Time for TIM-3: Beyond Immune Checkpoint Inhibition

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Meeting Summary

This symposium took place during the 2020 virtual European Hematology Association (EHA)–Scientific Working Group (SWG) Scientific Meeting on Immunotherapy for Hematological Disorders. The session focussed on the T-cell Ig and mucin domain containing protein-3 (TIM-3) receptor and its potential as a new target for drug development in the treatment of patients with higher-risk myelodysplastic syndrome (HR-MDS) and acute myeloid leukaemia (AML). Prof Kuchroo set the scene by describing the discovery of TIM-3 and the *TIM* family of genes. This included the identification of TIM-3 as a Th1-specific molecule, and of galectin-9 as a ligand for TIM-3. The role of TIM-3 as a negative regulator of Th1 immunity was discussed. Prof Kuchroo described how TIM-3 germline mutations induce an autoinflammatory disease called subcutaneous panniculitis-like T-cell lymphoma (SPTCL) and discussed the role of TIM-3 in myeloid cell function. Key findings were that TIM-3 is coexpressed with programmed cell death protein 1 (PD-1) in exhausted T cells and that coblockade of TIM-3 with PD-1 induces tumour regression. Prof Platzbecker introduced the concept of TIM-3-based checkpoint inhibition treatment in patients with myeloid malignancies, primarily MDS and AML. The rationale for TIM-3 as a promising therapeutic target in MDS and AML includes the role it has in regulating adaptive and innate immune responses. TIM-3 is expressed on most leukaemic progenitors, but not on normal haematopoietic stem cells (HSC). It also has a role in leukaemic transformation and disease progression in MDS and AML. He described studies showing that blockade of TIM-3 may restore

antileukaemic immune function while also directly targeting leukaemic stem cells (LSC) and blasts, and presented early clinical data for the anti-TIM-3 antibody sabatolimab demonstrating good safety and promising efficacy in HR-MDS and AML.

More Than Meets the Eye: Taking a Closer Look at TIM-3

Professor Vijay Kuchroo

TIM-3 was first discovered in Prof Kuchroo's laboratory in 2002. This lecture reviewed the history of the discovery of TIM-3, including its role in antitumour immunity.

Discovery of TIM-3 and the *TIM* Family of Genes

Identification of TIM-3 as a molecule specific for IFN-γ-producing Th1 and Tc1 cells

The discovery of TIM-3 arose from research to identify molecules that are expressed on subsets of differentiated T cells. Mosmann et al.[1] further described Th1 and Th2 cells, noting that when naïve T cells encounter antigens, they activate, expand, differentiate, and acquire different effector phenotypes. Th1 cells produce interferon-γ (IFN-γ) and IL-2, which induce autoimmunity and are also critical for inducing antitumour immunity. Th2 cells make IL-4, IL-5, and IL-13 and are essential for dealing with parasitic infections, but can also induce asthma, allergy, and atopy if their specificity is for allergens.

The finding that Th1 cells induce autoimmunity and antitumour immunity suggested that it was important to identify a molecule by which the cells can be extracted from the tissues. A series of monoclonal antibodies (mAb) that bind to Th1/Type 1 cytotoxic (Tc1) cells were generated by immunising rats with Th1 cells. Four different mAb were identified that bind to Th1/Tc1 cells but not to Th2 cells, including the two antibodies that were found to bind to the cell-surface protein now known as TIM-3. The next step was to clone the gene for the receptor bound by the antibody by undertaking expression cloning from a complementary DNA library of Th1 cells.

The gene was characterised as a 302-residue-long gene in mice and 296-residue-long gene in humans, with approximately 68% homology between the two species. The gene itself had a signal peptide, an Ig variable domain, a mucin domain, and a long tail with six tyrosines.[2] This allowed the identification of the gene's location and also revealed that it is the smallest member in a large family of genes;[3] in humans there are three different genes located on chromosome *5q33.2*, while in mice there are eight different genes on chromosome *11B1.1*. The chromosomal region has been repeatedly linked with a number of immune-mediated diseases such as asthma, allergy, and autoimmune conditions.[3]

Galectin-9 as a ligand for TIM-3

The next stage of the research was to pinpoint the ligand for TIM-3. For this purpose, a soluble protein of TIM-3 was created by inserting an Ig domain onto TIM-3 to form a soluble TIM-3–Ig fusion protein. This Ig fusion protein of TIM-3 was able to bind many tumour cells, including a T-cell lymphoma line, and TIM-3–Ig could bind to a putative ligand expressed on tumour cells. Immunoprecipitation coupled with mass spectrometry identified galectin-9 as the ligand expressed on many tumour cells to which TIM-3 was binding.[4]

TIM-3 germline mutations induce subcutaneous panniculitis-like T-cell lymphoma

Prof Kuchroo highlighted that germline mutations in *HAVCR2*, which encodes TIM-3, are seen in SPTCL, a type of autoinflammatory disease[5] that occurs at a median age of 38 years and is more common in females than males. The disease is characterised by a skin rash, followed by development of panniculitis with inflammation and activation, expansion, and infiltration of lymphocytes, CD8 T cells, and myeloid cells around the subcutaneous fat pads. The CD8 T cells hyperproliferate and ultimately form tumours. Approximately 30% of cases develop haemophagocytic lymphohistiocytosis, which worsens survival, and will ultimately develop lupus-like diseases. There is no standardised therapy for SPTCL, but patients have shown better responses to immunosuppression compared with standard chemotherapy.

TIM-3 as a negative regulator of Th1 immunity

In patients with SPTCL, three mutations have been found in the Ig variable domain of TIM-3: *Y82C*, *I97M*, and *T101I*.[5,6] All three germline mutations in patients with SPTCL coalesce on TIM-3 at the location where galectin-9 binds to TIM-3,[7] indicating that the mutations may regulate galectin-9 binding.

Patients with SPTCL show increased baseline activation of T cells and macrophages. Furthermore, patients with SPTCL have increased serum levels of inflammatory markers, including the chemokine CXCL10, soluble CD25, and IL-18. In addition, there is increased production of TNF-α and IL-1β by macrophages.[5] SPTCL mutations induce TIM-3 protein misfolding, abrogate cell surface expression, and mediate immune activation.[8]

Role of TIM-3 in Antitumour Immunity

TIM-3 is co-expressed with PD-1 in exhausted T cells

Because it is a coinhibitory molecule, Prof Kuchroo predicted that TIM-3 has a role in regulating antitumour immunity. His initial studies show that tumour-infiltrating lymphocytes acquired TIM-3 expression and became dysfunctional. CD8 T cells in the tumours of mice progressively express checkpoint molecules, e.g., TIM-3 and PD-1. Some cells do not express TIM-3 or PD-1 and are able to carry out their effector functions by secreting the cytokines IFN-γ, TNF-α, and IL-2. A fraction of tumour-infiltrating CD8 T cells express PD-1 only and lose some of their effector functions (only IFN-γ and TNF-α are secreted), but when tumour-infiltrating lymphocytes express both TIM-3 and PD-1, the cells become dysfunctional due to the loss of most of their effector functions (only IFN-γ is secreted). This demonstrates that TIM-3 and PD-1 are coinhibitory receptors (checkpoint molecules) that inhibit T-cell responses.

TIM-3 has been identified as one of the major checkpoint molecules in inducing T-cell exhaustion. T cells are activated by the T-cell receptor working together with costimulatory (activating) receptors, in order to activate, expand, and differentiate to attain effector functions. However, once activated, T cells are eliminated via inhibitory receptors including cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), PD-1, TIM-3, lymphocyte-activation gene 3 (LAG-3), and TIGIT, which trigger exhaustion and T-cell dysfunction. Tumours have co-opted these inhibitory receptors and readily induce their expression on tumour-infiltrating lymphocytes, thereby inhibiting antitumour immunity. A series of studies, including a study by Prof Kuchroo, have demonstrated that inhibitory (checkpoint) molecules are expressed together as a module in tumour-infiltrating lymphocytes during T-cell dysfunction or exhaustion.[9] IL-10 is the key cytokine made by these exhausted T cells, which suppresses the immune system inside the tumour microenvironment. Expression analysis by RNA sequencing of CD8 T cells from human tumours including non-small cell lung cancer,[10] colorectal carcinoma,[11] melanoma,[12] and hepatocellular carcinoma[13] has revealed a core programme of 18 genes that are common to all tumour-infiltrating lymphocytes and exhausted T cells. These include genes for TIM-3, PD-1, CTLA-4, TIGIT, and LAG-3, together with the transcription factor TOX, which has previously been implicated in the induction of T-cell exhaustion.

Coblockade of TIM-3 with PD-1 induces tumour regression

To investigate whether there is a role for TIM-3 in inducing antitumour immunity, especially in solid tumours, mice with tumours were given anti-TIM-3 antibodies alone, anti-PD-L1 antibodies alone, both anti-TIM-3 and anti-PD-L1, or neither (control group).[14] Combining anti-PD-1 and anti-TIM-3 together induced potent antitumour immunity and these mice were resistant to subsequent challenge with a transplanted tumour. Treatment with anti-PD-L1 and anti-TIM-3 resulted in loss of the exhausted PD-1+ and TIM-3+ fraction of cells, and the tumour-infiltrating lymphocytes acquired the ability to produce proinflammatory cytokines including IFN-γ, TNF-α, and IL-2, cytokines that are generally lost during T-cell exhaustion.[14] This may explain why the combination of anti-PD-1 and anti-TIM-3 antibodies can induce antitumour immunity. Although TIM-3 was originally identified as a T-cell surface protein, within tumours, T cells express very low levels of TIM-3 while the majority of TIM-3 expression

has been observed on myeloid cells, particularly on dendritic cells (dendritic cell 1 and migratory dendritic cells), followed by other myeloid cell populations.

In conclusion, TIM-3 was identified as a molecule that is differentially expressed on Th1 and Tc1 cells, where it is expressed on exhausted T cells in the tumour microenvironment. However, it appears that TIM-3 is also expressed on other cell types including FoxP3+ regulatory T cells, natural killer cells, and myeloid cells. In the tumour microenvironment, TIM-3 is predominantly expressed on myeloid cells. Combined TIM-3 and PD-1 expression mark terminally exhausted T cells in tumours (and chronic viral infections); coblockade of TIM-3 and PD-1 induces antitumour immunity in solid tumours.

On the Horizon: TIM-3 Inhibition in Myelodysplastic Syndrome and Acute Myeloid Leukaemia

Professor Uwe Platzbecker

This lecture introduced the concept of TIM-3-based checkpoint inhibition treatment in patients with myeloid malignancies, primarily MDS and AML.

An Unmet Medical Need

There is a tremendous unmet medical need in HR-MDS and AML, as shown by data obtained in patients receiving the standard of care, which is mainly the hypomethylating agents (HMA) azacitidine or decitabine. Patients with HR-MDS have a shorter survival time and greater likelihood of transformation to AML versus those with lower-risk MDS.[15] Patients with very-high-risk (vH) and HR-MDS, as defined by the Revised International Prognostic Scoring System (IPSS-R) have a median survival of <1 year with supportive care only, and many patients do not respond to azacitidine- or decitabine-based treatment and the duration of the response is short-lived.

The survival of patients with AML has improved only modestly over the last four decades, particularly among those aged ≥65 years.[16] This emphasises that even with the introduction of combination and novel treatment, many patients still do not respond or lose response. More therapy options are needed for patients with HR-MDS and AML, including targeted agents that could help restore antitumour immune function.

Modest Effect of Immune Checkpoint Inhibitor Therapy

Stimulating antitumour T-cell responses by using immune checkpoint inhibitors has revolutionised the treatment of solid malignancies and has become standard of care in diseases such as lung cancer. Overexpression of checkpoint molecules including PD-1, CTLA-4, TIM-3, and LAG-3 reduces T-cell-mediated tissue injury by preventing sustained T-cell activation. However in myeloid malignancies, immune checkpoint inhibition monotherapy has yielded only very modest efficacy results as well as safety concerns.[17-19] Treatment with ipilimumab (anti-CTLA-4) as a single agent in HMA-refractory patients with MDS yielded a very limited response rate and 20.7% of patients developed immune-related adverse events Grade ≥2.[18] The same treatment was more effective in patients who had received an allogeneic stem cell transplant, but 14% experienced dose-limiting graft-versus-host disease.[19]

Clinical trials of immune checkpoint inhibition combined with HMA have also yielded largely disappointing results in MDS and AML. For example, a study of azacitidine plus durvalumab versus azacitidine alone produced very limited response rates in patients with MDS or AML.[20] Complete response with combination treatment was achieved in 7% of patients with MDS and 17% of patients with AML. The findings suggested that unselected combinations of checkpoint inhibitors such as durvalumab with HMA may not improve outcomes in these patients.

Rationale for Targeting TIM-3

With advances in the understanding of checkpoint expression and the functional properties of these pathways, there are now data providing a rationale for moving beyond traditional checkpoint inhibition and moving towards targeting TIM-3. The reason for this is that TIM-3 is expressed not only on immune effector cells (T cells) but also on LSC and blasts.[21-24] While TIM-3 is expressed in LSC of most AML types at high levels, it is not expressed in normal HSC,[25] making it appealing for targeted interventions with anti-TIM-3 antibodies.

It has also been demonstrated that TIM-3 expression correlates with disease severity in MDS.[24] A low-to-high gradient is observed when comparing cell-surface TIM-3 expression on blast cells in control, low-grade MDS, high-grade MDS, or acute leukaemia transformed from MDS. This again highlights the potential of targeted treatment with anti-TIM-3 antibodies in these patients. From a functional perspective, the interaction of TIM-3 with the galectin-9 ligand has been shown to regulate the cell renewal of LSC.[23] The interaction can also promote clonal selection and by doing so contributes to leukaemic progression in myeloid malignancies, which includes the upregulation of NFκB and β-catenin, resulting in an autocrine loop, which improves the cell renewal capacity of these early progenitor cells.

TIM-3 Inhibitors in Development for the Treatment of Solid Tumours and Haematologic Malignancies

A number of studies of TIM-3 inhibitors are currently running in a variety of solid cancers. Preliminary data from a Phase I, open-label study in solid tumours showed that Sym023 (anti-TIM-3) combined with Sym021 (anti-PD-1) was generally well tolerated, with only mild side effects and treatment-related adverse events.[26] In addition, there was evidence of activity, with some patients responding for a promising period of time.

Sabatolimab for the Treatment of Myeloid Malignancy

Sabatolimab (MBG453; Novartis International AG, Basel, Switzerland) is an investigational, high-affinity, humanised, IgG4 mAb. Phase I and Phase II/III studies are underway with sabatolimab, an anti-TIM-3 inhibitor, in patients with myeloid malignancies, mainly MDS, chronic myelomonocytic leukaemia, and AML. The concept behind introducing sabatolimab into the treatment of myeloid malignancy is that it may provide dual targeting of TIM-3 on both immune cells but also LSC and blasts. Therefore, the proposed mechanism is unique, giving the potential for sabatolimab to be a first-in-class immunotherapeutic agent that could restore immune function while also directly targeting LSC and blasts.[14,25,27,28]

The targeting of TIM-3 by sabatolimab may have multiple antileukaemic mechanisms.[29] Firstly, it inhibits the TIM-3/galectin-9 autocrine feedback loop and the capacity for LSC self-renewal. Secondly, it promotes antibody-dependent cellular phagocytosis in FcγR-expressing myeloid cells or macrophages. Thirdly, it promotes an M1 phenotype in macrophages. Through these multiple effects, the agent promotes the killing and apoptosis of early progenitor cells in the bone marrow of patients with AML and MDS; this is the preclinical concept behind this potential treatment.

A Phase Ib study is underway, investigating sabatolimab in combination with HMA or spartalizumab (an anti-PD-1 inhibitor) in 11 trial centres in eight countries.[30] The following patient categories are eligible: IPSS-R vH/HR-MDS; unfit, newly diagnosed AML, ineligible for standard chemotherapy; and relapsed/refractory AML, ineligible for standard chemotherapy. Patients with prior HMA treatment for MDS/AML have been excluded. Patients receive decitabine for 1–5 days or azacitidine for 1–7 days, followed by sabatolimab at Days 8 and 22, in 28-day treatment cycles. Additional study arms include sabatolimab±spartalizumab; spartalizumab+decitabine; and sabatolimab+spartalizumab+decitabine. The primary endpoints are the maximum tolerated dose/recommended dose, safety, and tolerability. Secondary endpoints include preliminary efficacy (overall response rate [ORR], best overall response, progression-free survival, time to progression, and duration of response) and pharmacokinetics.

Preliminary data indicate that treatment with sabatolimab and HMA (decitabine or azacitidine) was safe and well tolerated in patients with HR-MDS and AML.[31] A total of 69 patients received the sabatolimab/decitabine treatment for a median of 4.3 (0.7–30.3) months, while 37 patients underwent sabatolimab/azacitidine therapy for a median of 3.1 (0.3–12.3) months. The most common treatment-emergent adverse events were consistent with those for HMA alone. The most common Grade 3/4 treatment-emergent adverse events with sabatolimab/decitabine and sabatolimab/azacitidine, respectively, were thrombocytopenia (41%; 52%), febrile neutropenia (46%; 21%), neutropenia (42%; 38%), and anaemia (25%; 28%). The majority (92%) of possible immune-mediated adverse

events related to study treatment were Grades 1/2, and few Grade 3 possible immune-mediated adverse events related to study treatment were observed.

Preliminary efficacy data have also demonstrated that sabatolimab/HMA therapy showed promising antileukaemic activity in patients with HR-MDS and AML (unpublished data, abstract at European School of Hematology [ESH] How to Diagnose and Treat: Acute Leukaemia 2020).[32] In HR-MDS, 11 of 18 (61.1%) patients achieved some response with sabatolimab/decitabine, for an ORR of 61.1%; the ORR with sabatolimab/azacitidine was 57.1% (eight of 14 patients). In newly diagnosed AML, the ORR was 47.1% (eight of 17 patients) with sabatolimab/decitabine, and 28.6% (four of 14 patients with sabatolimab/azacitidine. The ORR with sabatolimab/decitabine in patients with relapsed/refractory AML (26 evaluable) was 23% (all complete remission with incomplete haematologic recovery). Emerging durability of response was seen in patients with HR MDS, with some patients still responding after 1 year (unpublished data, abstract at ESH How to Diagnose and Treat: Acute Leukaemia 2020).[32]

Sabatolimab is being evaluated further in the STIMULUS clinical trial programme in HR-MDS and AML. STIMULUS-MDS1 is a Phase II study of sabatolimab plus HMA in patients with vH/HR or intermediate-risk MDS.[33] The Phase III STIMULUS-MDS2 study is investigating sabatolimab plus azacitidine in patients with vH/HR or intermediate-risk MDS or CMML-2.[34] STIMULUS-AML1 is a Phase II study of sabatolimab plus venetoclax and azacitidine in patients with AML who are unfit for intensive chemotherapy.[35]

In conclusion, traditional checkpoint inhibition, which is effective in solid cancers, has not been shown to be advantageous in MDS compared to HMA treatment alone. Multiple new pathways are therefore under exploration for the treatment of MDS[36] and AML. TIM-3 is emerging as a promising therapeutic target in MDS and AML. It has a role in regulating adaptive and innate immune responses, is expressed on most leukaemic progenitors but not on normal HSC, and has a role in leukaemic transformation and disease progression in MDS and AML. Blockade of TIM-3 may restore antileukaemic immune function while also directly targeting LSC and blasts. The majority of TIM-3 inhibitors in development are being investigated in solid tumours; however, early clinical data with sabatolimab demonstrated good safety and promising efficacy in HR-MDS and AML. With TIM-3 and other pathways and targets under investigation, a potential therapeutic revolution may be underway to improve treatment outcomes for patients with MDS and AML.

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