Board of Scientific Advisors (BSA)
BSA *Ad hoc* Subcommittee Meeting on Human Immunodeficiency Virus (HIV) and Acquired Immune Deficiency Syndrome (AIDS) Malignancy

Natcher Conference Center, Room D
National Institutes of Health
Bethesda, MD 20814
February 14, 2013
9:00 a.m. – 4:00 p.m. EST

SUMMARY

Participants

Subcommittee Members
Dr. Lawrence Corey, Chair (Fred Hutchinson Cancer Research Center)
Dr. Richard Ambinder (Johns Hopkins University)
Dr. Curt Civin (University of Maryland School of Medicine)
Dr. Kevin Cullen (University of Maryland School of Medicine)
Dr. Stanton Gerson (Case Western Reserve University, University Hospitals Case Medical Center)
Dr. Chanita Hughes-Halbert (Medical University of South Carolina)
Dr. Amy Justice (Yale University School of Medicine)
Dr. Elliot Kieff (Harvard Medical School, Brigham and Women's Hospital)
Dr. Ronald Mitsuyasu (University of California, Los Angeles)
Dr. Joel Palefsky (University of California, San Francisco)
Dr. Groesbeck Parham (University of North Carolina)
Dr. David Scadden (Harvard University, Massachusetts General Hospital)
Dr. Ren Sun (University of California, Los Angeles)

Other Participants
Dr. Geraldina Dominguez (NCI, Office of HIV and AIDS Malignancy)
Dr. Eric Engels (NCI, Division of Cancer Epidemiology and Genetics)
Dr. Paulette S. Gray (NCI, BSA Executive Secretary)
Ms. Claire Harris (NCI, Committee Management Officer)
Dr. Rebecca Huppi (NCI, Office of HIV and AIDS Malignancy)
Ms. Denise Jenkins (NCI, Office of HIV and AIDS Malignancy)
Dr. Mostafa Nokta (NCI, Office of HIV and AIDS Malignancy)
Dr. Lisa Stevens (NCI, Office of Science Planning and Assessment)
Dr. Harold Varmus (NCI Director)
Dr. Jack Whitescarver (NIH, Office of AIDS Research)
Dr. Robert Yarchoan (NCI, Subcommittee Executive Secretary)
Dr. Jennifer McCulley (The Scientific Consulting Group, Inc., Rapporteur)

Action Items

- It was decided that Drs. Lawrence Corey and Robert Yarchoan will develop a series of action items from the minutes and distribute the list to the BSA Subcommittee for review; these are now included at the end of the minutes. Communication between Subcommittee members will occur via email and/or teleconferences prior to the next in-person meeting.

Welcome and Introduction of Attendees—Dr. Robert Yarchoan

Dr. Yarchoan welcomed members of the BSA Subcommittee, NCI staff, and members of the public, and expressed appreciation for the Subcommittee members' time and contribution of expertise to the current discussion. The NCI is seeking guidance on two overarching and related issues: (1) how it should invest funding in research related to AIDS malignancy going forward; and (2) how it should spend the mandated funding on AIDS research. The issues do not entirely overlap because the NCI could use funding aside from that mandated for AIDS research to support specific programs and now uses some AIDS funding for "pure" HIV research not related to HIV-associated malignancies. BSA Subcommittee members and meeting attendees introduced themselves.

HIV and AIDS Malignancy Research in the NCI—Dr. Robert Yarchoan

Dr. Yarchoan provided a history of the NCI's involvement in AIDS research and informed Subcommittee members of the reasons why the NCI remains involved. The initial Centers for Disease Control and Prevention (CDC) reports of the AIDS epidemic had as one of two main points the recognition of clusters of Kaposi's sarcoma among homosexual men in 1981. Dr. Yarchoan explained that the NCI became involved very early with virology, immunology, and drug development. The first patient was admitted in the Metabolism Branch very soon after the initial CDC report was released. Other early NCI contributions included the identification of HIV-1 as the cause of AIDS 1984, the development of the first blood test to test for antibodies to HIV and screen the blood supply, and the development of and initial clinical testing of the first AIDS drugs, leading to the approval of AZT as the first AIDS drug in 1987 and approval soon thereafter of dideoxycytidine (zalcitabine) and dideoxyinosine (didanosine). These when combined with other advances in anti-HIV therapy, are estimated to have saved 14 million years of life worldwide.

The NCI pioneered the study of HIV protease and contributed to the early development of HIV protease inhibitors. These, in combination with reverse transcriptase inhibitors, are used in highly active antiretroviral therapy (HAART). The advent of HAART was accompanied by a significant decrease in deaths and new cases of AIDS. They have also led to a dramatic drop in the incidence of AIDS-defining cancers (ADC) in the United States, although this number has then remained fairly constant since approximately 1998. However, as therapies improve, the number of people living with AIDS has increased and overall this population has gotten older. When combined with an increase in the standardized incidence ratio (SIR) of certain non-AIDS-defining cancers (NADC), this has led to a substantial increase in the incidence of NACD since1998. Overall, while the total number of cancers in HIV-infected patients decreased around 1998, it has increased somewhat since then. Indeed, several recent studies have shown that cancer in the most frequent cause of death in HIV-infected patients where HAART is available.

In addition to numerous scientific achievements, the NCI also has accomplished administrative milestones in AIDS research. In 1987, the AIDS Vaccine Program was established in Frederick, MD. The AIDS Malignancy Clinical Trials Consortium, also called the AIDS Malignancy Consortium (AMC) was formed in 1995 to evaluate clinical interventions for the treatment and prevention of malignancies in people with HIV; investigate the biology of these malignancies; conduct Phase I, II, and II clinical trials; and contribute specimens and clinical data to the AIDS and Cancer Specimen Resource (ACSR). Furthermore, the AMC has begun to conduct international trials, including two such trials being conducted in collaboration with the NIAID-supported AIDS Clinical Trials Group (ACTG) for Kaposi's sarcoma in resource-limited countries. The NCI also initiated the AIDS and Cancer Specimen Resource (ACSR), which provides high-quality HIV-associated malignancy specimens (e.g., frozen tissues, plasma, body fluids, and formalin-fixed tissues) to qualified investigators at little or no cost.

In 1996, the HIV and AIDS Malignancy Branch was formed, and in 1997, the NCI held the First International Conference on Malignancies in AIDS and Other Acquired Immunodeficiencies . This annual conference was initiated because of the need to convene a critical mass of researchers to address the issue of AIDS malignancies. Intramurally, the HIV Drug Resistance Program was established in 1997, and the Center of Excellence in HIV/AIDS and Cancer Virology within the Center for Cancer Research was established in 2007. In 2007, the Office of HIV and AIDS Malignancy (OHAM) was established within the Office of the Director of the NCI to oversee certain HIV-specific research programs, including the AMC and the ACSR, and to coordinate the whole HIV research agenda in the NCI. More recently, OHAM has worked with the Cancer Therapy Evaluation Program (CTEP) to allow entry of HIV-infected patients on many NCI-sponsored clinical trials, conduct pharmacokinetic studies to support this initiative, and initiate a program of bone marrow transplantation for AIDS malignancies.

The Office of AIDS Research (OAR) determines the AIDS budget for the NCI for each fiscal year (FY). The OHAM then collaborates with NCI leadership, Divisions, and other Offices and Centers to manage the portfolio of AIDS malignancy research. Approximately $271 million of the FY 2012 NCI budget was administered as "AIDS dollars." The NCI is congressionally mandated to spend this funding on AIDS-related research, which is defined according to the *Trans-NIH Plan for HIV-Related Research*. With regard to research in HIV malignancies, the plan broadly dictates that "AIDS research", which can be funded with "AIDS dollars", directly involves HIV or AIDS patients or addresses malignancies or complications that substantially impact HIV or AIDS patients. Assuming a consistent budget and barring sequestration or unforeseen organizational changes, the NCI might have as much as $26 million to reprogram during the next 5 years. Importantly, the NCI needs to determine the best way to reinvest these funds.

Ongoing and new NCI projects are coded with a certain percentage of AIDS-related (e.g., hepatitis B virus [HBV] research is often coded as 20% of AIDS-related) to track the use of AIDS funds. The OAR reviews renewing projects for their HIV/AIDS focus and gives the NCI the opportunity to reprogram "low-priority" project funds on new OAR-approved "high-priority" projects (priority is related to the relevance of the project within the current AIDS research agenda). The review of OAR-funded AIDS research is conducted by OAR staff and outside advisors. In general, the OAR has been disallowing basic research that is only indirectly related to HIV, such as T-cell immunity, general lymphoma research, development of anti-cancer drugs that might be used to treat AIDS malignancies, and some research on Epstein-Barr virus (EBV) and human papillomavirus (HPV). They are more lenient in permitting the use of AIDS dollars on therapeutic research related to key malignancies that develop in patients with HIV/AIDS.

Much attention is focused on AIDS malignancy in the developing world. Africa is experiencing a co-epidemic of Kaposi's sarcoma-associated herpesvirus (KSHV) and HIV infection. The lack of research training and infrastructure is a major barrier to AIDS malignancy research in Africa. In the past 3 years, the OHAM has begun to develop an international effort in AIDS malignancies. Many of the efforts are coordinated with the Center for Global Health (CGH).

Open Discussion—Members

In response to a question, Dr. Yarchoan informed the Subcommittee members that the ACSR sites are located at George Washington University, Ohio State, and the University of California, San Francisco (UCSF). These and other affiliated sites across the country acquire specimens for the ACSR through a variety of mechanisms, including autopsies, biopsies, and longitudinal trials.

Dr. Amy Justice asked about the initiative to enter HIV-infected patients on CTEP-sponsored trials whenever possible. She questioned whether the analyses of such trials ensured a detection of different responses when HIV-positive patients are included in clinical trials. Dr. Yarchoan responded that HIV-

infected patients are included as a separate group in CTEP trials to collect safety information. In larger trials when there were enough patients to do so, researchers can perform subgroup analysis to monitor response rates in HIV-infected patients separately. Formerly, there was no physician guidance about the safety of various cancer regimens in HIV-positive individuals, and this initiative will help address this gap in knowledge. Pharmacokinetic studies also are being performed because protease inhibitors and other drugs used in AIDS can affect the metabolism of cancer drugs and vice versa.

Dr. Elliot Kieff expressed concern that international AIDS research is hindered by several barriers. One problem concerns medical care provided at African sites. He suggested that it is wise to have a relatively small number of state-of-the-art specimen collection facilities as a joint enterprise of the NCI and other government agencies. Drug distribution is another challenge in the African setting; Dr. Yarchoan noted that CGH is helping with this effort. Dr. Ronald Mitsuyasu commented that although the ACTG clinical trials infrastructure has decent capabilities in cancer-related activities such as pathology, chemotherapy administration, and the safe management of chemotherapy drugs, there are still are a number of logistical and administrative issues to work through even in joint trials with them, and that there are additional challenges in initiating trials separately from the ACTG.

Dr. Kieff asked about the quality of interactions between the NCI intramural program, the Frederick National Laboratory for Cancer Research's (FNLCR) primate program, and other groups doing vaccine work, such as the Division of AIDS (DAIDS) in NIAID, the Vaccine Research Center, and the US Army program. Dr. Yarchoan noted that there is good communication, often at the principal investigator (PI) level.

Dr. Kevin Cullen noted that the OHAM directly manages 10 percent of the total AIDS funding and asked what mechanisms were in place to coordinate the funding prioritization. Dr. Yarchoan explained the levels of coordination within the NCI, which occur through a variety of formal and informal mechanisms. Also, he noted that there is a lot of coordination between the OAR and the OHAM and between OHAM and DAIDS.

Dr. Corey commented that the NCI is a large institute that has grown organically over a long period of time. It will be useful to take a moment to question the responsibility of the NCI in spending AIDS dollars. The NCI would like the assistance of the BSA Subcommittee members in their deliberations concerning the current use of AIDS funding and the future direction of spending in the context of the NCI's mission and the entire AIDS portfolio.

Dr. David Scadden said that bone marrow transplant is potentially useful as curative therapy for HIV infection. The NCI has funded, along with then National Heart, Lung, and Blood Institute, an initiative to study bone marrow transplantation for HIV-positive individuals. Dr. Yarchoan noted that one consideration for the BSA Subcommittee is determining the appropriate involvement of the NCI for applying potentially curative therapies that were developed for cancer to HIV/AIDS. Dr. Scadden encouraged the NIH, which has that particular expertise, to seize the opportunity to pursue transplantation in this regard.

Charge From NCI Leadership—Dr. Harold Varmus

Dr. Varmus expressed appreciation to the Subcommittee members for their participation and reminded them of their advisory role to help the NCI make important decisions. Dr. Varmus told members that the AIDS research portfolio at the NCI should be given more scrutiny, and he provided three fundamental questions:

(1) What is their assessment of the current AIDS portfolio?

(2) How should the AIDS portfolio of the NCI be modified in response to needs, opportunities, and other scientific considerations that have arisen or that may arise in the near future?

(3) As an optional third question, is our current level of funding of the AIDS portfolio appropriate? He noted that the NCI receives a fairly large amount of money for AIDS research from the OAR, in part for historical reasons. There is a tendency to want to preserve this funding, but the Subcommittee should consider whether the funding amount is too much, too little, or just right. When an amount of funding is construed as an entitlement, the inclination is to use the allocated funding to do more of the same type of research, but that is not necessarily the best approach.

Dr. Varmus instructed the Subcommittee members to consider whether the current NCI portfolio is focused on addressing the most critical questions. He noted that studies of HIV replication and anti-HIV drug development might fit better in other Institutes and Centers (ICs). There is ongoing HIV vaccine research in the NCI, but this research is now a focus of the Vaccine Research Center, and DIADS has a large program. Subcommittee members should consider whether an NCI portfolio that focuses on HIV-related cancers is a more appropriate investment of OAR funds, or whether it is appropriate to continue to have some portion of the NCI portfolio consist of non-cancer HIV research. With respect to the future, individuals are living much longer and people with HIV are increasingly developing cancers. There are tremendous opportunities to learn more about HIV-related neoplasms. The somewhat arbitrary designation of what constitutes an "HIV-defining cancer" should be considered.

Dr. Varmus told members that the NCI has made a deliberate decision to foster work in global health. The new CGH fosters opportunities to study cancers arising locally and globally. Additionally, increasing rates of neoplasms are occurring in minority populations (e.g., drug users) infected by HIV, and there is an opportunity to address health disparities. The NCI is seeking to ascertain whether those topics are underinvested in funding, or if there are other actions that the NCI could be taking to encourage the research community through RFAs, program announcements, or other ways to bring people together to address sensitive issues. Finally, it will be important for the NCI to anticipate the consequences for people who live longer with HIV, and consider the implications of this shift in the epidemic for the increasing development of HIV-associated cancers.

Open Discussion—Members

In response to questions, Dr. Varmus informed members that a primary responsibility of the NCI is in dealing with the medical burden of cancer in specific populations (e.g., HIV-infected individuals). With regard to AIDS, other contributions could be made to understand the mechanistic aspects of HIV biology. Dr. Varmus stated that the Subcommittee members should assist the NCI in understanding how AIDS research fits into its primary mission.

Dr. Scadden commented that the study of HIV-infected populations provides an opportunity to research target-host interactions and the contribution of immunology to cancer. Dr. Varmus appreciated the suggestion and said that there was a strong opportunity to focus on the determinants of the immunological response. He noted that there were no limits to what the Subcommittee could propose for the NCI to prioritize; anything that then OAR may feel was not AIDS-related could be supported with other NCI funds.

Dr. Stanton Gerson commented that from an epidemiological perspective, the study of malignancies in the AIDS population allows for the determination of the relative contribution of age, as diseases in elderly populations act different in ways that are not genetically defined. The NCI's efforts could be combined with those of other ICs interested in understanding how to maintain human function over an increasing lifespan. Dr. Varmus solicited suggestions to use The Cancer Genome Atlas' (TCGA) genomic tools to study differences in biological behavior. Dr. Varmus commented that he had organized a workshop for

cancer immunology across age groups and this could be another opportunity to stimulate grant applications.

Dr. Justice suggested that the group define what characteristics are required for an ADC designation or a designation of HIV-associated cancers. She noted that as the population ages, the profile of malignancies will change, so it will be important to define criteria denoting "cancers of interest" to the NCI.

Dr. Varmus informed members that the "provocative questions" exercise has been highly successful as a means of getting the research community to identify and work on various important issues that are otherwise understudied. What are the provocative questions related to HIV and malignancy, and how best should those questions be addressed?

Dr. Yarchoan said that previous ad hoc meetings of HIV-malignancy researchers have been useful in providing ideas and articulating opportunities for HIV malignancy research. However, this formal Subcommittee is somewhat different in that it will culminate in specific messages to present to the full BSA for discussion. Dr. Yarchoan encouraged the Subcommittee to converge on specific points or action items.

Dr. Corey pointed out that the Subcommittee could either approach the discussion using the provocative questions approach or from the perspective of what mechanisms should be investigated. The group already had suggested several research priority possibilities, including the use of HIV as an experiment of nature to study the underlying biology of cancer through HIV-associated malignancies. It also might be useful to consider which malignancies associated with HIV will emerge throughout the next 4 to 6 years. Antiretroviral therapies are changing the spectrum of comorbidities, as HIV-infected people are dying of cancer rather than from opportunist infections. Dr. Corey suggested defining questions of importance to prioritize tumors and identify which questions could be answered and which programs should be enhanced or activated to make an impact.

OAR Perspective on AIDS Research—Dr. Jack Whitescarver

Dr. Whitescarver described the OAR's comprehensive evaluation of the NIH's AIDS research program, known as the "Levine Report," which had a major impact on how the OAR progressed forward with research priorities. Dr. Whitescarver noted that the NCI is the only IC that receives support from the OAR for HIV-related cancer research. The OAR funds provides some oversight for NCI AIDS projects; however, they do not review intramural research because the BSC provides a very rigorous review.

As a result of pressure from Congress and advocacy groups, the OAR was established in 1988 as a single focal point to coordinate HIV research in the NIH. Further legislation in 1996 strengthened the OAR because it was decided that an AIDS institute should not compete with existing research portfolios. Additionally, the complexity of the disease continues to increase and is best addressed by the experts residing in specific subject areas within the ICs. This strategy might be changing, which underscores the importance of the Subcommittee's review.

The OAR functions as a facilitator for trans-NIH issues. As instructed by Congress, the OAR has structured coordinating committees that reflect the areas of science (e.g., behavior and social science, epidemiology). Each OAR committee is comprised of representatives from ICs with portfolios in that area. The OAR is responsible for coordinating HIV-related science among the ICs. The budget is reviewed by the NIH Director to ensure that the AIDS allocation to ICs does not create a hardship on the non-AIDS portfolio; the research should not compete. The overall NIH AIDS and non-AIDS portfolios have generally grown at the same rate and AIDS funding is allocated according to scientific priorities. Projects are reviewed by OAR and IC staff to assign priority for the AIDS dollars. ICs are notified if any projects

should not be supported with AIDS dollars, which can be phased out if removing the funds abruptly will create a hardship.

Dr. Whitescarver emphasized that the OAR facilitates but does not directly manage AIDS research. Budget requests submitted to the OAR are reviewed to ensure that priorities are appropriate and there is no redundancy in research efforts. Collaborations might be suggested, and projects might be structured to include several ICs. The OAR will be looking to the NCI to help define its research priorities.

Open Discussion—Members

In response to a question, Dr. Whitescarver stated that the NIH AIDS budget has been approximately 10 percent of the total NIH budget for several years. This is in part the result of an agreement between the OAR and NIH Director.

Dr. Chanita Hughes-Halbert noted that two focal points for research include prevention and cures. She questioned whether the OAR was pursuing behavioral or vaccine prevention modalities. Dr. Whitescarver responded that all prevention topics are of interest, in addition to therapy.

Dr. Cullen commented that the nature of the disease has changed dramatically. Morbidity, however, is continuing to rise. The NCI is the only IC performing significant cancer research. Given that the morbidity of the cancer population is increasing rapidly, he recommended that more funding should go toward cancer research. Dr. Joel Palefsky asked whether a coordinating committee would facilitate these changes. No such coordinating committee exists, but it could be formed if the Subcommittee makes such a recommendation to the NCI.

Dr. Whitescarver emphasized that AIDS dollars can only be used for research, not treatment. Frequent trans-NIH workshops are held to solicit advice on where funding should be increased or shifted. Several recent examples include workshops addressing hepatitis B as well as diseases in at-risk groups of African Americans and Hispanics. A "think tank" with the National Institute on Aging (NIA) has brought together gerontologists and HIV experts to develop recommendations to share with the ICs. Regarding the proportion of AIDS funding for international versus domestic efforts, Dr. Whitescarver said that generally all international dollars are given to a U.S. PI and are used to fund the international component of a research project. Progress would occur more quickly with an international alliance leveraging various strengths of contributing countries.

Dr. Yarchoan encouraged the Subcommittee to consider whether the level of AIDS funding for the NCI is too high, too low, or ideal. Dr. Whitescarver clarified that there is no competition between AIDS and non-AIDS dollars for a given IC. Dr. Gerson commented on the tendency for incremental, rather than full, priority reassessments of existing research. He encouraged participants to consider a big leap in the future direction of NCI's research because issues are different now. Dr. Corey concurred and explained that the Subcommittee should define what needs to be accomplished scientifically and then leverage programmatic contributions to move the research agenda forward. The challenge is to provide specificity on pending issues with respect to HIV and malignancies in HIV-infected individuals.

Epidemiology of HIV Malignancies With an Eye to the Future—Dr. Eric Engels

Dr. Engels, a Senior Investigator with the NCI's Division of Cancer Epidemiology and Genetics (DCEG), described trends in malignancies among HIV-infected people. Dr. Engels told members that the epidemiology of HIV/AIDS-related malignancies has changed dramatically in the past decade. HIV-infected people are now at a high risk of NADC as well as ADC. The introduction of HAART in 1996 decreased overall AIDS mortality while also decreasing the incidence of ADC. Cancer trends in the HIV-

infected population reflect immune status, cancer risk factors, and demographic changes. The NCI's HIV/AIDS Cancer Match Study used a computerized method to link HIV/AIDS data and cancer registries in 14 U.S. regions and study various cancers in AIDS patients.

Dr. Engels provided an update on seven notable cancers in HIV-infected people that he said deserved research attention: the traditional ADCs of Kaposi's sarcoma, non-Hodgkin's lymphoma (NHL), cervical cancer, and the NADCs of lung cancer, Hodgkin's lymphoma, anal cancer, and liver cancer. The SIR for each of these cancers is significantly elevated in people with AIDS compared to the general population, especially Kaposi's sarcoma, NHL, and anal cancer. With the exception of lung cancer, these malignancies are associated strongly with viral agents. The cancers demonstrate some measure of a relationship with immune suppression (CD4 or AIDS), although the magnitude is different for different cancers.

One recent trend in the United States that has an important impact on cancer development is the aging of the AIDS population. The incidence of ADCs among people with AIDS has declined significantly since the introduction of HAART, although it has leveled off in the past several years. At the same time, the total cancer burden of NADCs among people with AIDS has increased, in part because people are living longer with HIV and AIDS. In terms of a public health impact, reducing the burden of NADC is becoming more important. The absolute numbers of cancer cases for people with HIV in the United States cannot be accurately calculated because the total number of people infected with HIV in the United States is unknown. The decline in ADCs occurred after the introduction of HAART. Anal cancer is increasing in both HIV and general populations, possibly due to an increase in HPV infection. Interestingly, the increasing anal cancer burden is experienced by more males than females in the HIV/AIDS population, while females with anal cancer outnumber males in the general population. The incidence of lung cancer is declining somewhat in the HIV population, although the number of cases per year is increasing, probably in part because of the aging of this population. Evidence suggests that HIV is an independent risk factor for lung cancer.

Much less is known about HIV-associated malignancies in the developing world. There are few reliable data on cancer trends in developing countries because the research is hindered by a lack of resources for pathology and cancer registries. As HAART use increases globally, a decline in ADCs and increase in aging and chronic comorbidities (including NADC) is expected.

Importantly, HIV-infected cancer patients might have worse cancer outcomes because of late presentation at advanced stages, poor access to medical care, comorbidities, and increased susceptibility to treatment toxicity. Interactions between chemotherapy drugs and HIV medications complicate treatment. Finally, there is limited practical data for guiding cancer treatment in HIV-infected people. Additional research is needed to understand the role of non-immunodeficiency pathways in cancer etiology, learn about epidemiology of cancer in the developing world, and optimize cancer treatment and outcomes.

Open Discussion—Members

Dr. Engels noted that HPV-related oral cancer is not common; the levels are increased in the HIV population but there is not a strong relative risk. Larynx and pharynx cancers, although rare in the HIV population, would be of interest. Ten-year cancer incidence projections are complicated and require many assumptions; those calculations have not been performed.

Dr. Hughes-Halbert asked whether the incidence rates differ by race and ethnicity. Dr. Engels noted that researchers have not looked in detail for cancer risks by race, but it is an important question. He gave the opinion that the proportion of deaths of people with HIV attributable to cancer is approximately 5 percent, although there are methodological challenges when contributing deaths to cancer. Dr. Yarchoan pointed

out that a recent article from France gave the percent of deaths in HIV patients attributable to cancer at 34%. Dr. Justice pointed out that the AIDS-cancer match technique being used by Dr. Engels would miss deaths occurring in HIV patients who had not developed AIDS, and that with the number of NADC increasing, this was an increasing percentage of the cancer deaths in HIV patients.

Dr. Corey questioned whether HIV-associated malignancy incidence could be estimated by country, and if the data were not available, what resources should be developed to understand the global HIV-related malignancy burden. He also asked whether it was possible to project the number of cases of HIV-associated malignancies in the United States in the near future. Dr. Engels noted that intramural researchers are mandated to study problems of the greatest scientific and public health impact. Although the DCEG is interested in African studies, its ability to do so is limited by financial and time resources. He noted that increasing the funding for cancer research and the development of cancer registries in Africa would produce valuable dividends.

Dr. Scadden questioned whether understanding the interactions between HIV and genetic predisposition to cancer might help to elucidate risk. Dr. Engels said that many studies look for additional risk factors or co-factors for cancer, and the research program is trying to address that question.

Center for Global Health—Dr. Lisa Stevens

Dr. Stevens presented an update on how the CGH is strengthening and coordinating global cancer research and health activities. Dr. Stevens noted that one of Dr. Varmus' top priorities is global health. The CGH, which was formed in September 2011, brings together existing global activities throughout the NCI. They are guided in this effort by the National Cancer Advisory Board (NCAB)'s Subcommittee on Global Health. Given the increasing incidence of cancer worldwide as other problems are addressed, the CGH has an important mission. In 2008, nearly 7.6 million people worldwide died from cancer, of which 64 percent were in the developing world.

The CGH engaged in strategic planning activities during the past year and decided on priority areas. One priority area includes supporting cancer research and cancer control planning by focusing on cancers related to chronic infections, research networks, and international partnerships for cancer control. They do this primarily by working with, coordinating, and supporting international efforts throughout the NCI. Another priority of the CGH is to leverage partnerships between the United States, nongovernmental organizations, and other countries. The NCI partners with the National Institute of Allergy and Infectious Diseases (NIAID), Fogarty International Center, and CDC to coordinate activities, and some countries (e.g., Brazil and China) are interested in contributing financially to help develop programs. A third priority area is monitoring research efforts through evaluations, country reports, and research activity summaries. The final priority area is catalyzing information dissemination and building capacity through data collection, training, and infrastructure.

The CGH and OHAM have collaborated on several workshops, including international scientific and grant writing workshops in Tanzania and South Africa. The key to the workshops is to encourage multiple partners to provide funds and expertise. The CGH, OHAM, and Office of Science Planning and Assessment (OSPA) collaborated on a project to measure outcome in OHAM D43 grants to build research capacity in Africa. Additional collaborations between the CGH and OHAM include upcoming meetings to explore future research topics (e.g., HIV-related and non-HIV-related malignancies) and an enhancement of collaborations between Centers for AIDS Research (CFARs) and the NCI. CFARs will be evaluated to explore ways to build on these successes. Dr. Stevens suggested several venues for further discussion, including regional interest groups with OHAM participants, open staff meetings, and CGH seminars and speaker lunches.

Open Discussion—Members

Dr. Mitsuyasu noted that, as the head of the AMC, he experienced a number of issues in developing the international consortium, such as the variation in regulations and requirements for trial studies between countries. He asked whether the CGH was interested in developing a coordinating center to assist cooperative groups in performing AIDS-related or unrelated trials. Dr. Mitsuyasu elaborated that assistance is needed in the logistical aspects of multinational collaborations, such as drug acquisition and distribution, material transfers, and legal documents. Dr. Stevens responded that the United States–Latin America Cancer Research Network provides a good example of how to approach this issue.

Some Ideas for Future Research Directions in AIDS Malignancies—Dr. Robert Yarchoan

Dr. Yarchoan highlighted some of the NCI's recent advances in HIV/AIDS malignancy. He said that Dr. Yarchoan numerous studies have elucidated the biology of KSHV, EBV, and HPV, and the mechanisms by which they cause tumors. He noted that one major accomplishment was the marked decline in the incidence of ADCs resulting from the development of and widespread use of HAART in developed countries. The NCI developed an effective HPV vaccine, licensed in 2006, and demonstrated that it can prevent the development of cervical cancer and premalignant lesions. The safety and efficacy of the vaccine was verified through NCI efforts. The development of effective screening and treatments for high-grade anal intraepithelial neoplasia (HGAIN) also is attributed to the NCI. The NCI demonstrated that HAART can effectively treat a high percentage of HIV and Kaposi's sarcoma cases. NCI researchers identified immunologic changes and genetic associations that accompany an increased risk of HIV-related lymphomas and improved the treatment and survival of patients with several therapies. Also the NCI had found evidence that the risk of breast cancer is reduced substantially in women with R4 HIV.

Dr. Yarchoan proposed several goals for the future for the committee to consider. He suggested that the prevention of HIV-associated malignancies could arguably be considered the most important goal. Other goals may be to (1) gain an improved understanding of the pathogenesis and immunobiology of HIV-associated malignancies, (2) development of improved therapies for cancer among HIV-infected people, and (3) region-appropriate prevention and treatment of HIV-associated malignancies in resource-poor regions.

Several possible strategies to meet these goals were presented as potential areas for consideration of increased investment. The NCI could study the prevention of virus-induced malignancies by developing vaccines based on the causative agent (e.g., EBV or hepatitis C virus [HCV]). Whether developing a vaccine for KSHV would be worthwhile depends on the likelihood of whether it would be administered widely in Africa. Public health measures could be used to reduce the spread of oncogenic agents. For example, KSHV is spread differently than HIV, but none of the current safe-sex guidelines address KSHV. Screening and treatment of premalignant conditions also could improve the prevention of HIV-associated malignancies. For example, improved screening and prevention algorithms for cervical cancer will improve detection in resource-poor regions. Prevention could be accomplished by addressing co-factors, such as malaria or smoking behavior.

A better understanding of the pathogenesis of HIV-associated tumors would be facilitated by identifying novel virus and oncogenic agents, studying the role of HIV in promoting tumor pathogenesis, and identifying the factors that affect the development of HIV-associated tumors. Several possible provocative questions to consider may be: What factors, other than increased smoking, contribute to increased lung cancer in HIV patients? How is HIV-associated lung cancer different from lung cancer in non-HIV patients? How do viral cancer-inducing genes interact with cellular mutations to induce cancer?

The development of improved therapies for ADC could involve novel pathogenesis-based approaches and studies of the underlying viral etiology. Even for cancers that do not show an increased incidence, understanding of how to best treat these tumors in the context of HIV disease will be important. Other strategies to improve therapies include pharmacokinetic studies of interactions between cancer drugs and antiretroviral drugs as well as the inclusion of HIV-infected individuals into general cancer trials. Aggressive therapies, such as bone marrow transplantations, in HIV-infected patients could be explored. Improving the prevention and treatment of HIV in resource-poor regions will require improved diagnostic capacity to identify the spectrum of tumors, additional epidemiology to identify the current disease burden and project future trends, and enhanced training and capacity for research. Region-appropriate treatment strategies should be developed, and therapies for HIV-associated tumors in children should be initiated.

Open Discussion—Members

Note: Compiled recommendations from this discussion are found as an Attachment at the end of this document. Following are some notes from the discussion as it took place.

Dr. Corey suggested that the members address specific issues before moving onto global considerations. He began with Dr. Engels' list of the seven tumors of interest (i.e., Kaposi's sarcoma, NHL, cervical cancer, lung cancer, Hodgkin's lymphoma, anal cancer, and liver cancer). Participants focused their discussion on seminal questions that should be answered for the cancers of interest.

Kaposi's Sarcoma

Kaposi's sarcoma is now a priority mostly in Africa and other areas in the developing world. Awareness of KSHV is an issue impacting public health measures; one UCSF study found that only 10 percent of men who had sex with men (MSM) knew the virus that caused Kaposi's sarcoma, and there was no awareness that saliva is a major transmission route. The Subcommittee recommended that the NCI should learn more about KSHV transmission and consider developing appropriate guidelines to prevent KSHV transmission.

Dr. Mitsuyasu noted the opportunity to understand differences in HIV/AIDS-related malignancies between racial populations throughout the world. Disease co-factors could be identified by investigating populations where disease persists and those where there is no disease. For example, one HIV-cancer match study in India found that none of the 700 cancer patients had KS. It is not clear whether this reflects a lack of KSHV or whether KSHV is less likely to cause KS in India. Studies need to be performed to confirm this and ascertain whether genetic or immunological differences in that population are contributing to the lack of KSHV infection and/or KS.

Hodgkin's Lymphoma

Very little research has been performed on Hodgkin's lymphoma in patients with HIV infection. The types of Hodgkin'sl ymphoma and their natural history are different in HIV-infected patient as compared to HIV-uninfected individuals. Dr. Richard Ambinder commented that he had seen relapses of Hodgkin's lymphoma in HIV patients that he has not seen in non-HIV patients, suggesting that the natural history of the malignancy might be different in the two groups.

Clinical Trials and Biobanks

Dr. Gerson commented that there is a need for longitudinal studies to monitor disease progression and evaluate contributing factors. HIV patients on average have poorer outcomes according to Surveillance Epidemiology and End Results (SEER) statistics. Some HIV patients have organ damage from HIV

infection or its treatment and are not included in clinical trials; their poor outcomes would not be reflected in trial statistics. Differences in outcomes also might reflect noncompliance issues.

Dr. Corey asked for opinions regarding the importance of large HIV cohort trials such as prevention studies. Several participants suggested that the NCI consider prospective studies. Combination analyses and meta-analyses are useful to increase the statistical power of trials, given that HIV cohorts are small and cancer data are limited. The NCI could provide incentives to include HIV patients in clinical trials.

Dr. Palefsky said that improving resources to collect additional specimens and data (e.g., sequential samples, cancer type) would be valuable; sequentially sampled cohorts could provide information with a modest investment. Some studies supply periodic collections, but they are small in number and it is difficult to find cohorts to follow over time. Another challenge is that tumor banks compete for patients.

Screening

Dr. Mitsuyasu stated that the literature shows that HIV patients are often not screened according to U.S. Preventive Services Task Force (USPSTF) guidelines. HIV-positive individuals are two- to four-fold less likely to receive mammogram and prostate exams; there is less focus on standard prevention.

Members agreed on the importance of determining whether cancer screening works for high-risk people. Promoting early detection could improve outcomes, and performing inexpensive interventions in high-risk populations might make sense. Caveats include the detriment of false positives for high-risk individuals, resource constraints, and finding screening and early intervention approaches that in fact lead to improved morbidity and mortality.

Given the increased prevalence of lung cancer, screening the HIV-positive smoking population subgroup may be worthwhile. However, it has not been established whether approaches that have been shown to yield improved care in HIV-uninfected patients would similarly be useful in HIV-infected smokers, and this is an area worthy of study. An important unanswered question is whether screening for anal cancer or its precursor (high-grade anal intraepithelial neoplasia) would improve outcomes in this disease. The best long-term approach for anal cancer prevention is widespread use of a preventive vaccine against HPV, which has been developed in the NCI. The activity of such a vaccine in HIV-infected patients is worthy of study. For people who are now adults and have been exposed to HPV, there is little evidence that a preventive vaccine will be effective. For this population, the NCI is considering a large multicenter trial to determine if screening for and treating HGAIN will prevent anal cancer. All participants agreed that it was a critical question that was worthy of study in a large trial. Dr. Cullen commented that a screening methodology for oropharyngeal cancer, which is increasing dramatically, is under development to identify people at risk.

Vaccines

Dr. Ren Sun suggested that an EBV vaccine is of interest for the prevention of mononucleosis in the United States. Private sector motivation is waning somewhat because of the lack of financial incentives; the NCI might be able to provide impetus for public-private partnerships to combine scientific expertise with financial resources. Dr. Ren Sun also commented that China is interested in developing a vaccine against EBV and might be interested in a global partnership. Members felt that although development of a KSHV vaccine was probably scientifically feasible, kn part because of the relatively poor transmission of this virus, there was almost no financial incentive for companies to participate, and that KSHV-associated disease might be better addressed by the development of nontoxic, low-cost, effective therapy.

Dr. Corey asked whether any members believed that the NCI should fund the development of an HCV vaccine. There was discussion of this point, and it was felt that this was worthy of consideration, although this would require an assessment of the activities of other ICs, non-profit organizations (like the Gates Foundation) and the private sector; partnership with those other groups should be considered if the NCI decides to undertake this effort.

Therapeutic Approaches

The NCI's previous focus has been to study HIV-associated tumors and their pathogenesis. Because these tumors may not be common enough to justify specific drug development, most of the therapeutic trials have involved the testing of drugs developed for other tumors. Dr. Mitsuyasu emphasized the importance of continuing interaction studies between standard cancer therapies and antiretroviral drugs, and several members agreed. Dr. Justice emphasized the uniqueness of the HIV population, whose organ functions are less robust and in whom polypharmacy may be a major concern.

Dr. Ambinder reiterated that investigating the biology of transplantation events might be useful and could contribute to efforts to eradicate HIV. Dr. Scadden noted that the NCI has the opportunity to use its expertise in such modalities as transplantation to contribute to the development of valuable cell-based therapies for HIV.

Dr. Palefsky stated the need for newer and more effective therapies against HIV-associated tumors. While antiretroviral therapy has reduced the incidence of several ADC, such as Kaposi's sarcoma and lymphoma, they have not been eradicated.

Genetic and Other Determinants

Members suggested evaluating disease genetics and studying the tumor microenvironment. HIV-positive individuals with lung cancer are relatively more likely to develop adenocarcinomas. Genetic profiling to identify genetic factors would help researchers understand the population differences. TCGA can be utilized to analyze tumor samples to correlate treatment with response and different genetic co-factors. The members discussed the best way to identify causal relationships between lung cancer and infection, given the multifactorial contribution to the disease. The study of anal infection of women is an interesting model system to compare cervical and anal cancers to elucidate the function of the cervical and anal microenvironment in dealing with infection. Dr. Yarchoan mentioned that the HIV is funding the HIV+ Tumor Molecular Characterization Project (HTMCP) which is sequencing several HIV-asociated tumor types, including diffuse large B cell lymphoma (DLBCL), cervical cancer, and lung cancer. The NCI funds the Tumor Microenvironment Network (TMEN), which emphasizes the contribution of stromal components to oncogenesis and provides a good leverage point.

Dr. Yarchoan asked what tumors should be prioritized and suggested that the NCI not only study HIV-associated tumors. If a cancer is commonly found in an HIV-infected individual, or its incidence is changed, it is potentially important to study, and we should assess the optimal treatment strategy. For example, breast cancer incidence is decreased in individuals with HIV so it would be difficult to study with AIDS dollars, but other funding could be used. Participants agreed that because infection with CXCR4-tropic HIV has been reported to be protective of breast cancer, it would be worth studying.

Immunology and Aging

Several Subcommittee members had suggested that the NCI use the natural experiment of HIV-related malignancies to learn about host-immune control of cancer in general and elucidate immune mechanisms related to HIV and other diseases. Understanding the contribution of infections to pathogenesis would be

valuable. The development of new therapeutic antibodies for individuals with altered immune function also would be useful.

Dr. Palefsky asked whether any cancers associated with HIV were unassociated with other immunodeficiency syndromes (e.g., transplant population). Dr. Ambinder suggested that Burkett's lymphoma might be an example of one such cancer. Dr. Scadden suggested that the group put forth a provocative question about how best to leverage subgroups of patients to gain mechanistic insights.

A suggestion to study the contribution of aging to the development of HIV malignancies was voiced by several Subcommittee members, who also recommended that the NCI collaborate with the NIA.

General Considerations

Dr. Yarchoan suggested that the NCI has funded supplements for collaborations between various groups; while this has been useful, it may be better to identify important areas for study. Understudied areas in the field of HIV malignancy could be funded with RFAs, possibly including a provocative question RFA in this area. Dr. Corey suggested that the NCI's participation at regional meetings, promulgating interest in HIV-positive malignancies, is a great way to attract new people into the field. The members discussed the importance of basic science contributions to translate findings into a clinical impact. The NCI could provide sustainable funds for projects that are not being funded by other ICs (e.g., HPV screening efforts by the NIAID).

Dr. Yarchoan reminded the participants that although a decreasing incidence, the cancer burden of HIV-associated cancers is increasing because the number of people with HIV/AIDS is increasing and they are living longer with HIV. Dr. Corey commented that knowing the number and incidence of cancers in the US and globally is needed in helping define priorities for future programs. Modeling the cancer epidemic in HIV infected persons would be helpful to both clinicians, health policy procedures and research.

Next Steps—Members

The Subcommittee members discussed scheduling a potential future meeting, but decided to operate via email at the present time. Teleconferences also could also be scheduled. The next in-person Subcommittee meeting will be scheduled to address Dr. Varmus' questions about optimizing resource use throughout the NCI. Drs. Corey and Yarchoan said they would develop a series of action items from the minutes and then distribute the list to the members for review; this is now included at the end of the minutes. The Subcommittee meeting adjourned at 3:40 p.m.

Preliminary Recommendations from the February 14, 2013 Meeting of the NCI BSA ad hoc Subcommittee on HIV and AIDS Malignancy

Charge to Committee from Harold Varmus:

With regard to our portfolio of research with AIDS dollars and research in HIV malignancy:

1. How does the portfolio look now?
2. In what ways should we change it in the future?
3. Consider whether our AIDS funding is too high, too low, or just right

Committee Deliberations:

There was substantial enthusiasm by the committee on the importance of the NCI developing a strategic plan for defining research priorities for malignancies occurring in HIV infected persons. Data were presented that in the US, the number of malignancies per year in HIV infected persons were increasing. This increase was largely associated with a shift in spectrum from AIDS-defining malignancies to a series of malignancies that were not AIDS-defining, but were clearly found in excess among HIV-infected versus HIV-uninfected persons. The risk of such selective malignancies was often 1.5 to >20 fold higher than in age-matched populations. The effectiveness of antiretroviral drugs in extending life and the aging population of persons living with AIDS were factors in these trends. There are challenges in assessing this parameter, but recent studies from areas where combination antiretroviral therapy (ART) is available suggest that 20 to 30% or even more of the deaths in HIV-infected persons were from cancer. As HIV-infected populations age, the burden of malignancies may increase further. The mechanisms responsible for this increasing number of malignancies are only partially understood. However, ART therapy, even among those with optimal virological control, is associated with inflammation and persistent abnormal immune responses.

Continued surveillance is needed to define the malignancy spectrum of persons living with HIV infection in the US and Europe. These data will help define the research spectrum in the coming decade.

Global Burden of Malignancies in HIV Infected Persons

Over 8 million people in Asia, sub-Saharan Africa, Latin America and the Caribbean are now on ART. It is yet uncertain if ART in these populations will produce the type of alteration in survival and age-related complications as seen in the US and Europe, but short-term results on survival are encouraging. As such, reasonable expectations are that a shift in the spectrum of malignancies in HIV+ persons will occur globally. Unfortunately, cancer registries are often disconnected from HIV registries and hence information on malignancies in HIV infected persons in countries with high HIV prevalence is not available. Moreover, oncological services are usually underutilized in high HIV prevalence countries and hence defining the spectrum of malignancies in HIV infected persons is largely a "data free zone."

There was near unanimity that increased effort to improve data on the numbers and types of malignancies in HIV infected persons in sub-Saharan Africa, Latin America, and Asia are needed. Leveraging sources (e.g. with the CDC and IARC) and perhaps selectively linking PEPFAR programs with cancer registries should be evaluated. It would be helpful to collect data in "representative centers" in each region so that some modeling of the epidemic globally could be performed. Having an overall prevalence of cancer burden, cancer morality and importantly cancer "type" is essential for optimal planning, and the committee thought it important to try to model future trends in HIV malignancy to help inform research decisions. This will require resources to support active endpoint determination.

The committee also noted the paucity of data involving malignancies in HIV infected persons in any of the NCI large cancer genome studies. As HIV accelerates tumorigenesis, defining the mutational pattern of malignancies in HIV infected persons and comparing it to HIV-uninfected individuals offers an important opportunity for understanding the underlying genetic biology of cancer. In addition to the current NCI initiative to conduct genetic typing of several HIV-associated malignancies, inclusion of HIV infected patients with cancer in ongoing genetic typing studies should be encouraged. Perhaps specific provocative questions/RFA could be initiated in this area.

Lastly, the general deliberations of the committee revolved around the greater HIV portfolio area. Development of an effective HIV vaccine and developing means to cure HIV-1 were noted to be the two highest priorities of the field and have been articulated by NIAID, NIH and the OAR. It was noted that many of the approaches toward cure used expertise that was concentrated within the NCI Caner Center Programs; use of chemotherapy, hematopoietic stem cell transplantation (HSCT) and gene therapy of hematopoietic stem cells. Inclusion of NCI investigators in such proposals and evaluation of the NCI portfolio in this area will be a potential topic of our next meeting.

Recommendations on Malignancies in HIV Infected Persons:

To provide structure to the meeting, the committee looked at 7 cancers that were felt to be the most common malignancies associated with HIV-1. The goal of these specific deliberations was to define what were the major unanswered questions or issues that should be discussed/undertaken. The seven malignancies discussed were 1) Kaposi sarcoma, 2) non-Hodgkin lymphoma, 3) Hodgkin's lymphoma, 4) cervical cancer, 5) anal cancer, 6) liver cancer, and 7) lung cancer.

Kaposi's sarcoma (KS)

KS has been reduced to nominal levels in the US and Europe. This was accomplished with the initiation of highly effective combination ART. However, even with ART, KS persists in Africa and is still a major clinical issue. The explanation for these differences in epidemiologic observations between KS incidence/prevalence post ART in the US and sub-Saharan Africa is unclear. Is this related to ART control or other co-factors?

Areas felt to be of importance to the research agenda for KS are:

1. Strategies to define those at risk of developing KS in Africa are needed. Concomitant with this is a strategy to prevent severe visceral KS.

2. The association between HHV-8 epidemiologically and KS is not completely defined, e.g., there is almost no KS in certain areas of the world (such as India). Is this because there is essentially no KSHV or because individuals are less likely to develop KS? Are there genetic / strain or other cofactors influencing KS development? Greater understanding of the pathogenesis with emphasis on how to prevent development of KS in high prevalence HIV areas were felt to be the focus of research.
3. While a KSHV vaccine might be helpful here, there was little enthusiasm in the committee for its development; it was felt that the uptake versus development costs could not be justified at present. Thus, studies of prevention and development of available cost-effective therapies were the areas of greatest research priority in the next 5 years.

Non-Hodgkin Lymphoma (NHL) and Hodgkin Lymphoma

The committee felt that reasonable therapies for these two malignancies were present in the US and Europe. However, this was not the case in resource poor settings. Classification of NHLs in sub-Saharan Africa are not known and there was an interest in identifying biomarkers for defining and classifying the histologic and genetic signatures of lymphoma in HIV+ persons in resource limited settings. Studies to develop strategies for intervening in high-risk populations should be developed, as well as therapies that could be used in low resource settings.

The discussion of the NCI's role in developing an EBV vaccine was robust with consensus that such an endeavor could and should be undertaken. Prevention of EBV associated malignancies via a vaccine that reduced acquisition (preferred) versus a vaccine that reduced the frequency of malignancy (acceptable) were worthy goals to pursue. The NCI should pursue such public-private partnerships and help establish an infrastructure that would assist development of such vaccines. Such vaccines were felt to have a "market" in resource-rich, as well as resource-poor countries. In addition, collaborating with Asian centers (especially China) should be considered due to the association between EBV and nasopharyngeal carcinoma (NPC).

HPV-associated tumors (especially cervical and anal cancer)

1. There was general endorsement of the HOST trial to determine if treating HGAIN would prevent anal cancer
2. There was some enthusiasm for studies of how to best screen and prevent cervical cancer using new methodologies, especially in resource-limited settings. However, there was inconsistent enthusiasm for implementation research in this area.

Liver Cancer in HIV Infected Persons

The high rate of HBV and HCV infection in HIV infected populations is associated with higher rates of liver cancer.

1. Development of effective screening analyses, the role current ART plays in reducing HIV related cancer, and the effect these co-infections have on ART therapy are all areas of current investigation. Defining what part of the liver cancer spectrum NCI should devote itself to requires some coordination with other Institutes, such as NIDDK and NIAID.
2. Should NCI participate in studies of "curing" latent HBV infection?
3. Screening, diagnosis, and treatment of liver cancer is NCI's area of purview. Inclusion of HIV-infected persons in treatment trials and specific approaches to HBV / HCV associated liver cancer in HIV-infected persons should be undertaken.

Lung Cancer

The increasing rate of lung cancer in HIV persons is intriguing. What are the implications for screening and diagnosis? To what extent is this related to traditional co-factors such as smoking and environmental pollutants? What are the drivers of lung cancer associated with HIV? What are the molecular signatures of lung cancer in HIV-positive persons? Are they similar to non-HIV-infected persons? Would antibodies to PD-1 work in HIV-infected persons? Are there high risk screening strategies that would be of benefit (e.g.,

CT screening – early detection biomarkers)? These were all questions that were raised. Initiating studies of lung cancer in this patient population should be performed.

General Infrastructure

The recent OHAM D43 Program in Africa has provided a snapshot for beginning to build the human resources and the training infrastructure to care for HIV related malignancies. Attention to training medical and nursing personnel in the use of therapies to treat curable cancers to the developing world through the AIDS treatment programs needs to be leveraged; integrating cancer prevention, screening and care into PEPFAR Programs and Global Fund Programs. This means obtaining cancer treatment drugs for the most common tumors. Workshops on treatment approaches for KS, NHL, Hodgkin's lymphoma and anal cancer should be initiated.

For malignancies in general there needs to be some coordination of how to improve diagnostic pathology, especially for accurately defining tumors, and providing classification for therapy. A better sense is needed as to what extent HIV-infected children are at risk of various malignancies in the developing world, what therapies will / should be needed, and what screening trials to initiate.

Overall, as discussed initially, there was an acknowledged underutilization of studies of cancer in HIV-infected persons in helping to increase understanding of cancer in general.

Several concepts were discussed:

1. There was substantial enthusiasm for molecular characterization of HIV-associated tumors and comparison with HIV-negative tumors.
2. There is a need to study pharmacokinetic (PK) interactions between antiretroviral drugs and cancer drugs in HIV patients.
3. HIV patients have some, although not all, aspects of early aging. How does this affect cancer development in HIV patients?
4. Studies to identify novel infectious agents that may be involved in this phenomenon. While high risk, any "hits" would be high yield.

5. For those tumors where there do not appear to be causative infectious agents, one needs studies to understand why these tumors are increased in HIV infection.
6. Enthusiasm for studying markers identified in the Early Detection Research Network (EDRN) and other markers predictive of tumor development to assess their utility in HIV-infected patients. This would be most useful if they could lead to strategies for tumor prevention.
7. Interest in studies of how the tumor microenvironment of HIV patients differs from that of the same tumor in other patients.
8. Studies of how HIV-associated immune dysregulation and inflammation as well as HIV proteins may influence development of tumors.
9. Learn what we can from changes in tumors with HIV infection as an experiment of nature. We can also learn from tumors that are decreased (such as a decrease in breast cancer in CXCR4+ HIV patients).

Additional themes of interest included:

1. Using HIV as a template to understand the interplay between chronic inflammation, immune suppression, and immune dysregulation / dysfunction; contrasting the pathophysiology among those with and without HIV with careful justification of the control group employed.
    - Compare pathology of cancer by level of immune suppression
    - Compare HIV cancer pathology to that among those with highly inflammatory but noninfectious, non-immunosuppressive conditions
2. Using HIV as a template to understand the roles of physiologic frailty (beyond a narrow focus on immune suppression / dysregulation) and polypharmacy in predisposing patients to experience major toxicities with cancer treatment:
    - To what extent are rates of cancer treatment toxicity higher among those with HIV, and what are the correlates of this increase?
    - How do these rates vary by level of organ system injury, viral suppression, or CD4?

- Is life expectancy substantially different among patients with HIV and cancer than with cancer alone and is this an important determinant of treatment disparities?
- How does the burden of disease compare among patients with and without HIV who are considering cancer treatment?

3. Using HIV as a template to identify the optimal approach to prioritizing screening and treatment for cancer in the normative context of multimorbidity and polypharmacy.
    - How should screening and treatment account for frailty, multimorbidity, and polypharmacy?

Provocative Questions Initiative focused on HIV-associated cancers

There was a tremendous level of enthusiasm for developing a Provocative Question RFA focused in the area of HIV malignancy. A suggestion was made to consider doing this with other ICs, such as with NIDDK (liver cancer issues) or NIA (role of aging). Some possible questions that were proposed:

1. Are there other infectious agents that contribute to HIV-associated cancers – either undiscovered agents or agents whose role we have not yet identified (e.g., hit-and-run)?
2. Do HIV proteins have a direct role in the induction of certain tumors? If so, what is the role?
3. Even with HAART, HIV patients have continued subtle immune defects and immune dysregulation. How does this promote the development of tumors? How do these defects interact with the immune defects of aging and HIV-associated premature aging to promote tumor development? What aspects of immunodeficiency or immune dysregulation are most important in the pathogenesis of KS, NHL, and other HIV-associated tumors?
4. HIV-infected patients have some aspects of premature aging. Which of these aspects are relevant to tumor development, and in what ways does this promote the development of various tumors?
5. In what ways do the inflammation and microenvironmental defects in HIV patients contribute to tumor development?

6. How do the oncogenes of tumor viruses interact with somatic mutations in the pathogenesis of HIV-associated tumors?

These recommendations will be considered further in subsequent deliberations of the Subcommittee by e-mail, teleconference, and/or face-to-face meetings.