

Prostate Program



Prostate Program

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James Mohler, MD

Professor and Chair, Urologic Oncology

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Overview and Themes

The unifying theme and common goal of the Prostate Program is the identification and targeting of unique changes which occur in prostate cancer (CaP) cells and their tissue microenvironment following androgen deprivation in order to develop new approaches to block or delay the development of “androgen-independent” – more properly castration-resistant or castration-recurrent – prostate cancer. Studies to identify unique targets that are related causally to the transition to metastatic, castration-resistant CaP, the lethal phenotype, are focused specifically on: 1) androgen receptor (AR) and vitamin D receptor (VDR) mediated signaling; 2) cellular targets in endothelial cells, pericytes and tumor stem cells; and 3) molecular targets, including prostate-specific antigen (PSA), tumor cell antigens, CaP-specific glycan signatures, 24-hydroxylase (CYP24) and cytokines. Targets validated in basic and pre-clinical investigations will be tested in the clinic.

Prostate cancer research at RPCI has a long and distinguished history. Among the many contributions of Roswell Park to prostate cancer research include the discovery of prostate specific antigen (PSA), prostate-specific membrane antigen (PSMA), the LNCaP cell line and RPMI-1640 media.

Research and clinical trials in the Prostate Program have crystallized around 3 themes:

1. Androgen Axis with a focus on androgen metabolism and the components of AR-mediated signaling and transactivation.

Advanced prostate cancer (CaP) is palliated by medical or surgical castration, but almost all men suffer recurrence in spite of castrate levels of circulating testicular androgens. Dr. Mohler and collaborators at the University of North Carolina showed that castration-recurrent CaP retains androgen receptor (AR) protein expression, and AR remains active in growth signaling despite castrate levels of circulating androgens. Dihydrotestosterone (DHT) levels were decreased by 91% in clinical specimens of castration-recurrent CaP (1.25 pmol/gm tissue) compared to

benign prostate tissue from hormonally intact men; however, these DHT levels were sufficient to transactivate AR in most specimens of castration-recurrent CaP. This observation suggests a paradigm shift: CaP that recurs after medical or surgical castration is not “androgen-independent” because castration-recurrent CaP tissue usually has testicular androgen levels sufficient to activate AR. The sources of prostate tissue “testicular” androgen and the altered metabolism of androgens probably of adrenal origin in castration-recurrent CaP are under investigation (PO1 CA77739). (Mohler *et al.*, *CI Cancer Res* 2004; 10:440; Titus *et al.*, *CI Cancer Res* 2005; 11:4653)

2. Angiogenesis with a focus on exploiting the innate biology of prostate endothelial cells and pericytes.

The work of Dr. Johnson and her collaborator Dr. Trump (MTET) has provided new insight into the potential role of calcitriol as an antiangiogenic agent as well as the role of vitamin D signaling in normal vasculogenesis. They found that tumor derived endothelial cells (TDEC) are sensitive to the antiproliferative effects of calcitriol while endothelial cells derived from a Matrigel environment (MDEC) are not. Sensitivity is not related to differences in VDR or VDR-mediated signaling. The enhanced sensitivity to calcitriol appears to be caused by transcriptional silencing of expression in TDEC of CYP24, the major vitamin D catabolic enzyme, through methylation of the CYP24 promoter. The CYP24 promoter in MDEC is not methylated. Further studies also indicate that vasculogenesis is abnormal in the VDR knockout mouse, suggesting a role of vitamin D signaling in tumor angiogenesis and normal blood vessel growth. (Chung, *et al.*, *J Biol Chem.* 2007; 282:8704; Chung, *et al.*, *J Steroid Biochem Mol Biol* 2007; 103:768; Flynn, *et al.*, *Oncology.* 2006; 70:447; and Chung, *et al.*, *Cancer Res* 2006; 66:8565)

3. Chemosensitization and Alternative Targets with a focus on vitamin D, tumor antigen/heat shock protein (HSP)-based vaccines, and novel targets, including prostate tumor stem cells, and CaP-specific glycan-signatures.

Dr. Smith and colleagues have characterized the phenotype of a putative prostate cancer stem cell and demonstrated that the signature phenotypic marker is linked mechanistically to the role of the androgen axis in differentiation. These stem cells express the ABCG2/BCRP-drug efflux pump. Blocking efflux of androgen from the prostate cancer stem cell could result in the forced induction of differentiation. Putative prostate tumor stem cells that express BCRP but not AR protein in TRAMP are the source of a BCRP-negative and AR-negative, Foxa2- and SV40Tag-expressing, transit amplifying compartment that progresses to the poorly differentiated carcinomas that arise rapidly after castration. Therefore, BCRP expression may isolate prostate stem/tumor stem cells from the prostate tissue microenvironment through constitutive efflux of androgen, making androgen deprivation less relevant and protecting the putative tumor stem cells from cytotoxic and other agents. (Huss, *et al.*, *Cancer Res* 2005 Aug 1; 65(15):6640-50)

Selected Scientific Accomplishments

Kailash Chadha, PhD

Associate Professor, Molecular & Cellular Biology

PSA levels in prostate tissue are 3 orders of magnitude higher than serum levels, and the majority of PSA in tissue is not complexed with inhibitors and is enzymatically active. Kailash Chadha, PhD has established and patented a simple, 2-step chromatographic procedure for isolation of enzymatically active, free PSA from human seminal plasma. The initial step in the separation of seminal plasma proteins is thiophilic interaction chromatography (T-gel) and the second step is molecular size chromatography on Ultrogel AcA54. Purity of the isolated free-PSA is verified using silver-staining of 2-D gels, and enzymatic activity is characterized using a fluorogenic substrate specific for PSA (Mu-His-Ser-Ser-Lys-Leu-Gln—AFC). The average yield of enzymatically active, free PSA was 0.5 mg/ml of seminal plasma. In the PC-3M human CaP cell line, Dr. Chadha showed that PSA (10 μ M), and enzymatically inactive PSA, down-regulated expression of multiple genes at the mRNA level, including VEGF, IL-8, EphA2, CYR61, Bcl2, Pim-1 oncogene and uPA, and, up-regulated expression/ production of several anti-angiogenic genes/proteins, including interferon, interferon-related genes and peptide inhibitors of angiogenesis (R21 CA113950). PSA (both enzymatically active and inactive) inhibited growth of PC-3M xenografted in nude mice; the average tumor volume in PSA treated animals was 267 mm³ (n=8) vs. 423.9 mm³ (n=8) in control animals. Drs. Chadha and Smith are testing whether PSA sequestered in the prostate tissue microenvironment targets prostate endothelial cells (directly and/or indirectly) to regulate angiogenesis in CaP tissue. (Bindukumar *et al.*, J Chromatogr B Analyt Technol Biomed Life Sci 2004; 813:113; Bindukumar *et al.*, Neoplasia 2005; 7:241; Kawinski *et al.*, Prostate 2002; 50:145)

Barbara Foster, PhD

Assistant Professor, Pharmacology & Therapeutics

The Mouse Tumor Model Resource (MTMR), an integral component of the Laboratory Animal Resource (LAR) was initiated with substantial input and guidance by Dr. Foster. MTMR is heavily used by prostate program investigators as it provides access to multiple pre-clinical models of CaP, including the TRAMP mouse (Dr. Foster), the androgen-dependent CWR22 human CaP xenograft (Dr. Mohler), and the most commonly utilized CaP cell lines, including CWR22-R1, LNCaP, LNCaP-C4-2, LAPC-4, PC-3, and DU145. Dr. Foster provided scientific

expertise in the use of TRAMP to study the role for spermidine/spermine N(1)-acetyltransferase (SSAT) in collaboration with Drs. Mazurchuk (MTET) and Porter (MTET) (Kee *et al.*, *J Biol Chem* 2004; 279:40076); gene methylation in collaboration with Drs. Smiraglia (GN) and Karpf (MTET) (Morey *et al.*, *Cancer Res* 2006; 66:11659); the synergistic action of docetaxel and methylselenocysteine on *in vitro* killing of PC-3 cells using a Loewe synergism/antagonism model to determine whether the combination effect was additive, synergistic, or antagonistic, in collaboration with Dr. Rustum (MTET) (Azrak *et al.*, *Mol Cancer Ther* 2006; 5:2540); the role of the retinoblastoma protein in CaP in collaboration with Dr. Goodrich (MTET)(R01 CA70292); combinatorial targeting of CaP cells, and tumor associated pericytes, with monoclonal antibodies in combination with cyclophosphamide (CTX) metronomic (chronic low dose) chemotherapy in collaboration with Dr. Ferrone (TII)(DOD-PC061351); methylselenocysteine for chemoprevention and augmentation of chemotherapy in collaboration with Dr. Ip (CPPS); chemopreventative capability of calcitriol and a less-calcemic vitamin D analog, QW-1624F₂-2 (QW) in collaboration with Drs. Johnson and Trump (MTET); the mechanism of action of 3 C-10 non-acetal trioxane dimers (Alagbala *et al.*, *J Med Chem* 2006; 49:7836); and novel targets of CpG island hypermethylation in primary, metastatic, and castration-recurrent tumors in collaboration with Dr. Smiraglia (GN)(R21 CA121216).

Allen C. Gao, MD, PhD

Professor, Medicine

Allen Gao, MD, PhD is examining the effects of selenium on AR transactivation. Selenium inhibits AR transactivation in LNCaP cells co-transfected with a wild-type AR expression vector by suppressing the binding of AR to the androgen responsive element. These initial findings in the LNCaP cell line were replicated in 5 additional androgen-dependent and androgen-independent cell lines in collaboration with Clement Ip, PhD (CPPS). In these studies selenium reduced AR mRNA expression, decreased the stability of AR mRNA after 8h which led to increased AR protein degradation and also reduced AR nuclear translocation. CHIP analyses showed that selenium diminished recruitment of AR, and AR co-activators such as SRC-1 and TIF-2, and enhanced recruitment of AR co-repressors, such as SMRT, to the promoter of the prostate-specific antigen (PSA) gene.

(Dong *et al.*, *Cancer Res* 2004; 64:19; Dong *et al.*, *Mol Cancer Ther* 2005; 4:1047; Chun *et al.*, *Mol Cancer Ther* 2006; 5:913) (R01 CA118887)

The multifaceted disruption of AR signaling suggests that selenium may be a therapeutic agent for CaP. Treatment of mice bearing LNCaP tumors with methylselenocysteine (MSC) decreased tumor growth, tumor tissue AR expression, and serum PSA levels. A DOD funded project (DOD-PC1051131) allowed Drs. Gao and Foster to evaluate combinations of 5 α -reductase inhibitors and selenium on CaP development and growth *in vivo* using TRAMP. These pre-clinical findings provide molecular evidence in support of Dr. Marshall's (CPPS) SWOG study of selenium for the chemoprevention of CaP in men with HGPIN (R01 CA116673), and Dr. Marshall's (CPPS) project in a PO1, Selenium for CaP Treatment (P01 CA126804).

Dr. Gao has expanded his investigative focus beyond ligand-independent AR transactivation to examine how interleukins act to hypersensitize AR to low levels of tissue androgens. Hypersensitization of the AR was demonstrated *in vitro* for both IL-4 and IL-6, an effect mediated through the PI3 kinase/AKT/NF- κ B pathway for IL-4 and through the Stat3 pathway for IL-6. These findings linked IL-4 to abnormal AR activation, and suggest that clinical data showing that serum IL-4 levels are elevated in CaP patients may provide a path for AR activation in the castrate situation. IL-4 levels are correlated with serum PSA levels in men with castration-recurrent CaP. In order to test these observations experimentally (R01 CA109441), Dr. Gao established LNCaP sublines that stably over expressed IL-4. These LNCaP cells demonstrated increased androgen sensitivity, activated Stat6, NF- κ B and AR signaling, and increased LNCaP cell proliferation and tumor growth in nude mice. Stat3 stimulated the transcriptional activity of AR, glucocorticoid receptor (GR), progesterone receptor (PR) and estrogen receptor (ER) in a hormone-dependent manner and acted in a synergistic fashion with coactivators, such as SRC-1, pCAF, CBP, and TIF-2, to alter transcriptional activity of AR, GR, PR and ER (DAMD-17-01-1-0089). Stat3 enhanced the recruitment of SRC-1 and TIF-2 to the promoter of the PSA gene in LNCaP cells, which is consistent with the findings by Prostate Program members that castration-recurrent CaP changed its coactivator profile from SRC-1 to TIF-2 in the CWR22 preclinical model and in clinical samples of castration-recurrent CaP. (Lee *et al.*, *Oncogene* 2003; 22:7981; Lee *et al.*, *Prostate* 2005; 64:160; De Miguel *et al.*, *Nucl Recept* 2003; 1:3; DeMiguel *et al.*, *Prostate* 2002; 52:123)

Candace Johnson, PhD

Robert, Ann, and Lew Wallace Chair in Translational Medicine
Chair, Department of Pharmacology & Therapeutics
Associate Director for Translational Research

Drs. Johnson and Trump (MTET) established that endothelial cells isolated from multiple tumor types were sensitive to killing by 1,25 dihydroxycholecalciferol (dihydroxyvitamin D₃, calcitriol) whereas a number of endothelial cell lines (HUVEC, aortic, yolk sac derived) as well as endothelial cells freshly isolated from Matrigel® implants were not sensitive. This suggests that the antitumor effects of calcitriol may be mediated in part through inhibition of angiogenesis (RO1 CA95001). The Johnson laboratory established a method for the isolation of fresh, tumor-derived endothelial cells (TDEC) that maintained phenotypic characteristics distinct from endothelial cell lines, those isolated from normal tissues and endothelial cells isolated from vessels that invade the environment established by Matrigel® plugs (MDEC). Calcitriol inhibited the growth of TDEC at nanomolar concentrations, a physiologic concentration of calcitriol. Furthermore, the combination of calcitriol and dexamethasone had greater activity than either agent alone. Calcitriol directly inhibited TDEC proliferation at concentrations comparable to those active in inhibiting proliferation of tumor cells, suppressed cell cycle progression and survival signaling in TDECs, and affected angiogenic signaling from cancer cells to endothelial cells. These inhibitory effects of calcitriol on TDEC were evaluated by comparing the effect on TDEC to the effect on MDEC or mouse embryonic yolk sac endothelial cells (MYSEC). MYSEC were studied because MYSEC were more primitive than MDEC, were morphologically similar to TDEC, and were not stimulated by the tumor microenvironment. VDR was present, VDR structure was normal, and VDR signaling axes were intact in all 3 cell types. However, only TDEC were growth-inhibited, underwent cell cycle arrest and enhanced apoptosis in response to calcitriol (Bernardi *et al.*, *Endocrinology* 2002; 143:2508; Chung *et al.*, *Cancer Res* 2006; 66:8565; Flynn *et al.*, *Oncology* 2006; 70:447).

Pre-clinical Characterization of Vitamin D Mechanism(s) of Action. Drs. Johnson and Trump (MTET) are leaders in the characterization of the anti-cancer effects of vitamin D (RO1 CA67267, CA085142, CA095045, W81XWH0410926, R21CA112914). Calcitriol is known classically for its effects on bone and mineral metabolism, however these investigators and many others have demonstrated that calcitriol also is a potent anti-proliferative and anti-tumor agent with activity against a

wide variety of malignant cell types, including the CaP model systems PC-3, LNCaP, DU145 and MAT-LyLu. Calcitriol induces cell cycle arrest, apoptosis and differentiation, and modulated growth factor receptor-mediated signaling in these models. Calcitriol caused G₀/G₁ arrest and modulated the cyclin-dependent kinase inhibitors p21(Waf/Cip1) and p27(Kip1). Furthermore, calcitriol-induced markers of pro-apoptotic activity, including PARP cleavage, increased the bax/bcl-2 ratio, reduced levels of phosphorylated mitogen-activated protein kinases (P-MAPKs, P-Erk-1/2), phosphorylated Akt (P-Akt), induced caspase-dependent MEK cleavage and up-regulated MEKK-1. Calcitriol, combined with dexamethasone, caused a time- and dose-dependent increase in VDR protein (RO1 CA85142). The ability of dexamethasone to inhibit calcitriol-induced hypercalcemia prompted Drs. Johnson and Trump (MTET) to investigate the potential for synergistic anti-tumor effects of calcitriol + dexamethasone and chemotherapeutic agents. Calcitriol increased mitoxantrone/dexamethasone mediated growth inhibition in PC-3 cells and enhanced regression of PC-3 xenografts. Furthermore, while calcitriol exhibited potent antitumor activity, the combination of calcitriol and cisplatin demonstrated even greater activity. Co-treatment up-regulated MEKK-1, enhanced apoptotic signaling through MEKK-1 and increased caspase-3 activation more than either agent alone. (Johnson *et al.*, *Cancer Metastasis Rev* 2002; 21:147; Ahmed *et al.*, *J Urol* 2002; 168:756; Hershberger *et al.*, *Mol Cancer Ther* 2002; 1:821)

Hyung L. Kim, MD

Assistant Professor, Urologic Oncology

Dr. Kim focuses on the development of tumor vaccines based on combinations of identified tumor antigens and immuno-chaperones. Dr. Kim and collaborators identified carbonic anhydrase IX (CA9) as a prognostic marker for renal clear cell carcinoma and in an approach applicable to CaP-associated antigens is producing a highly concentrated tumor vaccine by combining in vitro CA9 and heat shock protein 110 (hsp110) (K23 CA120075). In a tumor prevention model, the hsp110 + CA9 vaccine prevented the growth of the RENCA tumor in BALB/c mice, and produced an IFN-gamma response, and in a model of metastatic RCC, where RENCA cells were injected intradermally prior to vaccination, hsp110 + CA9 vaccination decreased tumor growth. (Bui *et al.*, *J Urol* 2004; 171:2461; Kim *et al.*, *Cancer Immunol Immunother* 2006)

Khushi Matta, PhD*Professor, Cancer Biology*

Khushi Matta, PhD hypothesizes that changes in the carbohydrate chains on cancer glycoproteins and glycolipids are dictated by tissue-specific regulation of glycosyl-transferase genes, availability of sugar nucleotides and competition between enzymes for acceptor intermediates during glycan elongation. Prostate, breast, colon, ovarian and hepatic cancer cell lines are distinguished by unique carbohydrate moieties in cancer-associated glycolipids and glycoproteins, and CaP cells demonstrate unique sulfo-, fucosyl- and sialo- transferases (RO1 CA35329). Dr. Matta developed technologies to synthesize specific substrates and acceptors to characterize the activity and specificity of the diversity of enzymes responsible for cancer cell-specific glycan signatures. In addition, cancer cell-specific selectin-ligand mimetics were characterized as competitive inhibitors of cell adhesion, and cell permeable, small molecule oligosaccharides interfered with biosynthesis of functional selectin-ligands. The acceptor specificities and kinetic properties of sulfotransferases, sialyltransferases and fucosyltransferases were characterized using cloned genes and enzymes purified from LNCaP cells. Identification of unique glycan signatures on CaP cells could provide a *CaP*-specific antigen instead of a *prostate*-specific antigen for improved early detection of CaP, and the enzymes responsible for these cancer-specific carbohydrate structures could provide new therapeutic targets (DOD-PC050420, 2005-2007). (Chandrasekaran *et al.*, *Carbohydr Res* 2006; 341:983; Beauharnois *et al.*, *Biochemistry* 2005; 44:9507; Beauharnois *et al.*, *Methods Mol Biol* 2006; 347:343; Chandrasekaran *et al.*, *Glycobiology* 2002; 12:153; Chandrasekaran *et al.*, *Carbohydr Res* 2003; 338:887; Chandrasekaran *et al.*, *J Biol Chem* 2004; 279:10032; Chandrasekaran *et al.*, *Biochemistry* 2005; 44:15619; Xia *et al.*, *J Org Chem* 2006; 71:3696)

James Mohler, MD*Chair and Professor, Urologic Oncology*

Prostate cancer (CaP) is more frequent and develops approximately 5 years earlier in African Americans than Caucasian Americans. The CaP mortality rate for African Americans is 3.1 times that of Caucasian Americans in men <65 years of age, and 2.3 times that of Caucasian Americans in men \geq 65 years of age. Dr. Mohler tested the hypothesis that CaP occurs at a younger age, and progresses more rapidly, in African Americans than Caucasian Americans due to racial differences in androgenic stimulation of the prostate (P01 CA77739). African Americans and Caucasian Americans who underwent radical prostatectomy for clinically localized CaP had similar tissue levels of testosterone, dihydrotestosterone (DHT), dehydroepiandrosterone (DHEA), and DHEA sulfate (DHEA-SO₄). However, African Americans had higher androstenedione (ASD) ($p=0.006$) and steroid hormone binding globulin (SHBG) ($p=0.009$) tissue levels. Racial differences in ASD ($p=0.015$) and SHBG ($p=0.008$) persisted after controlling for age, BMI, serum PSA and pathologic Gleason sum and stage. Dr. Mohler was the first to report that tissue SHBG levels were higher (38%) in African Americans than Caucasian Americans. Higher tissue levels of SHBG may enhance androgen action in prostate tissue of African Americans through cAMP-dependent pathways. Finally, AR protein expression was evaluated in malignant and benign prostate tissue from archived radical prostatectomy specimens obtained from 25 Caucasian Americans and 25 African Americans. In African Americans, malignant nuclei were 27% more likely to be immunostained for AR ($p=0.005$), and among immunopositive nuclei, AR protein expression was 81% greater ($p=0.002$). Racial differences in AR protein expression were not explained by age, pathologic grade or stage. (Mohler *et al.*, *J Urol* 2004; 171:2277; Gaston *et al.*, *J Urol* 2003; 170:990; Singh *et al.*, The IASTED International Conference on Software Engineering 2005; 95; Singh *et al.*, *Biomed Eng Online* 2005; 4:31)

The disproportionate mortality from CaP in African Americans compared to Caucasian Americans and these data comparing androgen metabolism and AR signaling in Caucasian and African-American men provided the impetus for the DOD Prostate Cancer Research Program to fund the North Carolina-Louisiana Prostate Cancer Project (PCaP), "Racial Differences in Prostate Cancer: Influence of Health Care and Host and Tumor Biology" (DAMD17-03-2-0052). PCaP seeks to capitalize on an experiment of nature: African Americans in North Carolina have among the highest incidence of, and mor-

tality from, CaP of any population in the US while African Americans in Louisiana have moderate risk, and Caucasian Americans from either state have lower risk. PCaP will study these racial differences in CaP aggressiveness in 3 domains: 1) interaction between men with CaP and their family, friends, physicians, and health care system; 2) characteristics of the host, including diet, frequency of CaP susceptibility genes and androgen axis; 3) characteristics of the tumor itself, including cellular apoptotic and proliferation rates, AR function, and androgen-regulated gene expression. PCaP is developing a repository of interview data, biological specimens and tumor specimens from 2,000 men with newly diagnosed CaP of both races from both states. (Schroeder *et al.*, Prostate 2006; 66:1162). The results of these studies are expected to shed considerable light on the nature and genesis of these regional and racial differences in CaP incidence and mortality.

Advanced CaP is palliated by medical or surgical castration, but almost all men suffer recurrence in spite of castrate levels of circulating testicular androgens. Dr. Mohler and collaborators at the University of North Carolina showed that castration-recurrent CaP retains AR protein expression, and AR remains active in growth signaling despite castrate levels of circulating androgens. Dihydrotestosterone (DHT) levels were decreased by 91% in clinical specimens of castration-recurrent CaP (1.25 pmol/gm tissue) compared to benign prostate tissue from hormonally intact men; however, these DHT levels were sufficient to transactivate AR in most specimens of castration-recurrent CaP. This observation suggests a paradigm shift: CaP that recurs after medical or surgical castration is not "androgen-independent" because castration-recurrent CaP tissue usually has testicular androgen levels sufficient to activate AR. The sources of prostate tissue "testicular" androgen and the altered metabolism of androgens probably of adrenal origin in castration-recurrent CaP are under investigation (PO1 CA77739). (Mohler *et al.*, *CI Cancer Res* 2004; 10:440; Titus *et al.*, *CI Cancer Res* 2005; 11:4653)

Gary Smith, PhD

Distinguished Professor, Urologic Oncology

Currently available pre-clinical models of tumor angiogenesis evaluate recruitment of vessels from the mouse host into an implant of transplanted cells. These models are not predictive of the performance of anti-angiogenic agents against established vascular networks in tumors. Dr. Smith has developed a pre-clinical model of human angiogenesis, and stable human vascular networks, in primary xenografts of benign and malignant human prostate and kidney tissue. Active angiogenesis is modeled during the initial 14 days after transplantation of the surgical specimen, and a stable vascular network is present by Day 30 after transplantation (PO1 CA77739). A 5-10 fold increase in human microvessel density in the xenografts occurred between Days 8 and 14 after implantation. The presence of erythrocytes, or lectin labeling after cardiac injection, in the neo-vasculature of the xenografts demonstrated that the new vessels were patent and had anastomosed with the circulatory system of the mouse host. The wave of angiogenesis was associated with massive up-regulation of VEGF expression by the prostatic stromal compartment, apparent as early as Day 1 after transplantation, and VEGF expression remained elevated through Day 6, preceding the strong angiogenic response between Days 8-14 after transplantation. Up-regulation of HIF-1 α expression was apparent after Day 4, and was limited to the epithelial compartment. (Gray *et al.*, *Cancer Res* 2004; 64:1712)

Xiang-Yang Wang, PhD

Assistant Professor, Urologic Oncology and Cell Stress Biology

Scavenger receptors, including scavenger receptor-A (SR-A), have been identified recently as putative receptors on APCs for HSPs. Dr. Wang, in collaboration with Drs. Subjeck (CSBT) and Repasky (TII) made an unexpected discovery that lack of SR-A in SR-A knockout mice enhanced HSP chaperone vaccine-generated antitumor immunity. These studies demonstrated, for the first time, that SR-A is an immune inhibitory receptor, which can attenuate immunostimulatory activities of 'danger' molecules (e.g., HSPs) in vivo. Dr. Wang is investigating whether down-regulating, or blocking, SR-A can enhance cancer vaccine efficacy in CaP (R01 CA129111). (Wang *et al.*, *Cancer Res* 2007; 67(10): 4996-5002)

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