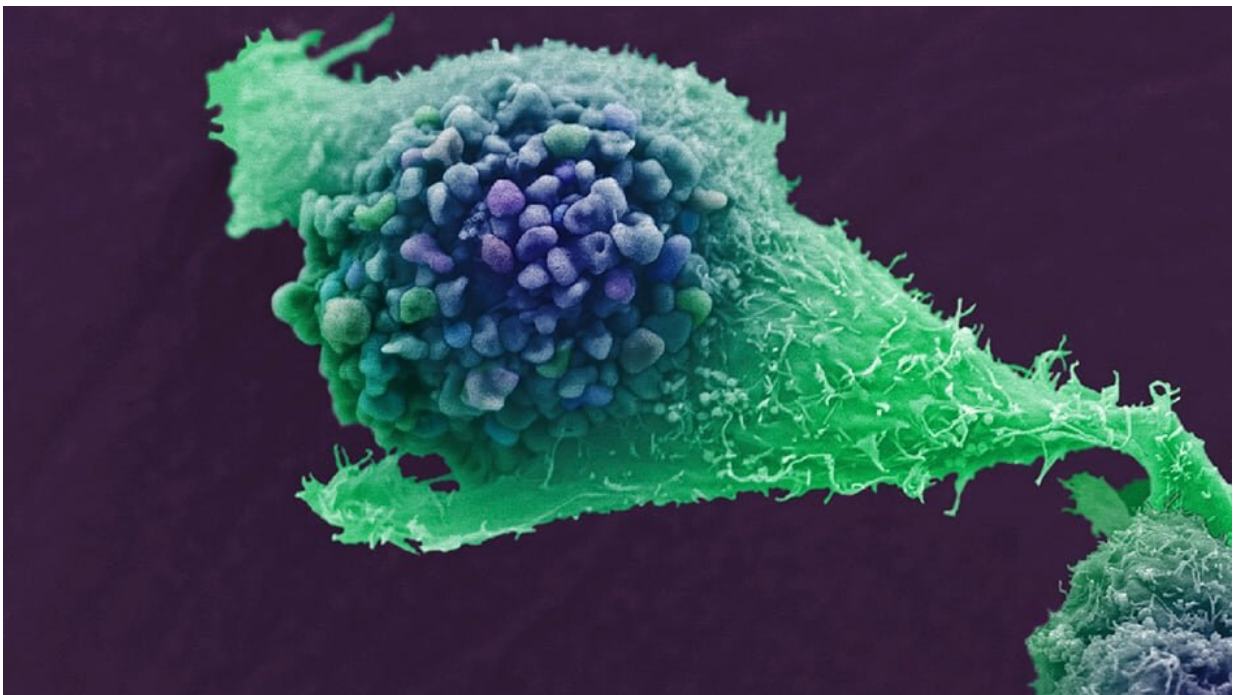


Scientists reverse drug resistance in prostate cancer by targeting 'hijacked' white blood cells

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Scanning electron micrograph of a single prostate cancer cell. Credit: Anne Weston, Francis Crick Institute

Prostate cancer's resistance to treatment can be reversed in some patients by stopping hijacked white blood cells from being 'pulled into' tumors, according to new research published in [*Nature*](#).

In an early clinical trial, researchers showed that blocking the messages [cancer](#) uses to hijack white blood cells can resensitize a subset of advanced [prostate](#) cancers to treatment—shrinking tumors or halting their growth.

Reverse drug resistance

The research provides the first proof in a human trial that targeting 'feeder' [myeloid white blood cells](#)—which are co-opted by tumors to help fuel cancer growth, progression, and resistance to treatment—can reverse drug resistance and slow tumor progression.

The research, led by The Institute of Cancer Research, London, The Royal Marsden NHS Foundation Trust, and The Institute of Oncology Research (IOR) in Switzerland, represents a major scientific advance following a decade of work into understanding how myeloid cells fuel treatment resistance.

Researchers tested a combination of AZD5069, an experimental drug which prevents myeloid cell recruitment to tumors, and enzalutamide, a hormone therapy commonly used to treat prostate cancer, in patients with advanced disease.

Five of 21 (24%) evaluable patients responded to the treatment, meaning their tumors shrunk by over 30%, they saw dramatic decreases in circulating levels of prostate specific antigen (PSA), a marker secreted by the prostate which is often elevated by cancer, or their blood levels of circulating tumor cells dropped, in response to the combination.

Blood levels of myeloid cells also dropped in patients who received treatment, and biopsies following treatment also revealed fewer myeloid cells within their tumors.

Building on a decade of research

The research builds on over a decade of work by teams at the ICR, The Royal Marsden and IOR working to understand how myeloid cells fuel prostate cancers.

This began with a surprising observation that patients with aggressive and resistant prostate cancer had much higher levels of myeloid RNA in their blood.

Research by this international team has since shown that myeloid cells within tumors enter a sleep state called "senescence," and become "hormone factories," manufacturing signals which support tumor growth, division and survival. They then send further signals to the bone marrow to recruit more "conspirator" myeloid cells to enter the tumor and the cycle continues.

The new study is the first to prove that blocking this pathway has anti-tumor activity in humans with prostate cancer. It is an example of a treatment that works by disrupting the cancer ecosystem—a pioneering approach to cancer treatment which is a key focus of the ICR's latest strategy, Defeating Cancer.

The treatment AZD5069 prevents myeloid cells being recruited to tumors by blocking a receptor on myeloid cells called CXCR2, which acts as a mailbox for recruitment messages sent by myeloid cells already residing in tumors.

These messages encourage myeloid cells to travel towards places of inflammation, such as tumors, and infiltrate them.

Study leader Professor Johann De Bono, professor in experimental cancer medicine at the Institute of Cancer Research, London, and

consultant medical oncologist at The Royal Marsden NHS Foundation Trust, said, "This research proves for the first time that targeting myeloid cells rather than the cancer cells themselves can shrink tumors and benefit patients. This is tremendously exciting, and it suggests we have an entirely new way to treat prostate cancer on the horizon.

"We've been studying these myeloid cells at the ICR for many years. More than a decade ago we first noticed that they were elevated in patients with much more aggressive tumors, and showed these tumors were more treatment resistant. Professor Andrea Alimonti at the Institute of Oncology Research (IOR) then demonstrated in laboratory studies that these cells could promote prostate cancer growth, with their inhibition blocking tumor progression.

"It's hugely rewarding to see our theory proven in a trial of patients with this disease. Myeloid cells may be implicated in treatment resistance in a range of cancers, so the impact of this research could be very broad, across multiple cancer types."

"It's a major achievement to plan and run a clinical trial on predominantly charity funding. We're incredibly grateful to the charities like Prostate Cancer UK, Cancer Research UK, the Prostate Cancer Foundation and Swiss Card Onco grant organization, who made this research possible."

Professor Kristian Helin, chief executive of the Institute of Cancer Research, London said, "It's fantastic to see such an innovative approach to treatment showing benefits in a clinical trial. It helps to act as a proof of principle for disrupting cancer's supportive ecosystem, as a smart new way of targeting tumors.

"I look forward to seeing how this work progresses and hope it will pave the way to a new treatment that is beneficial to people with prostate

cancer, and potentially also many other cancer types."

Dr. Matthew Hobbs, director of research at Prostate Cancer UK, said, "A man living with advanced prostate cancer needs treatments that will control his disease to give him years more life, feeling as well as possible. Sadly, for many men, their cancer resists treatments, ending too many lives far too soon."

"Six years ago, Prostate Cancer UK brought together some of the world's top experts in the field to work out how prostate cancer is using the immune system to evade treatments, and how we can disrupt this. Since then, we've moved from initial ideas to laboratory research, and now to a clinical trial that shows us a completely new, safe, effective way treat advanced [prostate cancer](#) without resistance."

More information: Christina Guo et al, Targeting myeloid chemotaxis to reverse prostate cancer therapy resistance, *Nature* (2023). [DOI: 10.1038/s41586-023-06696-z](#)

Provided by Institute of Cancer Research

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