

# Androgen Receptor May Explain Male Dominance in Liver Cancer

May 19, 2010



Left: liver cancer without androgen receptor; Right: liver cancer with androgen receptor

A University of Rochester study helps to explain why men get liver cancer more often than women and opens the door for a new treatment pathway, by showing a direct link between the androgen receptor, which is more active in men, and the hepatitis B virus as it relates to the deadly cancer.

The study is published May 19, 2010, in *Science Translational Medicine*, a new journal from the American Association for the Advancement of Science, AAAS.

**Primary liver cancer** is the fifth most common cancer in men. It often arises after infection from the **hepatitis B virus** (HBV), which is widespread across the globe and growing in the United States. Other studies of liver

cancer have focused on risk factors such as age, family history, and use of alcohol and cigarettes, but those epidemiology studies have not explained the mechanisms driving hepatocellular carcinoma and why men are more susceptible.

Now, corresponding author **Chawnshang Chang, Ph.D.**, the **George Hoyt Whipple Distinguished Professor of Pathology** at the University of Rochester Medical Center, and colleagues, showed that the androgen receptor (AR), a protein that mediates male sex hormones, promotes liver cancer when hepatitis B is present by altering DNA replication of the virus. Chang's laboratory created a mouse model for HBV-induced liver cancer and reported that knocking out AR suppressed the HBV-induced cancer.

According to an accompanying editorial in the journal, the identification of the AR pathway is a potential new treatment target that could translate to the clinic.

"Our study is the first in vivo evidence to demonstrate a direct connection between HBV-induced liver cancer and the AR," Chang said. "This is important because so far most work has focused on eliminating total serum androgen levels, a type of therapy that has shown little success."

"This important paper offers insight into something we have long observed but not entirely understood, namely that men with HBV are much more likely to develop cancer than women with the same infection," added **Aram Hezel, M.D.**, a gastrointestinal oncologist at the **James P. Wilmot Cancer Center** at University of Rochester Medical Center. "This is great use of the tools of genetics and mouse modeling to explain a clinical finding, and most importantly turn our attention to potentially more promising treatment approaches for patients with hepatocellular carcinoma."

"This study also raises the possibility of prevention among men with HBV infection through inhibition of the androgen receptor," Hezel said. "The potential impact on clinical care is great."

For decades Chang has focused on the particular role of the **AR** in human health. In 1988 he successfully cloned AR, which led to breakthroughs in several AR-related diseases such as prostate and bladder cancer, and Kennedy's neuron disease, a rare and progressive motor disorder similar to Lou Gehrig's disease, and that affects only men.

The AR is central to the action of testosterone and has a profound effect on many organs. In previous experiments, Chang has shown that mice without AR have dramatically lower rates of bladder cancer, a cancer that strikes men three times more often than women.

Male dominance in liver cancer suggested that the AR would be a key factor, as well. (About 74 percent of liver cancer cases occur in men.) Chang's objective was to locate a new pathway for treatment that would not require

depletion of androgen levels in the entire body, which amounts to castration and causes severe side effects for patients.

His study took the first step toward demonstrating this could be done, at least for early stage liver cancer. Researchers showed that an experimental drug, ASC-J9, attacked and degraded the faulty AR, and suppressed liver tumors in mice.

Chang developed ASC-J9 earlier this decade and first reported on its clinical potential in March 2007 in the journal *Nature Medicine*. The drug is a synthetic compound loosely based on the compounds found in curcumin, the polyphenol that gives the spice tumeric its yellow color. It has been used for centuries as a folk medicine in Asia and India. In this case, however, scientists significantly altered the natural substance to be more powerful, and are carefully screening it for safety and effectiveness.

**AndroScience Corp.**, a biotech company founded by Chang and others in 2000, is evaluating ASC-J9 in several clinical settings, although not yet in the treatment of liver cancer, Chang said. The URMCC owns a stake in AndroScience and has licensed several of Chang's research findings.

In the current study, researchers found that AR cooperates with the hepatitis B virus to trigger the expression of several oncogenes, resulting in normal liver cells transforming into cancer cells. Furthermore, they showed that liver tumors without the AR had fewer proliferating cancer cells, which helps to explain the gender disparity in the disease.

Some of the findings are in agreement with earlier studies by Chang's lab on the role of AR in prostate cancer. Just as in prostate cancer, the liver tumor microenvironment is rich in various cell types, each of which has a distinct role in promoting the cancer.

"It will be interesting to see if targeting AR at different stages or in different liver cancer cell types may also lead to differential effects during the progression of cancer," the paper concluded.

The hepatitis B and C viruses account for approximately 80 percent of primary liver cancer cases worldwide. Newborn vaccines and screenings for HBV and HCV, particularly in Asian and African countries, have reduced the incidence of liver cancer in later years. Still, an estimated 560,000 new cases are diagnosed annually. In high-risk areas such as China, Japan and sub-Saharan Africa the male-to-female ratio of liver cancer can be as high as 8 to 1. The current best treatment is surgery; median survival is generally six months.

**The National Institutes of Health** and the George Whipple Professorship Endowment funded the research. Co-authors from the Whipple Lab and the URMCC James P. Wilmot Cancer Center are: Ming-Heng Wu, Wen-Lung Ma, Cheng-Lung Hsu, Yuh-Ling Chen, Charlotte Kathryn Ryan and Shuyuan Yeh. Additional co-authors include Jing-Hsiung James Ou, of the Department of Molecular Microbiology and Immunology at the University of Southern California, Los Angeles; Yao-Ching Hung and Wen-Lung Ma, of the Sex Hormone Research Center at China Medical University/Hospital in Taiwan. Ming-Heng Wu is also associated with Cheng Gung University in Taiwan; and Cheng-Lung Hsu, with Chang Gong University in Taiwan.

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**Press release from Science-AAAs at Washington-DC at May19-2010**

## **Double the Danger for Males: Hepatitis B and Liver Cancer**

Sex hormones play a role in causing hepatitis B associated liver cancer and may help solve the decades-old mystery of why men with hepatitis B are struck with cancer far more than women, a new study suggests. The findings indicate that using drugs to destroy tumors' androgen receptors could be a new way to battle liver cancer at an early stage. Affecting the largest organ inside the body, liver cancer is the fifth most common cancer and the third leading cause of global cancer death. Hepatitis B infection (endemic in many Asian countries, including China) is uniquely associated with liver cancer, and accounts for about half of liver cancer cases worldwide.

Now, Ming-Heng Wu, Chawnshang Chang and colleagues have discovered why men with hepatitis B are more likely to than women to develop liver cancer; the answer lies deep in the genome of the virus, which contains a **special DNA sequence** that specifically attracts the receptor of the male sex hormone androgen. The androgen receptors in liver cells bind to this sequence and trigger a cascade of damage to liver tissue. The researchers found that by targeting the androgen receptor (rather than androgen itself), they could significantly inhibit cancer growth in mice. In the experiment, they created the first genetically modified mice with hepatitis B virus that could develop liver tumors upon low dose treatment with a carcinogen. Wu and Colleagues then showed that the androgen receptor could be destroyed with a chemical compound, which subsequently suppressed liver tumor growth. Treatment did not change overall androgen levels in the body, and had no obvious toxic effects in mice; hinting that drugs capable of targeting the androgen receptor rather an androgen could be a promising therapy for liver cancer.

## Science Translational Medicine Editor's Summary

Hepatocellular carcinoma represents the majority of cases of primary liver cancer; it is the fifth most common cancer and the third leading cause of cancer death worldwide. Several risk factors for hepatocellular carcinoma have been identified but gender and hepatitis B virus (HBV) infection have proven to be uniquely associated with the disease by undetermined mechanisms. HBV infection alone, which is endemic in many Asian countries, including China, accounts for approximately 53% of hepatocellular carcinoma cases worldwide. Decades of research have examined risk factor exposures like age, history of hepatitis, occupation, regular alcohol drinking, regular cigarette smoking, and family history of liver cancer to explain the gender disparities that are so prevalent among HBV-induced liver cancers, but alas none of these were fully accountable, suggesting that other unknown susceptibilities are lurking.

Liver cancer arises most frequently in the setting of chronic liver inflammation. After infection by the hepatitis virus, the host's inflammatory immune response to the viral antigens induces hepatocyte damage and is followed by the pathogenesis of liver cancer. While it has been postulated that sex hormones may interact with HBV infection in the process and lead to a dominant sex disparity in liver cancer risk, this has never been decisively shown. Now, Wu et al use a genetically modified mouse model of HBV-induced liver cancer to explore how sex hormones, specifically their receptors, play a role in promoting the disease. They find that targeting of the androgen receptor and not androgens as is frequently done in the clinic, hampers tumor formation at the gross and mechanistic levels. These results shed new light on a pathway previously unexplored, and provide an intervention modality that is translatable in the clinic, and the corollary of this may explain why men are more susceptible to liver cancer than women.

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## Researchers find link between male hormone and liver cancer

Taiwan News, Staff Writer

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2010-05-21 12:00 AM

A team of Taiwanese doctors have found a way to repress male hormones in what could lead to the prevention of liver cancer, reports said yesterday.

The team led by China Medical University Professor Chang Chawnshang used animal testing to prove for the first time that the androgen receptor can cause liver cancer, according to a report published in the United States by "Science Translational Medicine" magazine.

If the male hormone or androgen receptor could be suppressed, the number of incidences of hepatitis B and later liver cancer could be cut, Chang said.

Chang presented his research to the Cabinet-level National Science Council in a report yesterday about new medicine against liver cancer.

National Taiwan University hepatitis specialist Chen Ting-hsin had the experience of using the hepatitis B-virus vaccine to reduce the occurrence of hepatitis B in children as well as cases of liver cancer, reports said. Chen's experience proved that the two diseases were related, according to reports.

The role of the androgen receptor was extremely important, Chang said, because it causes hepatitis B in men to transform itself rather rapidly into liver cancer. His team's research was the first to use mice to show why men were more susceptible to fall prey to liver cancer than women, Chang said.

The team also extracted elements from ginger and curry it injected into mice to reduce the creation of cancer. The experience also showed there was a possibility that in the future doctors could develop a cure or a medicine that could prevent the emergence of liver cancer by repressing the androgen receptor.

"Science Translational Medicine" magazine held a news conference in Washington, D.C. on May 20 to announce the publication of the Chang team's research, reports said. The hepatitis story also featured on the magazine's cover.

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## Why men get liver cancer more often than women

ANI

Thu, May 20 02:30 PM

Washington, May 20 (ANI): A new research may help explain why men get liver cancer more often than women.

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Study co-author Chawnshang Chang, the George Hoyt Whipple Distinguished Professor of Pathology at the University of Rochester Medical Center, and colleagues, showed that the androgen receptor (AR), a protein that mediates male sex hormones, promotes liver cancer when hepatitis B is present by altering DNA replication of the virus.

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Source: [Eurekalert](#)

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s 8 to 1. The current best treatment is surgery; median survival is generally six months.



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Some of the findings are in agreement with earlier studies by Chang's lab on the role of AR in prostate [cancer](#). Just as in prostate [cancer](#), the [liver](#) tumor microenvironment is rich in various cell types, each of which has a distinct role in promoting the [cancer](#).

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Male dominance in [liver cancer](#) suggested that the AR would be a key factor, as well. (About 74 percent of [liver cancer](#) cases occur in men.) Chang's objective was to locate a new pathway for treatment that would not require depletion of androgen levels in the entire body, which amounts to castration and causes severe side effects for patients.

His study took the first step toward demonstrating this could be done, at least for early stage [liver cancer](#). Researchers showed that an experimental drug, ASC-J9, attacked and degraded the faulty AR, and suppressed [liver](#) tumors in mice.

Chang developed ASC-J9 earlier this decade and first reported on its clinical potential in March 2007

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# AD HOC NEWS

20.05.2010 | 11:17 Uhr

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## Androgen Receptors Found to Affect Growth of Liver Cancer

**Dr Ming-Heng Wu of the Institute of Basic Medical Sciences at National Cheng Kung University (NCKU), Taiwan, in collaboration with Prof Chawnshang Chang's laboratory of University of Rochester (UR), United States, have discovered that androgen receptors (AR) can promote hepatitis B virus-induced hepatocarcinogenesis through modulation of hepatitis B virus (HBV) RNA transcription. The discovery has captured considerable attention of the field of hepatitis and liver research studies.**

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The discovery has captured considerable attention of the field of hepatitis and liver research studies. It was published in the internationally renowned medical journal *Science Translational Medicine* on May 20th. The American Association for the Advancement of Science (AAAS) has announced this major discovery in a press conference held on May 20th in Washington, D.C., capital of the United States of America.

Dr. Ming-Heng Wu expressed, "According to the statistics of epidemiology, the chronic hepatitis B virus infection is an important factor in causing liver cancer. The higher the amount of hepatitis B virus in the serum, the higher the chance of getting liver cancer. Particularly, men are up to seven times more likely than women to develop liver cancer. Among hepatitis B virus carriers, men are also more likely to develop liver cancer than women. The evidences have suggested that serum androgen concentration and androgen receptors may play a significant role in liver cancer induced by hepatitis B virus. However, there hasn't been any research done to validate the theory."

In view of this, advised by Associate Professor Yuh-Ling Chen of the NCKU Institute of Oral Medicine and the NCKU Institute of Basic Medical Sciences, then a PhD student, Dr. Ming-Heng Wu worked with Prof. Chawnshang Chang's laboratory at University of Rochester to engage in a research of androgen receptors and hepatitis B virus.

The research team used transgenic technology to create the first mouse in the world that was genetically modified to lack androgen receptor in its liver hepatocytes and infected with hepatitis B virus for subsequent animal experiments. In the animal experiment, it was proved that androgen receptors will increase the replication of hepatitis B virus and enhance the incidence of liver cancer. Since previous research studies have revealed that lowering the concentration of androgen in the serum could not effectively treat liver cancer, a new method to treat liver cancer by restraining androgen receptors in the liver cells has been discovered.

In the experiment, the team injected low doses of carcinogen, diethylnitrosamine (DEN), into normal mice and mice that were infected with hepatitis B virus, sixteen days after they were born. By week 22, only mice that were infected with hepatitis B virus had developed liver tumors.

The team further explored the role of androgen receptors in the process of hepatitis B virus causing liver tumors. They used normal mice and HBV transgenic mice lacking androgen receptors only in the liver hepatocytes. These mice were infected with hepatitis B virus and injected with diethylnitrosamine sixteen days after their birth. By week 22, mice that were infected with hepatitis B virus were six times more likely to develop liver tumors than mice infected with hepatitis B virus and lacking in androgen receptors in their liver hepatocytes. The evidences have shown that androgen receptors can promote hepatitis B virus in the growth and development of hepatoma cells. Furthermore, their results have demonstrated that targeting the androgen receptors, rather than the androgen, could be developed as a new therapy to battle HBV-induced hepatocellular carcinoma.

Additional Information:

Graduated from the Department of Biochemistry and Molecular Biology in 2004, Ming-Heng Wu chose to study in the laboratory of Associate Professor Yuh-Ling Chen of the Institute of Oral Medicine and the Institute of Basic Medical Sciences because of his interest in cancer research. Prof. Yuh-Lin Chen's laboratory has been conducting related research of cancer metastasis and carcinogen mechanisms, devoting itself to the formation and metastasis of oral cancer influenced by specific genetic abnormality.

In his third year of doctoral study, Dr. Ming-Heng Wu was recommended by Prof. Yuh-Lin Chen to participate in the Graduate Student Study Abroad Program (GSSAP) sponsored by the National Science Council and to engage in a cancer-related research in Prof. Chawnshang Chang's laboratory at University of Rochester to broaden his international perspectives and expand his academic training.

Dr. Ming-Heng Wu joined the research team of University of Rochester and participated in the liver cancer joint project in 2007. Within two and a half years, they conducted animal experiment and proved that men are more likely than women to develop liver cancer among hepatitis B virus carriers.

The first author of the paper entitled "Androgen Receptor Promotes Hepatitis B Virus-Induced Hepatocarcinogenesis Through Modulation of Hepatitis B Virus RNA Transcription" in *Science Translational Medicine* is Dr. Ming-Heng Wu, then a PhD student, of the Institute of Basic Medical Sciences at National Cheng Kung University, and the co-authors also include Assistant Professor Wen-Lung Ma of China Medical University and physician Chen-Luna Hsu of Chang Gung Memorial Hospital.

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20/05/2010 01:43:00

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“This important paper offers insight into something we have long observed but not entirely understood, namely that men with HBV are much more likely to develop cancer than women with the same infection,” added **Aram Hezel, M.D.**, a gastrointestinal [oncologist](#) at the [James P. Wilmot Cancer Center](#) at University of Rochester Medical Center. “This is great use of the tools of genetics and mouse modeling to explain a clinical finding, and most importantly turn our attention to potentially more promising treatment approaches for patients with hepatocellular carcinoma.”

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“It will be interesting to see if targeting AR at different stages or in different liver cancer cell types may also lead to differential effects during the progression of cancer,” the paper concluded.

The hepatitis B and C viruses account for approximately 80 percent of primary liver cancer cases worldwide. Newborn vaccines and screenings for HBV and HCV, particularly in Asian and African countries, have reduced the incidence of liver cancer in later years. Still, an [estimated](#) 560,000 new cases are diagnosed annually. In high-risk areas such as China, Japan and sub-Saharan Africa the male-to-female ratio of liver cancer can be as high as 8 to 1. The current best treatment is surgery; median survival is generally six months.

[The National Institutes of Health](#) and the George Whipple Professorship Endowment funded the research. Co-authors from the Whipple Lab and the URMC

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# # #

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## Androgen receptor may explain male dominance in liver cancer

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The study is published May 19, 2010, in *Science Translational Medicine*, a new journal from the American Association for the Advancement of Science, AAAS.

Primary liver cancer is the fifth most common cancer in men. It often arises after infection from the hepatitis B virus (HBV), which is widespread across the globe and growing in the United States. Other studies of liver cancer have focused on risk factors such as age, family history, and use of alcohol and cigarettes, but those epidemiology studies have not explained the mechanisms driving hepatocellular carcinoma and why men are more susceptible.

Now, corresponding author Chawnsiang Chang, Ph.D., the George Hoyt Whipple Distinguished Professor of Pathology at the University of Rochester Medical Center, and colleagues, showed that the androgen receptor (AR), a protein that mediates male sex hormones, promotes liver cancer when hepatitis B is present by altering DNA replication of the virus. Chang's laboratory created a mouse model for HBV-induced liver cancer and reported that knocking out AR suppressed the HBV-induced cancer.

According to an accompanying editorial in the journal, the identification of the AR pathway is a potential new treatment target that could translate to the clinic.

"Our study is the first in vivo evidence to demonstrate a direct connection between HBV-induced liver cancer and the AR," Chang said. "This is important because so far most work has focused on eliminating total serum androgen levels, a type of therapy that has shown little success."

"This important paper offers insight into something we have long observed but not entirely understood, namely that men with HBV are much more likely to develop cancer than women with the same infection," said Aram Hezel, M.D., a gastrointestinal oncologist at the James P. Wilmot Cancer Center at University of Rochester Medical Center. "This is great use of the tools of genetics and mouse modeling to explain a clinical finding and most importantly turn our attention to potentially more promising treatment approaches for patients with hepatocellular carcinoma."

"This study also raises the possibility of prevention among men with HBV infection through inhibition of the androgen receptor," Hezel added. "The potential impact on clinical care is great."

For decades Chang has focused on the particular role of the AR in human health. In 1988 he successfully cloned AR, which led to breakthroughs in several AR-related diseases such as prostate and bladder cancer, and Kennedy's neuron disease, a rare and progressive motor disorder similar to Lou Gehrig's disease, and that affects only men.

The AR is central to the action of testosterone and has a profound effect on many organs. In previous experiments, Chang has shown that mice without AR have dramatically lower rates of bladder cancer, a cancer that strikes men three times more often than women.

Male dominance in liver cancer suggested that the AR would be a key factor, as well. (About 74 percent of liver cancer cases occur in men.) Chang's objective was to locate a new pathway for treatment that would not require depletion of androgen levels in the entire body, which amounts to castration and causes severe side effects for patients.

His study took the first step toward demonstrating this could be done, at least for early stage liver cancer. Researchers showed that an experimental drug, ASC-J9, attacked and degraded the faulty AR, and suppressed liver tumors in mice.

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Posted on : 2010-05-20 | Author : National Cheng Kung University

News Category : PressRelease

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In view of this, advised by Associate Professor Yuh-Ling Chen of the NCKU Institute of Oral Medicine and the NCKU Institute of Basic Medical Sciences, then a PhD student, Dr. Ming-Heng Wu worked with Prof. Chawnshang Chang's laboratory at University of Rochester to engage in a research of androgen receptors and hepatitis B virus.

The research team used transgenic technology to create the first mouse in the world that was genetically modified to lack androgen receptor in its liver hepatocytes and infected with hepatitis B virus for subsequent animal experiments. In the animal experiment, it was proved that androgen receptors will increase the replication of hepatitis B virus and enhance the incidence of liver cancer. Since previous research studies have revealed that lowering the concentration of androgen in the serum could not effectively treat liver cancer, a new method to treat liver cancer by restraining androgen receptors in the liver cells has been discovered.

In the experiment, the team injected low doses of carcinogen, diethylnitrosamine (DEN), into normal mice and mice that were infected with hepatitis B virus, sixteen days after they were born. By week 22, only mice that were infected with hepatitis B virus had developed liver tumors.

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Photo :

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## Why men get liver cancer more often than women

ANI  
Thursday, May 20, 2010 15:25

A new research may help explain why men get liver cancer more often than women.

The study, conducted by University of Rochester researchers, shows a direct link between the androgen receptor, which is more active in men, and the hepatitis B virus as it relates to the deadly cancer.

Study co-author Chawnsang Chang, the George Hoyt Whipple Distinguished Professor of Pathology at the University of Rochester Medical Center, and colleagues, showed that the androgen receptor (AR), a protein that mediates male sex hormones, promotes liver cancer when hepatitis B is present by altering DNA replication of the virus.

Chang's laboratory created a mouse model for HBV-induced liver cancer and reported that knocking out AR suppressed the HBV-induced cancer.

The identification of the AR pathway is a potential new treatment target that could translate to the clinic.

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## Why men get liver cancer more often than women

From ANI

Washington, May 20: A new research may help explain why men get liver cancer more often than women.

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May 20, 2010 05:17 AM Eastern Daylight Time 

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Science Centric

20 May 2010 13:58 GMT

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### Study explains male-dominance in liver cancer

**Updated:** 2010-05-21 19:25:48 CST **Category:** [Liver](#)

A liver [cancer test](#) may benefit men more than women, especially those with hepatitis B, as a new study from the University of Rochester has found that men are at a higher risk for developing the disease.


The research team found that the hepatitis B virus interacts with the androgen receptor, a protein that regulates male hormones, in a way that can often lead to liver cancer.

The study's lead author, Chawnsang Chang, said that the discovery is important because it could help doctors spot individuals at higher risk for cancer, and aid in developing more effective treatments.

"Our study is the first in evidence to demonstrate a direct connection between hepatitis B-induced liver cancer and the androgen receptor," Chang said. "This is important because so far most work has focused on eliminating total serum androgen levels, a type of therapy that has shown little success."

Chang added that the findings may also benefit treatments for bladder cancer, which similarly strike men at a higher rate than women, as the androgen receptor may also be involved in that disease.

More than 80 percent of the 22,620 individuals diagnosed with liver cancer in 2009 died from the disease, according to the National Cancer Institute.




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## Androgen receptor may explain male dominance in liver cancer

May 19th, 2010 in Medicine & Health / Cancer

**A University of Rochester study helps to explain why men get liver cancer more often than women and opens the door for a new treatment pathway, by showing a direct link between the androgen receptor, which is more active in men, and the hepatitis B virus as it relates to the deadly cancer.**

The study is published May 19, 2010, in *Science Translational Medicine*, a new journal from the American Association for the Advancement of Science, AAAS.

Primary [liver cancer](#) is the fifth most common cancer in men. It often arises after infection from the [hepatitis B virus](#) (HBV), which is widespread across the globe and growing in the United States. Other studies of liver cancer have focused on risk factors such as age, family history, and use of alcohol and cigarettes, but those epidemiology studies have not explained the mechanisms driving hepatocellular carcinoma and why men are more susceptible.

Now, corresponding author Chawnsang Chang, Ph.D., the George Hoyt Whipple Distinguished Professor of Pathology at the University of Rochester Medical Center, and colleagues, showed that the [androgen receptor](#) (AR), a protein that mediates male sex hormones, promotes liver cancer when hepatitis B is present by altering [DNA replication](#) of the virus. Chang's laboratory created a mouse model for HBV-induced liver cancer and reported that knocking out AR suppressed the HBV-induced cancer.

According to an accompanying editorial in the journal, the identification of the AR pathway is a potential new treatment target that could translate to the clinic.

"Our study is the first in vivo evidence to demonstrate a direct connection between HBV-induced liver cancer and the AR," Chang said. "This is important because so far most work has focused on eliminating total serum androgen levels, a type of therapy that has shown little success."

"This important paper offers insight into something we have long observed but not entirely understood, namely that men with HBV are much more likely to develop cancer than women with the same infection," said Aram Hezel, M.D., a gastrointestinal oncologist at the James P. Wilmot Cancer Center at University of Rochester Medical Center. "This is great use of the tools of genetics and mouse modeling to explain a clinical finding and most importantly turn our attention to potentially more promising treatment approaches for patients with hepatocellular carcinoma."

"This study also raises the possibility of prevention among men with HBV infection through inhibition of the androgen receptor," Hezel added. "The potential impact on clinical care is great."

For decades Chang has focused on the particular role of the AR in human health. In 1988 he successfully cloned AR, which led to breakthroughs in several

AR-related diseases such as prostate and bladder cancer, and Kennedy's neuron disease, a rare and progressive motor disorder similar to Lou Gehrig's disease, and that affects only men.

The AR is central to the action of testosterone and has a profound effect on many organs. In previous experiments, Chang has shown that mice without AR have dramatically lower rates of bladder cancer, a cancer that strikes men three times more often than women.

Male dominance in liver cancer suggested that the AR would be a key factor, as well. (About 74 percent of liver cancer cases occur in men.) Chang's objective was to locate a new pathway for treatment that would not require depletion of androgen levels in the entire body, which amounts to castration and causes severe side effects for patients.

His study took the first step toward demonstrating this could be done, at least for early stage liver cancer. Researchers showed that an experimental drug, ASC-J9, attacked and degraded the faulty AR, and suppressed liver tumors in mice.

Chang developed ASC-J9 earlier this decade and first reported on its clinical potential in March 2007 in the journal *Nature Medicine*. The drug is a synthetic compound loosely based on the compounds found in curcumin, the polyphenol that gives the spice turmeric its yellow color. It has been used for centuries as a folk medicine in Asia and India. In this case, however, scientists significantly altered the natural substance to be more powerful, and are carefully screening it for safety and effectiveness.

AndroScience Corp., a biotech company founded by Chang and others in 2000, is evaluating ASC-J9 in several clinical settings, although not yet in the treatment of liver cancer, Chang said. The URMC owns a stake in AndroScience, and has licensed several of Chang's research findings.

In the current study, researchers found that AR cooperates with the hepatitis B virus to trigger the expression of several oncogenes, resulting in normal liver cells transforming into cancer cells. Furthermore, they showed that liver tumors without the AR had fewer proliferating cancer cells, which helps to explain the gender disparity in the disease.

Some of the findings are in agreement with earlier studies by Chang's lab on the role of AR in prostate cancer. Just as in prostate cancer, the liver tumor microenvironment is rich in various cell types, each of which has a distinct role in promoting the cancer.

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Provided by University of Rochester Medical Center

"Androgen receptor may explain male dominance in liver cancer." May 19th, 2010. [www.physorg.com/news193492573.html](http://www.physorg.com/news193492573.html)

Tuesday, May 25, 2010

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## ▶ International

**Orient Europharma partners with AndroScience to develop, market new acne medicine**

Tuesday, May 25, 2010 11:00 IST

**Taipei, Taiwan**

Orient Europharma Co. Ltd announced a partnership agreement with US biopharmaceutical company AndroScience Corporation (ASC) to develop and market ASC-J9 acne cream. Under the terms of the agreement, OE holds the exclusive right to market the drug in Taiwan, Hong Kong, Korea, Australia, New Zealand, and various countries in Southeast Asia. ASC-J9 is a new patented drug developed by ASC for the treatment of acne.

Acne vulgaris, or acne, is the most common condition seen in dermatology clinics. It is a skin problem that usually occurs during adolescence, although it can affect people from 12 years old to those well in their forties. According to statistics, as much as 85 percent of people have suffered from acne at one point in their lives. Business information provider Visiongain estimates the market for acne treatment products to be US\$2.6 billion, with the Asian market taking up US\$280 million, or 11 percent.

Acne is a skin disease originating from follicular inflammation. Acne develops as a result of blockages in follicles and can occur on the face and upper body areas including the neck, chest, back, shoulders and upper arms. Factors linked to acne include hyperactive sebaceous glands, cleansing habits, hormonal activity, diet, stress, irregular sleeping habits, lack of sleep, genetic history, and work environment. No one defining factor can be pinpointed to explain its formation.

Androgens, or male sex hormones, are typically the main cause for acne outbreak. Androgen receptors are present in human sebaceous glands. The activation of androgen receptors causes the follicular glands to grow larger and secrete more sebum, which can lead to acne. Among women, irregular lifestyle or menstrual cycle may trigger the production of progesterone which can increase the incidence of acne as well. Generally, women who have relatively higher levels of androgens are also more prone to acne. ASCJ9 is a small molecule with a novel mechanism of action that can selectively enhance androgen receptor degradation (ARD) to effectively reduce androgen activities.

Dr Chawn-Shang Chang of University of Rochester was invited by Taiwan's National Science Council and US science journal, "Science", to announce his research team's newest findings on androgen receptors and HVB-enhanced liver cancer. Dr. Chang pointed out yesterday in a press conference that androgen receptor (AR) is the key target in treating liver cancer. Androgen receptor degradation enhancer such as ASC-J9, has been proven to treat androgen receptors related diseases such as HVB-enhanced liver cancer, Bulbar Muscular Atrophy (or Kennedy's disease), prostate cancer and bladder cancer.

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ARD enhancer (ASC-J9) acts on the key cause of acne, the androgen activation system, through reducing levels of androgen receptors in the sebaceous gland to minimize sebum secretions in order to effectively treat acnes. The 0.025% cream formulation dose of ASC-J9 delivers the same efficacy as other marketed acne drugs, however, ASC-J9 exhibits lower systemic absorption and side effects, and can be used to treat both male and female patients. This is an unprecedented approach different from all other current acne treatments on the market.

AndroScience recently announced results of the phase-2a dose-ranging study of ASC-J9. Following the signing of the partnership agreement, OE will participate in the US and Taiwan phase-2b clinical studies. The introduction of this drug will provide more treatment options for acne patients in the future.

Founded in 2000, AndroScience Corporation (ASC) is a privately held San Diego, CA based biopharmaceutical company dedicated to the research, development, and commercialization of a proprietary series of small molecules which target the androgen receptor (AR).

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**Androgen receptor may explain male dominance in liver cancer**

20.05.2010 03:34

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The National Institutes of Health and the George Whipple Professorship Endowment funded the research. Co-authors from the Whipple Lab and the UPMC James P. Wilmot Cancer Center are: Ming-Heng Wu, Wen-Lung Ma, Cheng-Lung Hsu, Yuh-Ling Chen, Charlotte Kathryn Ryan and Shuyuan Yeh. Additional co-authors include Jing-Hsiung James Ou, of the Department of Molecular Microbiology and Immunology at the University of Southern California, Los Angeles; Yao-Ching

Hung and Wen-Lung Ma, of the Sex Hormone Research Center at China Medical University/Hospital in Taiwan. Ming-Heng Wu is also associated with Cheng Gung University in Taiwan; and Cheng-Lung Hsu, with Chang Gong University in Taiwan.



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#### **E. coli O157:H7 present but not common in wildlife of nation\'s salad bowl**

25.05.2010 | 23:53

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E. coli O157:H7 present but not common in wildlife of nation\'s salad bowlThe disease-causing bacterium E. coli O157:H7 is present but rare in some wildlife species of California\'s agriculturally rich Central Coast region, an area often referred to as the nation\'s "salad bowl," reports a team of researchers led by a UC Davis scientist.

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#### **Novel anti-malarial drug candidate found by UT Southwestern researchers**

25.05.2010 | 23:53

## Androgen Receptors Found To Affect Growth Of Liver Cancer

20 May 2010 [Click to Print](#)

Dr. Ming-Heng Wu of the Institute of Basic Medical Sciences at National Cheng Kung University (NCKU), Taiwan, in collaboration with Prof. Chawnschang Chang's laboratory of University of Rochester (UR), United States, have discovered that androgen receptors (AR) can promote hepatitis B virus-induced hepatocarcinogenesis through modulation of hepatitis B virus (HBV) RNA transcription.

The discovery has captured considerable attention of the field of hepatitis and liver research studies. It was published in the internationally renowned medical journal *Science Translational Medicine* on May 20th. The American Association for the Advancement of Science (AAAS) has announced this major discovery in a press conference held on May 20th in Washington, D.C., capital of the United States of America.

Dr. Ming-Heng Wu expressed, "According to the statistics of epidemiology, the chronic hepatitis B virus infection is an important factor in causing liver cancer. The higher the amount of hepatitis B virus in the serum, the higher the chance of getting liver cancer. Particularly, men are up to seven times more likely than women to develop liver cancer. Among hepatitis B virus carriers, men are also more likely to develop liver cancer than women. The evidences have suggested that serum androgen concentration androgen receptors may play a significant role in liver cancer induced by hepatitis B virus. However, there hasn't been any research done to validate the theory."

In view of this, advised by Associate Professor Yuh-Ling Chen of the NCKU Institute of Oral Medicine and the NCKU Institute of Basic Medical Sciences, then a PhD student, Dr. Ming-Heng Wu worked with Prof. Chawnschang Chang's laboratory at University of Rochester to engage in a research of androgen receptors and hepatitis B virus.

The research team used transgenic technology to create the first mouse in the world that was genetically modified to lack androgen receptor in its liver hepatocytes and infected with hepatitis B virus for subsequent animal experiments. In the animal experiment, it was proved that androgen receptors will increase the replication of hepatitis B virus and enhance the incidence of liver cancer. Since previous research studies have revealed that lowering the concentration of androgen in the serum could not effectively treat liver cancer, a new method to treat liver cancer by restraining androgen receptors in the liver cells has been discovered.

In the experiment, the team injected low doses of carcinogen, diethylnitrosamine (DEN), into normal mice and mice that were infected with hepatitis B virus, sixteen days after they were born. By week 22, only mice that were infected with hepatitis B virus had developed liver tumors.

The team further explored the role of androgen receptors in the process of hepatitis B virus causing liver tumors. They used normal mice and HBV transgenic mice lacking androgen receptors only in the liver hepatocytes. These mice were infected with hepatitis B virus and injected with diethylnitrosamine sixteen days after their birth. By week 22, mice that were infected with hepatitis B virus were six times more likely to develop liver tumors than mice infected with hepatitis B virus and lacking in androgen receptors in their liver hepatocytes. The evidences have shown that androgen receptors can promote hepatitis B virus in the growth and development of hepatoma cells. Furthermore, their results have demonstrated that targeting the androgen receptors, rather than the androgen, could be developed as a new therapy to battle HBV-induced hepatocellular carcinoma.

### Additional Information

Graduated from the Department of Biochemistry and Molecular Biology in 2004, Ming-Heng Wu chose to study in the laboratory of Associate Professor Yuh-Ling Chen of the Institute of Oral Medicine and the Institute of Basic Medical Sciences because of his interest in cancer research. Prof. Yuh-Lin Chen's laboratory has been conducting related research of cancer metastasis and carcinogen mechanisms, devoting itself to the formation and metastasis of oral cancer influenced by specific genetic abnormality.

In his third year of doctoral study, Dr. Ming-Heng Wu was recommended by Prof. Yuh-Lin Chen to participate in the Graduate Student Study Abroad Program (GSSAP) sponsored by the National Science Council and to engage in a cancer-related research in Prof. Chawnschang Chang's laboratory at University

of Rochester to broaden his international perspectives and expand his academic training.

Dr. Ming-Heng Wu joined the research team of University of Rochester and participated in the liver cancer joint project in 2007. Within two and a half years, they conducted animal experiment and proved that men are more likely than women to develop liver cancer among hepatitis B virus carriers.

The first author of the paper entitled "Androgen Receptor Promotes Hepatitis B Virus-Induced Hepatocarcinogenesis Through Modulation of Hepatitis B Virus RNA Transcription" in Science Translational Medicine is Dr. Ming-Heng Wu, than a PhD student, of the Institute of Basic Medical Sciences at National Cheng Kung University, and the co-authors also include Assistant Professor Wen-Lung Ma of China Medical University and physician Cheng-Lung Hsu of Chang Gung Memorial Hospital.

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## Sex hormone explains higher liver cancer risk in men

Reuters

HONG KONG (Reuters) - Male sex hormones may explain why men who suffer from the hepatitis B liver disease are more likely to develop liver cancer than women, researchers in Taiwan have found.

In a paper published in *Science Translational Medicine* on Wednesday, the researchers said hepatitis B viruses attach themselves to receptors of the male sex hormone androgen before going on to damage liver tissue and cause cancer.

"The findings indicate that using drugs to destroy ... androgen receptors could be a new way to battle liver cancer at an early stage," they wrote.

Liver cancer is the fifth most common cancer and the third leading cause of global cancer death.

Hepatitis B virus infection, which is endemic in many Asian countries including China, is a leading cause of liver cancer and accounts for half of liver cancer cases worldwide.

Men are up to seven times more likely than women to develop liver cancer. Among hepatitis B virus carriers, men are up to three times more likely to develop liver cancer than women.

Led by Ming-Heng Wu at the Institute of Basic Medical Sciences in National Cheng Kung University in Tainan, Taiwan, researchers found that hepatitis B viruses have a special DNA sequence which draws it to androgen receptors.

"The androgen receptors in liver cells bind to this sequence and trigger a cascade of damage to liver tissue," they explained.

In their experiment, the researchers created mice that were infected with the hepatitis B virus and could easily develop liver tumors upon exposure to cancer-causing agents.

Some of these were genetically modified to be lacking in androgen receptors in their livers.

By week 22 in the experiment, more than 90 percent of those mice with androgen receptors had developed liver tumors compared to 27 percent of the mice without androgen receptors.

Tinkering with the receptors did not change overall androgen levels or leave any obvious toxic effects in the mice.

"Targeting the androgen receptor rather than androgen could be a promising therapy for liver cancer," the researchers said.

(Reporting by Tan Ee Lyn, editing by Miral Fahmy)

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science

# Androgen receptor may explain male dominance in liver cancer

May 19, 2010 – [University of Rochester Medical Center](#)

A University of Rochester study helps to explain why men get liver cancer more often than women and opens the door for a new treatment pathway, by showing a direct link between the androgen receptor, which is more active in men, and the hepatitis B virus as it relates to the deadly cancer.

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According to an accompanying editorial in the journal, the identification of the AR pathway is a potential new treatment target that could translate to the clinic.

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the same infection," said Aram Hezel, M.D., a gastrointestinal oncologist at the James P. Wilmot Cancer Center at University of Rochester Medical Center. "This is great use of the tools of genetics and mouse modeling to explain a clinical finding and most importantly turn our attention to potentially more promising treatment approaches for patients with hepatocellular carcinoma."

"This study also raises the possibility of prevention among men with HBV infection through inhibition of the androgen receptor," Hezel added. "The potential impact on clinical care is great."

For decades Chang has focused on the particular role of the AR in human health. In 1988 he successfully cloned AR, which led to breakthroughs in several AR-related diseases such as prostate and bladder cancer, and Kennedy's neuron disease, a rare and progressive motor disorder similar to Lou Gehrig's disease, and that affects only men.

The AR is central to the action of testosterone and has a profound effect on many organs. In previous experiments, Chang has shown that mice without AR have dramatically lower rates of bladder cancer, a cancer that strikes men three times more often than women.

Male dominance in liver cancer suggested that the AR would be a key factor, as well. (About 74 percent of liver cancer cases occur in men.) Chang's objective was to locate a new pathway for treatment that would not require depletion of androgen levels in the entire body, which amounts to castration and causes severe side effects for patients.

His study took the first step toward demonstrating this could be done, at least for early stage liver cancer. Researchers showed that an experimental drug, ASC-J9, attacked and degraded the faulty AR, and suppressed liver tumors in mice.

Chang developed ASC-J9 earlier this decade and first reported on its clinical potential in March 2007 in the journal *Nature Medicine*. The drug is a synthetic compound loosely based on the compounds found in curcumin, the polyphenol that gives the spice turmeric its yellow color. It has been used for centuries as a folk medicine in Asia and India. In this case, however, scientists significantly altered the natural substance to be more powerful, and are carefully screening it for safety and effectiveness.

AndroScience Corp., a biotech company founded by Chang and others in 2000, is evaluating ASC-J9 in several clinical settings, although not yet in the treatment of liver cancer, Chang said. The URMC owns a stake in AndroScience, and has licensed several of Chang's research findings.

In the current study, researchers found that AR cooperates with the hepatitis B virus to trigger the expression of several oncogenes, resulting in normal liver cells transforming into cancer cells. Furthermore, they showed that liver tumors without the AR had fewer proliferating cancer cells, which helps to explain the gender disparity in the disease.

## Increased cancer risk of people with type 2 diabetes

05/19/10 – Cancer and diabetes – are risk factors the same for these two diseases? Or does diabetes cause processes in the body which promote the onset or growth of cancer? It is still unclear why diabetics have a higher rate of cancer than people who are not affected by this metabolic disorder. ...

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05/19/10 – A nationwide study has confirmed the benefit of giving estrogen-lowering drugs before surgery to breast cancer patients. The treatment increased the likelihood that women could undergo breast-conservation surgery, also called lumpectomy, instead of mastectomy. The study's chair, Matthew ...



## Can eGFR be a routine preoperative renal function test?

05/19/10 – The creatinine clearance (Ccr) test has been used as a gold standard for evaluation of preoperative renal function in patients with gastric cancer. However, it is known that Ccr is not strictly equivalent to glomerular filtration rate (GFR). It has been accepted that estimated GFR (eGFR) ...



## NASA's Terra sees ash plume pulled to the northeast by a low

NASA's Terra satellite continues to provide visible and infrared imagery of Iceland's Eyjafjallajökull Volcano ash plume, and the most recent imagery showed the plume being pulled in a northeasterly direction over the island nation. The brownish ash plume was being pushed ...

Some of the findings are in agreement with earlier studies by Chang's lab on the role of AR in prostate cancer. Just as in prostate cancer, the liver tumor microenvironment is rich in various cell types, each of which has a distinct role in promoting the cancer.

"It will be interesting to see if targeting AR at different stages or in different liver cancer cell types may also lead to differential effects during the progression of cancer," the paper concluded.

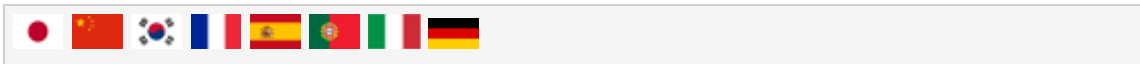
The hepatitis B and C viruses account for approximately 80 percent of primary liver cancer cases worldwide. Newborn vaccines and screenings for HBV and HCV, particularly in Asian and African countries, have reduced the incidence of liver cancer in later years. Still, an estimated 560,000 new cases are diagnosed annually. In high-risk areas such as China, Japan and sub-Saharan Africa the male-to-female ratio of liver cancer can be as high as 8 to 1. The current best treatment is surgery; median survival is generally six months.

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The National Institutes of Health and the George Whipple Professorship Endowment funded the research. Co-authors from the Whipple Lab and the URM Cancer Center are: Ming-Heng Wu, Wen-Lung Ma, Cheng-Lung Hsu, Yuh-Ling Chen, Charlotte Kathryn Ryan and Shuyuan Yeh. Additional co-authors include Jing-Hsiung James Ou, of the Department of Molecular Microbiology and Immunology at the University of Southern California, Los Angeles; Yao-Ching Hung and Wen-Lung Ma, of the Sex Hormone Research Center at China Medical University/Hospital in Taiwan. Ming-Heng Wu is also associated with Cheng Gung University in Taiwan; and Cheng-Lung Hsu, with Chang Gung University in Taiwan.



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## Male sex hormone linked to liver cancer risk

Updated on Monday, May 24, 2010, 12:21 IST

Tags: [Male sex hormone](#), [Liver cancer risk](#)

Taiwan: Male sex hormones may explain why men who suffer from the hepatitis B liver disease are more likely to develop liver cancer than women, researchers in Taiwan have found.

In a paper published in the journal *Science*, the researchers said hepatitis B viruses attach themselves to receptors of the male sex hormone androgen before going on to damage liver tissue and cause cancer.

"The findings indicate that using drugs to destroy ... androgen receptors could be a new way to battle liver cancer at an early stage," they wrote. Liver cancer is the fifth most common cancer and the third leading cause of global cancer death.

Hepatitis B virus infection, which is endemic in many Asian countries including China, is a leading cause of liver cancer and accounts for half of liver cancer cases worldwide. Men are up to seven times more likely than women to develop liver cancer.

Among hepatitis B virus carriers, men are up to three times more likely to develop liver cancer than women. Led by Ming-Heng Wu at the Institute of Basic Medical Sciences in National Cheng Kung University in Tainan, Taiwan, researchers found that hepatitis B viruses have a special DNA sequence which draws it to androgen receptors.

"The androgen receptors in liver cells bind to this sequence and trigger a cascade of damage to liver tissue," they explained. In their experiment, the researchers created mice that were infected with the hepatitis B virus and could easily develop liver tumours upon exposure to cancer-causing agents.

Some of these were genetically modified to be lacking in androgen receptors in their livers. By week 22 in the experiment, more than 90 per cent of those mice with androgen receptors had developed liver tumours compared to 27 per cent of the mice without androgen receptors.

Tinkering with the receptors did not change overall androgen levels or leave any obvious toxic effects in the mice. "Targeting the androgen receptor rather than androgen could be a promising therapy for liver cancer," the researchers said.

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