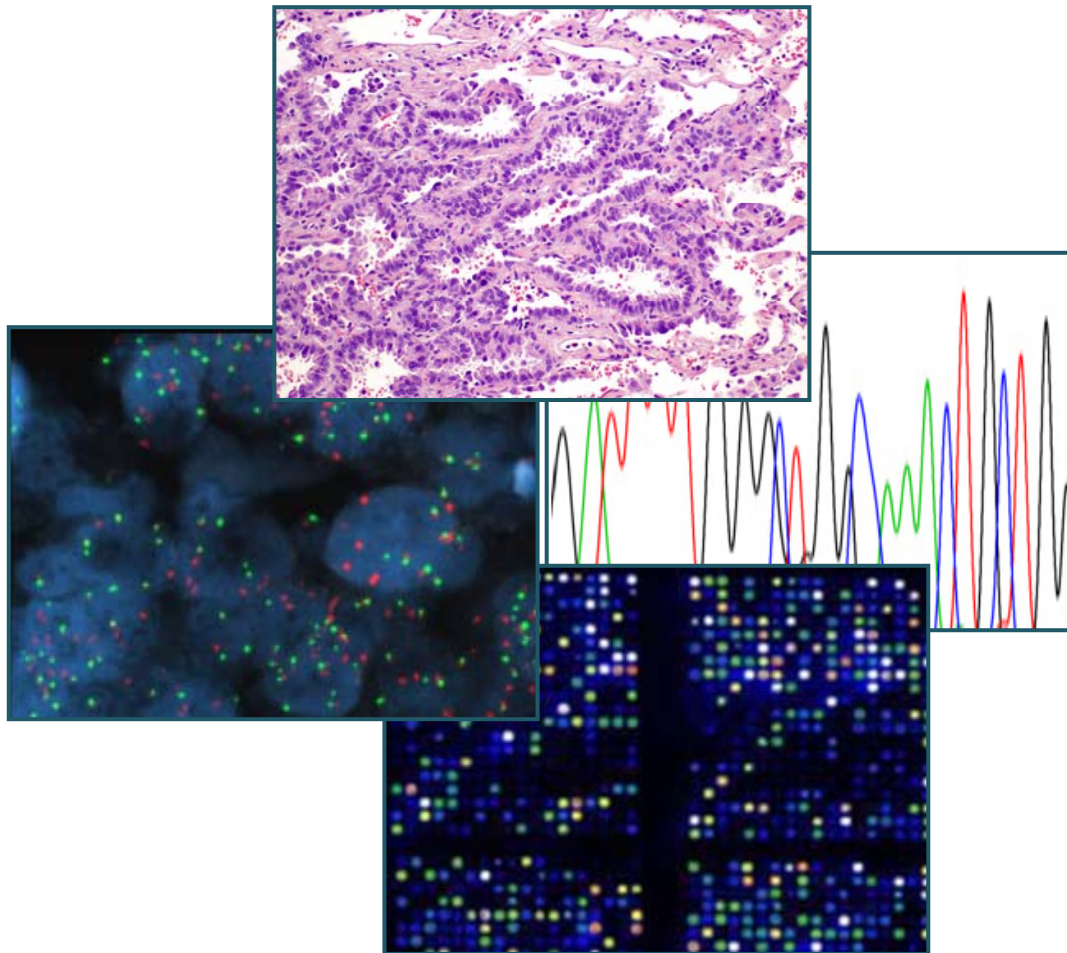


Institute for Personalized Cancer Therapy (IPCT) Annual Report



October 2008 – September 2009

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What is Biomarker-Based Personalized Cancer Therapy?

Since the sequencing of the human genome was completed in 2001, our molecular and genetic knowledge of healthy and diseased cells has increased dramatically. Accurately targeting cancer cells has become a realistic goal at M. D. Anderson Cancer Center, one of the few institutions with the breadth and depth of expertise and resources necessary to lead way in personalized cancer medicine. Integrated efforts in basic science, translational medicine, clinical research, bioinformatics and pathology, as well as research administration make M. D. Anderson the best place to meet a challenge of such magnitude.

Faculty members at M. D. Anderson have made significant progress in developing new technologies and approaches to look at the genetic makeup of an individual or of a specific tumor and to identify the mechanisms of action of specific drugs or treatments. Molecular driven, targeted therapy trials in areas such as lung, colon, brain, breast and prostate cancer are underway in our clinics, but a greatly expanded and cohesive effort is needed to accelerate new treatments for all types of cancer.

Therefore, we are developing an Institute for Personalized Cancer Therapy with Centers of Excellence (the first being the Center for Biomarker-Based Clinical Trials),

How Does the Institute Work?

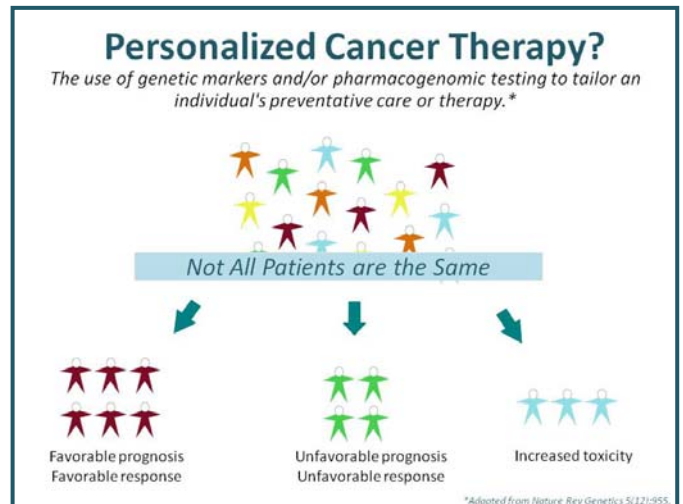
The Institute for Personalized Cancer Therapy is the largest of four institutes that will be established at M. D. Anderson over the next six years. As unified enterprises, the institutes will encourage collaborations that support innovative research; facilitate sharing of expensive and limited resources, such as major equipment; provide informatics technology and core laboratory services for assessing genetic and molecular abnormalities; and give us a competitive edge in recruiting top faculty and obtaining research funding.

Working with other M. D. Anderson researchers, faculty in the Institute for Personalized Cancer Therapy will identify laboratory discoveries – both here and at other institutions – with the greatest potential to lead to innovative anti-cancer agents and diagnostics. The institute's Center for Biomarker-Based Clinical Trials will provide the resources to expedite the testing and evaluation of these agents in Phase I and II trials in M. D. Anderson's multidisciplinary care centers or in the Department of Investigational Cancer Therapeutics. Promising agents will then be studied in Phase III trials and in registration trials aimed at regulatory approval by the Food and Drug Administration.

The Institute for Personalized Cancer Therapy encompasses the clinical research activities of all the clinical divisions and departments involved in our multidisciplinary care centers:

- | | | |
|------------------------------|------------------------|------------------------|
| • Brain and Spine | • Gastrointestinal | • Lymphoma and Myeloma |
| • Breast | • Genitourinary | • Melanoma and Skin |
| • Cancer Prevention | • Gynecologic Oncology | • Sarcoma |
| • Cardiopulmonary | • Head and Neck | • Targeted Therapies |
| • Children's Cancer Hospital | • Internal Medicine | • Thoracic |
| • Endocrine | • Leukemia | |

Each multidisciplinary center has established a steering committee to review progress and recommend priorities for future research. Both internal and external review boards oversee planning, conduct scientific reviews, measure progress and advocate nationally for changes in the way clinical trials for targeted therapy are conducted and evaluated.



At M. D. Anderson, personalized cancer therapy also encompasses exploring new surgical and radiation therapy techniques; diagnostic imaging and pathologic evaluation of cancer; the short and long-term effects of cancer and cancer treatment on the body's major organ systems, such as the brain, heart, lungs and immune function; as well as symptom management, palliative care and integrative medicine.

The Center for Biomarker-Based Clinical Trials in the Institute for Personalized Cancer Therapy will be a unique clinical research enterprise, unmatched at any other university or pharmaceutical company.

Our goal is to determine the specific genetic and molecular abnormalities of each patient's cancer, and then prescribe the appropriate therapies that target those abnormalities.

Institute Progress: A Time Line of Accomplishments

February 2, 2008 – Feasibility Retreat

Key Leaders throughout the institution met to discuss developing personalized medicine, and each areas representatives leaves with a charge to form a steering committee, create a roster of current personalized therapy activities for their area, identify infrastructure needs and develop a budget and a funding strategy. Plans to be submitted to the institutional steering committee.

Spring 2008 – Report to Institutional Senior Leadership

Comprehensive presentation to leaders made with details of the personnel, scientific resources and funding needed to launch the Institute for Personalized Cancer Therapy.

Summer 2008 – Project Funding Requests Submitted

Each Multidisciplinary care center was invited to submit two projects to be considered for funding. Twenty-seven projects from 15 care centers received funding and began implementing new studies in personalized medicine.

Fall 2008 – Institute Administrator Named

Carol Farhangfar, PhD, was hired to work with fellows and faculty to develop and fund new projects. She has experience in academia and the pharmaceutical industry and is a respected researcher, educator, and administrator.

November 2008 – Monthly Working Group Meetings Begin

Meetings feature scientific presentations on the accomplishments and challenges in personalized medicine. All faculty and staff are invited to attend and exchange ideas.

January 2009 – IPCT Website Launched

Website is launched which enables frequent, easily accessible updates for faculty, staff, and the public. The site contains meeting announcements, summary of current research programs, resources for investigators to identify National Cancer Institute, foundation, and society opportunities for funding specific to personalized medicine research, and other links of interest.

March 2009 – Center for Biomarker-Based Clinical Trials Created

This center of excellence within the institute will expedite testing and evaluation of anti-cancer agents and diagnostics in Phase I and II clinical trials, and promising agents will then be studied in Phase II trials. The philanthropic goal of the center is \$75 million to be raised over six years.

Summer 2009 – Molecular Pathology Working Group Created

Molecular pathology is one of the most essential components to the development and implementation of personalized cancer therapy. Multiple disease sites have well-developed molecular pathology research groups and the Molecular Pathology Working Group was created to integrate their efforts, minimize the overlap, and accelerate the pace of research.

Building Infrastructure to Lead Personalized Cancer Therapy

Of critical necessity to lead the development of personalized cancer therapy is building the essential infrastructure to support the research with consistent, high-quality assays performed efficiently and in real-time to support clinical decisions for each patient. Dr. Stanley Hamilton, Division Head of Pathology and Lab Medicine and Director of the IPCT, is leading the effort for molecular pathology, bringing research from the laboratory to the clinic rapidly through the Molecular Targets and Molecular Testing Facility (MTMTF). The advent of targeted therapy poses new opportunities and challenges for personalized cancer therapy. These challenges and opportunities begin with the design of marker-directed clinical trials based on translational research and lead to the development of levels of evidence that justify routine clinical usage of markers in directing patient management. Identification in an individual patient's tumor of the target for a targeted agent is

essential in selecting patients for inclusion in a trial with the presence of the target as a specific inclusion criterion. Few marker-directed clinical trials have been initiated, but the number is expected to increase dramatically as the therapeutic marker knowledge base continues to expand. Laboratory support for clinical trials of cancer therapy directed by molecular targets and markers must also be provided with regulatory compliance. The MTMTF is based in the clinical laboratories of the Division of Pathology and Laboratory Medicine that are compliant with the Clinical Laboratory Improvement Act of 1998 (CLIA-88). This “laboratory without walls” provides the framework for a resource to enhance clinical trials performed at M. D. Anderson by developing marker assays for marker-driven trials that meet regulatory requirements for treatment assignment for patients. The MTMTF “laboratory without walls” requires additional resources in six existing clinical laboratories in the Division of Pathology and Laboratory Medicine: the Molecular Diagnostics Laboratory at Naomi Street; the Flow Cytometry and Immunology Laboratory in the Love Clinic Building; the Immunohistochemistry Laboratory in the Alkek Hospital; the Image Analysis Laboratory in the Alkek Hospital; the Cytogenetics Laboratory in the Clark Clinic Building; and the Core Laboratory (Clinical Chemistry) in the Love Clinic Building. The tried-and-true sequence of Phase I, Phase II, and Phase III trials has been enhanced by correlative marker studies that permit assessment of drug mechanisms and molecular effects as well as tumor response. The clinical trial system is made especially complex because numerous cytotoxic and cytostatic drugs with a wide variety of targets and mechanisms of action are currently available or in development, and these agents are used routinely in various combinations. In the past year, CLIA-compliant assays have been developed for multiple markers including mutations in PI3KCA, BRAF, FLT3, NPM1, CEBPA, JAK2, to name a few. In collaboration with Dr. Gordon Mills and the team at the Kleberg Center for Molecular Markers, the latest sequencing technology, Sequenom, which allows detection of mutations in multiple genes in a single assay, is being brought to the CLIA-compliant MTMTF.

Brain Tumor Research

Although brain tumors (Gliomas) are not among the most common of neoplasms, they are among the most devastating. To date, little is known about the molecular pathways involved in their genesis, progression and clinical behavior. Despite the advances in treatment, glioma remains the leading cause of cancer death in children, the second most common cause of cancer death in young adults and accounts for a substantial percentage of cancer deaths in older adults. This is partly due to the fact that the therapy that is most effective for other cancers, surgical removal, cannot be used to cure brain tumors. In addition, brain tumors are relatively insensitive to radiation and chemotherapy resulting in a relatively small number of patients responding favorably to treatment. IPCT investigators at M. D. Anderson are working on multiple approaches to advance the prospects for patients with brain tumors.

Prediction using Genes

Drs. Howard Colman and Kenneth Aldape, in collaboration with multiple investigators, have identified a group of nine genes which can predict the outcome for patients diagnosed with glioblastoma multiforme. By looking at the genes expressed in the tumor of newly diagnosed patients, they can predict the outcome to the most common chemotherapy treatment, temozolomide, and determine how best to proceed. Two clinical trials are currently underway to test this predictive gene signature: 1) 2008-0059, a Phase I/II study of sorafenib with radiation and temozolomide; and 2) RTOG 0825, a Phase III study of bevacizumab with radiation and temozolomide. A third trial is to test an expanded 45 gene assay a phase III clinical trial (RTOG 0525).



Kenneth Aldape, MD



Howard Colman, MD PhD

MGMT Enzyme Activity as a Modulator of Glioma Treatment Outcome

Dr. Randa El-Zein and collaborators are working on another approach to identify patients who would benefit from treatment with temozolomide for glioblastoma multiforme. They have developed a novel assay to measure the activity of an enzyme, O⁶-methylguanine-DNA methyltransferase (MGMT), which is responsible for repair of the lesions induced by temozolomide. MGMT reverses the chemotherapeutic effect of temozolomide and may hinder its effect. Thus, determining the levels of MGMT enzymatic activity prior to initiation of temozolomide treatment could constitute a critical factor in determining treatment response and, in turn, clinical outcome. The assay they developed can detect levels in a blood sample making this a very non-invasive test for patients.



Randa El-Zein, MD, PhD

Molecular Triaging of Newly Diagnosed Stage II-III Breast Cancer for Neoadjuvant Therapy

M. D. Anderson oncologists, pathologists, surgeons, systems biologists and statisticians have developed a Breast Medical Oncology Personalized Medicine Program. The goals of the program are to develop and validate molecular markers that identify patients for specific therapies, and to use molecular data to identify new therapeutic targets to bring these results to test in the clinic. The program focuses on three areas of research: pharmacogenomics, systems biology, and minimal residual cancer.

The pharmacogenomics effort – led by Drs. Lajos Pusztai and W. Fraser Symmans – seeks to understand the interaction between the genetic makeup of a patient's breast cancer and her or his response to a particular drug therapy. Drs. Pusztai and Symmans recently reported on three genomic guides to breast cancer treatment decisions that provide important information to physicians and patients requiring only a single microarray analysis of the patient's tumor biopsy. The three genomic tests independently predict 1) the likelihood that the patient's breast cancer will recur after surgery; 2) the cancer's vulnerability to chemotherapy; and 3) the cancer's vulnerability to hormone therapy. Dr. Pusztai explains that this information could assist in deciding which patients can safely forego chemotherapy after surgery and which patients will require all three treatment modalities – surgery, chemotherapy and hormonal therapy – in order to maximize the chance of cure. A prospective clinical trial at M. D. Anderson will use these predictors to select treatment options for new patients. In collaboration with Dr. Ana Gonzalez-Angulo, they are investigating which patients will respond to the standard T/FAC chemotherapy

regimen alone and in combination with targeted agents (bevacizumab, trastuzumab). Their goal is to demonstrate that “molecular triaging” is beneficial through a proof-of-concept study to select patient treatment based on pharmacogenomic tests. Their clinical trial “*MDACC 2007-0574: Personalized treatment selection for Dasatinib in metastatic breast cancer*” is the first, ongoing, gene-expression profile-based treatment selection trial for a molecularly targeted drug in breast cancer. Dr. Symmans research was also chosen for award from the NCI to develop standard procedures for collection and analysis of human biospecimens to ensure that the results from all studies of this type are valid and comparable so that research such as this gives the most valuable information possible.



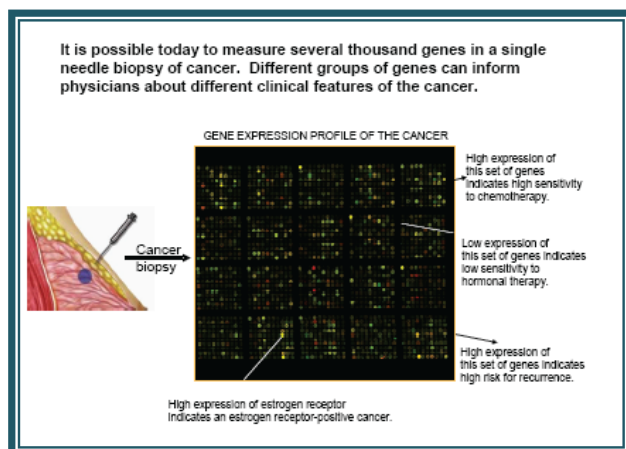
Lajos Pusztai, MD, DPhil



W. Fraser Symmans, MD



Ana Gonzalez-Angulo, MD



Improved Personalized Therapy through the Eradication of Micrometastases

Dr. Anthony Lucci's research focuses on quiescent disseminated tumor cells (DTCs) present in the distant organs of patients, such as the bone marrow. Blood is also collected to search for circulating tumor cells (CTCs) as another means of assessing micrometastatic spread within cancer patients. He and his team of collaborators have shown that the presence of DTCs or CTCs in breast cancer patients is a strong predictor for the risk of recurrence. Monitoring and eradication of DTCs will be an important component of personalizing cancer therapy. He has thus established a comprehensive clinic-based collaborative micrometastasis program at M. D. Anderson Cancer Center. They are working on several fronts: 1) optimizing methods of DTC detection and their clinical application in collaboration with Rice University, 2) investigating primary tumor characteristics that predict dissemination and long-term survival of tumor cells, and 3) developing assays in the laboratory to model dormant cells such as DTCs. They have made significant progress in all these areas to date. Two large clinical studies on DTCs (04-0657) and CTCs (04-0698) are ongoing here at M. D. Anderson.



Anthony Lucci, MD

Nested Enrichment Trial Design in Refractory Metastatic Colorectal Cancer

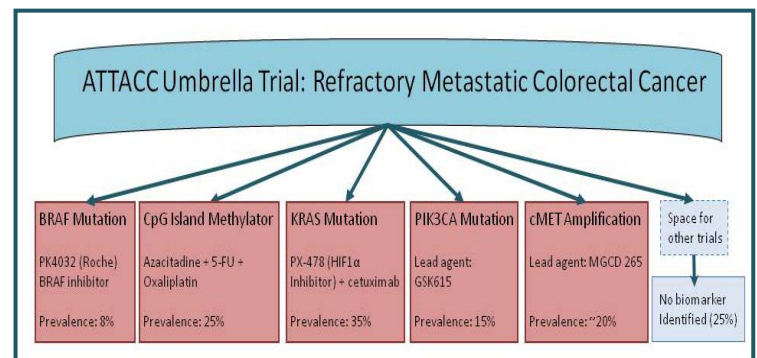
Drug development is changing rapidly. The Food and Drug Administration (FDA) Critical Path initiative has specifically called for innovative clinical trials, new statistical tools, and an increased push for biomarkers. As Dr. Scott Kopetz recently reviewed in the *Journal of Clinical Oncology*, in the field of metastatic colorectal cancer, this approach has not been adopted. In fact, of the 102 trials planned or ongoing, only three utilized an enriched design. Colorectal cancer is a heterogeneous disease, with subsets apparent based on pathologic, molecular, and genetic characteristics. In order to address this challenge, Dr. Kopetz and his collaborators (Drs. Jim Abbruzzese, Lee Ellis, Stanley Hamilton, Jean-Pierre Issa, Michael Overman, Gordon Mills, Gary Gallick, Asif Rashid, Bryan Hennessy, Cathy Eng, Hartmut Koeppen, Lynne Abruzzo) developed an enrichment approach for personalized therapy with novel therapeutics in refractory metastatic colorectal cancer. The long-term goal is to improve identification of agents that provide clinical benefit for subsets of colorectal cancer. Their design includes one protocol for enrollment, biopsy, and screening of patients (termed the “umbrella” protocol) and several separate protocols (termed the “enriched” protocols) for each of the proposed treatment trials. Each of the “enriched” protocols requires the presence of a biomarker predicted to identify a subset of patients with a higher likelihood of response. Patients undergo biopsy of a metastatic lesion and real-time assessment of the tumor for the relevant biomarkers to be assigned to an “enriched” protocol. Because of the open nature of this approach, two more trials have already been added (opening soon): 1) a combination Akt/Mek inhibitor for patients with KRAS mutation, and 2) Src-inhibitor dasatinib for patients with and without KRAS mutations. This design remains open-ended and moves toward the development of an iterative, personalized medicine approach in the GI Center.



Scott Kopetz, MD

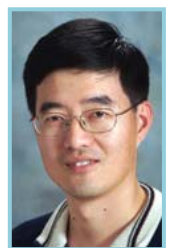
The study incorporates four clinical trials:

- 1) BRAF inhibitor in mutant BRAFV600E patients (opened with 15 patients to date)
- 2) Demethylating agent for patients with the hypermethylated phenotype in combination with 5-FU and oxaliplatin (approved, opening soon)
- 3) PIK3CA drug (approved, beginning soon)
- 4) c-Met inhibitor (assay development begun).



Predictors of Risk for Esophageal Cancer and Treatment Outcomes: An Integrative approach

The efficacy of treatment for esophageal cancer has improved only marginally over the past few decades. Chemoradiotherapy continues to have a narrow therapeutic index, and efficacy and toxicity are unpredictable, and drug resistance presents a major obstacle. For patients with local-regional cancer, chemotherapy is often combined with radiation therapy prior to surgery. 5-FU and platinum agents are the cornerstones of this approach, with approximately 95% patients receiving preoperative chemoradiation at M. D. Anderson. However, the inability to predict 5-FU or platinum toxicity and radiation-induced toxicity in individual patients limits drug efficacy. Moreover, most patients who do show initial tumor shrinkage with 5-FU or platinum subsequently relapse. Cellular events that are modulated by sets of interacting genes may partly explain such unpredictable outcomes. Dr. Gu and his collaborators, Drs. Jaffer Ajani and Xifeng Wu, believe that genetic differences in an individual impact the efficacy and toxicity of this regimen and this information can be used to predict individual drug response with great potential to facilitate therapy customization based on the individual patient's genetic makeup, thereby both increasing treatment efficacy and reducing undesired toxicity. In the past year, Dr. Gu has abstracted data and is assessing genes that are involved in relevant pathways. For patients with a specific genetic change in a gene for mTOR, they had a more than three-fold increased risk of death with current therapy, and for patients with a variation in the gene known as AKT, a better treatment response was found, indicating this was an important treatment to try for these particular patients.



Jian Gu, PhD

Esophageal cancer is associated with an increase in the body mass index, gastroesophageal reflux disease, and Barrett's esophagus (BE). In clinical practice today, no biomarkers are available to identify BE patients at high risk of developing esophageal cancer. The overall goal of Dr. Jaffer Ajani's research is to determine if

biomarkers in tissue of patients with esophageal cancer undergoing preoperative chemoradiation in conjunction with the results of an 'early' PET scan can help individualize therapy, creating a robust predictive model that will allow implementation of a change in clinical decision to personalize therapy for esophageal cancer patients. Protocol 2008-0752 (*FDG-PET-CT and Biomarkers to Assess Pathologic Response in Surgical Specimens of Patients with Localized Esophageal Cancer After Chemoradiation*) is underway and has enrolled 11 of 18 patients total, and is expected to be completed in 2010.

Genitourinary Cancer Research

Response and Resistance to Targeted Therapy in Renal Cell Carcinoma

In 2008, renal cell carcinoma will affect approximately 40,000 individuals per year in the US, resulting in 13,000 deaths. In deciding which patients to treat with the targeted agents available, an understanding of the mechanisms and pathways responsible for resistance and response is required to match patients to effective therapy. Dr. Eric Jonasch and his collaborators recently completed a 50 patient trial for patients with metastatic renal cell carcinoma who underwent cytoreductive nephrectomy after receiving bevacizumab. His goal is to understand the molecular determinants of response and resistance to targeted therapy to improve treatment for renal cell carcinoma patients. He performed reverse phase protein lysate array (RPPA) analysis of the tissue to look at the proteins and how they were affected by treatment and found a clear increase in the PI3K pathway in patients who did not respond as well to the treatment. Further analysis showed that the gene AKT possessed the strongest predictive power for decreased response to therapy. Other findings included:



Eric Jonasch, MD

1. AMPK was identified as being significantly associated with survival in patients treated with bevacizumab.
2. Gene expression data from same study was analyzed and compared with protein data in collaboration with Dr. Bin Teh at the Van Andel Institute in Michigan.
3. Associated genetic changes are being analyzed in collaboration with Dr. Federico Monzon. They have shown that duplication of chromosome 5 is strongly associated with improved survival in patients who received antiangiogenic therapy (like bevacizumab).
4. In collaboration with Dr. Amado Zurita and Dr. John Heymach, they have demonstrated a cytokine and angiogenic factor (CAF) profile which predicts for differential response to treatments with sorafenib versus sorafenib plus interferon therapy.

All of this research is leading to a better understanding of which treatment to use for which patient with renal cell carcinoma.

Genome-wide Association Study on Bladder Cancer Recurrence, Survival, and Treatment Response

Dr. Xifeng Wu and her collaborators (Drs. Colin Dinney, Barton Grossman, David, McConkey, Jian Gu, Jie Lin, and Yuanqing Ye) are focused on identifying the influence of epidemiologic profiles, clinical variables, and novel genetic components on recurrence, survival, and treatment response for bladder cancer patients through a genome-wide scan approach. This is the first genome-wide scan program for bladder cancer clinical outcome.



Xifeng Wu, MD, PhD

The IPCT provided funding to Dr. Wu to purchase the Illumina BeadXpress platform. Her lab now has a full repertoire of genotyping platforms that will greatly enhance our ongoing and future research. They, and collaborators in bladder cancer and multiple other disease sites, have used these platforms to identify important genetic components and SNPs (single-nucleotide polymorphisms which are DNA sequence variations that occur when just on single nucleotide A, T, C, G differs between individuals common to a geographical or ethnic group and different from a mutation) that indicate risk of developing cancer, having recurrence, the aggressiveness of the disease, and the response to different treatments. For example, they recently identified a novel bladder cancer susceptibility locus in the prostate stem cell antigen (PSCA) gene which that correlates to clinical outcomes. This study was enabled not only by the technology and expertise of her group but by the thousands of patients who allowed their blood to be used for this purpose. In bladder cancer, they are currently collaborating with researchers in New Hampshire, the Netherlands, and the United Kingdom to validate their findings.

Clinical Development of Therapeutic siRNA in Ovarian Cancer

Despite major advances in cytotoxic therapy and innovative attempts at screening and early detection, ovarian cancer remains the most common cause of mortality from a gynecologic malignancy. Therefore, discovery of novel therapeutics is urgently needed. The research of Dr. Anil Sood, Dr. Robert Coleman, and their collaborators, has culminated in bringing to the clinical setting a new therapeutic approach with RNA Interference (RNAi). RNAs are the direct products of genes, and these small RNAs, RNAi, can bind to other specific RNAs and either increase or decrease their activity. The ability to specifically bind a target gene of interest has made RNAi an attractive strategy for gene therapy. The inability to target many novel, but promising targets with other approaches prompted Drs. Sood and Coleman to utilize RNAi-based gene therapy and they have recently developed strategies for systemic delivery using a neutral nanoparticle that allows therapeutic targeting of genes that would otherwise not be “drugable”. Therefore, such a strategy could allow rapid development of personalized therapies based on the molecular profile of a given tumor.



Anil Sood, MD



Robert Coleman, MD

EphA2 is a member of the largest subfamily of receptor tyrosine kinases which is largely absent in normal tissues. While its functions are not completely understood, this protein plays a role in proliferation, survival, migration, invasion, and angiogenesis – all hallmarks of cancer. Drs. Sood and Coleman have shown that using RNAi specific for EphA2 resulted in significant advances in treatment of ovarian cancer in mouse models and they have worked to bring this to the FDA for a clinical trial.

PI3K Pathway Mutations and Progressive or Recurrent Endometrial Cancer

The standard treatment for endometrial cancer, the most common gynecologic cancer in the US, consists of a total hysterectomy with or without radiation therapy. Therapeutic options for advanced disease have included radiation, chemotherapy and hormonal therapy. However, none of these options have helped significantly. Ongoing research by our investigators, like Dr. Bryan Hennessy, is teasing apart the intricate molecular differences between various gynecologic cancers. His thorough analysis has identified several important differences which he plans to explore clinically in hope of improving treatments and outcomes for patients. He has found, for the first time, PIK3R1 (p85 α) mutations in 20% endometrial cancers. Thus, not only is the PI3K pathway targeted in a greater number of endometrial tumors than previously reported, PIK3R1 mutations are also present at a higher frequency than in any other tumor type. He has found PIK3CA, KRAS, PIK3R1 and PTEN mutations occur frequently, AKT1 mutations rarely, and BRAF mutations were not detected. This is very different from the breast cancer or gliomas. In collaboration with Dr. Kurzrock, chair of the Department of Investigation Cancer Therapeutics, these findings will be taken rapidly to the clinic with novel targeted drugs currently in clinical trials at M. D. Anderson in hopes of improving response: dual PI3K and mTOR inhibitors (GSK2126458A), PI3K-specific (GDC0941), AKT PH domain (MK2206) and catalytic domain (GSK690693B) inhibitors, rapalogs (RAD001/Everolimus) and mTOR catalytic domain (TORC) inhibitors (AZD8055), and the MEK inhibitor (GSK2B). To date, 18 women with chemoresistant metastatic endometrial cancer have been enrolled in these phase I studies with responses observed in four patients and stabilization of disease in five more, a rate of 50% – a remarkable achievement.



Bryan Hennessy, MD

PHASE I CLINICAL TRIAL NAME	DRUG CLASS
A Phase I Dose-Escalation Study of XL147 in Combination with Taxol/Carboplatin	PI3K inhibitor
Phase I study of IMC-A12 in Combination with CCI-779 in Patients with Biopsiable Advanced Cancers	IGF-IR and mTOR inhibitors
A Phase I Trial of Doxil, Bevacizumab and Temsirolimus	anthracycline, antibody, mTOR inhibitor
A Phase I/II, Multi-Centre Study to Assess the Safety, Tolerability, and Efficacy of the Tor Kinase Inhibitor AZD8055 Administered Orally to Patients with Advanced Solid Tumours, Lymphomas and Endometrial Carcinoma	mTOR inhibitor
A Phase I Study of Temsirolimus, Topotecan, and Bortezomib in Patients with Advanced Malignancy	mTOR inhibitor, combined with topoisomerase and proteasome inhibitors
A Phase I Trial of Sirolimus and Cetuximab in Cancer	mTOR inhibitor, anti-EGFR monoclonal antibody
A Phase I/II Open-Label, Dose-Escalation Study of the PI3K Inhibitor GSK1059615 in solid Tumors or lymphoma	PI3K inhibitor
A Phase I Trial of Bevacizumab and Temsirolimus in Patients with Advanced Malignancy	Monoclonal antibody and mTOR inhibitor
Histology-Independent Study of the mTOR Inhibitor, Torisel, in Patients with Advanced Cancer and PI3 Kinase Mutations	mTOR inhibitor
A Phase I Trial of ABI-009 (nab-rapamycin) Administered Weekly in Patients with Advanced Malignancies	Albumin-tagged mTOR inhibitor
A Phase I Trial of Oral PX-866 (a PI3K Inhibitor) in Patients with Advanced Solid Tumors	PI3K inhibitor

Surgery- and Radiation-Sparing Gene-expression Profiles for Patients with Laryngeal Cancer

There are more than 12,000 cases a year of laryngeal cancer in the US, making it more common than cervical cancer. A team of US surgeons and medical oncologists has demonstrated that chemotherapy alone can cure laryngeal cancer, published by M. D. Anderson in March 2009 (*Journal of Clinical Oncology*). This approach is a radical departure from either surgery or radiation therapy with concurrent chemotherapy – both of which are associated with significant acute and long-term toxicity. Dr. Chris Holsinger is working to identify biomarkers that predict response to treatment and how to select patients for chemotherapy alone as definitive treatment. He has identified genes that were differentially expressed between patients with good clinical outcome to this regimen and those who did not. He now has a genomic signature of 19 genes to predict overall survival to platin-based chemotherapy for laryngopharyngeal carcinoma. Identifying prognostic biomarkers may enable us to move towards a model of personalized cancer medicine, in which the selection of therapy will be based on individual patient and tumor characteristics, preventing unnecessary surgeries while providing the best possible outcome for patients based on this careful molecular screening.



Chris Holsinger, MD

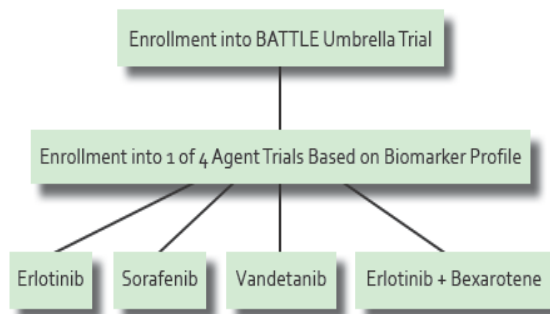
Lung Cancer Research

M. D. Anderson began conducting the first-ever clinical trials to test biomarker-based, personalized therapies in patients with advanced, treatment-resistant lung cancer in 2006. Dr. Waun Ki Hong, head of the Division of Cancer Medicine and professor of thoracic/head and neck medical oncology, leads the groundbreaking study called *BATTLE – Biomarker-Based Approaches of Targeted Therapy for Lung Cancer Elimination*, along with co-principal investigators Drs. Roy Herbst, and Edward Kim. BATTLE is examining multiple genetic and molecular biomarkers related to four signaling pathways frequently disrupted in non-small cell lung carcinomas (NSCLC). Patients are grouped according to their biomarkers in one of four clinical trials using agents known to disrupt the signaling pathways for cancer development and progression. The protocol is designed to determine whether treatment with agents known to target these pathways produces an enhanced clinical benefit for the individual patient.

The agents and their targets are:

- Erlotinib (Tarceva) targeting EGFR
- Sorafenib (Nexavar) targeting KRas and BRAf
- Vandetanib (Zactima) targeting VEGF and EGFR
- Bexarotene (Targretin) targeting RXR and cyclin D1

The goal is to first define the biomarkers that predict the activity of different agents, then enhance the probability of the patient receiving an active drug. For example, the initial hypothesis is that a patient whose lung tumor exhibits the biomarkers KRAS and BRAF could enter the clinical trial for sorafenib, the agent that specifically targets those two markers. In this way, each patient receives the agent most likely to effectively treat his or her cancer. The results of BATTLE are informing personalized therapy for lung cancer, and the design of the trial serves as a model for clinical research into many other malignancies. We are very excited as this trial draws to a close to see the results which will determine how to next move this field forward as well as inform lung cancer care.



Waun Ki Hong, MD



Roy Herbst, MD, PhD



Edward Kim, MD



Since this program was initiated, exciting new markers and signaling pathways have been discovered, and several new, promising targeted agents are now available. These new discoveries will be studied in our planned BATTLE-2 program, led by Dr. Roy Herbst. BATTLE-2 will expand our personalized medicine efforts and explore new targeted agents in patients with advanced NSCLC that have failed prior therapies.

Successful BATTLE Trial Ushered in New Era of Personalized Medicine

"Let the biology of the patient's tumor teach us how to treat the tumor" is the driving concept behind a unique proof-of-principal study—the Biomarker-Based Approaches of Targeted Therapy for Lung Cancer Elimination (BATTLE) trial. **Wan Ki Hong, MD**, division head, is the principal investigator, while **Roy Herbst, MD, PhD** and **Edward Kim, MD**, above, left, Department of Thoracic/Head and Neck Medical Oncology, are co-principal investigators of this study, and **Christine Alden, RN**, above, right, is the research nurse supervisor. The BATTLE trial demonstrated that personalized medicine is not only feasible, but also that matching molecularly targeted agents to dysregulated pathways may improve clinical response or disease control. Using an adaptive Bayesian design, biomarker classification of the patient's tumor biopsy, conducted in the Thoracic Molecular Pathology Lab by Ignacio Wistuba, MD, was used to assign patients to one of four treatment groups—erlotinib, sorafenib, vandetanib, and erlotinib with bexarotene—according to whether they were positive for EGFR, K-ras or B-raf, VEGF or VEGFR, RXR or cyclin D1, or possessed none of these biomarkers. In this design, response to treatment of the first 50 patients randomly assigned to one of the four study arms informed subsequent patient accruals to each arm of the study. Over 150 patients had been treated on the trial by end of fiscal year 2008, with the expectation that the goal of 200 enrolled at the M. D. Anderson site would be met early in 2009. The biomarker discovered the most frequently was EGFR, found in more than half of patients. The BATTLE trial design also offers the flexibility to add new targeted drug combinations that target other signaling pathways discovered in the biopsy analyses, especially to overcome drug resistance, or to suspend ineffective study groups.

Cytokine/angiogenic Factor (CAF) Profiling in Patients with Non-Small Cell Lung Cancer (NSCLC)

Targeted agents, such as VEGFR and EGFR inhibitors, have been shown to provide clinical benefit for patients with NSCLC and other solid tumors; however, benefits to date have been modest, are seen only in subsets of patients, and inevitably yield to therapeutic resistance. Dr. John Heymach and his collaborators are investigating potential blood-based biomarkers in trials of targeted agents for a number of malignancies including NSCLC, head and neck squamous cell carcinoma (HNSCC), renal cell carcinoma, and colorectal cancer to identify markers predictive of response and resistance.



John Heymach, MD, PhD

Their research has focused on proteins that can be found in the blood that may indicate the utility of these targeted drugs such as cytokines, which indicate the state of inflammation and the immune response, and angiogenic factors, which may indicate the response of blood vessels in tumors that keep the tumor growing strong. This approach is known as cytokine and angiogenic factor (CAF) profiling. Dr. Heymach's group has identified blood-based markers that predict improved progression-free survival in each of these disease types. For example, in randomized phase II trials of vandetanib, a dual VEGFR/EGFR inhibitor, they identified individual markers such as hepatocyte growth factor (HGF) associated with resistance

to vandetanib as compared to standard chemotherapy and signatures associated with greater benefit from the combination of vandetanib with chemotherapy. Similarly, in renal cell carcinoma, markers such as osteopontin were identified that predicted improved benefit in patients treated with sorafenib and interferon as compared to sorafenib alone. A CAF profile was also identified that was associated with decreased oxygen in the tumor (hypoxia) and recurrent disease in HNSCC and associated with EGFR or KRAS activation in NSCLC. Thus, they believe that broad profiling of CAFs in blood of cancer patients can be used to identify groups of patients that receive different degrees of benefit from a given therapeutic regimen compared to a standard regimen. These results suggest that CAF profiling may be an attractive, non-invasive method for identifying markers of tumor pathway activation leading to better decisions for treatment of patients.

Molecular Analysis of EGFR and KRAS in a Large Cohort of Advanced NSCLC Patients

Lung cancer is the leading cause of cancer-related death in both the United States and worldwide. Although novel approaches have improved survival in certain subsets of patients, the overall five year survival rate is only about 15%, and there is a great need to improve systemic therapy. Recent therapeutic advances in lung cancer have demonstrated the need to define these tumors at the molecular level in order to provide therapy that is more specific and thus more effective. Targeted therapy with inhibitors of the epidermal growth factor receptor (EGFR) is effective in treating a subset of NSCLC patients. Early studies demonstrated that patients with EGFR mutations have a high response rate to EGFR tyrosine kinase inhibitors and those with KRAS mutations do not respond. However, more recent data suggests that these markers do not predict benefit from any specific therapy. The use of these biomarkers remains undefined and controversial in NSCLC. Consequently, Dr. Faye Johnson and her collaborators have begun an extensive program to perform molecular testing for EGFR and KRAS mutations on all new patients with NSCLC seen in the Thoracic Center. This data is being compared to their clinical treatments and outcomes to determine the correlation of these seemingly important mutations with how a tumor responds to treatment. This information will help us make better treatment decisions for each NSCLC patient in the future.



Faye Johnson, MD, PhD

Lymphoma Research

Biomarkers for Personalized Cancer Therapy of Lymphoma

The World Health Organization (WHO) classification of lymphoid neoplasms currently recognizes 40 distinct lymphoma subtypes but, unfortunately, they do not help determine which treatment is best for which patient. To move toward personalized lymphoma therapy, Drs. Anas Younes and Timothy McDonnell are collecting and analyzing high quality biospecimens from lymphoma patients that are accurately linked to comprehensive clinical data to facilitate the development and validation of more effective but less toxic new targeted therapies. They have focused on five biomarkers selected based on their potential predictive value in clinical trials involving targeted therapies: HDAC1, HDAC2, c-MYC, JAK2, and phospho-JAK2. In addition to beginning this important endeavor to develop personalized cancer therapy for lymphoma patients, they have leveraged this pilot study to obtain a prestigious award from the National Cancer Institute (NCI): The Lymphomas Specialized Program of Research Excellence (SPORE). This program unites basic researchers and clinical researchers with a goal of bringing new research to the clinic in five years.



Anas Younes, MD

Melanoma Research

Targeting c-KIT in Melanoma

The majority of patients with mucosal (e.g., sinuses, rectal, vagina, urethra) and acral (e.g., palms or soles) melanoma have localized disease treatable by surgery, yet the overall five year survival is 10-25% and 25-35%, respectively. In chronic sun-induced damage melanoma which spreads locally, it too carries a poor prognosis. Unfortunately, adjuvant therapies (chemotherapy, immunotherapy or radiotherapy) have not improved the prognosis. Recent reports show that an important protein, the tyrosine kinase receptor c-KIT, has genetic mutations in 21% of chronically sun-damaged, 36% of acral, and 40% of mucosal melanomas, similar to those found in the in patients with gastrointestinal stromal tumors (GIST). Targeted inhibition of c-KIT has revolutionized the treatment of GIST with c-KIT mutations. GIST, like melanoma, is minimally responsive to chemotherapies, but treatment with c-KIT inhibitors has resulted in substantial improvements in survival. Dr. Patrick Hwu and his team of collaborators have had very compelling responses in patients with unresectable metastatic mucosal melanoma harboring c-KIT mutations. Their project can be truly categorized as personalized cancer therapy – a target is present in every patient in the study, that target is a proven gene that causes the transformation of normal cells into cancerous tumor cells that when inhibited results in a markedly improved clinical outcome in another form of cancer. They are opening the first clinical trial to test this new approach to melanoma treatment.



Patrick Hwu, MD



Myeloma Research

Personalizing Multiple Myeloma Therapy by Using Programmed Cell Death

Multiple myeloma will be diagnosed in over 20,000 patients in the US in 2009 making it the second-most commonly diagnosed hematologic malignancy. Significant advances have recently been made in identifying active novel agents and rational combinations in the relapsed/refractory setting, such as the proteasome inhibitor bortezomib alone and with liposomal doxorubicin, and the immunomodulatory agent lenalidomide with dexamethasone. These and other approaches have for the first time improved the overall survival of multiple myeloma patients. Despite these advances, however, multiple myeloma remains incurable, and initial responses are invariably followed by relapse. Dr. Robert Orlowski and his collaborators believe that outcomes of multiple myeloma patients can be improved by applying rationally-designed regimens that target programmed cell death pathways – pathways that specifically tell a cell to die. While this research is still in the early stage, Dr. Orlowski has obtained exciting preliminary data supporting this concept and he and his team have used these results to apply to the NCI to become a Specialized Program of Research Excellence in Myeloma to accelerate the pace of this research substantially.



Robert Orlowski, MD, PhD

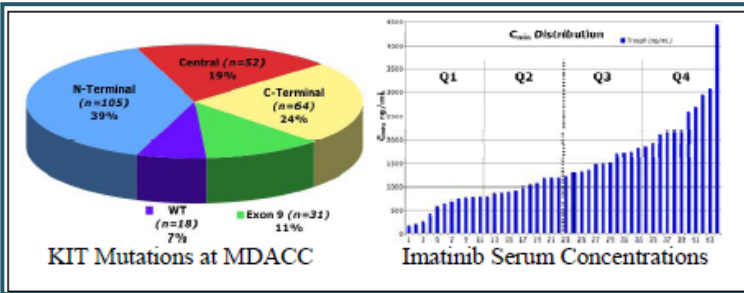
Sarcoma Research

Personalized Targeted Cancer Therapy of Gastrointestinal Stromal Tumors (GISTs)

Approximately 5,000 new cases of gastrointestinal stromal tumors (GISTs) occur in the US annually. Most commonly, GISTs arise from the stomach but may arise from multiple sites. Although half of patients present with primary GIST and are treated surgically, patients with advanced disease have historically had limited treatment options with response rates to chemotherapy typically of less than 5%. Imatinib was found to potently inhibit the tyrosine kinase receptor c-KIT, the key molecule involved in the tumorigenesis of GIST. Changes in the protein c-KIT are observed in more than 80% of GISTs. A phase III clinical trial showed that imatinib resulted in a dramatic 68% clinical benefit rate.



Jonathan Trent, III, MD, PhD



Dr. Jonathan Trent has studied in detail the response of various mutations in c-KIT to imatinib to identify why some patients respond better to the treatment than others. He has found that the response depends on the mutation and the dosage of imatinib and has been working to develop an easy blood test to determine which dose a patient should receive to have the best outcome. The goal of this research is to develop an individualized

approach using c-KIT mutations and imatinib blood levels to provide prospective, personalized, targeted cancer therapy of GIST with imatinib.

Thyroid Cancer Research

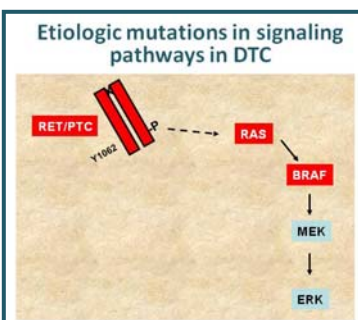
RET and BRAF mutations in Thyroid Cancer

The overall incidence of thyroid cancer has increased steadily such that it now ranks among the top six incident cancers in women. Surgical thyroidectomy remains the primary treatment for this cancer. Unfortunately, unresectable metastatic disease is associated with a poor prognosis. Advances in our understanding of the molecular mechanisms involved in the initiation and progression of thyroid tumorigenesis have led to the development of novel therapeutics to treat metastatic disease. For medullary thyroid carcinoma (MTC) aberrant activation of the RET tyrosine kinase receptor is observed in about 50-60% of patients. Similarly, RET receptor activation (via genetic rearrangement) or BRAF activation is observed at a similar frequency in papillary thyroid carcinoma (PTC). Early indications suggest that drugs targeting these molecules are effective in the treatment of advanced thyroid cancer, but with variable response rates. In addition, most patients undergoing treatment for metastatic disease have previously undergone thyroidectomy without having primary tumors tested for RET or BRAF mutations. Consequently, Drs. Gilbert Cote and Steven Sherman have been working to develop a method to collect circulating tumor cells (CTCs) or circulating DNA from the blood that can be used as a surrogate source to monitor RET and BRAF activity. Assessment of response through the assay of CTCs should contribute to personalization of treatment supporting a wide variety of future clinical trials.



Gilbert Cote, PhD Steven Sherman, MD

In collaboration with Dr. Herbert Fritsche, they have assessed whether methods already FDA approved for CTC capture for other tumor types such as the CellSearch system, which selectively isolates tumor cells from blood using a defined set of adenocarcinoma surface markers (EpCAM and cytokeratins 8, 18, and 19) could be used to capture the spectrum of thyroid cancer cell types. Molecular studies identified the expression of EpCAM in these 4 types of thyroid cancer supporting the use of this approach. They demonstrated that MTC and PTC cells could be efficiently retrieved from whole blood, but ATC cells could not. The successful capture of thyroid carcinoma cells led to the development of a protocol to examine the feasibility of using this tool in patients with differentiated thyroid cancer (PTC, FTC) or MTC (LAB09-0221). Their pilot studies clearly demonstrate, for the first time, the presence of EpCAM+ CTCs in patients with thyroid cancer. They provide a strong rationale for continued investigation of the utility of this new clinical assay.

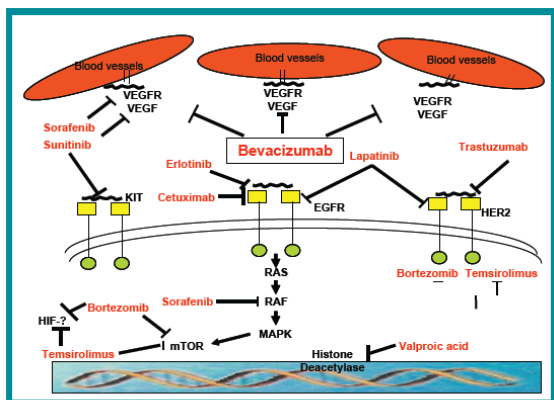


Initiative for Molecular Profiling and Advanced Cancer Therapy: The IMPACT Trial

Drs. Apostalia Tsimberidou, Razelle Kurzrock, and Jack Lee believe that the correlation of molecular features with clinical outcomes, starting in the phase I clinical trial setting for advanced cancers, will optimize the discovery of personalized, targeted treatments. Thus, they have developed an “umbrella” protocol that will facilitate blood and biopsy sampling from patients seen in the Clinical Center for Targeted Therapy. The main idea is that



Apostalia Tsimberidou, MD, PhD



THERAPEUTIC STRATEGIES TO INHIBIT TUMOR GROWTH

molecular profiles are created for patients as they enter the clinic. These profiles include characterization of the molecular and biologic signatures of the tumor through a variety of tissue-based and imaging techniques. These baseline profiles, as well as follow up after treatment, are correlated with response to specific agents or classes of targeted agents. Currently, there are 71 therapeutic trials in the Department of Investigational Cancer Therapeutics. Novel targets of the drugs currently under study include: FTase, mTor, Her2/neu, HIF-1alpha, glutathione, CDK, mdm2, histone deacetylase, notch, death receptor, IL-6 and multiple kinases (Raf, PI3K, AKT, FGFR, PDGFR, EGFR, VEGFR, MEK, aurora, MET, RET).

Experience with the BATTLE program has served as a model for this program. The IMPACT trial was approved and activated in February of 2009. They have collected hundreds of samples and will begin analysis of the samples shortly.

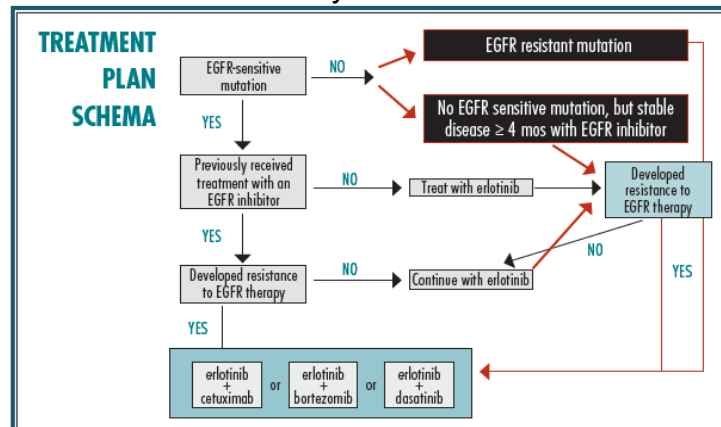
EGFR Mutations and Overcoming Resistance

In many different types of cancer, EGFR kinase activity is dysregulated through activating mutations, amplification, or overexpression of EGFR. This triggers a series of events leading to cancer cell growth, angiogenesis, and metastasis. EGFR inhibitors are approved for the treatment of NSCLC, HNSCC, colorectal, breast, and pancreatic cancers. Overall, the data suggest that expression levels of the EGFR do not predict who will respond to treatment with EGFR targeted drugs. The discovery that specific EGFR mutations are associated with a response to EGFR inhibitors in NSCLC suggests that the selection of patients through molecular screening of mutations may be feasible.



Jennifer Wheler, MD

Dr. Jennifer Wheler, along with Drs. Razelle Kurzrock and Jack Lee, developed a novel clinical trial to treat patients with the EGFR inhibitor erlotinib to determine if there is a correlation between the EGFR mutations in the tumors and response. This novel phase I clinical trial design consists of an “umbrella” protocol with separate module protocols of combination treatments. Patients will be screened for EGFR mutations and then treated with an EGFR inhibitor. For patients who lose their response after treatment, patients will have another drug added to their regimen. These studies are currently open and have been accruing rapidly. To date, 14 patients have been treated. Dr. Wheler has observed stable disease in two of these patients so far. In the future, molecular screening will become more cost-efficient as high-throughput technologies evolve and competitive commercialization decreases per unit costs. In contrast to the “one size fits all” approach to treatment, only a minority of patients screened will receive treatment on this study.



Individual Drug Discovery: A Proactive Approach

In a program looking at better ways to treat patients with lung metastases, a major problem in cancer, Drs. Anderson and Ryttinghas focused on performing the first clinical trial of aerosol gemcitabine. This treatment is expected to make home care more likely and reduce the time in the hospital and the cost of care for patients with lung metastasis (see figure below for the home equipment). In this study, they will also be looking at the changes in the protein known as the FAS death receptor to identify patients who are likely to benefit from this treatment. Dr. Anderson is working with multiple collaborators to move this project to the clinic rapidly: Dr. Koshkina for biomarker analysis, Dr. Robert Brown at The University of Texas for FAS detection



Pete Anderson, MD, PhD Michael Rytting, MD

methods, and Drs. Razelle Kurzrock and Aung Naing in Department of Investigation Cancer Therapeutics. An Investigational New Drug (IND) Application has been prepared for the FDA to pursue this novel treatment. Dr. Anderson is close to launching this first clinical trial of aerosol gemcitabine. This strategy shows the “art of the possible” for home chemotherapy and also may become a novel radio-sensitization strategy for cancers in the thorax.

An additional important milestone for Dr. Anderson’s research this past year was the completion by Dr. Lynn Harter (Ohio University Communications Professor) of a documentary on how personalized care is done at M. D. Anderson in the Department of Pediatrics. Viewing of the full documentary will be December 3, 2009, at noon in the AT&T auditorium at M. D. Anderson (contact Gail Goodwin or Sara Farris for details).



AeroEclipse breath actuated nebulizer and Salter AIRE Plus air compressor. Note how this model of air compressor has special shelf to facilitate filling of nebulizer bowl without spilling of detachment/reattachment of tubing.

Personalized Cellular Therapy

Applied Cell Therapy (ACT)

Drs. Laurence Cooper and Richard Champlin work to utilize what they have learned from the immune system to fight cancer. T cells can be made to specifically target a battery of hematologic and solid tumors that occur in children and adults. Using modern molecular biology techniques, they have created novel proteins that can specifically bind to and latch on to tumor cells signaling the immune system to attack the tumor cells. These modified T cells are called chimeric antigen receptor-positive (CAR+) T cells. To date, they have created CARs specific for:

- EGFR, expressed on solid tumors
- c-Met, expressed on solid tumors (in collaboration with Baylor College of Medicine)
- CD56, expressed on solid tumors
- HENV-K, expressed on breast cancer (in collaboration with Dr. Feng Wang-Johanning)
- Ror1, expressed on CLL (in collaboration with Dr. Tom Kipps at UCSD)
- Her2, expressed on solid tumors (in collaboration with Dr. Jon Weidanz at Texas Tech).

They have also worked on novel approaches to ensure that the effect is only targeted to the tumor itself. Tumors are known to have lower levels of oxygen and Dr. Cooper has taken advantage of this characteristic to have the CARs he created to only survive and be active under these conditions.

Dr. Cooper and Dr. Champlin have also developed the first ever trial with CD19-specific T cells (CD-19 is a receptor specifically found on B cells) to be used after autologous hematopoietic stem-cell transplantation (HSCT) and after allogeneic HSCT in patients with high-risk B-cell malignancies.



Another project underway is in collaboration with Dr. King Li at Methodist Hospital to put gold nanoparticles in the T cells to be able to visualize the cells and process in patients to further our understanding of the immune system and the role it can play in combating cancer.



Richard Champlin, MD



Laurence Cooper, MD, PhD

Identification of Biomarkers of Cardiotoxicity of Sunitinib

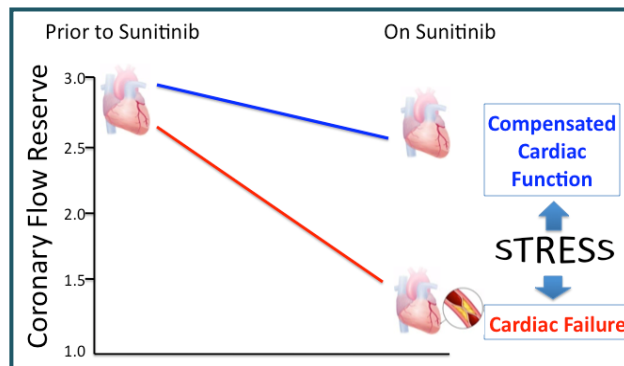
While the medical and surgical oncologists battle the tumor itself, doctors like cardiologist Dr. Aarif Khakoo, battle the toxic side effects of drugs that are essential for successful cancer therapy. This important research not only helps patients better tolerate their cancer treatment and manage these side effects, they have led to novel discoveries in cardiac biology that may also help heart disease.



Aarif Khakoo, MD, PhD

VEGF signaling inhibitors – a class of angiogenesis inhibitors – are commonly used in cancer therapy. Some cause significant hypertension while others (e.g., bevacizumab) are not significantly associated with heart failure. In addition, heart failure due to sunitinib appears to be more common and more severe than that due to imatinib, causing severe hypertension in large numbers of patients. In a study here at M. D. Anderson, 3% of sunitinib treated patients developed heart failure in an average of 21 days after beginning treatment. Dr. Khakoo has found the combination of severe, acute hypertension and inhibition of the molecule PDGFR in cardiomyocytes leads to cardiomyopathy due to sunitinib. He has also sought to characterize the cardiovascular toxicities of sunitinib and discover serum biomarkers that might identify patients at risk for the development of hypertension in the course of treatment with sunitinib. In addition to looking at established biomarkers of cardiovascular risk (e.g., BNP, troponin), he also measured levels of a panel of circulating angiogenic factors and cytokines that may also play an important role in blood pressure regulation.

Twenty-eight patients have so far completed six months follow-up in this study. Cardiovascular events associated with sunitinib treatment included hypertension and cardiac dysfunction at rates similar to those previously described. Strikingly, he noted that in those patients with a history of hypertension who developed significant increases in blood pressure with sunitinib, pre-treatment VEGF-A and IL-6 levels were substantially elevated. This preliminary data suggests that pre-treatment levels of pro-angiogenic factors may be critical biomarkers to help identify those patients at risk for development of hypertension due to sunitinib and other anti-angiogenic cancer therapies.



PREDICT - A multicenter study in Patients undergoing anthracycline-based chemotherapy to assess the Effectiveness of using biomarkers to Detect and Identify Cardiotoxicity and describe Treatment

Over the past two decades, there has been a significant improvement in cancer outcomes, resulting in a growing number of cancer survivors in the US, currently more than 10 million. Concurrently, there is an increasing appreciation of the impact of long-term side effects, including cardiovascular complications, on quality and length of life after cancer. As a result, there is a mandate from the Institute of Medicine to improve the detection and therapy of treatment-related side-effects in cancer survivors. Anthracyclines are a class of chemotherapeutic agents with wide-ranging applications that have a well-described substantial risk of cardiomyopathy and heart failure. The severity of myocardial damage is most often proportional to the cumulative dose received but also may occur unpredictably early or late in the course of therapy, especially when used in combination with other chemotherapeutic agents or radiation. Early detection of anthracycline cardiotoxicity could significantly reduce the development of clinical cardiotoxicity. Cardiac imaging, either with echocardiography (ECHO) or MUGA, is the standard for the routine follow-up of cancer patients receiving cardiotoxic chemotherapy but have significant limitations. Transient increases in B-type natriuretic peptide (BNP) are seen after administration of a single dose of anthracycline, but patients with sustained elevation appear to have the greatest risk for developing heart failure. Other biomarkers of cardiac damage, such as cardiac troponins I (TnI) and T (TnT), have been shown to be elevated prior to cardiac symptoms during anthracycline chemotherapy. Consequently, Dr. Daniel Lenihan and his colleagues have developed a clinical trial, PREDICT, to measure cardiac biomarkers, e.g., BNP and TnI, to identify the best biomarkers for anthracycline treatment-related cardiotoxicity, leading to prevention or better treatment of cardiotoxicity in cancer patients.