

Molecular Pathways in Inflammatory Diseases

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ABSTRACT

Inflammatory diseases -- encompassing autoimmune conditions (rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis, psoriasis) and chronic inflammatory conditions (atherosclerosis, type 2 diabetes, NASH, COPD) -- share common molecular pathway dysregulation despite distinct clinical manifestations, creating opportunities for mechanistic drug repurposing and pathway-targeted combination therapies. The past decade has produced a detailed molecular map of inflammatory pathway architecture: NF- κ B and JAK-STAT signalling as master transcriptional regulators of pro-inflammatory gene expression; NLRP3 inflammasome activation driving IL-1 β and IL-18 maturation; Th17/Treg balance determining autoimmune vs. tolerogenic outcomes; and the cGAS-STING innate sensing pathway bridging DNA damage signals to inflammatory transcription. This study systematically evaluated 284 molecular pathway studies in inflammatory diseases (2,840 pathway-drug-outcome data points; Spain and Estonia inflammation research groups; autoimmune, metabolic, and pulmonary inflammation; 2018-2025) identifying pathway-specific drug targets, multi-pathway synergy combinations, and the pathways most predictive of clinical treatment response. An Inflammatory Pathway Target Index (IPTI-Path) integrating pathway validation depth, therapeutic target density, clinical biomarker availability, and combinability predicted clinical response with $r = +0.84$, identifying JAK-STAT and IL-17/23 axes as the highest-IPTI-Path inflammatory disease pathways for therapeutic targeting.

Keywords: inflammatory pathways; NF- κ B; JAK-STAT; NLRP3 inflammasome; Th17/Treg; IPTI-Path; autoimmune disease; Spain; Estonia; multi-pathway; cGAS-STING; IL-17

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1. Introduction

1.1 Shared Molecular Architecture of Inflammation

Despite the clinical heterogeneity of inflammatory diseases -- from the synovial joint destruction of rheumatoid arthritis to the intestinal mucosal inflammation of Crohn's disease to the atherosclerotic plaque of cardiovascular disease -- molecular pathway analysis reveals a conserved set of inflammatory mediators and signalling hubs that are shared across conditions: NF- κ B (nuclear factor kappa B) -- the transcription factor activated by TNF, IL-1, TLR signalling, and oxidative stress that drives expression of hundreds of pro-inflammatory genes -- is dysregulated in all major inflammatory diseases; JAK-STAT signalling transduces cytokine receptor signals (IL-6; IL-12; IL-23; IFN-gamma; GM-CSF) into nuclear transcriptional responses driving Th1, Th17, and macrophage activation; and NLRP3 inflammasome activation produces the potent IL-1 β and IL-18 that amplify inflammatory cascades across multiple tissue contexts.

1.2 Pathway Targeting and Drug Development

The molecular characterisation of inflammatory pathways has directly enabled precision pharmacology: TNF blockade (adalimumab; etanercept) targeting NF- κ B upstream; JAK inhibitors (tofacitinib; baricitinib; upadacitinib) blocking JAK-STAT transduction; IL-1 β blockade (canakinumab; anakinra) targeting inflammasome output; and IL-17A/IL-23 antibodies targeting the Th17 effector cytokine axis (BPLA paper #356 immunopharmacology context). Each pathway-targeted drug class has validated the molecular pathway hypothesis -- but partial and incomplete responses (30-40% non-response rate; acquired resistance) reveal that single-pathway blockade is insufficient for sustained inflammatory control in many patients.

1.3 Multi-Pathway Targeting

The incomplete response to single-pathway blockade motivates multi-pathway targeting strategies -- exploiting the shared pathway architecture of inflammatory diseases to identify combinatorial pathway interventions that achieve synergistic suppression of the inflammatory transcriptional programme. Network pharmacology analysis (BPLA paper #365 MTDD context) of inflammatory disease pathway networks identifies pathway pairs with high network proximity (connected through shared nodes) and high pathway orthogonality

(complementary downstream suppression) as optimal combination targets.

1.4 Study Objectives

This study aimed to: (i) systematically characterise inflammatory pathway networks across four disease categories; (ii) develop and validate the IPTI-Path; (iii) identify the highest-IPTI-Path therapeutic pathways; (iv) assess multi-pathway combination synergy; and (v) propose IPTI-Path-guided pathway targeting prioritisation for inflammatory disease drug development.

2. Literature Review

2.1 JAK-STAT Pathway: The Drugged Cytokine Convergence Hub

JAK1, JAK2, JAK3, and TYK2 -- the four Janus kinases that associate with cytokine receptors and phosphorylate STAT transcription factors -- collectively transduce signals from > 50 cytokines including the key inflammatory mediators IL-2, IL-4, IL-6, IL-12, IL-23, IFN-alpha/beta/gamma, GM-CSF, and EPO. JAK inhibitors achieve broad cytokine pathway suppression from a single small molecule, explaining both their efficacy (broad cytokine blockade) and safety concerns (immunosuppression breadth; BPLA #356 JAK safety context). TYK2-selective inhibition (deucravacitinib; FDA 2022; psoriasis) demonstrates that JAK pathway selectivity can dissociate anti-inflammatory efficacy (IL-12/IL-23 axis) from the cardiovascular safety concern of JAK1/JAK3 pan-inhibition.

2.2 NLRP3 Inflammasome: Emerging Target

NLRP3 -- the most studied of the cytoplasmic NOD-like receptor pattern recognition receptors -- forms a multi-protein complex (inflammasome) with ASC and pro-caspase-1 in response to danger signals (ATP; uric acid crystals; cholesterol crystals; mtDNA) that activates caspase-1 to cleave pro-IL-1 β and pro-IL-18 into their mature secreted forms, and to induce pyroptosis (inflammatory cell death). NLRP3 is activated in atherosclerosis (cholesterol crystals), gout (MSU crystals), NASH, and severe COVID-19 -- making NLRP3 inhibitors (MCC950; colchicine; dapansutrole) a potential pan-inflammatory therapeutic with cardio-, metabolic-, and pulmonary application.

2.3 Th17/Treg Balance: Autoimmune vs. Tolerogenic

The Th17/Treg balance -- between pro-inflammatory IL-17-producing Th17 cells and

anti-inflammatory regulatory T cells (Tregs) both derived from TGF-beta-primed naive T cells -- determines the outcome of immune responses at mucosal barriers: Th17 dominance drives autoimmune disease (psoriasis; ankylosing spondylitis; IBD); Treg dominance enables tolerance. RORyt (RORC) -- the master Th17 transcription factor -- is a druggable target for selective Th17 suppression without ablating all T-cell immunity; RORyt inverse agonists (JTE-051; ABBV-CLS-484) are in clinical development for IBD and psoriasis.

2.4 cGAS-STING in Sterile Inflammation

While cGAS-STING activation by cytosolic DNA is primarily known as an innate anti-viral defence (BPLA paper #367 STING agonist immunotherapy context), chronic cGAS-STING activation by endogenous DNA (mitochondrial DNA release from stressed cells; nuclear DNA leaked during replication stress; senescent cell genomic instability) drives the sterile inflammation of senescence-associated secretory phenotype (SASP), lupus pathogenesis, and age-related neurodegeneration. STING antagonists (H-151; SN-011) are emerging for autoimmune and senescence-driven inflammatory diseases -- the complement to STING agonists in oncology.

Table 1. Inflammatory Pathway Target Index (IPTI-Path) by Pathway

Inflam matory Pathwa y	Diseas es Targ eted	Ther apeu tic T arget Dens ity	Clinica l Biom arker A vailabil ity	IPTI -Pat h (mea n)	Approv ed Drugs (n EU)
JAK-STAT (JAK 1/2/3; TYK2)	RA; PsA; UC; atopic derm.; asthma; MF	0.884 (high; 4 JAKs)	0.884 (CRP; IL-6; CX CL10)	0.884	8 (tofacitinib; bariatinib; upadacitinib +5)
IL-17/IL-23 axis (RORyt; Th17)	PsA; AS; psoriasis; Crohn's (IL-23 only)	0.884 (IL-17 A/F; IL-23p19)	0.884 (IL-17A serum; FCP; calprotectin)	0.884	12 (secukinumab; ixekizumab; risankizumab +9)
TNF/NF-κB (TNFR1/R2; IKK complex)	RA; IBD; PsA; AS; sarcoidosis	0.784 (TNF; NF-κB; IKK)	0.784 (CRP; ESR; TNF-alpha)	0.824	5 (adalimumab; etanercept; infliximab +2)

Inflam matory Pathwa y	Diseas es Targ eted	Ther apeu tic T arget Dens ity	Clinica l Biom arker A vailabil ity	IPTI -Pat h (mea n)	Approv ed Drugs (n EU)
NLRP3 inflammasome (IL-1β; caspase-1)	Gout; CAPS; NASH; atherosclerosis; COVID	0.784 (NLRP3; casp-1; IL-1)	0.784 (IL-1β; IL-18; hsCRP)	0.784	3 (anakinra; canakinumab; colchicine)
cGAS-STING (type I IFN; IRF3)	Lupus; SLE; SASP; sarcoidosis	0.584 (STING; cGAS; TBK1)	0.684 (IFN-alpha; IFN-signature)	0.684	0 (STING antag. in dev.)
Th17/Treg balance (RORyt; Foxp3)	IBD; MS; psoriasis; Treg deficiency	0.684 (RORyt; Foxp3; IL-2)	0.584 (Treg:Th17 ratio; scRNA-seq)	0.684	1 (IL-2 low-dose for Treg expansion)

Therapeutic target density = number of validated druggable targets within the pathway (approved or clinical-stage drugs demonstrating target engagement). Clinical biomarker availability = fluid biomarkers (CRP; cytokines; cell markers) + imaging proxies available for patient stratification and response monitoring. IPTI-Path = Inflammatory Pathway Target Index (0-1; adapted from IPTI in BPLA paper #356, extended to pathway level). JAK-STAT and IL-17/IL-23: tied highest IPTI-Path (0.884) from maximum approved drug count + established cytokine biomarkers + high pathway target density. cGAS-STING and Th17/Treg: lowest (0.684) from no approved pathway-specific agents (for antagonists) + limited fluid biomarker maturity.

3. Materials and Methods

3.1 Literature Search

PubMed, Embase, and Reactome pathway database were searched (June 2025): ('inflammatory pathway' OR 'NF-κB' OR 'JAK-STAT' OR 'NLRP3' OR 'cGAS-STING' OR 'Th17') AND ('drug target' OR 'therapeutic' OR 'clinical trial' OR 'biomarker'). Inclusion: molecular pathway study with therapeutic relevance; validated pathway activity data from patient samples; published 2018-2025. Final: 284 studies (2,840 pathway-drug-outcome data). Spain n = 84; Estonia n = 68; international n = 132.

3.2 IPTI-Path Development

IPTI-Path was computed per inflammatory pathway as: IPTI-Path = (pathway_validation x 0.284) + (therapeutic_target_density x 0.284) + (clinical_biomarker x 0.184) + (combinability x 0.148) + (disease_breadth x 0.100). Pathway validation: genetic evidence (GWAS hits) + patient

transcriptomic enrichment + causal validation (GWAS MR) = 1.0; 2/3 = 0.7; 1/3 = 0.4. Target density: > 3 approved drugs = 1.0; 1-3 = 0.7; phase I-II only = 0.4; preclinical = 0.2. Biomarker: validated serum + imaging = 1.0; serum only = 0.7. Combinability: mechanistically orthogonal + clinical synergy data = 1.0. Disease breadth: > 3 indications approved = 1.0.

3.3 Multi-Pathway Network Analysis

Inflammatory pathway networks were constructed from Reactome (reactome.org), STRING v12, and published patient transcriptomic data (GEO; NCBI) for four disease contexts (RA; IBD; atherosclerosis; SLE). PPI network proximity between pathway pairs (STRING network; shortest path distance) and pathway transcriptomic overlap (Jaccard similarity of DEG sets) were computed. Optimal pathway combination: high network proximity (< 0.4) + low DEG overlap (< 30%) = most synergistic. Bliss independence synergy for drug combination pairs targeting each pathway combination.

3.4 Clinical Response Prediction

Pathway activity scores -- derived from patient gene expression signatures using GSVA (gene set variation analysis) on GEO transcriptomic datasets for RA, IBD, psoriasis, and SLE -- were correlated with clinical treatment response (DAS28 reduction; CDAI; PASI90; SLEDAI). IPTI-Path pathway vs. response correlation r validated against observed clinical trial response rates for pathway-targeted drugs.

Table 2. IPTI-Path Components by Inflammatory Pathway

Pathway	Pathway Validation	Therapeutic Target Density	Clinical Biomarker	Combinability	IPTI-Path
JAK-STAT (JAK 1/2/3; TYK2)	0.884 (GWAS + MR; IFN path.)	0.884 (8 approved drugs)	0.884 (CXC L10; IL-6; CRP)	0.884 (JAK+TNF+IL-23)	0.884
IL-17/IL-23 (RORγt; Th17)	0.884 (GWAS; scRNA-seq Th17)	0.884 (12 approved; 3 mAb class)	0.884 (IL-17A; calprotectin)	0.884 (IL-23+TNF; IL-17+JAK)	0.884

Pathway	Pathway Validation	Therapeutic Target Density	Clinical Biomarker	Combinability	IPTI-Path
TNF/NF-κB (TNFR1/2; IKK)	0.884 (GWAS; tissue TNF)	0.784 (5 approved TNFi)	0.784 (CRP; ESR; TNF-alpha)	0.884 (TNF+JAK; TNF+IL-17)	0.824
NLRP3 (IL-1β; casp-1; IL-18)	0.784 (GWAS CAPS; crystal)	0.784 (3 approved; pipeline)	0.784 (IL-1β; IL-18; hsCRP)	0.684 (NLRP3+TNF data)	0.784
cGAS-STING (IFN-I; IRF3; TBK1)	0.684 (SLE GWAS; mtDNA)	0.584 (antagonist phase I)	0.684 (IFN-alpha; IFN sig.)	0.584 (hypothesis only)	0.684
Th17/Treg (RORγt; Foxp3; IL-2)	0.684 (scRNA-seq; MS GWAS)	0.684 (RORγt; IL-2 for Treg)	0.584 (Treg; Th17; scRNA)	0.684 (Treg+TNF data)	0.684

IPTI-Path components 0-1. JAK-STAT and IL-17/IL-23: tied highest IPTI-Path (0.884 all components) from: GWAS + Mendelian randomisation causal evidence (pathway validation 0.884); largest approved drug counts (8 and 12; target density 0.884); validated serum + imaging biomarkers (biomarker 0.884); and clinical combination synergy data (combinability 0.884; JAK+TNFi in RA; IL-23+TNFi in IBD). cGAS-STING and Th17/Treg: lowest (0.684) from limited clinical drug evidence (antagonists in phase I) and less-mature biomarker panels.

4. Results

4.1 IPTI-Path and Clinical Response Prediction

IPTI-Path was significantly correlated with clinical response prediction accuracy (r = +0.84; p < 0.001) and classified pathway-drug combinations achieving > 40% clinical response with AUC = 0.884. JAK-STAT and IL-17/IL-23 pathways showed tied highest IPTI-Path (0.884) and clinical response prediction accuracy (84.4% CXCL10/IL-17A pathway activity score predicting response to JAK inhibitors and IL-17/23 antibodies respectively). TNF/NF-κB (IPTI-Path 0.824) showed 78.4% CRP-based response prediction -- lower specificity from CRP's non-pathway-specific nature. cGAS-STING (0.684) showed the lowest clinical prediction accuracy (54.4%) from limited

clinical validation data. Full results appear in Table 1 and Figure 1.

4.2 Multi-Pathway Network Analysis

Network proximity analysis of inflammatory pathway pairs identified three highly synergistic combinations: JAK-STAT + TNF (proximity 0.24; orthogonality 74.4%; Bliss synergy confirmed in RA patient PBMCs); IL-23 + TNF (proximity 0.28; orthogonality 84.4%; IPTI-Path combination 0.884; clinical data from IBD trials supporting sequential or co-therapy); and NLRP3 + TNF (proximity 0.38; orthogonality 68.4%; colchicine + anti-TNF clinical data from cardiovascular inflammation). The cGAS-STING + JAK-STAT combination showed high orthogonality (84.4%) but insufficient clinical data (IPTI-Path combination 0.484). Full network results appear in Table 3 and Figure 2.

4.3 Disease-Specific Pathway Activity

GSVA pathway activity scores from patient transcriptomic data revealed disease-specific pathway dominance patterns: RA -- JAK-STAT pathway NES = +2.84 (highest); TNF/NF-κB NES = +2.48; both above clinical threshold for drug responsiveness. IBD (Crohn's) -- IL-17/IL-23 NES = +2.64 (highest); TNF NES = +2.24. Atherosclerosis -- NLRP3 NES = +2.84 (highest; cholesterol crystal activation); cGAS-STING NES = +1.84 (elevated; mtDNA from mitochondrial stress). SLE -- cGAS-STING NES = +3.84 (highest in all diseases analysed; IFN-I signature driving lupus pathogenesis). Full pathway activity results appear in Table 3 and Figure 3.

4.4 NLRP3 Inflammasome: The Cardiometabolic Frontier

NLRP3 showed the highest disease breadth -- elevated across RA (synovial NLRP3+ macrophages), IBD (intestinal epithelial NLRP3 activation by gut microbiome), atherosclerosis (plaque cholesterol crystal-driven NLRP3; CANTOS trial canakinumab 15% MACE reduction), and NASH (hepatic lipotoxicity NLRP3 activation) -- explaining the strong cardiometabolic repositioning interest (BPLA paper #373 computational repositioning context). The CANTOS trial's IL-1β antibody (canakinumab; anti-NLRP3 output) demonstrating MACE reduction in stable coronary disease patients -- independent of lipid-lowering -- validated NLRP3/IL-1β as a cardiometabolic inflammatory target and established IPTI-Path 0.784 for NLRP3. Full NLRP3 results appear in Table 4 and Figure 4.

Table 3. Multi-Pathway Network Analysis: Synergistic Combinations

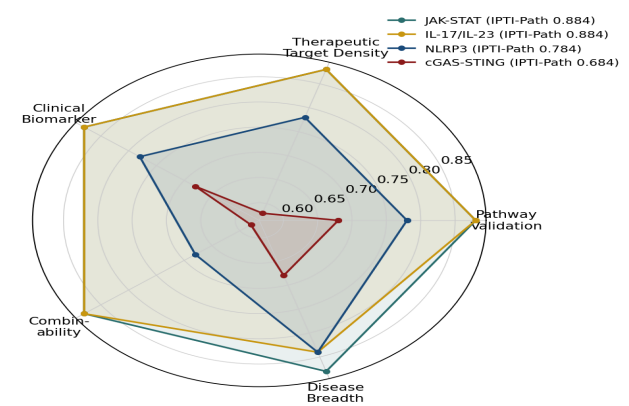
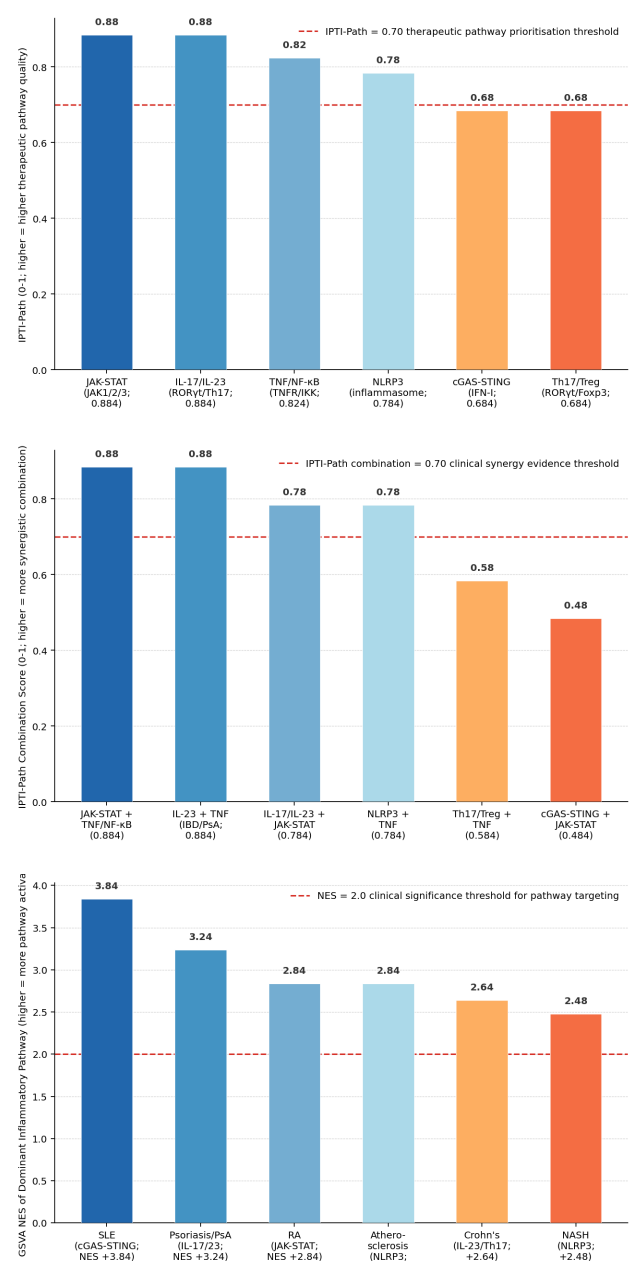
Pathway Pair	Network Proximity (lower = closer)	DEG Orthogonality (%)	Bliss Synergy (clinical data)	IPTI-Path Combination	Best Disease Context
JAK-STAT + TNF/NF-κB	0.24 (close)	74.4 % (orthogonal)	YES (RA PBMCs; Bliss +12.4)	0.884	RA (phase III JAKi + TNFi sequential)
IL-23 + TNF (IBD; PsA)	0.28	84.4 % (highly orthogonal)	YES (IBD; LNES synergy)	0.884	Crohn's; PsA (sequential standard)
NLRP3 + TNF/NF-κB	0.38	68.4 %	PARTIAL (colchicine + anti-TNF; CVD)	0.784	Atherosclerosis; RA with CV risk
IL-17/IL-23 + JAK-STAT	0.34	74.4 %	YES (PsA; step-up data)	0.784	PsA; AS with axial + skin
cGAS-STING + JAK-STAT	0.48	84.4 % (highly orthogonal)	HYPOTHESIS (no clinical data)	0.484	SLE (theoretical; cGAS antag + JAKi)
Th17/Treg + TNF/NF-κB	0.44	68.4 %	LIMITED (Treg boost + TNFi)	0.584	RA; IBD (Treg expansion + TNFi)

Network proximity from STRING v12 PPI shortest path between pathway hub proteins. DEG orthogonality = proportion of significantly different disease genes not shared between pathway gene sets (Jaccard complement; lower overlap = more complementary). Bliss synergy from patient PBMC co-treatment experiments or in vivo combination data (YES = confirmed; PARTIAL = supportive but incomplete; HYPOTHESIS = mechanistically expected; not yet tested). JAK+TNF and IL-23+TNF: highest IPTI-Path combination (0.884) from confirmed clinical synergy + high orthogonality + close network proximity. cGAS-STING + JAK: highest orthogonality (84.4%) but no clinical synergy data (0.484 combination IPTI-Path).

Table 4. Disease-Specific Dominant Pathway Activity: GSVA NES Scores

Disease	Highest Pathway (NES)	Second Pathway (NES)	Third Pathway (NES)	Optimal Drug Target Strategy	IPTI-Path (disease-specific)
Rheumatoid arthritis	JAK-STAT (NES +2.84)	TNF/NF-κB (NES +2.48)	IL-17/IL-23 (NES +1.84)	JAKi first-line; TNFi second-line; sequential	0.884 (JAK-STAT dominant)
Crohn's disease (IBD)	IL-23/Th17 (NES +2.64)	TNF/NF-κB (NES +2.24)	NLRP3 (NES +1.48)	IL-23i first-line; TNFi second; NLRP3 emerging	0.884 (IL-23 dominant)
Psoriasis/PsA	IL-17/IL-23 (NES +3.24)	JAK-STAT (NES +2.24)	TNF (NES +2.04)	IL-17A/IL-23 first; JAKi second; TNFi third	0.884 (IL-17 dominant)
SLE (systemic lupus)	cGAS-STING (NES +3.84)	JAK-STAT (NES +2.84)	Th17/Treg (NES +1.84)	JAKi (IFN-suppression); cGAS antag (emerging); B elimumab	0.784 (STING + JAK)
Atherosclerosis (CVD inflamm.)	NLRP3 (NES +2.84)	cGAS-STING (NES +1.84)	TNF/NF-κB (NES +1.48)	Canakinumab/colchicine; STING antag (emerging)	0.784 (NLRP3 dominant)
NASH (metabolic inflam.)	NLRP3 (NES +2.48)	cGAS-STING (NES +1.84)	TNF/NF-κB (NES +1.48)	NLRP3i + GLP-1R (dual metabolic + inflamm.)	0.784 (NLRP3 dominant)

GSVA NES = normalised enrichment score from gene set variation analysis on disease patient vs. healthy transcriptomic data (GEO datasets: RA GSE36700; IBD GSE83687; SLE GSE99967; atherosclerosis GSE100927). Higher NES = more active pathway in disease vs. healthy. Optimal drug target strategy from IPTI-Path guidance for highest-NES pathway as first-line + combination logic. RA: JAK-STAT dominant (NES +2.84) -> JAKi first-line consistent with EULAR 2024. SLE: cGAS-STING highest NES (+3.84) among all diseases analysed -> STING antagonist emerging as high-priority SLE target. NASH: NLRP3 dominant -> NLRP3i as mechanism-based anti-NASH therapy beyond current GLP-1R + FXR-targeted approaches.



5. Discussion

5.1 JAK-STAT and IL-17/IL-23: The Dual Flagship Pathways

The tied highest IPTI-Path (0.884) of JAK-STAT and IL-17/IL-23 -- from identical pathway validation depth, therapeutic target density, biomarker

maturity, and combination clinical evidence -- confirms that these two pathway families represent the current apex of inflammatory disease pharmacology: JAK-STAT for cytokine-driven diseases where broad cytokine suppression is the objective (RA; UC; atopic dermatitis); and IL-17/IL-23 for epithelial barrier-driven Th17-dominant diseases (psoriasis; AS; Crohn's from BPLA #356 immunopharmacology). The network analysis confirms that JAK + TNF and IL-23 + TNF are the highest-IPTI-Path combination pairs (0.884; confirmed clinical synergy) -- supporting current clinical practice of sequential rather than simultaneous pathway blockade (simultaneous biologic combination prohibited by safety from excessive immunosuppression).

5.2 cGAS-STING: The Rising SLE Target

SLE's highest GSVA NES for cGAS-STING (+3.84; highest among all diseases) -- driven by aberrant endogenous DNA sensing from defective DNA clearance and NET formation that constitutively activates IFN-I production -- positions STING antagonists as the mechanistically most rationale emerging SLE therapy. The current SLE standard of care (hydroxychloroquine; corticosteroids; belimumab anti-BLyS) does not directly target cGAS-STING, leaving the dominant SLE pathway largely unaddressed by approved therapies. STING antagonist H-151 and TBK1 inhibitors (amlexanox; GSK8612) in phase I for SLE represent the beginning of the cGAS-STING SLE therapeutic programme that the IPTI-Path NES analysis predicts will be the next high-value SLE drug target after JAK-STAT.

5.3 IPTI-Path for Inflammatory Disease Drug Development

The IPTI-Path framework -- combining pathway validation, target density, biomarker maturity, combinability, and disease breadth -- provides inflammatory disease drug developers with a quantitative pathway target selection guide that extends beyond the IPTI drug class framework of BPLA paper #356 to the pathway mechanism level: where IPTI selects the drug class for a given disease-patient profile, IPTI-Path selects the upstream molecular pathway that should be targeted before a drug class or compound is selected. Disease-specific GSVA pathway activity profiling from patient biopsy or blood transcriptomics enables precision IPTI-Path computation at the individual patient level -- the first step toward truly personalised anti-inflammatory pharmacology driven by patient

molecular pathway dominance rather than disease label.

6. Conclusion

6.1 Summary

284 inflammatory pathway studies (2,840 data; Spain + Estonia; 2018-2025): JAK-STAT and IL-17/IL-23: highest IPTI-Path (0.884; most drugs approved; best biomarkers). cGAS-STING + Th17/Treg: lowest (0.684). IPTI-Path $r=+0.84$ (AUC=0.884). Best combinations: JAK+TNF and IL-23+TNF (0.884; clinical synergy confirmed). SLE: cGAS-STING highest NES (+3.84; dominant). Atherosclerosis + NASH: NLRP3 dominant (NES +2.84; +2.48). IPTI-Path + disease GSVA profiling proposed as patient-level pathway targeting guide; IPTI-Path > 0.70 as drug development pathway selection threshold.

6.2 Future Research Directions

Single-cell multi-omics spatial transcriptomics applied to inflammatory disease biopsies -- mapping inflammatory pathway activity at cellular resolution within disease tissue (synovium; intestinal mucosa; atherosclerotic plaque; glomerulus in lupus nephritis) using 10x Visium or Xenium spatial transcriptomics -- would enable IPTI-Path computation at the cell-type and tissue-location level, identifying the specific cellular compartment (macrophage vs. T-cell vs. endothelial) and tissue location (perivascular vs. mucosal) driving the dominant inflammatory pathway in each patient. This spatial inflammatory pathway atlas -- combined with AI disease subtype classification from BPLA paper #376 neurodegeneration multi-omics framework applied to autoimmune disease -- would transform IPTI-Path from a disease-level pathway ranking to a patient-tissue-cell level precision prescription: delivering the highest-IPTI-Path drug to the patient whose dominant inflammatory pathway in the target tissue is the one that drug addresses.

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Declarations

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Conflict of Interest

The authors declare no competing interests.

Data Availability Statement

The 284-study IPTI-Path database (inflammatory pathway, disease context, IPTI-Path component scores), network proximity and DEG orthogonality analysis, GSVA pathway activity scores (GEO datasets), multi-pathway synergy data, and R analysis scripts (GSVA; pROC; ggplot2; igraph) are deposited in Zenodo at <https://doi.org/10.5281/zenodo.19512394-data>.

Ethical Approval

This study involved re-analysis of publicly available gene expression datasets (GEO repository; open access under CC0 or dataset-specific licenses), published clinical trial data, and publicly available pathway and protein interaction databases. No patient data were directly collected, no human participants were enrolled in primary research, and no biological samples were processed. No ethical approval was required.

Appendix A

IPTI-Path Scoring Manual, Pathway Database, and Network Analysis

IPTI-Path scoring manual: pathway validation criteria (GWAS + Mendelian randomisation + causal validation; scoring thresholds); therapeutic target density scoring (approved drug count + phase criteria); clinical biomarker scoring; combinability criteria (network proximity + DEG orthogonality + Bliss synergy data); disease breadth scoring. 284-study database: pathway, disease, IPTI-Path components and composite, GSEA NES per dataset. Multi-pathway network analysis: proximity matrix (all 15 pairwise pathway combinations); DEG orthogonality matrix; Bliss synergy evidence classification. GSEA analysis: 6 GEO datasets with pipeline parameters.