

Review

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The AIDS and Cancer Specimen Resource: Role in HIV/AIDS scientific discovery

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Abstract

The AIDS Cancer and Specimen Resource (ACSR) supports scientific discovery in the area 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 (43), specimen (15), and anatomical site (50) 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.

Review

Background

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. 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 tumor 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 speci-

mens 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.

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 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 ultrastructural studies of malignant, infectious, and reactive tissue processes. Specimens preserved in fixatives recently shown to enhance immunohistochemical and *in situ* 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 bio-repositories 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. Appendix I contains the list of these reports. Table 1 lists all publishing journals and Figure 1 depicts impact factors for them. Eighty-three podium and poster presentations have been made at local, national and international scientific meetings through 2006 by investigators using/promoting ACSR materials. Appendix II contains a list of these presentations.

Developments within the ACSR

Evaluation of HIV DNA in ACSR specimens

The ACSR tested the suitability of: banked tissues to evaluate *in vivo* HIV sequences using an HIV bioinformatics facility. HIV sequence analysis was performed using the HIVbase® software (GeneJohnson, Inc., St. Augustine, FL). HIV DNA was identifiable (at copy numbers greater than 1 per 10,000 cells) in:

- a) >50% of blood derived T cell preparations
- b) >33% of blood CD14+ monocytes
- c) AIDS lymphomas

Table 1: Journals publishing ACSR articles

Journals	Weighted*Impact Factor#	Number of Articles
Blood	9.654	9
Journal Of Virology	6.034	8
JAIDS – Journal Of Acquired Immune Deficiency Syndromes	3.345	5
Cancer Research	8.727	3
Journal Of Cellular Biochemistry	3.868	3
Nature Medicine	28.010	2
Lancet	20.158	2
Carcinogenesis	9.067	2
AIDS	5.517	2
Journal Of Neuroimmunology	3.598	2
Nature Genetics	24.695	1
JAMA – Journal Of The American Medical Association	9.522	1
Oncogene	6.872	1
American Journal Of Pathology	5.796	1
Cardiovascular Research	5.164	1
American Journal Of Epidemiology	3.978	1
Virology	3.540	1
American Journal Of Physiology – Heart And Circulatory Physiology	3.539	1
Journal Of Clinical Microbiology	3.503	1
AIDS Research And Human Retroviruses	3.069	1
Cellular Immunology	1.988	1
Journal Of Clinical Virology	1.744	1
Cancer Detection And Prevention	1.599	1
Journal Of Infectious Diseases	1.547	1
Anticancer Research	1.331	1
Ultrastructural Pathology	0.918	1
Cellular & Molecular Biology Letters	0.873	1
<i>Articles in journals with impact factors</i>		55
BMC Medical Informatics And Decision Making		2
Anatomical Record (Part B: New Anat.)		1
Annals Of Diagnostic Pathology		1
Current Opinion In Investigating Drugs		1
Humana Press		1
<i>Articles in journals without impact factors</i>		6
<i>Total articles</i>		61

* The impact factor of a journal varies by year. Each weighted impact factor is calculated by averaging the impact factor from the year of publication of each article.

As impact factors are calculated from citations in a three year window following publication date, the last published impact factor is used for some more recent articles.

d) AIDS lymphoid tissue

e) kidney and seminal vesicle tissues, and

f) >90% of brain tissues from patients with HIV dementia.

Studies of HIV gene sequence selection/evolution in human HIV infected tissues from patients with AIDS malignancies as compared to other classes of HIV related disease can therefore be facilitated by ACSR resources [19]. The ACSR has recently begun the development of an AIDS lymphoma DNA library that can be made available to interested and qualified investigators.

Tissue micro-arrays from ACSR specimens for translational research
 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

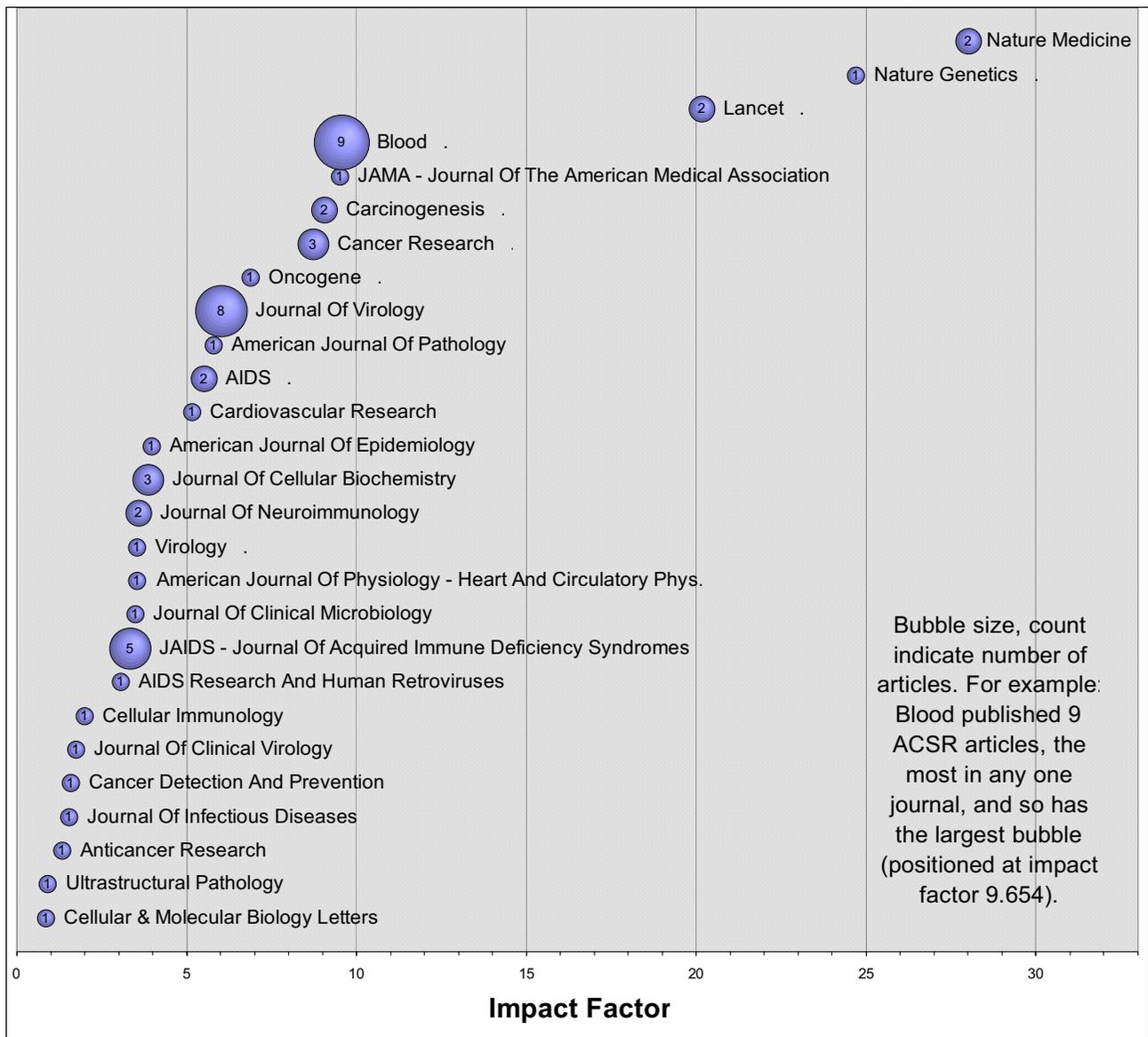


Figure 1

Impact of ACSR Articles. Journals that published ACSR related articles are shown with the bubble size representing the number of articles (count shown inside bubble) while the width represents the weighted average impact factor. For example, Nature Medicine, which published two ACSR articles, is shown at far right because it has the highest impact factor, 28.010.

approved researchers interested in characterizing these tumors using applicable tissue probes. Other TMAs are planned, e.g., various subtypes of lymphoma characterized by immunohistochemistry and DNA.

Preview and selection of TMAs by researchers are enhanced by the development and deployment of virtual whole slide images of digitized TMA stained sections and associated clinical data on an ACSR Internet site [23]. Online TMA and tissue core images (as in Figure 2), legends or data maps, and clinical data are linked for convenient browsing [24,25]. Data is available in an industry standard XML export format [26]. Printed data maps and images of TMA slides are also available. TMAs are offered as an enabling technology to expedite transitional research in HIV/AIDS and particularly in HIV-related malignancies, while conserving valuable specimens.

The quality of each TMA is directly related to the individual donor tissue core characteristics. Older archived paraffin embedded tissues may be antigen negative or weakly reactive and require optimal antigen retrieval methods and high antibody titres for positive results. Core donor tissues specifically prepared by optimal fixation and processing provide the most favourable TMA sections for studies with novel probes. Donor tissue characteristics are available with each TMA to provide guidance to the investigator. Cut sections from each TMA are stained by H & E to assure the presence of target tissues and by appropriate immunohistochemical stains (IHC) to assure tissue immunoreactivity for expected molecular targets prior to listing TMA availability on the Internet site.

Structure

Organization of the ACSR

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. An outside Research Evaluation and Decision Panel (REDP), comprised of experts in the field, evaluates requests for specimens as shown in Figure 3. See [6] for a detailed description of the program.

Privacy, Confidentiality, Authorization and Consent

Local Institutional Review Boards (IRBs) approve and monitor the activity of each ACSR site. The local ACSR maintains a research protocol to protect biologic sample donor privacy and to maintain confidentiality of clinical data as required by federal standards including the

requirements of HIPPA [27]. Local IRB approval is required for participation in the national ACSR program.

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.

Guidelines

The ACSR has quality practices for biorepository operation that are consistent with International Society for Biological and Environmental Repositories (ISBER) best practices [28], NCI Office of Biorepositories and Biospecimen Research (OBBR) guidelines [29] and AIDS Clinical Trials Group (ACTG) Biomedical Research Institute (BRI) guidelines [30].

Marketing

The ACSR has strategies to market the availability of HIV/AIDS-associated malignancy specimens. Through word of mouth, directed mailings, newsletters, and presence (handouts and a specially designed ACSR booth) at national and international meetings, the ACSR reaches increasing numbers of potential researchers interested in utilization of the resource and have steadily increased the number of applications. The ACSR seeks feedback from its investigator community to identify future needs, gaps, and shortcomings.

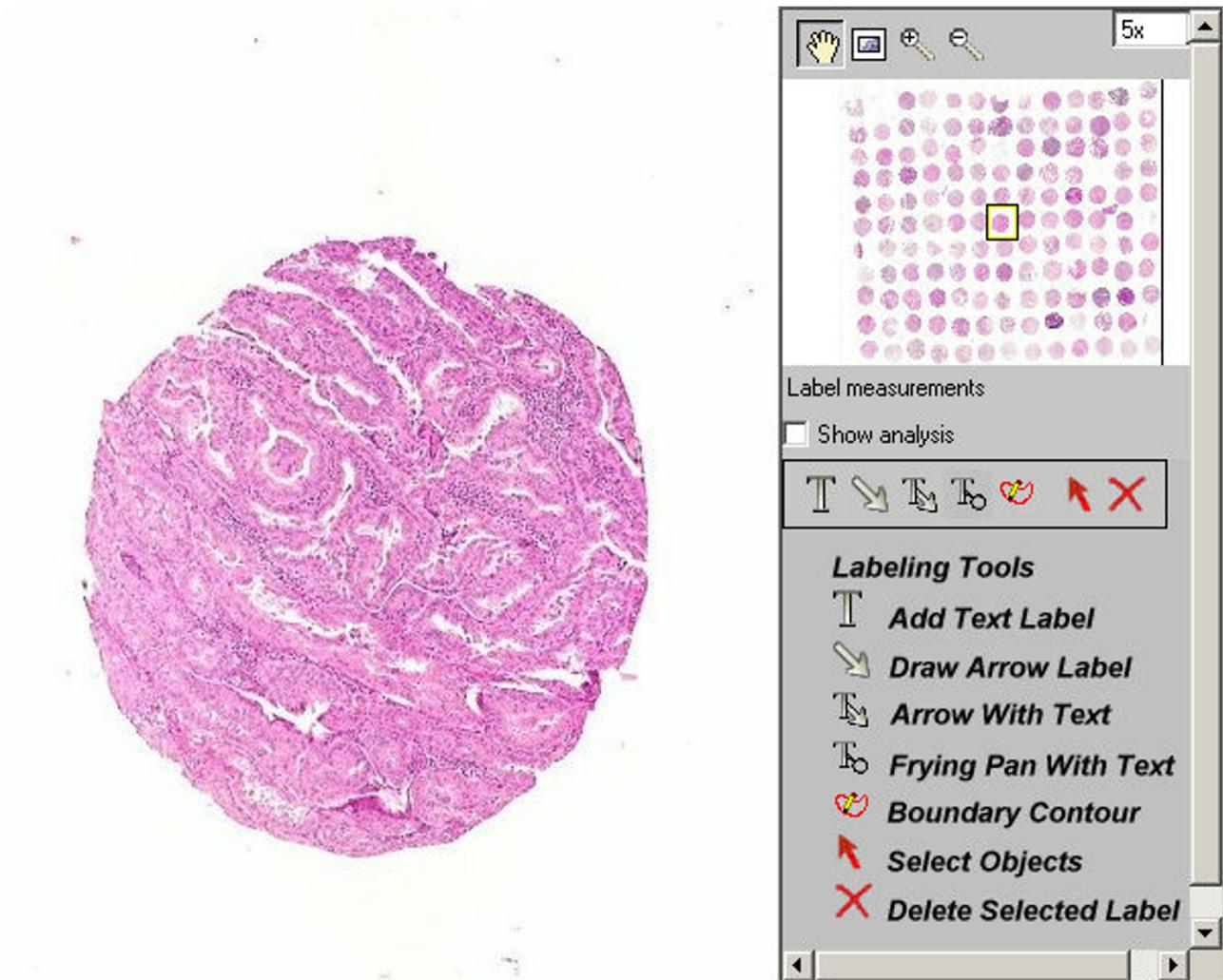
Specimen disbursement

Identifying researcher needs

Investigators search on-line (using the *Specimen Search* web page [6]) to identify specimen types that meet their research requirements. Once researchers find specimens of interest, they fill out a Letter of Intent (LOI) application for acquiring the specimens. The ACSR has two application types (short and long form) depending on the number of specimens needed. All of the requirements for researchers are available on the above Internet site. If the researcher is unsure of whether needed samples and data are available or has other questions regarding specimen and data availability, the ACSR or NCI program director can be contacted. Some of the general potential uses of ACSR specimens are outlined in Table 2.

Letters of Intent and tracking

Full and short form LOI applications are accepted from investigators throughout the year. Forms can be down-



Study: Species: human

Slide: acquired with 10.0x objective

Figure 2

Sample TMA image from the virtual microscope section on the ACSR Mid-region Internet site for viewing TMS core tissues by interested investigators.

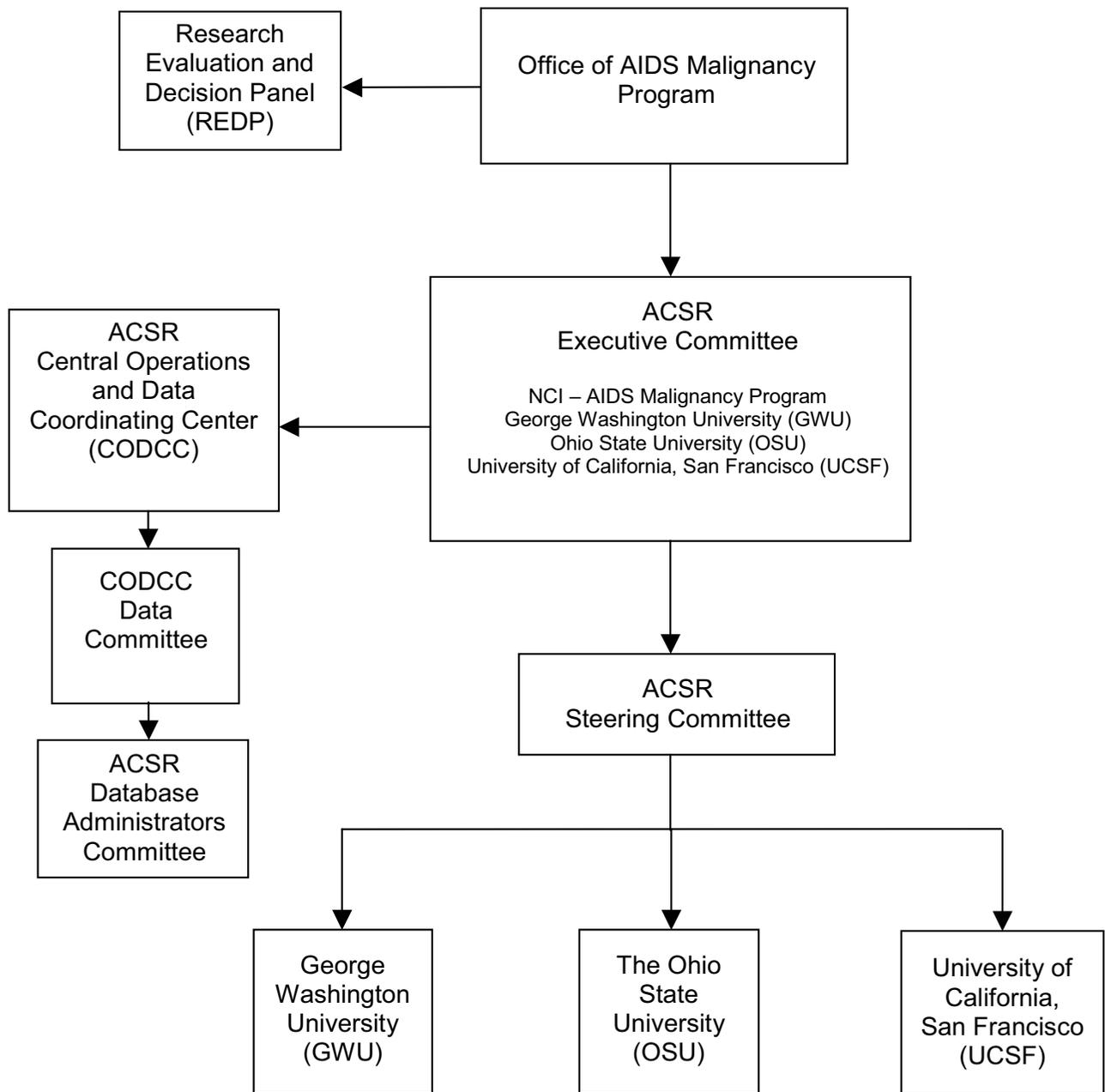


Figure 3
ACSR organization.

Table 2: Potential uses of ACSR banked specimens

Type	Use	
Autopsies (multi-site) frozen & fixed	DNA and protein studies within individuals; involved vs. uninvolved tissues	
	Tissue array analyses	Comparison of antigen expression between many patient tumors
		Diseased tissue specific cytokine, virus, antigen expression
Frozen lymphoma, KS and tumor tissues	DNA, RNA, and protein array studies; viral discovery/strain variation studies	
Non Hodgkin's lymphoma (AIDS & non-AIDS) epidemiology study (serum & fixed tissue)	Serologic studies on cases vs. controls for cytokine, viral antigen, serum proteins. Coupled with epidemiologic data in collaboration with Dr. Elizabeth Holly test disease associations, risk factors, transmission risk factors, resistance factors, lymphoma tissue, DNA/protein correlation with serum factors/disease associations.	
AIDS Malignancy Consortium clinical trial specimens	Longitudinal, trial associated specimens for analyses of disease specific markers in collaboration with AMC	
Serum specimens from cross-sectional survey in Thailand	Studies on low KS prevalence untreated HIV & serum cohort Infected vs. uninfected age & sex matched specimen comparisons	
		Studies on HIV, non-US viral isolates. Repeat blood draws from HIV+ individuals available for rate of variation studies.
Ano-genital specimens from men and women HIV+/HIV-	Study role of HIV strains in early stages of ano-genital carcinogenesis	
Plastic embedded tissue suitable for transmission electron microscopy	Evaluation of virus identity, morphogenesis, and cytopathology in various disease states	

loaded from the *Letter of Intent Application Form* web page [6]. The application process requires minimal paper work and is outlined in detail on the web site. When specimens are approved for delivery, they are packaged and shipped (on dry ice, when appropriate) according to International Air Transport Association (IATA) regulations. The ACSR works with other biological material resources and refers investigators to these resources if specimens are not available within the ACSR cooperative group. The confidential ACSR LOI tracking system allows inquiry tracking, providing details of requests and the status of shipments without disclosing research directions outside of the ACSR staff.

Sample Quality control

Investigators who receive ACSR specimens assist in the ACSR Quality Assessment Program by evaluating the quality of specimens they receive and returning a written evaluation document to the ACSR. For example, users have reported that blood stored by the ACSR yielded >90% high quality RNA and DNA and viability of PBMCs exceeding 50% in samples stored for up to five years. A

return evaluation card is included with each sample shipment.

Random samplings of specimens are regularly tested for preservation of RNA and DNA and the viability of cells in frozen storage. Many of the banked specimens, however, are too small to allow extensive pre-testing that requires destructive sampling. The quality of stored biological samples can generally be anticipated based on specimen type, type of fixative or processing, length of storage, storage method and the type of testing anticipated by the investigator [31,32]. Investigators are encouraged to verify the use of specified biological sample types before undertaking their planned study.

Cost to investigators

Samples are provided to approved, funded investigators working in non-profit research settings at no fee. Investigators working in a commercial setting may also obtain samples if approved by the REDP but a fee per sample and for service may be applied.

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.

Specimens donated individually

Each ACSR site has developed a consortium of pathologists and clinicians at participating sites who collect and contribute specimens and clinical information to the ACSR. If samples are specifically collected for the ACSR, each donor signs an ACSR informed consent document and a HIPPA document approved by the local IRB. Samples from archived paraffin embedded tissues and associated clinical data are acquired according to local hospital rules, IRB approved protocols including federal HIPPA waiver of informed consent for use of personal medical information preparatory to research [27]. All samples and clinical data are coded when they are entered into the local ACSR site, de-identified before being placed on the web and all samples and clinical data released to investigators are anonymous.

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 Inter-agency 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-center 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 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.

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.

Competing interests

The author(s) declare that they have no competing interests.

Authors' contributions

MSM wrote the initial draft of the manuscript. LWA had primary responsibility for rewriting, reviewing, incorporating comments and editing the manuscript. JMO also edited the manuscript. All authors provided comments of various drafts, participated in direction setting discussions and reviews and have read and approved the final version.

Appendix I – Articles using ACSR resources

1. Kaplan LD, Shiramizu B, Herndier B, Hahan J, Meeker TC, Ng V, Volberding PA, and McGrath MS. Influence of molecular characteristics on clinical outcome in HIV-associated non-Hodgkin's lymphoma: Identification of a subgroup with favorable clinical outcome. *Blood* 85:1727–1735; 1995.
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Appendix II – Presentation abstracts using ACSR resources

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