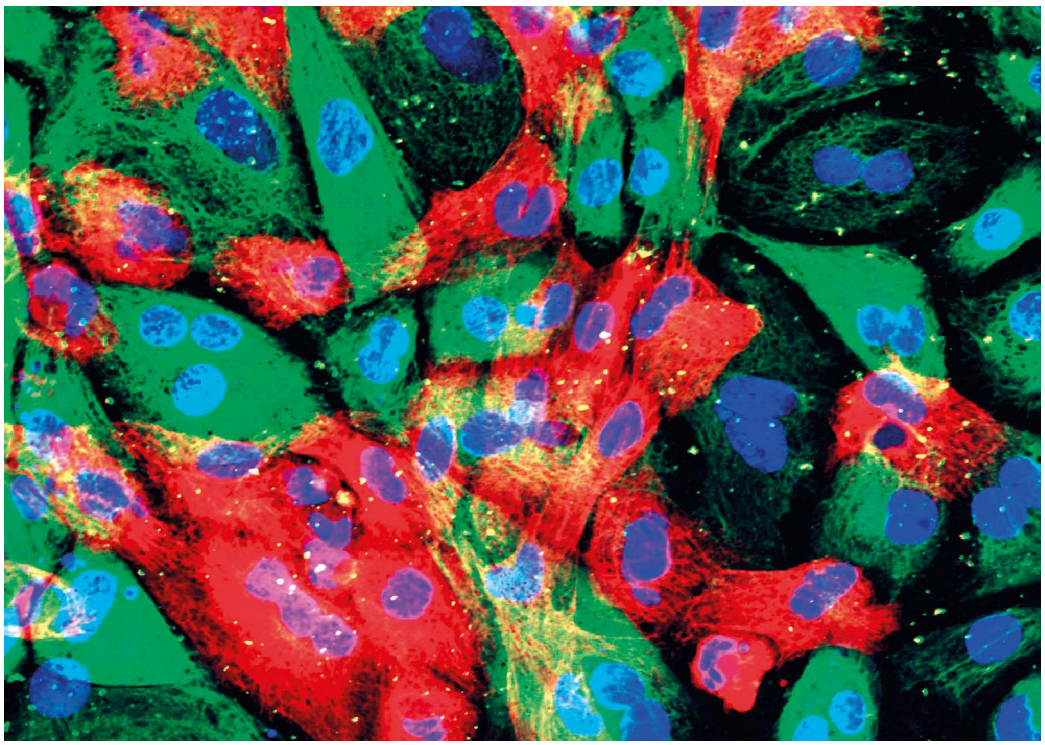
Research round-up

Highlights from prostate-cancer studies. By Annette Fenner



NCI/NIH/SPL

Fluorescent light micrograph of prostate cancer cells.

Armoured immunotherapy

Chimeric antigen receptor (CAR)-T cells — immune cells that have been modified to express an artificial receptor that enables them to recognize and attack tumours — are already used to treat blood cancers. However, solid tumours such as those in the prostate have posed more of a challenge, in part because of inhibitors present in the tumour microenvironment that limit CAR-T cell action. Now, a phase I trial led by researchers at the University of Pennsylvania in Philadelphia has suggested that CAR-T cells armoured against one such inhibitor, TGF-β, could form the basis of a successful treatment for prostate cancer.

The researchers developed CAR-T cells that target prostate-specific membrane antigen (PSMA) — a protein that is highly expressed in prostate cancer cells. The cells were also outfitted with a receptor for TGF-β that ties it up and limits its suppressive effects. In the trial, 13 men with metastatic castration-resistant prostate cancer were given the cells at a variety of doses.

The researchers evaluated the therapy's activity against tumours by monitoring levels of prostate-specific antigen (PSA) in the blood; prostate cancer cells can generate excessive amounts of PSA, so a decline could signal that the cancer is on the retreat. Four people demonstrated a decline in PSA of more than 30%; one had more than a 98% reduction in PSA.

The trial suggests that CAR-T therapy could be used to treat prostate cancer. However, the PSA responses seen were of limited durability. Moreover, although the treatment was generally well tolerated, an inflammatory condition known as cytokine release syndrome did arise in 5 of the 13 men — including the person who saw their PSA level fall the furthest, who died after developing sepsis. In addition, the use of PSMA to target tumours could be problematic, because although it is highly expressed in prostate cancer, it is also present in healthy tissue. A larger follow-up trial involving 50 people is now under way, and is expected to be completed by December 2022.

Nature Med. **28**, 724–734 (2022)

Tracking tumour metabolism

An emerging imaging technique, based on magnetic resonance imaging (MRI), has been used to visualize the metabolic response to immunotherapy in a person with metastatic castration-resistant prostate cancer.

The technique involves injecting a patient with biomolecules labelled with carbon-13 — an isotope of carbon. These molecules are incorporated into the body and can be tracked to assess metabolic activity *in vivo* in real time. This can show where a tumour is located and whether it is responding to treatment. For example, the conversion of a carbon-13-labelled pyruvate molecule into a lactate molecule, which are visible on MRI scans, can be used to identify tumours because the rate of this conversion is higher in malignant tissue than in healthy tissue.

In a study at the University of California, San Francisco, a person with prostate cancer who had undergone treatment with pembrolizumab — an immunotherapy that has shown effectiveness in a number of other cancers — was re-imaged using the new hyperpolarized 1-[^{13}C]-pyruvate MRI technique, as well as a more conventional multiparametric MRI. The multiparametric MRI suggested that the treatment had exerted only a mild effect — metastases in the person's bones appeared mostly unchanged, apart from a lesion in the pelvis that decreased in size. However, the hyperpolarized MRI could not detect any conversion of pyruvate to lactate in the shrunken tumours, indicating a complete metabolic response.

Furthermore, at nine weeks, PSA was also undetectable in the patient's blood.

The work suggests that hyperpolarized imaging could provide a more complete picture of a person's cancer and response to treatment. The team have since begun investigating the possibility of combining their hyperpolarized 1-[^{13}C]-pyruvate molecules with urea molecules labelled with both carbon-13 and nitrogen-15.

Eur. Urol. **81**, 219–221 (2022)

Gut microbes drive resistance

Androgen-deprivation therapy, in which the level of hormones such as testosterone in the body is chemically or surgically lowered, is widely used to treat people with prostate cancer. However, a considerable number of people develop resistance to this therapy, at which point alternative therapies must be sought.

Delaying the onset of this resistance could help to maximise the usefulness of androgen-deprivation therapy. One way to do this could be to target microbes in the gut. A study led by researchers at the Oncology Institute of Southern Switzerland in Bellinzona found that gut bacteria can produce male hormones, and that levels of these hormones increase in people with castration-resistant prostate cancer.

The researchers gave a cocktail of broad-spectrum antibiotics to mice with one of two models of castration-resistant prostate cancer, in order to deplete their intestinal microbiota. They found that the antibiotic treatment delayed tumour growth and improved survival in one model of the disease, and reduced prostate tumour volume in the other. Tumours in mice treated with antibiotics also appeared less aggressive, and the number of proliferating cancer cells was reduced.

Probing this effect, the researchers demonstrated that several microbes found in the gut of both mice and humans are able to directly synthesize androgens: the bacteria *Ruminococcus gnavus* and *Bacteroides acidifaciens* were shown to produce the androgen precursor dehydroepiandrosterone and testosterone. In addition, the sequencing of DNA from faeces showed that these bacterial strains are more common in people and mice receiving androgen-deprivation therapy.

In a mouse model of prostate cancer, a faecal transplant from a healthy mouse was found to control tumour growth and reduce cancer-cell proliferation, raising the possibility that transplants of this kind could be used to manage prostate cancer in the future.

Science **374**, 216–224 (2021)

Poorer outcomes for sexual minorities

People from sexual and gender minority groups who have prostate cancer typically experience worse physical- and mental-health symptoms following treatment than do heterosexual men, suggests a team of US researchers.

Men who have sex with men are an important clinical group in prostate cancer; a number of treatment considerations are unique to this population (see page S48). However, this group is often underrepresented in clinical trials, and few studies have investigated prostate cancer in these people.

Researchers asked 401 people taking part in the RESTORE-2 study — a trial of a rehabilitation programme for sexual-minority patients with prostate cancer — to complete a questionnaire designed to collect information on demographics and the treatments they had received, as well as their quality of life and mental health. Study participants had to identify as gay, bisexual, a man who has sex with men, or a transgender woman (although no transgender women took part).

When compared with previously reported prostate cancer outcomes for men who were presumed to be heterosexual, sexual-minority patients reported experiencing worse urinary, bowel and hormonal functions. They also reported poorer physical, social, prostate-specific and overall well-being, with poorer mental health and worse depression. They did, however, report better sexual function than heterosexual men. This might be due to differences in sexual behaviour between men from sexual minorities and heterosexual men, or strategies used by sexual-minority men to manage treatment effects, such as changes in sexual roles.

The authors note that such disparities illustrate the need for clinicians to ascertain a person's sexual orientation and consider it when counselling people regarding their treatment.

Front. Oncol. **12**, 812117 (2022)

Targeted radiation boosts survival

A phase III trial of a targeted therapy that delivers radioactive particles to prostate cancer cells has led the US Food and Drug Administration to approve the treatment for some people with metastatic castration-resistant prostate cancer.

The therapeutic agent comprises the radioisotope lutetium-177, which can deliver cancer-killing β-particle radiation, and a compound that binds to PSMA. PSMA is highly expressed on prostate cancer cells, both in the primary tumour and in metastatic lesions. So, by targeting cells that express high levels of PSMA, the combined radioligand — known as ^{177}Lu-PSMA-617 (Pluvicto) — can selectively deliver radiation to malignant cells and their microenvironment.

The trial, called VISION, was conducted across 84 sites in the United States and Europe, and involved people with PSMA-positive castration-resistant prostate cancer with at least one metastatic lesion that was visible on a standard radiological scan. Their disease also had to have progressed despite previous therapy with androgen-receptor-pathway inhibitors and taxane-based chemotherapy. The trial enrolled 831 people, who were randomized to receive either ^{177}Lu-PSMA-617 plus standard care or standard care alone. People in the treatment group received the experimental agent intravenously once every six weeks for four cycles, with the option to receive an extra two cycles at the discretion of the physician if there was evidence of a response.

At follow-up (on average, around 21 months later), men in the treatment group showed significantly longer progression-free survival — 8.7 months compared with 3.4 months for those in the control group. They also had longer overall survival (15.3 months versus 11.3 months). Levels of PSA in the blood, frequency of bone fractures, and health-related quality of life and pain score also improved with ^{177}Lu-PSMA-617 compared with standard care. Although adverse events were more common in people who received the treatment, their quality of life was not reduced.

N. Engl. J. Med. **385**, 1091–1103 (2021)

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