

**National Institutes of Health (NIH)
National Cancer Institute (NCI) Board of Scientific Advisors (BSA)
ad hoc Subcommittee Meeting on Human Immunodeficiency Virus (HIV) and
Acquired Immune Deficiency Syndrome (AIDS) Malignancy**

Teleconference
May 24, 2019
4:00 p.m. – 5:00 p.m. EDT

SUMMARY

Participants

Subcommittee Members

Dr. Blossom Damania, Chair (The University of North Carolina at Chapel Hill)
Dr. Robert Yarchoan, Subcommittee Executive Secretary (NCI, Office of HIV and AIDS Malignancy)
Dr. Richard Ambinder (Johns Hopkins University)
Dr. Otis Brawley (Johns Hopkins University)
Dr. Yuan Chang (University of Pittsburgh Cancer Institute)
Dr. Carol Ferrans (University of Illinois at Chicago)
Dr. Denise Galloway (University of Washington)
Dr. Amy C. Justice (Yale School of Public Health)
Dr. Jeffrey Martin (University of California, San Francisco)
Dr. Joel Palefsky (University of California, San Francisco)
Dr. Nancy Raab-Traub (The University of North Carolina at Chapel Hill)
Dr. Michael Saag (The University of Alabama at Birmingham)
Dr. Joseph Sparano (Albert Einstein College of Medicine)
Mr. Jeff Taylor (Positive Life Series Treatment Education Program)

Other Participants

Ms. Joy Wiszneaukas (NCI, Division of Extramural Affairs)
Dr. Geraldina Dominguez (NCI, Office of HIV and AIDS Malignancy)
Dr. Mostafa Nokta (NCI, Office of HIV and AIDS Malignancy)
Mr. Adam Gattuso (The Scientific Consulting Group, Inc., Rapporteur)

Welcome

Drs. Blossom Damania and Robert Yarchoan

Dr. Robert Yarchoan called the meeting to order.

Update from the Office of HIV and AIDS Malignancy

Dr. Robert Yarchoan

Dr. Yarchoan noted that Dr. Norman E. Sharpless has been named the Acting Commissioner of the U.S. Food and Drug Administration and that Dr. Douglas Lowy now serves as the Acting Director of NCI.

The request for applications (RFA) for the AIDS Malignancy Consortium was approved by NCI's BSA and will be moving forward. The grant application for the AIDS and Cancer Specimen Resource (ACSR) has been submitted and reviewed. The next step is for the application to undergo a secondary review. An

RFA has been released for the Latin America Cervical Cancers Consortia; a number of applications have been received and are under review.

The NCI has also released an RFA under the Provocative Questions Initiative that is focused on cancer with underlying HIV infection. Applications are due on August 1, 2019, and August 3, 2020. The questions are listed as follows:

1. Other than immune dysfunction (including inflammation) and known oncogenic mechanisms or risk factors that affect people living with AIDS (PLWA), by what other mechanism(s) does HIV infection promote the development or progression of tumors either directly or indirectly in patients with treated HIV infection?
2. What if any are the contributions of transposable elements or endogenous retroviruses to cancer development in people living with HIV (PLWH), and what role does HIV play in their mobilization across the genome?
3. Other than direct effects of HIV infection, what are the factors that contribute to the poorer survival of PLWH with cancer when compared to HIV-uninfected patients with the same tumor type? How can this knowledge inform improvements in cancer care in patients with HIV and cancer?
4. What are the determinants of the size and diversity of reservoirs of oncogenic agents that impact the development of malignancies in PLWH?
5. How does the biology of aging affect the development of cancer in PLWH?
6. Can novel *in vitro* and *in vivo* models of HIV/AIDS-associated malignancies be developed to study their development, pathogenesis, and the potential evaluation of novel treatments for common HIV/AIDS-associated malignancies?

The 17th International Conference on Malignancies in HIV/AIDS will be held on the NIH Campus on October 21–22, 2019. Dr. Geraldina Dominguez serves as Co-Chair of the Program Committee along with Dr. Yarchoan.

Summary and Discussion of Recommendations of the *ad hoc* Working Group on Immunology of Therapies and Vaccine and Research Structure

Dr. Blossom Damania

Dr. Yarchoan explained that the Subcommittee of the BSA must approve the recommendations of the Working Group; the Subcommittee also has the option of revising them. The recommendations then will be submitted to the BSA for approval. Once approved by the BSA, the recommendations will be forwarded to NCI for consideration.

Dr. Damania explained that the Working Group addressed several key questions in the field of AIDS malignancies as charged by the Subcommittee..

Topic 1: Research on Transmission and Biology of Initial Kaposi's Sarcoma–Associated Herpesvirus (KSHV) Infection

During its discussions, the Working Group considered the differences in KSHV transmission rates between developed and developing countries. The incidence of KSHV in the general U.S. population is very low but high among U.S. men who have sex with men (MSM). The incidence in the general

population in Africa is high, and transmission begins in childhood. The mechanisms responsible for these differences across geographical areas is not well understood but could be related to behavioral practices, host immune responses, or strain differences in the viral genome. The Working Group determined that knowledge gaps about KSHV transmission must be addressed.

Topic 2: Feasibility of a Vaccine for KSHV

The topic of creating a KSHV vaccine was a major focus of the Working Group's discussion. Group members expressed an interest in developing a KSHV vaccine, because such a vaccine would be beneficial to certain high-risk populations (e.g., populations in Africa, persons with an expectation of immune suppression). The Working Group compared KSHV vaccine development to that for Epstein-Barr virus (EBV); however, the feasibility and economic model for a KSHV vaccine are unclear. The Working Group identified a need to better understand KSHV transmission and the immune response to KSHV infection and then consider the likelihood of success in designing an efficacious vaccine. To this end, NCI's Office of HIV and AIDS Malignancy has released an RFA about KSHV transmission. Dr. Mostafa Nokta added that applications for this RFA have been reviewed and that some have been funded. Dr. Yarchoan explained that this RFA was released at the same time as two others and that the simultaneous release of the RFAs may have affected the quality and/or quantity of the applications. It may be worth considering whether the RFA should be reissued.

Topic 3: Research on Immunologic Control of Oncogene Virus Infection

The Working Group thought that an initiative to generate reagents and assays to assess the KSHV immune response would facilitate research in the field. The ability to systematically map T cell epitopes, soluble immune modulators, and antibody responses is a prerequisite for KSHV-targeted preventive or therapeutic applications. Because KSHV encodes many immune evasion genes, a detailed understanding of the virus and its tumor-intrinsic abilities to manipulate host immune responses would need to be developed to develop a vaccine or immunotherapy-based approaches for KSHV-associated cancer treatment.

Topic 4: The Availability of Clinical Materials and Data for the Study of AIDS-Associated Malignancies

There is a need for access to clinical data associated with well-characterized and phenotyped human subjects with and without cancer, as well as access to biological specimens collected before and after cancer detection. Access to clinical data and specimens will allow key studies on the pathogenesis of AIDS-associated malignancies and on potential biomarkers and outcomes. The Working Group discussed the various venues through which such a unified tissue bank could be developed.

One option is to link to health care systems that have banked clinical samples and patients who already have given consent; the utility of a given specimen, however, would be unknown at the time of collection. Another option is to leverage existing cohorts, such as the combined Multicenter AIDS Cohort Study and Women's Interagency HIV Study (now known as the MACS/WIHS Combined Cohort Study) network, the Veterans Aging Cohort Study (VACS), or Centers for AIDS Research Network of Integrated Clinical Systems (CNICS); the network of global centers for AIDS research (U54 sites) also could be used. The Working Group thought that it would be useful to have access to large cohorts of people living with HIV (PLWH), but the group also understands that the costs of such a large cohort would need to be balanced with respect to other needs and resources required to support AIDS malignancies research as a whole.

Topic 5: Availability of Reagents for the Study of AIDS-Associated Malignancies

The consensus opinion of the Working Group was that it would be useful to consider how to make clinical resources and laboratory reagents (e.g., cell lines) more available to the research community

through a centralized location or database. Although the ACSR currently performs some of these functions, expanded services would greatly benefit the AIDS malignancies research community.

Discussion

In response to a question from Dr. Carol Ferrans about the reasoning behind the Working Group's focus on KSHV, given the number of other oncogenic viruses of concern to PLWH, Dr. Damania stated that many of the Working Group discussions focused on KSHV because it is a key virus associated with HIV. In terms of AIDS-associated malignancies, the Working Group members thought that each oncogenic virus is important to study, especially with regard to obtaining samples and maintaining repositories. The Working Group contained two subgroups, with one focusing on AIDS-associated malignancies and the other focusing on KSHV. Dr. Yarchoan added that the Working Group was established to principally explore two items: (1) the transmission and immunologic control of oncogenic viruses, with a specific focus on KSHV, and (2) biorepositories and collection of specimens. The transmission of human papillomaviruses (HPV) is reasonably well understood, and a vaccine is available. An EBV vaccine currently is in development. By contrast, the research community has been hesitant to explore a KSHV vaccine, and more questions exist about KSHV transmission than other oncogenic viruses. Such questions include: What is the major mode of transmission between or among MSM? What practices in developing countries contribute to transmission? The BSA Subcommittee suggested that the Working Group focus on KSHV because of these knowledge gaps. Dr. Jeffrey Martin added that unless an individual already has developed Kaposi's sarcoma, a good deal of uncertainty exists regarding which individuals are infected with the virus because there is no "gold standard" assay at this time. Knowledge about KSHV is grossly behind the other oncogenic viruses in terms of basic epidemiology. Additionally, Topics 3 and 4 deal with all AIDS-associated malignancies.

Dr. Joel Palefsky asked whether the Working Group had discussed developing resources outside of North America to expand access to specimens from persons with or at risk for HIV-associated malignancies, particularly in sub-Saharan Africa and Latin America. Dr. Damania replied that the Working Group considered the U54 sites chartered in Africa as sources of biospecimens. Dr. Dominguez added that some of these sites have limited amounts of samples. It may be possible to determine what samples are available after the studies at these sites have been completed. The U54 sites, however, were not set up to serve as biorepositories. Dr. Yarchoan noted that the ACSR established a biobank in South Africa; another biobank is in the process of being set up in Latin America.

Dr. Yarchoan thought that it would be helpful to obtain insight from the Subcommittee about balancing the cost of a cohort with the advantages. Dr. Amy Justice reminded the Subcommittee members that the U.S. Department of Defense has a biorepository of blood specimens that can be linked to patients within the U.S. Department of Veterans Affairs (VA) health care system and VACS. Dr. Michael Saag stated that the mission of CNICS is to disseminate specimens and clinical data to as many investigators as possible. The logistics for creating a single portal clearinghouse must be considered, but the pieces are in place to work with other cohorts to share information and specimens. Dr. Palefsky suggested linking with ongoing and planned studies that target high-risk populations for prevention and screening (e.g., ANCHOR [Anal Cancer HSIL Outcomes Research] study or a low-dose computed tomography study of HIV-positive smokers currently being planned). Dr. Justice thought that a staged approach might work. The Subcommittee first could determine what can be done with the data and samples already being collected and then determine how to fill the gaps prospectively or with new efforts. Dr. Martin commented that, in terms of cost, it is important to remember that the cohorts are not being started from scratch, and the Subcommittee is discussing strategic biological sampling that does not cost nearly as much as clinical diagnosis and treatment within the cohorts.

Dr. Yarchoan summarized that the two options he identified in the discussion are to link to current and planned cohorts and/or to connect with health care systems to collect samples prospectively that otherwise would not be collected. A Subcommittee member commented that the MACS/WIHS Combined Cohort Study alone will not provide enough cancer cases for a robust study. The cohort selected will need to be large, much like CNICS, the VA system, or Kaiser Permanente. Dr. Justice added that these large cohorts could identify high-risk groups that could be followed with serial sampling. Another Subcommittee member asked whether this approach would be very focused on a specific cancer. Dr. Dominguez reassured the committee that it would not, and added that the NCI supports the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD), of which CNICS, the VA system, Kaiser Permanente, and the MACS/WIHS Combined Cohort Study are a part. NA-ACCORD has validated HIV treatment outcomes and cancer data¹. However, the ability of the cohorts to collect specimens is variable. Targeting larger cohorts will be more efficient, and the information would be able to be more standardized. Mr. Jeff Taylor explained that the Last Gift Study at the University of California, San Diego is planning on expanding its cohort and is another resource to consider. With regard to the initial suggestion of the Working Group that HIV-malignancy and other cancer researchers be encouraged to work together, the Subcommittee amplified this suggestion and suggested that the NCI develop funding opportunities to encourage these collaboration, as they have done this in the past and they were felt to be successful.

Recommendations

1. The consensus opinion from the group was to organize a KSHV symposium focused on current knowledge gaps regarding KSHV transmission and host immune responses to KSHV. Such a symposium could prompt the scientific community to share its research and perspectives to determine the best next steps. The symposium also could encourage the community to consider issues related to the development of a KSHV vaccine, including the need for and the economics and practicality of such a vaccine. The conference should include stakeholders (e.g., Bill and Melinda Gates Foundation) that might play a role in helping to fund the development, testing, and delivery of such a vaccine.
2. Obtaining precancerous samples of blood or other tissues may assist in the translation of AIDS malignancy research from basic science to clinical outcomes. The committee identified a need to assist the ACSR in collecting additional non-AIDS-defining, HIV-associated cancer samples and to evaluate new mechanisms and standard operating procedures for tumor specimen distributions. The scientific value of collecting samples from a large cohort should be weighed against the cost of establishing large infrastructures. Leveraging existing clinic-based cohorts (e.g., MACS/WIHS Combined Cohort Study, CNICS, VACS) to establish a virtual HIV malignancy cohort would be a useful approach for NCI to consider.
3. Another need is to develop methods to communicate across scientific disciplines to facilitate basic and translational science in the AIDS-associated malignancies research community. In the past, investigator-initiated research by a large scientific community has contributed significantly to the understanding of AIDS malignancies. Maintaining an active community and diversified approaches should remain a priority.

Discussion

Dr. Damania confirmed for a Subcommittee member that Recommendation 2 would be expanded beyond KSHV.

The Subcommittee members discussed the feasibility of collecting throat washings in a large cohort and determine whether saliva samples most likely would be sufficient. Cervical, vaginal, and analysis samples

are not difficult to obtain and could be included. Oral brush samples would be useful as well and are collected routinely in nasopharyngeal cancer cases. Samples are not applicable to cancer only; HIV researchers investigating a variety of end-organ noncommunicable diseases may be interested. The NCI, therefore, may not be the only NIH Institute interested in funding this effort. Dr. Yarchoan thought that other Institutes, particularly National Heart, Blood, and Lung Institute (NHLBI), might be interested in collaborating on the cohort project. Dr. Justice suggested designating certain risk groups that "travel together." For instance, the NHLBI might be approached about diabetes and obesity and the cancers associated with these conditions. NIH Institutes that might be interested are those seeking mechanistic insights that are generalizable outside of HIV infection.

Dr. Yuan Chang observed that the need to develop methods to communicate across research and clinical communities is included in Recommendation 3 and may not need to be identified as a specific gap for KSHV in Recommendation 1. A symposium focusing on more than KSHV would be beneficial.

The Subcommittee reached consensus on Recommendation 1, with the amendment that the symposium would be enhanced by the inclusion of individuals outside of the field who can provide additional insight (e.g., HPV vaccine developers). The Subcommittee reached consensus on Recommendation 2, with the clarification that it is broadly applicable to all AIDS-associated malignancies and not focused on KSHV specifically. The Subcommittee reached consensus on Recommendation 3, with the addition of targeted language about specific mechanisms to encourage collaboration between HIV-malignancy researchers and other cancers researchers (e.g., requests for proposals that require cross-discipline cooperation).

Other Items of Discussion

Dr. Blossom Damania

Dr. Yarchoan explained that part of the dialogue between NCI and NIH's Office of AIDS Research (OAR) involves the funding of areas, particularly in the basic sciences, that involve HIV- and non-HIV-related issues. Beginning in fiscal year 2021, OAR will consider projects, proposals, or RFAs that include research areas that encompass HIV- and non-HIV-related issues (e.g., EBV).

Adjournment

Dr. Robert Yarchoan

Dr. Yarchoan thanked Joy Wiszneaukas, who stayed beyond the early dismissal of NCI employees for the holiday weekend to attend the teleconference. Dr. Damania thanked the Subcommittee members for their participation. The recommendations will be revised based on the discussion, and Joy Wiszneaukas will distribute the revised recommendations to the members. Dr. Damania adjourned the teleconference at 4:57 p.m. EDT.

B. Damania
Dr. Blossom Damania
Chair

6/20/2019
Date

R. Yarchoan
Dr. Robert Yarchoan
Executive Secretary

6/20/2019
Date