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LAG-3 in Cancer Immunotherapy: A Comprehensive Review

Dr. Prafulla R Tathe[1], Kishor B. Charhate[2], Dr. Purushottam R. Laddha[3], Dr. Gopal R. Sitaphale[4]

Professor, Department of Pharmacology, Samarth College of Pharmacy, Deulgaon Raja, Buldana[1]
Associate Professor, Department of Pharmaceutics, Samarth College of Pharmacy, Deulgaon Raja, Buldana[2]
Professor, Department of Pharmaceutical Chemistry, Samarth College of Pharmacy, Deulgaon Raja, Buldana[3]
Professor, Department of Pharmacognosy, Samarth College of Pharmacy, Deulgaon Raja, Buldana[4]
Corresponding author: Dr. Prafulla R Tathe
prtathe@gmail.com

Abstract: *LAG-3 (CD223) is a cell surface protein that is present on activated T cells, NK cells, B cells, and plasmacytoid dendritic cells. It plays a crucial but not yet fully understood role in the activity of these immune cells. LAG-3 primarily interacts with Class II MHC molecules, and this interaction is believed to influence dendritic cell function. Recent research has highlighted LAG-3's involvement in the exhaustion of CD8+ T cells, a state that impairs their effectiveness against tumors. Therapeutic approaches that block the interaction between LAG-3 and Class II MHC, such as the use of a LAG-3 Ig fusion protein, are currently being explored in clinical trials for cancer treatment. This review will provide an overview of the structural and functional aspects of LAG-3, followed by a discussion of preclinical and clinical findings relevant to its role in cancer immunotherapy.*

Keywords: Immune anergy; CD4 T cells; CD8 T cells; Immune checkpoint; Immune tolerance; Regulatory T cells (Tregs); Tumor immunity; Lymphocyte-activation gene 3 (LAG-3)

I. INTRODUCTION

STRUCTURAL ASPECTS OF LAG-3:

LAG-3 was identified during experiments aimed at isolating molecules specifically expressed in an IL-2-dependent natural killer (NK) cell line (Triebel et al., 1990). Researchers discovered a novel 489-amino acid membrane protein. Further investigation revealed that the gene encoding this protein is located on the short arm of human chromosome 12, near the gene for CD4. The amino acid sequence analysis of LAG-3 indicated that it belongs to the immunoglobulin (Ig) superfamily, featuring four Ig-like domains, which are structurally similar to those found in CD4. This homology has significantly influenced subsequent research into LAG-3's function and potential therapeutic applications.

a. Basic Structure of LAG-3

LAG-3 and CD4 share a common structural feature, consisting of four IgG domains. Despite this similarity, the amino acid sequence of LAG-3 shows less than 20% homology with CD4, suggesting an early divergence in their evolutionary paths. A distinctive aspect of LAG-3 is the “extra loop” in its D1 domain, which is absent in CD4 and has been targeted by specific antibodies. Unlike CD4, which engages MHC Class II molecules through a broad surface area involving multiple residues, LAG-3 interacts primarily via a small cluster of amino acids within its D1 domain. Additionally, the intracellular domain of LAG-3 is relatively short, featuring a unique KIEELE motif essential for modulating T cell functions.

b. LAG-3 Expression

LAG-3 expression serves as a marker of T cell activation and is found on both CD4 and CD8 T cells within a few days post-activation. It is also present on natural killer (NK) cells, although its role in these cells is not fully understood. Some evidence suggests its expression on activated B cells, though this finding requires further validation. LAG-3 mRNA is also detected in the thymic medulla, splenic red pulp, and cerebellum. Upon T cell activation, LAG-3 expression becomes noticeable after about 24 hours, peaks around the second day, and then gradually declines by day

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eight. While initial studies indicated that LAG-3 might distinguish TH1 from TH2 cells, more recent research has cast doubt on this, particularly in humans.

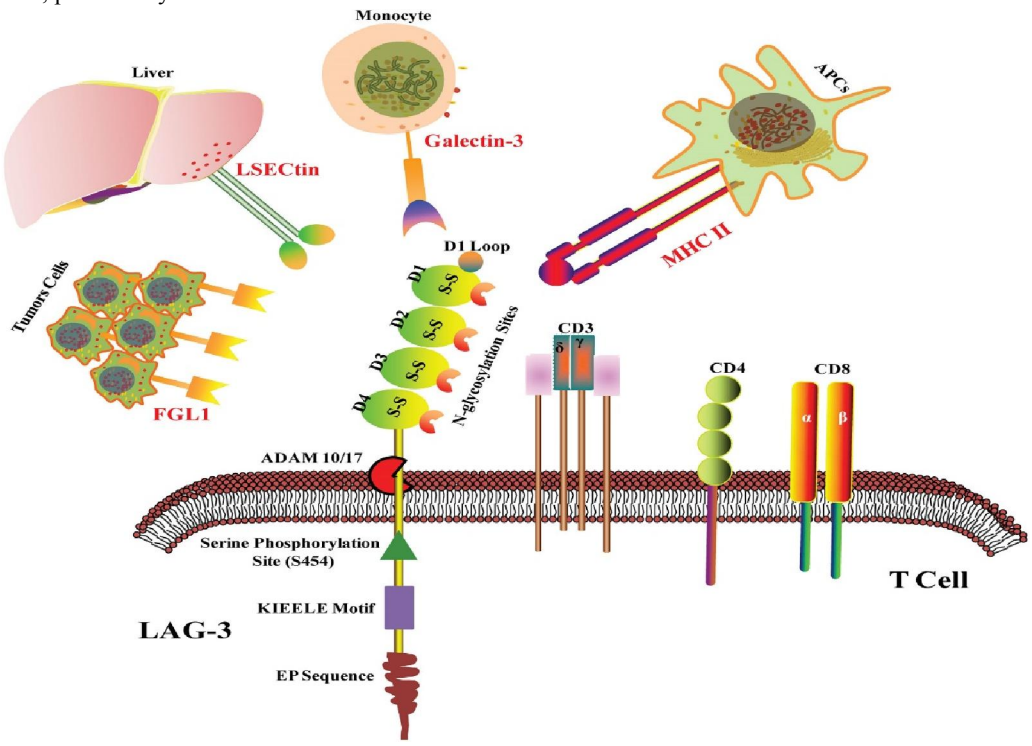

Figure 1: Structure and Ligands of LAG-3

(LAG-3 is characterized by its extracellular, transmembrane, and cytoplasmic domains. The extracellular segment features four immunoglobulin superfamily (IgSF) domains, labeled D1 through D4. The D1 domain includes a proline-rich loop and an intrachaindisulfide bond. Within the transmembrane and cytoplasmic regions, LAG-3 is cleaved from the cell membrane by the metalloproteinases ADAM10 and ADAM17. The cytoplasmic portion of LAG-3 is composed of three key elements: a serine phosphorylation site at S454, a highly conserved "KIEELE" motif, and a repeating glutamate-proline dipeptide sequence. In the tumor microenvironment, LAG-3 interacts with several ligands, including MHC class II, Galectin-3, LSECtin, and FGL1.)

c. Binding to MHC Class II

Given its structural similarity to CD4, early research explored whether LAG-3 might interact with MHC Class II molecules. Indeed, studies showed that cells expressing LAG-3 could bind specifically to MHC Class II, an interaction that could be blocked by antibodies targeting LAG-3 or HLA-DR. Further investigation using a LAG-3–Ig fusion protein revealed that LAG-3 binds to MHC Class II with an affinity significantly higher than that of CD4. Interestingly, this strong interaction is mediated by only a few residues within the D1 loop of LAG-3, contrasting sharply with the extensive contact area used by CD4 to engage MHC Class II molecules.

d. Localization of LAG-3 in T Cells

Although LAG-3 shares structural similarities with CD4, initial hypotheses suggested that LAG-3 might localize with CD4 during T cell activation. Contrary to this expectation, early research indicated that LAG-3 associates more closely with CD8 and CD3/TCR complexes rather than CD4 (Hannier and Triebel 1999). This finding was later corroborated by studies using a new murine anti-LAG-3 antibody, which confirmed that LAG-3 does not co-localize with CD4 either on the cell surface or intracellularly (Woo et al. 2010). Intriguingly, a considerable portion of LAG-3 in CD4 T cells was found in intracellular compartments near the microtubule organizing center, suggesting a potential mechanism for its rapid mobilization to the cell surface upon activation.

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Table No 1: The correlation between LAG-3 and TILs.

Types of TILs	LAG-3 expression	Correlations	Influence factors	Ref.
$CD4^+$ T cells	Elevated	LAG-3 negatively regulates $CD4^+$ T cell activation.	LAG-3/MHC-II interaction, KIEELE motif, gamma-chain cytokines (IL-2, IL-7, IL-12 and IFN-γ), and Tregs	[23, 50-53]
$CD8^+$ T cells	Elevated	LAG-3 dampens the effector function of $CD8^+$ T cells.	Co-inhibitory molecules especially PD-1, LSECtin and galectin-3	[15, 32, 37, 38, 40, 41, 44, 54-60]
Tregs	Elevated	LAG-3 promotes Tregs suppressor activity.	Co-inhibitory molecules, cytokines TGF-β and IL-10	[23,25, 61-64]
NK cells	Elevated	LAG-3 inhibits NKT cells proliferation.	IL-12	[26, 65-69]
pDCs	Elevated	LAG-3 suppresses pDCs activation.	IL-6 enrichment and IFN-α deficiency	[33, 70, 71]

MHC-II= Major histocompatibility complex-II; PD-1=Programmed death 1; LSECtin=Liver sinusoidal endothelial cell lectin; Tregs=T regulatory cells; NKT= Natural killer cells that can also express T cell receptors; pDCs=plasmacytoid dendritic cells; IL= Interleukin; IFN= Interferon; TGF= Transforming growth factor.

II. LAG-3 FUNCTION

a. Role in CD4 T Cell Function and Expansion

Early investigations using monoclonal antibodies against LAG-3 revealed that blocking LAG-3 led to sustained proliferation of human CD4 T cell clones in vitro (Huard et al. 1995). This enhanced proliferation was associated with increased cytokine production, including IL-2, IL-4, and IFN-γ, but was specific to antigen-dependent stimulation and not observed in CD8 T cells. These findings initially pointed to a negative regulatory role for LAG-3 in T cell activity, a notion supported by subsequent studies with human cells (Macon-Lemaitre and Triebel 2005). Further research involving LAG-3 knockout mice (Miyazaki et al. 1996) provided deeper insights, showing that LAG-3 plays a role in controlling the expansion of both CD4 and CD8 T cells, reinforcing its role as a negative regulator (Workman et al. 2002). Studies on LAG-3 mutants lacking the KIEELE domain highlighted the importance of this motif for LAG-3's regulatory function, as LAG-3 molecules without this domain were unable to modulate T cell function effectively (Workman and Vignali 2003).

Despite this, there is some debate regarding the LAG-3/Class II MHC interaction. One study using mixed lymphocyte reactions found that soluble LAG-3 reduced human CD4 T cell function in vitro, suggesting a stimulatory role for LAG-3 in this context (Subramanyam et al. 1998). This effect was not observed in CD8 T cells, indicating potential differences in how LAG-3 interacts with Class II MHC in CD8 versus CD4 T cells. These findings contrast with other studies that have demonstrated LAG-3–Ig as an activator of dendritic cells both in vitro and in vivo, adding complexity to our understanding of LAG-3's function.

b. Role of LAG-3 on Regulatory T Cells

Microarray analyses conducted by our research team revealed that LAG-3 expression is notably increased on CD4 T cells that encounter self-antigens in vivo and adopt a regulatory phenotype (Huang et al. 2004). In studies of self-tolerance, blocking LAG-3 with specific antibodies was observed to diminish the function of regulatory T cells (Tregs) in vivo. Additionally, transfecting antigen-specific CD4 T cells with full-length LAG-3, as opposed to truncated forms, imparted regulatory properties in vitro. This observation is corroborated by data from Hodgkin's lymphoma patients, who exhibited elevated levels of Tregs during active disease. Further in vitro experiments indicated that removing LAG-3+ CD4 T cells led to increased reactivity of tumor-specific CD8 T cells, suggesting that LAG-3 plays a role in inhibiting antitumor immune responses (Gandhi et al. 2006). More recent research has confirmed that LAG-3+ CD4+ CD25+ cells from cancer patient tumor sites have a greater suppressive capacity compared to LAG-3− cells

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(Camisaschi et al. 2010). Additionally, LAG-3 has been implicated in a FoxP3+ subset of CD8 T cells with regulatory functions, a novel and noteworthy discovery given the renewed interest in regulatory CD8 T cells (Joosten et al. 2007; Kapp and Bucy 2008).

c. Role of LAG-3 on CD8 T Cells

Initially, the involvement of LAG-3 in CD8 T cells was debated, despite evidence showing a substantial increase in LAG-3 expression—five to eight times higher—in activated CD8 T cells compared to CD4 T cells, as well as the concurrent presence of LAG-3 and CD8 in these cells. Subsequent research with LAG-3 knockout mice established its role in regulating the proliferation of CD8 T cells and their response to superantigens (Workman et al. 2004). Our own experiments confirmed these findings by adopting antigen-specific CD8 T cells into mice with either self or tumor antigens. The LAG-3 knockout CD8 T cells demonstrated greater proliferation and cytokine production in this context (Grosso et al. 2007). Additionally, administering an anti-LAG-3 antibody during adoptive T cell transfer also enhanced immune responses, indicating a direct effect of the antibody on CD8 T cells. However, when the antibody was given to mice receiving LAG-3 knockout T cells, no further effects were observed. This aligns with recent findings on CTLA-4 antibodies, which suggested a direct action on effector T cells, highlighting that immune checkpoint blockade can sometimes operate through cell-intrinsic mechanisms (Peggs et al. 2009). Furthermore, research into exhausted CD8 T cells during chronic viral infections revealed that these cells can express multiple checkpoint molecules, including both LAG-3 and PD-1. Blocking both PD-1 and LAG-3 simultaneously improved antiviral responses compared to targeting either checkpoint alone (Blackburn et al. 2009). Similar findings were observed in models of self-antigen tolerance, where nonfunctional CD8 T cells co-expressing LAG-3 and PD-1 were identified (Grosso et al. 2009). These results have been corroborated by studies on human ovarian cancer, where a significant proportion of tumor-specific CD8 T cells also co-express LAG-3 and PD-1 (Matsuzaki et al. 2010). Collectively, these findings suggest that effective immunotherapy for chronic infections and cancers may necessitate targeting multiple immune checkpoints.

d. Mechanisms of LAG-3 Action

The exact mechanisms through which LAG-3 inhibits T cell activity are not fully elucidated. It is established that the KIELLE domain within LAG-3 is crucial for its regulatory effects. Initial research identified a soluble variant of LAG-3 in the blood of some patients, suggesting a potential physiological role for LAG-3 cleavage (Triebel et al., 2006). Subsequent research by the Vignali group provided further insights, demonstrating that LAG-3 is cleaved at the cell surface by the metalloproteases ADAM 10 and ADAM 17, members of the TNF alpha converting enzyme (TACE) family (Li et al., 2007). Their work showed that expressing a form of LAG-3 resistant to cleavage led to a persistent impairment in T cell function, indicating that the cleavage of LAG-3 is a significant mechanism through which its inhibitory effects are mediated. Notably, these studies found that the cleaved form of LAG-3 did not play a significant role, contrasting with findings from studies involving a LAG-3–Ig fusion protein.

III. LAG-3 IN CANCER IMMUNOTHERAPY:

a. Preclinical Studies:

The initial investigations into LAG-3 involved creating a LAG-3–Ig fusion protein for biochemical and functional analysis. Subsequent in vivo studies using murine tumor models demonstrated that soluble LAG-3–Ig effectively controlled and reduced tumors in mice with RENCA (kidney), MCA 205 (sarcoma), or TS/A (mammary) cancers, contrary to the outcomes observed in human mixed lymphocyte reactions and the cleaved molecule portion (Prigent et al., 1999).

These results were replicated by introducing LAG-3 into tumor cells, suggesting that LAG-3 might exert its anti-tumor effects by interacting with Class II MHC molecules on antigen-presenting cells, potentially affecting their maturation or function. Supporting this, in vitro experiments with human monocyte-derived dendritic cells revealed that LAG-3–Ig increased the expression of co-stimulatory molecules and IL-12 production in these cells (Andreae et al., 2002). Consequently, dendritic cells matured by LAG-3–Ig demonstrated an enhanced ability to promote TH1 responses, as evidenced by elevated IFN-γ production by T cells.

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Furthermore, LAG-3–Ig showed potential as an adjuvant by significantly boosting the CD8 T cell response to a soluble antigen vaccine (Ovalbumin) and enhancing the humoral response to a particulate antigen (hepatitis B surface antigen) in mice (El and Triebel, 2000). This adjuvant effect extended to cancer vaccines, where LAG-3–Ig prevented mammary carcinogenesis when used alongside a weak DNA vaccine in HER-2/neu transgenic mice (Cappello et al., 2003).

Despite these promising findings, they seem somewhat at odds with the generally recognized negative impact of LAG-3 on T cell proliferation and function. It appears paradoxical that LAG-3 interaction with Class II MHC can both downregulate T cell activity and simultaneously provide a pro-inflammatory maturation signal to Class II-expressing dendritic cells. In this context, recent studies suggest a contrasting effect, where LAG-3 on regulatory CD4 T cells may actually inhibit dendritic cell function (Liang et al., 2008).

b. Clinical Studies:

Following the identification of LAG-3, research revealed that patients with renal cell carcinoma (RCC) often have a marked increase in LAG-3+ CD4+ tumor-infiltrating lymphocytes (Angevin et al., 1997). Subsequent studies showed that the proportion of LAG-3+ TILs in RCC ranged from 11% to 48%, while levels of other checkpoint molecules such as CTLA-4 or 4-1BB were not significant (Demeure et al., 2001).

Despite this, LAG-3 blockade did not enhance CD8 T cell-mediated cytotoxicity in these studies, suggesting that LAG-3 inhibition might be more effective during the initial phase of T cell activation or might be influenced by the challenges associated with using expanded human TILs as a reagent. Building on promising results from murine models using LAG-3–Ig, this agent is being commercially developed (IMP321, Immutep, Paris) and evaluated in clinical trials. In an initial Phase I trial, IMP321 was administered in increasing doses alongside a standard influenza vaccine (Brignone et al., 2007a). The treatment was well-tolerated with minimal adverse effects, though no significant enhancement of the humoral vaccine response was observed.

However, a TH1 CD4 T cell response was detected in some participants. A follow-up Phase I trial combined IMP321 with a commercial hepatitis B vaccine (Brignone et al., 2007b), and at higher doses, detectable CD4 and CD8 T cell responses were observed after a single dose of IMP321. This agent was then tested in patients with RCC in a dose-escalation trial (Brignone et al., 2009). The treatment was again well-tolerated and appeared to induce an effector phenotype in CD8 T cells, though not in CD4 T cells.

As is common in Phase I cancer immunotherapy trials, there were no objective responses, but several patients had stable disease. A more recent trial combined IMP321 with taxane-based chemotherapy in women with breast cancer (Brignone et al., 2010). This single-arm trial reported an objective response rate of 50%, compared to a historical rate of around 25%. Although single-arm trials require careful interpretation, additional Phase II trials are planned or ongoing (www.clinicaltrials.gov; www.immutep.com).

Table No 2: LAG-3-targeted immunotherapy in clinical trials (Clinical Trials.gov)

Trial number/ Ref.	Study population	Interventions	Phase	Status/ Outcomes
IMP321 (a soluble LAG-3 Ig)				
NCT00351949 [16]	Stage IV renal cell carcinoma	IMP321	1	Completed, October 2008 *Induction of effector $CD8^+$ T cells in all patients *Reduced tumor growth and better progression-free survival with high doses
NCT00349934 [17]	Metastatic breast carcinoma patients receiving first-line paclitaxel	IMP321	1	Completed, January 2010 *Sustained increase/activation of APCs, NK and $CD8^+$ effector/memory cells *50% ORR with IMP321 and paclitaxel compared with 25% ORR with paclitaxel alone
NCT00324623 [18]	Melanoma (skin)	Lymphodepletion, vaccine, IMP321 adjuvant	1	Completed, November 2011 *Induction of more robust and durable cellular antitumor immune responses
NCT03252938	Solid tumors Peritoneal carcinomatosis	IMP321	1	Recruiting Estimated completion, February 2019
NCT02614833	Hormone receptor-positive metastatic breast cancer	Paclitaxel + IMP321/ Placebo	2	Recruiting Estimated completion, December 2020
NCT02676869	Stage IV melanoma Stage III melanoma	IMP321 + Pembrolizumab (Anti-PD-1)	1	Recruiting Estimated completion, December 2018

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BMS-986016 (Relatlimab, anti-LAG-3 mAb)				
NCT01968109 (CA224-020) [19, 20, 92]	Advanced solid tumors	Relatlimab (BMS-986016) ± Nivolumab (BMS-936558, Anti-PD-1)	1/2a	Recruiting Estimated completion, October 11, 2019 *The response rates triple in LAG-3 positive melanoma patients (LAG-3 expression ≥1%). *A safety profile similar to nivolumab monotherapy.
NCT02966548 (CA224-034)	Advanced solid tumors	BMS-986016 ± Nivolumab (BMS-936558, Anti-PD-1)	1	Recruiting Estimated completion, July 1, 2020
NCT03470922 (CA224-047)	Previously untreated metastatic or unresectable melanoma	Nivolumab (Anti-PD-1) ± Relatlimab	2/3	Not yet recruiting Estimated completion, March 16, 2022
NCT03459222 (CA224-048)	Advanced malignant tumors	Relatlimab ± Nivolumab (Anti-PD-1) + BMS-986205 (anti-IDO1)/Ipilimumab (Anti-CTLA-4)	1/2	Not yet recruiting Estimated completion, May 16, 2022
NCT02488759	Virus-positive and virus-negative solid tumors	BMS-986016 + Nivolumab (Anti-PD-1)	1/2	Recruiting Estimated completion, December 31, 2019
NCT02060188	Recurrent and metastatic microsatellite high (MSI-H) and non-MSI-H colon cancer	BMS-986016 + Nivolumab (Anti-PD-1)	2	Recruiting Estimated completion, December 31, 2019
NCT02061761	Hematologic neoplasms	BMS-986016 ± Nivolumab (BMS-936558, Anti-PD-1)	1/2a	Recruiting Estimated completion, January 15, 2020
NCT02658981	Glioblastoma Gliosarcoma Recurrent brain neoplasm	A1: BMS 986016 A2: Urelumab (Anti-CD137) B1: BMS-986016 + Nivolumab (Anti-PD-1) B2: Urelumab (Anti-CD137) + Nivolumab (Anti-PD-1)	1	Recruiting Estimated completion, December 2019
NCT02935634	Advanced gastric cancer	BMS-986016 + Nivolumab (Anti-PD-1)	2	Recruiting Estimated completion, November 18, 2021
NCT02750514	Advanced non-small cell lung cancer	Nivolumab (Anti-PD-1) ± BMS-986016	2	Recruiting Estimated completion, April 29, 2021
NCT02996110	Advanced renal cell carcinoma	Nivolumab (Anti-PD-1) + Relatlimab / BMS-986205 (anti-IDO1)/Ipilimumab (Anti-CTLA-4)	2	Recruiting Estimated completion, January 18, 2022
NCT03335540	Advanced cancer	Nivolumab (Anti-PD-1) + Relatlimab/ Radiation Therapy	1	Recruiting Estimated completion, January 31, 2022
LAG525 (anti-LAG-3 mAb)				
NCT03365791	Advanced solid and hematologic malignancies.	LAG525 + PDR001 (anti-PD-1)	2	Recruiting Estimated completion, February 1, 2021
NCT02460224	Advanced solid tumors	LAG525 + PDR001 (anti-PD-1)	1/2	Recruiting Estimated completion, April 23, 2019
REGN3767 (anti-LAG-3 mAb)				
NCT03005782	Malignancies	REGN3767 ± REGN2810 (Anti-PD-1)	1	Recruiting Estimated completion: October 6, 2020
TSR-033 (anti-LAG-3 mAb)				
NCT03250832	Advanced solid tumors	TSR-033 ± Anti-PD-1	1	Recruiting Estimated completion, May 2021
MGD013 (a PD-1/LAG-3 bispecific DART® protein)				
NCT03219268	Advanced solid tumors Hematologic neoplasms	MGD013	1	Recruiting Estimated completion, August 2022
FS118 (a LAG-3/PD-L1 bispecific antibody)				
NCT03440437	Advanced malignancies that have progressed on or after prior PD-1/PD-L1 containing therapy	FS118	1	Not yet recruiting Estimated completion, May 16, 2020

PD-1=Programmed death 1; PD-L1= Programmed death ligand 1; CTLA-4=Cytotoxic T lymphocyte antigen 4; IDO-1= Indoleamine 2,3-dioxygenase; mAb=monoclonal antibody; DART= Dual-Affinity Re-Targeting.

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IV. CONCLUSION

LAG-3 is a fascinating cell surface protein with a notable evolutionary history, believed to have emerged early and possibly sharing a common origin with CD4. It plays a crucial role in regulating T cell expansion and activity. Blocking LAG-3 using monoclonal antibodies has shown promise in enhancing T cell responses across various experimental models. However, the precise mechanisms by which LAG-3 influences its physiological functions are not yet fully understood. One known mechanism of its attenuation is the cleavage by metalloproteases. Additionally, the intracellular signaling pathways involved in LAG-3's function remain underexplored, offering potential areas for future research into its effects on T cell differentiation and polarization. Despite encouraging preclinical findings supporting the use of LAG-3 inhibitors in cancer treatment, much of the research has focused on LAG-3–Ig fusion proteins, which affect dendritic cell activity both in vitro and in vivo. The clinical efficacy of LAG-3–Ig will ultimately be determined by ongoing clinical trials, with results eagerly anticipated.

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