Reframing Chronic Inflammation

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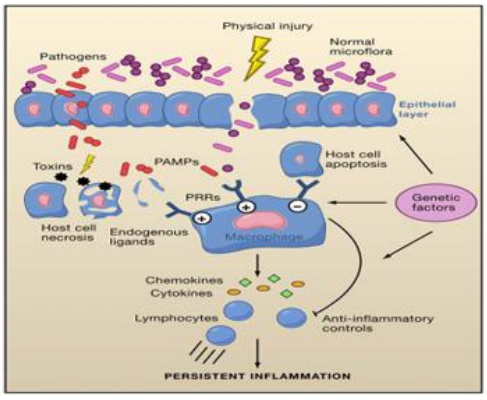
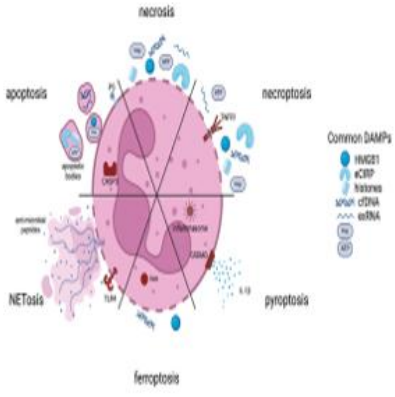
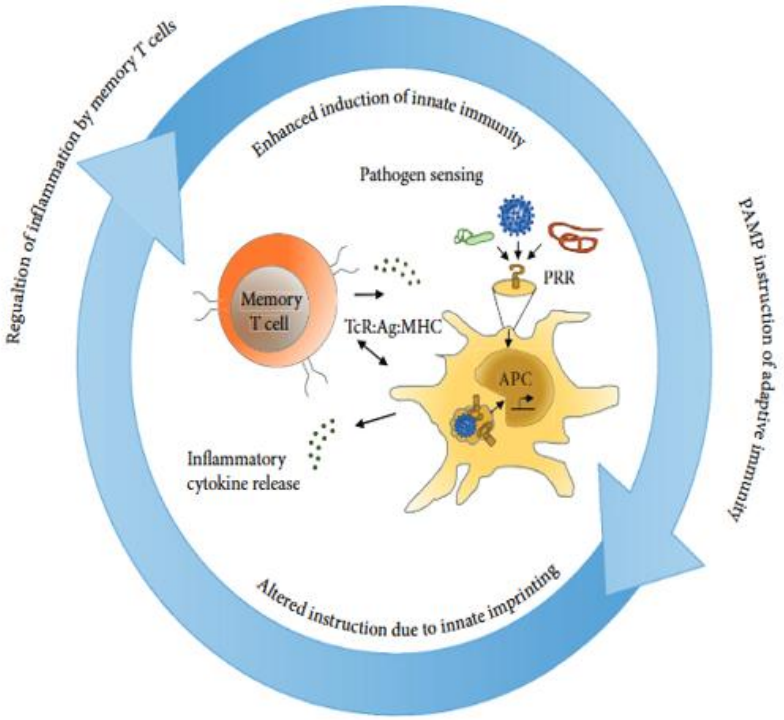
Chronic inflammatory disorders are increasingly being reframed as failures of innate immune regulation, not just adaptive autoimmunity, and that shift is driving a wave of novel targets and new modalities now moving from discovery into deals and the clinic. Recent M&A and licensing activity demonstrate that big pharma is willing to collaborate on innate-targeted programs.

Innate cells (myeloid, NK, innate lymphoid cells) drive persistent tissue inflammation through trained immunity, epigenetic reprogramming and sensing of cell-death signatures (pyroptosis/PANoptosis), creating self-sustaining inflammatory circuits distinct from acute responses.

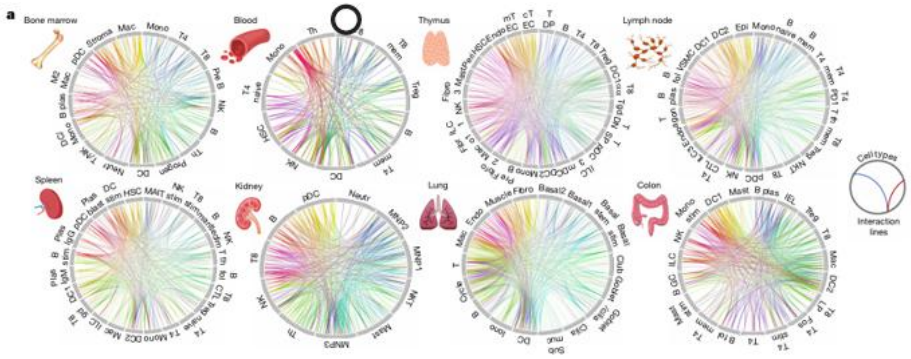


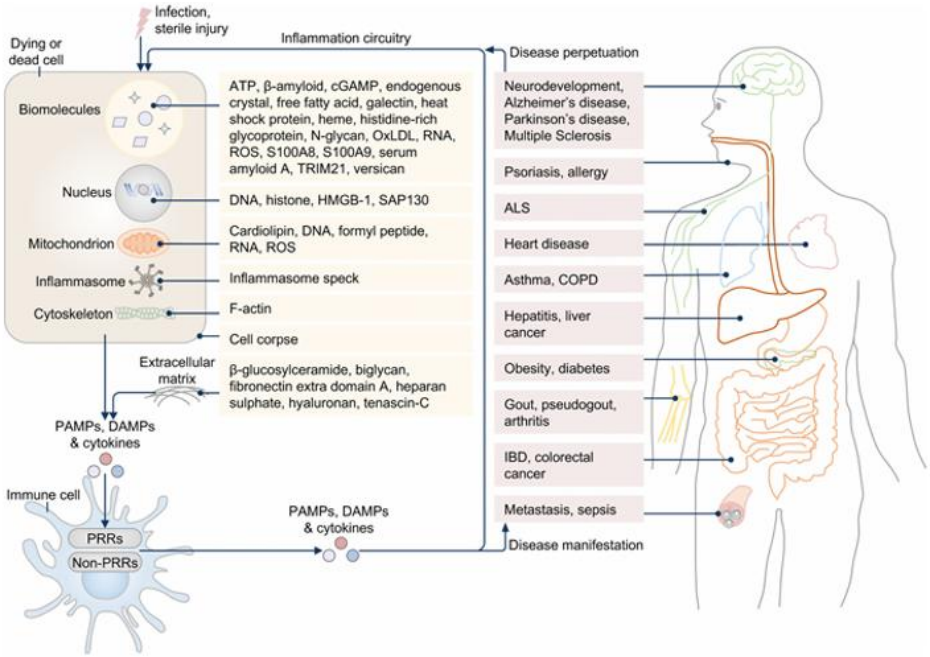




Innate Immune Targets Represent a Huge Therapeutic Landscape

The breadth and depth of soluble extracellular, membrane bound and intracellular sensing, priming and activation targets that drive innate immune dysfunction by tissue and cell interaction in human diseases of chronic inflammation is enormous.



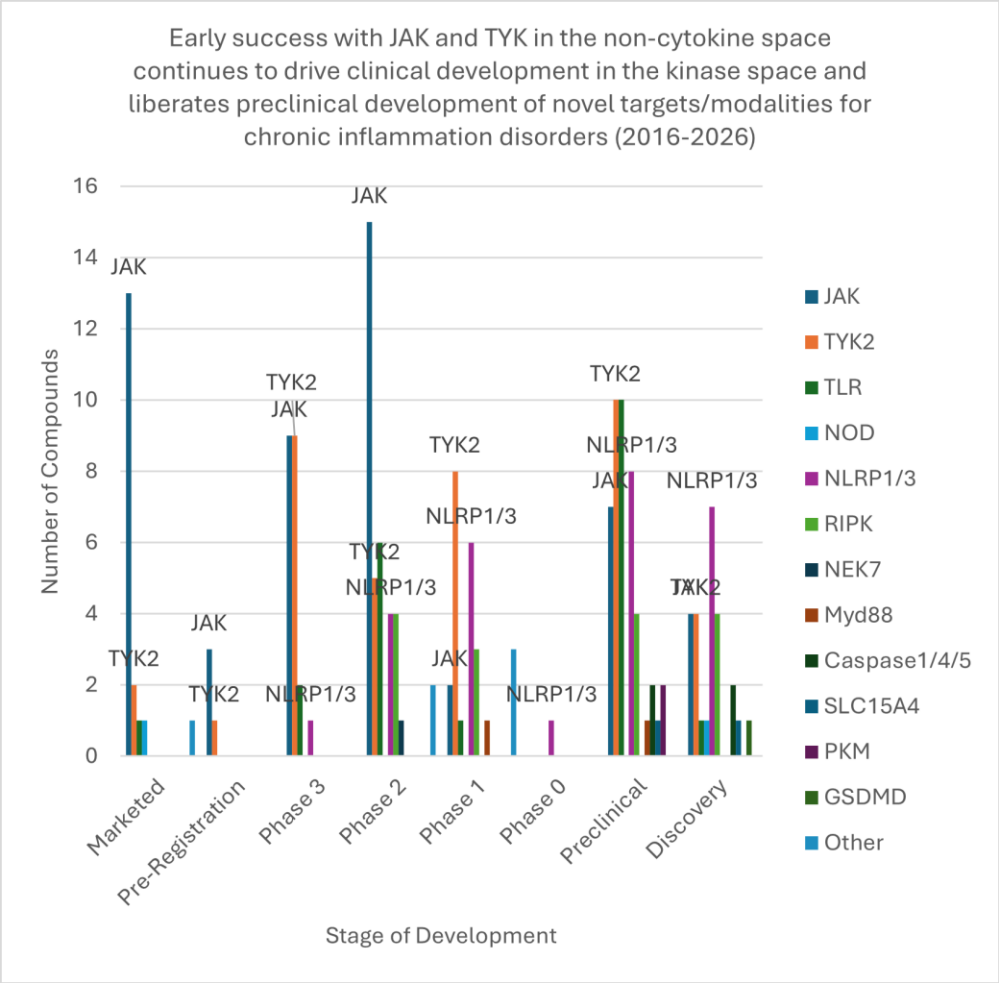


Despite this immense diversity, progress is being made at many cytokine and non-cytokine targets, including antagonism of proinflammatory pathways and activation of anti-inflammatory pathways:

- Interleukins: IL-1/6/12/17/18/23/36/37/38 (and receptors)

- Toll-Like Receptors: TLR2, TLR4, TLR7, TLR8, TLR9

- Intracellular machinery: (sensing, adaptors and effectors): NLRP3, NLRP1, NLRC2, NLRC4. AIM2, SLC15A4, Gasdermin D, Caspase 1/4/5, JAK1/2/3, TYK2, RIPK1, MLKL, hK2, PKM2, ACLY and MYD88



Therapies that reset innate cell state or block innate sensors can, in principle, stop inflammatory cycling without broadly suppressing adaptive immune responses. Small molecule inhibitors of NLRP and RIPK predominate and leverage potential for broad access and combination strategies in multi-organ indications.

Oral small molecules remain a commercially attractive modality for innate-immune targets given:

- **Intracellular access**: inflammasomes, caspases, metabolic enzymes, and endolysosomal transporters are all inside the cell.

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- **Chronic-disease suitability**: oral dosing supports long-term adherence.
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- **Payer alignment:** small molecules are easier to reimburse than high-cost biologics.

In Jan 2026 Eli Lilly announced acquisition of Ventyx (~$1.2bn; $14/share, 62% premium to 30 d VWTP) to secure NLRP3 and oral inflammation assets.

Ventyx VTX2735 showed POC, leading to clinically meaningful impacts on key biomarkers (IL-6, hsCRP) and inflammatory disease activity.

Innovative Therapeutic Modalities and Approaches

Advances into specialized cell therapies and precise molecular tools are being driven by knowledge related to innate immune target regulation in oncology research:

- Regulatory T-Cells (Tregs) and Exosomes: Coya Therapeutics aims to restore immune homeostasis by enhancing Treg function. Treg-derived exosomes are being explored as potentially more potent anti-inflammatory agents than those derived from mesenchymal stem cells.

- Innate Immune Engagers: Bispecific or trispecific molecules from companies like Affimed are designed to recruit and activate NK cells and macrophages directly at the site of

disease and could conversely be applied to targeted immune cell suppression.

- Allogeneic NK and iNKT Cells: Companies like Artiva and MiNK Therapeutics are using "off-the-shelf" Natural Killer (NK) and invariant Natural Killer T (iNKT) cells to bridge innate and adaptive immunity, offering a better safety profile than T-cell therapies, with a lower risk of Graft-versus-Host Disease (GvHD).

Targeted protein degradation (PROTACs/MGDs) represents a major shift in modality, as they physically remove the target protein rather than just blocking its activity:

- Advantages: Degraders can address "undruggable" targets and often achieve more potent efficacy by removing the protein's entire scaffolding function.

- Key Programs: Degraders for IRAK4 , STAT3/STAT6 , and NEK7 (a critical component for NLRP3 activation) are in development for conditions like atopic dermatitis and asthma.

Resolution biology and barrier function approaches aim to amplify/accelerate immune resolution before chronic cycling is established and protect barrier function against activating stimuli:

- Instead of suppressing the immune system, FPR2 agonists aim to actively resolve inflammation by limiting neutrophil recruitment and reprogramming macrophages into a pro-resolutive state.

- Targeting the constitutively expressed DR3 receptor aims to provide barrier protection and more durable protection from gut inflammation.

- AhR (Aryl Hydrocarbon Receptor) modulators are being developed to induce anti-inflammatory cytokines while simultaneously improving intestinal tissue barrier function.

- Suppression of cytokine expression in response to stimuli and barrier dependent innate immune amplification are also on the resolution radar.

Key Pipeline Assets and Developers (modality examples)

Target	Modality	Lead Candidate	Indications	Developer
NLRP3	Small molecule	BGE-102	Obesity, DME, GA	BioAge Labs
IRAK4	Degrader	SAR447971	Inflammatory Disease	Sanofi
miR-124	Small molecule	Obefazimod	Ulcerative Colitis	Abivax
C1s	Antagonist mAb	Riliprubart	Chronic Inflammatory Demylenating Polyneuropathy	Sanofi
IL-18	Fusion protein	EVO301	Atopic Dermatitis	Evommune
NEK7	Molecular glue degrader	MRT-8102	Inflammatory Disease	Monte Rosa
DPP1	Small molecule	INS1033	RA, IBD	Insmed
FPR2	Agonist mAb	OSE-230	Chronic Inflammation	OSE Immunotherapeutics
DR3	Antagonist mAb	SL-325	IBD	Shattuck Labs
IL1-RA	Gene therapy	PCRX-201	OA	Pacira Biosciences
IL-15/21	Stapled oral peptide	EQ302	Celiac	Equillium Bio
AhR	Small molecule	EQ504	Ulcerative Colitis	Equillium Bio

Targeted Degraders vs. Traditional Inhibitors: NLRP3 and IRAK4

The transition from traditional inhibitors to advanced modalities like protein degraders is redefining the management of chronic inflammation.

NEK7 is a structural protein essential for the assembly of the NLRP3 inflammasome; by degrading NEK7, therapeutic agents like MRT-8102 (Monte Rosa) can prevent the inflammasome from ever forming, whereas traditional NLRP3 inhibitors target an already firing complex.

The shift toward IRAK4 degraders is in some instances driven by the biological limitation of traditional small-molecule inhibitors, which only block enzymatic (kinase) activity while leaving signaling related to structural functions intact.

Efficacy advantages of degraders have driven expanded IRAK4 development:

- Scaffolding Function: Traditional inhibitors only block the kinase domain, but IRAK4 also serves a critical structural "scaffolding" role that regulates the stability and activity of the MYD88 complex. Estimates suggest that scaffolding can account for up to 50.00% of signaling activity, meaning degraders can achieve a more profound pathway blockade than inhibitors.

- Superior Cytokine Suppression: Preclinical data for GS-6791 and other degraders show more robust inhibition of IL-1 , IL-36 , and TSLP compared to kinase inhibition alone.

- "Genetic Knockout" Mimicry: By physically removing the entire protein, degraders effectively mimic a genetic knockout, which has shown superior efficacy in models of atopic dermatitis (AD)

and hidradenitis suppurativa (HS) where traditional inhibitors like Pfizer's PF-06550833 showed limited activity.

Company / Partner	Drug Candidate	Target / MOA	Target Indication(s)	Notes	Stage of Development
AstraZeneca	AZD-6793	IRAK4 inhibitor	COPD	AZN is currently recruiting a large-scale (~1,160 patient) Ph2 COPD study; Ph1 MAD results showed a ≥75% mean reduction in release of IL-6 and TNF-α from blood (ERS 2025)	Ph2 (PRESTO)
GILEAD	Edecesertib (GS-5718)	IRAK4 inhibitor	Cutaneous lupus erythematosus	-	Ph2 (COSMIC)
BeOne	BGB-45035	IRAK4 degrader	Moderate-to-severe RA, skin diseases (PN, AD)	Chimeric Degradation Activating Compound (CDAC); Ph1 data presented at ACR 2025 showed a favorable safety/PK profile over 14 days, with substantial IRAK4 degradation (95% in skin tissue in healthy volunteers); long half-life of ~60-96 hrs	Ph2
NURIX GILEAD	NX-0479 / GS-6791	IRAK4 degrader	RA and other inflammatory diseases	GILD to report Ph1 SAD/MAD HV data in 2026; preclinical data presented at EADV showed near-complete IRAK4 knockdown in human blood and keratinocytes with deep cytokine pathway inhibition (e.g., TSLP)	Ph1a
KYMERA sanofi	KT-485	IRAK4 degrader	Immunology & Inflammation (Th1/Th17/Th2)	Ph1 initiation expected in 2026; Prioritized over KT-474 due to superior potency, deeper skin distribution, and absence of QTc signal	Ph1 (in 2026)
Biogen	BIIB142	IRAK4 degrader	Autoimmune disease	-	Ph1
LeadingFarma	LT-002	IRAK4 degrader	AD, HS, psoriasis	First patient was dosed in Ph1 study in Jul '25	Ph1
Artivila Biopharma	ARD-885	IRAK1/4 inhibitor	RA, SLE	-	Ph1/2
Kamplon	P001 (topical / oral)	IRAK4 degrader	Autoimmune diseases	IND-cleared in Dec '25; developed using company's proprietary AI-driven discovery platform, ASTRIDE	IND-cleared
Photys Polymed	PHT-776 / HPB-143	IRAK4 degrader	AD, UC	Program was in-licensed in Feb '25, but no recent updates	IND-cleared
ODYSSEY THERAPEUTICS	n/a	IRAK4 scaffolding inhibitor	AD, HS, osteoarthritis	-	Preclinical

Degraders: Impact on Therapeutic Durability

The physical removal of the protein via degradation offers distinct advantages for sustained efficacy but may still confer broad immunosuppression.

- Ablation vs. Tuning : While kinase inhibitors only "tune down" enzymatic activity, degraders physically remove the entire protein, mimicking a genetic knockout and shutting down the scaffolding needed for the formation of the myddosome complex.

- Upstream action: Unlike downstream biologics like Canakinumab (anti-IL-1β) or Ziltivekimab (anti-IL-6), NEK7 degraders can block pyroptosis, an inflammatory cell death

process that is not addressed by current cytokine-targeted therapies.

- Sustained Response : Degraders like KT-474 have demonstrated significant durability, with IRAK4 levels remaining suppressed for up to 2.00 weeks post-dosing in some subjects. In contrast, inhibitors require continuous, high-level exposure to maintain pathway suppression against an increasingly abundant target.

- Clinical Differentiation : This mechanistic gap is cited as the reason many companies discontinued internal IRAK4 inhibitor programs in favor of degraders like GS-6791 and KT-485.

Degraders: Safety and Development Opportunities

Selectivity and Off-Target Risks: First-generation degraders like KT-474 faced developmental pivots due to potential selectivity issues. Sanofi deprioritized KT-474 in favor of KT-485 (SAR447971), which reportedly offers improved potency and a better selectivity profile.

Toxicity Mitigation: Targeted degradation may help mitigate specific toxicities, such as bone marrow toxicity, by allowing for more precise dosing compared to broader inhibitors.

Pharmacokinetics: Degraders like BGB-45035 have demonstrated long half-lives (60 to 96 hours) and deep tissue penetration, which are essential for treating skin-based inflammatory conditions.

Degraded Immune Suppression: Safety and Development Concerns

IL-17 Safety Barriers: While IL-17 inhibitors (e.g., Secukinumab) are generally well-tolerated, they are associated with class-specific risks such as Candida infections and must be used with caution in patients with inflammatory bowel disease.

TNF-α Safety Concerns: Conventional TNF-α inhibitors are described by clinicians as having a "broader risk of adverse events" due to their less specific mechanism, which blocks ubiquitous inflammatory mediators across multiple organ systems.

Degrader Platforms: Key Comparators

Technological and strategic divergence

Company & Platform	Primary Goal	Target Niche
Monte Rosa QuEEN™	Rational design of Molecular Glue Degraders (MGDs)	Undruggable G-loop and non-canonical degrons
Captor Optigrade™	Discovery of MGDs, Bifunctional Degraders, and Novel E3s	Intrinsically Disordered Proteins (IDPs) and neuroinflammation
C4 Therapeutics TORPEDO®	Catalytic turnover of oncology and CNS targets	Highly catalytic, brain-penetrant degraders
Aclaris KINect	Solving kinase selectivity and biochemical efficiency	Multi-specific antibodies and covalent kinase inhibitors

Modality and mechanist approaches

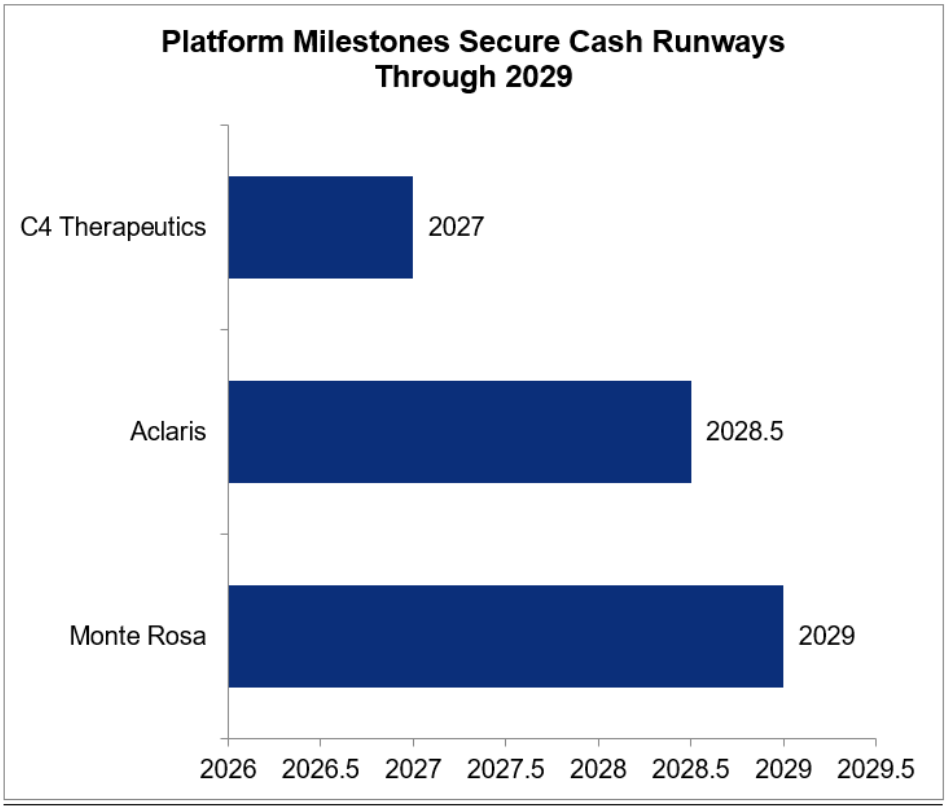
Company & Platform	Core Technology	Modality Focus	E3 Ligase Focus
Monte Rosa QuEEN™	AI/ML surface-based prediction (fAlceit)	Exclusively Molecular Glue Degraders (MGDs)	Primarily Cereblon (CRBN)
Captor Optigrade™	Structure-guided lead optimization (LILIS)	MGDs and Bifunctional Degraders	CRBN; focus on KLHDC2 and Kelch family
C4T TORPEDO®	DNA-encoded libraries & ternary complex models	MonoDACs (Glues) and BiDACs (Bifunctionals)	Agnostic toolkit (Primarily CRBN)
Aclaris KINect	Proprietary kinase library and SBDD expertise	Covalent inhibitors and diverse degraders	Agnostic; focus on kinase-scaffolding functions

Degrader Platforms: Commercial Metrics

Pipeline and commercial validation

Company	Lead Asset(s)	Primary Targets	Lead Indications	Strategic Partners
Monte Rosa	MRT-2359, MRT-8102	GSPT1, NEK7, VAV1	mCRPC, Inflammation	Novartis, Roche
Captor	CT-01, CT-02	GSPT1, NEK7, MCL-1	HCC, Autoimmune	Ono Pharmaceutical
C4 Therapeutics	Cemsidomide (CFT7455)	IKZF1/3, BRAF, EGFR	Multiple Myeloma	Roche, Biogen, Betta
Aclaris	ATI-2138, ATI-9494	ITK, JAK3	Immuno-inflammatory	Biosion

Collaborations secure extended capital runways



Degraders: Stated Advantages for CNS Specificity

Degraders are positioned as potentially superior to inhibitors in the CNS for several reasons:

- Lower Exposure Requirements: Because one degrader molecule can sequentially eliminate many target proteins, these drugs do not require the high maximal concentrations (Cmax) often needed for inhibitors to drive brain exposure, which can reduce systemic toxicity spikes.

- Avoidance of "Hook Effects": Molecular glue platforms, such as Monte Rosa's , claim their compounds exhibit more "regular" pharmacokinetics and avoid the "hook effect" (where high concentrations lead to decreased efficacy) often seen with heterobifunctional degraders.

- Deeper Target Inhibition: In the context of the inflammasome, Monte Rosa argues that degrading NEK7 before the NLRP3 complex can even assemble provides a deeper and more durable blockade than inhibitors that must compete for binding on an already activated complex.

- Selectivity Profiles: Captor Therapeutics has reported that its NEK7 degraders achieve over 90% degradation without affecting cell viability or proliferation, specifically demonstrating high selectivity against potential teratogenic targets like SALL4.

Pipeline Developments

Beyond the well-established NLRP3 and TYK2 pathways, several novel targets are gaining traction for treating chronic inflammation linked to metabolic and neurological health.

Target	Primary Application	Lead Candidate / Developer	Mechanism
CK1δ	ALS, FTD	NMRA-215 (Neumora)	Inhibiting phosphorylation of TDP-43 to reduce protein aggregation in neurodegeneration.
IL-22R	Obesity, MASH	CK-0045 (Cytoki)	Agonism of the IL-22 receptor to improve gut barrier function and insulin sensitivity.
APJ	Metabolic Aging	Platform Assets (BioAge)	Exercise-mimetic pathways aimed at improving body composition and muscle health.

Key Degradation Targets Outside of IRAK4 and NEK7:

- STAT6 (Signal Transducer and Activator of Transcription 6): Nurix and Sanofi are collaborating on SAR448272 (NX-3911), a STAT6 degrader designed to disrupt the integration of multiple inflammatory signal inputs.

- IRF5 (Interferon Regulatory Factor 5): Kymera is developing KT-579 , a first-in-class IRF5 degrader. IRF5 is a transcription factor inducing proinflammatory cytokines and type I interferons, with

potential roles in lupus, RA, and inflammatory bowel disease (IBD).

Novel Kinase Targets:

- RIPK2 (Receptor-Interacting Protein Kinase 2): RIPK2 acts downstream of NOD1 and NOD2 to mediate immune responses to bacterial signals. Preclinical research suggests RIPK2 inhibitors could normalize immune responses in IBD, metabolic, and liver diseases without broad immunosuppression.

- ITK (IL-2-inducible T-cell Kinase) and JAK3: Aclaris Therapeutics is developing ATI-2138 , a dual ITK/JAK3 inhibitor, and ATI-9494 , a JAK-sparing ITK inhibitor, for chronic inflammation using their KINect platform.

Complement Pathway Targets

- MASP-2 (Mannan-binding lectin-associated serine protease-2): Omeros Corp is in the final stage of drug candidate selection for small-molecule inhibitors targeting the lectin pathway. Omeros is also assessing candidates for

- MASP-3 small-molecule inhibitors to treat alternative pathway disorders.

- C1s: Dianthus's DNTH103 selectively inhibits the classical complement pathway by binding to active C1s, aiming to

reduce the pro-inflammatory cascade while leaving host defense pathways intact.

Mast Cell and Myeloid-Specific Targets

- MRGPRX2 (Mas-related G-protein coupled receptor X2): This receptor is a major regulator of mast cell function. Arcus Biosciences and Evommune (with EVO756) are developing oral inhibitors to treat chronic spontaneous urticaria and atopic dermatitis by blocking mast cell-driven inflammation.

- BSSL (Bile Salt-Stimulated Lipase): Lipum has identified BSSL as a novel target for chronic inflammation; their monoclonal antibody SOL-116 is being developed to treat RA.

- DPP1 (Dipeptidyl Peptidase 1): Insmed is developing next-generation DPP1 inhibitors (INS1033) to target neutrophil biology in RA and IBD, aiming to block the release of neutrophil serine proteases like elastase.

- Melanocortin Receptors (MC1r and MC3r): SynAct Pharma is utilizing resomelagon to modulate M1/M2 macrophages, increasing efferocytosis and phagocytosis to promote inflammation resolution.

Emerging Discovery and Bispecific Programs

- TL1A-Directed Bispecifics: Harbour BioMed is developing HBM2001 (TL1A x IL23p19) and Xencor is advancing XmAb942 ,

a next-gen anti-TL1A mAb designed for enhanced cytokine signaling inhibition in IBD.

- AhR (Aryl Hydrocarbon Receptor): Abivax and Equillium are exploring AhR modulation; Equillium's EQ504 is an oral, colon-targeted modulator designed to restore mucosal barrier protection in ulcerative colitis.

- SPPL2a (Signal Peptide Peptidase-like 2a): Incyte is researching novel SPPL2a inhibitors, which target a protease involved in the development of antigen-presenting cells like B and dendritic cells.

Signal Transduction and Transcription Targets to Watch

- ETS2 and VAV1: Recent research identifies ETS2 as a central regulator of human inflammatory macrophages; MEK inhibitors are being repurposed to suppress this pathway. VAV1 is also being targeted (InnoCare's ICP-538) to modulate dysregulated immune signaling in systemic autoimmune inflammation.

- WSTF: Under chronic stress, WSTF moves from the nucleus to the cytoplasm, where it is degraded by lysosomes. This loss of WSTF (a, "nuclear inhibitor of inflammation") increases chromatin accessibility and triggers the transcription of pro-inflammatory genes such as IL8 and IL1B).

Clinical and Strategic Outlook

- Beyond Symptoms: The goal for many new therapies is to move care from symptom management to immune system recalibration and durable disease control. Learnings from multiple modalities, targets and indications will provide

valuable insights into potential for target/modality combinations that can used to synergistic effect in many indications. Companies like beeline Medicines (top) and Kymera (bottom) may be well placed to leverage such multiplicity:

Why Innate Targets Are Commercially Attractive

Three reasons:

(1) many sit upstream of cytokine release,

(2) they offer oral small-molecule opportunities as 1st generation approach, (3) they may deliver disease modification rather than

symptom control and (4) innate-targeted platforms have established commercial relevance.

Large pharmaceutical companies are increasingly acquiring or licensing mid-to-late clinical-stage assets—particularly those targeting NLRP3, IL-6, and IL-1β—to address residual inflammation in cardiometabolic and neurological diseases.

Major 2025/2026 Deals in Innate Immunotherapeutics

Acquisitions

- Eli Lilly / Ventyx Biosciences (~$1.2B): Announced in January 2026 but driven by 2025 clinical progress, this acquisition centred on VTX3232 (CNS-penetrant NLRP3 inhibitor) and VTX2735 (peripheral NLRP3 inhibitor). The deal provides Lilly with oral small molecules to address neuroinflammation and cardiovascular risk, complementing its existing Alzheimer's and cardiometabolic portfolios.

- Novartis / Tourmaline Bio (~$1.4B): Novartis acquired Tourmaline and its lead anti-IL-6 monoclonal antibody, pacibekitug, in October 2025. This move followed positive data showing reductions in inflammatory and CVD risk markers, positioning Novartis to compete in the high value cardiometabolic space.

Licensing and Partnership Highlights

- InnoCare / Zenas BioPharma (>$2B total deal value): InnoCare licensed non-oncology rights for Orelabrutinib and several pre-clinical assets, including a CNS-penetrant TYK2 inhibitor and an

IL-17 inhibitor ($100.00 million upfront cash payment and tiered royalties in the high-teens).

- Captor Therapeutics / Undisclosed US Partner ($ undisclosed): In November 2025, Captor signed a licensing option agreement for its NEK7 protein degraders for selected (undisclosed) disease groups. The partner gained paid exclusivity to test these degraders, which are being developed for both neuroinflammatory and peripheral autoimmune diseases.

- Otsuka Pharma / Cantargia ($613M): Otsuka licensed the CAN10 program, which targets IL1RAP to simultaneously inhibit IL-1 and IL-18 signaling. The asset was in Phase 1 development at the time of the 2025 deal.

- Neurocrine / TransThera ($882M): In November 2025 Neurocrine acquired the ex-China rights to TransThera's portfolio of NLRP3 inhibitors leaving regional rights with the partner.

Final Thoughts

Innate immunity is not just an adjunct to adaptive immunity in the chronic inflammation setting. It is a primary architect of chronicity cycling in inflammatory disease as modulated through exaggerated stimulus response, muted response resolution in magnitude and over time, and peak engagement of the adaptive immune system.

Companies that have internalised innate concepts scientifically, clinically, and commercially and can expedite cross-fertilization of mechanism, modality and indication learnings will define the next generation of inflammation therapeutics. The varied matrix of

stimulants, targets, cells, and tissues in disease should foster robust therapeutic growth in the decades to come.