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*Review Article*

# Drugging the Inflammasome Gasdermin Axis: Toward Precision Control of Pyroptosis

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## About Article

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**ABSTRACT**

Pyroptosis, an inflammasome-driven, gasdermin-mediated form of lytic cell death, has emerged as a unifying mechanism in disorders ranging from sepsis to Alzheimer's disease. Canonical and non-canonical pathways converge on caspase-1/4/5/11 cleavage of gasdermin D, releasing IL-1β and IL-18; basal epithelial IL-18 preserves barrier integrity, whereas unchecked cytokine efflux fuels cardiovascular, metabolic, and neuro-inflammation. Early translational successes include the oral NLRP3 inhibitor dapansutrile, which lowered synovial IL-1β by 72% and halved pain scores in a phase II gout-flare trial, and tadekinig alfa, a recombinant IL-18-binding protein now in phase II for NLRC4-MAS. Repurposed disulfiram blocks gasdermin pores pre-clinically, while AI-guided structure screens and nanocarrier delivery are accelerating next-generation candidates. Yet inhibiting pyroptosis may heighten infection risk and demand brain-penetrant, cost-effective molecules. Judicious, biomarker-guided modulation of this fiery death program is therefore a promising but complex therapeutic strategy. This approach offers an increasingly tangible route to precision immunotherapy.

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## 1. INTRODUCTION

Pyroptosis is a form of programmed necrotic cell death marked by inflammasome activation, caspase-mediated cleavage of gasdermin proteins, and release of proinflammatory mediators. First recognized in the context of infection, pyroptosis has emerged over the past decade as a pivotal mechanism in many sterile inflammatory conditions (Yu *et al.*, 2021; Zhang *et al.*, 2025). Unlike apoptosis, pyroptosis leads to cell swelling, breaking open, and the quick release of cytokines, which is why it is called "fiery" (Yu *et al.*, 2021; Zhang *et al.*, 2025). Its main process includes NLRP-family inflammasomes (like NLRP3 and AIM2) that bring in ASC and caspase-1, while a different process involves caspase-4/5/11 sensing LPS in the cytoplasm (de Vasconcelos *et al.*, 2019; Zhang *et al.*, 2025). Gasdermin D (GSDMD) is the main effector: inflammatory caspases cleave GSDMD to liberate an N-terminal fragment that oligomerizes into membrane pores (Xia *et al.*, 2021; Yu *et al.*, 2021). These pores, which are about 1–2 μm wide, allow small IL-1β/IL-18 molecules (around 4.5 nm) to leave the cell while also letting water in, causing the cell to swell and eventually burst (Xia *et al.*, 2021; Yu *et al.*, 2021). NINJ1 functions after pore formation to drive terminal plasma-membrane rupture and the release of larger intracellular contents (Zhang *et al.*, 2025). This sequence links danger recognition in the cytosol to extracellular inflammatory signaling.

## 2. LITERATURE REVIEW

Early descriptions of pyroptosis framed it as an antibacterial self-destruct mechanism in macrophages, but over the past decade, the field has widened dramatically. Structural biology first clarified the molecular choreography: cryo-EM studies resolved the helical ASC speck and the 33-subunit gasdermin-D pore, revealing a negatively charged lumen that selectively releases mature IL-1β/IL-18 (Xia *et al.*, 2021). Single-cell imaging then showed pyroptosis proceeds through discrete stages—ion-selective membrane perforation, osmotic swelling, and then catastrophic rupture (de Vasconcelos *et al.*, 2019). Parallel genetics linked gain-of-function NLRP3 mutations to cryopyrin-associated periodic syndromes, cementing clinical relevance (Huang *et al.*, 2018). Despite this advancement, major uncertainties limit translation: the circumstances under which pyroptosis acts as a driver versus a byproduct across diseases; the intervention nodes (sensor, caspase, and gasdermin) that offer efficacy without unacceptable host-defense trade-offs; how to identify responsive patients using validated biomarkers; and how timing and dosing influence benefits in acute versus chronic inflammation.

### 2.1. Neuro/GI block

From 2018 onward, disease-focused work exploded. In cardiovascular research, the CANTOS trial proved IL-1β neutralization can cut recurrent myocardial infarction risk by 15 % (Ridker *et al.*, 2017), while murine studies demonstrated that NLRP3 or caspase-1 knockout shrinks atherosclerotic lesions (Zeng *et al.*, 2021). Neuroinflammation studies link microglial NLRP3 activation to pathology in Alzheimer's and Parkinson's. In a post-symptomatic 5xFAD model, pharmacologic NLRP3 inhibition improved cognitive readouts (Auger *et al.*, 2025). In the gut, epithelial IL-18 supports barrier function, while microbiota-driven GSDMD activation has been associated with worse colitis in experimental systems (Gao *et al.*, 2021; Nowarski *et al.*, 2015).

### 2.2. Therapeutics block

Therapeutic development is shifting from downstream cytokine neutralization toward upstream nodal blockade. The oral NLRP3 inhibitor dapansutrile has reported phase-II data in gout and heart failure with acceptable tolerability (Klück *et al.*, 2020). Disulfiram's inhibition of gasdermin offers an orthogonal strategy at the executioner step (Hu *et al.*, 2020). In parallel, structure-guided virtual screening that leverages AlphaFold models of NLRP3 has produced early small-molecule leads with sub-micromolar activity (Yin *et al.*, 2022). These lines of work position the inflammasome–gasdermin signaling as targets under active evaluation across multiple disease models

## 3. METHODOLOGY

Evidence was gathered from PubMed/MEDLINE, Embase, Scopus, and Web of Science Core Collection, with supplementary searches of Cochrane CENTRAL, ClinicalTrials.gov, and WHO ICTRP. Coverage spanned each database's inception through the last search on 3 September 2025.

Search strings combined controlled vocabulary and keywords for pyroptosis and its components (e.g., "pyroptosis," "gasdermin," "GSDMD," "inflammasome," "NLRP3," "caspase-1," "IL-1β," "IL-18") with disease terms (e.g., "atherosclerosis," "colitis," "neurodegeneration," "metabolic disease") using Boolean operators and field tags. English-language, peer-reviewed primary studies were eligible across human, animal, and cell models. Exclusions were conference abstracts, letters, editorials, preprints, single-patient anecdotes, and non-original commentary. Titles/abstracts were screened, and full texts assessed for relevance to pyroptosis mechanisms, disease involvement, or therapeutic targeting. Reference-list snowballing and forward citation checks identified additional records.

Data extracted included model/system, pathway component(s), intervention/target, outcome measures, and safety signals for clinical reports. Quality prioritization favored replicated findings, validated assays, appropriate controls, and adequate sample size for clinical evidence. Findings were integrated using narrative synthesis only; no meta-analysis was performed. A recency-first strategy was applied with selective reach-back to pivotal earlier work.

## 4. RESULTS AND DISCUSSION

### 4.1. Mechanisms of pyroptosis

#### 4.1.1. Inflammasome Assembly And Activation

Canonical pyroptosis is initiated by inflammasome sensors that detect danger signals. NLRP3 is the most extensively studied sensor, but NLRC4, AIM2, pyrin, and others also form inflammasomes. Inflammasome activation typically requires a priming step (e.g., NF-κB upregulation of NLRP3 and pro-IL-1β) followed by an activation step (e.g., $K^+$ efflux, reactive oxygen species) that induces oligomerization (Zeng *et al.*, 2021; Zhang *et al.*, 2025). Activated NLRP3 recruits ASC (apoptosis-

associated speck-like protein), which nucleates a large helical "speck" that polymerizes caspase-1. Caspase-1 autocleavage yields the active p20/p10 subunits, which process pro–IL-1β and pro–IL-18 into mature cytokines and also cleave gasdermin D (de Vasconcelos *et al.*, 2019; Zeng *et al.*, 2021). There is a noncanonical pathway: in mice, cytosolic LPS directly binds caspase-11, and in humans, caspase-4/5, triggering pyroptosis without need for a sensor (de Vasconcelos *et al.*, 2019; Zhang *et al.*, 2025). Activated caspase-11/4/5 can also amplify canonical inflammasomes indirectly. Real-time imaging suggests inflammasome assembly is rapid (minutes) and culminates in a single ASC speck per cell (de Vasconcelos *et al.*, 2019; Zhang *et al.*, 2025). Recent studies have identified additional regulators; for example, the transmembrane protein NINJ1 forms filaments that perforate the membrane late in pyroptosis, facilitating full cell rupture (Zhang *et al.*, 2025). Overall, the assembly of the inflammasome is a series of steps that firmly push a cell toward inflammation and death, resulting in the activation of caspase-1 and the breakdown of other important proteins.

#### 4.1.2. Gasdermin pore formation and cytokine efflux

Central to pyroptosis is gasdermin-mediated membrane permeabilization. GSDMD is cleaved by caspase-1 (or by caspase-4/5/11 in noncanonical pyroptosis) between its N- and C-terminal domains (de Vasconcelos *et al.*, 2019; Zhang *et al.*, 2025). The liberated N-terminal domain (GSDMD-N) oligomerizes into 27–30-mer arc-, slit-, or pore-like structures. Cryo-EM and liposome assays reveal that GSDMD pores have a negatively charged inner surface, which influences cargo passage (Xia *et al.*, 2021). Xia *et al.* (2021) showed GSDMD pores preferentially release positively charged mature IL-1β and IL-18 while retarding their more acidic precursors (Xia *et al.*, 2021). In practice, cleavage of GSDMD forms ~10–15 nm inner-diameter pores through which ~4.5 nm cytokines and small ions can exit (Yu *et al.*, 2021). High-resolution live imaging indicates pyroptosis proceeds in phases: initial formation of small, ion-selective pores leads to $Ca^{2+}/Na^{+}$ influx and $Cl^{-}$ efflux, causing swelling; this is followed by osmotic lysis when full-size pores form (de Vasconcelos *et al.*, 2019; Yu *et al.*, 2021). During this process, IL-1β and IL-18 are secreted (they cannot exit via conventional ER/Golgi routes). Cryo-EM studies indicate that GSDMD pores let mature cytokines escape, which helps explain how IL-1β builds up outside the cell without going through the usual secretion process (Xia *et al.*, 2021; Yu *et al.*, 2021). Thus, gasdermin pores are the literal "exit gates" for inflammatory mediators during pyroptosis.

#### 4.1.3. Crosstalk with other cell death pathways

Pyroptosis intersects with apoptosis, necroptosis, ferroptosis, and the emerging concept of PANoptosis. Apoptotic caspases modulate pyroptosis: caspase-3/7, hallmarks of apoptosis, can cleave GSDMD at Asp87 to inactivate it, effectively aborting pyroptosis (Zhang *et al.*, 2025). Conversely, caspase-3 can cleave gasdermin E (GSDME) to trigger a pyroptosis-like death in cells with GSDME expression (e.g., tumor cells) (Yu *et al.*, 2021). Caspase-8 has been shown to directly cleave GSDMD under certain stimuli, converting death receptor signals into pyroptosis (Yu *et al.*, 2021). Necroptosis and pyroptosis are both lytic death programs. Necroptosis proceeds through the RIPK1–RIPK3–MLKL axis, while pyroptosis is executed by inflammasome-dependent caspase activation and gasdermin D pore formation. Viral infection and TNF-family signaling intersect with these modules; for example, TNFα under caspase-8 inhibition or RIPK1 deficiency can bias cells toward necroptosis, and pathogen sensing can license inflammasome activation. The PANoptosis framework describes inflammatory settings in which apoptotic, pyroptotic, and necroptotic effectors are co-engaged via a higher-order "PANoptosome"; during influenza A virus infection in macrophages, concurrent activation of caspase-1, caspase-8, and RIPK3 has been reported (Nguyen & Kanneganti, 2022). Ferroptosis, an iron-dependent lipid-peroxidation pathway, uses distinct machinery. It does not share a canonical execution step with pyroptosis; however, oxidative stress generated during ferroptotic stimuli (e.g., GPX4 inhibition) can provide signals that prime or activate NLRP3. Pyroptosis is not isolated: apoptotic machinery can either inhibit or redirect it, and signals may trigger hybrid death modes. This plasticity emphasizes the need to consider context when targeting pyroptosis therapeutically.

### 4.2. Pyroptosis in disease pathogenesis

#### 4.2.1. Infectious diseases

Pyroptosis evolved as a host defense against infection, yet it can be double-edged. Pattern recognition of pathogens initiates inflammasomes; for example, bacterial flagellin activates NLRC4, viral DNA activates AIM2, and many pathogens induce NLRP3 via cellular damage (Zhang *et al.*, 2025). Importantly, cytosolic Gram-negative LPS binds caspase-11/4/5, rapidly triggering pyroptosis without a sensor (noncanonical pathway) (de Vasconcelos *et al.*, 2019; Zhang *et al.*, 2025). This disposes of infected cells and releases IL-1/IL-18 to recruit neutrophils. "Pyroptosis drives CD4 T cell depletion in HIV-1," as abortive HIV infection causes caspase-1–mediated pyroptotic death of lymphoid CD4 T cells (Doitsh *et al.*, 2014). Thus, pyroptosis helps clear intracellular microbes.

Excessive pyroptosis can drive pathological inflammation. Widespread inflammasome activation in sepsis contributes to organ failure, and septic shock elevates circulating IL-1 and IL-18. Consistent with this biology, mice lacking caspase-1 or NLRP3 show relative protection from endotoxic shock (Bader *et al.*, 2025). Early clinical work signals a similar direction: treatment with the recombinant IL-1 receptor antagonist anakinra improved survival in sepsis patients with macrophage activation–like syndrome (Wu *et al.*, 2025). The same pathway, however, supports antimicrobial defense; caspase-1–deficient mice are more susceptible to selected infections, including Salmonella (Zhang *et al.*, 2025).

In viral pneumonia, including influenza and SARS-CoV-2, inflammasome activity is frequently observed. SARS-CoV-2 can activate NLRP3 in monocytes and macrophages, and higher IL-1β levels correlate with greater disease severity (Datta *et al.*, 2021). Even so, one mouse study reported similar disease severity in NLRP3−/− and ASC−/− lines compared with controls, suggesting that inflammasome signaling is not strictly required and that parallel pathways can sustain pathology (Nguyen & Kanneganti, 2022). Overall, the contribution of pyroptosis in

infection varies with pathogen, tissue context, and timing.

Finally, the release of chemokines and alarmins during pyroptosis recruits immune cells. This process is beneficial in the early stages but can lead to a cytokine storm later on. For example, during severe malaria or tuberculosis, inflammasome activation in immune cells contributes to pathologic lung or brain inflammation (Miller *et al.*, 2018). Thus, in infectious diseases, pyroptosis provides a key defense but also drives immunopathology if uncontrolled.

#### 4.2.2. Cardiovascular diseases

Sterile inflammation in the vasculature often engages pyroptosis. Oxidized lipids and cholesterol crystals in atherosclerotic plaques activate NLRP3 in macrophages, leading to IL-1β/IL-18 production and inflammasome-dependent cell death (Zeng *et al.*, 2021). Macrophage pyroptosis contributes to the formation of necrotic cores that destabilize plaques. Indeed, ApoE^−/− mice deficient in NLRP3 or IL-1β develop smaller atherosclerotic lesions (Zeng *et al.*, 2021). Blocking IL-1 signaling has proven beneficial: the CANTOS trial showed that canakinumab (anti–IL-1β) lowered recurrent myocardial infarction, stroke, and cardiovascular death in ~10,000 post-MI patients with elevated CRP (Zeng *et al.*, 2021). Canakinumab reduced major adverse cardiovascular events by ~15% over 3.7 years (Zeng *et al.*, 2021), providing proof-of-concept that inflammasome-derived IL-1β is pathogenic in human atherothrombosis. However, infection risk increased (sepsis deaths were higher on canakinumab (Zeng *et al.*, 2021), highlighting the host-defense trade-off.

Beyond atherosclerosis, pyroptosis is implicated in ischemia-reperfusion injury (e.g., myocardial infarction). Ong *et al.* (2018) showed that reperfusion releases DAMPs, which switch on NLRP3 in cardiomyocytes and recruit macrophages, leading to caspase-1 activation, IL-1β maturation, and added tissue injury (Ong *et al.*, 2018). Zeng *et al.* (2021) reported smaller infarcts in small colchicine trials, consistent with an inflammatory component (Zeng *et al.*, 2021). With encouraging preclinical results, selective NLRP3 blockers, including dapansutrile, are being evaluated in heart failure and myocardial infarction.

In stroke, similar mechanisms occur: NLRP3 is activated by dying neurons, fueling IL-1β release that worsens neuroinflammation. In mice, NLRP3 or ASC deletion reduces infarct size. Small stroke trials in humans showed that anakinra (an IL-1 receptor antagonist) was safe. Overall, pyroptosis in cardiovascular disease involves macrophages and parenchymal cells, creating a feed-forward inflammatory loop that drives chronic injury and remodeling.

#### 4.2.3. Inflammatory bowel disease

In the gut, pyroptosis has complex roles. Intestinal epithelial cells (IECs) and lamina propria macrophages express inflammasomes; their activation releases IL-18 (maintains barrier) and IL-1β (promotes inflammation). Patients with ulcerative colitis often show increased mucosal IL-18 and ASC specks (Arrè *et al.*, 2023). In studies with mice, removing NLRP3 or caspase-1 can sometimes make colitis worse because it stops the healing effects of IL-18, but in other cases, it can help by reducing IL-1 levels (Arrè *et al.*, 2023). This pattern reflects dual roles: basal IL-18 supports epithelial integrity, while excessive IL-1 drives pathology.

Recent work shows microbiota can directly trigger pyroptosis: Gao *et al.* (2021) found that gut flora induce GSDMD cleavage in IECs, releasing IL-18 that exacerbates colitis (Gao *et al.*, 2021). Conversely, Nowarski *et al.* showed that balanced epithelial IL-18 is protective (cis-Pyroptosis) and that IL-18 deficiency leads to barrier breakdown (Nowarski *et al.*, 2015). A new monoclonal antibody targeting mature IL-18 improved DSS colitis in mice, reduced IFNγ/TNF, and restored goblet cell function (Ikegami *et al.*, 2024). IL-1β's role in IBD is not very clear; stopping it had only small effects in studies, likely because intestinal epithelial cells don't produce much IL-1β, and blocking it throughout the body can lead to infections.

Importantly, genetic inflammasomopathies highlight pyroptosis in gut disease. NLRP3 gain-of-function variants cause CAPS, which can manifest as GI inflammation. Moreover, agents like entecavir (HBV drug) and cholinergic neurotransmission have been shown to modulate gut NLRP3 activity. Clinical translation includes a phase II trial of dapansutrile in ulcerative colitis (NCT01636141) (Arrè *et al.*, 2023), and small studies of NLRP3 inhibitors in experimental colitis. Biomarkers like fecal IL-18 or GSDMD fragments are under investigation to monitor pyroptosis in IBD.

#### 4.2.4. Neurodegenerative diseases

Neuroinflammation in disorders like Alzheimer's (AD) and Parkinson's (PD) involves pyroptosis. Activated microglia in AD brains contain ASC specks and high IL-1β, implicating NLRP3. Aggregated amyloid-β can prime and activate NLRP3 in microglia, leading to IL-1β release that fuels tau pathology (Auger *et al.*, 2025). Genetic or pharmacologic NLRP3 inhibition in AD mouse models mitigates cognitive decline. For example, Auger *et al.* (2025) found that a selective NLRP3 inhibitor reversed memory deficits and reduced amyloid and tau pathology in 5xFAD mice, even when given after disease onset (Auger *et al.*, 2025). The evidence suggests pyroptosis contributes to neuron loss and synaptic dysfunction.

In PD, dying neurons release α-synuclein aggregates that activate NLRP3 in adjacent glia. Amo-Aparicio *et al.* (2023) treated MPTP-lesioned mice with dapansutrile (OLT1177); it crossed the blood-brain barrier and preserved motor function and dopaminergic neurons (Amo-Aparicio *et al.*, 2023). OLT1177 reduced NLRP3 activation and α-synuclein pathology in the substantia nigra, supporting translation to humans. In amyotrophic lateral sclerosis (ALS) and multiple sclerosis (MS), similar inflammasome activation is noted, though clinical data are sparse. It is crucial to have inhibitors that can enter the brain: the Nguyen study shows that stopping NLRP3 in lung macrophages helps with COVID, but for brain diseases, it's essential that these inhibitors can cross the blood-brain barrier (Nguyen & Kanneganti, 2022).

In stroke, NLRP3 activation in microglia and endothelial cells worsens injury; in mouse stroke models, MCC950 or caspase-1 inhibitors reduce infarct volume. Early human trials of anakinra in stroke have shown safety and some biomarker improvements.

#### 4.2.5. Metabolic diseases and diabetes

Metabolic stress triggers low-grade inflammasome activation.

In obesity, saturated fatty acids and cholesterol crystals activate NLRP3 in fat tissue macrophages, leading to the release of IL-1β that disrupts insulin signaling. Benetti *et al.* (2013) reported that both obese patients and high-fat diet mice show NLRP3-driven IL-1β production (Benetti *et al.*, 2013). Conversely, NLRP3 or IL-1β knockout mice fed a high-fat diet are protected from insulin resistance. In human type 2 diabetes, IL-1 blockade has metabolic benefits: Larsen *et al.* (2007) showed that daily anakinra for 13 weeks lowered HbA1c by ~0.4% and improved β-cell function (Larsen *et al.*, 2007). These results suggest that NLRP3-caspase-1–mediated IL-1β in adipose and islets drives inflammation in diabetes.

NLRP3 may also link to atherogenesis (overlap with CV) and non-alcoholic fatty liver disease. In NAFLD, hepatocyte pyroptosis (via caspase-1/GSDMD) releases IL-1β, promoting liver inflammation and fibrosis. Caspase-1 –/– mice fed a NASH diet have less steatosis. However, $IL^{-1}$ blockers in T2D have side effects (e.g., neutropenia), so metabolic disease therapies targeting pyroptosis remain investigational.

#### 4.2.6. Autoimmune and autoinflammatory diseases.

Monogenic autoinflammatory syndromes exemplify pyroptosis in human disease. Cryopyrin-associated periodic syndromes (CAPS), familial cold autoinflammatory syndrome, Muckle–Wells syndrome, NOMID, are caused by NLRP3 gain-of-function, leading to constitutive IL-1β/IL-18 release and periodic fever. IL-1 blockade is transformative in CAPS: anakinra, canakinumab, or rilonacept induce rapid remission (Arnold *et al.*, 2022). Similarly, systemic juvenile idiopathic arthritis and adult-onset Still's disease involve IL-1-driven inflammation. Familial Mediterranean fever (MEFV mutations) and gout (urate crystals) activate NLRP3; here too, IL-1 antagonists and colchicine are effective.

In classic autoimmunity (RA, lupus), the role of pyroptosis is more nuanced. Synovial macrophages in RA show NLRP3 activation (Chen *et al.*, 2024), but IL-1 blockade (e.g., anakinra) had limited efficacy in RA trials (den Broeder *et al.*, 2006). In lupus, self-DNA immune complexes can trigger AIM2 inflammasomes (Antiochos *et al.*, 2022), and lupus flares have elevated IL-18. A recent review suggests pyroptosis of neutrophils (NETosis crosstalk) may amplify SLE inflammation (Wei *et al.*, 2024). Anti-IL-18 therapies are being explored in lupus nephritis.

Thus, pyroptosis drives autoinflammation primarily through IL-1/IL-18, and IL-1 biologics are the standard of care for many IL-1–mediated syndromes (Arnold *et al.*, 2022). The limitations of cytokine blockade, such as loss of specificity and infection risk, motivate the exploration of upstream approaches like NLRP3 inhibitors.

#### 4.2.7. Cancer

Pyroptosis has a paradoxical role in cancer. On one hand, pyroptotic death of tumor cells can be immunogenic and tumoricidal. Many chemotherapeutics (e.g., anthracyclines) and immune cells can induce pyroptosis in $GSDME^{+}$ cancer cells. For instance, Granzymes from cytotoxic T cells and NK cells cleave GSDME (when expressed) to cause tumor cell swelling and IL-1 release (Liu *et al.*, 2024). Rogers *et al.* (2017) showed that restoring GSDME expression in tumor cells shifts cisplatin-induced death from silent apoptosis to inflammatory pyroptosis, enhancing dendritic cell activation (Rogers *et al.*, 2017). This suggests GSDME reactivation (via epigenetic drugs) might improve anti-tumor immunity.

On the other hand, inflammasome-mediated cytokines can promote tumor growth. Chronic IL-1β fosters angiogenesis and metastasis in colon and lung cancer. As noted in a broad review, inflammasome activation often correlates with poor prognosis in epithelial cancers (Arrè *et al.*, 2023), and tumor-associated macrophages with NLRP3 often support tumors (Zheng *et al.*, 2020). Mariani *et al.* (2022) observed high caspase-1, IL-1β, and IL-18 in ovarian carcinoma tissues (Arrè *et al.*, 2023).

Recent immunotherapy strategies attempt to harness pyroptosis. Yin *et al.* (2024) discuss nanoparticle and oncolytic-virus approaches, e.g., tumor-targeted delivery of gasdermin N-terminus or inflammasome activators to induce local pyroptosis (Yin *et al.*, 2024). One example is a zirconium-based nanoparticle that generates ROS, activates caspase-1 and GSDMD in situ; in mice, this enhanced dendritic cell maturation and T cell responses, reducing tumor growth (Yin *et al.*, 2024). Combining checkpoint inhibitors with pyroptosis inducers is an active area of research. However, blocking IL-1 throughout the body might weaken the body's ability to fight tumors, so the approach to promoting or stopping pyroptosis needs to be customized for each disease.

### 4.3. Therapeutic landscape

Several strategies target the pyroptosis cascade (Table 1). Considerations related to pharmacokinetics and clinical use are also included. For biologics, dosing frequency is dictated by half-life and route: anakinra requires daily subcutaneous dosing (half-life ~6 h) Zeng *et al.*, 2021); canakinumab has a ~26-day half-life (Zeng *et al.*, 2021), permitting every 1–2 month administration, and rilonacept is weekly, profiles that improve adherence but carry class-typical infection risk. For small molecules, oral agents enable chronic use if safety and exposure are adequate. MCC950 (diarylsulfonylurea) potently blocks NLRP3 but encountered hepatotoxicity during development, highlighting a liver-safety constraint (Zeng *et al.*, 2021). Dapansutrile (OLT1177), an oral β-sulfonyl nitrile NLRP3 inhibitor (Arrè *et al.*, 2023), has shown acceptable tolerability across phase II settings and crosses the blood–brain barrier in preclinical models, a requirement for neuroinflammatory indications (Amo-Aparicio *et al.*, 2023). VX-765 (belnacasan) is an orally bioavailable prodrug of VRT-043198; its active metabolite is brain-penetrant, aligning with CNS applications, and phase II experience (psoriasis, epilepsy) supports safety with measurable IL-1β PD effects (VX-765-Cognitive-Vitality-For-Researchers, 2019). Disulfiram (a dithiocarbamate approved for alcoholism) covalently modifies GSDMD (Cys191) and blocks pore formation (Hu *et al.*, 2020); its long human safety history is advantageous for repurposing, though definitive human anti-inflammatory efficacy remains pending. Tranilast indirectly dampens NLRP3 signaling and is approved (allergy), with repurposing under study (Huang *et al.*, 2018); reports of hepatotoxicity in some contexts warrant monitoring. In practice, half-life and route govern dosing burden, BBB penetration conditions CNS

suitability, and organ-specific safety (notably hepatic) shape feasibility for long-term inflammatory indications. The most direct are NLRP3 inhibitors. MCC950 (also called CRID3) is a highly selective diarylsulfonylurea that binds NLRP3's NACHT domain and blocks ASC assembly (Zeng *et al.*, 2021). In human/mouse macrophages, MCC950 abrogates both canonical and noncanonical NLRP3 activation (Zeng *et al.*, 2021). MCC950 dramatically reduces atherosclerosis and colitis in mice (Arrè *et al.*, 2023; Zeng *et al.*, 2021). However, its clinical development was halted due to hepatotoxicity. Dapansutrile (OLT1177) is an oral β-sulfonyl nitrile NLRP3 inhibitor that completed phase II trials (gout flares, heart failure, knee osteoarthritis). OLT1177 was safe and showed some efficacy; it crosses the blood–brain barrier and, in mice, prevented PD-related neurodegeneration (Amo-Aparicio *et al.*, 2023). Tranilast, an anti-allergy drug, indirectly inhibits NLRP3 and is being repurposed for CAPS and gout in Japan (Huang *et al.*, 2018). Figure 2 maps the leading pyroptosis-targeted agents, NLRP3, caspase-1, gasdermin, and cytokine modulators, onto the drug-development continuum, providing an at-a-glance view of halted, dormant, ongoing, and approved programs before the compound-specific discussion that follows.

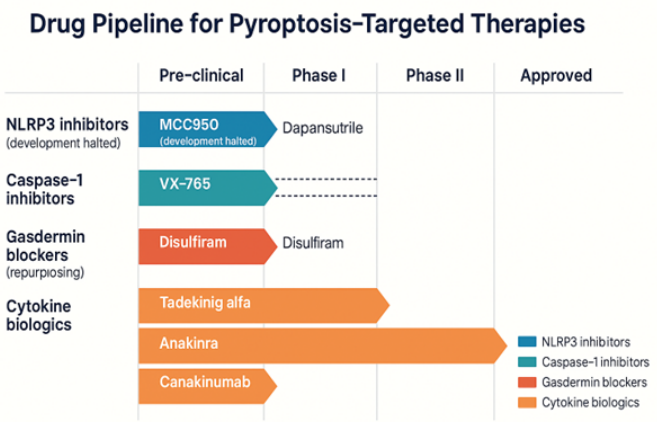


**Figure 1.** Developmental pipeline for pyroptosis-targeted therapeutics.

Downstream, caspase-1 inhibitors have been tested. VX-765 (belnacasan) is a prodrug of VRT-043198 that selectively inhibits caspase-1. It has completed Phase II trials (n≈60–64) in psoriasis and partial epilepsy (VX-765-Cognitive-Vitality-For-Researchers, 2019), demonstrating safety and some pharmacodynamic IL-1β reduction. Its active metabolite is brain-penetrant. Disulfiram (an FDA-approved aldehyde dehydrogenase inhibitor) was serendipitously found to covalently modify GSDMD (at Cys191) and block its pore formation (Hu *et al.*, 2020). Hu *et al.* (2020) showed that disulfiram stops pyroptosis and IL-1β release in vitro and protects mice from LPS-induced shock (Hu *et al.*, 2020). Disulfiram's long history of safe use makes it an attractive repurposed gasdermin blocker, although human data are pending.

Cytokine biologics form the most established class. Anakinra (IL-1 receptor antagonist) and canakinumab (anti–IL-1β antibody) are approved for autoinflammatory diseases and have been tried off-label in gout, rheumatoid arthritis, and sepsis. Rilonacept (IL-1 trap) is approved for CAPS. Their pharmacokinetics vary: anakinra requires daily injection (half-life ~6 hours), canakinumab has a ~26-day half-life (dosing every 1–2 months), and rilonacept weekly. All carry infection risk (particularly neutropenia and serious infections) (Zeng *et al.*, 2021). Tadekinig alfa, a recombinant IL-18 binding protein (Novartis), has shown promise in phase II trials for adult-onset Still's disease and NLRC4-MAS, normalizing free IL-18 levels without major toxicity (Ikegami *et al.*, 2024). There are also experimental IL-18 antibodies (e.g., GSK1070806) and GM-CSF inhibitors as upstream modulators. Combination approaches (e.g., IL-1 blockade plus TNF blockade) are sometimes used in refractory cases.

Pharmacodynamic biomarkers are guiding development: serum IL-1β/IL-18 levels reflect target engagement, though low baseline levels in some diseases (e.g., certain autoinflammations) complicate interpretation. Hence, stratifying patients by inflammasome activity (e.g., high CRP in CANTOS) has been key in trials.

FDA and regulatory note: Only the IL-1 blockers and colchicine have FDA approval for inflammation-related indications (Regeneron Pharmaceuticals, 2008; Sadiq *et al.*, 2025); none of the small-molecule inflammasome inhibitors are yet approved (Cabral *et al.*, 2025). Dapansutrile has the Fast Track designation for gout and is being evaluated for heart disease (phase II) (Klück *et al.*, 2020). Anakinra and canakinumab are approved for CAPS, rheumatoid arthritis, and juvenile arthritis (anakinra also for gout flares), with off-label use in cardiovascular disease and diabetes (Everett *et al.*, 2020; Larsen *et al.*, 2007). In the clinic, safety profiles guide use: IL-1β blockade requires vigilance for infection; gasdermin inhibitors, if used in humans, might spare cytokine processing (as disulfiram does), potentially reducing infection risk.

**Table 1.** Selected agents targeting pyroptosis and related pathways.

| Agent (Target) | Mechanism | Indications/Status | Notes/Adverse Events |
|---|---|---|---|
| MCC950 (NLRP3) | Binds NLRP3 NACHT domain, prevents ASC oligomerization (Zeng *et al.*, 2021) | Preclinical/Phase I (development halted due to toxicity) | Potent (IC_50 ~7 nM); hepatotoxicity in trials (Zeng *et al.*, 2021) |
| Dapansutrile (OLT1177, NLRP3) | Oral small molecule; covalent NLRP3 inhibitor (Arrè *et al.*, 2023) | Phase II: gout, heart failure, colitis (e.g., NCT01636141) | Well-tolerated in 1000–2000 mg/day (Arrè *et al.*, 2023); crosses BBB (neuro models) (Amo-Aparicio *et al.*, 2023) |
| Tranilast (NLRP3 modulator) | Inhibits NLRP3 (indirect) via NF-κB/ROS suppression | Approved (Japan, Europe) for allergy; Phase II (CAPS) (Huang *et al.*, 2018) | Off-patent antihistamine with NLRP3 effects; some hepatotoxicity reported (Huang *et al.*, 2018) |

| | | | |
|---|---|---|---|
| VX-765 (belnacasan) (caspase-1) | Orally bioavailable prodrug; irreversible caspase-1 inhibitor (VX-765-Cognitive-Vitality-For-Researchers, 2019) | Phase II completed (psoriasis, epilepsy) (VX-765-Cognitive-Vitality-For-Researchers, 2019) | Active metabolite BBB-permeant; no efficacy yet shown in CNS diseases |
| Disulfiram (GSDMD) | Covalently modifies GSDMD Cys191 to block pore formation (Hu *et al.*, 2020) | Approved (alcoholism); preclinical for inflammation | Generic drug; minor toxicity (neuropathy); mice protected from LPS shock (Hu *et al.*, 2020) |
| Anakinra (IL-1R) | Recombinant IL-1 receptor antagonist | Approved (RA, CAPS, gout flares); trial in sepsis/MI (Cavalli & Dinarello, 2018) | Daily subcutaneous injection; injection-site reactions, neutropenia |
| Canakinumab (IL-1β) | Human anti–IL-1β monoclonal antibody | Approved (CAPS, gout, JIA); CANTOS (CV disease) (Zeng *et al.*, 2021) | 8-week dosing; infection risk (CANTOS: ↑fatal sepsis) (Ridker *et al.*, 2017) |
| Rilonacept (IL-1 trap) | Soluble decoy receptor for IL-1α/β | Approved (CAPS) (Hoffman *et al.*, 2008) | Weekly injection; similar safety to other IL-1 blockers |
| Tadekinig alfa (IL-18BP) | Recombinant IL-18 binding protein | Phase II (Adult Still's, NLRC4-MAS) (Ikegami *et al.*, 2024) | Normalizes free IL-18; well tolerated (no opportunistic infections in trials) (Ikegami *et al.*, 2024) |
| Anti–IL-18 mAb (e.g. GSK1070806) | Neutralizes IL-18 | Early-stage trials (autoinflammation) (McKie *et al.*, 2016) | Humanized Ab; development ongoing |
| NLRP3 vaccine (experimental) | Induces neutralizing Abs to NLRP3 domains | Preclinical (mouse RA) (Zahid *et al.*, 2019) | Conceptual, no human data yet |

*Abbreviations: NLRP3 – nucleotide-binding oligomerization domain-, leucine-rich repeat-, pyrin domain-containing 3; IL-1R – interleukin-1 receptor; IP – intraperitoneal; IV – intravenous.*

### 4.4. Biomarkers and precision medicine

Monitoring pyroptosis in patients requires sensitive biomarkers. Circulating IL-1β and IL-18 are classic indicators of inflammasome activation. Elevated serum IL-18 often parallels disease activity in conditions like CAPS, systemic lupus, and cardiac disease (though IL-1β is usually cell-associated and hard to measure reliably) (Arrè *et al.*, 2023; Larsen *et al.*, 2007). The presence of cleaved GSDMD-N-terminal fragments in plasma has been proposed as a direct pyroptosis biomarker (for example, GSDMD N-terminus was detected in septic shock patients by immunoblot), though commercial assays are lacking. A breakthrough is measuring circulating ASC specks: these stable prion-like aggregates are released from dying myeloid cells and can be quantified by flow cytometry (Basiorka *et al.*, 2018). Basiorka *et al.* (2018) showed plasma ASC-speck levels were markedly elevated in myelodysplastic syndrome patients (where pyroptosis drives ineffective hematopoiesis) and distinguished them from healthy controls (Basiorka *et al.*, 2018). Future platforms (e.g., microfluidic assays) could use this principle.

Advanced imaging may also detect pyroptosis noninvasively. A novel near-infrared probe for activated caspase-1 has been tested in arthritis models (fluorescence detected in inflamed joints). PET tracers that focus on translocator protein (TSPO) are used to see if microglia are active, but they don't specifically show pyroptosis. Fluorodeoxyglucose (FDG) PET uptake can reflect general inflammation (e.g., in vasculitis), indirectly capturing IL-1–driven disease. Multi-omic signatures (e.g., transcriptomic profiling of inflammasome genes in blood) are being developed to stratify patients. For instance, "inflammasome expression scores" correlate with response to IL-1 blockade in arthritis (preliminary data). Proteomic approaches may identify patterns of alarmins (HMGB1, S100A8/A9) that complement IL-1/IL-18 measurements as readouts of pyroptotic inflammation.

Precision medicine will likely use such biomarkers for patient selection and PD readouts. For example, in a trial of an NLRP3 inhibitor for Parkinson's (in progress), cerebrospinal fluid IL-18 and amyloid PET imaging (for coexisting AD pathology) might stratify responders (Lobo, 2025). In cardiovascular disease, high-sensitivity CRP plus IL-18 genotyping could identify patients with "inflammasome-driven" atherosclerosis (Rajesh Kumar *et al.*, 2015). In summary, while IL-1β/IL-18 remain the oldest markers, emerging tests for ASC specks and GSDMD fragments promise direct monitoring of pyroptotic cell death, enabling more targeted therapeutic strategies.

### 4.5. Discussion

Pyroptosis, while a common thread in diverse inflammatory diseases and a rich therapeutic target, presents substantial challenges in translating this biology into clinical practice.

One major concern is infection risk: inhibiting pyroptosis blunts innate defenses. Patients on IL-1 blockers or NLRP3 inhibitors must be screened for latent infections (e.g., tuberculosis), and we may see increased viral or bacterial infections, as seen with IL-1β monoclonal therapy (Zeng *et al.*, 2021). Balancing immune suppression against benefits will require careful

patient selection and possibly intermittent dosing.

Blood–brain barrier (BBB) penetration is a challenge for neuroinflammatory indications. Many small molecules fail to reach brain parenchyma at therapeutic levels. The promising dapansutrile results in PD models suggest that some pyroptosis inhibitors can cross the BBB (Amo-Aparicio *et al.*, 2023), but development of CNS-optimized compounds (e.g., more lipophilic analogs or intranasal delivery) is needed.

Drug delivery technology could aid targeting: nanoparticle carriers or antibody–drug conjugates could selectively deliver inhibitors to diseased tissues, reducing systemic exposure. For example, macrophage-targeted liposomes carrying MCC950 might focus on plaques (Zeng *et al.*, 2021). Gene therapy is also a theoretical option: CRISPR/Cas9 editing to knock out NLRP3 in autoinflammatory syndromes or to correct gain-of-function mutations (though off-target and delivery issues loom large) (Xu *et al.*, 2018).

Cost and access are nontrivial: biologics like canakinumab cost >$100,000/year, limiting use (Michael O'Riordan, 2019). Small molecules (if safe) could be more affordable, but manufacturing high-complexity proteins (IL-18BP, GSDMD antibodies) is expensive. Equitable access will require global partnerships, especially for diseases like gout or cardiovascular disease affecting low-income countries.

Regulatory pathways for pyroptosis modulators will likely follow those of other anti-inflammatory drugs. FDA Fast Track designations (e.g., for dapansutrile in gout) reflect unmet need. Demonstrating clinical efficacy beyond biomarker changes is the key hurdle. CRISPR-based diagnostics might help identify hyperinflammatory patients; AI could expedite drug discovery, using deep learning to predict inflammasome inhibitor candidates (similar to recent efforts for NLRP3 structures).

### 4.6. Future directions

The landscape is rapidly evolving. AI-guided screening (using AlphaFold-predicted NLRP3 structures) may yield novel inhibitors with better safety. A 2022 benchmarking analysis confirmed the AlphaFold model captures the ATP-bound "active" conformation of the NACHT domain with sub-Å accuracy, allowing reliable pocket mapping (Yin *et al.*, 2022). Nanocarriers or exosomes could deliver pyroptosis modulators directly to macrophages or tumor cells (Nandi *et al.*, 2024). CRISPR editing to inactivate gasdermin genes has even been proposed as a gene therapy in hyperinflammatory disorders (still theoretical).

A particularly exciting avenue is engineered oncolytic viruses and cell therapies that exploit pyroptosis. One could imagine CAR-T cells armed with truncated gasdermins to enforce pyroptosis in target tumors or oncolytic viruses expressing inflammasome components to induce localized inflammation and immunogenic death (Chen *et al.*, 2024; Huang *et al.*, 2025; Lin *et al.*, 2023). These pyroptotic oncolytic tactics are in early exploration but hold promise to turn the "inflammatory death" weapon against cancer.

In summary, the dual nature of pyroptosis, protective in host defense yet harmful in chronic inflammation, demands nuanced approaches. Future successes will hinge on patient stratification (who benefits from dampening pyroptosis?), combination strategies (e.g., inflammasome inhibitor plus immunosuppressant), and vigilance for immune suppression side effects.

## 5. CONCLUSION

Pyroptosis has shifted from a biological curiosity to a central paradigm in inflammatory disease. Recent discoveries in inflammasome structure, gasdermin pore biophysics, and cell-death crosstalk have illuminated how pyroptosis drives pathologies from atherosclerosis to neurodegeneration. Simultaneously, therapeutic advances, from small-molecule NLRP3 inhibitors to repurposed disulfiram, are translating these insights into treatments. Utilizing pyroptosis can have both positive and negative effects: while reducing it can reduce chronic inflammation, utilizing it can enhance anti-tumor immunity. The next frontier will likely see precision-targeted therapies guided by pyroptosis biomarkers, combined approaches that temper infection risk, and innovative drug discovery aided by AI. Understanding and controlling this fiery form of cell death promises to redefine our fight against many inflammatory diseases.

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