

## **Current research in our laboratory focuses on the following areas (updated January 2008)**

### **Prostate Cancer (CaP)**

**Purification and function of resveratrol targeting proteins, RTPs** (Drs. Hsieh and Wu). Resveratrol is a grape-derived polyphenol shown to suppress proliferation and induce apoptosis in AD and AI CaP cells, and reduce PSA expression. We hypothesize that resveratrol affects responsive CaP cells by binding and interacting with cellular proteins, denoted RTPs. An affinity approach linking resveratrol to epoxy-activated agarose forms a platform to profile, capture, and purify RTPs, which has resulted in the identification of NQO2 as an RTP in CaP cells and archived CaP tissues. We advance the central hypothesis that NQO2 functions as a mediator and/or facilitator of CaP chemoprevention by resveratrol, via operational consequences involving NQO2 interaction with other proteins, concomitant with alterations in their spatiotemporal intracellular location in responsive cells.

**Control of EMT (epithelial:stromal transition) by resveratrol in CaP** (Dr. Hsieh). Metastasis – the ability of tumor cells to breach the confines of the primary tumor site, and survive the long journey to multiple locations in the body where they establish local presence with robust growth, is considered the primary complication contributing to failure in CaP management and treatment.

The acquisition of metastasis is tightly coupled to the transformation of tumor epithelial cells to a motile, migratory phenotype, which is in part regulated in the tumor microenvironment, by epithelial-stromal cell interaction. We hypothesize that chemopreventive agents, e.g., resveratrol and green tea polyphenols act by disrupting stroma:epithelium interplay, remodeling the cytoskeleton necessary for cell motility and initiation of an epithelial-to-mesenchymal transition.

**Herbals as modulators of prostate carcinogenesis** (Drs. Hsieh and Wu). A third area of our research relates to use of botanicals and herbals as management adjuncts for CaP. Our interest in this area is based on the fact that no curative therapies currently exist for hormone-refractory prostate cancer (HRPC). We reason that failures in treating HRPC may relate to its multifactorial, multi-stage, and multi-faceted nature. It is our hypothesis that HRPC can best be managed by intervening the establishment of clinically important CaP and/or the progression of HRPC from its latent stage. Namely, postponement or total aversion of the onset of HRPC would result in a largely chronic instead of fatal CaP. Epidemiologic studies have suggested that diets and/or ethnic foods can confer protection against the transition to HRPC. The nature and mechanism of the protective agents remain largely unknown.

We are exploring botanicals/herbals as alternatives for managing/treating CaP. Our working hypothesis is that complex herbals contain multiple bioactive ingredients, each present in sub-pharmacological dosage, which, in combination, elicits coordinated changes (increases and decreases) that directly/indirectly impact the transition and/or progression to HRPC. We are currently studying several poly-herbal formulations as well as novel flavonoids purified from complex botanicals, in regards to: a) regulation of cell cycle checkpoints, b) restoration of apoptosis, and c) control of androgen receptor AR and PSA.

### **Liver Cancer (Dr. Hsieh)**

**Control of AFT gene expression in cultured human hepatoma cells by amino acid deprivation.** This research focuses on how the deprivation of specific amino acids, e.g., methionine, elicits cellular defects, exemplified by suppression of cell proliferation, induction of apoptosis and/or autophagy, and regulation of cancer-specific genes, in cultured hepatoma cells. Our current focus is the study of AFP gene expression, in the context of IGF-1 axis.

### **Breast cancer (Dr. Wu)**

**Molecular Synergy and Novel Targets of Anti-Breast Cancer Phytochemicals.** Breast cancer (BCa) is a significant cause of death in American women. Hormonal therapies and surgery both provide relief. However, treatment options are lacking when the disease relapses at local or distant sites. Choices are also limited for BCa without estrogen receptors since they are resistant to hormonal therapies but occur in 30% of primary BCa and also frequently in recurrent BCa.

Asian females have lower BCa risk, as inverse correlates of foods rich in phytochemicals. Asian women who immigrated to America have BCa risks comparable to Caucasian females, suggesting that dietary protection against BCa has been lost. The manner by which Asian diets exert their BCa-protective effect remains to be completely elucidated.

We hypothesize that traditional Asian diets contain anti-BCa phytochemicals in combination.

We propose to develop an anti-BCa cocktail using EGCG and resveratrol from tea and grape, with vitamin E derivative,  $\gamma$ -tocotrienol. These agents are likely found in abundance in Asian diets.

We hypothesize that these agents in combination, exert molecular synergy in affecting BCa growth and gene expression.

### **Cardioprotection by resveratrol (Dr. Wu, Dr. Wang and Dr. Hsieh)**

**Signaling mechanisms mediated by resveratrol in cardiovascular diseases.** Resveratrol has cardioprotective activities, stemming from the epidemiological observation known as the “French paradox”. We hypothesize that resveratrol exerts its cardioprotective effects by preserving endothelial integrity, resulting from its ability to modulate the actin-mediated cytoskeletal changes, secondary to upregulation of p38 MAPK (mitogen-activated protein kinase), MAPKAPK2 (MAPK-activated protein kinase) and HSP27; the resulting cell morphology changes afford protection against damage that may be triggered by the circumferential distending forces in disturbed flow regions and conceivably, may also reduce the severity of local thrombosis.