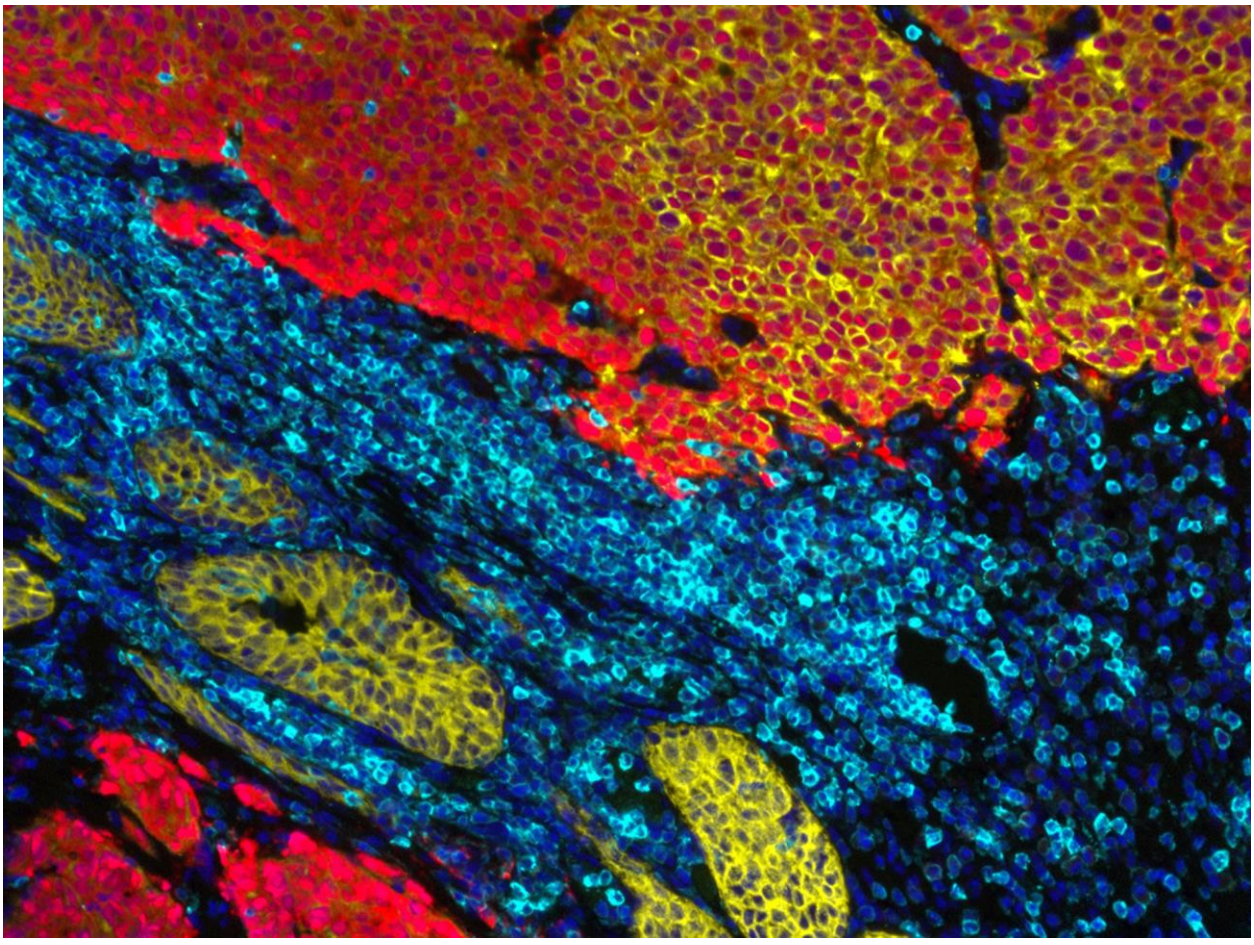

New drug hope for prostate cancer patients

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Prostate cancer that has become resistant to hormone therapy could be treated using a new drug that is currently in clinical trials for ovarian and bile duct cancer, according to research **published in the journal *Clinical Cancer Research***.

Scientists from The Institute of Cancer Research, London, showed that the drug, **NXP800**, discovered at the same institute, slowed the growth of prostate cancer cells, including in cancer cells that are resistant to the hormone therapy enzalutamide.

Searching for ways to overcome treatment resistance

Although hormone therapies like enzalutamide and abiraterone transform the lives of thousands of men with advanced prostate cancer every year, most patients will eventually become resistant to these treatments. Researchers are searching for new ways to overcome drug resistance.

NXP800 works in an innovative way, by targeting the Heat Shock Factor 1 (HSF1) pathway – a 'master switch' in cells that is hijacked to support the growth of cancer cells, helping them withstand the stresses they come under as a tumour develops. The pathway controls the production of heat shock proteins that help to protect the cancer cell during stressful conditions.

Heat shock proteins are associated with worse outcomes

The team at The Institute of Cancer Research (ICR) studied data from 439 advanced prostate cancer samples. In research funded largely by **Prostate Cancer UK**, **Movember**, and the **Prostate Cancer Foundation**, they found an association between higher levels of heat shock proteins and more androgen receptor signalling, which drives the development and growth of prostate cancer.

They also found an association between patients who had higher levels of these proteins and poorer overall survival. In one cohort they studied, patients with more of these proteins survived for 22.0 months, compared with 33.5 months for those with fewer heat shock proteins, suggesting that prostate cancers with more of these proteins may be better equipped to survive and harder to treat.

Targeting the heat shock proteins

The researchers attempted to block these heat shock proteins using the drug NXP800, which was discovered at the ICR in its **Centre for Cancer Drug Discovery**. **The drug underwent an early clinical trial in advanced cancer**, led by the ICR and its hospital partner **The Royal Marsden NHS Foundation Trust**, and sponsored by **Nuvectis Pharma**.

In the lab, the researchers found that NXP800 slowed the growth of prostate cancer cells – even for cells which were resistant to the hormone therapy enzalutamide.

In biopsies of patients with advanced prostate cancer grown as mini tumours in the laboratory, the new drug slowed the growth of the tumours, whereas enzalutamide only had a small effect at very high concentrations.

The drug significantly slowed tumour growth

In mice with hormone therapy-resistant prostate cancers, NXP800 significantly slowed tumour growth. Without the drug, 100 per cent of tumours had doubled in size by 38 days – when treated with the drug, only 37.5 per cent of tumours had reached that size in that time.

The researchers from the ICR, which is both a research institute and a charity, hope these findings will lead to trials of NXP800 for advanced prostate cancer, to provide patients with alternative treatments when hormone therapies have stopped working.

The team carried out mechanistic studies which confirmed that NXP800 blocks the activity of HSF1 in prostate cancer cells and reduces the levels of heat shock proteins. They also discovered that it modulates a pathway called the unfolded protein response – a pathway connected to the cells' response to stress – and impacts other protein molecules that are important in controlling gene activity in prostate cancer. Understanding the mechanism of the drug's action will be important for future research to discover which patients will respond best.

NXP800 has been granted Fast-Track and Orphan Drug Designation by the US Food and Drug Administration (FDA) for its potential to treat ARID1a-deficient ovarian, fallopian tube, and peritoneal cancers, and Orphan Drug Designation for hard-to-treat bile duct cancer. This is to speed up the review of, and provide financial benefits for, drugs which show promise to treat rare diseases. Until this study, it had not been considered for use in prostate cancer.

Tackling the problem from a new angle

Study co-leader Dr Adam Sharp, Leader of the **Translational Therapeutics Group** at The Institute of Cancer Research, London, and Honorary Consultant Medical Oncologist at The Royal Marsden NHS Foundation Trust said:

"While hormone therapies have extended the lives of lots of men with advanced prostate cancer, drug resistance is inevitable. We need to tackle the problem from a new angle.

“With this research, we’ve shown that targeting the heat shock response pathway – a pathway responsible for enabling tumours to withstand stress and keep growing – is a potential new avenue for treating advanced prostate cancer. The pathway impacts the hormone signalling that drives cancer, but it’s not susceptible to the usual mutations that drive drug resistance.

“Excitingly, we’ve shown that targeting this pathway can slow the growth of prostate cancer tumours – even for tumours that are resistant to hormone therapy. The next step will be to assess if certain prostate cancer patients would respond better than others.

“The researchers Jon Welti, Denisa Bogdan and Ines Figueredo, played a critical role in this research to establish the effect of NXP800 on prostate cancer.”

'Finding drugs that can slow down cancer's growth is critical'

Study co-leader Professor Johann de Bono, Regius Professor of Cancer Research at The Institute of Cancer Research, London, and Consultant Medical Oncologist at The Royal Marsden NHS Foundation Trust said:

“We have shown that people with prostate cancers with higher levels of heat shock proteins have significantly worse outcomes. If targeting these proteins proves effective in clinical trials, patients with advanced prostate cancer will be able to look forward to longer and better-quality lives.”

The ICR's track record is 'unrivalled in the academic world'

Professor Kristian Helin, Chief Executive at The Institute of Cancer Research, London, said:

“Drug resistance is one of the biggest problems we face in treating cancer. Finding drugs that can slow down cancer’s growth when all other treatments have stopped working is critical.

“This research uses an innovative drug to target prostate cancer through a novel mechanism of action. We’ve been delighted to see the ICR-discovered NXP800 drug make great progress in clinical studies for ovarian cancer, so it is very exciting to see that it could potentially also benefit prostate cancer patients for whom hormone therapy has stopped working.

“NXP800 is one of the 13 ICR-discovered drugs we’ve taken into clinical trials for cancer patients since 2005. That track record is unrivalled in the academic world.”

'Highly innovative mechanism'

Professor Paul Workman, Harrap Professor of Pharmacology and Therapeutics at The Institute of Cancer Research, London, who led the original research at the ICR to discover NXP800 and is a co-author of this study, said:

“The NXP800 drug is an example of the incredible drug discovery and development that is possible through partnerships between academics, clinicians and private enterprise. Through our Centre for Cancer Drug Discovery and our close partnership with The Royal Marsden, the ICR has unparalleled capabilities for discovering and developing totally new types of treatment for patients with hard-to treat cancers.

“I’m thrilled about the exciting results we’ve obtained in prostate cancer models, which means that the drug could benefit even more patients beyond the current focus on ovarian and bile duct cancer.

“NXP800 works through a highly innovative mechanism and I very much hope to eventually see the drug, now licenced to the US biotechnology Nuvectis Pharma, progress into additional trials including for advanced prostate cancer.”

Simon Grieveson, Assistant Director of Research at Prostate Cancer UK, said:

"For men with advanced prostate cancer, treatment with hormone therapy can be very effective at delaying cancer progression, however eventually these treatments are likely to stop working. This is a critical problem we need to address through continued research into brand new approaches to treating prostate cancer, and this is a fantastic example.

“We’re thrilled to have funded this research in partnership with Movember, which could make a marked impact on the lives of men with hormone resistant prostate cancer and who have very few treatment options remaining. These findings provide valuable insight into the role of heat shock proteins, which we now know are at a higher level among advanced prostate cancer patients and associated with worse outcomes. Targeting these proteins with this novel drug could give men with hormone resistant prostate cancer a new option for treatment and, crucially, more valuable time with their loved ones. Clinical trials are now needed, but this is an exciting step towards a new solution to tackling treatment resistance in prostate cancer."

Howard R. Soule, PhD, Executive Vice President and Chief Science Officer of the Prostate Cancer Foundation, said:

“These findings fill a therapeutic gap for patients with advanced prostate cancer. We applaud the discovery and clinical translational expertise of the ICR in advancing a new target and novel experimental therapy to the patients PCF serves.”