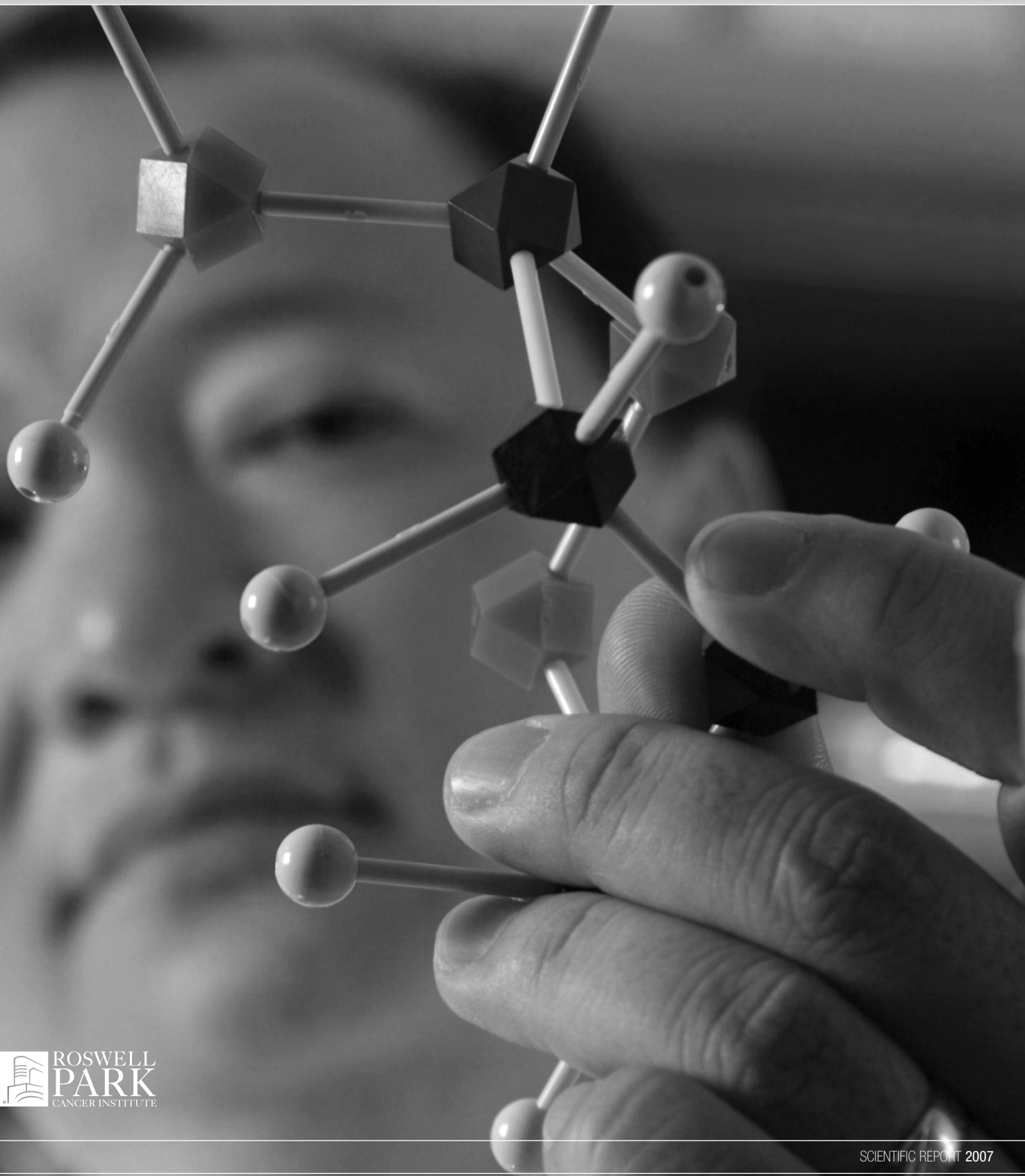


Molecular Targets and Experimental Therapeutics Program



Molecular Targets and Experimental Therapeutics Program

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Overview and Themes

The unifying goals of the Molecular Targets and Experimental Therapeutics Program are (a) to better understand the molecular circuitry of cancer cells and the mechanisms underlying drug action and resistance, and (b) to exploit this understanding for the development of improved mechanism-based anticancer therapies. To address these goals, the Program has three overlapping themes, each of which integrates basic science and translational activities (e.g., biomarker studies, clinical trials) and includes basic, translational, and clinical investigators.

The themes are:

1. Targeting signal transduction and growth control; and
2. Targeting cell survival and drug resistance; and
3. Targeting gene expression

Theme 1: TARGETING SIGNAL TRANSDUCTION AND GROWTH CONTROL

The **Targeting Signal Transduction and Growth Control** theme focuses on understanding signaling pathways that regulate cell growth, cell cycle progression, and DNA damage-induced checkpoint functions, and identifying related abnormalities in tumor cells that can be exploited for cancer therapy. Members of this group aim to promote rapid translation of basic discoveries of cancer mechanisms into therapeutic and prevention strategies and potential diagnostic and prognostic markers. New targets/strategies are validated using state-of-the-art *in vitro* and *in vivo* preclinical models. Candidate drugs are tested against validated targets to establish specificity and to optimize effectiveness, and new strategies are ultimately tested in the clinic. Research interests include vitamin D signaling, growth factor signaling networks, cell cycle control and DNA damage checkpoints, and growth-related metabolic flux pathways. Examples of anticancer agents being investigated, alone and in combination, include calcitriol, non-calcemic vitamin D analogs, ErbB antagonists, MEK inhibitors, src kinase inhibitors, radiomimetic enediynes, platinum drugs, and polyamine analogs.

Dr. Black and colleagues have provided the first evidence that the tumor suppressor properties of PKC α signaling in the intestine may involve regulation of cyclin D1 expression, at the level of mRNA accumulation and cap-dependent translational initiation. (Guan *et al.*, *J Biol Chem* 2007; 282:14213; Hizli *et al.*, *Biol Chem* 2006; 281: 14596; Clark *et al.*, *J Biol Chem* 2004; 279:9233; Leontieva *et al.*, *J Biol Chem* 2004; 279:5788)

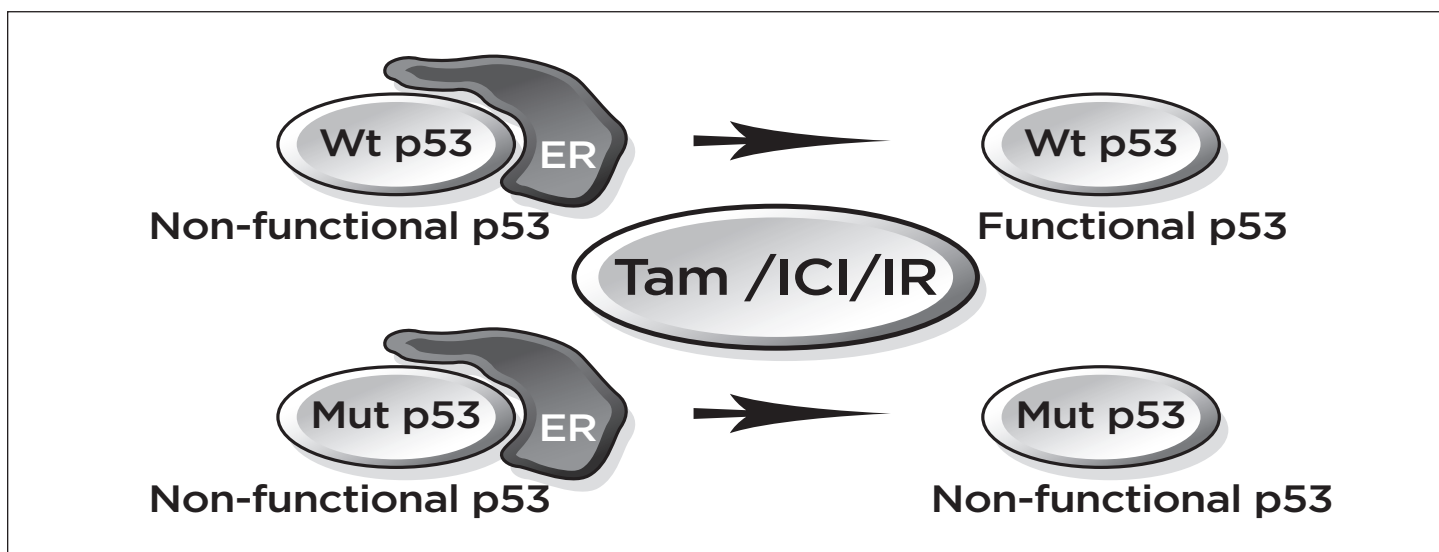
Dr. Porter's group has identified activated polyamine catabolism as a novel approach for cancer therapy and provided the first definitive link between polyamines and fat metabolism, a finding that has important implications for new anti-obesity strategies. Effects are attributed to altered metabolic flux through the polyamine pathway due to increased activity of the polyamine catabolic enzyme SSAT. This group has an effort in the discovery of new small molecule SSAT-inducers. (Hector *et*

al., Mol Cancer Ther 2004; 3:813; Kee *et al.*, J Biol Chem 2004; 279:40076; Kee *et al.*, J Biol Chem 2004; 279:27050). In related studies, Drs. Pendyala, Porter, and Fakih have provided the pharmacogenetic identification and validation of SSAT as a determinant of platinum drug action in ovarian and colorectal cancer cells. Clinical validation is provided by evidence of SSAT induction in rectal biopsies from patients receiving oxaliplatin therapy. Oxaliplatin/5-FU/DENSPM is identified as a novel combination for improved colon cancer therapy.

Drs. Fakih, Trump, and Johnson (PR) reported the first determination of the MTD of intravenous calcitriol and demonstrated that high dose, intermittent administration schedules result in calcitriol concentrations that exceed those associated with antitumor activity in preclinical models. These important findings pave the way for future clinical trials testing calcitriol as a single agent or in combination with other cytotoxics. (Fakih, Trump, Johnson, Black, *et al.* Clin Cancer Res 2006; RO1 CA67267).

Theme 2: TARGETING CELL SURVIVAL AND DRUG RESISTANCE

Members of the **Targeting Cell Survival and Drug Resistance** theme focus on understanding basic mechanisms of cancer cell survival and the basis for resistance to the apoptosis-inducing effects of classical and experimental anticancer agents. Approaches to circumvent drug resistance and optimize selectivity and antitumor action are also explored. Following pre-clinical antitumor studies, innovative clinical trials of new agents and combinations are developed. Research is also focused on achieving a mechanistic understanding of these agents/combinations in the clinic through pharmacokinetics, pharmacodynamics and biomarker studies based around the targeted effector molecule. Specific areas of interest include survival factors (survivin, Bcl-2 family members), survival effects of the tumor microenvironment, drug resistance, multidrug resistance proteins/modulators, and modulation of therapeutic efficacy (i.e., drug delivery, uptake and selectivity, drug combinations, and protection from toxicity). Examples of drugs and agents being studied include taxanes, survivin inhibitors, Genasense (Bcl-2 antisense), thalidomide analogs, methotrexate, and selenomethionine.



ER α -p53 interaction in breast cancer- novel concepts in tamoxifen and IR resistance

Dr. McGuire's group describes the identification of the first small molecule that regulates reduced folate carrier (RFC) activity. The study reports that MTX influx and metabolism to polyglutamates in human childhood ALL cells by the RFC is potentiated by the clinically relevant agent 5-amino-4-imidazolecarboxamide riboside. Since clinical findings indicate that a selective increase of 2- to 3-fold in intracellular polyglutamates may increase long-term survivors of childhood ALL, these findings have important implications for the use of methotrexate and other antifolates in cancer chemotherapy. (McGuire *et al.*, *Cancer Res* 2006; 66:3836-3844)

Collaborating with Dr. Nowak (GN), Drs. Trump, Johnson (PR) and Karpf first demonstrated that the vitamin D catabolic enzyme, CYP-24, is epigenetically silenced by methylation in tumor-derived endothelial cells, and that treatment with methylation inhibitors results in loss of sensitivity to calcitriol growth inhibitory effects. (Trump, Johnson, Karpf, Nowak, *et al.*, *J Biol Chem* 2007; RO1 CA095045).

A series of joint papers from Drs. Rustum, Fakih, Pendyala, Mazurchuk, and Bellnier (CSBT) reported that selenium is a highly selective modulator of the therapeutic efficacy of a variety of anticancer drugs and radiation in multiple human tumor xenograft models. These preclinical studies paved the way for clinical trials exploring the ability of selenium to modulate therapeutic efficacy in patients. (Rustum, Fakih, Pendyala, Mazurchuk, Bellnier *et al.* *Clin Cancer Res* 2004; 2005; 2007 (*in press*); *Mol Cancer Therap* 2006; *Oncogene* 2006; *Biochem Pharmacol* 2007.)

Dr. Chanan-Khan, collaborating with Drs. Porter and Goodrich, published studies that report the efficacy of IMiDs in the treatment of B-cell malignancies. The clinical demonstration of lenalidomide efficacy against relapsed and refractory CLL identifies a new treatment paradigm for the disease. (Chanan-Khan, Porter and Goodrich, *et al.* *Leuk Lymphoma* 2005; 2006; *Blood* 2005; *Lancet Oncol* 2006; *J Clin Oncol* 2006.)

Theme 3: TARGETING GENE EXPRESSION

Tight control of gene expression is critical for maintaining tissue homeostasis. Regulation can occur at the genetic, epigenetic, and post-transcriptional levels [i.e., at the level of transcriptional initiation, chromatin remodeling (for gene silencing or activation), and alternative RNA processing]. Studies of the **Targeting Gene Expression** theme focus on transcription factors, transcription factor interactions, transcriptional repression/activation, DNA methylation and gene silencing, histone deacetylase inhibitors (HDAC-I), and mRNA processing. Anticancer agents being investigated include methylation inhibitors and HDAC-I.

Studies by Dr. Das provide new understanding of breast cancer response to tamoxifen. These papers report the seminal discovery that ER α binds to the tumor suppressor p53 and inhibits p53-mediated transcriptional function in human breast cancer cells. While 17 β -estradiol augments the ER α -p53 interaction, anti-estrogens such as tamoxifen disrupt the binding of these factors. Analysis of breast tumors from tamoxifen-treated patients demonstrates that the presence of wild-type p53 in ER-positive breast tumors is associated with better response to tamoxifen therapy and significantly increased overall survival, and indicates that tamoxifen resistance is associated with expression of mutant p53. This represents an important paradigm shift regarding mechanisms of resistance to tamoxifen therapy.

Dr. Goodrich and colleagues recently reported that the pRb-associated protein, Thoc1, an RNA processing factor, is required for normal embryonic development in the mouse, and for oncogene-mediated transformation *in vitro*. Thoc1 expression is elevated in 50% of human lung cancers, and expression of this factor correlates with poorer patient survival in certain lung cancer subtypes. (Goodrich *et al.* *Mol Cell Biol* 2005, 2006; *Int J Oncol* 2006; *Cancer Res* 2006; R01 CA125665).

Selected Scientific Accomplishments

Alex Adjei, MD, PhD

*Katherine Anne Gioia Chair in Cancer Medicine
Associate Director for Clinical Research*

Two critical pathways that are activated by engagement of ErbB family members and other RTKs include the ERK/MAPK cascade and the PI3K/AKT pathway. Abnormalities in these pathways are also characteristic of a variety of tumor types. Inappropriate activation of the ERK/MAPK pathway is observed in up to 50% of all human cancers, indicating that inhibition of ERK/MAPK signaling may be a useful therapeutic strategy. In phase I studies with the highly potent and selective MEK inhibitor AZD6244, Alex Adjei, MD, PhD showed that ERK/MAPK activity is effectively inhibited in target tumor tissues and that prolonged stable disease can be achieved with this agent in several tumor types (Adjei *et al.*, *Eur J Cancer* 2006; 4:26). Six of twenty melanoma patients had stable disease for \geq 5 months. However, target inhibition did not necessarily correlate with clinical benefit. In an excellent example of bidirectional flow from bench-to bedside and back to the bench, preclinical studies in lung cancer cell lines identified a correlation between upstream phospho-MEK levels and AZD6244 sensitivity. Drug-induced phospho-MEK accumulation requires Raf activity and likely involves relief of feedback inhibition of Raf by ERK/MAPK (Friday *et al.*, *Proc. AACR* 2006; 47:4868; Friday *et al.*, *Cancer Res* 2007; submitted). Based on these findings, a phase I study led by Dr. Adjei will explore combinations of MEK and Raf (e.g., sorafenib) inhibitors to overcome this effect. A phase II clinical trial of AZD6244 in melanoma is in progress with Michael Wong, MD, PhD (TII).

Ralph Bernacki, PhD

Professor, Pharmacology & Therapeutics

Multidrug resistance (MDR) is a major impediment to successful cancer chemotherapy. Ralph Bernacki, PhD has long-standing interests in the discovery, biochemical characterization, and preclinical evaluation of doxorubicin analogs, tamoxifen analogs, and taxoid-lipid conjugates that demonstrate improved properties over "parent compounds" with respect to overcoming MDR. He collaborates with a number of medicinal chemists including Drs. Ojima and Parker (SUNY Stony Brook), Dr. Preibe (MD Anderson), Dr. Kingston (Virginia Tech), and Dr. Huw Davies (UB), in this discovery process. Recent studies with Dr. Preibe identified a novel 4'-O-benzylated synthetic doxorubicin analogue, WP744, that overcomes MDR mediated by P-glycoprotein, multidrug resistance protein-1, and breast cancer resistance protein (BCRP) in cell lines over-expressing these molecules (Brooks *et al.*, *Invest New Drugs* 2007; 25:115). These studies identified WP744 as a promising agent for clinical development in malignancies with broad-spectrum MDR. Dr. Bernacki has also evaluated a series of tamoxifen analogs synthesized by Dr. Davies, and identified an agent with the ability to partially overcome tamoxifen resistance. Recent findings with Dr. Ojima indicate that polyunsaturated fatty acids such as docosahexaenoic acid (DHA), linolenic acid, and linoleic acid linked to the C-2' position of second-generation taxoids (previously developed by Dr. Ojima) overcome MDR caused by over-expressed ABC transporters. The new conjugates, tested *in vivo*, exhibit strong activity against drug-resistant colon tumor xenografts in mice. Two of the conjugates, DHA-SB-T-1214 and DHA-SB-T-1213, were found to achieve total regression of drug-resistant and drug-sensitive tumors, respectively, in animal models, with substantially reduced systemic toxicity (Kuznetsova *et al.*, *Bioorg Med Chem Lett* 2006; 16:974). DHSB-1214 is considered a lead agent for further preclinical drug development leading to clinical trial. In other collaborative studies supported by a new consortium grant, R01 GM074776, Drs. Bernacki and Kathlyn Parker (SUNY Stony Brook) are evaluating natural products SNF 4435 C and D and related structures, synthesized by Dr. Parker, as MDR modulators.

Jennifer Black, PhD

Professor, Pharmacology & Therapeutics

The protein kinase C (PKC) family member, PKC α , is a downstream target of both vitamin D and EGFR signaling. Extensive evidence supports a role for PKC α signal transduction in mediating the growth-inhibitory effects of calcitriol and in negatively regulating EGFR activity. The laboratory of Jennifer Black, PhD has a long-standing interest in understanding the role of PKC signaling in control of intestinal epithelial homeostasis and transformation. In a series of R01-supported studies (R01 DK054909, R01 DK060632), this group has demonstrated that PKC α signaling triggers a program of cell cycle withdrawal in intestinal cells, characterized by rapid down-regulation of cyclin D1, increased expression of Cip/Kip cdk inhibitors, and activation of the growth suppressor function of pocket protein family members. The effect is dependent on sustained activation of PKC α and the ERK/MAPK pathway (Clark *et al.*, *J Biol Chem* 2004; 279:9233; Bateman *et al.*, *J Biol Chem* 2004; 279:12093). Notably, down-regulation of cyclin D1 occurs via PKC α -mediated inhibition of cap-dependent translation initiation (Hizli *et al.*, *J Biol Chem* 2006; 281:14596; Guan *et al.*, *J Biol Chem* 2007; 282:14213). Dr. Black's group has made the novel observation that PKC α modulates the activity of key translational regulators, including eIF4E and eIF4E-binding protein 1 (4E-BP1), to repress cyclin D1 protein synthesis during intestinal epithelial cell cycle withdrawal. The engagement of translational rather than transcriptional mechanisms ensures a rapid effect, with disappearance of cyclin D1 protein preceding other hallmark events of cell cycle exit. The relevance of translational regulation of cyclin D1 to intestinal homeostasis is highlighted by the fact that overexpression of eIF4E, together with associated up-regulation of cyclin D1, has been implicated in the development of colon tumors. Notably, Dr. Black's group was the first to demonstrate that, unlike normal proliferating intestinal cells, a majority of human colon tumors lack expression of PKC α . Loss of PKC α -mediated control of critical translational regulators and cell cycle control molecules is likely to play an important role in colon tumorigenesis. Ongoing studies in collaboration with Drs. Karpf and Rajput are (a) determining the mechanisms underlying loss of PKC α during intestinal carcinogenesis (Leontieva and Black, *J Biol Chem* 2004; 279:5788), (b) exploring approaches for restoration of PKC α expression in colon cancer cells, and (c) investigating the effects of PKC α expression on the malignant phenotype of these cells *in vivo*.

Terry Beerman, PhD

Professor, Pharmacology & Therapeutics

Terry Beerman, PhD studies DNA damage-inducing agents and response mechanisms as an approach to cancer therapy. Dr. Beerman has recently reported several unusual properties of C-1027, a clinically relevant radiomimetic enediyne. Studies with Sei-Ichi Matsui, PhD (GN) have shown that C-1027 induces genomic instability and altered cell cycle progression by preferentially damaging telomeres (McHugh *et al.*, *Cancer Res* 2005; 65:5344). In addition, C-1027 is unique among radiomimetics in that cellular responses to DNA double strand breaks induced by this agent do not require the ATM protein kinase, and are only diminished in the absence of both ATM and ATR (Kennedy and Beerman, *Biochemistry* 2006; 45:3747; Kennedy *et al.*, *Cancer Res* 2007; 67:773). Dr. Beerman has also shown that ionizing radiation (IR) potentiates the cytotoxic effects of C-1027. Follow-up studies will (a) optimize the C-1027/IR combination in regard to induction of genomic instability and cell death, and (b) explore the impact of abrogating the G2 checkpoint with the kinase inhibitor UCN-01. Studies of the combination will then be performed in mice, in collaboration with Mohamed Khan, MD, PhD (CSBT). Dr. Beerman's group has also demonstrated that C-1027 and the analogue desmethyl uniquely induce DNA interstrand crosslinks under low oxygen conditions, raising the possibility of using these agents to target the highly IR- and radiomimetic-resistant hypoxic centers of tumors (Kennedy *et al.*, *Proc Nat'l Acad Sci* 2007; submitted). Building on this novel finding, Dr. Beerman will test whether C-1027 and desmethyl interstrand crosslink activity and cytotoxicity are enhanced in hypoxic cells, as a prelude to evaluation of these agents in hypoxic tumor models. These studies led to new joint R01 funding to Drs. Beerman and Matsui (R01 CA106312).

Asher Chanan-Khan, MD

Associate Professor, Medicine

The tumor cell microenvironment is increasingly recognized for its role in cancer cell growth, progression and resistance to therapy. Immunomodulating agents (i.e., the IMiDs) represent a new class of drugs with the ability to favorably modulate the tumor cell microenvironment by down-regulating critical pro-survival cytokines and affecting angiogenesis. Because the bone marrow provides a critical milieu for proliferating and differentiating blood cells, Drs. Chanan-Khan, Porter, and others were among the first to investigate the potential of the IMiDs, thalidomide and lenalidomide (Revlimid), in the treatment of B cell malignancies such as MM and CLL. Dr. Chanan-Khan leads a nationally recognized, multidisciplinary research group engaged in preclinical and clinical activities related to these diseases, and including members from the MTET (Chanan-Khan, Porter, Goodrich, Bernacki), TII (Bangia, Czuczman, Lee), GN (Coignet, Hawthorn), and CPPS (Moysich) Programs. In phase II and phase III clinical studies performed in MM, this group showed superiority of the thalidomide analog, lenalidomide, compared with standard treatment (Scarpace *et al.*, *Leuk Lymphoma* 2005; 46:239; Chanan-Khan and Miller, *Leuk Lymphoma* 2005; 46:1103; Miller *et al.*, *Leuk Lymphoma* 2006; 47:2339). These and other studies resulted in FDA approval of lenalidomide for myeloma patients. The RPCI Multiple Myeloma clinic is a member of the Multiple Myeloma Research Consortium, which facilitates access to state-of-the-art therapeutic molecules for preclinical evaluation and clinical trials. Studies by this group have led to development of an additional phase I and II clinical trial, to be initiated through the CALGB cooperative group, investigating a novel combination of Velcade, Doxil and lenalidomide (VDR).

In the case of CLL, Dr. Chanan-Khan's group was the first to report the antileukemic activity of thalidomide and to demonstrate that the microenvironment is an important therapeutic target (Chanan-Khan *et al.*, *Blood* 2005; 106:3348; Chanan-Khan and Porter, 2006; *Lancet Oncol* 7:480; Chanan-Khan *et al.*, *J Clin Oncol* 2006; 24:5343). Response rates of 100% were achieved in a phase I and II clinical trial combining thalidomide with standard treatment fludarabine. Subsequent investigation of lenalidomide in a phase II trial as a single agent indicates that this compound modulates the CLL tumor cell microenvironment, resulting in remarkable antileukemic activity and sustained remissions in patients with relapsed or refractory CLL. These findings identify a new treatment paradigm for this disease. Several clinical trials have been initiated nationwide and

Dr. Chanan-Khan will lead an international clinical registration trial. Ongoing investigator-initiated clinical trials at RPCI include a phase I and II study of fludarabine/thalidomide for the treatment of newly diagnosed CLL, and a phase II study of lenalidomide for the treatment of relapsed/refractory CLL.

Gokul Das, PhD

Assistant Professor, Pharmacology & Therapeutics

Gokul Das, PhD studies interactions between p53 and estrogen receptor (ER) signaling in control of cell proliferation and oncogenesis (RO1 CA079911, Susan G. Komen for the Cure). His group has made the seminal discovery that ER α binds

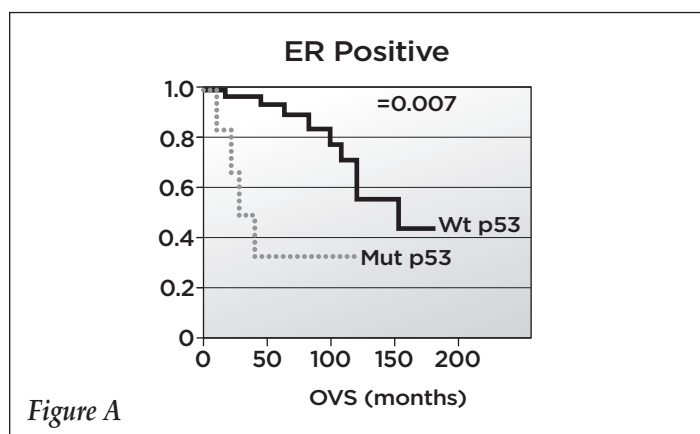


Figure A

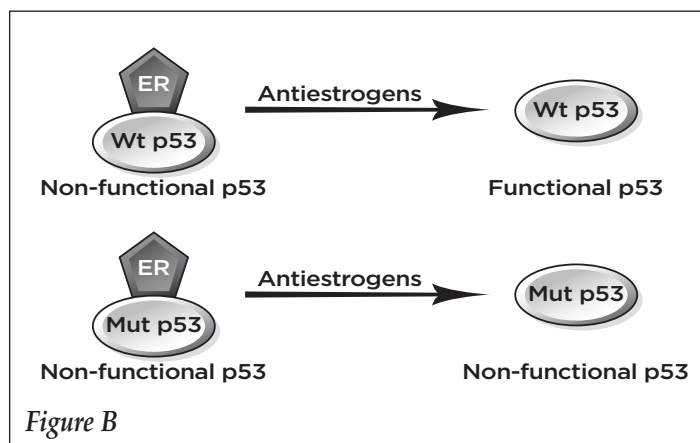


Figure B

Figure A: ER α -p53 interaction in breast cancer—novel concepts in tamoxifen and IR resistance. Wild-type p53 in ER positive breast tumors is associated with better response to tamoxifen. Kaplan-Meier analysis of overall survival (OVS) of tamoxifen-treated patients with ER-positive breast cancer expressing wt or mutant p53.

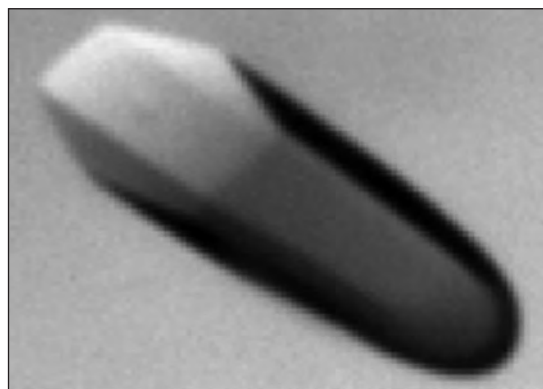
Figure B: Proposed model for the role of p53 in resistance to tamoxifen therapy.

directly to the tumor suppressor p53 in human breast cancer cells, resulting in inhibition of p53 function (Liu *et al.*, *J Biol Chem* 2006; 281:9837, *accelerated report*). p53-bound ER α recruits transcriptional corepressors leading to inhibition of p53-mediated transcriptional activation. Notably, 17 β -estradiol augments the ER α -p53 interaction, whereas anti-estrogens such as tamoxifen and ionizing radiation disrupt the binding of these factors. In a retrospective breast cancer patient analysis, Dr. Das showed that the presence of wild-type p53 in ER-positive breast tumors is associated with better response to tamoxifen therapy and increased survival (Sayeed *et al.*, *Cancer Res* 2007; *in press*). Together with published evidence that adjuvant therapy with tamoxifen is of less value for tumors with mutant p53, these studies support the novel hypothesis that relief of ER α -mediated repression of wild-type p53 function could be an important mechanism underlying tamoxifen action on breast tumors, and that resistance to tamoxifen may be associated with the expression of mutant p53. This represents an important paradigm shift regarding mechanisms of tamoxifen resistance. Collaborative studies with Margot Ip, PhD (CPPS) are now underway to develop a human breast cancer xenograft model in mice to analyze ER α -p53 interaction and how it is affected by radiation and hormone therapy. In addition, a pilot prospective clinical study to determine if this interaction occurs in human breast cancer patient tumors (on endogenous p53-target gene promoters) and if it is disrupted by tamoxifen therapy has been approved at RPCI with Drs. Edge (CPPS), Kulkarni (CPPS), and Hicks (GN). In RO1 GM062794-supported studies that are relevant to therapy of estrogen-dependent breast cancer and to the ER α -p53 interaction identified by Dr. Das, Debashis Ghosh, PhD has elucidated the structure of human steroid sulfatase, an integral membrane enzyme of the endoplasmic reticulum that regulates local production of estrogens and androgens from systemic precursors in several tissues (Thomas *et al.*, *J Endocrinology* 2007; *in press*). These studies revealed the steroid recognition mechanism and involvement of the lipid bilayer in catalytic function of the enzyme. Dr. Ghosh is currently applying structure-guided design and virtual screening techniques for the identification and optimization of novel inhibitors of steroid sulfatase.

Debashis Ghosh, PhD

*Associate Professor, Pharmacology & Therapeutics
Hauptman-Woodward Research Institute*

Aromatase is a unique cytochrome P450 that catalyzes the critical step of aromatization of the A-ring of androgens for the synthesis of estrogens. All human estrogens are synthesized by this enzymatic aromatization reaction. Aromatase inhibitors, thus, have become important modern drugs for the treatment and prevention of estrogen-dependent breast cancer. Despite being at the focus of decades of biochemical and biophysical investigation in many laboratories, all efforts to determine the precise atomic arrangement of its active site have thus far failed because of the difficulties in handling this membrane-bound and unstable enzyme. Knowledge about its active site is crucial for design and synthesis of the next generation aromatase inhibitors with superior medicinal properties. The laboratory of Dr. Debashis Ghosh has now been able to overcome these difficulties and grow the first crystals of human aromatase. These crystals have permitted Dr. Ghosh to determine the detailed atomic structure of the active site by X-ray diffraction. The structure reveals the molecular basis of exquisite substrate selectivity of the enzyme and its mechanism of action. This information will now be exploited for design and synthesis of highly specific aromatase inhibitors.



*A single crystal of human aromatase
(Debashis Ghosh, PhD)*

David Goodrich, PhD

Professor, Pharmacology & Therapeutics

The retinoblastoma tumor-suppressor gene (Rb1) is centrally important in cancer. Mutational inactivation of Rb1 causes the pediatric cancer retinoblastoma, while deregulation of the pathway in which it functions is common in most human cancer types. The Rb1-encoded protein (pRb) is well known as a cell cycle regulator, and this activity is likely critical for pRb-mediated tumor suppression. Recent evidence, however, shows the existence of additional, cell type-specific pRb functions in cellular differentiation and survival. Analysis of Rb mutants indicates that the varied functions of pRb are genetically separable and mediated by distinct regions of the molecule. In studies supported by R01 CA070292, David Goodrich, PhD is investigating how these additional pRb functions contribute to tumor suppression (Xiao and Goodrich, *Oncogene* 2005; 24:8105, *Featured Article*; Sun *et al.*, *Mol Cell Biol* 2006; 26:1527; Goodrich, *Oncogene* 2006; 25:5233). Using sophisticated targeted mutagenesis in animal models, he has shown that pRb retains some of its function in supporting normal embryonic development in the absence of Rb/E2F interaction. His group also determined that pRb uses E2F-independent, tissue-specific mechanisms to suppress prostate carcinogenesis, and has developed a new mouse model of prostate cancer based on conditional ablation of Rb1 and p53 (Zhou *et al.*, *Cancer Res* 2006; 66:7889). Clinical exploitation of pRb as a therapeutic target will require a better understanding of its complex functions in tumor suppression within given tissues. Ongoing studies with Dr. Barbara Foster (PR) are, therefore, using systematic proteomic approaches to explore Rb pathway alterations during prostate carcinogenesis (joint NIH APRC grant).

Adam Karpf, PhD

Assistant Professor, Pharmacology & Therapeutics

Innovative epigenetic therapeutics, involving the use of demethylating agents such as 5-aza-2'-deoxycytidine (decitabine, DAC) and HDAC inhibitors such as suberoylanilide hydroxamic acid (SAHA) are being actively developed at RPCI. An Epigenetics Group, including Drs. Karpf, Held, Smiraglia, and Higgins (GN), meets weekly to promote the development of these approaches. Dr. Karpf studies epigenetic gene deregulation in human cancer and develops novel therapeutic strategies based upon targeting these defects. Using an epigenomic screening approach, he discovered that a major cellular response to DNA methyltransferase (DNMT) inhibitors is

the robust activation of a family of medically important genes termed cancer/germline antigens, or CG antigens (Karpf *et al.*, *Mol Pharmacol* 2004; 65:18; Karpf, *Curr Opin Mol Therap* 2007; *in press*). These proteins were the first bona fide tumor antigens to be characterized, and vaccines targeting these molecules are undergoing active clinical testing for a variety of malignancies. Dr Karpf found that DNA methylation and histone modification status play a major role in regulating the expression of CG antigen genes in human cancer cells (Karpf, *Epigenetics* 2006; 1:116). NY-ESO-1 is a CG antigen gene that is under investigation as a target of vaccine therapy clinical trials in ovarian cancer conducted by Kunle Odunsi, MD, PhD (TII) at RPCI. Dr. Karpf's group determined that DNMT inhibitors, including DAC, robustly induce NY-ESO-1 expression in ovarian cancer cells *in vitro* (James *et al.*, *Oncogene* 2006; 25:6975), and that the methylation status of the NY-ESO-1 promoter predicts NY-ESO-1 protein expression levels in human ovarian cancer specimens from patients. These data have led to a clinical trial of the effect of decitabine treatment on the efficacy of NY-ESO-1 vaccines in women with recurrent ovarian cancer. Studies are supported by a joint R01 (Karpf and Odunsi, R01 CA11674).

Fengzhi Li, PhD

Associate Professor, Pharmacology & Therapeutics

MTET members have documented expertise in targeting survival molecules for cancer therapy. Fengzhi Li, PhD is an expert in the regulation and function of the anti-apoptotic protein survivin and its role in response to chemotherapeutic drugs. Survivin is undetectable in most normal adult tissues but is often highly expressed in cancer cells. In studies with Drs. Bernacki and Brattain, Dr. Li showed that transcriptional induction of survivin is an early event following paclitaxel treatment and, contrary to the accepted paradigm, occurs independently of paclitaxel-mediated G2/M arrest (Ling *et al.*, *J Biol Chem* 2004; 279:15196).

Additional studies identified survivin induction as a novel resistance pathway for paclitaxel; inhibition of paclitaxel-mediated survivin accumulation by siRNA markedly increases taxol-mediated cell death. Thus, abrogation of this new survivin-associated survival pathway may provide the basis for novel approaches for anticancer therapy. These studies led to new funding for Dr. Li (R01 CA109481, Susan G. Komen grant BCTR63806). Building on these findings, Dr. Bernacki is seeking analogues that lack the ability to induce survivin. In addition, Dr. Li, in collaboration with Drs. Brattain and Astellas (Japan), is testing a novel survivin transcription repressor, YM155. In

collaboration with Dr. David Hangauer (UB) and PrimaNova Biosciences in Buffalo, several small molecule inhibitors of survivin have been identified and characterization is underway; one patent has been filed. Studies with Drs. Rustum and Foster (PR) indicate that methylselenocysteine may potentiate the effects of paclitaxel via downregulation of survivin, indicating that selenium/paclitaxel combinations may be useful as a therapeutic modality (Zhang *et al.*, *J Exp Clin Cancer Res* 2006; 25:391; Azrak *et al.*, *Mol Cancer Ther* 2006; 5:2540).

Lakshmi Pendyala, PhD

Associate Professor, Medicine
Pharmacokinetics/Pharmacodynamics Resource Director

Lakshmi Pendyala, PhD focuses on optimizing the use of platinum compounds for cancer therapy. Using gene expression profiling, Drs. Pendyala, Porter, and Hawthorn (GN) showed that oxaliplatin and cisplatin are potent inducers of SSAT mRNA in human ovarian carcinoma cells (Hector *et al.*, *Mol Cancer Therap* 2004; 3:813) and other *in vitro* cell models. Further work showed that combination of platinum drugs and the clinically relevant polyamine analog DENSPM results in >1600x increase in SSAT mRNA and enzyme activity, leading to depletion of polyamine pools and markedly enhanced growth inhibition in several ovarian and colon cancer cell lines. Oxaliplatin is used in combination with 5-FU for colon cancer therapy; 5-FU similarly induces SSAT and, in HCT116 colon cancer cells, the combination of oxaliplatin/5-FU/DENSPM promotes higher induction of SSAT mRNA and activity relative to any single drug or dual combination. Notably, collaborative studies with Marwan Fakih, MD detected SSAT induction in rectal biopsies from patients receiving oxaliplatin therapy. Affymetrix gene expression profiling further showed that, in addition to up-regulation of SSAT, platinum drugs down-regulate the polyamine biosynthetic pathway genes ornithine decarboxylase and S-adenosylmethionine decarboxylase (Varma *et al.*, *Cancer Chemother Pharmacol* 2007; 59:711). Together, these studies confirm that the polyamine pathway is an important target for platinum drugs. Pending development through *in vivo* dose-optimization studies, these findings will be translated to a clinical trial of oxaliplatin/5-FU and DENSPM in colorectal cancer (supported by Genzyme). This effort has resulted in new joint R01 support for Drs. Pendyala and Porter (CA109619).

Carl Porter, PhD

Professor, Pharmacology & Therapeutics

Carl Porter, PhD has a long-standing interest in targeting the polyamine pathway for cancer therapy. Polyamines are essential for cancer cell growth, and levels of these molecules are tightly controlled in cells. While most polyamine-directed anti-cancer approaches have targeted polyamine biosynthesis, in recent years Dr. Porter has explored the possibility of engaging polyamine catabolic processes for cancer therapy development (R01 CA022153, R01 CA076428). His group has shown that increased expression of the polyamine catabolic enzyme spermidine/spermine N1-acetyltransferase (SSAT) in LNCaP prostate cancer cells, using genetic approaches or treatment with the polyamine analogue DENSPM, results in markedly increased metabolic flux through the polyamine pathway, depletion of acetyl-CoA, and inhibition of cell growth (Kee *et al.*, *J Biol Chem* 2004; 279:27050) (DOD DAMD17-03-1-0024). *In vivo* studies, performed in collaboration with Barbara Foster, PhD (PR), showed that SSAT overexpression in TRAMP mice (a transgenic model of prostate cancer) by cross-breeding with SSAT overexpressing transgenic mice markedly suppresses outgrowth of prostate tumors (Kee *et al.*, *J Biol Chem* 2004; 279:40076). Using MRI, Drs. Porter and Mazurchuk (Preclinical Imaging Resource) further demonstrated that the bigenic mice have reduced body fat composition, presumably due to acetyl-CoA depletion (R01 CA022153). They also report that mice that globally overexpress SSAT have lowered acetyl-CoA pools and a lean phenotype, while mice with global depletion of SSAT are prone to an obese phenotype (Jell *et al.*, *J Biol Chem* 2007; 282:8404, *Cover Article*). In addition to validating activated



Research in polyamine directed therapies: SSAT suppresses tumor development published as the cover story for The Journal of Biological Chemistry

polyamine catabolism as a new strategy in cancer chemotherapy (also see Nilsson *et al.*, *Cancer Cell* 2005; 7:1), these findings provide the first definitive link between polyamines and fat metabolism and have important implications for novel anti-obesity strategies. Dr. Porter is pursuing discovery of small molecule SSAT-inducers by high throughput screening of chemical libraries via a recently awarded NCI R•A•N•D grant. He also collaborated with Dr. Liang Tong at Columbia University to determine the structure of a bacterial polyamine acetyltransferase as a prelude to the development of specific inhibitors of this enzyme (Forouhar *et al.*, *J Biol Chem* 2005; 280:40328). Additional targets are being sought using a functional genomic approach in collaboration with Ping Liang, PhD (GN and Bioinformatics Core). These studies have resulted in the identification and characterization of three new polyamine catabolic enzymes - spermine oxidase, polyamine oxidase, and a second spermidine/spermine *N1*-acetyltransferase (Vujcic *et al.*, *Biochem J* 2003; 370:19-28; Chen *et al.*, *Biochem J* 2003; 373:661-667) (RO1 CA076428).

Ashwani Rajput, MD

Assistant Professor, Surgery

Deregulation of PI3K/AKT signaling is common in tumors and aberrant PI3K activation plays important roles in sustaining the malignant phenotype. Indeed, gain-of-function mutations in PIK3CA, which encodes the p110 α catalytic domain of PI3K, are seen in approximately 30% of colon cancers and 40% of breast tumors. To gain insight into the role of aberrant PI3K activation in colon cancer metastasis, the laboratory of Ashwani Rajput, MD in collaboration with Dr. Brattain, performed *in vivo* studies using isogenic pairs of GFP-labeled colon cancer cells expressing only wild-type or mutant PIK3CA alleles (CA 34432, CA54807). With the assistance of Richard Mazurchuk, PhD (Preclinical Imaging Resource), these cells were tested for metastatic potential in a novel orthotopic implantation model established by Dr. Rajput (Rajput *et al.*, *J Surg Res* 2007; *in press*). Notably, colon cancer cells harboring mutant PIK3CA were significantly more metastatic than those bearing wild-type PI3K in this model, exhibiting metastatic spread to the liver and lungs in a pattern consistent with that seen in humans (Guo *et al.*, *Cancer Res* 2007; *in press*). Cells harboring mutant PI3K were hypersensitive to PI3K inhibition, suggesting "oncogenic addiction" to

this pathway. Thus, mutant PI3K confers a more aggressive phenotype in colon cancer cells, and aberrant PI3K activity may represent a novel therapeutic target in colon cancer. The discovery phase of this project continues in a study with Dr. Fakih, in which the status of PI3K is being analyzed in colorectal tumors from patients treated with the monoclonal antibody cetuximab (Erbix) to determine if clinical response correlates with the activation status of downstream PI3K.

Youcef Rustum, PhD

Professor and Chair, Cancer Biology

Youcef Rustum, PhD leads a multidisciplinary initiative to investigate the role of selenomethionine (SLM) as a selective modulator of the therapeutic efficacy of anticancer drugs and radiation in multiple preclinical and clinical studies. *In vivo* studies by Dr. Rustum and others have shown that SLM and methylselenocysteine increase the cure rates of nude mice with human tumor xenografts treated with various anticancer drugs while providing protection from organ-specific toxicity and lethality (Cao *et al.*, *CI Cancer Res* 2004; 10:2561; Hu *et al.*, *CI Cancer Res* 2005; 11:2379; Azrak *et al.*, *Mol Cancer Therap* 2005; 4:845; Azrak *et al.*, *Mol Cancer Therap* 2006; 5:2540). Synergy was demonstrated with a number of chemotherapeutic agents and radiation in multiple human tumor xenografts. Potentiation of drug (irinotecan) sensitivity by methylselenocysteine is associated with down-regulation of molecular markers of angiogenesis and apoptosis, such as COX-2, inducible NO synthase, and hypoxia-inducible factor 1 α , as well as enhanced intratumoral drug accumulation due in part to stabilization of blood vessel density (Bhattacharya *et al.*, *CI Cancer Res* 2004; 10:8005; Yin *et al.*, *Oncogene* 2006; 25:2509; Park *et al.*, *CI Cancer Res* 2007; *in press*). Thus, SLM appears to exert dual effects on the tumor vasculature: inhibition of new tumor vessel proliferation; and stabilization of established tumor vessels by recruitment of pericytes/smooth muscle coverage. Recent studies showed that therapeutic synergy is highly dependent on SLM dose and schedule in relation to cytotoxic therapy (Azzak *et al.*, *Biochem Pharmacol* 2007; 73:1280).

Donald L. Trump, MD, FACP

*President and Chief Executive Officer,
Principal Investigator, CCSG*

Donald L. Trump, MD and Candace Johnson, PhD (PR) study the anti-proliferative effects of 1,25 dihydroxycholecalciferol (calcitriol, the most active form of vitamin D) using pre-clinical models and in phase I and II clinical trials. The approach is based on substantial epidemiological and preclinical data for anticancer growth inhibitory and apoptosis-inducing activities of vitamin D in murine and human tumor model systems (Muindi *et al.*, *Oncology* 2004; 66:62; Johnson *et al.*, *Anticancer Res* 2006; 26:2543; Ma *et al.*, *Cancer Res* 2006; 66:8131). Antitumor effects of calcitriol have been demonstrated in many tumor types (colorectal, prostate, breast, ovarian, and pancreas). Studies by this group have further shown that vitamin D potentiates the effects of other anticancer agents such as platinum analogues, taxanes, antimetabolites, alkylating agents, topoisomerase inhibitors, and ErbB1 (EGFR) small molecule antagonists (R01 CA067267, DOD grant PC040238). Potentiation of cisplatin and taxane effects appears to involve induction of the p53 family member, p73, and enhancement of apoptosis. These findings have been translated into a large number of NCI-, ACS-, DOD- or foundation-supported clinical trials led by clinician scientists Drs. Trump, Fakih, Ramnath, Chanan-Khan, and Iyer (Beer *et al.*, *CI Cancer Res* 2005; 11:7794; Trump *et al.*, *Anticancer Res* 2006; 26:2551; Trump *et al.*, *Cancer* 2006; 106:2136; Beer *et al.*, *Cancer Chemother Pharmacol* 2007; 59:581; Muindi *et al.*, *Cancer Chemother Pharm* 2007; 59:97).

The therapeutic potential of calcitriol has been limited by the inability to dependably achieve high systemic exposure with oral administration. Drs. Trump and Johnson (PR) have used two different approaches to circumvent this problem: intravenous calcitriol administration, and combination with inhibitors of calcitriol catabolism (R01 CA067267, ACS Grant MRS04-270-01-CCE). A phase I trial led by Dr. Fakih, in collaboration with Drs. Creaven, Black, and Hutson (Biostatistics), was performed to determine the maximum tolerated dose (MTD) of intravenous calcitriol (Fakih *et al.*, *Clin Cancer Res* 2006; 13:1216). Based on evidence for pre-clinical synergy with EGFR inhibitors, the trial also addressed the effects of calcitriol in combination with gefitinib. This study determined, for the first time, that high intravenous weekly doses of calcitriol up to

74 mcg can be safely administered in cancer patients in combination with oral gefitinib. Importantly, calcitriol concentrations achieved at the MTD of 74 µg/wk exceed *in vivo* concentrations associated with antitumor activity in preclinical models. The data suggest that optimal antitumor effects of calcitriol may be achieved through high-dose, intermittent administration schedules. These important findings pave the way for future clinical trials testing calcitriol as a single agent or in combination with other cytotoxics.

Vitamin D-based therapeutics are being further developed through a collaboration with Cornell College of Veterinary Medicine. Drs. Trump, Iyer, Ramnath, and Johnson (PR) from RPCI and Drs. Page, Rassnick, and Johnson from Cornell University meet monthly to develop animal models of spontaneous malignancies, which may be more relevant to human disease than transplantable or transgenic tumors. Several major projects involving calcitriol alone or in combination with cisplatin, the NSAID piroxicam, paclitaxel, or carboplatin have been completed or are underway in dogs with advanced spontaneous tumors, woodchucks with virally-induced hepatocellular carcinoma, and chickens with ovarian cancer. Phase I studies of intravenous high dose calcitriol + cisplatin in dogs resulted in 60% complete response rates, leading to award of an R21 grant to Dr. Ramnath and to an ongoing phase I and II clinical trial of high dose intravenous calcitriol + docetaxel + cisplatin in NSCLC.

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