Proposal for a New RFA

Translational Research Toward Development of a Kaposi Sarcoma Herpesvirus (KSHV) Vaccine

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NIH NATIONAL CANCER INSTITUTE

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Purpose of RFA

To support basic and translational research that will guide the development of a preventive and/or therapeutic Kaposi sarcoma herpesvirus (KSHV) vaccine, with the goal to prevent, attenuate, and/or treat Kaposi sarcoma (KS) and other KSHV-associated diseases

Background

Four KS Types epidemiologically:

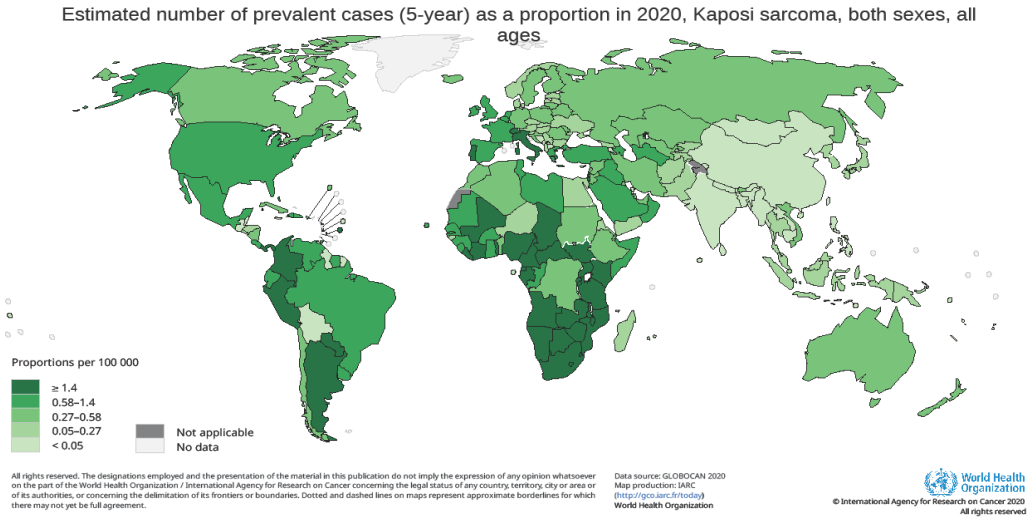
- *Classic KS:* Typically affects elderly men of Mediterranean descent
- *Endemic KS:* Primarily in central and southeast Africa; aggressive
- *Iatrogenic/immunosuppression-associated KS:* Transplant patients
- *Epidemic KS (AIDS-related KS):* One of the most common HIV-associated tumors in the US, and the most common in Africa
  - Often involves lymph nodes and visceral organs

Background (Cont.)

- KSHV (also called human herpesvirus 8) discovered in 1994, is the causative agent of Kaposi sarcoma and 4 other tumors or severe diseases:
  - Primary effusion lymphoma (PEL)
  - Multicentric Castleman disease (KSHV-MCD)
  - Lymphoma associated with KSHV-MCD
  - KSHV inflammatory cytokine syndrome (KICS)

Prevalence of Kaposi Sarcoma

One year proportion per 100,000 both sexes



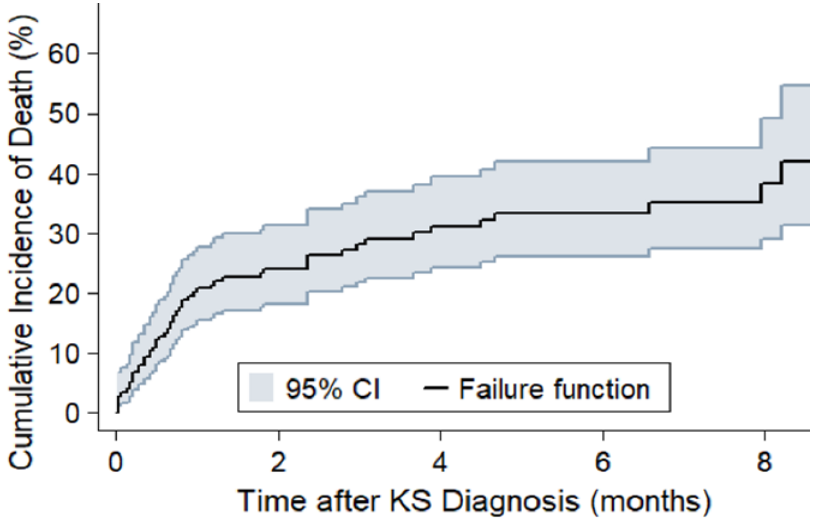
Globocan 2020

Kaposi Sarcoma

- A common malignancy in individuals with HIV/AIDS
- Caused by KSHV
- >90 % of cases in low- and middle-income countries (LMICs)
- KS is a frequent cause of morbidity and mortality in sub-Saharan Africa
- Most common tumor overall in men <65 years of age in some countries in sub-Saharan Africa

Continued High Mortality in Adults with HIV-KS in East Africa

- Patients with HIV-KS continue to have a very high mortality rate in East Africa even in the age of combination anti-retroviral therapy (cART)
- This study by Jeff Martin and colleagues followed 180 adults with newly diagnosed HIV-KS in Kenya and Uganda
- 95% of the patients were taking cART, and the median CD4 count was 197 cells/μL
- **33% mortality at 6 months**



*Byakwaga, H. et al. (2022) A Contemporary Update on Disease Stage at Diagnosis and Survival Among Adults with HIV-Associated Kaposi Sarcoma in East Africa. Poster presented at the *International Conference in Malignancies in HIV* October 24-26, 2022

KSHV Seroprevalence and Incidence of KS & KSHV-related Diseases

- In sub-Saharan Africa, children infected early in life, and some countries have an 83% prevalence by age 19
- In North America and most of Europe, overall seroprevalence is low (< 5%), but higher in men who have sex with men (MSM) and persons from endemic areas
- In the US, KSHV seroprevalence is 30-65% in HIV^+ MSM and 20-30% in HIV^- MSM
- Incidence of KS in US PWH is decreasing with combination antiretroviral therapy (cART). However, incidence is increasing in young black men in the south
- In parts of Africa (e.g. Malawi), incidence of KS remains high even after widespread use of cART. Also, KSHV-related multicentric Castleman disease has been found to represent 10-15% of all lymphoproliferative diseases in PWH in Malawi
- Classical KS is primarily a disease of the elderly, and the HIV-infected population is aging in the US. There are concerns that we may see an increase in KS as both HIV+ **and HIV-** MSM with KSHV infection age

KSHV Transmission

- KSHV is often found in oral fluids and *evidence to date indicates that this is the main route of spread.* However, many questions remain regarding principal modes of transmission
- In endemic areas such as Africa, acquisition primarily occurs during childhood
- In non-endemic areas, sexual transmission appears to be the primary route and occurs particularly in MSM
- The role of heterosexual transmission remains inconclusive and appears to vary in different parts of the world

Investigation of the Transmission of KSHV RFA-CA-18-013 and RFA-CA-20-046

- Nine R01 grants awarded
- The goal of the RFA was to advance our knowledge of KSHV transmission. Areas of research addressed in funded grants included:
  - Understanding the initial steps in KSHV infection of individuals and the biologic factors protecting against such infection
  - Identification of the characteristics of the initial immune response to KSHV in children/adults that may thwart establishment of infections
  - Identification of the principal modes of KSHV transmission in high-risk groups in the US and in LMIC
  - Understanding the behavioral, environmental, or genetic risk factors for KSHV transmission in endemic and/or non-endemic areas

NCI BSA Subcommittee on HIV and AIDS Malignancy

- **2017**
  - A need for both a better understanding of KSHV transmission and of the immune responses to KSHV infection
  - This information could help inform the development of a KSHV vaccine
- **2018-2019 NCI BSA Ad hoc Working Group: Immunology of Therapies and Vaccines**
  - Recommended further exploration of the feasibility and potential approaches to developing a vaccine against KSHV

This recommendation was enthusiastically endorsed by the BSA Subcommittee and then the BSA

October 2021: Virtual Kaposi Sarcoma-Associated Herpesvirus (KSHV) Vaccine Workshop

State-of-the-science workshop:

- Included expertise across the spectrum of HIV, oncology, virology, vaccinology and immunology
- Discussed the potential benefits and feasibility of developing a vaccine against KSHV
- Discussed gaps in knowledge regarding KSHV transmission, epidemiology, and immunity to herpesviruses
- Lessons learned from vaccine development to other viruses (including ongoing work developing an EBV vaccine)
- Discussions on the challenges in vaccine development, formulation, testing and implementation

October 2021: Virtual Kaposi Sarcoma-Associated Herpesvirus (KSHV) Vaccine Workshop (continued)

Consensus view:

While there may be challenges in developing and implementing a KSHV vaccine, the public health benefits make it a worthwhile endeavor at this time

The meeting was open to the public and a state-of-the-science paper was generated:

- KSHV (HHV8) Vaccine: Promises and Potential Pitfalls for a New Anti-cancer *Vaccine.* Casper C, Corey L, Cohen JI, Damania B, Gershon AA, Kaslow DC, Krug LT, Martin J, Mbulaiteye SM, Mocarski ES, Moore PS, Ogembo JG, Phipps W, Whitby D, Wood C. NPJ *Vaccines*. 2022 Sep 20;7(1):108

Scope and Expectations of RFA

- Research to better define the initial steps of infection with KSHV and the primary means of person-to-person transmission in different populations that can be targeted with a vaccine
- Identification and evaluation of KSHV structural and non-structural targets for a potential KSHV vaccine
- Development of animal models to study a prototype KSHV vaccine or vaccines
- Development and testing of a candidate KSHV vaccine or vaccines
- Studies to assess how the efficacy of a promising KSHV vaccine can be optimized for people with HIV
- Optimization and/or standardization of KSHV detection methods

The overall goal is to expand the research scope and leverage the gains made through the "Investigation of the Transmission of KSHV" RFA, to support basic and translational research that will guide the development of a preventive and/or therapeutic KSHV vaccine

Portfolio Analysis

- Two active research project grants (NIAID and NIDCR funded) that specifically address KSHV vaccine development
- Currently (FY2021, FY2022), the NCI has 56 funded grants that in some way address KS or KSHV/HHV-8, nine of which have been funded through the *"Investigation of the Transmission of KSHV"* RFA
- Six NCI funded grants address issues such as KSHV virology, early infection, KSHV pathogenesis and development of animal models that could potentially be important in vaccine development
- Other ICs in the NIH portfolio fund approximately 17 grants that in some way address KS or KSHV/HHV-8. It is notable that this is a >50% reduction of investment in KS or KSHV/HHV-8 research at other NIH I/Cs when compared to our portfolio review of FY2015 and 2016

Budget

- $3 Million is requested for each of two receipt dates
- $15 Million overall requested for 5 years for each of two receipt dates ($30 million total)
- Support of 3-4 U01s for each of two receipt dates
- Funds will come from our AIDS budget received through the NIH Office of AIDS Research (OAR). (It has been reviewed by the OAR and deemed AIDS-aligned)
- A U01 mechanism is being proposed:
  - Breadth of interest and complexity of the scope of science that needs to be catalyzed through this initiative
  - International partnerships in low- and middle-income countries will be facilitated by program engagement to optimize success

Questions

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