



## Scientists Find One Reason Why Bladder Cancer Hits More Men

April 17, 2007

Scientists have discovered one of the reasons why bladder cancer is so much more prevalent in men than women: A molecular receptor or protein that is much more active in men than women plays a role in the development of the disease. The finding could open the door to new types of treatment with the disease.

In an article in the April 4 issue of the *Journal of the National Cancer Institute*, **Chawnsang Chang, Ph.D.**, of the University of Rochester Medical Center and colleagues show that the androgen receptor, which is central to the action of testosterone and other hormones that are much more plentiful in men than women, appears to play a key role in the disease.

In experiments reported in the journal, mice without the receptor had dramatically lower rates of bladder cancer compared to normal mice with the receptor, and human cancer cells with the receptor were much more aggressive than those without it. Mice develop bladder cancer for many of the same reasons people do, and the molecular signals that control cancer development in mice mirror those in humans.

The disease hits about three times as many men as women, including estimates of 50,000 men and 17,000 women in the United States in 2007, according to the American Cancer Society. Some scientists have suspected that male hormones working in concert with the androgen receptor might play a role, but hard evidence has been minimal until now, said **Edward Messing, M.D.**, a bladder cancer expert and chair of Urology. Instead, scientists have suspected that factors like greater exposure of men to cigarettes and industrial chemicals has been responsible.

"For many years, people have recognized that men are more likely than women to get bladder cancer," said Messing, one of the authors of the paper. "More and more women are smoking and working with chemicals in the workplace, yet their bladder cancer rates have not really changed much. There is no longer any question that the androgen receptor is playing a role in bladder cancer."

The work by a team of collaborators from Rochester and from Yokohama City University Graduate School of Medicine in Japan was led by Chang, director of the George Whipple Laboratory for Cancer Research at the University of Rochester Medical Center and a faculty member in the departments of Urology and Pathology and the James P. Wilmot Cancer Center.

Chang is an expert on the androgen receptor, which is central to many diseases and conditions, most notably prostate cancer. For that disease, hormone therapy to block the supply of hormones that turn on the receptor is a staple of treatment for men with advanced disease. The new findings open the possibility that perhaps someday, drugs that target male hormones, like those used against prostate cancer, might help men with bladder cancer.

The strongest evidence for the involvement of male hormones in bladder cancer was what happened when Chang's team disabled the androgen receptor in mice. While their normal counterparts with the androgen receptor got significant levels of bladder cancer when exposed to a carcinogen – 92 percent of the males and 42 percent of the females – not a single mouse whose androgen receptor was knocked out developed bladder cancer. The mice without the receptor also had significantly fewer premalignant changes in their bladder.

Besides opening the door to possible new treatments, Chang says the findings could help doctors decide which cases of bladder cancer are most likely to re-occur. His team found a correlation between the frequency of the androgen receptor in tumor cells and the recurrence of the tumor – tumors more likely to re-appear had more of the protein. If the finding holds up in wider testing in human tumors, it would help doctors know which patients to treat aggressively right from the start.

The *JNCI* paper is the latest installment in a body of research Chang has compiled that shows that the story of the androgen receptor and male hormones like testosterone is much more complex than was once thought. For years it's been widely thought by doctors and scientists that all male hormones, and only male hormones, work through the androgen receptor.

But he felt there was more to the story. If anyone would know, it would be Chang, who in 1988 was the first

person to clone the androgen receptor, and was the first to discover that the protein needs molecular allies called co-factors to accomplish many of its tasks. Now more than 80 co-factors are known, offering many new targets to stop conditions like male-pattern baldness and diseases like prostate cancer.

Nearly a decade ago, Chang showed that molecules other than male hormones like testosterone are able to activate the androgen receptor. That finding isn't simply gathering dust in textbooks; it likely explains why hormone therapy for men in the advanced stages of prostate cancer ultimately fails. His work explained a long-baffling phenomenon in these patients, where drugs that work well for a few years suddenly make the cancer grow again late in the course of the disease.

In the recent paper, Chang continued this line of work, only in bladder cancer instead of prostate cancer. He took a closer look at the nearly disease-free male mice that didn't get bladder cancer despite exposure to a carcinogen. Some of those mice then received a drug known as DHT, a male hormone. In theory, such a drug only works if the androgen receptor is present, so the drug should not have had an effect. But 25 percent of these mice then got bladder cancer, clear evidence that the hormone is able to somehow side-step the traditional, receptor-mediated, pathway and still have an effect.

The work shows starkly that simply cutting off the supply of hormones like testosterone will have only a limited effect. The androgen receptor can still play a crucial role in the development of cancer, even without the hormones. The team has shown in other studies that even female hormones such as estrogen can turn on the androgen receptor.

"The activity of the androgen receptor is different from the activity of hormones that target the receptor," said Chang. "We've shown very clearly that even without these hormones, the receptor is still active in the development of cancer. This is crucial information as doctors seek to develop treatments for diseases like prostate or bladder cancer in men."

To knock out the androgen receptor, the team used a compound known as ASC-J9, a synthetic chemical compound that is loosely based on a compound found in curcumin. Chang's laboratory, in collaboration with San Diego-based AndroScience Corp., has screened hundreds of compounds for their activity involving the androgen receptor. Just last month, the team showed that ASC-J9 offers promise against a rare neuromuscular disease known as Kennedy's disease.

The compound is now being tested as a cream to treat acne in a clinical trial run by AndroScience, a biotech company founded by Chang, Charles C-Y Shih, and Por-Hsiung Lai in 2000. The University owns a stake in the company, which has licensed several of Chang's research findings.

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Other authors of the paper, in addition to Chang and Messing, are Zhiming Yang, a former graduate student now at Zhejiang University and 2<sup>nd</sup> Hospital in Hangzhou, China; Yei-Tsung Chen and Yueh-Chiang Hu, former graduate students and now researchers at Harvard; Yu-Jia Chang, formerly a post-doctoral researcher with Chang, now an assistant professor at Taipei Medical University and Hospital in Taipei, Taiwan; former graduate student Meng-Yin Tsai, now at Chang Gung Memorial Hospital in Kaohsiung, Taiwan; and Shuyuan Yeh, associate professor of Urology.

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### One Reason Why Bladder Cancer Hits More Men Than Women

*ScienceDaily (Apr. 23, 2007)* — Scientists have discovered one of the reasons why bladder cancer is so much more prevalent in men than women: A molecular receptor or protein that is much more active in men than women plays a role in the development of the disease. The finding could open the door to new types of treatment with the disease.

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"For many years, people have recognized that men are more likely than women to get bladder cancer," said Messing, one of the authors of the paper. "More and more women are smoking and working with chemicals in the workplace, yet their bladder cancer rates have not really changed much. There is no longer any question that the androgen receptor is playing a role in bladder cancer."

The work by a team of collaborators from Rochester and from

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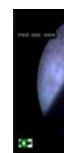
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Chang is an expert on the androgen receptor, which is central to many diseases and conditions, most notably prostate cancer. For that disease, hormone therapy to block the supply of hormones that turn on the receptor is a staple of treatment for men with advanced disease. The new findings open the possibility that perhaps someday, drugs that target male hormones, like those used against prostate cancer, might help men with bladder cancer.

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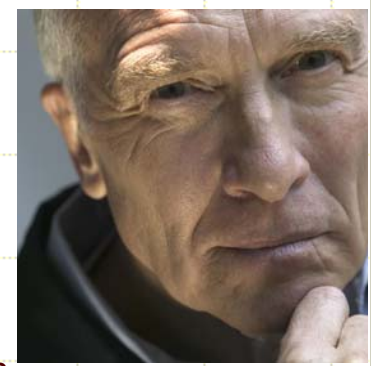
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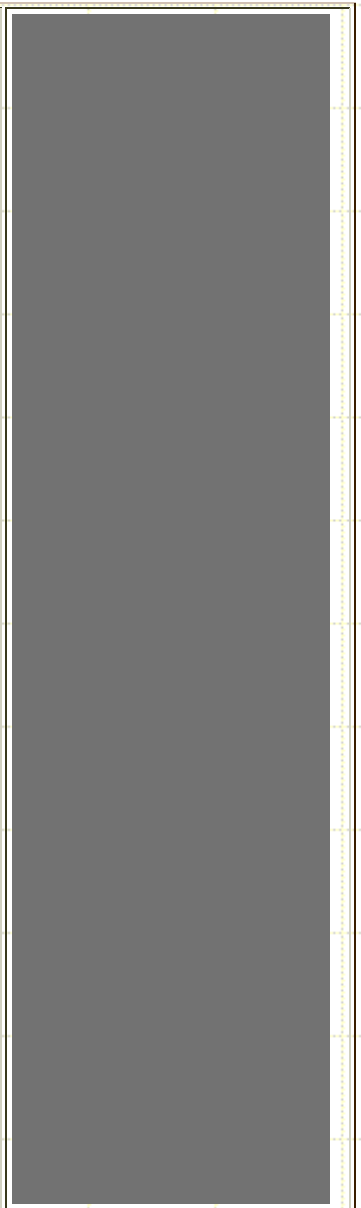
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"For many years, people have recognized that men are more likely than women to get bladder cancer," said Messing, one of the authors of the paper. "More and more women are smoking and working with chemicals in the workplace, yet their bladder cancer rates have not really changed much. There is no longer any question that the androgen receptor is playing a role in bladder cancer."

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| Non-Invasive Detection       |  | But he felt there was more to the story. If anyone would know, it would be Chang, who in 1988 was the first person to clone the androgen receptor, and was the first to discover that the protein needs molecular allies called co-factors to accomplish many of its tasks.   |  |
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| Preventing Cancer            |  | In the recent paper, Chang continued this line of work, only in bladder cancer instead of prostate cancer. He took a closer look at the nearly disease-free male mice that didn't get bladder cancer despite exposure to a carcinogen. Some of those mice then received a drug known as DHT, a male hormone. In theory, such a drug only works if the androgen receptor is present, so the drug should not have had an effect. But 25 percent of these mice then got bladder cancer, clear evidence that the hormone is able to somehow side-step the traditional, receptor-mediated, pathway and still have an effect. |  |
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| Prostate Cancer News         |  | The work shows starkly that simply cutting off the supply of hormones like testosterone will have only a limited effect. The androgen receptor can still play a crucial role in the development of cancer, even without the hormones. The team has shown in other studies that even female hormones such as estrogen can turn on the androgen receptor.   |  |
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|                          |  |   |  |
|--------------------------|--|---|--|
| Screening Benefit        |  | clearly that even without these hormones, the receptor is still active in the development of cancer. This is crucial information as doctors seek to develop treatments for diseases like prostate or bladder cancer in men."  |  |
| Screening Importance     |  |   |  |
| Self-Fulfilling Prophecy |  |   |  |
| Skin Cancer News         |  |   |  |
| Smelling Cancer?         |  |   |  |
| Historic 'Brain Trust'   |  |   |  |
| Smoking Hurts Recovery   |  | To knock out the androgen receptor, the team used a compound known as ASC-J9, a synthetic chemical compound that is loosely based on a compound found in curcumin. Chang's laboratory, in collaboration with San Diego-based AndroScience Corp., has screened hundreds of compounds for their activity involving the androgen receptor. Just last month, the team showed that ASC-J9 offers promise against a rare neuromuscular disease known as Kennedy's disease.  |  |
| Soy Helps                |  |   |  |
| Spicing Up Cancer Fight  |  |   |  |
| Stat3 Protein Link       |  |   |  |
| Stomp Out Cancer         |  |   |  |
| Stopping Metastasis      |  |   |  |
| Stop Stomach Cancer      |  |   |  |
| Stress & Cancer          |  |   |  |
| Stress, Cervical Cancer  |  | The compound is now being tested as a cream to treat acne in a clinical trial run by AndroScience, a biotech company founded by Chang, Charles C-Y Shih, and Por-Hsiung Lai in 2000. The University owns a stake in the company, which has licensed several of Chang's research findings.   |  |
| Surgery Best Option      |  |   |  |
| Surgery Delay Deadly     |  |   |  |
| Survivors' Music         |  |   |  |
| Survival Priority        |  |   |  |
| Spouses Impacted         |  |   |  |
| Standup2Cancer           |  | ###   |  |
| Survivor Transition      |  |   |  |
| Survivor Depression      |  | The first author of the paper is Hiroshi Miyamoto, M.D., Ph.D., who was a post-doctoral researcher in Chang's laboratory and is now a medical resident in the Department of Pathology and Laboratory Medicine. Miyamoto was joined by several of his former colleagues at Yokohama City University Graduate School of Medicine in Yokohama, Japan, who did much of the work with the human bladder cancer cell lines and analyzed levels of the androgen receptors. Collaborators there include Hitoshi Ishiguro, Hiroji Uemura, Yoshinobu Kubota, and Yoji Nagashima.        |  |
| Take Part in Program     |  |   |  |
| Theismann on Prostate    |  |   |  |
| Tea Helps Skin           |  |   |  |
| Test for Cancer Cure     |  |   |  |
| Thyroid Cancer Increase  |  |   |  |
| Tips in Recovery         |  |   |  |
| Toad Venom               |  |   |  |
| Tongue Cancer            |  |   |  |
| Treat Bladder Cancer     |  |   |  |
| Treatment Doubts         |  |   |  |
| Treating Cancer Spread   |  |   |  |
| Treatment Barrier        |  |   |  |
| Treatment Differences    |  |   |  |
| Treatment Risk           |  |   |  |
| Trials Started           |  | Other authors of the paper, in addition to Chang and Messing, are Zhiming Yang, a former graduate student now at Zhejiang University and 2nd Hospital in Hangzhou, China; Yei-Tsung Chen and Yueh-Chiang Hu, former graduate students and now researchers at Harvard; Yu-Jia Chang, formerly a post-doctoral researcher with Chang, now an assistant professor at Taipei Medical University and Hospital in Taipei, Taiwan; former graduate student Meng-Yin Tsai, now at Chang Gung Memorial Hospital in Kaohsiung, Taiwan; and Shuyuan Yeh, associate professor of Urology. |  |
| Tumor Blocker            |  |   |  |
| Tumors Can't Hide        |  |   |  |
| Unsubstantiated Claims   |  |   |  |

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### Testosterone Induces Three Times More Bladder Cancer in Men than Women

By **Stefan Anitei**, Science Editor  
 23rd of April 2007, 10:40 GMT  
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Bladder cancer turns into a nightmare the life of its victims, triggering excruciating piss problems. The disease affects about three times as many men as women: 50,000 men are estimated to develop it this year compared to 17,000 women in the US.

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Now a team led by Dr Chawnshang Chang, of the [University of Rochester](#) Medical Center can explain why: this cancer development appears to be determined by the testosterone molecular receptor protein, which is much more active in men than women.

Mice with the receptor removed displayed dramatically lower percentages of bladder cancer than normal mice, and human [cancer cells](#) with the receptor intact were much more active than those lacking it. Mice get bladder cancer for the same reasons as women.

"Some scientists have suspected that male hormones working in concert with the androgen receptor might play a role, but hard evidence has been minimal until now," said co-author Dr. Edward Messing, a bladder cancer expert and Chair of Urology.

Rather hard smoking and industrial chemicals have been blamed till now. "More and more women are smoking and working with chemicals in the workplace, yet their bladder cancer rates have not really changed much. There is no longer any question that the androgen receptor is playing a role in bladder cancer." said Messing.

Androgen receptor triggers many other diseases and conditions, most known being the prostate cancer. Perhaps chemicals used against prostate cancer could work with bladder cancer.

Normal mice exposed to cancer-inducing chemicals got high levels of bladder

cancer: 92 % of the males and 42 % of the females, while in the case of engineered mice lacking the protein not a single individual developed bladder cancer, and they also displayed much less premalignant changes in their bladder.

"The findings could help doctors decide which cases of bladder cancer are most likely to re-occur." said Chang.

Cancer tumors were more likely to re-appear if the receptor protein was more abundant.

Some of those mice lacking the receptor received DHT, a male hormone drug. 25 % of these mice got bladder cancer, thus the hormone can elude receptor pathway to inflict an effect.

Simply cutting off the testosterone supply will have only a limited effect. Other researches revealed that even estrogen (female sex hormone) can activate the androgen receptor.

"The activity of the androgen receptor is different from the activity of hormones that target the receptor. We've shown very clearly that even without these hormones, the receptor is still active in the development of cancer. This is crucial information as doctors seek to develop treatments for diseases like prostate or bladder cancer in men." said Chang.

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### Bladder Cancer Linked To Androgens And Androgen Receptor In Mice

*ScienceDaily* (Apr. 5, 2007) — Male sex hormones and their receptors may be involved in the development and progression of bladder cancer, according to a study in mice published in the April 4 Journal of the National Cancer Institute.

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Men have a considerably higher incidence of bladder cancer than women, though the reasons remain a mystery. Bladder cancer has been linked to exposure to cigarette smoke and industrial chemicals, but it was not previously considered to be influenced by male sex hormones, called androgens.

Chawnschang Chang, Ph.D., of the University of Rochester Medical Center in Rochester, N.Y., used a chemical carcinogen to induce bladder cancer in normal male and female mice and in mice lacking functional androgen receptors. They also treated human bladder cancer cell lines to reduce androgen levels or androgen receptor activity. Some

of these cell lines were injected into mice.

None of the androgen receptor-free mice developed bladder cancer when treated with the carcinogen, whereas more than 92 percent of the normal male mice and 42 percent of the normal female mice did. Human bladder cancer cells with reduced androgen levels or androgen receptor activity grew more slowly in culture and in mice than cells with normal androgen and androgen receptor levels.

"The results presented here have the potential to provide the basis for the development of new preventive or therapeutic approaches for bladder cancer, via targeting androgens and the [androgen receptor]," the authors write.

Note: The Journal of the National Cancer Institute is published by Oxford University Press and is not affiliated with the National Cancer Institute.

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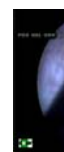
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## One Reason Why Bladder Cancer Hits More Men

21 Apr 2007 [Click to Print](#)

Scientists have discovered one of the reasons why bladder cancer is so much more prevalent in men than women: A molecular receptor or protein that is much more active in men than women plays a role in the development of the disease. The finding could open the door to new types of treatment with the disease.

In an article in the *Journal of the National Cancer Institute*, Chawnshang Chang, Ph.D., of the University of Rochester Medical Center and colleagues show that the androgen receptor, which is central to the action of testosterone and other hormones that are much more plentiful in men than women, appears to play a key role in the disease.

In experiments reported in the journal, mice without the receptor had dramatically lower rates of bladder cancer compared to normal mice with the receptor, and human cancer cells with the receptor were much more aggressive than those without it. Mice develop bladder cancer for many of the same reasons people do, and the molecular signals that control cancer development in mice mirror those in humans.

The disease hits about three times as many men as women, including estimates of 50,000 men and 17,000 women in the United States in 2007, according to the American Cancer Society. Some scientists have suspected that male hormones working in concert with the androgen receptor might play a role, but hard evidence has been minimal until now, said Edward Messing, M.D., a bladder cancer expert and chair of Urology. Instead, scientists have suspected that factors like greater exposure of men to cigarettes and industrial chemicals has been responsible.

"For many years, people have recognized that men are more likely than women to get bladder cancer," said Messing, one of the authors of the paper. "More and more women are smoking and working with chemicals in the workplace, yet their bladder cancer rates have not really changed much. There is no longer any question that the androgen receptor is playing a role in bladder cancer."

The work by a team of collaborators from Rochester and from Yokohama City University Graduate School of Medicine in Japan was led by Chang, director of the George Whipple Laboratory for Cancer Research at the University of Rochester Medical Center and a faculty member in the departments of Urology and Pathology and the James P. Wilmot Cancer Center.

Chang is an expert on the androgen receptor, which is central to many diseases and conditions, most notably prostate cancer. For that disease, hormone therapy to block the supply of hormones that turn on the receptor is a staple of treatment for men with advanced disease. The new findings open the possibility that perhaps someday, drugs that target male hormones, like those used against prostate cancer, might help men with bladder cancer.

The strongest evidence for the involvement of male hormones in bladder cancer was what happened when Chang's team disabled the androgen receptor in mice. While their normal counterparts with the androgen receptor got significant levels of bladder cancer when exposed to a carcinogen - 92 percent of the males and 42 percent of the females - not a single mouse whose androgen receptor was knocked out developed bladder cancer. The mice without the receptor also had significantly fewer premalignant changes in their bladder.

Besides opening the door to possible new treatments, Chang says the findings could help doctors decide which cases of bladder cancer are most likely to re-occur. His team found a correlation between the frequency of the androgen receptor in tumor cells and the recurrence of the tumor - tumors more likely to re-appear had more of the protein. If the finding holds up in wider testing in human tumors, it would help doctors know which patients to treat aggressively right from the start.

The JNCI paper is the latest installment in a body of research Chang has compiled that shows that the story of the androgen receptor and male hormones like testosterone is much more complex than was once thought. For years it's been widely thought by doctors and scientists that all male hormones, and only male hormones, work through the androgen receptor.

But he felt there was more to the story. If anyone would know, it would be Chang, who in 1988 was the first person to clone the androgen receptor, and was the first to discover that the protein needs molecular allies called co-factors to accomplish many of its tasks. Now more than 80 co-factors are known, offering many new targets to stop conditions like male-pattern baldness and diseases like prostate cancer.

Nearly a decade ago, Chang showed that molecules other than male hormones like testosterone are able to activate the androgen receptor. That finding isn't simply gathering dust in textbooks; it likely explains why hormone therapy for men in the advanced stages of prostate cancer ultimately fails. His work explained a long-baffling phenomenon in these patients, where drugs that work well for a few years suddenly make the cancer grow again late in the course of the disease.

In the recent paper, Chang continued this line of work, only in bladder cancer instead of prostate cancer. He took a closer look at the nearly disease-free male mice that didn't get bladder cancer despite exposure to a carcinogen. Some of those mice then received a drug known as DHT, a male hormone. In theory, such a drug only works if the androgen receptor is present, so the drug should not have had an effect. But 25 percent of these mice then got bladder cancer, clear evidence that the hormone is able to somehow side-step the traditional, receptor-mediated, pathway and still have an effect.

The work shows starkly that simply cutting off the supply of hormones like testosterone will have only a limited effect. The androgen receptor can still play a crucial role in the development of cancer, even without the hormones. The team has shown in other studies that even female hormones such as estrogen can turn on the androgen receptor.

"The activity of the androgen receptor is different from the activity of hormones that target the receptor," said Chang. "We've shown very clearly that even without these hormones, the receptor is still active in the development of cancer. This is crucial information as doctors seek to develop treatments for diseases like prostate or bladder cancer in men."

To knock out the androgen receptor, the team used a compound known as ASC-J9, a synthetic chemical compound that is loosely based on a compound found in curcumin. Chang's laboratory, in collaboration with San Diego-based AndroScience Corp., has screened hundreds of compounds for their activity involving the androgen receptor. Just last month, the team showed that ASC-J9 offers promise against a rare neuromuscular disease known as Kennedy's disease.

The compound is now being tested as a cream to treat acne in a clinical trial run by AndroScience, a biotech company founded by Chang, Charles C-Y Shih, and Por-Hsiung Lai in 2000. The University owns a stake in the company, which has licensed several of Chang's research findings.

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*Article adapted by Medical News Today from original press release.*  
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The first author of the paper is Hiroshi Miyamoto, M.D., Ph.D., who was a post-doctoral researcher in Chang's laboratory and is now a medical resident in the Department of Pathology and Laboratory Medicine. Miyamoto was joined by several of his former colleagues at Yokohama City University Graduate School of Medicine in Yokohama, Japan, who did much of the work with the human bladder cancer cell lines and analyzed levels of the androgen receptors. Collaborators there include Hitoshi Ishiguro, Hiroji Uemura, Yoshinobu Kubota, and Yoji Nagashima.

Other authors of the paper, in addition to Chang and Messing, are Zhiming Yang, a former graduate student now at Zhejiang University and 2nd Hospital in Hangzhou, China; Yei-Tsung Chen and Yueh-Chiang Hu, former graduate students and now researchers at Harvard; Yu-Jia Chang, formerly a post-doctoral researcher with Chang, now an assistant professor at Taipei Medical University and Hospital in Taipei, Taiwan; former graduate student Meng-Yin Tsai, now at Chang Gung Memorial Hospital in Kaohsiung, Taiwan; and Shuyuan Yeh, associate professor of Urology.

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