

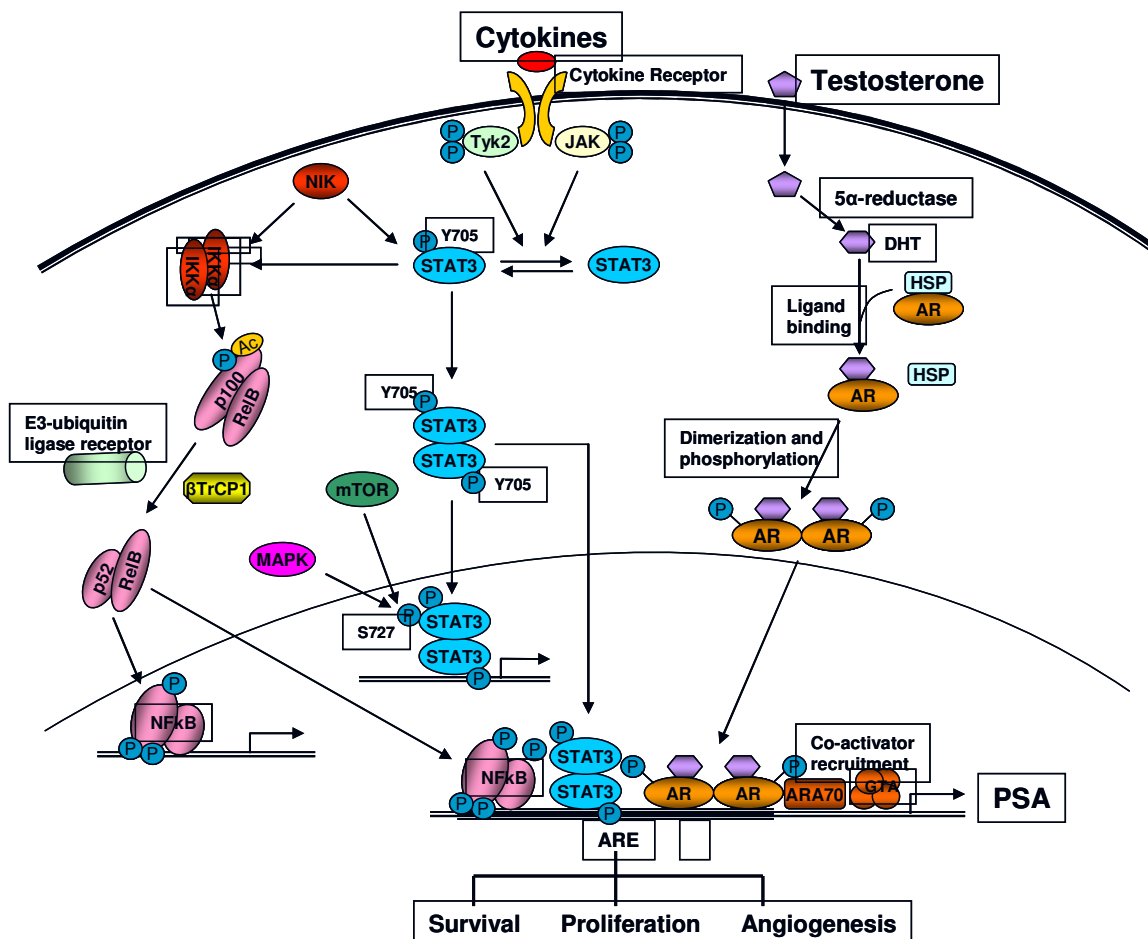
Elucidation of signalling pathways in prostate cancer

Contact Information

<p>Allen Gao, M.D., Ph.D. Professor and Director of Urologic Research Co-Leader, Prostate Cancer Program Department of Urology and Cancer Center University of California, Davis Phone: 916-734-8718 (office) Fax: 916-734-8714 Email: acgao@ucdavis.edu</p>	<p>Kate Marusina, Ph.D., MBA Manager, Industry Alliances Clinical and Translational Sciences Center UC Davis School of Medicine Phone 916-452-1827 Cell: 530-979-1522 Email: kate.marusina@ucdmc.ucdavis.edu</p>
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A major research Theme of **Prostate Cancer Program** at **UC Davis** is to study the mechanisms of aberrant activation of androgen receptor (AR) in castration resistant prostate cancer (CRPC). If this process can be understood, it will totally change all aspects of CaP therapy.

Diagram of pathways of AR activation. UC Davis Prostate Cancer Team consists experts on most of the targets in the pathway.



Drs **Gao** and **Kung** have demonstrated that interleukin-6 plays bi-functional roles during castration resistant prostate cancer progression: it induces neuroendocrine differentiation by paracrine fashion and it activates androgen receptor by autocrine fashion. Currently, these investigators are jointly investigating the mechanisms of IL-6 mediated neuroendocrine differentiation and CRPC. Strategies of targeting IL-6 signaling for treatment of CRPC are currently under investigation jointly by Drs. **Gao, Kung, Evans** and **Pan**.

Drs. **Mudryi** and **Kung** discovered that AR can be cleaved by calpain to generate a truncated AR that is missing in the LBD [ligand binding domain]. The truncated AR exhibits aberrant activation and is frequently present in castration resistant prostate cancer. Inhibition of cleavage by calpain inhibitors in Rv1 cells also inhibited tumor growth. Very interestingly, in an *in vivo* model, an HIV protease inhibitor amprenavir can prevent such AR cleavage and so stop CaP growth in nude mice.

Drs **de Vere White** and **Kung** found that *miR-125b* is differentially expressed in androgen-dependent and independent CaP cells; androgen signaling was able to upregulate the expression of *miR-125b* and stimulated the androgen receptor loading onto the 5'-region of *miR-125b*. In addition, transfection of synthetic *miR-125b* stimulated androgen-independent growth of prostate cancer cells and downregulated the expression of Bak1. These results suggest that 1) *miR-125b* acts as an oncogene in prostate cancer; 2) there is an androgen-androgen receptor-miRNA signal pathway that plays a key role in the pathogenesis of prostate cancer

In collaboration with Dr. **Kit Lam**, Dr. **Kung** developed small molecule and peptide inhibitors which inhibit Etk. These inhibitors induce autophagy and apoptosis on prostate cancer cells and block tube formation of HUVEC cells.

The group has published a number of papers on the role of p53 gain of function (GOF) as a cause of AI. This year, **Drs de Vere White and Hsing-Jien Kung** have investigated the ability of Relaxin, which is secreted by p53 GOF mutants, to support AI. The mechanism involved deals with Relaxin signaling through its receptor LGR-7 which results in B-Catenin translocation to the nucleus where it acts as a co-activator with the human androgen receptor (HAR), providing an additional pathway for the induction of hormone resistance. A p53 mutant transgenic mouse was generated for our group by Dr. **Alexander Borowsky**. The R270H p53 mutant is the equivalent of the human R273H p53 mutant. Our group has shown that the R273H mutant is one of several p53 mutants that have gain-of-function properties in CaP. One of these GOFs is to allow for AI growth of LNCaP. We have also shown a connection between this mutant and H2 relaxin. ChIP analysis revealed that the R273H p53 mutant can bind to the relaxin promoter and cause transactivation. The R270H gets PIN within 6 weeks.

AR coactivators are being pursued by a number of members in the group. Dr. **Chen's** work was addressed in the Program One Molecular Oncology narrative. Dr. de Vere White's present R01 evaluates in a yeast model the role that different CAG repeat lengths, different types of HAR receptors, different ligands and different coactivators play both in tumorigenesis and disease progression. Dr. **Gao** has demonstrated that CBP/p300 plays critical roles in cytokine-mediated AR activation and acetylation. This large body of work is completed and will be submitted for publication this year. Dr. **Ghosh** is investigating the ability of 90KDA Filamin A to

localize in the nucleus in CaP cells and thence sustain them in an androgen dependent state.

Prostate Cancer Xenograph Models

We have developed several androgen-independent prostate cancer xenograph models that can be used to screen and test potential experimental drugs.

1. IL-6 induced androgen-independent growth in LNCaP cells.

Lee SO, Chun JY, Nadiminty N, Lou W, and Gao AC. Interleukin-6 undergoes transition from growth inhibitor associated with neuroendocrine differentiation to stimulator accompanied by androgen receptor activation during LNCaP prostate cancer cell progression. *Prostate* 15;67(7):764-773, 2007.

Lee SO, Lou W, Demiguel F, Hou M, Gao AC. Interleukin-6 promotes androgen-independent growth in LNCaP human prostate cancer cells. *Clin. Cancer Res.*, 9: 370-376, 2003.

2. NF-κB induced androgen-independent growth in LNCaP cells.

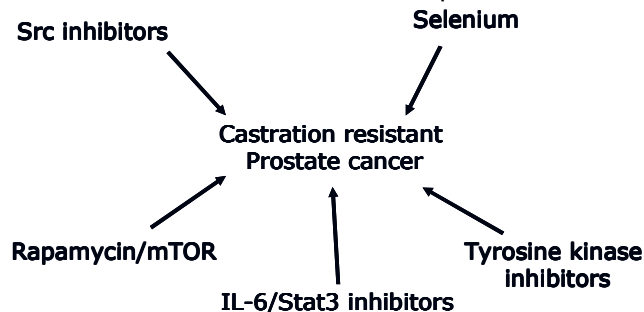
Nadiminty N, Chun JY, Lou W, Lin X, and Gao AC. NF-κB2/p52 enhances androgen-independent growth of human LNCaP cells via protection from apoptotic cell death and cell cycle arrest. *Prostate*, 68: Sept 9, 2008

3. GRP (bombesin) induced androgen-independent growth in LNCaP cells.

Yong J and Evans CP. *Cancer Res* (in press).

Targeting AR Cross-Talk Signals

UC Davis is actively engaged in finding industry partners for evaluation of small molecules and antibodies in our prostate cancer models.



In collaboration with Dr. **Chris Evans**, Dr. **Kung** tested the biological effects of Src inhibitors, PP2 and AZD0350 (Astra Zenca) and found that they inhibit cell cycle progression but in contrast to Etk inhibitor, they do not induce apoptosis. A combination of the Src and Etk inhibitors are likely to be useful as a treatment regimen. This team also developed a neuropeptide-autocrine, hormone-refractory prostate cancer model permitting the analysis of androgen-insensitivity *in vivo* and the test the efficacies of potential tyrosine kinase inhibitors. Drs. **Kung, Hongwu Chen, de Vere White and Evans** have jointly investigated the role of MAK (male germ cell-associated kinase) as a potential therapeutic target in AI.

Dr. **Ghosh** is evaluating Her2/3 inhibitors (i.e. Pertuzumab, Genetech) in prevention of CRPC. Simultaneous administration of Her3 inhibitors and castration therapy may prevent AR upregulation.

Diagram of current molecular targeting for prostate cancer at UC Davis

