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## **Cancer Researchers Add Spice To Research Against Rare Neuromuscular Disease**

Scientists who focus on the molecular signaling that underlies prostate cancer have discovered a compound that shows promise against a debilitating neurodegenerative condition known as Kennedy's disease, which is caused by a mutant gene. Currently there is no treatment for the inherited disorder, which resembles a slowly progressive form of Lou Gehrig's disease and affects only men.

The compound, a distant chemical relative of a component of the spice curry, dramatically slowed the progression of the disease in mice that carried the mutant human gene that causes the disease. The mice were able to walk much more normally, their muscles were much stronger, and they had near-normal levels of a vital molecule crucial for keeping nerve cells healthy.

While a great deal more research needs to be done to see if the compound could be developed into a drug to help people with the disease, scientists say it's a promising development in a field where progress has been slow.

The research by scientists at the University of Rochester Medical Center appears in the March 6 issue of the journal *Nature Medicine*.

In their search for new treatments for prostate cancer and other diseases, Chawnshang Chang, Ph.D., and his colleagues have taken a few cues from centuries of Asian tradition, where curcumin – the bright yellow spice found in curry powder – has been used to treat a variety of ills. In the last decade, Western medicine has been putting curry to the test, finding that the spice offers promise against breast cancer, melanoma, Alzheimer's disease and the blisters that come with radiation treatments for cancer.

Chang notes that ginger, a family of spices that includes curcumin, is widely used in China as a folk medicine to treat male-pattern baldness. That condition is caused largely by the activity of the androgen receptor, the protein that is central to the action of testosterone and other male hormones. Chang's laboratory, in collaboration with San Diego-based AndroScience Corp., has screened hundreds of compounds for their activity

involving the androgen receptor, which is also involved in prostate cancer, acne, and enlarged prostate, as well as Kennedy's disease.

Among the compounds tested is ASC-J9, a synthetic chemical compound that is loosely based on a compound found in curcumin. Significantly, however, ASC-J9 has been chemically modified compared to its natural counterpart to make it much more powerful. Despite the promise it offers for Kennedy's disease, Chang notes that ASC-J9 must be rigorously screened for side effects and effectiveness, through clinical studies in people, before it can be considered as a possible treatment for any disease.

"The compound we are studying has been significantly modified from the original ingredient found in food like curry or ginger," said Chang, a faculty member in the departments of Urology and Pathology and the James P. Wilmot Cancer Center. "It still must be tested in people. We certainly don't want to mislead people to think these foods themselves have any benefit for Kennedy's disease."

Just last month, a clinical trial evaluating the use of ASC-J9 as a cream to treat acne began. The tests are being conducted by AndroScience Corp., 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.

As the director of George Whipple Laboratory for Cancer Research at the University of Rochester Medical Center, much of Chang's research focuses on prostate cancer. His research has explained some previously baffling developments late in the course of that disease, opening the door to newer treatments.

In 1988 Chang was the first to clone the androgen receptor, and he was the first to discover that the protein needs molecular allies called co-factors to accomplish many of its tasks. Now more than 70 co-factors are known, offering many new targets to potentially stop conditions like Kennedy's disease that involve the receptor itself.

Chang's work has led to an understanding of the genetic basis of Kennedy's disease, which affects the motor neurons that go from the spine to certain muscles, causing muscle weakness and wasting throughout body. Symptoms typically include difficulty speaking and swallowing, and weakness in the arms and legs. Patients are often diagnosed in their 30s and 40s, and while most live a normal life span, many patients end up using a wheelchair and have serious health difficulties. Currently there is no way to slow the progression or prevent the disease, which is estimated to affect a few thousand Americans, perhaps 4,000 or so.

In the experiments reported in *Nature Medicine*, mice carrying the human gene that were treated with ASC-J9 experienced a remarkable improvement. They were more mobile than their untreated counterparts, walking more normally and dragging their legs less often. Their muscles appeared to work normally, and they lived 40 percent longer than the untreated mice. In addition, the mice treated with ASC-J9 were able to mate and produce offspring, while their counterparts could not.

ASC-J9 appears to work by breaking up a sort of molecular clog in neurons affected by Kennedy disease. The biology of the disease is bit like Huntington's disease, a more common neurodegenerative disease that is inherited, fatal, and unyielding in its progression. Both are caused by an abnormal repeat of three nucleotides, CAG, though not in the same gene – a kind of molecular stutter that results in extra copies of the amino acid glutamine.

In such diseases, the extra amino acids become part of abnormal proteins that clump up inside neurons, creating a clog that can bring normal molecular activity to a standstill. The clumps of material eventually become toxic to neurons.

In Kennedy's disease, a vital molecule known as CREB-binding protein or CBP becomes bound up or entangled by the clumps in motor neurons. This smothers CBP's normal activity which involves turning on another molecule known as VEGF, a growth factor that is crucial for life and essential to the health of motor neurons.

Chang's team found that ASC-J9 breaks up the clumps by separating the androgen receptor from some of its helper molecules, or co-factors. As the clumps dissolve, CBP moves throughout the cell as it normally would, producing more VEGF.

Ultimately, the work brought about healthier mice whose symptoms were much improved. Chang's team also found that the amount of abnormal clumps in the neurons and spinal cords of the mice was slashed by half, and that VEGF activity in the neurons went up more than four times in the treated mice compared to untreated mice.

The new research is a signal that new avenues for treating conditions like prostate cancer, baldness and Kennedy's disease – all of which rely on the androgen receptor – are opening up, thanks to the dozens of molecular players that Chang and others have identified in the past decade.

“Traditionally, when scientists have wanted to affect the androgen receptor, they have taken away substances like testosterone that bind to and activate the receptor,” said Chang. “But this can cause many unwanted, systemic side effects. We take another approach: Instead of taking away the substances that turn on the receptor, we look for ways to attack the faulty receptor directly. In this experiment, for instance, the mice treated with ASC-J9 have normal fertility and are completely healthy sexually, which wouldn't be the case if we simply took away testosterone.”

The first author of the study, funded by the National Institutes of Health and the Kennedy's Disease Association, is Zhiming Yang, a former graduate student who earned his doctorate under Chang and is now at Zhejiang University and 2<sup>nd</sup> Hospital in Hangzhou, China. Other authors include Yu-Jia Chang, formerly a post-doctoral researcher with Chang, now an assistant professor at Taipei Medical University and Hospital in Taipei, Taiwan; graduate student I-Chen Yu; Shuyuan Yeh, associate professor of Urology; medical student Cheng-Chia Wu; post-doctoral researcher Hiroshi

Miyamoto; Diane Merry of Thomas Jefferson University in Philadelphia; Gen Sobue of Nagoya University in Japan; and former post-doctoral researcher Lu-Min Chen and physician Shu-Shi Chang, both at China Medical University and Hospital in Taichung, Taiwan.

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