NCI Board of Scientific Advisors (BSA)
Ad hoc Subcommittee on HIV and AIDS malignancies

Working Group on Immunology of Therapies & Vaccines, and Research Structure

June 10, 2019
Cancer is one of the leading causes of death in HIV+ individuals in North America

- AIDS defining cancers (ADC) and non-AIDS defining cancers (NADC) combined, kills more HIV-infected individuals on antiretroviral therapy (ART) compared to any other cause. *(Silverberg et al. 2015; Gill et al. 2010)*

**AIDS-defining cancers continue to remain a problem in the HIV infected globally**

- Although rates have declined since the early days of the HIV epidemic, KS and NHL, continue to remain a great problem globally, and KS is the leading cause of cancer in sub-Saharan Africa.

- For example, in Malawi, KS is the leading cancer overall accounting for 34% of all malignancies recorded in the national cancer registry *(Host et al. 2017)*. This is a combination of both HIV-related KS and endemic KS in the region

- KS is now seen in HIV+ individuals on ART with CD4 counts >300 in the U.S. *(Krown et al. 2008)*
Kaposi’s Sarcoma

• Caused by KSHV infection
• A common malignancy in individuals with HIV/AIDS
• Most common tumor in men in areas of sub-Saharan Africa
• >44,000 new cases/year and 27,000 deaths/year
HIV infection is associated with a higher risk of many cancers in the elderly in the U.S. *(Yanik et al. AIDS 2016)*

Excess and increasing incidence over time for non-AIDS defining cancers in the U.S. *(Shiels et al. J Natl Cancer Inst. 2011; Robbins et al. JNCI 2015)*
NCI BSA Subcommittee on HIV and AIDS malignancies

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Specific recommendations for research on malignancies in the HIV-infected population. The areas described below were deemed to be of particular high priority.

- Kaposi sarcoma associated herpesvirus (KSHV)-associated cancers
- Non-Hodgkin lymphoma (NHL), Hodgkin disease (HD), and EBV-associated cancers
- Human papillomavirus (HPV)-associated cancers
- Liver Cancer including hepatitis C (HCV) and hepatitis B (HBV)-related cancers
- Non-AIDS defining cancers (NADC)
- Addressing disparities in the HIV-infected population related to social determinants of health
- International Efforts
- General Infrastructure
At the BSA Subcommittee on HIV and AIDS Malignancy it was proposed that two working groups be created to address gaps in our knowledge:

1) One Working Group to discuss issues related to oncogenic virus transmission, immune responsiveness, and vaccine development

2) A second Working Group to discuss research infrastructure for HIV-associated malignancies.

Subsequently, 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 (WG) on Immunology of Therapies & Vaccines and Research Structure was formed
Immunology of Therapies & Vaccines and Research Structure WG Members

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**Charge to the Working Group**

The Working Group was tasked with providing their recommendations to the NCI Board of Scientific Advisors (BSA) and the Subcommittee on HIV and AIDS Malignancy.

The purpose of this Working Group was to prioritize:

(i) Immunological aspects of developing therapeutic and preventative therapies and vaccines for virus-induced malignancies seen in the context of HIV infection

(ii) Understanding the interactions between the immune system and oncogenesis in tumor development

(iii) Understanding transmission of oncogenic viruses that cause HIV malignancies, especially Kaposi’s sarcoma-associated herpesvirus (KSHV)

(iv) Ways that the research infrastructure for AIDS-associated malignancies could be enhanced.
Functioning of the Working Group

The chair convened two meetings of this Working Group on June 13, 2018 and November 8, 2018 via conference calls.

(i) One call focused on oncogenic virus infections. As recommended by the BSA Subcommittee on HIV and AIDS Malignancy, a substantial amount of this discussion focused on KSHV.

(ii) The second 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.
Working Group Discussion Topics

1) Research on Transmission and Biology of Initial KSHV Infection
The consensus opinion was that there was a great need to address the gaps in our knowledge about KSHV transmission.

2) Feasibility of a Vaccine for KSHV
In order to consider the likelihood of success and to design an efficacious vaccine, there was a need to better understand KSHV transmission and the immune response to KSHV infection.

3) Research on Immunologic Control of Oncogene Virus Infection
Cross-disciplinary approaches are needed to advance the field. An initiative to generate reagents and assays to assess immune responses to oncogenic virus infection would facilitate research in the field.

4) Availability of Clinical Materials and Data for the study of all HIV-associated malignancies
It would be useful to have access to large cohorts of HIV-infected individuals. 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.

5) Availability of Reagents for the study of all HIV-associated malignancies
The consensus opinion was that it would be useful to consider how to improve access for clinical resources and laboratory reagents and make them available to the research community through a centralized location and/or database.
KSHV transmission:
- In endemic areas like Africa, much of acquisition is believed to occur during childhood by salivary exchange. It is unclear what specific practices are responsible for its spread.
- In non-endemic areas, sexual transmission appears to be the primary route for transmission.
- In the U.S. and Europe, KSHV seroprevalence and the incidence of new infection is still substantially higher among men who have sex with men (MSMs) as compared to the rest of the population.

KSHV vaccine:
- If a sterilizing vaccine were developed, it could prevent all KSHV-associated tumors and other diseases.
- However, there are questions about feasibility and practicality as no sterilizing vaccine has been successfully developed against a gammaherpesvirus.
- Additionally, most places where KSHV is highly prevalent have limited resources for health care.

Research approaches:
- Cross-disciplinary research efforts to systematically map T cell epitopes, soluble immune modulators, and antibody responses to oncogenic virus infection were considered important.
Working Group Discussion #2 (Research Structure)

Topics #4, 5

Clinical Materials and Data for the study of all viral and non-viral HIV-associated malignancies:
- There is need for access to clinical data associated with well-characterized human subjects with and without cancer, and to biological specimens collected before and after cancer detection.
- 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.
- Another option 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), 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).

Reagents for the study of all viral and non-viral HIV-associated malignancies:
- Improve making 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 AIDS Cancer Specimen resource (ACSR) does include some specimens and cell lines, there is currently no central repository of other laboratory reagents for HIV-associated malignancy research.
# Working Group Recommendations

#1) Among oncogenic viruses, the transmission of KSHV was felt to be the most poorly understood.

- Organize a symposium on KSHV focused on gaps in our current knowledge on KSHV transmission and host immune responses to KSHV. The symposium would also consider the pros, feasibility, and barriers to developing a KSHV vaccine.

#2) Obtaining cancer biospecimens from HIV-infected individuals is important to advance scientific research in all HIV-associated malignances.

- Need for NCI to establish a biorepository of specimens from HIV patients who would then be followed for the development of cancer. One approach may be to explore and leverage existing clinic-based cohorts such as the MACS-WIHS, CNICS, VACS, U54 sites.

#3) Individual investigator-initiated research within the HIV malignancy field has contributed significantly to our understanding of HIV-associated cancers.

- Targeted funding opportunities that bolster cross-disciplinary research were felt to be important to stimulate new research frontiers and advance our understanding of HIV malignancies.