NCI Board of Scientific Advisors

***Ad hoc* Working Group on Immunology of Therapies & Vaccines and Research Structure**

Final Working Group Report

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NATIONAL CANCER INSTITUTE
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***Ad hoc* Working Group on Immunology of Therapies & Vaccines and Research Structure**
ROSTER

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Background

At the last meeting of the BSA *ad hoc* Subcommittee on HIV and AIDS Malignancy on June 21, 2017, it was proposed that two working groups be created, one to further discuss issues related to oncovirus transmission, immune responsiveness, and vaccine development, and the other to discuss research infrastructure for HIV malignancies. With regard to the first, the subcommittee had noted that the transmission of KSHV was particularly poorly understood and that the development of a KSHV vaccine could be highly beneficial but that there were some barriers; they asked the working group to specifically consider these issues as they pertained to KSHV. It was decided that forming two working groups would be unwieldy, and a decision was made to form one working group to consider both issues. A BSA *ad hoc* Working Group on Immunology of Therapies & Vaccines and Research Structure was formed.

Charge to the Working Group

The purpose of this ad hoc Working Group was to provide further discussion and prioritization of the immunological aspects of developing therapeutic and preventative therapies and vaccines for virus-induced malignancies; understanding the interactions between the immune system and oncogenesis in tumor development; and understanding transmission of oncogenic viruses that cause HIV malignancies, especially Kaposi sarcoma-associated herpesvirus (KSHV) and ways that the research infrastructure for AIDS-associated malignancies could be enhanced. The Working Group was tasked with providing their recommendations to the NCI Board of Scientific Advisors (BSA) and the *ad hoc* Subcommittee on HIV and AIDS Malignancy.

In terms of the immunological aspects, oncogenesis, and understanding the transmission of oncogenic viruses, some of the following issues were to be discussed and prioritized: identifying public health measures to reduce transmission; predicting immunologic responders and utilizing immune responses to prevent disease and transmission; identifying target populations for vaccines; and the potential for leveraging established methods used for the HPV vaccine. The discussion and prioritization activities were also to be centered around several factors that are needed to continue to support and sustain the general infrastructure for AIDS-associated malignancy research while also addressing disparities in the HIV-infected population related to social determinants of health. Such factors included some of the following: analyzing the immune approaches to viruses associated with cancer; the need for mechanisms to fund ongoing cohorts to collect, standardize, and store specimens; and the need for mechanisms to optimally coordinate cancer trials. The resulting recommendations of the Working Group will seek to advance the NCI's research portfolio in AIDS and HIV-associated malignancy.

Functioning of the Working Group

Dr. Blossom Damania (chair), convened two meetings of this Working Group on June 13, 2018 and November 8, 2018 via conference calls. One call focused on oncogenic virus infections. As recommended by the BSA *ad hoc* Subcommittee on HIV and AIDS Malignancy, a substantial amount of this discussion focused on KSHV. The other call focused on the organization and collection of biospecimens of all HIV-associated cancers (these included both viral and non-viral

cancers). Creation of a collection of biospecimens from all HIV-infected individuals with and without cancer was considered to be highly desirable.

The working group summarized their deliberations into five key summary topics and proposed several recommendations for consideration. The summary topics and proposed recommendations were discussed at a teleconference of the BSA *ad hoc* Subcommittee on HIV and AIDS Malignancy on May 24, 2019 and they were accepted with some clarifications and modifications.

Summary Topics

1: Research on Transmission and Biology of Initial KSHV Infection

The discussion centered around the differences in KSHV transmission rates between developed and developing countries. In the United States, the prevalence is low in the general population but high among men who have sex with men. In Africa, the prevalence is high in the general population and transmission begins in childhood. The explanation for this difference in prevalence across geographical areas is not well understood. It may be because of behavioral practices, host immune responses or possibly strain differences in the viral genome. The role of the immune response, including the role of neutralizing antibodies, in influencing transmission is not well understood in any of these affected populations. The differences in prevalence across geographical areas are not well understood and could be attributed at least in part to the differences in the mode of transmission. *It was felt that there was a great need to address the gaps in our knowledge about KSHV transmission.*

2: Feasibility of a Vaccine for KSHV

The topic of creating a KSHV vaccine was a major part of the discussion. There was interest in developing a KSHV vaccine as it was felt it would be beneficial to certain high-risk populations such as in Africa or for persons with an expectation of immune suppression, e.g. in the organ transplant settings. Comparisons to the vaccine development of EBV were made. However, the feasibility and economic model for such a vaccine is unclear. *It was felt that there was a great need to better understand KSHV transmission and the immune response to KSHV infection in order to consider the likelihood of success and to design an efficacious vaccine.*

3: Research on Immunologic Control of Oncogene Virus Infection

It was felt 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. Since KSHV encodes many immune evasion genes, a detailed understanding of the virus and KS tumor-intrinsic abilities to manipulate host immune responses would need to be manipulated in order to make a vaccine or develop immune-therapy-based approaches for KSHV- associated cancer treatment.

4: The Availability of Clinical Materials and Data for the study of HIV associated malignancies

There is need for access to clinical data associated with well-characterized and phenotyped human subjects with and without cancer and to biological specimens collected before and after cancer detection. This will allow for key studies on the pathogenesis of HIV associated malignancies and on potential biomarkers and outcomes. This would require specimens obtained prior to the development of tumors and then access to actual tumor specimens. Members queried whether the ACSR can support precancerous biospecimens as well as the logistics of procuring these specimens. Members discussed resources that could be used in part to aid in this effort. Currently, the ACSR is a repository that stores, catalogs, and disseminates samples from clinical trials (e.g., AIDS Malignancy Consortium) but it is not charged to actively design and set up infrastructures to procure specimens prospectively. As HIV malignancies are a global phenomenon, many of the tumor specimens can most easily be obtained in areas of high HIV prevalence. One option to obtain more samples would be to link to health care systems with banked clinical samples and patients who have already given consent for prospective sampling. The utility of a given biospecimen would be unknown at the time of collection.
Another would be to leverage existing cohorts, such as the combined Multicenter AIDS Cohort Study (MACS)/Women's Interagency HIV Study (WIHS) network, the Veterans Aging Cohort Study (VACS), and/or the Centers for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS) or to utilize the network of global centers for AIDS research (U54 sites). The North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) collects longtitudinal data on the aforementioned HIV-infected cohorts and could also be harnessed for epidemiological studies.

Through electronic medical records, several health care systems are already following and documenting the clinical course (including the development of cancer) of many HIV-infected patients throughout the U.S. Examples include the Veterans Aging Cohort Study (VACS), the Centers for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS), and the Kaiser system. These systems could be leveraged by adding standard interval biological specimen collection (e.g., annual blood draw). Some systems, such as CNICS, have already consented patients for regular blood draw for research but lack resources for implementation. It was noted that the size of the cohort of HIV-infected people that would be needed to study any particular cancer would vary according to the cancer. This is because the incidence of cancer is measured in the realm of 100,000 person-year units. Hence access to these large cohorts would be ideal and would reduce costs.

However, other cohorts used to study HIV infection (e.g., the Multicenter AIDS Cohort Study (MACS) and the Women's Interagency HIV Study (WIHS), which are smaller cohorts could also be accessed to reduce costs. Access to specimens from cohorts would allow for identification of biomarkers in high-risk populations and allow for data and outcomes to be measured over time. The Working Group thought it would be useful to have access to large cohorts of HIV-infected individuals but the Working 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 HIV malignancies research as a whole.

5: Availability of Reagents for the study of HIV associated malignancies

The consensus opinion was that it would be useful to consider how to better make clinical resources and laboratory reagents (cell lines, etc.) available to the research community through a centralized location and/or database. There is also a need to generate new reagents, e.g. antibodies and RNA detection probes. While the ACSR does include some cell lines, there is currently no central repository of other laboratory reagents for HIV-malignancy research. The development of novel, and much needed new therapies for AIDS malignancies is crucially dependent on such reagents.

Final Recommendations

The Board of Scientific Advisors *Ad Hoc* Subcommittee on HIV and AIDS Malignancy accepted the recommendations of the Working Group with some modifications and clarifications. The final recommendations based on input from the *ad hoc* Subcommittee are as follows:

1: The consensus opinion from the group was to organize a KSHV symposium focused on gaps in our current knowledge on KSHV transmission and host immune responses to KSHV. It was felt that such a symposium would induce the scientific community to share their research and perspectives in order to determine the best next steps in the field. It could also consider issues related to the development of a KSHV vaccine, including the need, economics, and practicality of such a vaccine. The conference should include stakeholders, scientists from outside the discipline, as well as organizations like the Gates Foundation, that might play a role in helping to fund the development, testing, and/or delivery of such a vaccine.

2: Obtaining cancer biospecimens from HIV-infected individuals is important to advance scientific research in all HIV-associated malignances. This includes both viral associated cancers as well as non-viral associated cancers in the HIV infected population. It was also felt that 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 felt that there was a need to assist the AIDS and Cancer Specimen Resource (ACSR) in collecting additional non-AIDS defining, HIV-associated cancer samples and evaluate new mechanisms and standard operating procedures (SOPs) for tumor specimen distributions. The scientific value of collecting samples from a large cohort should be weighed against the cost of establishing large infrastructures. Leverage existing clinic-based cohorts—such as the MACS, WIHS, CNICS, and VACS—to establish a virtual HIV malignancy cohort would be a useful approach for NCI to consider. Linkage with NA-ACCORD was also felt to be beneficial.

3: Individual investigator-initiated research within the HIV malignancy field has contributed significantly to our understanding of HIV-associated cancers. The group felt there was a need to develop strategies to communicate across scientific disciplines to facilitate basic and translational research in the community. Targeted funding opportunities that bolster cross-disciplinary research were felt to be important. For example, NCI has previously issued several such RFAs (e.g. the link between HIV, cancer, and aging), which helped stimulate new research frontiers and advanced our understanding of HIV malignancies. The issuance of such targeted opportunities was thought to be a priority to bolster an active research community that uses diversified approaches to understanding HIV-associated cancers.