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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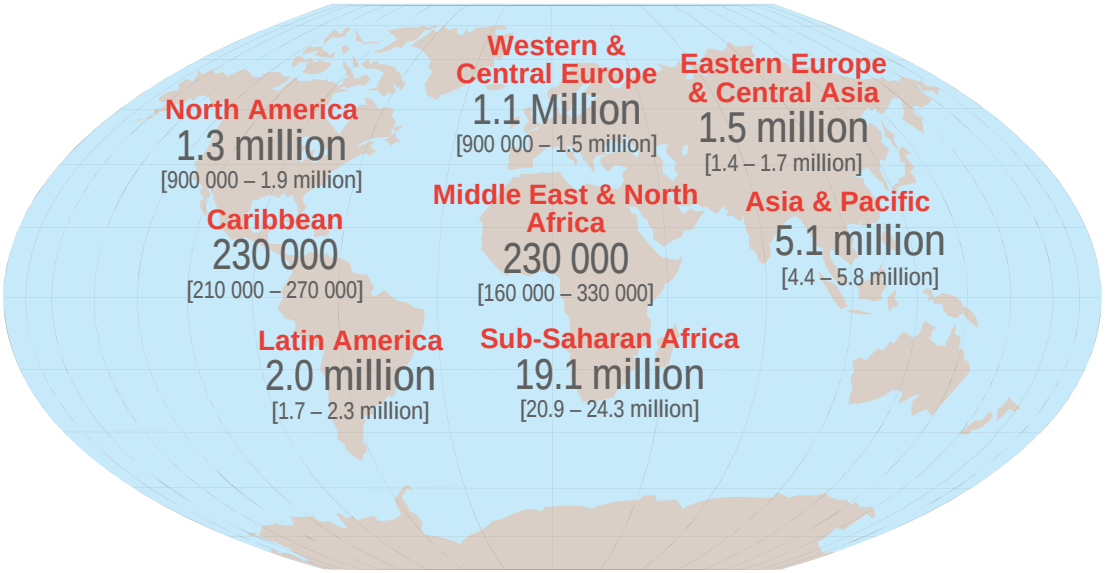
Purpose of RFA

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



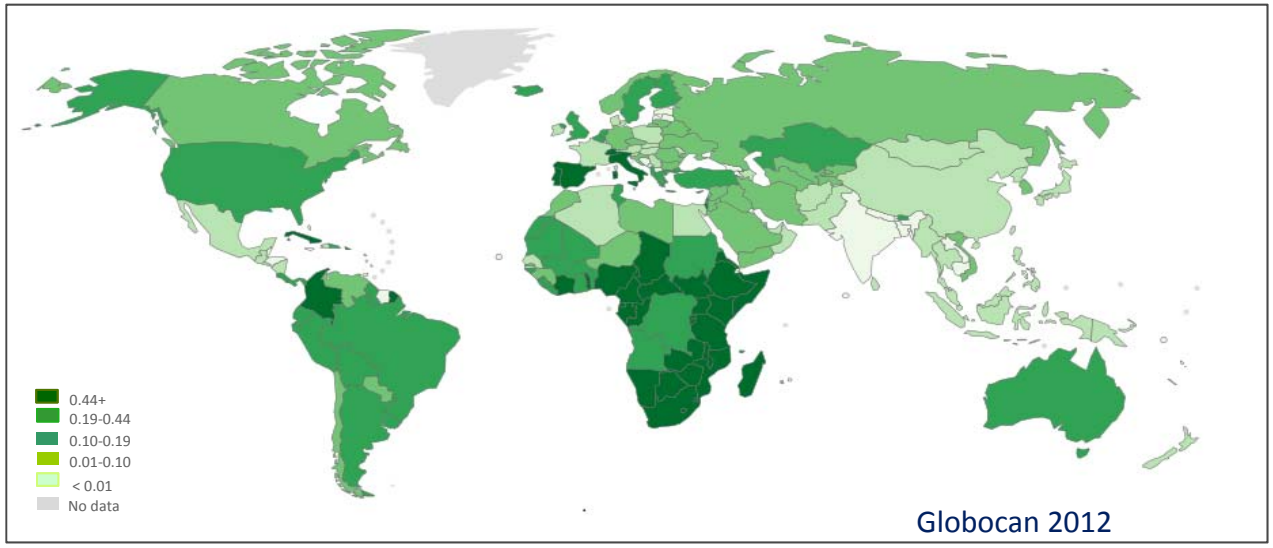
- 2.1 million new cases/year
- ~50% women
- ~90% in low- and middle-income countries (LMICs)
- 1.1 Million deaths/year

Total: 36.7 (34 – 39.8) million

December 2016

Prevalence of Kaposi Sarcoma

One year proportion per 100,000 both sexes



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 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. Cutaneous and often visceral

Background (Cont.)

- KSHV is the causative agent of 3 principal tumors or proliferative diseases:
  - 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

The virus was discovered in 1994

KSHV Transmission

- While KSHV can be detected in blood and occasionally in semen, it is frequently secreted in saliva and *this is believed to be the main route of spread*
- However, nearly 25 years after the identification of KSHV, the predominant modes of KSHV transmission, viral entry/host cells, and risk factors for infection are still not well understood
- It is believed that the predominant modes of KSHV transmission vary in different parts of the world

KSHV Transmission

- In endemic areas such as in SSA, much of acquisition is believed to occur during childhood by saliva exchange. It is unclear what 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 still substantially higher among men who have sex with men (MSMs) as compared to the rest of the population. The practices most responsible for this are unclear and may include deep kissing, oral-anal sex, or use of saliva as a lubricant
- The role of heterosexual transmission remains inconclusive and depends on which part of the world the studies where conducted

KSHV Seroprevalence and KS Risk with Age

- Sub-Saharan Africa has a 30% prevalence of KSHV by age 9, and some countries have an 83% prevalence by the age of 19
- In North America and most of Europe, seroprevalence in the general population is low (< 10%)
- People living with HIV are more likely to be KSHV seropositive than HIV-negative individuals
- In the United States, KSHV seroprevalence is 30-60% in HIV^+ MSM and 20-30% in HIV^- MSM
- 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 Prevention

- If KSHV infection could be halted, it would prevent the development of KS and other KSHV-related diseases
- Although logical and probably feasible, a vaccine is unlikely to be developed for a number of reasons, primarily economic
- The spread of KSHV can potentially be controlled 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
- Public health monitoring is hindered by the lack of an FDA-approved or gold standard serological assay to accurately diagnose KSHV infection
- In 2013, the the NCI BSA Ad Hoc Subcommittee on HIV and AIDS Malignancies recommended research on KSHV prevention.

KS Risk Awareness

- Though the risk of KS in MSM in the United States is quite high, awareness of KS, the role of KSHV as the causative agent in KS, and the routes of transmission of KSHV are generally quite low
- In sub-Saharan Africa there is also a lack of KS awareness among front line clinical staff and thus leads to diminished access to appropriate and timely antiretroviral therapy and chemotherapy

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

Scope and Expectations of RFA

- Identification of the principal modes of KSHV transmission in high risk groups
- Understanding the behavioral, environmental, or genetic risk factors for KSHV transmission in endemic and/or non-endemic areas
- Understanding the initial steps in KSHV infection of individuals and the biologic factors protecting against such infection
- Identification of the characteristics of the immune response to KSHV in children/adults that may thwart establishment of infections
- Development of robust diagnostic serological assays for KSHV that improve upon or simplify existing serological assays

Ultimately, the goal of the RFA is to advance our knowledge to inform measures 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
- A 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

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 appropriated AIDS funds as established by the NIH Office of AIDS Research (OAR)
- A request to use NCI's AIDS funds for this specific research initiative has already been submitted to the OAR

Questions

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

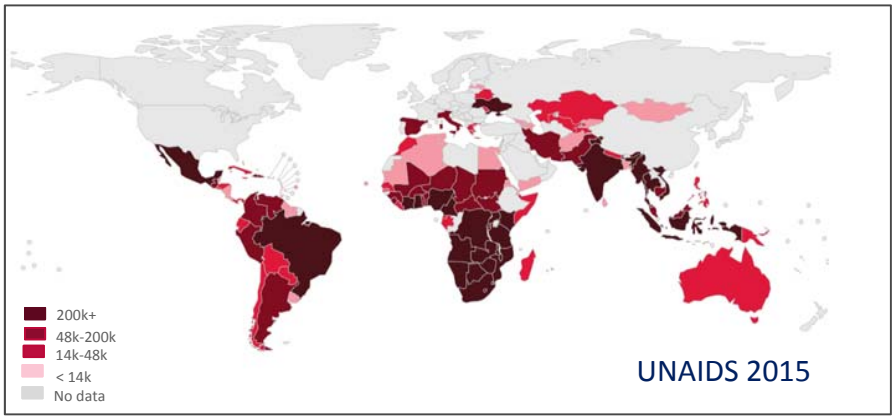
Justification for Use of RFA Mechanism

- HIV-associated malignancies are rare cancers, and historically, there has been a distinct need to stimulate participation in this cancer field
- Despite the advances in the fields of KS and KSHV epidemiology, virology and immunology, researchers have not been able to determine the principal routes of KSHV transmission or their relative importance, or to develop a successful KS prevention strategy for non-endemic or endemic, at risk populations
- The current knowledge of KSHV epidemiology and biology along with the existence of research-quality KSHV serological assays could serve as the stepping stones to high quality, properly evaluated, prospective cohorts, in both North America and sub-Saharan Africa
- Focused, sustained support for this area of science could reinvigorate the field and yield substantial benefit for these defined, at risk populations

Evaluation Criteria of RFA

- A committee (OHAM and DOCs) to track all applications from receipt and evaluations of responsiveness through funding plan approval
- The number of and quality of grants received, as judged by their scores
- The progress and accomplishments during the funding period
- The number and impact of publications and subsequent new awards resulting from this RFA
- Ultimately, an evaluation of the success of the RFA will involve an assessment of the increased understanding of KSHV transmission acquired and the ability to translate this understanding into effective public health measures
- The committee will periodically solicit input from the BSA *ad hoc* sub-committee on HIV and AIDS Malignancies to gain feedback on the success of the RFA

Number of People Living with HIV



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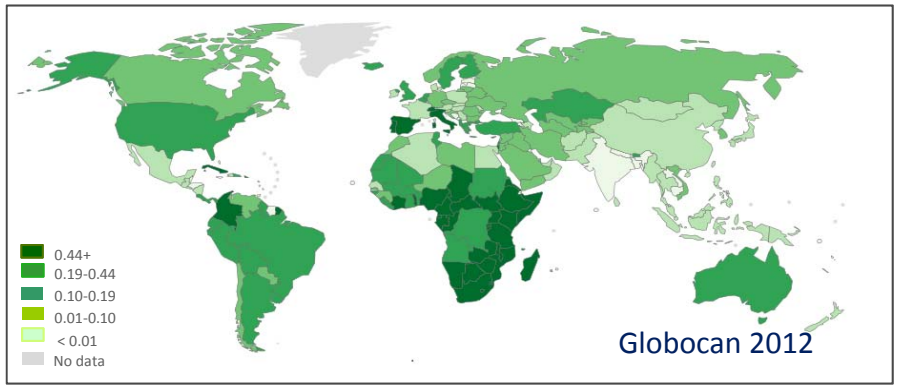

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