SWOG Cooperative Group Biorepository Resource: Access for Scientific Research Studies

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Abstract

SWOG (formerly the Southwest Oncology Group), a National Cancer Institute–supported cooperative group, conducts multi-institutional, multidisciplinary clinical trials for adult patients with cancer, covering a wide range of solid tumors and hematologic cancers. The group has amassed a large set of biospecimens, collected from patients in numerous studies over many years and linked to clinical data. SWOG is now actively promoting the use of this unique scientific resource by making it available to a much wider group of researchers. This biospecimen resource offers material for research on disease mechanisms, genomic changes associated with cancer progression, markers of response and resistance to therapies, diagnosis or detection of recurrence, and more. By collecting, storing, and distributing the specimens, SWOG provides the framework for translational scientists to complete the feedback loop from “bedside to bench.” This article provides an overview of the group’s biospecimen resources and guidelines for gaining access to them. Clin Cancer Res; 17(16); 5239–46. ©2011 AACR.

Introduction

SWOG (formerly the Southwest Oncology Group) conducts clinical trials of therapies for a wide range of adult cancers, including most types of solid tumors and hematologic malignancies. Approximately 6,000 individuals are enrolled in SWOG clinical studies each year, with about 32,000 people involved in ongoing SWOG clinical trials each year. The SWOG network is comprised of more than 5,000 oncology health care providers who represent more than 600 institutions, including National Cancer Institute (NCI)-designated Cancer Centers, community practices and hospitals across the United States. SWOG conducts phase-I–III studies across this network in numerous cancers: breast, gastrointestinal tract, genitourinary tract, gynecologic tract, leukemia, lymphoma, lung, melanoma, and multiple myeloma. The Group is structured around disease treatment and prevention committees, which are comprised of multidisciplinary teams of medical oncologists, surgical oncologists, radiation oncologists, pathologists, nurses, translational scientists, biostatisticians, clinical research associates, patient advocates, and epidemiologists. SWOG conducts clinical research of new cancer drugs, drug combinations, chemoprevention agents, and combined-modality therapies, with the goals of improving survivorship, lessening morbidity, and/or preventing cancer. The design of clinical trials incorporates experimental treatment regimens with specified eligibility requirements, and established clinical endpoints, such as survival, progression-free survival, or response, or toxicity, so that definitive conclusions on safety and efficacy may be obtained. The Group’s translational research is designed to advance understanding of disease mechanisms and the actions of drugs and other treatment modalities, as well as to improve classification and prognostication of cancer. To accomplish translational research objectives, the group systematically collects specimens during the course of cancer clinical trials that are linked ultimately to mature clinical outcomes data. The inherent value of SWOG’s biorepository lies in the prescribed standardized collection of specimens, and in the centralized processing, storage and tracking of biospecimen quality, quantity, use, and distribution. Use of the biorepository is aligned with the nationwide effort to advance the validation of biomarkers in cancer clinical trials and of companion diagnostics for targeted therapeutic strategies in phase II and III trials.

Materials and Methods

Rationale for biospecimen banking

Each SWOG clinical study may have scientific research aims that involve the collection of biospecimens for reasons that are either “integral” to the trial, i.e., necessary for the clinical study to proceed, or “integrated” into the trial as a prospective test of a research hypothesis or validation of
candidate biomarkers. In addition, for larger studies, SWOG may, with appropriate informed consent from the patients, collect specimens without a specific scientific research aim that is established prospectively (banking). The types of specimens collected in each clinical study are determined by the integral and/or integrated uses they will serve, and their methods of collection are specified within the study protocol in tandem with informed consent documents. At the conclusion of the clinical trial and completion of the research aims, SWOG provides to the scientific community access to banked specimens to support expanded scientific exploration. The intended use of these biospecimens is to conduct research of high scientific merit related to the unique feature of the SWOG resource: to evaluate associations with endpoints obtained from the clinical study. A request for access to biospecimens only, based on a research hypothesis that does not include association with a clinical endpoint, is considered a low priority use of this unique and finite resource; the investigator is advised to request biospecimens from alternative sources.

Table 1. SWOG biospecimen inventory as of January 2011

<table>
<thead>
<tr>
<th>Cancer type</th>
<th># Cases</th>
<th># Blocks (FFPE)</th>
<th># Unstained slides (FFPE)</th>
<th>Whole blood (1×10^6 cells/vial) # vials</th>
<th>Frozen tumor (1×10^6 cells/vial) # vials</th>
<th>MNC (1×10^6 cells/vial) # vials</th>
<th>Plasma (0.5–1 mL) # vials</th>
<th>Serum (0.5–1 mL) # vials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>7,712</td>
<td>5,178</td>
<td>32,742</td>
<td>110</td>
<td>0</td>
<td>3,405</td>
<td>7,434</td>
<td>30,179</td>
</tr>
<tr>
<td>GI</td>
<td>2,487</td>
<td>2,500</td>
<td>5,832</td>
<td>1,619</td>
<td>222</td>
<td>0</td>
<td>1,185</td>
<td>23,753</td>
</tr>
<tr>
<td>GU</td>
<td>920</td>
<td>104</td>
<td>2,197</td>
<td>102</td>
<td>0</td>
<td>621</td>
<td>1,765</td>
<td>1,871</td>
</tr>
<tr>
<td>Lung</td>
<td>1,997</td>
<td>625</td>
<td>3,123</td>
<td>102</td>
<td>4,431</td>
<td>8,486</td>
<td>3,482</td>
<td></td>
</tr>
<tr>
<td>Leukemia, lymphoid</td>
<td>633</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>8,145</td>
<td>2,860</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukemia, myeloid</td>
<td>3,110</td>
<td>0</td>
<td>0</td>
<td>42,190</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphoma</td>
<td>2,968</td>
<td>1,554</td>
<td>1,729</td>
<td>105</td>
<td>46</td>
<td>2,303</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Leukemia, myeloid</td>
<td>1,505</td>
<td>490</td>
<td>3,566</td>
<td>878</td>
<td>0</td>
<td>15</td>
<td>234</td>
<td>16,516</td>
</tr>
<tr>
<td>Melanoma</td>
<td>1,101</td>
<td>14</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>27</td>
<td>1,900</td>
</tr>
<tr>
<td>Total</td>
<td>22,556</td>
<td>10,680</td>
<td>49,253</td>
<td>3,063</td>
<td>50,365</td>
<td>10,166</td>
<td>47,288</td>
<td>62,960</td>
</tr>
</tbody>
</table>

Grand Total           | 233,775 |

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*Prostate cancer specimens from treatment trials. Additional biospecimens are available from chemoprevention studies in Cancer Control & Prevention Studies, including Prostate Clinical Prevention Trial (PCPT) and SELECT. More information is available on their respective websites (http://swog.org/Visitors/pcpt/) and (http://swog.org/Visitors/select/).

Abbreviations: FFPE, formalin-fixed paraffin embedded; MNC, mononuclear cells.
Overview of the SWOG Biorepositories

Table 2. Illustration of SWOG biospecimen collection for recently closed breast cancer studies

<table>
<thead>
<tr>
<th>Study trials.gov identifier</th>
<th>Phase</th>
<th>Histology</th>
<th>Stage</th>
<th>Study agent(s)</th>
<th>Study plan (n)</th>
<th>FFPE blocks</th>
<th>Slides</th>
<th>Whole blood</th>
<th>PBMC</th>
<th>Serum</th>
<th>Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td>S0215 NCT001041067 II</td>
<td>II</td>
<td>HER-2 pos</td>
<td>IV</td>
<td>Docetaxel/ Vinorelbine/ Filgrastim</td>
<td>29</td>
<td>29</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>S0430 NCT00107276 II</td>
<td>II</td>
<td>HER-2 neg</td>
<td>IV</td>
<td>Capcitabine/ Cyclophosphamide</td>
<td>96</td>
<td>0</td>
<td>0</td>
<td>10</td>
<td>146</td>
<td>357</td>
<td>321</td>
</tr>
<tr>
<td>S0226 NCT00075764 III</td>
<td>III</td>
<td>ER/PgR pos</td>
<td>IV</td>
<td>Anastrazole with or without Fulvestrant</td>
<td>690</td>
<td>341</td>
<td>2079</td>
<td>51</td>
<td>632</td>
<td>11001</td>
<td>1323</td>
</tr>
<tr>
<td>S0307 NCT00272205 II</td>
<td>III</td>
<td>HER-2 neg</td>
<td>I-III</td>
<td>Bisphosphonates (zoledronate, clodronate or ibandronate)</td>
<td>5400</td>
<td>3434</td>
<td>24547</td>
<td>20</td>
<td>2592</td>
<td>14257</td>
<td>5656</td>
</tr>
</tbody>
</table>

protocol treatment, demographics (e.g., gender, age, ethnicity) and outcome, as well as by type of specimen as shown in Table 1. An additional specimen inventory from chemoprevention trials in prostate cancer can be found on the SWOG website, related to PCPT and SELECT cancer control studies [PCPT (http://swog.org/Visitors/pcpt/) and SELECT (http://swog.org/Visitors/select/)]. SWOG specimens are stored in various formats, including frozen [tumor tissue, peripheral blood mononuclear cells (PBMC), whole blood, plasma, and serum] and fixed formalin-fixed paraffin embedded (FFPE) tissue blocks or slides. The number of patients represented by each collection is also available. As of January 2011, the collective inventory from the solid tumor and hematologic cancer banks represents more than 330,000 specimens contributed by more than 20,000 patients enrolled in SWOG cancer clinical trials since 1984.

The inventory of specimens from completed clinical trials is available for translational research. Details of the clinical trials can be retrieved in one of several ways: (i) using the clinical trials identifier number at trials.gov, (ii) accessing the protocol abstract posted on the SWOG website by SWOG Study Number, or (iii) via email to biospecimens@swog.org and publications, available in PubMed. The example in Table 2 provides an illustration of the diverse inventory of specimens at the SWOG solid tumor repository for 4 completed breast cancer clinical studies representing almost 7,000 patients, including specimens of FFPE tissue sections (Blocks), slides (FFPE slides), whole blood, serum, mononuclear cells (MNC), and plasma frozen in multiple aliquots (1 mL, 2 mL). Patient identifiers, however, are protected and kept confidential by the SWOG statistical center.

The repositories of specimens from patients with leukemias (myeloid and lymphoid) are composed primarily of frozen cells isolated from bone marrow aspirates and/or peripheral blood obtained at baseline (pretudy), during treatment or at follow-up (including relapses), depending on the study design. For many lymphoma and myeloma patients’ specimens of serum and FFPE blocks are obtained in addition to marrow and peripheral blood cells. The inventory of each tumor type reflects ease of specimen collection and types of trials (mostly phase 2 and 3 trials in advanced disease), for this reason, the number of cases from breast cancer exceeds lung and pancreas tumors. Access to specimens in both solid tumor and hematologic cancers follows the same process described below.

Operation and policies

Biospecimens contributed by patients enrolled on SWOG trials are centrally processed for use in protocol-specified research and, when patient permission is granted, banked for future studies. Protection of the participant’s privacy/confidentiality to donate tissues for research is emphasized through informed consent processes that are compliant with federal and local regulatory requirements and approved by institutional review boards (IRB). Individuals participating in SWOG clinical trials maintain their right to withdraw consent for biospecimen collection or for future use of specimen. Research investigators interested in using these specimens must submit an application (described below) and evidence of approval of the proposed research plan from their respective institutional review boards. In addition, investigators must provide sufficient proof of expertise and funding to complete the proposed studies. SWOG does not provide funding for translational research studies, however, will provide supporting letters in grant applications seeking funding for approved research. There is no cost associated with standard specimen processing, e.g., DNA extraction, PBMC isolation and creation of frozen cell pellets; however, investigators must pay cost for shipment of specimens to and from the research lab and the SWOG biorepository. The investigator has two years of the research plan from the date of approval to secure funding and initiate research. The research is expected to be completed within two years unless other considerations are mutually agreed upon.

Using established protocols for biospecimen handling, the biorepository staff complies with a manual of standard...
operating procedures for assisting in procurement, use of specimen collection kits, and specimen processing, storage, tracking, and distribution. The quality of the specimens is monitored at many levels beginning with verification of patient and specimen identifiers on receipt in the SWOG Biorepository. Specific quality assurance measures depend on specimen type, and range from assessment of color and turbidity of serum samples, to estimates of tumor cell content in histologic sections, to DNA quality and content in extracts of tumor-related specimens. The bank works closely with end users to ensure optimal specimen quality for the intended research platform and specimen requirements such as DNA quantitation or aliquots needed for genotyping assays, e.g., PCR, genotyping, genome analyses, mRNA or miRNA analyses using a variety of platforms. If biospecimens fail quality check using positive and negative internal controls in the recipient laboratories then the biorepository will replace the specimen when possible. The biorepository will isolate DNA, quantify it by Nanodrop method, and dispense to aliquots as specified or required by specific platforms for shipment to investigators. The lifecycle of each specimen is documented according to processing method, aliquots created of a specific type (DNA, RNA, serum) and specimen integrity. The details of specimen collection schema and methods are included in the clinical study protocol (Section 15, Special Instructions) and details of methods for processing are available upon request should an investigator wish to review a method (e.g., extraction of nucleic acids from a specimen) with the biorepository. The SWOG Operations Office, Statistical Center and Biorepository are governed by SWOG policies that provide oversight for protection of privacy and confidentiality in accordance with guidelines developed by the NCI and consensus statements for the ethical use of specimens in genetics research (1). SWOG conducts periodic performance reviews through audits at participating institutions to assure compliance with protocol stipulations for tissue collection, federal requirements and local IRB issues. Finally, biospecimen collections are audited annually to ensure accuracy of specimen tracking annotation, standard operating procedures and manual of operations, security and specimen processing, and storage methods and record keeping. In order to evaluate the quality of specimens, the sample integrity is noted on specimen intake, and pathologist review is carried out before and after specimens are processed as required by the clinical protocol or research study, for example, review of tumor cellularity, histopathologic review, and specific immunohistochemical assays. If the tumor integrity does not pass the initial evaluation, then a request is sent to the site to submit additional specimens, when available.

Access and distribution
To promote cancer research, SWOG provides an open access application procedure for use of specimens following publication of the primary results of the clinical trial. The process, templates, and details are also on the SWOG website (available from: http://www.swog.org/Visitors/TranslationalMed.asp). Submission and distribution of SWOG specimens are tracked using the online specimen tracking system, a tool developed by the SWOG statistical center.

The process for reviewing applications for access to specimens from the SWOG biorepository involves the following steps:

i. The investigator should become familiar with the clinical data obtained on the clinical trial(s) requested, preferably through review of the published manuscripts describing the patient population and the primary trial results. The investigator must provide preliminary evidence for their hypothesis and describe how achieving the proposed aims is likely to contribute meaningfully to the knowledge base of the research field related to the clinical trial, disease, or development of biomarkers.

ii. Investigator submits query by e-mail to ascertain feasibility of request, such as whether needed specimens from the trial(s) are available and whether sample format, quantity and quality are sufficient to carry out stated research. Request should be submitted in sufficient detail using forms provided on website http://swog.org/visitors/biorepository/application.asp and e-mailed to biospecimens@swog.org.

iii. Investigator consults with SWOG statisticians on the number of specimens with specified clinical or histopathologic criteria required for their study.

iv. Once notified that the request is feasible, the investigator submits a formal application using the SWOG Translational Medicine Research Proposal template. This formal application includes a scientific research plan with the following elements:
   a. Name of principal investigator and location of research
   b. Research hypothesis
   c. Preliminary data
   d. Experimental methods
   e. Statistical plan (justification of number of samples requested)
   f. Specimen request:
      i. Number of specimens
      ii. Type/amount/processing or special instructions
   g. Justification of request for use of SWOG biospecimen resource (specimen and associated clinical data) to confirm research hypothesis and advance scientific knowledge

v. The SWOG Triage Committee, consisting of internal and external advisors, meets weekly to review applications. The review follows NIH Grant Review criteria and the application is evaluated on the following categories: significance of proposed research, expertise of investigator(s), innovation, technical approach, and research environment.
Investigators are deemed qualified to complete the proposed research based on prior work and institutional support, such as the use of research labs, cores, and collaborations.

vi. A written response from the Triage Committee review is then provided to the investigator, indicating approval, revisions requested or rejection of application. Investigators may resubmit revised proposals.

vii. Once approved by the SWOG Triage Committee, SWOG will then submit the application to NCI Cancer Therapy Evaluation Program (CTEP; or appropriate CTEP Disease Steering Committee), if the request includes specimens from trials that were conducted by several cooperative groups (Inter-group trials) or from a SWOG trial with a tissue specimen request or patient cohort of 100 or greater.

viii. Following approval(s) of the research plan, authorization of specimen distribution takes place once the following steps are completed:

a. Confirmation of regulatory documents (IRB approval) at the submitting investigator’s institution
b. Material use agreement (MUA) completed by all parties
c. Contracts executed by SWOG
d. Evidence of adequate funding to complete the research

The overall process for obtaining SWOG specimens is depicted in Figure 1. The timeline for SWOG internal review of the research proposal [steps (v) and (vi) above] is approximately 7 to 10 days. NCI review, such as CTEP and the Disease Steering Committee, when required, typically takes an additional 30 to 60 days [step (vii)]. Once a research proposal is approved, the next steps are to initiate institutional review board (IRB) applications, negotiate contracts and complete a Material Use Agreement (MUA). The MUA includes provisions outlining use of the specimens, as approved in the research proposal and completion of the project through publication of results. The principal investigator and local host institutions control part of the process involving execution of contracts, MIAs and confirmation of IRB approval, and the timeline to complete these steps is dependent upon diligence at individual sites. Proof of funding sufficient to cover costs of specimen processing, shipment and research is provided by the investigator. Investigators often obtain funding from NIH grants, such as R01, R21, SPORE program project grants, program project (P) and K awards.

Once the lab research is completed, the principal investigator works with the SWOG Statistical Center to perform the linkage of the laboratory data with the outcome and other clinical data, and the analyses of prognostic or predictive associations. The SWOG Statistical Center maintains the link of codes to patient identification numbers in a secure database so that protection of patient’s confidentiality is upheld. In the course of the research, it may be helpful to consult with SWOG statisticians or study coordinators on specific clinical trial endpoints or secondary analyses in order to refine the research hypothesis.

Selected examples of use: Retrospective studies, data analysis, and clinical annotation

More recent examples of biospecimen use are shown in Table 3. FFPE tissue has been successfully used for creation of freshly cut tissue microarrays for immunohistochemistry (study SWOG-9313), for preparation of slides for extraction of RNA for measurement of expression of specific genes by quantitative RT-PCR (study SWOG-8814), for...
gene-expression profiling and copy number variation detection (study SWOG-8819), for FISH analysis of gene amplification (S0342), and for genotyping studies (SWOG-9321, C150105, S0124). Secondary research using biospecimens collected may have a significant impact on the primary clinical trial, such as C08405, a clinical study investigating the contribution of either cetuximab or bevacizumab to chemotherapy treatment regimens in advanced colorectal cancer. While this trial was ongoing, scientific evidence emerged from retrospective studies that genetic mutations in K-ras resulting in constitutive activation of epidermal growth factor receptor (EGFR) signal transduction pathways is associated with lack of benefit to cetuximab and chemotherap

The assays used for confirmatory studies were optimized and conducted in a centralized Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory of the SWOG biorepository (3). The clinical study was resumed with modified eligibility criteria incorporating an assay for detection of mutations in Kras for determination of eligibility of patients to enroll in the clinical study. Ultimately, the Food and Drug Administration (FDA) posted a guidance on the drug label advising molecular testing for the intended use of cetuximab in colorectal cancer(http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm172905.htm (valid as of 3-25-2011))

Research using biospecimens obtained from cancer clinical studies have informed new scientific hypotheses incorporated into new clinical trial designs, such as the following examples:

- Identification of gene-expression signatures in multiple myeloma (4) has been incorporated into a prospective study, S0124. "A Prospective Observational Biologic Study of Asymptomatic Patients With
Overview of the SWOG Biorepositories

- EGFR status by chromosomal and immunohistochemistry assays is prospectively tested in S0819, advanced nonsmall cell lung-cancer trial incorporating clinical endpoints compared by EGER FISH positive status (5, 6), and to prospectively test EGFR, K-ras, and other biomarkers in association with efficacy (https://swog.org/Members/ClinicalTrials/ViewProtocolDetails.asp?ProtocolID=2143)

- The prognostic value of the 21-gene recurrence score assay in postmenopausal women with lymph node-positive status treated with chemotherapy evaluated in retrospective studies (7) is currently being tested prospectively in a randomized phase III trial, S1007, A Phase III, Randomized Clinical Trial of Standard Adjuvant Endocrine Therapy +/- Chemotherapy in Patients with 1–3 Positive Nodes, Hormone-responsive, and Her2-Negative Breast Cancer focusing on Recurrence Score (RS; available from: https://swog.org/Members/ClinicalTrials/ViewProtocolDetails.asp?ProtocolID=2197).

Ongoing biospecimen studies also use serum for proteomics, plasma for miRNA profiles, whole blood, circulating tumor cells and peripheral blood mononuclear cells for genotyping and genome wide analysis studies.

Discussion

Future directions

Translational research using the unique resources of SWOG aims to improve existing treatment or to provide definitive data for developing new therapeutic approaches or validating drug targets, biomarkers, or molecular diagnostic markers. By associating such markers with a clinical database with mature endpoints, SWOG facilitates translational research in cancer treatment that ranges from discovery of molecular pathways involved in specific cancer subtypes, to validation and comparative effectiveness of new biomarkers to standard clinical prognostic tools.

New technologies allow more efficient use of any biospecimen resource. For example, genotyping studies now require 5 ng or less of input DNA, and multiplex biomarker assays allow multiples of markers to be interrogated, simultaneously. Innovations in isolation of nucleic acid that enable analysis of both RNA and DNA are especially important, given that much of the SWOG solid tumor inventory consists of formalin-fixed paraffin embedded tissues. Limitations presented by older fixation methods and best practices for specimen processing (8). The introduction of next generation sequencing technologies will enable more sensitive and robust detection of genomic variation and greater depth of understanding of both global changes in chromosomal structure and specific genomic rearrangements in tumor cells (9). Recent advances in detecting using archived serum and plasma biospecimens (10) enhance the possibility of using less invasive methods to monitor cancer disease state over time. Detection of epigenetic modulation of the cancer genome (11) is expanding, and this warrants systematic collection of tumor specimens and matched somatic tissues as part of each specimen collection protocol so that comparisons to germline (constitutive DNA profiles) may be determined.

The SWOG biorepository also preserves tissue slides so that molecular markers can be mapped onto the tumor architecture and features of the tumor tissue microenvironment. The introduction of “virtual” pathology and direct annotation of histomorphologic characteristics of the tissue slide provides instant access to this bioresource to a wider panel of experts and investigators. Biospecimen collection is a dynamic process, incorporating best practices to anticipate new technologies and faster turnaround times required by clinical trials that target therapies based on information about drug targets or pathways activated in individual tumors. Capturing these data will provide a database of great depth on populations treated in clinical trials and will offer an opportunity for in silico research on pathways across diseases. SWOG and the cooperative group system provide a valuable resource for retrospective translational research and prospectively planned validation of biomarkers (12, 13). Together, these tools and processes are intended to increase access to biospecimens and valuable annotated data related to SWOG clinical trials, and to advance cancer clinical trials into the era of genomic medicine.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References
