Nature Reviews Clinical Oncology | Published online 13 Jun 2017

IN BRIEF

BREAST CANCER

Microenvironment mediates differential resistance

Despite being effective, and approved for the treatment of a wide range of tumours, targeted therapies are generally less effective against brain metastases. Now, research using mouse models of brain metastases confirms that the PI3K inhibitor buparlisib is effective against tumours located in mammary fat pads, but not against those located in the brain, despite the established ability of buparlisib to cross the blood–brain barrier. A high-throughput screening approach indicated that exposure to neuregulins, from the tumour microenvironment, resulted in the upregulation of HER3. The relevance of this finding to anticancer drug resistance was confirmed by the sensitization of brain metastases to buparlisib resulting from inhibition of HER3: mice treated with this combination had a substantial delay in the growth of brain metastases, and prolonged survival. These findings demonstrate the importance of the tumour microenvironment in determining tumour sensitivity or resistance to targeted therapies.

ORIGINAL ARTICLE Kodack, D. P. *et al.* The brain microenvironment mediates resistance in luminal breast cancer to PI3K inhibition through HER3 activation. *Sci. Transl Med.* http://dx.doi.org/10.1126/scitranslmed.aal4682 (2017)

IMMUNOTHERAPY

Neuropilin-1 is required for T_{reg} stability

The development of an anticancer immune response is often precluded by an immunosuppressive microenvironment, which can be created by the presence of large numbers of regulatory T cells (T_{reg}). The findings of research using a mouse model of melanoma demonstrate the importance of neuropilin-1 (Nrp1) to T_{reg}-mediated immunosuppression: $Nrp1^{-/-}$ T_{reg} were found to enhance antitumour immunity, often resulting in tumour clearance. However, only a proportion of $Nrp1^{-/-}$ T_{reg} were required for this effect. These enhanced antitumour effects were found to be mediated by IFNγ release from $Nrp1^{-/-}$ T_{reg}. Further investigations revealed that IFNγ-induced T_{reg} fragility is required for a response to anti-programmed cell death protein 1 antibodies in mice, thus highlighting the central role of T_{reg} in the generation and maintenance of an immunosuppressed tumour microenvironment.

ORIGINAL ARTICLE Overacre-Delgoffe, A. E. *et al.* Interferon-γ drives T_{reg} fragility to promote anti-tumor immunity. *Cell* http://dx.doi.org/10.1016/j.cell.2017.05.005 (2017)

HAEMATOLOGICAL CANCER

Genomic disruption of CD7 avoids fractricide

The risk of T-cell fractricide, a situation in which chimeric antigen receptor (CAR) T cells are toxic to each other, owing to the expression of multiple shared antigens by malignant and nonmalignant cells, precludes the use of CAR T-cell-based therapies in patients with T-cell malignancies. New research indicates that targeted disruption of the CD7 gene in anti-CD7 CAR T cells largely avoids the risk of fractricide, and enables expansion of the anti-CD7 CAR T-cell population. Such an approach generated robust antitumour cytotoxicity in malignant T-cell lines and mouse models of T-cell malignancies. In *in vivo* experiments, anti-CD7 CAR T cells remained toxic to the unedited ($CD7^+$) T cells and natural killer cells of the host; however, anti-CD7 CAR T cells can themselves generate an immune response to pathogens, suggesting that such an approach could be tolerated by patients.

ORIGINAL ARTICLE Gomes-Silva D. *et al.* CD7-edited T cells expressing a CD7-specific CAR for the therapy of T-cell malignancies. *Blood* http://dx.doi.org/10.1182/blood-2017-01-761320 (2017)