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REVIEW

Cancer Focus

Inhibitory receptor agonists: Emerging strategies in immune modulation

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Inhibitory receptors (IRs) such as CTLA-4, PD-1, LAG3, TIM-3, and TIGIT are critical regulators of immune homeostasis, functioning to restrain excessive immune activation and prevent autoimmunity. While the blockade of IRs has transformed cancer immunotherapy by reinvigorating antitumor T cell responses, emerging strategies aim to harness the immunosuppressive potential of these receptors for treating autoimmune and inflammatory diseases. Agonistic antibodies that activate IR signaling have demonstrated promising results in preclinical models by promoting immune tolerance and suppressing pathological effector T cell functions. This review highlights recent progress in the development of agonistic IR-targeted therapies, examining their mechanisms of action, therapeutic efficacy, and the translational challenges that must be addressed to bring these innovative approaches into clinical practice for the management of autoimmunity and inflammatory disorders.

Introduction

Inhibitory receptors (IRs) are crucial regulators of immune tolerance and homeostasis. The IRs cytotoxic T lymphocyte–associated antigen 4 (CTLA-4), programmed cell death-1 (PD-1), lymphocyte-activation gene 3 (LAG3), T cell immunoglobulin and mucin domain 3 (TIM-3), and T cell immunoreceptor with Ig and ITIM domains (TIGIT) function to prevent excessive immune activation and autoimmunity by downregulating T cell responses (Fig. 1) (Francisco et al., 2010; Pardoll, 2012; He and Xu, 2020; Aggarwal et al., 2023; Joller et al., 2024). Their physiological role is to maintain a balanced immune response that can clear infections while avoiding chronic inflammation or tissue damage. While other IRs have been identified on various cells and discussed elsewhere (Liu et al., 2025; Lovewell et al., 2025), this review will focus on the receptors expressed on activated T cells whose depletion can induce autoimmunity and are advanced in clinical trials.

The therapeutic manipulation of IRs has gained prominence with success in oncology. Antagonistic antibodies that block IRs have shown remarkable efficacy in reinvigorating antitumor T cell responses (Sharma and Allison, 2015; Topalian et al., 2016). Alternatively, the concept of using agonistic antibodies is gaining attention in autoimmune and inflammatory diseases to restore immune tolerance by activating the inherent inhibitory function of co-IRs. By engaging these receptors, agonistic agents (antibodies or small molecular weight compounds) can promote immunosuppressive signaling and help re-establish immune homeostasis in autoimmune diseases like multiple sclerosis (MS) and type 1 diabetes (T1D). By promoting immune tolerance and dampening overactive immune responses, agonistic antibodies against these IRs offer a novel strategy to treat autoimmune conditions (Grebinoski and Vignali, 2020).

Recent advances in IR-targeted agonistic monoclonal antibodies (mAbs) have shown promise in preclinical models. This review focuses on recent advances in the understanding of mechanisms, development, and application of agonistic antibodies for autoimmune diseases, discussing their mechanisms, therapeutic potential, and challenges in clinical translation.

Inhibitory receptors: Structure and function

CTLA-4

CTLA-4 (CD152) was first identified from a cytotoxic T cell cDNA library (Brunet et al., 1987). Its gene encodes a 223–amino acid protein comprising a leader sequence, an IgV domain, a transmembrane region, and a cytoplasmic tail (Dariavach et al., 1988; Ling et al., 1999). Although expressed in multiple cell types,

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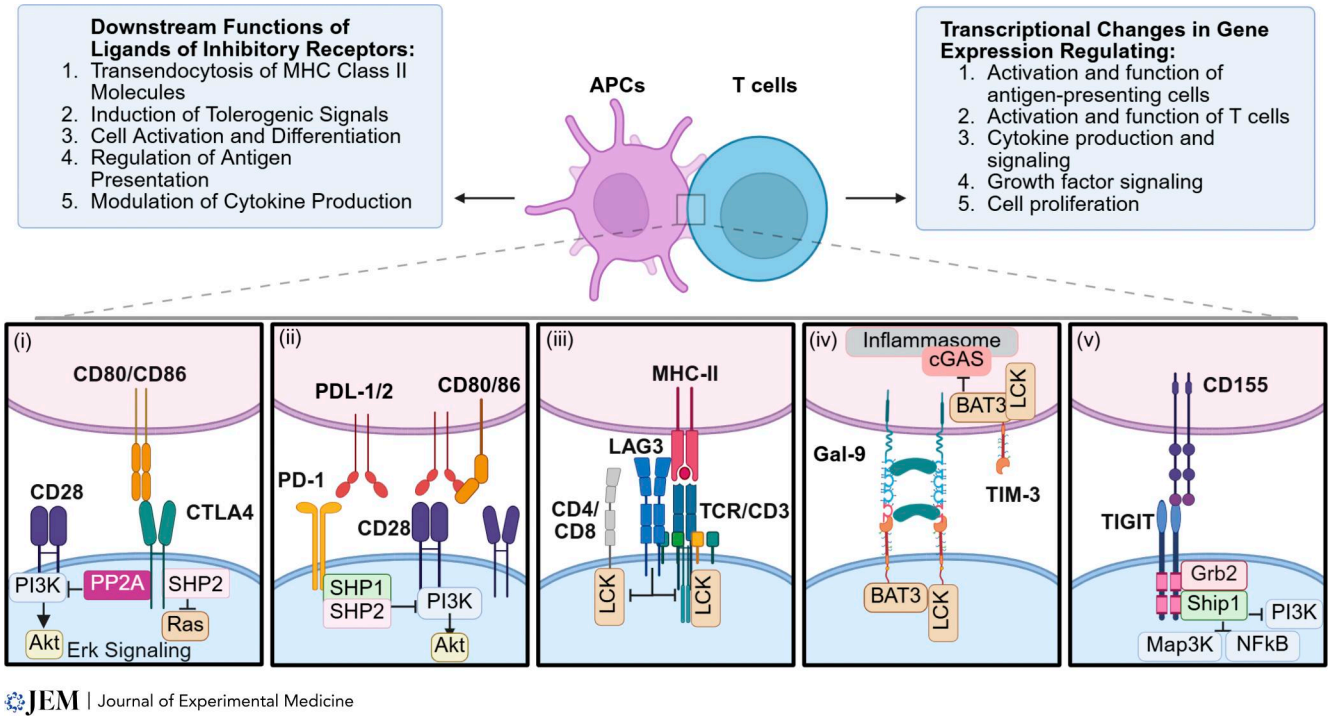

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Figure 1. **Downstream signaling pathways of immune IRs following ligand engagement.** (i) CTLA-4 competes with CD28 for CD80/CD86, limiting costimulation and antigen presentation. Its cytoplasmic tail recruits PP2A to inhibit AKT and SHP-2 to suppress ZAP70 and ERK signaling, while also mediating ligand removal via trans-endocytosis and trogocytosis. CTLA-4 on Tregs further enhances suppressive function by increasing IL-10 and TGF-β secretion. (ii) PD-1, through its ITIM and ITSM motifs, recruits SHP-1/2 upon PD-L1/PD-L2 engagement, leading to PI3K inhibition, CD28 dephosphorylation, and suppression of TCR signaling. (iii) LAG3 binds MHCII and associates with the TCR/CD3 complex, where its cytoplasmic motifs (FSALE, KIEELE, EP) disrupt Lck association from the coreceptors (CD4 and CD8) and the CD3ε-Lck interaction, thereby reducing ZAP70 activation. (iv) TIM-3 impairs antigen presentation and cytokine production in APCs. Its cytoplasmic tail is phosphorylated at Y256 and Y263 to recruit SH2-domain adaptors, while Bat3 binding prevents TIM-3–mediated exhaustion. (v) TIGIT binding to CD155 delivers inhibitory signals through ITIM and ITT-like motifs that recruit SHIP1 and GRB2, blocking PI3K, MAPK, and NF-κB pathways. CD155 engagement on APCs promotes a tolerogenic phenotype with elevated IL-10, while enhancing Treg activity and suppressing Teffs. The figure was created with BioRender.

including B cells, natural killer (NK) cells, dendritic cells (DCs), and certain types of leukemia and lymphomas, its role has been most extensively studied in T cells (Oyewole-Said et al., 2020).

Upon T cell activation, CTLA-4 is transported to the cell surface and colocalizes with the TCR at the immunological synapse (IS) (Chikuma et al., 2003; Darlington et al., 2002; Egen and Allison, 2002). The ligands for CTLA-4, CD80 (B7-1), and CD86 (B7-2) bind to CD28 at the IS. Although CD28 and CTLA-4 share ∼20% sequence similarity (Green et al., 1994; Linsley et al., 1991), CTLA-4 has ∼10-fold higher affinity for the B7 ligands compared with CD28, outcompeting and suppressing T cell activation (Greene et al., 1996; Harlin et al., 2002; Krummel and Allison, 1995; Linsley et al., 1994; Olsson et al., 1999; van der Merwe et al., 1997). The structural interactions between CTLA-4 and its ligands further contribute to its regulatory strength. CTLA-4 homodimerization and CD80/CD86 oligomerization are crucial for their high-affinity interactions (Greene et al., 1996; Linsley et al., 1994; Pentcheva-Hoang et al., 2004). Mutagenesis of CTLA-4 and structural analysis identified MYPPPY on the FG loop of the IgV domain as the binding interface, which is also conserved in CD28 (Metzler et al., 1997; Morton et al., 1996; Ostrov et al., 2000; Stamper et al., 2001). Thus, this competition between CTLA-4 and CD28 for B7 ligands is a critical mechanism for immune homeostasis.

At the molecular level, the CTLA-4 cytoplasmic tail can inhibit signaling cascades. The intracellular cytoplasmic tail contains four domains that interact with various kinases and phosphatases (He and Xu, 2020; Kim and Choi, 2022). Inhibitory signaling is provided by CTLA-4 recruitment of PP2A to inhibit AKT. Furthermore, the phosphorylation by SRC family kinases of tyrosine residues Y201 and Y218 recruits SHP-2 and suppresses ZAP70 and ERK signaling (Fig. 1) (Chuang et al., 1999; Teft et al., 2009). Similar to CD28, PI3K also associates with CTLA-4 at its SH2 domains but with 100 times less affinity (Iiyama et al., 2021; Schneider et al., 1995). While other molecules have been proposed to interact with the cytoplasmic tail, which of these are important remain unresolved (Walker and Sansom, 2015). Additionally, CTLA-4 exerts suppressive effects via trans-endocytosis and trogocytosis of CD80/CD86 from APCs, removing B7 ligands to prevent CD28 costimulation (Qureshi et al., 2011; Xu et al., 2023; Zenke et al., 2022). Unlike CD28, which recycles CD80 to the membrane, CTLA-4 targets it for lysosomal degradation. These mechanisms reinforce the role of CTLA-4 as a dominant negative regulator of T cell activation.

Translating this molecular understanding into clinical application has revolutionized cancer immunotherapy. While antibody blockade was shown to enhance T cell proliferation and IL-2 production (Krummel and Allison, 1995; Walunas et al., 1994), pioneering work from James Allison showed that CTLA-4 blockade in tumor-bearing mice enhances antitumor responses (Kwon et al., 1997; Leach et al., 1996), leading to the development of ipilimumab, the first IR inhibitor approved for cancer therapy. While ipilimumab blocks the interaction of CTLA-4 with B7-1 (Gao et al., 2020), the exact means of targeting CTLA-4 for the treatment of inflammation is still unresolved.

PD-1

PD-1 (CD279) was first identified as a gene upregulated during lymphoid cell death (Ishida et al., 1992). The *PDCD1* gene encodes a 288–amino acid receptor consisting of an IgV domain, stalk region, a transmembrane domain, and two tyrosine-based signaling motifs (Shinohara et al., 1994). PD-1 is expressed on activated B and T cells, NK cells, and DCs. It is notably upregulated on exhausted T cells during chronic infection and cancer, which has led to its therapeutic targeting (Barber et al., 2006; Chamoto et al., 2023; Day et al., 2006; Wherry and Kurachi, 2015; Zinselmeyer et al., 2013).

T cell function and activation are restrained when PD-1 interacts with its ligands, PD-L1 and PD-L2. PD-L1 (CD274) has two Ig-like domains, a transmembrane region, and an intracellular tail (Freeman et al., 2000) and is broadly expressed on hematopoietic and nonhematopoietic cells (Mueller et al., 2010), with its expression on nonhematopoietic cells protecting tissues during chronic LCMV infection. PD-L2, which shares ∼38% similarity to PD-L1, is primarily found on immune cells, has higher affinity for PD-1, and plays a significant role in immune evasion and oncogenesis (Cheng et al., 2013; Latchman et al., 2001; Philips et al., 2020; Wang et al., 2023). The expression of both ligands is upregulated by type 1 and 2 interferons (IFNs) and by specific inflammatory cytokines (Kuchroo et al., 2021). Both ligands interact with the PD-1 IgV domain (Zak et al., 2017). Thus, blockade of the PD-1 ligands has become an established and effective approach that complements traditional cancer therapies (Iwai et al., 2002; Miao et al., 2021).

Unlike CTLA-4, which dimerizes via its extracellular domain, PD-1 dimerizes through its transmembrane domain and mutations disrupting dimerization inhibit its function (Philips et al., 2024). The cytoplasmic tail contains two key motifs: immunoreceptor tyrosine-based inhibitory motif (ITIM) and immunoreceptor tyrosine-based switch motif (ITSM). Ligand-induced phosphorylation recruits SHP-2 to ITSM, inhibiting TCR signaling (Chemnitz et al., 2004; Latchman et al., 2001; Mariuzza et al., 2020; Morch et al., 2020; Okazaki et al., 2001; Patsoukis et al., 2020; Strazza et al., 2021b; Takehara et al., 2021; Tocheva et al., 2020). In humans, a PEQ motif enhances SHP-2 recruitment, while its absence in mice attenuates PD-1 inhibitory function (Masubuchi et al., 2025).

Although SHP2 has been implicated in PD-1 inhibitory function, its exact downstream targets in TCR signaling remain unclear, with several costimulatory and signaling molecules suggested to be inhibited (Bennett et al., 2003; Parry et al., 2005; Sheppard et al., 2004; Strazza et al., 2021a). It was shown that upon PD-L1 binding to PD-1, SHP2 is recruited to PD-1 and dephosphorylates CD28 (Hui et al., 2017). In a chronic LCMV model, PD-1 blockade enhanced $CD8^+$ T cell function, but dual PD-1/B7 blockade impaired it, suggesting CD28 is necessary for PD-1 blockade efficacy. Moreover, most proliferating $CD8^+$ T cells were $CD28^+$ in the periphery of non–small-cell lung cancer patients receiving PD-1 therapy, indicating its potential as a biomarker to predict anti-PD-1 response (Kamphorst et al., 2017). However, in another study PD-1 suppressed IL-2 without CD28, and CD28 ligation reduced PD-1 inhibition, implying CD28 may be one of several PD-1 targets (Mizuno et al., 2019).

PD-1 signaling suppresses T cell proliferation, cytokine production, and survival, informing both checkpoint blockade and agonist strategies to modulate inflammation and autoimmunity. Further investigation of the PD-1 interactome is crucial for optimizing efficacy of agonists and minimizing adverse events.

LAG3

LAG3 is a transmembrane protein upregulated on activated $CD4^+$/$CD8^+$ T cells, regulatory T cells (Tregs), activated B cells, and NK cells in response to inflammation, cancer, and viral infections (Datar et al., 2019; Grebinoski et al., 2022; Ruffo et al., 2019; Tian et al., 2015). However, persistent antigen stimulation leads to T cell exhaustion, impairing antitumor immunity (Andrews et al., 2024; Grosso et al., 2009; Ngiow et al., 2024; Wherry et al., 2003). As a result, LAG3 became the third IR antagonist to be approved for clinical use in cancer (Adam et al., 2024a; Aggarwal et al., 2023; Burnell et al., 2022; Chocarro et al., 2022). LAG3 contains four extracellular Ig-like domains: a V-type (D1) and three C2-type (D2, D3, and D4) Ig domains (Mariuzza et al., 2024; Triebel et al., 1990), and three conserved intracellular motifs that mediate its inhibitory function: "FSALE," "KIEELE," and a glutamic acid–proline-rich region "EP" (Aigner-Radakovics et al., 2023; Guy et al., 2022; Jiang et al., 2025; Li et al., 2004; Maeda et al., 2019; Workman et al., 2002a; Workman and Vignali, 2003; Workman and Vignali, 2005).

The identity and relative importance of LAG3 ligands in different disease settings remain controversial. Major histocompatibility class II (MHCII) (Fig. 1) is the canonical ligand which LAG3 binds to inhibit T cell effector functions (Baixeras et al., 1992; Huard et al., 1994; Huard et al., 1995; Huard et al., 1996; Huard et al., 1997; MacLachlan et al., 2021). LAG3 preferentially inhibits T cells with stable peptide–MHCII complexes, and disrupting this interaction worsened diabetes in NOD mice (Maruhashi et al., 2018; Maruhashi et al., 2022). Structural studies show that the LAG3 D1 interacts with the MHCII α2/β2 subdomains through residues Asn54, Arg57, Arg121, Gln124, and Arg125 (α2) and Gly103-P111 (β2) (Ming et al., 2024). In contrast, LAG3-HLA-DR1 interaction is mediated by residues Gly85-Leu87, Arg103, and Gln106 binding to the α chain, and Arg88-Gly90 binding to the β chain of HLA-DR1 (Petersen et al., 2024). Fibrinogen-like protein 1, which regulates hepatocyte metabolism, is another ligand of LAG3 involved in controlling T cell proliferation and promoting exhaustion (Wang et al., 2019; Yang et al., 2023). Several studies suggest the residues V104, R113, Q117, and V120 in human LAG3, and K27 in murine LAG3

can disrupt FLG1 binding (Maruhashi et al., 2022; Ming et al., 2022; Ming et al., 2024).

Several other ligands have been proposed to interact with LAG3. In the absence of MHCII, the TCR/CD3 complex serves as a ligand for LAG3 by mediating its translocation into the IS in both $CD4^+$ and $CD8^+$ T cells, thereby inhibiting TCR signaling (Guy et al., 2022). Antibodies that block LAG3:TCR/CD3 interaction prevent entry of the former but not the latter into the IS. This is supported by studies showing LAG3 clustering at the TCR and inhibiting IL-2 production in T cells (Hashimoto-Tane et al., 2024). Additional ligands include LSECtin, Gal-3 (Kouo et al., 2015; Xu et al., 2014), and α-synuclein, which causes neurodegenerative diseases like Parkinson's disease (Mao et al., 2016; Mao et al., 2024). However, their role in autoimmunity is not well understood and highlights the need to investigate which ligands modulate LAG3 function.

LAG3 forms homodimers through its D2 domain, which is essential for TCR/CD3 localization and ligand binding (Adam et al., 2024b; Li et al., 2004; Ming et al., 2022; Silberstein et al., 2024). Mutations in the D2 domain prevent dimerization, reducing its localization to the TCR/CD3 and inhibiting its function. Although LAG3 homodimers bind two HLA-II or MHCII molecules (Ming et al., 2024; Petersen et al., 2024), the higher affinity of LAG3 may be attributed to a larger binding site than the CD4-HLA-II binding site.

While LAG3 inhibits TCR signaling, the exact cytoplasmic motif responsible for this is debated (Li et al., 2004; Workman et al., 2002a; Workman et al., 2002b; Workman et al., 2004; Workman and Vignali, 2003; Workman and Vignali, 2005). Through association with the TCR/CD3, the LAG3 EP motif lowers the local pH, causing coreceptor (CD4 or CD8):Lck dissociation resulting in reduced ZAP70 signaling (Guy et al., 2022), while FSALE disrupts CD3ε-Lck association (Du et al., 2025). LAG3 is also modulated by E3 ligases to trigger its release from the membrane for signaling (Jiang et al., 2025). Moreover, LAG3 has been reported to modulate immunity by trans-endocytosing MHCII via TCR internalization, limiting antigen presentation and inflammation (Wakamatsu et al., 2024) as supported by a colitis model showing LAG3-mediated MHCII downregulation. In contrast, studies suggest a tight cell–cell interface mediates trogocytosis of pMHCII independent of TCR (Wang et al., 2025). While several inhibitory modalities exist, the dominant inhibitory mechanism remains unclear.

TIM-3

TIM-3 was identified and characterized in Th1 cells (Monney et al., 2002) and plays key regulatory roles in autoimmunity, cancer, neurodegenerative disease, and chronic viral infections (Fourcade et al., 2010; Golden-Mason et al., 2009; Jones et al., 2008; Kimura et al., 2025; Sabatos et al., 2003; Sakuishi et al., 2010; Sanchez-Fueyo et al., 2003; Wolf et al., 2020; Zhou et al., 2011). Its expression is increased on activated $CD8^+$ T cells but lower on Th1, Th17, and naive $CD8^+$ T cells (Baitsch et al., 2012; Hastings et al., 2009), with its expression driven by IL-27 in T cells (Zhu et al., 2015). TIM-3 is a type I transmembrane protein composed of an IgV domain, mucin domain, transmembrane segment, and cytoplasmic tail (Joller et al., 2024). Unique to the human IgV domain is the requirement of Ca^{2+} for ligand binding (Gandhi et al., 2018).

The cytoplasmic adaptor protein HLA-B–associated transcript 3 (Bat3) associates with the intracellular tail of TIM-3 to prevent premature T cell exhaustion and maintain effector function. Displacement of Bat3 from TIM-3 by certain ligands, such as galectin-9 (Gal-9), contributes to downstream inhibitory signaling, which promotes T cell exhaustion and generation of tolerogenic DCs when deleted from DCs (Rangachari et al., 2012; Tang et al., 2022; Zhu et al., 2005). Gal-9 is upregulated on T cells, B cells, and macrophages by IFNγ (Imaizumi et al., 2002). Moreover, soluble Gal-9 can bind TIM-3 on $CD4^+$ T cells to limit HIV-1 infection (Elahi et al., 2012). Gal-9 interacts with TIM-3 through its N- and O-glycans on Asn and Thr residues, respectively, within the IgV domain (Cao et al., 2007). TIM-3 also binds phosphatidylserine through FG and CC′ loops (DeKruyff et al., 2010; Nakayama et al., 2009; Weber and Zhou, 2017), in addition to the DAMP molecule high-mobility group protein B1 (HMGB1) when TIM-3 is expressed on DCs (Chiba et al., 2012). The last known ligand, carcinoembryonic antigen cell adhesion molecule 1 (CEACAM1), is expressed on activated T cells and myeloid cells, and can form cis and trans heterodimers through the N-terminal IgV domain with TIM-3 (Huang et al., 2015) at residues Glu62 and Arg69 (Gandhi et al., 2018). Reductionist approaches with T cells have demonstrated that Gal-9 and CEACAM1 are primarily inhibitory ligands when in trans on tumor cells, while CEACAM1 in cis with TIM-3 on T cells was stimulatory (Alamir et al., 2025). This suggests that the role of TIM-3 is context-dependent and can be either stimulatory or inhibitory.

Key tyrosines (Y256, Y263) are phosphorylated by Lck, Fyn, and ITK, enabling SH2-domain interaction (Lee et al., 2011a; van de Weyer et al., 2006). The cytoplasmic protein adaptor Bat3 also interacts with the TIM-3 cytoplasmic tail to suppress exhaustion and TIM-3–mediated cell death in Th1 cells (Rangachari et al., 2012). Bat3 also binds to TIM-3 in DCs to restrain T cell exhaustion. Bat3 deficiency promotes the accumulation of regulatory/exhausted T cells and dampens proinflammatory responses, thereby limiting autoimmunity but facilitating tumor progression (Tang et al., 2022). To explore the costimulatory and coinhibitory signalosomes associated with TIM-3, a systems approach identified both inhibitory (CBLB, SHP1, UBASH3A) and stimulatory (VAV1, LCK, P85A) partners of TIM-3 (Zhai et al., 2021). These findings not only validate previous TIM-3 binding partners but suggest that TIM-3 signaling is context-dependent, with potential inhibitory or stimulatory roles depending on the immune environment (Ferris et al., 2014).

The costimulatory role of TIM-3 has been demonstrated in various inflammatory diseases. In infections such as *Listeria monocytogenes*, LCMV, or HSV-1, it enhances $CD8^+$ T cell cytokine production but impairs memory formation, favoring short-lived effectors (Gorman et al., 2014; Avery et al., 2018; Carroll et al., 2020). This is most likely due to the strong binding of the adapter protein Bat-3 to the TIM-3 tail, which blocks TIM-3 inhibitory function both in T cells and in DCs (Tang et al., 2022; Zhu et al., 2021). In Tregs, deletion of TIM-3 enhanced virus-specific responses and reduced exhaustion in chronic LCMV (Nieves-Rosado et al., 2024). TIM-3 on DCs suppresses antitumor

immunity by limiting inflammasome activation (Dixon et al., 2021), and other groups have shown that TIM-3 may inhibit DC activation and function by inhibiting the cGAS-STING pathway (de Mingo Pulido et al., 2021). Therefore, TIM-3 might regulate innate immune cell activation by interfering with multiple innate pathways, promoting a regulatory program, and suggests that similar TIM-3–mediated control of innate immune activation may restrain inflammation in autoimmunity (Dixon et al., 2021). Also, TIM-3 maintains microglial homeostasis via TGF-β signaling, and its deletion enhances microglial phagocytosis, reduces amyloid pathology, and improves cognition in Alzheimer's disease models (Kimura et al., 2025). These findings highlight the complex, cell- and context-specific immune regulatory functions of TIM-3.

Synapse localization via the transmembrane domain is essential for TIM-3 function (Clayton et al., 2014). Moreover, posttranslational modifications affect TIM-3 localization at the membrane, with palmitoylation of TIM-3 preventing its degradation and stabilizing it at the membrane (Zhang et al., 2024). While TIM-3 is under investigation in several clinical trials, it has yet to produce a clear candidate for any malignancies (Lu and Tan, 2024). Further understanding of the ligands and their signaling is required to develop effective immunotherapies.

TIGIT

TIGIT (Vstm3, WUCAM, or VSIG9) is an IR of the immunoglobulin superfamily, first identified through gene expression profiling in human T cells and NK cells (Yu et al., 2009). It is a 244–amino acid protein comprising an extracellular IgV domain, a transmembrane region, and a cytoplasmic tail containing both an ITIM and an immunoglobulin tail tyrosine (ITT)–like motif (Levin et al., 2011; Stanietsky et al., 2009).

TIGIT is primarily expressed on activated and memory CD4$^+$/CD8$^+$ T cells, Tregs, and NK cells, with lower levels on T follicular helper (Tfh) cells, innate lymphoid cells (ILCs), and NKT cells (Johnston et al., 2014; Lozano et al., 2012). It acts as an IR with both intrinsic and extrinsic regulatory roles and is often co-expressed with PD-1, LAG3, and TIM-3 on exhausted T cells in cancer and chronic viral infections (Joller et al., 2014). In the tumor microenvironment, TIGIT expression is elevated on tumor-infiltrating lymphocytes, particularly on CD8$^+$ T cells and Tregs, and correlates with impaired effector function and poor clinical outcomes in cancers including melanoma, lung, and colorectal cancer (Zhang et al., 2018). TIGIT deficiency exacerbates central nervous system (CNS) inflammation (Joller et al., 2011) and is implicated in MS (Lavon et al., 2019; Lucca et al., 2019), rheumatoid arthritis (RA) (Zhao et al., 2016), systemic lupus erythematosus (SLE) (Luo et al., 2017; Mao et al., 2017), inflammatory bowel disease (IBD) (Battella et al., 2019; Joosse et al., 2019; Long et al., 2020), psoriasis (Wang et al., 2018a), and autoimmune uveitis (Muhammad et al., 2020).

TIGIT is related to CD226 (DNAM-1), a costimulatory receptor that competes with TIGIT for the shared ligands CD155 (PVR) and CD112 (PVRL2) (Fig. 1). These ligands are widely expressed on DCs, macrophages, endothelial cells, fibroblasts, and tumors (Martinet and Smyth, 2015; Yu et al., 2009). TIGIT binds CD155 with higher affinity, delivering inhibitory signals that counteract CD226-mediated activation (Johnston et al., 2014; Stanietsky et al., 2009). Structural studies show TIGIT binds CD155 via IgV domain–mediated β-strand interactions and forms stable homodimers (Stengel et al., 2012).

Upon ligand binding, TIGIT delivers inhibitory signals via ITIM and the conserved phosphorylation sequence–ITT-like motif on its cytoplasmic tail. Although TIGIT contains both ITIM (S/I/V/LYxxI/V/L) and ITT-like motif (YxN), the latter primarily mediates the inhibitory function by recruitment of SHIP1 and inhibition of PI3K, MAPK, and NF-κB pathways (Fig. 1), suppressing TCR and NK cell receptor signaling (Joller et al., 2011; Yu et al., 2009). In MS, TIGIT activation reduces IFNγ, enhances Treg suppression, and counters Th1 polarization via Akt-FoxO1-T-bet regulation (Lucca et al., 2019). Beyond T cells, TIGIT modulates DC function through CD155 binding, promoting a tolerogenic phenotype characterized by increased IL-10 and reduced IL-12 secretion, inhibiting Th1 priming further contributing to immune tolerance (Yu et al., 2009).

TIGIT suppresses Th1 responses and CD8$^+$ and NK cell cytotoxicity (Fourcade et al., 2010; Johnston et al., 2014; Kurtulus et al., 2015). A subset of Tregs expressing TIGIT and marked by Foxp3 and Helios have been shown to be highly suppressive (Kamada et al., 2013). TIGIT engagement with its ligand induces production of immunosuppressive molecules like IL-10 and fibrinogen-like protein 2, supporting a tolerogenic microenvironment (Fourcade et al., 2010; Fu et al., 2012; Joller et al., 2014). Anti-TIGIT therapy restores effector T cell (Teff) function resulting in improved tumor control, especially with PD-1/PD-L1 blockade (Dougall et al., 2017; Johnston et al., 2014).

Although anti-TIGIT antibodies together with anti-PD-1 antibodies have shown early promise in human non–small-cell lung cancer trials, subsequent phase III studies failed to achieve clinical benefit (Mullard, 2026; Recondo and Mezquita, 2022), indicating incomplete understanding of TIGIT's biology. Nonetheless, ongoing investigations reflect sustained interest in this pathway. The functional redundancy of TIGIT with other IRs underscores its continued therapeutic relevance both as a combinatorial target in cancer immunotherapy and as a potential agonistic target for the treatment of autoimmunity. This is especially important since TIGIT has an important function in regulating Foxp3$^+$ T cells, potentiating their function, which is of high relevance in using agonistic anti-TIGIT antibodies in the treatment of autoimmune diseases.

Inhibitory receptor biology in autoimmunity

Much of our understanding of IRs in tolerance comes from murine models involving genetic deletion or antibody blockade. CTLA-4–deficient mice develop fatal multiorgan inflammation due to dysfunctional Foxp3$^+$ Tregs (Tivol et al., 1995; Waterhouse et al., 1995; Wing et al., 2008). When tissue-infiltrating *Ctla4*$^{-/-}$ CD4$^+$ T cells were transferred into *Rag2*$^{-/-}$ mice, they accumulated in a tissue-specific manner, highlighting the role of CTLA-4 in limiting immune infiltration (Ise et al., 2010). Additionally, treatment with anti-CTLA-4 antibodies in mice induced gastric and intestinal inflammation (Liu et al., 2001; Read et al., 2000; Read et al., 2006). In experimental autoimmune encephalomyelitis

(EAE), CTLA-4 blockade increased T cell proliferation and proinflammatory cytokine production, which exacerbated the disease (Hurwitz et al., 2002; Karandikar et al., 1996; Perrin et al., 1996). However, inducible CTLA-4 deletion in adult mice showed attenuated EAE, possibly due to increased Treg numbers (Paterson et al., 2015). While Tregs constitutively express CTLA-4, the mechanism of anti-CTLA-4 antibodies may involve the depletion of Tregs, thereby reducing the Treg: autoreactive Teff ratio (Ingram et al., 2018; Simpson et al., 2013; Takahashi et al., 2000). Antibodies in the clinic can be either IgG1, which has moderate affinity to Fcγ receptors (FcγRs), that mediates antibody-dependent cellular toxicity (ADCC), or the lower affinity IgG4 or modified IgG1 with no ADCC activity. It has been suggested that Tregs are depleted through FcγR-mediated ADCC, as mice lacking FcγRs are protected from anti-CTLA-4 colitis (Lo et al., 2024). Overall, CTLA-4 is essential for controlling autoreactive T cells.

PD-1 also plays a key role in suppression of autoimmunity. PD-1–deficient B6 mice develop lupus-like disease, while its loss in nonautoimmune strains results in heart-specific autoantibodies and heart failure (Nishimura et al., 1999; Nishimura et al., 2001; Okazaki et al., 2003). Moreover, in autoimmune-prone MRL mice, PD-1 deficiency leads to T cell heart infiltration, elevated autoantibody titers, and fatal myocarditis (Wang et al., 2010), highlighting the role of genetic background in autoimmunity (Harroud and Hafler, 2023). In NOD mice, PD-1 deletion or blockade accelerated T1D by increasing T cell infiltration into islets (Ansari et al., 2003; Wang et al., 2005). Self-reactive CD4$^+$ T cells express high levels of PD-1 and CD73, and dual blockade enhances their expansion, indicating these molecules help restrain self-reactive T cell responses (Nettersheim et al., 2025).

LAG3 also contributes to self-tolerance. In mice expressing influenza HA as a self-antigen, LAG3 blockade or deletion enhanced CD8$^+$ T cell expansion and IFNγ production, with LAG3 and PD-1 showing synergistic effects in promoting inflammation (Grosso et al., 2007; Grosso et al., 2009). Their dual deficiency leads to lethal myocarditis, accelerated diabetes, and graft-versus-host disease (GVHD)–like autoimmunity (Okazaki et al., 2011; Woo et al., 2012). On its own, LAG3 can suppress inflammation, as either LAG3 blockade or LAG3-deficient NOD mice exhibited T cell infiltration in the islets and developed diabetes (Bettini et al., 2011). Mutations in LAG3 that prevent binding to MHCII exacerbated diabetes in NOD mice (Maruhashi et al., 2022). Additionally, autoreactive intra-islet CD8$^+$ T cells exhibit an exhaustion profile with expression of TOX and IRs that delays diabetes incidence (Grebinoski et al., 2022), and genetic ablation of LAG3 accelerated disease. Its function is cell type–specific as Treg-specific deletion increased proliferation and reduced diabetes (Zhang et al., 2017). In EAE, LAG3 on Tregs suppresses inflammation by inhibiting the PI3K-Myc axis, affecting Treg metabolism (Kim et al., 2024). In relapsing–remitting MS and T1D, LAG3 expression on T cells and *LAG3* mRNA expression on CD8$^+$ T cells were significantly lower compared with healthy controls (Jones et al., 2022). Moreover, the gut–immune axis has been implicated in autoimmune encephalomyelitis (Berer et al., 2011; Lee et al., 2011b; Miyauchi et al., 2023; Schnell et al., 2021). MOG-specific CD4$^+$ intraepithelial lymphocytes reduced EAE severity, and blocking LAG3 increased CNS infiltration (Kadowaki et al., 2016). In an ILC3 colitis model, LAG3$^+$ Tregs limited proinflammatory macrophages and their ablation promoted colitis, highlighting the potential role of the gut in modulating autoimmunity (Bauche et al., 2018).

TIM-3 was initially linked to tolerance via Th1 cells, as anti-TIM-3 blockade increased EAE inflammation (Monney et al., 2002). Treatment with TIM-3-Ig promoted Th1 proliferation and proinflammatory cytokine secretion, disrupting tolerance and accelerating diabetes in NOD mice (Sabatos et al., 2003; Sanchez-Fueyo et al., 2003). Analysis of cerebrospinal fluid from MS patients revealed TIM-3 expression on Th1 cells, and its role in inhibiting proliferation and IFNγ secretion (Khademi et al., 2004; Koguchi et al., 2006; Yang et al., 2008). In EAE models, TIM-3 deficiency affected Th1 and Th17 survival and CNS inflammation (Lee and Goverman, 2013), while overexpression on T cells increased MDSCs and reduced inflammation (Dardalhon et al., 2010). Its dysfunction or reduced expression has also been observed in other autoimmune diseases such as ulcerative colitis, RA, and psoriasis (Kanai et al., 2012; Liu et al., 2010; Shi et al., 2012). While its role in autoimmunity is still being defined, recent studies highlight its involvement in T cell exhaustion and cancer immunotherapy (Tang et al., 2019; Wolf et al., 2020).

Immune checkpoint blockade has improved survival in cancer patients, but often triggers immune-related adverse events (irAEs) resembling autoimmunity (Burke et al., 2021; Keam et al., 2024; Schnell et al., 2020; Young et al., 2018). Up to 85% of patients develop irAEs affecting the lungs, liver, gut, or endocrine glands. Single-cell studies suggest distinct tissue-resident T cells initiate these events (Bukhari et al., 2023), with combinatorial IR blockade increasing the risk of irAEs. Murine models in autoimmune-prone strains show immune infiltration similar to patients after dual PD-1/CTLA-4 blockade therapy (Adam et al., 2021; Wei et al., 2021). A mouse model examining skin-related irAEs used a contact hypersensitivity model with IR blockade, resulting in CD8$^+$ T cell infiltration (Ashoori et al., 2020). Furthermore, IR-induced colitis model demonstrated cytotoxic T cell phenotype that is dependent on IL-23 (Lo et al., 2023). Further research is needed to explore irAE mechanisms and the role of the tissue microenvironment in inflammation.

Genetic studies support the role of IRs in autoimmunity. For instance, the CTLA-4 +49A>G SNP (rs231775) exhibits a strong association with autoimmune diseases such as RA, SLE, T1D, and Addison's disease in European cohorts (Wang et al., 2017; Wolff et al., 2015; Yu et al., 2021). Similarly, CTLA-4 SNPs (rs733618, rs4553808, rs5742909, rs231775, rs3087243) are linked to myasthenia gravis (Li et al., 2018). On the PD-1 side, the rs10204525 SNP has been associated with altered PD-1 expression and susceptibility to immune-related conditions including colorectal cancer and other pathologies indicating potential modulatory roles in autoimmunity (Al-Harbi et al., 2022; Mirsharif et al., 2023). A start codon variant of LAG3, rs781745126-T, is associated with the development of autoimmune thyroid disease (Saevarsdottir et al., 2024). Pathogenic missense variants of TIM-3, p.Tyr82Cys and p.Ile97Met, cause misfolding, loss of cell surface expression and function contributing to hyperproliferation

of CD8⁺ T cells, increased myeloid cell activation, cytokine production, and the development of HLH-SPTCL (Gayden et al., 2018). These findings emphasize the genetic link between IRs and autoimmunity, supporting the development of agonistic therapies.

IRs are essential for maintaining tolerance by suppressing autoreactive T cells that escape central deletion. Mouse models reveal that IR loss leads to organ-specific autoimmunity, including colitis, diabetes, myocarditis, and CNS inflammation. These mechanisms are mirrored in irAEs observed with cancer immunotherapy, underscoring the delicate balance between immune activation and tolerance.

Agonistic approaches to IR modulation

IR agonists and inhibitors modulate immunity via opposing mechanisms. Inhibitors block IR–ligand interactions to enhance T cell activation and antitumor responses (Meng et al., 2024), while agonists activate IRs, mimicking ligand effects. This activation leads to the phosphorylation of intracellular motifs on the receptors, such as ITIMs, and recruits signaling proteins that inhibit cellular activation, consequently suppressing T cell activation and development of tissue inflammation (Paluch et al., 2018). Below, we summarize the concept and underlying mechanisms of inhibitory receptor agonism.

Concept of IR agonism for restoring tolerance

Autoimmune diseases, marked by immune attacks on self-tissues, remain a major clinical challenge. IR agonism offers a promising strategy to restore immune tolerance with more targeted immunosuppression than traditional therapies (Grebinoski and Vignali, 2020; Sharma and Allison, 2015; Wherry and Kurachi, 2015). By enhancing inhibitory signals, this strategy may not only inhibit Teffs but also promote Treg function, thereby restoring immune tolerance in autoimmune conditions while minimizing the risk of harmful inflammation. Autoimmune diseases, such as MS and T1D, arise when immune tolerance breaks down, disrupting the delicate balance between immune activation and regulation. IRs regulate T cell responses and maintain immune balance (Daei Sorkhabi et al., 2023; Paluch et al., 2018; Rousseau et al., 2023). Agonizing pathways modulated by IRs has shown potential to re-establish tolerance and controlling autoimmunity, with potential applications across autoimmune and cancer settings.

IR agonists specifically target autoimmune diseases in mouse models through several mechanisms (Chen et al., 2021; Curnock et al., 2021; Feng et al., 2024; Suzuki et al., 2023) that include but not limited to: (1) restoring tolerance by activating inhibitory pathways that suppress autoreactive T cells. For example, PD-1 agonist antibodies have demonstrated the ability to inhibit T cell activation by engaging FcγRs, thus facilitating colocalization of PD-1 and the TCR to promote tolerance; (2) reducing inflammation by lowering proinflammatory cytokine production in various autoimmune conditions; (3) inhibiting T cell function, suppressing cytokine release and CD8⁺ cytotoxicity; (4) restoring Foxp3⁺ Tregs and IL-10–producing Tr1 function, which are impacted on autoimmune diseases; (5) tissue-specific targeting using bispecific molecules to localize IR agonism to particular cell types or tissues involved in autoimmunity; and (6) mimicking natural signals by enhancing effects of endogenous ligands like PD-L1.

Agonistic IR antibodies are a novel class of immunotherapies that mimic natural ligands by binding IRs to suppress immune responses. Unlike their antagonistic counterparts used in cancer immunotherapy, these antibodies aim to amplify the downregulation of immune responses, offering a promising approach to restoring immune balance in autoimmune conditions. By engaging IRs, these antibodies can limit excessive immune responses, potentially halting the progression of autoimmune diseases. Early studies show their potential in conditions like psoriasis, IBD, and RA. Furthermore, human TIGIT knock-in mice treated with human anti-TIGIT agonist antibody demonstrated attenuated EAE disease, *in vitro* suppression of Tfh cells which are drivers of autoantibody production, and enhanced Treg function (Kojima et al., 2023). By activating IRs and suppressing overactive immune responses, these antibodies offer a novel strategy to target the root cause of autoimmunity (Feng et al., 2024; Luca, 2025; Wang et al., 2024b).

In summary, several IRs have been investigated in autoimmunity, with promising results in mouse models. Despite the potential, further research is needed to better understand the mechanisms of IR agonism and to design more effective agonists for clinical application in autoimmune diseases. This is even more important as agonism with antibodies can be achieved by multiple different ways; therefore, choosing an agonistic antibody will have to be carefully selected for optimal functional inhibition.

Potential advantages of agonistic antibodies over other immunosuppressive strategies

IR agonists can potentially be used in combination with other immunosuppressive therapies to enhance their effectiveness in treating autoimmune diseases (Lavon et al., 2019). The rationale for combining IR agonists with other immunosuppressive therapies is based on several factors, such as: (1) synergistic effects, which include targeting multiple inhibitory pathways simultaneously may lead to more potent inhibition of the activated immune system, (2) complementary mechanisms, where different immunosuppressive agents can act on distinct aspects of the immune response, thereby targeting multiple drivers of autoimmunity, and (3) dose reduction, based on the idea that combinations may allow for lower doses of individual agents, thereby reducing side effects while maintaining efficacy (Hui et al., 2017; Kamphorst et al., 2017; Larkin et al., 2015; Postow et al., 2015). In chronic autoimmune diseases, steroids, which are mainstay treatment in most autoimmune diseases, stop working or do not optimally inhibit the chronic autoimmune diseases. IR agonists may provide another avenue to inhibit tissue inflammation, limiting chronic use of high-dose steroids.

IR agonists have shown promising efficacy in various mouse models of autoimmunity. Agonistic anti-TIGIT mAbs inhibit T cell proliferation and reduce T-bet, GATA3, IRF4, and RORc expression, lowering IFNγ levels (Lozano et al., 2012). Agonistic antimouse TIGIT antibodies reduced T cell responses and

ameliorated autoimmune disease severity in the EAE model by decreasing T cell expansion and proinflammatory cytokine production. These antibodies also reduced IL-17$^+$ Th17 cells infiltration into the CNS (Dixon et al., 2018). The antihuman TIGIT agonistic mAbs were found to suppress the activation of CD4$^+$ T cells, particularly follicular helper T and peripheral helper T cells, which highly express TIGIT (Kojima et al., 2023). Additionally, these mAbs enhanced the suppressive function of Tregs. These findings suggest that agonists can restore T cell imbalance in autoimmunity, highlighting TIGIT as a therapeutic target, further supported by its effects in MS patient T cells (Lucca et al., 2019). These findings support further exploration of TIGIT-targeted therapies for autoimmune diseases.

PD-L1-Fc fusion proteins have demonstrated significant benefits in multiple autoimmune disease models. It reduced autoantibody production and tubular proteinosis in lupus models, decreased glomerular T cell infiltration, and extended survival in experimental autoimmune glomerulonephritis (Zhou et al., 2016). IMP761 is a LAG3-specific humanized agonist antibody with immunosuppressive effects in vivo (Angin et al., 2020). In a delayed-type hypersensitivity model using cynomolgus macaques, IMP761 suppressed T cell infiltration by self-antigen–specific T cells. However, it was unclear whether this was due to T cell depletion.

Challenge of making and evaluating agonists over antagonists

The development and evaluation of IR agonists present unique challenges compared with antagonists, particularly in the context of autoimmune diseases. One major concern is safety with these IR agonists, which could lead to excessive immunosuppression and increase the risk of infections or malignancies. For example, CD80-Fc and CD86-Fc, intended to inhibit T cells via CTLA-4, instead activated them through CD28, enhancing antitumor responses (Wei et al., 2019). Poor dosing may also trigger uncontrolled inflammation, such as cytokine storms. Determining the optimal sequencing and timing of agonist administration is crucial, as seen in cancer immunotherapy, where the order of treatment impacts both efficacy and safety. Additionally, patient selection is critical to identify those most likely to benefit from specific combinations, ensuring optimized outcomes (He et al., 2017).

Finding the therapeutic window to suppress autoimmunity without causing toxicity remains difficult. Chronic activation of pathways like STING can result in persistent cytokine generation, potentially promoting tumor growth rather than suppressing autoimmunity (Jiang et al., 2020; Liu et al., 2022; Wang et al., 2024a). Duration of treatment is another consideration as prolonged immunosuppression carries risks of infection and neoplasia in patients. Since IR agonists suppress autoreactive T cells, treatment should be limited to the period needed to restore immune tolerance, preferably short-term or intermittent until remission, which consequently would require clinical evaluation to balance efficacy and safety. Additionally, route of administration and tissue-specific effects further complicate therapeutic predictions, as IR pathways may have varying importance in different body regions. Furthermore, translating findings from animal models, such as knockout studies, to human outcomes is often unreliable, making the development process more complex.

Selecting appropriate autoimmune disease targets is also challenging, requiring careful analysis of pathway dependencies in various tissues. Designing effective agonistic antibodies without off-target activation is another technical hurdle. For combination therapies, selecting optimal pairings and patient-specific regimens is complex, and reliable biomarkers for predicting response are still lacking.

Targeting Teffs with IR agonists is a promising strategy for treating autoimmune diseases. In contrast, Tregs maintain peripheral tolerance and suppress inflammation, but their numbers and suppressive capacity are often reduced within affected tissues (Ge et al., 2024), especially in the autoimmune diseases where proinflammatory cytokines like IL-6 and TNFα are produced in copious amounts (Korn et al., 2007). As Tregs also express many IRs, they may also be targeted with agnostic antibodies. The impact of IR agonism on Tregs is highly context- and receptor-dependent. In Tregs, PD-1 and LAG3 agonism could lead to reduced suppressive function (Grebinoski and Vignali, 2020; Tan et al., 2021). In contrast, targeting CTLA-4, TIM-3, and LAG3, in different disease contexts, may lead to alternate effects and help in maintaining Treg stability and even enhance their suppressive activity (Huang et al., 2004; Kim et al., 2024; Nieves-Rosado et al., 2023; Sakuishi et al., 2013; Tan et al., 2021; Wing et al., 2008). In fact, activation of Tregs through CTLA-4 and TIM-3 results in enhancement of Treg function, not a decrease in their function. Thus, agonism of specific IRs may either inhibit or promote Treg function depending on the targeted pathway and should be carefully considered. These divergent effects highlight the importance of selectively modulating autoreactive Teffs while preserving or enhancing Treg activity, which is one of the mechanisms that fuels autoimmune disease. Future therapeutic strategies, such as bispecific antibodies (bsAbs) or cell type–restricted delivery approaches, may help achieve this balance and minimize off-target suppression of Tregs. Furthermore, potential ability of agonistic antibodies to delete Tregs can be mitigated by engineering the Fc portion of the agonistic antibodies.

In EAE, PD-1 restrains Treg functions, as Treg-specific PD-1 deletion enhances suppressive capacity and ameliorates disease severity (Tan et al., 2021). Similar observations have been reported in cancer, where PD-1 blockade can drive Treg expansion and suppressive activity, contributing to hyperprogression in gastric cancer (Kamada et al., 2019), an effect linked to CD30 signaling in the tumor microenvironment (Lim et al., 2025). Similarly, PD-L1 blockade has been shown to activate Tregs and enhance their suppressive function in murine tumor models (van Gulijk et al., 2023). In contrast, PD-1$^+$ Tregs suppress PD-L1$^+$ CD8$^+$ T cell function during chronic viral infection (Park et al., 2015), and PD-1 signaling supports the suppressive activity of tumor-infiltrating Tregs in murine lung cancer, as PD-1 deletion in these cells impairs their function (Kim et al., 2023). PD-1 intrinsically restrains Tregs, but its impact on Treg suppressive function is context-dependent and may vary across disease settings (Imianowski et al., 2025; Kuchroo et al., 2021).

LAG3 exhibits similar disease-specific effects on Tregs. In T1D, Treg-specific deletion of LAG3 reduces disease severity and is associated with diminished suppressive function within pancreatic islets (Zhang et al., 2017). Conversely, deletion of LAG3 in Tregs exacerbates disease in the EAE model (Kim et al., 2024), suggesting a role for LAG3 in supporting Treg function within the CNS. Thus, agonism of PD-1 and LAG3 could lead to reduced suppressive function depending on the disease or tissue (Tan et al., 2021; Zhang et al., 2017). Other IRs, including CTLA-4 and TIM-3, also exert context-dependent effects and may contribute to Treg stability and suppressive function (Huang et al., 2004; Wing et al., 2008).

Collectively, these observations underscore that IR agonism may either inhibit or promote Treg activity in a disease-specific manner and must be carefully evaluated. Therapeutic strategies should account for cell-specific effects to avoid unintended repression of Treg-mediated tolerance with these divergent effects highlighting the importance of selectively modulating autoreactive Teffs while preserving or enhancing Treg function. Future therapeutic strategies, such as bsAbs or cell type–restricted delivery approaches, may help achieve this balance and minimize off-target suppression of Tregs (Fig. 2).

Similarly, several challenges hinder the widespread adoption of combination therapies and IR agonists. A key obstacle is identifying effective combinations tailored to specific diseases and patient profiles. There is also a need to develop reliable biomarkers that can predict treatment response and stratify patients for personalized therapy. Future research should focus on developing specific agonists, exploring synergy with other immunomodulators, and conducting large-scale trials to assess long-term safety and efficacy in autoimmune diseases (Hellmann et al., 2018; Sharma and Allison, 2015; Wei et al., 2018). Consequently, deeper understanding of IR signaling mechanisms will be essential for successfully advancing these promising therapeutics for autoimmune diseases.

Development of agonistic IR antibodies

Soluble proteins of natural ligands such as Gal-9 are being explored in the treatment of autoimmune diseases (Grebinoski and Vignali, 2020). However, mAbs offer several advantages including higher affinity, specificity to single epitope, and extended serum half-life (Paluch et al., 2018; Unverdorben et al., 2016). Additionally, antibody engineering is well-established field that enables modulation of antibody function (Damelang et al., 2023). Mechanistically, agonistic antibodies can induce receptor clustering or stabilize ligand–receptor interactions by binding either orthosteric (ligand binding) or allosteric (non-ligand binding) sites (Carter and Lazar, 2018; Schardt et al., 2022). The development of therapeutic antibodies requires optimizing parameters, including epitope selection, valency, specificity, isotype, and Fc-meditated interactions to modulate agonist functions (Fig. 3). Unlike blocking antibodies, different agonist antibodies against the same inhibitory molecules that may agonize by different mechanisms therefore have different levels of efficacy. This should be considered while selecting agonistic agents for the treatment of autoimmune/inflammatory diseases.

The ligand binding site of immune IRs, the orthosteric site, is attractive for agonism due to its central role in receptor activation. Nonetheless, these sites may interact with multiple ligands. Structure-guided mutagenesis studies can identify residues or domains that regulate receptor activity, enabling the design of antibodies that bind idiotypically to modulate signaling. An alternative strategy involves targeting membrane-proximal regions of IRs to stabilize the receptor where metalloproteases cleave and release soluble receptor fragments from the cell, particularly for LAG3 (Andrews et al., 2020; Clayton et al., 2015; Li et al., 2007; Migita et al., 2020; Moller-Hackbarth et al., 2013). For example, anti-PD-1 mAbs binding membrane-proximal regions confer agonistic activity (Suzuki et al., 2023). While biparatopic antibodies targeting two different sites and/or domains may enhance binding via avidity (Niquille et al., 2024), using a biparatopic antibody to target different sites on an IR is a therapeutic strategy that requires further evaluation.

Avidity is the overall strength of interactions between two molecules and can drive surface clustering and promote effector function (Oostindie et al., 2022). Antibodies are typically bivalent and bind two sites, and increasing the valency can induce receptor clustering due to higher avidity. A unique i-shaped antibody consisting of Fab-Fab homotypic format targeting OX40 increased avidity and demonstrated enhanced agonist activity by increasing receptor clustering (Romei et al., 2024). While promising, its relevance to immune IRs remains to be assessed. Interestingly, reducing anti-PD-1 antibody affinity induced clustering and suppressed T cell activation, converting antagonism to agonism (Yu et al., 2023).

The choice of antibody isotype also impacts agonistic function. There are four subclasses of IgG: mice express IgG1, IgG2a, IgG2b, and IgG3, and humans express IgG1-4. The constant region of antibodies plays a significant role in antibody specificity and effector function (McConnell and Casadevall, 2025). IgGs have differences in flexibility of the Fab arms that is due to their distinct hinge regions, with IgG2 having the least flexibility and IgG3 having the greatest hinge flexibility due to a larger hinge length, with the order of flexibility being IgG2 < IgG4 < IgG1 < IgG3 (Damelang et al., 2023). This flexibility allows the Fab arms to interact with different epitopes and conformations to the Fc domain, which confer their effector function. A study demonstrated exchanging the CH1 hinges between IgG2 and IgG3 conferred agonistic activity in inactive anti-CD40 IgG3 (Liu et al., 2019). In addition to IgG subclass, posttranslational modifications can impact antibody function. A fucosylation of human IgG enhanced effector function through affinity to FcγRIII, which promotes ADCC instead of agonism (Nimmerjahn et al., 2023). The choice of IgG class is crucial as unmodified IgG1 has been posited to function by depleting IR-expressing cells in contrast to IgG4 and IgG1 with glycosylation modification or Fc-silenced variants.

IgG-Fc domains binding to activating FcγRs induce effector functions including phagocytosis and ADCC (Bournazos et al., 2020; Junker et al., 2020), and mutations can reduce FcγR binding while extending half-life (Saunders, 2019; Wang et al.,

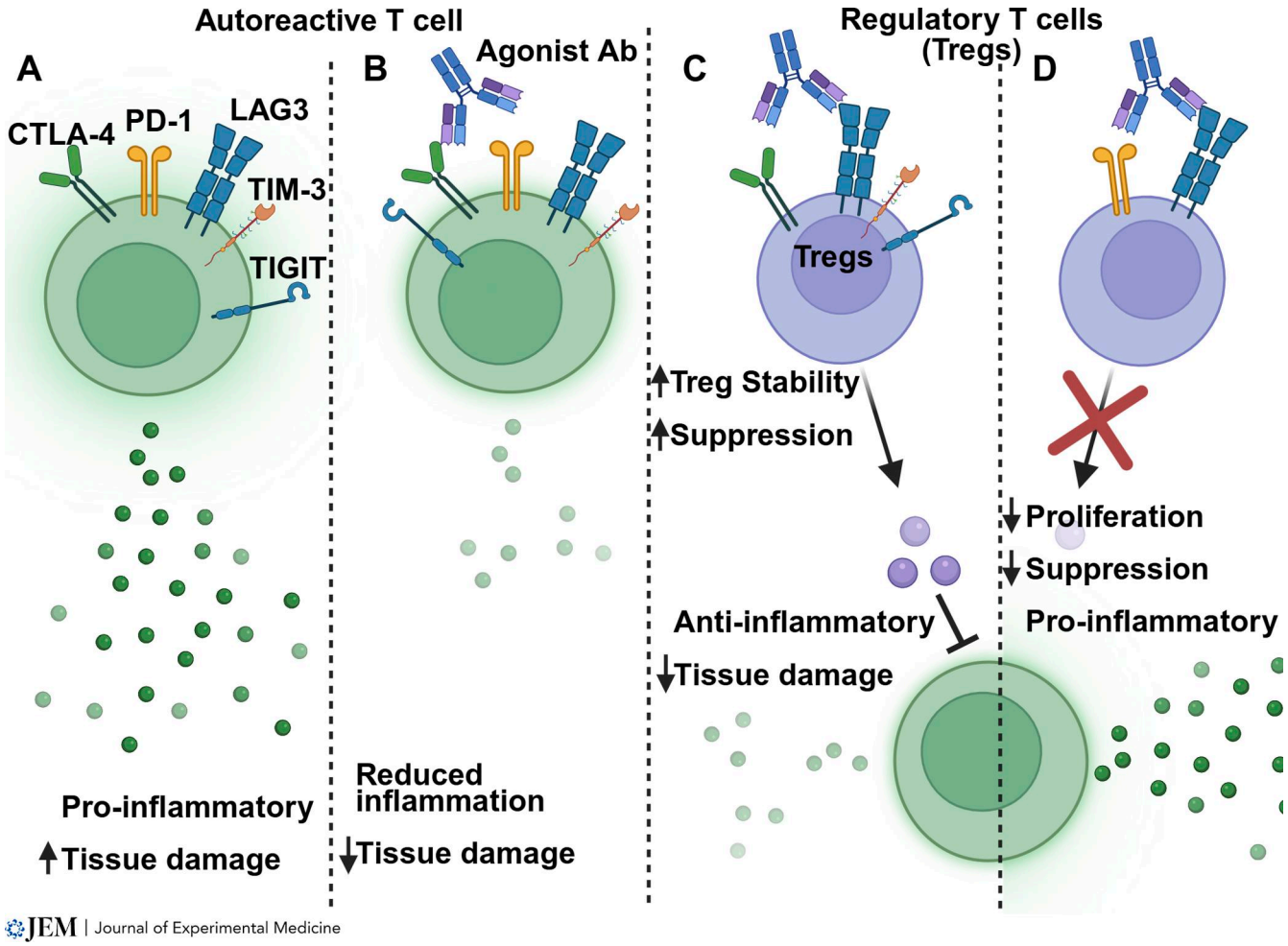

Figure 2. **Differential effects of IR agonism on Teffs and Tregs in autoimmune diseases. (A–D)** Pathogenic autoreactive T cells express multiple IRs, and agonist Abs targeting these IRs can suppress effector T cell (Teff) responses to reduce autoimmune inflammation. However, many IRs are also expressed on Tregs, which are critical for maintaining immune tolerance. The impact of IR agonism on Tregs is receptor dependent: signaling through CTLA-4, TIM-3, and TIGIT supports Treg stability and function, whereas PD-1 engagement decreases Treg suppressive capacity. In contrast, LAG3 activity appears to be context dependent, varying by disease state and tissue environment. Consequently, the overall therapeutic outcome depends on whether the balance between Teff inhibition and Treg preservation is maintained. Emerging strategies, such as bsAbs or cell type–restricted agonists, aim to preferentially target pathogenic Teffs while minimizing off-target effects on Tregs. The figure was created with BioRender.

2018b). However, differential expression of FcR between mice and humans impedes the translational aspect of antibody design. While the majority of FcγR expresses ITAMs, FcγRIIb is the only receptor expressing an ITIM. Enhancing an agonistic PD-1 mAb via binding to FcγRIIb inhibited IFNγ from primary human T cells (Suzuki et al., 2023). Furthermore, it was shown that FcγR binding is required for anti-PD-1 IgG agonism. Using anti-PD1 with similar antigen binding domains and with low-affinity Fc regions to FcγR failed to inhibit proliferation of human PBMCs and GVHD in a humanized mouse model (Feng et al., 2024). Although this study demonstrated FcγRIIIA as the dominant driver, this suggests that Fc engineering of mAbs is a promising approach in modulating antibody efficacy.

Agonistic antibodies targeting immune IRs lag behind their antagonistic counterparts. Advancing this field will require deeper investigation into optimal epitope targeting, IgG subclass selection, and Fc engineering to enhance agonistic activity and further IR biology.

Novel approaches and combination strategies

bsAbs offer enhanced specificity and potentially improved efficacy compared with traditional mAbs. bsAbs can be developed to be trans-targeting to recruit immune cells to the environment by engaging targets on two different cells or cis targeting to engage molecules on the same cells, thus having greater specificity, and minimize off-target effects (Oslund et al., 2024). A promising strategy to cluster and induce agonistic functions is to target immune IRs and molecules within the immune synapse. Recent studies have explored the use of bsAbs in various autoimmune conditions and have shown promise in preclinical and early clinical evaluation. A bsAb targeting TCR and LAG3 protected mice from pathogenic T cells in diabetes and EAE models (Du et al., 2025). While bsAbs show significant potential, optimizing their design and dosage, and identifying ideal patient groups remain key challenges.

Combining agonistic IR antibodies could also potentially offer synergistic effects, by targeting multiple immune regulatory

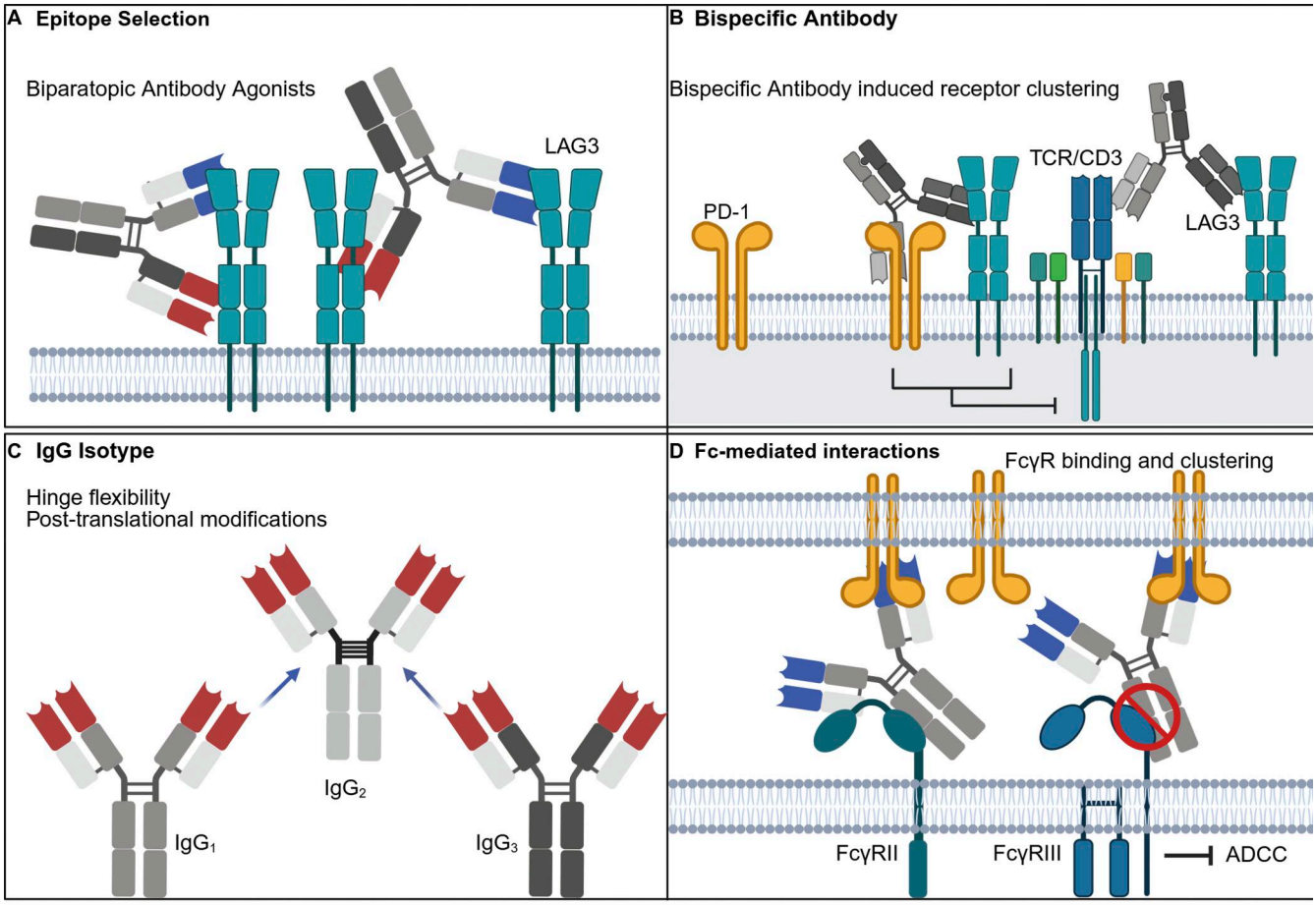

Figure 3. **Approaches to target IRs or disease/tissue. (A)** Biparatopic antibodies targeting both orthosteric and allosteric sites can enhance binding via avidity. **(B)** bsAbs can be cis targeting to engage molecules on the same cells to induce receptor clustering at the immune synapse (IS). **(C)** IgG subclass, hinge flexibility, and posttranslational modifications can impact antibody function. **(D)** FcγRII binding may stabilize antibody at the IS for agonism, and engineering of antibodies to prevent binding to other FcR can prevent depletion of cells through ADCC. The figure was created with BioRender.

pathways simultaneously, enhancing immune suppression and targeting specific disease pathways. These include (1) combining IR agonists targeting different receptors, such as CTLA-4, PD-1, and LAG3, (2) pairing IR agonists with conventional immunosuppressants, like corticosteroids or methotrexate, and (3) combining IR agonists with targeted therapies, such as biologics or small molecule inhibitors that focus on specific inflammatory pathways (Choi et al., 2021; Wei et al., 2019). The IR agonist therapies could be administered together with cytokine blockade therapies, where IR agonists could reset the function of pathogenic autoreactive T cells, thereby bringing back regulation and tolerance. Studies in various mouse models have shown that these combinations can effectively suppress autoimmune responses and inflammation. However, translating these findings to human diseases remains challenging due to species-specific differences in immune architecture, disease pathogenesis, and the limitations of murine models in fully recapitulating human immunopathology.

Among the most studied combinations, dual blockade of LAG3 and PD-1 has shown enhanced antitumor efficacy over monotherapies in preclinical models, due to their complementary suppression of T cell activity (Andrews et al., 2024; Cillo et al., 2024; Woo et al., 2012). This approach is effective even in models resistant to single-agent therapy and does not trigger significant autoimmunity (Andrews et al., 2017). Beyond LAG3 and PD-1, combinations like PD-1 with CTLA-4, TIM-3, or TIGIT are being tested to counter tumor-driven immune suppression (Hellmann et al., 2018; Sharma and Allison, 2015). In contrast to cancer, where IR inhibitors aim to enhance immunity, autoimmune diseases may benefit from the opposite approach activating multiple immune IRs to restore tolerance, especially when immune system is highly activated in autoimmune disease setting.

PD-1 and CTLA-4 remain the most well-characterized targets for agonistic therapies in autoimmune diseases. A study developed PD-1–bispecific agonist molecules, called ImmTAAI, that mimic PD-L1 by colocalizing PD-1 with the TCR at the immune synapse. These molecules effectively suppressed T cell function and cytokine production at low concentrations but remained inactive in soluble form, reducing the risk of systemic

immunosuppression (Curnock et al., 2021). Another study has shown agonistic anti-CTLA-4 antibodies increase Treg frequency in *in vitro* setting (Barnes et al., 2013). LAG3 also emerges as a compelling candidate due to its role in inhibiting T cell proliferation and maintaining immune homeostasis. Recent data suggest that LAG3 agonism can mitigate inflammation in autoimmune diseases (Angin et al., 2020). The development of agonistic IR antibodies, bispecific, and other multispecific constructs marks a major advance in autoimmune disease therapy. These approaches promise more targeted, effective, and safer treatments. Though challenges like design optimization and patient selection remain, ongoing research and clinical trials are key to unlocking their full potential and improving patient outcomes.

Future directions and perspectives

Agonistic antibodies targeting immune IRs are emerging as promising immunotherapies for autoimmune diseases, aiming to restore immune tolerance by enhancing inhibitory signaling. While preclinical data are encouraging, translating these findings to human therapies remains challenging. Key obstacles include resistance mechanisms such as compensatory immune activation or reduced receptor expression in chronically inflamed tissues. Optimizing dosing and administration through systemic, targeted, or transient approaches is crucial for balancing efficacy and safety (Zhang et al., 2018). Further development of bispecific or targeted agonists, such as ImmTAAI molecules that colocalize IRs with the TCR to mimic natural ligand interactions, represents a promising approach to selectively suppress autoreactive T cells while sparing protective immune responses. Such strategies could mitigate risks associated with systemic IR activation and enable more durable and safer therapeutic outcomes.

Beyond autoimmune diseases, IR agonists show potential in chronic infections and GVHD, where immune regulation is critical (Grebinoski and Vignali, 2020). They may also reverse T cell exhaustion and improve Treg function in chronic inflammation (Pauken and Wherry, 2015). Personalized approaches, including biomarker-driven stratification based on IR expression or genetic risk, could enhance outcomes and minimize side effects (Klocke et al., 2016). However, the transition from animal models to human trials remains difficult, as immune IR pathways are often species-specific, and many rodent models fail to fully replicate human autoimmune pathophysiology (Miyara et al., 2014). Future research should leverage single-cell and spatial profiling technologies, alongside computational modeling, to guide the rational design of IR-targeted therapies tailored to individual patients.

Agonistic IR antibodies represent a promising path in immunotherapy for autoimmune and inflammatory diseases. As our understanding of immune regulation deepens, these strategies may lead to more personalized and effective treatments, though further clinical validation is essential.

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