

## When Flutamide Stops Working: MAP Kinase Stimulation of Prostate Cancer Growth

### New Discoveries About Hormonal Therapy Failure in Treatment of Prostate Cancer

by J. STRAX

PSA Rising, New York, November 5, 2002 -- Scientists have discovered that the antiandrogen drug Flutamide, widely used to treat prostate cancer, actually switches on a non-hormonal molecule known to cause cancerous cells to grow and proliferate. This work, which earned an award from the American Urological Association, is described in the [November 1 issue of the journal Cancer Research](#). The authors says that their discovery "raises a concern for using [Flutamide] in the complete-androgen-ablation therapy in prostate cancer treatment and provides a possible pathway that might contribute to the [Flutamide] withdrawal syndrome."

"It's a real surprise, that the same compound that kills cancer cells also makes them grow," says Chawnshang Chang, Ph.D., corresponding author and director of the George Whipple Laboratory for Cancer Research at the University of Rochester Medical Center. "The effect of the drug reverses completely."

When prostate cancers first occur, they are dependent on androgens for growth and can be treated successfully with androgen ablation therapy. However, after prolonged antiandrogen therapy, eventually the cancer acquires the ability to proliferate. Finding out exactly how this happens is a key step to prevention and better treatment.

In 1998 Chang found molecular evidence of how antiandrogen drugs, which up to a point can halt the disease, under certain conditions can spur prostate-cancer cells to grow. Working with George Wilding of University of Wisconsin Comprehensive Cancer Center he reported that antiandrogens, hydroxyflutamide, (Flutamide) bicalutamide (Casodex), cyproterone acetate and other compounds such as genistein and RU486,



*Chawnshang Chang*

George Hoyt Whipple Professor of Pathology and Laboratory Medicine, Professor of Urology and of Radiation Oncology, U of Rochester Med Center

### BACKGROUND

[Androgen Deprivation Strategies for the Treatment of Recurrent and Metastatic Prostate Cancer](#), Cancer Medicine, Denmeade and Isaacs

Flutamide withdrawal  
[Prostate specific antigen decline after antiandrogen withdrawal: the flutamide withdrawal syndrome](#). Kelly & Scher, *J Urol* 1993 Reported falls in PSA after Flutamide was stopped.

"can promote the interaction between the androgen receptor (AR) and its coactivator."

He went on to show that [HER2/Neu oncogene could increase growth rate and raise PSA](#) "at a very low androgen concentration, a condition very similar to the prostate cancer patients undergoing androgen ablation therapy." At that time the researchers looked to see if Flutamide, widely used in androgen ablation therapy, could block this action of Her2/Neu, and found it could not.

In the most recent work on this problem of how anti-androgens fail, Yi-Fen Lee, Ph.D., now an assistant professor in the Department of Urology at Rochester, studied cancer cells from four men, comparing the cells from early in their disease to cells after hormonal therapy became ineffective. Chang and Lee's award-winning research found that, in addition to blocking uptake of testosterone by targeting a protein known as the androgen receptor, Flutamide switches on a molecule known as mitogen-activated protein (MAP) kinase. It is a signaling molecule which promotes cell growth and is known to play a role in diseases like breast and prostate cancer. Chang and Lee found it in much higher levels in the prostate cancer cells that had survived hormone therapy. Incidentally, this effect is not confined to chemical drugs. . Biopsies of men who had undergone orchiectomy (surgical castration) found that the reatment switched on the cancer-promoting molecule, (MAP) kinase.

"In all of the more than 30,000 men who die of prostate cancer each year, the cancer cells have become capable of growing even when we starve the cells of testosterone," says Edward Messing, M.D., professor and chair of urology who treats hundreds of men for prostate cancer each year.

"In each one of those men, there's been a fundamental change, so that the molecule we've targeted for stopping the cancer is no longer involved in the disease. It's at this point that the disease becomes a killer. Finding an additional potential target for preventing this switch is surprising and significant."

Despite the drawbacks, the scientists stress that current treatment, including hormonal therapy, is still the best option available for patients whose cancer has spread beyond the prostate gland. "These drugs are necessary for patients who otherwise have few options," says Lee. "However, these findings do raise some concerns that should be investigated further. Perhaps these findings will help lead to a new drug target so that men with this disease can be treated more effectively."

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*The project was done by Chang, Lee, Lin, Messing and Jiaoti Huang, Ph.D.,*

[The antiandrogen withdrawal syndrome in relapsed prostate cancer.](#) Scher & Kolvenbag, *Eur Urol.* 1997.

#### MAP Kinase and Cancer

[Discovery of Elevated MAP kinase in breast cancer](#) (Stonybrook, 1997)

[Blockade of Signal Transduction through MAP Kinase Pathway Presents a Novel Potential Anti-cancer Agents](#) iHumans.com

[Mitogen-Activated Protein Kinase Kinase Kinase 1 Activates Androgen Receptor-Dependent Transcription and Apoptosis in Prostate Cancer](#) Mol Cell Biol 1999 Jul Free full text article

#### The Androgen Receptor

[Map of Androgen Receptor Gene Mutations in Prostate Cancer](#)

[The Androgen Receptor in Prostate Cancer](#) brief article and graphics at Erasmus MC

[Lessons to be Learned from the Androgen Receptor](#) A. O. Brinkmann

[Androgen Receptor Gene and Prostate Cancer](#) Rovshan Ismailov, MD, MPH University of Pittsburgh

[Androgen Receptor Action](#) Oulu University Library

*assistant professor of pathology and laboratory medicine at The Cancer Center, University of Rochester Medical Center, Rochester, NY; Franky Chan of the Chinese University of Hong Kong; and medical oncologist George Wilding of the University of Wisconsin. The research was funded by the National Institutes of Health.*

*Read the Abstract:* Cancer Res 2002 Nov 1;62(21):6039-44 **Activation of Mitogen-activated Protein Kinase Pathway by the Antiandrogen Hydroxyflutamide in Androgen Receptor-negative Prostate Cancer Cells.** Lee YF, Lin WJ, Huang J, Messing EM, Chan FL, Wilding G, Chang C. George Whipple Laboratory for Cancer Research, Departments of Pathology, Urology, Radiation Oncology, and The Cancer Center, University of Rochester Medical Center, Rochester, New York 14642

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*FREE FULL TEXT:* Cancer Res 1999 Jan 15;59(2):279-84 **Activation of mitogen-activated protein kinase associated with prostate cancer progression.** Gioeli D, Mandell JW, Petroni GR, Frierson HF Jr, Weber MJ. Department of Microbiology and Cancer Center, University of Virginia Health Sciences Center, Charlottesville 22908, USA.

Life Sci 2002 Sep 27;71(19):2257-66 **Regulation of the expression of protein kinase C isoenzymes in rat ventral prostate: effects of age, castration and flutamide treatment.** Montalvo L, Sanchez-Chapado M, Prieto JC, Carmena MJ. Department of Biochemistry and Molecular Biology, University of Alcala, E-28871 Alcala de Henares, Spain.

FREE FULL TEXT: PNAS May 11, 1999 Vol. 96, Issue 10, 5458-5463 **From HER2/Neu signal cascade to androgen receptor and its coactivators: A novel pathway by induction of androgen target genes through MAP kinase in prostate cancer cells** Shuyuan Yeh, Hui-Kuan Lin, Hong-Yo Kang, Tin Htwe Thin, Ming-Fong Lin, and Chawnshang Chang. George Whipple Laboratory for Cancer Research, Departments of Pathology, Urology, Radiation Oncology, and The Cancer Center, University of Rochester, Rochester, NY 14642; and Department of Biochemistry and Molecular Biology, University of Nebraska Medical Center, Omaha, NE 68198

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## Cancer drug mystery solved

BY STAFF WRITER  
MICHAEL WENTZEL

University of Rochester scientists have discovered why a treatment for men with prostate cancer loses its effectiveness against the disease.

A drug that blocks the hormone that feeds the cancer eventually activates a protein that causes cancer cells to grow.

"The drug does good work at first but then, instead of suppressing, it stimulates prostate cancer growth," said Chawnschang Chang, director of the George Whipple Laboratory for Cancer Research at the University of Rochester Medical Center.

The findings, published this month in the journal *Cancer Research*, could provide a target for new drugs.

"No one had recognized that this process could even occur," said Dr. Edward Messing, chairman of UR's Department of Urology.

"This is another trick the



**Chawnschang Chang** is director of cancer research lab at UR Medical Center.



**Yi-Fen Lee** helped to track prostate cancer drug's double nature.

cells have. If we could understand the mechanism, we could work on drugs that would stop the trigger."

The university has applied for a patent on the concept and molecular pathways described in the research by Chang, Yi-Fen Lee, a UR assistant professor of urology, Wen-Jye Lin, a graduate student, and others.

Prostate cancer cells usually depend on the hormone testosterone for survival. To treat the disease when it has spread out of the prostate to other parts of the body, doctors use surgery and radiation to knock out the supply of the hormone.

In many cases, treatment also includes a drug known as an anti-androgen, which

blocks the molecule through which testosterone works, the androgen receptor.

"Somehow during the course of this treatment, the disease reoccurs," Messing said.

"This is true in almost every case. When it reoccurs, we stop anti-androgen and paradoxically the patients get better, but only for a period of time."

Chang and Lee studied a drug called hydroxyflutamide. Lee initially compared cancer cells from four men early in their disease with cells after hormonal therapy became ineffective. The team found a molecule known as MAP kinase at much higher levels in the cells that had survived hormone therapy.

This kinase promotes tumor cell growth and is known to play a role in several cancers. In cell studies in the lab, Lee and the team found hydroxyflutamide turned on MAP kinase in prostate cancer cells.

Surprisingly, the drug acted on cells independent of the androgen receptor, routinely believed to be its primary path.

In spite of the research findings, the scientists said hormonal therapy still is the best treatment for patients whose prostate cancer has spread.

"These drugs are necessary for patients who otherwise have few options," Lee said.

"Perhaps these findings will help lead to a new drug target so that men with this disease can be treated more effectively."

The work by the UR scientists earned an award for outstanding research recently from the American Urological Association. □

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