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Mesmerising study on HIV/AIDS-associated malignancies

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Abstract

In the present jargon of the AIDS Cancer and Specimen Resource (ACSR) research focused multiple spectrum on scientific discovery in the field of HIV/AIDS-associated malignancies. The ACSR was established as a cooperative agreement between the NCI (Office of the Director, Division of Cancer Treatment and Diagnosis) and regional consortia, University of California, San Francisco (West Coast), George Washington University (East Coast) and Ohio State University (Mid-Region) to collect, preserve and disperse HIV-related tissues and biologic fluids and controls along with clinical data to qualified investigators. The available biological samples with clinical data and the application process are described on the ACSR web site.

The ACSR tissue bank has more than 100,000 human HIV positive specimens that represent different processing, specimen (15), and anatomical site types. The ACSR provides special biospecimen collections and prepares speciality items, e.g., tissue microarrays (TMA), DNA libraries. Requests have been greatest for Kaposi's sarcoma (32%) and non-Hodgkin's lymphoma (26%). Dispersed requests include 83% tissue (frozen and paraffin embedded), 18% plasma/serum and 9% other. ACSR also provides tissue microarrays of, e.g., Kaposi's sarcoma and non-Hodgkin's lymphoma, for biomarker assays and has developed collaborations with other groups that provide access to additional AIDS-related malignancy specimens. ACSR members and associates have completed 63 podium and poster presentations. Investigators have submitted 125 letters of intent requests. Discoveries using ACSR have been reported in 61 scientific publications in notable journals with an average impact factor of 7.

The ACSR promotes the scientific exploration of the relationship between HIV/AIDS and malignancy by participation at national and international scientific meetings, contact with investigators who have productive research in this area and identifying, collecting, preserving, enhancing, and dispersing HIV/AIDS-related malignancy specimens to funded, approved researchers at no fee. Scientific discovery has been advanced by this unique biorepository. Investigators are encouraged to browse the ACSR Internet site for materials to enhance their own scientific initiatives.

Keywords: Human immunodeficiency virus, acquire immune, human immunodeficiency virus pathogenesis, human immunodeficiency virus sequence, data exchange specification

Introduction

Human Immunodeficiency Virus (HIV) infection continues its global spread with almost 40 million HIV-infected individuals worldwide. More than half are women [1]. While Acquired Immunodeficiency Syndrome (AIDS) is most associated with opportunistic infections, adults and children infected with HIV have well-recognized excess risks for the development of malignancies [2]. Many of these cancers are associated with known oncogenic viruses such as: Epstein Barr virus (EBV) with non-Hodgkin's lymphoma, human herpes virus 8 (HHV8) with Kaposi's sarcoma (KS), Hepatitis B (HBV) and Hepatitis C (HCV) viruses with hepatocellular carcinoma and human papilloma virus (HPV) with squamous cell carcinomas of cervix and anal canal. Other cancers, such as lung, are being studied for their relationship to HIV infection. In the developed world, cigarette smoking is common and HIV infected smokers have an increased incidence of smoking-related cancers of the lip, mouth, and pharynx [3]. With the advent of highly active antiretroviral therapy (HAART) in 1996, there was a dramatic reduction in the incidence of non-Hodgkin's lymphomas (NHL) and especially KS. However, apparently little reduction is suggested for the other excess risk cancers including Hodgkin's lymphoma, squamous cell carcinoma of anus, multicentric Castleman's disease in adults and leiomyosarcoma in children.

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Despite HAART and public education the total number of individuals living with HIV in the United States continues unabated with more than a 50% increase since 1996. HIV associated cancers in the HAART era are still among the top causes of death in HIV/AIDS [4]. Furthermore it is of concern that extended exposure of such a large population of HIV infected individuals of all ages to nucleoside analogs such as azidothymidine (AZT) and dideoxycytidine (DDC), as well as, other potent AIDS drugs may induce DNA damage leading to other significant associations with cancer in the future.

The need to obtain and provide tumour tissue from patients with AIDS was originally identified at a conference on AIDS Lymphoma in May, 1992. The request for a resource for such specimens was made both by investigators participating in clinical trials research and laboratory investigators. Thus the National Cancer Institute (NCI) established the unique AIDS Malignancy Bank (AMB) in 1994 as a cooperative agreement to collect HIV positive and control biological specimens, with associated clinical data, to support translational research into HIV/AIDS-related malignancies [5]. This AMB program continues as the AIDS and Cancer Specimen Resource (ACSR) [6], supporting broadened research interests in the area of HIV/AIDS and oncogenic viruses [7] through collaborative specimen assemblage. HAART associated reductions in certain HIV/AIDS-related malignancies make these specimens more difficult to acquire (e.g., KS and NHL), therefore the ACSR is a critical conduit for the collection, preservation, banking and disbursement of scarce HIV/AIDS-related malignant tissues and biological fluids to qualified investigators.

In addition to serving as a resource for specimens acquired from the consortia sites, the ACSR is a national repository of specimens that reflects the temporal changes, and thus the history, associated with HIV disease. During the course of the last decade, the ACSR has established itself as a singular specialized resource for collection, storage, and provision of specimens with associated clinical, diagnostic, and epidemiologic data collected from HIV-infected individuals participating in clinical trials, observational cohort studies, and other research studies conducted by AIDS investigators both domestically and internationally. During the life of the ACSR, the biorepository cost of specimens has decreased significantly making the ACSR a good value to support research by RO1/R21 funded investigators engaged in HIV/AIDS malignancy studies.

Review with the Specimens within the ACSR

The ACSR bank has more than 100,000 specimens from HIV infected and control patients available from different processing (43), specimen (15), and anatomical site (50) types. Specimens are representative of the HIV/AIDS evolving epidemic and are from a wide variety of patients, including those with early, as compared to late-stage disease, multi-site autopsy specimens with involved and uninvolved tissue, and specimens obtained from patients with defined anti-retroviral or chemotherapy histories. In addition, the inventory contains donations from the AIDS epidemics in developing countries outside the United States.

Special emphasis on specimen and data acquisitions

- Detailed viral typing studies: The ACSR has expanded tissue collection at international sites including Africa, Brazil, and Thailand to obtain specimens from patients who develop malignancies associated with infection from

different subtypes of HIV, HHV-8, EBV, and HPV. These types of specimens are critical for determining the role of virus associated carcinogenesis in the natural epidemic setting, as opposed to clinical settings where there is anti-viral therapy intervention.

- Neoplastic and non-neoplastic specimens from women: Gynaecologic tissues, breast, and obstetrical specimens from HIV-infected women come from collaborative efforts with ongoing clinical studies of HIV-disease in women, i.e. Women's Interagency HIV Study (WIHS). Expansion of this collection to include specimens for recently discovered agents and unusual malignancies associated with HIV-disease is ongoing. The coordinated study between WIHS and the Rwanda Women's HIV Study, provides fresh gynaecological specimens (LEEPs, uterine resections, and biopsies) and biological fluids from infected women including normal tissue through cervical cancer.
- Specimens from AIDS-related malignancies clinical treatment trials: AIDS-related malignancy clinical trial groups (ACTG) obtain specimens that are collected and stored longitudinally. Samples retained from the early clinical trials are now available through the ACSR to approved investigators.
- Specialty sub-bank samples: Disease specific (lymphoma, KS) tissue micro-arrays (TMAs) for rapid assessment of tissue molecular targets or reagents (antibody, *in situ* probes, etc.) are available. Specimens preserved specifically for transmission electron microscopy are available and provide optimal samples to carry out ultra-structural studies of malignant, infectious, and reactive tissue processes. Specimens preserved in fixatives recently shown to enhance immune-histochemical and dideoxycytidine hybridization results are currently available or could be developed by request of approved investigators.
- ACSR data interface: The ACSR has developed a national computerized database of specimens with patient information and clinical history. Over time, this system will interface with electronic databases of other cooperative banking groups, as well as with clinical trial groups. A version of the ACSR database, stripped of patient identifiers, is made available online; researchers can search for useful specimens using various patient, specimen and clinical criteria.

Investigator use of ACSR samples and clinical data

Investigators made 148 specimen availability inquiries to the ACSR, 88 resulted in *full* applications and 37 in *short* applications. Of the full applications, 73 were approved to receive multiple samples, 64 received samples, 8 are still waiting funding or identification of appropriate specimens, and 14 were not approved for a variety of reasons including scientific merit, sample request size, or lack of available specimens. The latter investigators were referred to other biorepositories or resources, when appropriate. Of the full approved applications, 83% were for tissue, 18% for serum/plasma and 9% for cell lines, bone marrow, or urine. Some applications were approved for mixed sample types. Of the 37 short form applications received, 36 were approved. The 23 remaining inquiries included 19 for which no final application for samples was received and researcher inquiries that were referred to other biological sample resources. Requests for Kaposi's sarcoma specimens accounted for 32% of the total served requests, lymphoma for 26%, and the

remainder were for a variety of other disease types and controls.

Investigators have used the ACSR's HIV infected and non-infected control biological samples and clinical data to contribute significant discoveries. Included are: markers of selective B cell activation during lymphomagenesis^[8], effect of HIV integration site on cancer development^[9], role of macrophages^[10], chemokines, cytokines and growth factors in cancer^[11], KHV induced transcriptional reprogramming in KS cell types^[12], correlation of interleukin, CD4+ lymphopenia, viral load and disease progression^[13], persistent infections associated with cancer, especially EBV^[14] and human papillomaviruses^[15] and diagnostic assay development and validation^[16].

Investigations into the pathobiology of HIV infection have used human tissue to provide translation from important discoveries made in cell culture or animal studies. HIV insertion sites within human tissues including somatic cells^[17], macrophages and malignancies^[18] have been defined using ACSR provided infected human tissue. The neuropathogenesis of AIDS dementia was explored^[19] using HIV infected brain tissue and technical resources within the ACSR. Likewise human associated vasculopathy^[20] and cardiomyopathy were elucidated by translation to HIV/AIDS human tissues relevant findings from a "murine AIDS" model^[21].

The use of ACSR resources has resulted in sixty-one scientific reports added to the scientific literature and others are in preparation.

Tissue micro-arrays from ACSR specimens for translational research

The national ACSR was formed as a cooperative agreement between the NCI, Office of the Director, Division of Cancer Treatment and Diagnosis (DCTD) and regional ACSR consortia: University of California, San Francisco for the West Coast, George Washington University for the East Coast and The Ohio State University for the Mid-Region. The ACSR steering committee, comprised of the principal investigators from each consortium, developed policies and procedures for standardized operation across the organization. Tissue micro-arrays (TMA)^[22] are useful for a wide range of research interests. One TMA tissue section can provide diagnostic tissue core sections (0.6 mm in diameter or greater) from literally hundreds of specimens, e.g., KS and NHL, from HIV-positive and negative individuals, for simultaneously testing. Immunohistochemical staining and *in situ* hybridization techniques are routinely employed on TMAs. In general, all ACSR TMAs also contain positive cores (e.g., cell culture lines) and negative control cores along with the disease specific cores allowing validation of novel tissue biomarkers. The ACSR provides non-Hodgkin's lymphoma and KS TMA slides to approved researchers interested in characterizing these tumors using applicable tissue probes. Other TMAs are planned, e.g., various subtypes of lymphoma characterized by immune-histochemistry and DNA.

ACSR Internet site and national database

The ACSR established a database containing information on ACSR specimen types and associated clinical data obtained from patients with HIV/AIDS-related malignancies and control specimens. Each consortium sends electronic de-identified data quarterly to the central ACSR database. Records are maintained at each local site in accordance with the local IRB approved protocol. Some specimen collections

have other databases that enable investigators to perform studies on specimens linked with a defined clinical or epidemiologic pedigree.

Specimen collection and processing

Specimens from a wide variety of HIV infected patients and selected controls are processed based on laboratory standard protocols described in the ACSR standard operating procedure manual, accessible through the *Process Specimens (Protocols)* web page^[6]. This manual provides instructions for the collection, preparation and shipment of specimens among the ACSR sites and to approved investigators. Cooperative groups interfacing with the ACSR can use the ACSR manual as a resource for their activities.

Samples donated by HIV/AIDS treatment and epidemiology groups

The ACSR is directly affiliated with the AIDS Malignancy Consortium (AMC)^[33], a national group that conducts clinical trials in patients with AIDS-related malignancies. This affiliation allows the banking of well-characterized, longitudinal specimens from a variety of clinical trials for ultimate use by approved researchers. This association provides material for the search for prognostic markers and promising therapeutic regimens. Using the AMC relationship as a model, further group affiliations have been developed, such as relationships with the Women's Interagency HIV Study (WIHS), the AIDS Clinical Trials Group (ACTG), the San Francisco gay men's health study, the national ano-genital cancer study, San Francisco lymphoma study of 1600 NHL patients and 2500 random controls, natural history study of HHV8/KSHV in homosexual men in the San Francisco area, the Rwanda HIV women's study, and a variety of smaller studies. The WIHS is a unique study, which provides interval blood specimens and fresh colposcopy specimens from 2809 HIV-positive and 959 negative women who have cervical lesions. This study provides valuable pre and post diagnostic biologic specimens.

Specimen collections donated or accessed through a referral process

Where large collections of specimens are in place within established programs, the ACSR can act as a broker between the ACSR research applicant and the "resource" tissue bank. Where there are biologic sample collections that have been placed at risk because of funding loss, tissue bank down sizing or other reasons, the ACSR can accept transfer of banked biological sample collections with their attendant databases, for inclusion in the overall ACSR program. Examples of the first type of relationship includes: interfaces with the National Neuro AIDS Bank (NNAB), the National Neurological disease Tissue Consortium (NNTC), the UCLA Brain Bank Program, various multi-centre AIDS cohort study (MACS) groups, the UCSF AIDS Specimen Bank (ASB) and the Hawaiian AIDS natural history cohort study. Examples of the second type, where specimens have been transferred to the ACSR include: the San Francisco gay men's HHV-8 natural history cohort, and the US Department of Defence Thailand vaccine trial serum specimen bank.

The magnificent ACSR approach to the changing epidemic

The USA alone has about 950,000 people living with HIV infection (about a quarter of whom are not aware of their infection). Prospective and longitudinal samples across the

time-line of the changes in the epidemic are critical to understanding the epidemic as it evolves. Collection of such specimens has been a goal of the ACSR. The ACSR is taking into consideration the evolution of HIV-associated cancers (e.g., the higher rate of head and neck cancer in HIV patients in Africa) by establishing pertinent collaborations. Through collaboration, the ACSR is reaching out to heavily HIV/AIDS affected areas, such as Africa, Brazil, Russia, and Thailand to acquire relevant specimens.

Discussion and conclusion

The ACSR makes available large numbers of HIV/AIDS-related malignancy specimens for funded, approved researchers at no fee. Scientific discovery has been advanced by this unique program through promotion of interest in and access to HIV/AIDS human tissues for primary and translational research. Investigators using ACSR specimens have shared their discoveries with the scientific community through publications in notable scientific journals and at meetings. Investigators are encouraged to browse the ACSR Internet site or contact the ACSR for specimens to enhance their own scientific initiatives.

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