinical assay development for later stage trials (F)
- Production of clinical dosage forms (N)
- Stability testing of clinical dosage forms (N)
- Regulatory support (N)

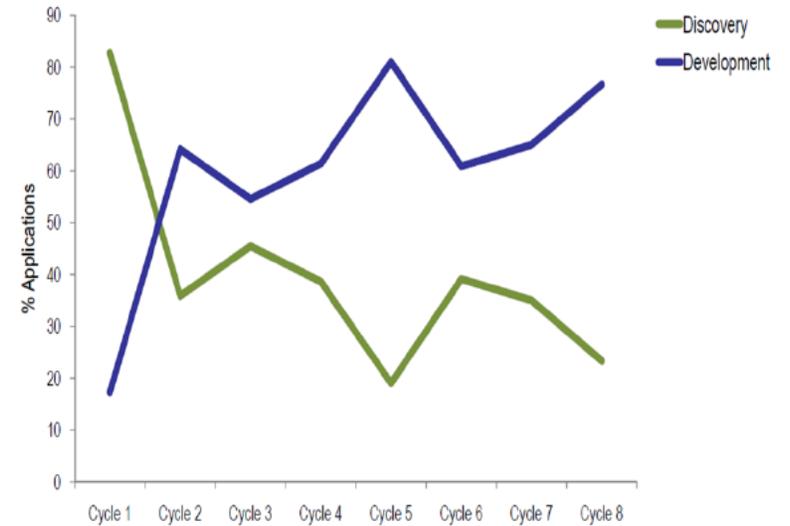
(N)=NCI; (F)=Frederick

265 NExT Applications Received in Cycles 1-8

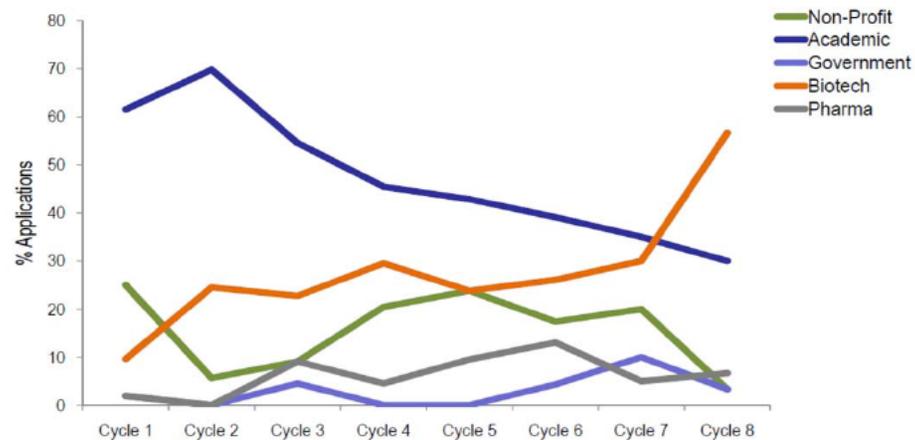


Overall, 17% of applications have been ranked in the top tier.

*Cycle 8 top tier TBD



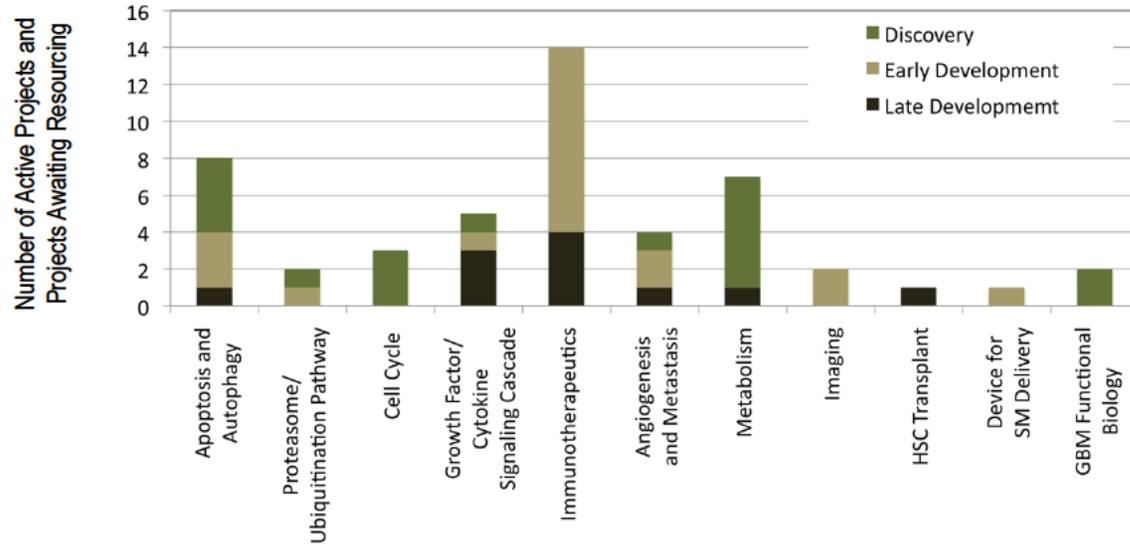
Overall, 44% of applications requested early-stage discovery resources, while 54% requested preclinical and clinical resources.



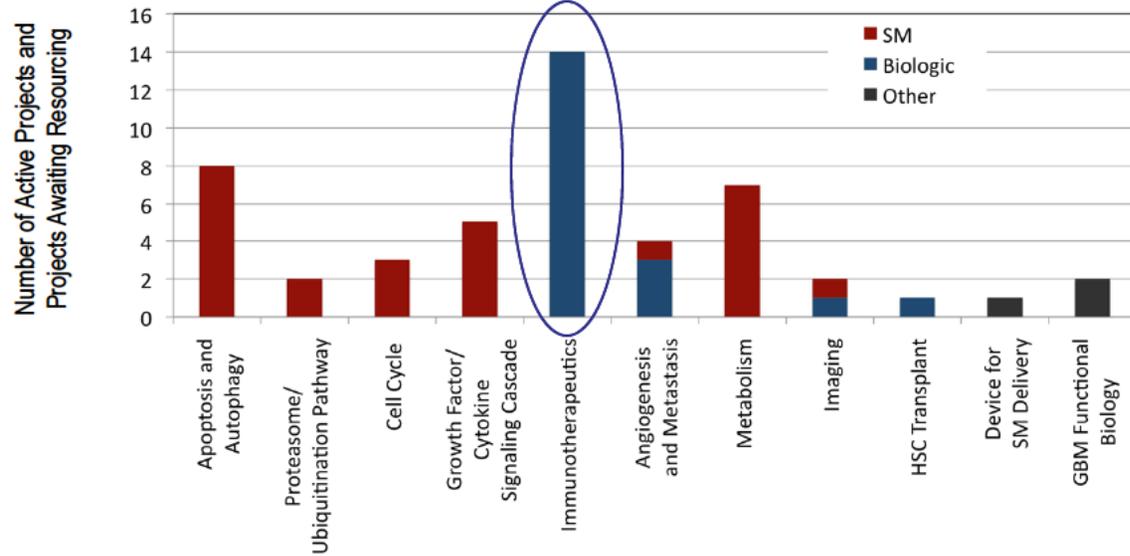
Source of NExT Applications

NExT Portfolio by Mechanism

Project Development Stage



Agent Type



Immunotherapeutic Projects: 14 as of 1/2011

Late
Development

1. Phase 3: **CD22 mAb** (CAT-8015) conjugated to Pseudomonas exotoxin A PI: Marapaka
2. Phase 2: **Vaccine** (CDX-1308) to elicit **HER2/neu**-specific immunity PI: Davis
3. Phase 2: A bispecific **CD19/CD3 mAb** (blinatumomab) that triggers a CTL reaction PI: Frankel
4. Phase 2: **IL-2/IL-15R β mAb** (Hu-Mik- β -1) for treatment of Celiac disease PI: Waldmann
5. Phase 1: **rhIL-15** that stimulates expansion of functionally educated NK cells PI: Miller

Early Development

6. CC: **CD22 mAb** (NSC 725179) PI: Tuscano
7. CC: **Viral oncolytic agent** based on affinity to **CD155** (PVS-RIPO) PI: Gromeier
8. CC: **Viral oncolytic agent** using herpes virus vector (**C134**) PI: Cassady
9. CC: **Viral oncolytic agent** using conditional adenovirus (Ad5- Δ 24RGD) PI: Alvarez
10. CC: **CMV-MVA vaccine** PI: Diamond
11. CC: **Hsp110-gp100** complex **vaccine** PI: Kane
12. CC: Plasmid **vaccine** against **HPV** (pNGVL4a-CRT/E7) PI: Pai
13. CC: **Vaccine** against **HPV16** (HPV L2E6E7) PI: Roden
14. CC: **Ig-4-1BB ligand** that stimulates T activation via **CD137** PI: Woo

Ongoing Prioritization of Biologics Portfolio

Special Emphasis Panel Biologics Portfolio Priority Subcommittee

Mac Cheever, MD Chair

Univ. of Washington

Louis Weiner, MD

Georgetown

Mario Sznol, MD

Yale

David Parkinson, MD

Nodality

Gwen Fyfe, MD

Formerly Genentech

Mike Morin, PhD

Formerly Pfizer

Stephen Russell, MD

Mayo Clinic

November 28, 2011

Prioritization Process Used To Ascertain Which Biologics To Move Forward?

- **This selection is based on the following criteria.**
 - **Scientific Merit**
 - **Feasibility**
 - **NCI Mission**
 - **Novelty**
 - **Clinical Need**
- **For Biologics: Focus on production of molecules required by the immunotherapy community; supply agents to the Cancer Immunotherapy Trials Network**
- **This evaluation process to provide guidance about the priority utilization of the capacity – based resources provided by NCI—in particular, the Biologics Development Program**

Changing Priorities of Biologics Portfolio

Initial NCI-BRB prioritization:

High Priority

- Ch 14.18 anti-GD2 monoclonal antibody
- IL-15 cytokine (Growth factor for activated T cell & NK cells)
- Ch11-1F4 anti-amyloidosis mAb
- GMP endotoxin*

Moderate Priority

- IL-7 cytokine
(Homeostatic T cell growth factor)
- hATN-658 uPAR mAb
- HSV C134 oncolytic Herpes virus (Glioma)
- H1299 cellular vaccine (Lung cancer)

Low Priority

- HPV16 TA-CIN + GPI-0100 vaccine for HPV (HPV16 L2/E6/E7 fusion protein)
- hlg-h4-1BBL protein (T cell activator)

Close: 1. CD22mAb; 2. Ad5RGD viral oncolytic; 3. CMV vaccine; 4. CD 155 polio viral oncolytic completed

Biologics Subcmte. revised prioritization:

High Priority

- Ch 14.18 anti-GD2 monoclonal antibody
- IL-15 cytokine
- Ch11-1F4 anti-amyloidosis mAb

Moderate Priority

- HSV C134 oncolytic Herpes virus (Glioma)
- hlg-h4-1BBL protein

Low Priority

- HPV16 TA-CIN + GPI-0100 vaccine for HPV
- hATN-658 uPAR monoclonal antibody
- H1299 cellular vaccine
- GMP endotoxin*

Hold

- IL-7 cytokine



***Moved to lowest priority at 12/7/2011 NExT SEP meeting.**

Monitoring the NCI-Frederick Biologics Facility

Ongoing interactions

- Daily interactions between NCI and SAIC-F
- Monthly report of projects and budget
- Annual budget assessment and adjustment

Need for change identified in FY 2011

- Budgetary issues (cost overruns; NCI constraints)
- Change in work focus/scope
- Operational issues

Change process

- On site extramural review with extensive documentation-2 days (4/11)
- Three independent evaluations obtained
- SAIC/NCI discussion, response, and initiation of changes

Training	Affiliation	Expertise
PhD	Director, Center for Biomedicine & Genetics Research Institute	Immunotherapy, founding Director of the Center for Applied Technology Development
MD, PhD	Director, Center for Cell and Gene Therapy Medical School	Gene Therapy, Immunotherapy
PhD	Director QA, GMP Facility Research Institute	Director QA, responsible for putting together the GMP program

BDP External Review: Summary & Outcomes

<u>Issue</u>	<u>Outcome</u>
Staffing: excessive for # projects	Decrease from 98 to 44 fte's with focus on redundant QC staff & enhanced cross-training; outsourcing
Cost Accounting: difficult to understand	Interface SAIC and NCI systems; initiate project-based cost tracking
Project Costs: overly costly	Increase outsourcing and subcontracting; require availability of initial starting material for QC; project development by PI not BDP
Facilities: underutilization of some areas	Space re-evaluation: 38% decrease in ATRF space requirements (22,291 vs. 35,721 sq.ft.)
Outsourcing: need to discern what projects <u>require</u> NCI manufacturing	Budget: Decreased from \$16 M (including \$5M ARRA) to \$9M total



Mechanisms for CCR Program Change at NCI-Frederick

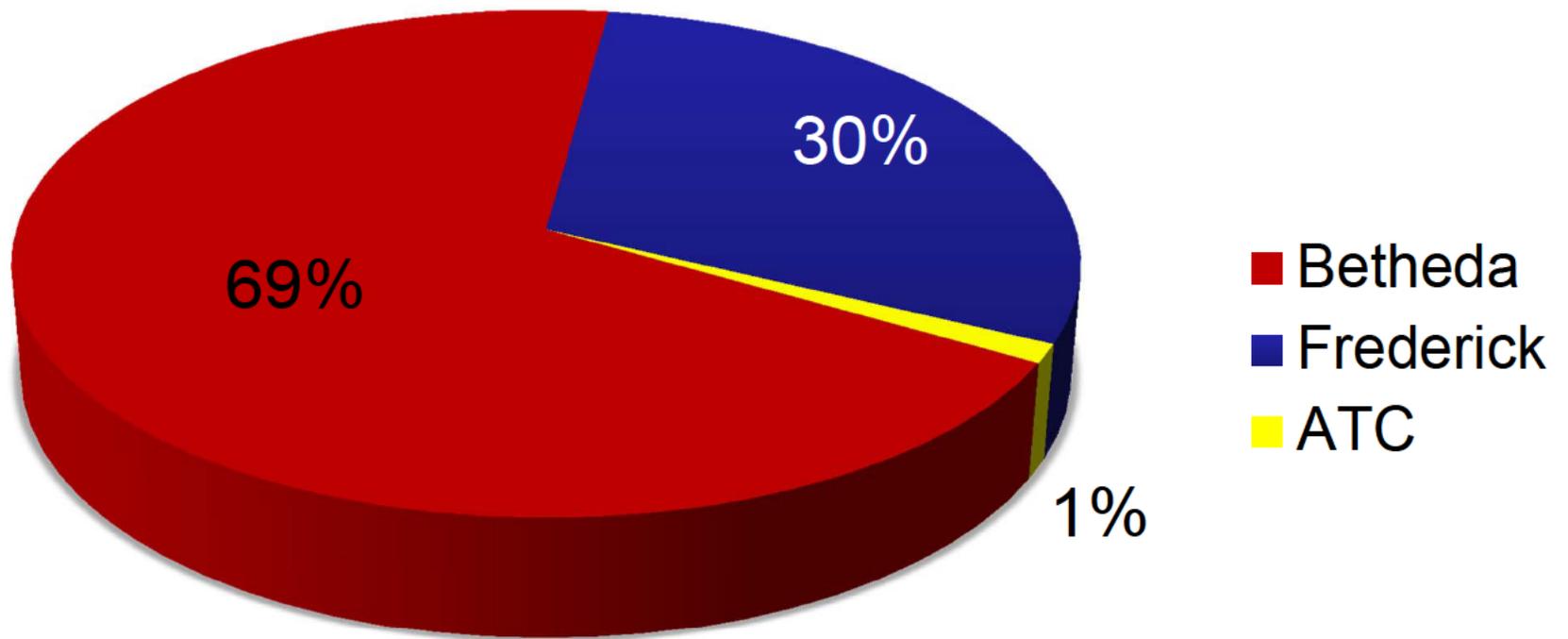
Robert H. Wiltrout, Director, SD for Basic Science

Lee J. Helman, SD for Clinical Research

January 2012

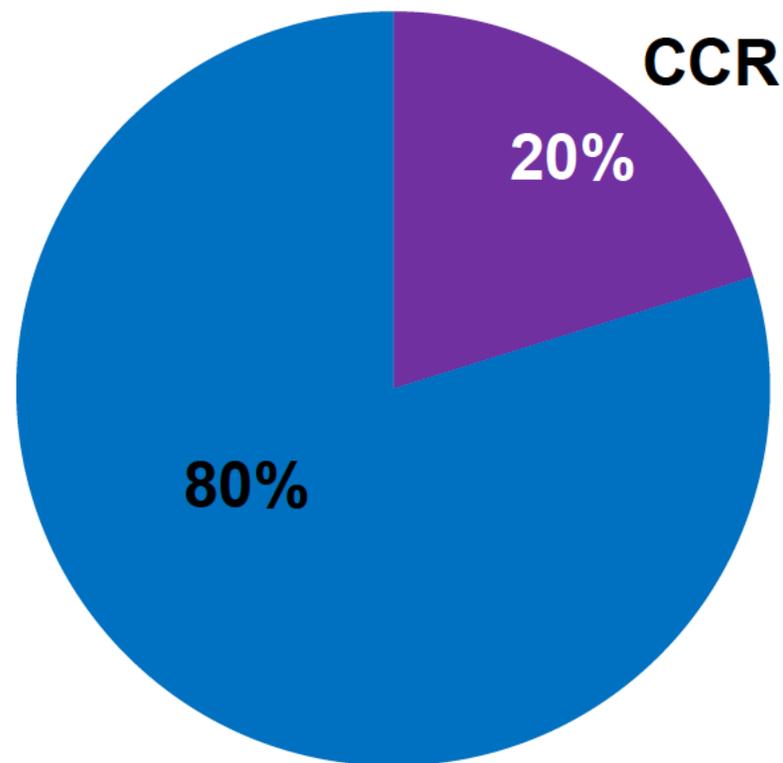


Current PI Distribution by Campus





CCR Portion of the NCI's Frederick Budget





Recommendations for Program Change Derive from Multiple Review Mechanisms

- **Ad hoc External Review**
 - NCAB ad hoc review the IRP (Bishop-Calabresi)
 - NCI Divisions can convene special ad hoc review
- **Quadrennial BSC Review of IRP Research**
 - Fully extramural site visit teams and NCI's Board of Scientific Counselors review Labs/Branches and CCR core services
 - BSC subcommittees can be used for specific tasks
- **NCI-Frederick Core Services Reviews**
 - Intramural users and extramural experts review the core services to assure they are cutting-edge, cost-efficient, and aligned with NCI's research priorities



NCI-Frederick Programmatic Changes Resulting From Bishop-Calabresi

- **Programs Realigned into Intramural and Extramural Divisions**

- Frederick components of DBS and DCTD created
DTP split between DBS and DCTD

- **Biological Response Modifiers Program Split**

- Clinical component aligned with DCS, moved to the Clinical Center

- Basic Research Laboratories aligned with DBS

- Biopharmaceutical Production Facility developed as contractor service,
opened to extramural

- **Contract PIs**

- SAIC PIs working in NCI Labs were recognized; retain SAIC affiliation, but
reviewed directly by the BSC

- ABL contract Labs were Federalized

- **Research Support Services**

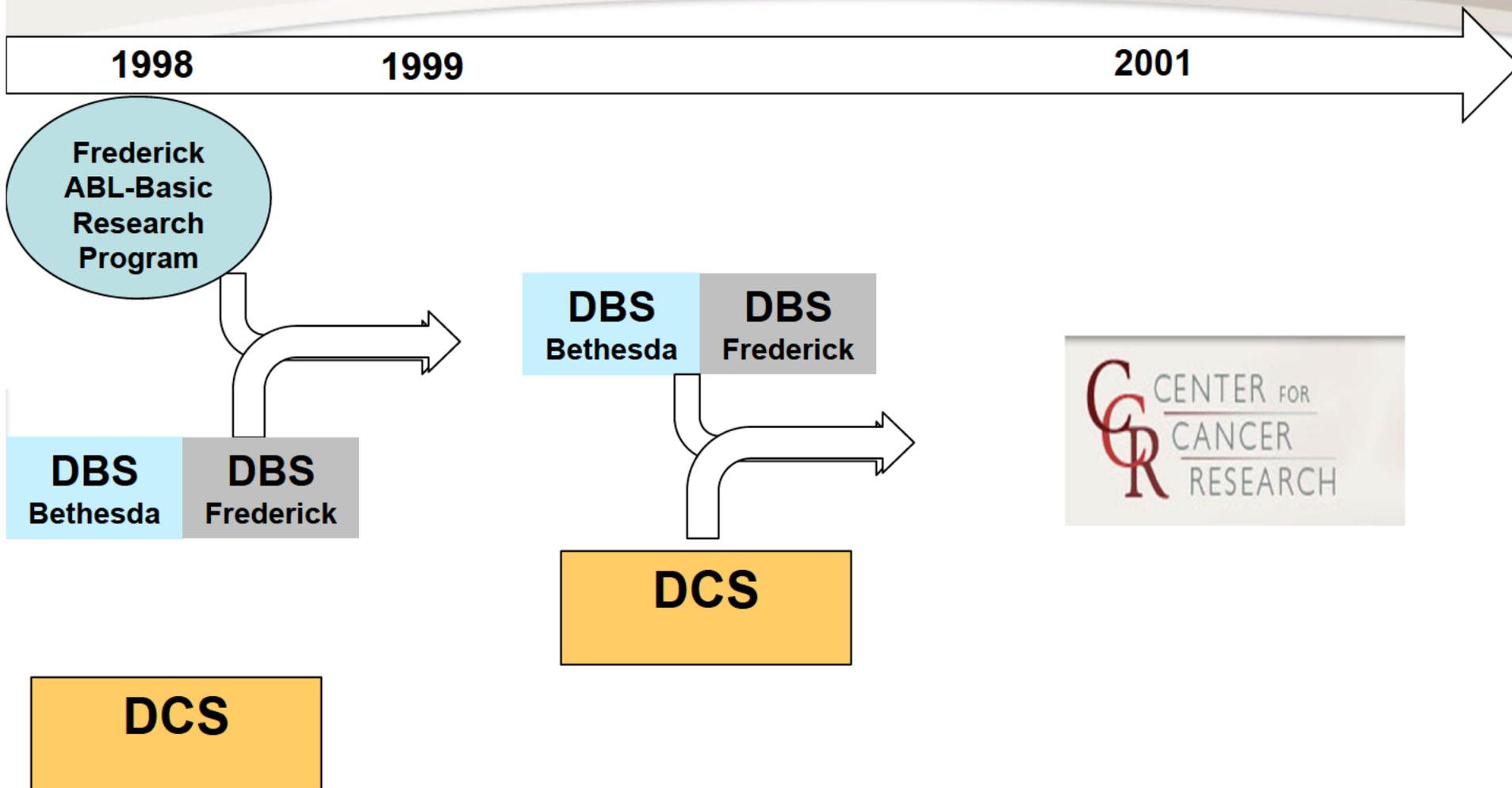
- Triennial reviewed process established

- Services offered reconfigured to reflect NCI needs and research priorities

- Opened to Extramural and Intramural



History of CCR in Frederick



A Rigorous BSC Process Drives Quality of Basic and Clinical Research

- **Four-year cycle**
- **Retrospective/prospective review**
 - Accomplishments
 - Future directions
 - Team science
 - Innovation
 - Mentoring and training
- **Site visit teams and Board of Scientific Counselors**
 - 100% Extramural participants
 - Evaluates the science being performed in light of its cost
 - Encourages high-risk approaches
- **Recommendation**
 - The site visit teams report their findings and provide recommendations to the BSC, which then advises the CCR Director whether research programs should continue to be supported, and at what level



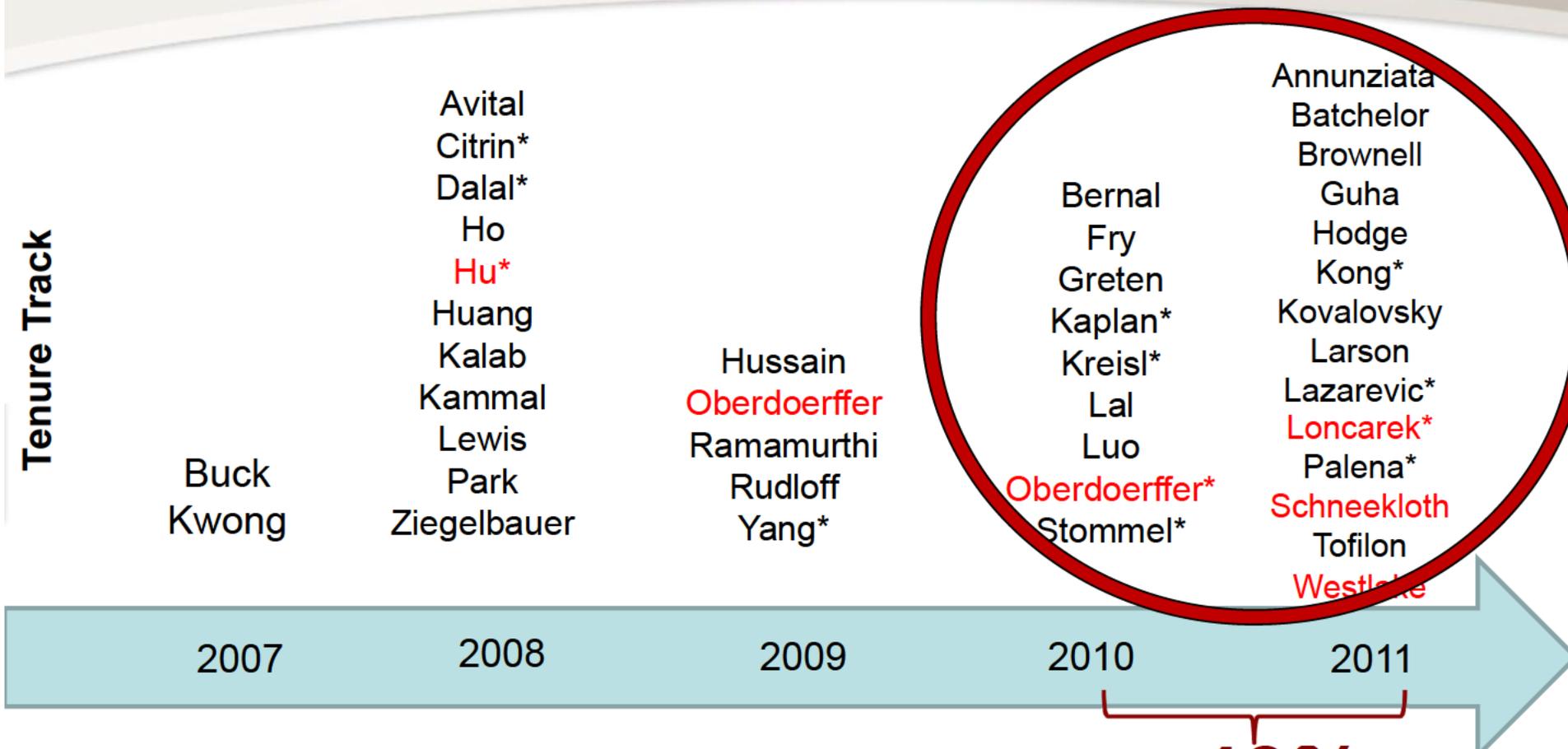


CCR Staffing in Frederick: Facts and Figures

- **In 2006 CCR Frederick had 95 PIs**
- **In 2012 CCR Frederick has 80 PIs**
- **Since 2006, 26 (31%) have departed**
 - 13 (50%) were directly or indirectly due to BSC
 - 5 (21%) departed for career advancement
 - 11 new hires-6 TT and 5 tenured (36% female)
 - ** 10 (13%) received substantial reductions/re-review
- **Anticipated closures/departures**
 - FY2012= 1
 - FY2013= 1
 - FY2014= 1



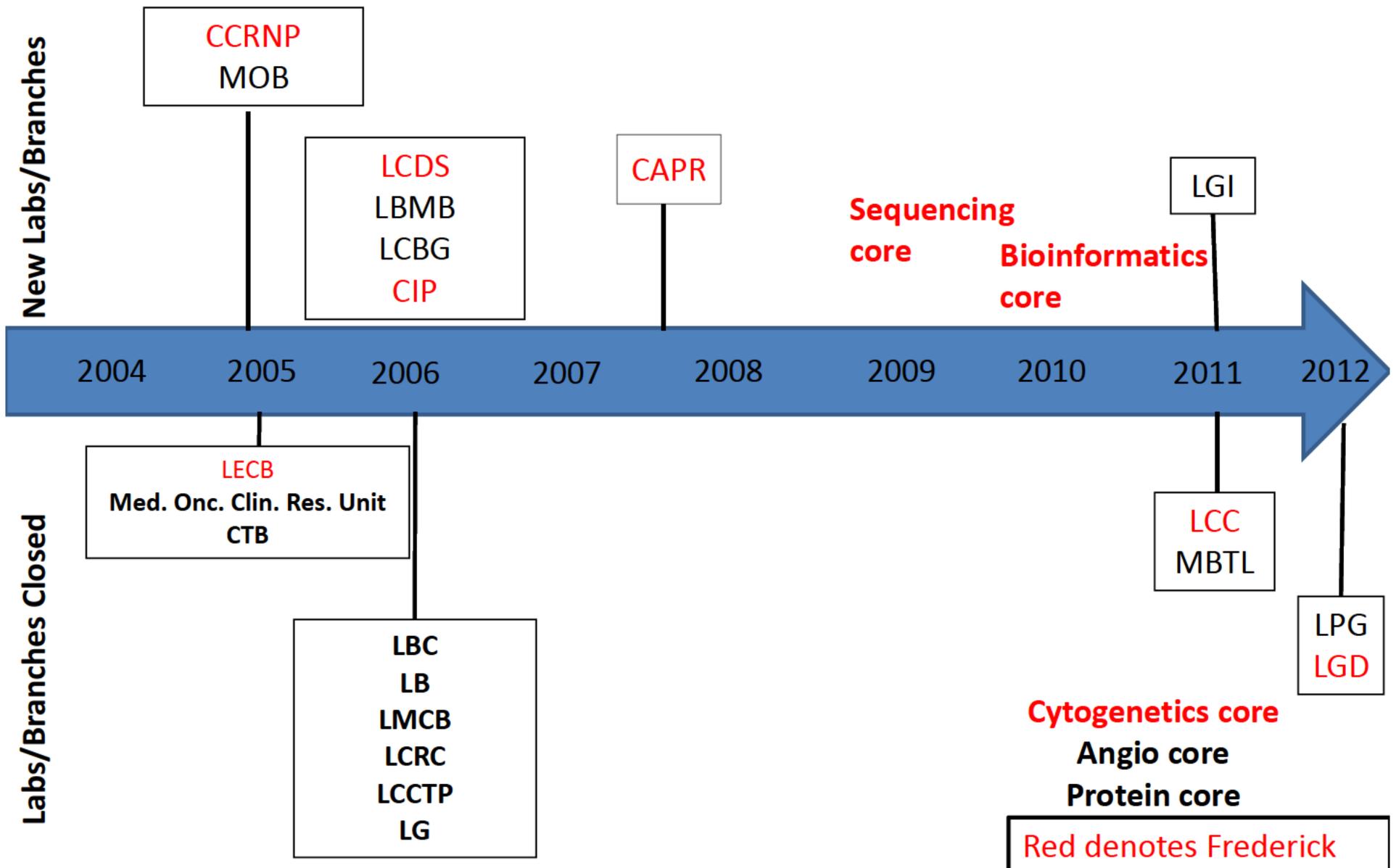
CCR TT Hires 2007-2011



43%
Female

Red denotes Frederick
* Denotes Female

Labs/Branches Created and Closed





Program Change: Capitalizing on Complementary Research Strengths

- **Cancer and Inflammation Program (CIP)-formed in 2005**
 - Recruited strong senior leader-**Giorgio Trinchieri**
 - Combined the Laboratory of Experimental Immunology with the Laboratory of Molecular Immunoregulation + additional cancer biology PIs
 - Provides leadership of CCR's inflammation and cancer initiative which melds NCI's expertise in inflammation and immunology with its broad-based cancer biology and carcinogenesis programs
- **Fostered closer collaborations among the 15 PIs in the Program and joint retreats and many collaborative studies on cancer and inflammation or cancer-related infections-very strong BSC review in 2010**
- **Stimulated Trans-CCR organization to propose and support a new Major Opportunity for Inflammation and Cancer associated with the re-engineering of CCR's clinical program**
- **Benefits by close proximity to NCI-F's animal models expertise**



Program Change: New Initiatives

- **The Center for Advanced Preclinical Research (CAPR) -**
 - formed in 2008 as a new initiative with the goals of:
 - using genetically engineered mouse models and gene expression profiling to accelerate cancer drug and biomarker development
 - more accurately assessing the potential of candidate drugs to succeed in clinical trials.
- **Built out in less than a year using SAIC staffing**
- **Envisioned as a national resource for the comprehensive preclinical testing of early stage candidate drugs. Candidate compounds will be primarily assessed for anti-tumor efficacy and selectivity in genetically engineered animal models.**
- **Program review mechanism: NFAC or BSC?**

Summary of Current CAPR Out-Reach Activities/Partnership Leads

<u>Partnership Lead</u>	<u>Project Concept</u>	<u>Contract Vehicle</u>	<u>% Complete</u>	<u>Projected Timeline</u>	<u>Expected Funds</u>
Foundation A/University Partner B/ Non-Profit Partner C	Fund raising: support an integrated preclinical/clinical drug development platform in NSCLC	MOU/Consortium	80%	Foundation Board approval (exp. February)	\$15M in total funds for three years
Pharma Partner D (recent IPO)	Testing novel RTKi's in EGFR-driven GEM models	Full CRADA	70%	NCI CRADA Subcommittee (exp. February)	\$100K-\$200K (first milestone)
Pharma Partner E	Testing two classes of compounds in ovarian cancer GEMs	Full CRADA	60%	Filing with NCI CRADA Subcommittee (exp. March-April)	\$150K-\$200K
Foundation F	Goal: Establish a cancer preclinical trial consortium based on GEM models	TBD/Consortium concept discussed	50%	White Papers/concept documents exchanged	Option 1: \$150K-\$200K Option 2: up to \$3.1M
Pharma Partner G	Multiple candidate drugs to be tested in GEM models for NSCLC, ovarian cancer and melanoma	Full CRADA	30%	Opportunities for joint projects identified	up to \$200K per compound tested



Mechanisms for CCR Program Change at NCI-Frederick

Robert H. Wiltrout, Director, SD for Basic Science

Lee J. Helman, SD for Clinical Research

January 2012

Resource

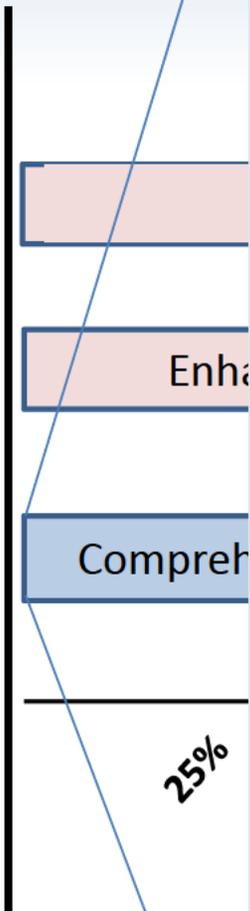
Value Added

Industry Benchmark/
Academic Lab

Dedicated
Preclinical Resource
(Animal Hospital)

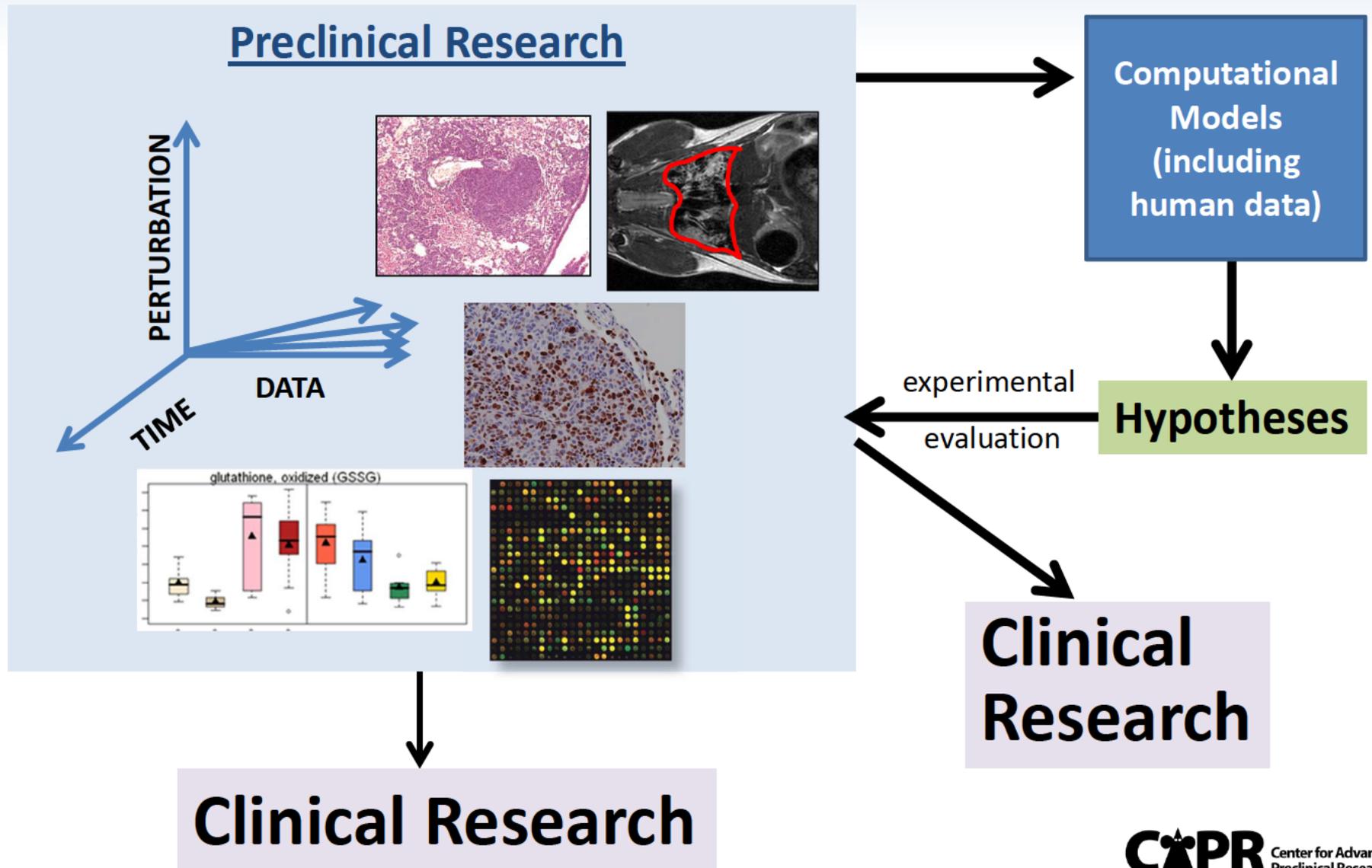


CPR
Integrated
Preclinical Center

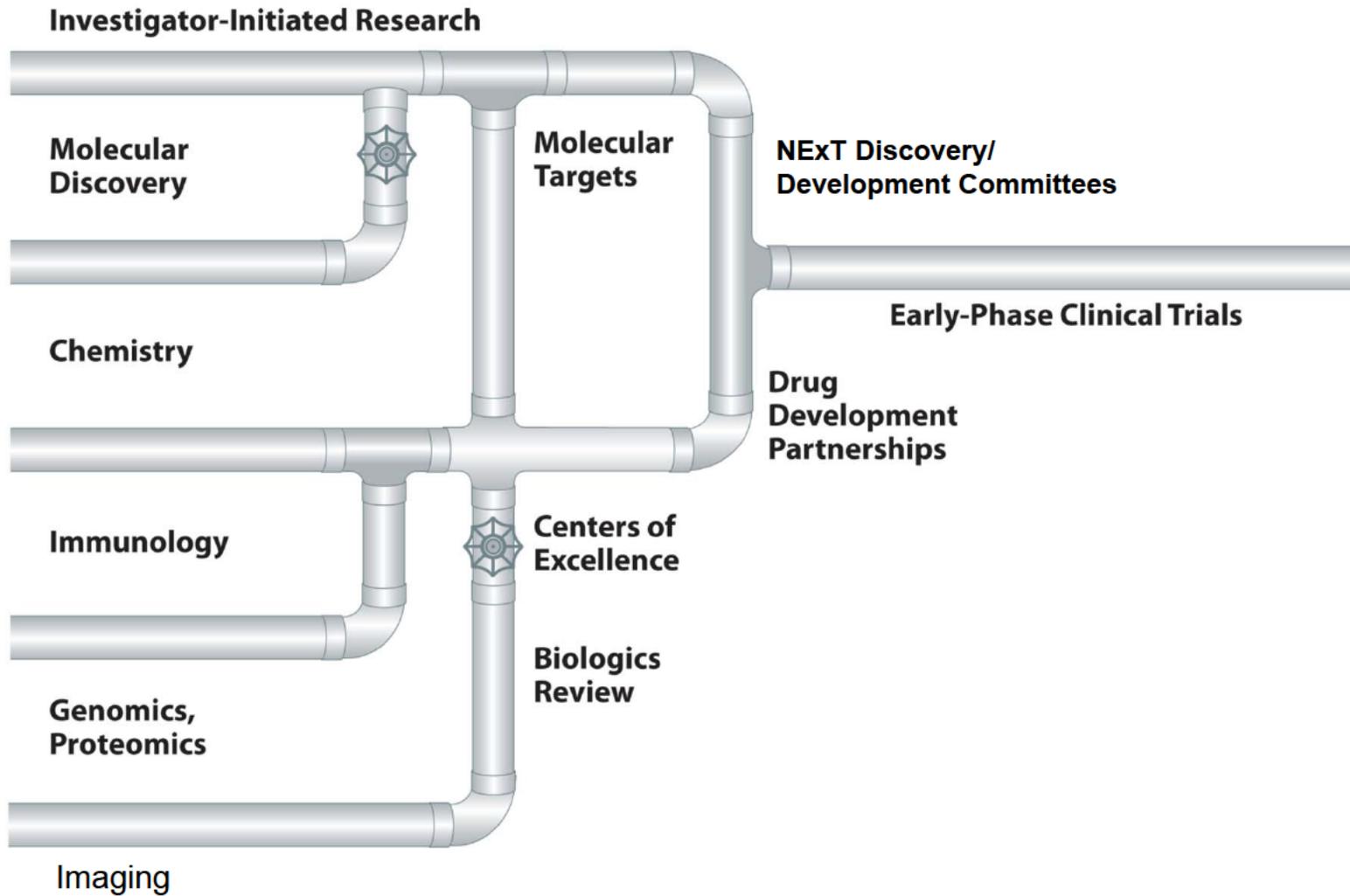


- Dedicated stable infrastructure and technology expertise
- Expert external scientific oversight maintained
- Statistically powered unbiased temporal evaluation (8-parameter systems biology) feedback/resistance → combination and relapse therapies hypothesis generation for human research therapeutic and disease biomarker prediction
- Integrated studies for imaging endpoints molecular pathology/heterogeneity
- Optimized model/cohort generation
- Standard of care comparisons
- Establishment and export of:
 - SOPs
 - retooled models
 - cross model predictive value
- Visiting scientists/training
- Frees resources for strong basic science/translational iteration

Systems Analysis of Disease and Treatment Response



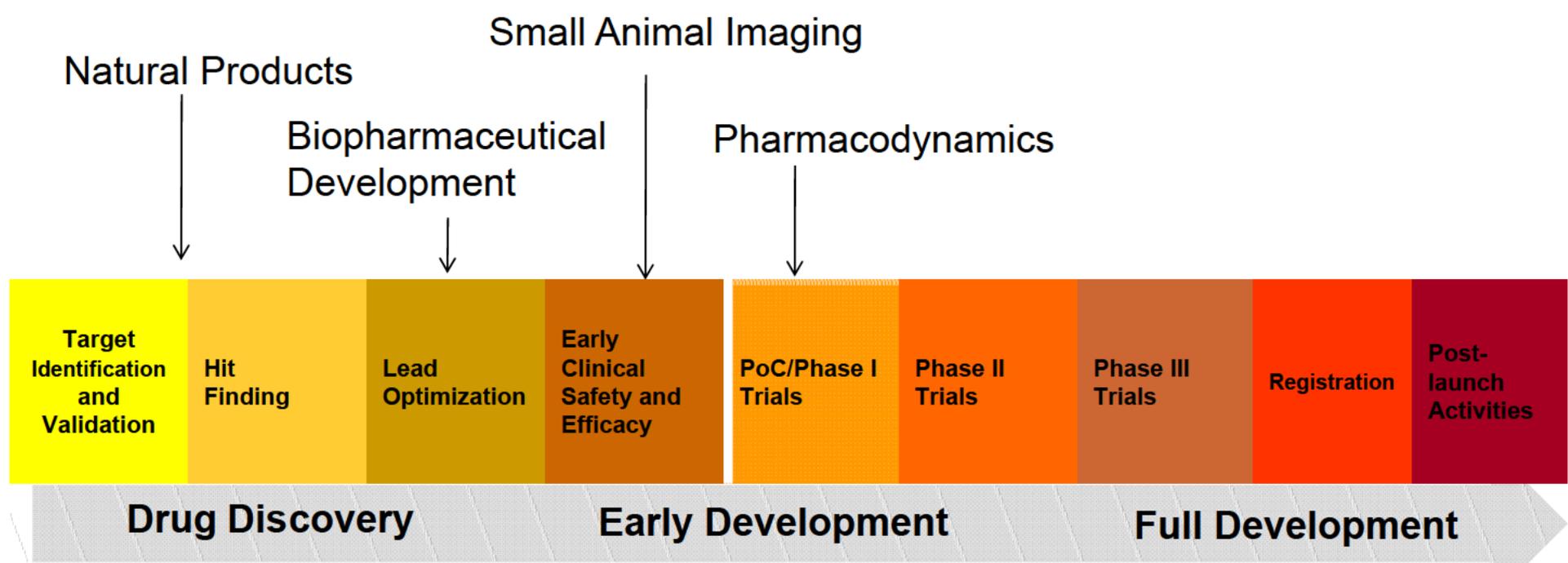
Translational Development Pipeline





Role of NCI-Frederick in NCI Therapeutics Development Program

Rapid translation of discoveries into public health benefits



Targets

- Includes:
- Investigational drugs and biologics
 - Investigational imaging agents
 - Academic, biotech, pharma projects
 - Includes Phase 0, I, II programs

Therapeutics



Commercial Successes in Fighting Cancer and HIV

Vaccines and Therapeutics

2-F-Ara-Fludara (1991) Berlex
Videx® (1991) Berlex
Hivid® (1992) BMS
Paclitaxel® (1992) BMS
Trimetrexate- Neu Trexin (1993) US Bioscience
Zenapax® (1997) Hoffman La Roche
Vitravene® (1998) Isis Pharma
Zevalin® (2002) IDEC Pharma
Kepivance® (2004) Amgen
Gardasil® (2006) Merck
Prezista® (2006) Tibotec Pharma
Cervarix® (2009) GSK

Diagnostics

Serological Detection of Antibodies to HIV-1 (1985)
Serological Detection of Antibodies to HTLV-1 (1988)
DNA Probe for Breast Cancer Diagnosis (1998)
Multi-Replica Blotting Kit for Proteins

Instrumentation/Devices

Laser Capture Microdissection



Knowledge Generation by CCR-Frederick PIs: FYs 10/11

Signaling and Gene Regulation

- Yamaguchi TP. Regulation of angiogenesis by a non-canonical Wnt-Flt1 pathway in myeloid cells. *Nature*. 2011
- Sharan S. Tumor Suppressor BRCA1 epigenetically controls oncogenic miRNA-155. *Nat. Medicine*. *In press*
- Burke Jr TR. Serendipitous alkylation of a Plk1 ligand uncovers a new binding channel. *Nat. Chem. Biol.* 2011
- Hurwitz AA. FOXO3 Programs Tumor-Associated DCs To Become Tolerogenic in Human and Murine Prostate Cancer. *J. Clin Invest.* 2011

Immunology and Inflammation

- Trinchieri G. Plasmacytoid dendritic cells: one-trick ponies or workhorses of the immune system? *Nat. Rev. Immunol.*
- Trinchieri G. Innate immune mechanisms of colitis and colitis-associated colorectal cancer. *Nat. Rev. Immunol.* 2011
- Tessarollo L, Klinman D, Wiltrout R, and Young H. IFN- gamma ARE-deleted mice reveal a role for chronic IFN-gamma in autoimmune disease. *Nat. Immunol.* *In press*
- Young H. and Trinchieri G. Interferon- γ links ultraviolet radiation to melanomagenesis in mice. *Nature*. 2011
- Trinchieri G. At 17, in-10's passion need not inflame. *Immunity*. 2011
- Trinchieri G. MyD88-mediated signaling prevents development of adenocarcinomas of the colon: role of interleukin 18. *J. Exp. Med.* 2010
- Wiltrout RH. Macrophage-dependent nitric oxide expression regulates tumor cell detachment and metastasis after IL-2/antiCD40 immunotherapy. *J. Exp. Med.* 2010



Knowledge Generation by CCR-Frederick PIs: FYs 10/11

HIV/AIDS and Cancer Virology

- Carrington M. HLA-A*3101 and carbamazepine-induced hypersensitivity reactions in Europeans. *New Eng. J. Med.* 2011
- Carrington M. Differential microRNA regulation of HLA-C expression and its association with HIV control. *Nature.* 2011
- Carrington M. The major genetic determinants of HIV-1 control affect HLA class I peptide presentation. *Science.* 2010
- Carrington M. Maternal activating KIR protect against human reproductive failure mediated by fetal HLA-C2. *J. Clin. Invest.* 2010

Proteomics

- Weissman AM. The predator becomes the prey: regulating the ubiquitin system by ubiquitylation and degradation. *Nat. Rev. Mol. Cell. Bio.* *In press.*
- Lipkowitz S and Weissman AM. RINGs of Good and Evil: RING finger ubiquitin-protein ligases at the crossroads of tumor suppression and oncogenesis. *Nat. Rev. Cancer.* *In press.*
- Weissman AM. Working on a chain: E3s ganging up for ubiquitylation. *Nature Cell Biol.* 2010

Genomics

- Hou SX. Kidney stem cells found in adult zebrafish. *Cell Stem Cell.* 2011

Developmental Biology

- Mackem S and Lewandoski M. Development: Limb cells don't tell time. *Science.* 2011

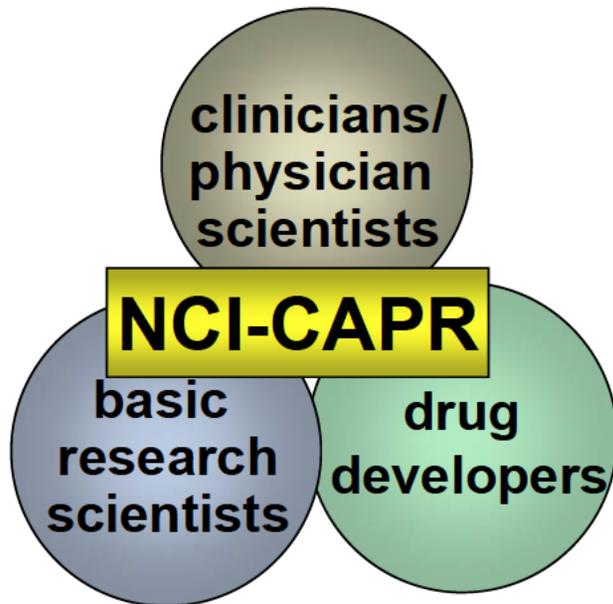
Chromosomal Biology

- Oberdoerffer, S. CTCF promotes pol II pausing and links DNA methylation to alternative splicing. *Nature.* *In press*

Program Changes: Center for Advanced Preclinical Research(CAPR)



To facilitate the improvement of preclinical assessment and clinical trial design for effective cancer diagnosis and treatment



Projected Interactome
*a new paradigm for
translational science*

- To accelerate the development of therapeutics and diagnostics for human diseases by providing state-of-the-art animal models genetically programmed to develop diseases in the same way they arise in humans for preclinical studies
- Genetically engineered mouse models will significantly reduce the time to identify promising candidate drugs and will provide improved systems for target discovery and validation, and biomarker discovery for early detection and treatment assessment



CCR Staffing: Facts and Figures

- **In 2003 CCR had 307 PIs**
- **In 2011 CCR has 252 PIs**
- **Since 2003, 110 (34%) have departed**
 - 57 (53%) were directly or indirectly due to BSC
 - 22 (20%) departed for career advancement
 - 55 new hires (25% female)
- **Anticipated closures/departures**
 - FY2012 =12
 - FY2013= 4
 - FY2014=3

History and Evolving Culture Shift Continuum for CCR



1994

1995

2001

→ →

→ →

2012

Marks-Castle Report
Bishop-Calabresi Report

**CCR
formed**

Emphasize multidisciplinary research to solve complex problems: Faculties, Working Groups, Centers of Excellence

Shifting the culture in CCR

- Reengineering the IRP has been a dynamic process
- Preserving and expanding outstanding PI-based research
- Encourage team science and collaboration
- Strategies for rewarding team science have been implemented
- Formation of Faculty and Working Groups and creation of Centers of Excellence around areas of strength
- Closer ties between clinical and basic research have led directly to translational research advances and new opportunities

Building Public-Private Partnerships

For the NCI-Frederick Advisory Committee
Jan 25, 2012

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

Advanced Technology Partnerships Initiative

ATPI Mission: Accelerate Translational R&D in Cancer & AIDS



**The National Cancer Institute
at Frederick:**

**Translating
Research
into Medicine**

Our priority is to speed up the development of new treatments for patients with cancer and AIDS.

Partnerships with Industry	From bench to bedside
Vaccines for Clinical Trials	Prevention and therapy
Improving Cancer Care	Reaching rural communities
Drug Development and Manufacturing	68 medicines to clinical trials

Paid for by SAIC-Frederick, Inc.. Our customer is the National Cancer Institute at Frederick

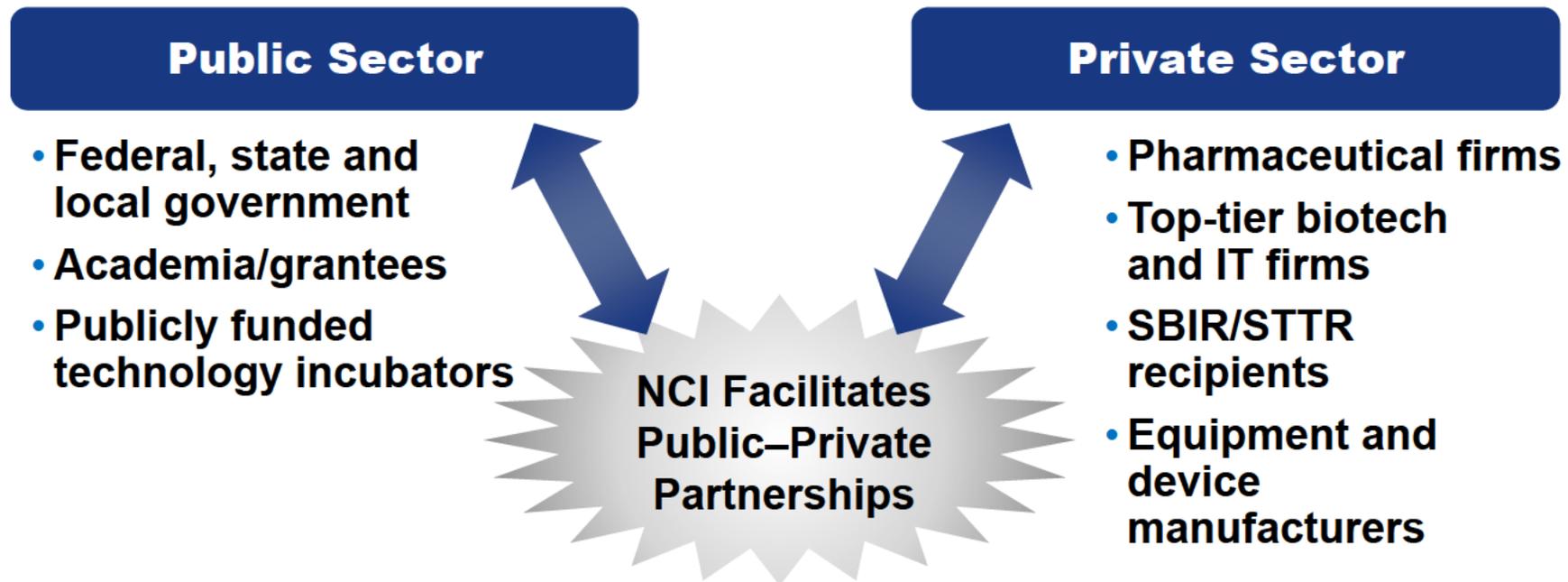
Origins

- Numerous studies by the NCI, FDA, and GAO in 2004–2007 highlighted the need to boost success in translational medical science through application of advanced technologies and improved public–private partnerships
- NCI developed the ATPI concept in 2007

Mission

To accelerate the delivery of new medicines to patients afflicted with cancer and AIDS through the strategic application of advanced technologies and effective translational research partnerships

The ATPI Concept: Public–Private Partnerships



Specific Areas of Partnership

- Advanced technologies; imaging, genomics, nanotechnology, *in silico* modeling, animal models, proteomics, bioinformatics
- cGMP capabilities: product development and pilot-scale manufacturing
- Clinical trials: first-in-man or drug combinations
- Biological and small molecules: develop lead molecules
- Education: training of integrated translational research teams
- Beta testing: testing and validation of new state-of-the-art equipment
- Diagnostics

Partnerships Facilitated through NCI Mechanisms



Material Transfer Agreement (MTA)

- Research materials transferred (in or out); research plan
- No fees; No IP; NCI can publish >90 days

β -Testing Agreement

- Technology development utilizing NCI resources
- No fees; No IP; NCI can publish >90 days

Collaboration Agreement

- Research materials transferred (in or out); research plan
- Both contribute intellectually; no \$\$ to NCI
- Useful for proof-of-concept with minimal IP concerns

Cooperative Research & Development Agreement (CRADA)

- R&D collaboration both partners contribute intellectually
- Both contribute resources; can include \$\$ to NCI
- Partner has first right to license CRADA inventions

"Umbrella" CRADA

- Same as above, useful for multiple lab projects

Clinical Trial CRADA

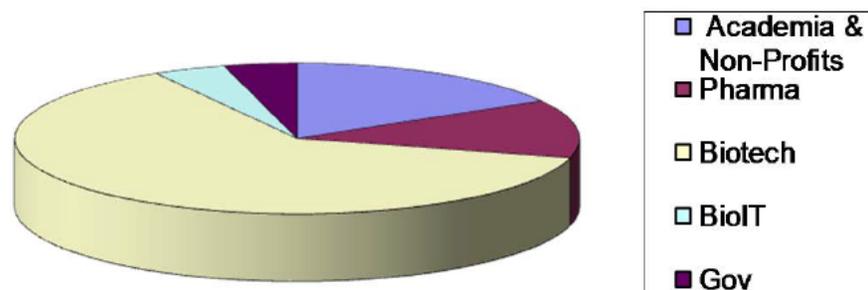
- Similar to CRADA above, specific to clinical trial R&D

ATPI: Agreements Summary Aug '08—Dec '11

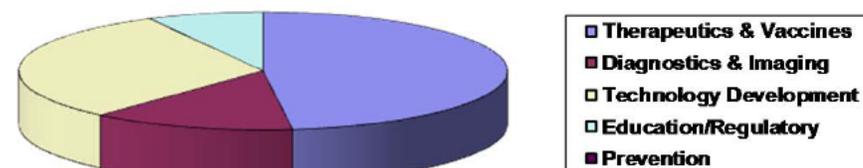
110 Partnerships—Majority with Biotechs



Partnership Projects by Market Segment



Partnership Opportunity Classification



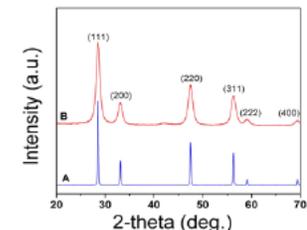
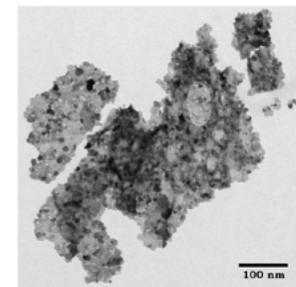
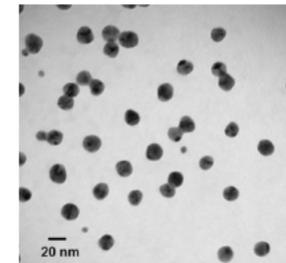
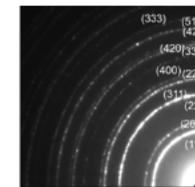
- **68** Material Transfer Agreements (MTA)
- **28** Collaboration Agreements
- **6** β - Testing Agreements
- **7** NCI CRADAs
- **1** NCI Umbrella CRADA

Inter-Agency Agreement : NIEHS

Plans for ATRF Co-location Underway



- Interagency agreement with NIEHS to provide physicochemical characterization for nanomaterial risk/hazard assessment studies.
 - NCL provides key infrastructure support for NIEHS' U01/U19 nanotechnology centers of excellence
 - NCL is characterizing 12 nanomaterials/year, including cerium dioxide, nanosilver, and carbon nanotubes.
 - \$1M/year, starting in 2010. Initial agreement for 2 years, with the possibility 3 years extension.
 - This work supports 5 NCL FTEs.



Collaboration Agreement : Sporian Microsystems and FDA

FFRDC Alliance Translates Lab Unit into Field Prototype

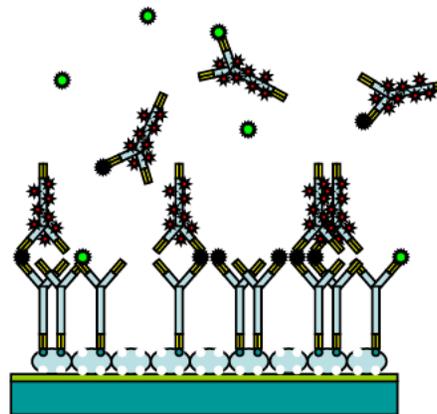


Optical-electronics and device engineering



Frederick

+



Assay reagent characterization and qualification

+



Field-based assay expertise and applied testing

Proof-of-Concept HIV detection assay for testing in remote regions

SAIC-Frederick, Inc.

FFRDC Partnering Authority - CRADAs



Cooperative Research and Development Agreements (CRADAs)

- Make Government facilities, intellectual property, and expertise available for collaborative interactions to further the development of scientific and technological knowledge into useful, marketable products
- Appropriate where collaborators make significant intellectual contributions to the research project or contribute research or materials not otherwise available to the NIH
- NIH Laboratory can contribute personnel, services, facilities, and equipment, with or without reimbursement; but not funding
- A Materials CRADA (m-CRADA) involves the transfer of proprietary material to the NIH laboratory where no collaborations is intended

NCI-F : CRADAs only through the NCI



SAIC-F scientists can enter into external CRADAs only through NCI processes using NCI agreements. This introduces certain NIH Policy-driven limitations :

- **Scope**
 - CRADAs for research and development
 - SAIC-F scientists can be Principal Investigators on a CRADA collaboration only with special individual approval by NCI
- **Timing**
 - OTT estimates an average of 4 to 8 months to negotiate and execute a CRADA, with more than 8 separate approval steps
- **Intellectual Property rights**
 - Collaborator is granted an option to negotiate a non-exclusive or exclusive commercial license
 - Terms not pre-determined

CRADA : General Electric

Move Novel Cancer Diagnostics to Clinic



- Pre-clinical Characterization of General Electric's Nanoparticle-based Diagnostics Imaging Agents
- First NCI CRADA with SAIC-F lab director approved as Principle Investigator (Contractor P.I.)
- Research plan:
 - Leverage NCL assay cascade and imaging knowledge
 - Evaluate feasibility of GE's proprietary nanoparticle diagnostic imaging agents

Partnership established 2008, extended in 2011 to new agents

Umbrella-CRADA : Amplimmune

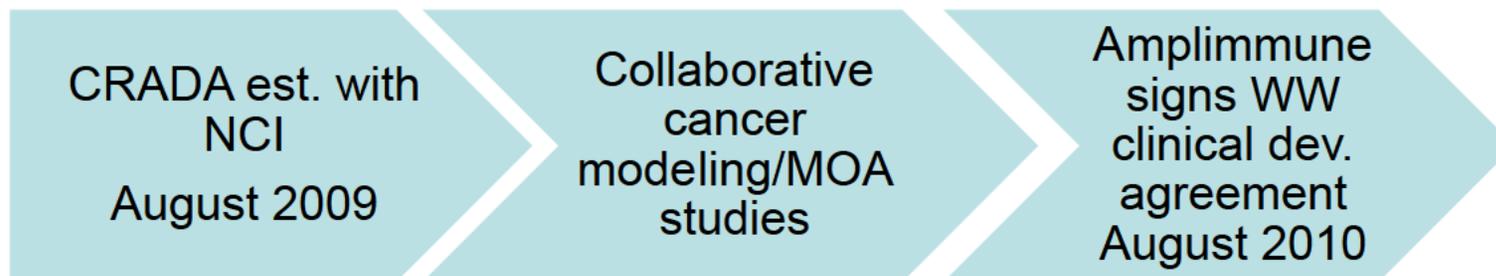
Accelerating Therapeutics to Clinic



“We look forward to collaborating with investigators at NCI and feel that these collaborations will have a significant impact on accelerating development and advancing AMP-224 and AMP-110 into the clinic...”

*Michael Richman, President & CEO
Amplimmune, Inc.*

NCI/Amplimmune Press Release, October 2009



NCI / Amplimmune Umbrella-CRADA: Using Internal Expertise to Explore MOA



Amplimmune

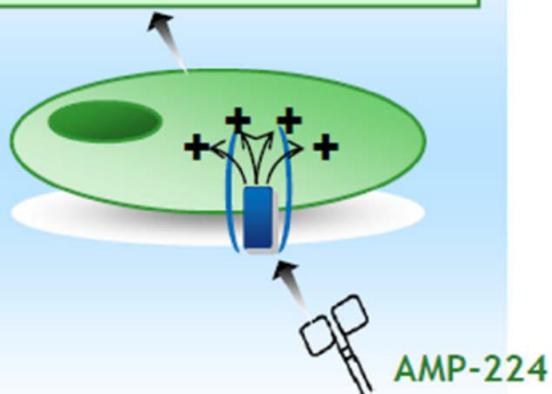
Novel Class of Protein Therapeutics: New Mechanisms of Action

Restoring Immune Function

Cancer/Infectious Disease

AMP-224

- Restores T Cell Function
- Kills Tumors/Treat Infectious Diseases
- Induces Memory Responses

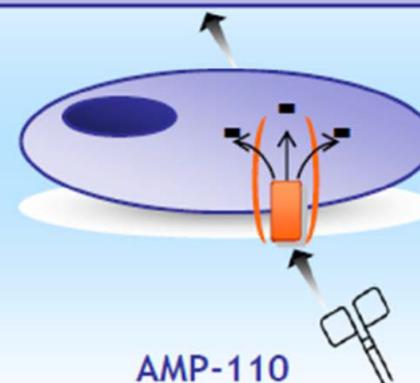


Attenuating Immune Response

Autoimmune/Transplantation

AMP-110

- Inhibits Inflammatory T Cells
- Promotes Treg Function
- Alleviates Autoimmune Disease



NCI/Amplimmune Umbrella-CRADA Partnership: Numerous Studies Performed to Accelerate Pre/Clinical Development



Amplimmune

Contribution of the NIH to Amplimmune's product development

- *As a result of our collaboration with the NIH/NCI through our broad CRADA, Amplimmune was able to test its product candidates in otherwise inaccessible infectious disease models and test novel therapeutic combinations*
- *In particular, based on combination therapy with a peptide based cancer vaccine (in collaboration with Samir Khleif) we were able to refine our understanding of the mechanism of AMP-224*
- *This led to the co-submission of manuscripts to JI that are under review:*

Treatment with CTX + B7-DC Ig Promotes Tumor Eradication Via A Novel PD-1 Targeted Mechanism

Shannon A. Marshall, Susannah D. Barbee, Monchou Fann, Thomas J. O'Neill, Karla Maloveste, Sarah Flies, Rong Zeng, Leighton Hyde, Nathaniel Macapagal, Erika McAfee, Sharon Polidoro, Paul Renaut, Jean N. Welch, Pauline Wong, James Bingham, David Fischer, Rena May, Linda Liu, Jeffrey Stavenhagen, Lieping Chen, Drew Pardoll, and Solomon Langermann

B7-DC-Ig enhances vaccine effect by a novel mechanism dependent on T cell subsets PD-1 expression level

Mikayel Mkrtichyan, Yana G. Najjar, Estella C. Raulfs, Shannon Marshall, Linda Liu, Solomon Langerman, Geoffrey Guittard, Laurent Ozbun, Samir N. Khleif

Expanding the Partnering Base

FFRDC CRADA opportunities



- **FFRDC's are permitted by federal law to have their own CRADA programs ("Contractor CRADA")**
 - Enables CRADA directly between contractor and partner
- **CRADAs are widely utilized by DOE FFRDCs to expand access to their technology and know-how**
- **Unlike DOE FFRDC's, SAIC-Frederick has no independent CRADA program**
 - Determination of Exceptional Circumstance (DEC) under the Bayh-Dole Act conveys all intellectual property developed by SAIC-F to the government, due to the exceptional access to specialized government programs conveyed by the FFRDC contract
 - SAIC-F cannot assign IP to any party other than the Government, as an independent Contractor CRADA would require

NCI-F Contractor CRADA



An independent contractor CRADA program will expand the impact of the FFRDC on the biological understanding, prevention, diagnosis, and treatment of cancer and AIDS

- **Key issues to address**

- Amend the DEC and OTS contract to enable SAIC-F to independently negotiate and manage CRADAs and CRADA-subject inventions
- Establishment of processes to support new agreements
 - Contracts, Workflow, IP, Funding, etc.
 - Build off of DOE FFRDC best practice

- **Status**

- DEC Amendment under review within NIH Office of the Director
- Work flow proposal and draft CRADA templates submitted to the NCI
- Contract modification drafted and ready for execution following the approval of the DEC Amendment

Contractor CRADA

Key anticipated features



- **Support for ongoing government programs under FFRDC OTS contract always has priority**
 - Excess or collaborator-funded new capacity available for contractor CRADAs
- **Use full CRADA authority under CRADA statutes**
 - CRADAs for Research, Development, and Testing collaborations
 - “M-CRADAs” for evaluation of proprietary partner materials, AIDS testing kits, etc.
- **Intellectual property rights**
 - SAIC-F is the custodian of joint or sole IP emerging from the CRADA
 - Streamlined assignment of exclusive commercialization rights
 - Any royalty streams support FFRDC R&D efforts
- **Processes**
 - Focus on speed
 - Local government review
 - Verify excess capacity and alignment of workplan with NCI mission

Contractor CRADA

Key Benefits to NCI-F

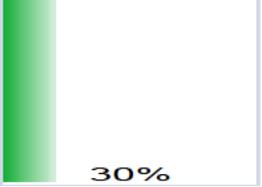
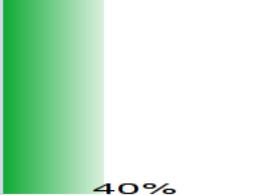
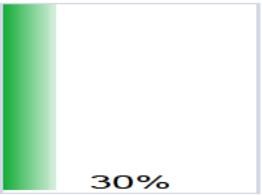
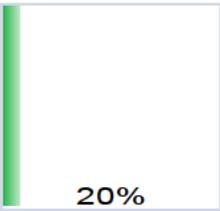
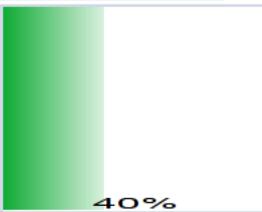


- Expands extramural and commercial access to FFRDC science, technology, and expertise with cost recovery capabilities
- Enables streamlined management of external collaborations
- Enhances the branding, recognition, and implementation of the unique capabilities of the Advanced Technology Research Facility and facilitates bringing in external partners
- Supports the Oct 28, 2011 Presidential Memorandum :
“Accelerating Technology Transfer and Commercialization of Federal Research in Support of High-Growth Businesses”

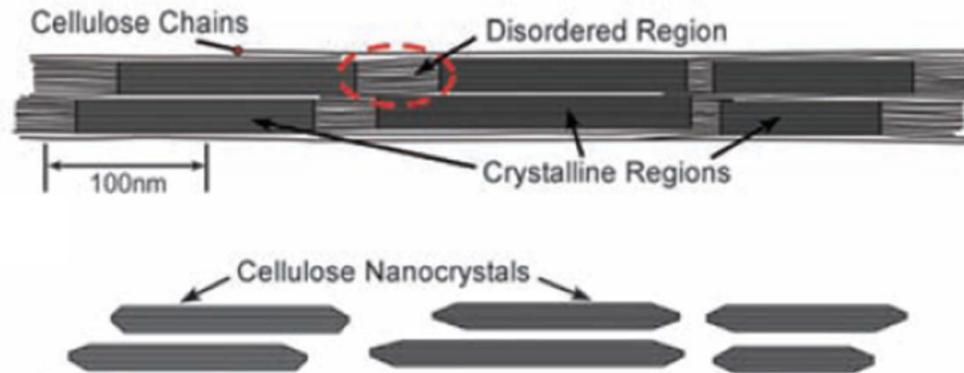
New Partnerships Under Discussion

Contractor CRADA is Likely Mechanism

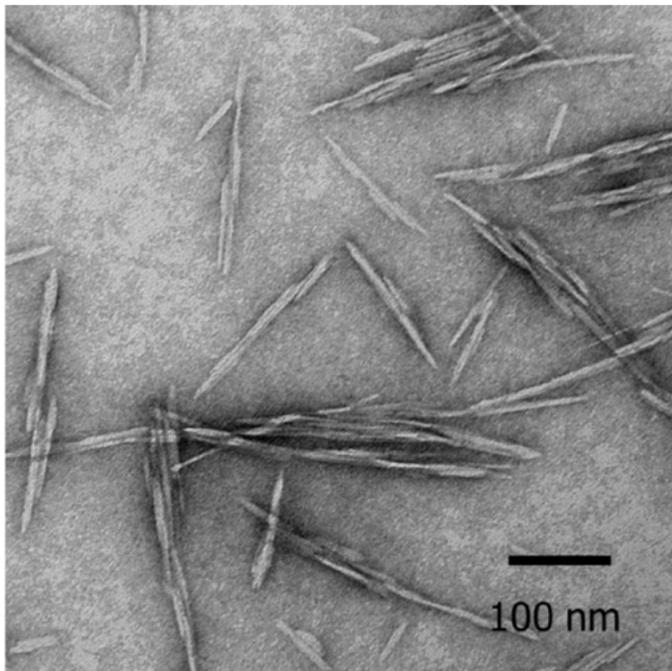


Partner	Project(s)	Business Development Stage
 Johnson & Johnson PHARMACEUTICAL RESEARCH & DEVELOPMENT, L.L.C.	Nanotechnology mAb therapeutics and assay development	 30%
Fluidigm 	Genome sequencing/expression array platforms for cancer biomarker applications	 40%
	Nanocellulose consortium seeking NCL co-development for production and testing	 30%
	Antibody engineering co-development platform and testing (ACL/clinical proteomics)	 20%
 FITCI Frederick Innovative Technology Center, Inc.	<ul style="list-style-type: none"> • Medigen viral vector gene delivery tech • Feldan Bio, Inc. interested in BDP access partnership 	 40%

Nanocrystalline Cellulose (NCC)



Chem. Soc. Rev., 2011, 40, 3941-3944



Micrograph from ATP's Electron Microscopy Lab (EML)

- Nanocrystalline form may be a “green” alternative to carbon nanotubes (CNTs)
 - NCC has 18X the strength of titanium, stronger than Kevlar
- It’s a “natural product”
 - Originates in the pulp/paper industry
- Potential applications in a wide variety of products

NCC Potential Collaboration



“Technical Association of the Pulp and Paper Industry.”



Advanced Technology Program

SAIC[®]

Frederick

- **Technical Association of the Pulp and Paper Industry (TAPPI) approached SAIC-F for:**
 - NCC characterization
 - Exploration of safety issues
 - Identification & evaluation of more efficient cellulases for production
- **Advanced Technology Program capabilities:**
 - Electron Microscopy Lab is performing imaging/characterization
 - The Nanotechnology Characterization Lab within ATP is conducting toxicity/safety testing
 - Protein Expression Lab is evaluating enzymes for NCC production

NCL= Nanotechnology Characterization Lab;
PEL = Protein Expression Lab;
EML = Electron Microscopy Lab;

SAIC-Frederick, Inc.

Building Public-Private Partnerships

Additional Outreach Activities



- Global Connect Summit Dec- completed
- Intramural Retreat Jan – completed
- Drug Delivery Partnerships Jan
- Pharma World Innovation Congress Feb
- Oncology Global Partnering Congress Feb
- FFRDC Capabilities brochure Mar
- External-Facing Website CRADA approval
 - *Julie Hartman (NCI) – presentation to follow*
- NCI-F “Branding” ?
 - *At Discussion session today*

Questions to the NFAC



- Does the planned Contractor CRADA and outreach activities meet your expectations to expand partnering with the FFRDC?
- Is there anything we can do to enhance the impact of the contractor CRADA for partners?
- Is there anything we can do to enhance the impact of our external-facing website?