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Title: First report of PSMA-targeted immunotherapy in prostate cancer...The Future is bright

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Efficacy against human prostate cancer by PSMA-specific, TGF- β insensitive genetically targeted CD8+ T cells derived from patients with metastatic castrate resistant disease .

Chicago.

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Text:

The field of prostate cancer research is becoming increasingly captured by the potential clinical utility of the transmembrane glycoprotein FOLH1 (also known as prostate specific membrane antigen, PSMA). The molecule's relative specificity as a prostate cancer cell-surface ligand¹, its emerging role in PET scanning and cell-directed therapy² are exciting new developments with unlimited potential. Is this excitement justified? Indeed, PSMA-PET scanning is starting to deliver^{3,4} and we eagerly await protocols and guidelines to optimise the utilisation of this novel, apparently sensitive staging modality in decision-making before and after radical treatment.

While researchers have started to consider the potential of PSMA in targeted therapy, to date, evidence remains scarce. In this issue of European Urology Zhang et al present interesting novel data using recombinant CD8+ T cells taken from a patient with prostate cancer and modified to target PSMA-expressing cells to resist host TGF- β . These modified immune cells were used to inhibit transformed PSMA-expressing PC-3 cells, a human cell-line model derived from a prostate bone metastasis, in both *in vitro* and *in vivo experiments*. The authors propose a means of modifying the host immune response to target prostate cancer cells expressing a specific cell-surface ligand (in this case PSMA).

This novel use of PSMA in cell-directed immunotherapy opens an intriguing and promising avenue of therapy for patients, with applications across the natural history of prostate cancer. To our knowledge, this is the first report of PSMA-targeted immunotherapy. It builds upon previous descriptions of the use of immunotherapy in prostate cancer, which to date is essentially limited to Sipuleucel T⁵, which was the first FDA-approved immunotherapy for any solid organ cancer type, although its use has been limited in clinical practice. In 2017 the FDA recommended CTL109, a chimeric antigen receptor (CAR) T Cell therapy, as a treatment for paediatric acute lymphoblastic

leukaemia (ALL), paving the way for a generation of recombinant T Cell therapies in leukaemia. But what about solid organ tumours such as PCa?

Molecular genetics data suggest that all individuals have cells with malignant change, whether they are in the circulating environment or within solid organs. Why do these mutated cells not form cancers more frequently? The answer to this question is almost certainly because we have a functioning immune system, which results in the frequent elimination of 'rogue' cancer cells, in a process known as "immunoediting"^{6,7}. In the absence of a competent immune system, tumours are more likely to develop. A classic example is the development of Kaposi's sarcoma in immunocompromised seroconverted patients with HIV⁸. Moreover, it is now clear that there is an inherent logic to harnessing the immune system in order to destroy cancer cells, as this is one of the body's natural cancer-fighting mechanisms.⁷

As T-cell mediated cell therapy is a relatively unknown conception in the management of urological malignancies, we refer the reader to Figure 1 which illustrates this process. The term chimeric antigen receptor (CAR) refers to the process by which a daughter cell is produced with an altered genotype (chimera), directing the antigen recognition complex to a specific molecular target such as PSMA (or the CD19 receptor in the case of the ALL therapy described above).

Multiple inhibitory mechanisms are thought to prevent the immune-mediated elimination of prostate cancer cells, including regulatory T-cells, tumour-associated macrophages, myeloid-derived suppressor cells and inhibitory molecules^{9,10}. As prostate cancer has a limited somatic mutation pattern^{11,12} and tumour-associated antigen (TAA) load¹³, it is thought that this malignancy may not be as amenable to immunotherapy as other solid organ cancers with a greater immunogenic load, such as lung or bladder cancer. Nonetheless, the immunogenicity of prostate cancer in potentially driving immunotherapy has been demonstrated by early studies combining conventional treatment with immune checkpoint modulators such as anti-PD-1/anti-PD-L1/anti-CTLA4 monoclonal antibodies¹⁴. It is therefore entirely plausible that a PSMA-directed immunotherapy such as that described by Zhang et al may yield clinical benefit for prostate cancer patients.

Whilst the ability to modify immune cells to target PSMA-expressing cells has achieved impressive results in pre-clinical models, it is not yet clear whether this will be the optimal approach and ideal target in a clinical setting. Further evidence is needed from imaging to demonstrate that PSMA-based PET detects reliably small volume metastatic disease. As a proof-of-principle, Zhang et al offer a template for ligand-based targeted immune therapy and, ultimately, for a translational loop from patient-to-lab-to-patient. Validation will, of course, require further patient-derived pre-clinical models before the technology is ready for clinical applications. However, at the current rapid rate of progress, one has to be optimistic that this will be achieved within the next few years.

The future utilisation of the near-ubiquitous cell surface molecule PSMA promises much in prostate cancer management and this study reveals another exciting avenue for harnessing this ligand. Alongside, T-Cell mediated tumour cell eradication holds significant potential for future clinical practice¹⁵. Several questions remain. At what point in the natural history of this relatively indolent disease do we envisage immunotherapy being implemented? Can other prostate cancer-specific ligands be used in place of PSMA? What other aspects of innate and acquired immunity could be bolstered to eradicate disseminated micrometastatic disease? And what proportion of men with prostate cancer harbour lethal circulating prostate cancer cells? There are few answers to date, but unprecedented opportunities for groundbreaking new research.

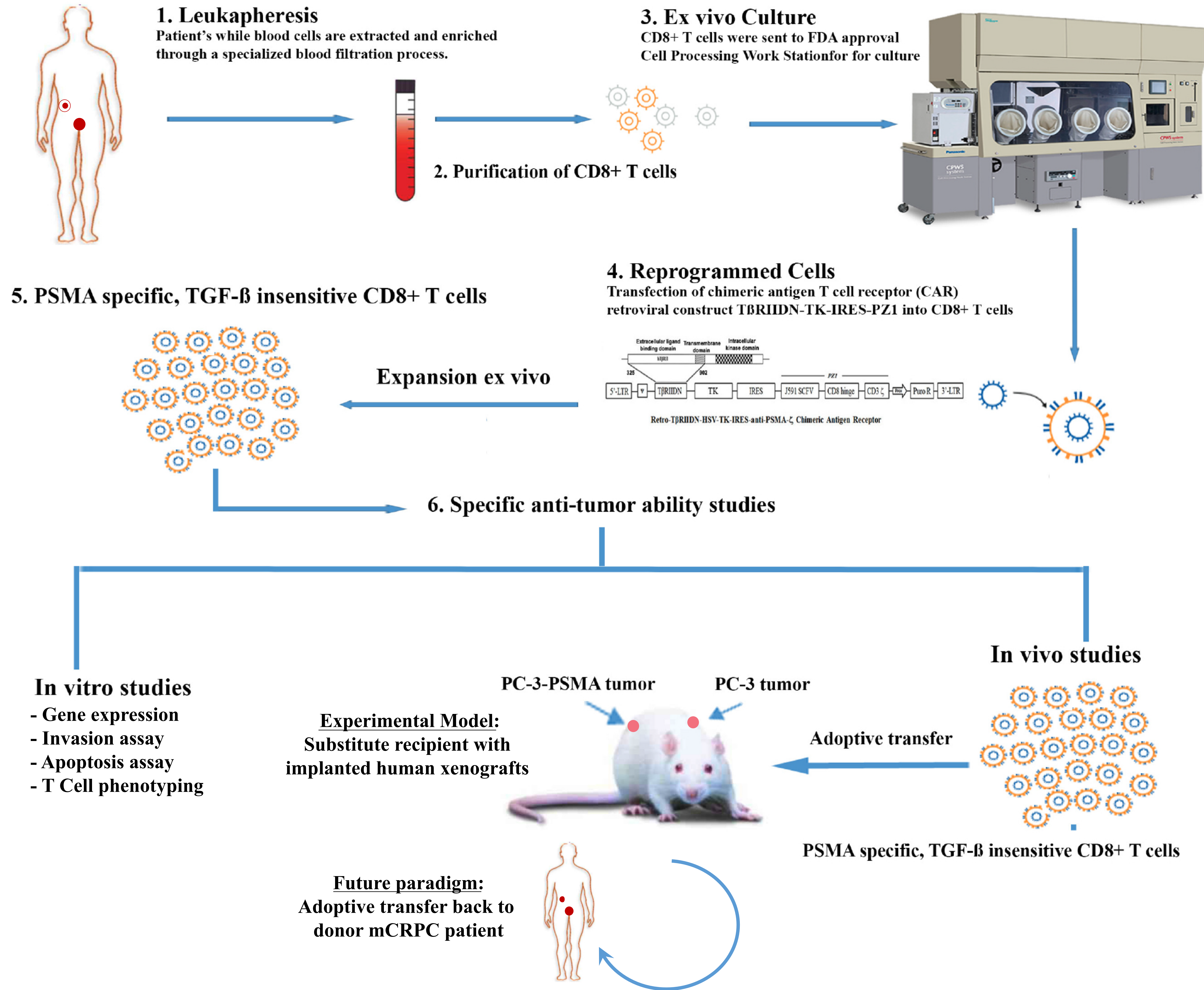
Figure Legend. Figure 1. Adoptive transfer strategy for lymphocytes taken from a donor with metastatic castrate resistant prostate cancer (mCRPC), reprogrammed in vitro to target PSMA and resist host TGF- β , and then re-injected to target PSMA-expressing host prostate cancer cells. In this study the 'host' is an immunocompromised mouse and the prostate cancer cells are xenografts. In future, the host could be the donor with mCRPC. [Modified from Supplementary Figure 6, Zhang et al]

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mCRPC patient



Disclosure

Three of the authors (ADL, RJB, FCH) are investigators on the PROMOTE Trial. Otherwise the authors have no conflicts to disclose.