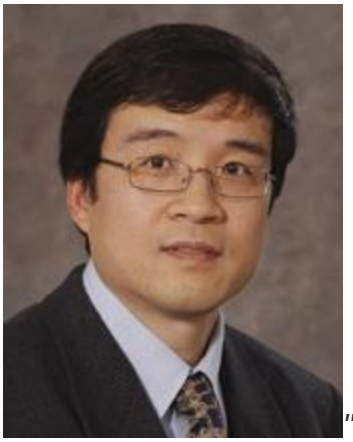
Message from the Director of Research

 *"We are the one of the largest urologic research programs in the nation with six research laboratories and over $4 million in research grants in 2014."*

Allen C. Gao, M.D., Ph.D.
Director of Research
Department of Urologic Surgery

Welcome to Urologic Research at UC Davis! We are the one of the largest urologic research programs in the nation with six research laboratories and over $4 million in research grants in 2014. We have active basic science, translational and clinical research programs in the areas of prostate, bladder, kidney, and pediatric urological diseases.

The central theme of urologic cancer research is to improve the treatment outcomes of prostate and urothelial cancers through translational research. The long-term goal of the program is to reduce mortality for advanced prostate and urothelial cancers, and improve outcomes for localized prostate and urothelial disease. We direct our research interests at three highly interactive research themes. First, to investigate mechanisms of drug resistance to current therapies. This theme is based on our long track record of research in studying castration-resistant prostate cancer (CRPC) and chemoresistance in urothelial cancer, and the translation of bench research into clinical trials. Androgen regulation is studied in mechanistic details with regards to aberrant AR activation by kinases and transcription factors, cytokines, intracrine androgens, microRNAs, and coregulations. Second, to identify molecular targets and develop therapeutic approaches. This theme was established based on our research of resistant mechanisms, research and deep sequencing of biopsy specimens to identify druggable genetic aberrations, and our patient-derived xenograft platform to assess the efficacy, study the resistant mechanisms, optimize treatment strategies, and translate these into the clinical application of precision cancer medicine. And third, to improve outcomes for localized cancers. This theme focuses on symptom self management, treatment decision support, sexual recover, social support network, and community of wellness/lifestyle of those patients with localized genitourinary malignancies. These three themes are addressed through a translational approach of preclinical models and clinical applications across disciplines that lead to mechanism-based transformative treatments for prostate and urothelial cancers to overcome resistance, optimize

response and minimize toxicity. The research programs within the Department created a mutually supportive research environment that fosters exchange and collaboration with Prostate and Urothelial Cancer Program at UC Davis Comprehensive Cancer Center.

We are actively participating in a $10 million Stand Up to Cancer Dream Team award, in a consortium including UCSF, UCLA, UC Davis, OHSU, UBC and UCSC. The grant, “Targeting Resistance Pathways in Metastatic Castration Resistant Prostate Cancer” is a 3-year award (2013-2015) with emphasis on discovery and translational science.

We have an active stem cancer program to investigate both the mechanisms and biological markers involved in cellular development. The studies on induction of human embryonic stem cells into becoming a more specialized cell type, urothelium will gain the potential of being able to regenerate a human organ such as the bladder, and obtain crucial insights into the causes of bladder cancer.

Research Highlights and Major Discoveries

- Anti-androgen therapies: We have identified several novel resistance mechanisms including AR-V7, AKR1C3, autophagy, IL6/Stat3, and miRNAs. Efforts are devoted to targeting these mechanisms. Clinical trials are currently being developed to target AR-V7 using niclosamide, and to target AKR1C3 using indomethacin to improve enzalutamide therapy for CRPC patients, which is supported by DOD IMPACT award.
- We discovered that niclosamide, an FDA approved medicine commonly prescribed to fight parasitic worms, is a potent inhibitor of AR-V7, and can dramatically enhances the efficacy of anti-androgen drugs such as enzalutamide and abiraterone (*Clin Cancer Res 2014, Oncotargets 2016)*. In animal models, when enzalutamide or abiraterone and niclosamide were given concurrently, AR-V7 expression was inhibited, staving off resistance to enzalutamide and abiraterone. These findings provide a warrant for investigation of niclosamide in patients with enzalutamide/abiraterone resistant CRPC. Based on these encouraging preclinical data, we have reformulate niclosamide and received IND approval for phase I/II clinical trials in CRPC patients, which are currently undergoing at UC Davis.
- We found that intracrine androgens and AKR1C3 are active in enzalutamide resistant cells in vitro and in vivo. Indomethacin can inhibit AKR1C3 activity and significantly inhibits enzalutamide resistant tumor cell growth. While indomethacin alone significantly suppressed tumor growth, the effect was further enhanced in combination with enzalutamide (*Cancer Res 2015*). Clinical trials to test targeting AKR1C3 pathways with indomethacin to improve enzalutamide therapy are currently under investigation at UC Davis, which is supported by DOD IMPACT award.
- We demonstrated that in mice orthotopically implanted with enzalutamide resistant cells, the combination of enzalutamide with metformin significantly reduced tumor growth when compared to the control groups. Our preclinical data have been translated into a Phase I-II trial of enzalutamide with

metformin, integrated into the SU2C West Coast Dream Team award. Bone marrow biopsies of patients with an AR gene signature will be used as an integrated biomarker.

- Targeting ABCB1 to overcome resistance to docetaxel. Docetaxel is currently the first-line chemotherapy for CRPC, however, docetaxel resistance rapidly develops. Identifying the critical mechanisms giving rise to docetaxel resistance is the major challenge in advanced prostate cancer. We found that ABCB1 was upregulated in docetaxel-resistant CRPC cells. Knockdown of ABCB1 genetically or with apigenin, a natural product of the flavone family that was identified as an inhibitor of ABCB1 expression, resensitized these cells to docetaxel treatment by enhancing apoptotic cell death (*Mol Can Ther 2013*). We further demonstrated that enzalutamide and bicalutamide could reverse ABCB1-mediated docetaxel resistance. The combination of bicalutamide with docetaxel had a significant anti-tumor effect in both AR-positive and AR-negative docetaxel resistant xenograft models (*Clin Cancer Res 2015*). We are currently testing if the combination of apigenin or bicalutamide with docetaxel could improve docetaxel treatment in CRPC.

New target makes end run against therapy-resistant prostate cancer

Date:

March 28, 2016

Source:

University of California - Davis Health System

Summary:

Suppressing the nuclear receptor protein ROR-?; with small-molecule compounds can reduce androgen receptor (AR) levels in castration-resistant prostate cancer and stop tumor growth, scientists have found.

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FULL STORY

Researchers at UC Davis, in collaboration with the other institutions, have found that suppressing the nuclear receptor protein ROR-γ with small-molecule compounds can reduce androgen receptor (AR) levels in castration-resistant prostate cancer and stop tumor growth.

This novel approach does not directly target the AR, but rather inhibits the gene that codes for the AR protein. Reducing AR levels could help patients overcome treatment-resistant prostate cancer and even rescue existing therapies. The research was published in the journal *Nature Medicine*.

"This is a new target and a totally new way of hitting prostate cancer," said Hongwu Chen, a professor in the Department of Biochemistry and Molecular Medicine and lead author on the paper. "This strategy targets the root cause of the problem -- the overexpression of the AR gene and its protein."

In the vast majority of prostate cancers, the AR gene becomes hyperactive, driving tumor growth and metastasis. Anti-androgen therapies can slow, and even stop, prostate cancer -- for a time. But quite often the gene mutates to resist the treatment.

However, suppressing ROR-γ circumvents this resistance. Because the protein is required for AR gene expression, ROR-γ inhibition strongly reduces AR protein levels in tumor cells. By preventing AR protein synthesis, ROR-γ antagonists can potentially short-circuit the resistance process.

"Essentially all existing therapies work on blocking either activation of the AR or the genes it regulates," said Christopher P. Evans, professor and chairman of the Department of Urology and a co-author of the study. "However, as patients become resistant to existing agents, the AR becomes mutated, amplified and spliced. This (ROR-γ suppression) mechanism blocks the actual expression of the AR and its spliced forms."

To illuminate the relationship between ROR-γ and the AR gene, Chen's team studied a number of small molecule ROR-γ antagonists, both in cell lines and human tumors in mice. In each model, suppressing ROR-γ reduced AR gene expression and AR protein levels, blocking tumor growth. These inhibitors showed broad effectiveness, inhibiting several AR variants, including AR-V7, which has been linked to resistance to advanced prostate cancer therapies enzalutamide and abiraterone.

"Blocking ROR-γ re-sensitizes castration-resistant prostate cancer to drugs that directly inhibit AR pathway signaling, such as enzalutamide," said Evans. "A combination approach can potentially be very effective."

In addition to reducing AR levels, ROR-γ suppression also can reduce the prevalence of several known oncogenes.

"ROR-γ suppression is quite remarkable," said the study's first author, Junjian Wang, a project scientist in the Department of Biochemistry and Molecular Medicine. "It can reduce levels of ERG and MYC, which are known to drive prostate cancer."

While ROR-γ was previously neglected in cancer research, it has been widely targeted for autoimmune diseases. As a result, there are a number of ROR-γ antagonists in the pipeline. These drugs could be retasked to fight prostate and possibly other cancers.

"ROR-γ has been extensively studied as a target for rheumatoid arthritis, inflammatory bowel disease, psoriasis and other autoimmune conditions," noted Chen. "Some of the drugs are orally available and have been found to be safe in early clinical trials. They could be a great help for patients with advanced prostate cancer."

Story Source:

Materials provided by **University of California - Davis Health System**. *Note: Content may be edited for style and length*