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> deletion of one or both copies of *PDCD1* reduced the time to the formation of lethal infiltrative lymphomas

TARGETED THERAPIES

# Strategies for mature T cell cancers

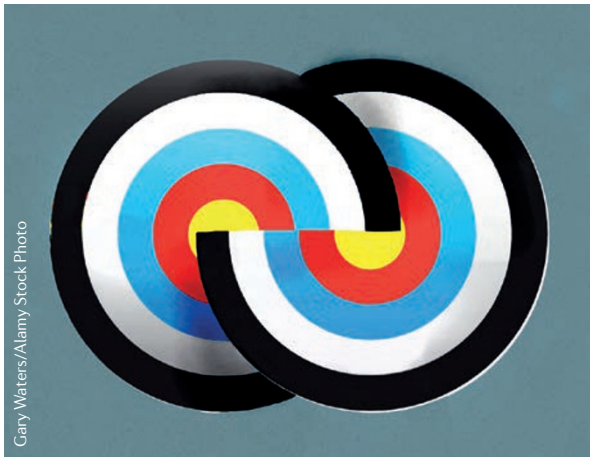
Cancers of mature T cells, such as T cell non-Hodgkin lymphoma (NHL), are aggressive and resistant to treatment. Two new papers provide insight into the future treatment of mature T cell cancers. Wartewig and colleagues demonstrate that *PDCD1*, which encodes programmed cell death protein 1 (PD1), is a haploinsufficient tumour suppressor in this cancer, suggesting that immuno-oncology strategies inhibiting PD1 could, unlike in other tumours, cause T cell NHLs to expand. In a second paper, Maciocia and colleagues exploit the clonal nature of tumours to specifically target one of the T cell receptor β-chain constant domains, TRBC1, using a chimeric antigen receptor (CAR) T cell approach.

Wartewig and colleagues began by generating mice that express a transgene that encodes a fusion protein, ITK–SYK, which is produced by a translocation found in human T cell NHL. ITK–SYK has constitutive tyrosine kinase activity and promotes oncogenic signalling from T cell receptor (TCR) pathways. Expression of the ITK–SYK transgene in $CD4^+$ cells resulted in fully penetrant, aggressive, clonal T cell lymphomas after 200–250 days, following an initial cell expansion and contraction phase.

This delay in tumorigenesis suggested that additional alterations are required. Using a transposon mutational screen, the authors identified *PDCD1* as the most common gene that, if disrupted, leads to rapid transformation. Indeed, in a meta-analysis of five published studies of human T cell lymphomas, *PDCD1* was altered in 36 of 158 cases.

In mice that express ITK–SYK in T cells, deletion of one or both copies of *PDCD1* reduced the time to formation of lethal infiltrative lymphomas to about 1 week ($Pdcd1^{-/-}$) or 1 month ($Pdcd^{+/-}$). Similarly, treating mice expressing ITK–SYK with inhibitors of PD1 or programmed death 1 ligand 1 (PDL1), a recently established class of immuno-oncology agent, led to an immediate and lethal expansion of ITK–$SYK^+$ cells.

In T cell lines, ITK–SYK drives PD1 expression. Normally, PD1 ligation dampens oncogenic signalling by increasing levels of phosphatase and tensin homologue (PTEN), thus providing a negative feedback loop: PTEN counteracts the effects of phosphoinositide 3-kinase (PI3K), a key downstream component of TCR signalling that is engaged by ITK–SYK. Treatment of ITK–SYK-expressing mice with the PI3K inhibitor idelalisib significantly extended their lifespan, underscoring the importance of this signalling pathway and also providing a potential therapeutic avenue.



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In another paper, Maciocia and colleagues generated CAR T cells that target TRBC1, but not TRBC2, to treat mature T cell cancers. Each T cell (and therefore each T cell cancer) irreversibly selects either TRBC1 or TRBC2 to incorporate into TCRs. Approximately 35% of normal and virus-specific T cells express TRBC1, and 65% express TRBC2. Thus, targeting tumours that express TRBC1 should deplete the tumour cells but leave enough T cells to fight infections.

T cells transduced with TRBC1-specific CAR constructs were able to kill $TRBC1^+$ cell lines, and allogenic or autologous CAR T cells were able to kill $TRBC1^+$ primary human malignant cells but not normal $TRBC2^+$ T cells. These CAR T cells were also effective in immunodeficient mice engrafted with $TRBC1^+$ T cells. A clinical trial of anti-TRBC1 CAR T cells for $TRBC1^+$ mature T cell malignancies is due to commence in 2018.

These findings suggest new therapeutic avenues for the treatment of mature T cell malignancies, and also caution against the use of PD1 or PDL1 inhibitors in these cancers.

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**ORIGINAL ARTICLES** Wartewig, T. *et al.* PD-1 is a haploinsufficient suppressor of T cell lymphomagenesis. *Nature* http://dx.doi.org/10.1038/nature24649 (2017) | Maciocia, P. M. *et al.* Targeting the T cell receptor β-chain constant region for immunotherapy of T cell malignancies. *Nat. Med.* http://dx.doi.org/10.1038/nm.4444 (2017)