CLDN18.2 — V4 Target Opportunity Report (Public Edition)

Whitespace & Trajectory, in one decision-first view

Target: CLDN18.2 — Claudin-18 splice-variant 2 (isoform 2). Gene CLDN18 (HGNC:2039; UniProt P56856; Wikidata gene Q18040098, protein Q21100780). A lineage-restricted tumor-associated antigen — the isoform-2-specific first extracellular loop (ECL1), de-repressed on gastric/GEJ, pancreatic and biliary adenocarcinomas. Reference drug: **zolbetuximab** (Vyloy/IMAB362; originator Ganymed/TRON; Astellas; FDA-approved 2024). **Date:** 2026-07-26 · **Substrate:** a full-landscape patent-family set (incl. the pre-2020 Ganymed foundational tail); **106 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*, necessary-but-not-sufficient for opportunity. Structural overlap and sequence identity are directional **lower bounds**. On an antibody target the dominant fence is the **binder sequence (CDRs)**, which this analysis flags but does not adjudicate. Verify any specific family before relying on it.
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> **Public edition note.** This is the public edition of the CLDN18.2 V4 Target Opportunity Report. It presents the whitespace and trajectory reads that accompany the LinkedIn 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

CLDN18.2 is a **crowded, young, China-dominated** single-epitope oncology target. There is little clean modality whitespace; the actionable plays are payload-lane differentiation, the still-pending redirection frontier, and one speculative mechanism. Detail in §2 (whitespace), §3 (the actionable chemical core), §4 (trajectory).

#	Opportunity	Status	Why it's actionable	Watch / design around
1	**Non-camptothecin ADC payload**	**Contestable now**	The CLDN18.2 ADC payload centre of	The anthracycline

#	Opportunity	Status	Why it's actionable	Watch / design around
	(e.g. anthracycline, novel-MoA, immune-agonist payload) — gastric/pancreatic		gravity is the **topoisomerase-I / exatecan / DXd camptothecin lane** and it is crowding; **all on-pathway ADC genera are pending** (no consolidated grants). A differentiated payload chemotype is the clearest in-cell structural room	lane is already partly occupied; the ADC genus is **binder-locked** (a different CDR + same payload class is a design-around)
2	**CAR-T / CD3 T-cell-engager** entrant (novel binder or logic) — solid-tumor	**Time-limited window**	The 2023-2026 redirection frontier is **almost entirely pending — 2 live grants of 19 families**; the grants have not consolidated	The pending CAR / T-cell-engager cohort is filling fast; one CD3-engager has now granted
3	**Single-domain / VHH binder** format — solid-tumor	**PARTIAL (not yet COVERED)**	The VHH/nanobody binder lane is the least-saturated antibody format (5 on-pathway, only 2 live) — a differentiated small-format binder or building block	A small number of granted VHH incumbents already anchor the lane
4 *(speculative)*	**CLDN18.2 degrader / tight-junction functional modulator**	**OPEN***	No family in the corpus claims degrading/functionally-modulating the CLDN18.2 protein itself — a mechanistic alternative to killing CLDN18.2+ cells	**Corpus-tested-and-absent but mechanistically hard (cell-surface structural protein); weakest call. A molecular-glue degrader-ADC payload filed off-pathway is the transfer chemistry to

#	Opportunity	Status	Why it's actionable	Watch / design around
				test
5	**RNA/vaccine · peptide/mimotope · next-gen diagnostic**	**THIN****	Each holds only 1 on-pathway *US-anchored* family	**Corpus artifact: the China/EP/WO ex-US tail (RNA, aptamer, cyclic-peptide, IHC families) is bibliographic-only — re-test after ex-US frack before relying
—	**naked-mAb / ADC-camptothecin / CD3-bispecific / CAR (generic)**	**AVOID**	COVERED & crowded: naked-mAb 39 families (16 live), ADC 16 (9 with a compiled genus), CD3-TCE 12, CAR 16	The foundational mAb estate plus the dense China fast-follower estates

The one-sentence read: on CLDN18.2 the defensible room is **not a new mechanism** — it is a **differentiated ADC payload lane**, an **entry into the still-pending CAR / T-cell-engager frontier before its grants consolidate**, and the **under-populated VHH binder format**, plus a speculative degrader hypothesis — all while designing around a dense, sequence-defined (CDR) binder thicket that is 70% China-origin.

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2. Whitespace map — the cells

The 106 on-pathway families were projected onto a scope grid (engagement-mode × modality/format × direction × 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 held only by pending applications.

Verdict rule: OPEN = 0 on-pathway families · THIN = ≤2, no broad live genus · PARTIAL = coverage but no broad live-granted genus · COVERED = broad live-granted genus OR dense (≥3) live-granted estate.

modality / format cell	verdict	on-path families	live grants
naked / Fc-engineered mAb	**COVERED**	39	16

modality / format cell	verdict	on-path families	live grants
ADC (small-molecule payload)	**COVERED**	16	4
CAR / cell therapy	**COVERED**	16	4
non-CD3 bispecific	**COVERED**	15	3
CD3 T-cell-engager	**COVERED**	12	4
single-domain / VHH	**PARTIAL**	5	2
RNA / vaccine / nucleic-acid	**THIN****	1	0
peptide / mimotope	**THIN****	1	0
diagnostic reagent	**THIN****	1	0
direction: degrader / functional-modulation	**OPEN***	0	0

* **`degrader/functional` OPEN caveat:** the classifier *has* a degrader/PROTAC/molecular-glue keyword path and **0 of the corpus families matched** — so this is tested-and-absent *in this corpus*, but degrading a cell-surface tight-junction protein is mechanistically hard; it is the **weakest** open call, a hypothesis prompt. ** **RNA/peptide/dx THIN caveat:** each holds only 1 *US-anchored* on-pathway family; the discovery pass surfaced China/EP/WO RNA/aptamer/peptide/IHC families at bibliographic tier only — these cells are THIN *in the US corpus*, not necessarily globally.

Read: the honest whitespace is narrow. Every established modality is COVERED. The genuine room is inside the COVERED ADC cell (payload-lane, §3), in time (the pending frontier, §4), in the PARTIAL VHH format, and in the speculative degrader direction.

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3. The actionable chemical core — the ADC payload/linker lane

CLDN18.2 is an antibody target: **binders are fenced by sequence (CDR sets), not by small-molecule genus.** Of the genus-bearing families corpus-wide, **only the ADC linker-payload chemistry compiles a small-molecule Markush genus** — and it is **binder-locked**: the canonical formula is `A-(L-T)n` (antibody `A` fixed to a CDR set; linker `L`; toxin/payload `T` at *class* level; DAR `n`). The chemical fence is therefore **(fixed CDR antibody) × (payload class) × (linker)**.

- **Topoisomerase-I / exatecan / DXd-class camptothecin is the crowding payload lane** — it appears in the large majority of CLDN18.2 ADC genera and is filling fast. This is where *not* to build.
- **Non-camptothecin payloads are thinner.** An anthracycline chemotype is differentiated and only lightly occupied; a maytansinoid lane appears mostly in combination. A CLDN18.2 ADC on a **non-camptothecin payload** is the clearest in-cell differentiation (Opportunity #1).
- **All on-pathway ADC genera are pending** — the payload/linker *grants* have not consolidated (temporal window), and the **binder-lock** means a different-CDR antibody with the same payload class is a design-around the genus does not reach.

4. Trajectory — where this target is going (real filing dates)

Composed from real `filing_date` on all 106 on-pathway families (no expiry proxy), by era × format × entrant origin.

era	n	live grants	dominant formats	entrant origin
pre-2017 (foundational)	5	5	naked-mAb (4) + first ADC	**EU** (Ganymed/TRON) + Japan
2017-2019	12	9	naked-mAb (8) + first CD3-bispecific + VHH	China (7), US (3), EU (1)
2020-2022 (the surge)	**70**	17	naked-mAb (25), non-CD3 bispecific (13), ADC (11)	**China (56)**, EU (4), US (4), Japan (3)
2023-2026 (frontier)	19	**2**	**CAR/cell (7), CD3-TCE (5), ADC (3)**	China (11), US (5)

Trajectory statement: *CLDN18.2 filing exploded off a small EU-origin foundational naked-mAb base (Ganymed, 2006-2013) into a 2020-2022 surge — 66% of the on-pathway estate,* ***overwhelmingly China-origin (56 of 70)*** *— that diversified formats (naked-mAb still leading, then non-CD3 bispecifics, ADCs, CD3-engagers). The 2023-2026 frontier has* ***pivoted to cell therapy (CAR-T/CAR-NK) and CD3 T-cell-engagers****, and — decisively —* ***these newest cells are almost entirely pending (2 live grants of 19).*** *Direction of travel: naked-mAb → format diversification → T-cell-redirection/cell-therapy; geography: EU-founded → China-dominated (****70% of the on-pathway estate****); maturity: the surge is consolidating into grants now while the redirection frontier remains contestable.*

The decisive dynamic — this estate is YOUNG, not decaying. Unlike a mature target with a lapsing first wave, CLDN18.2 has **0 lapse/discontinuation events among the 106 on-pathway families**; the foundational Ganymed families are all still maintained. The window is not decay-driven freedom but **grant-consolidation timing**: 33 of 106 are already granted-active, but the strategically-interesting newest cells (CAR/TCE, 2023-2026) are pending. **The window is *before those grants issue*, not *after old ones lapse*.**

5. Combination adjacencies + cross-class transfer

- **Combination interest:** CLDN18.2 is most co-claimed with **CD3** (T-cell-engager backbones), **4-1BB / CD40 / OX40** (co-stim), **CD47/SIRPα** (innate checkpoint), **PD-L1/PD-1** (checkpoint), and cytokine-armed cell platforms. **Unclaimed rational pairs** worth testing: CLDN18.2 × a non-CD3 redirection co-stim in one molecule for the pending frontier; CLDN18.2 ADC × checkpoint (the ADCs are mostly monotherapy-drafted).
- **Cross-class transfer (candidate generation; lower bounds):** the ADC payload/linker genera overlap generic ADC-platform chemistry filed for other

targets. A single **molecular-glue degrader ADC payload** filed off-pathway is the clearest transfer hypothesis into the OPEN degrader direction — proven degrader-conjugate chemistry, not yet aimed at CLDN18.2.

- **The dominant fence is sequence, not genus** — a dense CDR-similarity thicket means the real design-around problem for a new CLDN18.2 binder is epitope/CDR freedom, which this structural layer flags but does not adjudicate (not FTO).

PART II — METHOD & LIMITS (public summary)

How the reads were built

- **Discovery** across all four jurisdictions (US/EP/WO/CN; a large China-dominated ex-US tail), then a **full-landscape assembly including the pre-2020 Ganymed/TRON foundational anchors**, whole-family.
- **Scope binning** onto four externally-grounded axes (literature + Wikidata) — engagement-mode, direction, modality/format, indication — *not* derived from the patent set; each family carries a claim-scope `scope_evidence` string.
- **A load-bearing on/off-pathway screen:** of the full set, **only 106 families genuinely claim a CLDN18.2 mechanism**; a substantial share co-mention CLDN18.2 but their scored claim recites a generic platform (CAR backbone, cytokine receptor, CD3 arm, bare ADC linker, manufacturing) and are held out of the whitespace/trajectory denominator (retained only as combination/transfer signal). Treating raw hit counts as coverage would overstate the estate.
- **Structural genus/scope layer** over the genus-bearing families (ADC genus binder-locked; overlap is INDETERMINATE-dominated — candidate generation), and **real filing dates** on all 106 on-pathway families for the trajectory (no expiry proxy).
- **Independent adversarial review** of the analysis by an impartial reviewer with full data/script access (independent recompute + Wikidata re-query); headline integrity fixes were applied 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/THIN cell is a hypothesis prompt, not clearance.
- **The dominant fence on this antibody target is the binder SEQUENCE (CDRs)**, not a small-molecule genus — only the ADC payload/linker compiles a genus, and it is binder-locked. The sequence layer flags the CDR thicket but does not adjudicate epitope/CDR freedom.
- **`degrader/functional` OPEN is tested-and-absent in this corpus but mechanistically hard** — the weakest open call. The RNA/peptide/dx **THIN cells are US-corpus artifacts** — the China/EP/WO ex-US tail (bibliographic-only) holds such families; re-test after ex-US full-text frack.

- **The denominator is operator-defined** (the scope ontology); different axes → different whitespace. **Classification is a model read** emphasizing cell-level patterns over single-family calls.
- **Corpus-bounded & US-anchored.** Whitespace is relative to the ingested families; the large China/EP/WO ex-US landscape materializes at bibliographic tier (full-text analysis not yet run); genuinely un-filed art is invisible by construction.

This public edition presents the CLDN18.2 whitespace and trajectory reads. Every whitespace/trajectory number is computed on the 106 on-pathway families on real filing dates. Candidate generation, NOT freedom-to-operate.