Section 1: Scientific Progress and Achievements

A. Signal transduction and tumor analysis

Signaling pathways

The mTOR signaling pathway has been the focus of a number of studies in our program area. Two hyperactivating mutations of mTOR in human cancer, S2215Y and R2505P, were identified by Fuyu Tamanoi by mining human cancer genome database (Sato et al., Oncogene, 2010). Jing Huang carried out chemical genetics screen for enhancers of rapamycin and identified a specific inhibitor of an SCF family E3 ubiquitin ligase (Aghajan et al., Nature Biotechnol. 2010). Julian Martinez used Drosophila to examine abnormal organelle biogenesis (Cheli et al., Hum Mol Genet. 2010). The mTOR signaling pathway has been investigated in glioblastoma by a group of researchers in our program area including Paul Mischel, Linda Liao, Tim Claughesey and Stan Nelson (Akahavan et al., Neuro Oncol. 2010; Guo et al., PNAS 2009) (discussed more below in Clinical Translational Studies).

The Pten/Akt signaling was characterized by Hong Wu who carried out characterization of the PTEN complex and identified heterogeneous nuclear ribonucleoprotein C as a component of the complex (Mossessian et al., JBC 2009). The Hedghog signaling was characterized by Jim Waschek and Sotirios Tetradis (Kim et al. Mol Endocrinol. 2009). Kathleen Sakamoto continues to characterize CREB and published a paper discussing targeting CREB for cancer therapy (Xiao et al, Curr Cancer Drug Targets). Steve Cole reported an interesting observation that gamma-herpes virus inhibits CREB (Brown et al., JBC 2010). Cross-talk between signaling pathways has emerged as an important issue. Enrique Rozengurt and Guido Eibl showed that metformin disrupts cross-talk between G protein-coupled receptor and insulin receptor signalings and that this results in the inhibition of pancreatic cancer growth (Kisfalvi et al., Cancer Res 2009).

Tumor analysis has revealed a number of important changes in the tumor. Guido Eibl, Oscar Hines and David Dawson showed that prostaglandin E2 is increased in pancreatic cancer by the loss of 15-hydroxy prostaglandin dehydrogenase (Pham et al., Pancreas 2010). One of the recent exciting developments concerns metabolic changes in cancer cells. Heather Christofk is characterizing these changes by identifying small molecule inhibitors of pyruvate kinase M2 (Vander Heiden et al., Biochem Pharmacol 2010).

Global Analysis, Genomics, Proteomics

Gene expression analysis and high throughput sequencing are carried out in our program area by a number of people headed. The effort led by Stan Nelson, included large scale co-expression analysis of disease characterization (Day et al., Plos One 2009), developing BFAST, an alignment tool for large scale genome sequencing (Homer et al., PLoS One 2009) and determining the genomic sequence of a cytogenetically aberrant human cancer cell line U87MG (Clark et al., PLoS Genet 2010).

Phosphoproteome analysis of aortic endothelial cells activated by oxidized phospholipids was carried out by Tom Graeber (Zimman et al., J. Proteome Res. 2010). Global analysis of geranylgeranylated proteins were accomplished by Fuyu Tamanoi and Steve Young (Chan et al., Electrophoresis 2009). Using knockout mice, Steve Young studied functional significance of protein prenyltransferases in skin keratinocytes (Lee et al., Hum Mol Genet 2010).

David Wong has pioneered in the use of salivary for cancer detection. Salivary transcriptomic biomarkers for detection of resectable pancreatic cancer have been identified (Zhang et al., Gastroenterology 2010). Utility of salivary miRNA for oral cancer detection has been investigated (Park et al., Clin. Cancer Res. 2009). Increasing effort is being invested on the characterization of miRNA. One example is the detection of p53
inactivation mediated by the loss of miR-34a expression in malignant peripheral sheath tumors (Subramanian et al., J. Pathol. 2010).

Inhibitors, Nanodelivery, therapy

Chris Denny, Kathy Sakamoto and Noah Federman examined a small molecule inhibitor ABT-869 and showed that it inhibits proliferation of Ewing Sarcoma cells (Ikeda et al., Mol Cancer Ther. 2010). Use of nanoparticles to deliver anticancer drugs may be an effective approach to enhance the utility of currently used drugs. Federman and Denny have focused on the issue of targeting liposomes (Pediatr Res 2010). Fuyu Tamanom and Andre Nel have developed novel methods to deliver siRNA by using mesoporous silica nanoparticles (Hom et al., Small 2010; Xia et al., ACS Nano 2009). Polypeptide vesicles are being developed by Tim Deming (Macromol. Biosci. 2010).

Significance of cancer stem cells for cancer therapy, radiation therapy in particular, has been investigated by Frank Pajonk (Vlashi et al., J. Cell Biochem 2009; Vlashi et al., Mol. Cancer Res., 2010). Peter Butler and Sarah Dry reported that GLP-1 (Glucagon-like peptide-1) therapy enhances pancreatitis and pancreatic cancer (Butler et al., Diabetologia 2010).

B. Clinical Translational Studies

Members of the STT Program Area continue to collaborate in the Clinical/Translational Research Laboratory (CTRL), where each malignancy is represented by a panel of cancer cell lines that recapitulate clinical disease patterns. Anti-cancer drugs are studied across histologies to identify unifying patterns, and data generated is used in the design and implementation of phase I, II, and III clinical trials. Tumor specimens obtained from patients participating in STT clinical trials are also being brought back into the lab to study biomarkers. This year, we highlight projects involving ErbB, PTEN/MTOR, IGF-1R and Hsp90.

ErbB

Working in the CTRL, Zev Wainberg evaluated lapatinib, erlotinib, and trastuzumab in a panel of 14 molecularly-characterized human upper gastrointestinal cancer cell lines (Wainberg et al., Clin Cancer Res 2010). Lapatinib selectively inhibited the growth of HER2 amplified cell lines, where it also induced G1 arrest, and decreased activation of AKT and ERK. The combination of lapatinib and trastuzumab was highly synergistic, with greater decreases in AKT and ERK activation. In vivo studies confirmed the greater potency of lapatinib and trastuzumab in combination when compared to either drug as a single agent. This served as background for a randomized phase III clinical trial of chemotherapy plus or minus lapatinib in HER2 amplified gastric and esophageal cancer (the LOGIC trial), for which Randy Hecht is the lead investigator.

PTEN/MTOR

Working within their own robust laboratories, the neuro-oncology group (Linda Liau, Tim Cloughesy, Hong Wu, and Paul Mischel) investigated role of PTEN loss as an EGFR inhibitor response modifier. Together with colleagues from Memorial Sloan Kettering, they demonstrated PTEN inactivation impairs EGFR degradation through destabilization of newly formed ubiquitin ligase Cbl complexes (Vivanco et al., Proc Natl Acad Sci 2010).

IGF-1R

In the CTRL, Bill Tap applied AMG479, a monoclonal antibody against IGF-1R, across a panel of 28 Ewing sarcoma cell lines, and found that the EWS:ERG translocation predicted response and PTEN loss predicted resistance (Tap et. al., Proceedings of Connective Tissue Oncology Society 2009). The multicenter phase II study of AMG479 in Ewing Sarcoma, presented by Dr. Tap at ASCO 2010, demonstrated a few durable responses, but the overall response rate was low (Tap et al., J Clin Oncol 2010). The study sponsor is using Dr. Tap’s preclinical data to guide their analysis of tumor samples from study subjects in an effort to characterize responsive subsets.

Hsp90
Carolyn Britten participated in a large (> 100 patients) multi-center phase I clinical trial of the Hsp90 inhibitor, AUY922, presented at ASCO 2010. This trial demonstrated that AUY922 was generally well tolerated at doses up to 70 mg/m² IV per week, and that AUY922 induced Hsp70 in peripheral blood mononuclear cells (Samuel et al., J Clin Oncol 2010). In the CTRL, concurrent with the phase I trial, Zev Wainberg demonstrated potent anti-proliferative activity in the low nanomolar range in 13/15 of the upper GI cancer cell lines tested. The majority of these cell lines had LD50 values less than 100 nM. An anti-proliferative growth effect was seen in lines that over-amplified HER2 or c-MET. Based on these results, Dr. Wainberg collaborated with industry colleagues to design an ongoing randomized open-label phase II study in 2nd line gastric cancer, combining AUY922 with either docetaxel or irinotecan (Wainberg et al., Proceedings for the 100th Annual Meeting of the AACR Abstract #2753 2009).

Section 2: Role of the Cancer Center
Meetings
As outlined below, the JCCC has supported meetings and seminars organized by the Signal Transduction and Therapeutics Program Area. All members of the cancer center and UCLA campus are invited.

Roundtable discussions – We had two roundtable discussions. In September 2009, presentations were made by Paul Mischel, Hong Wu, and Gottfried Konecny on PI3K/mTOR/PTEN. In March 2010, a second roundtable was presented by Jing Huang and Ken Bradley on Pharmacology and Drug Screening. Dr. Huang spoke on DARTS: a general approach to identifying the target(s) of any small molecule. Dr. Bradley gave an update on approaches to drug screening.

Invited speakers – Together with the Heme Malignancies Program Area, we invited several outside speakers who met with members of both the STT and Heme Malignancies program areas. In September 2009, Mignon Loh (UCSF) spoke about “New Genetic alterations in Juvenile Myelomonocytic Leukemia – Lessons Learned from Studying Patients.” In June 2010, Ioannis Aifantes (NYU) presented “Molecular dissection of hematopoietic stem cell self-renewal and transformation.” In addition, other invited speakers included: October 2009, John Kuhn (UT San Antonio) spoke on Pharmacogenomics. In November 2009, Ram Mahato (UT Tennessee) presented “Polymeric Micelle-based Combination Therapy for Treating Advanced Prostate Cancer. In April 2010, Bill Matsui (Johns Hopkins) spoke on “Stem Cell Concepts in Translational Oncology.”

Business meetings – The purpose of these meetings was to discuss cancer center business and allow new members to present their research. The meetings were attended by the members of the STT program area. In December 2009, new members Heather Christofk gave a talk on “Regulation of Cancer Metabolism” and Alan Ikeda spoke about his research on a new multtargeted receptor tyrosine kinase inhibitor for Ewing’s sarcoma.

Hematopoietic Journal Clubs/Faculty Speaker Series (joint with Heme Malignancies) - Monthly journal clubs and faculty speaker seminars were attended by graduate students, postdoctoral fellows, and faculty from STT (Kathy Sakamoto, Hong Wu, Tom Graeber, John Colicelli), Heme Malignancies (Ken Dorshkind, Gay Crooks), Tumor Immunology (Steve Smale, Don Kohn), and Cancer Cell Biology (Mike Teitell, Luisa Iruela-Arispe, Hanna Mikkola) program areas. Speakers this past year were: Hanna Mikkola, Gay Crooks, John Colicelli, Steve Smale, and Mike Teitell.

CNSI Symposium on siRNA and microRNAs – Our program area co-sponsored siRNA/miRNA nanodelivery symposium on June 10, 2010. This one day symposium featured a keynote speech given by Mark Davis (Caltech) and Toni Ribas who spoke about clinical study of siRNA delivered by nanoparticles. A special lecture was given by Hua Yu (City of Hope). More than 250 people gathered to discuss biology and delivery of siRNA and miRNA.

Retention and Recruitment
Retention – Noah Federman (Pediatric Oncology, sarcoma)

Seed grants/fellowships
1. Fuyu Tamanoi, Ph.D. - “MTOR Cancer Mutations”
2. Tom Graeber, Ph.D. –“A Systems Biology Approach to the Integration of Signal Transduction and Metabolism”
4. Shuiming Qian (Hong Wu, M.D., Ph.D.) – “Studying Prostate Cancer Initiation Cells Using Mosaic Analysis with Double A Markers in Mouse Model”

Space
No changes in cancer center space for STT program area members during the past year.

**Section 3: Future plans**
The STT program area will continue to facilitate collaborations and interactions both intra and interprogrammatically. The program area will continue to invite outside speakers, organize journal clubs, and ask new members to speak at the weekly Thursday noon cancer center seminar series. A new format for the roundtable discussion will be implemented that focus on two specific signaling pathways: 1) The PI3K/Akt/mTOR signaling in glioblastoma and 2) cAMP and CREB. Members from the STT and other program areas will be invited to participate in these roundtable discussions. Several of the members will be asked to give a short (5-10 minute) presentation. Participants will include basic, translational, and clinical faculty and postdoctoral fellows.

Ongoing research developments in STT program area are:
1. Targeting transcription factors, CREB and LXR – new collaboration with Kathy Sakamoto, Steve Smale (Gene Expression), Farhad Parhami (new STT member), Steve Bensinger (Tumor Immunology).
2. Increasing numbers of investigator initiated clinical trials – Carolyn Britten, Noah Federman, Rich Finn, Zev Wainberg.
3. Leukemia Program Project grant – in progress, with project leaders Steve Smale (P.I.), Owen Witte, Ken Dorshkind, Markus Muschen (USC/CHLA), and Kathy Sakamoto.
4. Co-sponsored speakers with Heme Malignancies Program Area (Ken Dorshkind) and STT (Kathy Sakamoto). Invited speakers will include: Ben Ebert (Dana Farber), Ravi Bhatia (City of Hope), Alan D’Andrea (Children’s Hospital Boston), Akiko Shimamura (U Washington) and will be organized by Kathy Sakamoto, Ken Dorshkind, and Gary Schiller (Heme Malignancies Program Area). Drs. Sakamoto and Schiller are co-PIs on an ASH Alternative Training Pathway grant on Bone Marrow Failure and will be teaching a course together (Path 280 “Bone Marrow Failure Syndromes”) in Winter 2011.
5. Develop a Program Area newsletter that includes NIH/NCI news, funding opportunities, and highlight new members.
6. Nanotherapy working group – Fuyu Tamanoi, Chris Denny together with Mike Teitell are exploring ways to promote activities related to nanotherapy within JCCC.
7. Organize a two-day joint program area symposium on “Novel Cancer Therapies.” A committee will be formed to plan this event scheduled for spring 2011.
8. Continue to recruit new members and include scientists outside of the medical school and college of arts and sciences.

**Section 4: Selected Publications**


**Wainberg ZA**, Anghel A, Desai A, Adhani S, Safran B, **Hecht JR**, Jensen MR, Quad C, **Slamon DJ, Finn RS**. Biologic effects of NVP-AUY922, a novel small molecule inhibitor of HSP90 in human colon and gastric cancer
Section 5: New Key Personnel
No change in key personnel