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True Grit: The never-say-die attitude of men with advanced hormone refractory prostate cancer is an inspiration

By John Hoffman

Ten years ago, few people would have guessed that Gordon Dunn would still be around in 2008. Gordon has been fighting prostate cancer since 1995, and his illness has been considered hormone refractory since 2005.

That means he got to the point where his cancer was progressing in spite of the hormone treatments designed to keep it in check. When first line treatments like surgery or radiation fail to eradicate all cancer cells, men with prostate cancer are often put on hormone therapy, various treatments designed to reduce the influence of testosterone, which is the "food" that makes prostate cancer cells grow. Often a hormone treatment works well at first, but sooner or later, for reasons not quite clear to doctors, men "hit the wall." Their PSA rises in spite of the treatment. At that point, patients are often put on a different hormone treatment medication, which, again, usually works for a while but eventually loses its effectiveness. Once a man's cancer becomes resistant to all hormone treatments, his illness is considered hormone refractory.



Gordon Dunn has been on numerous medications and supplements. The most recent is ketoconazole, a synthetic antifungal drug that also happens to shut down production of the approximately 5 per cent of a man's testosterone produced by the adrenal glands. Ketoconazole is not generally used as a prostate cancer treatment in Canada. For the last few months, it has held his PSA steady at approximately 100.

Not only has Dunn survived far longer than expected, he has most likely helped other men do the same. In 1998, Dunn started The Vancouver Advanced Prostate Cancer Support Group, Canada's first support group specifically for men with advanced prostate cancer. "I had been attending a prostate cancer support group for about a year, but most men who came were recently diagnosed," Dunn explains. "There was no forum for those of us with advanced prostate cancer."

Before long, Dunn had become an expert researcher, spending many hours most weeks combing the Internet for new information. He's particularly good at ferreting out information about clinical trials that most patients would never hear about through the medical system. Just recently he got a call from a man with advanced prostate cancer who was running out of options. Dunn was able to tell him about an upcoming trial of abiraterone, a drug that, new research shows, can block the continued production of androgens after standard hormonal treatments lose their effectiveness by blocking androgens made by parts of the body (other than the testes), including the tumour itself.

[FACT CHECKING LINK](#)

The sad irony is that Dunn himself is not eligible for this particular trial because of factors related to his health condition. Nonetheless, he soldiers on, looking for new possibilities and feeling grateful that he is still well enough to enjoy simple pleasures like going for a walk or driving a car.

Now meet Ken Dreger, a 64-year-old from Calgary who describes his current state of health as "annoyed." Why so? For one thing, Dreger is certain he would not still be alive had he relied on his local medical system for his treatment. For example, Ken had been told by a local pathologist that his cancer had not spread to his seminal vesicles and lymph nodes, a finding that was later contradicted by pathologists in the United States and Germany. This "under staging" of his cancer meant that the treatment that had been recommended was inappropriate. "It took less than six months for me to see that I'd have to get off the pot and take care of myself," he says. "There are some great treatments out there, but most men never hear about them. The one thing I've learned, not just from my own experience but from the experiences of other men, is that if you're an enlightened, educated patient you're going to do a lot better."

Dreger has spent a lot of his own money to get these second and third opinions. He's also gone outside the country, hiring Oregon-based prostate cancer specialist Dr. Stephen Strum to coordinate the monitoring and treatment of his illness.

Currently, although Dreger has hit the wall with a number of drugs, he does not see himself as out of options. He's considering going on an Alzheimer's drug called Ebixa, which has been shown to help men with prostate cancer. He'd also like to try a drug called DCA (dichloroacetate), a relatively cheap substance used for decades to treat metabolic diseases in children, which has recently been shown to shrink cancer tumours in animals and humans. "It has amazing potential, but I can't get it in Canada. I'm going to see if Dr. Strum can help me get it."

One way Ken helps to keep himself and others enlightened is through participation in Prostaidd Warriors, Calgary's support group for men with advanced (mostly hormone refractory) prostate cancer. "We don't bring in speakers like most support groups," he says. "We sit around a table, talk about each guy's change from the previous month and share information about where to get treatment." Not only does this increase each man's chance of surviving longer, it improves the mental outlook of all members. "Men with prostate cancer fight and fight and fight, and then we wear out. But the group helps me to get back in the saddle and starting fighting again."

Gordon Dunn's selfless work has not gone unnoticed. In 2003, he was the recipient of a Governor General's Caring Canadian Award in honour of his extensive work providing information and support to other men with prostate cancer. As the government media release that announced his award stated "[Gordon Dunn's] expertise and commitment have brought hope and solace to many patients and their families."

Treating hormone resistant prostate cancer: Current responses to the challenge

There is an old adage among prostate cancer survivors: "Early detection is the only cure." Men say this because, once prostate cancer has spread beyond the prostate, once it has metastasized, it can only be controlled---not cured. Fortunately, hormonal therapy, while not a cure, can lead to the long-term remission of advanced prostate cancer and enable men to enjoy an excellent quality of life.

Hormonal therapy is treatment that stops the production of male hormones, such as testosterone, or that blocks the effects of these hormones. It works because male hormones, also called androgens, stimulate prostate cancer cell growth. So limiting or controlling androgens checks prostate cancer progression.



But there is a problem. With time, prostate cancer cells may learn to grow even when androgens like testosterone are curtailed. The cancer no longer responds to hormonal therapy as it did initially, and we say that the cancer is hormone resistant, meaning that it is resistant to hormone deprivation therapy. When metastatic prostate cancer reaches this stage, no therapy has been shown to be an effective cure. But researchers are working hard to discover better ways of treating men with hormone resistant prostate cancer. Here are some of the promising areas of research:

Androgens, Again

Doctors now know that men whose cancers have developed a resistance to conventional hormone therapy can often be treated successfully using different methods of hormone deprivation. Many of the drugs used in this "second line" hormone therapy are antiandrogens, which block the effects of male hormones at the prostate tissue level. These include bicalutamide, flutamide, and nilutamide, all of which can be used in "first line" hormone therapy as well. Low dose corticosteroids, such as prednisone and dexamethasone, can also be part of second line hormone therapy. These drugs work by diminishing adrenal androgen production.

Other drugs work to prevent steroidogenesis---the synthesis of steroid hormones (e.g., androgens). Ketoconazole and abiraterone acetate have this effect. The antifungal drug ketoconazole has been in use since the 1970s to treat a broad spectrum of fungi. As the drug became widely used as an antifungal agent, physicians noticed that a small number of male patients taking it developed enlarged breasts, and this observation led to the discovery of the drug's ability to inhibit the production of an enzyme necessary for the synthesis of androgens. Ketoconazole, while effective for some men with hormone resistant prostate cancer, can cause significant nausea, vomiting, rash, and fatigue in others. So researchers set out to find other agents that interfere with enzymes necessary in hormone synthesis. Dr. Johann de Bono and his colleagues developed and began testing one such drug, abiraterone acetate. The drug targets an enzyme called CYP17, which plays a key role in androgen synthesis throughout the body. Results from the phase I clinical trial of abiraterone were published in the October 2008 issue of the *Journal of Clinical Oncology*, and researchers concluded that "abiraterone acetate is safe and has significant antitumor activity" in men with hormone resistant prostate cancer. ([See an abstract of this article.](#))

An important principle behind the development of these "second line" hormone treatments, then, is that

hormone resistant prostate cancer commonly remains hormone driven and can respond to hormone deprivation. This is something that Dr. Charles Sawyer of Memorial Sloan-Kettering has believed for a while. "Until 5 years or so ago," remarks Dr. Joel Nelson, chair of the department of urology at the University of Pittsburgh, "we had started to think that hormone therapy did not work [for hormone resistant prostate cancer]. All along, a number of researchers, including Charles Sawyers, said: 'No, we need better hormone therapy.'"

Dr. Sawyers has been instrumental in the development of this "better hormone therapy" for men whose cancer has become resistant to hormone deprivation. MDV3100 is one result of his efforts. It is a selective androgen receptor modulator, which means that it works by inhibiting the activity of the androgen receptors in prostate cancer cells. These androgen receptors are proteins that enable male hormones to interact with cells. And hormone resistant prostate cancer cells seem to over-express (produce more than the normal amount of) androgen receptors. Consequently, interfering with the action of androgen receptors may result in a reduction in prostate cancer cell proliferation and, correspondingly, a reduction in prostate-specific antigen (PSA) level. A [phase 1 clinical trial](#) is due to report soon.

Targeting Other Cell Growth Mechanisms

Some researchers are investigating how to treat hormone resistant prostate cancer by disrupting other cell signalling or cellular growth processes, ones not directly related to androgens. An interesting area of study involves the tumour suppressor gene PTEN, which is frequently mutated or "lost" in advanced prostate cancer. PTEN regulates a critical cell signalling pathway involving the versatile proteins Akt, which inhibits programmed cell death (apoptosis), and mTOR, which regulates cell growth. Researchers have discovered that a drug called rapamycin, an antibiotic developed to prevent the rejection of organ and bone marrow transplants, inhibits these proteins. Two rapamycin analogues (drugs that are structurally similar to rapamycin) are currently being tested in clinical trials: everolimus and temsirolimus. (Click [here](#) to see a 2008 article on these two mTOR inhibitors).

Immune-Based Strategies

Encouraging the body's own immune system to fight prostate cancer has always seemed an attractive option. But, as you can imagine, this system is complex, involving many checks and balances that allow cells to recognize the body's own constituent parts as *self* and to avoid an immune response against the body's own healthy cells and tissues.

Key players in the body's immune response are the dendritic cells, which reside in the lymph nodes. In their immature state, these cells sample their environment, checking for "danger" signals. When they discover trouble, they transform into mature cells capable of initiating an immune response. This maturation is accompanied by the display of an antigen on the cell's surface, in a form that can be recognized by T cells---cells that can generate immune responses tailored to a specific danger or pathogen and "remember" each pathogen encountered, so they are able to fight it effectively again. These remembered battles are the basis for the effectiveness of vaccines.

Research into immune-based treatments for men with hormone resistant prostate cancer focuses either on stimulating specific immune responses or on "turning off" particular factors that check these responses.

One idea for stimulating an immune response to prostate cancer was to administer activated dendritic cells loaded up with tumour antigens as targets as well as granulocyte macrophage colony-stimulating factor (GM-CSF), which supports the survival, expansion, and differentiation of dendritic cells. This

approach led to the development of the vaccine sipuleucel-T (Provenge®), which contains mature dendritic cells that present the antigen prostatic acid phosphatase (PAP), an enzyme produced by the prostate and found in high levels in metastasized prostate cancer.

In October 2008, interim data from phase III of the IMPACT trial designed to assess the safety and efficacy of Provenge® reported a 20 per cent reduction in the risk of death among those who received the vaccine rather than the placebo. The final results should be ready in the spring of 2009. ([Get more information on this clinical trial.](#))

While the vaccine Provenge® modifies a man's own antigen-presenting cells so that they can initiate an immune response against his tumour, another approach uses a vaccine that is not patient specific. GVAX® is comprised of cells derived from two prostate cancer cell lines, one from a man with early-stage, metastatic prostate cancer that is still sensitive to hormones and the other from a man with more advanced, metastatic, hormone resistant prostate cancer. The hope was that the vaccine would stimulate both a broad immune response by introducing many antigens and a strong immune response by using cells that are not as weak or as compromised as those of a man with advanced hormone resistant prostate cancer. Although GVAX® immunotherapy reached phase III clinical trials, Cell Genesys, the company creating the vaccine, placed its further development on hold in October 2008 after an analysis indicated that the trial VITAL-1 had less than a 30 per cent chance of meeting its predefined endpoint of an improvement in survival.

Another area of immunotherapy research involves CTLA-4 (cytotoxic t-lymphocyte antigen 4), which acts as a check for T cells, thereby controlling immune responses. The idea is that CTLA-4 may hold back T cells from fighting off prostate cancer, allowing cancerous cells to multiply unchecked. So, by blocking CTLA-4, researchers hope to unleash the immune system. "CTLA-4 blockade works by removing the brakes on the immune system. Our results show that enhancing immune responses in prostate cancer patients can lead to clinical responses," said Dr. Lawrence Fong, a researcher at University of California, San Francisco. In prostate cancer, ipilimumab (MDX-010), an anti-CTLA-4 monoclonal antibody, is being tested as both a single-agent therapy and in combination approaches using radiation, chemotherapy, or other immunotherapy agents. (For current clinical trials of MDX-010, click [here.](#))

Bone Directed Therapy

Another approach to hormone resistant prostate cancer involves delaying the progression of metastatic disease in the bone. In men with advanced prostate cancer that has metastasized to the bone, osteoblasts, the cells responsible for bone formation, show high levels of endothelin-1 (ET-1) receptors, which researchers think are involved in several aspects of prostate cancer progression as well as in new bone formation. Atrasentan, a substance that blocks ET-1 receptors, is being studied in a [phase III trial](#) to see how docetaxel, prednisone, and atrasentan work compared to docetaxel and prednisone as a treatment for men who have advanced, hormone resistant prostate cancer with bone metastases.

Another drug, denosumab, is being studied for its potential to delay bone metastases and inhibit and treat bone destruction. This summer, researchers reported that denosumab improved bone mineral density significantly and reduced fractures in men undergoing androgen deprivation therapy (ADT) for non-metastatic prostate cancer. Denosumab works by targeting the RANK ligand, a signalling molecule that bonds to osteoclasts (the cells that break down bone). A [phase III trial comparing denosumab to a placebo](#) as a treatment to prolong bone metastasis-free survival in men with hormone resistant prostate cancer is underway and should report in 2010.

Chemotherapy Combinations

Currently, the standard treatment for men with hormone resistant, metastatic prostate cancer is the chemotherapy drug docetaxel (Taxotere®). This drug, made from the needles of the European yew tree, is a proven chemotherapy drug, which is known to extend the life of men with advanced prostate cancer. But survival benefits are modest with docetaxel (about 2 to 3 months) and the duration of the drug's effect is short (about 6 months). Consequently, researchers are looking at combining the drug with other therapies and potentially effective anti-cancer agents.

Two of these are bevacizumab, which inhibits tumour growth by blocking the formation of new blood cells, and DN-101, an investigational drug that contains high amounts of calcitriol. Calcitriol is the biologically active form of vitamin D, and lab experiments have associated higher levels of it with anti-cancer effects. [ASCENT](#) (the Androgen Independent Prostate Cancer Study of Calcitriol Enhancing Taxotere) reported in January 2008 that "DN-101 treatment was associated with improved survival" and "did not increase the toxicity of weekly docetaxel." More research is necessary to confirm improved survival. ([See this report in the Journal of Clinical Oncology.](#))

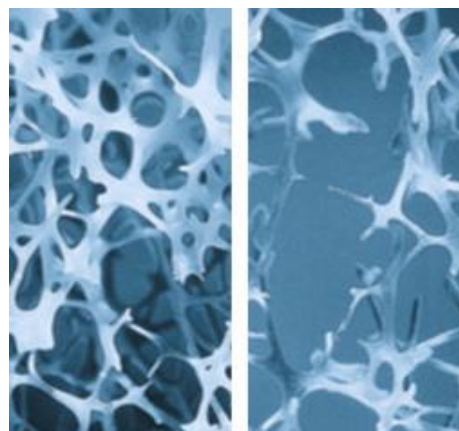
Bevacizumab, which blocks the activity of a protein called vascular endothelial growth factor (VEGF), is being studied in combination with docetaxel and prednisone. Many cancers use VEGF to help form the new blood vessels they need for continued growth, and high levels of VEGF in the blood and urine of patients with hormone resistant prostate cancer have been found to indicate a reduced likelihood of survival. "This phase III trial will answer the question of whether adding bevacizumab to docetaxel and prednisone actually does improve survival over the current standard of care," says Dr. William K. Kelly, the principal investigator. ([Click for more information](#) on this clinical trial.)

All of us at CPCN applaud these research efforts and look forward to the day when medical advances go even further to improve and extend the lives of men battling hormone resistant prostate cancer.

Them Bones: Osteoporosis and prostate cancer

"Male osteoporosis is really epidemic," reported Dr. Stephen Strum during his presentation *Osteoporosis in Men with Prostate Cancer*, given at the 2008 CPCN Prostate Cancer Conference held in Calgary last summer. "And I believe it is epidemic not just in the prostate cancer population," he continued.

Research supports his belief. "The current data indicate that one in four Caucasian men will suffer an osteoporosis-related fracture at some point in his lifetime, compared to about one in two women," says Dr. Felicia Cosman, associate professor of medicine at Columbia University. So, although osteoporosis is about half as common in men as in women, male osteoporosis is



still quite common. And osteoporosis (the abnormal loss of bone density resulting in weak and porous bones susceptible to fracture) is intrinsically linked to the burdens that face survivors of prostate cancer. Hormonal therapy for prolonged periods significantly increases a man's risk of developing osteoporosis.

Why should you care? Osteoporosis can have a major effect on quality of life. Bone fractures, especially hip fractures, are a serious problem and can lead to disability or even death. Following a hip fracture, for example, many people can no longer live independently. Also, as Dr. Strum points out, "bone integrity ... is all part of the integrated circuit that we call health." "Bone loss," he explains, "should be like an LED on your dashboard ... like an alert that you have a problem with your entire health system." Furthermore, "in the setting of a man newly diagnosed with prostate cancer, either osteopenia or osteoporosis occurs virtually 100 per cent of the time," reports Strum.

Once osteoporosis is detected, its treatment is both effective and non-invasive. It is in the technology usually used to detect osteoporosis that there is room for some improvement, according to Strum. The most common method used to determine bone density is an enhanced form of x-ray technology called dual-energy x-ray absorptiometry (DXA or DEXA). But a more sensitive test, says Strum, uses quantitative computed tomography or QCT. QCT is effective for men with prostate cancer since it can measure, in three dimensions, the true volumetric density of trabecular bone, which is some eight times more metabolically active than cortical bone. In other words, QCT is thought to be the most sensitive to short-term changes in bone density.

One flaw that critics of the QCT test are wary about is the significantly higher amounts of radiation given off during a QCT test than given off during the DXA. While the radiation from QCT is higher, the amount of radiation a man would be exposed to is far less than with many other preventative tests---dental scans, for example. And research suggests that the difference in sensitivity between these two tests is significant for men at risk for bone loss because of prostate cancer or its treatment.

But why do men, particularly men who have had prostate cancer, develop this bone degenerative disease? It all comes down to hormones, particularly when men have been on androgen deprivation therapy (ADT). "ADT immediately induces bone resorption," says Strum, because it lowers levels of male hormones (androgens), such as testosterone. Testosterone is an osteoclast inhibitor, so the less testosterone the more osteoclast activity and the more bone resorption. (Bone resorption is the process by which osteoclasts break down bone.)

Another "take home lesson" for men who have had prostate cancer is that bone degradation creates an environment "friendly" to tumour growth, and tumours can stimulate bone loss. A tumour cell elaborates (produces from more basic elements) various factors that stimulate the breakdown of bone and the creation of mature osteoclasts, the cells that function in the resorption of bone. Osteoclasts erode the bone and release growth factors, and some of these growth factors turn on other proteins and enzymes, which break down collagen, and this process leads to further breakdown of bone. Because the bone is a reservoir of bone-derived growth factors, which this cycle of bone erosion releases, osteoporosis potentially provides a fertile environment for the growth of tumour cells. "So this is not just about the risk of breaking a bone," Dr. Strum reminds us. "This is about pathogenesis; this is about disease that is growing, proliferating and is affected by the bony environment or the bone milieu." One main reason, then, that Dr. Strum is adamant in his advocacy of a holistic approach to prostate cancer treatment is that the body is a complex and unified system. So "anything that we can use to prevent an excess of this occurrence [the breakdown of bone] and to achieve a stabilization of bone integrity, has to result in helping the man with prostate cancer."

What sort of things can we use to prevent bone loss? Bisphosphonates are the most common treatment, but other important preventative measures are a healthy style of life and a good diet, one rich in vitamins and calcium. Calcium and Vitamin D are the two essentials that help to maintain bone density, and weight-bearing exercise encourages bone strength too. But lifestyle changes alone are sometimes inadequate, especially for men with prostate cancer. Bisphosphonates, such as pamidronate (Aredia®), alendronate (Fosamax®), ibandronate (Boniva®), and zoledronate (Zometa®), can prevent bone loss in these men. Bisphosphonates work, mainly, by blocking osteoclasts, thereby slowing bone resorption. But they do other things as well. According to Dr. Strum, bisphosphonates can

- kill the osteoclasts by affecting the mevalonate pathway,
- prevent the osteoclast from binding to the bone by binding to a mineral called hydroxyapatite,
- interfere with the precursors of the osteoclasts,
- affect the bone forming cells (the osteoblasts),
- interfere with the adhesion of the tumour cell to the bone matrix, and
- have a direct anti-tumour effect.

"They have an anti-prostate cancer effect by themselves," reports Strum, "and there are studies that show that the use of bisphosphonates can actually cause a drop in PSA." Current research indicates that bisphosphonates also play a role in preventing bone metastases in men with prostate cancer, women with breast cancer, and men or women with lung cancer.

The story of the interconnectedness of osteoporosis and prostate cancer can teach us crucial lessons, according to Strum. Indeed, we can greatly enhance medical research and improve health care and the treatment of men with prostate cancer if we remember that the human body is an integrated whole. "Osteoporosis," then, "is a 'signal' that a key integrative circuit of health has been breached."

But even more important are some larger ideas. All illnesses are linked to one another, as are all healthy bodily processes. So finding one illness should raise our concern regarding the presence of others. It follows, then, that the prevention or treatment of one disease will have some effect on the prevention, treatment, or risk of developing another. Sometimes, a treatment may be a double-edged sword that protects in one way and threatens in another, as hormone therapy keeps prostate cancer in check while increasing the risk of osteoporosis. Often, though, preventing or treating one disease keeps another at bay. Just look at how similar advice is about how to prevent heart disease, diabetes, cancer, osteoporosis, or the aging process itself. So Dr. Strum's main argument is to be logical and broad minded when assessing and healing illness---to look not only at the treatment of a single health concern but at the restoration of health itself.

For more information

Smith, M. R., McGovern, F., Fallon, M.A., Schoenfeld, D., Kantoff, P., Finkelstein, J. (2001) [Low bone mineral density in hormone naïve men with prostate cancer](#). *Cancer*, 91, 2238-2245.

Fort McKay: CPCN benefits from its tradition of sharing

Fort McKay First Nation is a small but growing northern community with a long history of doing big things---together. Located on the Athabasca River about 65 kilometres north of Fort McMurray, Alberta, the community has adapted to changing times while preserving its traditions of respect for and reliance on the land and of cooperation and sharing with others.

The people have lived in the region for about eight thousand years, since the arrival of, first, the Dene (Chipewyan), then the Cree, and then, in the 1820s, the Métis. Although Fort McKay's economy now centres on the development of the Athabasca oil sands, the Fort McKay Group of Companies, which is fully owned and operated by the community, works hard to create long-term and sustainable growth that values traditions.



And one of those traditions is generosity. The Canadian Prostate Cancer Network was the beneficiary of that generosity last November, when Executive Director Wally Seeley received a call from Melissa Dwyer, the Executive Assistant of CEO/Band Manager Phil Peddie. "She called me out of the blue," recalls Seeley, "and asked about prostate cancer awareness material and whether a donation would help."

Of course, CPCN receives many calls and emails each day, from newly diagnosed men and their loved ones, from support groups or people interested in starting them, and from other prostate cancer organizations, medical professionals, government agencies, and potential donors. "So, as soon as I had her address, I sent out a package right away and thought nothing more about it," says Seeley. "Then, we started receiving online donations from the Fort McKay First Nation."

"We decided to support the CPCN because we didn't think it got enough recognition," reports Melissa Dwyer. "To make it exciting, we came up with the goofy idea for the men in the office to grow beards and moustaches together, not only to raise money but as a way of team building." (Check out some of the before and after pictures below!)

"Our staff got the word out mostly by word of mouth, but I also sent emails to the different oil sands sites as well. I believe CPCN even received an online donation from Newfoundland because one of our staff members told parents back home, and they decided to get involved. Even the staff in the office made donations."

"The CPCN sent us prostate ribbon pins as well, which was a great idea," Melissa enthuses. "The pins were worn in the office with pride."

It was a most gratifying campaign, especially because of the donors' and organizers' very evident enthusiasm for giving. Perhaps the Fort McKay First Nation was living up to its namesake: Dr. Williams Morrison McKay was the first resident doctor in Alberta and became the first President of the Northern Alberta Medical Association. Perhaps the gift to CPCN was a reflection of the importance Fort McKay places on its people's welfare. (This progressive community has both a Health Centre and a Wellness

Centre.) But we at CPCN like to think that the donations were inspired by one of the most fundamental teachings of the community's elders---sharing.

