NEW STRATEGIES AGAINST CANCER

Perhaps from the outside, the battle against cancer appears unchanged. Yet, for those of us in the field of oncology, there are deep changes in the battle. The goal has remained the same—the cure of cancer; but the strategies and the weaponry for winning the battle are undergoing serious changes. This has occurred for three seminal reasons: (1) our thinking about the nature of cancer has changed, (2) we have acquired better techniques with which to interrogate cancer cells and (3) our knowledge about the role of the immune system in cancer has greatly expanded.

For decades, cancer has been viewed as a group of relatively homogenous diseases with biological features primarily based on the organ of origin of the cancer process. Relatively few distinctions were made. As such, colon cancers were viewed as being essentially all the same. The same was true for renal cancer, cancer of the liver and most other cancers. A few tumors, such as lung cancer and breast cancer were further divided based on cell type, creating some subgroups that appeared to behave differently and for which different treatment strategies were advised. Recently, however, a deeper appreciation for the uniqueness of each tumor’s molecular characteristics has emerged. It is increasingly apparent that tumors originating in the same organ demonstrate considerable diversity in clinical behavior, molecular patterns, response to therapy and patterns of drug resistance.

Not only is each tumor different, but each host is also different. Further, there is a relationship between the biology of the tumor cell, its local environment and the overall biology of the patient that is important in understanding the course of disease. This more complex understanding of individualized tumor biology has ushered in the era of “personalized or precision medicine.” Selecting therapies based purely on organ site is being abandoned. New techniques allow us to interrogate cancer cells yielding information not previously available. Peculiarities and specificity of each cancer can now be revealed. Their points of weakness can now be targeted and exploited. This new paradigm forms the basis for a new and better way to treat each patient.

Small quantities of tumor tissue obtained from biopsy or surgical material can now be interrogated using commercially available services such as Caris Molecular Intelligence Tumor Profiling or Foundation One Tumor Profiling, yielding detailed information about tumor mutations and available targeted drug therapies. An additional potential avenue is the use of circulating tumor

ABOUT US

The Angeles Clinic and Research Institute was established by a group of physicians who came from academic backgrounds and sought to establish an environment where world-class patient care was the top priority. Our institutional culture is defined by an unwavering commitment to excellence and continued innovation. The Clinic’s physicians include widely recognized oncologists and leaders in cancer medicine who, together with expert radiology services, radiation oncology, specialized oncology nurses, and a dedicated support staff, have created a state-of-the-art center for medical care in the Los Angeles area. In addition to superb clinical care, our physicians and Institute are known for world-class clinical research. The Institute has earned an international reputation for developing new cancer therapies, providing the best in traditional and experimental treatments, and expertly guiding and training the next generation of clinicians and researcher. Patients travel from all over the nation to seek care from the special team of experts found at The Angeles Clinic and Research Institute.

OUR PHYSICIANS

Ani Balmanoukian, MD
Peter D. Boasberg, MD
Ali R. Borghei, MD
Cathie T. Chung, MD, PhD
Kevin Drake, MD
Omid Hamid, MD
Daniel J. Lieber, MD
Silvana Martino, DO
Lawrence D. Piro, MD
Melani P. Shaum, MD
NEW STRATEGIES CONT’D …

cells isolated from peripheral blood samples for the specific purpose of performing tumor profiling and selecting drug therapies as is being performed in selected tumor types by Cynvenio Biosystems and others. This is particularly useful in patients where biopsy material is not available or is difficult to obtain. From these readily available assays, one can identify specific mutations and create a list of drugs most likely to be successful in clinical management.

Can this list of candidate drug therapies be narrowed further? Can we reduce the trial and error experience that each patient must go through to find an effective therapy? The answer is, yes. This step can now be achieved by creating personalized TumorGrafts™, a service available from Champions Oncology.

The process begins with the acquisition of fresh tumor tissue obtained from a biopsy (FNA, core, or surgical) which is then engrafted in its entirety along with its surrounding stromal compartment into a specialized mouse host. By implanting the tumor plus its microenvironment, the animal tumor grafts continue to closely resemble the patient’s own tumor with greater than 90% genetic correlation. Engraftment is successful from 70 to 80% of biopsies including solid tumors, lymphomas and many leukemias. Tumor growth and engraftment occur over a 20 week time period. At that point, molecular analysis of the tumor and drug sensitivity testing can be performed on multiple mice bearing the engrafted tumor. The drugs to be tested can be based on the patient’s clinical history and the results from tumor analysis described above. Multiple drugs (standard, experimental, targeted biological agents, antiangiogenics and combinations can be tested simultaneously on colonies of tumor bearing mice, thus avoiding the trial and error process that patients are exposed to in treating their disease. Concordance between patient clinical response and the response observed in tumor bearing mice appears to be above 80% based on presently available data. This level of predictability appears superior to other screening systems. Accumulating clinical evidence suggests that tumor response rates in patients are higher when therapy is selected in this manner. To confirm and expand this observation, The Angeles Clinic Foundation and The Angeles Clinic and Research Institute have established a collaboration with Champions Oncology. Our goal is to make this technology available to our patients and to follow and document their progress as they are treated with drugs selected based on results from their own TumorGrafts™.

Simultaneous to the development of more personalized drug selection, an expanded understanding of the immune system is revolutionizing the types of treatments that are available. The role of the immune system is to protect the body from invading agents by distinguishing self from non-self. When non-self-antigens are recognized as foreign, a complex cascade of events designed to destroy is initiated by the immune system. The same process should occur against cancer cells. However, cancer cells are cells that have become altered, but are essentially self. Therefore, they provide a particular challenge to the discriminating function of the immune system. Even so, an anti-tumor immune response is often mounted. Survival mechanisms within the tumor cells result in the evolution of skills that allow cancer cells to evade the immune response leading to a state of immune tolerance and result in a survival advantage for the cancer process. Immunotherapy now encompasses a range of therapeutic options that can alter the balance of power between tumor and the immune system.

In the past, therapies involving the immune system produced poor anti-tumor activity. More recent therapies, employing both passive and active immune mechanisms have been much more successful. Monoclonal antibodies, a form of passive immune strategies, have produced agents such as rituximab (Rituxan) and trastuzumab (Herceptin). Cancer vaccines, designed to actively engage the immune system have had a poor history. But newer versions are demonstrating much more promise as evidenced by the FDA approval of sipuleucel-T (Provenge) for the treatment of metastatic prostate cancer.

Understanding mechanisms of T-cell response and the balance of co-stimulatory and inhibitory signals, known as checkpoints that govern their activities, has led to the FDA approval of ipilimumab (Yervoy) in the treatment of melanoma. Other agents that influence T cell activities such as nivolumab (BMS-936558), lambrolizumab (MK-3475) and many others are in various stages of clinical development not only in melanoma but many other tumor types. It is...
The Angeles Clinic and Research Institute believe that oncology and perhaps all of medicine is poised to undergo a revolution fuelled by research and innovations at multiple levels. We believe the future to be exciting and very promising. Our patients and our community remain our source of inspiration.

NEW APPOINTMENTS

Congratulations to **Dr. Lawrence Piro** on his recent appointments to:

- The Board of Directors of Providence Saint John’s Health Center, Santa Monica, CA
- Co-Chair of the Stand Up to Cancer-Farrah Fawcett Foundation, Joint Scientific Advisory Committee

RECENT SCIENTIFIC PRESENTATIONS

The following presentations were made by members of our staff at the 105th annual meeting of the AMERICAN ASSOCIATION for CANCER RESEARCH held April 5-9, 2014, in San Diego, California.

- **Dr. Lawrence Piro** spoke on the President’s Cancer Panel Report “Accelerating HPV Vaccine Uptake: Urgency for Action to Prevent Cancer”—Scientific Advances to Help Achieve Policy Goals

- **Dr. Omid Hamid** had the following presentations:
  - Antitumor activity of the anti-PD-1 monoclonal antibody MK-3475 in melanoma (MEL): Correlation of tumor PD-L1 expression with outcome
  - A first-in-human phase 1 study of the safety and pharmacokinetic (PK) activity of DEDN6526A, an anti-endothelin B receptor (ETBR) antibody-drug conjugate (ADC), in patients with metastatic or unresectable melanoma

- **Dr. Ani Balmanoukian** and **Dr. Omid Hamid** presented:
  - MK-3475 (anti-PD-1 monoclonal antibody) for non-small cell lung cancer (NSCLC): Antitumor activity and association with tumor PD-L1 expression
SELECTED CLINICAL TRIALS CURRENTLY ENROLLING

Please visit our website, www.theangelesclinic.org, for a complete list.

ADVANCED SOLID TUMORS

- Genentech Protocol PIM4946g – A Phase 1b, Open-Label, Dose-Escalation Study of the Safety and Pharmacology of GDC-0980 in Combination with Paclitaxel and Carboplatin with or without Bevacizumab in Patients with Solid Tumors
- MedImmune CN-ON-MEDI4736-1108 - A Phase 1 Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of MEDI4736 in Subjects with Advanced Solid Tumors

BLADDER

- Genentech Protocol GO290293 - A Phase II, Multicenter, Single-Arm Study of MPDL3280A in Patients with Locally Advanced or Metastatic Urothelial Bladder Cancer

BREAST

- Abbott Protocol M12-895 – A Randomized, Phase 2 Study of the Efficacy and Tolerability of Veliparib with or without Paclitaxel in Patients with Locally Advanced or Metastatic Breast Cancer
- Novartis Protocol CLEE 01A2301(MonaLeesa-2 Trial) - A Randomized, Double-Blind, Placebo-Controlled Study of Letrozole plus Veliparib in Postmenopausal Women with Hormone Receptor Positive, HER2-Negative, Advanced Breast Cancer Who Received Prior Treatment for Advanced Disease

LUNG CANCER

- MedImmune Protocol D4880C00003 – A Phase 2, Randomized, Double-Blind Study Comparing Tremelimumab to Placebo in Second or Third-line Treatment of Subjects with Unresectable Pleural or Peritoneal Malignant Mesothelioma
- MedImmune Protocol D4190C00006 - A Phase 1b Open-label Study to Evaluate the Safety and Tolerability of MEDI4736 in Combination with Tremelimumab in Subjects with Advanced Non-Small Cell Lung Cancer
- Merck Protocol MK-3475-010 - A Phase II/III Randomized Trial of Two Doses of MK-3475(SCH900475) versus Docetaxel in Previously Treated Subjects with Non-Small Cell Lung Cancer
- Novartis Protocol CLE039A2303 - A Phase III, Multicenter, Randomized, Open-Label Study of ORAL LDK378 versus Standard Chemotherapy in Adult Patients with ALK-rearranged (ALK-positive) Advanced Non-Small Cell Lung Cancer Who Have Been Treated Previously with Chemotherapy (platinum doublet) and Crizotinib

LYMPHOMA

- Bayer Protocol BAY 80-6946/16349 - Open-label, Uncontrolled Phase II Trial of Intravenous PI3K Inhibitor BAY 80-6946 in Patients with Relapsed, Indolent or Aggressive Non-Hodgkin's Lymphomas

MELANOMA

- Incyte Protocol INC24360-201 – A Phase ½ Randomized, Blinded, Placebo Controlled Study of Ipilimumab in Combination with ICX001 or Placebo in Subjects with Unresectable or Metastatic Melanoma
- Mavis Protocol 103A-301 (Polyoma) - A Multicenter, Double-Blind, Placebo-Controlled, Adaptive Phase 3 Trial of POL-103A Polyvalent Melanoma Vaccine in Post-resection Melanoma Patients with a High Risk of Recurrence
- Merck EMD Serono Protocol EMR062235-005 - A Safety Study for MB0010445 in Combination with Stereotactic Body Radiation in Advanced Melanoma Subjects Following Prior Treatment with Ipilimumab
- Merck Protocol MK – 3475-001 – A Phase 1 Study of Single Agent MK-3475 in Patients with Progressive Locally Advanced or Metastatic Carcinoma, Melanoma, and Non-Small Cell Lung Carcinoma
- Merck EAP Protocol MK3475-030 - Expanded Access of MK-3475 in Metastatic Melanoma Patients with Limited to No Treatment Options
- OZM Protocol TH-CR-413 - A Phase 2 Biomarker-Enriched Study of TH-302 in Subjects with Advanced Melanoma
- Roche Protocol GO27826 (Brin G) - Phase III, Randomized, Double-Blind, Placebo-Controlled Study of Vemurafenib (RO5185426) Adjuvant Therapy in Patients with Surgically-Resected, Cutaneous BRAF Mutant Melanoma at High Risk for Recurrence
- Ziopharm Protocol ATI001-101 - A Phase I/II, Open Label Study of Ad-RTS-hIL-12, an Adenovirus Vector Engineered to Express hIL-12, in Combination with an Oral Activator Ligand, in Subjects with Unresectable Stage III or IV Melanoma