Proposal for a New RFA

Investigation of the Transmission of Kaposi Sarcoma-Associated Herpesvirus (KSHV)

OHAM, DCP, DCCPS, DCB and NIDCR

NIH NATIONAL CANCER INSTITUTE

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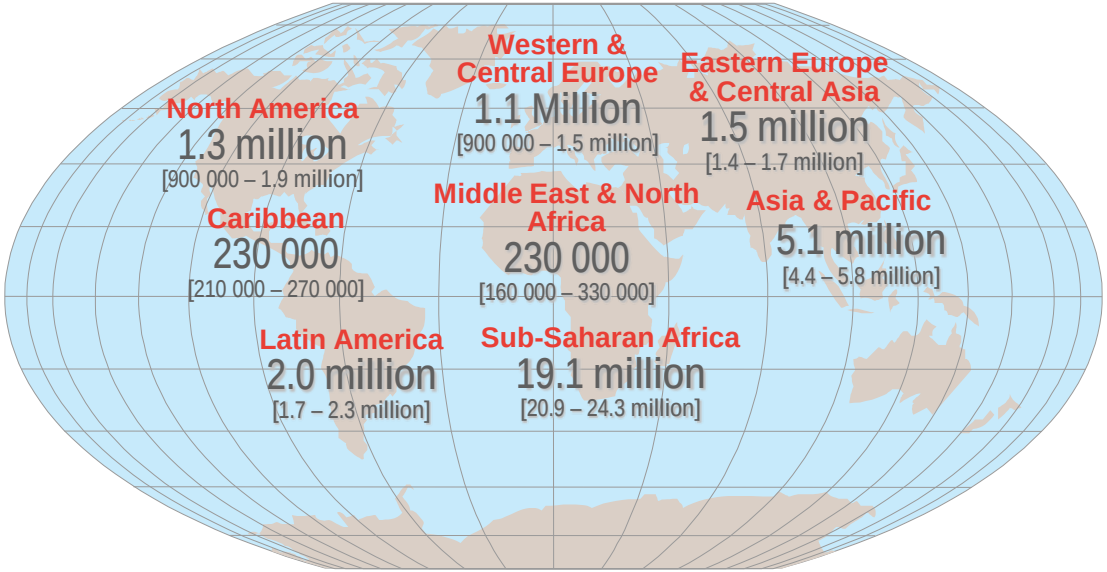
Purpose of RFA

Enhance our understanding of the modes of transmission of KSHV, also called human herpesvirus-8 (HHV-8), with the overall goal of preventing KSHV infection and thus preventing Kaposi sarcoma, KSHV-associated multicentric Castlemen's disease, primary effusion lymphoma, and other KSHV-induced diseases in populations living with HIV or at high risk of developing HIV

Adults and children estimated to be living with HIV, 2015



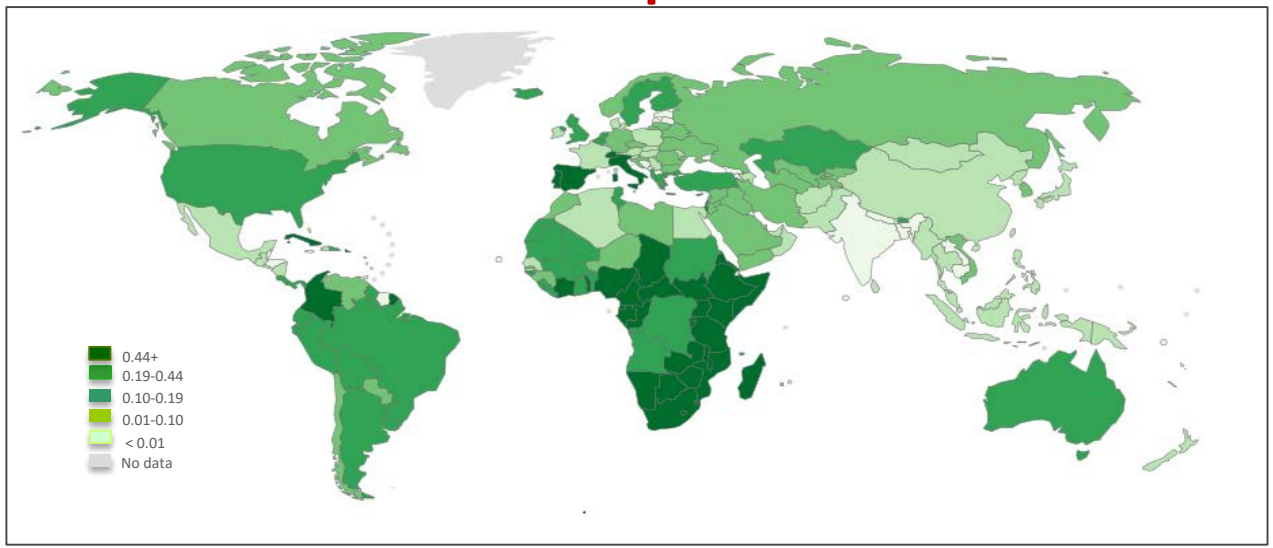
- 2.1 million new cases/year
- ~50% women
- ~90% in low- and middle-income countries (LMICs)
- 1.1 Million deaths/year

Total: 36.7 (34 – 39.8) million

December 2016

Prevalence of Kaposi Sarcoma

One year proportion per 100,000 both sexes



Globocan 2012

Kaposi Sarcoma

- A common malignancy in individuals with HIV/AIDS
- Caused by KSHV
- 44,000 new cases /year.
- Most common tumor in men in areas of sub-Saharan Africa
- 27,000 deaths/year
- > 90 % of cases in low and middle income countries (LMICs)

Background

Four KS Types:

- *Classic KS:* Typically affects elderly men of Mediterranean descent
- *Endemic KS:* Primarily in Sub-Saharan Africa (SSA)
  - Lymphadenopathic KS, primarily in children under 10
  - Cutaneous KS, young adults, primarily men
- *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 SSA
  - Often involves lymph nodes and visceral organs

Background (Cont.)

- KSHV, discovered in 1994, is the causative agent of 3 principal tumors:
  - Kaposi sarcoma (KS)
  - Multicentric Castleman disease (KSHV-MCD)
  - Primary effusion lymphoma (PEL)
- KSHV is also associated with:
  - KSHV inflammatory cytokine syndrome (KICS)
  - Lymphoma associated with KSHV-MCD

KSHV Seroprevalence and KS Risk

- In sub-Saharan Africa, there is a 30% prevalence of KSHV by age 9, and some countries have an 83% prevalence by age 19
- In North America and most of Europe, overall seroprevalence is low (< 10%), but higher in men who have sex with men (MSM) and persons from endemic areas
- In the United States, KSHV seroprevalence is 30-60% in HIV^+ MSM and 20-30% in HIV^- MSM
- Incidence of KS in US HIV+ persons is decreasing with combination antiretroviral therapy (cART). However, in parts of Africa (e.g. Malawi), incidence of KS remains high even after widespread use of cART
- 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

- While KSHV can be detected in blood and occasionally in semen, it is frequently secreted in saliva and *evidence to date indicates that this is the main route of spread*
- However, nearly 25 years after the identification of KSHV, the predominant modes of KSHV transmission, the biology of the initial steps of infection, and risk factors for infection are still not well understood
- There is epidemiologic evidence that the predominant modes of KSHV transmission vary in different parts of the world

KSHV Transmission

- In endemic areas such as in SSA, acquisition primarily occurs during childhood and is believed to occur primarily by saliva exchange. However, it is unclear as to which specific practices are most responsible for its spread
- In non-endemic areas, sexual transmission appears to be the primary route for transmission. For reasons that are not entirely clear, KSHV seroprevalence and the incidence of new infection is substantially higher among MSM as compared to the rest of the population. The practices most responsible for this may include deep kissing, oral-anal sex, or use of saliva as a lubricant; the relative importance of these is unclear
- The role of heterosexual transmission remains inconclusive and appears to vary in different parts of the world

KSHV Prevention

- If KSHV infection could be halted, it would prevent the development of KS and other KSHV-related diseases
- While logical and desirable, there are some impediments to the development of a KSHV vaccine, including the potential difficulties in developing a gammaherpesvirus vaccine and concerns about a lack of economic incentives. There is currently no active program to develop a KSHV vaccine
- The spread of KSHV can potentially be reduced through public health measures aimed at blocking the most important routes of transmission. However, such guidance is hindered by uncertainties regarding the principal routes of spread
- Also, public health monitoring of KSHV infection is hindered by the lack of an FDA-approved or gold standard serological assay to accurately diagnose KSHV infection

Special KS and KSHV Focus Session

International Conference on Malignancies in AIDS & Other Acquired Immunodeficiencies (2015)

Concluded:

- There are key areas of continued uncertainty regarding the principal routes of KSHV transmission
- While public health measures to prevent KSHV infection are a promising approach to reduce the spread of KSHV, the ability to make such recommendations, either among MSM in the United States or in SSA or other resource-limited regions, is hindered by the uncertainties regarding the principle routes of spread

2017 NCI BSA Subcommittee on HIV and AIDS Malignancy

Subcommittee members agreed there was:

- A need for better understanding of KSHV transmission in various populations
- A need for better understanding the immune responses to KSHV infection

Additionally:

- Information about transmission and the immune response to KSHV could help inform the development of a KSHV vaccine
- Lessons learned from development of other gamma herpesvirus vaccines (EBV) could inform potential KSHV vaccine development

Scope and Expectations of RFA

- The goal of the RFA is to advance our knowledge of KSHV transmission. Research can include:
  - Development of robust diagnostic serological assay(s) for KSHV that improve upon or simplify existing serological assays
  - 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

The ultimate goal is to inform strategies to prevent KSHV transmission

Portfolio Analysis

- Currently (FY2015, FY2016), the NCI has 59 funded grants that in some way address KS or KSHV/HHV-8. Most address basic virology, and only two (from the same PI) address issues regarding KSHV transmission in sub-Saharan Africa
- To the best of our knowledge, no current NCI funding is supporting questions regarding transmission and behavioral risk factors in the MSM population in the US
- Other ICs in the NIH portfolio fund approximately 39 grants. Again, most are focused on basic virology. Only one population-based grant from NIDCR in sub-Saharan Africa is addressing mucosal immunity to KSHV
- An FY 2017 NIH-wide search identified 8 applications related to KSHV transmission, and of the ones proposed to be paid, none were within the scope of this RFA
- In order to address the nuanced nature of the scope and expectations of this FOA, areas of research outside the scope of the FOA will be clearly identified

NIH Office of AIDS Research (OAR)-Designated Funds

- NIH HIV/AIDS Research Priorities and Guidelines for Determining AIDS Funding (NOT-OD-15-137)
- Mandates that AIDS funds can only be used for research addressing “high” or “medium” priority areas of AIDS research
- OAR-supported HIV-malignancy research is largely restricted to projects that either involve studies in HIV^+ patients; studies of a specific role of HIV in oncogenesis; or studies of tumors from patients with HIV-infection. KSHV research is also supported

Budget

- $4.5 Million is requested for Year 1
- $22.5 Million requested for 5 years
- Support of 8-10 R01s and R21s combined
- Funds for this RFA will come from the NCI AIDS funds that we receive through the NIH Office of AIDS Research (OAR)
  - Use of AIDS funds for this FOA already approved by the OAR

Questions

www.cancer.gov **www.cancer.gov/espanol**