TL1A — V4 Target Opportunity Report (Public Edition)

Whitespace & Trajectory, in one decision-first view

Target: TL1A (TNFSF15 / TNF-like ligand 1A; UniProt O95150; HGNC:11931; gene Wikidata Q18034921) → its receptor DR3/TNFRSF25 (Q18033239) **Date:** 2026-07-25 · **Substrate:** a full multi-jurisdiction landscape (US/EP/WO/CN, incl. the pre-2020 VEGI foundational tail); **100 on-pathway** families after claim-scope screening. **What this is for:** to let an inventor or BD&L reader *see where the defensible room is and where the field is going* — a whitespace/trajectory signal.

> **Read-me (the guardrails, once):** This is **candidate generation and a whitespace/trajectory signal — NOT a freedom-to-operate (FTO) opinion.** "Whitespace" = absence of *strong structural claim coverage*, which is necessary-but-not-sufficient for opportunity. Structural overlap and sequence identity are **lower bounds**. Ex-US members rest on machine-translated claims — a lower-fidelity tier. Verify any specific family before relying on it.
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> **Public edition note.** This is the public edition of the TL1A V4 Target Opportunity Report. It presents the whitespace and trajectory reads that accompany the article. The underlying patent-craftsmanship (KC) strength scoring, per-family score tables, machine-readable knowledge graph, and raw scored inputs are part of the internal analyst deliverable and are not reproduced here; the strength layer is relative-ordering, calibration-pending work and is deliberately not published as a ranking.

PART I — ACT ON THIS

1. Actionable summary — where to build

Ranked opportunities, each with the reason it is open and the standing claims to design around. Detail in §2 (whitespace), §3 (the actionable structural core), §4 (trajectory).

#	Opportunity	Status	Why it's actionable	Watch / design around
1	**Conformation- / cleavage-form-selective anti-TL1A** — IBD/fibrosis	**OPEN** (0 on-path families)	The only genuine novelty escapes in the corpus are conformational; no on-pathway family claims a conformation/cleavage/membrane-vs-soluble-selective anti-TL1A. Design *inside* the target, *outside* the CDR	The monospecific CDR thicket (56 families, dense sequence identity) is adjacent but

#	Opportunity	Status	Why it's actionable	Watch / design around
			thicket	does not reach a conformational epitope claim
2	**TL1A × second-target bispecific** (beyond IL-23/OSMR — e.g. × α4β7, × IL-13, × TNF)	**Contestable now (lower bound)**	Frontier direction, **0 live grants** in the scored set; several flagship players are still **unscored named absences**	Xencor TL1A×IL-23, Mirador TL1A×OSMR, Newsoara, Spyre α4β7+TL1A — all **named absences**; move before they land
3	**DR3 (TNFRSF25) receptor-side blockade** — autoimmune	**OPEN / near-open — decaying**	Only 5 families and **2 have lapsed** → receptor-side blockade is thin *and* partially undefended	A small number of live grants anchor the lane (a chimeric-protein autoimmunity estate + a receptor-blockade estate)
4	**DcR3-decoy tuning** (modulator / agonist direction)	**OPEN** (0 families in modulator/agonist directions)	Only 3 antagonist-direction DcR3 families exist; the decoy-receptor *tuning* lever is unclaimed	A pending DcR3-variant filing is the nearest art
5	**Downstream TL1A→DR3→ NF-κB signalling** inhibitor (intracellular / non-antibody)	**OPEN** (0 on-path families)	A non-antibody mechanistic route (small molecule / degrader) with no on-pathway family claiming it as the primary mechanism	Weakest-grounded open call — verify the axis is searched-and-empty, not empty-by-construction (§2 caveat)

#	Opportunity	Status	Why it's actionable	Watch / design around
6 *(indication-led)*	**Fibrosis / stricturing CD / PBC / MASH** with any TL1A mechanism	**THIN** (3 families)	Under-claimed relative to the **Wikidata TNFSF15→PBC genetic association**; the fibrosis axis is thin across nodes	Genentech/Roche MASH & AtD families are **named absences**; the indication axis is sparse (§method) — directional call
—	**Monospecific anti-TL1A composition for IBD** (generic CDR)	**AVOID**	COVERED & crowded: 56 families, 14 live grants, dense sequence-identity surface, US/China race	The consolidated US monospecific estates + the China follow-on cohort

The one-sentence read: the open, defensible room is in the **mechanistic alternatives to the crowded monospecific-mAb core — conformation-selective** binding, **receptor-side (DR3)** blockade (thin *and* decaying), **DcR3-decoy tuning**, and **downstream-signalling** inhibition — plus the **TL1A×second-target bispecific** frontier, which is being actively colonized by players not yet in the scored set. The monospecific-composition-for-IBD core is the least whitespace.

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2. Whitespace map — the open cells

The landscape was projected onto a scope grid (mechanism-node × direction × modality × indication). A cell is a **whitespace candidate** when it is *scientifically reachable* but *structurally thin*: few on-pathway families, no broad **live-granted** genus, and/or coverage held only by lapsing patents. **TL1A is antibody-dominated, so the actionable structural surface is sequence identity, not genus** — most cells legitimately carry no genus number (§3).

Verdict rule: OPEN = 0 on-pathway families · THIN = ≤2 families, no broad live genus · PARTIAL = coverage but no broad live-granted genus and <4 live grants · COVERED = broad live-granted genus present OR ≥4 live grants.

mechanism cell	verdict	on-path families	live grants	lapsed
TL1A_epitope_conformational / inhibitor	**OPEN**	0	0	0

mechanism cell	verdict	on-path families	live grants	lapsed
downstream_NFkB_signaling / inhibitor	**OPEN**	0	0	0
DcR3_decoy / modulator & agonist	**OPEN**	0	0	0
DR3_receptor_blockade / inhibitor	**PARTIAL — decaying**	5	3	**2**
bispecific_TL1A_x / inhibitor	**PARTIAL (lower bound)**	3	0	0
pathway_delivery_formulation / inhibitor	THIN	2	0	0
TL1A_Ig_fusion (agonist + inhibitor)	THIN/PARTIAL	4	1	0
DR3_agonism / agonist	THIN	2	1	0
pathway_biomarker_dx / diagnostic	COVERED	9	4	0
TL1A_ligand_neutralization / agonist (legacy VEGI)	COVERED	11	2	0
TL1A_ligand_neutralization / inhibitor	**COVERED**	56	14	1

Weakest open call: the `downstream_NFkB_signaling` cell is empty partly because the axis may be under-represented in an antibody-heavy corpus — verify with a dedicated small-molecule/degrader search before relying on it. (One `pathway_delivery_formulation` genus number in the internal data is an excipient-formulation parse artifact, not a real broad small-molecule genus, and is excluded from any coverage reading.)

Read: the open cells cluster on **conformation-selective binding, DcR3-decoy tuning, downstream-signalling inhibition, and the decaying DR3-receptor-blockade direction** — the mechanistic alternatives to the crowded ligand-side monospecific core. The bispecific cell reads PARTIAL but is a firm **lower bound** because its flagship members are unscored named absences. The monospecific-inhibitor and biomarker-Dx cells are covered.

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3. The actionable structural core — sequence surface, not genus

Because TL1A is a ligand–receptor antibody target, the actionable structural surface is **sequence identity**, and it is dense. Of the genus-carrying families, almost all are off-pathway small-molecule filings (an adjacent IRAK4 space); only a couple are on-pathway. So the "chemical genus" layer fences the **adjacent** small-molecule space, not TL1A itself.

What this means where you'd build (candidate-generation, lower bounds, NOT FTO):

- **Monospecific anti-TL1A composition (COVERED — a sequence thicket, avoid).** The anchor monospecific and methods estates carry hundreds of sequences and

large numbers of candidate identity hits, including near-identical different-assignee CDR matches. Near-identical CDR chemistry is already on file across multiple assignees — a new generic monospecific composition enters an occupied sequence space.

- **DR3-receptor-blockade (OPEN/near-open — decaying, priority #3).** 5 families, 2 lapsed. Receptor-side is a mechanistic alternative to the ligand-side thicket and is thinly + partially undefended.
- **DcR3-decoy (OPEN in the tuning directions — priority #4).** Only 3 antagonist-direction families; the decoy-receptor pharmacology lever on TL1A *availability* is under-explored.
- **Cross-class transfer:** the adjacent small-molecule (IRAK4) genus hubs reach a long tail of older small-molecule patents (INDETERMINATE-driven) — but these are transfer hypotheses on the **IRAK4 adjacency, not the TL1A core**, and are the weakest structural signal here.

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4. Trajectory — where this target is going

Composed from filing velocity × direction × modality × entrant origin, on **real filing dates** (all 100 on-pathway families dated; no proxy).

era	n	dominant modality	direction (agonist : inhibitor)	entrants
pre-2016 (foundational)	19	monospecific mAb (13), fusion (3), peptide (2)	**7 : 12**	US pharma/academic; the legacy VEGI cohort
2016–2020 (buildout)	24	monospecific mAb (11), dx-signature (5), fusion (3)	3 : 16	company-led; the core US estates form
2021–2026 (frontier)	57	**monospecific mAb (37)**, dx-signature (9), fusion (3), **bispecific (2)**	**6 : 47**	US ↔ **China (19 ex-US entrants)**

Trajectory statement: *TL1A has been an **autoimmune-inhibition, antibody-led** target from inception (inhibitor-dominant in every era — unlike cGAS-STING's agonist→inhibitor pivot), consistent with its Wikidata-confirmed TNFSF15→IBD/Crohn's genetic association. The center of gravity is a **crowded, maturing monospecific anti-TL1A mAb race for IBD** (37 of 57 frontier-era families are monospecific mAbs), now a **US ↔ China contest** (ex-US entrants 1→1→19). The dynamic edge is moving to (i) the **bispecific frontier** (TL1A×IL-23, TL1A×OSMR — mostly still unscored absences), (ii) **companion-diagnostic / SNP-haplotype patient selection**, and (iii) **indication expansion** beyond IBD into atopic dermatitis, MASH/fibrosis (the Wikidata PBC anchor), and asthma/COPD. Direction of travel: monospecific-composition → **bispecific + conformation-selective + companion-Dx**, IBD → **indication expansion**, US-core → **US/China race**.*

The decisive dynamic — no foundational genus is decaying; the decay is on the receptor side. Unlike cGAS-STING (where a broad first-wave systemic-CDN genus is lapsing), TL1A has **no lapsing broad foundational genus** — the foundation is antibody/sequence and the modern estates (2019–2026) are maintained and accreting (14 live grants in the core, none near expiry). The lapses (3 on-pathway) instead cluster in the **thin DR3-receptor-blockade** direction plus one first-generation (2006) ligand-neutralization filing — which is exactly why receptor-side blockade (§1 #3) is both open and undefended.

PART II — METHOD & LIMITS (public summary)

How the reads were built

- **Discovery** on TL1A/TNFSF15/VEGI across **all four jurisdictions** (US/EP/WO/CN), then a **full-landscape assembly including the pre-2020 VEGI/DR3 foundational tail**, materialized on-demand (publication- and INPADOC-family-anchored). Two provenance tiers are carried explicitly: US native-full-text and a distinct, lower-fidelity ex-US machine-translated tier.
- **Scope binning** onto four externally-grounded axes (literature + Wikidata SPARQL) — mechanism-node, direction, modality/chemotype, indication — *not* derived from the patent set; each family carries an LLM claim-scope `scope_evidence` string.
- **A load-bearing on/off-pathway screen:** only **100 of 136 families** genuinely claim the TL1A–DR3 axis; the rest co-mention TL1A but claim something else (IRAK4/PAD small molecules, anti-TNFR2 antibodies, IL-18R, diagnostics) and are held out of the whitespace/trajectory denominator (retained only as combination signal). Treating raw hit counts as coverage would overstate the estate by ~26%.
- **A sequence-identity structural layer** (the dominant surface for this antibody target) plus a genus/scope layer for the adjacent small-molecule space, **legal-status timelines** for the lapse/decay read, and **real filing dates** for the trajectory (no proxy).
- **Independent adversarial review** of both the strength read and the whitespace/trajectory read by impartial reviewers with full data/script access; a headline integrity fix — a classifier leak that had admitted six off-pathway families into the on-pathway core — moved the on-pathway count 111→100, removed a spurious core genus number, and cut the on-pathway lapse count 5→3 before release.

Limits — read before relying

- **Not FTO.** Whitespace = absence of *strong structural claim coverage* (necessary-not-sufficient). Structural overlap and sequence identity are lower bounds. An OPEN cell is a hypothesis prompt, not clearance.
- **The bispecific/combination frontier is understated by construction.** Several flagship bispecifics (Xencor TL1A×IL-23, Mirador TL1A×OSMR) and the Genentech

AtD/MASH families are named absences (biblio-only, unscored), so every bispecific/AtD/MASH verdict here is a **lower bound**.

- **The denominator is operator-defined** (the scope ontology); different axes → different whitespace. **Classification is a model read** (the 100/36 split and per-family bins are LLM claim-scope reads) emphasizing cell-level patterns over single-family calls.
- **The indication axis is sparse** (a majority of on-pathway families carry broad-autoimmune claims), so indication-axis calls (§1 #6) are directional, not quantitative.
- **The ex-US tier is lower-fidelity** (machine-translated claims); the China-origin trajectory surge rests partly on that tier — the trajectory *shape* is robust, individual ex-US placements are candidate-grade.
- **Corpus-bounded.** Whitespace is relative to the scored families; named absences and genuinely un-filed art are invisible by construction.

This public edition presents the TL1A whitespace and trajectory reads. Every whitespace/trajectory number is computed on the 100 on-pathway families on real filing dates. Candidate generation, NOT freedom-to-operate.