Clinical & Translational Immunology

Australian and New Zealand Society for Immunology Inc.

Clinical & Translational Immunology 2025; **14**: e70055. doi: 10.1002/cti2.70055
www.wileyonlinelibrary.com/journal/cti

REVIEW

T-cell subsets in *Pneumocystis* pneumonia

Yuxi Chen[1,a], Hengmo Rong[2,a], Ting Li[2], Chao Zhang[2], Huqin Yang[2], Han Sun[2], Dong Wang[2], Xiaoxia Zhou[2,3], Kan Zhai[2] & Zhaohui Tong[1,2]

1 Department of Critical Care Medicine, Zhongnan Hospital of Wuhan University, Wuhan, China
2 Department of Respiratory and Critical Care Medicine, Beijing Institute of Respiratory Medicine and Beijing Chao-Yang Hospital, Capital Medical University, Beijing, China
3 Department of General Medicine, Fu Xing Hospital, Capital Medical University, Beijing, China

Correspondence
K Zhai, Department of Respiratory and Critical Care Medicine, Beijing Institute of Respiratory Medicine and Beijing Chao-Yang Hospital, Capital Medical University, Beijing 100020, China.
E-mails: zhaikan@ccmu.edu.cn

Z Tong, Department of Critical Care Medicine, Zhongnan Hospital of Wuhan University, Wuhan 430000, China; Department of Respiratory and Critical Care Medicine, Beijing Institute of Respiratory Medicine and Beijing Chao-Yang Hospital, Capital Medical University, Beijing 100020, China.
E-mail: tongzhaohuicy@sina.com

[a]Equal contributors.

Received 26 May 2025;
Revised 2 October 2025;
Accepted 10 October 2025

doi: 10.1002/cti2.70055

Clinical & Translational Immunology
2025; **14**: e70055

Abstract

Pneumocystis pneumonia (PCP), caused by the opportunistic fungal pathogen *Pneumocystis*, remains a common fungal infection among immunosuppressed individuals. T cells are known to play a critical role in host defences against *Pneumocystis*. Two functional groups of T cells exist: $CD4^+$ T and $CD8^+$ T. Distinct subsets of $CD4^+$ and $CD8^+$ T cells have been shown to participate in PCP development through specific cytokines and interactions with other immune cells, significantly influencing the pulmonary fungal burden and disease severity. However, the host T-cell responses required for an effective adaptive immune response to PCP remain incompletely defined. In this review, we explore how an in-depth understanding of the integrated and well-defined functions of different T-cell subsets in the immune defence against *Pneumocystis* could provide insights into facilitating the development of anti-*Pneumocystis* treatment.

Keywords: Adaptive immune response, $CD4^+$ T cells, $CD8^+$ T cells, *Pneumocystis* pneumonia

Pneumocystis was thought to be a protozoan for approximately a century; however, it was reclassified as a fungus in 1988.[1] Despite this reclassification, the species' obligate dependence on the mammalian lung environment makes it difficult to cultivate *in vitro*, hindering research into its biology and treatment strategies.[2] As an opportunistic fungus, *Pneumocystis* can cause lethal pneumonia, particularly in individuals with compromised immune systems,[3] including those with congenital or acquired immunodeficiencies, such as human immunodeficiency virus (HIV),[4] and non-HIV individuals undergoing immunosuppressive therapies.[5–7] According to global burden research, *Pneumocystis* pneumonia (PCP) causes approximately 505 000 illnesses and 214 000 deaths worldwide per year.[8] Importantly, *Pneumocystis* is now recognised as one of the most common invasive fungal infections in infants worldwide,[9,10] as highlighted by the landmark Pediatric Emergency Research Network study.[11] The clinical symptoms of PCP are nonspecific and

commonly include dry cough, low-grade fever, progressive dyspnoea and chest pain.[12] *Pneumocystis jirovecii* remains to be a prevalent opportunistic pathogen, especially among immunocompromised individuals.

In immunocompromised individuals with PCP, there is a substantial reduction in T cells and B cells in the lungs, contrasting with the more robust immune cell presence in immunocompetent individuals; however, the proportion of myeloid cells remains relatively stable in these compromised hosts.[13] Innate immune cells, such as antigen-presenting cells, serve as the first line of defence and contribute to T-cell priming in response to *Pneumocystis*.[14] Over the past two decades, T cells have emerged as central players in PCP pathogenesis, acting as both drivers and regulators of the immune response.[14,15] Peripheral $CD4^+$ T cell counts are now routinely used to stratify infection risk in HIV-positive patients.[16–18] It was observed that the percentage of T cells gradually increased in the lungs during *Pneumocystis* infection.[19,20] We previously delineated the dynamic landscape of the host immune environment in *Pneumocystis*-infected mice from 0 to 5 weeks, revealing that T cells consistently represent one of the most predominant immune cell populations in the lungs.[21] A subsequent study has confirmed that pre-depletion of $CD4^+$ and $CD8^+$ T cells effectively prevents respiratory dysfunction and mortality in mice with PCP, even during progressive lung infection.[22] Our findings revealed that clonal $CD4^+$ T cells, characterised by elevated T-cell activation-related gene expression, constitute the primary responders to *Pneumocystis* infection. Additionally, a reduction in T-cell receptor (TCR) diversity among $CD4^+$ T cells and an increase in $CD8^+$ T-cell diversity have been observed in *Pneumocystis*-infected mice.[23] These findings underscore the critical role of T cells in orchestrating the immune response to *Pneumocystis* infection and highlight their potential as therapeutic targets.

T-cell heterogeneity has been shown to significantly influence disease progression and severity.[24,25] $CD4^+$ T cells have been extensively studied in the context of T-cell-mediated adaptive immunity to PCP, whereas fewer investigations have been conducted on the role of $CD8^+$ T cells.[26–30] This review focuses on the role of αβ T-cell subsets as evidenced in recent studies and summarises their central functions in adaptive immunity against *Pneumocystis* infection (Figure 1 and Table 1).

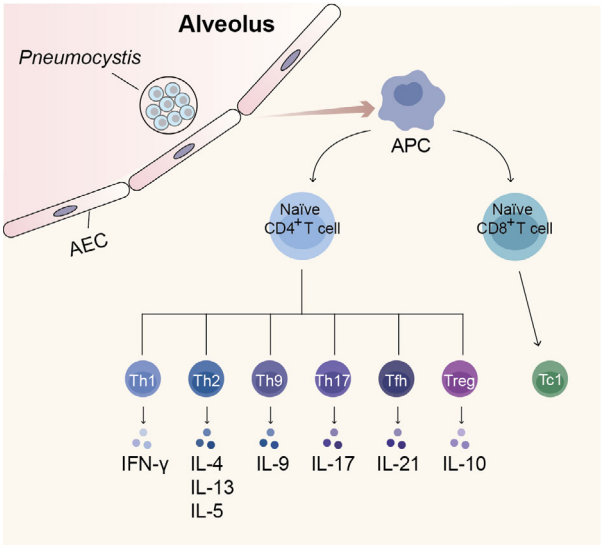

Figure 1. Graphical representation of T cells in PCP. Upon arrival in the lungs, *Pneumocystis* is recognised by APCs, which subsequently induce the differentiation of naïve T cells. Naïve $CD4^+$ T cells differentiate into more specialised functional subsets and exert immune responses by through the secretion of specific cytokines. Naïve $CD8^+$ T cells contribute to host defence a Tc1-type response. AEC, alveolar epithelia cell; APC, antigen presenting cell; Tc1, cytotoxic $CD8^+$ T cell; Tfh, follicular helper T cell; Th, T helper cell; Treg, regulatory T cell.

$CD4^+$ T CELLS

$CD4^+$ T cells serve as central regulators in the immune response by assisting other immune cells, such as B cells, macrophages, neutrophils, eosinophils, and basophils, through the secretion of various cytokines and chemokines.[45] $CD4^+$ T cells differentiate into distinct functional subsets that orchestrate immune responses, exerting effects that either enhance or suppress the activity of other immune cells while directly mediating pro-inflammatory or anti-inflammatory influences on resident cells.[45,46] This functional diversity underscores the vital role of $CD4^+$ T cells in PCP.

Clinical studies have highlighted the importance of $CD4^+$ T cells in PCP.[16,47] HIV-infected patients with $CD4^+$ T-cell counts below 200 per cubic millimetre are at a significantly higher risk of developing PCP.[27] Additionally, the *Pneumocystis* burden is negatively correlated with the level of circulating $CD4^+$ T cells.[48] Furthermore, the depletion of $CD4^+$ T cells, whether genetically or

Table 1. T - cell subsets and key cytokines that participate in PCP progression

T-cell subsets	Animal model of immunosuppression	Treatment	Final fungal burden	Lung inflammation	References
$CD4^+$ T cell	Reconstituted SCID mice	Anti-CD4 mAb	↑	n.d.	28
	Balb/c mice	Anti-CD4 mAb	↑	↑	31
	Reconstituted SCID mice	Anti-CD4 mAb	↑	↑	32
Th1	*Stat4*-deficient mice	—	↓	n.d.	33
	Ifn-γ-deficient mice	—	†	n.d.	34
	Ifn-γ receptor-deficient mice	—	†	↑	35
	γδ-TCR^+ T-cell-deficient mice	IFN-γ neutralisation	†	n.d.	36
	Reconstituted SCID mice	IFN-γ neutralisation	†	↑	37
Th2	*Stat6*-deficient mice	—	↓	n.d.	33
	Il-4-deficient mice	—	†	†	38
Th9	*Il-9*-deficient mice	—	†	n.d.	39
Th17	*Il-17*-deficient mice	-	†	↑	40
	C57BL/6 mice	IL-17 neutralisation	↑	n.d.	41
	$Stat3^{fl/fl}Cd4^{Cre}$ transgenic mice	—	↑	n.d.	33
Tfh	*Il-21*-deficient mice/*Il-21* receptor-deficient mice	—	↑	n.d.	33
Treg	*Il-10*-deficient mice	—	†	↓	42,43
	C57BL/6 mice	Anti-CD25 mAb	†	↑	44
$CD8^+$ T	Balb/c mice	Anti-CD8 mAb	†	†	31

†, not significant; mAb, monoclonal antibody; n.d., not done; SCID, severe combined immunodeficiency; *Stat*, signal transducer and activator of transcription; TCR, T-cell receptor; Tfh, follicular helper T cell; Th, T helper cell; Treg, regulatory T cell.

via antibody treatment, suppresses *Pneumocystis* infection progression.[28,31,32] This is most definitively demonstrated in humans by genetic conditions such as MHC class II deficiency (Bare Lymphocyte Syndrome), where the absence of antigen-specific $CD4^+$ T-cell responses invariably leads to PCP, as illustrated by clinical case reports of affected children.[49–51] Notably, anti-CD4 monoclonal antibodies significantly diminish the ability to control the fungal burden in severe combined immunodeficiency (SCID) mice with naturally acquired PCP that were previously transferred spleen cells to enable infection clearance, emphasising the critical role of $CD4^+$ T cells in immune defences.[28] In summary, the aforementioned studies highlight the pivotal function of $CD4^+$ T cells in PCP, demonstrating that identifying key mechanisms is crucial for further understanding the immunopathogenesis of this disease.

Th1

Th1 cells mediated inflammation and pathogen clearance.[52] The hallmark features of Th1 cells include high expression of T-box expressed in T cells and the presence of chemokine receptors CXC-chemokine receptor 3 and CC-chemokine receptor 5.[53] Cytokines produced by Th1 cells, such as IFN-γ and IL-2, have been found to play a significant role in influencing the course of PCP.[54–56] The proportion of pulmonary Th1 cells is significantly higher in infected lungs than in uninfected controls,[57] and a low Th1 cell frequency is associated with a poor prognosis.[57,58] Numerous studies have demonstrated that the proportion of Th1 cells among $CD4^+$ T cells increased following *Pneumocystis* infection.[23,57,59] Research focussing on intrinsic signal transducer and activator of transcription (STAT) family members that control T-cell differentiation has indicated that *Stat4*-deficient (Th1) cells show only a modest impairment in their ability to clear *Pneumocystis* infection.[33]

IFN-γ, a key cytokine produced by Th1 cells, has been implicated in conferring protection against immunopathogenesis while delaying fungal clearance during PCP.[60,61] Studies in rodent models have demonstrated that IFN-γ reduces the fungal burden.[62–64] IFN-γ acts directly by stimulating alveolar macrophages, which triggers the L-arginine-dependent cytocidal pathway,[65] and by priming $CD8^+$ T cells.[62] However, IFN-γ is not essential for *Pneumocystis* clearance, as mice deficient in IFN-γ or its receptor exhibit unimpaired fungal clearance.[34,35] Furthermore, IFN-γ neutralisation does not affect *Pneumocystis* elimination.[36,37] In contrast, IFN-γ plays an important regulatory role in controlling inflammation.[37] In a mouse model of graft-versus-host disease, anti-IFN-γ treatment exacerbated *Pneumocystis*-driven interstitial

pneumonia.[37] Consistent with this observation, SCID mice inoculated with *Pneumocystis* and reconstituted with splenocytes from IFN-$\gamma^{-/-}$ mice exhibited prolonged and exacerbated inflammatory responses compared with those reconstituted with splenocytes from wild-type (WT) mice.[37] Although IFN-γ is the most extensively studied Th1 cytokine in PCP, the involvement of other Th1-associated cytokines in PCP pathogenesis remains plausible. Notably, dedicated studies examining these alternative cytokines are currently lacking.

Th2

Th2 cells, regulated by GATA binding protein 3, play an important role in coordinating immune responses through the synthesis of IL-4, IL-5 and IL-13.[66,67] *Pneumocystis* acts as a respiratory allergen that can initiate a Th2-type immune response.[68,69] In immunocompetent mice, Th2 cells are dominant both in the lung and lymph nodes, with increases in Th2 cells in lung tissues persisting for 3 weeks before declining.[70] However, their role is not indispensable, as STAT6-deficient (Th2) mice exhibit only a modest decrease in their ability to clear *Pneumocystis* infection.[33] In further confirmation of the absence of complementary roles between Th1 cells and Th2 cells, infection experiments with STAT4/STAT6-deficient mice demonstrated no additional predisposition to *Pneumocystis murina*.[33] Interestingly, Th2-dominant immunity is associated with alleviated immunopathological outcomes. PCP mice treated with both anti-IFN-γ and Th2-promoting cytokines maintained enhanced fungal clearance capacity, demonstrating less severe pulmonary immunopathology and faster recovery rates compared to those receiving anti-IFN-γ alone.[61] Intriguingly, Th2 cells are involved in the development of inducible bronchus-associated lymphoid tissue, which may enhance host defences in PCP.[71]

Peripheral blood mononuclear cells obtained from HIV-infected patients with a history of PCP exhibited significantly elevated IL-4 secretion upon major surface glycoprotein stimulation.[72] Additionally, the effective fungal clearance observed in IL-4$^{-/-}$ mice indicates that *Pneumocystis* resistance mechanisms can operate independently of IL-4, suggesting that IL-4 may have a limited effect on PCP pathogenesis.[38] The levels of IL-13 in bronchoalveolar lavage fluid (BALF) were notably lower in infected versus uninfected individuals, whereas the levels of IL-5 showed no significant differences.[73] The use of plasmid-mediated IL-5 expression resulted in elevated eosinophil counts and reduced fungal infection in mice lacking CD4^{+} T cells.[74] These findings suggest that Th2 cells may not be essential for controlling fungal load but contribute to alleviating pulmonary inflammation.[38,74]

Th9

Th9 cells are characterised by the transcriptional factor PU.1[75]; however, their immunological function in combating PCP is less reported.[14] IL-9, the signature cytokine of Th9 cells, exerts multiple biological effects, including promoting the migration and activation of mast cells and eosinophils, and inducing mucus secretion from epithelial cells.[76] The role of the Th9/IL-9 axis in fungal immunity is complex and context-dependent. On the one hand, its proper function is crucial for host defence, as evidenced by patients with chronic mucocutaneous candidiasis who exhibit a broad T helper defect encompassing Th9 cells and significantly reduced IL-9 production.[77] On the other hand, its dysregulation can be pathogenic, as prominently displayed in allergic bronchopulmonary aspergillosis, where Th9 cells drive a deleterious allergic response to *Aspergillus fumigatus*, fuelling eosinophilic inflammation and mucus hypersecretion.[78]

Given these divergent roles, the function of Th9/IL-9 in PCP has been an open question. Addressing this gap, we have previously demonstrated that Il-9$^{-/-}$ mice exhibit no significant difference in the final clearance of *Pneumocystis* organisms from lung tissues; these gene-depleted mice demonstrate a markedly reduced pulmonary fungal burden 3 weeks after *Pneumocystis* infection compared with that observed in WT mice. This reduction was accompanied by an increased absolute number of Th17 cells in both BALF and lung tissues, along with an augmentation of IL-17A in BALF, suggesting an enhanced pulmonary Th17 response in Il-9$^{-/-}$ mice with PCP. *In vitro* differentiation experiments revealed that splenocytes from Il-9$^{-/-}$ mice are more prone to differentiate into Th17 cells, with higher concentrations of IL-17A in the

cell culture supernatant.[39] Thus, our study provides valuable insights into the immunoregulatory role of IL-9 in PCP. It suggests that, unlike its protective role in candidiasis, the IL-9 pathway may act as a negative regulator of protective immunity in PCP, potentially by constraining the Th17 response. This positions IL-9 signalling not merely as an understudied topic, but as a promising and novel immunotherapeutic target for modulating host defence in PCP.

Th17

The subset of $CD4^+$ T cells that generate IL-17A, known as Th17 cells, exhibits remarkable adaptability in the immunopathogenesis of various autoimmune disorders and is regulated by retinoid-related orphan receptor gamma t.[79] *Pneumocystis* colonisation in COPD patients is associated with elevated IL-17 levels.[80] Single-cell TCR sequencing of *Pneumocystis*-infected mice revealed that Th17 cells were predominantly clonal $CD4^+$ T-cell subsets, displaying characteristics similar to those of tissue-resident memory Th17 cells.[23] IL-17 depletion leads to delayed elimination of *Pneumocystis* and worsened pulmonary damage in comparison with observations in WT PCP mice,[40] emphasising the critical role of Th17 cells in controlling *Pneumocystis* infection. Notably, WT mice treated with anti-IL-17 antibodies showed a 36-fold increase in fungal burden 3 weeks after *Pneumocystis* inoculum.[41] Anti-IFN-γ treatment enhances fungal clearance, which can be blocked by anti-IL-17 antibodies.[61] Our previous study further demonstrated that IL-17 neutralisation exaggerates the fungal burden in an $Il\text{-}9^{-/-}$ mouse model of PCP.[39] Additionally, Th17 cells, together with Th2 cells, contribute to the formation of the inducible bronchus - associated lymphoid tissue structure.[71] Th17 cells not only influence the progression of *Pneumocystis* infection through the secretion of IL-17, but also exert their functions via complex interactions with other T-cell subsets.[39–41,71]

Tfh

Follicular helper T (Tfh) cells, which are characterised by the expression of the transcription factor B-cell lymphoma 6, reside in B-cell follicles and predominantly produce IL-21.[81,82] Despite the importance of Tfh cells in humoral immunity, few studies have been conducted on their role in *Pneumocystis* infection. Both $Il\text{-}21^{-/-}$ mice and patients carrying IL-21 receptor mutations show increased susceptibility to PCP, indicating a potential protective role for Tfh cells in combating *Pneumocystis* infection.[33,83] Moreover, our previous study provided further insights into the functions of Tfh cells, demonstrating that they might regulate cell proliferation, cell–cell adhesion and the positive regulation of B-cell differentiation, thereby highlighting their potential contribution to immune defence mechanisms during *Pneumocystis* infection.[21] The critical importance of Tfh is underscored by the susceptibility of patients with CD40L deficiency to PCP. As this gene is critical for Tfh function and germinal centre formation, its failure disrupts antibody affinity maturation. However, the fact that pure B-cell deficiencies (e.g. BTK deficiency) confer a much lower risk of PCP suggests that the essential role of Tfh extends beyond providing B cell help, likely encompassing direct effector mechanisms such as macrophage activation.[84]

Treg

Regulatory T cells (Tregs), a specialised subset of $CD4^+$ T cells, play an important role in suppressing immune responses and are characterised by the expression of the key transcription factor forkhead box protein 3 (FOXP3).[85,86] Treg cells suppress the function of other immune cells through IL-10, TGF-β, CTLA-4 and CD25.[87]

Patients with IPEX syndrome resulting from *FOXP3* mutations are at risk for developing PCP.[88,89] However, it remains challenging to definitively attribute this risk solely to the *FOXP3* mutation itself, as these patients frequently receive potent immunosuppressive therapies to manage their severe autoimmunity, which independently predisposes them to opportunistic infections.[90] Therefore, while *FOXP3* deficiency is clinically associated with PCP, iatrogenic immunosuppression is likely a significant contributing factor.[88] In rodent models, faster fungal clearance and heightened inflammation occur when IL-10 or Tregs are depleted,[42–44] indicating a complex role for Treg cells in balancing immune responses during PCP. The adoptive transfer of $CD25^+$ $CD4^+$ T cells to infected SCID mice alleviates inflammation without affecting the fungal load.[91] Similarly, intratracheal

administration of IL-10 in $CD4^+$ T-cell-depleted mice has been found to reduce inflammation without affecting *Pneumocystis* clearance.[92] These findings suggest that Tregs primarily modulate inflammation rather than directly influencing fungal clearance.

$CD8^+$ T CELLS

$CD8^+$ T cells play a critical role in identifying and eliminating pathogens and abnormal cells through cytotoxic mechanisms.[93,94] Clinical studies have delineated the importance of $CD8^+$ T cells in PCP outcomes.[95,96] In non-HIV patients diagnosed with PCP, a low $CD8^+$ T-cell count is identified as an independent risk factor for poor prognoses.[97] Furthermore, in another study, low levels of $CD8^+$ T cells were found to be strongly related to PCP and its mortality,[98] indicating their potential role in disease progression.

In contrast to $CD4^+$ T cells, the role of $CD8^+$ T cells in combating fungal infection during PCP is less clear and remains controversial. It has been suggested that $CD8^+$ T-cell deficiency alone does not impair the clearance of *Pneumocystis*; however, depletion of both $CD4^+$ and $CD8^+$ T cells exacerbates pulmonary infection,[31] implying an important interplay between $CD8^+$ T cells and $CD4^+$ T cells in PCP. However, $CD4^+$ cell-depleted mice presented opposite results.[62,99] It has been found that IFN-γ induces an increase in IFN-γ-positive $CD8^+$ T cells, resulting in stronger clearance of *Pneumocystis* infection.[62] Furthermore, $CD8^+$ T cells demonstrating a cytotoxic $CD8^+$ T (Tc1) response to *Pneumocystis* in BALB/c mice effectively killed the pathogen *in vitro* and facilitated its clearance in adoptive transfer models.[100] Subsequent evidence suggested that recombinant human IL-7 can increase the number of $CD8^+$ T cells in CD4-depleted mice, facilitating the clearance of *Pneumocystis*.[101] Additionally, it has been found that the fungal burden remains consistent across all time points, regardless of the presence of $CD8^+$ T cells, implying that the role of $CD8^+$ T cells in *Pneumocystis* clearance is not well-supported.[99] The conflicting findings regarding $CD8^+$ T cells in PCP may result from the heterogeneity within the $CD8^+$ T-cell population. Some subsets, such as Tc1 cells, exhibit protective functions; however, others may contribute to lung injury without significantly impacting fungal clearance.

Existing studies have documented that $CD8^+$ T cells play a causative role in lung injury during PCP. *Pneumocystis* infection triggers a strong infiltration of $CD8^+$ T cells into the alveolar and interstitial areas of the lung, especially when $CD4^+$ T cells are absent. This infiltration causes lung injury, evidenced by decreased pO_2 and albumin leakage into the BALF, similar to observations in other interstitial lung diseases mediated by $CD8^+$ T cells.[30,102,103] In one study, non-T cytotoxic-1 $CD8^+$ T cells showed no *in vitro* activity and were linked to lung damage when transferred.[100] Aligning with this conclusion, Tc1 $CD8^+$ T cells have also been identified as a good prognostic marker among autoimmune patients.[57] This diversity highlights the need for an in-depth investigation to clarify the specific roles of different $CD8^+$ T-cell subsets in PCP.

IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME AND PCP

Immune reconstitution inflammatory syndrome (IRIS) is characterised by the clinical deterioration or new onset of an infectious disease following the reversal of immune deficiency.[104] This reversal can be triggered by multiple events, including antiretroviral therapy (ART) in HIV patients, neutrophil recovery after chemotherapy or stem cell transplantation, suboptimal immunosuppression in solid organ transplant recipients, and postpartum immune reconstitution.[105,106] IRIS complicates 4–5% of cases of PCP in patients with HIV, occurring following the initiation of both ART and antimicrobial therapy for PCP.[107,108] The withdrawal of glucocorticoids or other immunosuppressants, which has been associated with clinical deterioration in a considerable proportion of patients, contributes to increasing PCP mortality rates in non-HIV populations.[109] According to one case series, elevated pre-ART HIV viral burden and reduced $CD4^+$ T cell counts are predictive of PCP-IRIS after ART initiation.[110]

The first experimental model of IRIS associated with PCP was established using *Rag1*$^{-/-}$ and SCID mice.[30,44] In this model, immunodeficient mice were infected with *Pneumocystis murina* for 2 weeks and subsequently reconstituted with whole splenocytes or $CD4^+$ T cells.[30,44] Studies using this system have demonstrated that $CD4^+$ T cells contribute to the pathological immune response in PCP-IRIS. Depletion of Tregs was found to exacerbate IRIS in this model.[44] Furthermore, IFN-γ is a critical

mediator in the exacerbated inflammatory response, decreasing the $CD8^+$ $Foxp3^+$ regulatory T cell subset in PCP-IRIS.[35] Moreover, $CD8^+$ T cells are the primary inflammatory mediators in the absence of $CD4^+$ T cells.[32]

OMICS APPROACHES IN PCP

The increasing accessibility of omics platforms has enabled research using high-throughput sequencing strategies to map dynamic alterations in the host pulmonary immune response and the pathogenic landscape of PCP.

Hu *et al*.[111] used transcriptome analysis to examine the immune response in the lungs of corticosteroid-treated PCP mice, revealing downregulated expression of genes associated with innate immunity, including antigen processing and presentation, inflammatory response and phagocytosis, as well as those involved in adaptive B- and T-cell-mediated immunity. These findings partly explain the susceptibility of patients using glucocorticoids to *Pneumocystis* and provide potential targets for clinical intervention. Unlike bulk RNA sequencing, single-cell RNA sequencing (scRNA-seq) enables the identification of specific groups of immune cell subtypes and the analysis of immune cell profiles during infection processes.[13,21] TCRs and B-cell receptors (BCRs) are key components of the adaptive immune system and play a crucial role in responding to pathogen infections.[112–114] Integrated scRNA-seq and BCR sequencing of murine lungs revealed that *Pneumocystis* infection induces persistent plasma cell expansion, reduced BCR diversity, biased V(D)J gene usage, and an expanded naïve B cell subset marked by high ATF3 expression, providing insights for biomarker and immunotherapy development.[115] In a complementary study, integrated scRNA-seq and TCR-seq analysis showed that clonally expanded $CD4^+$ T cells dominate the immune response in *Pneumocystis*-infected mice, accompanied by reduced TCR diversity and biased VDJ gene usage. A distinct population of clonal Th17 cells exhibiting a tissue-resident memory-like phenotype was also identified.[23] Qiao *et al*. collected TCR data from plasma of 10 patients with PCP and HIV-1 infection, eight asymptomatic HIV-infected patients, and eight healthy subjects, revealing that patients with PCP exhibited different immune cell proportions and reduced TCR pool diversity compared with healthy individuals. Furthermore, anti-PCP treatment could restore cytokine dynamics and TCR diversity, suggesting that the immune response plays a key role in host infection control.[116]

While Th1, Th2 and Th17 cell responses are all elicited during murine infection, studies using gene-deficient mouse models have demonstrated that these subsets are individually insufficient to mediate pathogen clearance.[33,38,40] These findings suggest that intercellular crosstalk among immune subsets, rather than isolated effector functions, may play a pivotal role in PCP immunopathogenesis. Current high-throughput sequencing studies predominantly focus on delineating alterations within discrete cell populations, as previously discussed.[13,21,115] However, the inability of single lineage-deficient models to recapitulate PCP susceptibility phenotypes implies that coordinated multicellular networks, mediated by cell–cell communication, are critical for host defences. This gap is underscored by the limited exploration of immune synapse dynamics, cytokine chemokine circuits, or receptor ligand interactions specific to the *Pneumocystis*-infected lung microenvironment.

FUTURE DIRECTIONS

Despite progress in defining the contributions of specific cell populations to the pathogenesis of PCP, an in-depth exploration of the crosstalk and cooperative networks among these cells remains lacking. Future studies should therefore prioritise elucidating these complex cellular interactions, both spatially and temporally, across the spectrum of infection. Key directions include applying high-dimensional single-cell technologies, such as spatial transcriptomics and multiplexed imaging, to map intercellular communication within the lung microenvironment. Unravelling this intricate cellular crosstalk will not only advance our fundamental understanding of PCP immunopathogenesis but also reveal novel therapeutic targets for modulating host immunity to improve disease outcomes.

The current standard therapeutic regimen for PCP remains trimethoprim-sulfamethoxazole (TMP-SMX), which serves as the first-line treatment.[4,117] Toxicities associated with TMP-SMX, such as rash, fever, nephrotoxicity, bone marrow suppression, electrolyte disorders and hepatotoxicity, necessitate a treatment change in up to 40% of patients.[118–120] Other alternative agents include dapsone, pentamidine, atovaquone, clindamycin and

primaquine,[121] which are less efficacious than TMP-SMX and possess their own profiles of serious toxicities.[122] Although T-cell therapies have not yet been explored for PCP, pioneering work in invasive fungal infection highlights their transformative potential.[123] Given the limitations of current pharmacotherapies, the development of T-cell-based immunotherapies for PCP represents a compelling and innovative direction. Ultimately, harnessing T-cell immunity may pave the way for targeted, toxin-sparing therapeutic modalities that overcome the drawbacks of existing antifungal regimens.

CONCLUSION

Host defence against *Pneumocystis* is uniquely dependent on functional T-cell immunity, a principle unequivocally demonstrated by the specific spectrum of human inborn errors of immunity. Profound susceptibility to PCP is observed in patients with severe T cell deficiencies, such as SCID (e.g. because of mutations in in *IL2RG*,[124] *IL7R*,[125] *RAG1*[126] and *STAT3*[127]) and in those with impaired function (e.g. *CD40L*[84]). A highly informative dichotomy, however, reveals the distinct nature of this defence: mutations affecting the IL-23/IL-17/Th17 axes (e.g. *IL12B*[128] and *RORC*[129]) or the IFN-γ signalling pathway[130] confer susceptibility to intramacrophage infections such as mycobacterial disease; however, they do not typically predispose otherwise healthy individuals to PCP. This key distinction indicates that the protective host response to *Pneumocystis* is less dependent on the classical Th1 and Th17 pathways required for intracellular pathogen control; instead, it is more reliant on other T-cell functions, potentially including $CD4^+$ T-cell-mediated macrophage activation through alternative pathways and B-cell help for antibody production. Furthermore, the occurrence of PCP in patients with certain forms of humoral immunodeficiency (e.g. agammaglobulinemia because of *BTK* mutations[131]) suggests that while antibodies may play a contributory role, they are individually insufficient to confer protection in the absence of adequate T-cell immunity.

While murine models have implicated numerous $CD4^+$ T helper subsets (Th1, Th2, Th9, Th17, Tfh) in fungal control, the findings are often inconsistent, and the roles of $CD8^+$ T cells and the precise mechanisms of inter-cellular crosstalk remain poorly defined. This heterogeneity underscores the complexity of the immune response to *Pneumocystis* and highlights a critical gap between phenomenological observations and mechanistic understanding.

Bridging this gap necessitates a paradigm shift in research strategies. Future efforts must prioritise the application of high-resolution tools, such as single-cell and spatial transcriptomics on human PCP samples, to move beyond murine models and directly map the landscape of protective versus pathological T-cell responses in the human lung. This refined understanding will be the foundation for rational therapeutic design, shifting the focus from broad-spectrum antimicrobials towards targeted immunotherapies. Promising avenues include engineering adoptive T cell transfers or modulating specific cytokine pathways (e.g. IL-9, IL-17) to augment defective immunity, particularly in immunocompromised hosts.

In conclusion, unravelling the intricate functional network of T-cell subsets in PCP is no longer just a biological question but a translational imperative. By defining the precise rules of T-cell-mediated host defence, we can pioneer a new class of immune-complementary therapies that overcome the limitations of current antifungals and finally improve outcomes for this challenging infection.

ACKNOWLEDGMENTS

The National Natural Science Foundation of China (No. 82270009, No. 82070005, No. 82400009) and Beijing Scholars Program (No. 062).

AUTHOR CONTRIBUTIONS

Yuxi Chen: Writing – original draft; visualization. **Hengmo Rong:** Writing – original draft; visualization; funding acquisition. **Ting Li:** Writing – original draft. **Chao Zhang:** Writing – original draft. **Huqin Yang:** Writing – original draft. **Han Sun:** Writing – original draft. **Dong Wang:** Writing – original draft. **Xiaoxia Zhou:** Writing – original draft. **Kan Zhai:** Conceptualization; writing – review and editing. **Zhaohui Tong:** Conceptualization; writing – review and editing; funding acquisition.

CONFLICT OF INTEREST

None.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

ETHICS APPROVAL STATEMENT

The authors have nothing to report.

REFERENCES

1. Gingerich AD, Norris KA, Mousa JJ. *Pneumocystis* pneumonia: immunity, vaccines, and treatments. *Pathogens* 2021; **10**: 10.
2. Liu Y, Fahle GA, Kovacs JA. Inability to culture *Pneumocystis jirovecii*. *MBio* 2018; **9**: 9.
3. Lécuyer R, Issa N, Camou F *et al*. Characteristics and prognosis factors of *Pneumocystis jirovecii* pneumonia according to underlying disease: a retrospective multicenter study. *Chest* 2024; **165**: 1319–1329.
4. McDonald EG, Afshar A, Assiri B *et al*. *Pneumocystis* jirovecii pneumonia in people living with HIV: a review. *Clin Microbiol Rev* 2024; **37**: e0010122.
5. Ghembaza A, Vautier M, Cacoub P, Pourcher V, Saadoun D. Risk factors and prevention of *Pneumocystis jirovecii* pneumonia in patients with autoimmune and inflammatory diseases. *Chest* 2020; **158**: 2323–2332.
6. Saadatzadeh T, Angarone M, Stosor V. *Pneumocystis jirovecii* in solid organ transplant recipients: updates in epidemiology, diagnosis, treatment, and prevention. *Curr Opin Infect Dis* 2024; **37**: 121–128.
7. Classen AY, Henze L, von Lilienfeld-Toal M *et al*. Primary prophylaxis of bacterial infections and *Pneumocystis jirovecii* pneumonia in patients with hematologic malignancies and solid tumors: 2020 updated guidelines of the infectious diseases working Party of the German Society of hematology and medical oncology (AGIHO/DGHO). *Ann Hematol* 2021; **100**: 1603–1620.
8. Denning DW. Global incidence and mortality of severe fungal disease. *Lancet Infect Dis* 2024; **24**: e428–e438.
9. Graham SM, Mtitimila EI, Kamanga HS, Walsh AL, Hart CA, Molyneux ME. Clinical presentation and outcome of *Pneumocystis carinii* pneumonia in Malawian children. *Lancet* 2000; **355**: 369–373.
10. Chintu C, Mudenda V, Lucas S *et al*. Lung diseases at necropsy in African children dying from respiratory illnesses: a descriptive necropsy study. *Lancet* 2002; **360**: 985–990.
11. Pneumonia Etiology Research for Child Health (PERCH) Study Group. Causes of severe pneumonia requiring hospital admission in children without HIV infection from Africa and Asia: the PERCH multi-country case-control study. *Lancet* 2019; **394**: 757–779.
12. Senécal J, Smyth E, Del Corpo O *et al*. Non-invasive diagnosis of *Pneumocystis jirovecii* pneumonia: a systematic review and meta-analysis. *Clin Microbiol Infect* 2022; **28**: 23–30.
13. Wang Y, Li K, Zhao W *et al*. Integrated multi-omics analyses reveal the altered transcriptomic characteristics of pulmonary macrophages in immunocompromised hosts with *pneumocystis* pneumonia. *Front Immunol* 2023; **14**: 1179094.
14. Otieno-Odhiambo P, Wasserman S, Hoving JC. The contribution of host cells to *pneumocystis* immunity: an update. *Pathogens* 2019; **8**: 52.
15. Charpentier E, Ménard S, Marques C, Berry A, Iriart X. Immune response in *pneumocystis* infections according to the host immune system status. *J Fungi (Basel)* 2021; **7**: 7.
16. Phair J, Muñoz A, Detels R, Kaslow R, Rinaldo C, Saah A. The risk of *Pneumocystis carinii* pneumonia among men infected with human immunodeficiency virus type 1. Multicenter AIDS cohort study group. *N Engl J Med* 1990; **322**: 161–165.
17. Kaplan JE, Hanson DL, Navin TR, Jones JL. Risk factors for primary *Pneumocystis carinii* pneumonia in human immunodeficiency virus-infected adolescents and adults in the United States: reassessment of indications for chemoprophylaxis. *J Infect Dis* 1998; **178**: 1126–1132.
18. Kaplan JE, Hanson DL, Jones JL, Dworkin MS. Viral load as an independent risk factor for opportunistic infections in HIV-infected adults and adolescents. *AIDS* 2001; **15**: 1831–1836.
19. Chesnay A, Gonzalez L, Parent C, Desoubeaux G, Baranek T. Description of a murine model of *pneumocystis* pneumonia. *Mycopathologia* 2024; **189**: 42.
20. Bishop LR, Curran SJ, Kovacs JA. Mucosal-associated invariant T cells accumulate in the lungs during murine *pneumocystis* infection but are not required for clearance. *J Fungi (Basel)* 2022; **8**: 8.
21. Yang HQ, Sun H, Li K, Shao MM, Zhai K, Tong ZH. Dynamics of host immune responses and a potential function of Trem2(hi) interstitial macrophages in *pneumocystis* pneumonia. *Respir Res* 2024; **25**: 72.
22. Bhagwat SP, Wright TW, Gigliotti F. Anti-CD3 antibody decreases inflammation and improves outcome in a murine model of *pneumocystis* pneumonia. *J Immunol* 2010; **184**: 497–502.
23. Yang HQ, Wang YS, Zhai K, Tong ZH. Single-cell TCR sequencing reveals the dynamics of T cell repertoire profiling during *pneumocystis* infection. *Front Microbiol* 2021; **12**: 637500.
24. Swain SD, Meissner NN, Harmsen AG. CD8 T cells modulate CD4 T-cell and eosinophil-mediated pulmonary pathology in *pneumocystis* pneumonia in B-cell-deficient mice. *Am J Pathol* 2006; **168**: 466–475.
25. Roths JB, Sidman CL. Both immunity and hyperresponsiveness to *Pneumocystis carinii* result from transfer of $CD4^+$ but not $CD8^+$ T cells into severe combined immunodeficiency mice. *J Clin Invest* 1992; **90**: 673–678.
26. Beck JM, Warnock ML, Kaltreider HB, Shellito JE. Host defenses against *Pneumocystis carinii* in mice selectively depleted of $CD4^+$ lymphocytes. *Chest* 1993; **103**: 116s–118s.
27. Shellito J, Suzara VV, Blumenfeld W, Beck JM, Steger HJ, Ermak TH. A new model of *Pneumocystis carinii* infection in mice selectively depleted of helper T lymphocytes. *J Clin Invest* 1990; **85**: 1686–1693.
28. Harmsen AG, Stankiewicz M. Requirement for $CD4^+$ cells in resistance to *Pneumocystis carinii* pneumonia in mice. *J Exp Med* 1990; **172**: 937–945.
29. An CL, Su XP, Harmsen AG. The role of $CD8^+$ T cells in the pathogenesis of *Pneumocystis carinii* pneumonia in mice depleted of $CD4^+$ T cells. *Zhongguo Ji Sheng Chong Xue Yu Ji Sheng Chong Bing Za Zhi* 2000; **18**: 207–212.

30. Wright TW, Gigliotti F, Finkelstein JN, McBride JT, An CL, Harmsen AG. Immune-mediated inflammation directly impairs pulmonary function, contributing to the pathogenesis of *Pneumocystis carinii* pneumonia. *J Clin Invest* 1999; **104**: 1307–1317.
31. Beck JM, Newbury RL, Palmer BE, Warnock ML, Byrd PK, Kaltreider HB. Role of $CD8^+$ lymphocytes in host defense against *Pneumocystis carinii* in mice. *J Lab Clin Med* 1996; **128**: 477–487.
32. Bhagwat SP, Gigliotti F, Xu H, Wright TW. Contribution of T cell subsets to the pathophysiology of *pneumocystis*-related immunorestitution disease. *Am J Physiol Lung Cell Mol Physiol* 2006; **291**: L1256–L1266.
33. Elsegeiny W, Zheng M, Eddens T *et al*. Murine models of *pneumocystis* infection recapitulate human primary immune disorders. *JCI Insight* 2018; **3**: 3.
34. Rudmann DG, Preston AM, Moore MW, Beck JM. Susceptibility to *Pneumocystis carinii* in mice is dependent on simultaneous deletion of IFN-gamma and type 1 and 2 TNF receptor genes. *J Immunol* 1998; **161**: 360–366.
35. Zhang ZQ, Wang J, Hoy Z *et al*. Neither classical nor alternative macrophage activation is required for *pneumocystis* clearance during immune reconstitution inflammatory syndrome. *Infect Immun* 2015; **83**: 4594–4603.
36. Steele C, Zheng M, Young E, Marrero L, Shellito JE, Kolls JK. Increased host resistance against *Pneumocystis carinii* pneumonia in gammadelta T-cell-deficient mice: protective role of gamma interferon and $CD8^+$ T cells. *Infect Immun* 2002; **70**: 5208–5215.
37. Garvy BA, Ezekowitz RA, Harmsen AG. Role of gamma interferon in the host immune and inflammatory responses to *Pneumocystis carinii* infection. *Infect Immun* 1997; **65**: 373–379.
38. Garvy BA, Wiley JA, Gigliotti F, Harmsen AG. Protection against *Pneumocystis carinii* pneumonia by antibodies generated from either T helper 1 or T helper 2 responses. *Infect Immun* 1997; **65**: 5052–5056.
39. Li T, Rong HM, Zhang C, Zhai K, Tong ZH. IL-9 deficiency promotes pulmonary Th17 response in murine model of *pneumocystis* infection. *Front Immunol* 2018; **9**: 1118.
40. Rong HM, Qian XJ, Zhang C, Li T, Tong ZH. IL-17 inversely correlated with IL-10 via the STAT3 gene in *pneumocystis*-infected mice. *Mediat Inflamm* 2019; **2019**: 6750861.
41. Rudner XL, Happel KI, Young EA, Shellito JE. Interleukin-23 (IL-23)-IL-17 cytokine axis in murine *Pneumocystis carinii* infection. *Infect Immun* 2007; **75**: 3055–3061.
42. Qureshi MH, Harmsen AG, Garvy BA. IL-10 modulates host responses and lung damage induced by *Pneumocystis carinii* infection. *J Immunol* 2003; **170**: 1002–1009.
43. Kurkjian C, Hollifield M, Lines JL *et al*. Alveolar macrophages in neonatal mice are inherently unresponsive to *pneumocystis* murina infection. *Infect Immun* 2012; **80**: 2835–2846.
44. McKinley L, Logar AJ, McAllister F, Zheng M, Steele C, Kolls JK. Regulatory T cells dampen pulmonary inflammation and lung injury in an animal model of *pneumocystis* pneumonia. *J Immunol* 2006; **177**: 6215–6226.
45. Künzli M, Masopust D. $CD4^+$ T cell memory. *Nat Immunol* 2023; **24**: 903–914.
46. Sun L, Su Y, Jiao A, Wang X, Zhang B. T cells in health and disease. *Signal Transduct Target Ther* 2023; **8**: 235.
47. Kaplan JE, Benson C, Holmes KK, Brooks JT, Pau A, Masur H. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV medicine Association of the Infectious Diseases Society of America. *MMWR Recomm Rep* 2009; **58**: 1–207.
48. Khalife S, Chabé M, Gantois N *et al*. Relationship between *Pneumocystis carinii* burden and the degree of host immunosuppression in an airborne transmission experimental model. *J Eukaryot Microbiol* 2016; **63**: 309–317.
49. Muhamad NDA, Kanie N, Otsubo Y, Suzuki K, Kinoshita K, Horikoshi Y. Letermovir-inclusive combination therapy for a refractory and resistant infection by cytomegalovirus with UL54 mutation following a hematopoietic stem cell transplant for MHC class II deficiency. *J Infect Chemother* 2025; **31**: 102627.
50. Clarridge K, Leitenberg D, Loechelt B, Picard C, Keller M. Major histocompatibility complex class II deficiency due to a novel mutation in RFXANK in a child of Mexican descent. *J Clin Immunol* 2016; **36**: 4–5.
51. Ahmed A, Reith W, Puck JM, Cheng LE. Novel mutation in the class II Transactivator associated with immunodeficiency and autoimmunity. *J Clin Immunol* 2015; **35**: 521–522.
52. Sheikh AA, Groom JR. Transcription tipping points for T follicular helper cell and T-helper 1 cell fate commitment. *Cell Mol Immunol* 2021; **18**: 528–538.
53. Zhu X, Zhu J. CD4 T helper cell subsets and related human immunological disorders. *Int J Mol Sci* 2020; **21**: 8011.
54. Shen HP, Tang YM, Song H, Xu WQ, Yang SL, Xu XJ. Efficiency of interleukin 6 and interferon gamma in the differentiation of invasive pulmonary aspergillosis and *pneumocystis* pneumonia in pediatric oncology patients. *Int J Infect Dis* 2016; **48**: 73–77.
55. Ripamonti C, Bishop LR, Kovacs JA. Pulmonary Interleukin-17-positive lymphocytes increase during *pneumocystis* murina infection but are not required for clearance of *pneumocystis*. *Infect Immun* 2017; **85**: e00434-16.
56. Alshahrani MY, Alfaifi M, Al Shahrani M *et al*. Increased mRNA expression of key cytokines among suspected cases of *Pneumocystis jirovecii* infection. *BMC Infect Dis* 2021; **21**: 28.
57. Zhang NN, Huang X, Feng HY *et al*. Circulating and pulmonary T-cell populations driving the immune response in non-HIV immunocompromised patients with *Pneumocystis jirovecii* pneumonia. *Int J Med Sci* 2019; **16**: 1221–1230.
58. Charpentier E, Marques C, Ménard S *et al*. New insights into blood circulating lymphocytes in human *pneumocystis* pneumonia. *J Fungi (Basel)* 2021; **7**: 7.
59. Zhang C, Rong HM, Li T, Zhai K, Tong ZH. PD-1 deficiency promotes macrophage activation and T-helper cell type 1/T-helper cell type 17 response in *pneumocystis* pneumonia. *Am J Respir Cell Mol Biol* 2020; **62**: 767–782.

60. Meissner N, Swain S, McInnerney K, Han S, Harmsen AG. Type-I IFN signaling suppresses an excessive IFN-gamma response and thus prevents lung damage and chronic inflammation during *pneumocystis* (PC) clearance in CD4 T cell-competent mice. *Am J Pathol* 2010; **176**: 2806–2818.
61. Wang J, Zhang ZQ, Gigliotti F, Wright TW. IFN-γ limits immunopathogenesis but delays fungal clearance during *pneumocystis* pneumonia. *J Immunol* 2023; **211**: 1397–1405.
62. Kolls JK, Habetz S, Shean MK *et al*. IFN-gamma and $CD8^+$ T cells restore host defenses against *Pneumocystis carinii* in mice depleted of $CD4^+$ T cells. *J Immunol* 1999; **162**: 2890–2894.
63. Ruan S, McKinley L, Zheng M *et al*. Interleukin-12 and host defense against murine *pneumocystis* pneumonia. *Infect Immun* 2008; **76**: 2130–2137.
64. Beck JM, Liggitt HD, Brunette EN, Fuchs HJ, Shellito JE, Debs RJ. Reduction in intensity of *Pneumocystis carinii* pneumonia in mice by aerosol administration of gamma interferon. *Infect Immun* 1991; **59**: 3859–3862.
65. Downing JF, Kachel DL, Pasula R, Martin WJ 2nd. Gamma interferon stimulates rat alveolar macrophages to kill *Pneumocystis carinii* by L-arginine- and tumor necrosis factor-dependent mechanisms. *Infect Immun* 1999; **67**: 1347–1352.
66. León B. A model of Th2 differentiation based on polarizing cytokine repression. *Trends Immunol* 2023; **44**: 399–407.
67. Zhang Y, Lan F, Zhang L. Update on pathomechanisms and treatments in allergic rhinitis. *Allergy* 2022; **77**: 3309–3319.
68. Eddens T, Campfield BT, Serody K *et al*. A novel $CD4^+$ T cell-dependent murine model of *pneumocystis*-driven asthma-like pathology. *Am J Respir Crit Care Med* 2016; **194**: 807–820.
69. Rojas DA, Iturra PA, Méndez A *et al*. Increase in secreted airway mucins and partial Muc5b STAT6/FoxA2 regulation during *pneumocystis* primary infection. *Sci Rep* 2019; **9**: 2078.
70. Shellito JE, Tate C, Ruan S, Kolls J. Murine $CD4^+$ T lymphocyte subsets and host defense against *Pneumocystis carinii*. *J Infect Dis* 2000; **181**: 2011–2017.
71. Eddens T, Elsegeiny W, Garcia-Hernadez ML *et al*. *Pneumocystis*-driven inducible bronchus-associated lymphoid tissue formation requires Th2 and Th17 immunity. *Cell Rep* 2017; **18**: 3078–3090.
72. Theus SA, Sawhney N, Smulian AG, Walzer PD. Proliferative and cytokine responses of human T lymphocytes isolated from human immunodeficiency virus-infected patients to the major surface glycoprotein of *Pneumocystis carinii*. *J Infect Dis* 1998; **177**: 238–241.
73. Carreto-Binaghi LE, Tenorio EP, Morales-Villarreal FR *et al*. Detection of cytokines and Collectins in bronchoalveolar fluid samples of patients infected with histoplasma capsulatum and *Pneumocystis jirovecii*. *J Fungi (Basel)* 2021; **7**: 7.
74. Eddens T, Elsegeiny W, Nelson MP *et al*. Eosinophils contribute to early clearance of *pneumocystis* murina infection. *J Immunol* 2015; **195**: 185–193.
75. Tu J, Chen W, Huang W *et al*. Positive feedback loop PU.1-IL9 in Th9 promotes rheumatoid arthritis development. *Ann Rheum Dis* 2024; **83**: 1707–1721.
76. Angkasekwinai P, Dong C. IL-9-producing T cells: potential players in allergy and cancer. *Nat Rev Immunol* 2021; **21**: 37–48.
77. Becker KL, Rösler B, Wang X *et al*. Th2 and Th9 responses in patients with chronic mucocutaneous candidiasis and hyper-IgE syndrome. *Clin Exp Allergy* 2016; **46**: 1564–1574.
78. Shankar J, Thakur R, Clemons KV, Stevens DA. Interplay of cytokines and chemokines in aspergillosis. *J Fungi (Basel)* 2024; **10**: 10.
79. Kanno T, Nakajima T, Miyako K, Endo Y. Lipid metabolism in Th17 cell function. *Pharmacol Ther* 2023; **245**: 108411.
80. Gantois N, Lesaffre A, Durand-Joly I *et al*. Factors associated with *pneumocystis* colonization and circulating genotypes in chronic obstructive pulmonary disease patients with acute exacerbation or at stable state and their homes. *Med Mycol* 2021; **60**: myab070.
81. Hinrichs CS, Spolski R, Paulos CM *et al*. IL-2 and IL-21 confer opposing differentiation programs to $CD8^+$ T cells for adoptive immunotherapy. *Blood* 2008; **111**: 5326–5333.
82. Vinuesa CG, Linterman MA, Yu D, MacLennan IC. Follicular helper T cells. *Annu Rev Immunol* 2016; **34**: 335–368.
83. Stepensky P, Keller B, Abuzaitoun O *et al*. Extending the clinical and immunological phenotype of human interleukin-21 receptor deficiency. *Haematologica* 2015; **100**: e72–e76.
84. Banday AZ, Nisar R, Patra PK *et al*. Clinical and immunological features, genetic variants, and outcomes of patients with CD40 deficiency. *J Clin Immunol* 2023; **44**: 17.
85. Ohkura N, Sakaguchi S. Transcriptional and epigenetic basis of Treg cell development and function: its genetic anomalies or variations in autoimmune diseases. *Cell Res* 2020; **30**: 465–474.
86. Bittner S, Hehlgans T, Feuerer M. Engineered Treg cells as putative therapeutics against inflammatory diseases and beyond. *Trends Immunol* 2023; **44**: 468–483.
87. Wang J, Zhao X, Wan YY. Intricacies of TGF-β signaling in Treg and Th17 cell biology. *Cell Mol Immunol* 2023; **20**: 1002–1022.
88. Bacchetta R, Roncarolo MG. IPEX syndrome from diagnosis to cure, learning along the way. *J Allergy Clin Immunol* 2024; **153**: 595–605.
89. Barzaghi F, Passerini L, Bacchetta R. Immune dysregulation, polyendocrinopathy, enteropathy, x-linked syndrome: a paradigm of immunodeficiency with autoimmunity. *Front Immunol* 2012; **3**: 211.
90. Huang Q, Liu X, Zhang Y, Huang J, Li D, Li B. Molecular feature and therapeutic perspectives of immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome. *J Genet Genomics* 2020; **47**: 17–26.
91. Hori S, Carvalho TL, Demengeot J. $CD25^+CD4^+$ regulatory T cells suppress $CD4^+$ T cell-mediated pulmonary hyperinflammation driven by *Pneumocystis carinii* in immunodeficient mice. *Eur J Immunol* 2002; **32**: 1282–1291.
92. Ruan S, Tate C, Lee JJ, Ritter T, Kolls JK, Shellito JE. Local delivery of the viral interleukin-10 gene suppresses tissue inflammation in murine *Pneumocystis carinii* infection. *Infect Immun* 2002; **70**: 6107–6113.

93. Sykulev Y. Factors contributing to the potency of $CD8^+$ T cells. *Trends Immunol* 2023; **44**: 693–700.
94. Kok L, Masopust D, Schumacher TN. The precursors of $CD8^+$ tissue resident memory T cells: from lymphoid organs to infected tissues. *Nat Rev Immunol* 2022; **22**: 283–293.
95. Kaminski H, Belliere J, Burguet L *et al*. Identification of predictive markers and outcomes of late-onset *Pneumocystis jirovecii* pneumonia in kidney transplant recipients. *Clin Infect Dis* 2021; **73**: e1456–e1463.
96. Tang G, Tong S, Yuan X *et al*. Using routine laboratory markers and immunological indicators for predicting *Pneumocystis jiroveci* pneumonia in immunocompromised patients. *Front Immunol* 2021; **12**: 652383.
97. Jin F, Xie J, Wang HL. Lymphocyte subset analysis to evaluate the prognosis of HIV-negative patients with *pneumocystis* pneumonia. *BMC Infect Dis* 2021; **21**: 441.
98. Li Y, Ghannoum M, Deng C *et al*. *Pneumocystis* pneumonia in patients with inflammatory or autoimmune diseases: usefulness of lymphocyte subtyping. *Int J Infect Dis* 2017; **57**: 108–115.
99. Gigliotti F, Crow EL, Bhagwat SP, Wright TW. Sensitized $CD8^+$ T cells fail to control organism burden but accelerate the onset of lung injury during *Pneumocystis carinii* pneumonia. *Infect Immun* 2006; **74**: 6310–6316.
100. McAllister F, Steele C, Zheng M *et al*. T cytotoxic-1 $CD8^+$ T cells are effector cells against *pneumocystis* in mice. *J Immunol* 2004; **172**: 1132–1138.
101. Ruan S, Samuelson DR, Assouline B, Morre M, Shellito JE. Treatment with Interleukin-7 restores host defense against *pneumocystis* in $CD4^+$ T-lymphocyte-depleted mice. *Infect Immun* 2016; **84**: 108–119.
102. Meissner NN, Lund FE, Han S, Harmsen A. CD8 T cell-mediated lung damage in response to the extracellular pathogen *pneumocystis* is dependent on MHC class I expression by radiation-resistant lung cells. *J Immunol* 2005; **175**: 8271–8279.
103. Wright TW, Notter RH, Wang Z, Harmsen AG, Gigliotti F. Pulmonary inflammation disrupts surfactant function during *Pneumocystis carinii* pneumonia. *Infect Immun* 2001; **69**: 758–764.
104. Dellière S, Guery R, Candon S *et al*. Understanding pathogenesis and care challenges of immune reconstitution inflammatory syndrome in fungal infections. *J Fungi (Basel)* 2018; **4**: 4.
105. Singh N, Lortholary O, Alexander BD *et al*. An immune reconstitution syndrome-like illness associated with *Cryptococcus neoformans* infection in organ transplant recipients. *Clin Infect Dis* 2005; **40**: 1756–1761.
106. Singh N, Perfect JR. Immune reconstitution syndrome and exacerbation of infections after pregnancy. *Clin Infect Dis* 2007; **45**: 1192–1199.
107. Achenbach CJ, Harrington RD, Dhanireddy S, Crane HM, Casper C, Kitahata MM. Paradoxical immune reconstitution inflammatory syndrome in HIV-infected patients treated with combination antiretroviral therapy after AIDS-defining opportunistic infection. *Clin Infect Dis* 2012; **54**: 424–433.
108. Roade Tato L, Burgos Cibrian J, Curran Fábregas A *et al*. Immune reconstitution inflammatory syndrome in HIV-infected patients with *pneumocystis* jirovecii pneumonia. *Enferm Infecc Microbiol Clin (Engl Ed)* 2018; **36**: 621–626.
109. Guo Y, Zhu L, Li H. Glucocorticoid-induced *pneumocystis* pneumonia mice developed immune reconstitution inflammatory syndrome after glucocorticoid withdrawal. *J Immunol* 2025; **214**: 2298–2306.
110. Jagannathan P, Davis E, Jacobson M, Huang L. Life-threatening immune reconstitution inflammatory syndrome after *pneumocystis* pneumonia: a cautionary case series. *AIDS* 2009; **23**: 1794–1796.
111. Hu Y, Wang D, Zhai K, Tong Z. Transcriptomic analysis reveals significant B lymphocyte suppression in corticosteroid-treated hosts with *pneumocystis* pneumonia. *Am J Respir Cell Mol Biol* 2017; **56**: 322–331.
112. Shah K, Al-Haidari A, Sun J, Kazi JU. T cell receptor (TCR) signaling in health and disease. *Signal Transduct Target Ther* 2021; **6**: 412.
113. Pai JA, Satpathy AT. High-throughput and single-cell T cell receptor sequencing technologies. *Nat Methods* 2021; **18**: 881–892.
114. Goldstein LD, Chen YJ, Wu J *et al*. Massively parallel single-cell B-cell receptor sequencing enables rapid discovery of diverse antigen-reactive antibodies. *Commun Biol* 2019; **2**: 304.
115. Sun H, Yang HQ, Zhai K, Tong ZH. Signatures of B cell receptor repertoire following *pneumocystis* infection. *Front Microbiol* 2021; **12**: 636250.
116. Qiao L, Cui X, Jia L *et al*. Peripheral immune phenotypes and T cell receptor repertoire in *pneumocystis* pneumonia in HIV-1 infected patients. *Clin Immunol* 2022; **237**: 108985.
117. Hänsel L, Schumacher J, Denis B, Hamane S, Cornely OA, Koehler P. How to diagnose and treat a patient without human immunodeficiency virus infection having *Pneumocystis jirovecii* pneumonia? *Clin Microbiol Infect* 2023; **29**: 1015–1023.
118. Hughes W, Leoung G, Kramer F *et al*. Comparison of atovaquone (566C80) with trimethoprim-sulfamethoxazole to treat *Pneumocystis carinii* pneumonia in patients with AIDS. *N Engl J Med* 1993; **328**: 1521–1527.
119. Utsunomiya M, Dobashi H, Odani T *et al*. An open-label, randomized controlled trial of sulfamethoxazole-trimethoprim for *pneumocystis* prophylaxis: results of 52-week follow-up. *Rheumatol Adv Pract* 2020; **4**: rkaa029.
120. Safrin S, Finkelstein DM, Feinberg J *et al*. Comparison of three regimens for treatment of mild to moderate *Pneumocystis carinii* pneumonia in patients with AIDS. A double-blind, randomized, trial of oral trimethoprim-sulfamethoxazole, dapsone-trimethoprim, and clindamycin-primaquine. ACTG 108 study group. *Ann Intern Med* 1996; **124**: 792–802.
121. Weyant RB, Kabbani D, Doucette K, Lau C, Cervera C. *Pneumocystis jirovecii*: a review with a focus on prevention and treatment. *Expert Opin Pharmacother* 2021; **22**: 1579–1592.
122. Helweg-Larsen J, Benfield T, Atzori C, Miller RF. Clinical efficacy of first- and second-line treatments for HIV-associated *Pneumocystis jirovecii* pneumonia: a tri-centre cohort study. *J Antimicrob Chemother* 2009; **64**: 1282–1290.

123. Seif M, Kakoschke TK, Ebel F *et al*. CAR T cells targeting *Aspergillus fumigatus* are effective at treating invasive pulmonary aspergillosis in preclinical models. *Sci Transl Med* 2022; **14**: eabh1209.
124. Rios X, Chinn IK, Orange JS, Hanson CI, Rider NL. T-cell lymphopenia detected by newborn screening in two siblings with an Xq13.1 duplication. *Front Pediatr* 2017; **5**: 156.
125. Gray PE, Logan GJ, Alexander IE, Poulton S, Roscioli T, Ziegler J. A novel intronic splice site deletion of the IL-2 receptor common gamma chain results in expression of a dysfunctional protein and T-cell-positive X-linked severe combined immunodeficiency. *Int J Immunogenet* 2015; **42**: 11–14.
126. Chen X, Jiang C, Song W *et al*. Case report: Identification of a Chinese patient with RAG1 mutations initially presenting as autoimmune hemolytic anemia. *Front Immunol* 2024; **15**: 1498066.
127. Lan J, Zhang Y, Song M *et al*. Omalizumab for STAT3 hyper-IgE syndromes in adulthood: a case report and literature review. *Front Med (Lausanne)* 2022; **9**: 835257.
128. Cheng A, Kashyap A, Salvator H *et al*. Anti-interleukin-23 autoantibodies in adult-onset immunodeficiency. *N Engl J Med* 2024; **390**: 1105–1117.
129. Okada S, Markle JG, Deenick EK *et al*. IMMUNODEFICIENCIES. Impairment of immunity to *Candida* and *Mycobacterium* in humans with bi-allelic RORC mutations. *Science* 2015; **349**: 606–613.
130. Zhang SY, Boisson-Dupuis S, Chapgier A *et al*. Inborn errors of interferon (IFN)-mediated immunity in humans: insights into the respective roles of IFN-alpha/beta, IFN-gamma, and IFN-lambda in host defense. *Immunol Rev* 2008; **226**: 29–40.
131. Fornes O, Jia A, Kuehn HS *et al*. A multimorphic mutation in IRF4 causes human autosomal dominant combined immunodeficiency. *Sci Immunol* 2023; **8**: eade7953.