

The GOG Foundation, Inc. Translational Science



Michael J Birrer, MD, PhD, and Heather A Lankes, PhD, MPH

Translational Science: The Challenges

Translational Science. The goals of translational science (TS) in the context of cancer clinical trials include (1) identifying individuals at risk; (2) preventing cancer development; (3) identifying early primary disease; (4) predicting which patients will likely respond to specific therapies and the durability of the response; (5) predicting recurrence prior to symptoms; and (6) determining why tumors become refractory to a given therapy. The challenges to successfully achieving these goals vary widely among the gynecological malignancies; however, there are several themes common to the different tumor types. These challenges are frequently related to the specific scientific/clinical question being addressed.

Identifying Gynecologic Cancer Risk. Perhaps the greatest strides in gynecologic cancer translational science have been made in the identification of patients at high risk for cancer development. About two decades ago, the only indication of inherited gynecologic cancer risk was a family history of the disease. Currently, it is known that germline mutations in BRCA1 and BRCA2 and a series of genes in the Fanconi DNA repair pathway, as well as the mismatch repair family of genes, account for the majority of inherited ovarian and endometrial cancer risk¹. Germline DNA can be screened for mutations in these genes and inherited risk ascertained. Despite this, several major challenges remain.

Outstanding Issues in Identifying Risk. To date, the gene(s) responsible for inherited risk in individuals with a strong family history of gynecologic cancer and no mutations in characterized genes remain(s) unidentified. Additionally, and perhaps more importantly, is the inability to determine the precise degree of risk in mutant gene carriers,

as it varies widely in different families. Addressing these issues requires tracking very large numbers of individuals at inherited risk of gynecologic cancer. Such an effort in the context of The GOG Foundation, Inc. (GOG-F), either within NRG Oncology (NRG) or GOG Partners (GOG-P), is hampered by the fact that the required population is generally healthy women, who are not usually seen by gynecologic oncologists. Further, the prospective collection of biospecimens and clinical data in such a cohort is a time consuming and expensive challenge.

Prevention. In an ideal world, the best strategy to eliminate death from gynecologic cancer is to prevent its occurrence. The question is how to test potential prevention strategies. To truly test a drug's ability to decrease gynecologic cancer development requires a large number of women treated for a prolonged period of time. This number could be decreased somewhat if only high-risk women were studied; however, even with this approach, the number required is large. For instance, large-scale phase III trials using HPV vaccines or potential chemoprevention agents are not practical in NRG or GOG-P. As an alternative, smaller phase II studies can be designed using surrogate endpoint biomarkers as an indication of a preventive effect. In such a setting, women can be treated with a preventive agent for a limited time prior to surgery. After such time, biopsies can be obtained and analyzed for modulation of the appropriate biomarkers.

Challenges to the Surrogate Endpoint Approach to Prevention. The validation of appropriate biomarker endpoints is critical to these trials and requires significant laboratory-based effort coupled with the careful collection of biospecimens. Since many of these patients are

essentially “normal” (i.e., without cancer), the ethics involved in treating these patients (e.g., performing invasive procedures and perhaps delaying treatment) needs to be carefully considered. It is important to note, based on these assumptions, current and proposed surrogate endpoint biomarker studies are likely under-powered. Furthermore, these high-risk women are healthy, making it difficult to identify and recruit them to such trials.

Early Detection. A major scientific/clinical goal is to identify cancer early during its development or recurrence. This is less of a problem for cervical and endometrial cancers than for ovarian because of the early symptoms and adequate screening for the former. Critical to the development of better screening assays for ovarian cancer is the development of new technologies and proper storage of clinically relevant biospecimens. One approach to improved ovarian cancer screening is to add additional biomarkers to CA125 to improve sensitivity and specificity.² Another approach, proteomic profiling, is being validated after an initial promising study.³ A third approach utilizes detection of abnormal DNA in serum or plasma as an indication of cancer.⁴

Procedural Problems Hindering Early Detection. There are a variety of practical problems with conducting these types of studies in a timely fashion. The obvious samples required are serial biospecimens from a population-based study where women are followed over time until disease occurrence. The overall incidence of ovarian cancer is modest compared to breast cancer; thus, these studies would need to be quite large.

Fortunately, such samples do exist, having been collected in several large population-based studies. The drawback being that there is limited sample volume available, and some laboratory testing methods require half or more of the samples. Hence, the groups controlling the samples from these population-based studies have been reluctant to release samples without some preliminary evidence of the detection strategy robustness. In lieu of collecting another set of samples in a population-based setting, investigators are faced with developing an alternative (e.g., collecting samples from individuals undergoing surgery for a pelvic mass or risk-reducing oophorectomy and age-matched, apparently healthy individuals). The goal is then to differentiate cancer from normal and benign disease in the pelvic mass cases and detect the rare cases of pre-clinical cancer in the prophylactic oophorectomy biospecimens.

Based on estimates of malignancy incidence in these settings, it is estimated at least 2,000 samples will be

needed. The issue here is whether validation in this setting will be at all predictive of a positive outcome in a population-based setting. There is also concern as to whether markers predictive of clinical disease will be the ones that detect preclinical disease and whether markers that detect sub-clinical cancer in individuals with genetic risk are the same as those needed to detect sub-clinical sporadic disease. The last major question relates to the natural history of ovarian cancer. That is, does early stage/curable disease exist sufficiently long enough that a highly sensitive and specific test performed on an annual basis will be effective at reducing mortality? This remains an important question to answer.

Prediction of Response. The ability to predict response to therapy requires the availability of predictive biomarkers and suitable patient material. At this time, highly predictive biomarkers have yet to be identified. The greatest progress is in the use of microarrays to interrogate tumors for gene expression patterns and gene copy number; the goal being to identify differences that track with treatment outcome and survival.⁵ Progress in this effort is impeded by insufficient numbers of high-quality tumor biospecimens with adequate follow-up from women receiving similar treatment. Currently, the ideal biospecimens are frozen tumors collected at the time of primary surgery from patients entered on phase III clinical trials. The problem is that, most often, tumor tissue is not frozen at the time of surgery because the surgeon is uncertain whether the patient will be entered on a phase III trial. Furthermore, primary surgery is often performed at non-NRG and/or non-GOG-P institutions and patients are later referred to NRG and/or GOG-P institutions for entry on protocols.

These issues are further complicated in recurrent disease and with experimental therapy. In the case of recurrent disease, there is often no surgical biospecimen available at the time of recurrence. In the case of experimental therapy, especially with agents targeting specific components of signal transduction pathways, there rarely are biospecimens available pre- and post-treatment. Hence, one cannot know whether the pathway has been perturbed and, if so, whether it correlates with clinical outcome. Some of these impediments, especially in prediction of primary response, may be alleviated in the future based on technological advances and theoretical possibilities. For instance, progress is being made in the use of formalin-fixed, paraffin-embedded tissue for molecular analysis. Further, there is the theoretical possibility that serum/plasma proteome may predict response and that polymorphisms in the individual's germline DNA may be predictive.

Therapy Resistance. The mechanism(s) involved when tumors become resistant to therapy is of both scientific and clinical interest. Obviously, if critical mechanisms for loss of sensitivity to drugs could be found, they would be prime drug target candidates. Much work has gone into trying to identify drug resistance mechanisms; however, most have been done in cancer cell lines and has not reliably translated to clinical material. The material needed for such studies would involve primary tumor biospecimens from individuals with a broad range of response to therapy. Work is proceeding in this area, but it is surprising how few biospecimens of this type are available. The more interesting question relates to acquired drug resistance. In this case, the patient might apparently become disease free for a period (e.g., 1.5 to 5 years), but ultimately recur. To ascertain resistance, mechanisms operating in such tumors require a primary tumor sample matched to one obtained at recurrence. Since surgery is often not warranted for recurrent disease, there are few paired biospecimens of this type and even fewer from equivalently treated patients. How to design phase III clinical trials to address this need for biospecimen collection at primary surgery and at recurrence is a major ethical and economic challenge.

Translational Science – Gynecologic Committee: The Solution

Origins and Goals. To address the critical importance of translational science in clinical trials, the legacy Gynecologic Oncology Group (GOG) established a separate committee to provide the expertise and direction needed to fully integrate this effort into its clinical trials structure. Originally, the Tumor Biology and Science Committee (TuBaSCo) was charged with bringing basic and translational science to the GOG. In that context, TuBaSCo initiated several protocols, provided seed money for translational science grants, and convened a multidisciplinary translational science retreat in 1995. Based upon the recommendations from that retreat, the Committee on Experimental Medicine (CEM), the successor of TuBaSCo, was established. In 1997, CEM became GOG's translational science committee, which was chaired by William Beck, PhD, and co-chaired by Thomas Hamilton, PhD. The goals of CEM were to integrate strong laboratory-based, hypothesis-driven translational science into GOG clinical protocols. Thus, the aims and responsibilities of CEM were designed to: (1) generate novel translational science ideas; (2) provide scientific consultation to legacy GOG membership; (3) approve scientific content in concepts and protocols; (4) fund seed grants using NIH-type review; (5) develop and oversee core labs; and (6) organize annual scientific meetings with experts from outside and within the legacy GOG.

In 2014, following the formation of NRG, CEM was reorganized into the Translational Science (TS) – Gynecologic (GYN) Committee. The first several years of the committee's existence were challenged by ongoing National Cancer Institute (NCI) National Clinical Trials Network (NCTN) policy changes regarding the inclusion of correlative biomarker studies in clinical trial protocols and access to biospecimens remaining after completion of these correlative studies. These changes were broad and impacted all NCTN Groups. TS-GYN, however, persevered throughout several years of changes – Ultimately upholding the original goals set forth by CEM.

Composition. NRG TS-GYN is composed of individuals with varying scientific expertise and designed to cover all major areas of scientific endeavor (e.g., molecular biology, cell biology, pharmacology, radiation biology). Scientists are selected based on expertise, independent funding, and international reputation. Young Investigators are also encouraged to participate and gain experience through the mentorship of senior committee members. Throughout the years, TS-GYN has maintained a diverse membership, balancing scientists with clinicians whose expertise spans all aspects of gynecologic cancers, as well as representatives from the biospecimen bank, statistical center, and operations office.

Organization. In 2014, Michael J Birrer, MD, PhD, was appointed Chair of the NRG TS Committee, with Drs. Adam Dicker (legacy Radiation Therapy Oncology Group [RTOG]) and Matthew Ellis (legacy National Surgical Breast and Bowel Project [NSABP]) serving as Co-Chairs. The TS Committee was initially established as an overarching committee where members of NRG, regardless of disease site interest, could collectively learn about the ongoing research efforts of NRG. This endeavor continues to date via the committee's semiannual workshop. Additionally, each NRG disease site has a committee dedicated to TS.

Established in 2014, the TS-GYN Committee is chaired by Dr. Birrer and co-chaired by Heather A Lankes, PhD, MPH. Additionally, in 2018, Dr. Lankes became the TS Co-Chair of the NRG GYN Cancer Committee. The GYN Cancer Committee also includes seven GYN disease site-specific TS co-chairs – Cervix: Dmitriy Zamarin, PhD, MPH; Ovary: Rebecca Arend, MD, and Elizabeth Swisher, MD; Rare Tumor: Gloria Huang, MD; Uterine Corpus: Victoria Bae-Jump, MD, PhD, and Katherine Fuh, MD, PhD; and Developmental Therapeutics: Panagiotis Konstantinopoulos, MD, PhD. All GYN Cancer Committee TS co-chairs are jointly appointed as TS-GYN committee members.

Concept and Protocol Review. Within legacy GOG, CEM es-

tablished review procedures for protocols and concepts. Each proposal was assigned a primary and secondary reviewer as discussion leaders. This procedure, with brief introductory remarks by the Principal Investigator (PI), permitted the appropriate review of concepts and protocols, but proved to be cumbersome and time consuming.

Accordingly, in 2002, CEM changed the process to streamline the procedure. The new format was to discuss all concepts and protocols in a closed-door session on the first evening of semiannual meetings. Reviewer assignments were made several weeks before the meeting and reviewers were asked to send their critiques to the CEM Chair prior to the closed-door session. Where it could be done, concepts and protocols were approved or disapproved at the closed-door session. The results were subsequently reported at the open session the following day, at which time PIs were allowed to respond to any specific questions that arose. The results (and any pertinent information from the reviews) were presented to the Protocol Development Committee and assigned prioritization. This process ensured that all protocols and concepts were thoroughly reviewed at each semiannual meeting and that all proposed translational science was scientifically sound. Further, this process afforded CEM an opportunity to integrate translational science endpoints and the appropriate biospecimen collections into GOG trials. As a result, there was a dramatic increase in translational science in phase III trials. This included all ovarian phase III trials (GOG 218, 212, 213, 262), endometrial trials (GOG 209, 210), cervical cancer trials (GOG 219, 239), and multiple phase II trials developed at the time. While this method proved efficient, in 2013, changes were made to the CEM meeting structure to accommodate the increasing need for interaction between CEM and the Developmental Therapeutics (DT) Committee.

Given the increasing focus on targeted molecular therapies and the pursuit of personalized medicine, it became evident that the roles and expertise of CEM and DT were of utmost importance. Accordingly, the closed-door CEM session was replaced with an open, joint CEM and DT meeting. This allowed CEM and DT to convene prior to the disease site committees and review and prioritize the science and drugs of interest that should be designated as high priority by the disease site committees. CEM protocol review subsequently took place the following day after the disease site committees met. This allowed CEM to review newly submitted concepts and protocols with some knowledge of the disease site committees' reviews and critiques of the proposals (an element that was missing from the previous review method).

In 2014, along with the formation of NRG, several new NCTN policies were implemented regarding the inclusion of correlative biomarker testing in clinical trial protocols. Multiple NCI biomarker review committees were established with the purpose of scientifically vetting proposals that included correlative biomarker testing in clinical trial protocols, as well as the use of biospecimens remaining after the completion of this testing. As the actual scientific review/approval of correlative biomarker testing and banked biospecimen requests was now under the purview of NCI, TS-GYN shifted focus to: (1) generating novel translational science ideas; and (2) providing scientific consultation to NRG GYN membership. The committee continues to convene at NRG semiannual meetings, and then meeting once after all GYN disease site workshops. During the meeting, each GYN disease site co-chair provides an update of their respective disease site – Thus, allowing membership to provide feedback and guidance, as needed. Additionally, throughout the lifecycle of a clinical trial or banked biospecimen project (e.g., concept/LOI through publication), the Director of Translational Science Operations works with the study team and TS Co-Chair(s) to ensure the timely completion of appropriate NCI biomarker reviews, biospecimen logistics, biomarker testing, publication and deposition of data (where required).

Review of Banked Biospecimen Applications. Prior to the formation of the NCTN, the oversight and use of the legacy GOG Tissue Bank was strengthened by changes in the administration and utilization of banked biospecimens. This included a close, integrated relationship between CEM and its Tissue Utilization Subcommittee (TUS). TUS was directly responsible for the creation and implementation of the bank's biospecimen acquisition and use rules. All members of TUS were also members of CEM; thus, there was a seamless integration between the two. In 2011, TUS was retired after much discussion regarding ways to improve the management of projects involving biospecimen requests.

The subsequent implementation of an updated banked biospecimen application allowed investigators to apply for use of clinically annotated and non-annotated banked biospecimens. This resource was formerly referred to as the GOG Internal and External Bank, respectively. The banked biospecimen application was easy to complete and provided sufficient information for reviewers to adequately assess scientific content. Applications for non-annotated biospecimens were reviewed directly by the GOG Tissue Bank on a rolling basis, whereas applications for clinically annotated biospecimens were reviewed by CEM. They reviewed these applications in person at semi-

annual meetings and electronically in between meetings. Once approved, all applications for clinically annotated biospecimens were developed into legacy GOG protocols. These protocols were given the support of the legacy GOG infrastructure and their progress tracked by the group. Investigators were expected to present the ongoings of their research at semiannual meetings and publish the results.

With the transition to the NCTN, NCI formed the Core Correlative Sciences Committee (CCSC) in 2015. The CCSC is charged with the scientific review and prioritization of all proposals to utilize banked biospecimens collected on NCTN clinical trials. The committee is comprised of representatives from the NCTN and NCI who have expertise in oncology, laboratory science, translational research, pathology, medicine, statistics, biobanking, and patient advocacy. Dr. Birrer served as the inaugural Co-Chair of the committee, along with Lee Ellis, MD, from SWOG. CCSC appointments are made for a six-year period, at which time committee membership is rotated. In 2021, Dr. Birrer fulfilled his term as Co-Chair and Dr. Lankes was appointed to the committee as the present Chair of the NCTN Banks Group Banking Committee (GBC) Steering Committee.

On April 3, 2018, the NCTN launched Navigator, an online resource for investigators seeking biospecimens to validate hypotheses generated from prior exploratory correlative studies. At present, all NCTN Groups are required to upload the biospecimen inventories of any federally funded (legacy or NCTN) phase III, randomized phase II/III, or large biospecimen collection protocols with clinical data activated after 1995. NRG Oncology was one of the first NCTN Groups to upload biospecimen data to Navigator and, to date, has the most biospecimens uploaded out of any NCTN adult Group, the Children's Oncology Group, or the Canadian Clinical Trials Group: 65 trials, 45,109 patients, and 711,461 biospecimens. Of the uploaded NRG biospecimens, GYN contributes: 24 trials, 14,090 patients, and 221,362 biospecimens.

Any investigator may search the Navigator database for available biospecimens. To submit a request, investigators must have (or register for) CTEP-IAM credentials. After logging in with these credentials, a letter of intent (LOI) can be submitted online. The LOI is then reviewed by the Navigator Front Door Service (FDS) to ensure all required fields have been completed correctly. The FDS will correspond directly with the investigator if any corrections need to be made. Once the LOI is complete, an electronic notification is sent to the NCTN Group's Navigator Concierge. The concierge reviews the LOI and sends

it to the Biospecimen Bank (BB) and Statistics and Data Management Center (SDMC) for a high-level feasibility assessment. This high-level review essentially confirms that the requested biospecimens and clinical data exist in the database. The BB and SDMC complete a Feasibility Report that is returned to the concierge, collated, and entered into Navigator online within 45 days of LOI receipt. If feasible, the FDS notifies the investigator and instructs them to complete the CCSC Proposal Submission Form. The proposal form is a 22-section document that requests detailed information from the investigator regarding the hypothesis, background information, pilot data, biospecimens requested, assays to be done and statistical analysis plans. Investigators are also required to attest to following NCI data sharing policies and provide letters of support from all collaborators, including any statistical collaborators named in the proposal. Investigators are given six months to complete the proposal form and submit the completed document along with all letters of support to the FDS. Upon receipt, the FDS reviews the proposal packet and works with the submitting investigator on any outstanding issues. Once the proposal packet is complete, it is forwarded for CCSC review. Since the launch of Navigator, turnaround time from proposal submission to review is approximately 2-3 months. In some instances, proposals will be triaged prior to committee review. This typically occurs if the proposal is not appropriate to use the irreplaceable, highly valuable, clinically annotated NCTN biospecimens. If the proposal is forwarded to the committee for review, the investigator will typically receive a set of Key Questions from the committee to be answered prior to the committee's monthly review call. Key Questions sent to the investigator must be returned within one week and specifically address all committee questions and/or concerns. CCSC review results in "Approved," "Revisions Requiring a Response," or "Disapproved." Disapproved proposals may not be submitted again; however, the investigator may submit a subsequent request for the same biospecimens if a different hypothesis is proposed. Revisions denoted "Requiring a Response" must address all comments and/or concerns expressed by the committee. The investigator's response is then subject to an up/down vote. If disapproved, the investigator may resubmit as described above. Approval guarantees the investigator access to the requested biospecimens and clinical data for one year. During this time, the investigator must secure funding and complete all regulatory paperwork necessary for biospecimen distribution (e.g., Material Use Agreement, Internal Review Board approval). If funding and paperwork are not in place within one year, the investigator will be required to start the process over. Following proposal approval, investigators are also required to submit an-

nual progress reports and follow NCI policies regarding publication and sharing of data.

As Navigator is currently limited to select trials, NRG has established a Biospecimen Access process that mirrors that of Navigator. This process allows investigators to apply for biospecimens from trials not included in Navigator. The NRG process follows a similar workflow and timeline as the Navigator process; however, LOIs are submitted via email to the NRG Oncology Biospecimen Access Mailbox. The disease site concierge reviews the LOI and sends for BB and SDMC feasibility assessments, similar to LOIs submitted via Navigator. For NRG Biospecimen Access LOIs, there is an additional feasibility review by the disease site TS Co-Chair, allowing the co-chair the opportunity to provide feedback regarding the request. Again, if the LOI is deemed feasible, the requesting investigator is notified and given six months to complete a CCSC proposal. Once completed, the investigator returns to NRG and the proposal packet is submitted to NCI by NRG. Depending on the trial(s) requested (e.g., phase, activation date, trial outcome), the proposal is sent to one of the various NCI biomarker review committees. If approved, as with Navigator, biospecimens are held for one year while the investigator secures funding and completes the regulatory documentation required for distribution.

Project Management. Prior to the NCTN transition, CEM effort resulted in the integration of translational science into nearly all phase II and III protocols and several phase I protocols. Since 2014, the NCTN has followed the adage, “no tissue, no trial,” and strongly encouraged (if not mandated) the inclusion of biospecimen collection in nearly all NCTN clinical trials. Additionally, online resources including NCTN Navigator and NRG Biospecimen Access publicly “advertise” the ability to request biospecimens from NRG GYN clinical trials. As such, a queue of over 50 clinical trial protocols including translational research, biospecimen access requests and/or other NCI translational collaborations exist at any given time. The successful execution of GYN translational science requires close and constant interaction between TS-GYN, the BB, the SDMC, the Operations Center and Finance Office, and investigators. It became evident that given the workload, additional management meetings (outside of semiannual meetings) would be necessary to maximize efficiency. To this end, in 2012, a monthly management call was established to track the progress of all translational science projects. The CEM Chair and Co-Chair, as well as representatives from the BB, SDMC, and Operations Center were in attendance. The call allowed for prioritization, as well as trouble shooting logistical issues, and ensured the

constant progress of GYN translational science.

In 2020, it was decided that this complete TS-GYN portfolio review would occur quarterly, either at semiannual meetings or via teleconference in between those sessions. A separate monthly biospecimen distribution status call was implemented, allowing Dr. Lankes, the NRG Director of Translational Science Operations, to convene with BB distribution staff. The monthly calls provide the opportunity to review distribution prioritization, as well as troubleshoot any pain points arising during the process. Additionally, Dr. Lankes remains in daily contact with BB staff regarding operational issues and best practices.

Funding Opportunities

Pilot Study Funding. A past goal of CEM was to fund pilot studies leading to national funding and/or publication. Although limited by the amount of funding available, the legacy Group Chair’s discretionary fund provided small amounts of money for scientific projects. As such, CEM proposed to fund scientific grants via a Request for Abstracts (RFA) mechanism. In 1997, three RFA grant recipients were able to obtain independent funding based upon their preliminary results. In 1999, with additional funding from the Group Chair, CEM initiated two additional RFA competitions (translational science and genomics) that were responsive to the NCI “Director’s Challenge” to develop genomic approaches to understand cancer. CEM was empaneled to review the applications and, in 1999, made two translational research awards of approximately \$50,000 each and one genomics award of \$86,000. All these awards eventually led to publications and independent federal funding.⁵⁻⁷

In 2004, CEM re-evaluated utilization of the RFA mechanism and concluded the best way to foster the scientific goals of legacy GOG was to design and fund more translational science efforts. This meant directing all monies to those proposals which involve scientific hypotheses that were directly applicable to questions of clinical importance. Additionally, CEM decided to focus on supporting peer-reviewed funding and industry monies for legacy GOG translational science initiatives.

This effort was successful in two regards. First, and most importantly, it allowed legacy GOG to incorporate translational science into its clinical trials. CEM members successfully competed for at least seven NIH-funded grants. Included in these applications were several large programmatic applications including two endometrial Specialized Programs of Research Excellence (SPoREs). CEM members’ success rate for grant applications was approx-

imately 25 percent. CEM also successfully engaged industry in supporting translational science efforts. This provided critical monies to test important translational science hypotheses. Secondly, this effort provided an independent peer review evaluation and NIH study section review has been an important external validation of the scientific value of these efforts. Further, industry supported projects were required to go through several levels of scientific review ensuring that the goals of the effort were important and scientifically sound.

Unfortunately, following the formation of NRG, pilot study funding for GYN translational science was no longer provided. The transition to the NCTN, however, provided other funding and biomarker collaboration opportunities for investigators including the NCI Cancer Moonshot initiatives.

NCI Cancer MoonshotSM. In December 2016, the United States Congress passed the 21st Century Cures Act authorizing \$1.8 billion in funding over seven years for the NCI Cancer Moonshot. The Cancer Moonshot endeavors to accelerate progress in cancer research via three ambitious goals: (1) to accelerate scientific discovery in cancer; (2) foster greater collaboration; and (3) improve sharing of data. Amongst Cancer Moonshot initiatives are the Molecular Profiling to Predict Response to Treatment (MP2PRT) Program and the Cancer Immune Monitoring and Analysis Centers-Cancer Immunologic Data Commons (CIMAC-CIDC) Immuno-Oncology Biomarkers Network.

MP2PRT. The NCI MP2PRT Program is one of the Cancer Moonshot initiatives intended to accelerate cancer research. Per recommendation of the Clinical Trials Working Group, NCI issued a 2019 solicitation for proposals to retrospectively analyze biospecimens and outcome data previously collected from patients enrolled on NCTN clinical trials. The MP2PRT Program provided a unique opportunity to determine whether specific genomic and molecular biomarkers are associated with exceptional responders and long-term survivors. In response to this solicitation, Krishna's Tewari, MD, was awarded MP2PRT funding for his proposal, "Genomic and molecular characterization of biomarkers associated with tumor angiogenesis, DNA repair, and immunologic tolerance among exceptional responders and long-term survivors in NRG Oncology/Gynecologic Oncology Group protocol 240, a phase III, randomized, open-label, multi-institutional, international trial of chemotherapy doublets with and without bevacizumab for primary treatment of women with recurrent, persistent, and/or metastatic cervical cancer." The award provides funding for biospecimen retrieval

and preparation by the BB, distribution to NCI genomic characterization laboratories, as well as bioinformatics and statistical support for the SDMC. The project, which is currently underway, will result in whole genome sequencing (WGS) and whole exome sequencing (WES) of all eligible GOG 240 patient tumors passing pathology review for set parameters. Following project analysis and publication, all genomic data will be publicly available – thus providing an infinite, valuable translational science resource.

Immuno-Oncology Biomarkers. The past decade has seen tremendous growth in the field of immuno-oncology, including the use of antibody-based therapies, IL-2, interferons and other cytokines, immunosuppression-reducing agents, cancer vaccines, CAR T cells and adoptive cell therapy (ACT), and oncolytic viruses. In recent years, checkpoint inhibitors have proved particularly promising and multiple NRG GYN clinical trials have been developed to evaluate checkpoint inhibitors in cervical (NRG GY002, NRG GY017), endometrial (NRG GY018, NRG GY020) and ovarian cancer (NRG GY003, NRG GY009, NRG GY021). Each of these trials include biospecimen collection and NCI-approved correlative studies. Furthermore, biospecimens remaining after completion of the protocol-specified correlatives are available to address future translational science questions.

NRG GY021, a phase II randomized trial of olaparib versus olaparib plus tremelimumab in platinum-sensitive recurrent ovarian cancer, is unique in that the translational science will be done in collaboration with the CIMAC-CIDC Immuno-Oncology Biomarkers Network (CIMAC). CIMAC is an NCI Cancer Moonshot initiative that provides cutting-edge technology and expertise in genomic, proteomic, and functional molecular analysis to enhance clinical trials in cancer immune therapies. The biospecimens collected from patients enrolled on immunotherapy trials will ultimately tested in one of four CIMAC laboratories, with data being jointly analyzed by the NRG SDMC and the CIMAC Cancer Immunologic Data Commons (CIDC).

CIMAC-NCTN collaboration requires NRG Operations, BB, and SDMC, to work with CIMAC and incorporate specialized biospecimen collection into selected immunotherapy protocols. Biospecimen collection must be harmonized with the CIMAC "Umbrella Protocol" to the extent permitted by NCTN resources and policies. Specialized CIMAC biospecimen processing includes, but is not limited to, provision of specialized kits, receipt, and immediate processing of blood biospecimens by Ficoll gradient to obtain peripheral blood cells for CIMAC analy-

sis, and receipt and processing of blood biospecimens collected in Streck (cell-free DNA) tubes to obtain plasma and nucleic acids. All biospecimens are shipped directly from sites to the NRG BB, where biospecimens are processed (if applicable) upon receipt. Biospecimens are stored at the biobank until batch distribution to CIMAC laboratories at agreed upon intervals. Additionally, the NRG SDMC is required to upload clinical data to the CIDC for subsequent biomarker analysis. Throughout the process, the NRG study team and CIMAC-CIDC work together to analyze data and publish results.

Scientific Symposia, Workshops, and Work-In-Progress. Another key element in CEM scientific efforts was the organization and hosting of annual scientific symposia. These symposia were viewed as quite valuable from an education standpoint and provided a basis for scientific direction within the GOG. Past scientific symposia topics included: ovarian carcinoma (1997); chemoprevention (1998); angiogenesis (January 1999); molecular biology of gynecologic malignancies (June 1999); cDNA arrays (2000), tumor vaccines (2001); proteomics (2002); new therapeutic agents (2003); drug resistance (July 2004); mouse models (January 2005); bevacizumab and angiogenic bio-markers (January 2006); pharmacogenomics (January 2007), hormone therapy (July 2007); reliable measurement of gene expression in formalin-fixed tissues (January 2008); novel methods of aCGH analysis (July 2008), Young Investigator presentations (January 2009); clinical application of genomic medicine (July 2009); cancer stem cell research and applications (January 2010); microRNA (January 2011); pathway identification (July 2011); new strategies to identify and screen women at risk for ovarian cancer (January 2012); targeting genomic chaos in gynecologic cancer (July 2012); legacy GOG translational science, highlighting GOG 199 and 210 and The Cancer Genome Atlas (TCGA) Project (January 2013); and state of the science in cervical cancer (July 2013).

With the formation of NRG in 2014, the TS Committee began hosting a semiannual TS Workshop. The two-hour workshop provided a venue for NRG to showcase some of the ongoing translational science within the group. The workshop is open to all NRG members and typically offers three translational presentations of various topics of current interest. Past topics included: genomics platforms (February 2014); PARP inhibitors and cell-free DNA (July 2014); checkpoint inhibitors and immunogenic modulation (February 2015); head and neck U10 update (July 2015), NRG immunotherapy trials (January 2016); proteomics and novel immunotherapy trials (July 2016); high-dimensional immune monitoring of immunotherapy trials and proteomics (January 2018); NCI's Clinical Pro-

teomic Tumor Analysis Consortium (CPTAC) and CIMAC initiatives (July 2018); proteomics and CPTAC (February 2019); radiomics and artificial intelligence approaches in glioblastoma (July 2019); imaging and informatics for big data in multi-site trials and biomarker-driven patient selection for breast cancer immunotherapy (January 2020); and current translational science efforts in genitourinary, brain and developmental therapeutics (July 2021).

Prior to the merger, CEM dedicated its final open session at semiannual meetings to "Work in Progress" presentations. Following the semiannual meeting restructuring in 2014, TS-GYN holds one session during which all disease site TS co-chairs present updates and, typically, one investigator is invited to present their "Work in Progress." These presentations allow investigators receiving GYN biospecimens to discuss the progress of their research with the translational committee and affords the investigators an opportunity to receive feedback and discuss future directions.

NRG GYN Biospecimen Banking and Biomarker Testing

The NRG Oncology Biospecimen Bank-Columbus. The NRG Oncology Biospecimen Bank (BB) – Columbus (formerly the GOG Tissue Bank) has been funded and managed as a direct subcontract with NRG, and previously the GOG, since 1991. The biobank is housed at the Biopathology Center (BPC), part of The Research Institute at Nationwide Children's Hospital, in Columbus, Ohio. BB-Columbus is among the best gynecologic cancer biospecimen repositories in the world. Biospecimen acquisition currently occurs via NRG treatment protocols; thus, all incoming biospecimens are highly annotated. All NRG protocols with biospecimen collection and translational science include a protocol-specific biospecimen manual detailing required biospecimens, standard operating procedures for collection and shipment, and other instructions for optimal banking. Biospecimen collection and shipping kits are provided for most NRG protocols. In addition, training sessions occur at NRG semiannual meetings and translational science and bank staffs are available daily to assist sites with biospecimen collection and translational science issues. The GOG, and now NRG GYN, translational science infrastructure has a track record of collecting over a million high-quality, clinically annotated and non-annotated biospecimens. Over the past ten years, on average, approximately 28,000 biospecimens have been submitted to the NRG BB-Columbus each year; almost 18,000 biospecimens are distributed annually to investigators for testing.

In 2004, in response to the GOG progress review, state of the science meetings, and site visit recommendations,

translational science objectives and biospecimen collection were instituted on all major GOG trials. This effort resulted in a greater than 40-fold increase in biospecimen accrual over the next grant period. A vast majority of these biospecimens (i.e., tissue, plasma, serum) were collected for GOG 199, a prospective study of risk-reducing salpingo-oophorectomy and longitudinal CA-125 screening among women at increased genetic risk of ovarian cancer (described below). This trial, opened to accrual from 2003 to 2006, provided a unique opportunity to prospectively collect clinically annotated serial biospecimens from approximately 2,600 high-risk women, establishing a valuable resource for future translational science. An additional legacy GOG initiative to collect whole blood for DNA isolation on all phase III trials resulted in a 75-fold increase in whole blood biospecimen submission from 2004 to 2014.

In 2014, with the formation of NRG, the GOG, NSABP and RTOG biobanks came together to form the NRG Oncology Biospecimen Bank (NRG BB). The NRG BB is composed of four physical locations and funded by one U24 award to NRG. This distributed model allows each of the four locations to focus on one or more of the NRG cancer disease sites – BB-Columbus: GYN, BB-Pittsburgh: colorectal and breast (tissue); BB-Baylor: colorectal and breast (blood); and BB-San Francisco: brain, head & neck, lung, genitourinary, non-colorectal gastrointestinal, and sarcoma.

As biospecimen demands have changed over the past decade, NCTN biobanking has shifted from the classic “tissue and blood” collection seen on many legacy cooperative group trials to more complex collections including cell-free DNA, Ficoll processed peripheral blood mononuclear cells (PBMCs), and stool. Throughout this progression, BB-Columbus has remained at the forefront of biobanking, providing a full range of services to accommodate the procurement, processing, biobanking, and distribution of GYN biospecimens to answer cutting edge translational science questions. In some instances, BB-Columbus has even extended its biobanking efforts beyond GYN to accommodate biospecimen procurement and processing for other NRG disease sites when their designated biobank is unable to do so.

Notably, in 2012, the BPC was the first biorepository to be accredited by the College of American Pathologists (CAP) Biorepository Accreditation Program (BAP). CAP accreditation is a peer-based program designed to drive the adoption of standards through consistent application of best practices and evidence-based policies. The accreditation process occurs in a three-year cycle, with on-site inspections by qualified biorepository peer reviewers occurring at the beginning of each cycle. The goal of this ac-

creditation is to continue to accomplish best practices for ensuring biospecimen handling to support clinical research, personalized medicine, and cures for genetic diseases. CAP has been accrediting medical laboratories for more than 60 years and is well recognized as the gold standard in laboratory accreditation. The BPC was one of the first 10 biorepositories in the United States to earn its certificate of accreditation. This institutional accreditation process benefits the BB-Columbus, ensuring that it is managed in a manner that results in the procurement, storage, and distribution of quality biospecimens that can be used to support new emerging technologies, cutting-edge medical research, and strengthen the quality of patient care. To date, BB-Columbus is the only NRG BB location to earn this designation.

Notable GYN Biospecimen Collections and Contributions. For nearly 30 years, the GOG and now NRG GYN have established a premier biorepository of high-quality, clinically annotated biospecimens. Included amongst this are several large, notable collections, as well as contributions to larger scientific efforts.

- *A Biorepository of Gynecologic Malignancies – GOG 136.* The legacy GOG banking study, GOG 136, opened to enrollment in 1992 and collected fixed and frozen tissue and pre-operative serum from women with a diagnosis of ovarian cancer. Enrollment was opened to endometrial and cervical cancer patients in 1997. In 2009, the protocol was amended to extend enrollment to several important populations – rare tumors and women with recurrent disease. The biospecimen requirements were also updated to accommodate the era of genomics and each patient was required to submit a whole blood specimen for DNA isolation. At this time, the protocol was given a major overhaul to conform to updated GOG translational science standard operating procedures and, as a result, enrollment increased to over 2,000 registrations per year. Unfortunately, in 2011, the NCI Cancer Therapy Evaluation Program decided to cease funding for banking protocols. As such, GOG 136 closed to patient accrual at the end of 2011 with more than 14,000 registrations over nearly 20 years.
- Biospecimens collected from women enrolled solely on GOG 136 (~11,000) are associated with very limited clinical data. In some cases, women have enrolled on both GOG 136 as well as another legacy GOG treatment trial (~3,000); thus, there is clinical information available for these biospecimens. All GOG 136 biospecimens are available for request via the NRG Biospecimen Access process (described above).

- *Prospective Biospecimen Collection on Cancer Prevention Trials - GOG 199 and NRG CC008.* Numerous banked biospecimens (tissue, plasma, and serum) were collected for GOG 199, a prospective study of risk-reducing salpingo-oophorectomy and longitudinal CA-125 screening among women at increased genetic risk of ovarian cancer. This trial, opened in 2003 and closed to patient accrual in 2006, provided a unique opportunity to prospectively collect clinically annotated serial biospecimens from high-risk women and provides a valuable resource for translational research. Following study closure, biospecimens from GOG 199 were contributed to the Consortium of Investigators of Modifiers of BRCA-Associated Cancer (CIMBA), a consortium formed to permit pooling of such scarce biospecimen by multiple investigators. This effort resulted in numerous publications. Currently, GOG 199 biospecimens are available for request via the NRG Biospecimen Access process (described above).
 - NRG CC008, a non-randomized prospective clinical trial comparing the non-inferiority of salpingectomy to salpingo-oophorectomy to reduce the risk of ovarian cancer among BRCA1 carriers [SOROCK], opened to patient accrual in June 2020 and has a target accrual of ~2,200. The trial will collect whole blood, plasma, and serum from participants at baseline and every year for five years. Additionally, formalin-fixed, paraffin-embedded tissue must be submitted for patients with evidence of serous tubal intraepithelial carcinoma or invasive cancer. Sites are also required to hold all tissue blocks from the patient's bilateral salpingectomy or bilateral salpingo-oophorectomy procedure until study termination as part of the protocol's "virtual bank" component. As with GOG 199, NRG CC008 will provide a valuable resource for future translational studies.
 - *GOG 210, A Molecular Staging Study of Endometrial Cancer.* GOG 210 is a molecular and surgico-pathological staging study of endometrial carcinoma. The overall goal of this protocol is to improve outcome and/or quality of life for patients with endometrial cancer. This fundamental goal will be accomplished through the development of more accurate risk models and identification of targets for therapeutic intervention and individualized treatments based on molecular characteristics identified in patient biospecimens. The specific objectives of this molecular staging study are to: (1) establish a repository of biospecimens with detailed clinical and epidemiologic data from patients with surgically staged endometrial carcinoma; (2) utilize genomic, proteomic, and immunoassay results from biospecimens to predict and discover molecular characteristics of endometrial carcinoma and to validate those characteristics associated with recurrence risk, clinical and histological characteristics, and epidemiologic factors; (3) improve the accuracy and resolution of the risk assessment models for predicting endometrial cancer recurrence using informative genomic, proteomic, and immunoassay results in combination with clinical, pathologic, and epidemiologic factors; (4) use the genomic, proteomic, and immunoassay results, along with the clinical, histological and epidemiologic data obtained for this research study, to identify targets of endometrial cancer prevention and/or treatment; and (5) to expand the current understanding of the biology, progression and responsiveness of endometrial carcinoma. To satisfy these objectives, tissue, serum and urine were collected. To date, over a dozen translational science projects have utilized GOG 210 biospecimens, resulting in ~30 abstracts and publications. Currently, GOG 210 biospecimens are available for request via Navigator.
 - *The Cancer Genome Atlas (TCGA) Project.* The GOG was called upon to serve as one of the major sources for ovarian, endometrial and cervical cancer biospecimens for TCGA. The GOG was selected as the main provider of ovarian cancer biospecimens for the initial pilot study due to CEM involvement in the design of GOG clinical trials and the collection of high quality, clinically annotated biospecimens. Dr. Birrer, CEM Chair at the time, served as principal investigator of the project, as well as a member of the TCGA steering committee and ovarian cancer working group. Additionally, the BPC served as one of the Biospecimen Core Resources.
- The GOG analyzed 315 ovarian biospecimens for inclusion in TCGA. Pathologic review consisted of histology (papillary serous), percent tumor (>70%), percent necrosis, and total sample size (200mg). Sectioning and pathology review was completed for all TCGA biospecimens; these efforts were led by gynecologic oncology pathologist, Nilsa Ramirez, MD, Director of the BPC. The GOG was the largest contributor of ovarian cancer biospecimens. In total, the GOG submitted 85 ovarian, 119 endometrial and 41 cervical cancer biospecimens to this effort.
- Assay Laboratories.* Despite efforts to develop protocols that improve treatment of women with gynecologic malignancies, there are many trials that do not improve the overall survival of these women. Of concern, the biologic

and/or pharmacologic mechanism(s) responsible for the success or failure of chemotherapy is not understood. Phase I/II studies have toxicologic and therapeutic end points, but little laboratory support to help explain the biologic basis for the result. Early on, there was little translational science, especially laboratory correlates, in most legacy GOG protocols. Thus, it was difficult to make sense of the clinical results of some protocols, as there was no information regarding the expression of the drug target. In most cases, it was not even known whether the drugs administered reached their targets in adequate amounts to be effective. In addition, very little pharmacokinetic data were available.

Consequently, CEM proposed that the legacy GOG establish core laboratories to run various molecular and analytical assays in support of selected protocols. In 1997, CEM established the Molecular Pharmacology and the Clinical Pharmacology Core Laboratories and obtained permanent funding for them with the 1999 grant renewal. In January 2001, with approval from legacy GOG leadership, CEM established an additional core laboratory, the Hormone Receptor Core Laboratory. In 2005, the Molecular Pharmacology and Clinical Pharmacology core laboratories were merged into one Pharmacokinetic (PK) Core Laboratory and the Hormone Receptor Core Laboratory was renamed the Receptors and Targets Core Laboratory to describe its function more adequately.

Unfortunately, with the transition to the NCTN and formation of NRG in 2014, funding for core laboratories was discontinued. However, over the next several years, NCI introduced several opportunities for investigators to collaborate with NCI-funded core laboratories through various programs, including the Cancer Moonshot initiatives. Additionally, new NCTN policies categorize clinical trial correlates into integral, integrated, and exploratory biomarkers. Integral biomarkers are assays required for the trial to proceed or are required to generate data to support the primary analysis. Integral assays are inherent to the design of the trial and must be done on all participants, usually in real time. Integrated biomarkers are assays intended to be validated for use as an integral biomarker in future trials or for use in clinical practice. Integrated biomarkers can be real time (i.e., must be done in real time during the trial) or non-real time (e.g., may be done at pre-specified intervals during the trial or upon trial completion). Inclusion of integral or integrated biomarker assays in NCTN clinical trial protocols prompts review by the NCI's Biomarker Review Committee (BRC), while inclusion of exploratory biomarkers is usually discouraged, and investigators are advised to seek approval after trial closure when biospecimens are available via

Navigator or the Biospecimen Access process (described above).

To receive BRC approval, investigators must include specific hypothesis, complete assay details (including pilot data), and a pre-specified statistical analysis plan in the clinical trial protocol. Investigators receiving BRC approval for a given assay are often able to successfully incorporate their assay on subsequent NCTN clinical trials, given that the subsequent use and objectives/hypothesis are warranted. To date, several GYN investigators have successfully sought BRC approval for various assays used on multiple NRG GYN trials, as well as other NCTN Group trials. Included among these are the BROCA-HR assay done in the laboratory of Elizabeth Swisher, MD, the plasma angiome assay done in the laboratory of Andrew Nixon, PhD, MBA, the assessment of T cell receptor repertoires done in collaboration with Adaptive Biotechnologies and the laboratory of Dmitriy Zamarin, MD, PhD, and cytometry by time of flight (CyTOF) analysis done in the laboratory of Katherine Fuh, MD, PhD.

Bench to Bedside: Translating Laboratory Successes to Federally Funded Clinical Trials. TS-GYN (and previously CEM) has always made a major effort to utilize work from its member's laboratories to impact NRG GYN clinical trial efforts. In ovarian cancer, Dr. Birrer's laboratory conducted large-scale genomics studies on a large number of tumor biospecimens collected via legacy GOG initiatives. The 2005 data from Dr. Birrer's laboratory strongly suggested that ovarian tumors of different histologies have completely differently genomic makeups and that tumors of similar histology, regardless of organ of origin, are very similar with respect to genomics.⁸ These data were discussed with the legacy GOG and provided a paradigm shift in the group's approach to ovarian cancer trials. All rare histology groups such as clear cell and mucinous tumors were removed from randomized phase III trials and are now the focus of histology-specific trials. Further, work from Dr. Birrer's laboratory demonstrated that ovary tumors of varying grade have very different gene expression patterns.⁹ Low-grade tumors have expression patterns that are very similar to borderline tumors suggesting that these are separate tumors and different from high-grade serous cancers. Based on these results, low-grade tumors were also removed from the phase III trials. Perhaps more importantly, these data identified rare tumors as a separate tumor group worthy of study and provided the rationale for a major change in the GOG committee structure and the creation of the Rare Tumor Committee within the GOG. With the formation of NRG Oncology, the Rare Tumor Committee continues operation as a subcommittee of the GYN Cancer

Committee. The Committee is currently chaired by Al Covens, MD, and co-chaired by Jubilee Brown, MD. Gloria Huang, MD, serves as the translational science co-chair. One notable rare tumor trial, GOG 239, examined the effects of a MEK inhibitor on low-grade serous tumors of the ovary. This trial was specifically based upon the finding that the MAP kinase pathway is activated in these tumors and all biomarker endpoints in this trial were genes previously identified in Dr. Birrer's studies. GOG 239 also included a translational science objective designed to investigate the relationship between BRAF and KRAS mutations and tumor response in patients given selumetinib. The results of GOG 239 suggested that selumetinib is an active agent, but not necessarily because of BRAF or KRAS mutational activation. This finding is important given recent recommendations for clinical trial designs restricting patient enrollment based on mutation status. Unless there is compelling evidence to restrict patient enrollment, trial designs should allow for adequate hypothesis testing.

In endometrial cancer, several legacy CEM members played important roles in identifying genetic factors that contribute to endometrial cancer risk. As a result of these research efforts, there have been changes in the clinical genetic management of patients with endometrial cancer and their family members. Paul Goodfellow, PhD, and his group demonstrated inherited (germline) mutations in MSH6 that are common among endometrial cancer patients. The validation of this finding by the Goodfellow laboratory has paved the way for a change in the clinical management of hereditary nonpolyposis colorectal cancer (HNPCC) patients. In addition, Dr. Goodfellow and colleagues (Pamela Pollock, PhD, and Matthew Powell, MD) pioneered a genomics discovery from laboratory to clinical trial. Drs. Goodfellow, Pollock and Powell identified FGFR2 activating mutations in patients with inherited genetic disease (craniosynostosis and skeletal dysplasia syndromes).

GOG-P

GYN Trials Committee. As part of the GOG-F restructuring process, a new committee, the GYN Trials Committee was formed. The Committee vision was to have a united group with representation from GOG-P committees, as well as the NRG GYN Cancer Committee. Currently, both Drs. Birrer and Lankes are both appointed to this GOG-F committee.

Biospecimen Banking. While many GOG-P clinical trials do not include a biospecimen banking component, or biobanking is done through investigator laboratories or commercial biobanks, some GOG-P trials have utilized

the BPC for biospecimen procurement, processing, and banking. As such, the BPC currently houses over 8,100 formalin-fixed, paraffin-embedded tumor tissue biospecimens, over 3,100 nucleic acid biospecimens, approximately 6,700 plasma biospecimens, and approximately 2,000 serum biospecimens from closed (GOG 3003, GOG 3005, GOG 3007, GOG 3008) and active (GOG 3026) GOG-P trials.

GOG 3005, veliparib with carboplatin and paclitaxel and as continuous maintenance therapy in adults with newly diagnosed stage III or IV, high-grade serous, epithelial ovarian, fallopian tube, or primary peritoneal cancer (VELIA), opened to patient accrual in 2015 and closed in 2019. While biospecimens were shipped directly from sites to a commercial biorepository, GOG-F negotiated the transfer of half of all biospecimens to the BPC. Biospecimens sent to the BPC are available via application to a joint GOG-F/AbbVie Translational Science Steering Committee (TSSC). The TSSC reviews all applications for use of BPC-housed GOG 3005 biospecimens for scientific merit.

The Long-Term Ovarian Cancer Survivor Project: A Department of Defense (DOD) Initiative. In response to a 2012 DOD Program Announcement, Dr. Birrer, along with Thomas Conrads, PhD; G. Larry Maxwell, MD; Samuel Mok, PhD; Kenneth Nephew, PhD; and Lari Wenzel, PhD, applied to form a long-term ovarian cancer survivor consortium. The consortium effort, endorsed by the GOG-F, sought to characterize long-term survivors to improve overall survival of all ovarian cancer patients and to characterize long-term survivors to better help their needs.

Three advisory boards oversee the consortium: an International Board chaired by Eric Pujade-Lorain, MD, PhD; a Scientific Board chaired by Edward Trimble, MD, MPH; and an Advocate Board chaired by Mary Jackson-Scroggins. The Coordinating Center (overseen by PI, Dr. Birrer, and Co-PI, Dr. Wenzel) directs the efforts of the scientific committee, research sites, biospecimen bank, and statistical collaborators. Key participants in the consortium include subject matter experts from a variety of areas: Quality of Life (QOL) - Dr. Wenzel; Biostatistics and Computational Biology - Austin Miller, PhD and Giovanni Parmigiani, PhD; Administration - Dr. Lankes; Biobanking - Nilsa Ramirez, MD; miRNAseq - Dr. Mok; MethylCap-seq - Dr. Nephew; Proteomics - Drs. Conrads and Maxwell; and Immunology - George Coukos, MD, PhD.

The overarching goal of the consortium is reflected in six specific aims: (1) to determine the genomic (RNAseq, miRNAseq, methylation patterns) and proteomic character-

istics of long-term (LT) versus short-term (ST) survivors; (2) characterize and quantify immune infiltrates and angiogenesis in LT versus ST survivors; (3) to validate a genetic signature that predicts for recurrence of early-stage, high-grade epithelial ovarian cancer; (4) determine the impact of host factors including genomic single nucleotide polymorphism profiles and key measures of patient stress on LT survival; (5) understand the extent to which health-related QOL measures, additional patient reported outcomes, and key Common Terminology Criteria for Adverse Events (CTCAE) criteria predict LT ovarian cancer survival; and (6) to examine, as an exploratory aim, the potential relationship between health-related QOL, PROs, and key CTCAE criteria and genomic features predicting disease recurrence.

To accomplish this, the consortium is utilizing the high-quality, clinically-annotated ovarian cancer biospecimens collected on the legacy GOG trials 172 and 182 for initial analysis, and 218 for validation. Biospecimens will be used for RNAseq, miRNAseq, MethylCap-seq, proteomics and immune analyses. Biomarker results will be analyzed in combination with clinical trial data, including QOL data.

The Future of Translational Science: Challenges

The future direction of TS-GYN will involve the continued integration of translational science into all NRG GYN clinical trials. Integral to this process is the accomplishment of three separate goals: (1) identification of appropriate laboratories and accomplished investigators with the required expertise; (2) obtaining adequate funding to conduct these studies; and (3) identification and prioritization of scientific areas of extraordinary opportunity.

Outreach to the Gynecologic Oncology Community. To effectively conduct translational science, it is necessary to involve the entire gynecologic cancer research community. This is necessary to actively and effectively engage established gynecologic cancer research programs including program project, SPORE, and mouse modeling groups. These programs involve multiple peer-reviewed funded investigators organized into interactive projects centered on an important biologic and clinical question involving GYN cancers. Thus, these are ideal groups to integrate into the NRG clinical trial structure to address important translational science questions. Moreover, it is critical to engage individual investigators with a proven track record of outstanding scientific investigation in GYN cancers. The composition of TS-GYN will assist in these efforts by including members who participate on SPORE and program project grants and have fully funded laboratories conducting GYN cancer research. Further, TS-GYN will provide a scientific forum where researchers

(NRG and non-NRG) can present and exchange “cutting edge” scientific concepts and new technological developments. This will include scientific retreats, semiannual meeting symposia, and work in progress presentations at semiannual TS-GYN committee meetings. Finally, TS-GYN will provide an opportunity for the NRG GYN committee to discuss translational science proposals utilizing NRG clinical trial biospecimens, including NCI review expectations, as well as operational and logistical challenges.

Funding Challenges. The success of translational science within the NRG is critically dependent upon adequate funding. It is anticipated that funding will remain a major challenge over the next several years. The major funding sources for translational science are the NCI, industry, and philanthropic sources. TS-GYN can facilitate the preparation of grant applications for translational science from qualified investigators by providing administrative support, letters of collaboration, statistical collaboration, and most importantly, proposal feedback. Grant applications utilizing NRG resources (e.g., clinically annotated biospecimens) and receiving NRG support will be stronger and thus, in a better competitive position.

Our industrial colleagues are also collaborators in the effort to translate scientific discoveries into clinical successes. Biotechnology and pharmaceutical companies are developing many of the new therapeutic agents that will be available for clinical testing. Thus, TS-GYN committee members will work closely with industry to design and implement the appropriate clinical trial protocols to effectively test these new agents. Further, this process will require research funds from these companies to specifically support the laboratory-based science attached to these clinical trials. This effort will include utilization of, and collaboration with, drug company research laboratories.

Prioritization and Areas of Opportunity. Perhaps the biggest challenge to conducting successful translational science within the NCTN is to effectively prioritize specific research areas that offer extraordinary opportunities. Many avenues of research are possible, but only a few can be reasonably achieved with available trials and resources. Thus, TS-GYN, working with the various GYN disease site TS Co-Chairs, will make a major effort to prioritize translational science directions. We have identified and prioritized three areas of extraordinary opportunity for translational science, including molecular targets, omics, and immuno-oncology.

- *Molecular targets.* New molecular targets will be pri-

oritized by TS-GYN as an important area of investigation for NRG. With the identification of the molecular basis of many GYN cancers, critical activated pathways can be identified in these tumors and targeted with novel agents. Indeed, the advent of small molecule inhibitors that target these pathways will form the basis of many phase II and III trials. It will be important in these trials to analyze intermediate molecular endpoints to determine adequate drug dosing and proper interpretation of clinical trial results. TS-GYN will utilize its membership's broad scientific expertise to assist investigators with the development of appropriate translational science endpoints on all phase II trials. Further, TS-GYN will propose the use of the R01-funded laboratories of its members and those of SPORE investigators to conduct these studies. These studies should be incorporated as integrated biomarkers in GYN clinical trials to validate any biomarkers as appropriate biologic endpoints for these experimental agents and provide standardized integral biomarker assays for phase III trials.

- Omics. Current genomics technologies (e.g., expression profiling by microarray, SNP) allow for a broad, in-depth genomic analysis and clinical correlation. These technologies are critical for a complete understanding of the molecular basis of GYN cancers. Additionally, these technologies can now be applied to formalin-fixed, paraffin-embedded tissue and thus, testing of large numbers of clinical biospecimens. Testing such large numbers provides the statistical strength needed to address important clinical questions (e.g., risk, early detection). Further, application of these technologies to clinical trials has the potential for prognosis and prediction of the clinical course of patients.
- In addition to genomic technologies, proteomic technologies have the potential to detect ovarian cancer when present in small volumes, such as during early tumor development and during recurrence. Integrating these technologies into trial design will be of critical importance. TS-GYN will ensure that all phase III trials include tissue collection; thus, providing adequate biospecimens to validate gene expression signatures and protein patterns needed to stratify patients for future trials. Ultimately, these investigations will lead to dramatic changes in phase III trial design in which patients are stratified according to their genomic/proteomic profile and these results can also be used to identify potential therapeutic targets. Immuno-Oncology. As the field of immuno-oncology continues to show promise, TS-GYN will

continue to incorporate appropriate immuno-biomarkers into NRG GYN clinical trials. Notably, two GYN investigator assays – assessment of T cell receptor repertoires done in collaboration with Adaptive Biotechnologies and the laboratory of Dr. Zamarin, and cytometry by time of flight (CyTOF) analysis done in the laboratory of Dr. Fuh – currently have NCI BRC approval and could likely be incorporated into future GYN trials, provided the appropriate hypothesis-testing primary or secondary objective(s). Additionally, as with NRG GY021, NRG GYN will continue to engage in successful collaborations with the CIMAC initiative. To support these efforts, the recent BB U24 award provides funding for provision of specialized biospecimen kits and processing of biospecimen types required for immune-biomarker assays.

Conclusions

To significantly impact the diagnosis, prevention, and treatment of women with GYN cancers, translational science is a critical element of all future studies. Empiric clinical trials will no longer be the standard approach. Trials with carefully selected and validated translational endpoints will be needed and are now a mainstay of the NCTN. Utilizing the expertise of TS-GYN membership and the infrastructure TS-GYN has created, NRG has and will continue to successfully apply translational science to its GYN clinical trial structure. This will usher in a new and exciting era where the rational application of new agents and individualization of care will become the standard.

References

1. Boyd, J., Hamilton, T.C., Berchuck, A. (2000) Oncogenes and tumor-suppressor genes. In W. Hoskins, Perez, C., Young, R. (ed.), Principles and Practice of Gynecologic Oncology. Lippincott, Williams & Wilkins, Philadelphia.
2. McIntosh MW, Drescher C, Urban N, Scholler N, Hellstrom I, Hellstrom K. (2004) Combining CA 125 and SMR serum markers for diagnosis and early detection of ovarian carcinoma. *Gynecol Oncol*. 95:9-15.
3. Petricoin, E. F., Ardekani, A. M., Hitt, B. A., Levine, P. J., Fusaro, V. A., Steinberg, S. M., Mills, G. B., Simone, C., Fishman, D. A., Kohn, E. C., Liotta, L. A. (2002) Use of proteomic patterns in serum to identify ovarian cancer. *Lancet* 359:572- 577.
4. Ibanez de Caceres, I., Battagli, C., Esteller, M., Herman, J. G., Dulaimi, E., Edelson, M. I., Bergman, C., Ehya, H., Eisenberg, B. L., Cairns, P. (2004) Tumor cell-specific BRCA1 and RASSF1A hypermethylation in

serum, plasma, and peritoneal fluid from ovarian cancer patients. *Cancer Res.* 64:6476-6481.

5. Ahluwalia A, Yan P, Hurteau JA, Bigsby RM, Jung SH, Huang TH, Nephew KP. DNA methylation and ovarian cancer. I. Analysis of CpG island hypermethylation in human ovarian cancer using differential methylation hybridization. *Gynecol Oncol.* 2001 Aug; 82(2): 261-8.
6. Wild R, Dhanabal M, Olson TA, Ramakrishnan S. Inhibition of angiogenesis and tumor growth by VEGF121-toxin conjugate: differential effect on proliferating endothelial cells. *Br J Cancer.* 2000 Oct;83(8): 1077-83
7. Freitas S, Moore DH, Michael H, Kelley MR. Studies of apurinic/apyrimidinic endonuclease/ref-1 expression in epithelial ovarian cancer: correlations with tumor progression and platinum resistance. *Clin Cancer Res.* 2003 Oct 15;9(13): 4689-94.
8. Zorn KK, Bonome T, Gangi L, Chandramouli GV, Awtrey CS, Gardner GJ, Barrett JC, Boyd J, Birrer MJ. Gene expression of serous, endometrioid, and clear cell subtypes of ovarian and endometrial cancer. *Clin Cancer Research.* 2005 Sep 15;11(18): 6422-30.
9. Bonome T, Lee JY, Park DC, Randonovich M, Pise-Masison C, Brady J, Gardner GJ, Hao K, Wong WH, Barrett JC, Lu KH, Sood AK, Gershenson DM, Mok SC, Birrer MJ. Expression profiling of serous low malignant potential, low-grade, and high-risk tumors of the ovary. *Clin Cancer Research.* 2005 Nov 15;11(22): 10602-12