MONASH University

MONASH INNOVATION

NEW TARGET FOR AGGRESSIVE PROSTATE CANCER

A key androgen independent pathway in prostate cancer progression and a crucial extracellular target that, if antagonized, could inhibit a highly aggressive sub-group of disease including castration-resistant disease. Neutralizing antibodies have been developed in mice to create novel compositions for patient stratification and single agent or combination use with androgen ablation therapy.

- **Potential target for development of prostate cancer-specific mAb-based drugs for all stages of disease progression including androgen-independent disease**
- **Potential neo-adjuvant and/or adjuvant therapy as single agent or in combination**
- **'Proof of Mechanism' *in vivo* using target knockout mice crossed onto a transgenic PCa invasion model**
- **Potential biomarker for the stratification of patients following biopsy for 'aggressive' vs. 'indolent' disease**

THE CHALLENGE

90% of men diagnosed with prostate cancer (PCa) have localized disease and face a major decision regarding the surgical removal of the organ or active monitoring for disease progression.

This decision is critical as prostatectomy is frequently associated with serious complications and often serves only to slow cancer growth. Left untreated, the PCa may grow slowly and have minimal impact on quality of life.

For men receiving surgery followed by radiation therapy, PCa is likely to reoccur. After this point virtually all treatment options involve the inhibition of androgen signalling. This is usually successful in the first instance but ultimately fails (after 2-3 years), leading to castration-resistant PCa, for which no viable treatment options remain.

The true challenge is to identify which men have high risk 'aggressive' disease and selectively treat them with targeted therapies that will inhibit all stages of PCa progression - including castration-resistant disease. Current blood-based markers, such as PSA, offer little discriminatory power in this respect.

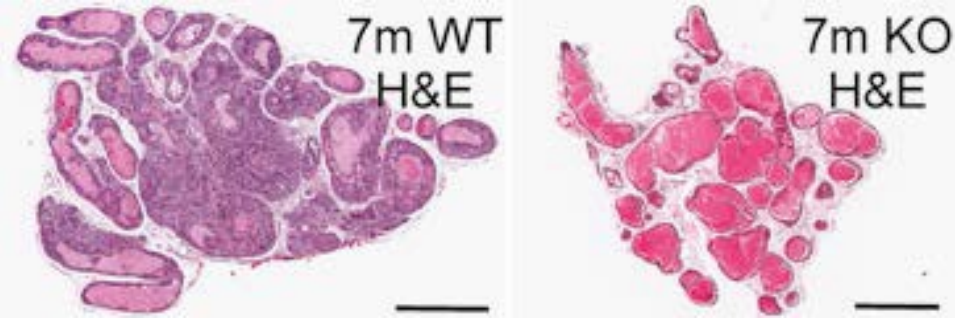

Figure 1. 7 month old lateral prostate showing the effect of target ablation (KO) on PCa progression in the mouse Hi-MYC model of prostate adenocarcinoma. WT mice develop invasive prostatic adenocarcinoma by 6 months while target KO mice retain a normal phenotype.

THE TECHNOLOGY

Monash Researchers have analysed a key pathway in prostate cancer progression and identified a crucial extracellular target. This target is drastically up-regulated in a significant percentage of human PCa cases and is clinically and experimentally associated with PCa progression (Fig.1).

Expression of the target in human PCa appears independent of androgen signalling, making the target a plausible therapeutic option for castration-resistant disease. The Monash data show that the target is pro-tumourigenic in the prostate, with a role in the promotion of an invasive phenotype. Our researchers hypothesize that antagonism of this target could inhibit all stages of PCa, including castration-resistant disease.

In collaboration with the Monash Antibodies Technologies Facility, the team is developing assays and making neutralizing antibodies (mAbs) in mice 'knocked-out' for the target. We aim to create novel compositions to be used in patient stratification and as single agents in a neo-adjuvant or adjuvant setting and/or in combination with androgen ablation therapy. We envisage clinical inhibition of target signalling could 'clean up' tumour margins prior to surgery and could inhibit metastases. The antagonists could also be used in containment and/or active ablation of invasive, metastatic or castration-resistant PCa.

THE OPPORTUNITY

We seek a partner to further develop novel compositions against this target. The Monash research team has extensive experience in all aspects of discovery stage therapeutic mAb development.

Reference

New biomarkers in prostate cancer. Crawford ED, Ventii K, Shore ND. *Oncology* 2014. Feb; 28 (2):135-42.

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