RFA Reissuance Request

AIDS and Cancer Specimen Resource

Office of HIV and AIDS Malignancy (OHAM)

NIH NATIONAL CANCER INSTITUTE

November 29, 2017

Purpose of ACSR RFA

- Facilitate research by basic, translational, and clinical researchers in HIV-associated malignancies by acquiring, storing and equitably distributing tumor tissues and biological fluids from these patients
- Support biobanking needs of the AIDS Malignancy Consortium (AMC) domestic and international clinical trials

Background - HIV Epidemic

- **United States**
  - More than 1.2 Million people live with HIV; only about 55% of those with an HIV diagnosis are virally suppressed
  - Little change in HIV transmission rate
  - Patients with AIDS or HIV infection are living longer, and the number of people living with HIV is increasing
- **Sub Saharan Africa (SSA)**
  - 19 Million People living with HIV
  - Approximately 960,000 new infections per year
- **Latin America**
  - 2.3 Million people living with HIV
  - Approximately 100,000 new infections per year

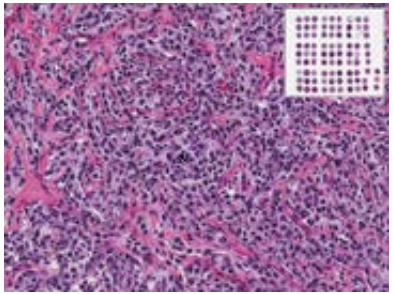
Cancer has been a prominent manifestation of HIV/AIDS since the beginning of the epidemic and is a leading cause of morbidity and mortality in HIV-infected people

Cancers in the US HIV+ Population

- Widespread use of combination antiretroviral therapy (cART) led to the decline of AIDS-defining tumors such as Kaposi sarcoma (KS) and AIDS-related lymphoma (ARL); however rates of decline have stabilized
- There has been a substantial increase in the incidence of non-AIDS-defining tumors such as anal cancer, hepatocellular carcinoma, and lung cancer
- In some recent studies, cancer was found to be the most frequent cause of death in HIV-infected patients

AIDS and Cancer Specimen Resource (ACSR)

- Established in 1993 to provide high-quality specimens from HIV-infected individuals with or at substantial risk for cancer, *with associated clinical data,* to qualified investigators at *little or no cost to the investigators*
- Main types of specimens:
  - Tissues - Frozen, formalin-fixed, H&E slides, unstained slides – 8% of inventory
  - PBMCs, plasma, body fluids (*e.g.*, saliva, urine, CSF) – 92% of inventory
  - Tissue micro-arrays (TMAs)



AIDS-related lymphoma (ARL) and ARL tissue microarray (TMA)

- Multiple cancers, including KS, ARL, Hodgkin disease, anal and lung cancers
- Special Collections: AMC studies, HIV multi-site autopsies, international collections

Changes Instituted with Current Funding Cycle

- The ACSR underwent a major restructuring at the time of the current award to substantially enhance its function and utility:
  - A single UM1 Cooperative Group replaced four independently managed U01 awards
  - Closed one biorepository, opened two domestic biorepositories (representing the growing HIV epidemic in the south), and one sub-Saharan Africa biorepository
  - Development and implementation of the ATLAS IT platform
  - Harmonization of administrative and technical processes
  - Developed strategies for coordinated scientific planning, biorepository accountability and fiduciary management
  - **Improvement of outreach and marketing approaches including redesign of the ACSR website and implementation of the Inventory Explorer**

We are just now reaping the benefits of these changes.

Current ACSR Organizational Structure

- **Five Regional Biospecimen Repositories (RBRs)**
  - George Washington University, Washington, DC
  - University of California, San Francisco, San Francisco, CA
  - Baylor College of Medicine, Houston, TX
  - Mayo Clinic Scottsdale, Scottsdale, AZ
  - Stellenbosch University, Cape Town, South Africa
- **Governed by an Executive Committee**
  - Leaders of the 5 RBRs
- **Central Operations and Data Coordinating Center (CODCC)**
  - University of California, San Francisco
- **Working Groups**
  - Science and Technology
  - Marketing & Outreach
  - Informatics
  - Quality Management

Recent ACSR Activity

	Previous Grant Cycle 1/1/2008-12/31/2011	Current Grant Cycle to date 9/1/2013 – 12/31/2016	
	All Samples	All Samples	Tumor Samples
Acquired	155,672 samples/7,349 pts	94,468 samples/2,385 pts	1266 samples
Disbursed	12,459 samples	13,651 samples	961 samples
TMAs Constructed	24	50	
TMA Cores disbursed	14,751 samples	24,268 samples	
Total disbursement	27,210 samples	37,919 samples	961 (not including TMAs)
Approved LOIs	119	81	

Special Initiatives and Special Collections

- **Tissue Microarrays (TMA)**
  - Custom built TMAs, upon request
  - Autopsy on a slide
- **Derivatives**
  - DNA and RNA (associated with TMAs)
  - Whole slide Aperio digital images of all TMA sections; broader data sharing initiatives
- **Special Collections**
  - Donated to the ACSR from NIH-funded research projects. These include:
    - UARTO: Uganda AIDS Rural Treatment Outcomes Cohort (750 pts.)
    - ARKS: Anti-Retrovirals for Kaposi Sarcoma (224 KS pts.)

Biorepository Support for the AIDS Malignancy Consortium (AMC)

- **George Washington University**
  - Simplify, streamline, and standardize the AMC's **domestic** biospecimen banking process since 2010
- **Stellenbosch University**
  - A 'within continent' biorepository to address biospecimen banking and curation issues that the AMC faces in **sub-Saharan Africa**
- **University of Arizona, Tucson**
  - Provide biorepository support for the **ANCHOR** (Anal Cancer HSIL Outcomes Research) trial (17,000 screened, 5,058 HIV+ enrolled participants) since 2014

Some Highlights of the Scientific Impact of ACSR on HIV Malignancy Research (1)

KS/KSHV

- Development of the BCBL-1 cell line (>200 publications) – major contributions to studies of KSHV, KS, primary effusion lymphoma (PEL), and multicentric Castleman disease (KSHV-MCD):
  - KSHV characterization and sequencing of the KSHV genome
  - Development of novel therapies for primary effusion lymphoma (PEL) and current recommended treatments for KSHV-MCD (AZT and ganciclovir) and KS (pomalidomide)
- Transcription profile of KSHV in primary KS lesions
- Development of an algorithm for diagnosis of KSHV infection
- Identification of a novel mechanism by which KSHV promotes cell survival and cellular transformation

Some Highlights of Scientific Impact of ACSR on HIV Malignancy Research (2)

Lymphoma

- Identification of pre-diagnosis biomarkers for AIDS-related non-Hodgkin lymphoma (NHL)
- mTOR activity in AIDS-related diffuse large B-cell lymphomas

Non-AIDS Defining Cancers

- Molecular changes in lung cancers in HIV+ subjects
- Genetic changes in anal intraepithelial neoplasia of HIV+ and HIV$^-$ men
- Disease-specific gene repositioning in breast cancer

ACSR Contributions to HIV Malignancy Research During the Current Grant Cycle

- 42 manuscripts/19 abstracts (current cycle, to date)
- 52 investigators/35 separate institutions received specimens from the ACSR
- AMC Biorepository serves >250 investigators in 25 domestic and 7 sub-Saharan sites
- ANCHOR Biorepository serves >50 research clinicians and scientists in19 sites
- HIV^+ Tumor Molecular Characterization Project (HTMCP)
- Young Investigator Pilot Award (4 awards in 2015; 3 awards in 2017)

Examples of Current NCI Projects and Important Questions that would benefit from ACSR Samples

- Studies of HIV/AIDS and the tumor niche (RFA-CA-17-030)
- Studies of the intersection of HIV/AIDS, aging, and tumor development (PAR-17-320 and PAR-17-321; Provocative Questions [PQ])
- Program announcements on the studies of AIDS-defining and HIV-associated non-AIDS-defining cancers (PA-16-425 and PA-16-426)
- Studies of differences between analogous tumors of the same tissue type or subtype in HIV vs. non-HIV infected patients (e.g. PQ, HTMCP)
- Studies on the nature of KS, including studies addressing uncertainties regarding clonality and mutations (proposed as PQ).
- The SSA (and Latin American) biorepositories will facilitate access to samples from these areas with high incidence of HIV malignancy

Mid-cycle External Evaluation

- Vital resource that serves the community of investigators who study HIV-associated malignancies
- Made great strides in fulfilling the difficult task of restructuring the group
- Made appropriate modifications in response to anticipated changes of the patterns of HIV malignancies
- Provided well-collected, processed, readily-accessible clinical specimens linked to clinical data in an excellent fashion
- Continually developing and consistently improving upon an excellent biorepository despite the difficulty of working with “rare” tumors
- Addition of Stellenbosch University was especially positive and plans to expand to South and Central America were deemed appropriate and enthusiastically supported

Mid-cycle Evaluation Recommendations

- Develop a clear succession plan with well-defined leadership positions (Complete)
- Engage junior members on the ACSR team (Started)
- Development of a comprehensive Quality Management Plan (In Process)
- Continue development of a strong scientific strategic agenda with a robust metrics-based evaluation plan that addresses scientific, administrative and fiduciary activities (In Process)
- **Develop a robust marketing plan for outreach and disbursements (In Process)**
- Decouple the physical location and management of the CODCC from the PI Institutions (In planning for the next grant cycle)

NIH Office of AIDS Research (OAR) Funds

- NCI supports HIV/AIDS research with designated funds it receives from the NIH OAR
- In 2015, NOT-OD-15-137 defined “high”, “medium”, and “low” priority areas of AIDS research and mandated that OAR funds can only be used for research addressing “high” or “medium” priority areas
- HIV-malignancy research supported by OAR is essentially 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
- **Availability of specimens from the ACSR will facilitate HIV-malignancy research that can be supported with OAR funds**
- In June 2015, BSA *Ad hoc* Subcommittee on HIV and AIDS Malignancy stressed the importance of infrastructure support for standardized collection and storage of and access to specimens to enable HIV-associated malignancy research

Proposed Budget

	Year 1	Year 2	Year 3	Year 4	Year 5
Basic RBR support	2,300,000	2,300,000	2,300,000	2,300,000	2,300,000
AMC Repository	500,000	500,000	1,000,000	1,000,000	1,000,000
Independent Procurement	300,000	300,000	300,000	300,000	300,000
Central operations & data management	700,000	700,000	700,000	700,000	700,000
ACSR Chair Office	200,000	200,000	200,000	200,000	200,000
Discretionary Fund	100,000	100,000	100,000	100,000	100,000
Total Cost	4,100,000	4,100,000	4,600,000	4,600,000	4,600,000
Grand Total					22,000,000

Proposed Budget (cont.)

- No increase in years 1 and 2 above FY2017 base funding
- Increase of $500,000 in years 3, 4 and 5 as compared to years 1 and 2
  - For support of the development of a Latin America based regional biorepository to serve Latin American investigators and US/Latin American collaborations
  - For support of AMC biorepository needs as they expand their clinical trials efforts into Latin America
  - Possibly serve to support other NCI research related efforts in Latin America
- Funds for this RFA will come from the NCI AIDS funds that we receive through the NIH Office of AIDS Research (OAR). (Already approved by OAR)

Summary

- The primary purpose of the RFA is to continue to provide investigators with access to high quality, HIV-associated tumor tissues with associated histopathologic and demographic data at no cost.
- The ACSR has had a substantial impact on HIV malignancy research to date. **Its functionality has been substantially improved since the last funding.**
- If renewed, it will facilitate the conduct of research into the pathogenesis of HIV-associated malignancies and the development of novel therapeutic strategies.

Summary (cont.)

- **If renewed, the ACSR will also be able to:**
  - Continue to serve as the biorepository for the AMC and ANCHOR trials conducted in the US and sub-Saharan Africa
  - Curate tumor tissues for MACS and WIHS cohorts
  - Enable investigators to do AIDS malignancy research using samples from LMIC
  - **Continue to maintain the existing repository of specimens**
  - Continue support of the HTMCP project
  - Continue support for investigators applying to NCI FOAs in HIV-associated malignancy research

Questions ?

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

Examples of the Impact of ACSR on HIV Malignancy Research During the Current Grant Cycle (cont.)

- Examples of research supported by the ACSR:
  - Identification of a novel mechanism by which KSHV promotes cell survival and cellular transformation *Zhu et al. PLoS Pathog, 2016*
  - Identified the *HGF/c-MET* pathway controlled genes as suitable for development of focused targeted therapy of PEL *Dai et al. Blood 2015*
  - Identified miRNA biomarkers that could be used for early detection markers of ARLs *Thapa et al. J Acquir Immune Defic Syndr 2014*
  - Shed insight into EBV and HIV expression programs in ARL that could be used as therapeutic targets in the post cART era *Arvey et al. Blood 2015*
  - Identification of potential HIV reservoirs in autopsy specimens, despite undetectable viral loads *Rose et al. J Virol 2016*