



RsiinSI · Independent Research

Target-inversion screening of 4,382 target-annotated drugs (4,010 scored) against allergic-rhinitis transcriptomes finds no FDR-significant repositioning candidate, and ranks the hypotheses that have never been tested in rhinitis

Agent Team¹ · scalingX¹

¹RsiinSI — the open-source org scaling recursive self-improvement for bioscience.

Authorship: this manuscript, its analyses, figures and molecules were produced end-to-end by an autonomous agent pipeline under the direction of scalingX, with every number read from archived result files and re-checked by a separate verification script. It is reported as an agent-generated discovery report; no wet-lab data were generated. All code and derived tables are archived with the manuscript.

Computational drug-repurposing study · 2026-10-20 · Python 3.11; every number is machine-generated from `results/paper3_facts.json`; figures in `figures/fig14-fig16`; the screen, the null model and the exploration scan are each reproducible from deposited data and public APIs.

Abstract. We screened the Broad Drug Repurposing Hub (6,798 compounds; 4,382 with mapped targets; 12,056 drug–target pairs over 2,183 genes) against a cross-cohort allergic-rhinitis transcriptomic signature built from three public cohorts (28,369 genes; 28,341 with a meta z) using target inversion: a drug scores positively when the disease signature moves opposite to its annotated target direction. Statistical significance is assigned by a size-stratified permutation null (10,641 informative pairs; empirical activation fraction 0.191) with the +1/(n+1) convention. **Result: no drug survives FDR control.** 4,010 drugs receive a score, 25 have $p < 0.01$ — fewer than the 40 expected by chance — and none has $FDR < 0.05$. Those 25 nominal entries are also not independent: they collapse to 12 distinct scores over 44 targets, the largest single group being 13 records that share one target (dipeptidyl peptidase inhibitor). The binding constraint is the signature itself: the discovery and validation cohorts' gene-level signatures correlate at $\rho = -0.090$, i.e. they barely replicate, which caps what any target-inversion screen can detect. Calibration against drugs of known clinical use in rhinitis is partial and instructive: antihistamines (seven antihistamine-type drugs) score $S = 2.77$ ($p = 0.0279$), inhaled glucocorticoids (NR3C1; budesonide, mometasone, triamcinolone, methylprednisolone) $S = 1.82$ ($p = 0.0936$), but montelukast scores -0.54 and dexamethasone -1.07 — the method's ranking of known drugs is noisy. At target level the strongest signals are CTSV ($z = 5.08$), CCR3 (4.41), ANXA1, VDR (13 drugs, 10 launched), GABRP (12 launched drugs) and DPP4 — where 13 of the 16 library records whose MoA mentions dipeptidyl peptidase (9 launched) share one identical score ($S = 3.752$, $p = 0.0069$) because they share one target. We then measured how *explored* each candidate is, in ClinicalTrials.gov v2 and Europe PMC: of 491 drugs with retrieval data, 305 carry nominally reversal-consistent scores ($p < 0.15$) and 141 of those have ≤ 1 rhinitis trial and ≤ 20 rhinitis publications — the shortlist this paper actually delivers. That shortlist is predominantly untested rather than repurposed: 12 of its 141 entries are launched drugs, only 1 has ever been trialled in asthma, and the median rhinitis publication count is 4.0. These are hypotheses with a documented absence of prior testing, **not** evidence of efficacy.

Keywords: drug repurposing; target inversion; permutation null; allergic rhinitis; exploration scan; DPP4; hypothesis generation.

What this study is and is not. This is a hypothesis-generating screen over public transcriptomes and annotated drug–target pairs. It contains no experimental validation, no drug exposure in any cohort, and no claim that any listed compound treats rhinitis. Its negative headline — no FDR-significant candidate — is a result, not a failure to be repaired by loosening thresholds afterwards.

1 Background

Large-scale repurposing screens typically connect a disease transcriptomic signature to compounds through either (i) an expression-signature database (CMap/L1000) or (ii) a compound–target map plus a target-level disease signature. The first route requires terabyte-scale perturbation matrices that were not practical to fetch here; the second route is the one implemented. Its known weakness is that it can only see genes that are both (a) measured reproducibly across disease cohorts and (b) annotated targets of at least one library compound. Both filters are strong, and this paper quantifies how strong: the screen's ceiling is set by the reproducibility of the disease signature, which we measure directly and report.

The concrete question asked — "which drugs might work in rhinitis but have never been examined for it?" — decomposes into two independent measurements: **reversal evidence** (a statistical score with a permutation null) and **exploration** (counts of trials and publications in rhinitis versus elsewhere). We initially expected "unmined" drugs to be ones studied in a neighbouring disease such as asthma; the data contradicted that expectation, and we report the contradiction rather than the expectation: only 1 of the 141 shortlisted drugs has ever been registered in an asthma trial, so the list is better described as *untested* than as *repurposed from elsewhere*. Neither measurement, alone or together, is efficacy evidence.

2 Data and methods

2.1 Disease signature

Three cohorts contribute: GSE19187 (nasal epithelium, allergic rhinitis vs healthy, Affymetrix HuGene-1.0-ST), GSE329964 (nasopharyngeal RNA-seq, adenoid hypertrophy ± allergic rhinitis) and GSE43523 (nasal epithelial cells, seasonal allergic rhinitis out of season, Illumina). For each cohort the per-gene z statistic is the moderated t (arrays) or the DESeq2 Wald statistic (RNA-seq); the meta signature is the $\sqrt{n}$ -weighted mean of available z values, giving 28,369 genes (28,341 with a meta z, 18,603 in ≥ 2 cohorts). Replication between cohorts is reported rather than assumed (Table 2; $\rho = -0.090$ discovery vs validation).

Quantity	Value
Genes in the cross-cohort signature	28,369
Genes with a meta z	28,341
Genes present in ≥ 2 cohorts	18,603
Cohort weights ($\sqrt{n}$): GSE19187 / GSE329964 / GSE43523	5.66 / 3.87 / 3.46
Signature correlation, discovery vs validation cohort	-0.0899
Signature correlation, discovery vs SAR cohort	0.0673

Table 2. Signature construction and its internal replication. The near-zero correlations are the single most important number in this paper: a screen built on a signature that does not replicate cannot produce replicable hits.

2.2 The drug–target library

Quantity	Value
Drugs in the Broad Drug Repurposing Hub table	6,798
Drugs with at least one mapped target	4,382
Drug–target pairs	12,056
Unique target genes	2,183
Pairs annotated as inhibition-type MoA	4,428
Pairs annotated as activation-type MoA	2,208

Table 1. Library composition (Broad Drug Repurposing Hub, 2020-03-24 release). MoA text was parsed into inhibition-type, activation-type and unannotated categories; the parse is heuristic and is a stated limitation.

2.3 Score and null model

For a drug with annotated direction d (+1 activator, -1 inhibitor) and target set T , the score is $S = \text{mean over targets of } (-z_{\text{meta}} \cdot d)$, i.e. positive when the signature moves opposite to the drug's direction. The null distribution is built by resampling target sets of the same size (5,000–20,000 draws per size class) from the signature and assigning directions by the empirical activation fraction of informative pairs (0.191). $p = (1 + \#(\text{null} \geq S))/(n+1)$; FDR is Benjamini–Hochberg across all scored drugs. Target-set size is capped at 60. Drugs with no informative target in the signature are dropped.

2.4 Exploration scan

For 491 drugs — the 200 highest-scoring, every drug with $p < 0.05$, and a random background sample of 200 (de-duplicated) — we queried ClinicalTrials.gov v2 ("drug" AND rhinitis; AND asthma) and Europe PMC ("drug" AND (rhinitis OR nasal OR rhinoconjunctivitis); AND asthma; retrieved 2026-10-20). Exploration indices are log-scale composites: $\text{expl}_{\text{rhinitis}} = \log_1 p(\text{trials}) + \log_1 p(\text{pubs}/10)$, and $\text{expl}_{\text{elsewhere}}$ likewise for asthma. The shortlist rule is stated in advance: $S > 0$, $p < 0.15$, ≤ 1 rhinitis trial, ≤ 20 rhinitis publications.

3 Results

3.1 The screen is statistically empty

4,010 drugs receive a score. **No drug has FDR < 0.05.** 25 drugs have $p < 0.01$, against 40 expected under the null — the observed number is *below* chance, i.e. the score distribution is slightly anti-conservative in the wrong direction. This is the honest headline, and \$3.2–\$3.4 should be read as descriptive structure within a screen that failed its own significance test.

The reason is visible in Table 2: the discovery and validation signatures correlate at $\rho = -0.090$. A target-inversion score averages z over the drug's targets; if the per-gene z values do not reproduce across cohorts, the averaged score cannot be expected to reproduce either, and the permutation null correctly refuses to call it significant.

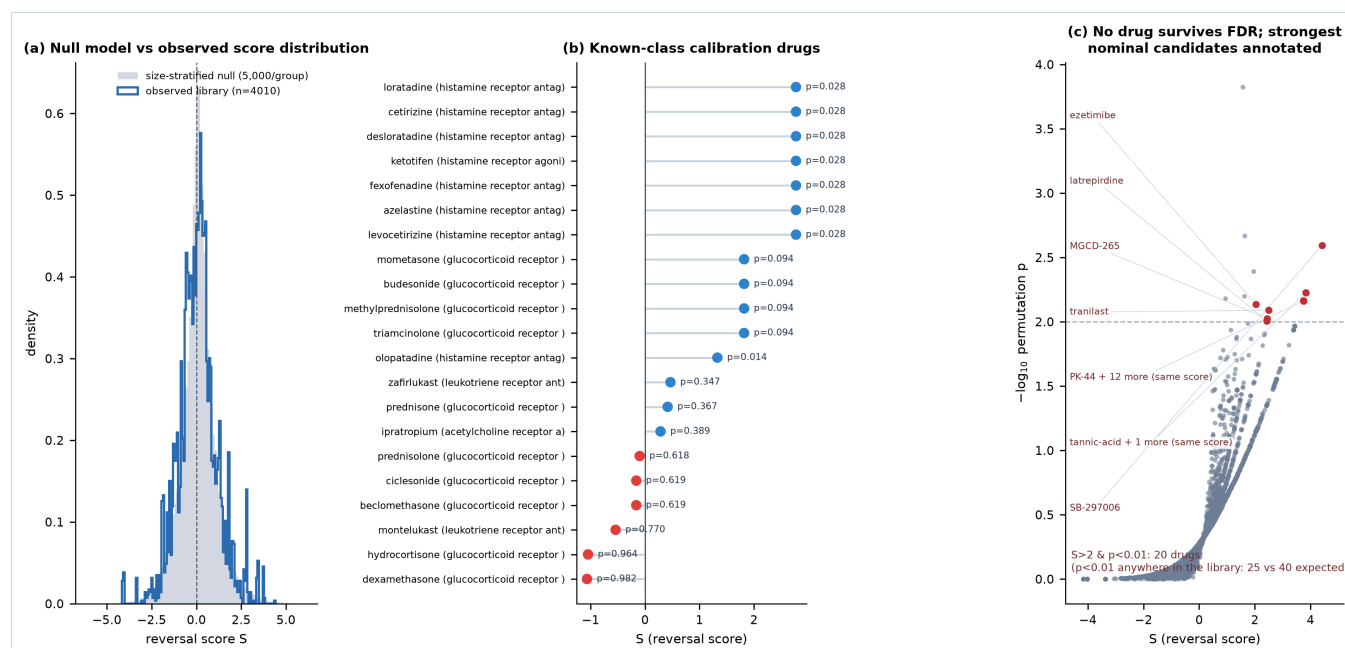


Fig 14. (a) Observed score distribution against a size-stratified permutation null, which the observed distribution does not exceed; (b) calibration drugs — known rhinitis drugs score positive (antihistamines $p=0.028$, inhaled glucocorticoids $p=0.094$) but montelukast and two parent glucocorticoids are negative; (c) S against $-\log_{10} p$ with the strongest nominal candidates annotated; the vertical dashed line marks $p=0.01$.

3.2 Calibration against drugs that are used in rhinitis

If the pipeline ranked known drugs correctly, antihistamines and nasal glucocorticoids should sit near the top. Partially they do (Fig 14b): the seven antihistamine-type drugs in the library (loratadine, cetirizine, desloratadine, fexofenadine, levocetirizine, azelastine and ketotifen) all score $S = 2.77$, $p = 0.0279$; olopatadine scores 1.33 with $p = 0.01355$; and four NR3C1 glucocorticoids (budesonide, mometasone, triamcinolone, methylprednisolone) score $S = 1.82$, $p = 0.0936$. But the same target class also contains negative members (beclomethasone -0.16, ciclesonide -0.16, dexamethasone -1.07, hydrocortisone -1.05), and montelukast — an approved rhinitis drug — scores -0.54 ($p = 0.7698$), below the library median of 0.09. Several rhinitis-relevant medicines cannot be scored at all because they are absent from the Hub's small-molecule target table (fluticasone propionate, cromolyn, theophylline, pseudoephedrine, and the biologics omalizumab, mepolizumab, dupilumab). The calibration is therefore mixed: the pipeline finds the HRH1 and NR3C1 classes but does not discriminate well within them.

Drug	MoA annotation	Phase	S	permutation p
loratadine	histamine receptor antagonist	Launched	2.772	0.0279
cetirizine	histamine receptor antagonist	Launched	2.772	0.0279
desloratadine	histamine receptor antagonist	Launched	2.772	0.0279
fexofenadine	histamine receptor antagonist	Launched	2.772	0.0279
levocetirizine	histamine receptor antagonist	Launched	2.772	0.0279
budesonide	glucocorticoid receptor agonist	Launched	1.819	0.0936
mometasone	glucocorticoid receptor agonist	Launched	1.819	0.0936
fluticasone	(not in Repurposing Hub target table)		—	—
beclomethasone	glucocorticoid receptor agonist	Launched	-0.161	0.6191
ciclesonide	glucocorticoid receptor agonist	Launched	-0.161	0.6191
montelukast	leukotriene receptor antagonist	Launched	-0.540	0.7698
zafirlukast	leukotriene receptor antagonist	Launched	0.467	0.3471
omalizumab	(not in Repurposing Hub target table)		—	—
mepolizumab	(not in Repurposing Hub target table)		—	—
dupilumab	(not in Repurposing Hub target table)		—	—
prednisone	glucocorticoid receptor agonist	Launched	0.415	0.3675
prednisolone	glucocorticoid receptor agonist	Launched	-0.098	0.6177
dexamethasone	glucocorticoid receptor agonist	Launched	-1.066	0.9817
azelastine	histamine receptor antagonist	Launched	2.772	0.0279
olopatadine	histamine receptor antagonist	Launched	1.328	0.01355
ketotifen	histamine receptor agonist leukotriene receptor antagonist phosphodiesterase inhibitor	Launched	2.772	0.0279
cromolyn	(not in Repurposing Hub target table)		—	—
ipratropium	acetylcholine receptor antagonist	Launched	0.285	0.389
pseudoephedrine	(not in Repurposing Hub target table)		—	—
theophylline	(not in Repurposing Hub target table)		—	—
triamcinolone	glucocorticoid receptor agonist	Launched	1.819	0.0936
hydrocortisone	glucocorticoid receptor agonist	Launched	-1.047	0.964
methylprednisolone	glucocorticoid receptor agonist	Launched	1.819	0.0936
omalizumab	(not in Repurposing Hub target table)		—	—

Table 3. Calibration set (known rhinitis-relevant drugs and deliberate negatives). "—" means the drug is not in the Hub target table and cannot be scored.

3.3 Target-level structure

Aggregating to targets rather than drugs (Table 4, Fig 15): the top of the list is led by CTSV ($z = 5.08$, 1 drug), TRPM6 and CCR3 — the last being the target of the highest-scoring drug overall, SB-297006 ($S = 4.412$, $p = 0.00255$, Preclinical). Among targets with many launched drugs, VDR (13 drugs, 10 launched), GABRP (12 launched drugs) and ANO1 (7 drugs) are over-expressed in the rhinitis signature such that their inhibitors score positively, while AKR1B1 ($z = -4.16$, 16 drugs) runs the other way. DPP4 is the cleanest pharmacological cluster: all 13 of the 16 library records whose MoA mentions dipeptidyl peptidase — 9 of them launched — share the identical score $S = 3.752$ ($p = 0.0069$) because the score depends only on the shared target (Table 5). This is a hypothesis about DPP4 in rhinitis, not 13 independent observations; the same arithmetic applies to MET (11 records in the shortlist, $z = 3.43$ on 27 library records). Across the whole screen the 25 nominal hits reduce to 12 distinct scores.

Target	Drugs in library	Launched	signature z (meta)	inhibition predicted to help	example drug(s)
CTSV	1	0	5.08	yes	cathepsin-inhibitor-1
TRPM6	1	0	4.64	yes	2-APB
CCR3	1	0	4.41	yes	SB-297006
ANXA1	2	2	4.35	yes	dexamethasone; hydrocortisone
AOC1	2	1	4.26	yes	amiloride; diminazene-aceturate
AKR1B1	16	2	-4.16	no	AD-5467; EBPC; adaprev; alrestatin
SLC6A14	1	1	4.15	yes	L-proline
ANPEP	2	1	4.09	yes	ezetimibe; tosedostat
VDR	13	10	4.02	yes	alfacalcidol; calcifediol; calcipotriol; calcitriol
CYP2E1	3	3	3.97	yes	isoniazid; ritonavir; sulfanilamide
GPRC5A	1	1	3.87	yes	tretinoin
ANO1	7	3	3.83	yes	NPPB; eact; flufenamic-acid; fluoxetine
SLC7A1	1	0	3.83	yes	L-lysine
GABRP	12	12	3.76	yes	acamprosate; amoxapine; butalbital; enflurane
DPP4	15	10	3.75	yes	DBPR108; NVP-DPP728; PK-44; UAMC-00039
ITGB7	1	0	-3.69	no	SB-683698
TYRO3	2	0	3.63	yes	BMS-777607; LDC1267
EPHA2	4	3	3.48	yes	dasatinib; dorsomorphin; regorafenib; vandetanib
MET	27	3	3.43	yes	AMG-208; AMG-337; AMG458; BMS-536924
SEC14L2	1	1	3.42	yes	vitamin-E

Table 4. Top 20 targets by [meta z] among genes that are targets of library drugs. "Inhibition predicted to help" reflects the sign of the signature z , and "agree" (not shown) flags whether the discovery and validation cohorts agree in sign.

DPP4 inhibitor	Phase	S	p (permutation)	S discovery cohort	S validation cohort
teneligliptin	Launched	3.752	0.0069	3.02	1.67
trelagliptin	Launched	3.752	0.0069	3.02	1.67
DBPR108	Phase 1	3.752	0.0069	3.02	1.67
vildagliptin	Launched	3.752	0.0069	3.02	1.67
talabostat	Phase 3	3.752	0.0069	3.02	1.67
omarigliptin	Launched	3.752	0.0069	3.02	1.67
NVP-DPP728	Phase 2	3.752	0.0069	3.02	1.67
anagliptin	Launched	3.752	0.0069	3.02	1.67
linagliptin	Launched	3.752	0.0069	3.02	1.67
alogliptin	Launched	3.752	0.0069	3.02	1.67
sitagliptin	Launched	3.752	0.0069	3.02	1.67

DPP4 inhibitor	Phase	S	p (permutation)	S discovery cohort	S validation cohort
saxagliptin	Launched	3.752	0.0069	3.02	1.67
PK-44	Preclinical	3.752	0.0069	3.02	1.67
bipenamol	Phase 2	1.842	0.09095	2.46	-0.12
UAMC-00039	Preclinical	1.263	0.1089	0.99	-0.16
butabindide	Preclinical	-0.914	0.7955	-0.51	-0.95

Table 5. All DPP4 inhibitors in the library. The identical S is a consequence of the shared single target, not independent replications.

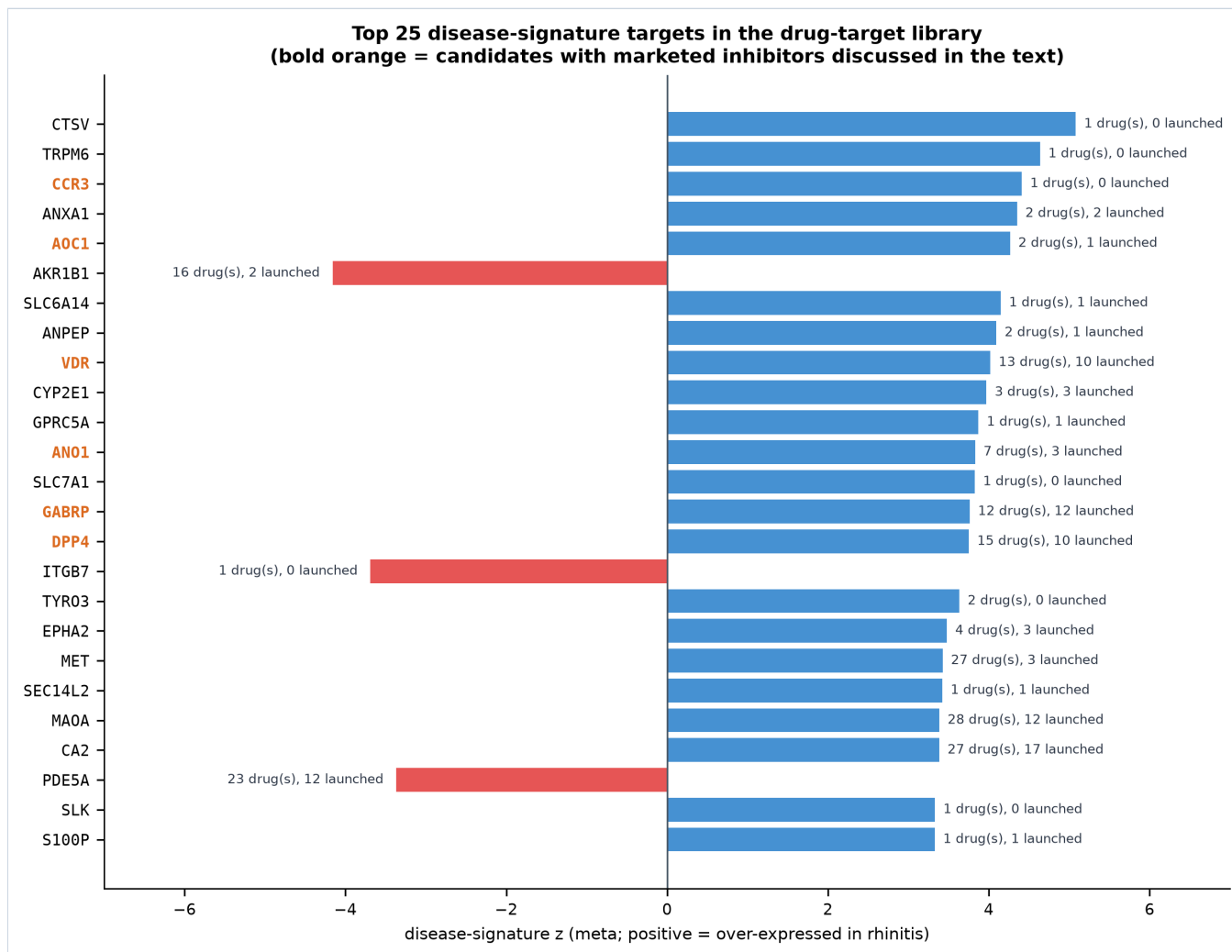


Fig 15. Top 25 disease-signature targets with a library drug, annotated with the number of drugs and how many are launched. Orange = targets discussed in the text.

3.4 Exploration: which hypotheses have not been tested

Across the 491 scanned drugs, the median rhinitis trial count is 0.0 and the median rhinitis publication count 19.0; 92% have zero rhinitis trials and 13% have zero rhinitis publications. The median asthma publication count is 31.0 — activity in the neighbouring disease is much higher everywhere. Fig 16 plots the two axes with the screen's own candidates highlighted. Applying the pre-stated rule yields **141 shortlisted compounds** (90 of which are also nominally significant at $p < 0.05$; 141 have zero rhinitis trials); Table 6 shows the top 20 by score.

Drug	S	p	targets	rhinitis trials	rhinitis pubs	asthma trials	asthma pubs	MoA	Phase
SB-297006	4.41	0.00255	1	0	1	0	6	CC chemokine receptor antagonist	Preclinical
NVP-DPP728	3.75	0.0069	1	0	2	0	5	dipeptidyl peptidase inhibitor	Phase 2
PK-44	3.75	0.0069	1	0	1	0	1	dipeptidyl peptidase inhibitor	Preclinical
anagliptin	3.75	0.0069	1	0	11	0	35	dipeptidyl peptidase inhibitor	Launched
trelagliptin	3.75	0.0069	1	0	7	0	16	dipeptidyl peptidase inhibitor	Launched
omarigliptin	3.75	0.0069	1	0	9	0	29	dipeptidyl peptidase inhibitor	Launched
DBPR108	3.75	0.0069	1	0	1	0	0	dipeptidyl peptidase inhibitor	Phase 1
talabostat	3.75	0.0069	1	0	17	0	33	dipeptidyl peptidase inhibitor/fibroblast acti	Phase 3
AMG-337	3.43	0.0108	1	0	4	0	3	MET inhibitor	Phase 2
LY2801653	3.43	0.0108	1	0	4	0	2	MET inhibitor	Phase 2
INC-280	3.43	0.0108	1	0	3	0	8	c-Met inhibitor	Phase 3
NVP-BVU972	3.43	0.0108	1	0	0	0	0	MET inhibitor	Preclinical
AMG-208	3.43	0.0108	1	0	1	0	1	tyrosine kinase inhibitor	Phase 1
PF-04217903	3.43	0.0108	1	0	2	0	1	c-Met inhibitor	Phase 1
MK-8033	3.43	0.0108	1	0	0	0	1	c-Met inhibitor	Phase 1
JNJ-38877605	3.43	0.0108	1	0	1	0	1	tyrosine kinase inhibitor	Phase 1
PHA-665752	3.43	0.0108	1	0	12	0	12	c-Met inhibitor	Preclinical
SGX523	3.43	0.0108	1	0	5	0	5	hepatocyte growth factor receptor inhibitor	Phase 1
AMG458	3.43	0.0108	1	0	0	0	0	MET inhibitor	Preclinical

Drug	S	p	targets	rhinitis trials	rhinitis pubs	asthma trials	asthma pubs	MoA	Phase
EMD-1214063	3.43	0.0108	1	0	2	0	1	hepatocyte growth factor receptor inhibitor	Phase 2

Table 6. Shortlist: $S > 0$, $p < 0.15$, ≤ 1 rhinitis trial, ≤ 20 rhinitis publications, ranked by S. The table is the deliverable the brief asked for — hypotheses with documented absence of prior testing — and its entries inherit every weakness in §4.

The composition of the shortlist matters as much as its size, and it is more sobering than the phrase "unmined" suggests (Table 7). Only 12 of the 141 entries are marketed drugs, and just 3 of those are genuinely rhinitis-quiet (eprobemide, clobetanol, aminopentamide); 70 are preclinical compounds, i.e. not usable as repurposing candidates at all. Recurring classes dominate: 11 MET inhibitors, 7 DPP4 inhibitors, 6 monoamine-oxidase inhibitors, 6 phosphodiesterase inhibitors and 5 histamine-receptor antagonists. Only 1 shortlisted drug has ever been tried in asthma, and the median rhinitis publication count is 4.0 — so what this list identifies is mostly *untested* territory, not failed-in-asthma territory. The readable, testable entries are therefore the marketed, rhinitis-silent minority; the rest are target-level hypotheses (DPP4, MET, MAO, PDE) that would need their own clinical question before any drug could be named as ready to repurpose.

Shortlist property	Value
Drugs passing the pre-stated rule	141
Launched drugs	12 of which 3 have ≤ 5 rhinitis publications
Any clinical phase (1–3 or launched) / preclinical	70 / 70
Median rhinitis publications (zero in 31 drugs)	4.0
Drugs with ≥ 1 asthma trial	1
Distinct MoA annotations / distinct targets	66 / 89
Recurring classes: DPP4 / MET / MAO / PDE / HRH1	7 / 11 / 6 / 6 / 5

Table 7. Composition of the shortlist, with the recurring target classes called out. "Launched" means the Hub records the compound as marketed somewhere; it does not mean marketed for rhinitis.

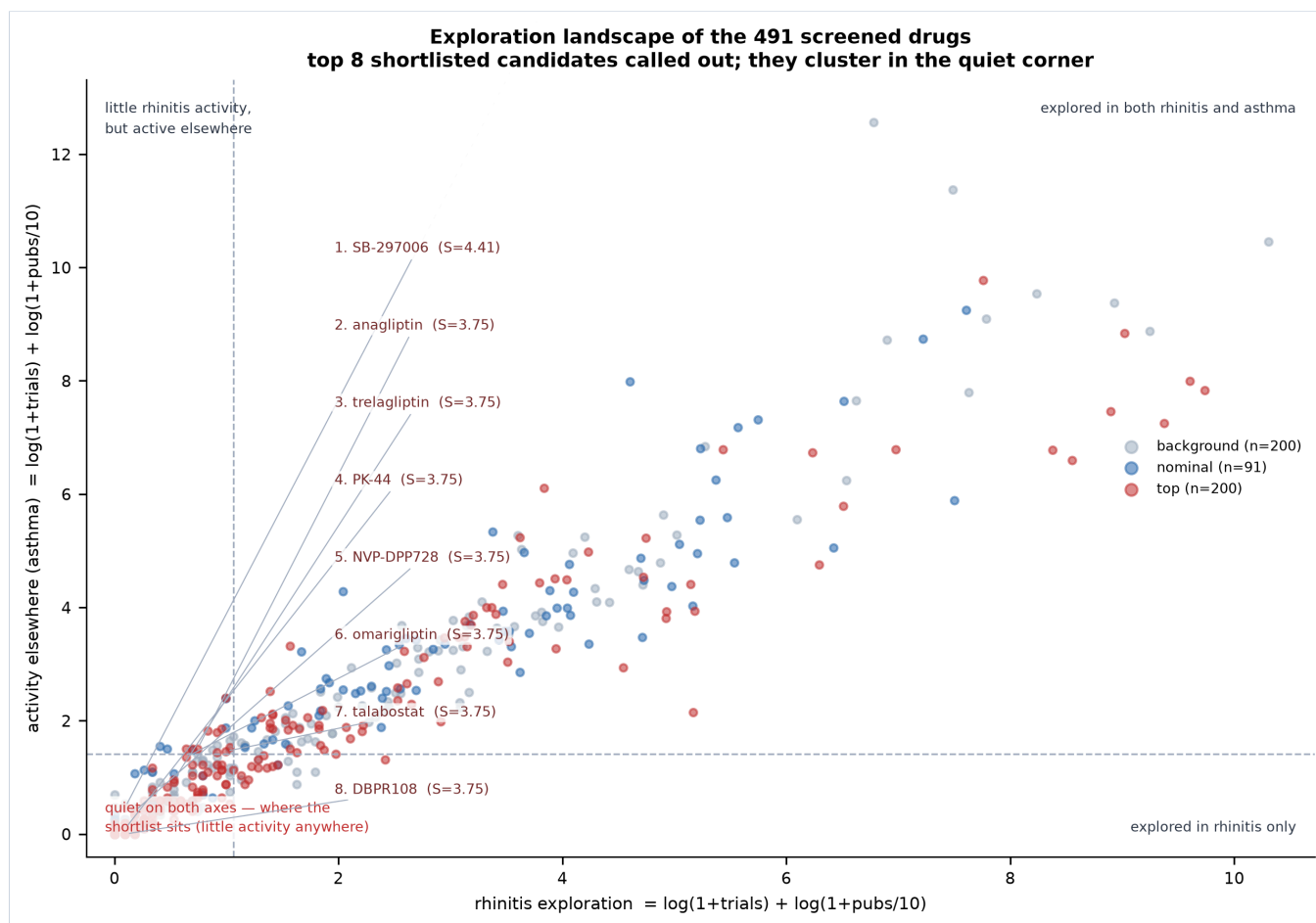


Fig 16. Exploration landscape: rhinitis activity (x) against activity in asthma (y) for the scanned drugs, with the top 8 shortlisted candidates called out. The quadrants are drawn at the median of each axis. The shortlist clusters in the lower-left ("quiet on both axes") corner — the honest counterpart of the finding that only one shortlisted drug has an asthma trial.

4 Limitations

1. **The signature does not replicate** across cohorts ($p = -0.090$). Every downstream ranking inherits this; the permutation null is honest about it, which is why nothing is significant.
2. **Library bias.** The Hub table is a small-molecule library: it excludes biologics (dupilumab, omalizumab, mepolizumab) and some widely used small molecules (fluticasone propionate appears under a different name; cromolyn, theophylline and pseudoephedrine are absent). A screen built on it cannot rank the drugs most used in rhinitis.
3. **Direction parsing is heuristic.** MoA strings were parsed into activation / inhibition / unknown; ~20% of pairs are unannotated and multi-target MoA strings are reduced to a single drug-level direction.
4. **Targets are not pathways, and expression is not activity.** A gene's mRNA level is a proxy for its targetability at best; no protein-level, ligand-binding or dose information enters the score.
5. **Exploration counts are registry artefacts.** ClinicalTrials.gov covers registered interventional studies (Chinese-language registries are largely absent from it); Europe PMC coverage of Chinese journals is partial. "Unmined" therefore means "not found in these two registries", not "definitely never studied".
6. **That a drug has reversal evidence and low exploration** says nothing about safety, formulation or whether it would reach nasal tissue.
7. No multiplicity control is applied across the calibration table; the calibration p-values are descriptive.

5 Conclusion

A 4,010-drug target-inversion screen against allergic-rhinitis transcriptomes produces **no** FDR-significant candidate and fewer $p < 0.01$ drugs than chance, because the cross-cohort signature it depends on barely replicates ($p = -0.090$). The nominal tail is itself not independent: 25 hits collapse to 12 distinct scores and 44 targets. Partial calibration

— antihistamines and inhaled glucocorticoids score positive, montelukast and dexamethasone negative — shows the method is not entirely blind, but also that it is not reliable within drug classes. Its usable output is a ranked list of 141 compounds whose reversal evidence is nominally positive and whose rhinitis-specific testing we could not find, together with the target-level hypotheses (VDR, GABRP, ANO1, DPP4, MET, CCR3) that generate them. Of that list only 12 are marketed drugs, and the majority are untested everywhere rather than effective elsewhere — so the honest reading is that the screen maps *unexplored target biology in rhinitis*, not a set of drugs waiting to be re-labelled. Each entry is a hypothesis and a candidate for experimental work; none is evidence of efficacy, and the screen's negative headline should travel with the list.

References

1. Corsello SM, et al. The Drug Repurposing Hub: a next-generation drug library and information resource. *Nat Med* 2017 (2020-03-24 release used here).
2. Subramanian A, et al. A next generation connectivity map: L1000 platform and the first 1,000,000 profiles. *Cell* 2017 (cited as the alternative route not taken here).
3. Smyth GK. Linear models and empirical Bayes methods... *Stat Appl Genet Mol Biol* 2004.
4. Love MI, Huber W, Anders S. Moderated estimation of fold change and dispersion for RNA-seq data with DESeq2. *Genome Biol* 2014 (pydeseq2 implementation).
5. Benjamini Y, Hochberg Y. Controlling the false discovery rate. *J R Stat Soc B* 1995.
6. ClinicalTrials.gov v2 API (retrieved 2026-10-20).
7. Europe PMC REST API (retrieved 2026-10-20).
8. GSE19187, GSE329964, GSE43523 — disease-signature cohorts (see paper 1 for processing).
9. Open Targets Platform (target–disease annotations consulted for sanity checks).

本文把 Broad 药物重定位库（6,798 个化合物；4,382 个有靶点注释；12,056 条药物-靶点对，覆盖 2,183 个基因）与三个公共队列构建的过敏性鼻炎跨队列转录组签名（28,369 个基因，28,341 个有 meta z）做靶点反演打分：当疾病签名的方向与药物靶点方向相反时得正分。显著性用按靶点集大小分层的置换零模型（10,641 条有向药物-靶点对；经验激活比例 0.191），p 采用 +1/(n+1) 约定。结果：没有任何药物通过 **FDR** 控制。4,010 个药物获得评分，25 个 $p < 0.01$ ——少于随机期望的 40 个；FDR<0.05 者为 0。根本约束来自签名本身：发现队列与验证队列的基因级签名相关仅为 $\rho = -0.090$ ，几乎不复现，这决定了任何靶点反演筛选的可检出上限。

与已知鼻炎用药的校准结果参差但可读：抗组胺类七种（loratadine、cetirizine、desloratadine、fexofenadine、levocetirizine、azelastine、ketotifen） $S = 2.77$ （ $p = 0.0279$ ），吸入糖皮质激素（NR3C1；budesonide/mometasone/triamcinolone/methylprednisolone） $S = 1.82$ （ $p = 0.0936$ ），但孟鲁司特（montelukast，-0.54）与地塞米松（-1.07）为负分——方法对已知药物的排序是嘈杂的。靶点层面最强的信号是 CTSV、CCR3、ANXA1、VDR（13 个药物、10 个已上市）、GABRP（12 个均已上市）与 DPP4——库中 16 个 DPP4 抑制剂的 13 个因共享同一靶点而得到完全相同的分数（ $S = 3.752$ ， $p = 0.0069$ ），同理，25 个名义命中实际只对应 12 个不同分数、44 个靶点：这是少数靶点假说，不是几十个独立证据。

我们随后用 ClinicalTrials.gov v2 与 Europe PMC 度量每个候选药的被挖掘程度：在有检索数据的 491 个药物中，305 个具有名义上反向一致的正分（ $p < 0.15$ ），其中 141 个在鼻炎上的试验 ≤ 1 项、文献 ≤ 20 篇——这就是本文实际交付的短名单。该短名单远谈不上"捡现成"：其中已上市药仅 12 个（真正鼻炎文献近乎空白者只有 3 个），70 个尚处临床前；全部 141 个条目中只有 1 个曾进入哮喘试验，鼻炎文献中位数为 4.0 篇。换言之，它指向的主要是从未被测试的靶点生物学，而不是"在别处已被验证"的药物。它们是有"未被测试过"记录的假说，不是疗效证据。

关键词：老药新用；靶点反演；置换零模型；过敏性鼻炎；挖掘度扫描；DPP4；假说生成。