J Appl Biomed
DOI: 10.32725/jab.2026.001
journal homepage: http://jab.zsf.jcu.cz

Journal of Applied Biomedicine

Review article

# Walking the tightrope: Balancing immune checkpoints and their inhibitors in host defence against bacterial infections

Anna Palounková [1], Andrea Frejlachová [1], Anna Kovaříková [1], Aleš Chrdle [1, 2], Helena Langhansová [1] *

[1] *University of South Bohemia in České Budějovice, Faculty of Science, Department of Medical Biology, České Budějovice, Czech Republic*
[2] *České Budějovice Hospital, Department of Infectious Diseases, České Budějovice, Czech Republic*

**Abstract**
Immune checkpoints are one of the mechanisms that maintain the balance between immunotolerance and immunopathology. These mechanisms are often exploited by tumour cells. Thanks to extensive global testing of anticancer drugs, a revolutionary cancer therapy based on immune checkpoint inhibitors (ICIs) has been developed. Some pathogens exploit regulatory checkpoint interactions, contributing to the establishment of hidden, long-term, or persistent infections in which the host is unable to eliminate the pathogen. However, a structured overview of immune checkpoint involvement in bacterial infections remains underrepresented in the current scientific literature. We conducted a literature review focusing on the documented role of selected immune checkpoints (specifically PD-1, PD-L1, TIM-3, LAG-3, CTLA-4, and TIGIT) during infections of humans and animals with clinically relevant bacterial pathogens from the Actinobacteria, Chlamydiae, Firmicutes, Proteobacteria, and Spirochaetae phyla. The current state of knowledge suggests that applied research into immune checkpoints and the controlled use of ICIs has great potential to improve the diagnosis, treatment, and prognosis of serious human bacterial infections.

**Keywords:** Bacteria; ICIs; Immune checkpoint; Infection; Therapy

**Highlights:**
- Immune checkpoints play a significant role during bacterial infections.
- Pathogenic bacteria exploit immune checkpoints in order to evade host immunity.
- Checkpoint inhibitors can improve multiple aspects of infectious disease management.

## Introduction

A fundamental property of the immune system is to correctly distinguish between self and non-self and to develop the appropriate immune response against invading pathogens. During infection, regulation of the inflammatory response is crucial to prevent excessive tissue damage due to host defence against pathogens. Prolonged immune activation is energetically demanding; timely control of the immune response and return to tissue homeostasis is beneficial for the host organism (Paludan et al., 2021). This delicate balance between tolerance and immunopathology is preserved by various pathways including anti-inflammatory cytokines, regulatory T cells, M2 macrophages and last but not least, by specific inhibitory immune checkpoints (IC), such as PD-1, PD-L1, CTLA-4, TIM-3, LAG-3, and TIGIT (Fig. 1) (Pauken and Wherry, 2015).

Programmed cell death protein 1 (**PD-1**; CD279) is a molecule that inhibits some lymphocyte functions, such as cytokine production, cell proliferation, and cytotoxicity. The interaction of PD-1 with its ligands PD-L1 (programmed death-ligand 1; CD274) and PD-L2 (programmed death-ligand 2; CD273) is important in the control of peripheral T lymphocyte activation in infectious diseases, since it limits the response of subpopulations of effector cells to avoid tissue damage (Sampedro-Nunez et al., 2018). T cell immunoglobulin and mucin domain-containing protein 3 (**TIM-3**; CD366) can have dual and context-dependent effects on the immune system through multiple ligands comprising galectin 9, phosphatidylserine, HMGB1 alarmin, and CEACAM1 (Gorman and Colgan, 2014; Wolf et al., 2020). Lymphocyte-activation gene 3 (**LAG-3**; CD223) binds to its canonical ligand MHC class II with higher affinity than CD4, thus compromising CD4+ T cell activation (Huard et al., 1997). The coinhibitory molecule cytotoxic T-lymphocyte-associated protein 4 (**CTLA-4**; CD152) competes with the costimulatory molecule CD28 for the binding to CD80 and CD86 on antigen-presenting cells (Berg and Zavazava, 2008). T cell immunoreceptor with Ig and ITIM domains (TIGIT) regulates T cell and NK cell-based immunity via high-affinity binding to CD155 and lower-affinity binding to CD112 on T and NK cells (Tang et al., 2023).

* **Corresponding author:** Helena Langhansová, University of South Bohemia in České Budějovice, Faculty of Science, Department of Medical Biology, Branišovská 31, 370 05 České Budějovice, Czech Republic; e-mail: hlanghansova@prf.jcu.cz
http://doi.org/10.32725/jab.2026.001

Submitted: 2025-12-10 • Accepted: 2026-03-06 • Prepublished online: 2026-03-06
J Appl Biomed 24/1: 1–9 • EISSN 1214-0287 • ISSN 1214-021X

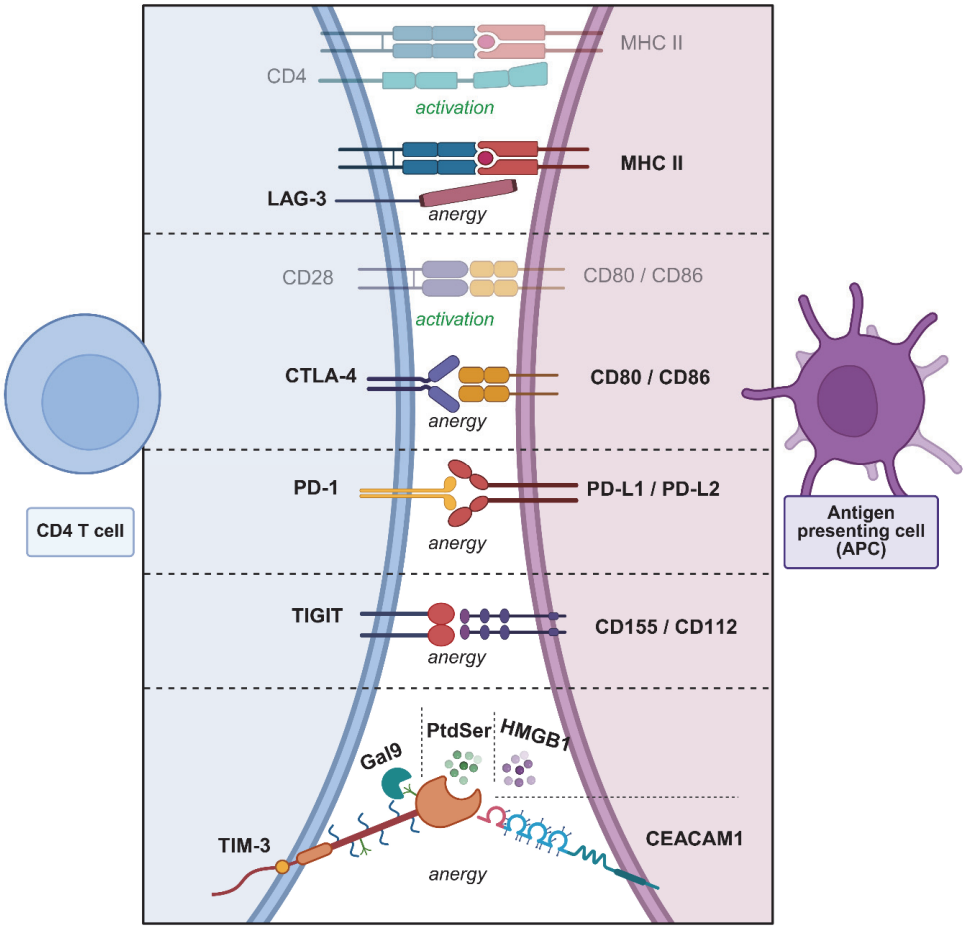


**Fig. 1.** Inhibitory immune checkpoints in immunological synapse. Interactions between key inhibitory immune checkpoints on a CD4 T cell and their ligands on an antigen presenting cell (APC) are highlighted in bold. T cell receptors such as LAG-3, CTLA-4, PD-1, TIGIT, and TIM-3 bind their corresponding ligands (MHC-II, CD80/CD86, PD L1/PD L2, CD155/CD112, and CEACAM1/HMGB1/PtdSer/Gal9) on the APC, leading to T cell anergy. Interactions resulting in cell activation, such as CD4–MHC II and CD28–CD80/CD86, are shown in grey and are diminished by the anergic effect. List of abbreviations: MHC II: major histocompatibility complex class II; LAG-3: lymphocyte-activation gene 3; CTLA-4: cytotoxic T-lymphocyte-associated protein 4; PD-1: programmed cell death protein 1, PD-L1: programmed death-ligand 1; PD-L2: programmed death-ligand 2; TIGIT: T cell immunoreceptor with Ig and ITIM domains; TIM-3: T cell immunoglobulin and mucin domain-containing protein 3; Gal9: galectin-9; PtdSer: phosphatidylserine; HMGB1: high-mobility group box 1 alarmin; CEACAM1: carcinoembryonic antigen-related cell adhesion molecule 1. Created in BioRender (Kovaříková, 2025).

Besides the traditional and well-described system of membrane-bound immune checkpoints and their ligands depicted in Fig. 1, soluble forms of these molecules also exist, produced through the alternative splicing of mRNA or the cleavage of membrane-bound checkpoint proteins. Soluble checkpoints can be present in body fluids, including plasma and cerebrospinal fluid, and also in extracellular vesicles. The functional significance of soluble immune checkpoints and their roles within both (patho)physiology and disease context have not yet been fully clarified (Joseph et al., 2022; Pitts et al., 2024).

Checkpoint molecules play an important role in two phases of the immune response: i) in immunological synapsis during antigen presentation where they prevent T cell hyperreactivity (Francisco et al., 2009); ii) during execution of immune cell effector functions in order to reduce collateral tissue damage. Tumour cells notoriously hijack these mechanisms to avoid the immune response and promote their own survival and progression. This insight led to the development of revolutionary cancer therapies based on immune checkpoint inhibitors (ICIs). Currently, multiple ICIs have either been approved or are undergoing clinical trials for treatment of various cancer types (Lee et al., 2022). The impact of ICIs on survival and prognosis across cancers is significant. In advanced melanoma, the combination of nivolumab (PD-1 inhibitor) and ipilimumab (CTLA-4 inhibitor) has been shown to increase the median overall survival to 72 months, compared with the previously used chemotherapeutic dacarbazine, which achieved a median survival of only 9.1 months (Robert et al., 2011; Wolchok et al., 2022).

Proper regulation of checkpoint immune response is crucial for optimal coping with infections. While there has been a breakthrough in the targeting of immune checkpoints in cancer, increasing evidence indicates that some pathogens exploit inhibitory checkpoint interactions, contributing to the chronicity of the viral, bacterial, and parasitic infections. In this review, we focus on examples of how important the checkpoints are during the infection of host organism with selected clinically relevant bacterial pathogens, and simultaneously highlight their potential as therapeutic targets.

## *The role of inhibitory immune checkpoints in selected bacterial infections*

### Actinobacteria

*Mycobacterium* spp.

It is well established that multiple immune checkpoints, including PD-1/PD-L1, TIM-3, and LAG-3, play an important role in the immune response to mycobacterial infections. Chronic mycobacterial infection can progressively impair antigen-specific T cell responses, resulting in a phenotype of exhausted T cells and inversely increased mycobacterial burden. In infected mice, TIM-3 neutralization via antibody or genetic knockout effectively reduces bacilli burden and prolongs survival (Jayaraman et al., 2016). Pan et al. (2022) observed elevation of PD-L1 in lung tissue from patients with pulmonary tuberculosis. Sporadic case reports mention a positive effect of anti-PD-1 therapeutics in resolving mycobacterial infection (Ishii et al., 2018; Liu et al., 2023). LAG-3 is upregulated during mycobacterial infection in non-human primates and its overexpression is characteristic for both pulmonary and extrapulmonary tuberculosis (Pan et al., 2024; Phillips et al., 2017). TIGIT is downregulated on NK cells from patients with latent tuberculosis (TB) (Harris et al., 2020), whereas in active TB patients, TIGIT expression on CD8+ T cells is significantly upregulated and positively correlates with disease severity. Moreover, TIGIT blockade reduces lung bacterial burden in *M. tuberculosis*-infected mice (Zhou et al., 2025).

It seems that a certain amount of immune checkpoint activation is necessary for optimal control of mycobacterial infection, since disruption of PD-1/PD-L1 signalling in *in vivo* animal models and human 3D model leads to increased *M. tuberculosis* burdens and greater vulnerability of the hosts (Barber et al., 2011; Kauffman et al., 2021; Tezera et al., 2020). Indeed, many studies acknowledge the association between the use of ICIs and increased risk of acute mycobacterial infections or reactivation of latent tuberculosis; reviewed e. g. in Anand et al. (2020), and case reports continue to accumulate (Anidi et al., 2024; Inada et al., 2025; Yamaba et al., 2022).

In patients infected with *M. leprae*, increased expression of LAG-3 and PD-1/PD-L1 in skin lesions and peripheral blood cells contributes to the hyporesponsive immune profile, which is characteristic of leprosy patients (de Castro et al., 2025; Tarique et al., 2023).

### Chlamydiae

*Chlamydiaceae*

Chlamydia infection represents a case in which the adaptive immune system is unable to protect against reinfection. This can be partially caused by type I interferon-induced upregulation of PD-L1 in the genital tract following *Chlamydia trachomatis* murine infection (Fankhauser and Starnbach, 2014; Reinhold-Larsson and Starnbach, 2025). On the other hand, an animal model showed that PD-L1 and TIM-3 signalling can reduce genital tract pathologies without significant suppression of immunity against *C. muridarium* infection (Peng et al., 2011). In the case of lung inflammation caused by *Chlamydophila pneumoniae*, the early targeting of abundantly upregulated PD-L1 has no effect on pathogen load but prevents infection-induced airway hyperresponsiveness (Starkey et al., 2016). Finally, in *C. psittaci*-infected mice, TIM-3 expression is upregulated, and its blockade leads to more effective pathogen clearance, diminishes lung pathology, and improves Th1 and Th-17 mediated immune response (Li et al., 2023b).

### Firmicutes

*Streptococcus* spp.

Multiple inhibitory immune checkpoint proteins, including PD-L1 and LAG-3, were upregulated at the maternal-fetal interface exposed to *Streptococcus agalactiae* experimental infection of *Macaca nemestrina* primates (Manuel et al., 2023). PD-1(-/-) mice, as well as wild-type mice treated with a PD-1 blocking antibody, exhibit significantly increased survival against lethal *Streptococcus pneumoniae* infection, since PD-1 expressed by B cells seems to play the central role in regulation of protection against *S. pneumoniae* (McKay et al., 2015). Moreover, blockade of the PD-1/PD-L1 pathway mitigates the symptoms of murine meningitis caused by *S. pneumoniae* (Ma et al., 2023).

*Staphylococcus aureus*

The PD-1/PD-L1 axis is strongly involved in the immune response to the common bacterium *Staphylococcus aureus* throughout life. Early in infancy, PD-L1 blockade during *S. aureus* stimulation reduces the induction of neonatal Tregs (Rabe et al., 2014). Likewise, both neonatal and adult CD4+ T cells upregulate PD-1 in response to *S. aureus* infection and the blockade enhances early *S. aureus*-initiated responses (Majer et al., 2023). Since the PD-1/PD-L1 axis contributes to immune dysfunction after burn injury, anti-PD-L1 treatment improves bacterial clearance and the survival of mice following post-burn systemic infection (Patil et al., 2018). Orthopaedic implant-associated *S. aureus* osteomyelitis is characterized by an immunosuppressive profile with upregulated PD-1 and PD-L1, which suppresses macrophage bactericidal function. PD-1/PD-L1 inhibitors not only reduce bacterial load in bone tissue but also promote healing and support memory T cells' development (Li et al., 2023a). Interestingly, a significant number of *S. aureus*-specific Tregs expressing TIGIT were found in healthy individuals, which may hinder vaccine responses (Clegg et al., 2024).

*Listeria monocytogenes*

The role of PD-1/PD-L1 axis during *Listeria monocytogenes* infection is unclear. Whereas PD-1 deficiency increases the resistance of mice to *L. monocytogenes* infection (Yao et al., 2009), some authors report a potential costimulatory effect of PD-L1 towards *Listeria* antigen-specific adaptive responses (Seo et al., 2008; Xu et al., 2013). However, TIM-3 helps *L. monocytogenes* to evade the immune system by inhibiting macrophage-mediated phagocytosis *in vitro* and MHC-I-restricted antigen presentation by murine macrophages *in vivo* (Wang et al., 2017b; 2020).

### Proteobacteria

*Brucella* spp.

Chronic infection of mice with *Brucella melitensis* leads, among other effects, to CD8+ T cell exhaustion with upregulation of PD-1 and LAG-3 (Durward-Diioia et al., 2015). Human brucellosis is accompanied by the upregulation of PD-1 during both acute and chronic infection, and CTLA-4+ Tregs in chronic disease (Sun et al., 2021). Moreover, a vaccine containing CTLA-4 together with *Brucella* surface proteins had higher antigenicity and immunogenicity (Guo et al., 2023). Also, *Brucella* antigen Omp25 significantly upregulates PD-1 in monocytes/macrophages and negatively regulates IL-12. PD-1 blockade restores IL-12 production and promotes Th1 responses (Cui et al., 2017).

Rickettsiales

PD-1 influences immune responses in different *Rickettsia* infections: patients infected with *R. rickettsii* had a higher percentage of CD8+PD-1+ cells, and patients infected with *R. typhi* had a higher number of cells corresponding to CD4+PD-1+ cells (Dzul-Rosado et al., 2023). Also, patients infected with rickettsial agent, *Orientia tsusugamushi*, the causative agent of scrub typhus, significantly upregulate PD-1, LAG-3, and TIM-3 on circulating NKT cells, resulting in their functional impairment (Kang et al., 2018). On the other hand, the blocking or silencing of TIM-3 signalling reduces intracellular killing and thus boosts rickettsial burdens in both *in vitro* and *in vivo* models of early phase *R. heilongjiangensis* infection (Yang et al., 2016).

Enhanced expression of PD-1 and LAG-3 on T cells following *Anaplasma marginale* infection in cattle contributes to the exhaustion of specific T cells and potentially leads to the persistence of this rickettsia in organism (Okagawa et al., 2016).

*Bordetella pertussis*

In contrast to *Bordetella pertussis* strains from the era before the whole-cell pertussis vaccines were introduced, recently circulating strains of *B. pertussis* induce higher levels of PD-L1 in a TLR2-dependent manner on human monocyte-derived dendritic cells. Emerging *B. pertussis* strains have thus evolved to induce a more regulatory response, which can be a pathogen strategy to increase its spreading in highly vaccinated population (Hovingh et al., 2017).

*Neisseria gonorrhoeae*

*Neisseria gonorrhoeae* is able to suppress the protective immune response at different levels, including polarization of macrophages into regulatory M2b phenotype and upregulation of PD-L1 on macrophages and dendritic cells upon cocultivation with gonococci (Ortiz et al., 2015; Zhu et al., 2012).

*Coxiella burnetti*

During the acute phase of Q fever caused by *Coxiella burnetti*, PD-L1 expression on T cells is upregulated, resulting in a decreased number of memory T cells (Ka et al., 2015). In chronic Q fever endocarditis, overexpression of PD-1 is observed in intermediate monocytes and CD4+ T cells (Ka et al., 2014).

*Pseudomonas aeruginosa*

Infection with *Pseudomonas aeruginosa* is common during immunopathologic conditions (e.g., extensive injuries, surgical traumas, cystic fibrosis). Blockade of PD-1/PD-L1 axis protects experimental mice against *P. aeruginosa* infection after burn injury, fracture surgery, or exposure to air pollutants (Luo et al., 2024; Patil et al., 2018; Zhang et al., 2019). In case of *P. aeruginosa* colonization of cystic-fibrosis-affected respiratory tract, PD-1/PD-L1 blocking assays improved the immune response and T cell effectivity (Avendano-Ortiz et al., 2019). In contrast, TIM-3/galectin-9 signaling is beneficial for the neutrophil-mediated killing of *P. aeruginosa* (Vega-Carrascal et al., 2014).

*Haemophilus* spp.

In cases of *Heamophilus* colonization of the lower respiratory tract, PD-1 and CTLA-4 pathways seem to play a complex regulatory role in controlling this opportunistic pathogen: patients with chronic obstructive lung disease produce more PD-1 and CTLA-4 in the airways, which makes them more susceptible to *H. influenzae* infections (Kalathil et al., 2014). In concordance, anti-PD-L1 antibodies enhance antibody production and improved the bacterial clearance of *H. influenzae* in a mouse model (Yoshinaga et al., 2025), and *Haemophilus* loads positively correlate with PD-L1 expression in mixed granulocytic childhood asthma (Kim et al., 2024). CTLA-4 positive Tregs contribute to the persistence of *H. ducreyi* genital ulcers (Li et al., 2010).

*Salmonella* spp.

According to current knowledge, multiple immune checkpoints play a significant role in the course of *Salmonella* infections. The infection of intestinal epithelial cells with *Salmonella enterica* serovar Typhimurium induces PD-L1 in both human and rodent cells, and this effect is potentiated by gamma interferon (Sahler et al., 2018). Also, *Salmonella*-infected B cells express more PD-L1, which leads to an impaired CTL response during persistent *Salmonella* infection (Lopez-Medina et al., 2015). PD-L1 upregulation is associated with *Salmonella* pathogenicity island 2 effector molecule SseL (Chopra et al., 2025). Effector responses during *Salmonella* Typhimurium infection are further inhibited by IL-10, originating from LAG-3-expressing the subpopulation of plasma cells (also co-expressing CD138, PD-L1 and PD-L2). This regulation leads to higher bacterial loads in murine tissues and the reduced survival of mice (Lino et al., 2018). Whereas TIM-3/galectin-9 interaction is important for the effective activation and bactericidal activity of intestinal macrophages during *S.* Typhimurium infection (Yu et al., 2018), TIM-3 antibody blockade restores Th1 responses dampened by iron overdose and improves bacterial control (Pfeifhofer-Obermair et al., 2021). Finally, antibody blockade of TIGIT in murine *in vivo* model is able to enhance immunity and improve the clearance of *S.* Typhimurium (McCulloch et al., 2024).

*Helicobacter pylori*

Infection with *Helicobacter pylori* is a well-established risk factor for the development of gastric cancer, where inhibitory immune checkpoints play a significant role. Whereas TIM-3 overexpression leads to reduced *H. pylori*-associated proinflammatory immune response in RAW264.7 macrophages *in vitro* (Wang et al., 2017a), the association between *H. pylori* and the PD-1/PD-L1 axis is in the spotlight, since *H. pylori* significantly increases PD-L1 expression in organoid cultures and gastric epithelium via Hedgehog signalling pathway, creating premalignant lesions (Holokai et al., 2019; Koh et al., 2021). Indeed, clearance of *H. pylori* is negatively affected by enhanced PD-L1 expression on gastric epithelial cells (Beswick et al., 2007; Das et al., 2006), and more importantly, *H. pylori* infection may reduce the efficacy of PD-1/PD-L1 blockade therapy of cancer (Oster et al., 2022; Shatila et al., 2025; Yang et al., 2025).

## Spirochaetae

*Spirochaetaceae*

In patients infected with *Treponema pallidum*, a notably higher percentage of follicular helper T cells expressing PD-1 is present in the stage of latent syphilis, characterized by no clinical symptoms and high antibody titres against *Treponema pallidum* (Shen et al., 2023). The exposure of dendritic cells and macrophages to live *Borrelia burgdorferi* spirochetes drives the expression of immunoregulatory molecules, including PD-L1, LAG-3, and TIM-3 (Gutierrez-Hoffmann et al., 2023; Helble et al., 2022). PD-1 knockout mice showed no differences in bacterial loads but the absence of PD-1 led to increased T cell expansion and accumulation in joints and draining lymph nodes of infected mice (Helble et al., 2022).

An overview of the literature addressing the role of checkpoints in bacterial infections is presented in Table 1.

**Table 1. Summary of the current knowledge about the involvement of immune checkpoints in the course of bacterial infections**

| Pathogen | PD-1/ PD-L1 | TIM-3 | LAG-3 | CTLA-4 | TIGIT | Reference |
|---|---|---|---|---|---|---|
| *Mycobacterium* spp. | • | • | • | | • | Anand et al., 2020; Anidi et al., 2024; Barber et al., 2011; de Castro et al., 2025; Harris et al., 2020; Inada et al., 2025; Ishii et al., 2018; Jayaraman et al., 2016; Kauffman et al., 2021; Liu et al., 2023; Pan et al., 2022, 2024; Phillips et al., 2017; Tarique et al., 2023; Tezera et al., 2020; Yamaba et al., 2022; Zhou et al., 2025 |
| Chlamydiaceae | • | • | | | | Fankhauser and Starnbach, 2014; Li et al., 2023b; Peng et al., 2011; Reinhold-Larsson and Starnbach, 2025; Starkey et al., 2016 |
| *Streptococcus* spp. | • | | • | | | Ma et al., 2023; Manuel et al., 2023; McKay et al., 2015 |
| *Staphylococcus aureus* | • | | | | • | Clegg et al., 2024; Li et al., 2023a; Majer et al., 2023; Patil et al., 2018; Rabe et al., 2014 |
| *Listeria monocytogenes* | • | • | | | | Seo et al., 2008; Wang et al., 2017b, 2020; Xu et al., 2013; Yao et al., 2009 |
| *Brucella* spp. | • | • | | • | | Cui et al., 2017; Durward-Diioia et al., 2015; Guo et al., 2023; Sun et al., 2021 |
| Rickettsiales | • | • | • | | | Dzul-Rosado et al., 2023; Kang et al., 2018; Okagawa et al., 2016; Yang et al., 2016 |
| *Bordetella pertussis* | • | | | | | Hovingh et al., 2017 |
| *Neisseria gonorrhoeae* | • | | | | | Ortiz et al., 2015; Zhu et al., 2012 |
| *Coxiella burnetti* | • | | | | | Ka et al., 2014, 2015 |
| *Pseudomonas aeruginosa* | • | • | | | | Avendano-Ortiz et al., 2019; Luo et al., 2024; Patil et al., 2018; Vega-Carrascal et al., 2014; Zhang et al., 2019 |
| *Haemophilus* spp. | • | | | • | | Kalathil et al., 2014; Kim et al., 2024; Li et al., 2010; Yoshinaga et al., 2025 |
| *Salmonella* spp. | • | • | • | | • | Chopra et al., 2025; McCulloch et al., 2024; Lino et al., 2018; Lopez-Medina et al., 2015; Pfeifhofer-Obermair et al., 2021; Sahler et al., 2018; Yu et al., 2018 |
| *Helicobacter pylori* | • | • | | | | Beswick et al., 2007; Das et al., 2006; Holokai et al., 2019; Koh et al., 2021; Oster et al., 2022; Shatila et al., 2025; Wang et al., 2017a; Yang et al., 2025 |
| Spirochaetaceae | • | • | • | | | Gutierrez-Hoffmann et al., 2023; Helble et al., 2022; Shen et al., 2023 |

## Discussion and future prospects

When exploring the relationship between bacteria colonizing the host and inhibitory immune checkpoints, it becomes evident that most existing literature focuses on their role in cancer immunotherapy and the interaction of ICIs with host microbiome. Indeed, gut microbiota has been identified as a key driver of ICIs efficacy against cancer (reviewed elsewhere, e.g., in Chen et al., 2025, Perl et al., 2025 and Vig and Dubey, 2025). Many studies have also explored how ICIs therapy may lead to bacteria-associated side effects, starting from *Clostridium difficile* infection during ICIs-induced colitis (Vuillamy et al., 2023) through pathogenic colonization of the genitourinary tract and skin (Ross et al., 2022), and ending with the reactivation of latent infections such as tuberculosis (Inada et al., 2025). Despite the extensive research on immune checkpoints in oncology, microbiome interactions, and experimental viral infections, their specific role in bacterial infections has received limited scientific attention.

To understand the potential role of immune checkpoints in bacterial infections, it is important to note that during the coevolution of bacteria and their hosts, the pathogens have evolved several immunity-based strategies that enable them to evade host immunity and establish hidden, long-term, or persistent infection with the host unable to eliminate the pathogen. Persistent antigenic stimulation, observed both in cancer and chronic infections, can lead to progressive T cell exhaustion, characterized by diminished effector functions and the increased expression of inhibitory immune checkpoints. This fact suggests that immune checkpoints may play a crucial role in determining the course of certain bacterial infections and therefore opens the possibility of their therapeutic use in human medicine.

While antibiotics remain the primary treatment for bacterial infections, their effectiveness is not universal – particularly in chronic or biofilm-associated conditions. Identifying strategies to enhance antibiotic treatment effectivity is therefore beneficial. Although some studies have shown that concomitant use of antibiotics reduces the efficacy of ICIs antitumour therapy (Wu et al., 2021), recent evidence suggests that immune checkpoint inhibition in certain conditions may enhance antimicrobial efficacy. For instance, PD-1/PD-L1 blockade significantly improved outcomes in a murine model

of *Staphylococcus aureus* osteomyelitis, acting as a potent adjuvant to antibiotic therapy and promoting bacterial clearance (Li et al., 2023a).

Another promising application of immune checkpoint modulation lies in enhancing vaccine responsiveness. In some healthy individuals, immune responses may be suppressed due to natural background checkpoint expression that can dampen the activation and proliferation of immune cells, resulting in suboptimal immune response following vaccination (Clegg et al., 2024). This pre-exposure immunosuppression can potentially be overcome through the administration of immune checkpoint inhibitor prior to vaccination.

In the discussion of using ICIs as immunomodulatory tools in human medicine, it is necessary to consider the potential risks associated with off-target effects of conventional ICIs, given the broad functional roles that checkpoints play in the body. However, evidence suggests that certain immune checkpoints may be pathogen specific. For instance, CD84 has been identified as a putative tuberculosis-specific inhibitory receptor (Zheng et al., 2022). The discovery of new, infection-specific checkpoints may bring fresh impetus to the treatment of chronic infections.

The potential of immune checkpoints and ICIs extends beyond immune modulation. Soluble immune checkpoints, which are elevated during infectious states like tuberculosis and bacterial sepsis, correlate with common laboratory markers and treatment responses. Moreover, elevated serum concentrations of some soluble inhibitory immune checkpoints correlate with higher mortality in bacterial sepsis. Taken together, certain soluble immune checkpoints may serve as potential biomarkers for disease surveillance and prognosis (Chen et al., 2022; Mearelli et al., 2025).

## Conclusion

Thanks to extensive global testing of anticancer drugs, we have a large amount of data on ICIs, which could also be transferred to other areas of human medicine – although we are aware of the challenges posed by the application of ICIs. In addition, there are many infections whose relationship to immune checkpoints remains poorly understood or unexplored. Taken together, modulation of immune response via immune checkpoints can be an emerging tool for the improvement of diagnosis, therapy, and determining the prognosis of important human infections. For this reason, we believe that future research should be directed towards this area.

### *Author contributions*

*H. Langhansová* conceived and designed the study. All authors performed the literature search. The first draft of the manuscript was written by *H. Langhansová* and *A. Palounková*, the figure was designed by *A. Kovaříková* and *A. Palounková*. All authors edited several drafts of the manuscript and read and approved the final version.

### *Acknowledgements*

The authors used AI-based tools (DeepL and Copilot) exclusively for language and stylistic editing. All intellectual content, interpretations, and conclusions are the sole responsibility of the authors. No copyrighted material was used.

### *Funding*

This work was supported by the Ministry of Health of the Czech Republic in cooperation with the Czech Health Research Council under project No. NU23-05-00302. The funder had no direct involvement in the study design, data collection and interpretation, or manuscript preparation.

### *Ethical aspects and conflict of interest*

The authors have no conflict of interest to declare.

## References

Anand K, Sahu G, Burns E, Ensor A, Ensor J, Pingali SR, et al. (2020). Mycobacterial infections due to PD-1 and PD-L1 checkpoint inhibitors. ESMO Open 5(4): e000866. DOI: 10.1136/esmoopen-2020-000866.

Anidi IU, Sakai S, Brooks K, Fling SP, Wagner MJ, Lurain K, et al. (2024). Exacerbation of CMV and Nontuberculous Mycobacterial Infections Following PD-1 Blockade for HIV-Associated Kaposi Sarcoma. Open Forum Infect Dis 11(5): ofae183. DOI: 10.1093/ofid/ofae183.

Avendano-Ortiz J, Llanos-Gonzalez E, Toledano V, Del Campo R, Cubillos-Zapata C, Lozano-Rodriguez R, et al. (2019). *Pseudomonas aeruginosa* colonization causes PD-L1 overexpression on monocytes, impairing the adaptive immune response in patients with cystic fibrosis. J Cyst Fibros 18(5): 630–635. DOI: 10.1016/j.jcf.2018.11.002.

Barber DL, Mayer-Barber KD, Feng CG, Sharpe AH, Sher A (2011). CD4 T cells promote rather than control tuberculosis in the absence of PD-1-mediated inhibition. J Immunol 186(3): 1598–1607. DOI: 10.4049/jimmunol.1003304.

Berg M, Zavazava N (2008). Regulation of CD28 expression on CD8+ T cells by CTLA-4. J Leukoc Biol 83(4): 853–863. DOI: 10.1189/jlb.0107065.

Beswick EJ, Pinchuk IV, Das S, Powell DW, Reyes VE (2007). Expression of the programmed death ligand 1, B7-H1, on gastric epithelial cells after *Helicobacter pylori* exposure promotes development of CD4+ CD25+ FoxP3+ regulatory T cells. Infect Immun 75(9): 4334–4341. DOI: 10.1128/IAI.00553-07.

Chen H, Zhou J, Zhao X, Liu Q, Shao L, Zhu Y, Ou Q (2022). Characterization of multiple soluble immune checkpoints in individuals with different *Mycobacterium tuberculosis* infection status and dynamic changes during anti-tuberculosis treatment. BMC Infect Dis 22(1): 543. DOI: 10.1186/s12879-022-07506-z.

Chen L, Li B, Zu M, Reis RL, Kundu SC, Xiao B (2025). Advances and mechanisms of gut microbiota modulation in enhancing immune checkpoint inhibitor efficacy. Semin Cancer Biol 114: 150–172. DOI: 10.1016/j.semcancer.2025.06.012.

Chopra U, Sabu MK, Rajmani RS, Chaudhary AD, Gupta SK, Chakravortty D (2025). *Salmonella* Effector SseL Induces Programmed Death Ligand 1 Upregulation and T-Cell Inactivation via the beta-Catenin Signaling Axis. J Infect Dis 232(2): 401–411. DOI: 10.1093/infdis/jiaf131.

Clegg J, Mnich ME, Carignano A, Cova G, Tavarini S, Sammicheli C, et al. (2024). *Staphylococcus aureus*-specific TIGIT(+) Treg are present in the blood of healthy subjects – a hurdle for vaccination? Front Immunol 15: 1500696. DOI: 10.3389/fimmu.2024.1500696.

Cui B, Liu W, Wang X, Chen Y, Du Q, Zhao X, et al. (2017). *Brucella* Omp25 Upregulates miR-155, miR-21-5p, and miR-23b to Inhibit Interleukin-12 Production via Modulation of Programmed Death-1 Signaling in Human Monocyte/Macrophages. Front Immunol 8: 708. DOI: 10.3389/fimmu.2017.00708.

Das S, Suarez G, Beswick EJ, Sierra JC, Graham DY, Reyes VE (2006). Expression of B7-H1 on gastric epithelial cells: its potential role in regulating T cells during *Helicobacter pylori* infection. J Immunol 176(5): 3000–3009. DOI: 10.4049/jimmunol.176.5.3000.

De Castro KKG, Da Silva PHL, Lara FA, Mendes MA, Leal-Calvo T, Leal JMP, et al. (2025). The role of cell exhaustion in lepromatous leprosy. J Immunol 214(7): 1517–1528. DOI: 10.1093/jimmun/vkaf056.

Durward-Diioia M, Harms J, Khan M, Hall C, Smith JA, Splitter GA (2015). CD8+ T cell exhaustion, suppressed gamma interferon

production, and delayed memory response induced by chronic *Brucella melitensis* infection. Infect Immun 83(12): 4759–4771. DOI: 10.1128/IAI.01184-15.

Dzul-Rosado K, Donis-Maturano L, Arias-Leon J, Machado-Contreras J, Valencia-Pacheco G, Panti-Balam C, et al. (2023). *Rickettsia* Vaccine Candidate pVAX1-OmpB24 Stimulates TCD4+INF-gamma+ and TCD8+INF-gamma+ Lymphocytes in Autologous Co-Culture of Human Cells. Vaccines (Basel) 11(1): 173. DOI: 10.3390/vaccines11010173.

Fankhauser SC, Starnbach MN (2014). PD-L1 limits the mucosal CD8+ T cell response to *Chlamydia trachomatis*. J Immunol 192(3): 1079–1090. DOI: 10.4049/jimmunol.1301657.

Francisco LM, Salinas VH, Brown KE, Vanguri VK, Freeman GJ, Kuchroo VK, Sharpe AH (2009). PD-L1 regulates the development, maintenance, and function of induced regulatory T cells. J Exp Med 206(13): 3015–3029. DOI: 10.1084/jem.20090847.

Gorman JV, Colgan JD (2014). Regulation of T cell responses by the receptor molecule Tim-3. Immunol Res 59(1–3): 56–65. DOI: 10.1007/s12026-014-8524-1.

Guo WH, Zhu YJ, Haimiti G, Xie XR, Niu C, Li M, et al. (2023). Bioinformatics-based design of a fusion vaccine with CTLA-4 variable region to combat *Brucella*. Braz J Med Biol Res 56: e12938. DOI: 10.1590/1414-431X2023e12938.

Gutierrez-Hoffmann M, Fan J, O'Meally RN, Cole RN, Florea L, Antonescu C, et al. (2023). The Interaction of *Borrelia burgdorferi* with Human Dendritic Cells: Functional Implications. J Immunol 211(4): 612–625. DOI: 10.4049/jimmunol.2300235.

Harris LD, Khayumbi J, Ongalo J, Sasser LE, Tonui J, Campbell A, et al. (2020). Distinct Human NK Cell Phenotypes and Functional Responses to *Mycobacterium tuberculosis* in Adults From TB Endemic and Non-endemic Regions. Front Cell Infect Microbiol 10: 120. DOI: 10.3389/fcimb.2020.00120.

Helble JD, Mccarthy JE, Sawden M, Starnbach MN, Hu LT (2022). The PD-1/PD-L1 pathway is induced during *Borrelia burgdorferi* infection and inhibits T cell joint infiltration without compromising bacterial clearance. PLoS Pathog 18(10): e1010903. DOI: 10.1371/journal.ppat.1010903.

Holokai L, Chakrabarti J, Broda T, Chang J, Hawkins JA, Sundaram N, et al. (2019). Increased Programmed Death-Ligand 1 is an Early Epithelial Cell Response to *Helicobacter pylori* Infection. PLoS Pathog 15(1): e1007468. DOI: 10.1371/journal.ppat.1007468.

Hovingh ES, Van Gent M, Hamstra HJ, Demkes M, Mooi FR, Pinelli E (2017). Emerging *Bordetella pertussis* Strains Induce Enhanced Signaling of Human Pattern Recognition Receptors TLR2, NOD2 and Secretion of IL-10 by Dendritic Cells. PLoS One 12(1): e0170027. DOI: 10.1371/journal.pone.0170027.

Huard B, Mastrangeli R, Prigent P, Bruniquel D, Donini S, El-Tayar N, et al. (1997). Characterization of the major histocompatibility complex class II binding site on LAG-3 protein. Proc Natl Acad Sci U S A 94: 5744–5749. DOI: 10.1073/pnas.94.11.5744.

Inada S, Omori K, Nomura T, Kitagawa H, Shigemoto N, Hattori N, Ohge H (2025). Non-tuberculous mycobacterial shoulder arthritis with acute exacerbation soon after initiation of immune checkpoint inhibitor: A case report. J Infect Chemother 31(3): 102596. DOI: 10.1016/j.jiac.2024.102596.

Ishii S, Tamiya A, Taniguchi Y, Tanaka T, Abe Y, Isa SI, et al. (2018). Improvement of *Mycobacterium abscessus* Pulmonary Disease after Nivolumab Administration in a Patient with Advanced Non-small Cell Lung Cancer. Intern Med 57(24): 3625–3629. DOI: 10.2169/internalmedicine.1195-18.

Jayaraman P, Jacques MK, Zhu C, Steblenko KM, Stowell BL, Madi A, et al. (2016). TIM3 Mediates T Cell Exhaustion during *Mycobacterium tuberculosis* Infection. PLoS Pathog 12(3): e1005490. DOI: 10.1371/journal.ppat.1005490.

Joseph J, Rahmani B, Cole Y, Puttagunta N, Lin E, Khan ZK, Jain P (2022). Can Soluble Immune Checkpoint Molecules on Exosomes Mediate Inflammation? J Neuroimmune Pharmacol 17(3–4): 381–397. DOI: 10.1007/s11481-021-10018-3.

Ka MB, Bechah Y, Olive D, Mege JL (2015). Programmed death ligand-1 expression and memory T-cell generation in *Coxiella burnetii* infection. Microb Pathog 80: 1–6. DOI: 10.1016/j.micpath.2015.02.002.

Ka MB, Gondois-Rey F, Capo C, Textoris J, Million M, Raoult D, et al. (2014). Imbalance of circulating monocyte subsets and PD-1 dysregulation in Q fever endocarditis: the role of IL-10 in PD-1 modulation. PLoS One 9(9): e107533. DOI: 10.1371/journal.pone.0107533.

Kalathil SG, Lugade AA, Pradhan V, Miller A, Parameswaran GI, Sethi S, Thanavala Y (2014). T-regulatory cells and programmed death 1+ T cells contribute to effector T-cell dysfunction in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 190(1): 40–50. DOI: 10.1164/rccm.201312-2293OC.

Kang SJ, Jin HM, Cho YN, Oh TH, Kim SE, Kim UJ, et al. (2018). Dysfunction of Circulating Natural Killer T Cells in Patients With Scrub Typhus. J Infect Dis 218(11): 1813–1821. DOI: 10.1093/infdis/jiy402.

Kauffman KD, Sakai S, Lora NE, Namasivayam S, Baker PJ, Kamenyeva O, et al. (2021). PD-1 blockade exacerbates *Mycobacterium tuberculosis* infection in rhesus macaques. Sci Immunol 6(55): eabf3861. DOI: 10.1126/sciimmunol.abf3861.

Kim YH, Park MR, Kim SY, Kim MJ, Kim KW, Sohn MH (2024). Respiratory Microbiome Profiles Are Associated With Distinct Inflammatory Phenotype and Lung Function in Children With Asthma. J Investig Allergol Clin Immunol 34(4): 246–256. DOI: 10.18176/jiaci.0918.

Koh V, Chakrabarti J, Torvund M, Steele N, Hawkins JA, Ito Y, et al. (2021). Hedgehog transcriptional effector GLI mediates mTOR-Induced PD-L1 expression in gastric cancer organoids. Cancer Lett 518: 59–71. DOI: 10.1016/j.canlet.2021.06.007.

Kovaříková A (2025). Inhibitory immune checkpoints in immunological synapse. Eur J Clin Microbiol Infect Dis [online] [cit. 2026-01-22]. Available from: https://BioRender.com/057g9hl

Lee JB, Kim HR, Ha SJ (2022). Immune Checkpoint Inhibitors in 10 Years: Contribution of Basic Research and Clinical Application in Cancer Immunotherapy. Immune Netw 22(1): e2. DOI: 10.4110/in.2022.22.e2.

Li K, Chen Y, Lin Y, Zhang G, Su J, Wu X, et al. (2023a). PD-1/PD-L1 blockade is a potent adjuvant in treatment of *Staphylococcus aureus* osteomyelitis in mice. Mol Ther 31(1): 174–192. DOI: 10.1016/j.ymthe.2022.09.006.

Li W, Tenner-Racz K, Racz P, Janowicz DM, Fortney KR, Katz BP, Spinola SM (2010). Role played by CD4+FOXP3+ regulatory T Cells in suppression of host responses to *Haemophilus ducreyi* during experimental infection of human volunteers. J Infect Dis 201(12): 1839–1848. DOI: 10.1086/652781.

Li Z, Wang Y, Zheng K, Lu X, He Z, He S, et al. (2023b). Tim-3 blockade enhances the clearance of *Chlamydia psittaci* in the lung by promoting a cell-mediated immune response. Int Immunopharmacol 116: 109780. DOI: 10.1016/j.intimp.2023.109780.

Lino AC, Dang VD, Lampropoulou V, Welle A, Joedicke J, Pohar J, et al. (2018). LAG-3 Inhibitory Receptor Expression Identifies Immunosuppressive Natural Regulatory Plasma Cells. Immunity 49(1): 120–133.e9. DOI: 10.1016/j.immuni.2018.06.007.

Liu L, Song Z, Xun J, Liu D, Wei J, Wang Z, et al. (2023). PD-1 Inhibitor for Disseminated *Mycobacterium avium* Infection in a Person With HIV. Open Forum Infect Dis 10(1): ofac700. DOI: 10.1093/ofid/ofac700.

Lopez-Medina M, Perez-Lopez A, Alpuche-Aranda C, Ortiz-Navarrete V (2015). *Salmonella* induces PD-L1 expression in B cells. Immunol Lett 167(2): 131–140. DOI: 10.1016/j.imlet.2015.08.004.

Luo L, Jiang M, Xiong Y, Xiong A, Zhang L, Wu D, et al. (2024). Fine particulate matter 2.5 induces susceptibility to *Pseudomonas aeruginosa* infection via expansion of PD-L1(high) neutrophils in mice. Respir Res 25(1): 90. DOI: 10.1186/s12931-023-02640-x.

Ma C, Zhang Y, Lei J, Zhang J, Li F, He X, et al. (2023). Programmed Cell Death Protein 1/Programmed Cell Death Ligand 1 Signaling Pathway Mediated Interleukin-10 and Bacterial Biofilm Formation to Drug Resistance Mechanism of Pneumoniae Meningitis. Cell Mol Biol (Noisy-le-grand) 69(4): 105–111. DOI: 10.14715/cmb/2023.69.4.16.

Majer C, Lingel H, Arra A, Heuft HG, Bretschneider D, Balk S, et al. (2023). PD-1/PD-L1 Control of Antigen-Specifically Activated

CD4 T-Cells of Neonates. Int J Mol Sci 24(6): 5662. DOI: 10.3390/ijms24065662.

Manuel G, Coleman M, Orvis AS, Munson J, Li A, Kapur RP, et al. (2023). Spatial profiling of the placental chorioamniotic membranes reveals upregulation of immune checkpoint proteins during Group B *Streptococcus* infection in a nonhuman primate model. Front Cell Infect Microbiol 13: 1299644. DOI: 10.3389/fcimb.2023.1299644.

McCulloch TR, Rossi GR, Miranda-Hernandez S, Valencia-Hernandez AM, Alim L, Belle CJ, et al. (2024). The immune checkpoint TIGIT is upregulated on T cells during bacterial infection and is a potential target for immunotherapy. Immunol Cell Biol 102(8): 721–733. DOI: 10.1111/imcb.12794.

McKay JT, Egan RP, Yammani RD, Chen L, Shin T, Yagita H, Haas KM (2015). PD-1 suppresses protective immunity to *Streptococcus pneumoniae* through a B cell-intrinsic mechanism. J Immunol 194(5): 2289–2299. DOI: 10.4049/jimmunol.1401673.

Mearelli F, Nunnari A, Rombini A, Chitti F, Spagnol F, Casarsa C, et al. (2025). Inhibitory Immune Checkpoints Predict 7-Day, In-Hospital, and 1-Year Mortality of Internal Medicine Patients Admitted With Bacterial Sepsis. J Infect Dis 231(3): 706–715. DOI: 10.1093/infdis/jiae370.

Okagawa T, Konnai S, Deringer JR, Ueti MW, Scoles GA, Murata S, et al. (2016). Cooperation of PD-1 and LAG-3 Contributes to T-Cell Exhaustion in *Anaplasma marginale*-Infected Cattle. Infect Immun 84(10): 2779–2790. DOI: 10.1128/IAI.00278-16.

Ortiz MC, Lefimil C, Rodas PI, Vernal R, Lopez M, Acuna-Castillo C, et al. (2015). *Neisseria gonorrhoeae* Modulates Immunity by Polarizing Human Macrophages to a M2 Profile. PLoS One 10(6): e0130713. DOI: 10.1371/journal.pone.0130713.

Oster P, Vaillant L, Riva E, Mcmillan B, Begka C, Truntzer C, et al. (2022). *Helicobacter pylori* infection has a detrimental impact on the efficacy of cancer immunotherapies. Gut 71(3): 457–466. DOI: 10.1136/gutjnl-2020-323392.

Paludan SR, Pradeu T, Masters SL, Mogensen TH (2021). Constitutive immune mechanisms: mediators of host defence and immune regulation. Nat Rev Immunol 21(3): 137–150. DOI: 10.1038/s41577-020-0391-5.

Pan SW, Shu CC, Huang JR, Lee CC, Tseng YH, Hung JJ, et al. (2022). PD-L1 Expression in Monocytes Correlates with Bacterial Burden and Treatment Outcomes in Active Pulmonary Tuberculosis. Int J Mol Sci 23(3): 1619. DOI: 10.3390/ijms23031619.

Pan Y, Yao Z, Huang L, Xu M, Chen R, Li D, et al. (2024). Overexpression of LAG-3: a potential indicator of low immune function in tuberculosis. Front Cell Infect Microbiol 14: 1410015. DOI: 10.3389/fcimb.2024.1410015.

Patil NK, Luan L, Bohannon JK, Hernandez A, Guo Y, Sherwood ER (2018). Frontline Science: Anti-PD-L1 protects against infection with common bacterial pathogens after burn injury. J Leukoc Biol 103(1): 23–33. DOI: 10.1002/JLB.5HI0917-360R.

Pauken KE, Wherry EJ (2015). Overcoming T cell exhaustion in infection and cancer. Trends Immunol 36(4): 265–276. DOI: 10.1016/j.it.2015.02.008.

Peng B, Lu C, Tang L, Yeh IT, He Z, Wu Y, Zhong G (2011). Enhanced upper genital tract pathologies by blocking Tim-3 and PD-L1 signaling pathways in mice intravaginally infected with *Chlamydia muridarum*. BMC Infect Dis 11: 347. DOI: 10.1186/1471-2334-11-347.

Perl M, Fante MA, Herfeld K, Scherer JN, Poeck H, Thiele Orberg E (2025). Microbiota-derived metabolites: Key modulators of cancer immunotherapies. Med 6(8): 100773. DOI: 10.1016/j.medj.2025.100773.

Pfeifhofer-Obermair C, Tymoszuk P, Nairz M, Schroll A, Klais G, Demetz E, et al. (2021). Regulation of Th1 T Cell Differentiation by Iron via Upregulation of T Cell Immunoglobulin and Mucin Containing Protein-3 (TIM-3). Front Immunol 12: 637809. DOI: 10.3389/fimmu.2021.637809.

Phillips BL, Gautam US, Bucsan AN, Foreman TW, Golden NA, Niu T, et al. (2017). LAG-3 potentiates the survival of *Mycobacterium tuberculosis* in host phagocytes by modulating mitochondrial signaling in an *in-vitro* granuloma model. PLoS One 12(9): e0180413. DOI: 10.1371/journal.pone.0180413.

Pitts SC, Schlom J, Donahue RN (2024). Soluble immune checkpoints: implications for cancer prognosis and response to immune checkpoint therapy and conventional therapies. J Exp Clin Cancer Res 43(1): 155. DOI: 10.1186/s13046-024-03074-z.

Rabe H, Nordstrom I, Andersson K, Lundell AC, Rudin A (2014). *Staphylococcus aureus* convert neonatal conventional CD4(+) T cells into FOXP3(+) CD25(+) CD127(low) T cells via the PD-1/PD-L1 axis. Immunology 141(3): 467–481. DOI: 10.1111/imm.12209.

Reinhold-Larsson NV, Starnbach MN (2025). Type I IFNs contribute to upregulation of PD-L1 during *Chlamydia trachomatis* infection. Infect Immun 93(4): e0004025. DOI: 10.1128/iai.00040-25.

Robert C, Thomas L, Bondarenko I, O'Day S, Weber J, Garbe C, et al. (2011). Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. N Engl J Med 364(26): 2517–2526. DOI: 10.1056/NEJMoa1104621.

Ross JA, Komoda K, Pal S, Dickter J, Salgia R, Dadwal S (2022). Infectious complications of immune checkpoint inhibitors in solid organ malignancies. Cancer Med 11(1): 21–27. DOI: 10.1002/cam4.4393.

Sahler JM, Eade CR, Altier C, March JC (2018). *Salmonella enterica* Serovar Typhimurium Increases Functional PD-L1 Synergistically with Gamma Interferon in Intestinal Epithelial Cells via *Salmonella* Pathogenicity Island 2. Infect Immun 86(5): e00674-17. DOI: 10.1128/IAI.00674-17.

Sampedro-Nunez M, Serrano-Somavilla A, Adrados M, Cameselle-Teijeiro JM, Blanco-Carrera C, Cabezas-Agricola JM, et al. (2018). Analysis of expression of the PD-1/PD-L1 immune checkpoint system and its prognostic impact in gastroenteropancreatic neuroendocrine tumors. Sci Rep 8(1): 17812. DOI: 10.1038/s41598-018-36129-1.

Seo SK, Jeong HY, Park SG, Lee SW, Choi IW, Chen L, Choi I (2008). Blockade of endogenous B7-H1 suppresses antibacterial protection after primary *Listeria monocytogenes* infection. Immunology 123(1): 90–99. DOI: 10.1111/j.1365-2567.2007.02708.x.

Shatila M, Sperling G, Machado AP, Vohra M, Baerman E, Toni EN, et al. (2025). *Helicobacter pylori* infection negatively affects response of gastric cancer to immunotherapy. Ann Gastroenterol 38(3): 262–269. DOI: 10.20524/aog.2025.0966.

Shen F, Shen Y, Xu Y, Zhao J, Zhao Z, Liu J, Ge Y (2023). Dysregulation of circulating T follicular helper cell subsets and their potential role in the pathogenesis of syphilis. Front Immunol 14: 1264508. DOI: 10.3389/fimmu.2023.1264508.

Starkey MR, Nguyen DH, Brown AC, Essilfie AT, Kim RY, Yagita H, et al. (2016). Programmed Death Ligand 1 Promotes Early-Life *Chlamydia* Respiratory Infection-Induced Severe Allergic Airway Disease. Am J Respir Cell Mol Biol 54(4): 493–503. DOI: 10.1165/rcmb.2015-0204OC.

Sun HL, Du XF, Tang YX, Li GQ, Yang SY, Wang LH, et al. (2021). Impact of immune checkpoint molecules on FoxP3(+) Treg cells and related cytokines in patients with acute and chronic brucellosis. BMC Infect Dis 21(1): 1025. DOI: 10.1186/s12879-021-06730-3.

Tang W, Chen J, Ji T, Cong X (2023). TIGIT, a novel immune checkpoint therapy for melanoma. Cell Death Dis 14(7): 466. DOI: 10.1038/s41419-023-05961-3.

Tarique M, Naz H, Suhail M, Turan A, Saini C, Muhammad N, et al. (2023). Differential expression of programmed death 1 (PD-1) on various immune cells and its role in human leprosy. Front Immunol 14: 1138145. DOI: 10.3389/fimmu.2023.1138145.

Tezera LB, Bielecka MK, Ogongo P, Walker NF, Ellis M, Garay-Baquero DJ, et al. (2020). Anti-PD-1 immunotherapy leads to tuberculosis reactivation via dysregulation of TNF-alpha. Elife 9: e52668. DOI: 10.7554/eLife.52668.

Vega-Carrascal I, Bergin DA, Mcelvaney OJ, Mccarthy C, Banville N, Pohl K, et al. (2014). Galectin-9 signaling through TIM-3 is involved in neutrophil-mediated Gram-negative bacterial killing: an effect abrogated within the cystic fibrosis lung. J Immunol 192(5): 2418–2431. DOI: 10.4049/jimmunol.1300711.

Vig M, Dubey S (2025). Gut microbiome and tumor immunotherapy. Int Rev Cell Mol Biol 394: 147–170. DOI: 10.1016/bs.ircmb.2024.12.014.

Vuillamy C, Arnault JP, Fumery M, Mortier L, Monestier S, Mansard S, et al. (2023). *Clostridium difficile* infection and immune checkpoint inhibitor-induced colitis in melanoma: 18 cases and a review of the literature. Melanoma Res 33(3): 192–198. DOI: 10.1097/CMR.0000000000000878.

Wang F, Mao Z, Liu D, Yu J, Wang Y, Ye W, et al. (2017a). Overexpression of Tim-3 reduces *Helicobacter pylori*-associated inflammation through TLR4/NFkappaB signaling *in vitro*. Mol Med Rep 15(5): 3252–3258. DOI: 10.3892/mmr.2017.6346.

Wang Z, Li G, Dou S, Zhang Y, Liu Y, Zhang J, et al. (2020). Tim-3 Promotes *Listeria monocytogenes* Immune Evasion by Suppressing Major Histocompatibility Complex Class I. J Infect Dis 221(5): 830–840. DOI: 10.1093/infdis/jiz512.

Wang Z, Sun D, Chen G, Li G, Dou S, Wang R, et al. (2017b). Tim-3 inhibits macrophage control of *Listeria monocytogenes* by inhibiting Nrf2. Sci Rep 7: 42095. DOI: 10.1038/srep42095.

Wolf Y, Anderson AC, Kuchroo VK (2020). TIM3 comes of age as an inhibitory receptor. Nat Rev Immunol 20(3): 173–185. DOI: 10.1038/s41577-019-0224-6.

Wolchok JD, Chiarion-Sileni V, Gonzalez R, Grob JJ, Rutkowski P, Lao CD, et al. (2022). Long-Term Outcomes With Nivolumab Plus Ipilimumab or Nivolumab Alone Versus Ipilimumab in Patients With Advanced Melanoma. J Clin Oncol 40(2): 127–137. DOI: 10.1200/JCO.21.02229.

Wu Q, Liu J, Wu S, Xie X (2021). The impact of antibiotics on efficacy of immune checkpoint inhibitors in malignancies: A study based on 44 cohorts. Int Immunopharmacol 92: 107303. DOI: 10.1016/j.intimp.2020.107303.

Xu D, Fu HH, Obar JJ, Park JJ, Tamada K, Yagita H, Lefrançois L (2013). A potential new pathway for PD-L1 costimulation of the CD8-T cell response to *Listeria monocytogenes* infection. PLoS One 8(2): e56539. DOI: 10.1371/journal.pone.0056539.

Yamaba Y, Takakuwa O, Tomita Y, Owaki S, Yamada K, Kunii E, et al. (2022). *Mycobacterium avium* complex lung disease in a patient treated with an immune checkpoint inhibitor: A case report. Mol Clin Oncol 16(2): 37. DOI: 10.3892/mco.2021.2470.

Yang HC, Fu CF, Qiao LJ, Long GH, Yang LF, Yao B (2025). Relationship between *Helicobacter pylori* infection and programmed death-ligand 1 in gastric cancer: A meta-analysis. World J Clin Oncol 16(4): 102397. DOI: 10.5306/wjco.v16.i4.102397.

Yang X, Jiao J, Han G, Gong W, Wang P, Xiong X, Wen B (2016). Enhanced Expression of T-Cell Immunoglobulin and Mucin Domain Protein 3 in Endothelial Cells Facilitates Intracellular Killing of *Rickettsia heilongjiangensis*. J Infect Dis 213(1): 71–79. DOI: 10.1093/infdis/jiv463.

Yao S, Wang S, Zhu Y, Luo L, Zhu G, Flies S, et al. (2009). PD-1 on dendritic cells impedes innate immunity against bacterial infection. Blood 113(23): 5811–5818. DOI: 10.1182/blood-2009-02-203141.

Yoshinaga K, Hirano T, Umemoto S, Kadowaki Y, Matsunaga T, Suzuki M (2025). Effect of Anti-Programmed Cell Death-1 Antibody on Middle Ear Mucosal Immune Response to Intranasal Administration of *Haemophilus influenzae* Outer Membrane Protein. Vaccines (Basel) 13(3): 313. DOI: 10.3390/vaccines13030313.

Yu X, Zhang H, Yu L, Liu M, Zuo Z, Han Q, et al. (2018). Intestinal Lamina Propria CD4(+) T Cells Promote Bactericidal Activity of Macrophages via Galectin-9 and Tim-3 Interaction during *Salmonella enterica* Serovar Typhimurium Infection. Infect Immun 86(8): e00769-17. DOI: 10.1128/IAI.00769-17.

Zhang H, Chen C, He J, Zhang J, Liu Z, Sun T (2019). Anti-PD-1 Antibody Administration following Hip Fracture Surgery Reverses Immune Dysfunction and Decreases Susceptibility to Infection. Mediators Inflamm 2019: 8492090. DOI: 10.1155/2019/8492090.

Zheng N, Fleming J, Hu P, Jiao J, Zhang G, Yang R, et al. (2022). CD84 is a Suppressor of T and B Cell Activation during *Mycobacterium tuberculosis* Pathogenesis. Microbiol Spectr 10(1): e0155721. DOI: 10.1128/spectrum.01557-21.

Zhou J, Yang Q, Xu H, Chen H, Jiang N, Ou Q, et al. (2025). TIGIT blockade improves anti-*Mycobacterium tuberculosis* immunity. PLoS Pathog 21(6): e1013228. DOI: 10.1371/journal.ppat.1013228.

Zhu W, Ventevogel MS, Knilans KJ, Anderson JE, Oldach LM, Mckinnon KP, et al. (2012). *Neisseria gonorrhoeae* suppresses dendritic cell-induced, antigen-dependent CD4 T cell proliferation. PLoS One 7(7): e41260. DOI: 10.1371/journal.pone.0041260.