Newsletter

Prostate Cancer 101, Inc.

http://prostatecancer101.org

April, 2010

The Prostate Cancer Information and Support Group of the Mid-Hudson

Coming: Vaccine That Fights Prostate Cancer

by Ford Vox | U.S. News & World Report | 12.04.2009

Women were the beneficiaries of the first cancer vaccine Gardasil, approved in 2006 to prevent cervical cancer. Several weeks ago, the same drug was made available to young males to prevent genital warts. And now it looks as if the first vaccine approved to fight cancer, by enhancing the body's immune response to cancer cells, will benefit males. Last month the Food and Drug Administration committed to deciding the fate of the prostate cancer vaccine Provenge by May 1, 2010. Prostate cancer is an appealing target because it moves slowly (even men whose cancer comes back after prostate surgery often live for well over a decade). That wide window of opportunity gives a vaccine time to prompt the immune system into fighting the body's own cells when they've become cancerous. (The immune system routinely fends off some tumors on its own, generally tiny cancers that are never detected, much less diagnosed.)

But while Provenge is on track to enter the market first, a less-sexy vaccine that hasn't caught the eye of biotech investors could work just as well at a much lower cost.

To the chagrin of patient advocates (and investors), the FDA ruled against allowing Provenge into doctor's hands back in 2007 when the results of its large Phase III trial came in. The trial supported the vaccine's effectiveness -- men with advanced prostate cancer lived several months longer after getting the vaccine. But Dendreon, the company that owns the technology, hadn't set out to judge the vaccine's value for extending life. The company had designed the trial, and had so informed the FDA, to assess disease progression -- how fast the cancer grew and spread. Those results didn't show that the drug offered a statistically significant improvement. New goal, new game, dictated the FDA. The company had to fund a second large trial, this time designed explicitly to test for survival benefit, if it was ever to see its product enter the U.S. market. The results, announced in April, showed that patients with advanced metastatic prostate cancer who had failed other treatments lived four months longer, on average, if they got the Provenge vaccine. That's statistically significant, but is it clinically significant? Dendreon wants patients and doctors, not the FDA, to decide.

Provenge isn't your typical vaccine. It's custom-made from each patient's dendritic cells. These specialized cells mop up foreign molecules (antigens) and then show them off to the immune system's T-cells. If the T-cells don't like what they see, they seek and destroy any cells that carry the antigen, even the body's own cells. To make the

Provenge vaccine, technicians must culture a patient's dendritic cells and expose them to an antigen called PAP, found in cancerous prostate tissue. After the cells take up the antigen, they are reintroduced into the patient's bloodstream in a series of three injections to begin schooling the immune system. Because of all this high-tech labor, Provenge will be very expensive, which has attracted the interest of a lot of investors. A few months more of life for a hefty price is all that most cancer therapies offer, and that won't change with this vaccine.

Now for the cheaper way—David Lubaroff's old-school approach. Lubaroff, director of urology research at the University of Iowa, has fashioned a vaccine from a common cold virus. It can be produced inexpensively in mass quantities like the influenza vaccine. Lubaroff and his team inserted the genetic code for prostate-specific antigen, which is generated by prostate cancer cells, into a weakened virus. When a prostate cancer patient gets Lubaroff's PSA vaccine, the weakened virus causes the body's immune system to think that PSA is a foreign intruder like rest of the virus's proteins, and the T-cells go on a search-and-destroy mission against the invading cancer cells. Lubaroff has already demonstrated this fact in animal models, and this month in the journal Clinical Cancer Research, he reports on the vaccine's first human trial. Only 32 men with advanced prostate cancer got the vaccine -- the group was so small because the goal of such a Phase I trial is only to determine whether a drug is safe. That's also why investigators only enrolled men with severe disease who were out of other options. There were no serious side effects. As for cancer fighting, over half of the patients lived longer than would be expected—three patients lived close to four years longer. But the study was too small to say much more.

Men with localized prostate cancer could end up benefiting from a vaccine, but they'd have to get the vaccine only after a prostatectomy to remove the prostate gland. Cancer-fighting vaccines are designed to target your own tissues, and even healthy prostates put out PSA. If you got Lubaroff's vaccine prior to prostatectomy, you'd have a painful inflammation of the prostate gland (prostatitis) as your immune system attacked PSA-producing cells. But while Lubaroff's vaccine and Provenge are being tested in men who have cancer that's spread elsewhere in the body, both vaccines may be more effective if given before that happens. For one thing, men who've received chemotherapy, like some of those in the vaccine trials, may have worn-out immune systems that can't take full advantage of the vaccine's stimulation. For another, it makes sense to nip a cancer in the bud.

If the FDA approves Provenge without specific and strong restrictions, some doctors are sure to use it on patients with localized prostate cancer, and they'll be theoretically correct in doing that. "We thought it would be a harder sell" to do a trial in men with less-advanced disease, says Lubaroff. He thinks cancer vaccines like his would work as effectively, perhaps even more so, in men with cancer that hasn't spread. He has a larger Phase II trial underway, funded by the Department of Defense. For a big Phase III trial like those backing up Provenge, Lubaroff knows he'll need pharmaceutical sponsorship. Will he get such backing? Lubaroff's vaccine is a one-shot, one-size-fits-all deal; there's little opportunity for big money to be made from its manufacture or on the healthcare provider's end. Even the seasonal flu vaccine, which goes out to a far larger "customer base," wouldn't be feasible without special government concessions and sponsorship. But if Provenge goes on the market and doctors offer it to men without advanced disease, the expense will put a huge strain on the healthcare system. If the government truly wants healthcare that is more efficient and affordable, wouldn't it make sense to seek out and accelerate the development and approval of simple, cheap drugs—like Lubaroff's vaccine?

Source: www.zerocancer.org

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In Memoriam
Ralph Calcavecchio
Aug. 22, 1929-Dec. 28, 2009

How best to express the many fine attributes of our valued member, Ralph Calcavecchio, other than to relate that at his funeral service moving tributes were made by people of many faiths; a psalm was sung by the Bruderhoff choir; a chant intoned by Buddhists and joined by the congregants. Everyone was there in admiration and respect of the man they considered a friend who had shown kindness and compassion throughout his life.

Ralph, before he became too ill, aided in the set up of the hall for our distinguished lecture series and was one of our official greeters. He was a staunch supporter of PCa101 and its mission for many years.

He and his lovely wife, Adele, joined us at our December 2008 Sharing and Caring meeting, at which he spoke kind words to us all. I, for one, will never forget, how much effort that must have taken for him, but he did what he felt in his heart, which might just have been his watchword.

Ralph worked for many years for IBM, inventing devices still in use and winning several awards. He was appointed the Standards Project Authority within IBM. He continued his work on electromagnetic compatibility and radio interference, even after his retirement.

A man for all seasons and varied interests including horsemanship, acting, the Arts Society and Library and many charitable endeavors, not to mention his craftsmanship in homebuilding and even an airplane. He and Adele owned and operated the Rondout Bed and Breakfast for many years.

Ralph Calcavecchio was a good man and lived his life as such. Would that we all could be remembered as he is; with a smile when we think of him and with thanks for the blessings of having known him. He will be sorely missed.

Diane Sutkowski

Prostate Cancer Treatment Guidelines Updated

by Henry L. Davis | The Buffalo News | 01.09.2010

The National Comprehensive Cancer Network has announced that it has updated its practice guidelines for physicians to stress active surveillance rather than treatment for many men with low-risk prostate cancer.

Roswell Park Cancer Institute played a key role in the new recommendations, with three physicians serving on the network's 23-member guideline panel, including Dr. James Mohler, who led the group.

A big change in the guidelines is the recommendation for active surveillance instead of treatment for men with very-low- risk prostate cancer and a life expectancy estimated at less than 20 years, and for men with low-risk prostate cancer and a life expectancy of less than 10 years. The very-low-risk category is new and represents patients with what's considered "insignificant" prostate cancer.

The new guidelines reflect the debate in medical circles over what is the most appropriate action to take with early-stage prostate cancer.

The problem starts with the PSA test to detect prostate cancer. It can't tell the difference between harmless tumors and those that will grow into dangerous cancers but has led to suspected tumors being diagnosed much earlier, leading many patients to rush into unnecessary therapies that drive up costs and risk complications.

The other dilemma for the 192,800 men who will be diagnosed with prostate cancer this year is that each therapy, such as surgery and radiation, has its advocates, as well as its pros and cons. But it's unclear which one is best. The federal Agency for Healthcare Research and Quality in 2008 concluded that not enough scientific evidence exists to identify a treatment as most effective at prolonging life or limiting such side effects as incontinence.

Active surveillance is considered an option because prostate cancer is generally slow-growing. Experts estimate that 40 percent of patients 65 and older will die of other causes before their cancer requires treatment.

Active surveillance involves monitoring the disease and intervening if the cancer progresses. Patients in active surveillance should obtain regular prostate exams and PSA tests, according to the guidelines.

"Growing evidence suggests that overtreatment of prostate cancer commits too many men to side effects that outweigh a very small risk of prostate cancer death," Mohler, chairman of urology at Roswell Park, said in a statement.

The National Comprehensive Cancer Network panel reviewed data showing that 23 percent to 42 percent of all prostate cancers detected in the United States by PSA tests and digital rectal exams are over treated.

Despite the greater emphasis on active surveillance, Mohler said final decisions on care should be based on a careful review of a patient's particular situation, including life expectancy, disease characteristics, general health condition, potential side effects of treatment and the patient's preferences.

Drs. Robert Huben, chief of urology at Roswell Park, and Michael Kuettel, chairman of radiation medicine, also served on the panel.

The head of one of the leading prostate cancer advocacy groups praised the changes in the guidelines. "The recognition of active surveillance in recent years has been a good development," said Thomas Kirk, president and chief executive officer of US TOO International, a network of more than 300 support groups around the world, including Buffalo.

Source: Zero – The Project to End Prostate Cancer

Tokai Pharmaceuticals Initiates ARMOR Clinical Development Program for TOK-001; First Ever Multi-Target Investigational Drug for Prostate Cancer

TOK-001 Offers Unique Multi-Target Approach Combining Three Separate Mechanisms of Action in One Compound; Phase 1/2 Trial Begins in Castration Resistant Prostate Cancer

CAMBRIDGE**, Mass., November 10, 2009** -- Tokai Pharmaceuticals, Inc., a biopharmaceutical company focused on developing new treatments for prostate cancer, today announced the initiation of a Phase 1/2 clinical trial of its lead candidate TOK-001 for the treatment of patients with castration resistant prostate cancer (CRPC). TOK-001 is the only compound in development that combines three distinct mechanisms of action for the treatment of CRPC. CRPC is an advanced, difficult-to-treat form of prostate cancer that does not respond to prostate cancer therapies. Nearly all men initially diagnosed with prostate cancer eventually advance to CRPC. Prostate cancer is the most frequently diagnosed cancer and the second leading cause of cancer related deaths among men in the U.S.

"TOK-001 delivers a three-pronged attack on CRPC cells, and has shown very promising results in preclinical models of prostate cancer," said Seth Harrison, M.D., chairman and acting chief executive officer of Tokai and managing general partner of Apple Tree Partners. "This proprietary multi-target mechanism marks a novel and promising approach to both treating CRPC and addressing the clear unmet medical need for a safe and effective CRPC therapy. We are looking forward to building upon our promising preclinical safety and efficacy data to establish clinical safety and proof of concept in this tumor type."

In preclinical studies, TOK-001 demonstrated a novel mechanism of action acting in three distinct ways to treat prostate cancer: as an androgen receptor antagonist, as a CYP17 lyase inhibitor and by decreasing overall androgen receptor levels in prostate cancer tumors. Androgen receptor antagonists have demonstrated clinical effectiveness in the treatment of prostate cancer, with one currently available to patients and another in Phase 3 clinical trials. There is also a CYP17 lyase inhibitor currently in Phase 3 clinical trials and the compound has demonstrated reduction in prostate-specific antigen (PSA) levels. Notably, TOK-001 is the first investigational new drug that decreases androgen receptor levels in prostate cancer cells and the only in which all three of these distinct mechanisms are combined in one drug. In fact, in preclinical models, TOK-001 has demonstra- prostate cancer compound in development ted improved efficacy compared with any individual therapy or investigational agent in development to treat prostate cancer.

"For patients suffering from advanced castration resistant prostate cancer, chemotherapy is the only option at this point that has been shown to prolong survival. There is an urgent need for new treatments for patients with prostate cancer since these chemotherapeutic agents extend survival for only a few months," said Philip Kantoff, M.D., chief clinical research officer, chief, division of solid tumor oncology, and director, Lank Center for Genitourinary Oncology at the Dana-Farber Cancer Institute; and professor of medicine, Harvard Medical School. "We now have a better

understanding of the unique mechanisms by which prostate cancer tumors survive. Androgen signaling remains critical to the survival of prostate cancer cells even in the castration resistant state. Preclinical studies suggest that TOK-001 can disrupt these unique mechanisms. We look forward to the results from this trial and learning more about the potential role TOK-001 may play for those patients facing castration resistant prostate cancer."

About ARMOR

ARMOR (A ndrogen **R** eceptor **M** odulation **O** ptimized for **R** esponse) is Tokai's clinical program for the evaluation of TOK-001. The first clinical trial in that program, ARMOR1, is a Phase 1/2 open-label trial that will assess both safety and efficacy of once-daily treatment with TOK-001 in patients with CRPC. The Phase 1 component of the trial is a dose-finding study to evaluate escalating dose levels of TOK-001 and is expected to enroll nine patients. The Phase 2 portion of the trial is expected to enroll 40 patients, who will receive one of two target dosing regimens as identified by the Phase 1 results. The primary endpoints of the Phase 1/2 trial are safety and reduction in **PSA levels from baseline levels measured at first visit. Patients who respond to therapy will have the opportunity to continue treatment with TOK-001 in an extension arm of the trial.**

"Patients, their families and physicians dealing with resistant prostate cancer are looking for a treatment that is well-tolerated, safe and effective against this disease," said Bruce Montgomery, M.D., lead investigator of ARMOR1 and associate professor, University of Washington School of Medicine. "The standard therapeutic options for this disease are limited and often toxic, and this clinical trial signals an exciting development for patients battling resistant prostate cancer and potentially other forms of prostate cancer."

The Phase 1/2 trial is being conducted at leading prostate cancer treatment centers in the United States, including the Cancer Centers of the Carolinas/Greenville Hospital System University Medical Center, Comprehensive Cancer Centers of Nevada, Dana-Farber Cancer Institute, Fred Hutchinson/University of Washington Cancer Consortium, Roswell Park Cancer Institute, San Bernardino Urological Associates, Sidney Kimmel Comprehensive Cancer Center and University of California, Los Angeles. Please refer to www.clinicaltrials.gov for clinical trial details and enrollment information.

About Castration Resistant Prostate Cancer (CRPC)

According to the American Cancer Society, prostate cancer is the most frequently diagnosed cancer among men in the United States and is the second leading cause of cancer related death in this group. Prostate cancer tumors are unique in that their growth is fueled by androgens, or male sex hormones, which are produced mainly in the testes. Current therapies designed to reduce androgens by medical or surgical castration can be effective initially in controlling prostate cancer, but resistance to these therapies usually occurs, rendering them ineffective after several years. CRPC is an advanced form of prostate cancer that does not respond to first-line prostate cancer treatment and continues to thrive after a period of successful castration therapy. It is estimated that there are 60,000 new cases of CRPC in the United States annually. The only therapy currently approved for the treatment of progression of CRPC is the chemotherapeutic docetaxel. New therapies are needed to specifically address the multiple mechanisms that allow CRPC tumors to grow.

About TOK-001

TOK-001 is a small molecule, oral drug that disrupts the growth and survival of cancer

cells by attacking three specific targets in the prostate cancer tumor, providing a novel and proprietary triple mechanism of action for the treatment of prostate cancer. In preclinical studies, TOK-001 acts as an androgen receptor antagonist as a CYP17 lyase inhibitor and decreases androgen receptor levels in prostate tumors – the only drug in development that has been shown to exhibit this property. In TOK-001 these three distinct mechanisms of action are combined in one therapy.

About Tokai Pharmaceuticals

Tokai Pharmaceuticals is a U.S. biopharmaceutical company focused on developing new treatments for prostate cancer. The company's lead drug candidate, TOK-001, is the first investigational new drug that can decrease overall androgen receptor levels in prostate tumors and in which three distinct mechanisms of action are combined in one oncotherapeutic. TOK-001 is currently in clinical development and is being studied in patients with castration resistant prostate cancer. Privately held Tokai is based in Cambridge, Massachusetts and is backed by Apple Tree Partners and Novartis Venture Fund. For more information on the company and TOK-001, please visit www.tokaipharma.com.

Source: www.psa-rising.com

Is robot prostate surgery best for quality of life?

Study looks at long-term quality of life after various treatments

By Amy Norton

Monday, April 5 (Reuters Health) - Despite the popularity of robot-assisted procedures for prostate cancer, when it comes to men's long-term quality of life, patients with earlier stage cancers generally fare better with non-surgical approaches than with surgery, according to a new study.

Researchers say the findings, reported in the Journal of Urology, offer men more information to consider when deciding on treatment.

Men with earlier stage prostate cancer have a number of treatment options, from "watchful waiting" to radiation to surgical removal of the prostate gland.

When it comes to surgery, robot-assisted laparoscopic surgery -- where the surgeon sits at a console, operating robotic "arms" that extract the prostate gland through small cuts in the abdomen -- has become the dominant approach in the U.S.

After hospitals invest the roughly $1.5 million for the machines, plus the costs of surgeon training and annual service contracts, they often aggressively market robotic surgery. That may include claims that it carries lower risks of long-term incontinence and impotence than traditional open surgery. Actual study data to prove that, however, are lacking.

In the new study, researchers at the Sentara Health System/Eastern Virginia Medical School in Norfolk followed 785 men who received one of four types of treatment for localized prostate cancer (cancer confined to prostate gland) at their center between 2000 and 2008.

Overall, 135 men underwent traditional "open" surgery to remove the prostate gland, while 447 had robotic surgery. Another 122 patients had radioactive "seeds" implanted in the prostate gland to kill the cancer cells. The remaining 81 patients had cryotherapy, where the doctor uses thin metal rods inserted through the perineum to freeze prostate gland tissue and kill the resident cancer cells.

In general, the researchers found, men treated with radioactive seeds tended to fare best in terms of quality of life, based on standardized questionnaires they completed before treatment and periodically for three years after-

ward.

Patients who had received either radioactive seeds or cryotherapy had higher average scores when it came to urinary function, versus men who had either type of surgery. And together, men who had radioactive seed implants or cryotherapy were three times as likely as surgery patients to return to at least 90 percent of their pre-treatment score for urinary function.

When it came to sexual function, radioactive seed patients reported a greater quality of life than those who had received any of the other three treatments. Three years after treatment, radioactive seed patients' scores for sexual function and "bother" -- the degree to which they thought their sexual side effects were a problem -- were higher than they were before treatment.

In contrast, scores remained below pre-treatment levels for men in each of the other treatment groups. Cryotherapy patients had the poorest scores long term.

However, there were no significant differences in quality of life between men who had undergone open surgery and those who'd had robot-assisted surgery.

"I think data like these give men more information to use in their decision-making," Dr. Michael D. Fabrizio, one of the researchers on the study, said in an interview.

As for the lack of difference between open and robotic surgery, Fabrizio said that while there are advantages to the robot -- including far less blood loss during surgery and shorter hospital stays -- that may not necessarily translate into better long-term quality of life.

He noted that there is a "big push" to promote robotic surgery, and many patients "assume it's the way to go."

But the current findings, the researchers write in their report, "serve as a reminder that popular enthusiasm for robotic prostatectomy merits temperance."

Nor do the findings come down in favor of any single therapy, however. "This study doesn't tell patients what's right for everyone," said lead researcher Dr. John B. Malcolm, and men still have to talk with their doctors about which treatment might be best for them.

The study did not look at the four treatments' effectiveness against the cancer, Malcolm told Reuters Health, but other research has suggested that surgery is more effective than radioactive seeds.

The study had a number of limitations as well, including a lack of information on any other patient health problems that might have been affecting their sexual or urinary function.

It was also not designed as a randomized, controlled clinical trial -- where patients are randomly assigned to receive a particular treatment, notes Dr. Stephan A. Boorjian, of Fox Chase Cancer Center in Philadelphia, in a commentary published with the study. Such trials are considered the gold standard for assessing a given treatment's outcomes.

A second commentary says that the findings point to a broader issue: the general lack of randomized clinical trials comparing prostate cancer treatments with each other -- in terms of cancer control or quality of life.

"If the standard for evaluating all treatments for prostate cancer were raised," writes Dr. Yair Lotan, of the University of Texas Southwestern Medical Center in Dallas, "then patients and physicians would be able to use more objective criteria in determining the optimal treatment."

Source: Prostate Cancer Foundation (www.pcf.org)

When It Comes to Prostate, Watch and Wait

Major Cancer Group Endorses Active Surveillance for Prostate Cancer

by Judith Graham | Chicago Tribune | 03.28.2010

Five years ago, when he was diagnosed with cancer, Kevin Brick gratefully accepted a doctor's offer to wait and see what happened to the tiny tumor in his prostate gland.

So far, there is no evidence the cancer is growing or becoming more aggressive.

"Everything seems to be going fine," says Brick, 60, whose doctor examines his prostate and administers tests every six months.

The approach is called active surveillance, and for the first time it's being endorsed for large numbers of men by a major medical organization: the National Comprehensive Cancer Network, an alliance of 21 leading cancer centers across the U.S.

In new guidelines, NCCN recommends active surveillance for men deemed to have "very low risk" prostate cancer and a life expectancy of less than 20 years. Also, the organization recommends the strategy if a man's prostate cancer is considered "low risk" and his life expectancy is less than 10 years.

Almost 40 percent of the 192,000 men diagnosed with prostate cancer each year could qualify for active surveillance under those standards, said Dr. James Mohler, chairman of the committee that prepared the guidelines and head of urology at Roswell Park Cancer Institute in Buffalo, N.Y.

NCCN's goal is to identify men likely to have slow-growing tumors and prevent unnecessary treatments that can render them incontinent or impotent.

"We know one in six men will be diagnosed with prostate cancer, but only one in 40 men will die of prostate cancer," Mohler said. "It's obvious that we don't need to treat every single man with this condition."

The problem is that "we can't determine which prostate cancers are harmless," said Dr. William Catalona, director of the prostate cancer program at Northwestern University's Robert H. Lurie Comprehensive Cancer Center.

With active surveillance, there's a possibility that an aggressive cancer will be missed and the window for potentially life-saving treatment missed, he said.

By that logic, it's safer to intervene than adopt a "wait and see" strategy. And indeed, most doctors recommend surgery, radiation or other therapies, and more than 90 percent of patients follow their advice.

But there's mounting evidence that active surveillance works without adding to prostate cancer's death toll.

The longest running trial of the strategy is at Johns Hopkins University, where experts have followed 800 men over the past 15 years. To qualify, a man must be at least 65. "We have a very strong bias that a younger man who gets diagnosed with prostate cancer should be treated," said Dr. H. Ballentine Carter, professor of urology at Hopkins.

Men who join the program get a PSA (prostate-specific antigen) blood test and digital rectal exam every six months and a biopsy every year, up to age 75. If signs indicate a cancer is growing or becoming more aggressive, a patient is referred to treatment.

No patients enrolled in the program have died of prostate cancer. Thirty-two percent have undergone medical treatments; 56 percent are still undergoing active surveillance; 2 percent died of other causes; and 10 percent have withdrawn or lost touch with the program.

Similarly, there have been no deaths from prostate cancer among 300 men enrolled in an active surveillance program at Roswell Park Cancer Institute.

More trials of active surveillance are being launched across the country. At NorthShore University Health System in the Chicago suburbs, for example, 70 men age 60 or older have signed up for a new program over the past year. One is Richard Henriksen, 65, whose first wife died of pancreatic cancer five years ago.

"I like the fact that I'm being followed closely and that I'm not being pushed into doing something drastic quickly," he said. "Frankly, I'm pretty conservative when it comes to my health, and surgery is the last thing I want to do."

Source: Zero The Project to End Prostate Cancer

Scientists Find Key to Gene That Promotes Cancer Metastasis

4-protein complex provides new target for thwarting cancer migration, invasion

by EurekAlert.org | 04.12.2010

The molecular machinery that switches on a gene known to cause breast cancer to spread and invade other organs has been identified by an international team led by scientists at The University of Texas M. D. Anderson Cancer Center. The paper was published Sunday in Nature Cell Biology's advanced online publication.

The discovery provides a target-rich environment for development of drugs to thwart expression of the RhoA gene, according to Hui-Kuan Lin, Ph.D., the paper's senior author and an assistant professor in M. D. Anderson's Department of Molecular and Cellular Oncology. RhoA overexpression has been implicated in cancer metastasis.

"There are four components to this complex, which starts RhoA expression by transcribing the gene, and we found that all of them are important to metastasis," Lin said. "Knock down any one of the four, and you can stop breast cancer metastasis by preventing RhoA expression."

Researchers built their case with a series of laboratory experiments on cell lines, followed by confirmation in a mouse model of breast cancer metastasis and then analysis of 64 prostate cancer tumors that showed overexpression of RhoA or three of its transcription complex components were strongly correlated with metastatic disease.

Transcription is the first step on a gene's path to expressing its protein. Transcription factors bind to the promoter region of the gene, causing a copy of RNA to be made from the DNA of the gene. The RNA is then translated into the corresponding protein.

The team first established the Myc protein as a transcription factor that binds to RhoA's promoter region. Knocking down Myc in cancer cell lines decreased RhoA expression, cell migration and invasion, while Myc overexpression increased all three.

Next, they found that the Skp2 overexpression also results in more RhoA, and that both Skp2 and Myc were required for the metastasis-producing RhoA to be overexpressed.

This cancer-promoting pathway is the second way Skp2 fuels cancer growth, Lin said. Skp2 has been shown to work through a separate E3 ligase pathway to destroy tumor-suppressing proteins, causing heightened cellular proliferation and the transition from normal cell to tumor.

"Skp2's E3 ligase activity is required for tumorigenesis, but not involved at all in metastasis," Lin said. Lin and colleagues also previously found that Skp2 blocks cellular senescence – a halt in cell division – in cancer cells.

The research team then found that Skp2 recruits two other proteins, p300 and Miz1, to join Myc and form the complex that transcribes RhoA.

Experiments in a mouse model of breast cancer metastasis to the lung showed that deficiency of either Myc, Skp2 or Miz1 restricted metastasis, while overexpression of each of the three proteins increased cell migration and invasion. Skp2 knockdown, for example, resulted in no metastatic nodules in the lung, compared with an average of 40 nodules when Skp2 was expressed.

Directly knocking down RhoA expression produced the same effect as blocking the Myc-Skp2-Miz1 complex. Knocking down expression of p300 resulted in decreased expression of RhoA.

In the analysis of prostate cancer tumors, expression of RhoA, Myc, Skp2 and Miz1 were significantly correlated with metastasis. Expression of the RhoA and the Myc-Skp2-Miz1 complex also were highly correlated.

Lin and colleagues note that Miz1 is thought to be a tumor-suppressor that contends with the oncogene Myc to regulate genes. In this case, the tumor-suppressor cooperates with the oncogene to launch RhoA and promote metastasis.

"Right now, there are no small-molecule agents to inhibit any of these targets," Lin said. "One future direction of research will be to find ways to target the entire transcription complex or its individual components."

Source: ZERO The Project to End Prostate Cancer

General Powell Discusses Prostate Cancer on Facebook

by Paul Bedard | U.S. News & World Report | 04.06.2010

He still loves his gadgets and Corvettes, but retired Gen. Colin Powell is also very attentive to his Facebook fans page. He has over 22,700 of them and word is that he reads every single comment that comes in.

Well he just turned 73 last weekend and noted that one of his fans referred to his prostate cancer. So in his comment box he announced that he is still cancer-free and a spokesman for prostate cancer screenings.

"Today was my 73rd birthday and the most valuable gift I received was all the well-wishes from so many of you. Thank you. As one of you noted, I am a prostate cancer survivor and a spokesman for prevention. Men should have regular prostate examinations. Black men are more susceptible to the disease than others. Regular exams allowed me to deal with this problem early and make a full recovery."

Even after his many years in the Army and public service, he is still a public leader on major issues. To quote one of his well-wishers, "If today's government leaders and officers had the same desire for leading by providing purpose, motivation, and direction as you do, this nation would be on a better standing."

Source: Zero The Project to End Prostate Cancer

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Poughkeepsie Man to Man Group
Our brothers in support and education

Meetings are held the First Thursday of the month at the Central Hudson Auditorium on South Road in Poughkeepsie, starting at 6:30 p.m. Various doctors and speakers are on the agenda and one on one help is available after the meeting.

Contact
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If you need or want to help:

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