haematologica
Journal of the Ferrata Storti Foundation

Janus kinase inhibitors as an evolving treatment for lymphomas and immune-mediated complications

by Caitlin Unkenholz, Sofia Huerga, Alison Moskowitz and Santosha Vardhana

Received: May 18, 2026.
Accepted: July 31, 2026.

Citation: Caitlin Unkenholz, Sofia Huerga, Alison Moskowitz and Santosha Vardhana.
Janus kinase inhibitors as an evolving treatment for lymphomas and immune-mediated complications.
Haematologica. 2026 Aug 13. doi: 10.3324/haematol.2026.301214 [Epub ahead of print]

Janus kinase inhibitors as an evolving treatment for lymphomas and immune-mediated complications

Caitlin Unkenholz[1], Sofía Huerga[2], Alison Moskowitz[1,2], and Santosha Vardhana[1,2,3]

[1] New York Presbyterian Hospital-Weill Cornell Medical College, New York, NY, USA.

[2] Lymphoma Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA.

[3] Immuno-Oncology Program, Memorial Sloan Kettering Cancer Center, New York, NY, USA.

Short title: JAK inhibition in lymphoid malignancies and inflammatory complications

Correspondence: vardhans@mskcc.org

Author Contributions: C.U. and S.H. wrote the manuscript with supervision from A.M. and S.V.

Disclosures: Research Support: Pfizer, Merck, Bristol-Myers Squibb, Incyte, and SecuraBio (A.M.), Bristol Meyers Squibb (S.V.). Honorarium: Merck, Pfizer, and Takeda (A.M). Consulting Generate Biomedicines (S.V.)

Abstract

The Janus kinase (JAK) and Signal Transducer and Activator of Transcription (STAT) signaling pathway orchestrates the cellular response to multiple cytokine families, including interleukins, hematopoietic growth factors, and interferons. JAK inhibitors were initially approved for the treatment of primary inflammatory disorders. The more recent identification of mutations that constitutively activate the JAK/STAT pathway in both myeloproliferative disorders as well as lymphoid malignancies has led to clinical exploration of JAK inhibitors for the treatment of hematopoietic cancers as well as immune-mediated complications of either hematopoietic cancers or treatment-associated, immune-mediated complications, such graft-versus-host disease (GVHD). In this review, we summarize the current understanding of the JAK/STAT pathway in the pathogenesis of both lymphoid malignancies and lymphoma-associated immune complications and discuss both the clinical efficacy and mechanisms of action of JAK inhibitors in lymphoid malignancies as well as their inflammatory complications, for which JAK inhibition has revolutionized the therapeutic landscape. In contrast, the variable clinical efficacy of JAK inhibitors across B- and T-cell malignancies highlights the need for biomarker-driven patient selection and rational combination approaches to maximize the efficacy across malignant disease contexts.

Introduction

Janus kinase (JAK) inhibitors are small-molecule agents that play an important role in the management of several hematologic disorders, including myelofibrosis (MF), polycythemia vera (PV), and graft-versus-host disease (GVHD). In addition, they are widely used in many chronic inflammatory diseases, such as psoriasis, inflammatory arthritis and spondylarthritis, and inflammatory bowel disease, among others[1]. JAK inhibitors target the JAK/STAT signaling pathway, a central regulator of immune responses and inflammation and a key pathway in both normal and malignant hematopoiesis[2].

Given the central role of JAK/STAT signaling in lymphoid biology, JAK inhibitors have recently emerged as an area of increasing interest in lymphoma research. Aberrant activation of this pathway, together with recurrent activating mutations in *JAK* and *STAT* genes, has been implicated in the pathogenesis of multiple lymphoma subtypes[3-12]. Accordingly, there is a growing body of literature on the use of JAK inhibitors across a broad spectrum of lymphoid malignancies, such as peripheral T-cell lymphomas (PTCL), extranodal NK/T-cell lymphoma (NKTCL), classical Hodgkin lymphoma (cHL), B-cell non-Hodgkin lymphomas (NHL), and large granular lymphocytic leukemia (LGL).

JAK inhibitors have also been used to manage immune-mediated complications associated with lymphoma and its treatment including GVHD, hemophagocytic lymphohistiocytosis (HLH), cytokine release syndrome (CRS), and immune effector cell-associated neurotoxicity syndrome (ICANS). In this review, we discuss the rationale, clinical efficacy, and mechanisms of action of targeting the JAK/STAT pathway in lymphoid malignancies and malignancy-associated complications.

JAK/STAT pathway: central regulators of inflammatory signaling

By the 1980s, several paracrine factors capable of eliciting rapid and diverse biological responses in hematopoietic cells, including interferons, interleukins, and growth factors, had been identified and biologically characterized. However, the question of how these paracrine factors exert rapid cellular effects remained elusive until the identification of the JAK family of tyrosine kinases and STAT family of

transcription factors in the late 1980s and early 1990s. Somatic cell complementation screens — in which mutant cell lines selectively unresponsive to interferon were rescued by transfection of candidate transcripts — led to the identification of TYK2 and subsequently JAK1 as kinases whose expression was necessary for interferon responsiveness[13,14]. In parallel, biochemical fractionation and affinity purification identified proteins containing SH2 domains that were rapidly tyrosine phosphorylated and underwent nuclear translocation upon interferon stimulation, where they bound specific promoter elements of interferon-responsive genes[15,16].

The unique architecture of the JAK/STAT family of proteins is critical for its functionality. JAKs are constitutively associated with the intracellular domain of cytokine receptors in an inactive state until ligand-induced receptor dimerization drives their reciprocal phosphorylation and transactivation. Activated JAKs then phosphorylate specific tyrosine residues on receptor intracellular tails, creating docking sites that recruit members of the STAT family of transcription factors (STAT1-6), which are themselves phosphorylated, dimerized, and translocated to the nucleus within minutes of cytokine exposure. Beyond their canonical role in cytokine receptor signaling, JAKs, particularly JAK2, also have non-canonical scaffolding and nuclear functions, including regulation of chromatin structure and gene expression [17,18]. The pathway's fidelity is enforced by negative regulatory circuits including the SOCS (suppressor of cytokine signaling) proteins, which are transcriptional targets of STATs and competitively bind phosphorylated receptor motifs, thereby directly suppressing JAK catalytic activity **(Figure 1)**.

Overall, the JAK/STAT pathway is deployed by more than fifty cytokines, interleukins, interferons, and colony-stimulating factors that are central to hematopoiesis, immune surveillance, and inflammatory resolution. This convergence is achieved through substantial promiscuity in which cytokines with distinct receptors activate overlapping sets of JAK-STAT components to produce coordinated transcriptional outputs. Importantly, certain JAK/STAT family members are more restricted in their activating inputs and downstream outputs, which reflect their preferential oncogenic activation in distinct

hematologic malignancy subtypes. For example, JAK2 is the principal kinase for homodimeric receptors that bind hematopoietic growth factors, and as such is preferentially mutated in myeloid neoplasms, whereas STAT6 exclusively transduces signals from IL-4 and IL-13 and is therefore preferentially mutated in B cell neoplasms (**Figure 2**).

JAK/STAT activation in lymphoma pathogenesis

The role of the JAK/STAT pathway in the pathobiology of lymphoid malignancies can be distinguished by the pathway members that are recurrently mutated in individual lymphoid malignancy subtypes (**Figure 3**). Classical Hodgkin lymphoma (cHL) and primary mediastinal large B-cell lymphoma (PMBCL) share many transcriptional features and are characterized by recurrent genomic alterations in the JAK/STAT pathway. Chief among these are recurrent amplifications of the 9p24.1 locus, which contains the *JAK2*, *CD274*, and *PDCD1LG2* genes[19]. In addition, activating mutations in STAT6 and inactivating mutations in SOCS1 are frequent[20,21]. Together, nearly all cHL/PMBCL tumors exhibit oncogenic activation of the JAK/STAT pathway[9].

Compared with cHL and PMBCL, oncogenic JAK/STAT activation is somewhat less common in other B-cell non-Hodgkin lymphomas (B-NHL), with most mutations being activating STAT6 or inactivating SOCS1 mutations[22,23]. Activating STAT6 mutations have also been described in follicular lymphoma, where they enhance oncogenic signaling and contribute to lymphomagenesis [24]. STAT6 is the primary transcription factor that transduces signals from IL-4 and IL-13; accordingly, STAT6 activation in B-cell lymphomas promotes B-cell proliferation as well as recruitment of immunosuppressive cells that interfere with tumor surveillance[25].

The overall mutational landscape of T-cell lymphomas is quite distinct from B-cell lymphomas, with more frequent mutations in *JAK1, JAK3*, and *STAT3*, as well as activating mutations in *STAT5B*, which are essentially never seen in B-cell lymphomas, and almost no activating mutations in *STAT6*. These mutations are even more common in specific rarer subtypes of T-cell lymphoma, including

monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL), T-cell large granulocytic leukemia (T-LGL), T-cell prolymphocytic leukemia (T-PLL), extranodal NK/T cell lymphoma (ENKTL), and certain gamma delta T cell lymphomas such as hepatosplenic T cell lymphoma (HSTCL) in which the prevalence is approximately 50%[6,26,27]. These mutations confer ligand-independent pathway activation and cytokine hypersensitivity, sustaining autonomous proliferation and resistance to apoptosis[7,10,12]. Constitutive *STAT3* activation also impairs antitumor immunity by inducing immunosuppressive cytokines and recruiting suppressive immune cells that inhibit surveillance by non-malignant cytotoxic T- and NK cells[5,28]. Together, these findings establish JAK/STAT dysregulation as a central feature of lymphoma biology and a target for therapy.

JAK inhibitors in lymphoid malignancies

Many JAK inhibitors are currently approved or under clinical investigation for a range of immune-related diseases, myeloproliferative neoplasms (MPNs), and lymphoid malignancies. Their use varies across diseases, reflecting differences in specificity for individual JAKs and JAK inhibitors. **Table 1** shows the major JAK inhibitors worldwide and their selectivity for the different JAK receptors as well as key approved indications and ongoing trials.

Monotherapy in B-cell lymphomas

Ruxolitinib has been shown to induce apoptosis in HL and primary mediastinal B-cell lymphoma (PMBCL) cell lines and to prolong survival in lymphoma xenograft murine models[29]. In B-NHL however, oncogenic JAK/STAT activation is predominantly mediated through STAT6 gain-of-function mutations and SOCS1 loss rather than direct JAK mutation, limiting the potential impact of upstream JAK inhibition. Unlike T-cell lymphomas, where constitutive JAK kinase activity drives autonomous proliferation, JAK/STAT signaling in B-NHL primarily functions to recruit immunosuppressive cells rather than as a primary cell-intrinsic survival signal. As oncogenic STAT6 mutants can signal semi-autonomously from JAK input, it is not effectively targeted by conventional JAK inhibitors. This

mechanistic distinction may explain the modest and heterogeneous clinical activity observed with single-agent JAK inhibition in B-NHL.

Clinical studies have reflected these limitations, with stronger signals in HL—where JAK2 amplification represents a more direct oncogenic dependency—than in B-NHL broadly. In a phase I study (NCT00741871) of patients with relapsed or refractory (R/R) Hodgkin and non-Hodgkin lymphomas, the JAK2 inhibitor pacritinib showed modest overall response (ORR 9%) but measurable tumor reductions in up to 55% of patients, with responses concentrated in indolent subtypes[30]. In a multicenter study (NCT01965119) of ruxolitinib in R/R HL and PMBCL (n=19), disease control was achieved in 7 of 13 HL patients, whereas all six PMBCL patients progressed. JAK2 amplification was assessed by fluorescence in situ hybridization (FISH) in patients with available tumor tissue. Among the four JAK2-amplified HL patients, three achieved clinical benefit, whereas neither of the two JAK2-amplified PMBCL patients responded, illustrating that pathway activation is not synonymous with pharmacologic sensitivity[31].

Combination strategies in B-cell lymphomas

The immunosuppressive microenvironmental role of JAK/STAT signaling in B-NHL provides a stronger mechanistic rationale for combination strategies than for monotherapy. A recent study demonstrated that JAK inhibition may paradoxically enhance antitumor immunity when combined with checkpoint blockade by reprogramming the myeloid compartment to an immunostimulatory phenotype[32]. In a phase I clinical trial (NCT03681561) in 19 patients with R/R HL who had progressed after prior PD-1 blockade, ruxolitinib plus anti-PD-1 achieved an ORR of 53%, including 6 metabolic CR, with transcriptomic analysis showing reduced JAK/STAT-driven myelopoiesis[32].

Combined PI3Kδ and JAK1 inhibition has also been explored. In a phase I study (NCT01905813), the addition of itacitinib to dezapelisib (INCB040093), a selective PI3Kδ inhibitor, amplified activity in HL (ORR 67%; CR 38%, median PFS 23 months) compared to monotherapy[33]. The dual JAK/SYK inhibitor

cerdulatinib produced tumor reductions ≥50% in CLL/SLL and FL patients, with biomarker evidence linking pSYK and pSTAT6 inhibition to response[33]. Efficacy in DLBCL was limited across both studies. Taken together, these results support rational combination strategies that leverage JAK inhibition's immunomodulatory effects rather than direct cytotoxicity in HL and indolent B-NHL.

T- and NK cell lymphomas

Mature T-cell and NK-cell neoplasms are a heterogeneous group of lymphoid malignancies that make up 5-10% of non-Hodgkin lymphomas (NHLs) in the Western World with the most frequent subtypes being angioimmunoblastic T-cell lymphoma (AITL), anaplastic large cell lymphoma (ALCL), and peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS)[34,35]. Given their rarity, subtype-specific clinical trials are challenging, and therapeutic decisions are often guided by small, non-randomized studies. With the exceptions of ALK-positive ALCL and early-stage NKTCL, prognoses are unfavorable.

In this context, the high prevalence of JAK/STAT pathway alterations in PTCL and NKTCL represents a promising therapeutic opportunity. JAK/STAT pathway activation is common across multiple PTCL entities, including a substantial proportion of patient with ALK-negative ALCL[36], ENKTL, gdTCL[37], MEITL, LGL, and PLL. Based on this, Moskowitz et al. conducted a phase II biomarker-driven study (NCT02974647), evaluating ruxolitinib in patients with R/R PTCL and CTCL. Fifty-three patients were enrolled and stratified into three groups: cohort 1 (JAK/STAT activating mutations), cohort 2 (phospho-STAT3 overexpression by immunohistochemistry), and cohort 3 (none of these)[38]. JAK/STAT pathway activation was observed in 68% of patients and was associated with higher clinical efficacy (ORR 33%, 29%, and 12%, respectively; clinical benefit rate (CBR; ORR plus stable disease lasting >6 months) 48%, 36%, and 18%). Median progression-free survival (PFS) and duration of response (DoR) were 2.8 (95% CI 1.8-4.5) and 8.4 months (95% CI 7.5-NR), respectively.

By histologic subtype, the best response was observed in T-cell large granular lymphocytic leukemia (T-LGL), an incurable lymphoproliferative disorder driven by clonal expansion of cytotoxic $CD8^+$ memory T-cells. While up to one third of patients are asymptomatic at the time of diagnosis, most eventually require treatment for cytopenias or autoimmune complications[39]. Current therapy relies on oral immunosuppressive agents such as methotrexate, cyclophosphamide, and cyclosporine, yet responses are frequently unsatisfactory and not durable. No standard therapy exists for R/R disease, underscoring a major unmet need. STAT3 is a driver of T-LGLL pathogenesis, with activating *STAT3* mutations in 30-60% of patients [39,40] and constitutive STAT3 activation in most cases.

Among five treated T-LGL patients, CBR with ruxolitinib reached 80% with two PR (40%) prompting a subtype-specific expansion in T-LGL patients[41]. Among 20 evaluable patients, ruxolitinib achieved an ORR of 55% and a CBR of 75%, including CR in 25%. Responses were durable, with a 14-month event-free survival (EFS) of 68%, and responses were significantly enriched in patients harboring *STAT3* mutations (EFS 100% vs. 40%, $p = 0.007$)[41]. Treatment was well tolerated, with only isolated cases of febrile neutropenia and herpes zoster. Plasma proteomics demonstrated a reduction in circulating interferon-driven inflammatory factors including CXCL9, CXCL10, PD-L1, and TNF. Additionally, single-cell RNA-sequencing of PBMCs showed a decrease in both circulating myeloid cell abundance and downregulation of JAK/STAT signaling in both myeloid and T-LGL cells from responding patients, supporting a model in which ruxolitinib restores hematopoiesis by disrupting JAK/STAT-dependent paracrine immune suppression[41]. A multicenter retrospective series (n=21) corroborated these findings with an ORR of 85.7% and a median PFS of 24 months[42]. A new phase II study evaluating ruxolitinib 20mg BID in R/R and untreated T-LGLL patients is ongoing (NCT05592015).

In contrast to T-LGL, clinical efficacy in PTCL was modest, potentially due to dose-limiting cytopenias by dual JAK1/2 inhibition. Golidocitinib, a selective JAK1 inhibitor, offered a potential strategy by sparing JAK2-driven hematopoiesis[43]. The pivotal JACKPOT8 Part B study (NCT04105010)

demonstrated an ORR of 44.3% in R/R PTCL and NKTCL, with particularly strong responses in PTCL with a follicular helper (FH) phenotype (ORR 62%)[44,45].

Beyond monotherapy approaches, some clinical trials are currently exploring either dual kinase inhibition or combination strategies that incorporate JAK inhibitors. Cerdulatinib, a dual SYK/JAK inhibitor, has also shown clinical activity in T-cell lymphomas in a phase IIa study (NCT01994382) with an ORR of 36.2% (21% CR) and strongest activity in AITL/TFH (ORR 51.9%)[46]. A phase I study of ruxolitinib combined with the PI3Kδ inhibitor duvelisib in R/R PTCL/CTCL and T-PLL demonstrated an ORR of 41% with superior activity in JAK/STAT-activated patients (52% vs 14%) and particularly high activity in TFH lymphomas (ORR 79%) and T-PLL (ORR 60%)[47]. These data highlight the importance of biomarker-enriched patient selection and rational kinase combination strategies for optimal efficacy in PTCL.

Cutaneous T cell lymphomas

Cutaneous T-cell lymphomas (CTCL), including mycosis fungoides (MF) and Sézary syndrome (SS), represent another T-cell malignancy subtype in which JAK/STAT pathway activation is well documented, due largely to copy number alterations in *STAT3* or *STAT5B* rather than gain-of-function mutations[48,49]. Clinical data for JAK inhibition in CTCL remain limited but are accumulating. In the Moskowitz et al. biomarker-driven study (NCT02974647), responses were observed in only 1 out of 7 CTCL patients[38]. Additionally, the dual SYK/JAK inhibitor cerdulatinib showed activity in CTCL in the phase IIa study (NCT01994382)[46]. Larger prospective studies specifically enrolling CTCL patients and incorporating molecular stratification are needed to define the role of JAK inhibition in this setting. For example, JAK2 fusions commonly occur in CTCL, with limited case series suggesting that these may be particularly susceptible to JAK inhibition[50-52]. Moreover, topical formulations, which achieve superior concentrations in the dermis compared with oral formulations, may enable more complete JAK inhibition without incurring excess toxicity[53].

Hemophagocytic lymphohistiocytosis

Hemophagocytic lymphohistiocytosis (HLH) is a severe hyper-inflammatory syndrome that can be classified as primary (pHLH) or secondary (sHLH). Primary HLH is driven by germline defects in cytotoxic lymphocyte function, whereas secondary arises in the context of infections, autoimmune disorders, or malignancies[54]. Malignancy-associated HLH accounts for approximately 28% of sHLH cases, with 76% of these being due to lymphoma, referred to as lymphoma-associated HLH (LAHS)[55]. Outcomes have been shown to be worse for patients with LAHS compared with patients with sHLH from other causes[56]. Allo-SCT remains the only curative option for pHLH and select cases of sHLH, but its role in LAHS is limited by disease aggressiveness and patient fitness. HLH is characterized by aberrant activation of cytotoxic T cells and excessive production of IFN-γ, IL-2, IL-6, and IL-10, which promotes macrophage activation and perpetuates immune-mediated tissue damage[57]. Accordingly, preclinical studies across multiple murine models demonstrated that ruxolitinib reduced IFN-γ-driven cytokine production and significantly improved survival[58,59].

Clinically, JAK inhibition has shown promising results in sHLH. In an open-label, single-center pilot study (NCT02400463), single-agent ruxolitinib was well tolerated and induced resolution of symptoms and disease-associated laboratory abnormalities in all five patients with sHLH [60]. A subsequent phase II study of ruxolitinib and dexamethasone (Ru-D) as first-line therapy in 28 adults with sHLH (including 16 with LAHS) achieved an ORR of 85.7%, with 2-year OS rates exceeding historical controls; however, LAHS cases had substantially worse outcomes than non-LAHS patients (2-year OS 37.5% vs. 75%) [61]. A systematic review pooling 75 HLH patients treated with ruxolitinib reported an ORR of 70.7%[62]. However, outcomes were not stratified by HLH etiology, precluding specific conclusions regarding efficacy in LAHS. Clinical experience with JAK inhibitors other than ruxolitinib in HLH is limited; however, itacitinib has shown efficacy in preclinical sHLH murine models, where it significantly improved survival[63]. Moreover, the addition of JAK1 inhibition to anti-IFN-γ therapy, which has shown substantial clinical activity in HLH[64,65], improved outcomes, while the addition of ruxolitinib to anti-IFN-γ

worsened outcomes, possibly due to the impact of JAK2 inhibition on hematopoiesis and underscoring the need for careful dosing strategies and selective JAK targeting in this disease[66].

JAK inhibition to treat lymphoma therapy-associated immune dysregulation

Immunotherapeutic strategies, including allogeneic stem cell transplantation (allo-SCT), bispecific antibody therapy (BsAb), bispecific T-cell engagers (BiTEs), and chimeric antigen receptor T-cell therapy (CAR-T), are increasingly mainstays of treatment for relapsed B- and T-cell lymphomas but are complicated by substantial inflammatory toxicity. Allo-SCT carries a substantial risk of graft versus host disease (GVHD) that can approach 40%. GVHD is driven by donor T-cell activation and inflammatory cytokine signaling through the JAK/STAT pathway[67,68]. CRS and ICANS are both hyperinflammatory toxicities associated with CAR-T therapy, BsAb, and BiTEs[69,70], in which excessive cytokine signaling and immune cell activation converge on JAK/STAT-dependent pathways.

Graft versus host disease

GVHD is a major complication of allo-SCT and results from donor-derived T-cells becoming sensitized to host antigens and mediating tissue damage through JAK/STAT-dependent inflammatory cytokine cascades (59,[71]. Ruxolitinib's activity in GVHD was first demonstrated in murine models showing reduced GVHD severity through suppression of T-cell proliferation and STAT3 phosphorylation alongside clinical evidence of rapid and durable responses in 6 patients[72]. A multicenter survey in 95 patients with GVHD established ORRs of 81.5% in acute GVHD (aGVHD) and 85.4% in chronic GVHD (cGVHD), with histologic regression of intestinal GVHD seen in biopsy samples, and evidence of decreased circulating inflammatory markers, IL-6**,** soluble IL-2 receptor, and activated $CD3^{+}HLA\text{-}DR^{+}$ T-cells[73]. The phase II REACH1 trial demonstrated an ORR of 55% in aGVHD[74], and the phase III REACH2 trial established ruxolitinib as the standard of care compared with investigator's choice for refractory aGVHD (ORR 62% vs. 39%, $p<0.001$)[75]. Subsequently, REACH3 established ruxolitinib as superior second-line therapy for cGVHD compared with investigator's choice (ORR 49.7% vs. 25.6%, $p<0.001$)[76].

Cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS)

CRS and ICANS are inflammatory toxicities associated with CAR-T therapy, BiTEs, and all BsAbs. CRS results from excessive immune activation with increased levels of IL-6, IFN-γ, and IL-1[69]. The pathophysiology of ICANS is not fully understood, but accumulating evidence implicates cytokines secreted predominantly by macrophages and monocytes, resulting in endothelial activation, increased vascular permeability, and disruption of the blood-brain barrier[70]. Standard management of CRS includes tocilizumab, an IL-6 antagonist, and corticosteroids, whereas ICANS is primarily treated with corticosteroids[77]. Additionally, anakinra, an IL-1 receptor antagonist, has shown efficacy in high-grade CRS and ICANS[78]. Nevertheless, a subset of patients continues to experience life-threatening toxicity, underscoring the need for additional therapies. JAK/STAT inhibition was evaluated in a phase II randomized controlled trial (NCT04071366) of prophylactic itacitinib for CRS/ICANS initiated three days prior to CAR-T infusion in patients with R/R large B-cell lymphoma[79]. The incidence of CRS was significantly reduced in the itacitinib arm compared with placebo (65% vs. 85%), with a marked decreased in grade 2 CRS (17.4% vs. 56.5%, $p = 0.003$)[79]. ICANS incidence and severity were also reduced (13% vs. 35%). Clinical experience with ruxolitinib in established CRS and ICANS is currently limited to case reports describing rapid resolution of steroid-refractory CRS following ruxolitinib administration without impairment of CAR-T efficacy[80-83].

Toxicity of JAK inhibitors: mechanisms and clinical implications

The therapeutic benefits of JAK inhibitors must be weighed against a toxicity profile that is directly attributable to the role of JAK/STAT signaling across normal tissues. The clinical consequences of JAK inhibition on hematopoiesis, immune surveillance, and cardiovascular homeostasis are discussed below and summarized in **Figure 4**.

Hematologic toxicity: JAK1 vs. JAK1/2 inhibition

Cytopenias are the most consistently observed class effect of JAK inhibitors used in lymphoma, and their severity is meaningfully influenced by isoform selectivity. Ruxolitinib and other dual JAK1/2 inhibitors suppress JAK2-dependent signaling downstream of hematopoietic growth factor signaling, leading to dose-dependent anemia and thrombocytopenia. For example, in the REACH2 trial, anemia (≥grade 3: 30%) and thrombocytopenia (≥grade 3: 33%) were the most frequent hematologic adverse events with ruxolitinib[75]. Similarly, in PTCL studies of ruxolitinib, dose-limiting cytopenias were identified as a barrier to sustained treatment exposure and contributed to the relatively modest efficacy signals when compared with golidocitinib, a selective JAK1 inhibitor, which by sparing JAK2-driven erythropoiesis and thrombopoiesis demonstrated improved hematologic tolerability[44,45]. This distinction is clinically meaningful when treating patients with pre-existing cytopenias from prior therapy or bone marrow involvement and provides the principal rationale for preferring JAK1-selective agents in PTCL. Similarly, in HLH, the JAK2 inhibitory component of ruxolitinib may paradoxically worsen disease-related cytopenias, and preclinical data suggest that selective JAK1 inhibition is preferable in this context[66].

Infectious complications

JAK inhibitors impair multiple arms of host defense by blocking signaling downstream of the common gamma-chain (γc) cytokine receptors, including IL-2, IL-7, IL-15, and IL-21, which are critical for T-cell and NK cell homeostasis and antiviral immunity. As a result, JAK inhibition is associated with increased susceptibility to opportunistic infections, including cytomegalovirus reactivation, *Pneumocystis jirovecii* pneumonia (PJP), and invasive fungal infections, including aspergillosis[75,76]. Given these risks, prophylaxis against PJP and/or invasive fungal infections may be considered in selected patients, particularly those receiving prolonged therapy, concomitant corticosteroids or other immunosuppressive agents, or with additional risk factors for opportunistic infections.

Cardiovascular and metabolic risks

Emerging evidence from large clinical trials of JAK inhibitors in rheumatologic diseases has raised important cardiovascular safety signals. The ORAL Surveillance trial, a post-marketing cardiovascular safety study of tofacitinib versus TNF inhibitors in rheumatoid arthritis, demonstrated an increased risk of major adverse cardiovascular events (MACE) and malignancy, particularly in patients ≥50 years with cardiovascular risk factors, leading to class-wide FDA black-box warnings for JAK inhibitors approved for inflammatory conditions[84]. These data are most directly derived from broader JAK1/2/3 inhibitors in inflammatory disease contexts and their applicability to the lymphoma setting—where patient populations, treatment duration, and underlying disease biology differ substantially—remains incompletely characterized. Venous thromboembolism (VTE), including deep venous thrombosis and pulmonary embolism, has also been associated with JAK inhibitor use[85]. The risk appears highest with first-generation, less selective JAK inhibitors that target multiple JAK family members, particularly at higher doses. In the lymphoma and GVHD literature, VTE rates have generally been reported at lower frequencies than in inflammatory disease cohorts, possibly reflecting differences in patient selection and concomitant anticoagulation practices. Finally, elevations in LDL and total cholesterol are a well-described class effect of JAK inhibitors[86]. These elevations are typically modest, responsive to statin therapy, and have not been directly linked to increased cardiovascular events in short-duration oncology studies. Clinicians should nonetheless monitor lipid panels in patients receiving prolonged JAK inhibitor therapy, particularly those with pre-existing cardiovascular risk factors.

Future directions

Several important questions will shape the future development of JAK inhibitors in lymphoma. First, biomarker-driven patient selection remains essential. The enrichment of responses in *STAT3*-mutated T-LGLL and JAK/STAT pathway-activated PTCL suggests that prospective incorporation of mutational profiling into clinical trial eligibility and stratification will be necessary to identify populations most likely to benefit. Second, JAK inhibitor selectivity is emerging as a clinically meaningful design parameter: JAK1-selective agents such as golidocitinib and itacitinib circumvent JAK2-associated

myelosuppression and may be preferable in patients with pre-existing cytopenias or in contexts where JAK2 inhibition is deleterious, such as in HLH. Third, rational combination strategies hold the greatest promise for B-cell malignancies, where JAK/STAT signaling operates predominantly through microenvironmental immunosuppression rather than cell-intrinsic oncogenic dependency; combinations with checkpoint blockade, PI3K inhibitors, and SYK inhibitors have demonstrated early proof-of-concept and warrant prospective evaluation. Finally, the development of agents targeting JAK/STAT effectors more selectively—including direct STAT3 inhibitors, STAT3-targeting PROTACs, and allosteric JAK modulators—may expand the therapeutic index of this pathway beyond what is achievable with current ATP-competitive kinase inhibitors.

Conclusion

JAK inhibitors have evolved from use in myeloproliferative disorders and inflammatory diseases to agents with increasing relevance in lymphoid malignancies and their immune complications. By modulating the JAK/STAT pathway, which is shared by malignant lymphoid cells and immune effectors, JAK inhibitors enable both antitumor activity and targeted immunomodulation. The clearest clinical benefit has emerged in T-LGLL, steroid-refractory GVHD, and HLH, where JAK/STAT-dependent inflammatory signaling is the primary disease driver. In contrast, direct antitumor activity in B-NHL remains modest, reflecting the indirect, microenvironmental role of JAK/STAT signaling in most B-cell contexts. Realizing the full therapeutic potential of this drug class in lymphoma will require biomarker-enriched trial designs, thoughtful agent selection based on isoform selectivity, and rational combination strategies.

References

1. Shawky AM, Almalki FA, Abdalla AN, Abdelazeem AH, Gouda AM. A comprehensive overview of globally Approved JAK inhibitors. Pharmaceutics. 2022;14(5):1001.
2. Bousoik E, Montazeri Aliabadi H. "Do We Know Jack" About JAK? A closer look at JAK/STAT signaling pathway. Front Oncol. 2018;8:287.
3. Zhu F, Wang KB, Rui L. STAT3 Activation and oncogenesis in lymphoma. Cancers (Basel). 2019;12(1):19.
4. Yuan J, Zhang F, Niu R. Multiple regulation pathways and pivotal biological functions of STAT3 in cancer. Sci Rep. 2015;5:17663.
5. Wang Y, Shen Y, Wang S, Shen Q, Zhou X. The role of STAT3 in leading the crosstalk between human cancers and the immune system. Cancer Lett. 2018;415:117-128.
6. Waldmann TA, Chen J. Disorders of the JAK/STAT pathway in T Cell lymphoma pathogenesis: Implications for Immunotherapy. Annu Rev Immunol. 2017;35:533-550.
7. Vicente C, Schwab C, Broux M, et al. Targeted sequencing identifies associations between IL7R-JAK mutations and epigenetic modulators in T-cell acute lymphoblastic leukemia. Haematologica. 2015;100(10):1301-1310.
8. Tosic I, Frank DA. STAT3 as a mediator of oncogenic cellular metabolism: Pathogenic and therapeutic implications. Neoplasia. 2021;23(12):1167-1178.
9. Tiacci E, Ladewig E, Schiavoni G, et al. Pervasive mutations of JAK-STAT pathway genes in classical Hodgkin lymphoma. Blood. 2018;131(22):2454-2465.
10. Roncero AM, Lopez-Nieva P, Cobos-Fernandez MA, et al. Contribution of JAK2 mutations to T-cell lymphoblastic lymphoma development. Leukemia. 2016;30(1):94-103.
11. O'Shea JJ, Holland SM, Staudt LM. JAKs and STATs in immunity, immunodeficiency, and cancer. N Engl J Med. 2013;368(2):161-170.
12. Chang YH, Yu CH, Jou ST, et al. Targeted sequencing to identify genetic alterations and prognostic markers in pediatric T-cell acute lymphoblastic leukemia. Sci Rep. 2021;11(1):769.
13. Velazquez L, Fellous M, Stark GR, Pellegrini S. A protein tyrosine kinase in the interferon alpha/beta signaling pathway. Cell. 1992;70(2):313-322.
14. Wilks AF, Harpur AG, Kurban RR, Ralph SJ, Zurcher G, Ziemiecki A. Two novel protein-tyrosine kinases, each with a second phosphotransferase-related catalytic domain, define a new class of protein kinase. Mol Cell Biol.1991;11(4):2057-2065.
15. Schindler C, Shuai K, Prezioso VR, Darnell JE Jr. Interferon-dependent tyrosine phosphorylation of a latent cytoplasmic transcription factor. Science. 1992;257(5071):809-813.
16. Shuai K, Schindler C, Prezioso VR, Darnell JE Jr. Activation of transcription by IFN-gamma: tyrosine phosphorylation of a 91-kD DNA binding protein. Science. 1992;258(5089):1808-1812.
17. Dawson MA, Bannister AJ, Gottgens B, et al. JAK2 phosphorylates histone H3Y41 and excludes HP1alpha from chromatin. Nature. 2009;461(7265):819-822.
18. Hu X, Li J, Fu M, Zhao X, Wang W. The JAK/STAT signaling pathway: from bench to clinic. Signal Transduct Target Ther. 2021;6(1):402.
19. Green MR, Monti S, Rodig SJ, et al. Integrative analysis reveals selective 9p24.1 amplification, increased PD-1 ligand expression, and further induction via JAK2 in nodular sclerosing Hodgkin lymphoma and primary mediastinal large B-cell lymphoma. Blood. 2010;116(17):3268-3277.
20. Mottok A, Renne C, Willenbrock K, Hansmann ML, Brauninger A. Somatic hypermutation of SOCS1 in lymphocyte-predominant Hodgkin lymphoma is accompanied by high JAK2 expression and activation of STAT6. Blood. 2007;110(9):3387-3390.
21. Ritz O, Guiter C, Castellano F, et al. Recurrent mutations of the STAT6 DNA binding domain in primary mediastinal B-cell lymphoma. Blood. 2009;114(6):1236-1242.
22. Duns G, Vigano E, Ennishi D, et al. Characterization of DLBCL with a PMBL gene expression signature. Blood. 2021;138(2):136-148.
23. Yildiz M, Li H, Bernard D, et al. Activating STAT6 mutations in follicular lymphoma. Blood. 2015;125(4):668-679.
24. Shao Q, Bedi K, Malek IA, Shedden K, Malek SN. STAT6 mutations compensate for CREBBP mutations and hyperactivate IL4/STAT6/RRAGD/mTOR signaling in follicular lymphoma. Leukemia. 2025;39(4):899-908.
25. Skinnider BF, Elia AJ, Gascoyne RD, et al. Signal transducer and activator of transcription 6 is frequently activated in Hodgkin and Reed-Sternberg cells of Hodgkin lymphoma. Blood. 2002;99(2):618-626.
26. Iqbal J, Inghirami G, Chan WC. New insights into the biology of T-cell lymphomas. Blood. 2024;144(18):1873-1886.
27. McKinney M, Moffitt AB, Gaulard P, et al. The genetic basis of hepatosplenic T-cell lymphoma. Cancer Discov. 2017;7(4):369-379.

28. Zhang L, Kuca K, You L, et al. Signal transducer and activator of transcription 3 signaling in tumor immune evasion. Pharmacol Ther. 2022;230:107969.
29. Lee S, Shah T, Yin C, et al. Ruxolitinib significantly enhances in vitro apoptosis in Hodgkin lymphoma and primary mediastinal B-cell lymphoma and survival in a lymphoma xenograft murine model. Oncotarget. 2018;9(11):9776-9788.
30. Younes A, Romaguera J, Fanale M, et al. Phase I study of a novel oral Janus kinase 2 inhibitor, SB1518, in patients with relapsed lymphoma: evidence of clinical and biologic activity in multiple lymphoma subtypes. J Clin Oncol. 2012;30(33):4161-4167.
31. Kim SJ, Yoon DH, Kang HJ, et al. Ruxolitinib shows activity against Hodgkin lymphoma but not primary mediastinal large B-cell lymphoma. BMC Cancer. 2019;19(1):1080.
32. Zak J, Pratumchai I, Marro BS, et al. JAK inhibition enhances checkpoint blockade immunotherapy in patients with Hodgkin lymphoma. Science. 2024;384(6702):eade8520.
33. Phillips TJ, Forero-Torres A, Sher T, et al. Phase 1 study of the PI3Kdelta inhibitor INCB040093 +/- JAK1 inhibitor itacitinib in relapsed/refractory B-cell lymphoma. Blood. 2018;132(3):293-306.
34. Vose J, Armitage J, Weisenburger D, International TCLP. International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. J Clin Oncol. 2008;26(25):4124-4130.
35. Fiore D, Cappelli LV, Broccoli A, Zinzani PL, Chan WC, Inghirami G. Peripheral T cell lymphomas: from the bench to the clinic. Nat Rev Cancer. 2020;20(6):323-342.
36. Crescenzo R, Abate F, Lasorsa E, et al. Convergent mutations and kinase fusions lead to oncogenic STAT3 activation in anaplastic large cell lymphoma. Cancer Cell. 2015;27(4):516-532.
37. Kucuk C, Jiang B, Hu X, et al. Activating mutations of STAT5B and STAT3 in lymphomas derived from gammadelta-T or NK cells. Nat Commun. 2015;6:6025.
38. Moskowitz AJ, Ghione P, Jacobsen E, et al. A phase 2 biomarker-driven study of ruxolitinib demonstrates effectiveness of JAK/STAT targeting in T-cell lymphomas. Blood. 2021;138(26):2828-2837.
39. Marchand T, Lamy T, Loughran TP Jr. A modern view of LGL leukemia. Blood. 2024;144(18):1910-1923.
40. Koskela HL, Eldfors S, Ellonen P, et al. Somatic STAT3 mutations in large granular lymphocytic leukemia. N Engl J Med. 2012;366(20):1905-1913.
41. Moskowitz AJ, Rahman J, Ganesan N, et al. Ruxolitinib promotes clinical responses in large granular lymphocytic leukemia via suppression of JAK/STAT-dependent inflammatory cascades. Blood. 2023;142(Supplement 1):183.
42. Marchand T, Pastoret C, Damaj G, et al. Efficacy of ruxolitinib in the treatment of relapsed/refractory large granular lymphocytic leukaemia. Br J Haematol. 2024;205(3):915-923.
43. Moskowitz AJ, Stuver RN, Horwitz SM. Current and upcoming treatment approaches to common subtypes of PTCL (PTCL, NOS; ALCL; and TFHs). Blood. 2024;144(18):1887-1897.
44. Song Y, Malpica L, Cai Q, et al. Golidocitinib, a selective JAK1 tyrosine-kinase inhibitor, in patients with refractory or relapsed peripheral T-cell lymphoma (JACKPOT8 Part B): a single-arm, multinational, phase 2 study. Lancet Oncol. 2024;25(1):117-125.
45. Song Y, Yoon DH, Yang H, et al. Phase I dose escalation and expansion study of golidocitinib, a highly selective JAK1 inhibitor, in relapsed or refractory peripheral T-cell lymphomas. Ann Oncol. 2023;34(11):1055-1063.
46. Horwitz SM, Feldman TA, Ye JC, et al. Results from an open-label phase 2a study of cerdulatinib, a dual spleen tyrosine kinase/janus kinase inhibitor, in relapsed/refractory peripheral T-cell lymphoma. Leuk Lymphoma. 2025;66(6):1100-1110.
47. Moskowitz AJ, Ganesan N, Chang T, et al. Dual-targeted therapy with ruxolitinib plus duvelisib for T-cell lymphoma. Blood. 2024;144(Supplement 1):463.
48. Kiel MJ, Sahasrabuddhe AA, Rolland DCM, et al. Genomic analyses reveal recurrent mutations in epigenetic modifiers and the JAK-STAT pathway in Sezary syndrome. Nat Commun. 2015;6:8470.
49. Tensen CP, Quint KD, Vermeer MH. Genetic and epigenetic insights into cutaneous T-cell lymphoma. Blood. 2022;139(1):15-33.
50. Geller S, Liao V, Lavin L, et al. JAK2 fusions in adult patients with mycosis fungoides and CD30 lymphoproliferative disorders. JAMA Dermatol. 2026;162(1):41-46.
51. Lee K, Evans MG, Yang L, et al. Primary cytotoxic T-cell lymphomas harbor recurrent targetable alterations in the JAK-STAT pathway. Blood. 2021;138(23):2435-2440.
52. Zhang Y, Yescas JA, Tefft K, et al. Addiction of primary cutaneous gammadelta T cell lymphomas to JAK/STAT signaling. J Clin Invest. 2025;135(8):e180417.
53. Persaud I, Diamond S, Pan R, et al. Plasma pharmacokinetics and distribution of ruxolitinib into skin following oral and topical administration in minipigs. Int J Pharm. 2020;590:119889.
54. Henter JI. Hemophagocytic lymphohistiocytosis. N Engl J Med. 2025;392(6):584-598.

55. Knaak C, Schuster FS, Nyvlt P, et al. Treatment and mortality of hemophagocytic lymphohistiocytosis in adult critically Ill patients: a systematic review with pooled analysis. Crit Care Med. 2020;48(11):e1137-e1146.
56. Zhang Q, Wang L, Zhou D, et al. Clinical features and prognostic analysis of lymphoma-associated hemophagocytic syndrome: a report of 139 cases. Oncol Lett. 2023;25(1):13.
57. Jordan MB, Hildeman D, Kappler J, Marrack P. An animal model of hemophagocytic lymphohistiocytosis (HLH): CD8+ T cells and interferon gamma are essential for the disorder. Blood. 2004;104(3):735-743.
58. Das R, Guan P, Sprague L, et al. Janus kinase inhibition lessens inflammation and ameliorates disease in murine models of hemophagocytic lymphohistiocytosis. Blood. 2016;127(13):1666-1675.
59. Albeituni S, Verbist KC, Tedrick PE, et al. Mechanisms of action of ruxolitinib in murine models of hemophagocytic lymphohistiocytosis. Blood. 2019;134(2):147-159.
60. Ahmed A, Merrill SA, Alsawah F, et al. Ruxolitinib in adult patients with secondary haemophagocytic lymphohistiocytosis: an open-label, single-centre, pilot trial. Lancet Haematol. 2019;6(12):e630-e637.
61. Zhou D, Huang X, Zhu L, et al. Ruxolitinib combined with dexamethasone for adult patients with newly diagnosed hemophagocytic lymphohistiocytosis in China. Blood. 2025;146(3):318-327.
62. Shahzad M, Sarfraz Z, Azam R, et al. Efficacy of ruxolitinib in patients with hemophagocytic lymphohistiocytosis: a systematic review. Blood. 2024;144(Supplement 1):5372.
63. Keenan C, Albeituni S, Oak N, et al. Differential effects of itacitinib, fedratinib, and ruxolitinib in mouse models of hemophagocytic lymphohistiocytosis. Blood. 2024;143(23):2386-2400.
64. Locatelli F, Jordan MB, Allen C, et al. Emapalumab in children with primary hemophagocytic lymphohistiocytosis. N Engl J Med. 2020;382(19):1811-1822.
65. Johnson WT, Epstein-Peterson ZD, Ganesan N, et al. Emapalumab as salvage therapy for adults with malignancy-associated hemophagocytic lymphohistiocytosis. Haematologica. 2024;109(9):2998-3003.
66. Chaturvedi V, Lakes N, Tran M, Castillo N, Jordan MB. JAK inhibition for murine HLH requires complete blockade of IFN-gamma signaling and is limited by toxicity of JAK2 inhibition. Blood. 2021;138(12):1034-1039.
67. Malard F, Holler E, Sandmaier BM, Huang H, Mohty M. Acute graft-versus-host disease. Nat Rev Dis Primers. 2023;9(1):27.
68. Malard F, Huang XJ, Sim JPY. Treatment and unmet needs in steroid-refractory acute graft-versus-host disease. Leukemia. 2020;34(5):1229-1240.
69. Tvedt THA, Vo AK, Bruserud O, Reikvam H. Cytokine release syndrome in the immunotherapy of hematological malignancies: the biology behind and possible clinical consequences. J Clin Med. 2021;10(21):5190.
70. Sterner RC, Sterner RM. Immune effector cell associated neurotoxicity syndrome in chimeric antigen receptor-T cell therapy. Front Immunol. 2022;13:879608.
71. Mannina D, Kröger N. Janus kinase inhibition for graft-versus-host disease: current status and future prospects. Drugs. 2019;79(14):1499-1509.
72. Spoerl S, Mathew NR, Bscheider M, et al. Activity of therapeutic JAK 1/2 blockade in graft-versus-host disease. Blood. 2014;123(24):3832-3842.
73. Zeiser R, Burchert A, Lengerke C, et al. Ruxolitinib in corticosteroid-refractory graft-versus-host disease after allogeneic stem cell transplantation: a multicenter survey. Leukemia. 2015;29(10):2062-2068.
74. Jagasia M, Perales MA, Schroeder MA, et al. Ruxolitinib for the treatment of steroid-refractory acute GVHD (REACH1): a multicenter, open-label phase 2 trial. Blood. 2020;135(20):1739-1749.
75. Zeiser R, von Bubnoff N, Butler J, et al. Ruxolitinib for glucocorticoid-refractory acute graft-versus-host disease. N Engl J Med. 2020;382(19):1800-1810.
76. Zeiser R, Polverelli N, Ram R, et al. Ruxolitinib for glucocorticoid-refractory chronic graft-versus-host disease. N Engl J Med. 2021;385(3):228-238.
77. Santomasso BD, Nastoupil LJ, Adkins S, et al. Management of Immune-related adverse events in patients treated with chimeric antigen receptor t-Cell therapy: ASCO guideline. J Clin Oncol. 2021;39(35):3978-3992.
78. Strati P, Ahmed S, Kebriaei P, et al. Clinical efficacy of anakinra to mitigate CAR T-cell therapy-associated toxicity in large B-cell lymphoma. Blood Adv. 2020;4(13):3123-3127.
79. Frigault MJ, Maziarz RT, Park JH, et al. Itacitinib for the Prevention of immune effector cell therapy-associated cytokine release syndrome: results from the phase 2 incb 39110-211 placebo-controlled randomized cohort. Blood. 2023;142(Supplement 1):356.
80. Zi FM, Ye LL, Zheng JF, Cheng J, Wang QM. Using JAK inhibitor to treat cytokine release syndrome developed after chimeric antigen receptor T cell therapy for patients with refractory acute lymphoblastic leukemia: a case report. Medicine (Baltimore). 2021;100(19):e25786.
81. Zavoriti A, Miossec P. Understanding the effects of Janus kinase inhibitors on the cardiovascular system in comparison to main biological DMARDs in rheumatoid arthritis. Autoimmun Rev. 2025;24(11):103892.

82. Wei S, Gu R, Xu Y, et al. Adjuvant ruxolitinib therapy relieves steroid-refractory cytokine-release syndrome without impairing chimeric antigen receptor-modified T-cell function. Immunotherapy. 2020;12(14):1047-1052.
83. Li S, Wang X, Yuan Z, et al. Eradication of T-ALL cells by CD7-targeted universal CAR-T cells and initial test of Ruxolitinib-based CRS management. Clin Cancer Res. 2021;27(5):1242-1246.
84. Ytterberg SR, Bhatt DL, Mikuls TR, et al. Cardiovascular and cancer risk with tofacitinib in rheumatoid arthritis. N Engl J Med. 2022;386(4):316-326.
85. Charles-Schoeman C, Fleischmann R, Mysler E, et al. Risk of venous thromboembolism with tofacitinib versus tumor necrosis factor inhibitors in cardiovascular risk-enriched rheumatoid arthritis patients. Arthritis Rheumatol. 2024;76(8):1218-1229.
86. Li N, Gou ZP, Du SQ, et al. Effect of JAK inhibitors on high- and low-density lipoprotein in patients with rheumatoid arthritis: a systematic review and network meta-analysis. Clin Rheumatol. 2022;41(3):677-688.
87. Roskoski R Jr. Janus kinase (JAK) inhibitors in the treatment of neoplastic and inflammatory disorders. Pharmacol Res. 2022;183:106362.
88. Singer JW, Al-Fayoumi S, Taylor J, Velichko S, O'Mahony A. Comparative phenotypic profiling of the JAK2 inhibitors ruxolitinib, fedratinib, momelotinib, and pacritinib reveals distinct mechanistic signatures. PLoS One. 2019;14(9):e0222944.
89. Vainchenker W, Leroy E, Gilles L, Marty C, Plo I, Constantinescu SN. JAK inhibitors for the treatment of myeloproliferative neoplasms and other disorders. F1000Res. 2018;7:82.
90. Li T, Yang X, Zhu J, et al. Current application status and structure-activity relationship of selective and non-selective JAK inhibitors in diseases. Int Immunopharmacol. 2023;122:110660.
91. Virtanen A, Palmroth M, Liukkonen S, et al. Differences in JAK isoform selectivity among different types of JAK inhibitors evaluated for rheumatic diseases through in vitro profiling. Arthritis Rheumatol. 2023;75(11):2054-2061.
92. Konzett V, Smolen JS, Nash P, et al. Efficacy of Janus kinase inhibitors in immune-mediated inflammatory diseases a systematic literature review informing the 2024 update of an international consensus statement. Ann Rheum Dis. 2025;84(5):680-696.
93. Drugs@FDA. Approved Drug Products with Therapeutic Equivalence Evaluations (102nd ed.). Available at https://www.fda.gov/drugs/drug-approvals-and-databases/drugsfda-data-files Accessed on 2025, October 10.
94. Agency PaMD. List of approved products. Available at https://www.pmda.go.jp/english/review-services/reviews/approved-information/drugs/0002.html Accessed on 2025, October 10.
95. Agency MaHpR. UK-wide licensing for human medicines. Medicines and Healthcare products Regulatory Agency. Available at https://products.mhra.gov.uk/ Accessed on 2025, October 10.
96. (EMA) EMA. Medicines for human use. https://www.ema.europa.eu/en/medicines
97. Administration NMP. National Medical Products Administration database. Available at https://www.nmpa.gov.cn/datasearch/en/search-result-en.html?nmpaItem=82808081889a0b5601889a251e33005c Accessed on 2025, October 10.
98. Cerami E, Gao J, Dogrusoz U, et al. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. Cancer Discov. 2012;2(5):401-404.

Table 1. Globally available JAK inhibitors, their selectivity, approvals, and ongoing clinical trials.

JAK Inhibitor	JAK1	JAK2	JAK3	TYK2	Approvals	Clinical trials	References
Ruxolitinib	+	++	+/-	+/-	MF, PV, GVHD, AD (US, EU, Japan, China, Australia, Canada)	Vitiligo, PTCL, HL, PMBCL, LGLL (US, EU, Japan, China)	[87], [1], [88], [89]
Golidocitinib	+++	+/-	+/-	+/-	PTCL (China, conditional approval)	PTCL, others	[90]
Pacritinib	+/-	++	+/-	+/-	MF (esp. thrombocytopenia) (US)	MPNs, HL, other B-cell malignancies (US)	[1], [87,88]
Itacitinib	++	+/-	+/-	+/-	None	RA, SSc, HL, other B-cell malignancies, GVHD (US, EU, Japan)	[91]
Fedratinib	+/-	++	+/-	+/-	MF (US, EU, Australia, Canada)	MPNs (US, EU)	[1], [87,88]
Cerdulatinib	++	++	++	++	PsA in Japan	PTCL and R/R B-cell malignancies (US, EU)	[1]
Momelotinib	+	++	+/-	+/-	MF (US, EU)	MPNs (US, EU)	[88]
Baricitinib	+	+	+/-	+/-	RA, COVID-19, AD (US, EU, Japan, China, Australia, Canada)	SLE (US, EU, Japan, China)	[91,92]
Tofacitinib	+	+	+	+/-	RA, PsA, JIA, AS, UC (US, EU, Japan, China, Australia)	AA, SLE (US, EU, Japan, China)	[87,91,92]
Upadacitinib	++	+/-	+/-	+/-	RA, PsA, AS, SpA, UC, CD, AD, JIA (US, EU,	Takayasu arteritis, GCA (US, EU, Japan)	[87,91,92]

JAK Inhibitor	JAK1	JAK2	JAK3	TYK2	Approvals	Clinical trials	References
					Japan, Australia, Canada)		
Filgotinib	++	+/-	+/-	+/-	RA, UC (EU, Japan, Australia)	CD (EU, Japan)	[91,92]
Delgocitinib	+	+	+	+	AD (EU, Japan)	chronic hand eczema (EU, Japan)	[1]
Peficitinib	+	+	+	+/-	RA (Japan, South Korea)	RA (US, EU, Japan)	[91,92]
Abrocitinib	++	+/-	+/-	+/-	AD (US, EU, Japan, Australia, Canada)	None	[1,87,92]
Ritlecitinib	+/-	+/-	+++	+/-	AA (US, EU, Japan)	RA, vitiligo (US, EU, Japan)	[91,92]
Deucrava-citinib	+/-	+/-	+/-	+++	PsA (US, Japan)	SLE, CD, UC (US, EU, Japan)	[91,92]

Table 1. JAK inhibitors available globally, their selectivity for the JAK family members graded by low (+/-), moderate (+), high (++), or very high (+++) selectivity, key approved indications and their countries, ongoing clinical trials and their countries, and references. The approvals/governing bodies for each of the countries/regions listed are cited here[93-97].

Abbreviations: polycythemia vera (PV), myelofibrosis (MF), rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), graft-versus host disease (GVHD), juvenile idiopathic arthritis (JIA), axial spondyloarthritis (SpA), systemic lupus erythematosus (SLE), systemic sclerosis (SS), ulcerative colitis (UC), Crohn's Disease (CD), alopecia areata (AA), atopic dermatitis (AD), giant cell arteritis (GCA), myeloproliferative neoplasms (MPNs)

Figure 1. Overview of the canonical JAK/STAT signaling pathway. Cytokine binding to its receptor leads to dimerization and reorientation of receptor-associated JAK kinases (JAK1, JAK2, JAK3, and TYK2), leading to their trans-phosphorylation, activation, and subsequent phosphorylation of the STAT family of transcription factors. Activated STATs dimerize and translocate to the nucleus, where they regulate the transcription of genes involved in immune responses, cell proliferation, and survival. SOCS1 acts as a key negative regulator of the pathway by inhibiting JAK signaling, thereby maintaining signaling homeostasis. JAK: Janus kinase. STAT: signal transducer and activator of transcription. SOCS1: suppressor of cytokine signaling 1. IFNs: interferons. IL: interleukin.

Figure 2. Differential specificity of JAK/STAT family members and relationship to oncogenic potential. Key members of the JAK/STAT signaling pathway range from broad (SOCS1, which negative regulates all JAK family members) to specific (STAT6, which exclusively transduces signals from IL-4 and IL-13). The respective prevalence of these mutations in hematologic malignancy subtypes is listed. T-NHL: T-cell non-Hodgkin lymphoma. cHL: classical Hodgkin lymphoma. B-NHL: B-cell non-Hodgkin lymphoma. MPN: myeloproliferative neoplasm.

Figure 3. Distribution of JAK/STAT family mutations across lymphoma subtypes. (a) Prevalence of the 6 most commonly mutated genes in the JAK/STAT family in B-NHL and T-NHL from MSKCC's clinical IMPACT sequencing cohort[98]. (b) Integrated prevalence of somatic mutations in B-NHL and T-NHL subtypes as indicated. (c) Lollipop plots depicting SNV frequency in the 6 most commonly mutated genes in the JAK/STAT family. SV: structural variant. SNV: single nucleotide variant.

Figure 4. Mechanisms of JAK inhibitor toxicity. The three most common toxicities with JAK inhibition are organized by organ system along with their mechanism of action, including hematologic effects (JAK2-dependent erythropoiesis and thrombopoiesis), infectious complications (JAK-dependent T- and NK cell surveillance), and cardiovascular risks (dyslipidemia, venous thromboembolism). The relative contribution of JAK1 versus JAK2 to these toxicities is also displayed.

Cytokines
(e.g., IL-6, IL-10, IL-2, IL-4, IL-13, IL-21, IFNs)

Cytokine receptor

Cytoplasm

JAK1 JAK2 JAK3 TYK2

STAT phosphorylation

STAT1 STAT3 STAT5 STAT6

Dimerization

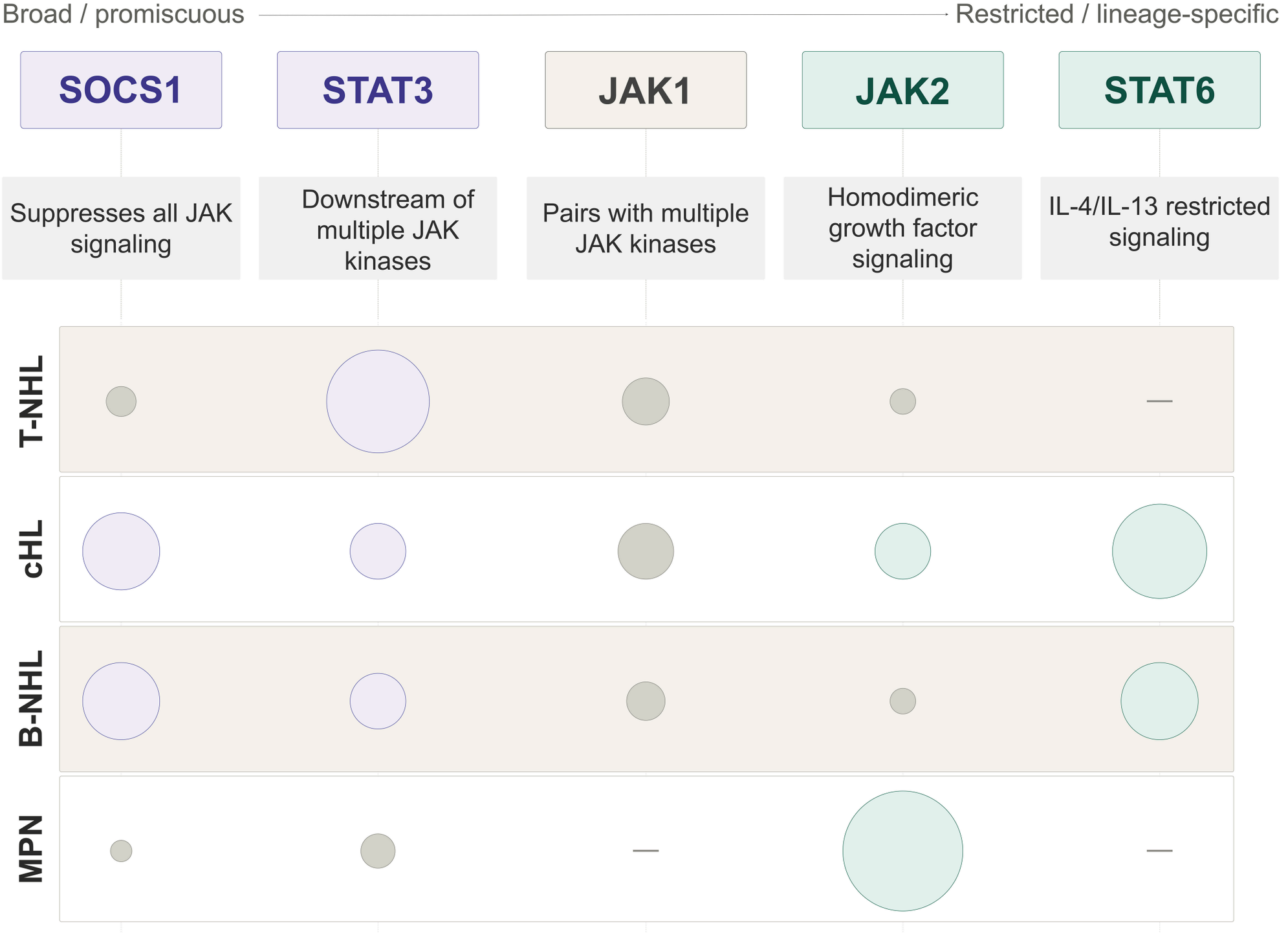
SOCS1

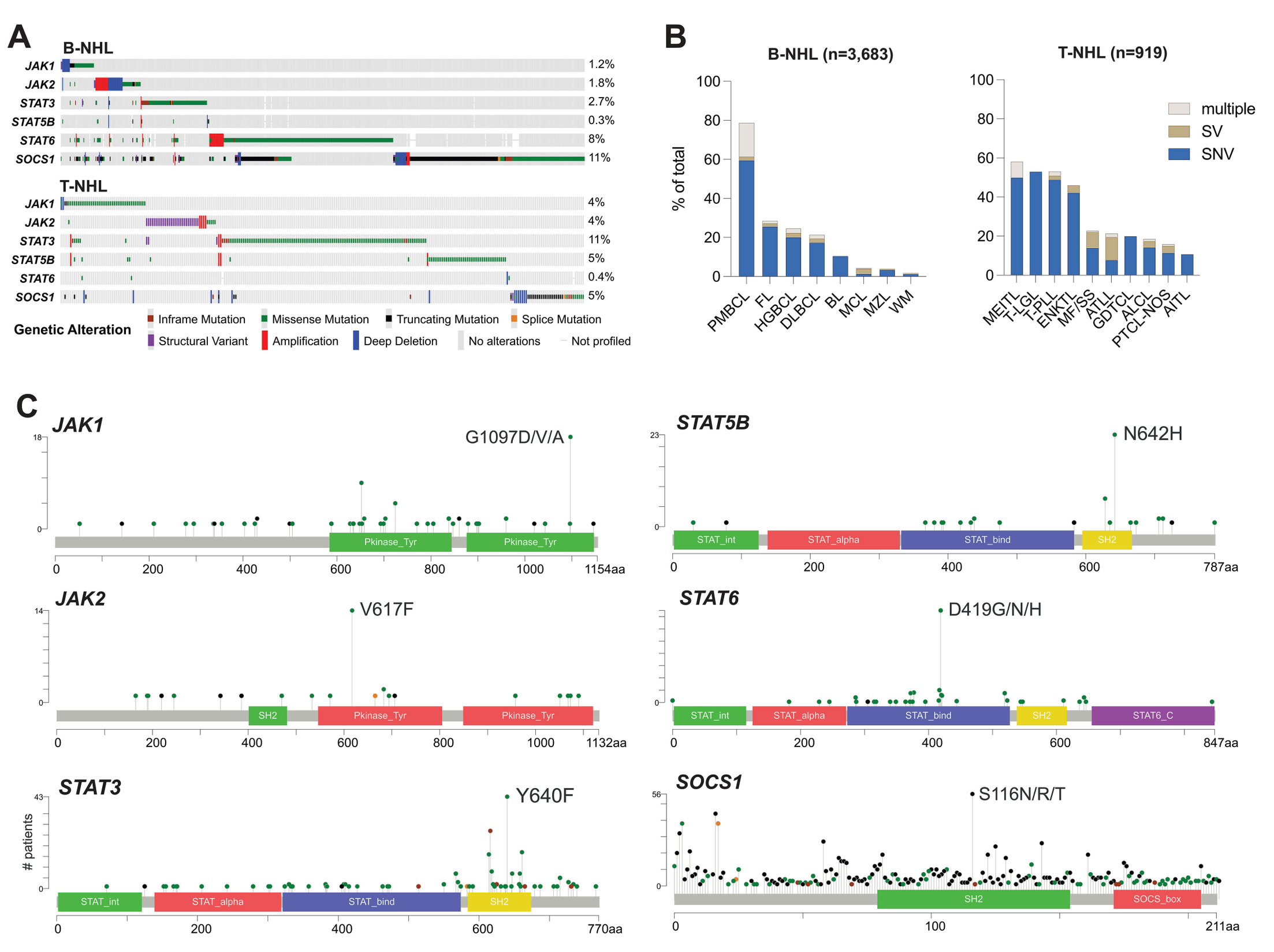
Negative feedback loop

Nucleus

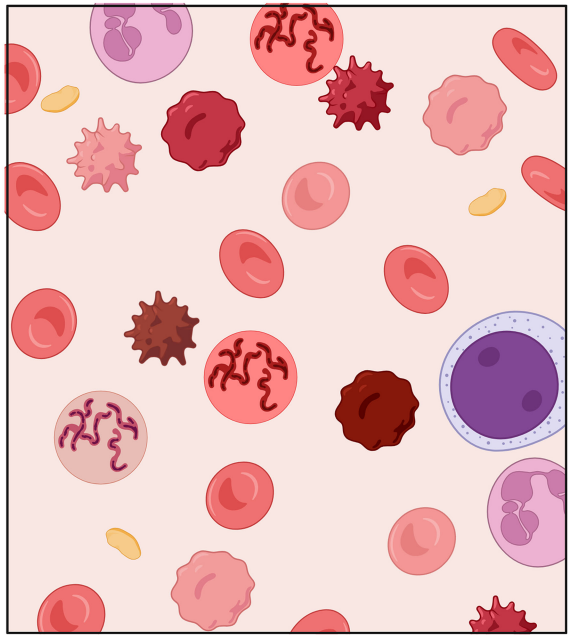
Transcription of target genes

Proliferation / Survival / Immune regulation

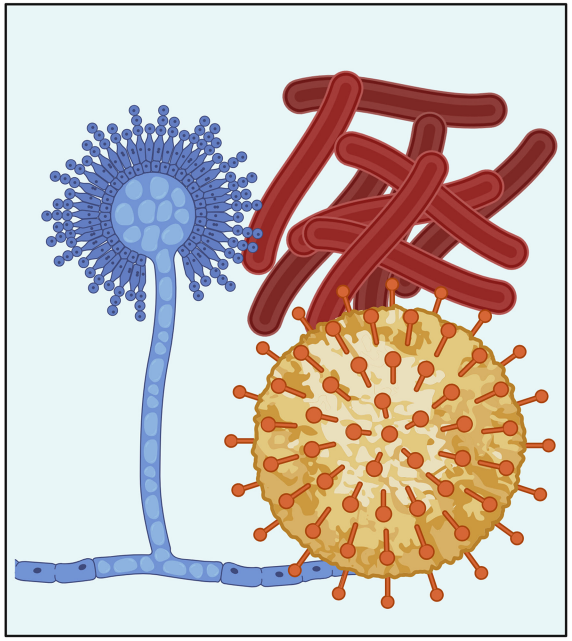

Broad / promiscuous
Restricted / lineage-specific
SOCS1
STAT3
JAK1
JAK2
STAT6
Suppresses all JAK signaling
Downstream of multiple JAK kinases
Pairs with multiple JAK kinases
Homodimeric growth factor signaling
IL-4/IL-13 restricted signaling
T-NHL
cHL
B-NHL
MPN
Bubble size = relative mutation / dysregulation frequency
Broad / cross-lineage (SOCS1, STAT3): mutations recur across T-cell lymphomas, B-cell NHL, and HL
Restricted / lineage-specific (JAK2, STAT6): mutations concentrated in one disease context
Intermediate or pathway-level activation without recurrent direct mutation


A
B-NHL
JAK1 1.2%
JAK2 1.8%
STAT3 2.7%
STAT5B 0.3%
STAT6 8%
SOCS1 11%
T-NHL
JAK1 4%
JAK2 4%
STAT3 11%
STAT5B 5%
STAT6 0.4%
SOCS1 5%
Genetic Alteration
Inframe Mutation
Missense Mutation
Truncating Mutation
Splice Mutation
Structural Variant
Amplification
Deep Deletion
No alterations
Not profiled
B
B-NHL (n=3,683)
T-NHL (n=919)
% of total
multiple
SV
SNV
PMBCL
FL
HGBCL
DLBCL
BL
MCL
MZL
WM
MEITL
T-LGL
T-PLL
ENKTL
MF/SS
ATLL
GDTCL
ALCL
PTCL-NOS
AITL
C
JAK1
G1097D/V/A
Pkinase_Tyr
1154aa
STAT5B
N642H
STAT_int
STAT_alpha
STAT_bind
SH2
787aa
JAK2
V617F
SH2
1132aa
STAT6
D419G/N/H
STAT6_C
847aa
STAT3
Y640F
patients
770aa
SOCS1
S116N/R/T
SOCS_box
211aa

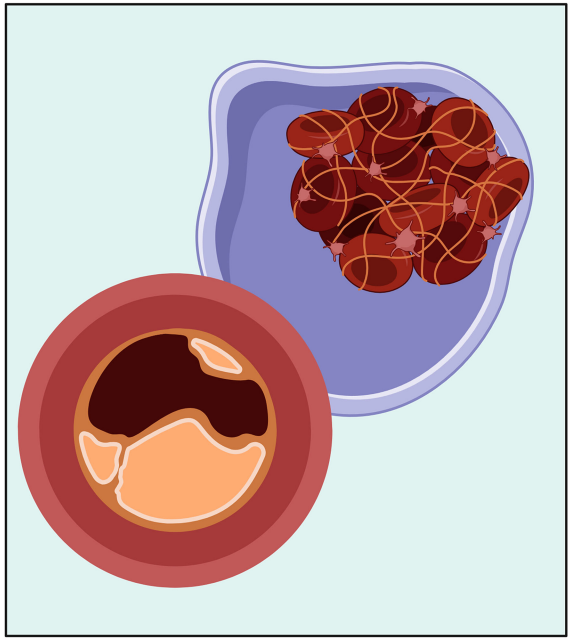
Myelosuppression



Immunodeficiency



Cardiovascular



JAK1

JAK2

JAK2-dependent hematopoiesis

JAK1/2-dependent T cell surveillance

JAKi-driven dyslipidemia, thrombotic events