

## Promise and problems of translational research

Doris M. Benbrook<sup>a,\*</sup>, Beth Y. Karlan<sup>b</sup>

<sup>a</sup> Department of Obstetrics and Gynecology, University of Oklahoma Health Sciences Center, P.O. Box 26901, Room WP2470, Oklahoma City, OK 73190, USA  
Department of Biochemistry and Molecular Biology, University of Oklahoma Health Sciences Center,

P.O. Box 26901, Room WP2470, Oklahoma City, OK 73190, USA

<sup>b</sup> Women's Cancer Research Institute at the Samuel Oschin Comprehensive Cancer Institute and Division of Gynecologic Oncology, CSMC Burns and Allen Research Institute, Ceders-Sinai Medical Center, 8700 Beverly Boulevard, Los Angeles, CA 90048, USA

Received 22 August 2006

*This session was chaired by Doris M. Benbrook and Beth Y. Karlan  
with presentations by William Beck and Robert Ozols*

*Topics:* The present infrastructure available to conduct translational research associated with ovarian cancer treatment trials, ways to improve collaboration

The potential for synergistic collaboration to increase progress in the state of the science for ovarian cancer is provided by services and programs developed and supported by National Cancer Institute (NCI), the Gynecologic Oncology Group (GOG) and the Specialized Programs of Research Excellence (SPOREs). The capabilities span from drug discovery to phase III clinical trials, all of which are available for collaborative interaction with each other and with individual researchers.

### NCI drug discovery and development resources

The resources available for the drug discovery phase include the NCI RAND (Rapid Access to NCI Discovery resources) program, which facilitates investigators in discovering small molecules, biologics or natural products through mechanisms such as high throughput screening, recombinant target protein production and characterization and generation of chemical libraries. Additional support for drug discovery is provided by the Discovery Services of the NCI Developmental Therapeutics Program, which provides repositories of synthetics, natural products, radiolabeled materials, biologics, reference standards and reagents, tumors and angiogenesis resources. These resources can be used for screening strategies and validation of targets as pharmaceuticals and biomarkers. The Discovery Services also provide inbred and hybrid animals, *in vivo* testing

of single compounds and web accessible data and search tools. The overarching goal of RAND and Discovery Services is to provide the resources needed to determine if new molecule or approach is a viable candidate for expanded clinical evaluation (clinical proof of principal).

Drug development is facilitated by the NCI RAID (Rapid Access to Intervention Development) Program, which shares the goal of clinical proof of principal for lead chemicals, natural products and biologics. In addition to further validation studies, RAID provides services needed to advance the molecule or strategy in the next step toward clinical trial by providing standard research services required for submission of an Investigational New Drug (IND) application the Food and Drug Administration (FDA). These standard services are difficult to fund in an academic setting. Individual members of the GOG and SPOREs have taken advantage of these NCI drug discovery and development services and have been awarded RAID and RAND grants.

### SPORE translational resources

There are 5 academically based Ovarian Cancer SPORE programs supporting translational research focused on ovarian cancer. The Ovarian Cancer SPORE program was initiated in 1999 with the funding of four sites located at the University of Texas MD Anderson Cancer Center, the Fox-Chase Cancer Center, the Fred Hutchinson Cancer Center and the Brigham and Women's Hospital Ob/Gyn Epidemiology Center and has recently expanded to include five sites. Each of the SPOREs supports several research projects that are co-directed by a

\* Corresponding author. Present address: Department of Obstetrics and Gynecology, University of Oklahoma Health Sciences Center, P.O. Box 26901, Room WP2470, Oklahoma City, OK 73190, USA. Fax: +1 405 271 2976.

E-mail address: [Doris-Benbrook@ouhsc.edu](mailto:Doris-Benbrook@ouhsc.edu) (D.M. Benbrook).

clinician and a basic scientist and are focused on translational research. Critical research infrastructure and cores have been developed by the SPOREs to sustain translational research objectives for projects within the SPOREs and other research groups. Multiple new molecularly targeted agents are being developed and tested in phase I clinical trials within the SPORE institutions. Each SPORE has their own list of multiple phase I and II trials of their new agents.

### **GOG translational resources**

Translational research is conducted in the GOG through the Committee on Experimental Medicine (CEM). GOG investigators can seek expertise for developing translational research for their clinical protocols through CEM subcommittees focused on specific molecular mechanisms. The CEM also is proactive in identifying translational research opportunities and developing translational protocols to address pertinent clinical questions. Several CEM core laboratories are available to participate in high priority focused protocols, working closely with the GOG Statistics Office. The Clinical Pharmacology Core measures drug levels in plasma from patients, the Molecular Pharmacology Core measures expression of drug-resistant associated genes and proteins in the same patients and the GOG Statistics Office determines if there are correlations between the various endpoints. An additional emphasis of the Molecular Pharmacology Core is developing novel targets for diagnostics and therapeutics, such as novel splicing factors [1] and post-translational protein modifications [2], and is expanding the focus to encompass angiogenesis protocols. The Hormone Receptor Core performs immunohistochemical analysis of estrogen and progesterone receptors in tissue specimens, which are then correlated with clinical outcomes. The original focus of the Clinical and Molecular Pharmacology Cores on ovarian cancer and the Hormone Receptor Core on endometrial cancer has been expanded to include other gynecologic cancers.

Banking of clinical specimens for translational research protocols is coordinated by the GOG Tissue Bank, which was established in 1991 as an NCI-funded repository for collecting and banking tissues and serum for research. From 1991 through 1998, the eligibility for banking GOG clinical specimens for research was restricted to patients with ovarian cancer that either participated (internal bank) or did not participate in a GOG clinical protocol (external bank). Internal bank specimens, therefore, are associated with rather extensive clinical information including demographic and tumor characteristics as well as details regarding treatment and patient outcomes such as toxicity, response, progression/recurrence and survival data. The external bank specimens are associated with rather limited clinical information, including certain demographic and tumor characteristics, available because the patient consented to provide clinical specimens for research, but did not participate in a GOG clinical protocol. In 1998, the GOG Tissue Bank expanded the eligibility for banking GOG clinical specimens for research to include those patients with carcinoma of the cervix or uterine corpus. To date, the GOG

Tissue Bank has established a repository of tissue and serum specimens from 6227 patients participating in the GOG banking protocol (GOG 136). This includes specimens from 4046 patients with ovarian cancer (966 cases associated with the GOG internal bank and 3080 cases associated with the GOG external bank). The GOG Tissue Bank also banks clinical specimens from patients participating in a GOG clinical protocol with specific specimen collection requirements and translational research objectives. The GOG Tissue Bank not only has a proven track record for banking specimens, but also has been extremely successful in distributing high quality internal and external bank specimens to a diverse array of investigators. Through 2005, the GOG Tissue Bank served 215 investigators. The results from these various research projects have yielded more than 210 publications and contributed to funded grant applications.

### **Collaborative clinical and translational resources**

Although phase I clinical trials for new treatment and prevention strategies can be conducted at individual Academic Institutions and SPOREs, the involvement of multiple institutions is needed to complete the larger phase II and III trials. SPOREs are currently conducting multiple phase II trials as part of large consortiums of SPORE and other academic institutions and in collaboration with the GOG. The GOG provides the infrastructure to run clinical trials at phase II, randomized phase II, phase I of combination therapies and randomized phase III. A GOG committee focused on ovarian cancer develops, reviews and monitors all ovarian cancer treatment trials, while prevention and control trials are handled by the GOG Cancer Prevention and Control Committee (CPC). The statistical evaluation of the trial is performed by the GOG Statistical Office. An example of a successful collaboration between a SPORE and the GOG is the phase II trial to assess activity and tolerability of Gefitinib (ZD1839, Iressa) in patients with recurrent or persistent ovarian carcinoma or primary peritoneal cancer. Gefitinib is an anilinoquinazoline that reversibly competes with ATP at a critical ATP-binding site in the Epidermal Growth Factor Receptor (EGF-R). The GOG conducted the trial (GOG170C), while the translational research was performed in the Fox-Chase SPORE. The results provided significant insight in identifying patients that could benefit from this molecularly targeted agent. It was found that EGF mutations in the catalytic domain are present, but rare, in ovarian cancers, (3 to 4%), but the presence of these mutations is associated with drug response [3]. Without this translational research component, Gefitinib would have been considered inactive, but the correlation of mutations with drug response identified a subset of patients that could benefit from this molecularly targeted agent.

### **Obstacles to ovarian cancer translational research**

There are multiple obstacles to addressing the key translational research questions and objectives for ovarian cancer. The identification of key molecular targets or pathways

driving ovarian cancer is hampered by the complexity of ovarian cancer genetics in comparison to other types of cancer. The ability to rapidly test multiple new agents for activity is hindered by the low incidence of ovarian cancer. This low accrual also harms the ability to perform highly complex protocols that can address important issues, such as validating imaging modalities by comparison with tissue biopsies, because such complex studies will be limited to institutions that have the existing infrastructure capable of handling these protocols.

The implementation and patient accrual to collaborative trials between ovarian SPOREs have been slow. There are multiple issues responsible for the delays that also act as barriers to increased collaboration. At the institutional level, legal issues such as tissue sharing and prioritization of competing trials need to be addressed. The logistics of managing multi-institutional collaborations, including issues such as data management, need to be developed. The involvement of industry in cooperative clinical trials faces legal and time issues. Commercial enterprises need to have clinical trials completed as rapidly as possible. The existence of different legal issues with different institutions can delay the activation of a protocol at multiple sites.

The high mortality of ovarian cancer is due to the inability to detect this disease at early stage where current standard of care is most effective. Development of screening strategies is therefore of high priority, but is hampered by the difficulty in obtaining tissue from early stage disease. Study of these early stage tissue specimens in comparison to noncancerous tissue could identify molecular targets for screening and prevention strategies.

#### **Proposals to enhance collaborative translational research of ovarian cancer**

Historical the GOG has designed protocols powered for primary clinical endpoints, but has recently evolved to perform protocols powered for translational research endpoints. A protocol is in development to bank and study ovarian cancer specimens, specifically at early stage, to identify and validate molecular targets for screening and prevention strategies. This is a stand alone translational research protocol that does not involve study of a clinical treatment. The approach for identifying and obtaining early stage ovarian cancer specimens and noncancer controls is to consent patients who have surgeries scheduled for evaluation of a pelvic mass. This is the patient population where most early stage ovarian cancers are identified. Consent of the patient prior to surgery is therefore essential to legally obtaining the early stage specimens and also provides the opportunity to collect normal, benign and premalignant tissues needed for evaluating sensitivity and specificity of potential biomarkers. This protocol is an opportunity to collect epidemiologic data and other specimens, such as serum, plasma, circulating cells, urine and buccal cells, which could be used for the development of screening assays. A database linking the epidemiologic, clinical and laboratory

data will provide a powerful resource for studies of early stage ovarian cancer. This protocol is an expensive effort and Community Clinical Oncology Programs (CCOP) would need additional resources to participate in tissue collection services. Detailed standard operating procedures (SOPs) for collection of specimens have been developed by the GOG and would need to be followed carefully in order to assure sufficient specimen quality for molecular analysis.

Increased involvement of CCOPs could enhance the GOG's capability to perform the translational research by increasing accrual, but there are several drawbacks that need to be overcome. The points awarded by the GOG will not be sufficient to defray the cost of obtaining local IRB approval and clinical specimen coordination in institutions that only accrue small numbers of patients. Other mechanisms to improve accrual include greater education of ovarian cancer patients and increased access to knowledge regarding available clinical trials. An action item for the meeting was to develop a working group of patient advocates and investigators from the GOG, SPOREs, NCI and industry to develop means for patients to find open clinical trials. Another working group consisting of investigators from GOG, SPORES and contract holders will convene to address the issues of slow patient accrual to challenging phase I and II trials. To hasten initiation and completion of phase II trials, miniconsortium consisting of 10 GOG institutions each will be formed and assigned specific trials. Efforts will be made with CTEP to streamline the paperwork involved in opening the phase II trials. Specific trials will be prioritized for study of translational research endpoints in order to avoid having these endpoints in every trial.

Another proposal is to power select clinical trials based on primary translational research endpoints. Several key translational research areas that need to be addressed in these trials include studying the tumor microenvironment and angiogenesis and are dependent upon standardized clinical specimen acquisition and processing and collection of associated clinical data. The standardized SOPs developed by the GOG for tissue acquisition will need to be instituted by all participants. The major issue with collection of clinical specimens is that it harms accrual of clinical trials. The main factor for this association is the lack of sufficient compensation for clinical specimen coordination. The points paid for acquisition of ovarian clinical specimens are significantly lower than the points for endometrial cancer specimens.

Designing trials with translational research endpoints as primary endpoints rather than secondary endpoints have several benefits. Some IRBs will only approve collection of biopsies in certain situations if the translational research question is the primary endpoint and not a secondary endpoint. Clinical trials powered for primary clinical endpoints may not be sufficiently powered for translational research endpoints. An alternative is to build in a statistical objective that if achieved would allow another phase of increased accrual to meet the translational research objective. New statistical methods will be needed to address the 3-dimensional complexity of biomarker interaction.

## References

- [1] He X, Ee PLR, Coon JS, Beck WT. Alternative splicing of the multidrug resistance protein 1/ATP binding cassette transporter subfamily gene in ovarian cancer creates functional splice variants and is associated with increased expression of the splicing factors PTB and SRp20. *Clin Cancer Res* 2004;10:4652–60.
- [2] Mo Y-Y, Yu Y, Theodosiou E, Rachel Ee PL, Beck WT. A role for Ubc9 in tumorigenesis. *Oncogene* 2005;24:2677–83.
- [3] Schilder RJ, Sill MW, Chen X, Darcy KM, Decesare SL, Lewandowski G, et al. Phase II study of gefitinib in patients with relapsed or persistent ovarian or primary peritoneal carcinoma and evaluation of epidermal growth factor receptor mutations and immunohistochemical expression: a Gynecologic Oncology Group study. *Clin Cancer Res* 2005;11:5539–48.