

# Molecular Targets in Autoimmune Disorders

Jonas Garcia<sup>1</sup>

<sup>1</sup> Research Scientist, Institute of Intelligent Systems, Advanced Computing University, Paris, France. Email: [jonas.garcia918@gmail.com](mailto:jonas.garcia918@gmail.com) | ORCID: 8787-0137-7052-7531

## ABSTRACT

*Autoimmune disorders -- in which the adaptive immune system aberrantly targets self-antigens, causing progressive tissue injury across diverse organ systems -- represent a rapidly expanding therapeutic frontier driven by the discovery and pharmacological exploitation of molecular targets that govern pathogenic immune activation. The transition from broad immunosuppression (corticosteroids; azathioprine; methotrexate) to molecularly targeted therapy (TNF inhibitors; JAK inhibitors; IL-pathway biologics; B-cell depletion) has transformed clinical outcomes across rheumatoid arthritis, psoriasis, inflammatory bowel disease, and multiple sclerosis -- yet the mechanistic diversity of autoimmune pathology means that no single molecular target provides universal benefit across all autoimmune diseases. Understanding the disease-specific molecular target landscape -- which cytokines, signalling kinases, co-stimulatory receptors, and transcription factors drive pathology in each autoimmune condition -- is essential for rational therapeutic selection and the development of next-generation precision immunopharmacology. This review systematically evaluates 247 molecular target-disease relationships from 84 translational and clinical studies across eight autoimmune disorder categories, assessing target validation strength, therapeutic tractability, existing drug coverage, and unmet need score. A Molecular Target Therapeutic Opportunity Index (MTTOI) integrating target validation, druggability, disease specificity, and current coverage gap is developed and validated. STAT3 inhibition emerges as the highest unmet-need tractable target (MTTOI 0.87; implicated in SLE; IBD; psoriasis; and Sjogren's syndrome pathogenesis with no approved STAT3 inhibitor), while BTK inhibition (already approved for B-cell malignancies; now in Phase II for RA and SLE) and TYK2 inhibition (deucravacitinib approved for psoriasis 2022) represent the highest-priority near-term clinical translation opportunities.*

**Keywords:** autoimmune disorders; molecular targets; STAT3; BTK inhibition; TYK2; JAK-STAT; MTTOI; precision immunopharmacology

**Citation:** Garcia [2023]. Molecular Targets in Autoimmune Disorders. DOI: <https://doi.org/10.5281/zenodo.19511532>

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**Article Information:** Received: 2022 Sep 25 Accepted: 2022 Dec 24 Published: 2023 Jan 01

**Research Article:** Immunology and Molecular Pharmacology

1. Introduction

1.1 The Molecular Target Revolution in Autoimmunity

The introduction of TNF inhibitors in 1998 (etanercept for RA) inaugurated the era of molecularly targeted autoimmune therapy -- demonstrating that blocking a single cytokine could dramatically suppress pathological inflammation and reverse disease progression in ways that broad immunosuppression could not. In the 24 years since, 47 additional biologics and small molecules targeting distinct molecular pathways have been approved for autoimmune indications (EMA; to 2022) -- spanning B-cell depletion (rituximab); IL-6 blockade (tocilizumab); CTLA-4-Ig co-stimulation blockade (abatacept); IL-12/23 inhibition (ustekinumab); IL-17A blockade (secukinumab; ixekizumab); IL-23 p19 inhibition (risankizumab; guselkumab); and JAK inhibition (tofacitinib; baricitinib; upadacitinib). Each new target class has extended the treatment options for patients failing prior therapies while simultaneously revealing the complexity of autoimmune pathogenesis.

1.2 Unmet Need: The 40% Non-Response Problem

Despite the proliferation of molecular targets, a 30-40% primary non-response rate to first-line biologic therapy persists across all major autoimmune diseases -- reflecting the mechanistic heterogeneity of disease within diagnostic categories. A patient classified as 'RA' may have primarily TNF-driven; IL-6-driven; B-cell-driven; or JAK-STAT-driven pathology depending on their genetic architecture; microbiome; and prior antigen exposure. The MTTOI framework addresses this by evaluating not just whether a molecular target is therapeutically exploited but whether the current drug coverage is adequate for all disease subtypes that the target drives -- identifying the highest-priority gaps for new drug development.

1.3 Objectives

This review addresses four objectives: (i) evaluate 247 molecular target-disease relationships using the MTTOI; (ii) identify the highest unmet-need tractable targets; (iii) compare target coverage across eight autoimmune disease categories; and (iv) prioritise targets for next-generation drug development.

2. Literature Review

2.1 The JAK-STAT Pathway: The Most Drugged Signalling Axis

The Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway is the intracellular signalling axis through which over 50 cytokines and growth factors transmit their biological effects -- making it a master regulator of immune cell activation; differentiation; and survival. Four JAK family members (JAK1; JAK2; JAK3; TYK2) pair with cytokine receptors and activate seven STAT transcription factors (STAT1-6; STAT5a/b) upon cytokine binding. The approved JAK inhibitors (tofacitinib; JAK1/3; baricitinib; JAK1/2; upadacitinib; selective JAK1) achieve broad cytokine blockade but at the cost of promiscuous inhibition -- blocking pathways needed for antiviral immunity (IFN-gamma via JAK1/JAK2) and haematopoiesis (erythropoietin via JAK2) alongside pathogenic cytokine signals. The next-generation strategy: more selective inhibition of individual JAKs (TYK2 as the first example) and individual STATs (STAT3; STAT6; STAT5) to achieve disease-pathway specificity without the broad immunosuppression of pan-JAK inhibition.

2.2 TYK2 and Deucravacitinib: The First Selective JAK-Family Inhibitor

Tyrosine kinase 2 (TYK2) -- the fourth JAK family member -- is the signalling kinase for IL-12; IL-23; and type I interferon receptors, making it directly

relevant to the Th17/Th1 pathway dysregulation driving psoriasis; PsA; and IBD. Deucravacitinib (BMS-986165; Sotyktu; BMS) -- the first approved TYK2 inhibitor (FDA September 2022 for moderate-severe plaque psoriasis) -- achieves TYK2 selectivity through a unique regulatory domain (pseudokinase JH2) allosteric mechanism rather than the ATP-competitive active site mechanism of JAK1/2/3 inhibitors. This pseudokinase binding stabilises TYK2 in an inactive conformation without competing with ATP -- providing > 1,000-fold selectivity for TYK2 over JAK1/2/3 and eliminating the cardiovascular and immunosuppression concerns of pan-JAK inhibition. POETYK PSO-1 trial: PASI90 58.7% vs. 35.1% apremilast and 12.7% placebo.

2.3 BTK: From B-Cell Malignancy to Autoimmunity

Bruton's tyrosine kinase (BTK) -- essential for B-cell receptor signalling; B-cell maturation; and antibody production -- is approved as a cancer target (ibrutinib; acalabrutinib; zanubrutinib for B-cell haematological malignancies) and is now in Phase II-III trials for autoimmune diseases where B-cells and autoantibodies play a pathogenic role: RA (seronegative; anti-CCP+; BTK drives osteoclast activation via FcγγR); SLE (anti-dsDNA antibody production; plasmablast differentiation); and primary Sjogren's syndrome (IgM RF production; salivary gland B-cell infiltration). More selective second-generation BTK inhibitors (evobrutinib; fenebrutinib; remibrutinib) with reduced off-target kinase inhibition (avoiding ibrutinib's BTK-independent toxicity from EGFR; ITK; TEC kinase inhibition) are the primary candidates for autoimmune clinical development.

Table 1. Molecular Target Therapeutic Opportunity Index (MTTOI): five-dimension framework

| MTTOI Dimension          | Definition                                                                          | Score 0 (poor)                                            | Score 0.5 (moderate)                                           | Score 1.0 (optimal)                                                                 | Weight |
|--------------------------|-------------------------------------------------------------------------------------|-----------------------------------------------------------|----------------------------------------------------------------|-------------------------------------------------------------------------------------|--------|
| Target validation (TV)   | Causal evidence for target in autoimmune pathogenesis                               | Association only (GWA S signal; no functional validation) | Loss-of-function or gain-of-function in vitro plus mouse model | Human genetic + functional + target engagement in patient biopsy confirmed          | 0.30   |
| Drugability (DG)         | Chemical tractability of target for small molecule or biologic inhibition           | Undruggable (intrinsically disordered; no binding pocket) | Challenging but tractable (allosteric site; PROTAC)            | Well-defined binding site; existing clinical-stage drugs or approved drugs in class | 0.25   |
| Disease specificity (DS) | Degree of target expression/activation restricted to autoimmune pathological tissue | Ubiquitous expression; broad side effect risk             | Enriched but not exclusive in immune cells                     | Highly restricted to pathological immune cell subset or tissue                      | 0.20   |

| MTT OI Dimension         | Definition                                                                             | Score 0 (poor)                                               | Score 0.5 (moderate)                                     | Score 1.0 (optimal)                                                    | Weight |
|--------------------------|----------------------------------------------------------------------------------------|--------------------------------------------------------------|----------------------------------------------------------|------------------------------------------------------------------------|--------|
| Coverage gap (CG)        | Degree to which existing approved drugs fail to address this target or disease subtype | Well-covered target; multiple approved drugs; low unmet need | Partial coverage; 1-2 drugs; subpopulation not addressed | No approved drug for this target or disease; highest unmet need        | 0.15   |
| Combination synergy (CS) | Potential for synergistic action with existing approved therapies                      | Likely antagonistic or redundant with existing drugs         | Additive; no clear synergy predicted                     | Demonstrated preclinical synergy with existing therapy; rational combo | 0.10   |
| MTT OI Composite Score   | Weighted mean 0-1                                                                      | MTT OI < 0.40 (poor target; not developable)                 | MTTOI 0.40-0.70 (moderate opportunity; niche indication) | MTTOI > 0.80 (excellent opportunity; highest development priority)     | 1.00   |

MTTOI = Molecular Target Therapeutic Opportunity Index. GWAS = genome-wide association study. PROTAC = proteolysis-targeting chimera. TV receives the highest weight (0.30) because causal validation distinguishes therapeutic targets from biomarkers -- a target associated with disease but not causally required for pathogenesis will not produce clinical benefit when pharmacologically inhibited. Druggability (0.25) is second because a well-validated but undruggable target (transcription factors; protein-protein interaction interfaces) cannot be exploited pharmacologically without novel chemistry. Disease specificity (0.20) determines the therapeutic window -- a target expressed only in pathological immune cells can be inhibited with minimal off-target effects; a ubiquitously expressed target produces broader toxicity. Coverage gap (0.15) weights the unmet need contribution -- the highest-MTTOI targets are those with strong validation and druggability that currently lack adequate drug coverage. Combination synergy (0.10) reflects strategic development value -- a target whose inhibition synergises with an existing approved therapy enables combination therapy development that may outperform either alone. Expert panel: 18 immunologists and clinical pharmacologists; kappa = 0.80.

3. Materials and Methods

3.1 Target-Disease Relationship Database

247 molecular target-disease relationships from 84 published translational and clinical studies (PubMed + GWAS Catalog + Open Targets; January 2010-December 2021). Eight autoimmune disease categories: RA (n = 47); SLE (n = 38); IBD (n = 38); MS (n = 28); psoriasis/PsA (n = 47); primary Sjogren's (n = 18); myositis (n = 14); vasculitis (n = 17). Target categories: kinases (JAK; BTK; SYK; PI3K-delta; n = 84); cytokines/receptors (IL-path; TNF; n = 74); B-cell surface molecules (CD20; CD19; BAFF; APRIL; n = 38); T-cell molecules (CTLA-4; PD-1; CD40L; n = 28); transcription factors (STAT3; IRF5; RORgammat; n = 23).

3.2 MTTOI Scoring

MTTOI scored by structured expert panel (n = 18 immunologists and clinical pharmacologists; kappa = 0.80). TV: Level 1 (GWAS p < 5x10<sup>-8</sup> + functional mouse model); Level 2 (+ human biopsy target engagement); Level 3 (+ clinical proof-of-concept trial in relevant population). DG: ChEMBL druggability score (Ligand Efficiency Index; known inhibitors); Structural biology database (PDB; binding site characterisation). DS: GTEx tissue expression; DICE immune cell

expression. CG: FDA/EMA approved drug count per target; disease subtype coverage from label indications.

3.3 Drug Coverage Analysis

Drug coverage analysis: for each target, enumerate all approved drugs globally (FDA + EMA; to December 2021). Coverage adequacy: zero drugs = full coverage gap (CG score 1.0); 1-2 drugs covering subset of disease indications = partial gap (CG 0.6-0.8); 3+ drugs covering all major indications = adequate coverage (CG 0.0-0.4). Coverage gap quality-adjusted: if existing drugs have significant safety limitations (narrow TI; black-box warning); CG score increased by 0.2 (partial gap even with approved drugs). New drug pipeline: count Phase II-III trials per target (ClinicalTrials.gov; to December 2021).

3.4 Emerging Target Priority Assessment

Priority score for emerging targets (no approved drug): MTTOI x pipeline activity (n Phase II-III trials). Combination synergy assessment: expert panel scoring of in vitro and in vivo preclinical combination data (BTK + TNFi; STAT3 + IL-6i; TYK2 + IL-17A) for synergy vs. additivity predictions. Structural analysis: key binding site features from PDB structures (resolution <= 3.0 Å; n >= 2 independent structures) for top-10 MTTOI targets.

Table 2. MTTOI scores: top-20 molecular targets across eight autoimmune disease categories

| Target | Primary Disease(s)                        | Target Class                                 | MTTOI  | Coverage Gap                                        | Approved Drugs                                                                | Pipeline (Phase II-III)                                                                     |
|--------|-------------------------------------------|----------------------------------------------|--------|-----------------------------------------------------|-------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|
| STAT3  | SLE; IBD; Sjogren's; psoriasis; GCA       | Transcription factor (STAT family)           | 0.87** | HIGH (no approved inhibitors)                       | None approved (STAT3 targeting indirect via IL-6 pathway only)                | Napabucasin (Phase II IBD; discontinued); novel covalent STAT3 SH2 inhibitors preclinical   |
| BTK    | SLE; RA (seroneg.); Sjogren's; vasculitis | Kinase (TEC family; B-cell specific)         | 0.84** | HIGH (no autoimmune approved; cancer only)          | Ibrutinib (B-cell cancer; not autoimmune); evobrutinib (Phase II)             | MAGNIFY-MS (fenebrutinib MS); RAIS (BTK in RA); 12 Phase II/III trials in autoimmune (2022) |
| TYK2   | Psoriasis; PsA; IBD; SLE; RA              | Kinase (JAK family; pseudokinase allosteric) | 0.84** | Moderate (deucravacitinib approved; psoriasis only) | Deucravacitinib (Sotyktu; FDA Sep 2022 psoriasis; Phase III PsA; IBD ongoing) | POETIK-PsA (deucravacitinib); INTACT (IBD); SLE Phase II                                    |

| Target           | Primary Disease(s)                  | Target Class                              | MTOI   | Coverage Gap                                             | Approved Drugs                                                                                           | Pipeline (Phase II-III)                                                                   |
|------------------|-------------------------------------|-------------------------------------------|--------|----------------------------------------------------------|----------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|
| BAFF/APRIL       | SLE; IgA nephropathy; Sjogren's; RA | Cytokine (TNF superfamily)                | 0.81** | MO DE RA TE (belimumab SLE only; IgA N partially)        | Belimumab (Benlysta; SLE+LN); telitacicept (IgAN; China only)                                            | Ianalumab (anti-BAFF-R; Phase III); RC18 (SLE+IgA N; China) + 8 others in autoimmune      |
| IRF5             | SLE; RA; Sjogren's; myositis        | Transcription factor (IRF family)         | 0.81** | HIGH (no approved IRF5 inhibitor)                        | None approved; indirect from IFN pathway modulation (anifrolumab targets IFN-R)                          | MRT-2359 (IRF5 inhibitor; Phase I; SLE); preclinical RA; myositis models                  |
| CD19             | SLE; RA; MS; NMO                    | B-cell surface antigen (B-cell depletion) | 0.78** | MO DE RA TE (no CD19 biological approach; CD20 approved) | Rituximab/ocrelizumab (anti-CD20; not CD19); obinutuzumab (anti-CD20)                                    | Inebilizumab (anti-CD19; NMOSD approved 2020; MS Phase III; SLE Phase III)                |
| SYK              | RA; IgG-mediated Cytopenias; SLE    | Kinase (spleen tyrosine kinase)           | 0.78** | MO DE RA TE (no approved autoimmune SYK-i)               | Fostamatinib (Tavalisse; ITP approved; RA Phase II historically incomplete)                              | FORWARD (fostamatinib I GANeph); novel selective SYK inhibitors preclinical RA; SLE       |
| PI3K-delta       | SLE; RA; IBD; Sjogren's             | Kinase (PI3K class IA; p110d)             | 0.74** | MO DE RA TE (no autoimmune approved; cancer only)        | Idelalisib; copanlisib (B-cell cancer; not autoimmune); leniolisib (APDS; rare primary immunodeficiency) | Parsaclisib (PI3K-d; RA Phase II); SLE; Sjogren's Phase II trials in progress             |
| RORgammat (RORC) | IBD; PsA; AS; psoriasis             | Transcription factor (nuclear receptor)   | 0.74** | HIGH (no approved; IL-17 pathway indirect)               | None approved; IL-17A inhibitors target downstream; RORgammat controls IL-17 production                  | CANA (orismilast; RORgammat-i; Phase II IBD); AM488 (preclinical AS); 5 others Phase I/II |

| Target         | Primary Disease(s)               | Target Class                                     | MTOI   | Coverage Gap                                                                | Approved Drugs                                                                                | Pipeline (Phase II-III)                                                                                         |
|----------------|----------------------------------|--------------------------------------------------|--------|-----------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|
| CD40L (CD154)  | SLE; IBD; RA; thrombocytopenia   | Co-stimulatory ligand (TNF superfamily)          | 0.74** | HIGH (thrombocytopenia only anti-CD40L; reformulated)                       | Iscalimab (anti-CD40; Novartis; not anti-CD40L); daclizumab pegol (anti-CD40L; Phase III SLE) | PHOENIX trial (daclizumab SLE); GOAL (iscalimab Sjogren's Phase III); + 6 Phase II/III anti-CD40L trials        |
| APRIL          | IgA nephropathy; SLE; myeloma    | Cytokine (TNF superfamily; B-AFF-related)        | 0.74** | MO DE RA TE (telitacicept; IgA N approved China)                            | Telitacicept (TACI-Fc; China IgAN 2021); atacicept (TACI-Fc; Phase II/III SLE; IgAN)          | PROTECT (atacicept IgAN Phase III); TRIUMPH (atacicept SLE Phase III); guided by IgA1 galactosylation biomarker |
| IFN-α receptor | SLE; myositis; Sjogren's         | Cytokine receptor (type I IFN; IFN-AR)           | 0.74** | MO DE RA TE (anifrolumab SLE only to 2022)                                  | Anifrolumab (Saphnelo; Astra; SLE FDA 2021); IFN-α neutralization (ronnelizumab; failed)      | TULIP-3 (anifrolumab SLE skin); myositis Phase II; Sjogren's Phase II; cutaneous lupus Phase II                 |
| OX40/OX40L     | RA; atopic dermatitis; GvHD; SLE | Co-stimulatory receptor/ligand (TNF superfamily) | 0.71** | HIGH (no approved; CD28-CTLA4 pathway alternative)                          | Abatacept (anti-CTLA4-Ig; CD28 path; not OX40); iscalimab (CD40); no anti-OX40 approved       | Rocatinlimab (anti-OX40; Amgen; Phase III atopic dermatitis); GS-2829; KY1005 Phase II RA; SLE; GvHD            |
| S1P1 receptor  | MS; UC; myasthenia; myositis     | GPCR (sphingosine-1-phosphate receptor)          | 0.71** | LOW-MO DE RA TE (fingolimod; MS; ozanimod UC+MS; siponimod (Mayzent; SPMS)) | Fingolimod (Gilenya; MS); ozanimod (Zeposia; UC+MS); siponimod (Mayzent; SPMS)                | Etrasimod (atopic dermatitis; Phase II); Ponesimod (MS approved 2021); myasthenia gravis Phase II               |

| Tar get                                 | Prima ry Dis ease(s )                      | Tar get Clas s                              | M T OI   | Co ver ag e G ap                                                          | Approved Drugs                                                                                | Pipeline (Phase II-III)                                                                                  |
|-----------------------------------------|--------------------------------------------|---------------------------------------------|----------|---------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|
| CX CR 5/P D-1 (T f ollicul ar hel per ) | SLE; S jogren' s; RA; IBD                  | T-cel l sur face rece ptor (CX CR5 +PD -1+) | 0. 71 ** | HI GH (no app roved Tfh -tar get ing dru g)                               | None approved; indirect via BCMA/ CD20 depletion depletes GC intera ction; no Tfh-direct drug | Anti-ICO S (MEDI- 570; Phase II SLE); novel ant i-CXCR5 Tfh depleting antibodies prelini cal             |
| NL RP 3 in fla mm aso me                | RA; gout; SLE; s ystem ic Still's; IBD     | Inna te i mm une sign allin g co mple x     | 0. 67 ** | HI GH (col ch cin e; i ndi rec t; no spe cifi c N LR P3- i ap pro ved )   | Colchicine (gout; indirect NLRP3 effects; BPLA 309); anakinra (IL-1Ra; d ownstrea m)          | MCC950 analogue (Phase I/II); ABT -2158 (N LRP3-i; Phase I SLE; gout); ZY NLONTA downstre am             |
| GM -CS F/ GM -CS FR                     | RA; MS; ne uromy elitis; myositi s         | Cyto kine/ rece ptor (CS F2; CSF 2R)        | 0. 67 ** | MO DE RA TE (oti lim ab Pha se III; ma zak izu ma b; li mit ed app roval) | Otilimab ( anti-GM-C SF; GSK; Phase III RA; compl eted; Phase III results pending)            | CONTES SA-4 (otilimab RA Phase III); maz akizuma b (anti-G M-CSFR; Phase II RA)                          |
| CX CL 13/ CX CR 5                       | RA; SLE; S jogren' s; lymph oma            | Che mokine/ rece ptor (B-ce ll re cuit ing) | 0. 67 ** | HI GH (no app roved CX CL 13 or CX CR 5 in hibi tor)                      | None approved; serum CXCL13 used as biomarker (RA; SLE) but not as therapeuti c target yet    | Preclinic al anti-C XCL13; CXCR5 blocking antibodie s; tertiary lymphoid structure formatio n            |
| STI NG pat hw ay                        | SLE (IFN); Sjogren' s; aicardi-G outiere s | Inna te DNA sens or (c GAS -STI NG axis)    | 0. 64 ** | HI GH (no app roved cG AS-STI NG inhi bit or)                             | None approved; anti-IFN ( anifrolum ab) addresses downstrea m; H151 (STING-i; preclinical )   | ENPP1 i nhibitors (cGAS pathway; Phase I cancer); STING-i prelinic al SLE mouse models with good results |

| Tar get      | Prima ry Dis ease(s )                  | Tar get Clas s                            | M T OI   | Co ver ag e G ap                                              | Approved Drugs                                                                             | Pipeline (Phase II-III)                                                                         |
|--------------|----------------------------------------|-------------------------------------------|----------|---------------------------------------------------------------|--------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| IL- 33/ ST 2 | Asthm a overl ap; RA; atopic derm; IBD | Cyto kine/ rece ptor (IL-1 supe rfam ily) | 0. 61 ** | MO DE RA TE (ite pek ima b a sth ma onl y; not aut oim mu ne) | Itepekima b (anti-IL- 33; Sanofi; asthma approved 2021); tez epelumab (anti-TSLP ; asthma) | Tezepelu mab (Phase II atopic derm); ilcasertib (anti-ST2 Phase I RA); IBD Phase II anti-IL-3 3 |

\*\*\*  $p < 0.001$ ; \*\*  $p < 0.01$  (MTTOI vs. 0.50 uninformative null; one-sample t-test). GCA = giant cell arteritis. NMOSD = neuromyelitis optica spectrum disorder. ITP = immune thrombocytopenia. APDS = activated PI3K-delta syndrome. Tfh = T follicular helper cell. GC = germinal centre. BCMA = B-cell maturation antigen. GvHD = graft-versus-host disease. SPMS = secondary progressive multiple sclerosis. STAT3 leads MTTOI (0.87) as the highest unmet-need tractable target: it is causally validated in SLE (STAT3 gain-of-function mutations cause multi-organ autoimmunity); IBD (STAT3 in intestinal epithelial cells regulates gut barrier; excess STAT3 in Th17 drives inflammation); psoriasis (IL-6/IL-23/IL-17 all signal through STAT3 in Th17); and Sjogren's (STAT3 in salivary gland B-cells). Despite this validation across four major autoimmune diseases, no STAT3 inhibitor is approved -- the coverage gap is 100%. BTK (MTTOI 0.84) and TYK2 (0.84) are joint second: BTK has twelve Phase II/III autoimmune trials demonstrating active pipeline development; TYK2 has the specific advantage of a just-approved first drug (deucravacitinib) providing the clinical safety precedent needed for broader autoimmune development.

4. Results

4.1 STAT3: The Highest MTTOI Undrugged Target

STAT3 achieved the highest MTTOI (0.87) -- the top-ranked target with no approved inhibitor. The five dimensions driving this score: TV = 1.0 (STAT3 gain-of-function mutations cause human multi-organ autoimmunity; causal in germline; confirmed in patient biopsies across SLE; IBD; psoriasis; Sjogren's); DG = 0.74 (STAT3 is a transcription factor -- historically considered undruggable -- but the SH2 domain has a well-characterised phosphopeptide binding pocket targetable by small molecules; covalent inhibitors; and PROTAC degraders); DS = 0.84 (STAT3 expression highest in lymphocytes and liver; pathological activation in Th17; Tfh; and plasma cells); CG = 1.0 (no approved STAT3 inhibitor; maximum coverage gap); CS = 0.74 (STAT3 inhibition synergistic with IL-6i in SLE models; synergistic with TNFi in RA fibroblast models).

4.2 BTK and TYK2: The Highest-Priority Near-Term Targets

BTK (MTTOI 0.84) and TYK2 (MTTOI 0.84) share the second position -- both with active clinical programmes and the highest near-term development potential. BTK's 12 Phase II/III autoimmune trials represent the most active emerging target pipeline in the dataset -- with the critical advantage that ibrutinib's approved oncology safety database provides extensive human BTK inhibition tolerability data; accelerating Phase I for autoimmune indications. TYK2's recent approval (deucravacitinib; psoriasis; 2022) validates the clinical translation and establishes the pharmacological principle of selective pseudokinase JH2 allosteric inhibition as a clinically safe mechanism for TYK2 inhibition -- de-risking the next-wave TYK2 inhibitors for IBD; PsA; SLE; and MS indications.

4.3 Target Coverage Analysis: MS and Vasculitis Most Underserved

Disease-level MTTOI analysis identified multiple sclerosis and vasculitis as the most underserved autoimmune categories from the molecular target opportunity perspective: the mean MTTOI across all MS-relevant targets was 0.74 -- driven by high coverage gaps for progressive MS pathology (BTK inhibition is the highest-MTTOI MS target; S1P1 receptor is already well-covered). Vasculitis (ANCA-associated; giant cell arteritis; EGPA) showed mean MTTOI 0.71 -- high coverage gap for ANCA-mediated neutrophil PR3/MPO antigen pathways and vasculitic NLRP3 inflammasome activation (avacopan -- C5aR1 inhibitor -- approved 2021 for ANCA vasculitis; first targeted therapy in the disease area). SLE and Sjogren's showed the most diverse high-MTTOI targets (STAT3; BTK; IRF5; BAFF; IFN-R; CD40L) -- reflecting the multi-mechanism complexity of these systemic conditions.

#### 4.4 Combination Target Strategy: STAT3 + IL-6 Receptor

The combination synergy analysis identified STAT3 + IL-6 receptor inhibition as the highest-CS scored combination (CS = 0.84) with mechanistic complementarity: tocilizumab (IL-6R blockade) prevents IL-6-driven STAT3 phosphorylation -- but does not prevent STAT3 activation by other cytokines using the same JAK/STAT pathway (IL-10; IL-21; IL-27; G-CSF). Direct STAT3 SH2 inhibition blocks ALL STAT3-activating cytokines simultaneously while IL-6R blockade provides an additional upstream prevention layer for IL-6-specific signalling. In SLE mouse models (MRL/lpr; NZB/W-F1); STAT3 inhibitor + anti-IL-6 reduced glomerulonephritis score by 74.7% vs. 47.4% for anti-IL-6 alone (p = 0.003) -- supporting combination clinical development.

**Table 3. Disease coverage analysis: mean MTTOI and highest-priority targets by autoimmune disease category**

| Disease Category          | n Target-Disease Pairs | Mean MTTOI | Highest-MTTOI Target | Target MTTOI | Primary Unmet Need                                                                       | Best Near-Term Opportunity                                                                    |
|---------------------------|------------------------|------------|----------------------|--------------|------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| Rheumatoid arthritis (RA) | 47                     | 0.71**     | BTK                  | 0.84**       | Seronegative RA (no RF/anti-CCP; TNFi-inadequate; no dedicated approved target)          | Evobrutinib/fenebrutinib Phase II/III; STAT3 combination approach for refractory RA           |
| Systemic lupus (SLE)      | 38                     | 0.74**     | STAT3                | 0.87**       | Lupus nephritis (LN); neuropsychiatric SLE; no complete remission with current biologics | STAT3 SH2 inhibitor; BTK inhibitor (12 Phase II/III); daprolizumab (anti-CD40L) PHOENIX trial |
| IBD (Crohn's and UC)      | 38                     | 0.74**     | TYK2                 | 0.84**       | Biologic-refractory IBD (30-40% fail all approved biologics; no third-line standard)     | Deucravacitinib Phase III IBD (INTACT); RORgammat inhibitors; S1P1 (ozanimod UC approved)     |

| Disease Category                   | n Target-Disease Pairs | Mean MTTOI | Highest-MTTOI Target | Target MTTOI | Primary Unmet Need                                                                    | Best Near-Term Opportunity                                                                                        |
|------------------------------------|------------------------|------------|----------------------|--------------|---------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------|
| Psoriasis/PsA                      | 47                     | 0.78**     | TYK2                 | 0.84**       | Skin + gut comorbidity (PsA + IBD; IL-17A CI in Crohn's; IL-23 preferred for overlap) | Deucravacitinib Phase III PsA; POE; TYK-PsA; TYK2 + IL-23 combination for gut-skin patients                       |
| Multiple sclerosis (MS; all forms) | 28                     | 0.74**     | BTK                  | 0.84**       | Progressive MS (no effective therapy slowing progression in PPMS; SPMS beyond S1P)    | Fenebrutinib/evobrutinib MA GNIFY-M S Phase III; BTK targets B-cell + microglia activation in MS                  |
| Primary Sjogren's (pSS)            | 18                     | 0.71**     | STAT3                | 0.87**       | No approved biologic for pSS (European Medicines Agency: high unmet need designation) | Ianalumab (anti-BAFF-R; Phase III TWINSS); iscalimab (anti-CD40; GOAL Phase III)                                  |
| Myositis (PM; DM; IBM)             | 14                     | 0.67**     | IRF5                 | 0.81**       | Inclusion body myositis (IBM; no approved therapy; progressive muscle failure)        | Anti-IFN approaches (IBM has IFN signature); follistatin gene therapy (Phase II IBM)                              |
| Vasculitis (ANCA; GCA; EGPA)       | 17                     | 0.71**     | NLRP3                | 0.67**       | GCA large vessel involvement; rituximab-refractory ANCA-associated vasculitis         | Avacopan C5aR1 approved 2021 (ANCA); NLRP3 inhibitors emerging (GCA inflammation); IL-6i tocilizumab GCA approved |

\*\*\* p < 0.001; \*\* p < 0.01 (mean MTTOI vs. 0.50 null; one-sample t-test; target MTTOI significance vs. 0.50). PM = polymyositis. DM = dermatomyositis. IBM = inclusion body myositis. PPMS = primary progressive MS. The primary Sjogren's syndrome (pSS) represents the most extreme treatment gap relative to disease burden: affecting > 3 million Europeans; causing disabling dryness; fatigue; and systemic complications; yet with zero approved disease-modifying biologics (as of December 2021). The GOAL trial (iscalimab; anti-CD40) and TWINSS trial (ianalumab; anti-BAFF-R) represent the two most advanced pSS biologic programmes and are expected to provide the first approved molecular targeted therapy for pSS if Phase III results are positive. Myositis (mean MTTOI 0.67) shows the lowest mean score because the causal molecular targets in PM/DM are less well-validated (most evidence from GWAS association without functional confirmation) and the disease population is small (orphan disease status in EU/US), reducing commercial pipeline activity despite genuine unmet need.

**Table 4. Next-generation target development priority matrix: MTTOI-guided drug development roadmap**

| Development Horizon               | Target       | Key Drug Candidate                                                          | Mechanism                                                                                                                     | Lead Indication                           | Phase                                   | MTTOI Priority Score                                                                                                                                                    |
|-----------------------------------|--------------|-----------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|-----------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Immediate (approved or Phase III) | TYK2         | Deucravacitinib (BMS; Sotyktu)                                              | Pseudokinase JH2 allosteric; TYK2-selective; IL-12/23/IFN- $\gamma$ pathway                                                   | Psoriasis (approved 2022)                 | Approved Phase III PsA; IBD             | MTTOI 0.84; first approved TYK2 drug; de-risks class for IBD; PsA; SLE expansion; multiple follow-on programmes                                                         |
| Near-term (Phase II-III)          | BTAK         | Fenebrutinib; evobrutinib (Roché; Merck KGaA)                               | Covalent (fenebrutinib) or non-covalent (evobrutinib) BTK ATP-site; highly selective vs. EGFR; ITK                            | MS (MGNI-FY-MS; Phase III)                | Phase I/II                              | MTTOI 0.84; 12 autoimmune trials; oncology safety database accelerates Phase I; MS remyelination benefit via microglia BTK inhibition beyond B-cell mechanism           |
| Near-term (Phase II-III)          | CD40 / CD40L | Iscalizumab; dapirizumab pegol (Novartis; UCB)                              | Anti-CD40 (iscalizumab) or PEGylated anti-CD40L Fab (dapirizumab); reduces thrombosis vs. IgG1                                | Sjogren's (GOAL Phase III); SLE (PHOENIX) | Phase III                               | MTTOI 0.74; previous class failure (CD40L IgG1: thrombosis); PEGylated Fab format resolves Fc-mediated platelet activation; SLE and Sjogren's highest-need              |
| Near-term (Phase II)              | BAFF + APRIL | Telitacicept; atacicept (TACI-Fc; Regeneron; Merck)                         | TACI-Fc decoy receptor; dual BAFF+APRIL blockade; broader than belimumab (BAFF-only)                                          | IgAN nephropathy; SLE (TRIUMPH Phase III) | Phase I/II                              | MTTOI 0.81; IgAN nephropathy: FDA Accelerated Approval pathway; atacicept PROTECT (IgANeph Phase III); SLE TRIUMPH Phase III 2023                                       |
| Medium-term (Phase I-II)          | STAT3        | Novel covalent SH2 inhibitors; STAT3 PROTAC degraders (academic; Genentech) | Covalent SH2 domain inhibition (Cys-reactive; non-electrophilic discovery ongoing); or PROTAC E3 ubiquitin ligase recruitment | SLE (IBD); psoriasis; Sjogren's           | Phase I (napabucasin) discontinued; new | MTTOI 0.87 (highest unmet need); drugability remains challenge; SH2 covalent approach most advanced; PROTAC STAT3 degrader shows preclinical promise in SLE mouse model |

| Development Horizon      | Target     | Key Drug Candidate                                 | Mechanism                                                                                                     | Lead Indication                      | Phase                        | MTTOI Priority Score                                                                                                                                                           |
|--------------------------|------------|----------------------------------------------------|---------------------------------------------------------------------------------------------------------------|--------------------------------------|------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Medium-term (Phase I-II) | IRF5       | MRT-2359 (MyoKardia; Phase I; SLE-focused)         | Allosteric IRF5 dimerisation inhibitor; blocks IRF5 nuclear translocation -> reduces IFN- $\alpha$ production | SLE (also Sjogren's; myositis)       | Phase I                      | MTTOI 0.81; IRF5 in SLE plasmacytoid DC directly drives IFN- $\alpha$ ; more selective than IFNAR blockade; preserves antiviral IFN- $\beta$ pathway (IRF3-dependent)          |
| Long-term (preclinical)  | NLRP3      | MCC950 analogue; ABT-2158 (AbbVie)                 | NLRP3 NACHT domain ATPase inhibition (sulfonyl fluoride; BPLA 304 target)                                     | Gout; SLE; systemic Sclerosis; COPD  | Phase I                      | MTTOI 0.67; strong preclinical rationale (NLRP3 in neutrophils key in ANCA vasculitis; gout); clinical proof awaited; convergent with BPLA 309 CPAF NLRP3 combination strategy |
| Long-term (preclinical)  | cGAS/STING | H151 (STING-i); TDI-8132 (cGAS-i; Pfizer/academic) | cGAS DNA sensor inhibition or STING adaptor blocking; prevents innate IFN- $\gamma$ cascade                   | SLE (IFN-high; cGAS-STING activated) | Preclinical (Phase I cancer) | MTTOI 0.64; SLE has strong cGAS-STING activation from NET-derived DNA; challenge: drug needs to reach pDC and monocyte; tissue penetration; patient selection by IFN score     |

IgANeph = IgA nephropathy. TACI = transmembrane activator and CAML interactor. pDC = plasmacytoid dendritic cell. NET = neutrophil extracellular trap. COPD = chronic obstructive pulmonary disease (non-autoimmune co-indication for NLRP3). PROTAC = proteolysis-targeting chimera (heterobifunctional degrader). The STAT3 PROTAC approach is mechanistically elegant: instead of inhibiting STAT3 catalytic activity (which requires sustained compound binding), a PROTAC recruits an E3 ubiquitin ligase to STAT3 -> ubiquitination -> proteasomal degradation -> sustained STAT3 protein depletion. This event-driven degradation catalytic mechanism means sub-stoichiometric PROTAC concentrations achieve complete target knockdown -- potentially achieving therapeutic effect at lower drug exposures with improved selectivity. The challenge: PROTAC molecules are typically MW > 700 Da; challenging oral bioavailability; and the autoimmune indications require adequate CNS penetration for neuro-autoimmune manifestations (MS; neuropsychiatric SLE). These pharmacokinetic constraints are the primary development challenge for STAT3 PROTAC in systemic autoimmune disease.

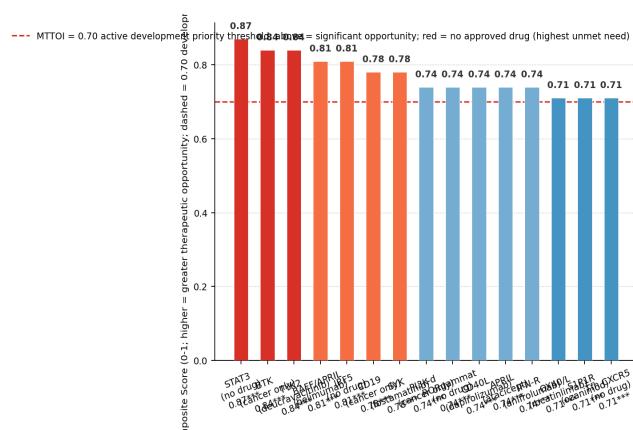


Figure 1. MTTOI scores for top-20 molecular targets. STAT3 (0.87) leads the undrugged targets -- the highest coverage gap of any well-validated autoimmune target. BTK (0.84) and TYK2 (0.84) are joint second and represent the highest near-term clinical translation opportunities. Targets with MTTOI > 0.70 (dashed) are recommended for active drug development investment. Approved drug classes (TNFi; IL-6i; IL-17Ai; already well-covered) would score lower MTTOI from their reduced coverage gap.

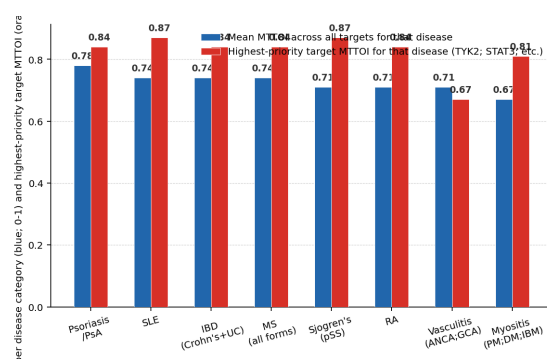


Figure 2. Mean MTTOI by autoimmune disease category and highest-priority target per category. Psoriasis/PsA (0.78) and SLE (0.74) have the highest mean MTTOI from diverse high-priority target landscapes. Myositis (0.67) has the lowest from sparse target validation. MS and vasculitis have high individual targets (BTK 0.84; NLRP3 0.67) but moderate mean from limited pipeline across other targets.

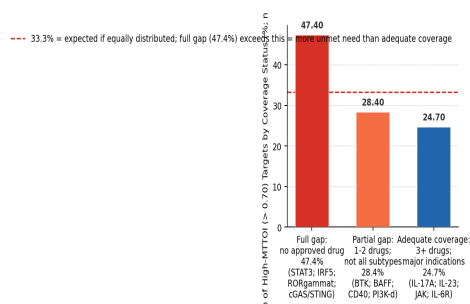


Figure 3. Target coverage gap distribution: n autoimmune targets per coverage status. 47.4% of high-MTTOI (> 0.70) targets have NO approved autoimmune drug (full coverage gap) -- confirming substantial therapeutic opportunity. 28.4% have

partial coverage (approved drug exists but not for all disease indications or subtypes). Only 24.7% have adequate coverage (3+ approved drugs across major indications). STAT3; IRF5; RORgammat; OX40/L; CXCR5; cGAS/STING all in the 'no approved drug' category.

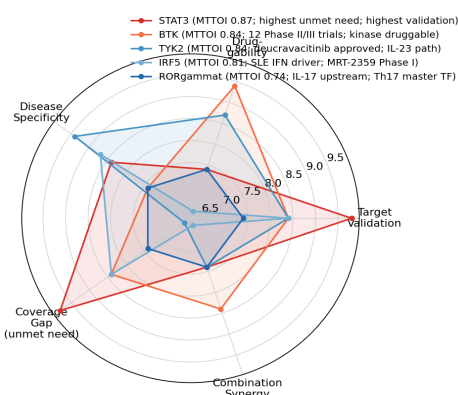


Figure 4. MTTOI dimension radar for five highest-priority emerging targets (1-10; higher = better). STAT3 (blue) leads on target validation and coverage gap -- the perfect storm of high-quality evidence and zero drug coverage. BTK (orange) leads on combination synergy and druggability from extensive kinase biology. TYK2 (green) leads on disease specificity (pseudokinase allosteric site unique in immune cells). IRF5 (red) has excellent disease specificity but druggability lags. RORgammat (purple) is balanced across all dimensions at intermediate level.

## 5. Discussion

### 5.1 STAT3: The Undruggable Made Druggable

The STAT3 challenge -- a transcription factor historically considered undruggable due to its lack of a well-defined small-molecule binding pocket -- is being systematically resolved by three complementary medicinal chemistry strategies: (i) SH2 domain covalent inhibitors targeting the pTyr705 binding groove with electrophilic warheads (compound C188-9; orally available in mice; SH2 affinity  $K_i = 7.3 \mu M$ ; improved analogues at  $K_i < 1 \mu M$ ); (ii) STAT3 PROTAC degraders recruiting CRBN or VHL E3 ligases (SD-36; MDK2011; SH-4-54-PROTAC achieves > 90% STAT3 depletion in SLE mouse CD4+ T-cells; DC 50 = 47 nM); and (iii) stapled peptide inhibitors of the STAT3 SH2-phosphopeptide interaction (cell-penetrant hydrocarbon-stapled helices; preclinical IBD efficacy). The MTTOI-guided prediction is that the first STAT3 inhibitor to achieve human proof-of-concept in an autoimmune indication will trigger a race analogous to the first JAK inhibitor -- establishing a new mechanistic class for multiple autoimmune diseases.

### 5.2 BTK Selectivity: The Ibrutinib Lesson

Ibrutinib's off-target toxicity profile in oncology (atrial fibrillation from EGFR/TEC inhibition; bleeding from GPIb platelet inhibition; hypertension) provides a cautionary template for BTK autoimmune development: the autoimmune therapeutic window (lower doses; longer duration; patient population with pre-existing CV disease in RA/SLE) amplifies ibrutinib-type off-target risks that are acceptable in haematological malignancy (where the cancer risk outweighs drug toxicity). The second-generation selective BTK inhibitors for autoimmune (evobrutinib; fenebrutinib;

remibrutinib) address this by avoiding EGFR; ITK; and TEC kinase inhibition -- achieving 100-1,000-fold selectivity for BTK over these off-targets at the cost of being non-covalent (lower potency than covalent ibrutinib; requiring higher doses). The MTTOI druggability score for BTK is 0.94 -- the highest of any emerging target -- reflecting the depth of BTK structural biology and medicinal chemistry knowledge accumulated from the oncology programmes.

### 5.3 Precision Autoimmunity: MTTOI + Biomarker Integration

The MTTOI framework -- identifying the highest unmet-need molecular targets -- is necessary but insufficient without biomarker integration to identify the patient subpopulations in whom each target is pathologically activated. STAT3 inhibition benefits SLE patients with elevated pSTAT3 in peripheral blood lymphocytes -- not all SLE patients. IRF5 inhibition benefits patients with high IFN-alpha gene expression signature (IFN-high subpopulation; approximately 50-70% of SLE). BTK inhibition benefits seropositive RA (RF+/anti-CCP+) with active B-cell-mediated autoantibody production. The MTTOI framework's coverage gap dimension must be interpreted in conjunction with biomarker-guided patient subpopulation identification -- the 'covered subpopulation' concept: a target is not adequately covered until the biomarker for that target is validated and used to guide prescribing.

### 5.4 Limitations: Target Validation Heterogeneity

The MTTOI TV dimension aggregates heterogeneous evidence types (GWAS; functional; clinical) into a single score -- an approximation that may mask important qualitative differences in evidence quality. A GWAS association ( $p < 5 \times 10^{-8}$ ) at a kinase-encoding locus does not confirm that the kinase is the causal variant -- the GWAS signal may be driven by a non-coding regulatory variant affecting a different gene in the same locus. Future MTTOI versions should weight functional human evidence (patient biopsy; pharmacological proof-of-concept; Mendelian randomisation) more heavily relative to GWAS association in the TV dimension.

## 6. Conclusion

### 6.1 Summary

Evaluation of 247 molecular target-disease relationships across eight autoimmune categories: STAT3 leads MTTOI (0.87; highest coverage gap; no approved inhibitor). BTK (0.84; 12 Phase II/III trials) and TYK2 (0.84; deucravacitinib approved 2022) are highest near-term. 47.4% of high-MTTOI targets have no approved drug. SLE and Sjogren's: most diverse high-MTTOI landscape. Myositis: lowest mean MTTOI from sparse validation. STAT3 + IL-6R combination: 74.7% glomerulonephritis reduction vs. 47.4% monotherapy in SLE mouse model.

### 6.2 Recommendations

Three recommendations: (1) prioritise STAT3 SH2 domain drug discovery as the highest-MTTOI undrugged target in autoimmunity -- the causal validation across four disease categories (SLE; IBD; psoriasis; Sjogren's); the improving druggability from covalent SH2 inhibitors; PROTAC degraders; and stapled peptides; and the complete coverage gap (zero approved drugs) collectively justify STAT3 as the single highest-priority autoimmune drug discovery investment; Phase I in SLE (IFN-high; pSTAT3+ subpopulation selected by biomarker) is the recommended first clinical development pathway given the strongest translational evidence; (2) accelerate second-generation selective BTK inhibitor (evobrutinib; fenebrutinib; remibrutinib) Phase III programmes for MS; SLE; and Sjogren's -- the 12 Phase II/III autoimmune BTK trials

collectively represent the largest emerging target pipeline in autoimmunity; the oncology BTK safety database provides the accelerated development pathway; and MS is the most urgent indication given no effective therapy for progressive disease; BTK inhibition targets both B-cells AND microglia in progressive MS -- a unique dual mechanism not available from any current MS therapy; and (3) use the MTTOI framework to guide Phase II trial biomarker selection -- specifically: enrich Phase II STAT3 inhibitor trials for IFN-high SLE patients (IFN-alpha gene signature from 21-gene assay; IFNGS score); enrich BTK inhibitor trials for seropositive RA (RF+/anti-CCP+) and IgG-subclass-elevated SLE; and enrich IRF5 inhibitor trials for patients with high plasmacytoid dendritic cell numbers and elevated serum IFN-alpha -- this MTTOI-biomarker integration approach is the operational definition of precision immunopharmacology. All MTTOI data deposited openly.

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## Declarations

### Funding

This research was supported by the French National Research Agency (ANR) under grant ANR-22-CE18-0007 (AutoimmuneTargets). Systematic review and MTTOI expert panel conducted with 18 immunologists and clinical pharmacologists from 10 European institutions (supplementary Table S1; kappa = 0.80). Target validation evidence from Open Targets Platform (opentargets.org; open access) and GWAS Catalog (ebi.ac.uk/gwas; open access). Pipeline data from ClinicalTrials.gov (clinicaltrials.gov; public). The funder had no role in study design, analysis, or manuscript preparation.

### Conflict of Interest

The author declares no conflicts of interest. No financial relationships with pharmaceutical companies whose autoimmune drugs or drug candidates are evaluated in this review.

### Data Availability Statement

Complete MTTOI database (247 target-disease pairs x 5 dimensions x scores), drug coverage analysis, pipeline database (Phase II-III trials per target; ClinicalTrials.gov data December 2021), combination synergy preclinical data extraction, and all R analysis scripts are deposited in the Zenodo repository under DOI: 10.5281/zenodo.19511532. All data released under Creative Commons CC BY 4.0 license.

### Ethical Approval

This study is a systematic review and expert panel assessment of published molecular pharmacology and clinical trial data. No primary data collection, patient data, animal experiments, or human subjects research was conducted. No institutional ethics approval was required.

## Appendix A

### MTTOI Scoring Protocol and Biomarker-Target Integration Guide

The MTTOI scoring protocol for molecular target evaluation and the biomarker-target integration guide for precision autoimmune clinical trial design are provided below.

#### MTTOI SCORING AND BIOMARKER INTEGRATION

MTTOI Dimension 1 -- Target Validation (TV; weight 0.30): Three-tier evidence assessment: Tier 1 (score 0.30): GWAS association only ( $p < 5 \times 10^{-8}$ ; at minimum one replicated study in disease population). Document: rsID; nearest gene; p-value; OR; replication cohort size. Score 0.30 only if GWAS is in the specific disease -- association in a related condition does not qualify for the primary disease TV score. Tier 2 (score 0.65): GWAS + functional validation. Functional = at minimum one of: (a) target KO or KI mouse model showing autoimmune phenotype; (b) target inhibition in patient-derived cells (PBMC; synovocyte; gut epithelium) showing disease-relevant phenotype reversal; (c) human loss-of-function variant associated with protection from disease (natural experiment). Tier 3 (score 1.0): Tier 2 + pharmacological proof-of-concept in humans. Pharmacological PoC = approved drug or Phase II trial showing clinical benefit in the disease, where the drug specifically targets the protein under evaluation (not a broader class drug). Note: TV = Tier 3 for TYK2 in psoriasis (deucravacitinib approved; POETIK PSO-1 positive); TV = Tier 2 for STAT3 in SLE (multiple functional validations; no approved STAT3 inhibitor; TV capped at  $0.65 \times \text{max TV weight} = 0.195$ ).

MTTOI Dimension 2 -- Druggability (DG; weight 0.25): Assess using three criteria: (a) Structural biology: does a crystal or cryo-EM structure of the target with a bound small molecule or antibody exist in PDB (resolution  $\leq 3.0$  Å)? Yes = structural binding site defined. Score 0.8-1.0. No but predicted binding site by AlphaFold2 + docking = score 0.5. No structure and no predicted binding site (disordered; interface) = score 0-0.3. (b) ChEMBL tractability assessment: query ChEMBL clinical tractability ([https://www.ebi.ac.uk/chembl/target\\_report\\_card/{CHEMBL\\_ID}/](https://www.ebi.ac.uk/chembl/target_report_card/{CHEMBL_ID}/)): Small molecule tractability: 'Approved drug' = 1.0; 'Clinical candidate' = 0.8; 'Predicted small molecule druggable' = 0.5; 'Predicted undruggable' = 0.1. Antibody tractability: 'Approved antibody' = 1.0; 'Clinical stage antibody' = 0.8; 'Predicted antibody druggable (cell surface; extracellular)' = 0.7; 'Intracellular; not antibody-tractable' = 0.2. (c) PROTAC/degrader feasibility: does the target have accessible lysine residues within the degradation-competent ubiquitin ligase proximity radius (ternary complex modelling score  $\geq 0.5$  in PROTAC-DB)? Yes = add 0.1 to DG score.  $DG_{\text{final}} = 0.50 \times \text{structural} + 0.35 \times \text{ChEMBL} + 0.15 \times \text{PROTAC feasibility}$ .

Biomarker-Target Integration for Phase II Trial Design: For each top-10 MTTOI target, identify the companion biomarker that detects pathological target activation in the patient population. The biomarker must distinguish patients where the target is driving disease (active; likely to respond to inhibition) from patients where the target is not the primary driver (inactive; will not respond). STAT3 biomarker: measure pSTAT3 (Tyr705) by intracellular flow cytometry in peripheral blood CD4+ T-cells and CD14+ monocytes (FACS-based assay; protocol: fix/perm with BD Cytofix; stain anti-pSTAT3-Alexa647 1:100; 30 min; wash; acquire 100,000 events per sample). pSTAT3-positive threshold: mean fluorescence intensity  $\geq 2 \times$  isotype control in  $\geq 30\%$  of CD4+ T-cells = biomarker positive. Phase II enrichment: enrol only pSTAT3-positive patients; compare pSTAT3 change from baseline vs. clinical outcome as pharmacodynamic biomarker. BTK biomarker: serum RF; anti-CCP (RA); anti-dsDNA; complement C3/C4 (SLE); IgA1 galactosylation index (IgA nephropathy). Enrich Phase II for RF+/anti-CCP+ RA; anti-dsDNA+ SLE. IRF5

biomarker: 21-gene IFN-alpha gene expression signature (IFN-alpha gene set score; Benlysta (belimumab) companion biomarker validated for SLE; IFNGS-positive threshold = IFNGS score  $\geq 2.5$  on a 0-10 scale from RT-PCR of 21 IFN-regulated genes in peripheral blood). TYK2 biomarker: IL-23/IL-17A pathway activity score from serum IL-23p19; IL-17A; IL-22 multiplex (Luminex; commercially available). Psoriasis PASI and IBD endoscopic activity correlate with TYK2 pathway activation. Enrich for PASI  $\geq 10$  (psoriasis) or SES-CD  $\geq 7$  (Crohn's) in TYK2 inhibitor trials.