Levine Cancer Institute
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UPDATES IN CANCER FOR CLINICIANS

JANUARY 2013

Updates from ASH 2012:

Gene Encoding and Sequencing to Personalize Therapy

Edward Copelan, MD *(right)*
Chair of the Department of Hematologic Oncology and Blood Disorders

Belinda Avalos, MD *(left)*
Vice Chair of the Department of Hematologic Oncology and Blood Disorders

Two important themes of the 2012 ASH meeting emerged from special lectures given by Carl June, MD, from the University of Pennsylvania and recipient of the Ernest Beutler Award, and Tim Ley, MD, from Washington University and E. Donnall Thomas Award recipient. Dr. June presented striking results using tumor-specific cellular immunotherapy in two lymphoid malignancies, CLL and ALL. June and colleagues introduced genes encoding artificial receptors called chimeric antigen receptors (CARs) into patients' autologous T cells in vitro in order to redirect the specificity of these immune effector cells to the B cell-specific CD19 antigen. CAR proteins expressed on T cells were composed of an antibody that could bind to a specific target (here the CD19 antigen found on B cell leukemias) fused to a transmembrane domain followed by one or more cytoplasmic signaling domains to generate proliferative and antitumor activity. A T cell engineered with this design could specifically recognize a leukemia cell, kill it, disengage and kill another—then divide and make more engineered T cells so that one cell could kill more than 1,000 leukemia cells following injection, meriting it the moniker "serial killer." In addition to achieving sustained complete remissions in four of nine evaluable patients with refractory CLL, complete remission was also obtained in a child with ALL who experienced life-threatening cytokine storm associated with tumor lysis that was successfully treated with TNF and IL-6 antagonists. Along with accrual of larger numbers of patients with B-Cell malignancies, new protocols are currently being developed to extend the groundbreaking work of cancer-specific T cells to pancreatic, prostate and breast cancer.

Dr. Ley summarized his own work and that of others, including several presentations at the meeting, using whole genome sequencing to study clonal evolution in large numbers of patients with AML. By sequencing several hundred primary tumor and relapse genomes, Ley and colleagues have provided an unprecedented view of the development and evolution of AML. A series of non-transforming mutations appear to accumulate with age in pre-leukemic stem cells. A dominant mutation cluster consisting of genes recurrently mutated in AML leads to leukemic transformation by a founding clone. Extensive mutational analysis can be used to discriminate intermediate risk AML patients into clinically relevant groups with distinct prognoses and to delineate patients who would and would not benefit from intensified chemotherapy and/or transplantation. Relapse of AML results either from a founding clone which gains mutations that confer a survival advantage or from a subclone of the founding clone, detectable at diagnosis, which survives initial therapy, gains new mutations and expands at

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Message from the President of Levine Cancer Institute

Derek Raghavan, MD, PhD, *President*

Carolinas HealthCare System's Levine Cancer Institute is built on the concept of cancer care without walls, spanning throughout the system's network of affiliated hospitals and providers in the Carolinas. The Institute is working to define the future of cancer care – where innovations in research, clinical trials, patient support and treatment are brought closer to home for patients.

We continue to build an elite cancer program, with the recruitment of internationally renowned experts to lead the clinical teams. From the University of Texas MD Anderson Comprehensive Cancer Center, Edward S. Kim, MD, will serve as chair of the Department of Solid Tumor Oncology. Edward A. Copelan, MD, FACP, from Cleveland Clinic's Taussig Cancer Institute will serve as chair of the Department of Hematologic Oncology and Blood Disorders. We have recruited more than 50 faculty from the Carolinas and across the USA.

Updates in Cancer for Clinicians will inform you on exiting news from Levine Cancer Institute.

We welcome your feedback at levinecancerinstitute@carolinashealthcare.org *and look forward to bringing you more news in the future!*

Levine Cancer Institute Research and Administrative Headquarters.

A view of the infusion floor at Levine Cancer Institute.

Translational Science

Pharmacogenic Approaches to Personalize Cancer Therapy

Ram Ganapathi, PhD *(left)*
Chair of Cancer Pharmacology

Marukh Ganapathi, PhD *(right)*
Senior Scientist

Complexities in the genetic landscape of tumors significantly impact the design of optimal strategies for effective treatment of cancer. The goal of Cancer Pharmacology/Translational Research at Levine Cancer Institute is to support and develop novel paradigms for cancer care. As such, our ongoing translational research has focused on the areas of acute myeloid leukemia (AML), renal cell carcinoma and ovarian cancer.

A key event in the development of AML is the disruption of the myeloid differentiation program and aberrant self-renewal of leukemic stem cell. Differentiation therapy with the retinoic acid analog, all-trans retinoic acid (ATRA) has been successful in treating acute promyelocytic leukemia, a cytogenetically distinct subtype of AML characterized by the PML-RARα gene translocation. However, ATRA has shown little promise in differentiation therapy of other subtypes of AML. To develop strategies that would improve differentiation therapy for other forms of AML, including relapsed/refractory disease, we studied the role of a key nuclear enzyme, topoisomerase II, in ATRA-induced differentiation of AML cells. Using different AML cell lines and AML blast cells from relapsed/refractory patients, we were able to demonstrate that by targeting topoisomerase II, either by deleting the enzyme or inhibiting its activity, the therapeutic efficacy of ATRA could be potentiated. Specifically, the combination of ATRA and topoisomerase II inhibitors, such as ICRF-193 or dexrazoxane (a clinically active topoisomerase II inhibitor), led to enhanced differentiation and preferential activation of the cell death pathway, as compared to differentiation coupled growth arrest induced by ATRA alone. Based on this preclinical finding, we were able to formulate a clinical hypothesis that the combination of ATRA with the clinically relevant topoisomerase II catalytic inhibitor, dexrazoxane, leads to improved response in AML patients. We are now poised to test this hypothesis in

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Novel Treatments for Lung Cancer Patients With EGFR Mutations

Edward S. Kim, MD *(left)*
Chair of the Department of Solid Tumor Oncology and Investigational Therapeutics

Kathryn Mileham, MD *(right)*
Medical Oncology

Lung cancer remains the leading cause of cancer-related deaths in the United States, (1) and non-small cell lung cancer (NSCLC) accounts for more than 85 percent of the cases. With most patients presenting with advanced disease, there is an urgency to maximize treatment efficacy while minimizing drug toxicity. Through a deeper understanding of the biology driving NSCLC, novel treatment paradigms are based on disease biomarkers with corresponding targeted therapy. This has been best achieved with advanced treatment options for the two-thirds of adenocarcinoma patients in whom driver mutations are identified.

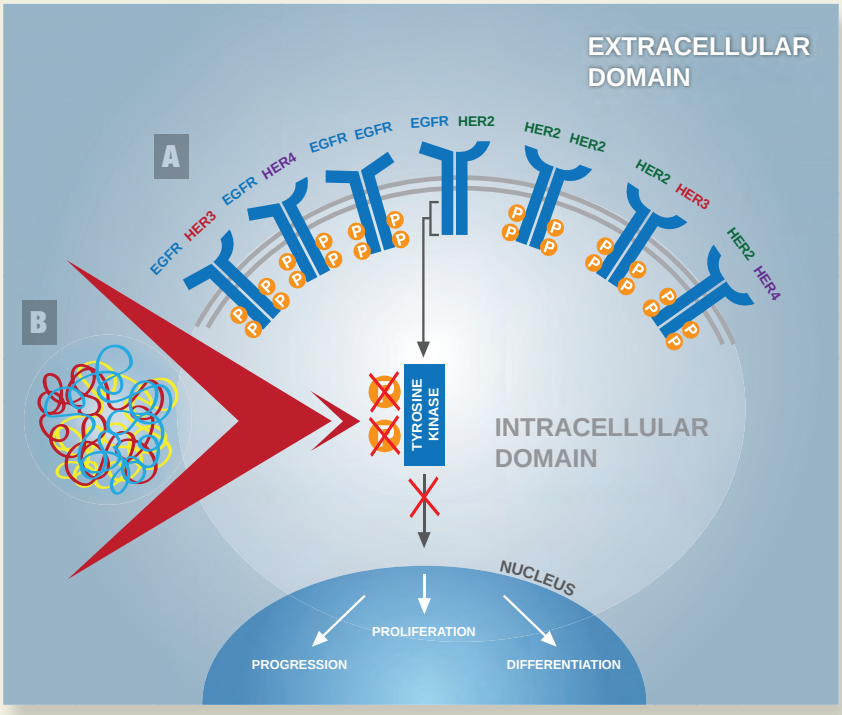
Somatic mutations in the tyrosine kinase domain of the epidermal growth factor receptor (EGFR) are found in 15-20 percent of lung adenocarcinomas.

Afatinib is an oral small-molecule EGFR-tyrosine kinase inhibitor that binds irreversibly to EGFR and HER2. Recent compelling data from the LUX-Lung 3 trial have been reported. In this randomized phase III study, patients with EGFR-mutated, advanced lung adenocarcinomas were treated frontline with afatinib versus pemetrexed-cisplatin. The study enrolled 345 patients and met its primary endpoint demonstrating significantly prolonged progression free survival (PFS) in patients treated with afatinib (11.1 vs 6.9 months; HR, 0.58; p=0.0004). In preplanned analysis, those patients with common mutations (Del19 or L858R) had a median PFS of 13.6 versus 6.9 months (HR, 0.47; p<0.0001). (2) Additionally, objective response rate, disease control, cancer-related symptoms and quality of life were also improved with afatinib. The most frequent adverse events were diarrhea and rash, although no patients discontinued afatinib for rash. LUX-Lung 3 is the first randomized study to demonstrate benefit of an oral targeted therapy versus chemotherapy in a molecularly selected population. Based on these results, afatinib is currently available through an open label expanded access program at a starting dose of 40 mg/daily.

While management of lung cancer is in rapid evolution the standard of "chemotherapy for all" no longer exists. National guidelines concur that molecular profiling is necessary in order to provide the best available therapy. This requires sufficient tissue sampling for precise pathologic diagnosis. While patients with unknown driver mutations are still treated with chemotherapy, those with EGFR mutations or ALK rearrangements have expanding options for targeted personalized treatment.

REFERENCES
1. http://seer.cancer.gov/statfacts/html/lungb.html

2. Yang JC, Schuler MH, Yamamoto N, et al. LUX-Lung 3: A randomized, open-label, phase III study of afatinib versus pemetrexed and cisplatin as first-line treatment for patients with advanced adenocarcinoma of the lung harboring EGFR-activating mutations. J Clin Oncol 2012;30(suppl): LBA7500.



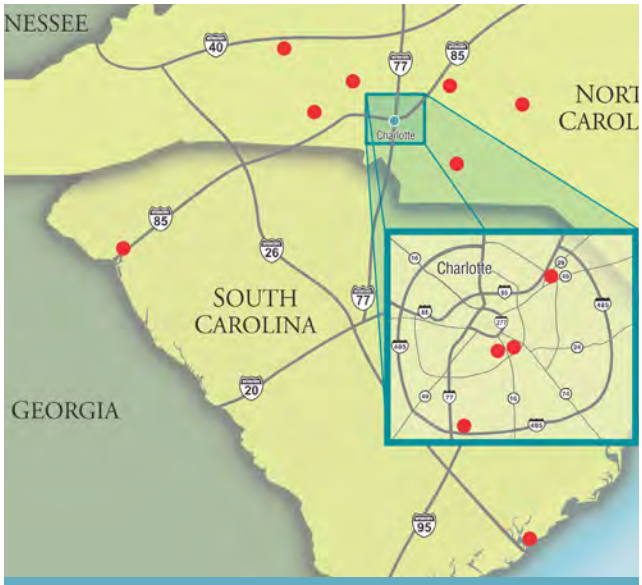
A: The epidermal growth factor family of extracellular protein ligands includes cell surface receptors EGFR (ErB-1), HER2 (ErB-2), HER3 (ErB-3), and HER4 (ErB-4). When EGFR is dimerized, intrinisic intracellular tyrosine kinase activity is stimulated by autophosphorylation causing downstream activation and signaling leading to DNA synthesis and cell proliferation.

Mutations in EGFR are clustered near the tyrosine kinase domain possibly providing stabilization and additive gain. Therapeutic approaches targeting EGFR tyrosin kinase halt this signaling cascade.

B: Afatnib is an oral, small-molecule, EGFR-tyrosine kinase inhibitor that irreversibly binds to the ErbB family homo- and heterodimers inhibiting signal transduction.

Levine Cancer Institute: Built on the Strength of a Network

At Levine Cancer Institute we've developed a sophisticated academic and clinical cancer institute without walls, spanning Carolinas HealthCare System (CHS) and providing state-of-the-art treatment and research programs are closer to where our patients live.



CHANGING THE COURSE OF CANCER CARE

The Institute's research and administrative headquarters located in Charlotte, NC, opened in October 2012. While the Institute functions as a series of integrated cancer programs distributing high-quality cancer care system-wide, this building serves as its center for communication, research and administration. It houses the technology infrastructure to seamlessly connect physicians and care teams and share best practices and programs.

The building features nine cancer clinics, infusion therapy, palliative care, as well as cutting-edge teleconferencing technology that allows physicians to collaborate long-distance, further breaking down geographic barriers and improving care across CHS. With six floors and more than 171,000 square feet of space, the building includes an extensive clinical trials operation with a special Phase I therapeutic unit designed to evaluate new treatment options, and multidisciplinary clinics to treat complex and rare cancers.

"The opening of the building is symbolic of the entire Levine Cancer Institute network being fully functioning, for the advancement of patient care across the Carolinas," said Dr. Derek Raghavan. "The new resources and technology this space affords will enable us to be better connected to our partner institutions across the Carolinas to share knowledge, standard protocols and research, while offering patients in Charlotte a state-of-the-art place to receive their cancer care."

Integration of Roper St. Francis Cancer Care Into Our Network

Steve Akman, MD,
Medical Director, Roper St. Francis Cancer Care

In 2012, Carolinas HealthCare System's Levine Cancer Institute announced its charter member institutions, including Roper St. Francis Cancer Care, as part of the system's new cancer care network.

Roper St. Francis Cancer Center was established in 2010 through a partnership between Roper St. Francis Healthcare and Charleston Hematology Oncology Associates. The 76,000 square-foot outpatient cancer center is home base for many of the services provided by Roper St. Francis Cancer Care physicians, who help more than 1,700 newly diagnosed cancer patients each year. Top tumor sites include breast, prostate, lung and colorectal cancers. Roper St. Francis Cancer Care is the market leader by volume for breast, prostate and colorectal cancers*.

The relationship between Levine Cancer Institute, Roper St. Francis Cancer Care and other member institutions brings increased access to cancer specialists, research and innovative programs and services to patients closer to where they live.

"We take cancer care very seriously. Through our elite network of affiliated hospitals and physicians across the Carolinas, we are able to bring patients the best cancer care in a more convenient way," said Derek Raghavan, MD, PhD, and President of the Institute. "Levine Cancer Institute is a national model that shows how we are investing in our community and the lives of patients by removing barriers that separate them from access to breakthrough research and treatments."

" The providers and patients of Roper St. Francis Healthcare are excited about our partnership with Levine Cancer Institute," said Steven Akman MD, Medical Director of Roper St. Francis Cancer Care. "This partnership facilitates rapid access to advanced cancer therapies and technologies in our Charleston community that heretofore had only been available to institutions of the size and scale of Levine Cancer Institute."

**Based upon 2010 data provided by the Commission on Cancer of the American College of Surgeons*

Highlights from SABC 2012


Wendy Brick, MD *(left)*
Medical Oncology

Richard White, MD, FACS *(right)*
Surgical Oncology


Steven Limentani, MD *(left)*
Medical Oncology

Teresa Flippo-Morton, MD, FAC *(right)*
Surgical Oncology

The ATLAS Trial: Treatment Implications

While current treatment guidelines recommend that women with estrogen receptor positive breast cancer receive anti-estrogen therapy for five years, the recently published results of the Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) results suggest that 10 years of adjuvant treatment should be considered for some women.

The international trial recruited patients from 1996-2005 and enrolled patients were randomized to stop tamoxifen at five years (control) or continue for a total of 10 years. Allocation to continue tamoxifen for 10 years versus stopping at five years reduced breast cancer recurrence (617 recurrences in 3,428 women allocated to continue versus 711 in 3,418 controls p=0.002) and breast cancer mortality (311 deaths with recurrence in women allocated to continue versus 397 in controls p=0.01). Risk of recurrence during years 5-14 was 21.4 percent for continuing tamoxifen versus 25.1 percent for controls (absolute risk reduction 3.7 percent). Breast cancer mortality during these same years was 12.2 percent versus 15 percent, for an absolute mortality reduction of 2.8 percent. The greatest additional benefit was seen in the second decade after diagnosis, as there was almost no difference in death and recurrence between the two groups during the five years of extra tamoxifen. The difference came in later years, consistent with the understanding that tamoxifen has an effect that lasts long after women stop taking it. Breast cancer mortality during the second decade after diagnosis was decreased almost 30 percent in women who continued tamoxifen for 10 years.

These results are relevant for any woman currently taking tamoxifen and may be even more so for premenopausal women, who have little risk of tamoxifen causing uterine cancer or venous thrombotic events. Women and their doctors should consider this evidence when deciding how long to continue tamoxifen or any other endocrine therapy.

Evaluation of the long-term side effects of longer term tamoxifen will require lengthier follow up and meta-analysis of all relevant trials for final assessment.

REFERENCE:
The Lancet, 2012 DOI: 10.1016/S0140-6736(12)61963-1

Racial and Staging Disparities

Racial disparities in the care of women with breast cancer have become the norm rather than the exception (MMWR 2012, Lund 2008, van Ravesteyn 2011). Investigators from MD Anderson Cancer Center used SEER Medicare data to assess the utilization of the relatively new technology of axillary sentinel lymph node biopsy (SLNB) in the staging of women with breast cancer. The use of SLNB was compared in white women versus the use in black women.

5.7 percent of 31,274 women retrieved from the database were black while 89 percent were white. 74 percent of the white women underwent SLNB, compared to 62 percent of the black women (p<0.001). Further analysis noted differences between 7 and 15 percent for every year from 2002 to 2007. With adjusted analysis, black women were 33 percent less likely to undergo SLNB than white women (relative risk=0.74, 95 percent CI 0.67-0.81, p<0.001).

Black women in the U.S. have a 41 percent higher breast cancer death rate than white women despite a lower incidence. 45 percent of black women are diagnosed with regional or distant disease versus 35 percent of white women [MMWR 2012]. Van Ravesteyn [2011] proposed a model suggesting that differences in screening use explained 8 percent and differences in adjuvant therapy explained 19 percent of these disparities. Methods to address disparities are being tested throughout the U.S. and are critical to changing the course of cancer care.

REFERENCE:
Black DM, San Antonio abstract 2012

Axillary Node Dissection May Not Be Needed For Everyone

ACOSOG Z-1071 studied the use of sentinel node biopsy in a group of women with breast cancer who had previously been considered contraindicated for this procedure; biopsy-proven node positive women. This multicenter trial enrolled 756 women with node positive breast cancer.

All patients received neoadjuvant chemotherapy prior to surgery. All women had re-evaluation of the axilla with ultrasound and then surgery with a sentinel lymph node procedure (encouraging both blue dye and radionucleotide for mapping), followed by complete axillary node dissection.

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Highlights from SABC 2012

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Results demonstrated that 40 percent of patients with positive sentinel lymph node prechemotherapy had a complete pathologic response in the axilla. The false negative rate of the procedure was 12.6 percent, though the SLN procedure was able to correctly identify nodal status in 91 percent of patients. Further evaluation of the data is needed before this can routinely change practice, but it does give hope that a subset of women with node positive disease in the axilla may, in the future, be able to omit an automatic axillary node dissection.

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2. Johnson K, " In Node-Positive Breast Cancer, Sentinel Biopsy Could Avert ALND", Medscape, Dec 6, 2012.

TDM-1, Docetaxel and Pertuzumab in Breast Cancer Patients

T-DM1 is a drug in which Trastuzumab has been covalently linked to a novel chemotherapeutic emtansine, also known as DM1. Pertuzumab, in contrast, interferes with her2- her3 dimerization, a novel action different from the mechanism action of Trastuzumab.

This phase I dose escalation study was performed beginning with stage IV disease patients, but also those with stage II and stage III breast cancer treated in the neoadjuvant setting followed by an expansion cohort. Sites for this study included Levine Cancer Institute, Baylor College of Medicine and multiple sites in Europe.

The study demonstrated that doublet and triplet combinations were well tolerated. Early analysis of patients treated in the neoadjuvant setting revealed eight of nine (88 percent) treated with the doublet and three of five (60 percent) treated with the triplet regimen achieved a pathologic complete response in the breast and lymph nodes. More data will be available once all patients have undergone the surgical portion of their treatment. Although the numbers are small, the rate of pathologic complete response is encouraging. Data will be utilized as the basis for a phase III randomized trial that will compare these combinations to the current standard of care for women with breast cancer treated in the neoadjuvant setting.

REFERENCE:
Martin Miguel; "Interim Results From a Phase 1b/2a Study of Trastuzumab Emtansine and Docetaxel, With and Without Pertuzumab, in Patients With HER2-Positive Locally Advanced or Metastatic Breast Cancer", presented at San Antonio Breast Cancer Symposium, Dec. 5, 2012, San Antonio, Texas.

Updates from ASH 2012: *Gene Encoding and Sequencing to Personalize Therapy*

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relapse. A comparison of relapse versus primary tumor mutations demonstrated increased numbers of transversions at relapse, likely resulting from cytotoxic chemotherapy.

In addition, Francesco Lo-Coco, MD, from the University of Rome Tor Vergata, presented interesting results from a phase III, randomized, prospective trial from the Italian GIMEMA group and German SAL and AMLSG groups at the Plenary Session. Data demonstrated a two-year, non-inferior EFS in adult patients with newly diagnosed non-high-risk APL (WBC ≤10x109/L) treated with a chemotherapy-free regimen of ATRA and arsenic trioxide compared to standard ATRA + Idarubicin.

Together, these presentations demonstrate that the leukemic genome in an individual patient is a "moving target", whose cure requires eradication of the founding clone and its subclones, but offers clinicians better tools for risk assessment and selection of existing initial therapy and new weapons, including "serial killer" cells, for the melee.

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3. Fisher A, Daniel C, et. all; 54th American Society of Hematology Annual Meeting, Atlanta, GA, 2012 Abstract 706.
4. Porter David L, et. all; 54th American Society of Hematology Annual Meeting, Atlanta, GA, 2012 Abstract 717.
5. Kalos Michael, et. all; 54th American Society of Hematology Annual Meeting, Atlanta, GA, 2012 Abstract 756.
6. Ley Timothy J; 54th American Society of Hematology Annual Meeting, Atlanta, GA, 2012, E. Donnal Thomas Lecture: The AML Genome.
7. Blazar BR, June CH; 54th American Society of Hematology Annual Meeting, Atlanta, GA, 2012, Ernest Beutler Lecture: T-Cell Infusions: A New Tool for Transfusion Medicine That Has Come of Age.

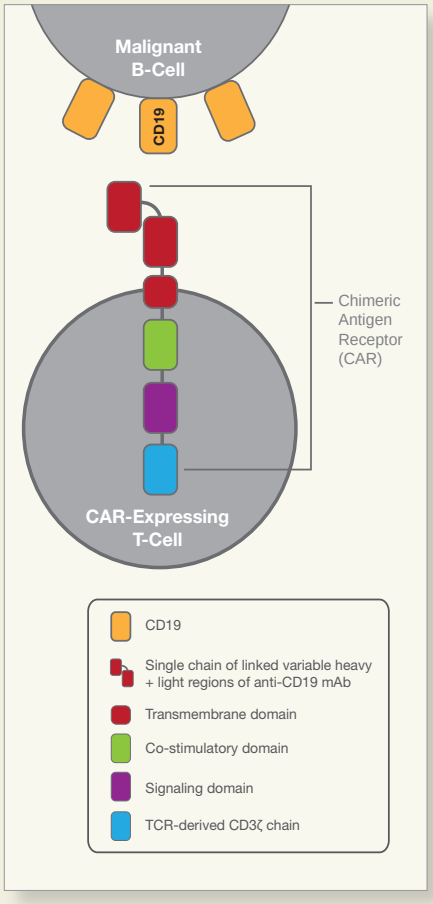

Figure 1: Genetically Engineered Adoptive Cell Therapy Via Car-Expressing T-Cells.

Translational Science

Pharmacogenic Approaches to Personalize Cancer Therapy

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preclinical mouse models that mimic relapsed/refractory AML. This study will serve as a platform in the development of a clinical protocol for treating AML.

In the past few years, treatment of renal cell cancer has included the discovery and approval of drugs that target angiogenesis related pathways. However, the rapid entry of these drugs in clinical practice has not kept pace with our understanding of treatment associated toxicity and mechanisms governing response to optimize therapy. We have embarked on a pharmacogenomic approach of screening for DNA polymorphisms in gene(s) associated with angiogenesis related pathways that can be exploited to maximize efficacy and reduce toxicity of targeted therapy for kidney cancer. Studies analyzing polymorphisms in vascular endothelial growth factor (VEGF) and VEGF-receptor (VEGFR) suggest that specific single nucleotide polymorphisms (SNPs) in the VEGF gene and the combination of VEGF and VEGF-receptor may be useful as markers to define treatment associated toxicity and overall survival, respectively.

Ovarian cancer is a major cause of mortality among gynecologic malignancies in the United States and Western Europe. The standard of care for patients with advanced disease includes surgical cytoreduction of tumor burden followed by adjuvant chemotherapy with a platinum-based regimen that in most cases includes a taxane. Although response rate with this approach is high (>70 percent), resistance to primary therapy and subsequent recurrence (relapse) is substantial. A further complication is the limited success of second line therapy in patients failing primary therapy or those with recurrent disease.

Using high throughput sequencing strategies, we sought to identify genes that are deregulated in ovarian cancer and contribute to failure of adjuvant treatment or disease recurrence following an initial complete response. Our preliminary studies have identified a subset of genes that can distinguish tumors that respond well to therapy and those that potentially lead to early relapse or recurrence. Following validation of these genes in a larger patient cohort, we plan to carry out prospective clinical trials using the gene signature to predict treatment failure or recurrent disease. Results from these studies could allow us to offer alternate therapeutic strategies to patients with resistant or recurrent disease.

REFERENCE:
Genome Med. 2011 Dec 30;3(12):79; Cancer 118: 1946-1954, 2012.

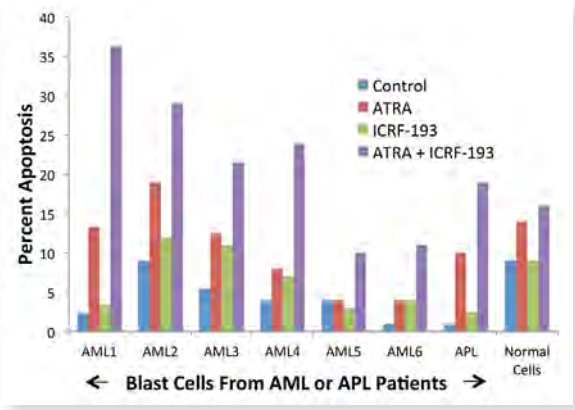

Figure 1: Preclinical Studies in AML Evaluating Response of Patient Blast Cells to the Combination of ATRA and ICRF-193.

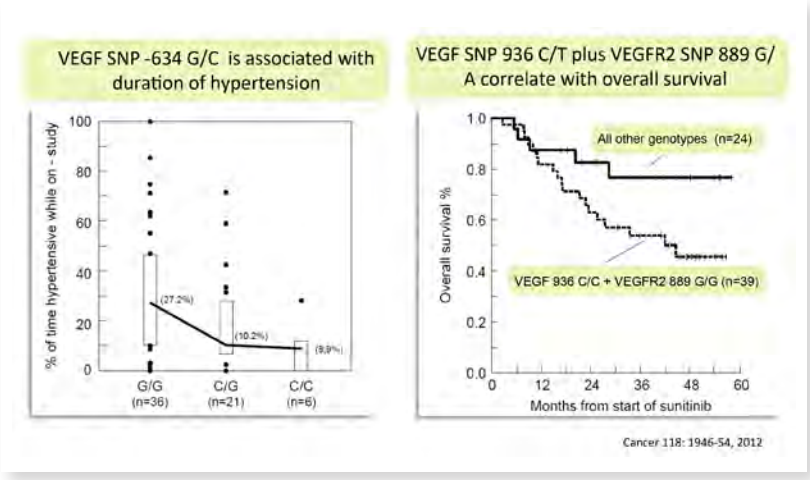

Figure 2: Association of VEGF and VEGFR2 SNPs with Toxicity (P = .01) and Overall Survival (P = .03) in Renal Cell Carcinoma Patients Treated with Sunitinib.

Targeted Folate Receptor Therapy for Ovarian Cancer

The PRECEDENT Study

Wendel Naumann, MD, FACOG, FACS, *(left)*
Gynecologic Oncologist

James Symanowski, PhD *(right)*
Biostatistician

Epithelial ovarian cancer is the second most common gynecologic malignancy in the United States.[1] The combination of aggressive surgery, platinum-based chemotherapy, intraperitoneal chemotherapy and the development of new drugs has resulted in a median survival of approximately five years in women with advanced ovarian cancer.[2] When patients become resistant to platinum, response rates are less than 20 percent and overall survival (OS) is less than one year [3]. The development of new drugs is needed, but until recently, no clinical trial has generated any advantage over single agent therapy.

Folate is a vitamin required for DNA replication and cell division. Folate receptor (FR) is strongly expressed in many cancers, including over 80 percent of epithelial ovarian cancers but not in normal tissues, making FR an excellent molecular candidate for targeted cancer therapy.[6] Further, FR expression appears to be a negative prognostic factor in ovarian cancer patients and may allow targeting of cells that are resistance to conventional chemotherapy.[4, 5]

The therapeutic agent vintafolide is a folate-chemotherapy conjugate designed to deliver desacetylvinblastine monohydrazide (DAVLBH) directly to FR-expressing cells while minimizing exposure of vintafolide to non-FR-expressing cells.[6] Normally, DAVLBH is so toxic that it cannot be used systemically. However, it can be conjugated with folate in such a way that the drug is only active when taken up into the cell and the linkage is broken by the lower intracellular pH. Toxicity from this agent is minimal due to nonspecific hepatic breakdown resulting in constipation.

We conducted the first randomized, open label, international phase II clinical trial with this compound in the PRECEDENT trial comparing vintafolide in combination with pegylated liposomal doxorubicin (PLD) versus PLD alone, in women with platinum-resistant recurrent ovarian cancer.[7] The primary objective was to compare the PFS population of patients with measurable disease, and results were statistically significant (HR=0.626; p=0.031). Previous studies suggested patients in whom all lesions expressed the folate receptor by scan had the best clinical response [8] and this hypothesis was supported by results from the PRECEDENT trial. In this group, the hazard ratio for disease progression was 0.381 (p=0.013) resulting in a median PFS increase from 1.5 to 5.5 months. This is the first randomized trial to show a significant benefit to combination chemotherapy in platinum resistant ovarian cancer.[7]

Based on the success of the randomized phase II trial, the PROCEED trial has been launched as an international phase III approval trial for vintafolide in women with FR-positive ovarian cancer by etrafolatide scan. The trial will be conducted in approximately 600 participants, with a primary objective to compare PFS between the study arms in FR-positive participants.

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8. Symanowski J., et al., Use of 99m-Tc-EC20 (a folate-targeted imaging agent) to predict response to therapy with EC145 (folate-targeted therapy) in advance ovarian cancer. J Clin Oncol, 2010.28(15_suppl): p. 5034.