2nd NCI Epidemiology Leadership Workshop: Understudied Rare Cancers

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OPENING SESSION

Session Chair: Margaret R. Spitz, M.D., M.P.H.
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Welcome and Meeting Overview

Edward Trapido, Sc.D.
Associate Director, Epidemiology and Genetics Research Program (EGRP)
Division of Cancer Control and Population Science (DCCPS)
National Cancer Institute (NCI)

Dr. Trapido opened the meeting by describing how investigators were chosen to attend the meeting. Attendees included EGRP-funded investigators working on rare cancers, defined as cancers of organ sites with 40,000 or fewer cases per year. The purpose of the meeting was to facilitate a broadening of EGRP's portfolio of research grants to include more understudied and rare cancers.

The following types of cancers are being addressed by this workshop, and EGRP-funded investigators working on them were included:

- Brain and ocular cancer
- Oral cavity and pharynx cancer
- Head and neck cancer
- Endometrium, ovary, and testis cancer
  - including cancers of the vulva, vagina, and penis (no studies are currently funded on these cancers)
  - excluding cervical cancer because the etiology is well understood
- Digestive and urinary systems cancer
  - including esophagus, stomach, liver, and kidney cancer
  - also including small intestine, anus, gallbladder, and ureter (no studies are currently funded on these cancers)
- Larynx, bones, joints, soft tissues, thyroid, and other endocrine systems
- Non-Hodgkin's lymphoma, which has more than 40,000 cases per year but is understudied, Hodgkin's disease, leukemia, myeloma, and Kaposi's sarcoma.

Pancreatic cancer was excluded for the purposes of this workshop because a Program Announcement (PA) on the disease recently was issued, and another funding opportunity is planned.[1]

[1] Program Announcement for Pilot Studies in Pancreatic Cancer (PA-05-116) *NIH Guide for Grants and Contracts* Web page: grants.nih.gov/grants/guide/pa-files/PA-05-116.html.

EGRP-funded investigators were asked to suggest the names of junior investigators, who were also invited to the workshop to promote interest in the study of rare cancers.

Design Issues in the Study of Rare Cancers
Rare Cancers Working Group Report of the 1st NCI Epidemiology Leadership Workshop
Isis S. Mikhail, M.D., M.P.H., Dr.P.H.
Program Director, Clinical and Genetic Epidemiology Research Branch (CGERB)
EGRP, DCCPS, NCI

Dr. Mikhail reported on a workshop, held at the 1st NCI Epidemiology Leadership meeting, to gather input from NCI investigators on why and how best to study rare cancers. The workshop focused on adult tumors. Rare adult cancers were defined as those with an incidence of less than 15 per 100,000 or fewer than 40,000 cases per year.

Workshop participants indicated a number of reasons why the study of rare cancers is worthwhile. As a group, rare cancers can have a large impact, especially in certain populations. The total incidence from all rare tumors is substantial, and rates of some have risen steadily over the last several years (for example, esophageal cancer). Some rare cancers are highly lethal, and those that occur at a young age result in significant years per life lost. Some otherwise rare cancers occur disproportionately in specific ethnic groups, such as male breast cancer in Zambians or nasopharyngeal cancer in Asians.

In addition, the study of rare cancer etiology could improve our understanding of all cancers. Some rare tumors tend to have a simpler etiology (for example, retinoblastoma, angiosarcoma), which if understood might provide insight into the etiology of common, more complex cancers. Family studies have shown that some rare cancers tend to be heritable, thus perhaps shedding light on genetic mechanisms. Also, the first study of a rare tumor is more likely to give useful results than the 101st study of a more common and complex tumor that has thus far proven intractable.

There are ethical reasons to study rare cancers as well. Rare tumors have been given much less attention by the research community. Patients who have rare cancers should not carry the burden of disease alone and should be allowed some hope that a cure is in the future.

Workshop participants also addressed the question of how best to study rare cancer etiology. Several methods were proposed, including the use of descriptive data from the Surveillance, Epidemiology and End Results (SEER) Program, the use of existing cohorts, and piggy-backing onto existing clinical trials. Multiple existing cohorts, while modest in size individually, could be combined to potentially identify moderate to strong risk factors. A potential caveat would be whether or not questionnaire data and biospecimens had been collected and, if they had, whether these materials would be obtainable. Existing clinical trials have been used before to gather etiologic data on childhood cancers. There is a potential for bias because clinical trial cases are likely to have the worst prognosis. Workshop participants noted that we cannot afford to be overly fastidious in studying rare cancers as strong apparent risk factors should be robust to small biases. Dr. Mikhail urged researchers to stay “open minded” about this approach.

The participants also highlighted the importance of new studies that could be designed to address specific hypotheses, to generate fresh samples for use in phenotypic assays, or to allow molecular characterization of subgroups within a specific rare cancer type. These new studies could be integrated with prognosis and treatment studies, and pool baseline data from multiple rare tumor types. The studies could be simplified by creating a common rare tumor protocol, including a single questionnaire and a common biospecimen collection protocol. Participants recommended that such studies be hospital-based since “that’s where the money is.”

Dr. Mikhail concluded by noting that both the use of existing cohorts and clinical trials, and the design of new studies will depend on building partnerships among researchers, along with a supportive infrastructure for collaboration. Workshop participants proposed that NCI set aside supplemental funds to

explore the feasibility of using the NCI-designated Comprehensive Cancer Centers (www3.cancer.gov/cancercenters) to facilitate such partnerships.

Statistics on Rare Cancers From the SEER Program
Benjamin F. Hankey, Sc.D.
Chief, Cancer Statistics Branch (CSB)
Surveillance Research Program (SRP), DCCPS, NCI

The next two speakers described how tumor registries could be used to advance study of rare cancers. Dr. Hankey provided a series of tables and graphs showing statistics on rare cancers from the SEER database. The tables and graphs, which showed incidence rates, mortality rates, trends, survival data, and other statistics were intended for use in the working group sessions if needed.

In addition to statistical data, Dr. Hankey described a number of services that SEER provides. Researchers can access SEER's public-use file through the Internet, along with software tools that can facilitate their own statistical analyses. For example, SEER software can be used to calculate different types of survival rates, including crude, net, observed, and relative. It can be used to calculate frequencies, incidence rates, and prevalence. Such tools might be useful for generating etiologic hypotheses. Researchers who do not have time to learn how to use the tools can also ask the SEER staff to perform desired analyses.

Two main Web sites give researchers access to SEER cancer data and statistical tools:

The SEER Program at the Cancer Statistics Branch:

Web site: www.seer.cancer.gov

Contains the SEER public-use file, SEER statistics tutorials, and cancer statistics.

The Statistical Research and Applications Branch:

Web site: srab.cancer.gov

Contains software tools, such as CancerServ, for cancer survival analysis; CompPrev, for prevalence analysis; and DevCam, for calculating the probability of developing or dying of cancer.

SEER's data and advanced statistical tools might be especially valuable for the study of rare cancers, Dr. Hankey said.

Cancer Registry Issues in Studying Rare Cancers: A NAACCR Perspective
Holly L. Howe, Ph.D.
Executive Director
North American Association of Central Cancer Registries

In a presentation on population-based cancer registries, Dr. Howe described the work of the North American Association of Central Cancer Registries (NAACCR), an umbrella organization of all cancer registries and surveillance programs in the United States and Canada. NAACCR defines standards for data collection and incidence statistics, trains registration professionals on these standards, certifies registries achieving high data quality, releases an annual statistical monograph, conducts population-based cancer research and surveillance, and promotes the use of population-based cancer incidence data in cancer research conducted by others.

Dr. Howe revisited the question of rare cancer definition. She suggested that no standard definition exists and many are used: cancers with rare organ/histology combinations; rare subtypes of common cancers (for example, inflammatory breast cancer); and rare, exposure-related cancers, such as mesothelioma. She also noted that some cancers are only rare in specific age groups or populations. She suggested

that a rare cancer might also be defined as an orphan cancer, one with no support, no advocates, and no population-based information. Without a standard definition, studies on rare tumors will not be compatible and surveillance statistics used for directing research of rare tumors will also be inconsistent.

In addition to definition, registries face other challenges in registering rare cancers. There are questions about the validity of diagnosis. If a cancer appears to be very rare in a given data set, is it due to reporting or coding errors or inconsistency in pathology interpretation? These errors will affect statistics for rare cancers, and even the definition of a rare cancer itself.

Dr. Howe presented rare cancer data from the NAACCR Cancer in North America (CINA) aggregated data set, from seven Canadian provinces, 42 U.S. States, and Washington, D.C. These data represent cancer cases from about 60 percent of the U.S. population and one-third of the Canadian population. These data tables can be used in the working group sessions, if needed, along with the SEER data.

Her group is planning an overview paper of rare tumors in the NAACCR aggregated data set that will first establish a rare tumor definition for inclusion in the manuscript, a data quality assessment, and then provide some descriptive statistics for all included sites. Rare tumors with sufficient numbers to enable more detailed epidemiologic descriptions will be identified, and a consortium will be convened to prepare a series of manuscripts that may be compiled into a monograph on rare tumors.

Dr. Howe proposed that NAACCR could help rare tumor research by acting as a coordinating center for a rapid case ascertainment network (RCAN), which could include all registries in the U.S. and Canada. A NAACCR RCAN could provide quality control for diagnoses, obtain patient consents, collect biospecimens, and refer consented participants to investigators for interviews. This population-based RCAN would promote consistency and efficiency among studies conducted in various states and regions. The large number of cases and population-based research capability that would be offered by an NAACCR RCA network should be especially valuable for the study of rare tumors, she said.

KEYNOTE ADDRESS

My 30-Year Love Affair with Hodgkin's Lymphoma—Lessons Learned
Nancy Mueller, Sc.D.
Professor, Department of Epidemiology
Harvard School of Public Health

In the keynote address, Dr. Mueller described her experiences studying the rare cancer Hodgkin's lymphoma (HL). Hodgkin's is noted for a "perplexing" bimodal U.S. age-incidence curve that peaks in young adulthood, around age 25, followed by a drop in incidence and another peak after age 45. The young adult form of HL is associated with higher socioeconomic status, a smaller number of siblings, a more highly educated mother, and living in a single family home. All of these factors can influence the age of first childhood infections, which led to the hypothesis that young adult HL was associated with delayed infection by a common oncogenic agent.

Epstein-Barr virus, or EBV, was the "prime candidate," Dr. Mueller said, because it is B-cell tropic, and HL is a malignancy of B cells. Moreover, HL patients often showed an abnormal antibody profile against EBV at first diagnosis, and multiple studies have shown that altered EBV antibody levels can be present years before and after HL diagnosis.

But molecular evidence for an EBV-HL link was lacking. Such evidence was difficult to obtain before the availability of molecular biology techniques because very few cells in an involved HL lymph node are actually malignant. The breakthrough came in 1989 with the demonstration of clonal EBV genomic DNA in about 30 percent of HL cases. The presence of clonal DNA implied a very early role in HL pathogenesis, but if EBV was central to HL pathogenesis, "Why not 100 percent?" asked Dr. Mueller.

Epidemiologic data presented several other paradoxes. EBV-genome-positive HL cases were primarily older adults, not the young adults the hypothesis would have predicted. EBV-positive status was found to be associated with poorer living conditions, greater age at diagnosis, and other factors that lead to poorer immune response. These results led to the further hypothesis that EBV starts the oncogenic process in all HL, but is "kicked out" in patients with adequate immune function and thus no longer detectable.

In the 1990s Dr. Mueller obtained a program project grant to test this hypothesis. The project included a population-based case-control study carried out by her group, a cohort study on pre-diagnosis specimens, and functional immunologic analyses on biosamples from EBV-positive and EBV-negative cases. This study found no evidence that EBV was involved in EBV-negative HL cases. Moreover, there appeared to be no difference in the susceptibility of younger EBV-negative HL cases to late infections, including EBV. She has since concluded that EBV-negative HL may be due to another, as yet unknown virus, with a similar transmission pattern to EBV and a greater oncogenic potential in immune-competent persons.

Dr. Mueller followed this summary of her HL research by describing what she has learned about the rewards and pitfalls of studying a rare cancer. While post-childhood HL is highly curable, she said, it remains a significant health problem for survivors and an intriguing scientific problem. However, because HL is so rare, she found few epidemiologists with whom to share data, and few basic scientists interested in collaboration. Funding was also a problem, as HL receives a low priority in peer review and attracts few advocates. She also highlighted the need for academic scientists to diversify their portfolio by doing parallel research on another disease, both to gain additional perspective and to maintain a good publication record. She said that it took a good 10 years for her case-control study to be completed, from the time of application through data acquisition and analysis.

Dr. Mueller concluded her talk by saying that the reward of rare cancer research lies in the opportunity to make a difference. "It's really a labor of love...you do it because you care," she said.

At the conclusion of her talk, Dr. Mueller was honored with a certificate of appreciation for her contributions to epidemiology. "Nancy has been an important leader in the epidemiological community, both within NCI and in the wider scientific community," Dr. Trapido said.

Closing, Charge, and Mission
Edward Trapido, Sc.D.
Associate Director, EGRP, DCCPS, NCI

Dr. Trapido closed this opening session by describing NCI's mission and how EGRP and the present meeting fit into that mission. He noted that the NCI challenge goal to eliminate the suffering and death due to cancer by 2015 is getting ever closer. "We have our work cut out for us," he said. One of NCI's primary goals is a better understanding of gene/environment interactions, part of the mandate of EGRP.

Within the context of NCI, Dr. Trapido emphasized that although there are budget issues, NCI spends the bulk of its $6.17 billion budget on extramural research projects led by individual investigators. Budget issues include a lack of increases, institutional "taps" for new initiatives, and out-year commitments for multiyear awards. These pressures have increased appreciation for the value of resource sharing, leading to the current data sharing policy. Despite these pressures, however, he noted that NCI still receives "the lion's share" of funding, and there is still a lot money for extramural research.

EGRP's research portfolio runs the gamut from understanding subcellular mechanisms of cancer to health outcomes in cancer patients. EGRP also has budgetary issues with respect to its approximately 500 grants. Pay lines are tougher, grant proposals are more closely scrutinized, and consortia are becoming increasingly attractive as a means of maximizing resources. But even with these issues, Dr. Trapido emphasized that there are still many opportunities for individual investigators, particularly in rare cancers.

The purpose of this meeting is to gather together research leaders to explore the scientific issues, identify the common roadblocks, and update researchers on the funding available for rare cancers. Junior scientists were invited to give them a chance to learn from experienced NCI-funded scientists. In turn, NCI leaders have been invited to gather suggestions about new approaches to the study of rare cancers that might enable them to justify new programs and funding opportunities.

Ultimately, said Dr. Trapido, these new approaches are likely to include transdisciplinary research in areas like behavioral and survivorship studies. He also suggested that increased use of the Specialized Programs of Research Excellence (SPOREs) (spores.nci.nih.gov) and the Comprehensive Cancer Centers (www3.cancer.gov/cancercenters) would be likely to play a role. "Reaching out towards other people really is the name of the game" for more effective research, he said.

EARLY MORNING SESSION

NCI-Supported Opportunities for Training and Career Development in Cancer Research
Lester S. Gorelic, Ph.D.
Program Director, Cancer Training Branch, Office of the Deputy Director for Extramural Science (DES), NCI

In a special session for young investigators in the early stages of their careers, Dr. Gorelic described the two major types of extramural funding that are available from NCI: institutional grants (grants awarded to the institution to which the applicant applies for funding) and individual grants (applicant applies directly to the National Institutes of Health (NIH)/NCI, and the award is made directly to the applicant).

STEPS IN THE GRANTS PROCESS: Dr. Gorelic stated that the first step in the grant process is for a young investigator to assess what his/her career goals are before initiating a search for extramural funding opportunities. For example, individuals with a doctoral degree should determine what their research focus in for the immediate future, where they currently are in their career development, how much research experience they already have, and what their strengths and deficiencies are. For clinicians, it is also necessary to determine whether their research career will be patient- or laboratory-focused, or whether they plan to pursue a career in translational research. It is also important that they conduct an assessment of the proposed research environment to determine the level of support for research career development including sources of funding, availability of appropriate onsite mentors, opportunities for collaboration and other resources including accessibility to patients. For clinicians, it is also important to assess the institutional culture as it relates to the support of clinical research versus clinical practice.

After formulating a career development plan, young investigators should search for extramural funding from Federal sources, professional societies, and foundations, and can do so by accessing their Web sites. Published compendia and professional colleagues are also good sources of information. After selecting potential funding sources, it is very important for individuals to identify the appropriate contact person at the funding agency who can help determine which program is the most appropriate for the applicant's needs.

NIH/NCI FUNDING TRAINING OPPORTUNITIES: Dr. Gorelic then described 14 NIH and NCI grant mechanisms that are appropriate for various stages in the career track of young investigators and span the continuum from the earliest stages of mentored career development awards to those awarded to established investigators.

- Institutional awards made directly to an institution include the National Research Service Award (NRSA) T32 program, which provides research training for those with very limited research experience as well as for postdoctorals; the K12 award that provides funding for clinicians who wish to conduct patient-oriented research; and the NCI R25T program, one of the fastest growing segments in NCI's grant portfolio, which supports a research career development experience that is directly relevant to epidemiologists.

- Individual awards include the F32 postdoctoral fellowships or career (K) awards which can be *mentored* for individuals early in their research career development, *unmentored* for individuals who are transitioning to their first independent position or are within the first 2 years of a first independent research position, or for established principal investigators who need protected time to expand their own research programs and to mentor those of young investigators.

Individuals who are early in their epidemiologic research careers should consider the NIH F32, K08, or K23 awards, or the NCI K07, which is an award specifically for individuals pursuing a career in cancer prevention, control, behavioral, or population sciences research. The NCI K22 should be considered by mentored individuals (Ph.D., health professional degree) who are pursuing a research career in cancer prevention, control, behavioral, or population sciences, or who have health professional degrees and are pursuing careers in basic or patient-oriented cancer research and are ready to transition to their first

independent position, or who are within the first 2 years of their first independent research position. Federally employed Ph.D.-basic scientists are also eligible to apply for the NCI K22. A unique feature of the NCI K22 is that applicants do not need a sponsoring institution to apply for an award and have up to 12 months to identify an appropriate sponsoring institution to "activate" an award should it be made. Finally, mid-career investigators in patient-oriented research or established investigators in cancer prevention, control, behavioral, or population sciences, are eligible for the NCI K05 award, which provides protected time to expand their research program and to mentor young investigators.

Individuals from groups underrepresented in biomedical research should refer to the NCI Comprehensive Minority Biomedical Branch (CMBB) for additional opportunities for support of research training and career development.

Web sites: Training Opportunities Supported by NCI: www.cancer.gov/researchandfunding/training; and CMBB: minorityopportunities.nci.nih.gov.

GUIDELINES FOR PREPARING A GRANT APPLICATION: Dr. Gorelic presented general guidelines that young investigators should follow when they are considering submitting an application for extramural funding. First and foremost, they should work with their mentor(s) and with the NIH/NCI grant program contact person to identify the funding mechanism(s) that are appropriate considering the stage in their career and their desired research career plans.

The "K" Awards: Dr. Gorelic also focused on the elements that are critical to preparing a successful application for mentored individual NIH/NCI career (K) awards. Major elements for the "K" awards are the career development plan (that includes a description of the research plan), the didactic plan, and the expertise of the selected mentors/co-mentors/collaborators. The proposed sponsors (mentors) must have expertise and current research support in the proposed area of training, as well as a proven track record in training researchers.

Dr. Gorelic advised that the research plan should be focused and should include a small number of well-defined, hypothesis-driven specific aims. Preliminary data should be introduced to show that the applicant has some experience in the methodology to be used to achieve the objectives of the research plan, and must be introduced in a situation where there is a question of feasibility of the proposed studies. The research plan must parallel the objectives of the proposed career development plan. The application should identify potential pitfalls and explain how the pitfalls will be circumvented and should cite, in the *Background* section, the critical research by others in the field. Everything in the career development and research plans should be developed through careful consultation with the sponsor (for a mentored award).

If one is applying for a career transition award (K22), it is important to demonstrate that the applicant is ready to begin an independent research program and that he/she will be able to submit a research-type ("R") application before the third year of the grant. If additional expertise is needed, individuals should be brought on as collaborators, but not as mentors.

Process for Submitting an Application: Dr. Gorelic advised that applicants should submit their NIH application using the most current electronic PHS Form 398 and should pay attention to the required criteria and format, including the required font size.[2] The application should include the applicant's biosketch (and for mentored awards those of their mentor(s) including information on the mentor(s)' current research support) and documentation pertaining to human subjects and inclusion of women, minorities, and children in research.

If an application submitted to the NIH includes research that falls within the mission of more than one NIH Institute (for example, National Institute of Child Health and Human Development (NICHD), National

[2] **NIH is transitioning to electronic submission of grant applications and the new SF 242 Research and Related (R&R) application form. See Web site for deadlines, instructions, and application form: era.nih.gov/ElectronicReceipt.**

Institute on Aging (NIA)), the applicant should include a cover letter with the application and in that letter request that the primary assignment should be made to the Institute that represents the major focus of the application, and a secondary assignment to the other Institutes providing a scientific justification for this request. This alerts the NIH staff that this application is being considered by more than one Institute, and they can collaborate with one another on its review and possible award.

At the end of his talk, Dr. Gorelic described the process that a grant application follows through the NIH system. Applications are sent to the NIH Center for Scientific Review (CSR), where they are assigned through the referral process either to an Institute study section or to a CSR special emphasis panel (for example, F32 awards). (At the NCI, K award and T32 applications are assigned to different study sections, with care taken not to review basic and clinical research applications in the same Institute review group.) In the event that an application is not funded, Dr. Gorelic encouraged the investigators "*not to give up,"* but that once they receive the Summary Statement, they should contact the Program Director who is assigned to their application. The Program Director will assist an applicant in interpreting the critiques, and provide additional input on the review that will be useful in assembling the revision of their original application. For mentored career development awards, the applicant should discuss the critiques with their mentor(s) prior to contacting their Program Director.

PLENARY SESSION
Creating Consortia: Rationale, Roadblocks, and Successes

Session Chair: Leslie Bernstein, Ph.D.
Professor, Norris Comprehensive Cancer Center
University of Southern California

Consortia: A Tool for Interdisciplinary Research in Epidemiology

Daniela Seminara, Ph.D., M.P.H.
Program Director, CGERB, EGRP, DCCPS, NCI

Dr. Seminara presented her work on the characteristics and formation of consortia and other large-scale collaborative scientific projects. She described consortia as an "emerging new research paradigm" in which large interdisciplinary teams of scientists work together collaboratively, using common protocols and methods and performing coordinated parallel or pooled analyses. This approach to research creates synergy by exposing scientists from different disciplines to new concepts and approaches, she said. For epidemiologists, consortia can provide the resources necessary to study the effects of environmental exposures, identify genetic factors, evaluate GXE interactions, unravel the etiologic heterogeneity of tumor subgroups, and determine prognostic factors. Consortia can facilitate the rapid replication of findings, the pooling of data to increase sample size, and the initiation of new large-scale studies.

EGRP supports epidemiology consortia with several different types of designs, including cohort studies designed to track multiple outcomes and identify converging mechanisms; more specialized case-control studies, generally focusing on less common tumors; and family-based studies that might identify high or intermediate penetrance genes and show effects of environmental modifiers. Another large segment of the EGRP-supported consortia concentrates on research infrastructures with hybrid design, such as the Breast and Colon Cancer Family Registries (BC-CFR) (Web site: epi.grants.cancer.gov/CFR). Dr. Seminara emphasized the growing importance of this approach to the conduct of research by listing established or emerging consortia focusing on 15 different cancers.

The EGRP works to foster consortia development by identifying research priorities, assessing needs and providing resources, facilitating communication, and aiding in study implementation. A program task is also to evaluate consortia's performance, develop milestones, and incorporate best practices for high research standards. The recently established EGRP Consortia Working Group reviews the status of EGRP-supported consortia, identifying issues and obstacles, and proposing solutions. Through the soon-to-be-established consortia Web site, EGRP plans to disseminate information about how to plan, develop, and evaluate consortia to give the general research community the benefit of its expertise in this area.

Dr. Seminara said that the Consortium Working Group has developed a set of criteria with which to evaluate proposed consortia. First they look at the scientific rationale: are there scientific questions that only this consortium can address? Clearly defined leadership roles and an appropriate organizational structure are also very important. The proposal should address issues such as data and specimen sharing, and publication policies. It should also address potential difficulties due to differences in design, data variables, and specimen acquisition and storage among the different research groups involved.

She addressed some of the funding issues faced by consortia. Consortia require larger financial commitments over longer periods of time, which are difficult to obtain given current infrastructure and funding mechanisms, especially with tighter pay lines. She illustrated potential new funding mechanisms for consortial grants and satellite grants that are currently under development at NIH. For consortial grants, RFAs could be issued to solicit additional applications to become an integral part of a specific consortium. These applications would be reviewed within the context of that consortium. Satellite grants, for proposals that are affiliated with the consortium only by scientific serendipity, would not become an integral part of the consortium. In both cases, continued funding would depend on the success of both the individual project and the overall consortium.

She described a number of other challenges faced by consortia. These include effective communication and coordination among the research groups belonging to the consortium, sufficient informatics and analytical support to handle very large data sets, and overcoming institutional boundaries that separate scientists working in different disciplines. Consortia must also find ways to rapidly integrate cutting-edge technologies, including genomic methods, and to form biorepositories that can facilitate the storage and use of critical biosamples. She mentioned the sharing of intellectual property rights and authorship as additional challenges. The Consortium Working Group can provide suggestions and support to help emerging consortia for deal with these and other difficulties.

Lastly, Dr. Seminara gave some examples of consortia that have recently published results or commentaries. These included the Human Genome Epidemiology Consortium (HuGE), the International Consortium for Prostate Cancer Genetics (ICPGG), and the Genetic Epidemiology of Lung Cancer Consortium (GELC). She said that she expects such very large consortia to provide additional challenges in the future, as consortia "superstructures" will be needed to support their activities.

An Example From the Brain Tumor Consortium

Melissa L. Bondy, Ph.D.
Professor of Epidemiology
The University of Texas M. D. Anderson Cancer Center

Dr. Bondy described her work with the Brain Tumor Epidemiology Consortium (BTEC). It is estimated that there will be 17,000 new brain tumor cases and 13,100 deaths from brain tumors in the United States in 2005. Brain tumor rates are increasing, especially for adults over age 65, although the apparent increase might be attributable to advances in detection technology. However, brain tumors are still quite rare, and research consortia are needed to provide adequate numbers for epidemiologic study, she said.

The BTEC, which was initiated at a meeting organized by NCI in 2003, was formed to promote multicenter, interdisciplinary collaborations leading to the understanding of etiologies, outcomes, and prevention of brain tumors. Pooled or parallel analyses from different labs could provide sufficient data to study statistically difficult questions, such as the roles of gene-gene and gene-environment interactions. The consortium also aims to help its members keep up with the latest molecular and genomic advances, so that brain tumor epidemiology can be understood at the molecular level.

The consortium consists of an international, multidisciplinary group of investigators including epidemiologists, statistical geneticists, neurosurgeons, oncologists, neuropathologists, and basic scientists. It also includes brain tumor advocates and fundraising organizations. The consortium is overseen by a coordinating committee, with U.S. and European chairs, and includes four research focus groups concentrating on adult glioma etiology, family studies, meningiomas, and pediatric brain tumors.

The BTEC's first funded initiative will undertake the first large epidemiological study of meningiomas. This multicenter study will examine environmental, genetic, pathological, and clinical variables associated with meningioma risk. Dr. Bondy described some of the difficulties the consortium encountered in applying for funding. She said there was initially some uncertainty as to how to submit the proposal to NCI, but that they succeeded by submitting a group of linked R01s. At review time, the study section had difficulty finding outside reviewers since almost everyone in the field was involved in one of the linked proposals.

The National Brain Tumor Foundation (NBTF) has also funded two multicenter pilot studies initiated by the BTEC. One study will look at single nucleotide polymorphisms in the DNA repair gene pathway to gather clues about the etiology of glioblastomas. A second study will focus on the descriptive epidemiology of oligodendroglioma, seeking to classify and identify risk factors for this very rare tumor.

The BTEC is now seeking funding for a large consortium to be called GLIOGENE, which would target the genetic epidemiology of familial and sporadic gliomas. This consortium would build on a number of previously established relationships among centers in the United States and Europe, including several SPORE programs. It will include a steering committee, made up of principal investigators from each site, and an advisory committee, made up of experts in genetics, molecular biology, and brain tumors. Dr. Bondy stressed the importance of having such outside advisors to maintain high scientific standards.

Dr. Bondy closed by describing some of the reasons for BTEC's success. In terms of logistics, the Central Brain Tumor Registry provides administrative support for handling meeting planning and finances, a difficult task to accomplish through individual institutions. The BTEC has attracted long-term support for meetings and pilot projects through foundations such as NBTF and from NCI. Scientifically, the BTEC consists of a highly collaborative and committed group of investigators, who are gathering retrospective data for merged analyses, initiating prospective studies, and creating opportunities for young investigators. They are also developing criteria for publications so that all participants can receive proper credit for their work. These activities should greatly increase our knowledge about the little understood etiology of brain cancers.

PANEL DISCUSSION

Opportunities for Partnerships Along the DCCPS Cancer Control Continuum
Session Chair: Robert T. Croyle, Ph.D.
Director, DCCPS, NCI

Dr. Croyle opened the session on partnership opportunities in cancer control research by describing the organizational structure of the Division of Cancer Control and Population Sciences (DCCPS). DCCPS includes the Office of Cancer Survivorship (OCS) and four programs: Epidemiology and Genetics Research Program (EGRP), Behavioral Research Program (BRP), Applied Research Program (ARP), and Surveillance Research Program (SRP). He highlighted a variety of DCCPS resources of potential interest as sources of data, resources, and collaborators for EGRP-funded investigators: SRP's biostatistics group and funded investigators, and the BRP-funded Centers of Excellence in Cancer Communications Research, Transdisciplinary Tobacco Research Centers (TTURC), and the Transdisciplinary Research on Energetics and Cancer (TREC) Centers (awarded Oct. 2005). DCCPS also conducts research on how to assess health disparities and collaborates with NCI's Center to Reduce Cancer Health Disparities.

He said that when DCCPS considers funding by exception grant applications that are outside the payline, it looks at whether the investigator is taking advantage of existing resources and the most effective strategies for achieving the research aims. He encouraged investigators to piggyback on existing resources, for example, the SEER-Medicare linked database, HMO Cancer Research Network (CRN), and NCI's Cancer Information Service (CIS).

(Web sites for the above mentioned resources: SRP biostatistics group and funded investigators, statfund.cancer.gov; Centers of Excellence in Cancer Communications Research,

dccps.nci.nih.gov/hcirb/ceccr; Transdisciplinary Tobacco Research Centers (TTURC), dccps.nci.nih.gov/TCRB/tturc; Transdisciplinary Research on Energetics and Cancer (TREC) Centers, cancercontrol.cancer.gov/TREC; SEER/Medicare-linked database, healthservices.cancer.gov/seermedicare; HMO Cancer Research Network (CRN), crn.cancer.gov; NCI Center to Reduce Cancer Health Disparities, crchd.nci.nih.gov; Cancer Information Service (CIS), cis.nci.nih.gov/research/research.html.)

Surveillance Research Program
Benjamin F. Hankey, Sc.D.
Chief, Cancer Statistics Branch (CSB), SRP, DCCPS, NCI

Dr. Hankey described the Surveillance Research Program (SRP) which includes two branches: the Cancer Statistics Branch and the Statistical Research and Applications Branch.

The Cancer Statistics Branch collects and analyzes data to answer questions about cancer incidence, mortality, and the cancer-related health status of various regions and populations in the United States. This branch provides a number of resources for the study of rare cancers, including the SEER Program. The 2006 release of the SEER public-use file will include ecologic data from the Census Bureau and other sources at the county level. SEER data are also linked to cohort data from the National Longitudinal Mortality Study, which includes 26,000 linked cases from 11 registries. The SEER registries themselves provide high-quality data and mechanisms for rapid case ascertainment and rapid-response surveillance studies.

The Cancer Statistics Branch is also interested in promoting geographic information systems (GIS) studies and held a workshop in June to address the development of future GIS methods. SEER also holds an annual meeting to explore topics for study using the rapid response surveillance mechanism, one of a number of meetings that might be useful to research consortia.

The Statistical Research and Applications Branch, develops statistical methods for analyzing trends in cancer rates, evaluating the impact of cancer control interventions, and for evaluating the impact of geographical, social, behavioral, genetic, and health care delivery factors on the cancer burden. This branch develops software tools for generating epidemiologic statistics using the SEER public-use file. It also is investigating the use of GIS methods.

Dr. Hankey provided a list of Web sites that can be used to obtain more information about SRP activities and resources:

Surveillance Research Program
Web site: surveillance.cancer.gov

SEER Program
Web site: seer.cancer.gov

Cancer Statistics Branch
Web site: surveillance.cancer.gov/csb

Statistical Research and Applications Branch
Web site : srab.cancer.gov

Geographic Information Systems
Web site : srab.cancer.gov/gis

Rapid Response Surveillance Studies
Web site: seer.cancer.gov/rapidresponse

National Longitudinal Mortality Study

Web site: www.census.gov/nlms

Resources for Studying Rare Cancers
Martin L. Brown, Ph.D.
Chief, Health Services and Economics Branch (HSEB), Applied Research Program (ARP), DCCPS, NCI

Dr. Brown described the mission of the Applied Research Program (ARP) and how its work might be of interest to those studying rare cancers. ARP supports the evaluation of patterns and trends in cancer-associated health behaviors, practices, genetic susceptibilities, health services, economics, and outcomes. Its staff also monitors and evaluates cancer control activities in the United States and determines the influences of these factors on cancer incidence, morbidity, mortality, survival, cost, and health-related quality of life. It can provide technical assistance with databases and surveys, and advise on grant issues.

ARP has a number of resources applicable to rare cancers. One is the Breast Cancer Surveillance Consortium, which includes study of prognostic factors for the rare cancer ductal carcinoma *in situ* (DCIS). Another important resource is the HMO Cancer Research Network, or CRN. This is a network of cancer research centers associated with large nonprofit HMOs. The network, which covers a population of 10 million, provides a large scope of data including pharmacy information, and large diverse populations. These populations include large numbers of cases of rare cancers such as multiple myeloma, esophageal cancer, and glioblastoma. The CRN is carrying out several multicenter studies, including one on pancreatic cancer etiology and one on multiple myeloma. Outside investigators can access the CRN by submitting a proposal to collaborate with CRN investigators. Initial estimates of cancer cases and related health care and pharmaceutical use can be obtained through the CRN Virtual Data Warehouse.

Dr. Brown described another resource known as SEER-Medicare, which is a linkage of SEER data with Medicare data. This resource provides detailed information about elderly persons with cancer and represents a retrospective, longitudinal data set that can be used for a number of types of epidemiologic and health services studies. It includes huge numbers of Medicare recipients and will continue to grow as the population ages. More than 150 studies have already taken advantage of this resource. The database is not for public use but access can be gained by a straightforward process.

Dr. Brown listed several Web sites for further information on access to data and collaboration with these resources:

Breast Cancer Surveillance Consortium
Web site: breastscreening.cancer.gov

HMO Cancer Research Network
Web site: crn.cancer.gov

SEER-Medicare Linked Database
Web site: healthservices.cancer.gov/seermedicare.

The Epidemiology/Cancer Survivorship Interface
Julia H. Rowland, Ph.D.
Director, Office of Cancer Survivorship (OCS), DCCPS, NCI

According to Dr. Rowland, cancer survivorship research seeks to identify and control adverse cancer- and treatment-related outcomes to provide a knowledge base that will allow optimal follow-up care and surveillance of cancer survivors, and to optimize health after cancer treatment. She said that epidemiologic studies should focus not only on survival but on all the things that make survival possible, including long-term effects and predisposing factors that might make for a poor trajectory. Survivorship

studies can use classic epidemiological research designs such as cohort and case-control studies, and trial/intervention designs.

She provided some examples of epidemiologic research germane to survivorship, including studies on the incidence and risk factors of physiological late effects, such as cardiotoxicity; examination of lifestyle and health behaviors, such as exercise and smoking, on morbidity; and identification of protective factors, especially in "extraordinary" survivors. She also identified a number of gap areas that epidemiologic research could address, such as the influence of predisposing factors on survivorship outcomes, health outcomes in long-term survivors, the role of co-morbidity, and the roles of socio-cultural and behavioral factors, family, and post-treatment care on outcomes.

Dr. Rowland suggested that existing studies and databases supported by NCI could be leveraged to collect data about survivorship and provide answers for some of these gap questions. New multidisciplinary studies could also be used to link epidemiologic data such as risk factors to survivorship outcomes.

The CIS Research Program
Susan E. Rivers, Ph.D.
Senior Research Coordinator, New England Cancer Information Service
Yale Cancer Center

Dr. Rivers explained that the Cancer Information Service, or CIS, is an NCI program that operates through contracts with academic institutions, hospitals, and Comprehensive Cancer Centers. The CIS operates three component services, including an Information Service, a Partnership Program, and a Research Program.

The CIS provides answers to individuals seeking information on cancer through toll-free phone numbers, instant messaging, and by e-mail through NCI's Web site (cancer.gov). Comprehensive information is provided on cancer risks and prevention, symptoms and diagnosis, and treatments and clinical trials.

The Partnership Program collaborates with trusted community organizations to reach minority and medically underserved populations with cancer information. The outreach effort helps to enroll these populations into cancer detection and prevention programs as well as into clinical trials. It also provides training to those organizations on cancer-related topics and the use of NCI resources, links organizations with similar goals, and helps plan and evaluate programs.

The Research Program seeks to understand, apply, and disseminate effective communication approaches to educate the public about cancer and contribute to cancer control efforts. Research themes include testing novel health communication and education interventions, increasing access and use of cancer-related information, discovering effective models for disseminating cancer information, and understanding general information seeking behaviors.

Dr. Rivers said that the CIS provides an opportunity for investigators to collaborate with highly skilled researchers who have access to large numbers of cancer information seekers, many eager to participate in research. The CIS provides multiple venues for dissemination of information, often in partnership with organizations that can reach minority and underserved populations. Its staff is highly trained and can provide cancer content expertise, design research methodology, obtain informed consent, and design and administer eligibility assessments and baseline questionnaires.

LUNCHEON KEYNOTE ADDRESS

Health Informatics, caBIG, and Population Sciences and Cancer Control
Deborah M. Winn, Ph.D.
Chief, Clinical and Genetic Epidemiology Research Branch (CGERB), EGRP, DCCPS, NCI

Dr. Winn presented the work of the Health Informatics Steering Committee, whose mission is to apply health informatics tools to DCCPS research activities in order to optimize new data collection as well as the use of existing data. The committee also promotes the application and sharing of data and research advances with individuals and communities. Key focus areas include cancer care and surveillance, data collection and analysis strategies in population science, behavioral and cancer survivorship research, and the application of GIS methods to cancer data and bioimaging.

She described an NCI initiative known as caBIG, for cancer Biomedical Informatics Grid (https://cabig.nci.nih.gov). The grid represents a network of individuals and institutions, designed to facilitate the sharing of cancer-related data, tools, and infrastructure. The network includes about 50 NCI-designated Cancer Centers, including participants from the cancer and biomedical research communities, private industry, and patient advocacy groups.

Working groups within caBIG are taking open-source, open-data approaches to such tasks as clinical trials management, integrative cancer research, and tissue banks and pathology tools. Other groups are planning systems architecture, vocabularies, and common data elements. Strategic-level groups are involved in strategic planning, addressing data sharing and intellectual capital issues, and training efforts. Tools are under development to handle data from cutting edge technologies such as microarrays, proteomics and computational genomics.

The Health Informatics Steering Committee joined with the extramural community and the NCI Center for Bioinformatics, which developed caBIG, to create the Population Sciences Special Interest Group within the Integrated Cancer Research Working Group. This interest group is focusing its efforts on developing tools and resources to facilitate epidemiologic and cancer control research.

DCEG and DCCPS also have created a joint project to develop common data elements (CDEs) for population sciences and cancer control. These CDEs, which are being developed for subject areas like demographics, tobacco history, and body mass index, will be placed in the Cancer Data Standards Repository, or caDSR, along with common vocabularies. Thus, the caDSR will provide unambiguous semantics for the data collected in all cancer studies and trials. The caDSR will also provide a Form Builder tool that can build standardized questionnaires and forms using the CDEs and vocabularies. These standardized forms will be stored in the repository for use by others in the research community. They should allow for more consistent data collection and analysis, reduction of errors, and vastly enhanced data sharing and data pooling capabilities.

PLENARY SESSION AND PANEL DISCUSSION
Transdisciplinary Science: Partnering Population, Basic and the Clinical Sciences

Session Chair: Graham A. Colditz, M.D., Dr.P.H.
Professor of Medicine, Brigham and Women's Hospital
Harvard University

Merging Basic Science and Population Science to Elucidate Mechanisms of Breast Cancer Development

Jonine L. Bernstein, Ph.D.
Associate Attending Epidemiologist, Memorial Sloan-Kettering Cancer Center

Dr. Bernstein discussed her work with the Women's Environment, Cancer and Radiation Epidemiology Study, also known as the WECARE Study. This interdisciplinary, multicenter study was designed to investigate the joint roles of radiation exposure and genetic susceptibility in second primary cancers in women with breast cancer.

Only 5 to 10 percent of women with breast cancer develop a second primary cancer in the contralateral breast, making this a rare cancer. Breast cancer patients are two to five times more likely to develop a second breast cancer than are women in the general population without breast cancer to develop a first cancer. The risk of developing a second primary persists for at least 30 years. Although epidemiologic

data are scarce, the only other consistently identified risk factors for second primary breast cancer are: early age at diagnosis of the first primary breast cancer, lobular histology of the first primary, a family history of breast cancer, and carrying mutations in the cancer genes BRCA1 and 2.

Radiation treatment for the first primary also elevates the risk of developing a second primary, while tamoxifen and chemotherapy do not, which led to the idea that risk might be associated with DNA damage and damage repair pathways. ATM (for ataxia-telengectasia gene mutation) is activated by DNA damage, such as that from radiation exposure. ATM lies upstream and controls a number of damage control proteins, including the Chk2 protein, which interacts with the P53 tumor suppressor. Homozygous mutations in the ATM gene cause the disorder ataxia telengectasia (A-T), an autosomal recessive disease characterized by progressive neuronal degeneration, immunologic deficiency, and premature aging and death.

A-T is also characterized by increased radiosensitivity and susceptibility to cancer. This led to the hypothesis tested by the WECARE Study that women who carry a single ATM gene mutation may be more susceptible to radiation-induced breast cancers than those with no mutations. To improve the chances of detecting the effects of these relatively rare mutations, in the WECARE Study, women with asynchronous bilateral breast cancer serve as cases and women with unilateral breast cancer serve controls. Preliminary results show that women who carry a deleterious ATM mutation and who received radiation treatment for their first primary have a much higher risk of developing a second breast cancer than do women who do not. Ongoing studies are looking at genes in the entire ATM-Chk2 DNA repair pathway, as well as the roles of BRCA1 and 2.

Dr. Bernstein also described the organization of this large successful collaborative study. Since the cancer is rare, and a large sample size was required to achieve adequate statistical power, the study involves multiple data collection centers. Multiple genotyping laboratories are also needed to analyze the very large, complex ATM gene, as well as laboratories with experience in the technical challenges of measuring radiation exposure. The study includes more than 70 investigators from 25 institutions, 5 countries, and 7 time zones.

The WECARE field organization includes working groups that direct different aspects of data collection and analysis, such as Radiation Dosimetry, Genotyping, and Biostatistics. These groups are coordinated by a Steering Committee and an Internal and External Advisory Committee, which Dr. Bernstein credits with helping to keep the study moving. There are also subcommittees formed to deal with practical issues such as biorepository use, budgets, and publications, and to deal with the data analysis.
Dr. Bernstein ended her presentation by describing some of the “lessons learned” from the WECARE Study about interdisciplinary partnerships. The study team worked well, she said, because it included deep expertise in every scientific aspect of the study, along with a prior track record of collaboration among many of the investigators. For the follow-up study, they are planning to include more junior investigators. Communication within the Working Groups was constant and effective, but she found that annual meetings and e-mails were only barely adequate as a means of overall communication with the team as a whole. Support from NCI was helpful but funding is an issue now that the initial WECARE:ATM funding is finished. Additional funding is needed to maintain the group’s infrastructure so that this work can be built upon and future studies completed.

Integration of Oncogenomics and Population Science to Improve Patient Outcome in Myeloma
Kenneth C. Anderson, M.D.
Director, Jerome Lipper Multiple Myeloma Center
Dana-Farber Cancer Institute

Dr. Anderson presented his work using both genomic and epidemiologic data to guide clinical research on potential chemotherapeutic agents for the treatment of myeloma. “Teamwork is the only way to go,” he said, making the case for multidisciplinary approaches to rare cancer research. Dr. Anderson leads a SPORE in myeloma.

Multiple myeloma is a disease resulting from excess plasma cells in the bone marrow. The disease is incurable, although the median survival of 3 to 4 years with conventional therapy can be improved slightly with high-dose therapy and bone marrow transplant. Myeloma accounts for 2 percent of cancer deaths in the United States, and there are 14,400 new cases each year. Incidence is especially high in African Americans and Pacific Islanders. Predisposing factors include environmental exposures such as radiation or petroleum products, and occupations such as farmer, paper producer, furniture manufacturer, or wood worker.

Another predisposing factor for myeloma is the presence of a clinical syndrome known as Monoclonal Gammopathy of Unclear Significance, or MGUS. MGUS occurs in about 2 percent of individuals older than 50 years and is characterized by less than 3.5 grams/liter monoclonal immunoglobulin and less than 5 percent monoclonal bone marrow plasma cells. Individuals with MGUS have a 25-fold higher risk of developing multiple myeloma within 20 years, as well as greatly increased risks for other blood disorders such as macroglobulinemia, plasmacytoma, and primary amyloidosis.

Dr. Anderson's group is investigating how gene expression profiles change in the progression from normal to MGUS to myeloma. They have identified a large number of genes whose expression is either up-regulated or down-regulated at different stages in the progression. These genes and their protein products represent potential targets for therapy against myeloma. Dr. Anderson refers to this research strategy as "oncogenomics."

A total of 258 expressed oncogenes were identified. In order to target myeloma-specific genes, genes that were over-expressed in more than one cancer were eliminated. Some of the remaining genes were only over-expressed in certain patients. For example, only 20 percent of patients over-expressed fibroblast growth factor receptor 3 (FGFR30), a tyrosine kinase. A kinase inhibitor is in clinical trials, but only those patients will be expected to show a response.

By these and other methods, Dr. Anderson's group has identified seven potential targets for anti-myeloma therapy. They have developed compounds against six of these. In addition to the anti-FGFR3 agent, they are testing inhibitors of angiogenesis, telomerases, the proteasome, and the stress response. They are also working on an Mcl-1 antisense RNA as an anti-apoptotic agent.

Most of these studies involve cells in culture. But Dr. Anderson said that it is important to remember that cells live in a particular microenvironment, and this can change gene expression patterns. His group has identified many of the genes that control the interactions of multiple myeloma cells with cells in the bone marrow microenvironment. These studies have led to the use of thalidomides to manipulate these interactions. One thalidomide compound, revlimid, has been very successful in Phase III clinical trials.

Another drug that blocks tumor/microenvironment interactions is Velcade (bortezomib). This drug gained FDA approval in less than 3 years from bench to bedside, which Dr. Anderson attributes to the power of collaborative research. Further demonstrating the value of teamwork, he said that two companies have joined together to test bortezomib and revlimid together, a combination that is successful in some patients who have failed treatment with one or the other alone.

Dr. Anderson's group is also using gene expression microarrays to help predict clinical responses to drugs. He said that population studies are needed to identify gene targets associated with drug sensitivity or resistance. His group found that heat shock protein 27 (Hsp27) was over-expressed in people who were resistant to his new proteasome inhibitor. He is now directing a clinical trial to determine whether inhibiting Hsp27 indirectly, by inhibiting p38 MAP kinase, will affect proteasome inhibitor resistance in these patients.

Dr. Anderson's latest project, on IGF gene variation and multiple myeloma risk, is funded by a SPORE career development award, which he called a "wonderful model" for team-related integrated research. This study will investigate the role of IGF-1 mediated signaling cascades in myeloma, combining molecular biology and biochemistry, animal models, and epidemiological research. The results could be useful in other cancers where this pathway has been implicated, including breast cancer. Another new

collaborative project will investigate genetic risk factors for myeloma using single nucleotide polymorphisms and epidemiologic studies.

Dr. Anderson concluded with two lessons learned from his studies of rare cancers. First, he has developed a new treatment paradigm that targets both the cancer cell and its microenvironment. This paradigm may prove useful for other cancers. Second, the SPORE collaborative oncogenomic and population studies have proven very useful for identifying new therapeutic targets and for informing the design of clinical protocols.

Translational Research: Trends of the Future
Jorge Gomez, M.D., Ph.D.
Chief, Organ Systems Program
National Cancer Institute

Dr. Gomez followed Dr. Anderson's talk with a discussion of some of the general issues involved in multidisciplinary research, and how NCI can facilitate this research. He defined multidisciplinary research as studies performed by a team of experts, based on common scientific goals. There are many projects now that cannot be accomplished using single investigator research, although the R01 is still the basis of most biomedical research.

He said that the NCI staff can facilitate such research in a number of ways. They can help initiate and promote interactions among scientists. They can provide administrative advice, including pre-application consultation and advice on funding opportunities and program requirements. They can also help coordinate with other NCI programs and help to establish partnerships with private industry. He emphasized that their role should be facilitative rather than regulatory.

Dr. Gomez described a number of trends occurring in translational research. This research is incorporating new technologies into patient research and supporting the development of new drugs and novel clinical interventions. It is also opening up new, more creative ways of interacting with private industry and involving patient advocacy groups.

Translational research requires flexible management of the interactions between grantees, NCI, and NIH programs, and other government agencies. A high level of leadership is needed to coordinate and support these interactions, in the context of an appropriate organizational structure. It also requires the resources to respond quickly and efficiently to newly identified gaps. "Rare diseases are outside the line," Dr. Gomez concluded, and will require new models for management and funding that can support translational, multidisciplinary approaches.

Remarks
Shelia Hoar Zahm, Sc.D.
Deputy Director, Division of Cancer Epidemiology and Genetics (DCEG), NCI

Dr. Zahm brought forward another perspective on the challenges facing transdisciplinary, integrative, and translational research. First, she noted that such research requires sufficient funding and resources to enable adequate communication, including in-person meetings, to plan and ensure successful conduct of complex projects. Adequate and continued funding is also a necessity to fully exploit the resources developed by the study.

A major challenge is the increasing complexity of projects as disciplines are added to a study. With each discipline often needing unique data, biospecimens, or environmental specimens, there is the risk that the protocol may become a crushing burden for staff and subjects. Lengthy questionnaires, complicated environmental and biospecimen collection, shipping, and storage procedures, and other requirements can be logistically challenging, expensive, decrease response rates, and lead to staff burnout. In the face of decreasing response rates, transdisciplinary studies, in particular, may need to increase incentives paid to subjects and may need to grapple with the best method to inform subjects of the possible study components without jeopardizing participation. Researchers launching transdisciplinary projects need to

seek the best scientific collaborators, but it helps to also seek collaborators who are reasonable, communicate well, and are willing to compromise appropriately, if necessary. This is especially important because as the science becomes more complex, it becomes harder to judge the value of proposals for study components that are outside one's own discipline.

Transdisciplinary research is challenging but well worth it, she said, providing a "veritable goldmine" of data. Factors that promote success include good communication, mutual respect, real-time monitoring of each component, and sufficient resources.

FINAL SESSIONS

PANEL DISCUSSION
Rare Cancer Advocates and Survivors: The Few and Far Between

Session Chair: Julia H. Rowland, Ph.D.
Director, Office of Cancer Survivorship, DCCPS, NCI

Panelists:
Douglas Bank
President and Editor
Testicular Cancer Resource Center

Richard N. Boyajian, R.N., M.S.
Lance Armstrong Foundation Adult Survivorship Clinic
Perini Family Survivors Center
Dana-Farber Cancer Institute

Cary Zahrbock
National Coalition for Cancer Survivorship

In this discussion, the moderator, Dr. Rowland, asked the panelists to respond to a series of questions about the role of epidemiology in the life of cancer survivors and members of the public who have never had cancer.

1) How accessible is epidemiology to consumers?

Panelists responded that many people do not understand what epidemiology is and have difficulty understanding how risk factors apply to them (for example, the difference between relative, absolute, and individual risk). They felt that many people get their information from television in a form that may not be accurate or readily understandable. People need to know how they can apply epidemiologic data to themselves and their families in practical ways. They would benefit from information that emphasizes the key, most important messages. People are also especially attuned to messages that give them hope.

2) How effective are consumer advocacy programs in research and related activities, such as the Director's Consumer Liaison Group (la.cancer.gov/dclg.html)**?**

Panelists noted that there are a number of consumer advocates who have been trained to provide input in research-related activities. However, they also felt that many of these individuals are underutilized. They advocated for a more open process that includes consumer advocates and cancer survivors on review panels for many types of grants and on Request for Applications (RFA) review panels as well. They see this involvement as an important avenue for communication between the public and scientists. They noted that the training of advocates varies greatly and suggested that it may be useful to have a way to review the training and or standardize the approach to orienting advocates who wish to serve in this capacity, such as done in NCI's CARRA (Consumer Advocates in Research and Related Activities) Program (liaison.cancer.gov/CARRA).

3) What are the biggest barriers preventing collaboration between scientists and consumer advocates?

Scientists need to incorporate advocates into the process before the research is created, they said. The advocates may bring about changes in protocols by introducing a "human factor" that addresses whether a given protocol is reasonable for the subjects participating. They did note that some advocates who are survivors are unable to separate their emotions from the science. Careful screening should be used to make sure advocates are emotionally ready to participate in the research review and planning process. Accessing survivors through groups, such as the CARRA Program, or established advocacy groups can help scientists identify and enlist the input of trained, articulate advocates.

4) What are the questions that consumers want to know about?

Panelists described a number of concerns and questions:

- What are the long-term and late effects of treatment?
- Should the chronic and late effects of cancer be studied by treatment exposure and not based solely on disease? This would provide a larger population and stop the discussions about relevance by disease and perhaps also reveal differences in patterns of effects experienced. It was acknowledged that this would require a large effort in monetary levels and manpower.
- How can scientists best study/validate late effects and side effects of treatment?
- What should cancer survivors expect and what screening tools should they be using after treatment ends?
- What should they be doing to promote a longer life and prevent late effects?
- How can they promote their overall quality of life after cancer?
- What is a cancer cluster? How do you know if a number of cancers experienced by members of a group is significant and who would you report it to?
- How does lack of insurance coverage affect cancer outcomes?
- Better morbidity and mortality data could help cancer survivors who face discrimination from life insurance companies and potential employers.

5) What are the lifestyle and family effects of cancer?

People with a cancer diagnosis want to know how to lessen the impact of disease both on themselves and their families. Often they want to make their lifestyles healthier, and they need information about how to do this, the panelists said. They also need tools to help them make such changes, like smoking cessation programs. Further, they need to know what they should tell their families about risks both to themselves and to other family members.

If a cancer is hereditary, what steps should they take to protect their family? What is the level of evidence regarding lifestyle modification and reduction of cancer risk? Could this information help families reduce their cancer burden? To what extent are factors that may be associated with risk of cancer also be predictors of survival or morbidity after a cancer diagnosis? This, they felt, is where we need more answers. Finally, genetic links or risks need to be looked at in larger study populations instead of smaller cohorts.

Many also have psychosocial needs that are going unmet the panelists pointed out. Their quality of life may be poor because of psychological rather than physical effects of cancer. Psychologists need more training to deliver this care and more programs need to be developed to help survivors and their loved ones deal with these problems.

6) How can advocates help with epidemiologic research?

Panelists said that cancer survivors are often eager to share information about their lifestyles and participate in research, but are not asked to do so. They suggested several ways that advocates/survivors could help researchers. For example, scientists wishing to find survivors of rare cancers could go to cancer survivor groups. These groups might also be able to help set up community-based research and be trained to carry it out. They felt that outreach and study enrollment carried out by survivors might be more effective because they are peers or fellow patients. The panel also suggested that giving tax credits to participants might be an effective way to enroll more survivors and more cases and controls for studies. Scientists could also team up with advocates when going to policymakers to seek funding because the survivors, by bringing their personal experience, would allow the scientists to tell a more compelling story. In summary, the panel felt consumers and cancer advocacy groups are eager to be part of the research process and can contribute valuable perspectives and practical assistance to epidemiologists.

WORKING GROUPS REPORT BACK
Session Chair: Hoda Anton-Culver, Ph.D.
Professor and Chief, Epidemiology Division
University of California, Irvine

In the last session of the meeting, Dr. Anton-Culver presented a comprehensive summary of information and action items generated by the working groups in response to the following questions:

Discussion Questions:

a) What is the state of the science—what do we know?
b) What are the scientific gaps—what do we not know?
c) What obstacles (scientific, infrastructure, technical) impede progress, and what needs to be done to remove the obstacles? Are there solutions to some of these problems that work?
d) What expertise, disciplines, and linkages do we need to "bring to the table" to enhance progress?
e) What are the partnering opportunities with other DCCPS programs?

(Answers to questions "d" and "e" were not explicitly discussed but are included in the individual working groups' summaries.)

Question a) What is the state of the science—what do we know?

The working groups concluded that while at least some descriptive data are available for all but the rarest subtypes, the amount of data available varies widely by cancer type. Some cancers are well studied with respect to age, gender, and ethnicity, but others are not. For some types, most research data come from international studies, which may or may not be applicable to American populations.

Action items:

- Find ways to translate international data to American populations
- Include international investigators in new studies
- Initiate new research into differences among racial groups with respect to etiology, response to treatment, and expression of different rare cancer subtypes.

Question b) What are the scientific gaps—what do we not know?

Dr. Anton-Culver reported that the biological mechanisms underlying most rare cancers are unknown. There is also a need for molecular markers that could distinguish between subclasses within rare cancer types, especially in complicated types such as head and neck, leukemia, and brain. Lack of knowledge about the latency period between exposure and effect also hampers understanding of etiology.

Action items:

- Identification and study of prediagnostic lesions could lead to understanding of biological mechanisms

- Study of people with predisposing conditions could also provide information about mechanisms and latency period
- Study of susceptibility could lead to identification of molecular markers for classification and early detection
- General research on major physiological processes, such as energy balance, the blood-brain barrier, viral load, immune mechanisms, and assessment of environmental exposures, could shed light on mechanisms common to all cancers.

Question c) What obstacles (scientific, infrastructure, technical) impede progress, and what needs to be done to remove the obstacles? Are there solutions to some of these problems that work?

The working groups identified two major types of obstacles: those affecting data collection and those affecting the ability of researchers to collaborate.

Data collection is plagued by a number of problems. There are standardization issues, such as the lack of histological definitions for some cancers, lack of standard core questionnaires, and lack of standard bioinformatics methods and analyses. Practical issues may also impede data collection, including difficulties in getting appropriate biospecimens (for example, skin biopsies and other specialized samples); a need for ultra-rapid case ascertainment in cancers with rapid mortality; Health Insurance Portability and Accountability Act (HIPAA) and Institutional Review Board (IRB) issues; and the high costs of data collection. Data analysis is impeded by the small sample sizes available for most rare cancers. This is particularly a problem for junior investigators because of their limited funding.

Problems preventing effective collaboration included limited contact between scientists in different disciplines and a lack of appropriate funding mechanisms for consortia and interdisciplinary research.

The groups proposed a number of solutions to these problems:

Action items:

- Increased funding for rare cancer research
- Cross-training for new investigators to encourage interdisciplinary research
- Training for international fellows to facilitate study in other countries
- Coordination of resources by a central agency such as NCI
- Increased involvement of advocacy groups and private organizations
- Encouraging universities to be flexible in giving academic credit to investigators involved in multiple principal investigator projects
- Formation of new consortia and expansion of existing consortia by adding new investigators.

DISCUSSION

At this point in the presentation, Dr. Anton-Culver opened the floor to the session chairs and any other participants who wished to discuss these or other potential solutions to the challenges facing investigators of rare cancers.

Four major themes emerged from the discussion:

- Need for improvements to the review process for rare cancer research proposals
- Need for targeted funding for rare cancers research
- Suggestions for promoting consortia formation
- Potential usefulness of greater involvement of the cancer registries in research.

Improvements to the review process: Because rare cancers require the study of large populations to achieve adequate sample size, the price tag for such research is generally expensive. This is particularly true if extra funds are needed for consortium building. Grant reviewers, who often are not epidemiologists but instead are clinicians, generally do not appreciate the reasons for these extra expenses. These

reviewers can be very critical, especially when the cancer involved is very rare and the research might be considered to benefit only a small number of people.

One suggestion was to ask the CSR to form a special study section that could take into account these special challenges. Because it is very difficult to get CSR to form a new standing committee, it was suggested that ad hoc study sections might be formed instead. However, even if this could be done, there might be difficulty in getting enough researchers who could act as outside reviewers because almost all of them would likely be involved in the consortium covering their field. Another suggestion was to hold workshops to educate reviewers from outside epidemiology on the specific challenges of rare cancer research. It was also pointed out that, as multidisciplinary consortia were formed, more basic scientists would be needed on study sections to ensure adequate scientific review.

Epidemiologists attending this meeting were encouraged to take ownership of the problem by acting as advocates for rare cancer research while serving on study sections and when interacting with colleagues in other settings.

Another suggestion was that reviewers be asked to use the NIH CRISP database (crisp.cit.nih.gov) to ensure that the proposals that they are reviewing are really novel. This would cut down on duplication of existing research and perhaps free up funding for more rare cancer research proposals.

Funding targeted specifically to rare cancers
Several workshop participants suggested that difficulties in competing against other grants could be at least somewhat alleviated if more money were targeted specifically to rare cancers—for example, through a RFA. A RFA would also emphasize to reviewers NCI's commitment to rare cancer study. However, other participants felt that reviewers do not really pay attention to whether a grant proposal targets a specific RFA.

Another suggestion was the creation of a funding level slightly above the R03 so that junior investigators could obtain enough funding to get started on rare cancer research.

Formation of consortia
Several participants discussed how to develop an infrastructure that would support emerging consortia. Consortia planning grants could be used to defray the costs of getting people face-to-face in order to start a new consortium. Such funding would need to include an ongoing mechanism, so that groups could have multiple meetings as needed without continually applying for more funds. It was suggested that consortium grants include a required mentoring component to help junior investigators get involved.

Participants noted that consortia should be investigator-driven and should include new investigators as well as those from other disciplines. Consortia could include both extra- and intramural NCI investigators if careful attention were paid to keeping funds separate. Selection of consortium members could use the criteria developed by Dr. Seminara (described earlier in the meeting).

Involvement of cancer registries
Representatives from several cancer registries said that the registries would like to help with rare cancer research. They suggested including the state registries in research plans, in addition to the SEER Program. NCI could set aside some funds to help registries develop their ability to actively participate in research, above and beyond funding for building the actual research resources.

Better communication between NCI and outside organizations could also help support the registries. The Centers for Disease Control and Prevention (CDC) and the American Cancer Society (ACS) provide some support for registries. This support could be coordinated with that of NCI through NAACCR as an umbrella organization.

Other suggestions were to use the Comprehensive Cancer Centers for ultra-rapid case registry and to form specific national registries for some rare cancers, if needed.

MEETING EVALUATION, WRAP-UP, AND THE BOTTOM LINE...
Edward Trapido, Sc.D.
Associate Director, EGRP, DCCPS, NCI

Dr. Trapido wrapped up the session by stating that NCI would use the working groups' comments and suggestions to help prioritize funding mechanisms and write new initiatives, and when discussing review issues with the CSR. He addressed researchers' frequently expressed concerns about funding mechanisms for consortia by stating that NIH is already working on a mechanism for funding multiple principal investigator grants. He said that NCI will also ask the American College of Epidemiology and other professional organizations to help set standards that will guide academic departments in evaluating the work of junior investigators on multiple principal investigator, multidisciplinary projects.

# # #

Appendices:

A – Cancer Site Working Group Report: Brain and Eye Cancer
B – Cancer Site Working Group Report: Endometrial Cancer
C – Cancer Site Working Group Report: Esophageal, Liver, Stomach, and Renal Cancer
D – Cancer Site Working Group Report: Head and Neck Cancer
E – Cancer Site Working Group Report: Hodgkin's Disease and Leukemia
F – Cancer Site Working Group Report: Non-Hodgkin's Lymphoma, Myeloma, and Kaposi's Sarcoma
G – Cancer Site Working Group Report: Ovarian and Testicular Cancer
H – Working Group Participants List

Appendix A:

Cancer Site Working Group Report: Brain and Eye Cancer

Chair: Melissa L. Bondy, Ph.D.; **Co-Chair:** Daniela Seminara, Ph.D.

Discussion Questions:
a) What is the state of the science—what do we know?

Much descriptive epidemiology is available for brain and eye cancer, including information on sex, age, and race differences. Several important scientific advances have been made in brain cancer research since 2000, including evidence for a connection with immunologic factors, studies of angiogenesis, identification of molecular markers, and the role of 1p/19q deletions in oligodendromas. However, there is still a great deal of uncertainty about the factors causing brain tumors. Progress has not been as fast as hoped, partially because most studies thus far have included only small sample sizes.

b) What are the scientific gaps—what do we not know?

The working group came up with a long list of knowledge gaps, including:

- Problems with molecular and histological classification and unknown effects of misclassification
- Unknown role of the blood-brain barrier
- Lack of information about latency periods
- Lack of information about indicators such as epilepsy
- Lack of animal models with which to study exposures
- Need for better measures of and biomarkers for exposures
- Lack of imaging and biomarkers for early and differential diagnoses
- No genes identified yet for familial predispositions
- Lack of understanding of brain tumor progression and pathways at the molecular level.

c) What obstacles (scientific, infrastructure, technical) impede progress, and what needs to be done to remove the obstacles? Are there solutions to some of these problems that work?

The working group identified six major areas that impede brain cancer research:

1) **Biospecimens**—lack of normal tissue and cerebrospinal fluid (CSF) banks and access to brain tumor samples. These problems might be solved by creating CSF repositories, brain tumor tissue banks, autopsy brain banks, or by using discarded Guthrie cards.

2) **Data quality**—lack of early exposure data, which could be solved by familial studies and registries.

3) **Ascertainment**—rapid mortality in some tumor types leads to bias in data collection. This could be avoided with ultra-rapid ascertainment and reporting and by utilizing the cancer registries.

4) **HIPAA and confidentiality**—impedes sharing of biospecimens and data. Master biospecimen sharing agreements among multiple institutions could solve this problem.

5) **Collaboration**—competition for funding and publications impede collaborative studies in the United States, while differences in ownership, privacy, and healthcare structures impede international collaborations. These problems could be eased by increasing funding for consortia and enhancing the international brain tumors epidemiology consortium.

6) **Communication**—lack of communication could be eased by Web portals and a semi-private database for use by physicians and scientists.

d) What expertise, disciplines, and linkages do we need to "bring to the table" to enhance progress?

The working group listed:

- Neurodevelopmental scientists
- Cancer, neuro-, and nutritional epidemiologists
- Immunologists
- Infectious disease experts
- Industrial hygiene experts
- Radiation and environmental scientists
- Neurologists and neurological surgeons
- Physicians, including hematologists
- Communications and IT staff
- Cancer advocates
- Geriatrics experts
- Genomicists
- Molecular and cancer biologists
- Biostatisticians and bioinformaticians.

e) What are the partnering opportunities with other DCCPS programs?

The working group mentioned a SEER project in which samples and data from discard repositories are made available to the general scientific community. Members also suggested collaborations among the different Institutes. Researchers could also take advantage of NCI cooperative groups such as the HMO Cancer Research Network (CRN) and the Mouse Model Consortium. (The Mouse Model Consortium is funded by NCI, but it is not a DCCPS program.)

The group highlighted technology integration as a priority for action because microarrays, proteomics, and methylation studies have been used successfully in other cancers.

Appendix B:

Cancer Site Working Group Report: Endometrial Cancer

Chair: Pamela L. Horn-Ross, Ph.D.; **Co-Chair:** Virginia W. Hartmuller, Ph.D., R.D.

Discussion Questions:
a) What is the state of the science—what do we know?

Endometrial cancer rates are highest in Caucasian women (26 per 100,000) and lower in other groups (17 per 100,000), and recent observations suggest increasing rates in African-American women. The 5-year relative survival is substantially higher in Caucasian women (87%) compared with African-American women (61%). Primary risk factors include obesity and hormone therapy (HT), particularly estrogen-only therapy. The "unopposed estrogen hypothesis" explains a portion of the relationship between obesity and endometrial cancer.

b) What are the scientific gaps—what do we not know?

The working group came up with a long list of knowledge gaps, including:

- Role of obesity, body fat distribution, metabolic syndrome, and hormone and insulin levels
- Role of inflammatory, immune, and DNA repair mechanisms
- Effects of plant foods
- Effects of NSAIDS and other pharmaceuticals
- Clarified role of continuous combined HRT
- Genetic factors and the role of gene-environment interactions
- Differences in risk factors and mechanisms by histologic type
- Racial/ethnic differences in risk factors
- Biomarkers for endometrial cancer development that might serve as prevention and intervention targets
- Factors influencing survival following endometrial cancer diagnosis
- Factors influencing endometrial cancer metastasis
- Challenges with pathology and classification.

c) What obstacles (scientific, infrastructure, technical) impede progress, and what needs to be done to remove the obstacles? Are there solutions to some of these problems that work?

The working group identified scientific, infrastructure, and technical obstacles:

- Scientific obstacles included a lack of better histological classifications; small sample sizes in individual studies; need to address multiple factors, pathways, and mechanisms simultaneously; need for biomarkers; and the need for bioinformatics to synthesize large amounts of data. The problems could be addressed through transdisciplinary, multicenter, and/or consortial studies. Partnership with the established Breast Cancer Family Registry (B-CFR) can provide guidance in setting up a consortium for endometrial cancer. Partnering with NAACCR and pathologists can be instrumental in improving the uniformity of histologic classification.

- The major infrastructure problems were the need for initial funding to establish consortia, as well as identification of leaders and inclusion of junior investigators. It was suggested that DCCPS could help provide this support with new funding mechanisms (e.g., consortia planning grants), and provide logistical support for emerging consortia, including maintenance of a database and tissue archive. Identification of community-based advocates

and foundations interested in endometrial cancer could potentially provide funding opportunities.

- The technical obstacles also included budgetary concerns such as the lack of appropriate consortium funding mechanisms, lack of funding for major instruments, and standard NCI budget cuts on all grants. Data issues included problems with HIPAA, with maintaining uniformity, and lack of genotyping platforms.

d) What expertise, disciplines, and linkages do we need to "bring to the table" to enhance progress?

The list included:

- Epidemiology, genetics, molecular biology, biochemistry, pathology, surgical oncology, gynecology, biostatistics, bioinformatics, nutritionists, analytic chemists, biologists, behavioral scientists, endocrinologists, marketing, food companies
- High through-put genetic technology
- Laboratory resources for the collection, processing, and storage of biospecimens
- Cancer registries.

e) What are the partnering opportunities with other DCCPS programs?

The working group suggested that NCI's Cancer Information Service (CIS) could help with minority recruitment. Corporate partnerships might be sought to help fund consortium meetings. The DCCPS-funded HMO Cancer Research Network (CRN), DCCPS Applied Research Program (ARP), and other databases could also be pressed into service for endometrial cancer research.

This group also suggested the following major priorities for action:

- Establish endometrial cancer consortia and identify leadership
- Establish ground rules (leadership and membership roles, authorship, publications)
- Identify collaborators in the United States and Europe
- Establish a mission statement around priorities (in-person meetings would be vital in successfully and efficiently accomplishing this)
- Partner with breast/prostate consortia to learn from their successes/failures
- Determine scope, including single vs. dual consortia with case-control and cohort studies, and include survivorship issues
- Identify outside funding opportunities
- Include junior investigators.

Appendix C:

Cancer Site Working Group Report: Esophageal, Liver, Stomach, and Renal Cancer

Chairs: Marilie D. Gammon, Ph.D., and Alexander S. Parker, Ph.D.; **Co-Chair:** Mukesh Verma, Ph.D.

Discussion Questions:
a) What is the state of the science—what do we know?

The incidences of renal and liver cancers are increasing, while the incidence of gastric cancer is declining in the United States. However, gastric cancer remains high elsewhere in the world. Obesity is a risk factor in all of these cancers. Other risk factors include smoking and hypertension for renal cancer; hepatitis viruses B and C and alcohol for liver cancer; tobacco, alcohol, and low fruit and vegetable intake for esophageal cancer; and *H. pylori* infection, nitrosamines, and smoking for gastric cancers.

b) What are the scientific gaps—what do we not know?

The working group defined the following knowledge gaps:

- Mechanisms linking these cancers with known risk factors, including viruses
- Other risk factors including genetic susceptibility
- Reasons for racial, socioeconomic, and gender differences
- Need for better detection and improved treatments
- Prognostic concerns

c) What obstacles (scientific, infrastructure, technical) impede progress, and what needs to be done to remove the obstacles? Are there solutions to some of these problems that work?

The working group identified data collection as a special challenge in these rare cancers, resulting in high costs and an underappreciation of the difficulties by others in the scientific community. There are also problems translating study results from international populations to the United States and attracting good new investigators. The solutions suggested were to establish a rare tumor study section as well as specific RFAs. Members also suggested special considerations for new investigators in the review process.

d) What expertise, disciplines, and linkages do we need to "bring to the table" to enhance progress?

The working group suggested epidemiologists, geneticists, molecular biologists, biochemists, pathologists, clinicians, bioinformaticians, statisticians, behavioral biologists, health disparities researchers, and exposure assessment experts. Members also emphasized a need for cross-training at the junior level.

e) What are the partnering opportunities with other DCCPS programs?

Potential partners include the Epidemiology and Genetics Research Program (EGRP), SEER Program and Cancer Statistics Branch of the Surveillance Research Program (SRP), Applied Research Program (ARP); and Office of Cancer Survivorship (OCS), and collaborations with intramural NCI scientists.

This working group identified three main priorities for further action: find NCI scientists to act as partners, get the main players together face-to-face at a meeting to begin forming a consortium, and send a message to NCI indicating the need for special consideration for rare tumor proposals at review time.

Appendix D:

Cancer Site Working Group Report: Head and Neck Cancer

Chair: Qingyi Wei, M.D., Ph.D.; **Co-Chair:** Deborah M. Winn, Ph.D.

Discussion Questions:
a) What is the state of the science—what do we know?

The existing head and neck consortium has brought together more than 10,000 cases and 10,000 controls for pooled analysis. This analysis is considering risk factors such as occupation and the etiology of head and neck cancer among non-tobacco users and alcohol abstainers. The consortium will also look at mechanistic factors such as the influence of DNA repair genes, virus infections (such as human papillomavirus (HPV)), and associations with single nucleotide polymorphisms (SNPs). HPV infection has been linked to certain head and neck cancers, such as tonsillar cancer.

b) What are the scientific gaps—what do we not know?

The working group defined the following knowledge gaps:

- Lack of clear definitions and classifications
- Small sample sizes
- Need for biomarkers for prognosis and diagnosis
- Follow up and treatment issues—do we overtreat?
- Identification of SNPs and other genetic markers
- Reasons for variation by geographic regions
- Contribution of lifestyle factors
- Environmental factors
- Role of HPV in etiology and prognosis
- Lack of understanding of gene/environment interactions.

c) What obstacles (scientific, infrastructure, technical) impede progress, and what needs to be done to remove the obstacles? Are there solutions to some of these problems that work?

Like many of the working groups, this one identified both scientific and technical/infrastructure obstacles:

- Scientifically, the heterogeneity of these tumors prevents the detection of associations for head and neck cancer anatomic subsites, a problem that could be solved with better classification methods. A common protocol is also needed, with common controls and sampling methods. The treatment issues mentioned above could be approached by starting with small-scale, simplified studies and moving to standardized consortial studies.

- Definitions and classification were seen as a technical problem as well because different registries are using different standards. Standard databases, classifications, and protocols would help ease this problem. The group also suggested that better coordination of studies would improve access to specimens, while the formation of consortia would increase sample sizes. These efforts would be improved by building centralized Web portals that contained study protocols and questionnaires. Ready availability of standardized tools might also allow consortia to respond more quickly to changes in the cancer field.

d) What expertise, disciplines, and linkages do we need to “bring to the table” to enhance progress?

DCCPS partnerships were not specifically addressed by this group.

e) What are the partnering opportunities with other DCCPS programs?

The working group singled out the Office of Cancer Survivorship (OCS) and SEER Program. It also suggested caBIG, SPORE-type programs, and collaborations with intramural NCI scientists.

This working group identified a number of priorities for further action:

- Develop working groups to focus on standardized definitions, protocols, and follow up
- Facilitate interactions among existing consortia
- Develop new collaborative projects and support their infrastructures
- Initiate studies in diverse and international populations
- Investigate understudied lifestyle and genetic risk factors
- Gather information on HPV status of tumors and
- Better understand genetic susceptibility.

Appendix E:

Cancer Site Working Group Report: Hodgkin's Disease and Leukemia

Moderators: Sara S. Strom, Ph.D.; **Co-Chair:** Isis S. Mikhail, M.D., M.P.H., Dr.P.H.

Discussion Questions:
a) What is the state of the science—what do we know?

For Hodgkin's disease, risk factors include Epstein-Barr Virus (EBV) and socioeconomic status (SES). This disease also shows a bimodal age distribution, and gender and race differences.

Leukemias are a heterogeneous group for which there is scarce data. A few risk factors are known for certain types, for example, smoking, and chemical and occupational exposures. Leukemias also show gender differences.

b) What are the scientific gaps—what do we not know?

Hodgkin's disease:

- Many hypotheses to be studied
- Need to better understand biology of EBV
- Heterogeneity of exposures could be addressed by studies in countries with differing SES
- Insufficient data on women due to very low incidence.

Leukemias:

- Insufficient research in this area—"It is all gaps."

c) What obstacles (scientific, infrastructure, technical) impede progress, and what needs to be done to remove the obstacles? Are there solutions to some of these problems that work?

These diseases share many of the same obstacles, according to the working group. Research on both suffers from a scarcity of patients, which could be remedied by inter-institutional and international collaborations. These collaborations should include clinical, epidemiological, and basic researchers. Such collaborations could be facilitated by funding mechanisms that promote multiple grant collaborations and that recognize multiple principal investigators on single grants.

Funding is also an issue for both diseases. This could be eased by increasing Federal funding, and enlisting the help of patient advocacy groups and foundations.

There is a lack of standardized methodologies—for example, control selection and data collection instruments. Collaborations would also be aided by the development of common methodologies. Certain leukemias also present an ascertainment obstacle due to their rapid mortality rates. This problem could be solved by rapid patient identification and enrollment at the time of diagnosis.

d) What expertise, disciplines, and linkages do we need to "bring to the table" to enhance progress?

For Hodgkin's disease, a multidisciplinary team should include virologists, molecular biologists, B-cell biologists, geneticists, immunologists, hematologists, and epidemiologists. For leukemias, the team should include hematologists, epidemiologists, molecular biologists, geneticists, and immunologists.

e) What are the partnering opportunities with other DCCPS programs?

The programs most relevant to these diseases include the Epidemiology and Genetics Research Program (EGRP) and its Analytic Epidemiology Research Branch (AERB), Applied Research Program (ARP), and the Surveillance Research Program (SRP).

This working group identified a number of priorities for further action:

For Hodgkin's disease:

- Establish an independent Hodgkin's group separate from the InterLymph consortium but linked to it
- Build on the existing InterLymph by taking advantage of existing committees
- Identify researchers to be members of the group
- Approach InterLymph leadership to propose a Hodgkin's disease group and work out logistics
- Create a RFA for rare cancers (urgent).

For leukemias:

- Identify and invite interdisciplinary researchers to be part of a brainstorming group
- Build connections with cancer survivorship groups and consumer advocates
- Approach private foundations to initiate communications and provide support
- Create a RFA for rare cancers (urgent).

Appendix F:

Cancer Site Working Group Report: Non-Hodgkin's Lymphoma, Myeloma, and Kaposi's Sarcoma

Moderators: James R. Cerhan, M.D., Ph.D., and Vaurice Starks, B.S.

Discussion Questions:
a) What is the state of the science—what do we know?

This working group defined a number of areas of knowledge:

1) Pathobiology—In non-Hodgkin's lymphoma (NHL), malignancy originates mainly in B cells, sometimes in T cells, and rarely in other primary immune cells. Malignancy arises from molecular mistakes resulting from normal physiological responses. In multiple myeloma (MM), MGUS is a known precursor lesion, and cytokines and growth factors appear to be very important. Kaposi sarcoma (KS) is characterized by the presence of HHV-8/KSHV virus in all cases. KSHV has a latency period and codes for several gene products that play a role in cellular transformation.

2) Classification—WHO classification system (developed to incorporate the revolution in our understanding of immunology) appears to be robust and reproducible. There is some evidence for specific risk factors in specific NHL subtypes. MM has a standard clinical definition. KS is well-classified and often clonal.

3) Descriptive epidemiology—NHL rates are higher in men than women (a notable exception is follicular NHL) and in Caucasians relative to other racial/ethnic groups. Incidence and mortality rates have increased dramatically since the 1950s. NHL subtypes have different descriptive epidemiologies. For MM, incidence rates are higher in men and in African Americans and Hispanics. Classic KS shows male predominance while HIV-associated KS does not.

4) Genetic risk factors—NHL shows modest familial influence; the others have limited data in this area.

5) Environmental risk factors—For NHL, risk factors are EBV, immunosuppression, local inflammation/chronic antigenic stimulation, and HIV. MM is associated with high-dose ionizing radiation. KS is associated with HHV-8/KSHV and immunosuppression.

b) What are the scientific gaps—what do we not know?

Non-Hodgkin's lymphoma

- Need to define factors that contribute to the molecular errors that characterize different NHL subtypes
- Many WHO-defined NHL subtypes remain heterogenous at the molecular level
- Uncertain how histologic subtypes relate to etiology and the best groupings of subtypes for etiologic studies
- Cause of the slowing in the rate of increase in the incidence of NHL not fully understood
- Changing classifications make historical trend and risk factor data difficult to interpret
- Role of EBV and other viruses in NHL etiology; other mechanisms by which EBV (and other viruses) might influence lymphomagenesis; differences in risk factors for EBV-positive versus EBV-negative lymphomas
- Role of immune function in NHL in immunocompetent persons
- Role of immune function in HIV+ patients who do not develop NHL

- Is there a precursor state that leads to NHL (analogous to the MGUS to MM paradigm).

Multiple myeloma

- Molecular events that cause the transition from MGUS to MM
- Contributions of SES, diet, lifestyle, and genetics to risk
- Why is MGUS more prevalent in non-Caucasian populations?

Kaposi's sarcoma

- Molecular events leading from KSHV infection to KS
- How does KSHV remain latent and what activates it?
- Need to identify the many gene products involved in KSHV pathogenesis and understand how KSHV infection can lead to cellular transformation
- What is the immune response to KSHV?

c) What obstacles (scientific, infrastructure, technical) impede progress, and what needs to be done to remove the obstacles? Are there solutions to some of these problems that work?

The working group identified a number of scientific obstacles and solutions for each cancer. For NHL and MM, the basic immunology and virology needs to be translated into valid, reliable, robust, and cost-effective measurements for use in epidemiological studies. Exposure assessments for both cancers need to be better developed and standardized. The molecular classification of NHL is incomplete. MM suffers from a lack of funding. KS needs more studies in populations with a high prevalence of KS, which are mostly in developing countries.

Technical and infrastructure needs were many and varied. For NHL, multicenter studies are needed to obtain sufficient sample sizes, particularly to address rarer subtypes. There is a need for prediagnostic specimens. Central pathology review and classification is difficult and expensive, and needs to be standardized. Money is needed to develop infrastructure such as control registries so that population-based controls can be obtained more easily. Access to minority populations is needed.

For MM, the use of prediagnostic specimens and cohort studies requires a very large study size or very long follow up to accrue sufficient cases. Case-control studies are made difficult by high case fatality. There is a need for centralized communication and resources, perhaps by Web portals. MM researchers need better access to minority and non-Western populations. The group suggested that the SPOREs could increase their emphasis on epidemiological projects to alleviate some of these problems.

For KS, there is a lack of research infrastructure in the developing countries where it is most prevalent. This could be alleviated by establishing functional research sites in those countries. These centers could also attract and train needed international collaborators. Another suggestion was to use AIDS cohort studies as a resource for KS research.

For all cancers, there are multiple obstacles to consortium participation (academic recognition; authorship; meaning of independence; indirect costs; review at study section). Funding mechanisms are also problematic (R03 too small; R01 size not flexible enough). Few (or almost no) studies result in slow follow up of promising leads (literature evolves slowly).

d) What expertise, disciplines, and linkages do we need to "bring to the table" to enhance progress?

For all cancers, immunology (better measures of immune function), virology/microbiology (pathogen identification; new models of how pathogens lead to cancer), pathology (classification), molecular biology (relevant pathways), genetics (host, viral, and tumor), epidemiology, bioinformatics, and biostatistics (analysis of complex pathways and interactions).

e) What are the partnering opportunities with other DCCPS programs?

The following suggestions were made:

- Support of consortia (meetings, Web sites, communications, etc.)—for example, InterLymph model
- Intramural and extramural
- Survivorship research (add on to cohort and case-control etiology studies)
- Diagnostics
- SPOREs
- CaBIG

The working group identified a large number of action items and priorities for each disease:

Non-Hodgkin's lymphoma

- Maintain InterLymph by adding resources, easing review concerns, holding targeted workshops, and increasing researchers' incentives to participate
- Maintain funding of individual R01s as incubators of new discoveries that can be validated in consortia
- Obtain long-term support for biospecimen repositories and databanks
- Produce standardized definitions for distinct lymphoid malignancies
- Maintain support for SEER and epidemiology/population based projects in SPOREs
- Increase R03 funding to $75,000 per year and increase use of R21 mechanism
- Incorporate new biology into population studies to address interactions of infectious agents and immune function.

Multiple myeloma

- Develop an MM consortium, possibly as a working group linked to InterLymph
- Strengthen existing multidisciplinary collaborative groups
- Use pancreatic cancer model to jump-start myeloma funding
- Investigate understudied lifestyle and genetic risk factors.

Kaposi's sarcoma

- Develop a KS consortium
- Establish international research sites, fund and train collaborators
- Increase collaboration with AIDS malignancies consortium
- Establish cancer registries in developing countries
- Develop working groups focusing on different areas such as epidemiology, animal models, and treatment.

General (all three types)

- Have NCI coordinate/facilitate access to prediagnostic specimens from cohort studies
- Support infrastructure for consortium (leadership, communication, working groups, Web sites; meetings, etc.) and provide incentives for participation
- Improve consortia review by including transdisciplinary researchers on study sections
- Support studies in diverse and international populations
- Facilitate career development of junior scientists
- Support long-term storage of valuable samples
- Encourage research on the epidemiology of survivorship
- Support whole genome studies and other new technologies as appropriate
- Encourage novel study designs
- Increase awareness of epidemiological research.

Appendix G:

Cancer Site Working Group Report: Ovarian and Testicular Cancer Working Group

Moderators: Roberta Ness, M.D., M.P.H., and J. Fernando Arena, M.D., Ph.D.

Discussion Questions:
a) What is the state of the science—what do we know?

The working group concentrated primarily on ovarian cancer, which shows significant heterogeneity of tumors. There are three well-recognized protective effects: child bearing, breastfeeding, and oral contraceptive use. The incidence is approximately 15 per 100,000 and 1.5 percent of women will develop ovarian cancer sometime in their lifetime. There is virtually no cancer under the age 40, and it is less common in African Americans. The presence of BRCA1 and 2 increases the risk of ovarian cancers, and BRCA carriers generally have a lower age of incidence.

b) What are the scientific gaps—what do we not know?

- More studies needed on pregnancy outcomes and possible effects on ovarian cancer, for example, the role of preeclampsia
- Lack of international studies comparing rates in other countries
- Need to start testing current hypotheses by looking at biomarkers using cohorts
- Need to consider testing some biomarkers as markers of diagnosis
- Better understanding of the biology of ovulation
- Better integration of animal models and epidemiologic observations
- Risk stratification (are there strata of women that would benefit from known preventive strategies?)
- Latency periods (are pre- and post-menopausal cancers the same or different?)
- Correlation between inflammatory markers and ovarian cancer
- Need to understand the cellular mechanisms of ovarian cancer
- Need for studies to understand the North-South gradient for ovarian cancer
- Disease outcome, response to treatment, and survivorship by race.

c) What obstacles (scientific, infrastructure, technical) impede progress, and what needs to be done to remove the obstacles? Are there solutions to some of these problems that work?

This working group concentrated primarily on the solutions, suggesting that an ovarian cancer consortium be formed. The consortium could perform case-control studies to identify genetic polymorphisms, and cohort studies to identify biomarkers and other prognostic factors, and could pool data and resources. The group suggested using the template of the brain consortium and taking advantage of international studies and active survivor groups. Inclusion of multidisciplinary investigators would promote understanding of the biology of infertility and ovarian cancer.

The group had several other proposed solutions to improve study of ovarian cancer. Members suggested leveraging ongoing clinical trials to gather epidemiological data and using cohorts from other diseases, such as cardiovascular disease. Case-control studies could be used for pooling to examine gene-gene and gene-environment interactions; whereas cohort pooling would be best used for the study of biomarkers. Common data elements and common histologic definitions would also be useful. This group also suggested special study sections for rare cancers.

d) What expertise, disciplines, and linkages do we need to “bring to the table” to enhance progress?

The working group suggested multidisciplinary teams including pathologists, cellular and molecular biologists, epidemiologists, geneticists, immunologists, gynecologists, and oncologists.

e) What are the partnering opportunities with other DCCPS programs?

DCCPS partnerships were not specifically addressed by this group.

The working group identified priorities for both ovarian and testicular cancer:

Ovarian cancer

- Produce a standardized core questionnaire
- Investigate molecular profiling of tumors to complement histology
- Identify genetic polymorphisms in key pathways, such as hormonal and inflammatory
- Study the biology of ovulation
- Pool cohort studies and look for biomarkers that are related to current hypotheses
- Establish trans-division and trans-institute collaborations for use of various cohorts
- Access the NCI-funded Gynecology Oncology Group for clinical trials and other resources
- Obtain funding for consortium building.

Testicular cancer

- Hold meeting next spring in Bethesda and identify relevant investigators
- Find ways to get larger sample sizes
- Establish type of study design to be used
- Partner with other studies, such as prostate cancer, to get African cases
- Increase standardization of studies
- Collect information about existing studies
- Examine the role of hormones and quality-of-life issues in survivors (what are the later-life effects of different treatments?).

Appendix H:

Working Groups Participants

Brain and Eye Cancer
Working Group

Melissa Bondy, University of Texas M.D. Anderson Cancer Center– **Chair**
Daniela Seminara, National Cancer Institute – **Co-Chair**
Emily Dowling, National Cancer Institute – **Recorder**
Julie Buring, Harvard Medical School
Dominique Michaud, Harvard School of Public Health
John Neuberger, University of Kansas School of Medicine
Judith Schwartzbaum, Ohio State University
Maria Schymura, New York State Cancer Registry
Margaret Wrensch, University of California, San Francisco
David Lee, Sylvester Comprehensive Cancer Center/University of Miami
Manuela Orjuela, Columbia University
James Fisher, Ohio State University
Dora Il'yasova, Duke University Medical Center
Colleen McLaughlin, New York State Department of Health
Peter Inskip, National Cancer Institute
Ania Pollack, University of Kansas School of Medicine
Michael Scheurer, University of Texas M.D. Anderson Cancer Center
Ben Hankey, National Cancer Institute

Endometrial Cancer
Working Group

Pamela Horn-Ross, Northern California Cancer Center – **Chair**
Virginia Hartmuller, National Cancer Institute – **Co-Chair**
Nancy Emenaker, National Cancer Institute – **Recorder**
Chu Chen, Fred Hutchinson Cancer Research Center
Immaculata Devivo, Brigham and Women's Hospital/Harvard Medical School
Anne Zeleniuch-Jacquotte, New York University School of Medicine
Jiali Han, Brigham and Women's Hospital/Harvard Medical School
Holly Howe, North American Association of Central Cancer Registries
Susan Reed, Fred Hutchinson Cancer Research Center/University of Washington
Herbert Yu, Yale University School of Medicine
Dana Christo, Johns Hopkins Bloomberg School of Public Health
Jennifer Doherty, Fred Hutchinson Cancer Research Center
Monica McGrath, Brigham and Women's Hospital/Harvard Medical School

Head and Neck Cancer
Working Group

Qingyi Wei, University of Texas M.D. Anderson Cancer Center – **Chair**
Deborah Winn, National Cancer Institute – **Co-Chair**
Shannon Lynch, National Cancer Institute – **Recorder**
Gerry Funk, University of Iowa Hospitals and Clinics
Anna Giuliano, H. Lee Moffitt Cancer Center & Research Institute
Karl Kelsey, Harvard School of Public Health

Miriam Rosin, British Columbia Agency Cancer Research Centre
Elaine Smith, University of Iowa College of Public Health
Margaret Spitz, University of Texas M.D. Anderson Cancer Center
Yin Yao, Johns Hopkins University
John Lee, University of Iowa Hospitals and Clinics
Guojun Li, University of Texas M.D. Anderson Cancer Center
Sheila Zahm, National Cancer Institute
Heather Nelson, Harvard School of Public Health

Hodgkin's Disease and Leukemia Working Group

Sara Strom, University of Texas M.D. Anderson Cancer Center – **Chair**
Isis Mikhail, National Cancer Institute – **Co-Chair**
Megan Stephan (contractor) – **Recorder**
Jonine Bernstein, Memorial Sloan-Kettering Cancer Center
Hoda Anton-Culver, University of California, Irvine
Elizabeth Corder, Duke University
Randa El-Zein, University of Texas M.D. Anderson Cancer Center
William Field, University of Iowa
Sally Glaser, Northern California Cancer Center
Thomas Mack, Norris Comprehensive Cancer Center, University of Southern California
Theresa Keegan, Northern California Cancer Center
Xiaomei Ma, Yale School of Medicine
Nancy Mueller, Harvard School of Public Health

Liver, Renal, Esophageal, and Stomach Cancer Working Group

Marilie Gammon, University of North Carolina, Chapel Hill – **Chair**
Alexander Parker, Mayo Clinic College of Medicine – **Chair**
Mukesh Verma, National Cancer Institute – **Co-Chair**
Sheri Schully, National Cancer Institute – **Recorder**
Joe Patel, National Cancer Institute
Cheryl Marks, National Cancer Institute
Jay Choudhry, National Cancer Institute
Alison Evans, Fox Chase Cancer Center
Sherri Stuver, Boston University School of Public Health
Manuela Gago-Dominguez, Norris Comprehensive Cancer Center/University of Southern California
Marsha Frazier, University of Texas M.D. Anderson Cancer Center
Jinyun Chen, University of Texas M.D. Anderson Cancer Center
Radoslav Goldman, Georgetown University
Karen Pawlish, New Jersey Department of Health and Senior Services
Kathryn McGlynn, National Cancer Institute
Leslie Bernstein, Norris Comprehensive Cancer Center/University of Southern California
Catherine Hoyo, Duke University Medical Center
Jie Lin, University of Texas M.D. Anderson Cancer Center
Christian Abnet, National Cancer Institute

Non-Hodgkin's Lymphoma, Myeloma, and Kaposi's Sarcoma Working Group

James R. Cerhan, Mayo Clinic College of Medicine – **Chair**
Vaurice Starks, National Cancer Institute – **Co-Chair**
Carmina Valle, National Cancer Institute – **Recorder**

Wendy Cozen, Keck School of Medicine, University of Southern California
Elizabeth Holly, University of Southern California, San Francisco
Francine Laden, Harvard School of Public Health
Otoniel Martinez-Maza, David Geffen School of Medicine, University of California
Kenneth Anderson, Dana-Farber Cancer Institute
Graham Colditz, Brigham and Women's Hospital/Harvard Medical School
Charles Wood, Nebraska Center for Virology
Brenda Birmann, Harvard School of Public Health
Paige Bracci, University of California, San Francisco
Christine Skibola, University of California, Berkeley
Shumin Zhang, Brigham and Women's Hospital/Harvard Medical School/Harvard School of Public Health
Mulugeta Gebregziabher, University of Southern California
Dalsu Baris, National Cancer Institute
Jill MacKinnon, Sylvester Comprehensive Cancer Center/University of Miami

Ovarian and Testicular Cancer Working Group

Roberta Ness, University of Pittsburgh – **Chair**
Fernando Arena, National Cancer Institute – **Co-Chair**
Scott Rogers, National Cancer Institute – **Recorder**
Julia Rowland, National Cancer Institute
Daniel Cramer, Brigham and Women's Hospital
Joanne Dorgan, Fox Chase Cancer Center
Susan Hankinson, Brigham and Women's Hospital/Harvard School
Betsy Kohler, New Jersey Department of Health and Senior Services
Leigh Pearce, Norris Comprehensive Cancer Center/University of Southern California
Harvey Risch, Yale University School of Medicine
Joellen Schildkraut, Duke University Medical Center
Victoria Cortessis, University of California, Los Angeles
Stephen Schwartz, Fred Hutchinson Cancer Research Center
Julia Greer, University of Pittsburgh
Kathryn Terry, Brigham and Women's Hospital
Russ Hauser, Harvard School of Public Health
Lynn Rosenberg, Boston University Medical Campus
Yawei Zhang, Yale University
Michael Thun, American Cancer Society
Anita Ambs, National Cancer Institute
Katherine McGlynn, National Cancer Institute