Scientists identify new family of drugs which could combat prostate cancer

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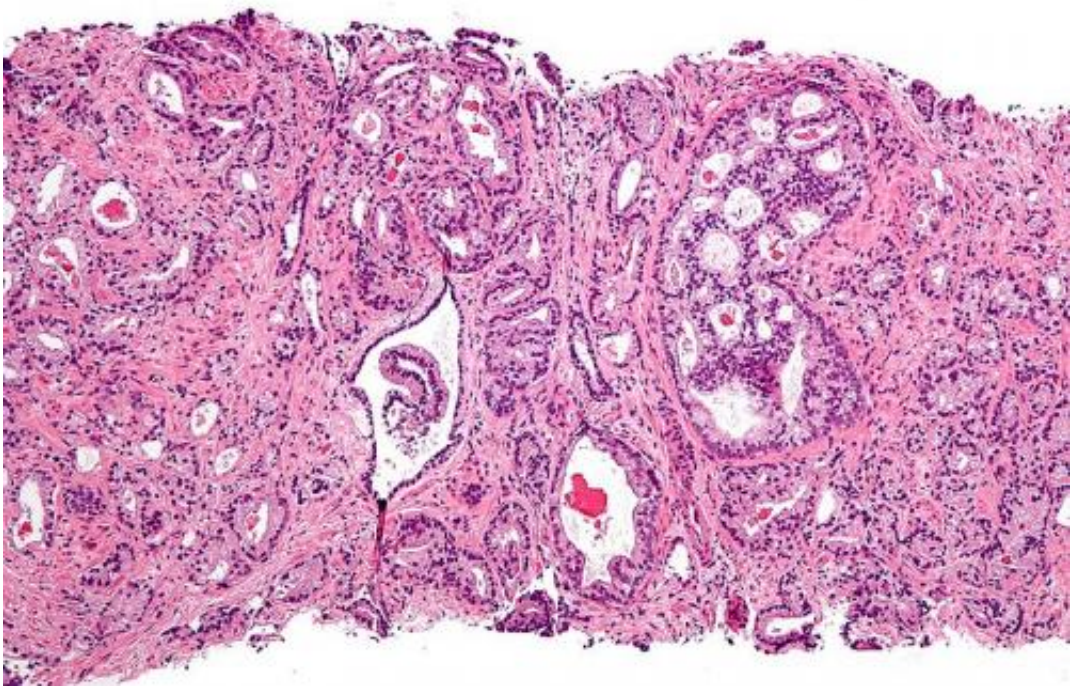

Micrograph showing prostatic acinar adenocarcinoma (the most common form of prostate cancer) Credit: Wikipedia, CC BY-SA 3.0

A new family of drugs which inhibit the activity of a protein associated with prostate and other cancers has been reported by scientists from the University of Bath.

They provide a promising avenue for research to potentially develop new therapies to treat a range of cancers thanks to the design of the study,

which rationally investigates how the drugs work. The research team from the Departments of Pharmacy & Pharmacology and Chemistry study a protein called α-methylacyl-CoA racemase (AMACR). Levels of the AMACR protein and its activity are increased by ~10-fold in all prostate cancers, and a number of other cancers as well.

Reducing levels of AMACR in prostate cancer cells using genetic techniques makes them less aggressive, and their behaviour becomes more like normal cells.

Until recently it was difficult to accurately measure AMACR activity and therefore hard to determine the effectiveness of drugs designed to reduce AMACR activity. This means that few studies on developing AMACR-targeted drugs had been carried out, and those that had been did not systematically investigate the structural features which contribute to high effectiveness. In this study a new family of drugs which inhibit AMACR is reported. The structure of a feature called a side-chain was systematically varied in order to identify important structural features which are required for highly effective inhibition of AMACR activity. This work resulted in a 20-fold increase in effectiveness in the drugs compared to those already known, such as ibuprofenoyl-CoA. The reported new drugs proved to work in a different way to ibuprofenoyl-CoA and similar drugs.

The study is published in the journal *Bioorganic Chemistry*.

Lead author Dr. Matthew Lloyd, from the Department of Pharmacy & Pharmacology, said "This study is really significant because it gives detailed information about the structure of these drugs and provides a rational basis for understanding their behaviour. That means that we have some really promising avenues to explore as we work towards developing new treatments against prostate cancer, and other cancers where AMACR is involved.

"It is also particularly nice that this study provided important training to the next generation of researchers at Bath."

Synthesis of the new drugs was performed by post-doc, Dr. Maksims Yevglevskis, Bath Pharmacy undergraduate Suzanne Al-Rawi (who undertook this is a part of a Biochemical Society Summer Vacation Studentship), and Shandong Pharmacy undergraduate Tingying Jiao (as part of a Bath-Shandong Visiting Student Exchange Programme). Biological testing of the drugs was undertaken by post-doc Dr. Amit Nathubhai, and Masters in Drug Discovery with Chemistry student Katty Wadda.

Prostate Cancer UK funded part of this research with support from Movember.

Simon Grieveson, Head of Research Funding at Prostate Cancer UK said: "With one man dying from prostate cancer every 45 minutes in the UK there is a desperate need to develop new and effective treatments for the disease, and that's why it's so important that we continue to fund explorative studies like this. The protein AMACR has been shown to be present in larger quantities in aggressive prostate cancer cells, and this research group have successfully developed a technique to find the protein and monitor its activity. Further to this, they have now found certain compounds that can target this protein's activity in the lab, and stop the cancer cells in their tracks. The research is still in its infancy and is some way off from clinical investigation, however this is certainly promising and we look forward to seeing how this research progresses over the coming years."

In the United Kingdom, prostate cancer is the most common male-specific cancer with 47,151 new diagnoses reported in 2015 and 11,287 deaths in 2014. It accounts for 26% of all cancers diagnosed in men, with one in eight men being diagnosed with prostate cancer in their

lifetime. Although 84% of men will survive for at least 10 years with the disease, new treatments are urgently needed especially for those men diagnosed with more advanced disease.

More information: Maksims Yevglevskis et al, Novel 2-arylthiopropanoyl-CoA inhibitors of α-methylacyl-CoA racemase 1A (AMACR; P504S) as potential anti-prostate cancer agents, *Bioorganic Chemistry* (2019). DOI: 10.1016/j.bioorg.2019.103263

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