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Targeting CDK9 in Autoimmune Diseases: A New Approach to Inflammation Control (Title)

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ABSTRACT

Cyclin-dependent kinase 9 (*CDK9*), the kinase associated with positive transcription elongation factor b (P-TEFb), enhances transcription elongation by phosphorylating RNA polymerase II and transcription elongation factors. The critical function of P-TEFb is in mediating networks of transcription that are induced by cytokines. More specifically, P-TEFb is involved in STAT3 signaling induced by IL-6 and TNF-inducible NF-κB activation. Within these signaling cascades, the pathways become hyperactivated due to abnormal *CDK9* activity, which in turn increases inflammation and causes tissue damage. Pharmacological research has recently made great strides, and new *CDK9* inhibitors are being considered as potential treatment options for regulating abnormal inflammatory responses. The efficacy of these inhibitors in reducing inflammation and symptom severity has been demonstrated in preclinical studies of inflammatory diseases, including psoriasis, inflammatory bowel disease, rheumatoid arthritis, and atherosclerosis. The advancement of next-generation *CDK9* inhibitors with improved selectivity and diminished off-target effects provides considerable promise for the treatment of many inflammatory disorders.

Keywords: Cyclin-dependent kinase 9; Immune-mediated inflammatory diseases; Inflammation; Rheumatoid arthritis; Transcription elongation factor B

INTRODUCTION

Inflammation is a fundamental host defense response that facilitates pathogen clearance and initiates tissue repair. Innate leukocytes, including neutrophils, monocytes/macrophages, and eosinophils, orchestrate these processes through directed migration to sites of tissue injury and the production of inflammatory mediators.[1] Effective resolution of inflammation requires the timely termination of these responses, which is often accomplished by tightly regulated leukocyte apoptosis followed by efferocytic clearance, thereby preventing progression to sustained tissue damage.[4,5] When such regulatory mechanisms fail, chronic inflammation ensues, driving persistent injury and pathological tissue remodeling through prolonged release of histotoxic mediators.[6] Although current anti-

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inflammatory therapies have substantially improved clinical outcomes, they also reveal important therapeutic limitations. Glucocorticoids, for example, are highly effective in eosinophil-dominant inflammatory conditions such as asthma, yet confer limited benefit in many neutrophil-dominant diseases, including chronic obstructive pulmonary disease (COPD). Mechanistically, this disparity reflects the ability of glucocorticoids to induce eosinophil apoptosis while paradoxically prolonging neutrophil survival.[7] Nonsteroidal anti-inflammatory drugs (NSAIDs) suppress inflammation primarily through inhibition of cyclooxygenase (COX) activity; however, nonselective COX inhibition disrupts constitutive COX-1–mediated homeostatic functions, leading to adverse gastrointestinal effects and prompting the development of COX-2–selective inhibitors.[8] Collectively, these observations underscore the need for therapeutic strategies that attenuate inflammatory programs while actively promoting resolution.[9] One emerging approach is the targeting of transcriptional control nodes that sustain inflammatory cytokine expression and leukocyte survival. Cyclin-dependent kinases (CDKs) comprise both classical cell-cycle regulators and transcription-associated kinases, including CDK7, CDK8, CDK9, CDK12, and CDK13.[10] Among these, CDK9—a serine/threonine kinase—constitutes the catalytic core of the positive transcription elongation factor b (P-TEFb) complex and drives productive transcriptional elongation through phosphorylation of RNA polymerase II and associated regulatory factors.[11] Given that inflammatory phenotypes rely on rapid, stimulus-responsive transcriptional activation, CDK-dependent transcriptional control has emerged as a compelling target for modulating inflammatory responses, including the regulation of apoptosis and survival pathways in leukocytes.[12] Consistent with this concept, pharmacological inhibition of transcriptional CDKs, particularly CDK7 and CDK9, has been shown to accelerate the depletion of short-lived granulocytes by promoting apoptosis and to modulate macrophage inflammatory transcriptional programs.[13] In this review, we evaluate the role of CDK9 inhibition in the control and resolution of inflammation, with a focus on the following: (i) mechanistic links between transcriptional elongation and leukocyte survival, (ii) evidence supporting granulocyte apoptosis and its downstream consequences for efferocytosis and resolution, (iii) reported effects on macrophage inflammatory programs and cytokine production, and (iv) limitations, contradictory findings, and critical knowledge gaps that define priorities for future investigation and therapeutic development. By integrating both supportive and opposing evidence, we aim to clarify the contexts in which CDK9 inhibition may be beneficial, identify areas of uncertainty, and delineate the experimental and clinical questions that must be addressed to advance this strategy from basic biological insight toward rational therapeutic application. However, the majority of evidence supporting CDK9 inhibition as a means of inflammatory control derives from cellular studies and animal models. Given that CDK9 is a central regulator of transcriptional elongation, translation of these findings to human disease presents substantial challenges. Successful clinical application will depend on (i) defining a tolerable therapeutic window that minimizes on-target toxicity, (ii) achieving effective delivery to disease-relevant compartments, such as the gut mucosa, airways, or synovium, while limiting systemic exposure, and (iii) establishing pharmacokinetic- and pharmacodynamic–linked biomarkers of target engagement in human tissues. Accordingly, in addition to summarizing preclinical efficacy, this review explicitly highlights key translational barriers and outlines the data required to de-risk clinical development. Figure 1 summarizes the role of CDK9/P-TEFb in regulating stimulus-responsive transcription and highlights the therapeutic potential of CDK9 inhibition in controlling pathological inflammation.

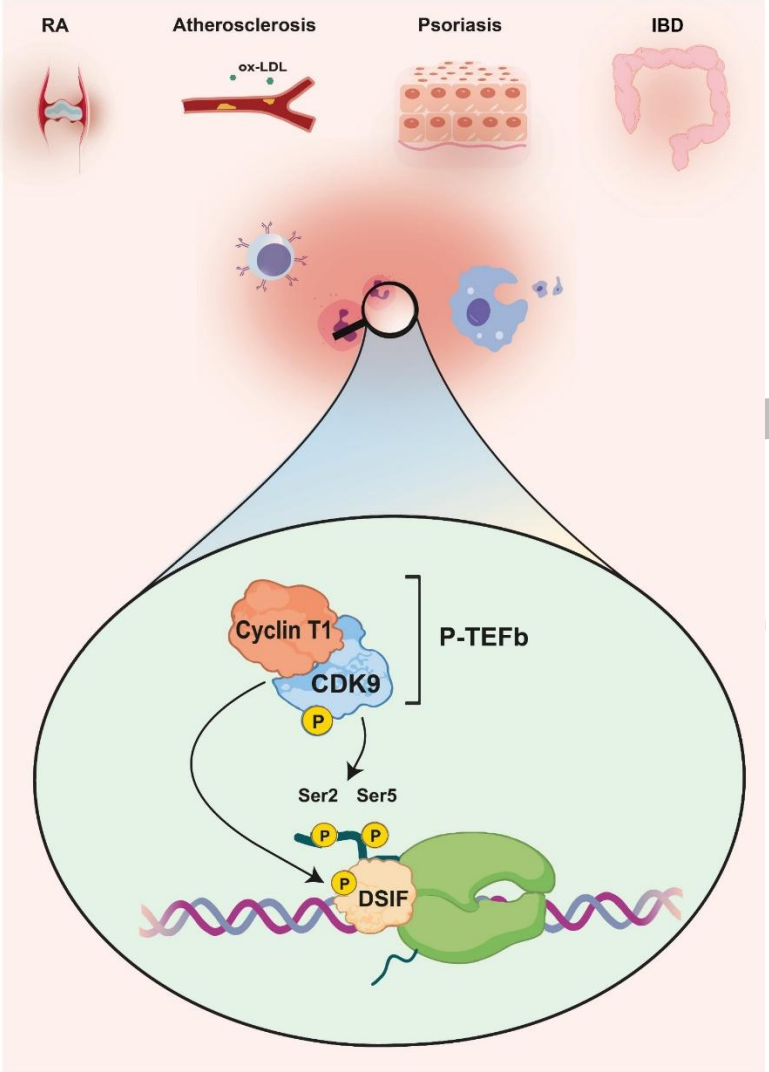

Figure 1. Graphical Abstract. Overview of CDK9/P-TEFb as a convergence node for stimulus-responsive transcription in immune-mediated inflammatory diseases. Inflammatory cues activate transcription factors (eg, NF-κB, STAT3, T-bet) that recruit P-TEFb (CDK9/cyclin T) to promoter-proximally paused RNA polymerase II (Paused Pol II is stabilized by the protein complexes DRB sensitivity-inducing factor [DSIF]) to drive cytokine and survival gene programs. Pharmacologic CDK9 inhibition can dampen pathological inflammatory transcription and, in granulocyte-dominant settings, accelerate apoptosis to support resolution.

Structural Insights into Cdk9

CDK9 was first identified by Grana et al in 1994, during efforts to characterize kinases related to CDC2 (CDK1). It is a 42-kDa protein comprising 372 amino acids and was originally designated PITALRE based on the presence of a Pro-Ile-Thr-Ala-Leu-Arg-Glu motif, which corresponds to the highly conserved PSTAIRE box found in several CDKs.[16] Structurally, CDK9 exhibits the canonical bilobal kinase fold, consisting of an N-terminal lobe primarily composed of 5 β-sheets and a single α-helix, and a C-terminal lobe dominated by α-helices. The α-helix within the N-terminal lobe plays a critical role in mediating interactions with cyclin T1; this peptide sequence is highly conserved among CDKs and facilitates cyclin binding upon kinase activation.[17] The ATP-binding site of CDK9 contains structural features that can be exploited for the design and optimization of high-affinity inhibitors. Structural analyses of CDK9 inhibitor complexes have identified a conserved glycine-rich loop that adopts a downward

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conformation. In contrast, the C-terminal region of the ATP-binding pocket displays limited sequence conservation- a feature that warrants careful consideration when evaluating inhibitor affinity and selectivity, as it may influence local conformational dynamics. Incorporation of this kinase-targeting domain into the transcriptional inhibitor 5,6-dichloro-1-β-D-ribofuranosyl-benzimidazole (DRB) has been shown to enhance its inhibitory activity against CDK9.[18] Enzymatic assays and differential fluorescence scanning techniques have further demonstrated the dependence of inhibitor binding on the C-terminal region of the kinase domain.[19] CDK9 is expressed as two major isoforms: a predominant 42-kDa form ($CDK9_{42}$) and a longer 55-kDa form ($CDK9_{55}$). The $CDK9_{55}$ isoform contains an N-terminal extension of 117 amino acids relative to $CDK9_{42}$.[20] Although both isoforms arise from a shared genetic locus, their expression is regulated by distinct promoter regions, with the $CDK9_{42}$ promoter characterized by GC-rich sequences.[21] Despite exhibiting identical phosphorylation patterns, the two isoforms display distinct subcellular localization. $CDK9_{42}$ is predominantly localized within the nucleoplasm, whereas $CDK9_{55}$ is enriched in the nucleolus.[22,23] Accumulating evidence indicates that further investigation is required to delineate the specific functional roles of $CDK9_{42}$ and $CDK9_{55}$. The extended N-terminus of $CDK9_{55}$ may provide additional regulatory interfaces that influence subcellular targeting and protein–protein interactions, while the divergent nucleoplasmic versus nucleolar localization of $CDK9_{42}$ and $CDK9_{55}$ suggests non-redundant functions in transcriptional regulation. However, isoform-resolved data in immune cells and inflamed tissues remain scarce. Defining isoform-specific interactomes, transcriptional programs, and differential sensitivity to CDK9 inhibitors therefore represents an important knowledge gap with potential therapeutic implications.[20–23]

Function of Cdk9 in Transcription

CDK9 associates with Cyclin T1 or Cyclin T2 (CycT1, CycT2), thereby constituting the fundamental element of P-TEFb, which influences gene transcription through the phosphorylation of critical substrates at serine and threonine residues.[24] Elimination of P-TEFb from a DNA template inhibits synthesis of long RNA transcripts but does not affect short-length RNA levels.[25] The role of P-TEFb in transcriptional pausing was elucidated through the discovery that phosphorylation of the carboxyl-terminal domain (CTD) on the largest subunit of RNA polymerase II (RNAP II) is required for productive elongation. The hypo- and hyper-phosphorylated phases, which were associated with a pausing and a productive elongation, respectively, are remarkable.[26] Consistent with this finding, the RNAP II CTD contracted, leading to a decrease in long RNA production. Researchers discovered that P-TEFb had kinase activity that specifically targeted the CTD.[27] In human cells, the majority of gene expression regulation happens during the elongation phase of transcription, not during the initiation phase. CDK7 activates CDK9, which contributes to both stopping and enhancing transcription.[28,29] Consequently, CDK7 and CDK9, pivotal regulators of transcriptional activity through RNAP II phosphorylation, are critical for transcription activity. Transcriptional CDKs (tCDKs), particularly CDK9, act downstream of inflammatory signaling by enabling transcriptional elongation of genes induced by pro-inflammatory transcription factors such as STAT3, NF-κB, and T-bet (Table 1).[30–32]

Upon stimulation, these transcription factors recruit P-TEFb to promoter-proximal paused RNAP II, where CDK9 phosphorylates RNAP II and negative elongation factors to release productive elongation. Consistent with this model, RNA interference targeting CDK9 suppresses NF-κB–dependent IL-8 transcription.[33,34] In addition, CDK9 plays a role in IL-6-regulated gene transcription, which occurs when IL-6 induces the binding of STAT3 to the promoter of the *p21CIP1* gene, after which CDK9 is recruited to promote Ser2 phosphorylation of RNAP II CTD and transcription elongation. The recruitment of tyrosine-phosphorylated STAT3 to the γ-fibrinogen promoter in liver cells was found to be associated with the presence of CDK9 upon IL-6 stimulation.[35] By evaluating more than 2000 high-throughput gene expression experiments, researchers were able to detect both basal and inducible modulators of CDK9 activity in a thorough analysis. Hypoxic signaling, angiogenesis, wound healing, stress and defensive responses, and innate immune response regulation are each regulated by target gene networks that are controlled by the inducible CDK9 modulator complex. The innate immune response profoundly influences the functions and gene targets regulated by the CDK9 complex.[36] Flavopiridol, which inhibits transcription by deactivating the positive transcription elongation factor P-TEFb,[37] enhances apoptosis through the intrinsic apoptotic pathway, inducing the activation

of the caspase cascade, which involves Bid, cytochrome *c* release, and the sequential activation of caspase 9 and caspase 3.[38,39] Flavopiridol treatment has been observed to suppress the activity of other key anti-apoptotic factors, including inhibitor of apoptosis protein 1 (IAP-1), Bcl-2, Mcl-1, and Bcl-xL.[38] Flavopiridol also prevents activation of the pro-inflammatory transcription factor NF-κB. The NF-κB pathway has been thoroughly investigated for its role in the cancer development and progression. It also helps control the expression of genes involved in transformation and survival.[38] Flavopiridol suppresses NF-κB via blocking IκBα kinase phosphorylation and degradation, thereby preventingNF-κB nuclear translocating. Consequently, cyclin D1, COX-2, and matrix metalloproteinase-9 synthesis isinhibited, these factors are implicated in neoplastic tumorigenesis and metastasis.[40] Flavopiridol also affects levels of pro-inflammatory markers such as interleukins in addition to the aforementioned pathways. Since flavopiridol exerts its effects by disrupting P-TEFb, it represses CDK9-STAT3 complex formation and leads to decreased development of acute phase proteins by inhibiting the production of IL-6. This indicates that CDK9 is crucial for the initiation of inflammation-related transcription and translation.[41] It also is critical for the expression of certain NF-κB target genes. This process relies on ATM-mediated phosphorylation of the NF-κB specific subunits, facilitating the interaction of CDK9 and subsequently with the components such as P-TEFb. This enables CDK9 to phosphorylate the CTD at Ser2 to enhance elongation of RNA transcript.[42]

Table 1. Representative CDK9-targeting compounds discussed in this review.

Compound	Selectivity/modality	Primary use in cited studies	Key limitations/notes (refs)
Flavopiridol	First-generation pan-CDK inhibitor (incl. CDK9)	Models of inflammation; broad transcriptional suppression	Limited selectivity; dose-limiting toxicity in oncology experience (37–39, 60).
R-roscovitine (seliciclib)	Pan-CDK inhibitor with CDK2/CDK7/CDK9 activity	Resolution of inflammation; RA/GVHD-related models	Off-target CDKs; context-dependent outcomes (77, 109, 116, 117).
Dinaciclib	Multi-CDK inhibitor (CDK1/2/5/9)	Preclinical inflammation and oncology settings	Selectivity and safety considerations; PK/PD optimization required (73, 118).
Atuveciclib	Selective CDK9 inhibitor (clinical)	Psoriasis-related inflammatory programs	Clinical experience largely in oncology; immune safety needs evaluation (75, 84).
VIP152 (enitociclib analogs)	Next-generation selective CDK9 inhibitor	Transcriptional dependency targeting; potential for intermittent dosing	Still primarily oncology-focused; inflammation applications require dedicated trials (76).
AZD4573/other selective CDK9 inhibitors	Selective CDK9 (varies by compound)	Mentioned as emerging tools to reduce off-target CDK inhibition	Differential kinase selectivity and dosing schedules complicate cross-study comparisons.

CDK: cyclin-dependent kinase; GVHD: graft-versus-host disease; PD: pharmacodynamics; PK: pharmacokinetics; RA: rheumatoid arthritis.

CDK9 and Mechanisms of the Inflammatory Responses

CDK9 activity increases during lymphocyte activation. Human peripheral blood leukocytes and resting $CD4^+$ T cells stimulated with phytohemagglutinin (PHA) show increased CDK9 mRNA and protein levels, and cyclin T1 expression rises in parallel, consistent with enhanced P-TEFb activity.[43,44] Subsequent studies extended these observations and linked CDK9 to lymphocyte proliferation and differentiation.[45–47] In B-cell compartments, activated and memory leukocytes exhibit higher CDK9 expression than naive cells.[52] Collectively, these findings suggest that pharmacologic CDK9 inhibition (e.g., flavopiridol) can dampen lymphocyte-driven inflammation by limiting activation-associated

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transcriptional programs and promoting apoptosis in highly dependent populations.[34] In neutrophils, CDK9-dependent transcription supports survival by maintaining short-lived anti-apoptotic programs, and CDK9 activity has been implicated in delayed apoptosis and amplified inflammation in both in vitro and in vivo settings.[48,49] Inhibition of CDK9 with R-roscovitine has been reported to induce neutrophil apoptosis and mitigate neutrophil-predominant inflammatory responses.[48] Consistent with a pro-resolving mechanism, CDK9 inhibition has been shown to delay arthritis onset and reduce disease severity in collagen-induced arthritis models.[50,51] CDK9 also shapes macrophage inflammatory outputs through gene-specific transcriptional elongation checkpoints. IL-10 suppresses TNF transcription by limiting CDK9 recruitment to the TNF locus while sparing the NFKBIA (IκBα) promoter, indicating that pause-release control can act as a negative regulatory node during innate immune activation.[14] Although CDK9 levels may remain relatively stable during macrophage differentiation,[53] flavopiridol has been reported to reduce LPS-induced TNF-α production and to attenuate upstream kinase signaling (ERK, JNK, IKK) and NF-κB activation in a leukemic/monocytic cell model.[54] Mechanistically, many NF-κB-driven inflammatory genes require recruitment of P-TEFb to promoter-proximal paused RNA polymerase II. NF-κB can bind and recruit P-TEFb/CDK9, and inhibition with DRB or expression of a kinase-inactive CDK9 mutant reduces NF-κB-dependent transcription, supporting a requirement for CDK9 kinase activity in productive elongation.[58] In this framework, inflammatory stimuli activate NF-κB (eg, via TNF-α/IL-1 signaling), NF-κB engages coactivators such as BRD4 that deliver P-TEFb, and CDK9 phosphorylates RNAP II and associated elongation factors to release pausing and drive cytokine transcription.[59] This model helps explain observations that CDK9 inhibition lowers expression of selected NF-κB targets (e.g., IL-8) and reduces leukocyte-adhesion programs such as ICAM-1 in endothelial cells, whereas upstream NF-κB activation events (IKK activation, IκBα phosphorylation/degradation, nuclear translocation, and DNA binding) may remain largely intact depending on the inhibitor and context.[33,40,60] Beyond vascular inflammation, IL-1β-driven NF-κB activity is attenuated by the CDK9 inhibitor LDC067 in articular chondrocytes, with concomitant suppression of inflammatory cytokines and matrix metalloproteinases (MMPs), supporting relevance to osteoarthritis.[61,62] CDK9 similarly intersects with IL-6/JAK/STAT signaling. IL-6 engagement of IL-6Rα/gp130 activates Janus kinases and promotes STAT3 phosphorylation and recruitment to target loci.[64–67] Hou et al reported that IL-6 induces assembly of a STAT3/CDK9 complex during the hepatic acute-phase response and that CDK9 activity is required for IL-6-driven overexpression of γ-fibrinogen, as shown using flavopiridol or a kinase-inactive CDK9 mutant.[41] Taken together, these findings support a coherent pathway in which inflammatory signals activate transcription factors such as NF-κB and STAT3 that recruit P-TEFb to paused RNAP II, making CDK9 a convergence node for stimulus-responsive transcriptional elongation and a plausible target to blunt cytokine and pro-survival gene programs.

CDK9 Inhibitors

The identification of flavopiridol as one of the first clinically tested cyclin-dependent kinase (CDK) inhibitors fueled efforts to develop small molecules with improved potency and selectivity, including agents that more precisely target CDK9. Flavopiridol represents a first-generation CDK inhibitor: it is relatively nonselective but displays strong inhibitory activity toward CDK9.[71] Roscovitine (seliciclib) was another potent CDK inhibitor evaluated in clinical trials, although it is generally less potent against CDK9 than flavopiridol (Table 2).[72]

Table 2. Mechanistic interfaces between CDK9/P-TEFb and disease-relevant transcriptional modules.

Upstream module/TF	How CDK9/P-TEFb is engaged	Representative outputs	Disease contexts (examples)	Key notes/evidence
NF-κB	Recruitment of P-TEFb (CDK9/cyclin T) to paused RNAPII at inducible promoters	TNF, IL-8, adhesion molecules, chemokines	RA, IBD, vascular inflammation	NF-κB–P-TEFb interaction supports transcriptional elongation of inflammatory genes (40).
STAT3 (IL-6/JAK)	STAT3-bound promoters can recruit CDK9 to promote RNAPII Ser2 phosphorylation and elongation	Acute-phase and survival gene programs	RA, SLE and other IL-6–driven states	CDK9 participation in IL-6/STAT3-regulated transcription reported in cell models (35).
T-bet (Th1)	Lineage TFs coordinate pause release for IFNG/TNF loci via P-TEFb	IFN-γ and Th1 effector programs	IBD, MS (Th1-dominant)	CDK9 inhibition can modulate T-cell effector transcriptional programs (90–93).
RORγt/IL-17 axis	Cytokine-driven epithelial programs can depend on P-TEFb activity downstream of IL-17 family inputs	IL-17-responsive epithelial genes; neutrophilic inflammation programs	Asthma endotypes; barrier inflammation	P-TEFb involvement in IL-17F signaling in airway epithelium reported (110).
AP-1	MAPK/AP-1 inducible genes may require elongation control mediated by transcriptional CDKs	MMPs and inducible inflammatory mediators	Psoriasis; systemic sclerosis; RA	CDK-dependent regulation of c-Jun phosphorylation/AP-1 activity described (30); CDK9 inhibition may modulate AP-1 outputs (114).
BRD4/enhancer control	BRD4 recruits P-TEFb to super-enhancer-associated inflammatory loci	Clustered cytokine/chemokine programs	Multiple inflammatory tissues	Conceptual framework: BRD4–P-TEFb coupling helps explain selective sensitivity of inducible genes to CDK9 blockade (45).

AP-1: activator protein 1; BRD4: bromodomain-containing protein 4; IBD: inflammatory bowel disease; IL: interleukin; JAK: Janus kinase; MAPK: mitogen-activated protein kinase; MMPs: matrix metalloproteinases; MS: multiple sclerosis; RA: rheumatoid arthritis; RNAPII: RNA polymerase II; RORγt: RAR-related orphan receptor gamma t; SLE: systemic lupus erythematosus; TF: transcription factor.

Despite extensive evaluation, first-generation pan-CDK inhibitors were frequently limited by restricted efficacy and dose-limiting toxicities, and complete response rates remained low in several clinical settings.[24,74] Dinaciclib, a more potent CDK inhibitor, has demonstrated improved antitumor activity in preclinical and early clinical studies, particularly in combination regimens such as anti-PD-1 therapy. Dinaciclib has also been reported to trigger immunogenic cell death, potentially promoting an antitumor response.[73] Consequently, second-generation compounds were engineered to improve selectivity for transcriptional CDKs, including CDK9. Atuveciclib was among the first reported CDK9-selective inhibitors.[75] Further optimization has yielded more potent and selective agents such as enitociclib (VIP152; previously

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BAY 1251152), which exibits nanomolar inhibitory activity against CDK9 .[76] From an inflammation perspective, a key observation is that CDK9 inhibition can override survival and inflammatory programs induced by stimuli such as db-cAMP, GM-CSF, and LPS, which converge on NF-κB and JAK/STAT signaling (particularly STAT3). These transcription factors promote recruitment of P-TEFb to promoter-proximal paused RNA polymerase II at target genes; CDK9 then phosphorylates RNAP II and associated elongation factors to enable productive transcription. Accordingly, blocking CDK9 can attenuate NF-κB/STAT-driven expression of pro-survival and cytokine genes, accelerating granulocyte apoptosis and potentially promoting resolution.[77] It is important to acknowledge that neither selective CDK9 inhibitors nor CDK9 degraders have yet received FDA approval.

Cdk9 as A Novel Target in Inflammatory Disease

Inflammatory disease represents a comprehensive category that includes various pathological conditions that affect numerous organs and tissues, including psoriasis, inflammatory bowel disease, rheumatoid arthritis, atherosclerosis, multiple sclerosis, and asthma.[78] Disease-specific CDK9-dependent signaling pathways and the corresponding experimental and therapeutic evidence across these conditions are summarized in Table 3. Many inflammatory diseases, whether of infectious or noninfectious origins are characterized by unusual buildup of inflammatory cells such as monocytes, macrophages, granulocytes, plasma cells, lymphocytes, and platelets. These cells, in conjunction together with fibroblasts, secrete a complex mixture of lipid mediators and cytokines that contribute to localized tissue damage. The tissue damage observed in various inflammatory diseases characterized by neutrophil predominance, such as bacterial infections, active phases of rheumatoid arthritis, COPD, and cystic fibrosis, primarily results from the activation of neutrophils. This activation triggers the release of proteinases and an augmented production of reactive oxygen species.[79]

Psoriasis

Psoriasis represents a complex interplay of autoimmune and autoinflammatory mechanisms affecting the skin. Psoriatic skin lesions are marked by an overproduction of keratinocytes and a significant influx of immune cells, including neutrophils, macrophages, and TH17 cells.[80] Psoriasis treatment with neutralizing antibodies against IL-17 is highly efficacious; nonetheless, it presents drawbacks, including challenging administration methods, substantial expenses, systemic adverse effects such as upper respiratory tract infections, and the potential for long-term therapeutic resistance due to the formation of antidrug antibodies.[81,82] Consequently, innovative therapeutic strategies for psoriasis are essential. The transcription factor STAT3, as a principal regulator of inflammatory and immunological responses, has become a crucial element in the process of expansion and pathophysiology of psoriasis. STAT3 excessive activation has been documented in every cell type associated with disease onset and persistence. This is consistent with its importance in TH17 cells and IL-6 and IL-23, key cytokines for TH17 differentiation.[83] The irregular stimulation of the STAT3 signaling pathway facilitated by CDK9 is crucial in the pathogenesis of psoriasis, resulting in the buildup of inflammatory mediators and the advancement of lesions on the skin in a study. Zhao et al have reported atuveciclib, a highly specific CDK9 inhibitor, which has been accompanied by a reduction in the release of inflammatory factors and mitigating skin damage in psoriasis animal models. Atuveciclib markedly suppressed STAT3 molecular functions in murine skin and decreased the concentrations of critical immunomodulators in both murine skin and plasma. These findings indicated that CDK9 inhibition can markedly eliminate the inflammatory signaling and diminish the expression of pro-inflammatory markers including IL-1, IL-6, TNF-α, and IFN-γ.[84] Prior research in this area has focused on palbociclib and abemaciclib as CDK4/6 inhibitors that reduce inflammation in psoriasis-like skin lesions.[85] Further clinical trials are required to assess the efficacy of CDK inhibitors as novel therapeutic agents for psoriasis treatment.

Inflammatory Bowel Disease

Crohn's disease and ulcerative colitis are the two primary types of inflammatory bowel disorders (IBD) in humans.[86] While the etiology of this disease remains unidentified, it has been proposed that the provoking of the mucosal immune system in response to bacterial antigens, along with subsequent pathological cytokine production and activation of matrix metalloproteinases, is pivotal in its pathogenesis.[87,88] Cytokines generated by T cells seem to trigger and sustain persistent intestinal

inflammation.[89] T-bet, a transcription factor, functions as a primary regulator of the TH1 subset of $CD4^+$ T cells development and the modulation of T cell cytokine production and cytotoxic activity.[90] Numerous studies utilizing experimental colitis models have demonstrated elevated T-bet expression within lamina propria T cells, which subsequently leads to the activation of IFN-γ and TNF.[91,92] In a model of immune-mediated murine colitis and in colonic lymphocytes derived from patients with inflammatory bowel disease, Omer et al observed the immunosuppressive effect of CDK9 inhibition seemed to be limited to colonic T cells, indicating that its potential effectiveness is highest among activated lymphocytes in inflammatory areas. $CD4^+$ T cells from both mice and humans showed a decrease in the production of IFN-γ and TNF-α in T cell transfer colonic explants. The observation was made that inhibiting CDK9 led to a decrease in TH1 and TH17 cytokine production by colonic $CD4^+$ T cells, which improved the colitis score. Reduced production of IFN-γ and TNF-α was the outcome of CDK9 inhibition, indicating that these small molecule inhibitors are easily absorbed into the intestinal mucosa and efficiently inhibit resident immune cells.[93] Furthermore, numerous models of inflammation-driven gastrointestinal disease provide compelling evidence that ABC1183, a selective inhibitor of GSK3α/β and CDK9, effectively reduces the levels of proinflammatory cytokines TNF-α and IL-6, enhances the levels of the anti-inflammatory cytokine IL-10, alters immune cell infiltration, and alleviates disease symptoms. The findings underscore the significance of GSK3 and CDK9 in various diseases due to their proinflammatory functions.[94]

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is characterized by the infiltration of immune cells, synovial hyperplasia and infiltration, and the subsequent compromised joint integrity.[95] The notion exists that the dysfunction of apoptosis in potentially pathogenic auto-reactive T and B cells may play a significant role in the severity and progression of the disease.[96] Moreover, evidence suggests that the expression of Mcl-1 is crucial for the prolonged survival of plasma cells. Auto-reactive plasmacytes are instrumental in the synthesis of rheumatoid factor (RF), which significantly contributes to the pathogenesis of RA (Figure 2).[97]

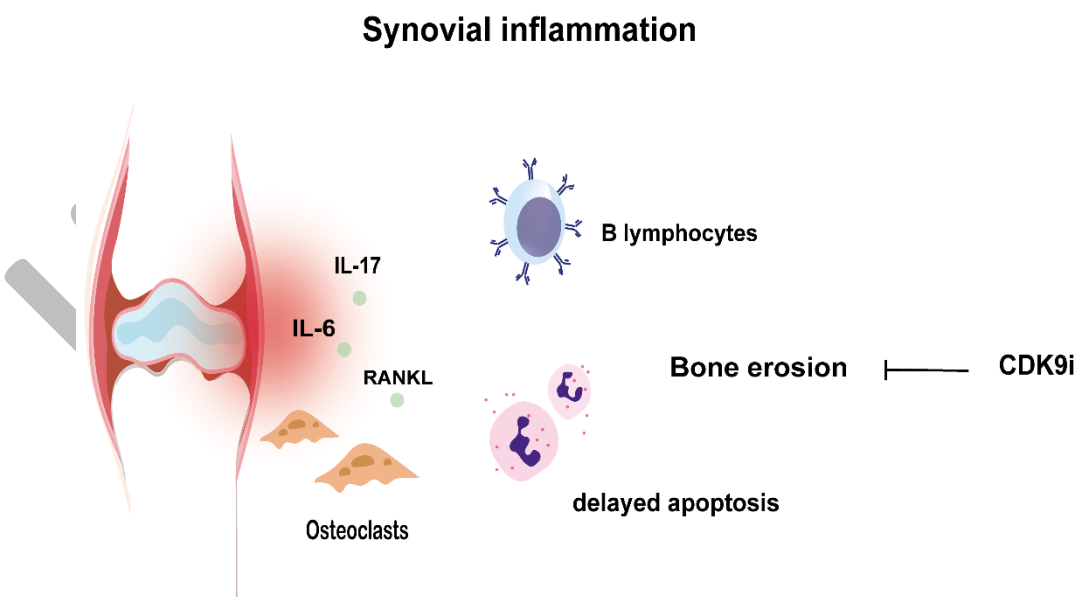

Figure 2. Synovial inflammation involves coordinated interactions among macrophages, neutrophils, dendritic cells, T cells (including T_H1/T_H17), and synovial fibroblasts. Key mediators (eg, TNF-α, IL-6, IL-1β, IL-17, GM-CSF) drive leukocyte recruitment and activation, and CDK9/P-TEFb supports transcriptional elongation of these inducible inflammatory programs. CDK9 inhibition is proposed to reduce cytokine/chemokine production and, in granulocytes, promote apoptosis to facilitate resolution.

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To alleviate and prevent RA aggressiveness, a new class of immunosuppressive and immunomodulatory medications called disease-modifying antirheumatic drugs (DMARDs) is required, as NSAIDs and corticosteroids have undesirable side effects.[98] Flavopiridol and roscovitine are compounds that inhibit CDK9 and thereby decrease Mcl-1 expression.[99] Hellvard et al evaluated Mcl-1 concentrations in mice subjected to systemic treatment with CDK9 inhibitors. Treated mice exhibited reduced Mcl-1 expression compared with the control group, inducing a pro-apoptotic state.[51] As a result, CDK9 is effective for the terminating inflammation in immune responses driven by neutrophils.[49] Pharmacological inhibition of CDK9 effectively controls the resolution of inflammation by promoting neutrophil apoptosis. Consistent with this, genetic modification to inhibit CDK9 in vertebrate model organisms resulted in a subsequent decrease in the neutrophil population.[49] A novel approach to modifying immune responses modulates CDK9 activity in a manner distinct from traditional cell cycle inhibitors.

Atherosclerosis

Atherosclerosis is a chronic inflammatory disease that results from hyperlipidemia and lipid oxidation. It is a progressive vascular disease affecting the entire circulatory system.[100] The concept that atherosclerosis is an inflammatory disease was initially proposed by Russell Ross in 1999, based on observations of circulating monocytes infiltrating the growing fatty streak.[101] A large amount of evidence indicates that significant antigens implicated in atherosclerosis may encompass neoepitopes produced by oxidized LDL (ox-LDL), which are formed within the vessel wall or during the process of apoptotic cell death.[102] Han et al observed that CDK9 levels were significantly increased in the serum of individuals with atherosclerosis, and there was a notable correlation between the high presence of $CD14^+$ monocytes/macrophages in arterial plaques and the expression of CDK9. The findings suggest that CDK9 may play a significant role in the inflammatory processes underlying the pathogenesis of atherosclerosis and could serve as a potential biomarker for this condition.[103] Ox-LDL significantly activates the NF-κB signaling pathway through its interaction with the membrane surface receptor LOX-1, subsequently leading to the upregulation of inflammatory signals, particularly TNF-α and IL-6.[104] Huang et al verified the role of NF-κB in ox-LDL-induced inflammation through using LDC000067 in another investigation. They also found that this CDK9 inhibitor diminished ox-LDL-induced inflammatory responses by inhibiting the NF-κB pathway, thereby ameliorating atherosclerosis.[105]

Other Inflammatory Diseases

Beyond the major immune-mediated disorders discussed above, CDK9/P-TEFb has also been implicated in additional inflammatory disease models. These examples highlight emerging opportunities as well as the need for more in-depth mechanistic works and improved translational alignment across endotypes and tissues.

Osteoarthritis

Osteoarthritis (OA) is increasingly recognized as a whole-joint disease with inflammatory contributions that include synovitis and cytokine-driven cartilage catabolism.[107] In particular, chondrocytes require P-TEFb-dependent pause release for IL-1β–driven NF-κB programs, and CDK9 inhibition has been reported to reduce inflammatory cytokines and matrix metalloproteinases, consistent with a potential disease-modifying mechanism in OA models.[61,62] In addition, experimental work combining matricellular pathway perturbation with CDK9 inhibition supports the concept that transcriptional CDKs can modulate cartilage-degradative programs, although these findings remain preclinical and require validation in human OA tissues and clinically relevant delivery approaches.[108]

Graft-versus-host Disease

In allogeneic immune settings, pharmacological inhibition of CDKs has been proposed as a strategy to restrain the rapid, activation-induced transcriptional programs that drive alloreactive T-cell responses. For instance, the CDK inhibitor R-roscovitine (seliciclib/CYC202) has been shown to suppress clonal expansion of alloreactive T cells and to confer protection against acute graft-versus-host disease in preclinical models.[109] These findings support a CDK9-centered hypothesis in which activated effector T cells exhibit heightened dependence on sustained transcriptional elongation. At the same time, they emphasize the critical need to rigorously assess the extent of immunosuppression and the associated risk of infection when considering translation of this approach to human clinical settings.

Airway Inflammation (Asthma/COPD Endotypes)

Airway inflammatory diseases span eosinophilic, type 2–skewed asthma phenotypes and neutrophil-dominant, steroid-refractory endotypes that are common in COPD. Mechanistically, P-TEFb has been implicated in IL-17F signaling in airway epithelial cells, linking TH17 cytokine inputs to transcriptional elongation control.[110] These observations motivate testing whether selective, compartment-targeted CDK9 inhibition (eg, inhaled delivery) can attenuate pathogenic airway cytokine programs while preserving host-defense transcriptional responses. At present, direct evidence in COPD remains limited and represents an important gap for future studies.

Acute Innate Activation (LPS/Endotoxemia Models)

Several reports in macrophage/monocytic systems show that CDK9 inhibition can reduce LPS-induced TNF-α production and dampen upstream NF-κB pathway activation, consistent with a role for P-TEFb in sustaining rapid inflammatory transcription.[54] However, such models capture acute transcriptional bursts and may not fully reflect chronic tissue remodeling or long-term safety; translation will require PK/PD-linked target engagement biomarkers and infection-aware efficacy models.

Integrative Mechanistic Model Across Diseases

A unifying feature of inflammatory and immune-mediated diseases is the persistence of pathogenic phenotypes driven by rapid and sustained transcriptional reprogramming.[1] Within this framework, CDK9 (through its central role in positive transcription elongation factor b [P-TEFb]–mediated release of promoter-proximal pausing) acts as a convergence node that couples extracellular inflammatory signals to transcriptional programs controlling cytokine and chemokine production, cell adhesion, tissue remodeling, and leukocyte survival.[2] Inflammatory stimuli, including TNF-α and IL-1, IL-6, and Toll-like receptor ligands, activate inducible transcription factors such as NF-κB, STAT3, and AP-1, along with lineage-specifying regulators such as T-bet.[3] These factors, in turn, recruit co-activator complexes, including BRD4 and related chromatin-associated regulators, which facilitate the delivery of P-TEFb to promoter-proximally paused RNA polymerase II.[4] CDK9 subsequently phosphorylates Ser2 residues within the RNA polymerase II C-terminal domain, as well as associated negative elongation factors, thereby releasing transcriptional pausing and enabling productive elongation of stimulus-responsive genes.[5] The downstream transcriptional output of this process includes pro-inflammatory mediators such as TNF, IL-6, and IL-8; tissue-remodeling enzymes including matrix metalloproteinases; adhesion molecules such as ICAM-1; and short-lived pro-survival transcripts that sustain activated leukocyte populations.[6] From a therapeutic standpoint, the objective is not global suppression of transcription, but rather selective attenuation of disease-driving transcriptional modules, ideally achieved through optimized dosing strategies, tissue-targeted delivery, and biomarker-guided pharmacokinetic and pharmacodynamic approaches that preserve essential host-defense and tissue-repair programs.[7]

Limitations and Contradictions

Despite growing interest in CDK9 inhibition as a strategy to modulate inflammation and promote resolution, the current literature contains important limitations and apparent contradiction that should be considered when interpreting the evidence and defining its translational potential.

Attribution to CDK9 Is Complicated by Inhibitor Selectivity and Experimental Design

A major source of inconsistency is that many "CDK9 inhibitors" used in inflammation studies have multi-kinase/CDK activity, and effects attributed to CDK9 may partly reflect inhibition of CDK7 or other CDKs.[8] For example, widely used compounds such as R-roscovitine and DRB have broader CDK profiles (commonly including CDK7/9 and additional CDKs depending on the compound), whereas newer agents (and genetic approaches) enable more direct interrogation of CDK9-specific effects.[9] One practical consequence is that differences in compound selectivity, potency, exposure time, and achievable intracellular concentrations can lead to divergent outcomes across studies even when the nominal "target" is CDK9. This issue is highlighted in work comparing CDKi classes, where CDK9-focused approaches were distinguished from broader CDK inhibition and where macrophage readouts were carefully separated from granulocyte apoptosis phenotypes.[10]

Cell-type Dependence: Granulocytes vs Macrophages Show Distinct Sensitivities

Evidence consistently shows that CDK inhibition

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promotes granulocyte apoptosis and accelerates inflammatory resolution in neutrophil-dominant models, supporting a pro-resolving mechanism linked to the transcriptional dependence of short-lived survival proteins such as Mcl-1.[11] In vivo, treatment with CDK inhibitors, including R-roscovitine, enhances the resolution of established neutrophil-driven inflammation across multiple experimental models, with pharmacological inhibition of caspases abrogating these pro-resolving effects, supporting an apoptosis-dependent mechanism. Mechanistic studies further indicate that inhibition of RNA polymerase II phosphorylation by transcriptional CDKs, particularly CDK7 and CDK9, reduces neutrophil transcriptional capacity and triggers apoptosis, thereby contributing to inflammatory resolution.[12] In contrast, macrophage responses to CDK9 inhibition are more heterogeneous. In human monocyte-derived macrophages, CDK9 inhibition does not induce caspase-dependent apoptosis under conditions that trigger neutrophil apoptosis, despite concomitant downregulation of Mcl-1. This may reflect the presence of compensatory anti-apoptotic pathways in macrophages. Such cell type-specific divergence can give rise to apparently conflicting interpretations, namely that CDK9 inhibition is pro-apoptotic vs CDK9 inhibition does not induce apoptosis, which may both be valid depending on the leukocyte population under investigation.[13]

Anti-inflammatory Suppression Does Not Always Equal "Pro-resolution": IL-10 and Efferocytosis Considerations

Another nuance is that CDK9 inhibition can reduce both pro-inflammatory and regulatory cytokines. For example, CDK9-targeting CDKi have been reported to downregulate LPS-induced macrophage cytokine production (including TNF and IL-6), but also reduce IL-10 in some settings.[10] This creates a potential tension: while suppression of TNF/IL-6 may be beneficial in hyperinflammation, reduction of IL-10 could theoretically blunt counter-regulatory pathways that support restoration of homeostasis. Moreover, although short-term CDK9 inhibition did not impair macrophage efferocytosis of apoptotic neutrophils in one study, the impact on sustained/serial efferocytosis, macrophage reprogramming over time, and tissue-repair programs remains less certain and may vary across inflammatory contexts.[14]

Context Dependence and Host-defense Trade-offs (Especially Relevant to Mucosal Inflammation)

CDK9 inhibition suppresses activated T-cell cytokine programs (including T_H1/T_H17 outputs) in ex vivo human colonic lymphocytes and improves pathology in an immune-mediated colitis model, supporting therapeutic relevance in inflammatory bowel disease (IBD), including anti-TNF-resistant disease signatures.[15] However, immune pathways suppressed by CDK9 inhibition (eg, IFN-γ/IL-17-related programs) can be double-edged: prior clinical experiences targeting individual cytokines in IBD illustrate that blocking certain pathways (eg, IL-17A or IFN-γ) has failed to meet endpoints and in some cases worsened disease activity.[16] Although CDK9 inhibition operates upstream at the transcriptional level (rather than single-cytokine blockade), these observations emphasize the need to delineate when transcriptional suppression is beneficial vs when it risks impairing barrier immunity, antimicrobial defense, or tissue repair.[17]

Translational Constraints to Human Application: Safety, Drug Delivery, and PK/PD Bridging

A consistent limitation in the CDK9-inflammation literature is that most supportive data come from cellular systems and animal models, while human disease involves greater heterogeneity, comorbidities, concomitant therapies, and longer treatment horizons. As a result, translation depends not only on mechanistic plausibility, but on whether a clinically usable exposure profile can be achieved in humans with demonstrable target engagement and an acceptable safety margin. Because CDK9 is a core regulator of transcriptional elongation, systemic inhibition raises predictable concerns around on-target toxicity in non-diseased tissues, particularly those with high turnover or transcriptional demand (eg, gastrointestinal epithelium and hematopoietic compartments).[18] These risks are amplified for chronic inflammatory indications that may require repeated dosing. In addition, upstream transcriptional suppression can create host-defense trade-offs, where beneficial attenuation of inflammatory programs must be balanced against maintaining antimicrobial and barrier-protective immunity. Translational studies should therefore define the minimal exposure required for immunomodulation, evaluate whether short "pulse" inhibition can separate efficacy from cumulative toxicity, and assess infection-relevant outcomes when appropriate.[19] Many target

diseases are anatomically compartmentalized (airways, gut mucosa, synovium, skin), and inadequate delivery to the inflamed compartment can lead to apparent lack of efficacy even when cellular mechanisms are valid.[20] Conversely, excessive systemic exposure increases toxicity without improving local benefit. Development paths that bias exposure toward the disease site (eg, inhaled delivery for airway disease or gut-targeted release for IBD) and/or use cell- or tissue-directed strategies may be necessary to establish a favorable benefit-risk profile.[21]

Cellular Adaptation, Compensatory Pathways, and Potential Resistance

A largely under-discussed issue in the inflammation literature is whether repeated or prolonged CDK9 inhibition could elicit cellular adaptation.[22] Because CDK9 lies within a highly redundant transcriptional network, immune and stromal cells may partially compensate by engaging alternative transcriptional CDKs (eg, CDK7, CDK12/13) and elongation regulators, or by rewiring stimulus-responsive signaling modules (eg, NF-κB, MAPK, JAK-STAT) that restore pro-inflammatory gene expression despite CDK9 pressure.[23] At the level of survival and resolution, compensatory responses could include increased reliance on parallel anti-apoptotic programs (for example, induction of Bcl-xL, A1/BFL-1 or other stress-response pathways), altered metabolic support, or shifts in macrophage polarization that reduce pro-resolving efferocytosis over time.[24] These possibilities are particularly relevant if CDK9-directed strategies are considered for chronic diseases requiring repeated dosing, where selective pressure may favor tolerant phenotypes. To address this gap, future studies should incorporate time-course and re-challenge designs that model chronic exposure, quantify target engagement longitudinally, and use unbiased profiling (transcriptomics/proteomics) to identify compensatory pathways. Such datasets would also inform rational combination strategies (eg, pairing transient CDK9 inhibition with agents that block dominant escape pathways) and help define biomarkers that predict durable versus transient responses.

CONCLUSION

CDK9, in conjunction with cyclin T1, forms the P-TEFb complex, which is instrumental in gene expression by enabling RNAP II to effectively promote the next step of transcription, elongation. Their roles extend beyond transcriptional elongation to include functions in differentiation, DNA repair, transcription initiation, and termination.[16] Currently, therapies utilizing small-molecule inhibitors targeting CDK9 are designed to regulate the proliferation and growth of cancer cells.[111,112] The increasing number of studies utilizing CDK9 inhibitors for the treatment of inflammatory diseases has led to a heightened recognition of the significance of transcription-regulating CDKs in the resolution of inflammation.[77] The evidence supports a potent anti-inflammatory and inhibitory effect of CDK9 on the pro-inflammatory transcription factor, NF-κB. NF-κB, a pro-inflammatory transcription factor, is dependent on interaction with P-TEFb to facilitate transcription elongation of target genes.[58] It is noteworthy that gene silencing, along with treatment using flavopiridol, led to significant restriction of NF-κB recruitment in vascular endothelial cells. This intervention resulted in a considerable reduction in ICAM-1 expression, a key factor in the recruitment of lymphocytes to inflamed tissues.[60] Furthermore, research indicates that STAT3 pathways are crucial for sustaining the constitutive production of Mcl-1 in macrophages,[113] CDK9 interacts with STAT3 upon IL-6 stimulation.[35] This review elucidates recent findings that underscore the pivotal role of P-TEFb in facilitating transcription from ytokine-induced promoters.. While BRD4 plays a crucial role in P-TEFb activation, numerous studies indicate that P-TEFb targets specific inducible genes. Consequently, given the changing function of CDK9 in inflammation, further experimental investigation is needed to facilitate the clinical approval of novel CDK9 inhibitors for human inflammatory conditions. Finally, because most supporting evidence remains preclinical, a major priority is to de-risk human translation through PK/PD-guided target engagement, optimized delivery to disease compartments, and rigorous safety evaluation adapted to chronic dosing needs and host-defense requirements. Another important translational unknown is whether cells develop tolerance through compensatory transcriptional and pro-survival pathways during prolonged exposure. Longitudinal human-relevant models and biomarker-guided studies will be needed to detect adaptation early and to design dosing schedules or combination approaches that preserve durable immunomodulatory effects.

Table 3. Disease-specific CDK9-dependent pathways and evidence base.

Condition/model	Dominant inflammatory drivers	Putative CDK9-dependent nodes	CDK9-targeting evidence	Notes on translation/limitations
Psoriasis	IL-23/T_H17 and keratinocyte inflammatory circuits	NF-κB/AP-1-dependent cytokine programs; keratinocyte activation	Selective CDK9 inhibition reported to reduce inflammatory mediators in preclinical models (84, 85)	Human tissue validation and long-term safety needed; risk of broad transcriptional suppression must be monitored.
Inflammatory bowel disease	Dysregulated mucosal immunity; T_H1/T_H17 cytokines	T-cell effector transcription; macrophage cytokines (NF-κB/STAT)	CDK9 inhibition reduces cytokine production and supports resolution in experimental settings (90, 93, 94)	Delivery to gut and infection-aware endpoints are key translational constraints.
Rheumatoid arthritis	Synovial inflammation; neutrophil and macrophage cytokine networks	NF-κB-driven cytokines/chemokines; granulocyte survival modules	Roscovitine/flavopiridol-class inhibitors reported to dampen inflammatory outputs and improve models (95–99)	Need to balance anti-inflammatory efficacy with immunosuppression and hematologic toxicity.
Atherosclerosis	Lipid oxidation and chronic vascular inflammation	Leukocyte–endothelium activation; NF-κB-dependent adhesion/cytokines	CDK9 implicated in leukocyte–endothelial interaction and vascular inflammatory transcription (100–105)	Translation requires vascular-targeted delivery and biomarkers of endothelial target engagement.
Osteoarthritis	Cytokine-driven cartilage catabolism; synovitis	IL-1β/NF-κB-dependent MMPs and inflammatory mediators in chondrocytes	CDK9 inhibition reported to reduce cytokines/MMPs in chondrocyte-focused models (61, 62, 108)	Evidence remains preclinical; intra-articular delivery and effects on repair programs require study.
Graft-versus-host disease	Alloreactive T-cell expansion	Activation-induced transcriptional elongation in effector T cells	R-roscovitine reported to limit T-cell clonal expansion and protect in preclinical GVHD (109)	Immunosuppression/infection risk and dosing schedules are central barriers.
Airway inflammation (asthma/COPD endotypes)	Type-2 and/or T_H17/neutrophilic programs	P-TEFb coupling to IL-17-responsive epithelial transcription	P-TEFb involved in IL-17F signaling in airway epithelium (110)	Direct COPD-focused evidence is limited; inhaled delivery may improve therapeutic window.
Acute innate activation (LPS)	TLR4-driven cytokine burst	NF-κB–dependent TNF and early-response transcription	CDK9 inhibition reduces LPS-induced TNF and inflammatory activation in cell models (54)	Acute models may not predict chronic remodeling; requires PK/PD-linked biomarkers and safety profiling.

AP-1: activator protein 1; COPD: chronic obstructive pulmonary disease; GVHD: graft-versus-host disease; IBD: inflammatory bowel disease; IL: interleukin; LPS: lipopolysaccharide; MMPs: matrix metalloproteinases; NF-κB: nuclear factor kappa B; PD: pharmacodynamics; PK: pharmacokinetics; P-TEFb: positive transcription elongation factor b; RA: rheumatoid arthritis; STAT: signal transducer and activator of transcription; T_H1: T helper 1 type; T_H17: T helper 17 type; TLR4: Toll-like receptor 4; TNF: tumor necrosis factor.

STATEMENT OF ETHICS

This study did not involve human participants or clinical interventions.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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DATA AVAILABILITY

Data supporting the findings in this study are immediately available upon reasonable request.

AI ASSISTANCE DISCLOSURE

The authors used an artificial intelligence (AI) tool (Grok3) solely for language refinement, paraphrasing, and improving the structure and readability of the manuscript. No AI tool was used for scientific writing, generation of scientific content, literature search, reference selection, data interpretation, or drawing conclusions. All content, references, and final manuscript revisions were independently prepared, reviewed, and approved by the authors.

REFERENCES

1. Leitch AE, Duffin R, Haslett C, Rossi AG. Relevance of granulocyte apoptosis to resolution of inflammation at the respiratory mucosa. Mucosal Immunol. 2008;1(5):350-63.
2. Savill JS, Wyllie AH, Henson JE, Walport MJ, Henson PM, Haslett C. Macrophage phagocytosis of aging neutrophils in inflammation. Programmed cell death in the neutrophil leads to its recognition by macrophages. J Clin Invest. 1989;83(3):865-75.
3. Haslett C, Savill J, Meagher L. Macrophage recognition of senescent granulocytes. Biochem Soc Trans. 1990;18(2):225-7.
4. Ozato K, Tsujimura H, Tamura T. Toll-like receptor signaling and regulation of cytokine gene expression in the immune system. Biotechniques. 2002;Suppl:66-8, 70, 2 passim.
5. Fox S, Leitch AE, Duffin R, Haslett C, Rossi AG. Neutrophil apoptosis: relevance to the innate immune response and inflammatory disease. J Innate Immun. 2010;2(3):216-27.
6. Rossi AG, Hallett JM, Sawatzky DA, Teixeira MM, Haslett C. Modulation of granulocyte apoptosis can influence the resolution of inflammation. Biochem Soc Trans. 2007;35(Pt 2):288-91.
7. Meagher LC, Cousin JM, Seckl JR, Haslett C. Opposing effects of glucocorticoids on the rate of apoptosis in neutrophilic and eosinophilic granulocytes. J Immunol. 1996;156(11):4422-8.
8. Rossi A, Kapahi P, Natoli G, Takahashi T, Chen Y, Karin M, et al. Anti-inflammatory cyclopentenone prostaglandins are direct inhibitors of IkappaB kinase. Nature. 2000;403(6765):103-8.
9. Stewart AG. Mediators and receptors in the resolution of inflammation: drug targeting opportunities. Br J Pharmacol. 2009;158(4):933-5.
10. Roskoski R, Jr. Cyclin-dependent protein serine/threonine kinase inhibitors as anticancer drugs. Pharmacol Res. 2019;139:471-88.
11. Romano G, Giordano A. Role of the cyclin-dependent kinase 9-related pathway in mammalian gene expression and human diseases. Cell Cycle. 2008;7(23):3664-8.
12. Leitch AE, Haslett C, Rossi AG. Cyclin-dependent kinase inhibitor drugs as potential novel anti-inflammatory and pro-resolution agents. Br J Pharmacol. 2009;158(4):1004-16.
13. Leitch AE, Lucas CD, Marwick JA, Duffin R, Haslett C, Rossi AG. Cyclin-dependent kinases 7 and 9 specifically regulate neutrophil transcription and their inhibition drives apoptosis to promote resolution of inflammation. Cell Death & Differentiation. 2012;19(12):1950-61.
14. Smallie T, Ricchetti G, Horwood NJ, Feldmann M, Clark AR, Williams LM. IL-10 inhibits transcription elongation of the human TNF gene in primary macrophages. J Exp Med. 2010;207(10):2081-8.
15. Wang S, Fischer PM. Cyclin-dependent kinase 9: a key transcriptional regulator and potential drug target in oncology, virology and cardiology. Trends Pharmacol Sci. 2008;29(6):302-13.
16. Graña X, De Luca A, Sang N, Fu Y, Claudio PP, Rosenblatt J, et al. PITALRE, a nuclear CDC2-related protein kinase that phosphorylates the retinoblastoma

protein in vitro. Proceedings of the National Academy of Sciences. 1994;91(9):3834-8.
17. Baumli S, Lolli G, Lowe ED, Troiani S, Rusconi L, Bullock AN, et al. The structure of P-TEFb (CDK9/cyclin T1), its complex with flavopiridol and regulation by phosphorylation. Embo j. 2008;27(13):1907-18.
18. Baumli S, Endicott JA, Johnson LN. Halogen bonds form the basis for selective P-TEFb inhibition by DRB. Chem Biol. 2010;17(9):931-6.
19. Vedadi M, Niesen FH, Allali-Hassani A, Fedorov OY, Finerty PJ, Jr., Wasney GA, et al. Chemical screening methods to identify ligands that promote protein stability, protein crystallization, and structure determination. Proc Natl Acad Sci U S A. 2006;103(43):15835-40.
20. Shore SM, Byers SA, Maury W, Price DH. Identification of a novel isoform of Cdk9. Gene. 2003;307:175-82.
21. Liu H, Rice AP. Genomic organization and characterization of promoter function of the human CDK9 gene. Gene. 2000;252(1-2):51-9.
22. Liu H, Herrmann CH. Differential localization and expression of the Cdk9 42k and 55k isoforms. J Cell Physiol. 2005;203(1):251-60.
23. Shore SM, Byers SA, Dent P, Price DH. Characterization of Cdk9(55) and differential regulation of two Cdk9 isoforms. Gene. 2005;350(1):51-8.
24. Whittaker SR, Mallinger A, Workman P, Clarke PA. Inhibitors of cyclin-dependent kinases as cancer therapeutics. Pharmacol Ther. 2017;173:83-105.
25. Marshall NF, Price DH. Purification of P-TEFb, a transcription factor required for the transition into productive elongation. J Biol Chem. 1995;270(21):12335-8.
26. O'Brien T, Hardin S, Greenleaf A, Lis JT. Phosphorylation of RNA polymerase II C-terminal domain and transcriptional elongation. Nature. 1994;370(6484):75-7.
27. Marshall NF, Peng J, Xie Z, Price DH. Control of RNA polymerase II elongation potential by a novel carboxyl-terminal domain kinase. J Biol Chem. 1996;271(43):27176-83.
28. Mbonye U, Wang B, Gokulrangan G, Shi W, Yang S, Karn J. Cyclin-dependent kinase 7 (CDK7)-mediated phosphorylation of the CDK9 activation loop promotes P-TEFb assembly with Tat and proviral HIV reactivation. Journal of Biological Chemistry. 2018;293(26):10009-25.
29. Chen FX, Smith ER, Shilatifard A. Born to run: control of transcription elongation by RNA polymerase II. Nat Rev Mol Cell Biol. 2018;19(7):464-78.
30. Vanden Bush TJ, Bishop GA. CDK-mediated regulation of cell functions via c-Jun phosphorylation and AP-1 activation. PLoS One. 2011;6(4):e19468.
31. Fukada T, Ohtani T, Yoshida Y, Shirogane T, Nishida K, Nakajima K, et al. STAT3 orchestrates contradictory signals in cytokine-induced G1 to S cell-cycle transition. Embo j. 1998;17(22):6670-7.
32. Zinatizadeh MR, Schock B, Chalbatani GM, Zarandi PK, Jalali SA, Miri SR. The Nuclear Factor Kappa B (NF-kB) signaling in cancer development and immune diseases. Genes Dis. 2021;8(3):287-97.
33. Nowak DE, Tian B, Jamaluddin M, Boldogh I, Vergara LA, Choudhary S, et al. RelA Ser276 phosphorylation is required for activation of a subset of NF-kappaB-dependent genes by recruiting cyclin-dependent kinase 9/cyclin T1 complexes. Mol Cell Biol. 2008;28(11):3623-38.
34. Krystof V, Baumli S, Fürst R. Perspective of cyclin-dependent kinase 9 (CDK9) as a drug target. Curr Pharm Des. 2012;18(20):2883-90.
35. Hou T, Ray S, Brasier AR. The Functional Role of an Interleukin 6-inducible CDK9·STAT3 Complex in Human γ-Fibrinogen Gene Expression*. Journal of Biological Chemistry. 2007;282(51):37091-102.
36. Yang J, Zhao Y, Kalita M, Li X, Jamaluddin M, Tian B, et al. Systematic Determination of Human Cyclin Dependent Kinase (CDK)-9 Interactome Identifies Novel Functions in RNA Splicing Mediated by the DEAD Box (DDX)-5/17 RNA Helicases*. Molecular & Cellular Proteomics. 2015;14(10):2701-21.
37. Chao SH, Fujinaga K, Marion JE, Taube R, Sausville EA, Senderowicz AM, et al. Flavopiridol inhibits P-TEFb and blocks HIV-1 replication. J Biol Chem. 2000;275(37):28345-8.
38. Gupta SC, Kim JH, Prasad S, Aggarwal BB. Regulation of survival, proliferation, invasion, angiogenesis, and metastasis of tumor cells through modulation of inflammatory pathways by nutraceuticals. Cancer Metastasis Rev. 2010;29(3):405-34.
39. Byrd JC, Shinn C, Waselenko JK, Fuchs EJ, Lehman TA, Nguyen PL, et al. Flavopiridol induces apoptosis in chronic lymphocytic leukemia cells via activation of caspase-3 without evidence of bcl-2 modulation or dependence on functional p53. Blood. 1998;92(10):3804-16.
40. Takada Y, Aggarwal BB. Flavopiridol inhibits NF-kappaB activation induced by various carcinogens and inflammatory agents through inhibition of IkappaBalpha kinase and p65 phosphorylation: abrogation of cyclin D1,

cyclooxygenase-2, and matrix metalloprotease-9. J Biol Chem. 2004;279(6):4750-9.
41. Hou T, Ray S, Brasier AR. The functional role of an interleukin 6-inducible CDK9.STAT3 complex in human gamma-fibrinogen gene expression. J Biol Chem. 2007;282(51):37091-102.
42. Fang L, Choudhary S, Zhao Y, Edeh CB, Yang C, Boldogh I, et al. ATM regulates NF-κB-dependent immediate-early genes via RelA Ser 276 phosphorylation coupled to CDK9 promoter recruitment. Nucleic Acids Research. 2014;42(13):8416-32.
43. Arguello F, Alexander M, Sterry JA, Tudor G, Smith EM, Kalavar NT, et al. Flavopiridol induces apoptosis of normal lymphoid cells, causes immunosuppression, and has potent antitumor activity In vivo against human leukemia and lymphoma xenografts. Blood. 1998;91(7):2482-90.
44. Herrmann CH, Carroll RG, Wei P, Jones KA, Rice AP. Tat-associated kinase, TAK, activity is regulated by distinct mechanisms in peripheral blood lymphocytes and promonocytic cell lines. J Virol. 1998;72(12):9881-8.
45. Garriga J, Peng J, Parreño M, Price DH, Henderson EE, Graña X. Upregulation of cyclin T1/CDK9 complexes during T cell activation. Oncogene. 1998;17(24):3093-102.
46. Ghose R, Liou LY, Herrmann CH, Rice AP. Induction of TAK (cyclin T1/P-TEFb) in purified resting CD4(+) T lymphocytes by combination of cytokines. J Virol. 2001;75(23):11336-43.
47. Ramakrishnan R, Dow EC, Rice AP. Characterization of Cdk9 T-loop phosphorylation in resting and activated CD4(+) T lymphocytes. J Leukoc Biol. 2009;86(6):1345-50.
48. Hu Z, Yik JH, Cissell DD, Michelier PV, Athanasiou KA, Haudenschild DR. Inhibition of CDK9 prevents mechanical injury-induced inflammation, apoptosis and matrix degradation in cartilage explants. Eur Cell Mater. 2016;30:200-9.
49. Hoodless LJ, Lucas CD, Duffin R, Denvir MA, Haslett C, Tucker CS, et al. Genetic and pharmacological inhibition of CDK9 drives neutrophil apoptosis to resolve inflammation in zebrafish in vivo. Sci Rep. 2016;5:36980.
50. Wang K, Hampson P, Hazeldine J, Krystof V, Strnad M, Pechan P, et al. Cyclin-Dependent Kinase 9 Activity Regulates Neutrophil Spontaneous Apoptosis. PLOS ONE. 2012;7(1):e30128.
51. Hellvard A, Zeitlmann L, Heiser U, Kehlen A, Niestroj A, Demuth HU, et al. Inhibition of CDK9 as a therapeutic strategy for inflammatory arthritis. Sci Rep. 2016;6:31441.
52. De Falco G, Leucci E, Onnis A, Bellan C, Tigli C, Wirths S, et al. Cdk9/Cyclin T1 complex: a key player during the activation/differentiation process of normal lymphoid B cells. J Cell Physiol. 2008;215(1):276-82.
53. Liou LY, Herrmann CH, Rice AP. Transient induction of cyclin T1 during human macrophage differentiation regulates human immunodeficiency virus type 1 Tat transactivation function. J Virol. 2002;76(21):10579-87.
54. Haque A, Koide N, Iftakhar EKI, Noman AS, Odkhuu E, Badamtseren B, et al. Flavopiridol inhibits lipopolysaccharide-induced TNF-α production through inactivation of nuclear factor-κB and mitogen-activated protein kinases in the MyD88-dependent pathway. Microbiol Immunol. 2011;55(3):160-7.
55. Holgate ST. Cytokine and anti-cytokine therapy for the treatment of asthma and allergic disease. Cytokine. 2004;28(4-5):152-7.
56. Chung KF. Cytokines as targets in chronic obstructive pulmonary disease. Curr Drug Targets. 2006;7(6):675-81.
57. Williams RO, Paleolog E, Feldmann M. Cytokine inhibitors in rheumatoid arthritis and other autoimmune diseases. Curr Opin Pharmacol. 2007;7(4):412-7.
58. Barboric M, Nissen RM, Kanazawa S, Jabrane-Ferrat N, Peterlin BM. NF-kappaB binds P-TEFb to stimulate transcriptional elongation by RNA polymerase II. Mol Cell. 2001;8(2):327-37.
59. Brasier AR, Tian B, Jamaluddin M, Kalita MK, Garofalo RP, Lu M. RelA Ser276 phosphorylation-coupled Lys310 acetylation controls transcriptional elongation of inflammatory cytokines in respiratory syncytial virus infection. J Virol. 2011;85(22):11752-69.
60. Schmerwitz UK, Sass G, Khandoga AG, Joore J, Mayer BA, Berberich N, et al. Flavopiridol protects against inflammation by attenuating leukocyte-endothelial interaction via inhibition of cyclin-dependent kinase 9. Arterioscler Thromb Vasc Biol. 2011;31(2):280-8.
61. Xue S, Shao Q, Zhu L-B, Jiang Y-F, Wang C, Xue B, et al. LDC000067 suppresses RANKL-induced osteoclastogenesis in vitro and prevents LPS-induced osteolysis in vivo. International Immunopharmacology. 2019;75:105826.
62. Xue S, Zhu L, Wang C, Jiang Y, Lu H, Liu Y, et al. CDK9 attenuation exerts protective effects on catabolism and hypertrophy in chondrocytes and ameliorates osteoarthritis development. Biochemical and Biophysical Research Communications. 2019;517(1):132-9.
63. MacLachlan TK, Sang N, De Luca A, Puri PL, Levrero M, Giordano A. Binding of CDK9 to TRAF2. J Cell Biochem. 1998;71(4):467-78.

64. Hou T, Tieu BC, Ray S, Recinos Iii A, Cui R, Tilton RG, et al. Roles of IL-6-gp130 Signaling in Vascular Inflammation. Curr Cardiol Rev. 2008;4(3):179-92.
65. Boulanger MJ, Chow DC, Brevnova EE, Garcia KC. Hexameric structure and assembly of the interleukin-6/IL-6 alpha-receptor/gp130 complex. Science. 2003;300(5628):2101-4.
66. Heinrich PC, Behrmann I, Haan S, Hermanns HM, Müller-Newen G, Schaper F. Principles of interleukin (IL)-6-type cytokine signalling and its regulation. Biochem J. 2003;374(Pt 1):1-20.
67. Kurdi M, Booz GW. Can the protective actions of JAK-STAT in the heart be exploited therapeutically? Parsing the regulation of interleukin-6-type cytokine signaling. J Cardiovasc Pharmacol. 2007;50(2):126-41.
68. Rébé C, Ghiringhelli F. STAT3, a Master Regulator of Anti-Tumor Immune Response. Cancers (Basel). 2019;11(9).
69. Yu H, Kortylewski M, Pardoll D. Crosstalk between cancer and immune cells: role of STAT3 in the tumour microenvironment. Nat Rev Immunol. 2007;7(1):41-51.
70. Berberich N, Uhl B, Joore J, Schmerwitz UK, Mayer BA, Reichel CA, et al. Roscovitine blocks leukocyte extravasation by inhibition of cyclin-dependent kinases 5 and 9. Br J Pharmacol. 2011;163(5):1086-98.
71. Chao SH, Price DH. Flavopiridol inactivates P-TEFb and blocks most RNA polymerase II transcription in vivo. J Biol Chem. 2001;276(34):31793-9.
72. McClue SJ, Blake D, Clarke R, Cowan A, Cummings L, Fischer PM, et al. In vitro and in vivo antitumor properties of the cyclin dependent kinase inhibitor CYC202 (R-roscovitine). Int J Cancer. 2002;102(5):463-8.
73. Hossain DMS, Javaid S, Cai M, Zhang C, Sawant A, Hinton M, et al. Dinaciclib induces immunogenic cell death and enhances anti-PD1-mediated tumor suppression. J Clin Invest. 2018;128(2):644-54.
74. Judith EK, Elizabeth G-M, Elihu HE, Michelle AR, Smith BD, Jacqueline MG, et al. Randomized phase II study of two schedules of flavopiridol given as timed sequential therapy with cytosine arabinoside and mitoxantrone for adults with newly diagnosed, poor-risk acute myelogenous leukemia. Haematologica. 2012;97(11):1736-42.
75. Lücking U, Scholz A, Lienau P, Siemeister G, Kosemund D, Bohlmann R, et al. Identification of Atuveciclib (BAY 1143572), the First Highly Selective, Clinical PTEFb/CDK9 Inhibitor for the Treatment of Cancer. ChemMedChem. 2017;12(21):1776-93.
76. Lücking U, Kosemund D, Böhnke N, Lienau P, Siemeister G, Denner K, et al. Changing for the Better: Discovery of the Highly Potent and Selective CDK9 Inhibitor VIP152 Suitable for Once Weekly Intravenous Dosing for the Treatment of Cancer. J Med Chem. 2021;64(15):11651-74.
77. Rossi AG, Sawatzky DA, Walker A, Ward C, Sheldrake TA, Riley NA, et al. Cyclin-dependent kinase inhibitors enhance the resolution of inflammation by promoting inflammatory cell apoptosis. Nat Med. 2006;12(9):1056-64.
78. Bloomfield SF, Stanwell-Smith R, Crevel RW, Pickup J. Too clean, or not too clean: the hygiene hypothesis and home hygiene. Clin Exp Allergy. 2006;36(4):402-25.
79. Witko-Sarsat V, Rieu P, Descamps-Latscha B, Lesavre P, Halbwachs-Mecarelli L. Neutrophils: Molecules, Functions and Pathophysiological Aspects. Laboratory Investigation. 2000;80(5):617-53.
80. Nestle FO, Kaplan DH, Barker J. Psoriasis. N Engl J Med. 2009;361(5):496-509.
81. Wasilewska A, Winiarska M, Olszewska M, Rudnicka L. Interleukin-17 inhibitors. A new era in treatment of psoriasis and other skin diseases. Postepy Dermatol Alergol. 2016;33(4):247-52.
82. Jullien D, Prinz JC, Nestle FO. Immunogenicity of biotherapy used in psoriasis: the science behind the scenes. J Invest Dermatol. 2015;135(1):31-8.
83. Wegenka UM, Buschmann J, Lütticken C, Heinrich PC, Horn F. Acute-phase response factor, a nuclear factor binding to acute-phase response elements, is rapidly activated by interleukin-6 at the posttranslational level. Mol Cell Biol. 1993;13(1):276-88.
84. Zhao F, Wang Y, Zuo H, Ru Y, Wang Y. Cyclin-Dependent kinase 9 (CDK9) inhibitor Atuveciclib ameliorates Imiquimod-Induced Psoriasis-Like dermatitis in mice by inhibiting various inflammation factors via STAT3 signaling pathway. Int Immunopharmacol. 2024;129:111652.
85. Müller A, Dickmanns A, Resch C, Schäkel K, Hailfinger S, Dobbelstein M, et al. The CDK4/6-EZH2 pathway is a potential therapeutic target for psoriasis. J Clin Invest. 2020;130(11):5765-81.
86. Podolsky DK. Inflammatory bowel disease (1). N Engl J Med. 1991;325(13):928-37.
87. Shanahan F. Inflammatory bowel disease: immunodiagnostics, immunotherapeutics, and ecotherapeutics. Gastroenterology. 2001;120(3):622-35.
88. Elson CO, Sartor RB, Tennyson GS, Riddell RH. Experimental models of inflammatory bowel disease. Gastroenterology. 1995;109(4):1344-67.
89. Breese E, Braegger CP, Corrigan CJ, Walker-Smith JA, MacDonald TT. Interleukin-2- and interferon-gamma-

secreting T cells in normal and diseased human intestinal mucosa. Immunology. 1993;78(1):127-31.
90. Szabo SJ, Kim ST, Costa GL, Zhang X, Fathman CG, Glimcher LH. A novel transcription factor, T-bet, directs Th1 lineage commitment. Cell. 2000;100(6):655-69.
91. Neurath MF, Weigmann B, Finotto S, Glickman J, Nieuwenhuis E, Iijima H, et al. The transcription factor T-bet regulates mucosal T cell activation in experimental colitis and Crohn's disease. J Exp Med. 2002;195(9):1129-43.
92. Jenner RG, Townsend MJ, Jackson I, Sun K, Bouwman RD, Young RA, et al. The transcription factors T-bet and GATA-3 control alternative pathways of T-cell differentiation through a shared set of target genes. Proc Natl Acad Sci U S A. 2009;106(42):17876-81.
93. Omer OS, Hertweck A, Roberts LB, Lo JW, Clough JN, Jackson I, et al. Cyclin-dependent Kinase 9 as a Potential Target for Anti-TNF-resistant Inflammatory Bowel Disease. Cell Mol Gastroenterol Hepatol. 2022;14(3):625-41.
94. Schrecengost RS, Green CL, Zhuang Y, Keller SN, Smith RA, Maines LW, et al. In Vitro and In Vivo Antitumor and Anti-Inflammatory Capabilities of the Novel GSK3 and CDK9 Inhibitor ABC1183. J Pharmacol Exp Ther. 2018;365(1):107-16.
95. Smolen JS, Aletaha D, Barton A, Burmester GR, Emery P, Firestein GS, et al. Rheumatoid arthritis. Nat Rev Dis Primers. 2018;4:18001.
96. Zheng B, Marinova E, Switzer K, Wansley D, He H, Bheekha-Escura R, et al. Overexpression of Bcl(XL) in B cells promotes Th1 response and exacerbates collagen-induced arthritis. J Immunol. 2007;179(10):7087-92.
97. Peperzak V, Vikström I, Walker J, Glaser SP, LePage M, Coquery CM, et al. Mcl-1 is essential for the survival of plasma cells. Nat Immunol. 2013;14(3):290-7.
98. Huang J, Fu X, Chen X, Li Z, Huang Y, Liang C. Promising Therapeutic Targets for Treatment of Rheumatoid Arthritis. Front Immunol. 2021;12:686155.
99. Bettayeb K, Oumata N, Echalier A, Ferandin Y, Endicott JA, Galons H, et al. CR8, a potent and selective, roscovitine-derived inhibitor of cyclin-dependent kinases. Oncogene. 2008;27(44):5797-807.
100. Hennekens CH, Gaziano JM. Antioxidants and heart disease: epidemiology and clinical evidence. Clin Cardiol. 1993;16(4 Suppl 1):I10-3; discussion I3-5.
101. Ross R. Atherosclerosis--an inflammatory disease. N Engl J Med. 1999;340(2):115-26.
102. Miller YI, Choi SH, Wiesner P, Fang L, Harkewicz R, Hartvigsen K, et al. Oxidation-specific epitopes are danger-associated molecular patterns recognized by pattern recognition receptors of innate immunity. Circ Res. 2011;108(2):235-48.
103. Han Y, Zhan Y, Hou G, Li L. Cyclin-dependent kinase 9 may as a novel target in downregulating the atherosclerosis inflammation (Review). Biomed Rep. 2014;2(6):775-9.
104. Pirillo A, Norata GD, Catapano AL. LOX-1, OxLDL, and atherosclerosis. Mediators Inflamm. 2013;2013:152786.
105. Huang S, Luo W, Wu G, Shen Q, Zhuang Z, Yang D, et al. Inhibition of CDK9 attenuates atherosclerosis by inhibiting inflammation and phenotypic switching of vascular smooth muscle cells. Aging (Albany NY). 2021;13(11):14892-909.
106. Medzhitov R. Origin and physiological roles of inflammation. Nature. 2008;454(7203):428-35.
107. Bannuru RR, Osani MC, Vaysbrot EE, Arden NK, Bennell K, Bierma-Zeinstra SMA, et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. Osteoarthritis Cartilage. 2019;27(11):1578-89.
108. Fukui T, Yik JHN, Doyran B, Davis J, Haudenschild AK, Adamopoulos IE, et al. Bromodomain-containing-protein-4 and cyclin-dependent-kinase-9 inhibitors interact synergistically in vitro and combined treatment reduces post-traumatic osteoarthritis severity in mice. Osteoarthritis Cartilage. 2021;29(1):68-77.
109. Li L, Wang H, Kim J, Pihan G, Boussiotis V. The cyclin dependent kinase inhibitor (R)-roscovitine prevents alloreactive T cell clonal expansion and protects against acute GvHD. Cell Cycle. 2009;8(11):1794 - 802.
110. Nakajima M, Kawaguchi M, Matsuyama M, Ota K, Fujita J, Matsukura S, et al. Transcription Elongation Factor P-TEFb Is Involved in IL-17F Signaling in Airway Smooth Muscle Cells. Int Arch Allergy Immunol. 2018;176(2):83-90.
111. Cai D, Latham VM, Jr., Zhang X, Shapiro GI. Combined depletion of cell cycle and transcriptional cyclin-dependent kinase activities induces apoptosis in cancer cells. Cancer Res. 2006;66(18):9270-80.
112. MacCallum DE, Melville J, Frame S, Watt K, Anderson S, Gianella-Borradori A, et al. Seliciclib (CYC202, R-Roscovitine) induces cell death in multiple myeloma cells by inhibition of RNA polymerase II-dependent transcription and down-regulation of Mcl-1. Cancer Res. 2005;65(12):5399-407.
113. Liu H, Huang Q, Shi B, Eksarko P, Temkin V, Pope RM. Regulation of Mcl-1 expression in rheumatoid arthritis synovial macrophages. Arthritis Rheum. 2006;54(10):3174-81.

114. Yang X, Luo W, Li L, Hu X, Xu M, Wang Y, et al. CDK9 inhibition improves diabetic nephropathy by reducing inflammation in the kidneys. Toxicology and Applied Pharmacology. 2021;416:115465.
115. Yik JH, Hu Z, Kumari R, Christiansen BA, Haudenschild DR. Cyclin-dependent kinase 9 inhibition protects cartilage from the catabolic effects of proinflammatory cytokines. Arthritis Rheumatol. 2014;66(6):1537-46.
116. Siebert S, Pratt AG, Stocken DD, Morton M, Cranston A, Cole M, et al. Targeting the rheumatoid arthritis synovial fibroblast via cyclin dependent kinase inhibition: An early phase trial. Medicine (Baltimore). 2020;99(26):e20458.
117. Meijer L, Nelson DJ, Riazanski V, Gabdoulkhakova AG, Hery-Arnaud G, Le Berre R, et al. Modulating Innate and Adaptive Immunity by (R)-Roscovitine: Potential Therapeutic Opportunity in Cystic Fibrosis. J Innate Immun. 2016;8(4):330-49.
118. Shen X, Kretz AL, Schneider S, Knippschild U, Henne-Bruns D, Kornmann M, et al. Evaluation of CDK9 Inhibition by Dinaciclib in Combination with Apoptosis Modulating izTRAIL for the Treatment of Colorectal Cancer. Biomedicines. 2023;11(3).
119. Palermo A, Doyonnas R, Bhutani N, Pomerantz J, Alkan O, Blau HM. Nuclear reprogramming in heterokaryons is rapid, extensive, and bidirectional. FASEB J. 2009;23(5):1431-40.