3 Improving ovarian cancer diagnosis and treatment with translational research

6 3-D mammography increases detection and decreases call-backs

7 Advances in the diagnosis and treatment of small cell lung cancer
In this issue of Innovations in Cancer, we highlight how we strive to bring innovation to patient care, both by translating basic science into new therapies and technologies and by designing unique clinical trials to validate their safety and effectiveness.

Analisa DiFeo, PhD, provides an excellent example of innovation in her work in ovarian cancer at Case Comprehensive Cancer Center, Case Western Reserve University. The University’s Gynecologic Oncology Translational Research Program brings together a multidisciplinary group of investigators who strive to understand the molecular defects associated with this disease. Dr. Difeo also describes the program’s extensive tumor biobank, including primary cancer cell lines and patient-derived xenografts, and how the group employs it for patient-centered research.

Marcos de Lima, MD, demonstrates creativity in designing new therapies for our patients with his state-of-the-art clinical trials of novel cell therapies for patients with hematologic malignancies. He also discusses how we foster pioneering single-site trials in addition to large cooperative group trials, and he explains how both types of trials benefit our patients.

Donna Plecha, MD, brings us the results of a large multicenter study of a new technology in imaging, tomosynthesis, that both improves breast cancer detection and reduces false positive results and recall rates.

Afshin Dowlati, MD, updates us on the oncogenic somatic mutation at amino acid 918 in the RET (rearranged during transfection) protein that he has identified in small cell lung cancer (SCLC) tumors. He explains how he is applying this research to better understand SCLC and to develop a new target for therapy in a subset of patients with SCLC.

Each of these investigators demonstrates our commitment to groundbreaking research that brings our patients new hope, novel clinical trials and treatments that are not available elsewhere.

Warm regards,

Stanton L. Gerson, MD
Director, University Hospitals Seidman Cancer Center and Case Comprehensive Cancer Center at Case Western Reserve University
Asa and Patrick Shiverick – Jane Shiverick (Tripp) Professor of Hematologic Oncology
Case Western Reserve University School of Medicine
Director, National Center for Regenerative Medicine

The commitment to exceptional patient care begins with revolutionary discovery. University Hospitals Case Medical Center is the primary affiliate of Case Western Reserve University School of Medicine, a national leader in medical research and education and consistently ranked among the top research medical schools in the country by U.S. News & World Report. Through their faculty appointments at Case Western Reserve University School of Medicine, physicians at UH Case Medical Center are advancing medical care through innovative research and discovery that bring the latest treatment options to patients.
COMBATING OVARIAN CANCER
Translational research supporting personalized medicine  By Analisa DiFeo, PhD

The Gynecologic Oncology Translational Research Working Group (GOTRWG) at Case Comprehensive Cancer Center was created to ensure translation of laboratory discoveries into a better understanding of the molecular defects that underpin epithelial ovarian cancer (EOC).

We have assembled a dedicated multidisciplinary group that includes gynecologic oncologists, pathologists, basic scientists, translational research scientists, information scientists and clinical fellows. I work especially closely with Steven Waggoner, MD, Division Chief, Gynecologic Oncology, UH Seidman Cancer Center, and Associate Professor, Obstetrics and Gynecology, Case Western Reserve University School of Medicine.

An important aspect of the program is our extensive gynecologic tumor biobank, one of only a few in the United States, which supports patient care and translational research.

GYNECOLOGIC TUMOR BIOBANK
After a patient has given informed consent and the surgeons have removed an ovarian or uterine cancer, the tumor sample is rushed from the operating suite to our tissue bank. There, researchers divide the sample, freeze a portion and start both a primary cell culture line and, in a mouse model, a patient-derived xenograft (see “Mouse Avatars” sidebar). A serum sample from each participant is also stored. In its nearly two years of existence, the biobank has collected more than 175 tumor samples.

FOSTERING PATIENT-FOCUSED RESEARCH
To support patient care, GOTRWG researchers test each mouse xenograft (avatar) with the chemotherapy that the patient is receiving. If the tumors recur or do not respond, this is a red flag for the clinician that may indicate a patient whose tumor needs more careful monitoring. The avatar can then be tested with other FDA-approved drugs and drugs being developed as part of the translational research program. If that patient’s tumor does recur, then the clinician has advance information about which other FDA-approved drugs worked in the avatar.

One caution is that the avatar may not always adequately predict the behavior of a patient’s cancer. While the avatar will reflect the sample received in the biobank, that sample may not always represent the most aggressive part of a patient’s tumor.

UNDERSTANDING OVARIAN CANCER
One of GOTRWG’s key goals is to develop ways to diagnose ovarian cancer at an early stage. Currently, only 10 percent of these cancers are detected at stage I.

In my laboratory, we identified a microRNA biomarker, miR-181a, and discovered that it is a molecular driver of EOC. Because we have access to the biobank tumor samples, we were able to determine that this microRNA is associated with tumor recurrence and that it is highly expressed in cancer stem cells isolated from the patients’ tumors.

We showed that elevated levels of miR-181a are associated with chemotherapy resistance and disease progression. We also determined that miR-181a blocks the expression of the Smad7 gene, which shuts down the TGF-ß signaling pathway, a potent inducer of metastases. We are now looking for small molecules that can block the interaction between miR-181a and Smad7, stop TGF-ß activation and, hopefully, prevent the spread of ovarian cancer.

For more information about the Gynecologic Oncology Translational Research Working Group at Case Western Reserve University and its biobank program, contact me at analisa.difeo@case.edu.

MOUSE AVATARS
When tumor samples are implanted in mice, they form patient-derived xenografts, called mouse avatars. Researchers can use an avatar as a personalized in vivo tumor model to identify which drug or drug combinations are most likely to be effective, while also identifying regimens that are unlikely to work well. Clinicians can improve patient care while avoiding toxicities associated with measures that are unlikely to help.
Our University Hospitals Seidman Cancer Center
Stem Cell Transplant Program has three priorities:
first, provide donors for every patient who needs a
donor cell transplant; second, reduce toxicities; and
third, reduce relapse rates. These priorities guide all
of our research, including our clinical trials. Some are
smaller, innovative trials set only at our site, while
others are larger, multicenter cooperative trials.
Both types of trials benefit our patients and advance
transplantation research.

CORD BLOOD TRANSPLANTS
Cord blood is more forgiving of mismatches between
donor and recipient and has the potential to serve
as a source of stem cells for more patients than do
adult donor stem cells. Cord blood can also extend
transplantation to people who cannot find a full
match from an adult donor, including minorities who
are underrepresented in the transplant registry.

One problem with cord blood is the small sample
size; a single cord blood donation contains too few
cells for an adult transplant. UH Seidman Cancer
Center is one of only a few centers in the country
participating in a national trial to test our ability to
multiply cord blood stem cells in culture. We are
comparing transplant using two cord blood units
per patient with transplant containing one standard
cord blood sample plus one whose cell numbers have
been extended in cell culture.

The routine loss of some of the cord blood cells
between the site of intravenous injection and the
bone marrow is another problem. One way to limit
this loss is to inject cord blood directly into the
bone marrow. We discovered that if we combine
human cord blood cells with mesenchymal stromal
cells (MSCs) from an unrelated human and inject
the combined cells into a recipient mouse, we see
better engraftment with more donor cells remaining
in the marrow. In a single-site study at UH Seidman
Cancer Center, we will soon be performing similar
transplants in humans. MSCs will be harvested
from an adult volunteer, who does not need to be
matched with the donor or the recipient, and these
will be injected into the bone marrow immediately
before the cord blood is injected.

HAPLOIDENTICAL
DONORS
The use of haploidentical (half-match) transplants
from a close relative such as a parent increases
the number of potential donors but also increases
the risk of graft-versus-host disease (GVHD). We
are investigating a way to selectively kill the donor
cells if GVHD develops. In an ongoing trial at UH
Seidman Cancer Center and at a few other centers
nationally, T lymphocytes are removed from a
haploidentical donor. A subset of these cells is
isolated, and a “suicide gene” is inserted to render
them susceptible to a “suicide” drug that induces
apoptosis (cell death). The genetically altered T
lymphocytes are transplanted into the patient. If
severe GVHD develops, we can immediately give the
patient the “suicide” drug, and the transplanted
cells will self-eliminate.
REDUCING TOXICITY AND RELAPSE
Before a bone marrow transplant, a patient receives some form of radiation and/or chemotherapy to kill some of the malignancy and tamp down the immune response to help prevent graft rejection. However, if a patient is older or frailer, we have to compromise on the dose of chemoradiation, despite the fact that this increases relapse rates. We initiated a single-site study at our institution to test targeted marrow irradiation (TMI) in place of traditional radiation regimens. We hope this will avoid toxicity in older, frailer patients while reducing relapse rates.

One study in the planning stage involves natural killer (NK) cells, a cytotoxic lymphocyte that does not cause GVHD yet has the potential to kill leukemia cells. Previous attempts to use NK cells suffered both from difficulties harvesting enough cells to transplant and from a lack of sufficient effectiveness. We are multiplying NK cells in the laboratory and, at the same time, incubating them with a glycogen synthase kinase 3 (GSK3) inhibitor developed by David M Wald, MD, PhD, Assistant Professor, Case Western Reserve University School of Medicine, to increase their ability to kill leukemia cells. We hope this approach will allow us to generate NK cells from mismatched but related donors, increase the cell numbers in cell culture and improve their killing ability so that we can use them as a potential therapy for difficult-to-treat leukemias and other cancers.

ADVANTAGES OF SINGLE-SITE TRIALS
Traditionally, the large cooperative trial format is the best way to answer questions that arise from smaller studies that precede it. We offer these trials to our patients, but we also initiate smaller, innovative single-site trials that enable us to test early hypotheses. If successful, these can lead to the larger multicenter trials necessary to fully prove safety and effectiveness to the FDA.

Small pioneering trials can be difficult to fund. Often the money must come from a mixture of sources, including institutional funds, NIH funds that support some of the preclinical steps and donor/community funds. Unfortunately, NIH has little money to support a state-of-the-art early clinical trial and prioritizes most funding for preclinical studies.

An institution like ours has a huge role in initiating single-site studies, and we are very thankful that UH provides this critical support. It enables us to offer access to additional groundbreaking studies with the potential to help patients with difficult cancers that we might not otherwise be able to treat.

For more information about clinical trials involving stem cell transplantation, please contact me at Marcos.deLima@UHhospitals.org.
University Hospitals Case Medical Center recently took part in a large multicenter trial comparing tomosynthesis (3-D mammography) with traditional mammography for the detection of breast cancer. Thirteen academic and non-academic centers from across the country participated, evaluating nearly one-half million breast examinations (approximately 281,000 by digital mammography and 174,000 by digital mammography plus tomosynthesis).

Results were recently published in the Journal of the American Medical Association. The bottom line: With the addition of tomosynthesis, our detection of breast cancers improved substantially, while our recall rate decreased.

**INCREASED DETECTION RATE**

We were able to show a 41 percent relative increase in the invasive cancer detection rate for combined tomosynthesis and digital mammography, compared with digital mammography alone. We concluded that tomosynthesis is a much better examination for finding cancers that may otherwise hide within normal breast tissue on a regular mammogram. This makes sense because 3-D mammography provides many more images, each sliced at one-millimeter intervals throughout the breast. Instead of looking at four views from a regular mammogram in a woman with average-size breasts, for example, I may be looking at 200 images with tomosynthesis.

**DECREASED CALL-BACK RATE**

In addition to missing too many cancers in patients, traditional mammography has often been criticized for producing a large number of false positives. If we see something slightly suspicious or irregular on a mammogram, we call a woman back for additional imaging, which causes anxiety and extra cost to that patient. In this study, we saw a 15 percent relative decrease in these call-backs using tomosynthesis, compared with 2-D digital mammography alone.

We looked further to determine how often we would find a cancer in the women called back. The relative increase in the positive predictive rate was 49 percent after tomosynthesis, compared with traditional mammography – an impressive jump.

We also wanted to know whether the use of tomosynthesis affected the positive predictive value of a biopsy. We found a relative increase of 21 percent. We are planning additional investigations of the large database from this study, including whether certain subpopulations separated by age and/or breast density benefit more from tomosynthesis than do others.

**ADDING TOMOSYNTHESIS**

The bottom line of this study: Adding tomosynthesis to traditional mammography is a game-changing technology that makes us much better at what we do.

At our University Hospitals-affiliated mammography sites, we have a mixture of locations with traditional plus 3-D mammography (hybrid sites) or traditional mammography only. Patients at the hybrid sites are offered the choice of tomosynthesis in addition to traditional mammography, but they may have to check with their private insurers to determine whether they will be required to pay an additional out-of-pocket cost or deductible.

The Centers for Medicare and Medicaid Services (CMS) plans to implement the new CPT code and a reimbursement fee for tomosynthesis sometime in 2015. Earlier studies of the technology were much smaller, single-site investigations. We hope that this larger, more powerful multicenter trial may help drive approval for reimbursement for tomosynthesis by private insurers as well.

For more information about this study, see the article in JAMA 2014;311(24):2499-2507, or contact me at Donna.Plecha@UHhospitals.org.
ADVANCES AGAINST SMALL CELL LUNG CANCER
TRANSLATING BASIC SCIENCE INTO CLINICAL IMPACT  By Afshin Dowlati, MD

During the past 30 years, little progress has been made in the treatment of small cell lung cancer (SCLC), which accounts for about 13 percent of all lung cancers. Approximately 20,000 to 25,000 cases are diagnosed each year in the United States, but many more SCLC cases occur worldwide. Virtually all cases are linked to cigarette smoking. SCLC is one of the most aggressive and fastest-growing solid tumors. Without treatment, survival is only about four to eight weeks.

University Hospitals Seidman Cancer Center is a center of excellence in the diagnosis and treatment of SCLC, with considerable expertise not only on the clinical side, but also in basic and translational research.

IDENTIFYING RET MUTATIONS IN SCLC
In my laboratory, we have focused on finding new targets for the treatment of SCLC. We recently identified a mutation in the RET (rearranged during transfection) protein in the tumor of one of our patients, and we found this same mutation in a small number of other SCLC patients.

When we artificially implant this mutation into SCLC lines growing in the laboratory, those cells become extremely sensitive to RET inhibitors. This tells us that we must think about whether patients with SCLC have RET mutations. If they do, they should be considered for treatment with RET inhibitors.

Based on this work, a multicenter trial has been proposed that will identify and treat the subset of patients who have RET mutations present in their SCLC tumors, and UH will participate.

PINPOINTING POTENTIAL DRUGS
We have also used resources from the bioinformatics group at UH Case Medical Center and Case Western Reserve University School of Medicine to identify additional molecular targets for SCLC treatment. We analyzed biologic data from a large series of SCLC cell lines and identified three molecular targets and three corresponding groups of drugs that may be very effective in treating SCLC. The drugs are polokinase (PLK) inhibitors, heat shock protein inhibitors and cyclin-dependent kinase inhibitors, none of which has been studied previously in SCLC.

To validate the work further, we looked more closely at the responses of individual cell lines to PLK inhibitors. We found that approximately 50 percent of SCLC cell lines are sensitive to this class of drugs at very low, nanomolar concentrations.

PERSONALIZING MEDICINE
Because only half of the SCLC lines were sensitive to PLK inhibitors, we developed a genomic signature to personalize our approach, determining which patients may benefit from this class of drugs.

We then looked prospectively at human SCLC tumors to determine whether the same genomic predictor that we found in the cell lines also exists there. It does. This paves the way to start clinical trials of PLK inhibitors in patients whose SCLC contains this genomic signature. This study is being proposed as a national trial in which UH will participate.

Our progress in SCLC is an excellent example of practical research that translates directly into improved patient care. Additional genomic studies in SCLC are ongoing.

For more information on our SCLC clinical trials, please contact me at Afshin.Dowlati@UHhospitals.org.
DR. GERSON TO LEAD ASSOCIATION OF AMERICAN CANCER INSTITUTES

Stanton L. Gerson, MD, Director, University Hospitals Seidman Cancer Center and Case Comprehensive Cancer Center at Case Western Reserve University; Asa and Patrick Shiverick – Jane Shiverick (Tripp) Professor of Hematologic Oncology, Case Western Reserve University School of Medicine; and Director, National Center for Regenerative Medicine, has been elected Vice President and President Elect, Association of American Cancer Institutes’ (AACI) board of directors.

Being elected to the six-year term (two as Vice President, two as President and two as Past President) is an important peer recognition of institutional leadership, because the major cancer centers in the country elect the AACI board and officers.

The AACI, which comprises 93 leading cancer research centers in the U.S., is dedicated to reducing the burden of cancer by enhancing the impact of these academic cancer centers. As Dr. Gerson points out, “The AACI is unique for being the only organization that promotes the needs, values and directions of the nation’s major cancer centers.”

Dr. Gerson says he intends to prioritize three critical aspects of the nation’s cancer centers program during his term by:

1. Encouraging the centers to work more closely together to lower health care costs and improve outcomes through nationally coordinated research and translation. Examples include sharing best practices for introducing new drugs and the use of clinical trials; evaluating new technologies such as cell therapy, imaging and minimally invasive surgery; and developing proper strategies for referral from community sites to the major cancer centers.

2. Expanding the use of cancer patient data to further health improvements and research discoveries. Dr. Gerson further explains, “We are on the verge of being able to assemble and interpret huge data sets accumulated from large patient data repositories, and we have the opportunity to use these to improve decision-making, cost management and quality control.”

3. Making optimal use of the cancer center director and administrative leader network, including partnering with funding agencies to set the policy agenda for cancer research, dissemination of discoveries and cancer health care.

Dr. Gerson assumed the role of Vice President/President Elect during the AACI and Cancer Center Administrations Forum (CCAF) annual meeting in Chicago in October 2014.