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Perspective

Interleukin-1 Receptor-Associated Kinase 4 (IRAK4) Degraders for Treating Inflammatory Diseases: Advances and Prospects

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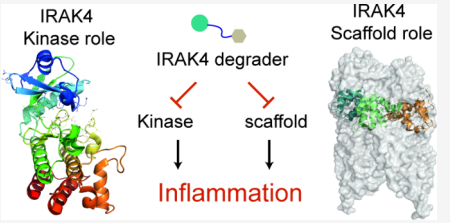
ABSTRACT: Interleukin-1 receptor-associated kinase 4 (IRAK4) is involved in various inflammation-related diseases. Both the kinase and scaffolding functions of IRAK4 initiate pro-inflammatory factor transcription and expression. The scaffolding function of IRAK4 is essential for Myddosome assembly and NF-κB activation. Conventional small-molecule inhibitors effectively inhibit the kinase function of IRAK4 but do not block its scaffolding function. Recently, various IRAK4 degraders have shown promising therapeutic potential in inflammatory diseases. The most advanced IRAK4-selective degrader, KT-474 (SAR444656), significantly reduced inflammatory biomarker levels in patients and demonstrated high safety and tolerability. This perspective introduces and discusses the physiological biology of IRAK4, its associated diseases, and the current development of IRAK4 degraders, thereby offering insights into future research directions.



SIGNIFICANCE

- IRAK4 plays a crucial role in the pathophysiology of various inflammation-related diseases, making it a promising therapeutic target.
- Conventional IRAK4 inhibitors may have limited efficacy, because they fail to address the scaffolding functions of IRAK4.
- IRAK4 degraders have recently emerged as innovative candidate drugs for treating inflammation and autoimmune diseases.
- KT-474 is the first heterobifunctional degrader evaluated in a nononcological setting and investigated in humans with encouraging clinical activity.

1. INTRODUCTION

Inflammation is the response of the immune system to an invading virus or bacteria.[1] It is a pleiotropic process linking innate and specific immunity to metabolism and events that impact cell and organelle integrity.[2,3] The inflammatory response primarily involves inflammatory mediator release, white blood cell infiltration and activation, and tissue repair and regeneration. However, a cytokine storm resulting from excess and uncontrollable inflammatory reactions can cause multiple organ dysfunction syndrome, leading to tissue cell death and severe damage to human health.[4] Therefore, research on key signal nodes in the inflammatory response signaling pathway and corresponding drug development is crucial for treating inflammation-related diseases.

Toll-like receptors (TLRs) are crucial in host defense and inflammation as they recognize damage- and pathogen-associated molecular patterns.[5] Interleukin-1 receptor-associated kinase 4 (IRAK4) is essential for TLR and interleukin-1 receptor (IL-1R) signaling, as it is involved in the TLR/IL-1R-mediated myeloid differentiation primary response 88 (MyD88)-dependent pathways.[6] Upon TLR activation, IRAKs and MyD88 form a signalosome, termed the "Myddosome," via death domain (DD) interactions (Figure 1).[5,7,8] The IRAK family includes IRAK1, IRAK2, IRAK3, and IRAK4. Among these, IRAK4 is a critical kinase in TLR/IL-1R signaling pathways.[9−11] Targeting IRAK4 is a promising therapeutic strategy for autoimmune and inflammatory disorders.[6] Several IRAK4 kinase domain inhibitors, including PF-06650833,[12] BAY-1830839,[13] zabedosertib (BAY1834845),[14] edecesertib,[15] and emavusertib (CA-4948),[16] have advanced to clinical trials.

IRAK4 has dual roles within the Myddosome complex: kinase and scaffold functions.[17,18] Conventional small-molecule inhibitors selectively target the kinase function but fail to inhibit the scaffold function, which may limit their clinical efficacy.[19] For instance, PF-06650833 demonstrated modest therapeutic effects in rheumatoid arthritis (RA); however, it exhibited no significant activity in a phase II trial for hidradenitis suppurativa (HS) compared to a placebo.[20] In

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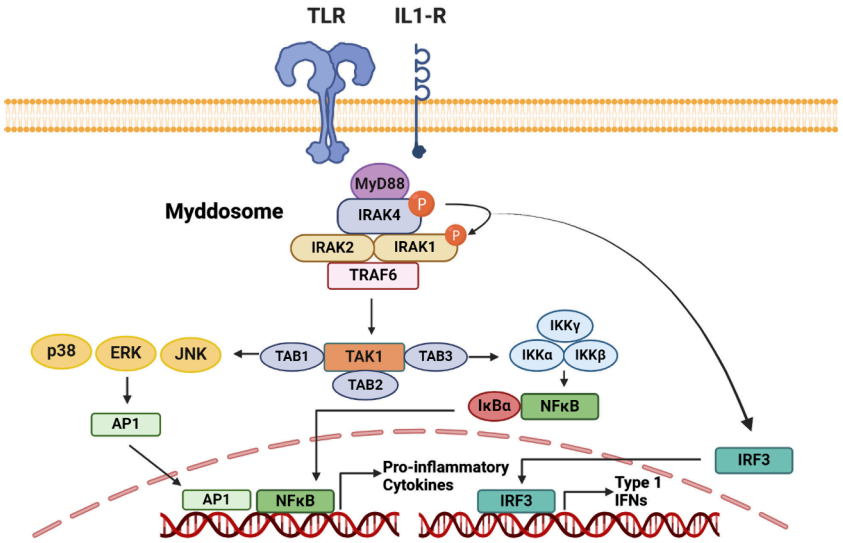

Figure 1. Interleukin-1 receptor-associated kinase 4 (IRAK4) is involved in interleukin-1 receptors (IL-1Rs) and toll-like receptor (TLR) signal transduction, leading to inflammation. The figure was created with BioRender.

addition, the phase II clinical trail (NCT05656911) of Bayer-developed compound zabedosertib (BAY1834845) for treating moderate-to-severe atopic dermatitis (AD) has been terminated, which implies that its clinical development might have been suspended.[14,21,22] Consequently, targeting the catalytic and scaffold functions of IRAK4 could enhance its efficacy in treating inflammatory and autoimmune diseases.

Proteolysis-targeting chimeras (PROTACs) are heterobifunctional molecules that induce ubiquitylation and subsequent protein of interest (POI) degradation through the ubiquitin−proteasome system.[23] Heterobifunctional degraders can simultaneously regulate both catalytic and nonenzymatic functions of POIs, presenting a promising strategy to overcome the limitations of traditional inhibitors.[24−26] Increasingly, degraders are being designed to target the nonenzymatic functions of kinases, such as focal adhesion kinase (FAK), discoidin domain receptor 1, and Aurora.[21−27] By eliminating the IRAK4 scaffold from the Myddosome, heterobifunctional degraders can inhibit all downstream TLR signaling, thus blocking inflammation and cytokine production. Recently, more IRAK4 degraders have been developed, with KT-474 being the first to be tested in humans after displaying promising results in phase 1 clinical trials.[20] This perspective provides an overview and analysis of current research on IRAK4-associated inflammatory diseases and discusses recent advances in IRAK4 degraders, aiming to inspire the development of novel agents for treating inflammatory diseases.

2. IRAK4 IN INFLAMMATORY SIGNAL TRANSDUCTION

Innate and adaptive immunity are crucial for maintaining normal physiological functions and preventing disease development.[28] The innate immune system acts as the primary defense against pathogens, identifying them through few genetically encoded pattern-recognition receptors (PRRs).[1] These PRRs detect pathogen-associated molecular patterns, conserved molecules in pathogens, and damage-associated molecular patterns (DAMPs) produced by damaged cells.[29] The discovery of TLR4 in humans in 1997 marked a significant breakthrough, establishing TLRs as a critical class of PRRs expressed by various immune cells.[4,30] Currently, 13 known TLR family members are found in numerous innate immune cells, such as macrophages and dendritic cells, and nonimmune cells, such as epithelial and fibroblast cells.[31,32] TLR1−5 are primarily located on the cell membrane surface and recognize bacterial and fungal components, while TLR3 and TLR7−13 are mainly intracellular, recognizing viruses, microbial nucleic acids, and endogenous stimulatory molecules.[33]

IRAK4 has kinase and scaffold functions that transmit signals during the inflammatory and immune responses (Figure 1), playing a crucial role in TLR and IL-1R family signaling pathways.[34] All TLR/IL-1R family members, except TLR3, utilize the TIR domains at the carboxy terminus of MyD88 for recruitment. MyD88 contains DD that recruits to IRAK4. The MyD88−IRAK4 complex then recruits IRAK4 substrates, IRAK2 or IRAK1. This forms a left-handed helical oligomer, the Myddosome signaling complex, comprising six MyD88, four IRAK4, and four IRAK1 molecules.[35,36]

TLR/IL-R activation brings the kinase region of IRAK4 into proximity, activating these two kinases through transautophosphorylation and subsequent IRAK1 phosphorylation. IRAK4 kinase activity can directly lead to the nuclear entry of interferon response regulatory factor (IRF) to transcribe inflammatory signaling factors.[37] Additionally, the C-terminal extension of IRAK1 contains the Pro−Xaa−Glu motif, which interacts with TNF receptor-associated factor 6 (TRAF6).[38] TRAF6, a vital protein in the TLR signaling pathway, facilitates Lys63 (K63)-linked polyubiquitin chain production.[39] This type of polyubiquitin attracts two downstream kinase complexes: transforming growth factor-activated kinase-1 (TAK1) and IκB kinase (IKK).[40−42] The presence of these complexes on polyubiquitin promotes their phosphorylation and activation. IKK eventually phosphorylates IκB protein, leading to its degradation by proteasomes. IκB degradation removes its inhibitory effect on NF-κB, allowing NF-κB to enter the nucleus. Inside the nucleus, NF-κB, IRF, and AP-1 trigger target gene expression. The products of this mechanism significantly facilitate immune and inflammatory responses (Figure 1).[43,44]

In addition to autophosphorylation, IRAK4 activation is regulated by K63 ubiquitylation.[35] During ubiquitylation, the C-terminal tail of ubiquitin (Ub) is covalently docked to the

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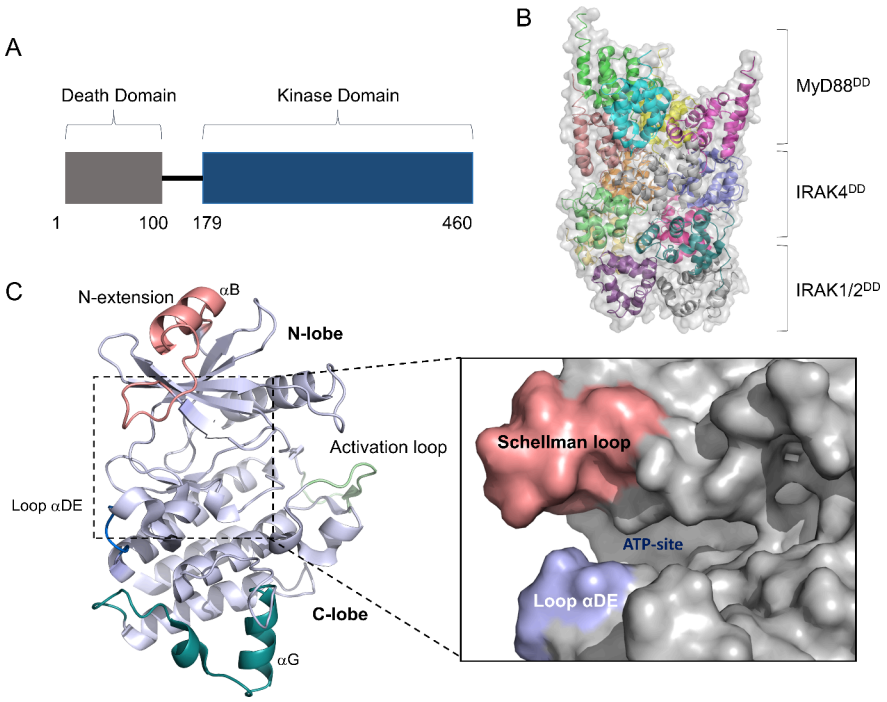

Figure 2. Interleukin-1 receptor-associated kinase 4 (IRAK4) structure. (A) Schematic illustration of IRAK4 domains. (B) Cartoon representation of the Myddosome complex comprising MyD88, IRAK4, and IRAK1/2 death domains (PDB ID: 3MOP). (C) Crystal structure of the IRAK4 kinase domain (PDB ID: 2NRU).

lysine residue of IRAK4. First, the Ub moiety is activated by the E1 enzymes. Second, the E2 Ub-conjugating enzyme transfers Ub from E1 to E3 Ub ligase and then to the substrate protein IRAK4. The Ub moiety contains several lysine residues, including the first methionine amino acid (M1) at the N-terminus, K48, and K63, which can recruit additional Ub to form a polyUb chain. K48-linked polyUb chains mediate the 26S proteasomal degradation pathway. In contrast, K63-linked polyUb chains offer additional structural scaffolding that facilitates protein interaction and signaling activation. IRAK4 ubiquitylation contain both Ml−Ub and K63−Ub linkages, which are essential for NF-κB activation.[45] Several Myddosome subunits, including MyD88, IRAK4, and IRAK1, are regulated by K63-linked ubiquitylation, suggesting that polyUb chains may be particularly important in the TLR/IL-1R pathway. IRAK4 is the key subunit of the Myddosome, and IRAK4 kinase activity-dependent and -independent mechanisms may work parallelly to activate the Myddosome and proinflammatory cytokine production.[35,46] Thus, further investigation of post-translational IRAK4 modifications may reveal the underlying kinase-independent function in signaling activation.

3. IRAK4 STRUCTURE

All IRAK family members, including IRAK4, contain a kinase domain, an N-terminal DD, and a linker chain (Figure 2A). Upon TLR activation, the IRAK4 DD interacts with MyD88 and IRAK1 DDs, forming the Myddosome complex (Figure 2B).

The IRAK4 kinase domain displays a typical double-leaf structure with an ATP-binding pocket between the leaves. Three autophosphorylation sites, Thr342, Thr345, and Ser346, are present within the kinase domain.[47] The N-terminal ATP-binding pocket of the IRAK4 kinase domain, termed the "Front Pocket," features a unique kinase leaf extension comprising the Schellman loop, an amphiphilic α-helix, ASX motif, ST motif, and C-terminal Gly-rich loop.[48] The Schellman loop, a highly solvent-exposed loop, exhibits hydrogen bonding between the G188/G189 backbone amino acids and P184/I185 carbonyls.[49] Notably, the I185 residue within this loop is positioned immediately adjacent to the ATP-binding site, distinguishing IRAK4 from other kinases. Moreover, the IRAK4 N-terminus includes a distinctive hinge loop and the gatekeeper residue Tyr262. The size and flexibility of Tyr262 side chain typically determine the presence of an additional lipophilic subpocket near the ATP-binding site, referred to as the "Back Pocket".[50−52]

4. IRAK4 AND INFLAMMATORY DISEASES

IRAK4 signaling dysregulation contributes to numerous inflammatory conditions and inflammation-related cancers, including sepsis, psoriasis, systemic lupus erythematosus (SLE), and RA (Figure 3).[53] Moreover, IRAK4 serves as a therapeutic target in chronic inflammatory skin diseases.[54] Consequently, targeting IRAK4 represents an appealing therapeutic approach for autoimmune and inflammatory disorders.[6]

4.1. SLE. SLE is an autoimmune disease characterized by complex multigene involvement.[55] It manifests through the production of pathogenic antibodies against nuclear autoantigens, systemic inflammation, and an exaggerated response to these autoantibodies, leading to the progressive accumulation of damage across multiple organ systems.[56,57] Impaired apoptotic and necrotic cell clearance allows autoantibodies access to nuclear antigens, initiating immune complex formation and subsequent activation of various immune cell types.[58] Genome-wide association studies (GWAS) have identified IRAK4 as part of the SLE risk locus. IRAK4,

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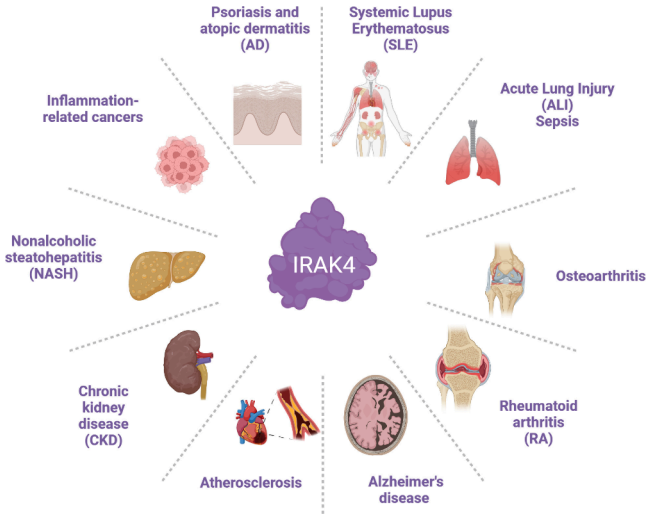

Figure 3. Interleukin-1 receptor-associated kinase 4 (IRAK4)-related inflammatory diseases. The figure was created with BioRender.

which is coexpressed with IRF5 in immune cells, functions as a kinase and scaffold protein in numerous signaling pathways.[59] An enhanced TLR7 response has been linked to SLE, with some studies suggesting the essential role of IRAK4 in TLR7 signaling. Therefore, targeting IRAK4 is a promising treatment strategy for SLE.[60,61]

4.2. Acute Lung Injury and Sepsis. Among the spectrum of IRAK4-linked diseases, sepsis is the most severe and is characterized by an exaggerated response of the human body to external pathogens, leading to multiple organ dysfunction syndrome (MODS).[62,63] Bacteria-induced septic shock is characterized by elevated lipopolysaccharide (LPS) levels in the blood, excess pro-inflammatory cytokine production, coagulation system activation, and fibrinogen degradation product accumulation. This results in local and systemic damage to the circulatory system and endothelial cell impairment through the TLR signaling pathway. Notably, sepsis can also be a complication of severe influenza, in which abnormal TLR4 activation by DAMPs produced during virus-induced acute lung injury (ALI) plays a pivotal role. Upon TLR4 polymerization, signaling transduction into the cell binds to the carboxyl-terminus of MyD88. Subsequently, IRAK4, the main regulator in this signaling pathway, establishes the Myddosome complex and activates NF-κB, MAPK, and IRF5/7, producing various sepsis-associated pro-inflammatory cytokines.[64] Wang et al. demonstrated that the combined administration of IRAK4 inhibitors and ubiquitin-specific peptidase 13 (USP13) improved LPS-induced inflammatory responses in primary bone marrow-derived macrophages and septic mice.[65] Consequently, targeting IRAK4 holds potential as a therapeutic strategy for managing inflammation in sepsis and ALI.

4.3. Osteoarthritis. The primary pathological symptoms of osteoarthritis include synovitis, osteophyte formation, subchondral sclerosis, and cartilage damage.[66,67] Osteoarthritis, a prevalent degenerative disease affecting joints and bones, often expresses TLRs in both the articular cartilage and synovial tissue of affected individuals.[68,69] Studies have confirmed that IRAK4 activation induces osteoclastogenesis, inhibits foreign body giant cell (FBGC) formation, and consequently promotes inflammatory osteolysis.[10,70] Conversely, IRAK4 absence or inhibition can restore FBGC formation, improve M2 macrophage marker expression, and mitigate osteoarthritis progression. Li et al. have further reported the significant role of IRAK4 in osteoarthritis, as ad-shIRAK4 effectively reduces inflammatory factor expression in chondrocytes in an osteoarthritis rabbit model.[71] These results collectively underscore the critical involvement of IRAK4 in osteoarthritis pathogenesis and progression.[72]

4.4. RA. In addition to conventional osteoarthritis, which affects the entire joint, including the articular cartilage, subchondral bone, and bone marrow compartments, RA represents one of over 100 different types of arthritis, with its prevalence increasing globally.[73,74] Extensive research has demonstrated that TLR/MyD88 signaling pathway activation in fibroblast-like synoviocytes contributes to inflammatory factor production and RA development.[75] Clinically, patients exhibit elevated expression of autoreactive TLRs in circulating immune cells and synovial tissues.[76] Furthermore, the inhibition of IRAK4 and its associated metabolic factors (HIF1α and cMYC) reduced TLR7-mediated metabolic activity in RA macrophages and fibroblast-like synoviocytes, consequently alleviating RA-related inflammation.[77] Consequently, targeting TLR/MyD88-mediated IRAK4 activation and its downstream pathways has emerged as a promising therapeutic approach for treating RA.[78]

4.5. Alzheimer's Disease. Alzheimer's disease is the most prevalent neurodegenerative disorder, characterized by excess amyloid-beta peptide (Aβ) accumulation in the brain.[79] Studies have elucidated that hyperphosphorylation of microtubule-associated protein Tau forms paired spiral fibers and neurofibrillary tangles, thereby triggering neuronal dysfunction and death, mediated by Aβ induction.[80,81] Moreover, the neuroinflammation hypothesis highlights neuroinflammation as a common feature of neurodegenerative diseases, a confirmed pathological hallmark.[82,83] Phenotypic microglial activations, attributed to fibrillar β-amyloid deposition in the brains of patients with Alzheimer's disease, generates inflammatory molecules.[84,85] Studies have demonstrated the selective regulation of microglial phagocytosis by pro-inflammatory cytokines and affirmed the efficacy of anti-inflammatory therapy in mitigating Alzheimer's disease risk and treating affected individuals.[86] Furthermore, IRAK4 activation in the microglia determines their differentiation into a more inflammatory M1 state, hampering amyloid protein clearance.[87] Additionally, studies revealed the impact of IRAK4-dependent signaling on Aβ homeostasis and deposition in the later stages of Alzheimer's disease pathogenesis.[88] Collectively, these findings underscore the pivotal role of IRAK4-dependent signaling in the brain, influencing Aβ homeostasis and microglial phenotypes.[89]

4.6. Atherosclerosis. Atherosclerosis, a chronic inflammatory disease, encompasses various characteristic features such as vascular inflammation, endothelial dysfunction, plaque formation, impaired blood flow, and cholesterol deposition resulting from dyslipidemia.[90] Endothelial cells undergo damage due to mechanical, biological, and toxic effects, releasing diverse compounds, including proteins and small nucleic acids, which serve as endogenous DAMPs.[91] Previous research has highlighted the involvement of the pro-inflammatory cytokine IL-1 in atherosclerosis progression. The depletion of IL-1 or its receptor IL-1R diminish inflammation within blood vessels and reduce atherosclerosis in ApoE$^{-/-}$ mice.[40,92] Initial investigations indicate the essential role of IRAK4 kinase activity in Tak1-dependent

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NF-κB activation and mRNA stability induced by TLR/IL-1R signaling. This is evidenced by the impaired aortic sinus lesion formation in ApoE$^{-/-}$ mice with inactive IRAK4 kinase and reduced pro-inflammatory mRNA expression in arterial tissues due to IRAK4 dysfunction.[93] Consequently, anti-inflammatory therapies targeting IRAK4 hold promise for atherosclerosis treatment.[94]

4.7. Chronic Kidney Disease. Chronic kidney disease (CKD), encompassing conditions such as diabetic nephropathy, represents a hazardous state characterized by a progressive and irreversible decline in kidney function.[95] Presently, diabetes and hypertension stand as the primary causes of CKD, although other common etiologies include infectious glomerulonephritis, renal vasculitis, ureteral obstruction, genetic alterations, and autoimmune disorders.[96] Recent research has confirmed the presence of a chronic low-grade inflammatory state in patients with CKD and end-stage kidney disease, characterized by elevated levels of pro-inflammatory cytokines and markers such as IL-1, IL-6, TNF-α, and C-reactive protein.[60] Moreover, IRAK4-induced inflammation plays a pivotal role in CKD progression, whether caused by diabetes or other factors, and inhibiting IRAK4 activation can effectively confer renoprotective effects. Consequently, IRAK4 activity modulation, which is pivotal in CKD pathogenesis, has emerged as a promising therapeutic avenue for managing various inflammatory disorders.[10,97]

4.8. Inflammation-Related Cancers. Drug discovery for the activated B-cell-like (ABC) subtype of diffuse large B-cell lymphoma (DLBCL) remains unsuccessful. Certain conditions such as chronic pleurisy, chronic osteomyelitis, and chronic skin ulcers, as well as metal implants within the bone and surgical mesh, have been implicated in DLBCL pathogenesis.[98−100] A subset of ABC DLBCL cancers is driven by activating mutations in MyD88, such as L265P. In ABC-DLBCL cells, the pathogenic MyD88 mutation induces the Myddosome formation, increasing IRAK4 kinase activity and constitutive NF-κB activation to promote B-cell proliferation and survival.[101−103] Consequently, IRAK4 acts as a crucial mediator to promote tumor growth in MyD88 mutant lymphoma, and IRAK4-targeting molecules should be further investigated for ABC-DLBCL treatment.[104,105]

Since IRAK4 signaling activity is highly dependent on both kinase activity and scaffolding roles, inhibiting the IRAK4 kinase activity alone is insufficient to block NF-κB activity.[17,106] Thus, three heterobifunctional IRAK4 degraders have been developed for treating DLBCL.[107−109] However, those studies have shown that IRAK4 degradation has limited efficacy to induce DLBCL cell apoptosis, indicating the presence of alternative IRAK4 signaling-independent NF-κB activation mechanisms. One of the reported underlying mechanisms includes the transcription factor interferon regulatory factor 4 (IRF4)-mediated NF-κB activation.[110] These studies suggested that only IRAK4 degradation is not sufficient to treat IRAK4-related cancers such as DLBCL.[111] The molecules both degrade IRAK4 and related transcription factors such as Ikaros show robust pro-apoptotic effect in MyD88 mutant DLBCL.[112]

4.9. Skin Diseases. Psoriasis, characterized by skin involvement, is a visible manifestation of a broad systemic immune disorder marked by generalized inflammation.[113] Psoriasis pathogenesis involves intricate interactions among various immune system components, including crosstalk between the innate and adaptive systems, the IL-17/IL-23 axis, and the impact on resident T cells in the skin.[114] AD, another prevalent inflammatory skin disorder, is closely associated with dysregulated T cell-mediated immune responses and diverse cytokine release patterns.[115] Lavazais et al. have underscored the efficacy of IRAK4 inhibition in human and murine models of psoriasis and AD, highlighting the pivotal role of IRAK4 in the innate and adaptive immune processes implicated in inflammatory skin disease pathogenesis.[54] In a phase 1 trial involving KT-474, an IRAK4 degrader, circulating inflammatory biomarkers reduced in AD, with a notable trend toward IL-1α, COX2, OX40, CXCL13, and IL27RA downregulation.[20] These findings advocate further investigation of IRAK4 modulators as a promising therapeutic avenue for managing inflammatory skin diseases.

5. DUAL ROLES OF IRAK4

In contrast to most kinases, IRAK4 serves as a kinase that phosphorylates downstream signaling molecules and is a scaffold protein crucial for Myddosome formation. While the catalytic activity of IRAK4 is essential for IRAK1 recruitment, it is dispensable for IRAK4 recruitment to MyD88.[116] Inhibiting IRAK4 kinase activity with a kinase domain inhibitor further stabilizes the Myddosome complex.[17] Moreover, IRAK4 kinase function is not indispensable for TLR4 signaling, but its scaffold role is critical for NF-κB activation in TLR4-activated macrophages.[18] The IRAK4 DD plays a vital role in inflammatory signaling by mediating TLR-induced NF-κB activation.[117] Hence, IRAK4 demonstrates a crucial scaffold function in Myddosome formation, while its kinase activity is not imperative for Myddosome assembly. Understanding this molecular mechanism highlights the potential limitations of IRAK4 inhibitors, which mainly target IRAK4 kinase activity while exhibiting weaker effects on its scaffold role. PF-06650833 is the first IRAK4 inhibitor to enter clinical trials with low nanomolar potency against IRAK4 (IC_{50} = 0.2 nM).[118] It demonstrates a favorable safety and pharmacokinetic profile, with a modified-release formulation having PK characteristics suitable for QD dosing.[12] However, another phase 2 clinical trial (NCT04092452) revealed that PF-06650833 induced clinical response in only 34% patients with HS (16/47), comparable to the 33.3% observed in the placebo group, indicating that it failed to exhibit significant therapeutic effects in patients with HS.[119,120] The limited clinical success of IRAK4 kinase inhibitors in treating chronic inflammatory and autoimmune diseases may be attributed to their inability to target the crucial scaffolding function of IRAK4.[121] Consequently, inhibiting the scaffolding function of IRAK4 may enhance the efficacy of treatments for inflammatory and autoimmune diseases.

6. IRAK4 DEGRADERS

Targeted protein degradation (TPD) has recently emerged as an important modality in drug development. Target protein ligands, E3 ubiquitin ligase ligands, intermediate linkers, and heterobifunctional degraders facilitate TPD via the ubiquitin−proteasome system. Compared with traditional small-molecule inhibitors, TPD is more efficient for targeted regulation. Protein degraders have several significant advantages over conventional inhibitors, including event-driven pharmacology, the ability to target nonenzymatic proteins, which are regarded as "undruggable" targets, and the potential to address proteins with scaffolding roles.[122] Consequently, IRAK4 is an ideal

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Table 1. Representative IRAK4-Targeting Heterobifunctional Degraders in Preclinical and Clinical Development

Degrader	Company or Inventor	IRAK4 DC_{50} in cells	Target	Indications	Route of administration	E3 ligase	Status
Degrader-1	GlaxoSmithKline	151 nM (PBMCs); 36 nM (Dermal fibroblasts)	IRAK4	Autoimmune and inflammatory diseases	Undisclosed	VHL	Preclinical
Degrader-2	Janssen	405 nM (HEK293T)	IRAK4	DLBCL	Undisclosed	CRBN	Preclinical
Degrader-3	Chinese Academy of Sciences	Undisclosed	IRAK4	DLBCL	Undisclosed	CRBN	Preclinical
Degrader-4 (LC-MI-3)	Hangzhou Medical College	47.3 nM (RAW264.7)	IRAK4	Acute lung injury, sepsis, psoriasis	Oral	CRBN	Preclinical
Degrader-5 (KT-474)	Kymera	2.6 nM (Monocytes); 1.8 nM (Lymphocytes)	IRAK4	Hidradenitis suppurativa, atopic dermatitis	Oral	CRBN	Phase II (NCT06028230, NCT06058156)
Degrader-6 (KT-413)	Kymera	6 nM (OCI-LY10)	IRAK4 Ikaros/ Aiolos	DLBCL	i.v.	CRBN	Phase I (NCT05233033) discontinued
LT-002−158	Leadingtac	Undisclosed	IRAK4	suppurativa, atopic dermatitis, acute myeloid leukemia	Oral	CRBN	Phase I (NCT06082323)

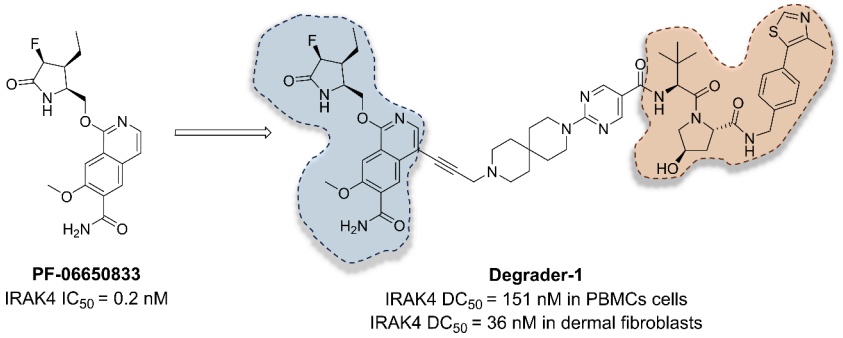

Figure 4. Degrader-1.

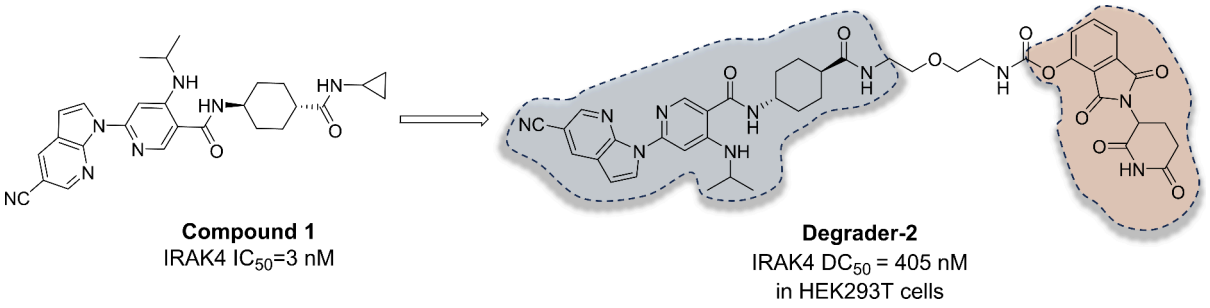

Figure 5. Degrader-2.

protein for TPD, an approach that enables the complete elimination of this target. This dual action could potentially yield superior therapeutic outcomes by disrupting the MyD88−IRAK4−NF-κB signal transduction pathway.[19] IRAK4 degraders are emerging as a promising class of molecules, providing powerful tools for studying IRAK4 biology while also offering novel therapeutic approaches for autoimmune, inflammatory, and oncological disorders (Table 1).

6.1. PF-06650833-Based Degrader. In 2019, the GlaxoSmithKline Medicine Research Center reported the discovery of degrader-1 using PF-06650833 as the target protein ligand and VHL as the E3 ligand, demonstrating 151 and 36 nM half-maximal degradation concentration (DC_{50}) in peripheral blood mononuclear cells (PBMCs) and human dermal fibroblasts, respectively (Figure 4).[107,123] Degrader-1 exhibited high selectivity over the closely related IRAK1 kinase. Treatment with degrader-1 inhibited multiple cytokines in PBMCs, including IL-1β, IFN-γ, IL-6, IL-8, IL-10, and TNF-α. However, compared to that, for the parent compound PF-06650833, no increase in potency was observed for degrader-1. Furthermore, despite the potent IRAK4 degradation, degrader-1 failed to inhibit TNF-α and IL-6 release in IL-1β-activated dermal fibroblasts.[107] The result is inconsistent with that of the previous study that IL-6 was completely inhibited in IRAK4-deficient dermal fibroblasts.[106] A plausible explanation is that the remaining portion of protein in dermal fibroblasts that is not degraded by the degrader activates IL-1R signaling.[107] Since degrader-1 did not exhibit a superior pharmacological profile over PF-06650833, further investigations are warranted to enhance the physicochemical properties of degrader-1, potentially owing to its high molecular weight (>1000 Da) and gain insights into IRAK4 biology.[107]

6.2. Compound 1-Based Degrader. Compound 1 was a highly selective IRAK4 kinase inhibitor with an impressive IC_{50} (3 nM). Zhang et al. observed no discernible effect of compound 1 on the survival of MyD88-mutated ABC DLBCL.[109] In 2020, to explore the scaffolding functions of

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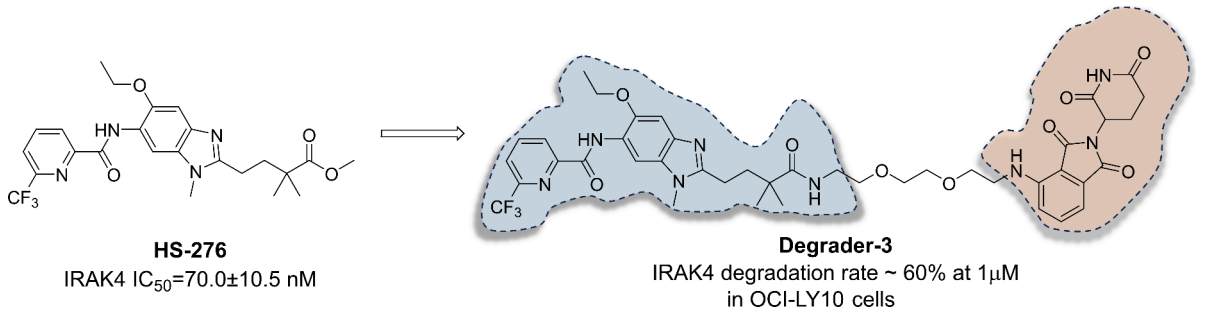

Figure 6. Degrader-3.

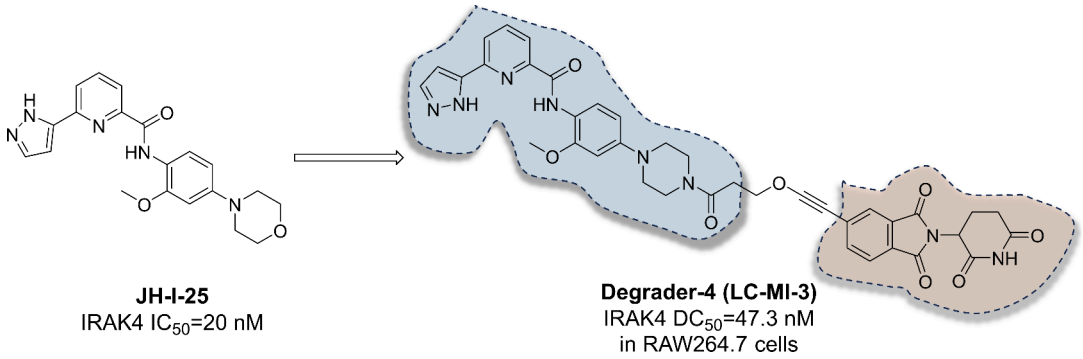

Figure 7. Degrader-4.

IRAK4, Janssen designed degrader-2 based on compound 1 to induce CRBN E3 ligase-mediated IRAK4 degradation, demonstrating a DC_{50} value of 405 nM in HEK293T cells (Figure 5). Degrader-2 exhibited remarkable proteome-wide degradation selectivity for IRAK4 among 9,741 targets in OCI-LY3 cells. Further investigations revealed that degrader-2 disrupted LPS-induced Myddosome downstream signaling by inhibiting IKKβ, JNK, and p38 phosphorylation, consequently reducing the level of cytokine production in THP-1 cells. However, IKKβ, JNK, and p38 phosphorylation in ABC-DLBCL cell lines remained unaffected by degrader-2, implying that the IRAK4 protein might partially contribute to $MyD88^{L265P}$ mutant-mediated downstream signaling. Considering the pivotal role of IRAK4 as a key kinase in inflammatory signaling, it is likely involved in modulating immune cell activity and the inflammation-related tumor microenvironment. Hence, further investigations using IRAK4 degraders are warranted to gain insight into these processes.[109]

6.3. HS-276-Based Degrader. In 2020, Chen et al. utilized an *N*-acyl-2-aminobenzimidazole inhibitor (HS-276) to target protein ligands and developed a series of IRAK4 degraders by conjugation with pomalidomide (Figure 6).[108] Among these, degrader-3, featuring a PEG2 linker, exhibited the most pronounced reduction in IRAK4 protein levels time and concentration dependently (DC_{50} value unreported). Notably, degrader-3 effectively hindered NF-κB signal transduction activation and outperformed the original inhibitor. Moreover, compared with IRAK4 kinase inhibitors, degrader-3 demonstrated significant advantages in reducing the cellular viability of the OCI-Ly10 and TMD8 cell viability. These findings underscore the potential of targeting both the kinase and scaffold functions of IRAK4 to yield superior and broader therapeutic effects than solely inhibiting kinase activity.[108] Hence, this compound merits further investigation for treating inflammation-related diseases linked to constitutively active NF-κB signaling.[124]

6.4. JH-I-25-Based Degrader. JH-I-25 is an IRAK4 kinase inhibitor featuring a thiazole amide core that exhibits excellent kinome selectivity.[125,126] Utilizing the JH-I-25−IRAK4 cocrystal structures, a JH-I-25-based chimera molecule, degrader-4 (LC-MI-3), was synthesized. Degrader-4 was validated as a potent IRAK4 degrader (DC_{50}: 47.3 nM, Figure 7).[127] It displayed high selectivity among 468 human protein kinases based on kinome screening results and TMT-labeled quantitative proteomic analysis. Degrader-4 effectively blocked both the kinase and scaffolding functions of IRAK4, demonstrating superior anti-inflammatory activity *in vitro* than JH-I-25. Studies have revealed the potent therapeutic activity of degrader-4 in both TLR4-mediated acute inflammation and TLR7-mediated chronic skin inflammatory models.[127]

6.5. Other Patented IRAK4 Degraders. The patent landscape surrounding IRAK4 degraders is evolving rapidly, and numerous innovative strategies are being explored to harness its therapeutic potential. Bristol-Myers Squibb and Celgene Corporation jointly developed piperazinylisoindolyl-piperidin-2,6-dione compounds and compositions for modulating IRAK4, and have verified their safety and efficacy.[128] Wuhan Humanwell Innovative Drug Research and Development Center Co., Ltd. has prepared imidazopyridine compounds as IRAK4 degraders (DC_{50}: 1.05 nM).[129] Hangzhou Polymed Biopharmaceuticals, Inc. has disclosed a series of indazole and isoindoline derivatives that possess targeted degradation capabilities against IRAK4.[130] Novartis has developed dihydropyrimidine derivatives capable of degrading IRAK4 under nanomolar conditions.[131] Additionally, companies such as Gilead Sciences, Inc. and Genentech, Inc. have also made strategic deployments in the development of IRAK4 degraders reported patents.[132,133] As research

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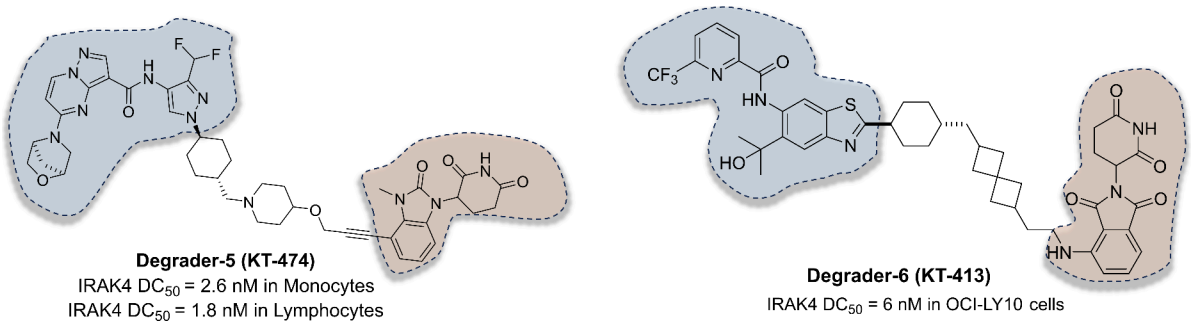

Figure 8. Degrader-5 (KT-474) and degrader-6 (KT-413).

progresses, the conversion of these patents is anticipated to identify effective IRAK4 degraders that can be translated into clinical applications for treating inflammatory and oncological diseases.

6.6. IRAK4 Degraders Entered Clinical Trials. In 2023, Kymera Therapeutics published the discovery and first-in-human clinical trial results of the oral heterobifunctional molecule degrader-5 (KT-474, also known as SAR444656) for treating TLR- and IL-1R-driven autoimmune diseases, specifically HS and AD.[20,121] Similar to most IRAK4 degraders, KT-474 induces an IRAK4−degrader−CRBN ternary complex formation, leading to IRAK4 protein ubiquitination and subsequent degradation (DC_{50} = 2.6 nM in monocytes, Figure 8).[134] KT-474 is a highly selective compound confirmed by KINOMEscan screening of 468 kinases. The degradation selectivity of KT-474 was assessed by using TMT-labeled quantitative proteomic analysis in human PBMCs and induced pluripotent stem cells (iPSCs). Both studies indicated a high selectivity for KT-474. IRAK4 was the only protein that was significantly degraded, and none of the immunomodulatory imide drug (IMiD) substrates were downregulated.[121] In addition, KT-474 showed favorable stability in human liver microsomes and exhibited moderate to high plasma clearances, moderate terminal half-lives ($t_{1/2}$) and steady-state high volumes of distribution (10−14 L·kg). The $t_{1/2}$ value of KT-474 was 3.6 and 7.5 h in rat and dog, respectively. The across species oral bioavailabilities (F%) of KT-474 were 13%, 12%, and 35% in monkey, rat, and dogs, respectively.[121]

In a randomized, double-blind, placebo-controlled phase 1 trial, healthy volunteers who received KT-474 displayed significantly reduced IRAK4 protein levels in the blood, with over 90% reduction after a single high dose (600−1,600 mg) or 14 daily doses (50−200 mg). In patients with HS or AD, IRAK4 levels in the skin are approximately twice those in healthy volunteers. KT-474 administration reduced inflammatory biomarkers (IL-6 and IL-1β) in the blood and skin and improved skin lesions and symptoms. Notably, no infections were observed during KT-474 administration, indicating IRAK4 is a safe and promising drug target for TLR- and IL-1R-driven diseases.[20] The robust activity and acceptable safety profile of KT-474 based on the phase 1 trial results support its progression to phase 2 trials (Table 1).

Additionally, Kymera Therapeutics recently identified and characterized degrader-6 (KT-413), a dual-functioning compound for treating MyD88-mutated DLBCL.[112,135] Global proteomic profiling in human PBMCs and OCI-Ly10 cells revealed that degrader-6 degrades not only IRAK4 but also the transcription factors Ikaros and Aiolos, known as IMiD substrates.[112,136] The DC_{50} of degrader-6 against IRAK4 and Ikaros in the OCI-Ly10 cells was 6 and 1 nM, respectively. Notably, degrader-6 exhibited a dual-functioning role, acting as both a heterobifunctional degrader and a molecular glue. *In vivo*, OCI-Ly10 and patient-derived xenograft studies demonstrated the promising *in vivo* therapeutic activity of 20 mg/kg degrader-6. Based on its verified potency and safety in preclinical studies, degrader-6 has advanced to a phase 1 clinical trial in patients with B-cell lymphoma, however the development of this compound has discontinued for strategic reasons (Table 1).[112]

LT-002-158 is an oral IRAK4 protein degrader developed by Shanghai Leadingtac Pharmaceutical Co., Ltd.[137] It is currently under development for treating autoimmune diseases and inflammation, including HS and AD and is in a phase 1 clinical trial to characterize its safety, tolerability, and PK/PD of single and multiple ascending doses in healthy volunteers (NCT06082323).[138]

7. CONCLUSION AND PROSPECT

TLRs (except TLR3) and IL-1Rs signal through the intracellular Myddosome, a protein supercomplex that includes IRAK4. As a primary inflammation regulator, IRAK4 is the key kinase in the MyD88-dependent pathway and has both scaffolding and kinase functions indispensable for complete signal activation.[17,139] The scaffolding role of IRAK4 is essential for Myddosome assembly and signal activation through NF-κB and MAPK, producing pro-inflammatory cytokines.[140]

Several IRAK4 inhibitors have been designed and evaluated in preclinical and clinical trials. Based on clinical data, blocking IRAK4 kinase activity alone may not be satisfactory for anti-inflammatory therapy owing to the dual roles of IRAK4. Over the past decade, an increasing amount of IRAK4 targeting heterobifunctional molecules has been developed. Based on the powerful PROTAC strategy, IRAK4 degraders have been designed to block both kinase and scaffold functions. These bifunctional molecules serve as valuable tools for enhancing our understanding of IRAK4 biology and offer novel therapeutic approaches for autoimmune, inflammatory, and oncological disorders. Interestingly, despite the low DC_{50} in cell-based studies, only some degraders have yielded better therapeutic outcomes.[19] The recently published promising clinical trial results of KT-474 in patients with HS and AD confirmed the efficacy and safety of the IRAK4 degraders in humans.

To date, most heterobifunctional degraders that have entered clinical trials are designed for cancer therapy by degrading androgen receptors, estrogen receptor (ER), Bruton's tyrosine kinase (BTK), or bromodomain-containing

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protein (BRD). IRAK4 degraders have therapeutic potential for various inflammatory diseases. Whether these degrader-based therapies can become clinical drugs for treating inflammatory disorders and oncological diseases remains to be determined.

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Notes

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ABBREVIATIONS

AD, atopic dermatitis; ABC DLBCL, activated B cell-like diffuse large B-cell lymphoma; ALI, acute lung injury; AP-1, activator protein 1; BTK, bruton's tyrosine kinase; BRD, bromodomain; CRBN, cereblon; CKD, chronic kidney disease; DLBCL, diffuse large B-cell lymphomas; DC_{50}, half-maximal degradation concentration; DAMP, damage-associated molecular pattern; DD, death domain; HS, hidradenitis suppurativa; IRAK, interleukin-1 receptor associated kinase; IMiD, immunomodulatory drug; IL-1R, interleukin-1 receptor; IRF, interferon response regulatory factor; IKK, IκB kinase; JNK, c-Jun N-terminal protein kinase; LPS, lipopolysaccharides; MyD88, myeloid differentiation primary response protein 88; NASH, nonalcoholic steatohepatitis; NF-κB, nuclear factor-kappa B; PBMC, peripheral blood mononuclear cells; PDGF, platelet-derived growth factor; POI, protein of interest; PROTAC, proteolysis-targeting chimera; PPR, pattern-recognition receptor; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; TAK1, factor-activated kinase-1; TLR, toll-like receptor; TRAF6, tumor necrosis factor receptor-associated factor 6; USP13, ubiquitin-specific peptidase 13; VHL, von Hippel-Lindau

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