

## Antibody targeting of TIRC7 with

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### What is known about TIRC7?

**Nalân Utku:** TIRC7 (T cell immune response cDNA7) is a seven membrane protein of 614 amino acid length that was identified as an induced cDNA fragment from 24 h alloactivated T cells via DDRT-PCR analysis (1). TIRC7 contains multiple putative sites of posttranslational modification, including phosphorylation and N-linked glycosylation sites, as well as an immunoreceptor tyrosine-based inhibitory motif. No amino acid homology was found with any known proteins involved in immune cell activa-

tion. Results of several *in vitro* and *in vivo* studies, including those with TIRC7 null mice, indicate that TIRC7 is a key negative T cell regulatory molecule upstream of other inhibitory pathways. Signals downstream to TIRC7 induce suppression in both T and B cell immune responses. Unlike the knock out of its splice variant OC116, which is exclusively expressed in osteoclasts (2), disruption of the TIRC7 gene resulted in hyperreactivities in T- and B-cell responses to stimuli (3).

### Is something known about up-regulation of TIRC7?

**Nalân Utku:** TIRC7 is upregulated after allo or mitogen activation in T cells, in subsets of B cells and monocytes, but not in CD16<sup>+</sup> NK cells (4). Confocal microscopy demonstrated that the cell surface distribution of TIRC7 molecules is enriched towards antigen binding sites and co-localizes with the T cell receptor (TCR)/CD3 (5). Moreover, TIRC7 is upregulated in infiltrating mononuclear cells in human kidney allografts undergo-

ing rejection; in human synovial tissues of patients with Rheumatoid Arthritis and in infiltrates in the neural tissues of patients with Multiple Sclerosis. TIRC7 mRNA is found to be increased in rejected allografts and decreased in PBL of patients undergoing heart transplant rejection (6). Accordingly, mRNA is induced in urine samples of patients undergoing kidney transplant rejection (unpublished data).

### What is the effect of anti-TIRC7 antibody administration?

**Nalân Utku:** The effects of TIRC7 ligation are quite similar to those described by targeting other co-stimulatory molecule pathways, such as CTLA-4 which suggests that TIRC7 might mediate negative co-stimulatory signals. Consistent with this, lymphocytes from TIRC7 deficient mice exhibit signs of immunological hyperactivity such as enhanced proliferation as well as cytokine and antibody secretion following *in vitro* stimulation (3). Spleen cells isolated

from TIRC7 null mice produced higher levels of both Th1 and Th2 cytokines, suggesting a broader regulatory role of TIRC7 (3). Crosslinking of TIRC7 by bivalent antibodies is required to induce inhibitory effects (4). In several *in vitro* and *in vivo* studies, anti-TIRC7 antibodies are shown to inhibit proliferation and Th1 cytokine expression of T cells stimulated with mitogen, recall and alloantigens. Ligation of TIRC7 results in down regulation of the

CD69, CD25 and HLA DR expression whereas CTLA-4 is induced (4,7). Anti-TIRC7 mAb treated allograft recipients exhibited an intragraft up-regulation of CTLA-4 suggesting that sustained up-regulation of CTLA-4 results in transduction of negative sig-

nals to allo-activated T cells inducing hyporesponsiveness to the stimulatory allo-antigens (7). These results, together with the phenotype of TIRC7 null mice, indicate that anti-TIRC7 antibodies act as agonists, inducing inhibitory effects in T cell activation.

### Do you believe in a therapeutic potential of TIRC7 targeting?

**Nalân Utku:** TIRC7 has been shown to serve as a potential immunoregulatory target in various *in vitro* and *in vivo* preclinical assays and therefore seems to be a highly promising candidate for the development of novel therapies to treat immunological disorders (1,4,7). Treatment with anti-TIRC7 mAb results in marked therapeutic effects in collagen-induced arthritis in mice and in organ transplantation in mice cardiac and rat kidney models. An induction of donor-specific anergy is observed, resulting in a significant prolongation of graft survival, including long-term graft survival (7). Moreover, synergy with Calcineurin inhibitors resulted in prolonged graft survival at doses that would be ineffective as

monotherapy in rat kidney transplantation (unpublished data). Targeting of TIRC7 has great potential to open the door for the induction of immune tolerance as well as being a promising target in combination therapy allowing a dose reduction and consequently diminishing the side effects of immune suppressive therapy. The results obtained so far strongly support the therapeutic potential of TIRC7 pathway-mediated T cell suppression in controlling various immunological disorders. If translated into clinical use, the unique mode of action and expression dynamics of TIRC7 might provide highly advantages to treat and monitor immune related diseases.

### REFERENCES

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