TL1A V4 Whitespace & Trajectory Analysis

Public edition: the whitespace/trajectory reads only; the per-family patent-craftsmanship strength scoring is held in the internal analyst deliverable and is not reproduced here. **Target:** TL1A (TNFSF15 / TNF-like ligand 1A; UniProt O95150; HGNC:11931; gene Wikidata Q18034921) **Date:** 2026-07-25 **Analyst:** OpenCode (Opus 4.8) for Mark Edwards **Substrate:** 136 native-scored families → **100 on-pathway** (36 excluded as off-pathway co-mentions) **Basis:** structured-IP reading layer (native KC + compiled Markush genus + scope-neighbors + sequence-FTO) projected onto a literature+Wikidata-grounded scope ontology **Framing:** This is **candidate generation and a whitespace/trajectory signal — NOT a freedom-to-operate (FTO) determination.** Genus membership/overlap is 3-valued (IN/OUT/INDETERMINATE) and recall is a **lower bound**; sequence identity is a **lower bound**; native KC is **not calibrated** (Gold Set 0/200–300 pending). "Whitespace" here means *absence of strong structural claim coverage*, which is necessary but not sufficient for opportunity — it must be read against the reachable biology (the ontology denominator).

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0. Why this report exists

The V4 KC portfolio report grades *what exists*. It does not tell an inventor *where the defensible room is* or *where the field is going*. Whitespace is the structured **complement** of claim coverage; it only exists relative to a coordinate system. This companion adds the three layers the KC report lacked:

1. a **scope-coordinate system** (mechanism-node × direction × modality × indication) — the whitespace denominator, grounded externally (literature + Wikidata), not derived from the patent set;
2. a **coverage-density read + thin-cell detector** integrating live-granted status, lapse events, genus breadth, and sequence-FTO surface; and
3. the **dynamic layer** — lapse-driven decay, the bispecific/combination frontier, cross-class transfer, and a trajectory vector on **real filing dates**.

Everything is exported as a **knowledge graph** (`tl1a_knowledge_graph.json`, 265 nodes / 731 edges) so the whitespace question is answerable as a graph query.

The central structural fact about TL1A (which shapes every finding below): unlike a small-molecule enzyme target, TL1A is a **TNF-superfamily ligand–receptor axis** (TL1A ligand → DR3/TNFRSF25 death-domain receptor, with the soluble decoy DcR3). The therapeutic core is the **neutralizing antibody**, so the actionable structural surface is **sequence identity**, not Markush genus. Of the 15 genus-carrying families in the substrate, **13 are off-pathway Gilead small-molecule** (IRAK4 / PAD / indole / MK2 — a downstream-innate adjacency); only **2 are on-pathway** (Novo Nordisk's antagonistic DR3-ligand construct, and a Cephalon excipient-formulation whose "genus" is a parse artifact, §4). The TL1A antibody core itself carries essentially

no small-molecule genus coverage. This inverts the cGAS-STING picture and is why the sequence-FTO layer (§4) carries the structural signal here.

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1. Headline findings

1. **Only 100 of 136 native-scored families genuinely claim the TL1A–DR3 axis.** An LLM claim-scope read (card summary + title + assignee + genus/sequence flags), hardened by a second adversarial pass, reclassified **36 families as off-pathway** — they co-mention TL1A/TNFSF15 but claim something else: **14 Gilead small molecules** (IRAK4 / PAD / indole / MK2), **4 MGH anti-TNFR2 / Fc-engineering** antibodies, **4 no-TL1A-token generic/process/ocular** filings (Cephalon chromatography wash buffers, an MGH Fc-modification family, a Legend ocular-disorder method), **2 anti-IL-18R**, **2 anti-TNFα-response diagnostics**, **2 Cedars RNASET2 diagnostics**, and one each of Beth Israel's NF-κB-conformation antibody (the native-KC #3 family), Senti's cell circuit, Burnham's NOD-like and GSK3 families, Neurimmune's anti-SARS-CoV-2 antibody, Ikena's kynureninase, Anaphore's anti-IL-23R, and a Cedars IL-17 family. Treating raw hit counts as coverage overstates the TL1A estate by ~26%.

2. **The field was inhibitor-led from inception and is intensifying** (on real filing dates). Agonist:inhibitor ran **7:12** pre-2016, **3:16** in 2016–2020, and **6:47** in 2021–2026. Unlike cGAS-STING (which *pivoted* from agonist to inhibitor), TL1A has been an **autoimmune-inhibition target from the start** — consistent with the TNFSF15→IBD/Crohn's genetic association (Wikidata P2293). The frontier era (2021–2026) is 57 of the 100 on-pathway families, dominated by monospecific anti-TL1A mAbs (37 of 57).

3. **A China-origin antibody wave is the defining recent entrant shift.** Ex-US (CN/WO machine-translated) entrants went **1 → 1 → 19** across the three eras. The native #1 and #2 families overall are Chinese anti-TL1A estates (Sunshine Guojian, Truelab) — scored on the lower-fidelity `exus-gp-mt` tier (verify against native claims). The monospecific-mAb core is now a US/China race.

4. **The monospecific anti-TL1A ligand-neutralization core is the crowded, well-defended center** (56 on-pathway inhibitor families, **14 live grants**, 26 pending, 15 unknown-status). This is the *least* whitespace, and — as expected for an antibody axis — it carries **no on-pathway small-molecule genus at all**. New monospecific composition entrants face a dense, mutually-prior-arted CDR thicket and a heavy sequence-identity surface (the anchor monospecific estate alone carries hundreds of sequences and many candidate identity hits; §4).

5. **Four reachable mechanism cells are genuinely OPEN or near-open** (0–1 on-pathway families): **conformation/cleavage-form-selective anti-TL1A** (a novelty-differentiated binding sub-node — the KC report's Beth-Israel-adjacent escape category), **downstream TL1A→DR3→NF-κB signalling inhibition** (mechanistically distinct from binding the ligand), **DcR3-decoy modulation** (the modulator/agonist direction of the decoy axis), and the **DR3-receptor-blockade** direction — which is populated (5 families) but **decaying**: 2

of its 5 families have lapsed (Xencor, Meylan/Siegel-NIH), so it is thin *and* partially undefended.

6. **The bispecific / combination frontier is real but barely claimed in the scored set** — and its most important members are **named absences, not scored families**. Only 3 on-pathway bispecifics are scored (Amgen TL1A×TNF-α 2016; Earendil TL1A×IL-23 2025; one more 2025). The headline bispecific programs — **Xencor TL1A×IL-23** (WO-2026055669) and **Mirador TL1A×OSMR** (WO-2026060117) — are in the KC report's **22 named absences** (biblio-only, unscored). So the bispecific count here is a firm **lower bound**; this is the single biggest coverage caveat for a forward-looking read.

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2. The scope-coordinate system (ontology / whitespace denominator)

Four axes, human-gated and **externally grounded** (V4 §2.3 — the denominator cannot be derived from the patent set). Full definitions in `data/ontology.json`.

- **mechanism_node** (11 values incl. the off-pathway screen bucket): where on the axis the claim acts — `TL1A_ligand_neutralization`, `TL1A_epitope_conformational`, `DR3_receptor_blockade`, `DR3_agonism`, `DcR3_decoy`, `TL1A_Ig_fusion`, `bispecific_TL1A_x`, `downstream_NFkB_signaling`, `pathway_delivery_formulation`, `pathway_biomarker_dx`, plus `TL1A_adjacent_offpathway` (the off-pathway screen).
- **direction**: antagonist-inhibitor / agonist-activator / modulator / diagnostic.
- **modality_chemotype** (9 values): monospecific mAb / humanized-optimized mAb / bispecific-multispecific / fusion protein / peptide / small molecule / nucleic-acid-gene / formulation-dosing / dx-signature.
- **indication**: IBD-UC/CD / fibrosis-stricture / atopic-dermatitis / asthma-COPD / rheum-systemic-AI / sarcoidosis-granuloma / IO-oncology / other.

Grounding (Wikidata SPARQL, confirmed 2026-07-25): TNFSF15 gene **Q18034921** (HGNC 11931, Entrez 9966), encoding TL1A protein **Q21124632** (UniProt **O95150**); the signalling receptor DR3/**TNFRSF25** = **Q18033239**. Critically, the **gene→disease genetic associations (P2293)** for TNFSF15 are **Crohn's disease (Q1472)**, **inflammatory bowel diseases (Q917447)**, **primary biliary cholangitis (Q1072420)**, and **leprosy (Q36956)**. These four Wikidata-confirmed associations anchor the indication axis and the KG disease nodes — IBD/Crohn's is the lead clinical indication (tulisokibart/duvakitug/RVT-3101); PBC anchors the fibrotic-cholestatic axis; leprosy anchors the granulomatous axis. The mechanism/direction/modality axes are literature-grounded (Migone 2002 TL1A-DR3 discovery; Bamias/Siakavellas; Croft & Siegel TNFSF review; the ARTEMIS-UC/APOLLO-CD, RELIEVE, and TUSCANY clinical programs).

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3. Coverage-density grid + thin-cell whitespace

3.1 Mechanism-node × direction (on-pathway families; `whitespace_grid_node_dir.json`)

`live` = granted **and currently maintained** (lapsed patents propagated out of the live count); `laps` = granted/pending-then-lapsed; `pend` = **`legal_verdict == "pending"` only**; `null` = family with **unknown legal status** (no USPTO verdict on the anchor member — foundational/ex-US/empty-summary families; `live + laps + pend + null = n`); `medRcl(N)` = median `family_best` genus recall over N genus-carrying families in the cell (recall is a **lower bound**; blank = no genus family in the cell — expected for an antibody axis).

mechanism_node	direction	n	live	laps	pend	null	genus fams	medRcl	verdict
TL1A_ligand_neutralization	antagonist_inhibitor	56	14	1	26	15	0	–	**COVERED**
TL1A_ligand_neutralization	agonist_activator	11	2	0	1	8	1	0.473	COVERED*
pathway_biomarker_dx	diagnostic_none	9	4	0	4	1	0	–	COVERED
pathway_biomarker_dx	antagonist_inhibitor	5	1	0	3	1	0	–	PARTIAL
DR3_receptor_blockade	antagonist_inhibitor	5	3	**2**	0	0	0	–	PARTIAL / **decaying**
bispecific_TL1A_x	antagonist_inhibitor	3	0	0	1	2	0	–	PARTIAL (lower bound — see §5.2)
DcR3_decoy	antagonist_inhibitor	3	2	0	1	0	0	–	PARTIAL
TL1A_Ig_fusion	agonist_activator	3	0	0	0	3	0	–	PARTIAL
pathway_delivery_formulation	antagonist_inhibitor	2	0	0	1	1	1	0.941	THIN (genus = excipient artifact, §4)
DR3_agonism	agonist_activator	2	1	0	0	1	0	–	THIN
TL1A_Ig_fusion	antagonist_inhib	1	0	0	0	1	0	–	THIN

mechanism_node	direction	n	live	lapsed	pend	null	genus fams	medRcl	verdict
	itor								

* The `agonist_activator` ligand-neutralization cell is the legacy **VEGI** angiogenesis/oncology cohort (the 1998–2012 Human Genome Sciences / ProteomTech / Nankai lineage) — same protein (TNFSF15/VEGI), opposite therapeutic framing (anti-angiogenic activity rather than immune neutralization). It is genuinely populated but old and largely lapsed/biblio.

(A patent-craftsmanship-strength column is deliberately omitted: the strength scoring is uncalibrated, and pairing a high strength score next to a thin cell invites over-reading. Strength scoring is held in the internal deliverable and is not used to grade whitespace here.)

3.2 Thin-cell + open-cell verdicts (`whitespace_thin_cells.json`)

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

cell	verdict	evidence
TL1A_epitope_conformational / inhibitor	**OPEN**	0 on-pathway families claim a conformation/cleavage-form/membrane-vs-soluble-selective anti-TL1A. This is the KC report's novelty escape category (Beth Israel's conformation antibody is *NF-κB*, off-pathway) — the differentiated sub-node of the crowded ligand-neutralization core.
downstream_NFkB_signaling / inhibitor	**OPEN**	0 on-pathway families claim intracellular TL1A→DR3→NF-κB/apoptosis modulation as the primary mechanism — mechanistically distinct from binding the ligand or receptor. (Weakest-grounded open call — verify the axis is searched-and-empty, not empty-by-construction.)
DcR3_decoy / modulator & agonist	**OPEN**	0 families in the modulator/agonist directions of the decoy-receptor axis (only 3 antagonist-direction DcR3 families exist — Kyowa Kirin DcR3 variant + 2). The decoy-tuning direction is unclaimed.
DR3_receptor_blockade / inhibitor	**PARTIAL — decaying**	5 families but **2 lapsed** (Xencor US-2012014950, Meylan/Siegel-NIH US-2011217310). Receptor-side blockade is thinly held and partially undefended vs the ligand-side core.

cell	verdict	evidence
bispecific_TL1A_x / inhibitor	**PARTIAL (lower bound)**	3 scored, 0 live grants — but the two flagship bispecifics (Xencor TL1A×IL-23, Mirador TL1A×OSMR) are **named absences**, so true coverage is understated. Contestable *now*, before these land.
pathway_delivery_formulation / inhibitor	THIN	2 families; the one genus (Cephalon US-20250263494, recall 0.941) is an **excipient-formulation parse_failed artifact** (§4), not a real broad small-molecule genus.
TL1A_Ig_fusion (both directions)	THIN	4 families total (University of Miami IL-2/TL1A + TL1A-Ig-Treg); a small, specialized fusion-protein niche.
pathway_biomarker_dx / diagnostic	COVERED	9 families, 4 live grants — the SNP-haplotype + companion-Dx cluster is well-populated (incl. a haplotype-B dosing estate).
TL1A_ligand_neutralization / inhibitor	**COVERED**	56 families, 14 live grants, 26 pending — crowded, mutually prior-arted, a US/China monospecific-mAb race.

Read. The genuinely open/near-open cells cluster on the **mechanistic alternatives to the crowded monospecific-mAb core**: (i) **conformation/cleavage-form-selective** anti-TL1A (the novelty-differentiated binding sub-node), (ii) **downstream NF-κB-signalling** inhibition, (iii) **DcR3-decoy tuning**, and (iv) the **receptor-side (DR3) blockade** direction, which is thin *and* decaying. The monospecific-ligand-neutralization inhibitor cell and the biomarker-Dx cell are covered; the bispecific cell reads PARTIAL but is a firm lower bound because its flagship members are unscored absences.

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4. The actionable structural core — sequence-FTO, not genus

Because TL1A is antibody-dominated, the actionable structural surface is **sequence identity**, and it is dense. From `data/genus_scope_layer.json` (candidate-generation, lower bounds, NOT FTO):

- **The monospecific-mAb core is a sequence thicket.** The Pfizer/BMS anchor US-11474112 carries **498 sequences / 134 candidate hits** (top different-assignee identity 97.96%); the Pfizer/BMS methods estate US-20240059799 carries **296 sequences / 1,749 hits** (1,517 candidate); the Earendil TL1A×IL-23 bispecific US-20260062472 carries **382 sequences / 885 candidate hits** (two 100%-identity different-assignee hits on short CDR segments). A new monospecific composition here is entering a space where near-identical CDR chemistry is already on file across multiple assignees — the sequence-identity analog of the KC report's novelty ceiling.
- **The genus layer is almost entirely off-pathway small-molecule.** Of 15 genus families, **13 are Gilead** (IRAK4 / PAD / indole / MK2 — off-pathway), and the two hubs are Gilead pyrrolo[1,2-b]pyridazine benzamides: **US-10336762** (recall **0.746**, 7 cores, 864 genus-

overlap edges) and **US-11046686** (recall **0.655**, 10 cores, 860 edges). These are a well-drafted, broad small-molecule thicket — but they fence the **IRAK4-adjacent** chemistry, **not TL1A itself**. A TL1A small-molecule (were one to exist) would design around Gilead's IRAK4 genus, which is a different target. The **2 on-pathway genus families** are Novo Nordisk US-9713644 (antagonistic DR3-ligand construct, recall 0.473, structurally moderate) and the Cephalon formulation below.

- **One genus "breadth" number is a formulation artifact.** Cephalon US-20250263494 reports recall **0.941** — but its genus `markush_status` is **parse_failed** and its 898 genus-overlap edges are **spurious cross-class excipient-SMARTS matches** (histidine/Arg-HCl/sucrose cores matching generic chemistry, incl. 1970s patents). It is an anti-TL1A **biologic formulation**, not a broad small-molecule estate; its real signal is its 50 sequence edges. **Do not read 0.941 as broad small-molecule coverage** (a recall-artifact caught in review, analogous to the cGAS-STING audit's recall-field bug).

Cross-class transfer candidates: the Gilead genus hubs' long tail of lower-ECFP edges reaches older/unrelated small-molecule patents (all INDETERMINATE-driven, frac=1.0) — chemistry proven elsewhere, structurally adjacent to the Gilead IRAK4 scaffolds, filed for other purposes. These are **transfer hypotheses on the adjacency, not the TL1A core**, and are the weakest of the structural signals here.

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5. Dynamic layer

5.1 Lapse-driven decay timeline (`dynamic_signals.json`; real abandonment dates)

Three **on-pathway** families have lapsed (all US, all `withdrawn_abandoned`; abandonment dates from the USPTO legal record, not a proxy). *(The adversarial review pulled two further "lapses" — Burnham GSK3 and Anaphore anti-IL-23R — off this list because they are off-pathway distinct-target families, not TL1A neutralization.)*

patent	assignee	node / direction	lapse event	date	filed
US-2012014950	**Xencor**	DR3_receptor_blockade / inhibitor	Abandoned — failure to respond	2014-04-08	2011-08-24
US-2011217310	Meylan/Siegel (**NIH**)	DR3_receptor_blockade / inhibitor	Abandoned — failure to respond	2012-03-21	2008-01-10
US-2009317388	Biogen (Burkly et al.)	TL1A_ligand_neutralization / inhibitor	Abandoned — failure to respond	2015-05-14	2006-05-25

Combinatorial whitespace-as-lapse. Two of the three on-pathway lapses are in the **DR3 receptor-blockade** direction (Xencor + NIH), which is *already* thin (5 families) — so receptor-side blockade is now both under-populated and partially undefended, an actionable near-open call. The third (Biogen 2006) is a first-generation ligand-neutralization filing that predates the modern anti-TL1A antibody generation. The

current ligand-neutralization core (2019–2026 filings) is fresh and accreting — none of its 14 live grants is near expiry. Unlike cGAS-STING, there is **no lapsing broad foundational genus** here (the foundation is antibody/sequence, and the recent estates are maintained).

5.2 Bispecific / combination frontier (the key forward signal)

The emergent frontier is **TL1A × second-target** bispecifics. In the scored set only 3 exist (Amgen TL1A×TNF-α 2016; Earendil TL1A×IL-23 2025; one more 2025), **0 live-granted**. But the field's most-watched bispecifics are **named absences** in the KC report (biblio-only, unscored):

- **Xencor TL1A×IL-23** (WO-2026055669) — named absence
- **Mirador TL1A×OSMR** (WO-2026060117) — named absence
- plus Newsoara TL1A×IL-23, Spyre α4β7+TL1A combo (from the discovery frontier)

So the bispecific cell's "PARTIAL, 0 live grants" is a **firm lower bound**: the direction is being actively colonized, but by families not yet in the scored substrate. **This is the single most important caveat for a forward-looking read** — a next run must full-text-frack these absences before the bispecific whitespace can be graded. Combination *adjacencies* revealed by the off-pathway co-claims (IRAK4, IL-18R, TNFR2, IL-17, NF-κB) suggest biologically-rational unclaimed pairs — notably **TL1A-inhibitor × IL-23** (partly claimed) and **TL1A-inhibitor × α4β7** (Spyre, an absence).

5.3 Trajectory vector — "what is the trajectory of this target?"

Composed from filing velocity × direction × modality × entrant origin by era, on **real filing dates** (all 100 on-pathway families carry a real `filing_date`; no proxy) — `dynamic_signals.json`:

era	n	direction (ago:inh)	dominant modality	dominant node	ex-US entrants
pre-2016 (foundational)	19	**7 : 12**	monospecific mAb (13), fusion (3), peptide (2)	ligand-neutralization (12), DR3-blockade (4)	1
2016–2020 (buildout)	24	3 : 16	monospecific mAb (11), dx-signature (5), fusion (3)	ligand-neutralization (15), biomarker-dx (5)	1
2021–2026 (frontier)	57	**6 : 47**	**monospecific mAb (37)**, dx-signature (9), fusion (3)	ligand-neutralization (40), biomarker-dx (9), **bispecific (2)**	**19**

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** (the Cedars/Prometheus/MSD*

cluster, a maturing cell), and (iii) ***indication expansion*** *beyond IBD into atopic dermatitis (Genentech/Roche — absences), MASH/fibrosis (Wikidata PBC anchor), and asthma/COPD. Genuine defensible whitespace concentrates in the* ***conformation/cleavage-selective binding, downstream-NF-κB, DcR3-decoy-tuning, and (decaying) DR3-receptor-blockade*** *cells.* Node-emergence timing (real dates): monospecific mAbs surge from 2019; biomarker-Dx builds 2016+; the first scored bispecific is 2016 (Amgen TL1A×TNF-α) but the modern IL-23/OSMR bispecific wave is 2025+.

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6. Knowledge graph

`data/tl1a_knowledge_graph.json` — **265 nodes, 731 edges**, generic nodes/edges JSON (Cytoscape / networkx / Neo4j-loadable).

- **Node types:** target_pathway, mechanism_node, direction, modality, indication, **disease** (Wikidata-grounded), assignee, patent_family, year.
- **Edge types:** `part_of_pathway`, `acts_on`, `directed_as`, `uses_modality`, `targets_indication`, `assigned_to`, `filed_in`, `co_claims` (off-pathway adjacency, 36 edges), `lapses_on` (family→year), `genus_overlaps` (structural, 8 edges), `sequence_identity` (structural, 13 edges), `node_associates_disease` (mechanism_node→disease, Wikidata P2293, 6 edges), `indication_is_disease`.

The 6 `node_associates_disease` edges each source from a real `node:` id (verified at build time): `node:TL1A_ligand_neutralization` and `node:DR3_receptor_blockade` → Crohn's / IBD; `node:TL1A_ligand_neutralization` → PBC / leprosy — each carrying the Wikidata QID (Q1472/Q917447/Q1072420/Q36956) and `p_ref: Wikidata:P2293`. The disease-grounding subgraph is queryable.

The whitespace query becomes a graph query: *mechanism_node reachable in the biology (has a `node_associates_disease` edge or ontology entry) with no incident `acts_on` edge from a live-granted family* → returns the OPEN cells of §3.2. **The trajectory query:** family nodes grouped by real `filed_in` year, projected on `directed_as` / `uses_modality` → the §5.3 vector. **The lapse-whitespace query:** cells whose `acts_on` families carry `lapses_on` edges → the decaying DR3-receptor-blockade cell.

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7. Limits & honest framing

- **Not FTO, not calibrated.** Whitespace = absence of *strong structural claim coverage*, a necessary-not-sufficient condition for opportunity. Genus recall and sequence identity are lower bounds; native KC is uncalibrated (Gold Set 0/200–300) and is deliberately **not** used to grade whitespace here. An OPEN cell is a *hypothesis-generation prompt*, not clearance.
- **The bispecific/combination frontier is understated by construction.** The two flagship bispecifics (Xencor TL1A×IL-23, Mirador TL1A×OSMR) and the Genentech atopic-dermatitis/MASH families are in the KC report's **22 named absences** (biblio-only, no fracked claims), so they are **not** in this whitespace substrate. Every bispecific/AtD/MASH

cell verdict here is a **lower bound**; a next run must recover those absences before those cells can be graded.

- **Classification is a model read, and ~30% of on-pathway placements rode a default.** The 100/36 on/off-pathway split and the per-family bins come from an LLM claim-scope read of card summary + title + assignee + genus/sequence flags; each family carries `scope_evidence`. A meaningful fraction of on-pathway families (mostly empty-summary Cedars/Prometheus IBD-genetics families) were placed by a **default-to-ligand-neutralization fallback** that fires only when the family sits in a TL1A-primary therapeutic-area bin and carries no distinct-target token; families with no TL1A token AND a non-TL1A-primary TA are pushed off-pathway by an explicit guard. This guard, added after an adversarial review that caught six leaks (an MK2 kinase small molecule, a GSK3 family, an anti-IL-23R polypeptide, an anti-SARS-CoV-2 antibody, an RNASET2 family, and a kynureninase family) sitting in the on-pathway core, moved the on-pathway count from 111 to 100. The report emphasizes **cell-level patterns over single-family calls** accordingly.
- **The indication axis is sparse.** 58 of 100 on-pathway families (58%) carry `indication = other_unspecified` (broad-autoimmune claims with no resolved indication). So indication-axis whitespace calls (fibrosis under-claimed, AtD/asthma thin) are **weaker than the node/direction calls** and should be read as directional, not quantitative.
- **The `exus-gp-mt` tier is lower-fidelity.** 21 of 136 families were scored on Google-Patents-scraped machine-translated claims; the China-origin trajectory surge (§5.3) and the two top-ranked ex-US families rest partly on that tier. The trajectory *shape* (inhibitor-led, China-rising, bispecific-emerging) is robust to it, but individual ex-US cell placements are candidate-grade.
- **Denominator is operator-defined.** The reachable space is set by the ontology axes (literature + Wikidata P2293), not the patent corpus. Different axes → different whitespace. The axes are auditable in `ontology.json`.
- **One genus recall number is a formulation artifact** (Cephalon 0.941, parse_failed excipient cores) and is explicitly excluded from any "broad genus" reading (§4).
- **Corpus-bounded.** Whitespace is relative to the 136 native-scored families. Genuinely un-filed art, and the 22 named absences, are invisible-by-construction to the grid.

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8. Actionable summary for an inventor

priority	where	why
1	**Conformation- / cleavage-form-selective anti-TL1A** (membrane-vs-soluble, or a specific cleaved form) — IBD/fibrosis	**OPEN** cell, 0 on-pathway families; the differentiated binding sub-node that escapes the crowded monospecific-mAb novelty ceiling (the only genuine novelty escapes in the corpus are conformational). Design *inside* the target, *outside* the CDR thicket.
2	**TL1A × second-target bispecific** (beyond IL-23/OSMR — e.g. × α4β7, × IL-13, × TNF for	Frontier direction, **0 live grants** in the scored set; flagship players (Xencor, Mirador) are still **unscored absences** → contestable *now*, but

priority	where	why
	a specific indication)	move before they land.
3	**DR3 (TNFRSF25) receptor-side blockade** — autoimmune	**PARTIAL & decaying**: only 5 families and **2 have lapsed** (Xencor, NIH). Receptor-side is a mechanistic alternative to the ligand-side core and is thinly + partially undefended.
4	**DcR3-decoy tuning** (modulator/agonist direction)	**OPEN** direction; only 3 antagonist-direction DcR3 families exist. Decoy-receptor pharmacology is an under-explored lever on TL1A availability.
5	**Downstream TL1A→DR3→NF-κB signalling** inhibitor (intracellular)	**OPEN**; a non-antibody mechanistic route (small molecule or degrader) with no on-pathway families claiming it as the primary mechanism. Weakest-grounded of the open calls (verify the axis is searched-and-empty, not empty-by-construction).
6 *(indication-led)*	**Fibrosis / stricturing CD / PBC / MASH** with any TL1A mechanism	THIN across nodes despite the **Wikidata PBC genetic association**; the fibrosis-stricture indication axis (3 families) is under-claimed relative to its genetic grounding — but note the indication axis is sparse (§7), so read this as directional.
— avoid	**Monospecific anti-TL1A composition for IBD** (generic CDR)	**COVERED**, crowded (56 families, 14 live grants), dense sequence-identity surface, US/China race — the least whitespace.

Artifacts: `data/ontology.json`, `families_binned.json` (136, with on/off-pathway + 4-axis bins + scope_evidence), `card_scope_reads.json` (37 claim-scope reads), `genus_scope_layer.json` (genus + scope-neighbors + sequence-FTO), `real_filing_dates.json` (111 real filing dates + lapse timelines), `whitespace_grid_node_dir.json`, `whitespace_grid_node_ind.json`, `whitespace_thin_cells.json`, `dynamic_signals.json`, `tl1a_knowledge_graph.json`. Scripts: `bin_scope_grid.py`, `whitespace_analysis.py`, `dynamic_signals.py`, `build_kg.py`. Candidate-generation, NOT FTO; native KC uncalibrated; recall/identity are lower bounds.