IL-23R–p19 Inhibition for Psoriasis

Small-molecule discovery strategies and target product profile

Public information reviewed through 4 September 2026.

Executive assessment

Recommendation: pursue a gated hit-discovery program, not candidate nomination. The IL-23 pathway is strongly validated in plaque psoriasis by human genetics, anti-p19 antibodies and an orally active IL-23R antagonist peptide. The remaining uncertainty is chemical: can a *nonpeptidic* molecule disrupt the extracellular p19–IL-23R interaction selectively, with sustained free exposure in skin? An oral route by itself is no longer sufficient differentiation.[1–5]

The most actionable structural opportunity is a **peptide-induced pocket on p19**, resolved in 8UUI. A 2025 study combined a peptide co-structure, peptide optimization, a fluorescence-polarization (FP) screen and orthogonal support for four weak nonpeptidic IL-23 binders. This improves the case for starting discovery; it does not establish potent small-molecule antagonism. The pocket is offset from the native receptor-binding surface, so a compact binder might occupy it without blocking receptor recruitment.[6]

Table 1. Evidence strength and the decisions it supports.

Evidence layer	Established observation	Remaining gap
Human target validation	Genetics, antibody efficacy and oral receptor-peptide efficacy support IL-23 inhibition.	Does not establish nonpeptidic tractability or safety.
Structural opportunity	Native receptor complexes and the peptide-induced p19 pocket are experimentally resolved.	No co-structure of the reported nonpeptidic fragments; pocket occupancy is not equivalent to antagonism.
Chemical starting points	Four fragment hits have reported IL-23 binding support; SI values are 180–434 μM.	Weak affinities, assay inconsistencies, mixtures and incomplete mechanistic characterization.
Program readiness	Reagents, structural templates and assay concepts are available.	Human-cell selectivity, oral PK, skin exposure and efficacy remain to be demonstrated.

Evidence-quality finding. The 2025 paper's main text gives fragment K_D values of 180 μM–1.95 mM, while Figure 4E and supporting Table S2 list 180–434 μM for the four supported hits. The discrepancy is retained rather than silently reconciled. Neither range justifies a lead-stage designation.[6]

Priority order. (1) Reproduce and expand cytokine-directed fragment binding at the induced pocket; (2) test receptor-side, hotspot-mimetic chemistry in parallel at smaller scale; (3) investigate alternative allosteric pockets only when supported by solution-state data. Advance only when direct binding, receptor displacement and selective human-cell signaling inhibition agree.

Proposed product concept. An oral, systemically available, reversible nonpeptidic inhibitor for adults with moderate-to-severe plaque psoriasis, ideally once daily, with IL-12 sparing and a low monitoring burden. All numerical TPP and candidate-selection thresholds below are *proposed program objectives*, not observed properties of a molecule or predictions of clinical success. Table 1 summarizes the distinction between target validation and modality validation.

1 Target biology and disease rationale

IL-23 is a secreted, disulfide-linked heterodimer of p19 (*IL23A*; Q9NPF7) and p40 (*IL12B*; P29460). The signaling receptor comprises IL-23R (Q5VWK5) and IL-12Rβ1 (P42701). The p19-facing IL-23R arm provides cytokine specificity; p40 engages the shared receptor arm. IL-12 instead contains p35/p40 and uses IL-12Rβ1/IL-12Rβ2. Thus, p19–IL-23R blockade offers a rational route to preserve IL-12, whereas p40 blockade does not.[7, 8]

IL-23R-associated JAK2 and IL-12Rβ1-associated TYK2 drive downstream signaling, notably STAT3 activation and pathogenic type-17 effector responses. In psoriasis, these responses contribute to IL-17A/F- and IL-22-dependent keratinocyte activation and epidermal inflammation. IL-23 is important for maintenance and effector function of these responses; it should not be described as the sole initiator of human Th17 differentiation. Figure 1 locates the intended intervention relative to downstream small-molecule mechanisms.[2, 9]

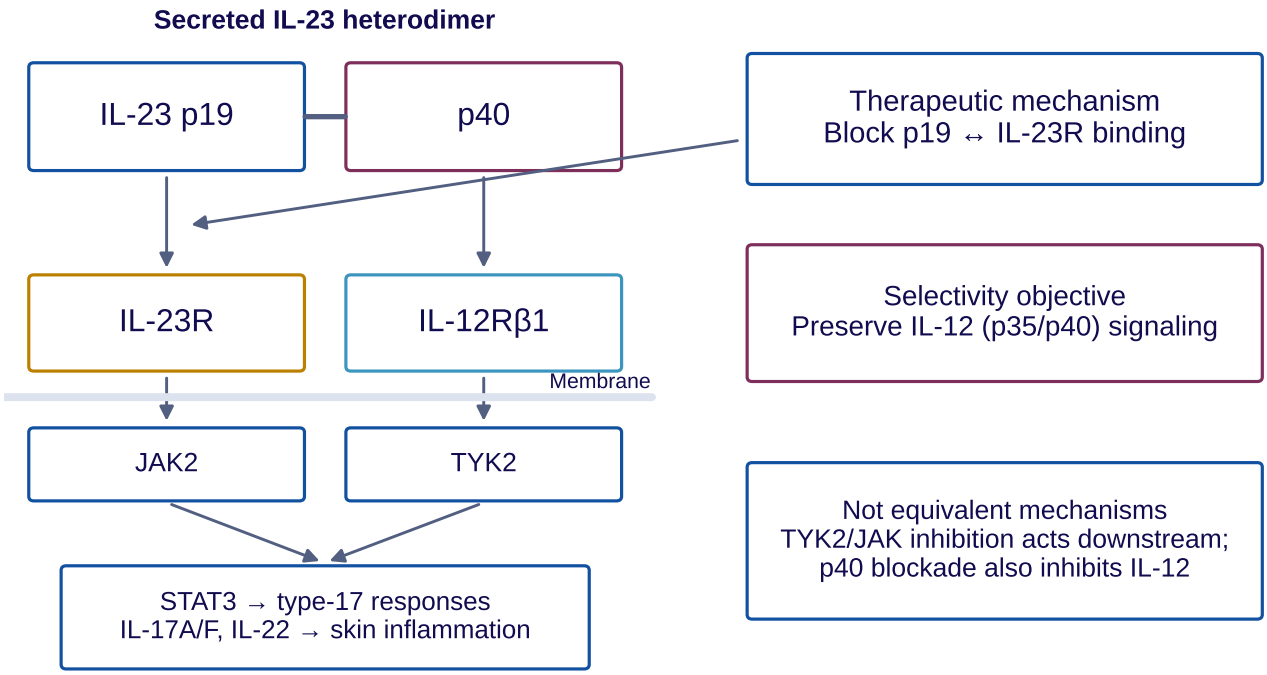

Figure 1. Selective extracellular blockade within the IL-23 pathway. Schematic, not a membrane-scale structural model. The target is binding between p19 and IL-23R, either through a ligand on p19 or on the receptor. Inhibiting TYK2/JAK signaling or reducing IL-23 production is mechanistically distinct.

1.1 What human genetics does and does not establish

A psoriasis association study in 1,446 cases and 1,432 controls identified IL23R and confirmed IL12B susceptibility loci. Functional studies of the protective IL23R R381Q variant showed reduced IL-23-induced STAT3 phosphorylation and IL-17A production in human Th17 cells. This supports the therapeutic direction of pathway attenuation. R381Q is not an extracellular binding-pocket residue and is not a direct blueprint for interface inhibitors. Genetic association also does not specify a clinically effective occupancy threshold.[1, 2]

1.2 Safety boundary

IL-12 sparing avoids an additional immunological mechanism, but does not eliminate IL-23-dependent host-defense risk. Human studies published in 2025–2026 associate homozygous hypomorphic IL23R variants with chronic mucocutaneous candidiasis and tuberculosis susceptibility. These lifelong genetic contexts differ from reversible drug exposure and cannot quantify treatment risk. They nevertheless argue for explicit fungal and mycobacterial risk assessment rather than a claim of infection-free selectivity.[10, 11]

2 Clinical benchmarks and competitive positioning

Table 2 gives source-checked benchmarks. PASI90 means a reduction of at least 90% in a patient's Psoriasis Area and Severity Index; it does *not* mean that 90% of patients are clear. Differences in population, endpoint handling and trial design prevent an efficacy ranking across unrelated trials.

Table 2. Published psoriasis benchmarks at week 16; active treatment versus placebo.

Therapy / modality	Trial and study dose	Endpoint / response	Interpretation
Risankizumab anti-p19 antibody	UltIMMa-1/-2; 150 mg SC, weeks 0 and 4	PASI90: 75.3/74.8% vs 4.9/2.0%	Strong p19 target validation; injection and long-lived biologic exposure.[3]
Guselkumab anti-p19 antibody	VOYAGE-1; 100 mg SC, weeks 0 and 4	PASI90: 73.3% vs 2.9%	Independent confirmation of p19-directed efficacy.[12]
Icotrokinra oral IL-23R **peptide**	ICONIC-LEAD; 200 mg once daily	PASI90: 50% vs 4%; IGA0/1: 65% vs 8%	Validates oral extracellular receptor antagonism, not nonpeptidic chemistry.[4]
Icotrokinra oral IL-23R **peptide**	ICONIC-ADVANCE-1/-2; 200 mg once daily	PASI90: 55/57% vs 4/1%	Active-comparator trials also reported superiority over deucravacitinib.[13]
Deucravacitinib oral TYK2 inhibitor	POETYK PSO-1; 6 mg once daily	**PASI75**: 58.4% vs 12.7%	A nonpeptidic oral competitor, but intracellular and not a direct p19–IL-23R blocker.[14]

2.1 Current status and what now constitutes differentiation

Icotrokinra (JNJ-77242113; JNJ-2113) is an orally administered receptor-binding peptide. A June 2026 peer-reviewed first-approval review reports US approval as ICOTYDE in March 2026 for moderate-to-severe plaque psoriasis in adults and eligible adolescents. This status was checked against that publication; direct regulator and current-label access was unavailable. The exact current label and non-US status require a separate regulatory refresh. Describing the program as only a phase-2 proof of concept would be outdated.[5]

The 2026 ICONIC-ADVANCE report supports durability through one year, but placebo and active-control crossover mean that the week-52 results are not a continuing randomized comparison. An August 2026 pooled safety publication included 2,400 exposed participants and 1,840 participant-years through one year. Longer-term and rare-event risks remain distinct from short-term tolerability.[15, 16]

For a new nonpeptidic inhibitor, credible differentiation would therefore combine oral convenience with at least one of: stronger clearance, more reliable exposure without food restrictions, lower dose/tablet burden, simpler manufacturing and cost, or a demonstrably favorable long-term benefit–risk profile. None follows automatically from smaller molecular size. Biologic-like efficacy is a development aspiration, not an inference from binding potency.

2.2 A useful pharmacology control, not a small-molecule template

Published JNJ-77242113 data report IL-23R $K_D = 7.1$ pM, proximal human-cell $IC_{50} = 5.6$ pM and psoriasis whole-blood functional $IC_{50} = 9$ pM, with IL-12 sparing. These are assay-specific peptide benchmarks. They demonstrate that selective systemic pathway pharmacodynamics can be measured; they should not be imposed as the initial potency requirement for fragments or treated as evidence that an oral nonpeptide can reproduce the peptide's exposure.[9]

3 Structural landscape and targetable surfaces

3.1 Experimental templates and construct limitations

Table 3 selects structures that distinguish native-like cytokine geometry, receptor recognition and inhibitor-induced rearrangement. The complete downloaded inventory includes additional antibody, nanobody and scaffold-protein complexes. None should be described as an experimentally solved drug-like nonpeptidic inhibitor complex.

Table 3. Selected human IL-23 structural templates. Author chain identifiers are used. Resolutions and construct features were checked against public coordinate records.

PDB	Method / resolution	Contents and design use	Key qualification
5MXA	X-ray 2.50 Å	Unliganded IL-23: A, p40; B, p19. Baseline for peptide-induced changes.	Receptor-free heterodimer, not isolated p19; unresolved loops remain.[7]
5MZV	X-ray 2.80 Å	A, p40; B, p19; C, IL-23R; D, nanobody 22E11. Native p19–receptor contact template.	Crystallization nanobody and truncated receptor ectodomain; not a full signaling complex.[7]
6WDQ	X-ray 3.40 Å	A, p40; B, p19; C, IL-23R; D, IL-12Rβ1. Demonstrates the shared-receptor recognition arm.	Only D1 of IL-12Rβ1 is resolved; IL-23R contains L310P. No membrane or intracellular domains.[8]
8OE4	Cryo-EM 3.60 Å	Complete folded-domain extracellular architecture; p19 B, p40 A, IL-23R C, IL-12Rβ1 D.	Engineered pre-dimerized fusions; p40 N303D. IL-23R 317–353 and fusion segments are unmodeled. No membrane/JAK machinery.[17]
8CR8	X-ray 2.00 Å	Receptor-free IL-23; A, p40; B, p19. Additional cytokine conformer for comparison.	p40 N303D and unresolved p19 loops; do not treat as a complete wild-type reference.[17]
8UUI	X-ray 2.43 Å	A, p40; B, p19; D, cyclic peptide 23–446. Induced-pocket template for cytokine-directed discovery.	Peptide, not small-molecule complex. p19 47–67 and 138–153 are unresolved; surface geometry at these gaps is uncertain.[6]

3.2 What to preserve in structure-based work

The p19 subunit is a four-helix cytokine bundle, whereas IL-23R uses its N-terminal immunoglobulin-like D1 domain for the main cytokine interface. Native IL-23R contacts also include a smaller p40 contribution, so an isolated p19 surface is an incomplete representation of the ligand. Soluble ectodomain structures omit membrane context and receptor conformational constraints.[7, 8]

Glycosylation and construct context require deliberate controls, especially on p40 and IL-23R. For example, 8UUI resolves a p40 Asn222 glycan, but this does not constitute a complete native glycan model. The 2025 work used a glycosylation-restricted expression system. Compare native-like and structural-grade reagents experimentally rather than assuming that an accessible surface in a stripped coordinate model is exposed on cells.[6]

For the main p19/IL-23R structures above, the interface residues discussed here use human UniProt precursor numbering. In 5MZV, p19 chain B and receptor chain C author numbers match that numbering at the interface. Older structures can use mature-chain numbering; coordinate indices must not be transferred between entries without mapping.

3.3 Native interface versus induced pocket

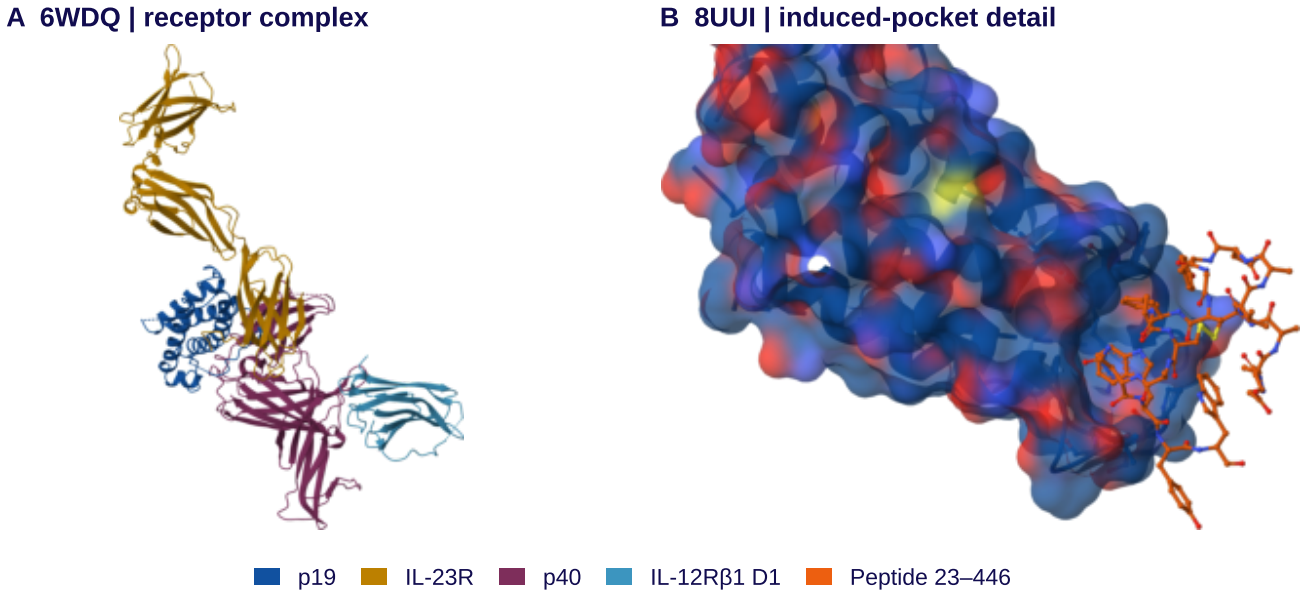

Figure 2. Two complementary experimental templates. **A:** 6WDQ, a crystallographic extracellular receptor complex: p19, blue; p40, purple; IL-23R, gold; IL-12Rβ1 D1, light blue. It is not a full membrane receptor model. **B:** 8UUI, p19 with cyclic peptide 23–446, orange carbons; p40 omitted for clarity. The translucent surface uses only resolved p19 atoms; N/O/S retain element colors. Missing loops can create artificial openings and are not validated pockets. Independent structures are not superposed. Images generated from public coordinates in the molecular viewer.

Figure 2 distinguishes native receptor recognition near Trp156 from the offset, induced 23–446 pocket. Peptide bulk appears to contribute to receptor exclusion; a smaller ligand may preserve binding but lose antagonism. Human single-residue dependence cannot be inferred from the mouse hotspot experiments.[6, 7, 18]

Table 4. Geometric contacts versus functional evidence. Distances are new measurements from 5MZV, model 1, chains B/C. Mutagenesis results are species- and assay-dependent.

Human p19	IL-23R contacts $\leq$4.0 Å	Functional interpretation
Trp156	Ser98, Gly116, Lys117, Asp118; minimum 3.15 Å	Mouse W157A loses binding/signaling and skin-inflammatory activity. Human W156A retains signaling in engineered human-receptor cells; W156A/L160E disrupts it. Not a universal single-residue knockout.[7, 18]
Leu160	Ile28; 3.91 Å	Mouse L161E loses measurable BLI binding but retains impaired cellular activity. Human double-mutant evidence supports a distributed interface.[7, 18]
Lys164	Gly24, Ile25, Asn27; minimum 2.62 Å	Mouse K165S moderately impairs binding; a contributory polar contact rather than a uniquely dominant anchor.[7]
Leu56	Thr102, Gln110, Glu111; minimum 3.33 Å	Published mouse L56E retains near-wild-type binding. Local sequence alignment permits mouse L56/L57 mapping; the experimental designation is retained.[7]

The human counterevidence used engineered Hyper-IL-23 and Ba/F3 receptor systems, not primary human cells. It motivates native human-reagent confirmation rather than a universal energetic assignment.[18] At 4.0/5.0 Å, the interface has 31/58 residue pairs (15/19 p19; 18/24 receptor residues). Half-total protein-only SASA loss is 891 Å^2 (total 1,783 Å^2), not a pocket volume or binding energy. Table 4 separates geometry from function.

4 Chemical evidence: promising, but still at hit level

4.1 The induced p19 pocket is the best-supported starting point

Lecomte and colleagues resolved IL-23 with the 20-residue disulfide-cyclized peptide 23–446 at 2.43 Å (8UUI). The peptide-bound structure differs from unliganded IL-23 in loop Thr110–Pro120 and several helices. Peptide Trp18 occupies the deepest region near p19 Arg162; Tyr10/Phe14 contact the Phe163 region, with additional backbone interactions near Ser114 and Leu116. These observations motivate aromatic anchor and polar-rim designs, but are not yet a validated nonpeptidic pharmacophore.[6]

Peptide optimization produced peptide 14 (K_D = 16 nM; PPI IC_{50} = 64 nM) and peptide 15 (K_D = 20 nM; PPI IC_{50} = 28 nM). Both remain peptides. Their success supports energetic tractability of the site and enables displacement assays; it does not establish oral absorption or small-molecule efficacy.[6]

Table 5. Nonpeptidic IL-23 fragment hits: values in supporting Table S2 and Figure 4E of Lecomte et al. (2025). These are binding results, not cellular inhibition potencies.

Hit	Enamine identifier	MST K_D	Quality and interpretation
1	Z3060590163	200 μM	Intrinsic fluorescence; apparent FP inhibition exceeded 100%. Spectral controls reported; independent confirmation remains essential.
2	Z4158155057	434 μM	Diastereomeric mixture; affinity approaches the maximum MST compound concentration.
3	Z7611593044	Not confirmed	No DSF/MST binding support; exclude from the validated-hit count.
4	Z7611605541	180 μM	Pyrazole tautomer assignment and two HPLC peaks with the same mass require chemical-resolution work.
5	Z3383056062	289 μM	Diastereomeric mixture; determine which component carries activity.

4.2 A validation issue that should determine the first experiments

The pilot screen tested 12,800 compounds at 9.4 μM. Binding support for hits 1, 2, 4 and 5 came from MST and downward DSF shifts; receptor counterscreens were negative. As shown in Table 5, the main-text range (180 μM–1.95 mM) conflicts with the figure/SI values (180–434 μM). MST tested up to 500 μM, limiting saturation for the weakest hits.[6]

A simple consistency calculation gives $[L]/(K_D + [L])$ = 2.1–5.0% occupancy at 9.4 μM for K_D = 434–180 μM. This is much lower than the reported approximately 37–45% FP effects of hits 2/4/5. Different assay conditions, tracer competition and possible non-ideal behavior mean occupancy is *not* a prediction of FP inhibition; the mismatch is a reason to repeat experiments, not proof of false binding. Downward DSF shifts can also reflect destabilization rather than productive inhibition.

Decision implication. Repurchase/resynthesize the supported fragments, verify identity and purity, resolve mixtures where possible, then require label-free SPR and ligand-observed NMR with solubility, aggregation and fluorescence controls before committing to medicinal chemistry. No fragment co-structure, definitive p19 site map, human-cell potency, oral PK or psoriasis efficacy is established by this study.

5 Discovery strategies and structural design priorities

Table 6 ranks strategies by current experimental support rather than docking score. The core design problem is to obtain enough interaction energy and steric or conformational leverage to prevent receptor recruitment without simply making a large, insoluble mimic of the peptide.

Table 6. Ranked structural strategies for nonpeptidic discovery. All work packages are proposed.

Priority / site	Design and screening approach	Required proof / principal failure mode
1. Induced p19 pocket	Reconfirm published fragments; screen diverse fragments by NMR/SPR plus peptide-FP displacement. Use 8UUI and unliganded structures as an ensemble. Grow aromatic anchors toward the receptor-occluding rim; optimize polar contacts and 3D shape.	Co-structure or HDX/NMR site support, followed by native IL-23–IL-23R inhibition. A small ligand may bind the pocket without sterically excluding the receptor.
2. Receptor D1 surface	Search for nonpeptidic mimics of the p19 Trp156-centered recognition element. Use receptor-directed display/DEL or fragment screening with peptide and cytokine competition. Consider nonpeptidic macrocycles only with a credible oral-property path.	Direct receptor binding, native cytokine competition and no partial agonism. Peptide epitopes and binding energy may not transfer to a compact scaffold.
3. Peptide-informed scaffold replacement	Reduce the 23–446 contact network into constrained, nonpeptidic scaffolds; preserve geometry of productive anchors rather than sequentially deleting residues.	Define modality explicitly. A shortened cyclic peptide is still a peptide; maintaining affinity alone is insufficient.
4. New allosteric pockets	Probe solution ensembles of intact IL-23 or IL-23R; prioritize pockets reproducibly connected to loss of receptor assembly. Use HDX, NMR and functional mutations.	Demonstrate allosteric antagonism experimentally. Predicted cavities, receptor stabilization or MD-open states do not prove inhibition.
Deprioritize: p40/shared arm	Avoid primary screening aimed at p40–IL-12Rβ1 or generic cytokine destabilization.	Risks loss of IL-12 sparing; may suppress IL-23 but fails the intended selectivity mechanism.

5.1 A disciplined computational contribution

Use experimental structures first. Prepare native, peptide-bound and receptor-bound conformers separately; preserve disulfides and investigate nearby glycans rather than indiscriminately deleting them. Unresolved loops need explicit uncertainty ensembles. A cavity next to a missing segment is not evidence of a druggable cryptic pocket.

Apply pocket characterization and ensemble docking to *prioritize testable analogues*, not to declare binding. Once a reliable co-complex and a congeneric active series exist, restrained pose exploration and relative free-energy calculations may support optimization. Before then, predicted affinities and long MD residence in a starting pose are weak evidence. Proposed mixed-solvent MD should be followed by solution-state validation of any new pocket. No docking, MD or free-energy calculations were executed for this assessment.

5.2 Exclude pathway-active compounds from the direct-binding count

A DT40 reporter screen yielded IL-23-pathway inhibitors, but reporter activity does not establish binding to extracellular p19 or IL-23R. A 2026 Inh-31 report includes HEK-Blue cellular screening plus computational work; the accessible abstract did not establish a quantitative direct-binding mechanism. ZINC20572287/r3-7 remains computational evidence in the reviewed source. TYK2/JAK, RORγt, transcriptional or IL-23-production inhibitors are separate mechanisms, not direct PPI validation.[19–21]

6 Assay cascade: bind, displace, function, translate

The cascade in Fig. 3 is designed to falsify false-positive mechanisms early. Use intact, mammalian-expressed human p19:p40 as the primary cytokine reagent, with monodispersity and biological activity confirmed. Isolated p19, Fc fusions and immobilized ectodomains can be useful secondary tools but may not preserve native conformation or avidity.[6, 22]

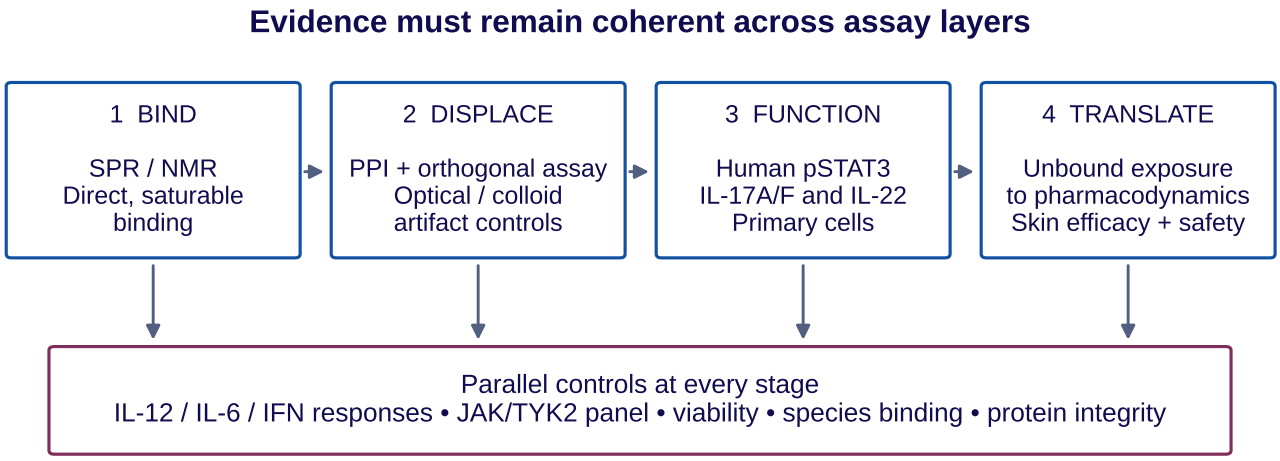

Figure 3. Proposed evidence chain for a selective extracellular inhibitor. Progression requires concordant binding, receptor displacement, primary-cell inhibition and exposure-linked pharmacodynamics. Counterassays run in parallel rather than only after potency optimization.

Table 7. Mechanistic assay package and interpretation controls.

Layer	Preferred measurement	Essential discrimination
Reagent / binding	SEC and activity QC; SPR with alternative orientation; ligand-observed NMR; concentration series and stoichiometry.	Aggregation, detergent sensitivity, label effects, compound solubility, redox/disulfide disruption, p40-only binding and nonspecific protein binding.
PPI displacement	Native IL-23–IL-23R interaction by two formats, e.g. SPR competition and TR-FRET/NanoBRET. Determine maximal inhibition and cytokine-concentration dependence.	Tag-binding, optical effects, ligand depletion and preincubation artifacts. Include peptide-FP for site triage, not as the only proof of receptor blockade.
Human pharmacology	Early IL-23-induced pSTAT3 in responsive primary human cells; later IL-17A/F and IL-22. Multiple donors, then whole blood and psoriasis-relevant tissue.	IL-12–pSTAT4/IFNγ, IL-6–pSTAT3, type-I IFN responses, cell viability and JAK/TYK2 inhibition. No signal increase or receptor agonism.
Translation	Species-matched binding and cellular assays; plasma/skin free exposure, ex vivo cytokine challenge and skin biomarkers.	A systemic anti-inflammatory effect is not proof of p19–IL-23R blockade. Connect dose, unbound exposure, proximal PD and tissue efficacy.

Table 7 deliberately separates **cytokine-directed** and **receptor-directed** competition. An IL-23-binding small molecule need not displace a fluorescent peptide already bound to IL-23R. For example, the P630-derived receptor probes described by Lay et al. are appropriate for receptor-site pharmacology, whereas the Lecomte peptide-FP probe binds IL-23. Use the matching probe and retain a direct native cytokine–receptor assay as the mechanistic reference.[6, 22]

Measure concentration–response curves at documented cytokine and receptor concentrations; report IC_{50}, IC_{90}, Hill slope and maximal effect separately. Do not equate K_D with IC_{50} or use a fixed IC_{90}/IC_{50} conversion without validating the curve shape. Mutations used to establish mechanism must preserve folding, expression and baseline receptor responsiveness; otherwise resistance or lost activity is uninterpretable.

7 Target product profile

7.1 Clinical-facing product objectives

Scope: proposed adult systemic product, assessed at the preclinical stage. Table 8 defines the intended therapeutic profile, not a clinical prediction or regulatory commitment. A separate topical program would address a different population and would require demonstrable penetration to dermal immune-cell compartments; low systemic exposure alone would not validate efficacy.

Table 8. Proposed TPP for a nonpeptidic p19–IL-23R inhibitor. Numerical values are program aspirations, not observed efficacy.

Attribute	Minimum development objective	Preferred profile / preclinical implication
Indication / patients	Adults with moderate-to-severe plaque psoriasis eligible for systemic therapy; monotherapy positioning.	Effective in high-impact sites and systemic-treatment-experienced patients. Pediatric expansion is a later decision, not presumed from peptide approval.
Modality / mechanism	Chemically defined nonpeptidic inhibitor directly binding IL-23 or IL-23R and blocking their interaction.	Reversible selective extracellular action; no cytokine-production suppression or kinase inhibition needed for efficacy.
Route / regimen	Oral formulation; at most twice daily. Working total-dose feasibility target $\leq$300 mg/day.	Once daily, ideally $\leq$100 mg/day, without substantial food effect. Dose requires human PK projection; the numbers are formulation goals.
Efficacy benchmark	Future week-16 PASI90 response around $\geq$50%, with meaningful IGA and patient-reported benefit, in an appropriate controlled trial.	PASI90 $\geq$70–75% plus deep clearance and itch/QoL benefit. Direct comparisons are required; these are not preclinical go/no-go endpoints.
Onset / durability	Clinically meaningful benefit during induction and maintenance without unacceptable rebound.	Early benefit by weeks 2–4 and durable year-long control; establish sustained pathway coverage rather than relying on a peak exposure.
Safety / monitoring	Benefit–risk suitable for chronic immune-mediated disease; no broad JAK-like pharmacology, unacceptable organ toxicity or severe off-target liability.	Low routine monitoring burden; preserve IL-12. No claim of zero infection or malignancy risk; anticipate TB/infection screening consistent with final clinical evidence.
Convenience / access	Stable, manufacturable oral dosage form with feasible adherence and manageable drug interactions.	Room-temperature solid dose, low pill burden, scalable synthesis and cost advantage versus injectable or peptide modalities.
Comorbidities / scope	Avoid assuming efficacy in psoriatic arthritis or other inflammatory diseases.	Expansion only after independent exposure, mechanism and efficacy evidence; no extrapolation to axial disease.

These targets reflect an increasingly demanding market: oral icotrokinra already provides approximately 50–57% week-16 PASI90 in the cited phase-3 trials, while established p19 antibodies reach approximately 73–75%. Matching an endpoint in a different trial is not evidence of clinical equivalence. A program with weaker efficacy would need a clear compensating advantage in safety, convenience, cost or patient segment.[3, 4, 12, 13]

7.2 Preclinical candidate-selection profile

The thresholds in Table 9 are stricter than fragment-discovery gates and are not regulatory standards. Revisit them with exposure–response data. The exposure-based counterpathway gate is mandatory: an IC_{50} selectivity ratio alone does not establish sparing at an efficacious dose.

Table 9. Proposed candidate-selection criteria. All thresholds are prospective program choices.

Attribute	Minimum working gate	Preferred / decision logic
Mechanism	Two orthogonal direct-binding methods plus native PPI inhibition, with mapped binding site and no artifact explanation.	Co-structure and mechanistically informative, folding-competent mutants; reproduce with untagged native reagents.
Affinity / PPI	Human target K_D $\leq$100 nM; PPI IC_{50} $\leq$100 nM in a defined assay.	K_D $\leq$10 nM, PPI IC_{50} $\leq$30 nM; reconcile kinetics, cytokine concentration and functional effect.
Human-cell potency	Primary-cell IL-23 pSTAT3 IC_{50} $\leq$100 nM and $\geq$90% maximal inhibition without cytotoxicity.	IC_{50} $\leq$10 nM with a reproducible measured IC_{90} across donors and downstream cytokines. Confirm whole-blood activity.
Selectivity	$\geq$30-fold functional separation from IL-12, IL-6 and type-I IFN responses; no relevant JAK/TYK2 activity.	$\geq$100-fold as a screen; jointly require $<$ 20% IL-12/IL-6/IFN inhibition at projected free C_{max} and sustained exposure (preferably $<$ 10%). Ratios alone do not ensure sparing.
Free exposure / PD	Trough unbound concentration at the target compartment covers matrix-adjusted cellular IC_{90}, or sustained PD demonstrates an alternative coverage requirement.	Approximately 3-fold coverage as a robustness objective; quantify skin distribution and duration, not merely total plasma or homogenate concentrations.
Oral PK	Reproducible exposure in a pharmacologically relevant species; dose projection supports the TPP.	Bioavailability $\geq$40% as a useful goal ($\geq$20% working floor), low/moderate clearance and a half-life compatible with once-daily dosing. Favor exposure over any isolated PK number.
Physicochemistry	Adequate solubility and stability at assay and dosing conditions; no aggregation.	Soft design window: MW $\leq$500 Da (up to 650 with evidence), $logD_{7.4}$ about 1–3.5. Permeability/solubility must support absorption; extracellular action does not remove the oral-absorption requirement.
In vivo proof	Exposure-dependent improvement in an IL-23-driven skin model with matched proximal PD and tissue biomarkers.	Working efficacy target $\geq$50% reduction in disease-induced skin thickening; $\geq$70% preferred, benchmarked to a species-active antibody. Not a PASI surrogate.
Safety / DDI	Negative genotoxicity package as appropriate; no dose-limiting organ liability; assessed CYP/transporter and reactive-metabolite risks.	hERG margin $\geq$30-fold versus projected free C_{max} and exposure margins around 10-fold at repeat-dose NOAEL as working goals; refine by mechanism and relevant guidance.
Developability	Defined stereochemistry, purity and solid form; scalable synthesis and stable oral formulation.	Controlled impurities, suitable salt/form, low food effect and manufacturable cost profile.

Exposure principle. For plasma, $C_{u,p} = f_{u,p}C_{\text{total},p}$. Use a measured or justified unbound tissue distribution relationship, $C_{u,\text{skin}} = K_{p,uu}C_{u,p}$, as a model to test—not an assumption that a skin-homogenate ratio measures extracellular free drug. Binding kinetics and persistent PD may alter the necessary trough requirement. High plasma binding is not automatically disqualifying if free exposure is sufficient; low total plasma concentration is not automatically inadequate.

8 Translation, safety and staged decisions

8.1 Human-relevant proof before animal efficacy

Prioritize primary human pharmacology and confirm cytokine/receptor cross-reactivity before choosing animal species. The peptide precedent demonstrates IL-23 skin pharmacology in rats, but species activity of one peptide cannot be transferred to new p19-binding chemistry. Human-cytokine challenge, a validated species-active surrogate or humanized systems may be necessary.[9]

Use an IL-23-driven skin-inflammation model to connect exposure to epidermal thickness, histology and IL-17A/F/IL-22 biomarkers. Include vehicle, a species-active anti-p19 or anti-IL-23R control, a matched inactive analogue and a dose/exposure range. Randomize, blind histology and predefine endpoints and exclusions. Human psoriasis explants or relevant skin–immune cocultures can provide additional translational evidence, but disease heterogeneity and short culture viability limit interpretation.

Imiquimod (IMQ) inflammation is a useful complementary stress test, not sole proof of direct IL-23 blockade. It can respond to broad anti-inflammatory or cytotoxic mechanisms. A negative animal result without species binding and adequate unbound exposure is not an informative target test; a positive result without mechanism is not a validated hit. The structural hotspot work itself provides a precedent for linking altered IL-23 receptor engagement to skin inflammation.[7]

8.2 A chronic-disease safety package

Build selectivity and safety into optimization: broad pharmacology, cardiac ion channels, mitochondrial/cellular stress, genotoxicity, reactive metabolites, CYP/transporter liability and repeat-dose histopathology at relevant exposure. Choose toxicology species based on pharmacological relevance; apply small-molecule nonclinical guidance with immunomodulatory considerations, not a fixed antibody template. Reproductive, chronic and carcinogenicity requirements should be staged with the eventual clinical plan.

Maintain infection surveillance and an explicit fungal/mycobacterial risk hypothesis. Long-term anti-p19 experience is reassuring context—for example, a risankizumab analysis reported 1.2 serious-infection events per 100 psoriasis patient-years excluding COVID-related infection—but trial selection and modality differences preclude importing that numerical rate into a small-molecule TPP.[10, 11, 23]

Table 10. Proposed decision gates and stop criteria; durations are planning estimates, not forecasts.

Stage	Advance when	Stop, redesign or deprioritize when
0. Reagent and hit audit 0–3 months	Native reagents are active; fragment identities and orthogonal binding reproduce.	Only optical/aggregation effects, unstable protein or unresolved chemical mixtures explain activity.
1. Hit validation 3–9 months	At least two tractable series show consistent SAR, preferably $K_D \leq 10\,\mu$M, native PPI inhibition and a credible site.	Affinity improves but antagonism does not; activity requires insoluble concentrations or broad cytokine inhibition.
2. Lead optimization 9–18+ months	Human-cell selectivity and free-exposure feasibility approach candidate criteria; species/model strategy is validated.	Excessive size/lipophilicity, poor exposure or IL-12/JAK off-target effects are inseparable from potency.
3. Candidate decision	Replicated PK/PD and skin efficacy, developable formulation and safety margins support the intended human regimen.	Efficacy lacks proximal PD, therapeutic coverage is infeasible, or chronic safety/differentiation is inadequate.

Table 10 makes the first investment decision narrow: **is there reproducible, optimizable nonpeptidic binding that actually prevents receptor engagement?** A positive answer justifies lead generation. Docking rank, fluorescence displacement alone or isolated animal improvement does not.

9 Evidence validation, methods and limitations

9.1 Source hierarchy and audit trail

This focused assessment used PubMed/Europe PMC searches combining IL23/IL23R/p19 with structure, peptide, fragment, small molecule, inhibitor, psoriasis and named programs. Primary papers and supplements were prioritized, with PDB/UniProt metadata cross-checks and a 2025–2026 update. It is not an exhaustive systematic review; cached sources and scripts preserve the audit trail.

Table 11. Claim-level validation and explicit boundaries.

Claim type	Validation performed	Boundary
Clinical endpoints	Checked endpoint, time point, dose and percentages against primary trial records/abstracts.	Descriptive benchmarks, not a meta-analysis; PASI75 and PASI90 are not interchangeable.
Icotrokinra status	Verified a June 2026 first-approval publication reporting US approval in March 2026.	Secondary source; regulator/current-label access blocked. No claim of independent current global-label verification.
Nonpeptidic chemistry	Compared main text, Figure 4E and supporting Table S2; separated four supported hits from the unconfirmed hit.	Affinity discrepancy remains unresolved; biophysical binding is not validated cellular inhibition.
Structural observations	Checked PDB metadata, author chains and construct context; calculated geometric contacts from deposited coordinates.	Contacts are not energetic hotspots; missing atoms, glycans and crystal constructs affect interpretation.
Proposed TPP / experiments	Derived explicit working objectives from clinical context and pharmacological principles.	No candidate-specific potency, PK, efficacy or safety is measured or predicted here.

9.2 Reproducible coordinate analysis

New measurements use 5MZV biological assembly 1, p19 B/IL-23R C. Model 1 protein heavy atoms with positive occupancy were retained; alternate atoms were selected by highest occupancy, then blank/A tie priority. Waters, sugars, hydrogens and nanobody were excluded. Contacts are Euclidean distances $\leq$4.0 or $\leq$5.0 Å, not assigned energetic interactions.

SASA used BioPython Shrake–Rupley, default radii, a 1.4 Å probe and 960 points at fixed coordinates. Interface area is $[\mathrm{SASA}(B) + \mathrm{SASA}(C) - \mathrm{SASA}(BC)]/2$; total/per-partner losses are saved. Including p40 changes the definition: IL-23 (A+B) versus receptor C gives approximately 1,137 Å^2, rather than the p19-only 891 Å^2. Missing atoms and excluded glycans limit completeness.

Sequence mappings, construct changes, glycan links and metadata are saved in CSV/JSON. Reproduce with `scripts/analyze_interfaces.py`; versions, input hash and method are in `analysis/analysis_summary.json`. Viewer figures use 6WDQ and 8UUI. No density maps were re-refined, and no new binding/pharmacology experiments or molecular simulations were performed.

9.3 Remaining decision-critical uncertainties

The outstanding questions are whether fragments bind the induced p19 pocket; whether compact ligands retain receptor-blocking activity; whether human-cell potency can be covered by free skin exposure; and whether relevant animal pharmacology, chronic safety and commercial differentiation are achievable. These must be answered experimentally, not inferred from structural proximity.

Patent and competitive scope. Patent-platform and some regulatory/trial endpoints were inaccessible. No freedom-to-operate or exhaustive competitor-absence conclusion is justified; undertake claim-level patent review before scaffold commitment. No clinically validated direct nonpeptidic p19–IL-23R inhibitor was confirmed in the searched sources, a bounded finding rather than proof of absence. Table 11 distinguishes published observations, coordinate-derived measurements and proposed criteria for reuse.

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