Shrinking Prostate Tumors by Starvation

William L. Dahut, M.D., has always straddled both the clinic and the lab. He completed his clinical training in internal medicine at the National Naval Medical Center in Bethesda, Md., and in hematology and medical oncology at the Bethesda Naval Hospital and the Medicine Branch of NCI. When offered the opportunity to join CCR's Medical Oncology Branch and a clinical program in prostate cancer research, Dahut leapt at the chance. The draw was CCR's unique intramural program, in which the science drives the design and implementation of clinical trials.

When a man develops prostate cancer, he can expect any of a number of possibilities. The good news is that fewer than 10 percent of the estimated 230,000 men diagnosed in the U.S. each year succumb to the disease. In essence, there is life after a prostate cancer diagnosis.

Unfortunately, researchers have not yet found a cure. At CCR, we are working on the cutting edge to develop those cures. In the interim, there is treatment. It can delay the progression of disease, sometimes for a lifetime. Treatment also helps relieve pain and other complications that arise as the disease progresses.

Prostate tumors can grow slowly or more aggressively. They can remain contained in the glandular region, where the tumor originates. Or they can spread (metastasize) to other locations in the body, mainly the bones.

Long before patients arrive at NCI, their local physician probably detected the first signs of a problem—a continued rise in the blood levels of prostate specific antigen (PSA), a marker for replicating prostate cells (see "PSA and Its Vaccine Potential?"). A biopsy would have confirmed the diagnosis of cancer. The next step would have been either surgery, radiation therapy, or, if the tumor was growing very slowly, "watchful waiting" (simply monitoring the tumor over the course of time).

In about a third of these cases, however, the disease recurs or progresses, as signaled by a rise in PSA. At this stage, the malignancy is still not life-threatening. But once it spreads outside the prostate, as detected by a bone scan, the situation becomes more serious. At this stage, we say that the patient has metastatic prostate cancer and give him a choice: drugs that block the action of the male sex hormone testosterone (which can fuel prostate cancer growth), or orchiectomy (surgical castration).

If PSA levels begin to rise again, we consider the patient "castrate resistant." He may benefit from second- or third-line agents that block testosterone or its receptor on prostate cancer cells. But not everyone responds well to these therapies. At this point, patients come to us at NCI, where we are working with men whose tumors have metastasized to discover unique treatments and strategies that can delay the progression of disease.

At the Cutting Edge

Outside NCI, patients with metastatic prostate cancer are usually prescribed a regimen of chemotherapy, primarily a combination of an agent called docetaxel and the steroid prednisone. Patients receive this treatment every 21 days. But chemotherapy does not cure the disease; in some cases, it does not even prolong survival.

Our lab at the Medical Oncology Branch of CCR, in collaboration with others such as William Figg, Sr., Pharm.D., Senior Scientist and Head of the Molecular Pharmacology Section, is looking for other options. We have chosen to let the molecular discoveries made in our laboratories guide the design of our clinical trials, an approach that is made possible at CCR by its close connection (both in location and collaboration) to the clinics at NIH's Clinical Center.

Blocking Blood Vessels—Starving Tumors

A decade ago, we became intrigued by the concept of angiogenesis, or blood vessel growth and development. In 1971, Judah Folkman, M.D., at Children's Hospital Boston (CHB), published a seminal paper proposing that solid tumors need a supply of blood vessels to sustain their growth. Tumor cells create these blood vessel networks by producing so-called angiogenic proteins, molecules such as vascular endothelial growth factor (VEGF) that promote the shaping and sprouting of new blood vessels. Folkman hypothesized that if oncologists could somehow block

The Dahut team (clockwise from center front): Dahut, Lea Lathan, R.N.; Jackie Jones, R.N.; Phil Arlen, M.D.; James Gulley, M.D.; Yanh-Min Ning, M.D.; Kim Scott, R.N.; Marica Mulquin, R.N.

angiogenesis, they could starve tumors, and so shrink them. His laboratory went on to purify the first angiogenic tumor protein, discover the first molecules that could inhibit angiogenesis, and initiate clinical trials of anti-angiogenic therapies.

In 1994, Robert D'Amato, M.D., Ph.D., then in Folkman's CHB laboratory, demonstrated that the drug thalidomide inhibited angiogenesis by blocking fibroblast growth factor, a molecule that stimulates cell reproduction. While thalidomide was withdrawn from the market 30 years ago after it was linked to birth defects, researchers in the last two decades started looking at thalidomide as a potential anti-cancer drug, thinking that if thalidomide could prevent new blood growth to prostate tumors, it might provide a means to shrink them, and so help patients achieve remission.

We decided to apply these concepts to prostate cancer, designing a "hypothesis driven" clinical trial that used the basic science on thalidomide's putative anti-angiogenic capabilities to make predictions as to how it might act on prostate tumors in patients.

In our first trials, we learned that thalidomide alone is not enough by itself to stop prostate tumor growth. But we found that when we combined thalidomide with standard chemotherapy (docetaxel), more than half of patients experienced a 50 percent or greater drop in PSA levels after 26 months of treatment, compared to slightly more than a third of those treated with docetaxel alone. Even more promising, the combination of docetaxel and thalidomide prolonged overall survival.

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While this research was a step forward in improving pain management and survival, the treatment still was not a cure. Thus, we opened our third and current metastatic prostate cancer trial in 2004, this one combining two anti-angiogenic compounds (each with a different mechanism of action) with docetaxel and prednisone. While we know that thalidomide can hinder blood vessel growth, its precise tactics for doing so are still unclear. Thus, we hypothesized that we might improve our metastatic prostate cancer treatment even further by adding another anti-angiogenic drug, bevacizumab (Avastin®, Genentech), which works through a different biochemical pathway.

Our preliminary results show clearly that this combination is our most active yet. After receiving the combination in 21-day cycles, nearly every patient enrolled in the trial has experienced a drop in PSA levels of at least 50 percent. Typically, patients at this stage of disease survive about 18 months when treated with chemotherapy alone. Thus far, three-fourths of trial participants have passed the 18-month mark. As we go

forward with the analysis, we are accruing the data to support innitiation of a larger randomized trial including thousands of patients. And while patients do experience side effects, which are to be expected as we add more drugs to a regimen, most find that the benefits of therapy outweigh the side effects.

Another Vein of Trials

One caveat is that patients enrolling in these anti-angiogenic trials cannot have undergone chemotherapy before enrolling, as previous treatment would confound the results. Many patients who come to NCI do not fit that eligibility criterion, having exhausted their chemotherapeutic options beforehand. For these men, we have another clinical trial, this one focused on a small molecule called AZD2171 (Recentin™, AstraZeneca). It acts similarly to bevacizumab, which targets VEGF, except that AZD2171 actually targets the receptor for VEGF. One major benefit of AZD2171 is that patients can take it at home as a pill once daily for 28 days; with bevacizumab, they have to travel to NCI every three weeks for infusions.

Early data shows that AZD2171 can shrink tumors in patients' lymph nodes, another common site for metastasis. This activity gives us an opportunity to see whether we can use measurements of blood flow as a surrogate marker for blood vessel growth and, by extension, anti-tumor activity. If we can correlate changes in blood flow to stalled blood vessel growth to anti-tumor activity, we will have a way to better monitor patients' progress as well as a better understanding of disease progression and drug action.

The Road Ahead

In the future, we hope to personalize our prostate tumor research by studying the unique biology of each patient's tumor and the possible genetic differences that not only cause each tumor to grow at different rates, but also cause each person to respond differently to therapy. Researchers are genetically comparing tumor and normal tissue and are looking for differences in gene expression and markers of metabolism of various drugs. This tailored approach to medicine is just over the horizon in other types of cancer.

Prostate cancer research is often hindered by the difficulty in obtaining tumor cells from biopsies, which in our case have to come from bone since most of our patients have previously undergone surgery to remove the prostate (prostatectomy). We are working with collaborators on a method to capture cancer cells that have escaped the tumor and are circulating throughout the blood stream. Such an advance would improve our ability to conduct the kinds of molecular studies that will let us match the biology of the tumor to the age, cancer stage, and health of individual patients.

As we move forward, we have a clear goal in mind: to develop treatments that are beneficial for the patient and, at the same time, advance the field of cancer research. At CCR, we have the unique ability to determine not only if the drugs are working in patients, but also why they are working (or not), thanks to our close connection to the lab. We can only achieve this feat because of the heroes—the patients who volunteer to join our trials (see "Patient Perspectives").

PSA and Its Vaccine Potential?

At the most basic level, cancer starts as healthy cells gone awry. In many cases, these cells are still able to produce the proteins that they produced as normal cells, but in higher amounts. This difference is what has made prostate-specific antigen (PSA) a valuable tool for the last 20 years. PSA is normally produced by healthy prostate cells. However, as prostate cells turn cancerous and begin to increase in number, so does the level of PSA; this rise can be measured in the blood with the PSA test.

In addition to its value as a biomarker, researchers like Jeffrey Schlom, Ph.D., Head of the Immunotherapeutics Group in the Laboratory of Tumor Immunology and Biology at CCR, look at PSA as a means of creating prostate cancer vaccines. Unlike vaccines for influenza or chickenpox, though, these vaccines are therapeutic, not preventative. Schlom's group has come up with eight vaccines by inserting the PSA gene into large poxviruses (e.g., vaccinia, fowlpox), which are able to deliver considerable amounts of genetic material. When injected into patients, the viruses carry the gene into the body and trigger an immune response against the PSA-carrying prostate cancer cells. Other strategies include combining vaccines with hormonal therapy, radiation, chemotherapy, or, most recently, molecules that take the brakes off the immune response.

Schlom and his collaborators, including Clinical Immunotherapy Group directors Philip Arlen, M.D., and James Gulley, M.D., Ph.D., are targeting men who are castrate resistant (no longer respond to hormonal therapy) but whose tumors have not yet metastasized. The vaccine project also involves the design and development of novel immunoassays to analyze patients' immune responses both pre- and post-vaccination.

Patient Perspectives

Lenny Renner

For Lenny Renner, 63, it all began with a cholesterol test. In 2003, he went to his doctor's office in Minneapolis, Minn, simply to get blood drawn in a typical wellness check.

"And while you're at it, why don't you take my PSA?" Renner said, referring to the protein that signals whether a man may have prostate cancer.

The test came back with a high value, a sign that a tumor might be growing. His doctor felt Renner's prostate and found a lump. A local urologist confirmed the suspicion of cancer. But the definitive answer came after a local oncologist took a biopsy and made a positive diagnosis.

When given the options, Renner chose to have his cancerous prostate removed. During the procedure, however, his oncologist noted that the cancer had spread to Renner's bladder. That brought the more serious diagnosis of "metastatic prostate cancer" and the suggestion that Renner travel to Bethesda to join a prostate cancer trial at NCI.

Renner made his first trip in June 2005, expecting that because he was entering a research hospital, "people would be cold, aloof, clinical." But he experienced the opposite. Physicians, nurses, and staff were "the nicest, friendliest caretakers." A nurse gave him a hug. "It feels more like they are on your side," he said, "not like they are looking at me as if I am a guinea pig."

Renner chose to enter a trial of a cancer vaccine (see "PSA and Its Vaccine Potential?"). Given that he is the kind of person who "hated even taking aspirin for a headache," he liked the idea of using his body's own immune system to "fend off" the cancer. But after four months, his PSA levels began to rise again.

Thus, Renner joined William Dahut's combination clinical trial (see main text), taking two anti-angiogenic drugs, chemotherapy, and a steroid.

So far, the signs are good. Renner's PSA has "fluctuated a bit" but stayed within a healthy range. A pain in his hip—caused by the spread of his tumor cells—has now dissipated. And while he has experienced some side effects, he takes it all in stride. He knows that while he will not be "cured" with today's level of medical technology, he is not "terminal." Thus, he accepts that treatment at CCR, which he calls "the best in the country, if not the world," is now "a part of my life."

That acceptance has made him more philosophical. "I am hoping that regardless of my outcome," he said, "others will get some benefit out of my participation in this important research."

His advice to others considering clinical trials at CCR: "If there is any way to swing it, including the travel, I would highly recommend it."

David Thorpe

For David Thorpe, 69, a diagnosis of prostate cancer was the beginning of a journey, full of highs and lows, triumphs and disappointments.

His first sign of trouble came in 1992, with a PSA reading of 12 nanograms per milliliter (the healthy range is 0-4 ng/ml). A urologist confirmed the diagnosis through a biopsy. Thorpe, living in Connecticut, traveled to Yale, in New Haven, for surgery to remove his prostate.

Six years later, his PSA levels rose again, a sure sign that renegade cancer cells remained in his body despite the surgery. After seven weeks of radiation treatment, Thorpe's PSA levels dropped to zero, only to climb again after another two years. This time, treatment was hormonal therapy, which blocks the production of testosterone. His PSA levels went back down.

But again, the fix was temporary. Within seven years, Thorpe's PSA climbed to 4, even while taking the anti-hormonal drug. Doctors added a second anti-hormonal drug, one that blocks an additional source of testosterone in the adrenal glands. After six months, the second therapy stopped working, too.

Thorpe, now retired and living with his wife in Vero Beach, Fla., watched helplessly as his PSA levels rose; "It was not a fun situation," he recalled. He sought help from an oncologist in Vero Beach. There was nothing to do but wait and see, checking bone and CAT scans for signs that the cancer had spread. Five months later, the bad news came: Thorpe's tumor had metastasized into the lymph nodes in his pelvic area.

That was when Thorpe's oncologist in Vero Beach introduced him to William Dahut. After getting a second opinion at the Fox Chase Cancer Center in Philadelphia, Thorpe traveled to NCI in December 2006 and joined the same Phase II clinical trial as Renner.

When he started the trial, Thorpe's PSA was up to 17.6. Today, with the three-week cycles of therapy, it has dropped to 0.4. CAT scans show that his formerly enlarged, cancer-laden lymph nodes are either back to normal or near normal. His bone scan is stable. And his side effects are all manageable with drugs and vitamins. "Even though I am dealing with reduced energy and stamina levels," Thorpe noted, "I have been able to pursue normal activities."

While no one can make predictions about his specific outcome, 65 percent of the patients in Thorpe's trial are still in the protocol 18 months later, and some have been in it as long as 30 months.

"I'll take it," said Thorpe, who is now traveling to visit his children, grandchildren, and friends. "I know that I had better live today," he said, "because, at some point, there won't be a tomorrow. If you are dealing with a limited time horizon like I am, it is encouraging when you can realize a quality life for an additional 18 or 30 months, or longer."

"I have been very pleased," Thorpe said, "with the care and service of the dedicated professionals at NCI."

A Molecular View of Prostate Cancer Therapy

(Photo: Courtesy of Douglas Figg, CCR)

William Douglas Figg, Sr., Pharm.D.

Traditional chemotherapy has long produced disappointing results in prostate cancer patients. But William Douglas Figg Sr., Pharm.D., Head of the Molecular Pharmacology Section at CCR, is trying to change that reality. Figg's group is not only taking a molecular view of cancer—drilling down into the ways that small molecules might slow tumor growth—but is also describing how the body metabolizes new anti-cancer drugs.

Before introducing a promising new drug into patients, researchers first determine two parameters: the drug's pharmacodynamics (where in the body the drug will travel and how it will behave when it reaches its target) and pharmacokinetics (how long it will stay there before being broken down and eliminated). For instance, predicting liver enzyme metabolism is "huge for cancer," Figg said, because many drugs can interact with each other. Further, many anti-cancer drugs have a very narrow time frame in which to work. Therefore, a drug that does not reach a tumor by a specific time could be essentially useless.

Figg and his team are leading CCR's efforts to address these complexities, working with analytical chemists to develop assays to measure many different aspects of drug metabolism before a drug ever enters a patient's body.

For instance, Figg's team has developed assays that determine what concentration of drug builds up in different "compartments" of the body (e.g., the bloodstream, liver, kidneys). Liver enzyme tests they have developed can give an idea of how a drug is metabolized, information that can help pinpoint whether a person is likely to be a "slow" or "fast" metabolizer, which in turn affects how much drug they need to achieve a certain effect. And they have also created tests to determine how well a drug binds to a class of blood proteins called AAG plasma proteins; such binding can increase the time a drug remains intact and active (dubbed its "half-life"), but leaves less drug available to do its job.

Figg's group is also part of an international team that is synthesizing and screening 120 variants of the anti-angiogenic drug thalidomide (see main text). They have already flagged seven for additional study. The CCR team is able to test these and other anti-angiogenic agents—some provided by companies such as Pfizer, Novartis, and Aventis—in at least four model systems of blood vessel growth and development.

The key to this whole drug development system is collaboration—both outside CCR and within. Figg has teamed up with William Dahut, M.D., who conducts patient studies of drugs later in the development process. In this pairing, Figg focuses on pharmacokinetics and pharmacogenomics—the study of the unique genetic variations in each person's enzymes that determine how they metabolize drugs.

"Pharmacokinetics and pharmacogenomics are key to the drug development enterprise at CCR," Figg said. "Ours is a model for what most of CCR is moving to: tying a translational lab like mine to a clinician such as Bill Dahut."

Patient Perspectives (continued)

Jimmie Smith

For Jimmie Smith, 73, prostate cancer has been an odyssey—of doctors, institutions, and more than one clinical trial. His journey began July 3, 2002, with a PSA score of 17 and a biopsy confirming a diagnosis of metastatic prostate cancer.

Smith lives in the small town of Rocky Mount, N.C., where everybody knows everybody; his general practitioner and urologist are close friends. But the town held limited treatment options for him. Thus, Smith traveled to Duke University in Durham, then to University of North Carolina's Memorial Hospital in Chapel Hill. At UNC, he received a battery of treatments, including two chemotherapy agents and a steroid. By February 2003, his PSA had dropped to 0.3.

When his PSA rose again, a friend suggested a trip to MD Anderson Cancer Center. The oncologist there told Smith that he had six months to live. He made a trip to an oncology/hematology clinic in Los Angeles, Calif., that boasted alternative treatments, but none that Smith wanted to try. He called The Johns Hopkins Hospital; unfortunately, they had no prostate cancer clinical trials at the time.

Smith began to lose hope, until another friend told him about a family in Rocky Mount whose son who worked at the National Institutes of Health (NIH). The son told him about a clinical trial there for men with metastatic prostate cancer.

By March 2005, he had undergone castration surgery, his cancer had spread to a lymph node, and his PSA was 11. In short, he was running out of options. Thus, on April 18, 2005, he became the first patient to enter William Dahut's combination therapy trial, the same that Renner and Thorpe would later join.

Twenty-eight months later, Smith is still in the trial. His PSA initially dropped to 0.8 and the cancer seems to be at bay, a far cry from the six month pronouncement made previously. But more importantly, Smith is ebullient about his experience with the NIH doctors and staff.

"Everybody up there is just so intelligent and so caring, even the security personnel," he said. "And I can't think of anything to say that wouldn't be a real honor to them."

To this day, Smith believes if not for the friend and the tip about the NIH, he would have died sometime in 2005. Now, whenever he meets a person in his town with cancer, he tells them about NIH.

"I tell them, 'Go one time. One time. I'll even pay for your trip,'" he said. "I feel that strongly about NIH."