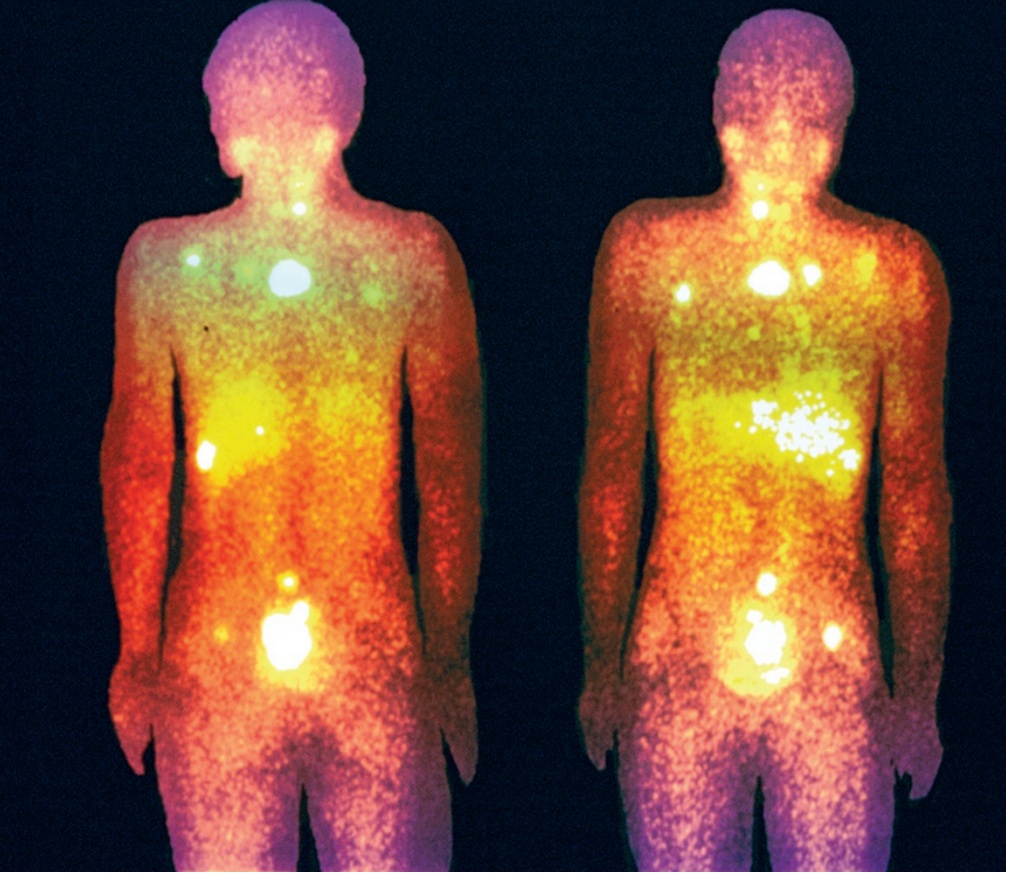

Scans that use γ-rays show the spread of cancer (white) from the prostate to the bones.

GJLP/CNRI/SPL

METASTASIS

Resistance fighters

Strategies to destroy treatment-defying tumours in men with prostate cancer are beginning to make a difference.

BY NEIL SAVAGE

When the patient entered a trial of an experimental prostate-cancer treatment, he was in bad shape. The disease had spread to at least ten different parts of his body, including his arm and leg bones, and his hip, spine and ribs. The tumours caused him so much discomfort that, despite heavy use of pain-relieving medication, he was unable to sit up. Chemotherapy had failed to halt the spread of the cancer. But now, nearly seven years after finishing the trial, the patient's tumours have disappeared, his pain has vanished and his blood levels of prostate-specific antigen (PSA; a protein biomarker used to monitor malignancy) give no indication of the disease.

"We always are cautious using the word 'cure'," says Fred Saad, a prostate-cancer researcher at the University of Montreal in Canada, who ran the study. "There are diseases we have cured in a very advanced stage, like lymphoma, like testicular cancer," he says. But despite individual successes, advanced prostate cancer is still considered to be incurable.

Many men with the disease have tumours that grow so slowly that they never cause a problem. Others can be cured by treating the tumour within the prostate gland. But in some, the cancer spreads to elsewhere in the body, usually to the bones. The first line of treatment for these men is to suppress the male sex hormones (androgens), such as testosterone, that stimulate prostate tumours to grow — a form of chemical castration. Within a year or two, however, tumours become resistant to this treatment.

Until the early 2000s, there were no available treatment options for castration-resistant prostate cancer (CRPC). Since 2010, a handful of therapeutic strategies for treating CRPC have emerged. But at best, they add a few months to patients' median survival time. So researchers are working to understand the mechanisms by which prostate cancer is able to resist efforts to overcome it, and to develop approaches that can permanently defeat the disease.

Saad's study is one such attempt[1]. The phase II trial focused on men with metastatic CRPC whose condition had worsened despite undergoing chemotherapy with docetaxel, a drug from the taxane family. The researchers focused on clusterin, a protein that increases in concentration when cells are stressed and seems to protect the cells from damaging agents. Researchers suspect that clusterin helps various types of tumour to become resistant to drugs used in chemotherapy. By inhibiting clusterin with a drug known as custirsen, the team hoped to once again make CRPC tumours vulnerable to the effects of chemotherapy.

REMARKABLE RESPONSE

The results of the trial were encouraging. Men who received custirsen together with docetaxel and the immunosuppressant drug prednisone showed a reduction in both pain and PSA levels. Saad's patient with the impressive results, who was 62 when he started the trial, had seen his PSA level shoot up from 74 to 115 nanograms per millilitre in the 3 weeks before treatment (a PSA level below 4 ng ml^{-1} is generally considered normal; a man who has had his prostate removed and is now cancer free should have a level of 0). Within 2 weeks of starting the trial, his PSA levels had dropped to around 70 ng ml^{-1}, and after 24 weeks, they had plummeted to less than 0.03 ng ml^{-1}. Seven years on, the patient's PSA level is undetectable. Although this particular case does not prove that custirsen can cure prostate cancer, Saad thinks that it is remarkable.

The larger story of custirsen — an example of a DNA-based 'antisense' drug that binds to RNA and switches a gene off — is less clear. A phase III trial that used custirsen alongside docetaxel and prednisone showed no statistically significant improvement in the survival of participants with advanced prostate cancer compared with those who received the same treatment, but without custirsen. The results of another phase III trial, which combines custirsen and prednisone with a different anticancer drug, cabazitaxel, are expected by early 2016.

Saad says that the key to finding effective treatments for advanced prostate cancer lies in identifying those men — like his star patient — who will respond to a given therapy, perhaps because of a particular mutation or variation in their tumour. That requires determining which molecular mechanisms help to confer resistance to drugs in certain people, and finding ways to test for them. Large studies that are unable to identify subgroups of patients who respond

to a therapy can lead researchers to dismiss drugs that would work well in the right individuals. "The ones that are actually responding are drowned in a sea of non-responders," says Saad.

SPLICE VARIANTS

The resistance of prostate cancer to chemical castration develops by several routes. One biomarker of a particular mechanism of resistance has already been found — a receptor protein that binds androgens within the cell. Two new anti-androgen drugs, enzalutamide and abiraterone, can extend the lives of men with metastatic prostate cancer by up to three years. Eventually, those drugs stop working in almost all men — but 20–40% of patients never respond at all[2]. The reason for this initial resistance is a variation in the messenger RNA sequence that is used as a template for building the androgen-receptor protein itself.

To make the receptor, the DNA of the androgen-receptor gene is first converted into a sequence of RNA that encodes all parts of the receptor protein. Any RNA that does not code for protein is cut out and the remaining pieces of RNA are joined or 'spliced' together to produce the receptor template. Occasionally, pieces of protein-coding RNA are also removed during splicing, which creates different versions — splice variants — of the receptor template. In one, androgen-receptor variant 7 (AR-V7), the receptor is missing its ligand-binding area, called the carboxyl terminal. This is what the androgen normally attaches to, but with no receptor mechanism to interfere with, the drugs are powerless. However, the area of the androgen receptor that triggers the cell to divide, found at the protein's opposite end, still works. "It can cause the cancer cell to grow and divide even without testosterone being present," says Emmanuel Antonarakis, an oncologist at Johns Hopkins Sidney Kimmel Comprehensive Cancer Center in Baltimore, Maryland, who helped to identify the variant.

Using a blood test, Antonarakis has compared men whose tumours contain AR-V7 with those whose tumours do not. Whereas men who tested negative for AR-V7 responded equally well to both anti-androgen drugs and chemotherapy with taxanes, those with AR-V7 did not respond to the anti-androgen drugs. But they did respond to chemotherapy with taxanes, which disrupt the microtubules that help cells to divide. Antonarakis's finding is supported by a study from the Erasmus University Medical Center Rotterdam in the Netherlands, in which investigators showed that AR-V7 does not diminish the effect of the taxane cabazitaxel[3]. A study from University Hospital Ulm in Germany confirmed the link between the variant and androgen resistance[4]. If these findings hold up, Antonarakis says that men with AR-V7 could skip the anti-androgen treatment and go straight for chemotherapy. Men who test negative can choose between the two.

Soon, there might also be more treatment options for men with AR-V7. The drug galeterone, for example, the subject of a phase III trial, works in three different ways. Like enzalutamide, it prevents androgens from binding to their receptors. And like abiraterone, it interferes with the production of testosterone. But galeterone also degrades the androgen receptor itself — an action that could prevent the cell from becoming resistant to the other two lines of attack. According to Antonarakis, galeterone is the first anti-androgen drug "that actually may be effective in men who have AR-V7". So far, testing has shown that PSA levels dropped in men with CRPC who took galeterone during phase II trials. Initial results of a phase III trial, which focuses specifically on men with AR-V7, are expected by the end of 2016.

"If the receptor can't bind to DNA, it can't switch on these genes to divide, multiply and spread."

Essa Pharma of Vancouver, Canada, is taking a different approach to the problem of resistance with its drug EPI-506, currently being prepared for phase I/II testing. Although most anti-androgen drugs target the end of the androgen receptor to which androgens bind, Essa's drug is the first to target the receptor's opposite end, which can interact with the DNA of the cell. By blocking this part of the receptor, the drug could prevent it from doing its job — stopping the cancer in its tracks. "If it can't bind to DNA, it can't switch on these genes to divide, multiply and spread," Antonarakis says.

DNA REPAIR

Splice variants are not the only way that prostate cancer can become resistant to anti-androgen drugs. When hit with a therapy, the disease — like any other cancer — mutates and develops mechanisms to help it to survive and grow. And anti-androgen drugs such as enzalutamide and abiraterone can inadvertently switch on the cancer-promoting mechanisms that androgens normally suppress. "You activate a sort of replacement pathway," says Timothy Thompson, an oncologist who is director of prostate-cancer research at the University of Texas MD Anderson Cancer Center in Houston.

Anti-androgen drugs actually "unrepress" oncogenes such as *c-MYB*, switching on pathways that help to promote the growth of cancer. In fact, drugs such as enzalutamide seem to stimulate mechanisms that repair DNA damage[5] — not enough to create normal cells, but sufficient to allow cancer cells to multiply and spread.

Researchers are searching for specific steps in the c-MYB pathway that they could target with new or existing drugs. Of particular interest is a class of enzymes called poly(ADP-ribose) polymerases, known as PARPs, which play a part in repairing damaged DNA[6]. Drugs that inhibit PARPs might disrupt the repair process and make cells more vulnerable to other forms of chemotherapy. PARP inhibitors are already being tested for the treatment of patients with breast cancer who have mutations in the genes *BRCA1* and *BRCA2*, and in December 2014, olaparib became the first such drug to be approved by the US Food and Drug Administration for treating ovarian cancers with the same *BRCA* mutations.

In April 2015, researchers from the Institute of Cancer Research and the Royal Marsden NHS Foundation Trust in London presented the results of a phase II trial of olaparib for men with metastatic prostate cancer. Lead researcher Johann De Bono says that a handful of patients showed "spectacular responses" to treatment with olaparib — their tumours disappeared from imaging scans. Others saw their PSA level cut in half. And all of the seven trial participants who had mutations in the gene *BRCA2* responded to the drug in some way.

Such discoveries could open the door to multipronged approaches in the fight against a disease for which there was no effective therapy just over a decade ago. That could revolutionize the treatment of advanced prostate cancer, says Saad, by bringing approaches in line with those for other cancers. "Prostate cancer is still one of the few, or only, solid tumours treated with a mono-treatment approach," he says. "Where we need to go in the future is combining therapies."

Although it might be a long time before the lives of most men with advanced prostate cancer can be significantly prolonged, Antonarakis agrees that combining therapies that block androgen receptors and destroy resistance mechanisms will soon stop the disease from being 100% fatal. "In the next five to ten years," he predicts, "we will be able to cure a small percentage of metastatic castration-resistant prostate cancer." ■

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