ACTH Receptor (MC2R) — V4 Target Opportunity Report

Whitespace & Trajectory, in one decision-first view — public edition

Target: ACTH receptor = **MC2R** (melanocortin subtype-2 receptor / ACTHR) — HGNC:6930, UniProt **Q01718 Date:** 2026-07-30 · **Substrate:** 25 ingested patent families; **23 on-pathway** after claim-scope screening; 90 members; real filing dates **1992-04-10 → 2025-08-28**. Plus **2 externally-discovered families ingested on demand** and reported as a separate layer.

> **Public edition.** Presents the whitespace/trajectory reads that accompany the article. The underlying KC strength scoring, per-family score tables, knowledge graph, and raw 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.

What this is for: to let an inventor or BD&L reader *act* — see where the defensible room is, where the field is going, and which existing claims stand in the way — without first reading how the analysis was built.

> **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. Genus recall is a **lower bound**. The strength-scoring layer that sits underneath this analysis is **uncalibrated** (Gold Set 0/200–300), is used only for *relative* ordering within this corpus, is never a valuation, and is **not published in this edition**. Verify any specific family before relying on it. Full method, reclassifications and limits are in **Part III**.
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> **One target-specific warning that outranks the rest.** This corpus **cannot read 26% of itself.** The six OMass Therapeutics families — the entire non-incumbent live small-molecule antagonist programme, with a named clinical candidate — have **zero claims ingested**, and re-ingest provably does not repair it. Every comparative statement about this target's competitive position is blocked on that gap. It is stated wherever it bites, and it is not worked around.

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 (structure), §4 (trajectory). Evidence in Part II.

#	Opportunity	Status	Why it's actionable	Watch / design around
1	**Acquire or revive**	**LAPSED,**	Granted claim 1 retains	2027-09-03 is the

#	Opportunity	Status	Why it's actionable	Watch / design around
	`US-8524664-B2` (Univ. of Denver) — a **method-of-use claim to selective MC2R antagonism for hypercortisolism**, functional preamble intact	**revivable**	*"an agent that significantly inhibits activation of a melanocortin 2 receptor (MC2R) without significantly inhibiting activation of a melanocortin receptor other than MC2R"*, narrowed only by a `wherein` proviso to two short peptides. Maintenance fee unpaid, operative **2025-09-03**; petitionable under 37 CFR 1.378(b) with **no hard bar**	threshold beyond which the Office wants extra explanation of the delay — **not** a deadline. Anticipated expiration 2031-06-02, so the residual term is short. The *peptide* scope is narrow; the value is the preamble and the prior-art position
2	**MC2R–MRAP accessory-protein interface blocker** (`N3`)	**OPEN — the only corroborated absence**	Zero families in-corpus **and** zero interface-blocking claims in three independent claim-scoped searches of the whole Google Patents corpus. Genetically validated (MRAP LoF → familial glucocorticoid deficiency 2, OMIM 607398) and structurally resolved (PDB **8GY7**, 3.30 Å)	**Two serious caveats, §2.2(iv)–(v).** MRAP's extracellular region acts as a *"seat-belt"* stabilising bound ACTH, so an interface blocker may read on **orthosteric-antagonist claim language** as a matter of construction. MRAP modulates **all five** melanocortin receptors, so the selectivity problem is inherited, not escaped. And this analysis **cannot assess feasibility at all**
3	**MC2R agonist for glucocorticoid deficiency 1**	**UNSEARCHED — not measured**	The **only** MC2R disease association in Wikidata via P2293 is **glucocorticoid deficiency 1** (Q5572316, OMIM 202200) — a **loss-of-function** phenotype. The human genetics on this receptor support	The operator gate deliberately excluded all ~47 verified-tier agonist terms, so the zero in this cell **measures our own search**. Marketed peptide agonists (cosyntropin, tetracosactide, corticotropin, seractide)

#	Opportunity	Status	Why it's actionable	Watch / design around
			agonism for a rare deficiency, while the entire commercial estate is *antagonism for excess*	are long off-patent. Treat as a hypothesis prompt requiring a dedicated slice
4	**Exploit the reagent layer that is now free** (N5)	**LAPSED / EXPIRED-OPEN**	The OHSU/Cone founding estate is dead: three members term-expired (filed 1992/1993/1995), two expired for non-payment and now also term-expired, one abandoned. Deltagen (knockout mouse) abandoned; Genaissance (haplotyping) dead with the company	**Structurally open is not free.** The disclosures survive permanently as §102/§103 prior art — *including the recombinant-cell screening method for "an inhibitor of agonist binding to a mammalian adrenocorticotropic hormone receptor."* The assay you would use to find antagonists is published art
5	**In-scaffold room inside the incumbent's *granted* fence**	**Contestable, narrower than it looks**	The broadest genus measured on an **issued** claim is **0.594** (US-12492181-B2, precision 0.995), not the 0.739 headline — that one is on a **pending** application. The same family's two granted compiles come in at recall **0.221** and **0.043**	Crinetics 76477827 is the real granted fence. But recall is a **lower bound** and a failed compile is **unmeasured, not zero** — three of six compiles failed
—	**N2 allosteric MC2R modulator**	**flagged — do not treat as whitespace**	Zero families, and no allosteric modulator reported anywhere	Its emptiness rests partly on the same instrument blind spot as N7's did: **no discovery slice targeted allosteric chemistry.** Newly flagged in this revision. It may be genuinely open; this analysis has not earned the right to say so
—	**N7 ligand supply / anti-ACTH biologic**	**AVOID — granted-occupied**	**H. Lundbeck A/S holds 8 US grants (2017-06-27 → 2025-09-30) plus EP-3835319-B1** across	This cell was reported as *unmeasurable whitespace* in the first pass. It is not. See §2.3 —

#	Opportunity	Status	Why it's actionable	Watch / design around
			two anti-ACTH antibody families, on the same indication set as the entire corpus	and note that the "antibody is a hard format here" argument was **wrong**: the play is against the **ligand**, not the 7TM receptor
—	**N1 orthosteric antagonist, generic chemotype**	**AVOID**	COVERED: 18 of 23 families, 13 live grants (all Crinetics), 5 families with live grants	Crinetics across nine families. **But** six competitor families sit in the same cell with **no readable claims**, so "how contested" is genuinely unknown

The one-sentence read: on this target the actionable surface is **legal-status decay and the modality axis, not genus geometry** — a lapsed method-of-use claim inside its revival window, one corroborated mechanistic absence at the MRAP interface that carries a claim-construction problem of its own, and a genetically-anchored agonist question nobody has searched — while the orthosteric small-molecule lane is held by a single incumbent whose broadest *granted* fence is narrower than its headline, and the biologic lane turned out to belong to Lundbeck all along.

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2. Whitespace map — the open cells

The landscape was projected onto a four-axis scope grid (mechanism-node × direction × modality × indication; §II-A), built from external sources and human-gated **before** any family was placed on it.

Verdict rule: OPEN = 0 on-pathway families · THIN = ≤2 families and no broad live genus · COVERED = broad validated live genus present · LAPSED/EXPIRED-OPEN = occupied only by time-barred families.

mechanism cell	verdict	on-path families	families w/ live grant	live grants	best recall (family-level)	best recall **granted**
N1 orthosteric / **antagonist**	**COVERED**	**18**	**5**	**13**	0.739 *(pending app)*	**0.594**
N1 orthosteric / agonist	**OPEN** ⚠	0	0	0	—	—
N2 allosteric / antagonist	**OPEN** ⚠	0	0	0	—	—
N2 allosteric /	**OPEN** ⚠	0	0	0	—	—

mechanism cell	verdict	on-path families	families w/ live grant	live grants	best recall (family-level)	best recall **granted**
agonist						
N3 **MRAP interface** / antagonist	**OPEN**	**0**	0	0	—	—
N4 transcript / knockdown	THIN	1	0	0	—	—
N5 gene / protein / reagent	**LAPSED / EXPIRED-OPEN**	3	0	0	—	—
N6 targeting address / non-modulating	THIN	1	0	0	—	—
N7 ligand supply / antagonist	**OPEN IN CORPUS — EXTERNALLY OCCUPIED** ⛔	0	0	0	—	—

⚠️ = artefact-flagged, **not** whitespace. ⛔ = **granted-occupied on external evidence.**

Of five cells reading zero, exactly one is a clean absence. One (N7) is occupied by a top-20 pharma. One (N1×agonist) measures our own operator gate. Two (N2, both directions) rest on the same instrument blind spot as N7 did. That leaves **N3**, whose emptiness was independently corroborated outside the corpus — and which carries the claim-construction caveat in §1 row 2.

Modality × node is almost degenerate, which is itself the story. N1 holds 17 small molecules and 1 peptide; N4 one oligonucleotide; N5 one reagent, one animal/cell tool, one genotyping method; N6 one radioconjugate. Two axis values are genuinely unpopulated and flagged (**degrader**, **gene/epigenetic editing** — neither searched). The third, **antibody**, is unpopulated *in the corpus* and populated *in the world* (§2.3).

A named lower bound on the COVERED cell, and the sharpest caveat in this report. Forfar *et al.* (LifeArc + Queen Mary University of London, *Endocr Connect* 2022, **PMID 36515667**) report *"a highly specific MC2R antagonist … having selectivity for MC2R amongst the human melanocortin receptors"* from a small-molecule screen. It is the **only other reported specific small-molecule MC2R antagonist**, and it has **no visible patent family** — absent from the 23, and absent from a targeted sweep of LifeArc's US portfolio (25 hits, no melanocortin family). A published, characterised, selective antagonist with no findable estate is direct evidence that this corpus is a **lower bound on the very cell called COVERED**.

3. The structural layer — what is actually fenced

Six families carry a compiled Markush genus. **Three of the six compiles FAILED**, and two of those three are the non-incumbent chemotypes — so the structural extent of the competition is **unmeasured, not zero**.

Publication	Family	Sponsor	Grant status of *this* publication	Compile	Precision	`family_best.recall`	Enumeration
US-20240300920-A1	68692821	Crinetics	**PENDING — `grant_date: null`**	candidate	0.980	**0.739**	—
US-12492181-B2	**76477827**	**Crinetics**	**granted 2025-12-09**	candidate	**0.995**	**0.594**	4.0×10^{8}
US-12479825-B2	75849034	Crinetics	granted 2025-11-25	candidate	**0.460**	0.523	2.1×10^{6}
US-12466829-B2	76576023	Crinetics	granted 2025-11-11	**failed**	0.980	0.065	3.8×10^{6}
WO-2024237266-A1	93519713	**Scohia**	pending (PCT)	**failed**	0.905	0.484	96
US-20230405157-A1	88730850	Radionetics	pending	**failed**	0.980	**0.000**	3.92×10^{10}

The headline number does not hold on the granted record. The only genus above 0.70 on this target is **claim 56 of a pending Crinetics continuation**. That family holds seven live grants — but the two granted members that were compiled return `failed` genera at recall **0.221** (`US-11566015-B2`, 22 structures enumerated) and **0.043** (`US-12479828-B2`, 14). What is measured broadly has not issued; what has issued compiles narrow.

So the design-around order is: `76477827` first (broad, precision 0.995, **granted**) → then the pending 0.739 as a forward-looking constraint → then `75849034` discounted on precision 0.460 → then `76576023`, where a design-around "outside the spirocyclic family" is relying on a compile that failed.

And the cross-class transfer lane that carried the cGAS-STING and PCSK9 analyses is not available here. The only non-empty genus-overlap edge sets belong to two Crinetics publications and are dominated by 1970s–80s US patents matching at `frac = 1.0` in both directions; `US-`

`12479825-B2`'s own genus has precision 0.460, and a low-precision genus matches promiscuously. These are a **precision artefact**, not competitive overlap. **No edge connects any Crinetics publication to either the Scohia or the OMass chemotype — because Scohia's compile is `failed` and excluded from the overlap graph, and OMass has no compiled genus at all. That is the absence of a measurement, not a measurement of absence.** `rdna_compare_claims` returned HTTP 500 on four attempts, so the Crinetics↔Scohia relationship stays **UNMEASURED**.

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4. Trajectory — where this target is going

Every date is a real member `filing_date`. **No expiry-minus-20 proxy is used anywhere.** Priority dates are not in the substrate (`earliest_priority_date_field` is null for all 25 families), so eras are cut on earliest member filing.

Era	Families	Modality mix	Sponsor origin	Live-grant families	Unreadable claims
pre-2010	4	reagent 1 · genotyping 1 · animal tool 1 · **small molecule 1**	US 4	0	0
2010–2018	1	**peptide 1**	US 1	0	0
2019–2022	7	small molecule 6 · oligonucleotide 1	US 6 · CN filing 1	**5**	1
2023–2026	11	small molecule 10 · radioconjugate 1	US 4 · **GB 6** · **JP 1**	**0**	**6**

Incumbent share reverses: 0/4 → 0/1 → **6 of 7 (86%)** → **4 of 11 (36%)**. The reversal is robust — recomputed under seven alternative era-boundary definitions plus equal-count quartiles, the penultimate era runs **80–100%** Crinetics and the final era **22–43%** in every one of them. Re-labelling Radionetics as third party (defensible: affiliated, not controlled) takes the final era to **27%**, so the finding strengthens. **Report the direction and the range, not the two decimals.**

This is not a pivot, and that is the interesting part. cGAS-STING pivoted agonist→inhibitor; PCSK9 pivoted antibody→oral. MC2R has done something different: **the direction of travel has never changed, and everyone who tried it before the incumbent stopped paying.**

- **pre-2010 is entirely dead and was never commercial** — an academic cloning estate, a mass knockout-mouse programme, a mass haplotype library, and one genuine attempt: ChemDiv's 2006 composition claim to compounds *"having an inhibitory effect on the MC2R receptor"*, **twelve years and eight months before Crinetics' earliest non-provisional filing**. It has one member, was **never nationalised in any jurisdiction**, so no exclusive right ever issued from it. Its significance is permanent §102/§103 prior art.
- **2010–2018 is the sharpest data point** — the University of Denver's functional-genus method-of-use, granted with the preamble intact and a `wherein` proviso limiting the agent to a decapeptide and an undecapeptide, then lapsed for non-payment on **2025-09-03**.

Someone tried to own selective MC2R antagonism for hypercortisolism as a method of use and left the Office holding two short peptides.

- **2019–2022 is the incumbent building essentially alone** — six Crinetics families and one Novo/Dicerna RNAi filing. **Every live grant on this target comes from this window.**
- **2023–2026 is where the field arrives — from outside the United States and entirely pre-grant.** Third-party share goes 1-of-7 → **7-of-11**; six of those seven are OMass (UK), the seventh Scohia (Japan, a 2017 Takeda carve-out). **Not one of the eleven holds a live grant, and six of the eleven have no readable claim scope at all.**

The honest consequence. The most active era on this target is also the least measurable, and the un-scorable set is *entirely* ex-US-anchored. Two readings are available and the data does not choose between them: the competitive picture is genuinely early (nothing has granted, so the cell is contested in prosecution and not in exclusion), **or** the instrument cannot see the current frontier (WO-only ex-US filings are exactly the shape this corpus reads worst). **Any claim about how the non-US entrants' positions compare to the incumbent's is not supported by this analysis.**

PART II — THE EVIDENCE

II-A. The scope-coordinate system (how "whitespace" is defined)

Whitespace only exists relative to a coordinate system. Four axes, externally grounded (Wikidata SPARQL ×14 queries with 69 raw responses, UniProt, PubMed, IUPHAR/BPS, the FDA label), human-gated — **not** derived from the patent set, which would be circular. Definitions: `V4_ACTH_whitespace/data/ontology.json`.

- **mechanism_node (7):** `N1` orthosteric · `N2` allosteric · `N3` **MRAP interface** · `N4` transcript · `N5` gene/protein/reagent · `N6` targeting address · `N7` ligand supply
- **direction (5):** agonist · antagonist · knockdown · non-modulating binder · none (tool/dx)
- **modality:** small molecule · peptide · oligonucleotide · radioconjugate · NA/protein reagent · animal/cell tool · genotyping · antibody/protein biologic · degrader · gene/epigenetic editing
- **indication:** CAH · Cushing's disease · ectopic ACTH · hypercortisolism · adrenocortical carcinoma · glucocorticoid deficiency · other

Three adjacent nodes are deliberately screened OUT and retained only as competitive context, because they share the indication and not the mechanism: **CRF1/CRHR1 antagonism** (crinecerfont / CRENESSITY, FDA-approved 2024-12-13, whose own label reads *"a selective corticotropin-releasing factor (CRF) type 1 receptor antagonist"* — it cuts ACTH *release* at the pituitary and never touches MC2R), **steroidogenic-enzyme inhibition** (osilodrostat, mitotane, levoketoconazole), and **glucocorticoid-receptor antagonism**. Screening them out matters: the upstream node is occupied by an approved drug, and lumping it in would have made the receptor look contested by agents that never bind it.

Two grounding findings that shaped the read.

1. **The genetic anchor points the opposite way from the therapeutic hypothesis.** The only MC2R P2293 edge in all of Wikidata is to **glucocorticoid deficiency 1** (Q5572316, OMIM 202200, Orphanet 361) — verified against both the gene item (Q14909766) and the protein item (Q410784), in both directions. Every indication the corpus claims was pair-tested and carries **no** P2293 edge to MC2R, POMC or MRAP. Those are hormone-**excess** phenotypes in which MC2R is the mediator, not the mutated gene.
2. **The target's lead asset is invisible to the ontologies.** `search_terms("MC2R")` returns ~47 verified-tier drug suggestions and **every one is an agonist or the ACTH-stimulation diagnostic**. Corroborated independently: **corticotropin is the only entity in all of Wikidata with a P129 edge to MC2R**, and it is the endogenous agonist. Meanwhile **atumelnant** exists only as a bare Wikidata stub (Q131735774, zero statements) and **CRN04894 does not exist at all**. The operator gate that rejected the agonist list and hand-supplied the lead compound is load-bearing, not ceremonial.

One curation inconsistency in our own pharmacology source, stated rather than dropped. GtoPdb lists corticotrophin-releasing hormone (`ligandId 912`) as an MC2R agonist with `primaryTarget: true` — inconsistent with screening CRF1 out. We treat it as a curation artefact and rely on it either way; but we cannot cite the file as authority for the interaction inventory and ignore one of its rows. Relatedly: all ten GtoPdb MC2R records carry an **empty `targetBindingSite`**, so "orthosteric" is our inference from ligand identity, **not** a GtoPdb annotation. The defensible form is the negative: *none of the ten carries an allosteric annotation.*

II-B. IP-portfolio strength — withheld from this edition

The analysis carries a family-scoped claim-strength layer underneath the whitespace map: it reports how well the coverage that *does* exist is drafted. It is **uncalibrated** — the Gold Set stands at 0 of a target 200–300 — so a published per-patent table would read as precision that does not exist, and a named-party quality ranking is an exposure the guardrails forbid. **It is withheld in full, along with the per-family tables, the weighting-basis comparison and the dispersion statistics.**

Two things from that layer are reportable because they are structural rather than evaluative, and both are load-bearing above:

- **The strength layer on this target measures one cell.** Twelve of the thirteen scored families sit on the orthosteric node and one on the targeting-address node. **Every other node in the ontology has no scored family at all** — either it holds no family, or the families it holds are named absences (§II-C). Whatever the strength layer says, it says it about the cell that is already COVERED.
- **Its novelty dimension carries no signal here, and we can prove it.** The off-pathway ZTE mobile-handset patent scores the exact modal on-pathway value on that dimension (§III-B). No ranking derived from it is published, and none should be relied on.

II-C. Named absences — ten families, and why they are not low scores

This is the integrity core of the run. **Ten of the 23 on-pathway families carry no native KC**, and none of them is a low score:

- **Seven are structurally un-KC-scorable** (`coverage.kc: deferred`, `claims.total_n: 0`) — the six **OMass** families and **Dicerna**. Re-ingest provably does not repair them (`source_max_produced_at` stays 2026-07-11). OMass is 26% of the corpus, 6 of the 11 most recent filings, and the entire non-incumbent live antagonist programme.
- **Three have no agent card at all** — OHSU, Deltagen, Genaissance, the dead pre-2010 reagent layer.

`absent_checked` ≠ 0. A family with no readable claim is not a weak family; it is an unmeasured one. Two further families report `claims_total_n: 0` and *are* readable because their claims were recovered from published documents — including Crinetics `93589762`, whose claims recite `Formula (I) ×36` and **never** recite MC2R, antagonism, melanocortin or ACTH. Its mechanism is specification-only (description ¶132). Its placement in the orthosteric cell rests on the spec, not the claims. *(The same weakness is disclosed for `83321094`, where "MC2R" appears in the title but not the claims. It is applied symmetrically because it cuts both for and against the incumbent.)*

II-D. Legal status — the temporal signal under §4, and why the rollup was not used

The corpus's own legal-status rollup verdict was wrong in *both* directions on 3 of 4 checkable grants — too generous on `US-8524664-B2` (called `granted_active` when it had lapsed) and too harsh on `EP-4077307-B1` and `EP-4081525-B1`, the latter an **in-force Unitary Patent**. Liveness throughout this analysis is derived from legal-event semantics instead, and the rollup is not relied on anywhere.

Date	Publication	Sponsor	Event	Final?
—	US-5280112-A · US-5554729-A · US-5773229-A	OHSU	expired by **20-year term** (filed 1992/1993/1995)	**yes**
—	US-6046011-A · US-6392027-B1	OHSU	expired for **non-payment**, now also term-expired	**yes**
—	US-20030044973-A1	OHSU	abandoned — failure to respond	yes
—	US-20020133843-A1 · US-20060174361-A1	Deltagen	abandoned — failure to respond	yes
2009-07-08	WO-2007133108-A1	ChemDiv	EP regional phase **not entered**	—
2024-10-02	WO-2023060141-A2	Dicerna (Novo)	EP regional phase **not entered** *(one event; the corpus duplicates the row)*	—
2025-09-	**US-8524664-B2**	**Univ. of**	**maintenance fee unpaid —**	**no —**

Date	Publication	Sponsor	Event	Final?
03		**Denver**	**11.5-year (final) window**	**revivable on petition**
2025-07-07 → 2026-06-29	EP-4077307-B1	Crinetics	**6** distinct PG25 *"lapsed in a contracting state"* notifications — designation pruning	partial
2025-10-13 → 2026-01-27	EP-4081525-B1	Crinetics	**7** such notifications — on a patent that then took **unitary effect**	partial
2026-02-18	WO-2024175925-A1 · WO-2024175927-A1	OMass	EP regional phase **not entered**	—

The lapse is verified on primary USPTO evidence and independently corroborated. Official Gazette **1539 OG 138** (2025-10-28), operative date **2025-09-03**, 11.5-year fee, application 13/152,233; no reinstatement in **39 consecutive Gazettes** to 2026-07-28. Independently: the IFI CLAIMS legal-event feed carries `FP · 2025-10-28 · Effective date: 20250903`, and the date is arithmetically forced — grant 2013-09-03 → 11.5-year fee due 2025-03-03 → six-month grace ends 2025-09-03. **What required the gazette was the *fact* of non-payment, not the *date*.**

On terminology. *"Expired"* is the statutory word (35 U.S.C. §41(b)(2)), the Gazette's word and the event-code word — including in our own decay data, which quotes the USPTO text verbatim as *"Patent **Expired** Due to NonPayment…"*. We use "lapsed" in prose only because in commercial reading "expired" is heard as term-expired and final. **A non-payment lapse inside the petition window is neither.** A landscape tool that renders that as a green cell is not conservative enough to be useful.

"13 live grants" broken down, because its composition is softer than the integer reads: 10 US + 2 EP + 1 CN. The two EP grants carry the PG25 partial-designation caveat — `PG25` notifications are per-state renewal cessations, the patent survives where renewals were paid, and both of these did, so **"one live EP grant" is not uniform European coverage** and the counts are lower bounds because the notifications do not name the states. The one CN grant, `CN-112533904-B`, is counted live on **two byte-identical `GR01` grant notices and nothing else** — no post-grant maintenance evidence of any kind. The other CN grant is `liveness_indeterminate` only because its timeline is empty. **Both CN grants are in the same epistemic state; CN liveness is unconfirmed for both.**

II-E. The external N7 estate — the finding that changed a verdict

Reported in the first pass as *unmeasurable whitespace*. It is granted-occupied. Found outside the corpus by adversarial review, then **ingested on demand and re-verified from primary corpus records**:

Publication	Family	Filed	Granted

Publication	Family	Filed	Granted
US-9688754-B2	53879059	2015-02-20	**2017-06-27**
US-10047157-B2	56127868	2015-12-18	**2018-08-14**
US-10544214-B2	56127868	2018-08-13	**2020-01-28**
US-10550180-B2	53879059	2017-06-05	**2020-02-04**
US-11117960-B2	56127868	2019-12-09	**2021-09-14**
US-11427631-B2	53879059	2020-02-03	**2022-08-30**
US-12351627-B2	53879059	2022-06-27	**2025-07-08**
US-12428475-B2	56127868	2021-08-09	**2025-09-30**
EP-3835319-B1	56127868	2015-12-18	**2025-11-19**

Two families, 27 members, eight US grants and a granted EP, assignee **H. Lundbeck A/S** — the earliest grant issued to **Alder BioPharmaceuticals, Inc.**, which Lundbeck acquired in 2019. Titles: *"Anti-ACTH antibodies"* and *"Humanized anti-ACTH antibodies and use thereof."* Claim 1 of US-12428475-B2 is a method of *"reducing at least one of cortisol, aldosterone, and corticosterone levels"* by administering an anti-human-ACTH antibody defined by six CDR SEQ IDs; its dependent indication claims recite **CAH (classical and nonclassical), familial glucocorticoid deficiency, Cushing's disease, Cushing's syndrome, ectopic-ACTH Cushing's, ACTH-driven hypercortisolism, hypertension and hyperaldosteronism** — *the same indication set as the entire on-pathway corpus.*

Two lessons, both kept in the record. First, the **antibody modality's** stated cause was the wrong diagnosis: "an antibody to a seven-transmembrane receptor is a hard format" is true of *receptor*-directed antibodies and irrelevant here, because the play is against the **circulating ligand**. Second, **a flag that says "unmeasurable" where the truth is "granted-occupied" is its own hazard** — worse than no flag, because it looks like diligence.

Named limits on this layer, none of which soften the verdict: the two families are **deliberately excluded from the 23-family denominator** (folding them in would silently change every count in this report); no genus is compiled (`genera: []` — a valid absence-first answer for antibody claims, not a zero); no agent card exists for either 2025 grant, so no coverage map, KC or legal rollup; claims are unfracked across all 11 members of family 53879059; verbatim claim text is unavailable from the corpus, so claim language is quoted from published documents; and the externally-reported adjusted expiry of 2036-04-09 for US-12428475-B2 is **not** verified in this pipeline.

II-F. Combination adjacency, and the sequence layer that was thrown away

Combination: exactly one architecture in-corpus — Dicerna's 85803732, co-claiming MC2R **and** CYP11B1 knockdown in one construct, the only family crossing the grid's own screened-out boundary into the steroidogenesis lane. Scope unread. The only other adjacency worth naming is **Scohia's claim-20 indication sweep, which is not four indications but eighteen** — including **obesity and type 2 diabetes**, the two largest markets on the list and an indication reach no other sponsor claims on this receptor.

The sequence layer is invalid on this target and is used nowhere. The `sequences-extract/v1` extractor is **falsified** on a 1976 Sumitomo small-molecule patent (`US-3979390-A`), is **non-idempotent** across family members, and returns **zero hits on the one family that actually holds ACTH peptides**. Rather than report it with a caveat, it is omitted entirely and the defect is filed upstream. An FTO-adjacent surface built on a 15-residue alignment is worse than no surface.

II-G. Knowledge graph

A typed knowledge graph underlies the analysis, and three of its design choices are worth stating because in each case the obvious default would have misled:

1. **The unoccupied mechanism nodes are nodes in the graph.** The allosteric surface and the MRAP interface carry zero incident "acts on" edges. **An unoccupied node is the analytical output, not missing data** — a graph built only from what was filed cannot express whitespace.
2. **External occupancy is typed and quarantined.** The ligand-supply node carries zero in-corpus edges and two explicit *external occupancy* edges under their own node type, so no corpus statistic silently absorbs them. The graph distinguishes *empty in the corpus* from *empty in the corpus and occupied in the world* — a distinction the first pass of this analysis got wrong.
3. **"Overlap unmeasured" is a typed edge.** The Scohia↔Crinetics relationship is represented as an explicit non-measurement carrying its reason, rather than as the absence of an edge — because the absence of an edge is exactly what a reader would misread as non-overlap.

The graph, the scope ontology and the machine-readable inputs are internal work-product and are not published.

PART III — METHODOLOGY, RECLASSIFICATIONS & LIMITS

III-A. How the substrate was built

1. **Discovery:** `search_terms` on the receptor (verified HGNC/UniProt tier + operator-reviewed drug tier — the operator **rejected all ~47 verified-tier agonist/diagnostic terms** and hand-supplied atumelnant/CRN04894, which no ontology carries); `discover_patents` across US/EP/WO/CN.
2. **Ingest:** 25 families materialised, 90 members with per-member text tiers; ex-US members at bibliographic tier where English claims were absent.
3. **Strength layer (not published here):** a family-scoped strength read was produced for **13 of the 23 on-pathway families**; the other **10 are named absences (§II-C), not low scores**. It is uncalibrated relative-ordering work and is deliberately excluded from this edition.
4. **Scope binning:** each family classified onto the four axes by a **claim-scope read**, not the title; each family carries a `scope_evidence` string. Where the corpus had no claims, the bin rests on titles plus named external evidence, and says so.

5. **Structural layer:** `get_patent_genus` + `get_scope_neighbors` over 19 probed publications — **8 return a `family_best` genus, 11 return none** (10 of them on-pathway).
6. **Legal layer:** liveness derived from legal-event semantics after the rollup verdict was found wrong in both directions; the headline lapse verified against the primary Official Gazette.
7. **Whitespace + graph layers:** the coverage-density grid, thin-cell detector, genus layer, decay timeline, trajectory signals and knowledge graph, each produced by a script so that every count in Part I is reproducible from the substrate rather than asserted in prose.

Comparison ≠ reliance. No prior V2/V3 score is an input to any V4 value. The prior run's `family_id` was used for identity/dedup only.

III-B. The load-bearing reclassifications

Two of 25 families are OFF-pathway, and the corrections matter because the earlier prose record had both wrong:

- **`60324583` is a ZTE mobile-handset battery-temperature patent.** OFF_TARGET_HARD. It survives in the corpus only as a **control**: on the strength layer's novelty dimension it scores the exact modal on-pathway value. A mobile-phone patent cannot share a property of the ACTH receptor, which is how we established that that dimension carries no signal on this target — and why no ranking derived from it is published.
- **`96700157` is a DKS testosterone family** with **zero occurrences of MC2R anywhere in the document.** OFF_PATHWAY.

Eight further corrections were applied to the inherited prose record, all evidence-backed — OMass has **6** families not 5; `93589762` is a **Crinetics CAH** family, not what the prose said; `38431686` is **ChemDiv 2006** with MC2R inhibition as an express claim limitation, a single WO member never nationalised, so **prior art only**; **Scohia Pharma is Japanese** (a 2017 Takeda carve-out — the CN "SCORHIA PHARM CO LTD" is a transliteration artefact of PCT/JP2024/017921); and **Radionetics is affiliated, not controlled** (Crinetics determines it is **not** the primary beneficiary and does not consolidate, *"due to lack of control over key decisions"*).

III-C. Adversarial audit — two rounds, both REJECT

Both layers were independently audited by impartial subagents with fresh context and full data + script + live-MCP + web access.

- **Strength layer (round 1): REJECT — 11 MUST-FIX + 11 SHOULD-FIX. All 22 applied.** Three findings changed conclusions: a claimed identity between weighting bases was **retracted**; a claim that the novelty dimension measured a property *of the target* was **withdrawn** as unattributable (the ZTE control settles it); and the **sequence layer was declared invalid** on this target and removed entirely rather than published with a caveat.
- **Whitespace / trajectory (round 2): REJECT — 8 MUST-FIX + 16 SHOULD-FIX. All 24 applied.** The reviewer reproduced 18/5/13, all nine cell verdicts, 27 of 28 trajectory cells, all six genus rows and the KG counts independently — **no cell verdict was bent.** Every defect was in prose written *about* a number, or in an external fact asserted without a live check. Three findings changed conclusions: **`N7` is granted-occupied** (§II-E); **the 0.739**

fence is on a pending application; and **"nobody has published on it" was false** (112 PubMed records). The audit records themselves are internal QA documents and are not published.

Every MUST-FIX in round 2 was re-derived here before it was applied, rather than accepted on the reviewer's word — including re-verifying the Lundbeck estate by ingesting it, re-checking `NCT05999292` against the live ClinicalTrials.gov API, and re-counting PubMed live. Two further defects were found in the process and are logged as SELF-1 and SELF-2 in the round-2 record; one of them (the unread-claims conflation propagating into the trajectory table) had **survived review**, because the number was reproducible from the field it was computed from while the prose gloss on it was wrong.

The process signal, stated for the methodology owner. Across both rounds the scripted layer was essentially flawless and the narration layer produced every defect. Five of the 24 round-2 findings were figures inherited from an earlier document rather than re-derived; three were external facts asserted without a live check. **A mandatory prose re-derivation pass belongs in the playbook before publication.**

III-D. Limits — read before relying

1. **Not FTO, not calibrated.** No cell in §2 is clearance. OPEN is necessary and not sufficient. Native KC is uncalibrated (Gold Set 0/200–300) and is never used to grade whitespace.
2. **The instrument cannot read 26% of its own corpus.** Six OMass families, zero claims, re-ingest non-repairing. This is the binding constraint on every competitive statement.
3. **Four of five zero cells are flagged and one of them is occupied.** Only `N3` is a corroborated absence — and it carries a claim-construction problem (limit 8) and no feasibility assessment (limit 9).
4. **The broadest measured genus is on a pending application.** 0.594 is the broadest on an issued claim. The grid's broad-genus rule can be satisfied by three different documents and does **not** require the genus to be granted; both predicates are now reported.
5. **Three of six genus compiles FAILED**, two of them the non-incumbent chemotypes. Recall is a lower bound; a failed compile is unmeasured, not zero. The large scope-neighbour edge counts are a **low-precision artefact**, not overlap.
6. **The sequence layer is invalid on this target** and is unused (§II-F).
7. **The corpus is US-anchored by construction history**, and **ex-US grant liveness is unconfirmed for both CN grants**; EP state-level pruning cannot be enumerated from member records. "13 live grants" is 10 US / 2 EP / 1 CN and a lower bound with a soft composition.
8. **`N3` is not cleanly axis-independent from `N1`.** On 8GY7 the MRAP extracellular region stabilises bound ACTH, so an interface blocker may read on orthosteric-antagonist claim language. The empty-cell finding is about claim *wording*; claim *scope* is not resolved here.
9. **This analysis cannot assess chemistry feasibility anywhere.** It reports the patent record.
10. **Priority dates are not in the substrate** (null for all 25 families), so all era cuts are on earliest member filing. The trajectory shape survives every cut tested; individual row counts do not.

11. **Verbatim claim text is unavailable from the corpus** (`gcs_verbatim_uri` 403; the claims API exposes structure only). Every claim quotation is from a published document, cited as such.
12. **`rdna_compare_claims` returns HTTP 500** (4 attempts), so Crinetics↔Scohia genus overlap is **UNMEASURED** — not zero.
13. **Failed verification legs, named not papered over:** USPTO ODP API 401 (key required); Patent Center OKTA; Maintenance Fee Storefront auth-gated; Maintenance Fee Events bulk file DNS unreachable; PatentsView DNS unreachable; **USPTO Patent Assignment Search DNS unreachable, so the assignment chain is unverified**; Espacenet/EPO OPS Cloudflare + 403.
14. **The scope ontology is an operator artefact.** Different axes → different cells. It is grounded externally and human-gated precisely so the empty cells are not artefacts of the patent set — but they remain artefacts of *these axes*.

III-E. What the next run should do

1. **Get claim text for the six OMass families.** Highest-value gap on the target by a wide margin. Until it closes, no comparative statement about OMass is supportable.
2. **Work the Lundbeck `N7` estate properly** — cards, claim fracking on family 53879059, post-grant status and term — and answer the question a BD&L reader asks next: do those claims reach a **receptor**-directed antagonist at all?
3. **Resolve Crinetics ↔ Scohia by manual claim construction.** The tool cannot do it and the compile will not improve on its own.
4. **Run the three searches whose absence produced flagged cells** — a deliberate **agonist** slice (`N1`×agonist), an **allosteric-modulator** slice (`N2`), and a **POMC/ACTH-sequestration** slice (`N7`) — so flagged cells become real measurements or real absences rather than statements about our own query design.
5. **Search MRAP-interface art directly** with spelled-out accessory-protein phrasing plus structural terms (PDB 8GY7), never the bare `MRAP` token — which collides with Mine Resistant Ambush Protected vehicles and 3GPP master radio access points and returned **17 of 17 pure string collisions**.
6. **Chase the LifeArc / Queen Mary antagonist (PMID 36515667) to a family or to a documented absence.** Unindexed family and genuine non-filing have opposite implications for the COVERED cell.
7. **Populate `earliest_priority_date`** so era cuts can run on priority as well as filing.
8. **File the `sequences-extract/v1` defect upstream** — chemistry-context guard, minimum length well above 15 residues, and idempotency across family members before its output feeds any FTO surface.
9. **Add a mandatory prose re-derivation pass to the playbook** (§III-C).

Sources: an IP-portfolio strength analysis and a whitespace/trajectory analysis, both independently audited to REJECT and both fully remediated before this edition was produced. Every whitespace and trajectory number is computed on the 23 on-pathway families on real filing dates. The strength-scoring layer, the knowledge graph, the scope ontology and the machine-readable inputs are internal

analyst deliverables and are not reproduced here. ***Candidate generation, NOT freedom-to-operate.***