# Gene of the month: T-cell immunoreceptor with immunoglobulin and ITIM domains (TIGIT)

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# ABSTRACT

Immune modulators play a crucial role in carcinogenesis and cancer progression by impairing cancer celltargeted immune responses. T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domains (TIGIT) regulates T-cell function and cancer cell recognition and was therefore identified as a promising target for cancer immunotherapy. TIGIT is expressed in T cells and natural killer (NK) cells and has three ligands: CD155, CD112 and CD113. CD155 binds TIGIT with the highest affinity and promotes direct and indirect downregulation of T-cell response. TIGIT signalling further inhibits NK function and secretion of proinflammatory cytokines. An association between TIGIT expression and poor survival was identified in multiple cancer entities. Blocking TIGIT with monoclonal antibodies, and a combination of TIGIT and programmed cell death protein 1 blockade in particular, prevented tumour progression, distant metastasis and tumour recurrence in in vivo models. Inhibition of TIGIT is currently evaluated in first clinical trials.

#### INTRODUCTION

T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domains (TIGIT) is a T-cell receptor involved in limiting T-cell function and adaptive immune responses in the context of cancer immune evasion mechanisms.<sup>1 2</sup> TIGIT was discovered in an effort to identify additional costimulatory or inhibitory molecules expressed on activated human T cells.<sup>3</sup> In this context, Yu et al performed genomic searches for genes specifically expressed in T cells that have a protein domain structure representative of immunomodulatory receptors. TIGIT is mostly expressed by T cells and natural killer (NK) cells. Different T-cell subsets like CD4+ T cells, CD8+ T cells, regulatory T cells (Tregs) and follicular T helper cells as well as NK cells show varying expression levels of TIGIT.<sup>34</sup> In healthy individuals, the highest expression of TIGIT is found in Tregs, memory and activated T cells and NK cells.<sup>5</sup> TIGIT acts as a negative modulator of cancer cell-targeted T-cell response and was identified as a potential target of immune checkpoint inhibition in different malignancies.67

### STRUCTURE

The TIGIT gene encodes a surface protein of the poliovirus receptor family of immunoglobin proteins that is expressed on regulatory, memory and activated T cells as well as NK cells.<sup>3 8</sup> Structurally,

TIGIT is composed of multiple domains: an extracellular immunoglobulin variable (IgV) domain, a type 1 transmembranous domain and a cytoplasmic tail consisting of an immunoreceptor tyrosine-based inhibitory motif (ITIM) and an immunoglobulin E tyrosine tail (ITT)-like motif. The phosphorylacopyright tion of the cytoplasmic tail initiates an inhibitory signalling cascade on TIGIT binding to its ligand (figure 1).<sup>3 8</sup>

The extracellular IgV domain binds a family of nectin proteins expressed on the surface of antigenpresenting cells or tumour cells in a lock-and-key mechanism: CD155, CD112 and CD113.8 TIGIT binds CD155 with the highest affinity as compared with competing receptors, followed by CD96, and the immunoactivator CD226 showing the lowest affinity for CD155.369 CD155 is mainly expressed on dendritic cells (DCs), T cells, B cells and macrophages,<sup>3 6 10 11</sup> but also on fibroblasts and endothelial cells.<sup>12</sup> Crystal structure analysis shows that on binding CD155, the newly formed TIGIT/CD155 dimers cluster into a heterotetramer which mediates cell adhesion and signalling between the cells.<sup>12</sup> CD155 is bound by the TIGIT receptor in a dosedependent manner competitively, thereby directly blocking CD155 binding to the competing receptor CD226. This inhibition is further supported by cellintrinsic signals directly by signalling cascades initiated on phosphorylation of TIGIT's cytoplasmic tail.<sup>6 13</sup>

## **FUNCTION**

TIGIT acts as an immune modulator and inhibits effector T cells and NK cells.<sup>6</sup> TIGIT effects are mediated by binding TIGIT's primary receptor CD155 and by direct inhibition of T-cell responses.<sup>6</sup><sup>13</sup><sup>14</sup>

TIGIT interacts with CD155 on DC, leading to technolog an increase in the secretion of interleukin (IL)-10 and a decrease in proinflammatory cytokines such as IL-12p40, IL-12p70 and IL-18.<sup>3</sup> These functionally impaired DC lead to an indirect decrease in T-cell response.<sup>3</sup> In the presence of TIGITmodulated DC, T-cell proliferation is reduced by at least 50% and T-cell activation is inhibited.<sup>3</sup> TIGIT also binds CD155 expressed on macrophages.<sup>15</sup> In mice, TIGIT promotes the polarisation of CD155expressing type 1 proinflammatory macrophages into immunosuppressive IL-10-secreting type 2 macrophages.

CD226 is a costimulatory receptor widely expressed by immune cells, including T cells, NK cells and monocytes. TIGIT impedes

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**Figure 1** TIGIT consists of three domains: an extracellular IgV domain, a type 1 transmembranous domain and a cytoplasmic tail consisting of an ITIM and an ITT-like motif. The phosphorylation of the cytoplasmic tail initiates an inhibitory signalling cascade on TIGIT binding to its ligand. The extracellular IgV domain binds a family of nectin proteins expressed on the surface of antigen-presenting cells or tumour cells in a lock-and-key mechanism: CD155, CD112 and CD113. CD155 is bound by the TIGIT receptor in a dose-dependent manner competitively, thereby directly blocking CD155 binding to the competing receptor CD226. IgV, immunoglobulin variable; ITIM, immunoreceptor tyrosine-based inhibitory motif; ITT, immunoglobulin tyrosine tail; NK, natural killer; PVR, poliovirus receptor; TIGIT, T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domains.

CD155-mediated CD226 activation, ultimately impairing T-cell function in different T-cell subsets.<sup>16</sup> TIGIT knock-down in human CD4+ T cells increased their expression of T-bet and interferon gamma (IFN- $\gamma$ ); however, this effect can be overcome by CD226 blockade.<sup>17</sup> Furthermore, TIGIT suppresses mouse CD8+ T-cell responses in a CD226-dependent manner.<sup>13</sup> The TIGIT–CD226 axis with TIGIT outcompeting CD226 for binding of CD155 is essential in TIGIT-mediated immune modulation.

TIGIT-CD155 signalling via the intracellular ITIM domain of TIGIT can restrict not only T-cell but also NK-cell response.<sup>14</sup> TIGIT plays a major role in NK-cell exhaustion and limits tumor cell-directed NK-cell cytotoxic effects.<sup>18</sup> TIGIT-positive NK cells showed characteristics of exhaustion and dysfunction such as weakened killing function, reduced cytokine production and proliferation.<sup>19</sup> TIGIT inhibits NK-cell degranulation, cytokine production and NK cell-mediated cytotoxicity against CD155-expressing tumour cells.<sup>20 21</sup> TIGIT-derived interference with NK toxicity and IFN- $\gamma$  production is mediated by the ITT motive via different signalling pathways.<sup>20 21</sup>

TIGIT is highly expressed in a subset of Tregs.<sup>22 23</sup> These TIGIT-positive Tregs specifically suppress T-helper type 1 and T-helper type 17 T-cell responses.<sup>22</sup>

Taken together, all direct and indirect pathways of TIGIT binding result in suppression of T-cell and NK-cell functions. This mechanism of immune evasion makes TIGIT an attractive target to study in the context of malignant disease.

#### TIGIT EXPRESSION IN MALIGNANCY

In healthy individuals, the immune system plays an important role in eliminating malignant cells.<sup>1 24</sup> Immune checkpoint mechanisms moderate immune responses to restrict excessive T-cell or NK-cell cytotoxicity. These modulating effects are important in preventing major tissue damage or autoimmunity. Immune checkpoint signalling, however, is used by tumour cells to evade immune surveillance.<sup>6</sup> These pathways involve receptor–ligand pairings that ultimately suppress the effector functions of T cells and NK cells and thereby downregulate antitumour immunity.<sup>17</sup>

pairings that ultimately suppress the effector functions of T cells and NK cells and thereby downregulate antitumour immunity.<sup>17</sup> In vivo models of TIGIT deficiency highlighted the crucial role of TIGIT in tumour progression. Compared with wild-type mice, growth of colon and breast cancer subcutaneous tumours was suppressed in TIGIT-deficient mice, and overall survival was increased in myeloma models.<sup>7 25</sup> TIGIT deficiency further protected mice against B16 experimental lung metastasis.<sup>26</sup> TIGIT is widely expressed across different cancer entities, and studies in both mice and humans report increased TIGIT expression on tumour-infiltrating lymphocytes (TILs) in melanoma, pancreatic cancer, breast cancer, non-small-cell lung carcinoma, colon adenocarcinoma, gastric cancer, acute myeloid leukaemia (AML) and multiple myeloma.<sup>67</sup> 13 27-30

A growing body of evidence suggests a role for TIGIT in disease recurrence and patient prognosis in patients with various malignancies. TIGIT expression on TILs of patients with melanoma or on peripheral blood CD8+ T cells of patients with gastric cancer correlated with metastases formation and impaired overall survival.<sup>28 31</sup> In patients with melanoma, a high TIGIT:DNAM-1 expression ratio on tumour-infiltrating Tregs was demonstrated to be associated with reduced overall survival rates.<sup>32</sup> There are now a couple of studies showing that TIGIT is highly expressed in pancreatic cancer, and this is mainly on Tregs, CD8+ T cells and NK cells.<sup>33 34</sup> Furthermore, in a recent article, in animal models of pancreatic cancer, monoclonals of TIGIT and PD-1 with CD40 agonists proved to have a significant survival benefit.<sup>35</sup> TIGIT is furthermore involved in AML recurrence and a strong correlation was observed between TIGIT expression on peripheral blood CD8+ T cells and AML relapse post-transplantation.<sup>29</sup> TIGIT overexpression is part of the highly immunosuppressive microenvironment of pancreatic cancer.<sup>36</sup> Mapping of the tumour and immune cell landscape in pancreatic cancer revealed an increase in TIGIT expression and a corresponding higher number of dysfunctional CD8+ T cells in advanced stage disease.<sup>34</sup>

The major role of TIGIT for cancer progression in various cancer entities makes TIGIT an attractive target for immune checkpoint inhibition.

#### **TIGIT-targeted monotherapy**

The rationale for targeting TIGIT is to reverse immune invasion of cancer cells and to re-establish cancer-targeted T-cell and NK-cell cytotoxicity. Different monoclonal antibodies (mAbs) binding the TIGIT receptor in T cells and NK cells were established over the past years.<sup>6 37</sup> Anti-TIGIT mAb therapy administered while establishing CT26 subcutaneous tumours and methylcholanthrene-induced fibrocarcinomas hindered tumour growth and protected mice against 4T1 or B16 experimental metastasis.<sup>26</sup> In melanoma patient-derived xenograft models reconstituted with human haematopoietic stem cells, etigilimab, a TIGIT-targeting mAb, impaired tumour growth.<sup>38</sup> Another group found that anti-TIGIT mAbs protected mice against Vk12653 myeloma recurrence after haematopoietic stem cell transplantation.<sup>39</sup> In another myeloma mouse model, TIGITblocking mAbs reduced tumour burden in a CD8+ T cell-dependent manner and prolonged overall survival.<sup>7</sup>

Despite these promising results, other studies found no effect of anti-TIGIT mAbs in xenograft models bearing advanced tumours.<sup>13 40</sup> These heterogeneous results of anti-TIGIT monotherapy highlight the need for combination therapies potentially enhancing the effect of immune checkpoint blockade.

#### **TIGIT-targeted combination therapy**

Since TIGIT-targeting mAbs alone may not have a sufficient effect on tumour progression, combination immune checkpoint inhibition strategies are evaluated in different cancer entities. In both mouse models and patient samples across cancer entities, TIGIT is often coexpressed with programmed cell death protein 1 (PD-1) on CD8+ TILs.<sup>13 41</sup> PD-1 checkpoint blockade proved a highly effective treatment in multiple cancer entities, including melanoma and non-small cell lung cancer.<sup>37 42</sup>

The mechanism behind combined TIGIT and PD-1 blockade is mainly based on shifting CD155 signalling towards CD226 activation since the TIGIT +PD-1 therapeutic effect can be abrogated by CD226 blockade.<sup>13 41</sup> Additionally, PD-1 induces SHP2-mediated CD226 dephosphorylation, further supporting the need for combined PD-1 +TIGIT blockade to promote CD226 signalling.<sup>43</sup> Jin *et al* suggest that CD226 may even qualify as a predictive biomarker of combined TIGIT +PD-1 targeted therapy.44 The authors found that high expression of CD226 in CD8<sup>+</sup> cells improved self-renewal capacity and

responsiveness to TIGIT-targeted therapy in pancreatic cancer. Interestingly, mFOLFIRINOX therapy increased the rates of CD8+ cells with high CD226 expression, potentially increasing the effects of combined TIGIT +PD-1 blockade.

In vivo studies of combined TIGIT+PD-1 blockade show impressive results inducing tumour regression and preventing distal tumour spread. Johnston et al investigated combined anti-TIGIT mAbs with PD-1 or PD-L1 blockade in xenograft models of colon (CT26) and breast (EMT6) cancer.<sup>13</sup> Combined therapy induced mostly complete tumour regression in a CD8+ T cell-dependent manner with an increase in IFN-γ production. In another mouse model of colon cancer (MC38), TIGIT+PD-1 blockade was associated with enhanced effector cell functions of both CD4+ and CD8+ T cells compared with either therapy alone, and combined therapy led to a 100% cure rate.<sup>40</sup> TIGIT+PD-1 blockade further protected mice from orthotopically implanted GL261 glioblastoma tumour formation.<sup>4</sup>

Besides the effects of TIGIT blockade on T cells, TIGIT blockade alone and in combination with PD-1 blockade can play a crucial role in reversing NK-cell exhaustion, unleashing NK-cell cytotoxicity and boosting synergetic effects with adaptive T-cell immunity.<sup>18</sup> TIGIT blockade enhanced degranulation and IFN- $\gamma$  production of NK cells in response to ovarian cancer tumour cells in vivo.<sup>46</sup> Blockade of TIGIT prevented NK-cell exhaustion and promoted NK cell-dependent tumour immuuses related to text nity in mouse models of colon cancer. Furthermore, blockade of TIGIT resulted in potent tumor-specific T-cell immunity in an NK cell-dependent manner, enhanced therapeutic effects with PD-1-targeted therapy and sustained memory immunity in tumour rechallenge models.<sup>26</sup> Novel anti-TIGIT monoclonal antibodies with the specific purpose of enhancing NK-cell immunity such as AET2010 are currently being developed and tested in in vivo settings.47 and

Besides TIGIT+PD-1 blockade, further TIGIT combination therapies are currently explored. TIGIT-positive NK cells were found to coexpress TIM-3, another inhibitory receptor.<sup>26</sup> TIGIT and TIM-3 synergise to suppress antitumor immune responses in mice and are therefore a promising target for combination ther-apies.<sup>25</sup> Chauvin *et al* investigated a combined TIGIT blockade with IL-15 stimulation in MHC class I-deficient melanoma, ≥ which is refractory to CD8+ T cell-mediated immunity.<sup>48</sup> The combination blockade increased NK cell-mediated cytotoxicity in vitro and decreased tumour metastasis in mouse melanoma models.

Antitumour effects of TIGIT combined therapy are impressive and call for further evaluation in first clinical trials.

#### **TIGIT blockade in clinical trials**

TIGIT checkpoint inhibition has entered clinical trials, and six different TIGIT-blocking mAbs are currently available.<sup>49</sup> The anti-TIGIT mAb etigilimab was entered into a phase I, dose-escalation study (NCT031119428) as monotherapy or in combination with anti-PD-1 mAb nivolumab to treat advanced or metastatic solid malignancies.<sup>50</sup> Etigilimab was well tolerated with low toxicity profiles at doses of up to 20 mg/kg. Rodriguez-Abreu et al evaluated combined TIGIT+PD-1 versus PD-1 blockade alone in a randomised phase II trial in patients with PD-1positive non-small cell lung cancer.<sup>37</sup> Combined TIGIT+PD-1 blockade was superior to PD-1 blockade alone as a first-line therapy in terms of overall response rates and progression-free survival despite similar toxicity profiles. Five clinical phase I and II trials are currently investigating combined TIGIT blockade alone or TIGIT+PD-1 blockade in patients with advanced or

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metastatic solid malignancies (NCT03628677, NCT02964013, NCT02913313, NCT03260322 and NCT03945253). Another phase II trial evaluates TIGIT+PD-1 blockade in advanced or metastatic non-small cell lung cancer (NCT03563716). One trial is testing agonistic anti-CD226 blockade in solid malignancies (NCT04099277).

#### CONCLUSIONS

TIGIT is a major immune checkpoint promoting tumour cell immune evasion from T-cell and NK-cell cvtotoxicity via binding of its primary ligand CD155. TIGIT overexpression was found in various malignancies and is associated with cancer progression, distant metastases and impaired patient prognosis. Combined checkpoint blockade of TIGIT+PD-1 shows impressive tumour regression in vivo, and first clinical trials yield encouraging results for this combination therapy. Several questions still need to be addressed. Can combined TIGIT blockade overcome the immunosuppressive microenvironment and is it effective even in advanced stages of cancer? Moreover, which cancer entities benefit most from TIGIT blockade and what criteria could be applied to select ideal candidates for TIGIT-targeted therapies? A more in-depth understanding of TIGIT interaction with other components of the tumour microenvironment and future clinical trials evaluating TIGIT combination blockade therapies are warranted.

#### Take home messages

- T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domains (TIGIT) is a T-cell immunoreceptor primarily binding CD155 as a ligand.
- It is found expressed on T cells and NK cells.
- TIGIT impairs T-cell and NK cell cytotoxicity directly and indirectly via binding CD155.
- Blockade of TIGIT and combined blockade of TIGIT+programmed cell death protein 1 (PD-1) in particular show impressive tumor regression in multiple cancer entities in vivo.
- Combined TIGIT+PD-1 blockade is currently evaluated in multiple clinical trials,;first results show no excess toxicity and promising effects on response rates of progression-free survival.

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Gene of the month

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