The Rare, Underfunded Condition Within VHL

A (Draft) Hemangioblastoma Research Agenda for 2027 and Beyond

Six research tracks · 45 directions for the brain and spine compartment of von Hippel–Lindau disease

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Abstract
A first draft of a proactive research agenda for brain and spine hemangioblastoma — six tracks, 45 directions — published so the field can correct it. We are asking for input before 1 January 2027, when the project begins directing and commissioning work against it. Each direction ends in a physical act — a stain, a scan, a consent form, a protocol — and carries a confidence tier and the cheapest test that would advance or kill it. Fourteen are verified absences: things never measured, published or attempted. Tell us which are wrong, which are already under way in your lab, and which are impossible in practice.

1 A draft, on purpose — and what happens to it on 1 January 2027

This is version 1.8 of a first draft, not a set of conclusions. Between now and 1 January 2027 we are collecting corrections, additions and objections from clinicians and researchers; the agenda will be revised and re-issued, with credit, before any of it is acted on. From that date the project will partner with and direct research against these directions, commission specific experiments where no lab is already doing them, and fund inbound proposals that address them. Across every track, the primary outcome the project cares about is the same: fewer lifetime surgical procedures for people with VHL. A separate page, How we fund, covers the mechanics.

2 Six tracks. The kinds of things we are looking at, and suggesting.

Ordered so that each track's output makes the next interpretable: measurement first, then tissue, then the contradictions tissue would settle, then the drug that already exists, then new agents. Every direction below is expanded in full further down the page.

§	Track	Nos.	Evidence tiers
§4	I — Measurement and endpoints	1–5	1 verified, 3 absence, 1 inference
§5	II — Tissue, models and the sampling gap	6–10	2 absence, 3 inference
§6	III — Contradictions the literature has left standing	11–14	2 absence, 2 inference
§7	IV — Optimizing the drug that already works	15–20	1 verified, 2 absence, 1 inference, 2 hypothesis
§8	V — New therapeutic axes carried in from other fields	21–32	2 verified, 1 absence, 4 inference, 5 hypothesis
§9	VI — Therapeutics for hemangioblastoma, with or without HIF-2α	33–45	1 verified, 4 absence, 7 inference, 1 hypothesis

Table 1. Index of the six tracks. Full treatment in §§4–9; each track opens with a per-direction summary table.

Track I · 5 directions · Measurement and endpoints. Report the enhancing nodule, the cyst and the edema as three separate numbers, always. Validate surgery-free survival as the endpoint the field actually cares about. Build the growth model that certifies a lesion safe to watch. Turn post-contrast FLAIR and the retina into readouts of the vascular leak.

Track II · 5 directions · Tissue, models and the sampling gap. No tissue from any patient progressing on belzutifan has ever been analyzed: bank it now under a shared protocol. One dual-label stain on archived blocks settles six therapeutic leads at once. A single-cell and spatial atlas, cell of origin from public data, and drug escape read from cyst fluid and CSF.

Track III · 4 directions · Contradictions the literature has left standing. Is HIF-1α a driver or a tumor suppressor in post-belzutifan tissue? SSTR2A in 37 of 40 graded samples, or 0 of 112? Has anyone measured whether the drug engages its target in this lesion at all? Does propranolol act on the tumor cell or the vessel?

Track IV · 6 directions · Optimizing the drug that already works. Belzutifan is effective and almost certainly mis-dosed, un-genotyped and under-combined for an indication measured in decades. Intermittent and de-escalated dosing, UGT2B17 genotyping before dosing, the combination a person can take for forty years, anemia and the EPO loop, radiosurgery bracketing, next-generation inhibitors.

Track V · 12 directions · New therapeutic axes carried in from other fields. Reasoning outward from targets measured in this tumor to every agent that exists against them anywhere in medicine: dual-HIF inhibition, the EGFR/TGF-α loop, PlGF for the cyst, NOX4 from hepatology, MIF from neurology, CXCR4 as a theranostic pair, CDK4/6, ferroptosis, pocket-independent HIF-2α removal, a HIF-PHI safety statement, folding correctors, the FGFR vessel wall.

Track VI · 13 directions · Therapeutics for hemangioblastoma. The domain the other five tracks circle without entering: what else could treat this tumor. Does the existing drug even reach it; the brain-penetrant successor; six HIF-independent synthetic-lethal targets never checked here; statins and differentiation; the proteostasis trial that was never given a growth endpoint; whether this tumor is immunologically visible at all; and radioligand therapy, where the question is deliverable dose rather than receptor expression.

Highest-leverage single item · The compartment stain. Six independent analyses converged on one experiment: a dual-label immunohistochemistry panel on archived hemangioblastoma tissue that assigns each candidate target to tumor cell or vessel. About $40–75K, sixteen weeks, no new patients. It promotes or eliminates six leads at once. Direction 7

3 How to read the tracks

Every direction carries a confidence tier, and the tiers are not decorative. They were applied by the same discipline that governs the project's own board — the standing record of every target, agent and citation behind this draft — and several directions were demoted during preparation of the draft when full-text checking showed the supporting claim reached further than the source.

Tier	Meaning	n
Verified	A primary finding with a citation checked against the live record.	5
Verified absence	Structured search establishes that something has never been measured, published or attempted. Bounded by what is indexed.	14
Inference	The pipeline's reasoning from verified parts, stated so it can be attacked.	18
Hypothesis	A proposal, usually an agent approved or in trials elsewhere, whose first step is a cheap test rather than a trial.	8

Table 2. Confidence tiers used throughout §§4–9.

A verified absence deserves particular attention from a funder, because it is the one category a conventional literature search cannot return: absences are not indexed. It also carries a specific fragility, stated here once and applying throughout — absence of indexing is not absence of knowledge, and an unindexed thesis, registry, institutional collection or conference abstract can falsify any of them. Where that happens the author would like to be told, because being corrected is cheaper than being wrong.

Where a direction names a drug, that drug is already approved or in clinical trials somewhere in medicine — simply not here. The "cheapest test" line attached to each direction is deliberate and is the most practically important field in the draft: almost every direction can be advanced or eliminated by a stain on tissue that already exists, long before anyone designs a trial.

The tracks are organized by the kind of act each one requires, not by mechanism, because the binding constraint in this compartment is rarely a shortage of plausible mechanisms.

4 Track I — Measurement and endpoints

Five directions that gate every trial that follows. None requires a new patient, a new drug or a new scanner; each is a reporting convention or a reanalysis of data that already exists. They are placed first because every later direction inherits whatever measurement error is left standing here.

4.1 Direction 1. Report the three compartments separately, in every paper and every trial

The enhancing nodule, the peritumoral cyst and the surrounding edema are different tissues with different biology. Cyst fluid has the protein composition of plasma rather than of tumor secretion, which means cysts form by extravasation through leaky tumor vessels, not by tumor growth.[1] Yet almost every published series reports one blended volume, or a single maximum diameter that spans all three.

No.	Direction	Tier	First concrete step
1	Three-compartment reporting standard	Verified	Consensus statement; no cost
2	Surgery-free survival endpoint	Verified absence	Reanalysis of existing procedure counts
3	Growth-prediction / safe-to-watch model	Verified absence	Train on existing NIH archive
4	Post-contrast FLAIR as leak biomarker	Inference	Reanalysis of existing imaging
5	Retina as an optical window on CNS leak	Verified absence	Pair existing ophthalmic and brain scans

Table 3. Track I at a glance. Full treatment in §4.1–4.5.

That single convention is why the same LITESPARK-004 population has been published at 30%, 44%, 48%, 50%, 63% and 76% response.[2,10,31] The 44% cyst-inclusive and 76% solid-component figures are the same patients, same scans, same timepoint — a 32-point swing produced by a measurement choice. The field's own natural-history study states the consequence plainly: unpredictable growth compromises the assessment of non-surgical therapy.[3] A one-page reporting convention would make every cohort in the field poolable, and it is the precondition for every drug trial that follows.

lever A reporting standard: enhancing-nodule volume, cyst volume and edema volume, reported as three separate numbers, always.

cheapest test Costs nothing. Adopt as a consensus statement.

evidence Verified [1,2,3,10,31]

4.2 Direction 2. Validate surgery-free survival as the endpoint the field actually cares about

No VHL trial has used surgery-free or intervention-free survival as its primary endpoint, and none has applied recurrent-event statistics to the lifetime count of procedures. Where time to surgery has been measured, in LITESPARK-004 and against an external control arm, it was a secondary, time-to-first-event analysis. That is striking given that 47.3% of patients name reducing the number of surgeries as their top treatment goal and 73% would take a pill that might delay surgery.[4] The German regulator ruled belzutifan's additional benefit "not proven" on precisely this gap.[74]

The methodology already exists and has simply never been ported. Five other tumor-predisposition syndromes solved this problem — NF with selumetinib, TSC with everolimus, Gorlin with vismodegib, hereditary angioedema, PNH — using annualized event-rate designs with negative-binomial statistics. The one published VHL procedure-rate figure, a fall from 0.35 to 0.08 procedures per patient-year,[5,31] comes from a retrospective single-system cohort and has no confidence interval attached in any prospective analysis. The platform-trial design most closely matched to this disease already exists in NF2-related schwannomatosis.[6]

LEVER An annualized procedure-rate endpoint with negative-binomial statistics, ported from the syndromes that have already validated one.

FROM Benign tumor-predisposition trial methodology (NF, TSC, Gorlin, HAE, PNH).

CHEAPEST TEST A reanalysis of existing trial and real-world procedure counts; no new accrual.

EVIDENCE VERIFIED ABSENCE [4,5,6,31]

4.3 Direction 3. Build the growth-prediction model that certifies a lesion safe to watch

Roughly half of hemangioblastomas never grow and only about 6% ever become symptomatic, yet there is no radiomics or growth model that predicts symptom onset for any VHL lesion. The thresholds have been derived and never operationalized: cerebellar growth above 112 mm^3 per month, or 69 mm^3 with combined tumor-and-cyst growth above 14 mm^3 per month, separates lesions that will become symptomatic at 100% sensitivity and 72% specificity;[7] location-dependent size predicts eventual symptom formation at AUC above 0.9.[3]

The cost of not having this is quantified in the same literature. Intervening on radiographic progression alone would have produced approximately four additional procedures per patient across a ten-year study period.[7] A model that reliably certifies "watch, do not cut" therefore prevents surgeries directly, and given the natural history its prevented-surgery yield is plausibly larger than that of any drug currently in development. The training data already exists in the NIH natural-history archive.

LEVER A per-lesion growth and symptom-onset model on serial volumetrics, with a calibrated "safe to watch" output.

FROM Radiology / radiomics.

CHEAPEST TEST Train on the existing NIH natural-history archive: 1,921 lesions across 15,819 lesion-years.

EVIDENCE VERIFIED ABSENCE [3,7]

4.4 Direction 4. Turn post-contrast FLAIR into a pharmacodynamic readout of the leak

Post-contrast FLAIR is more sensitive than T1 to gadolinium that has leaked into cyst fluid, and was proposed on that basis as a way to assess peritumoral fluid extravasation after pharmacological treatment.[8] The proposal was explicitly framed as future work and, as far as the structured search can establish, nobody has tested it.

In the drug era this matters more than when it was written. If the cyst is the compartment that escapes and that sends lesions to surgery, then an image of the leak itself is the first available pharmacodynamic biomarker for the thing being treated — distinct from measuring the consequence of the leak weeks later as a volume. The sequences required are already present in longitudinal archives, so this is a reanalysis rather than a study, and it can be validated against the surgical outcomes those archives already contain.

LEVER A validated post-contrast-FLAIR leak metric reported alongside compartment volumes.

FROM Neuroradiology.

CHEAPEST TEST Reanalysis of existing serial imaging; no new scans, no new patients.

EVIDENCE INFERENCE [3,8]

4.5 Direction 5. Use the retinal hemangioblastoma as an in-vivo optical window for CNS vascular leak

Retinal capillary hemangioblastoma is histologically and genetically the same lesion as the cerebellar and spinal tumors, responds to belzutifan,[2,10,31] and sits behind the only transparent window in the central nervous system. Where brain and spinal lesions need gadolinium MRI to infer vascular permeability indirectly, the retinal lesion allows non-invasive, micron-resolution imaging of capillary lumen, pericyte dropout and plasma extravasation in real time through optical coherence tomography angiography and fluorescein angiography.

No published study pairs quantitative retinal OCT-angiography leak metrics with simultaneous brain post-contrast FLAIR (Direction 4) in patients who carry both lesions. Establishing that retinal barrier tightening tracks peritumoral CNS cyst stabilization would give the field a radiation-free, contrast-free pharmacodynamic readout available within days of a dose change — and the scans needed to test it already sit in the NIH natural-history and LITESPARK archives.

LEVER Paired longitudinal retinal OCT-angiography and brain post-contrast FLAIR volumetrics in patients with synchronous ocular and CNS lesions.

FROM Ophthalmic imaging and retinal vascular biology.

CHEAPEST TEST Retrospective pairing of serial ophthalmic OCT-A and brain MRI already held in the NIH and LITESPARK cohorts.

EVIDENCE VERIFIED ABSENCE [2,8,10,31]

5 Track II — Tissue, models and the sampling gap

Hemangioblastoma is among the least-sampled solid tumors in medicine: no immortalized cell line, no xenograft, no CRISPR screen of any kind, and roughly ten human tumors ever RNA-profiled. These directions close that gap, and most run on archived or already-public material.

No.	Direction	Tier	First concrete step
6	Bank progressor tissue under shared protocol	VERIFIED ABSENCE	Write and adopt the protocol
7	The compartment stain (6 targets at once)	INFERENCE	$40–75K, 16 weeks, archived tissue
8	Single-cell and spatial atlas	VERIFIED ABSENCE	Port an existing VHL pipeline
9	Cell of origin by single-cell genotyping	INFERENCE	Free on existing public data
10	Liquid biopsy from cyst fluid and CSF	INFERENCE	ddPCR on banked fluid aliquots

Table 4. Track II at a glance. Full treatment in §5.1–5.5.

5.1 Direction 6. Bank tissue from patients progressing on drug, now, under a shared protocol

No hemangioblastoma tissue from any patient exposed to belzutifan or any other HIF-2α inhibitor has ever been analyzed and reported. Searches of PubMed, GEO, SRA, BioProject and ArrayExpress return no cohort, repository or case series. The only post-treatment hemangioblastoma dataset in existence comes from a seven-patient vorinostat trial with single-nucleus profiling[9] — a different drug class entirely.

This is the most time-critical item in the draft. Belzutifan has been approved since 2021; at 50 months of follow-up a substantial fraction of the original cohort remains on drug, and patients who progress are going to surgery now.[10] Every one of those operations that proceeds without a banking protocol destroys the only material that can answer why the drug stopped working. There is no retrospective substitute, the treated cohort is young, and the window closes quietly rather than with any announcement.

LEVER A pre-consented, multi-center banking protocol: tissue, CSF and plasma at any surgery for progression on drug, with a committed central molecular pipeline.

CHEAPEST TEST The protocol itself is the deliverable. The project will pay for it.

EVIDENCE VERIFIED ABSENCE [9,10]

5.2 Direction 7. One dual-label stain promotes or kills six therapeutic leads at once

Hemangioblastoma is definitionally vascular — roughly 36% of nuclei are endothelial in the only public single-nucleus dataset — so any gene expressed in blood vessels reads high in a bulk measurement of the whole tumor whether or not it matters to the neoplastic cell. Every expression-derived target in Track V is vulnerable to this single confound, and vascular genes elevated in a vascular mass are the expected null, not a finding.

Six independent cross-field analyses, run on six different targets drawn from six different source literatures, converged on the same decisive experiment without being asked to agree: co-stain a multi-marker stromal panel (inhibin-α with brachyury/TBXT, podoplanin/D2-40 and CA9/GLUT1[19,21]) against endothelial and pericyte markers on archived blocks, and assign each signal to a compartment. Dual labeling is required rather than optional, since single stains on a tumor this vascular are uninterpretable. Stratify by anatomical site and never pool, because methylation profiling splits this tumor into subgroups that track site.[11] The result either promotes six leads to real dependencies or clears them from the board, and settles the cell-of-origin question on the same tissue sections.

Before the wet-lab stain, the bulk fold-changes in Figure 1 can be deconvolved at no cost with single-cell reference deconvolution (CIBERSORTx or MuSiC) against the seven-patient single-nucleus dataset,[9] narrowing the target list the stain must adjudicate.

HIGHEST-LEVERAGE FUNDABLE ITEM

Approximately $40–75K, 16 weeks, archived tissue, no accrual

Six independent leads converge on this one experiment, and several newer directions extend the same stain. Funding it would resolve or eliminate a substantial block of the agenda.

LEVER Serial dual-label chromogenic IHC / RNAscope sections (each target paired with a stromal or vascular mask), or a single multiplex immunofluorescence panel, on archived FFPE blocks, pre-registered thresholds, two blinded readers including a neuropathologist.

CHEAPEST TEST The experiment itself: approximately $40–75K, 16 weeks, existing tissue, no accrual. The project pays full direct cost and claims no intellectual property, exclusivity or publication control.

EVIDENCE INFERENCE [9,11,13,19,21]

5.3 Direction 8. Run a single-cell and spatial atlas on hemangioblastoma tissue

There is still no spatial or multi-sample single-cell atlas of this tumor. Public human hemangioblastoma RNA profiling totals roughly ten tumors; Cellosaurus returns zero hemangioblastoma cell lines against 586 for renal carcinoma, and a search for any CRISPR screen in this tumor returns nothing at all.

In a lesion that is mostly blood vessel, spatial resolution is not a refinement — it is the only way to read the tissue, because bulk fold-change is close to uninterpretable without compartment deconvolution. The method development is already done: groups working on VHL kidney tissue run integrated single-cell and spatial pipelines at scale, and the marginal cost of pointing one of them at hemangioblastoma is tissue access and sequencing rather than protocol development. Deposit openly: the only existing human single-cell hemangioblastoma dataset sat under embargo for three years.

LEVER Integrated single-cell RNA/TCR sequencing plus high-definition spatial transcriptomics.

FROM An existing VHL single-cell pipeline, re-pointed from kidney to brain.

CHEAPEST TEST Port a pipeline a VHL group already operates; tissue and sequencing cost only.

EVIDENCE VERIFIED ABSENCE [9,11]

5.4 Direction 9. Settle cell of origin by genotyping single cells in data that is already public

Two bodies of work disagree flatly about what the vessels in this tumor are. One holds that tumor-derived vasculogenesis is constitutive — the neoplastic cell makes its own endothelium[14] — which would mean dissociated stromal culture discards a defining component of the disease. The one genetic mouse model reads the other way: when VHL is deleted in the hemangioblast lineage, microdissection finds the deletion in the stromal tumorlet cells, with the florid vasculature around them recruited rather than neoplastic.[58] Cell of origin is separately unresolved between a mesodermal hemangioblast and a PAX2-positive neuroectodermal progenitor; the group that proposed the neuroectodermal origin later found cerebellar lesions ZIC1-negative and PAX2-positive.[13]

This is not academic. Every mechanism transferred into hemangioblastoma from clear-cell renal carcinoma assumes a

lineage, and if the stromal cell is astrocytic it may carry death machinery the renal lines lack. Read haplotype-aware across the whole 3p arm (Numbat or inferCNV) rather than at one coordinate, since single-nucleus coverage over any individual VHL locus is sparse. Per-cell VHL allele status in a single-nucleus atlas then settles both questions definitively, and the first pass is runnable today, for free, on the one public dataset.

LEVER Haplotype-aware chromosome-3p copy-number and allelic-imbalance calling (Numbat or inferCNV, pooling phased germline SNPs across the whole arm) plus targeted long-read VHL-locus genotyping.

FROM Computational single-cell genomics.

CHEAPEST TEST Free on the existing public dataset; then confirmed in the atlas of Direction 8.

EVIDENCE INFERENCE [13,14,58]

5.5 Direction 10. Read drug escape from cyst fluid and CSF when the lesion cannot be biopsied

Many progressing brainstem and intramedullary hemangioblastomas cannot be safely resected or biopsied, which leaves the mechanism of drug escape unobservable by the one route — tissue — that would settle it. Bulk cyst fluid has the protein composition of plasma rather than tumor secretion,[1] but cyst fluid and cerebrospinal fluid also carry tumor-derived extracellular vesicles and cell-free DNA that do not reach peripheral blood, and that compartment has never been sampled serially in this disease.

Expanding the Direction 6 banking protocol to mandate paired CSF and Ommaya- or intraoperatively aspirated cyst fluid would allow digital-droplet PCR for the somatic second hit, chromosome-3p allelic imbalance and the on-target EPAS1 G323E gatekeeper mutation,[20] alongside vesicle-sorted proteomics for PlGF, EPO and VEGF-A. It is an addendum to a protocol the draft already proposes, not a new study, and it runs on fluid that surgical centers discard today.

LEVER A CSF and cyst-fluid liquid-biopsy addendum to the Direction 6 banking protocol: vesicle proteomics plus ddPCR for 3p loss and EPAS1 pocket mutations.

FROM Neuro-oncology CSF liquid biopsy and vesicle proteomics.

CHEAPEST TEST Run ddPCR and vesicle isolation on archived cyst-fluid and CSF aliquots already banked at surgical centers.

EVIDENCE INFERENCE [1,20]

6 Track III — Contradictions the literature has left standing

Places where real, unretracted papers disagree, or where the measurement that would settle the argument was never made. Each is settleable with a stain or a reanalysis rather than a trial, and each currently gates a therapeutic decision that is being made on assumption.

6.1 Direction 11. Measure HIF-1α in post-belzutifan tissue: driver, or tumor suppressor?

HIF-1α compensation is the most frequently repeated explanation for why HIF-2α inhibitors stop working. Twelve structured searches found no primary paper demonstrating it, for belzutifan or any HIF-2α inhibitor, in any tissue; a 2026 review enumerating resistance mechanisms does not list it.[36] Two things appear to have seeded the belief: the second-site mutation ARNT F446L is HIF-1β rather than HIF-1α and was found in mouse tumorgrafts, never in a patient;[20] and resistant tumorgrafts express higher baseline HIF-1α, which is a marker of HIF-2-independent biology rather than evidence of acquired compensation.

Meanwhile the direction may be inverted. In clear-cell renal carcinoma HIF-1α behaves as a tumor suppressor: the two isoforms are functionally opposed on c-Myc[16] and HIF1A undergoes focal homozygous deletion, with knockdown promoting tumor growth.[17] Yet primary cultures grown from VHL patients' own CNS hemangioblastoma tissue overexpress both isoforms and die to the dual inhibitor acriflavine.[15] Both observations are real. Which one governs this lesion is unmeasured, and it is an immunohistochemistry panel, not a program.

LEVER HIF-1α and HIF-2α immunohistochemistry on post-belzutifan hemangioblastoma tissue.

CHEAPEST TEST A panel on the tissue banked in Direction 6, or on any post-treatment block held today. Pair any HIF-1α-directed agent with renal imaging until the direction is settled.

EVIDENCE VERIFIED ABSENCE [15,16,17,20,36]

6.2 Direction 12. Resolve the SSTR2A contradiction, then open the radioligand pathway

One study of VHL-related hemangioblastomas reports some degree of somatostatin receptor 2A positivity in 37 of 40 graded samples — 43 were collected, and the published counts account for 40;[18] another, of 112 tumors, reports it in none.[19] Both are real, unretracted, and studied this lesion directly — a head-on disagreement inside the tumor's own literature rather than a transfer argument. The question gates cold somatostatin analogues and every receptor-maximizing strategy at once. It does not, on its own, gate radioligand therapy: in-vivo uptake in this tumor is reproduced across roughly ten independent patient reports and one 14-patient cohort using four different chelated peptides, so the receptor is demonstrably reachable. What gates therapy is the absorbed dose a bound ligand can actually deposit — expression, access, internalization and residence time are inputs to that one number, and it has never been measured in this tumor.

Independent in-vivo evidence makes a true 0% hard to credit: somatostatin-receptor PET positivity in hemangioblastoma is documented from at least six unrelated centers across four anatomical locations including spinal cord lesions, one

No.	Direction	Tier	First concrete step
11	HIF-1α: driver or suppressor?	VERIFIED ABSENCE	IHC panel on post-treatment tissue
12	SSTR2A: 40/43 versus 0/112	INFERENCE	Clone-matched re-stain exchange
13	Target engagement never measured	VERIFIED ABSENCE	Port an existing ccRCC assay
14	Propranolol / ADRB2 contradiction	INFERENCE	One antibody plus a cohort query

Table 5. Track III at a glance. Full treatment in §6.1–6.4.

at SUVmax 22.6. The likeliest reconciliations are mundane and testable — the positive study localizes the receptor to endothelium rather than stromal cells and bundles weak staining; the negative study's VHL fraction is unstated and its purpose was differential diagnosis; and the two used different antibody clones. That same negative paper contains a separate marker whose positivity swings from 0% to 63% on antibody choice alone, which is the best available argument that the discrepancy is technical.

LEVER An antibody-clone-matched, compartment-scored re-stain exchange between the two groups.

FROM Nuclear medicine / neuroendocrine radioligand therapy.

CHEAPEST TEST An email to the second group establishing VHL fraction, scoring method and clone; then a dozen blocks re-stained with both clones on whole sections. Weeks, not years, and no patients.

EVIDENCE INFERENCE [18,19]

6.3 Direction 13. Confirm the drug engages its target in this lesion at all

HIF-2α target engagement has never been measured in hemangioblastoma tissue. No HIF-2α immunohistochemistry study in this tumor exists, the newest HIF-target surrogate record dates to 2022,[21] and there is no human intratumoral concentration measurement for any HIF-2α inhibitor in any tissue.

The field is therefore several years into treating this lesion without knowing whether, or in which lesions, the drug reaches and engages its target — which is a different question from whether the lesion shrinks, and the only one that distinguishes pharmacological failure from biological resistance. The single human study that measured plasma drug, peripheral pharmacodynamics and tumor target engagement together did so in ten renal-carcinoma patients[20] and has never been repeated in this compartment. Validated HIF-2α assays exist in renal-cancer pathology and can be applied directly to banked blocks.

LEVER A HIF-2α target-engagement immunohistochemistry score, ported from renal-cancer pathology.

FROM Renal-cancer pathology assay development.

CHEAPEST TEST Apply an existing ccRCC HIF-2α assay to banked hemangioblastoma blocks.

EVIDENCE VERIFIED ABSENCE [20,21]

6.4 Direction 14. Settle the propranolol / ADRB2 question by compartment staining and cohort adjustment

For a decade, European groups have reported that propranolol reduces viability, downregulates HIF targets and triggers apoptosis in patient-derived VHL hemangioblastoma cultures[39] and leaves retinal lesions stable in a small phase 3 trial,[40] prompting orphan-drug designation and a randomized CNS trial. North American cohorts rarely use it, and no one has established whether β-adrenergic blockade acts on the neoplastic stromal cell or merely constricts reactive vessels.

The disagreement does not need a new trial to resolve. Adding a β2-adrenergic-receptor antibody to the Direction 7 compartment stain establishes whether the target sits on the inhibin-α/brachyury-positive stromal cell or on endothelium, and a retrospective covariate analysis of incidental β-blocker prescriptions already in the NIH and LITESPARK cohorts tests whether exposure alters lesion growth or cyst formation in patients. Both run on material that exists.

LEVER An ADRB2 antibody added to the Direction 7 stain, plus a time-varying covariate analysis of concomitant β-blocker use in existing longitudinal cohorts.

FROM Infantile-hemangioma vascular biology and pharmacoepidemiology.

CHEAPEST TEST Add one ADRB2 antibody to the Direction 7 run and query concomitant-medication logs in the NIH archive.

EVIDENCE INFERENCE [3,39,40]

7 Track IV — Optimizing the drug that already works

Belzutifan is effective and tolerable, and is almost certainly misdosed, un-genotyped and under-combined for an indication measured in decades. These directions treat the existing drug as a starting point rather than a settled regimen.

No.	Direction	Tier	First concrete step
15	Intermittent / de-escalated dosing	VERIFIED ABSENCE	Investigator-initiated trial
16	UGT2B17 genotype before dosing	VERIFIED	CNV assay on banked DNA
17	Which combination is tolerable for decades	INFERENCE	VHL-specific dose-finding
18	Does anemia correction feed the EPO loop?	VERIFIED ABSENCE	Merge two existing cohorts
19	Belzutifan bracketing radiosurgery	HYPOTHESIS	Retrospective on-versus-off comparison
20	Next-gen HIF-2α beyond UGT2B17	HYPOTHESIS	Measure CNS penetration first

Table 6. Track IV at a glance. Full treatment in §7.1–7.6.

7.1 Direction 15. Test intermittent, de-escalated and biomarker-guided dosing

No intermittent, pulsed, de-escalated or biomarker-guided belzutifan schedule has ever been studied, in any indication. None of the registered belzutifan trials asks whether a patient taking this drug for life could take less of it. Meanwhile real-world dose reduction in the VHL subgroup runs at 59%[5,24] — reactive, after anemia, with no evidence that lesion control is maintained.

The pharmacology already makes the case. Exposure-response for efficacy is flat while exposure-response for grade $\geq$3 anemia is positive and baseline-hemoglobin dependent;[22] a randomized comparison of 200 mg against 120 mg found response rates of 23.1% and 23.7%,[23] establishing flatness above 120 mg. The regulatory assessment carries dose-response data published nowhere else: erythropoietin suppression of -64.9% at 80 mg against -69.4% at 120 mg, with the document conceding a possible plateau, and 120 mg chosen because two of six patients in the 80 mg cohort

under-responded. This is the difference between a drug taken for four years and one taken for forty, and no commercial sponsor has an interest in running it.

LEVER A biomarker-guided intermittent-dosing and de-escalation trial, with anemia and treatment persistence as co-primary outcomes alongside lesion control.

CHEAPEST TEST Investigator-initiated or philanthropic. There is no commercial return in demonstrating that less drug works equally well.

EVIDENCE VERIFIED ABSENCE [5,22,23,24]

7.2 Direction 16. Genotype UGT2B17 before dosing

Approximately one in six White patients, and the majority of some East Asian populations, carry a UGT2B17 poor-metabolizer genotype that raises belzutifan exposure roughly 2.5-fold; combined with CYP2C19 poor metabolism the figure is 3.2-fold, making a 120 mg dose pharmacologically equivalent to 300–380 mg. Effective half-life roughly doubles and trough concentration rises more than threefold.

Nobody is genotyped. No genotype-outcome study exists in any indication, there is no CPIC guideline for this drug, and no clinical annotations exist in the major pharmacogenomic resources. Two technical points matter for anyone acting on this: the UGT2B17 variant is a whole-gene deletion requiring a copy-number-capable assay, so a standard SNP panel misses it entirely; and the frequently quoted "∼90% in Japanese" figure is the deletion allele frequency, not the poor-metabolizer rate, which is the homozygous-null frequency. Given a flat efficacy exposure-response and a positive toxicity exposure-response,[22] genotype is a rational basis for starting dose.

LEVER A copy-number-capable UGT2B17 assay as a pre-dosing or correlative test.

FROM Pharmacogenomics.

CHEAPEST TEST Add a copy-number assay to any existing belzutifan cohort with banked DNA; the exposure consequence is already in the label.

EVIDENCE VERIFIED [22]

7.3 Direction 17. Define which belzutifan combination is tolerable for a lifelong indication

The only strategy against HIF-2α monotherapy failure with randomized phase 3 support is belzutifan combined with lenvatinib — generated entirely in advanced sporadic renal carcinoma, at doses and for durations no VHL patient could sustain for decades. No belzutifan combination has ever been tested in VHL disease, and none approaches monotherapy's tolerability in this population, where only 3% of patients (2 of 61) stopped because of adverse events over a median of about four years, even though 41% stopped for any reason, most often by their own decision.

The question for this disease is therefore not whether a combination shrinks tumors, which the renal data already indicates, but which partner at what dose a person can take for forty years without losing the tolerability that makes the anchor drug usable at all. That is a different trial with a different primary outcome. The historical comparator is instructive: pazopanib produced responses in 52% of renal lesions but only 4% of CNS hemangioblastomas in the same patients, with one fatal CNS hemorrhage[25] — within-trial evidence that this compartment is not pharmacologically equivalent to the kidney. Any lifelong combination also needs vascular-remodeling safety endpoints — susceptibility-weighted (SWI/T2*) imaging for microhemorrhage — because rapid solid-nodule involution stresses a hyperpermeable vascular wall.[25]

LEVER A VHL-specific combination-tolerability trial, with long-term tolerability and persistence as the primary readout rather than response rate.

FROM Advanced renal-carcinoma combination trials.

CHEAPEST TEST Dose-finding in VHL patients, powered for tolerability over years rather than response over months.

EVIDENCE INFERENCE [5,25]

7.4 Direction 18. Ask whether correcting anemia feeds the tumor's own erythropoietin loop

Symptomatic hemangioblastomas carry roughly twofold higher erythropoietin message with increased phospho-EPO-receptor and phospho-STAT5, and erythropoietin is detectable in cyst fluid; the authors describe this as a signaling loop associated with loss of quiescence.[26] Anemia is the dominant toxicity of HIF-2α blockade and is routinely corrected, including with erythropoiesis-stimulating agents.

No published analysis in any indication examines ESA use during HIF-2α inhibitor therapy. That is a correlative question and must be framed as one: it is emphatically not a reason to withhold anemia treatment from anyone, and the confound runs in the awkward direction, since patients needing more ESA are those with more drug exposure. But two existing groups hold both ESA-exposure records and longitudinal lesion volumetrics, and merging them is an analysis rather than a study. Phospho-STAT5 staining on growing versus quiescent lesions would independently establish whether the switch is active in the tissue.

LEVER A correlative analysis of ESA exposure against lesion volumetrics; phospho-STAT5 immunohistochemistry on growing versus quiescent lesions.

CHEAPEST TEST Merge ESA-exposure and volumetric data that two existing cohorts already hold.

EVIDENCE VERIFIED ABSENCE [26]

7.5 Direction 19. Test time-limited belzutifan bracketing radiosurgery to prevent post-SRS cyst expansion

Stereotactic radiosurgery controls the solid nodule in 85% of VHL-associated intracranial hemangioblastomas at a median 52 months,[41] but radiation injury to hyperpermeable tumor vessels frequently provokes subacute cyst progression, forcing surgical decompression of a lesion whose solid component was successfully controlled.[8,41] The failure mode is the cyst, not the nodule.

Because belzutifan suppresses HIF-2α-driven permeability factors within weeks, a time-limited course bracketing radiosurgery — for example two months before through nine months after — could seal the leak during the radiation-reaction window and convert cyst-forming lesions into durable outpatient cures, sparing both craniotomy and lifelong systemic exposure. The first test needs no trial: compare post-SRS cyst expansion in patients irradiated while on belzutifan against those irradiated off it.

LEVER A time-limited peri-radiosurgical belzutifan bridge, monitored by post-contrast FLAIR leak (Direction 4) and three-compartment volumetrics (Direction 1).

FROM Radiosurgical neuro-oncology and anti-angiogenic radiation-necrosis management.

CHEAPEST TEST Retrospective comparison of post-SRS cyst expansion in VHL patients irradiated on versus off belzutifan.
EVIDENCE HYPOTHESIS [2,8,41]

7.6 Direction 20. Evaluate second-generation HIF-2α inhibitors that bypass UGT2B17 hyper-exposure

Direction 16 establishes that homozygous UGT2B17 deletion raises belzutifan exposure roughly 2.5-fold, and up to 3.2-fold with CYP2C19 poor metabolism, and drives the anemia that forces dose interruption; Direction 29 addresses on-target pocket mutations. Between them sits an immediate small-molecule opportunity: second-generation HIF-2α inhibitors — casdatifan among them, with a roughly 24-hour half-life and clearance that does not depend on UGT2B17 glucuronidation.[42]

Neither casdatifan nor its class peers has been tested in VHL-associated CNS hemangioblastoma, and their cerebrospinal-fluid penetration ratios are unpublished. For a UGT2B17-null patient who cannot tolerate standard belzutifan, a UGT2B17-independent oral HIF-2α inhibitor with confirmed CNS penetration would be a direct substitute rather than a new mechanism — the cheapest test is a brain-penetration measurement, not a trial.

LEVER A CSF-to-unbound-plasma partitioning measurement and a CNS hemangioblastoma cohort for a second-generation HIF-2α inhibitor, enriched for UGT2B17 poor metabolizers.
FROM Second-generation renal-carcinoma HIF-2α medicinal chemistry.
CHEAPEST TEST Measure CNS/CSF drug levels in preclinical brain-penetration models or opportunistically in ongoing trials.
EVIDENCE HYPOTHESIS [22,42]

8 Track V — New therapeutic axes carried in from other fields

The cross-field engine reasons outward from a target measured in this tumor to every agent that exists against it anywhere in medicine, then asks why nobody brought it here. Most of these are hypotheses whose first step is a stain, not a trial, and six of them share the single experiment described in Direction 7.

No.	Direction	Tier	First concrete step
21	Dual-HIF inhibition (acriflavine proof of concept)	VERIFIED	Gated by Direction 11
22	EGFR/TGF-α loop — proposed twice, never tested	VERIFIED	Patient-derived culture assay
23	PlGF blockade for the cyst compartment	INFERENCE	Gated on the compartment stain
24	NOX4 / setanaxib (from fibrosis)	HYPOTHESIS	Compartment IHC first
25	MIF / ibudilast (from neurology)	HYPOTHESIS	IHC with myeloid co-stain
26	CXCR4 theranostic (PET gates the drug)	HYPOTHESIS	IHC, then pentixafor PET
27	CDK4/6 inhibition, pending Ki-67	HYPOTHESIS	Routine Ki-67 stain decides it
28	Ferroptosis axis — does it survive HIF-2 blockade?	INFERENCE	In-vitro interaction assay
29	Pocket-independent HIF-2α removal	INFERENCE	Sequence the pocket in banked tissue
30	HIF-PHI safety guidance for carriers	VERIFIED ABSENCE	Consensus statement; no cost
31	Missense pVHL folding rescue	INFERENCE	Stratify outcomes by genotype class
32	FGFR2/4 wall plus TBK1/EZH1 lethality	HYPOTHESIS	Archival FGFR score plus culture assay

Table 7. Track V at a glance. Full treatment in §8.1–8.12.

8.1 Direction 21. Dual-HIF inhibition for the CNS compartment

The only agent shown to kill hemangioblastoma cells is acriflavine, a dual HIF-1α/HIF-2α dimerization inhibitor. In primary cultures grown from twelve VHL patients' own CNS hemangioblastoma tissue, both isoforms were overexpressed and acriflavine reduced viability with G2/M arrest and predominantly necrotic death; the paper frames this explicitly against belzutifan's limited efficacy in CNS lesions.[15]

The proof of concept here is the direction — dual inhibition — rather than the molecule, which has its own development problems. The result also carries a second finding worth more than it appears: in-vitro proliferation rate correlated with clinical tumor burden and with four-year recurrence, meaning donor variability in a primary-culture screen is signal rather than noise. One caution for anyone citing this area: an older and widely cited acriflavine/HIF paper is retracted[37] and must not be used to support the mechanism.

LEVER A developable dual-HIF or HIF-1α-adding strategy.
FROM HIF chemical biology.
CHEAPEST TEST The tissue question in Direction 11 decides whether to pursue this at all.
EVIDENCE VERIFIED [15,37]

8.2 Direction 22. Test the EGFR/TGF-α autocrine loop, the only target built on this tumor's own tissue

In 30 resected VHL-associated CNS hemangioblastomas, EGFR and TGF-α protein were significantly elevated relative to normal brain, with the same direction confirmed at message level in a subset, and phosphorylated EGFR strongly immunoreactive in the stromal — that is, the neoplastic — cell of every tumor examined.[27,28] This is the only mechanism in the project's resistance map constructed on hemangioblastoma tissue rather than borrowed from sporadic renal carcinoma.

Both source papers propose an EGFR inhibitor. Neither tests one, and no EGFR-directed agent has ever been tried in a hemangioblastoma, in a model or in a patient. The constraint

is CNS exposure, since EGFR tyrosine kinase inhibitors are efflux-limited with cerebrospinal-fluid penetration in the low single-digit percentages — but brain-penetrant EGFR chemistry developed for lung-cancer CNS metastases has moved substantially since these papers were written, and the first test is a patient-derived culture rather than a trial.

LEVER A brain-penetrant EGFR tyrosine kinase inhibitor, tested first in patient-derived culture.

FROM Lung-cancer CNS-penetrant EGFR chemistry.

CHEAPEST TEST A cell-based assay in patient-derived hemangioblastoma cultures before any trial.

EVIDENCE VERIFIED [27,28]

8.3 Direction 23. Target the leak rather than the vessel: PlGF blockade for cyst and edema

Belzutifan acts on the enhancing nodule; the cyst is what escapes, and the cyst is a plasma leak through vessels whose endothelium lacks tight junctions.[1,12] Placental growth factor is the most induced gene the pipeline found in this tumor, ahead of erythropoietin, and it is not covered by anti-VEGF-A therapy.

The negative history of anti-PlGF therapy in renal carcinoma does not transfer, and the reason is the receptor: those xenograft failures occurred where VEGFR-1 was not expressed, whereas in hemangioblastoma the pipeline's reanalysis places VEGFR-1 at parity with normal cerebellum rather than depleted, once the abundance-stratified null is applied. Receptor status is precisely the variable the negative literature identifies as decisive. Aflibercept traps both VEGF and PlGF and is the cheapest available test of the axis; TB-403 is a PlGF-specific antibody with an existing pediatric CNS program. This remains an expression-derived lead and is gated on the compartment stain.

LEVER Aflibercept (traps VEGF and PlGF) or the PlGF-specific antibody TB-403.

FROM Pediatric CNS oncology and ophthalmic PlGF biology.

CHEAPEST TEST Compartment immunohistochemistry for PlGF and FLT1, as part of Direction 7.

EVIDENCE INFERENCE [1,2,12]

8.4 Direction 24. NOX4: an oral, non-anti-angiogenic add-on from the fibrosis field

NOX4 is markedly elevated in hemangioblastoma tissue and runs in the opposite direction in clear-cell renal carcinoma, which means reasoning from kidney data actively misleads on this target. It carries almost no research attention in this disease — one card on the project's entire board.

Setanaxib is an oral dual NOX1/NOX4 inhibitor developed in fibrosis indications, where NOX1/4 inhibition has been carried toward therapy.[32] It is chronically dosed, orally available, and acts on an axis entirely distinct from HIF-2α and from angiogenesis — the profile required for something a patient might add to belzutifan for years rather than months. It was found by a field, hepatology, that has no reason to read CNS vascular-tumor literature, which is precisely why it was available to find. The lead rests on bulk transcript data and is a hypothesis until the compartment is established.

LEVER Setanaxib (GKT137831), oral, clinical-stage in fibrosis.

FROM Hepatology and fibrosis.

CHEAPEST TEST NOX4 immunohistochemistry scored by compartment on archived blocks, as part of Direction 7.

EVIDENCE HYPOTHESIS [32]

8.5 Direction 25. MIF: an oral brain-penetrant agent with a long human safety record, from neurology

Macrophage migration inhibitory factor is strongly expressed in this tumor. Ibudilast is an oral MIF inhibitor, long marketed in Japan, brain-penetrant, and carried into a randomized phase 2 trial in progressive multiple sclerosis[33] — an unusually long human exposure record for a CNS-active agent, which is the characteristic that matters most for a lifelong benign-tumor indication.

One thing must be ruled out before this goes further, and it is the same confound that governs this whole track in a different guise: MIF is abundantly produced by macrophages, and this tumor contains them. A myeloid co-stain on serial sections separates tumor-cell MIF from macrophage MIF and is the difference between a target and an infiltrate.

LEVER Ibudilast (MN-166), oral, CNS-penetrant.

FROM Neurology — progressive MS and ALS.

CHEAPEST TEST MIF immunohistochemistry with a CD68 or IBA1 myeloid co-stain on serial sections.

EVIDENCE HYPOTHESIS [33]

8.6 Direction 26. CXCR4: a theranostic pair where the scan is also the patient-selection test

CXCR4 is elevated in this tumor, though the one study that stratified by VHL status found VHL-related lesions carry roughly half the receptor density of sporadic ones (8% versus 16% of cells, p=0.002) — which means this project's own population is the weaker half, and the imaging gate below matters more here than it would elsewhere. Uniquely among these leads the confirmatory test is itself the patient-selection step. A gallium-68 pentixafor PET establishes whether a given lesion is CXCR4-avid at all,[34] and only an avid lesion would justify proceeding to oral mavorixafor, a CXCR4 antagonist already approved for WHIM syndrome and dosed chronically in a non-malignant indication.

The radioligand arm of this field is explicitly not what is proposed here: pentixather delivers therapeutic radiation and is inappropriate for a benign lesion in a patient who needs their marrow. The imaging arm is diagnostic and low-risk. CXCR4 drug development ran almost entirely through stem-cell mobilization, myeloma, leukemia and a rare congenital immunodeficiency — four fields with no reason to examine a CNS vascular tumor.

LEVER Mavorixafor (oral, approved for WHIM syndrome), gated by pentixafor PET.

FROM Hematology and nuclear medicine.

CHEAPEST TEST CXCR4 immunohistochemistry first; then a pentixafor PET over an already-monitored lesion.

EVIDENCE HYPOTHESIS [34,73]

8.7 Direction 27. CDK4/6 inhibition, if the proliferation index justifies it

Cyclin D1 is elevated in this tumor, and cyclin-D/CDK4-6 bypass is a documented escape route from HIF-2α blockade in renal carcinoma, where CRISPR-activation screens identified

CCND1 as the top hit for conferring resistance. Abemaciclib is the marketed CDK4/6 inhibitor with meaningful central nervous system exposure.[35]

This lead stands or falls on a single cheap number that nobody has measured: the Ki-67 fraction in hemangioblastoma. This is a slow-growing WHO grade 1 lesion, and if the proliferative fraction is low then cell-cycle arrest cannot plausibly change the growth curve regardless of cyclin D expression. VHL loss shows conserved, HIF-independent synthetic lethality with CDK4/6 inhibition across species,[38] so a low index narrows the question rather than closing it; a high index reopens it outright, with an approved, orally available, CNS-exposed drug. Ki-67 and Rb status are routine stains on material that already exists.

LEVER Abemaciclib, or a more brain-penetrant successor.

FROM Breast oncology, with CNS-penetrant chemistry from glioblastoma development.

CHEAPEST TEST Ki-67 and Rb-status immunohistochemistry on archived blocks, paired with a low-cost viability assay in patient-derived VHL-null cultures with and without belzutifan — all on existing material.

EVIDENCE HYPOTHESIS [15,35,38]

8.8 Direction 28. A ferroptosis vulnerability in the clear-cell state — but does it survive the drug?

The HIF-2α-driven clear-cell state carries a GPX4-dependent ferroptosis vulnerability.[29] That is an attractive axis because it is a death mechanism rather than a growth-arrest one, in a disease where the dominant therapeutic effect is cytostatic.

The decisive question is an interaction, not an expression level, and it is untested: a HIF-2α inhibitor may remove the very state that creates the vulnerability. This belongs to a general class of therapeutic antagonism the project's resistance map tracks explicitly — cases where blocking HIF-2α subtracts a vulnerability rather than exposing one. Because the question is an interaction, it is answerable in cell culture with commercially available reagents before any tissue or patient question arises. Sulfasalazine, an approved anti-rheumatic with decades of chronic-dosing safety data, is the clinically available lever on the pathway if the interaction proves favorable.

LEVER Sulfasalazine (system xc− blockade), contingent on the interaction result.

FROM Rheumatology and ferroptosis chemical biology.

CHEAPEST TEST A ferroptosis-sensitivity assay in a VHL-null line with and without belzutifan co-treatment.

EVIDENCE INFERENCE [29]

8.9 Direction 29. Pocket-independent removal of HIF-2α, for when the pocket mutates

Every approved and late-stage HIF-2α inhibitor is an allosteric PAS-B pocket binder, so a single pocket mutation defeats the class as a whole. The only human-confirmed on-target escape is the gatekeeper mutation G323E, identified in two of three progressors with evaluable tissue in a renal-carcinoma substudy;[20] the partner-side ARNT F446L mutation raises heterodimer affinity beyond the drug's reach but has so far been found only in mouse tumorgrafts.

Modalities that remove the protein or its message are not pocket-dependent and would be expected to retain activity against both. An interfering RNA against HIF-2α is the furthest advanced; targeted protein degradation is the other route. For a disease where patients remain on therapy for decades, class-wide vulnerability to a single point mutation is a structural risk worth pre-empting rather than discovering.

LEVER HIF-2α interfering RNA, or a targeted degrader.

FROM RNAi therapeutics and targeted protein degradation.

CHEAPEST TEST Sequence the PAS-B pocket in any progressor tissue banked under Direction 6, to size the need.

EVIDENCE INFERENCE [20]

8.10 Direction 30. Write the HIF-PHI safety guidance before a VHL carrier is prescribed one

Every normal cell in a VHL patient is already VHL-heterozygous. HIF prolyl-hydroxylase inhibitors — the oral drugs for anemia of chronic kidney disease — pharmacologically raise HIF-α in exactly those cells, pushing normal and pre-neoplastic tissue toward the HIF-high state that constitutes the initiating lesion, without requiring loss of the remaining allele. Human genetics supports the direction of concern, and the clinical evidence runs cleanly the other way: blocking HIF-2α shrinks VHL lesions.

Both approved agents carry an identical warning against use in patients with active malignancies. That wording misses the VHL patient precisely — no active malignancy, but multiple benign HIF-driven lesions under surveillance, and chronic kidney disease from repeated partial nephrectomy that makes them strong candidates for exactly this prescription. No published guidance, consensus statement, label contraindication or case report addresses HIF-PHI use in VHL disease or in germline VHL, EGLN1, EPAS1 or SDHx carriers. The reassuring pharmacovigilance literature covers CKD populations with no germline-predisposition subgroup and no power for rare tumors. A real population is walking toward this prescription today.

LEVER A short consensus statement or registry query, coordinated with the surveillance-guidelines group.

CHEAPEST TEST A consensus statement. This is the cheapest high-value output on the list.

EVIDENCE VERIFIED ABSENCE

8.11 Direction 31. Rescue germline missense pVHL by proteostasis modulation and folding correctors

Roughly a third to a half of VHL patients, and a high fraction of families with heavy CNS burden, carry germline missense mutations rather than deletions or truncations. Missense pVHL often keeps its intrinsic E3-ligase function in vitro but is recognized as misfolded by the Hsp70/TRiC chaperone system and destroyed prematurely.[9] The seven-patient vorinostat study with single-nucleus profiling[9] showed the principle in human CNS tissue — chaperone inhibition stabilized missense pVHL — though pan-HDAC inhibition is too toxic for multi-decade use.

Rescuing endogenous pVHL does what no HIF-2α inhibitor can: it restores degradation of both HIF-1α and HIF-2α and recovers the HIF-independent functions of the protein. Cystic fibrosis made exactly this turn, replacing broad proteostasis modulators with mutation-specific folding correctors. No high-throughput screen for selective, non-HDAC pVHL folding correctors has been taken to hemangioblastoma, and the first

step costs nothing: stratify existing belzutifan response and cyst-escape rates by missense versus truncating genotype.[2,5]

LEVER A genotype-stratified reanalysis of belzutifan outcomes (missense versus truncating VHL), then selective folding correctors in patient-derived missense cultures.

FROM Cystic-fibrosis chaperone discovery and VHL proteostasis biology.

CHEAPEST TEST Stratify existing LITESPARK-004 and real-world response and cyst-escape rates by germline missense versus truncating genotype.

EVIDENCE INFERENCE [2,5,9]

8.12 Direction 32. Attack the VEGF-refractory vessel wall (FGFR2/4) and HIF-independent synthetic lethality (TBK1, EZH1)

Two puzzles in the draft share a root: why multi-targeted VEGFR inhibitors fail in this compartment (4% response on pazopanib against 52% in renal lesions[25]), and how to kill VHL-null stromal cells without relying on a vulnerability belzutifan erases (Direction 28). On the vessel-wall side, immunohistochemistry across 139 hemangioblastomas found FGFR2 in 95% — enriched in VHL-mutated tumors ($p = 0.034$) — and FGFR4 in 61%, associated with larger diameter ($p = 0.018$),[43] against a dense PDGFRβ-positive pericyte coat (Figure 1); simple VEGFR2 blockade collapses neither the mature vessel nor the leak.

On the synthetic-lethal side, functional screens in VHL-deficient cells identify druggable, HIF-independent dependencies on TANK-binding kinase 1[44] and the histone methyltransferase EZH1[45] — driven by loss of pVHL itself rather than by HIF-2α, so they remain active during belzutifan co-treatment. Both arms are testable on existing material: score FGFR2/4 against cyst volume on archival blocks, and test CNS-penetrant TBK1 or EZH1/2 inhibition with and without belzutifan in patient-derived culture.

LEVER Compartment scoring for FGFR2/4 against cyst volume on archival blocks; in-vitro testing of CNS-penetrant TBK1 or EZH1/2 inhibitors with and without belzutifan.

FROM Vessel-wall FGFR biology and VHL synthetic-lethality functional genomics.

CHEAPEST TEST Add FGFR2/4 to the archival run and test TBK1 and EZH1/2 inhibition with and without belzutifan in VHL-null culture.

EVIDENCE HYPOTHESIS [25,43,44,45]

9 Track VI — Therapeutics for hemangioblastoma, with or without HIF-2α

The tracks above ask what to measure, what to bank, what to settle and how to use the drug that exists. This one asks the question none of them does: what else could treat this tumor. It runs from whether the existing drug even reaches the lesion, through mechanisms that kill rather than slow, to therapies delivered by a molecule the tumor itself captures. Two scope notes, because they decide what belongs here. The project does not pay to improve radiation delivery — beam, dose, fractionation and device are an established field with its own funders — but it does fund how systemic agents change what radiation does, and it does fund radioligands, where the targeting molecule is the therapy and the isotope is cargo. The test is simple: ***if the tumor has to catch the radiation, it is in scope; if someone has to aim it, it is not.***

No.	Direction	Tier	First concrete step
33	Measure the drug in the tumor before funding another drug	VERIFIED ABSENCE	Ten to fifteen already-scheduled operations. No new patients, no new surgeries, no new imaging.
34	The brain-penetrant second-generation inhibitor	INFERENCE	Ask for the penetration data before designing anything. Culture comparison second. A trial only after Direction 33 reads out.
35	One archived-tissue panel to triage six HIF-independent synthetic-lethal targets	INFERENCE	The panel itself. It de-risks six programs at once and needs no patients.
36	Statins, tested inside the cohort that already exists	INFERENCE	A retrospective cohort analysis on imaging that already exists. No drug, no consent for intervention, no new scans.
37	Ferroptosis, grounded in this tumor rather than borrowed	HYPOTHESIS	Add four markers to a panel that is already being run. Scope it together with the existing vitamin-K and FSP1 liability before committing.
38	Differentiation therapy against the arrested hemangioblast	INFERENCE	Six to eight primary cultures and a flow-cytometric differentiation readout.
39	Finish the vorinostat experiment: give proteostasis modulation a growth endpoint	VERIFIED	Seven patients and scans that have already been acquired. This is a request, not a grant.
40	Establish whether this tumor is immunologically visible at all	VERIFIED ABSENCE	A reanalysis request against an existing dataset. If it cannot answer the question, multiplex immunofluorescence on twenty to thirty archived blocks.
41	Build the two pieces of substrate that are actually missing	VERIFIED ABSENCE	The biobank is logistics rather than science and should be funded first. The CNS mouse is the single highest-value missing reagent in the field and the most expensive item on this agenda.

42	Treat the cyst, not the nodule	Inference	Reanalysis of imaging that already exists. It also supplies Track I with the endpoint it is missing.
43	Compute the deliverable dose before believing the picture	Inference	A desk-and-archive study on existing scans. If predicted dose is in single-digit gray, stop funding somatostatin-directed radioligand work and move to Direction 45.
44	Residence time: the measurement the whole radioligand question turns on	Verified absence	Archived frozen tissue. A negative result closes the entire radioligand therapy scope while leaving the imaging case intact, for roughly two percent of what a pilot trial would cost. Replicate the stromal-receptor claim on the same blocks at negligible marginal cost.
45	Carbonic anhydrase IX as the lead radioligand target	Inference	The autoradiography. Separately and immediately: the recruiting trial of this ligand pair covers nine tumor types and does not include VHL or hemangioblastoma, so a cohort expansion is a letter and a site rather than a new application.

Table 8. Track VI at a glance. Full treatment in §9.1–9.13.

9.1 Direction 33. Measure the drug in the tumor before funding another drug

No one has ever measured belzutifan concentration in a human hemangioblastoma, or in cerebrospinal fluid. Structured search returns no record of a CNS tissue level, a CSF level, or a partition coefficient for this lesion. The field is prescribing a CNS drug without knowing whether it arrives.

The 44% versus 76% split in the registration cohort — the same fifty patients scored with and without the cystic component[2] — is usually read as cystic biology. An exposure deficit in the solid nodule is untested and equally consistent with the data. The two readings point the portfolio in opposite directions, and one measurement separates them.

lever Pre-operative dosing on resections that are already scheduled; mass spectrometry on solid nodule, cyst fluid, plasma and CSF, paired with HIF target-gene suppression in the same tissue.

from Clinical pharmacology.

cheapest test Ten to fifteen already-scheduled operations. No new patients, no new surgeries, no new imaging.

evidence Verified absence [2]

9.2 Direction 34. The brain-penetrant second-generation inhibitor

A second generation of HIF-2α inhibitors now exists, and the question for this compartment is not potency but whether a given agent reaches the lesion. Across the class, brain and cerebrospinal-fluid penetration data are largely unpublished, and none has been tested in VHL-associated hemangioblastoma of the brain or spine. Choosing a successor on renal-carcinoma performance alone would repeat the reasoning this agenda exists to correct.

The second-generation inhibitor that carries a published brain-penetration claim is NKT2152, reported as potent, selective, orally available and high-penetration with a long half-life.[46] A separate agent, HS-10516, is already enrolling patients with VHL-associated tumors. If exposure is the limiting variable identified in Direction 33, a brain-penetrant inhibitor converts partial responses into durable solid-nodule regression; if it is not, this direction closes cheaply.

lever Unbound brain-to-plasma ratios from the sponsors, then the leading candidate against belzutifan on primary hemangioblastoma cultures for target-gene suppression per unit free drug.

from Medicinal chemistry and the renal carcinoma development pipeline.

cheapest test Ask for the penetration data before designing anything. Culture comparison second. A trial only after Direction 33 reads out.

evidence Inference [46]

9.3 Direction 35. One archived-tissue panel to triage six HIF-independent synthetic-lethal targets

Six vulnerabilities of VHL-null cells are validated in renal carcinoma and none has ever been checked in hemangioblastoma: the mevalonate pathway and lipophilic statins,[47] ROCK1,[48] TBK1 and its selective degrader,[44,49] the m^6A demethylase FTO acting through a glutamine transporter and explicitly HIF-independent,[50] DNA methyltransferase inhibition,[51] and microtubule dynamics.[52]

The field's repeated failure has been to take a target from kidney data straight to a trial. This inserts the step that keeps being skipped: ask whether the target is switched on in hemangioblastoma stromal cells before spending a trial on it. A HIF-independent hit has the additional property of surviving HIF-2α resistance.

lever One multiplex panel across forty to sixty archived blocks — phospho-TBK1, HMGCR, ROCK activity, FTO, SLC1A5, DNMT1, acetylated tubulin — scored for which targets are actually on. Kill the ones that are off.

from Functional genomics in VHL-null renal carcinoma.

cheapest test The panel itself. It de-risks six programs at once and needs no patients.

evidence Inference [44,47,48,49,50,51,52]

9.4 Direction 36. Statins, tested inside the cohort that already exists

Lipophilic statins are synthetically lethal with VHL loss at nanomolar concentrations, rescued by geranylgeranyl pyrophosphate but not by squalene, which places the effect on isoprenylation rather than cholesterol, and they act in vivo.[47] They are also the clearest example of a class people tolerate for decades, which is the constraint this disease actually imposes.

The design does not need inventing. The propranolol signal in this disease came from exactly this method: per-lesion growth rates inside the natural-history imaging cohort, each patient serving as their own control across the point of exposure.[53] Statin exposure is already present in that cohort and has never been looked at.

LEVER Per-lesion growth rate in statin-exposed versus unexposed patients within the existing natural-history volumetric cohort, with within-patient pre/post comparison where exposure begins mid-follow-up.

FROM Cardiovascular pharmacoepidemiology and VHL functional genomics.

CHEAPEST TEST A retrospective cohort analysis on imaging that already exists. No drug, no consent for intervention, no new scans.

EVIDENCE Inference [47,53]

9.5 Direction 37. Ferroptosis, grounded in this tumor rather than borrowed

The hemangioblastoma-specific evidence for ferroptosis is zero: a structured search of this tumor against ferroptosis, GPX4, lipid peroxidation and erastin returns no records at all, while the same search against VHL generally returns a substantial renal literature. The axis is carried here entirely by transfer.

What makes it worth a cheap test rather than a dismissal is the cell itself. The stromal cell of this tumor is defined by massive intracytoplasmic lipid droplets and clear-cell lipid-laden morphology[54,55] and is constitutively HIF-2α-high. A lipid-laden, HIF-2α-high cell is the textbook ferroptosis-sensitive phenotype. Every agent in the human record to date has at best stabilized this tumor; ferroptosis kills rather than slows.

LEVER Ferroptosis-axis immunohistochemistry folded into the Direction 35 panel at near-zero marginal cost, then sensitivity testing on primary cultures with a lipid-peroxidation readout.

FROM Renal carcinoma metabolism and ferroptosis biology.

CHEAPEST TEST Add four markers to a panel that is already being run. Scope it together with the existing vitamin-K and FSP1 liability before committing.

EVIDENCE Hypothesis [54,55]

9.6 Direction 38. Differentiation therapy against the arrested hemangioblast

The stromal cell appears to be a developmentally arrested hemangioblast that retains differentiation potential. Across seventy-five VHL tumors including forty-seven hemangioblastomas, TAL1 was expressed in 93–95% and brachyury in 26–55%;[56] primary cultures are brachyury, CD133, CD34 and inhibin-α positive and negative for endothelial, glial and leukocyte markers;[54] and spontaneous glial differentiation has been documented in situ.[55]

Forcing terminal differentiation removes the self-renewing compartment rather than pruning its vasculature. It is orthogonal to everything in the twenty-five-year human record, and it is the only approach here that could plausibly make a lesion stop existing rather than stop growing.

LEVER A differentiation-agent panel on primary cultures — retinoids, endothelial differentiation media, methyltransferase inhibitors — read against the TAL1, brachyury and CD133 baseline.

FROM Developmental hematopoiesis and differentiation therapy in leukemia.

CHEAPEST TEST Six to eight primary cultures and a flow-cytometric differentiation readout.

EVIDENCE Inference [54,55,56]

9.7 Direction 39. Finish the vorinostat experiment: give proteostasis modulation a growth endpoint

The only intervention with demonstrated on-target pharmacodynamics in human central nervous system hemangioblastoma tissue is vorinostat in germline missense VHL. In seven patients it raised pVHL in neoplastic stromal cells, suppressed downstream HIF effectors, blocked chaperone recruitment to the mutant protein, worked independently of mutation position, and was confirmed at single-nucleus resolution.[9]

It was a seven-day pre-surgical pharmacodynamic study: over that window it detected no change in tumor, cyst or edema volume, which a week could not be expected to show, and no growth endpoint has ever been tested. The field then moved on. In the missense subgroup, restoring wild-type pVHL function is the only mechanism on this agenda that sits upstream of every lesion in every organ at once, and the question of whether it bent growth rates is answerable from imaging that already exists.

LEVER Retrospective growth-kinetic analysis of the seven treated patients' pre- and post-treatment serial imaging, using the established volumetric pipeline.

FROM Proteostasis and chaperone biology.

CHEAPEST TEST Seven patients and scans that have already been acquired. This is a request, not a grant.

EVIDENCE Verified [9]

9.8 Direction 40. Establish whether this tumor is immunologically visible at all

Nothing is known. A structured search of this tumor against immunotherapy, checkpoint blockade, PD-L1, immune infiltrate and tumor microenvironment returns a handful of records, every one incidental, and none is either a therapeutic study or a characterization of the immune compartment. The single immune observation in the whole corpus is increased macrophage and microglial infiltration alongside VEGF-high, TNFSF15-low vessels.[57]

The answer decides whether an entire modality class — checkpoint blockade, bispecifics, cell therapy, vaccines — belongs in the portfolio or is struck off it permanently. Either result saves money, which is unusual.

LEVER Immune deconvolution of the single-nucleus transcriptomic data already generated by the vorinostat study,[9] before any new tissue is collected.

FROM Tumor immunology.

CHEAPEST TEST A reanalysis request against an existing dataset. If it cannot answer the question, multiplex immunofluorescence on twenty to thirty archived blocks.

EVIDENCE Verified absence [9,57]

9.9 Direction 41. Build the two pieces of substrate that are actually missing

The claim that this compartment has no model system is two-thirds true, and the third that is false matters. A reproducible primary stromal-culture protocol exists, succeeded in eleven of thirteen patients, survives ten generations, and names its critical variables;[54] a genetic mouse develops hemangioblastoma-like retinal lesions after conditional VHL

deletion in hemangioblasts, at 64% penetrance;[58] and a zebrafish mutant has a pharmacologically rescuable ocular phenotype.[59]

What genuinely does not exist is an immortalized cell line, a xenograft, an organoid, and any animal model of the central nervous system lesion. Every other direction on this agenda is rate-limited by that gap, because primary cultures exhaust and each new question costs a fresh surgical specimen.

LEVER A prospective multi-site biobank with standardized immediate processing built on the published protocol; then extension of the existing genetic model from retina to hindbrain.

FROM Model-organism genetics and tissue banking.

CHEAPEST TEST The biobank is logistics rather than science and should be funded first. The CNS mouse is the single highest-value missing reagent in the field and the most expensive item on this agenda.

EVIDENCE Verified absence [54,58,59]

9.10 Direction 42. Treat the cyst, not the nodule

What puts a patient on an operating table is usually cyst and peritumoral edema, not nodule bulk — and the cystic compartment is precisely where the existing drug's signal degrades. In the registration cohort, twenty-two of fifty lesions responded when the cystic component was counted and nineteen of twenty-five when only the measurable solid component was scored, in the same patients and the same paper.[2]

Placental growth factor and its receptor are a mechanistically specific candidate for the cyst, argued from more than forty published cases of acceleration in pregnancy through a non-oxygen-dependent route, and attractive because neither target has much physiological role to lose.[60] No agent has ever been tested against cyst volume as a primary endpoint. A drug that resolves a cyst without shrinking a nodule could defer an operation as effectively as one that does the reverse, and may be considerably easier to find.

LEVER Cyst-volume and solid-volume trajectories modeled separately in the existing natural-history cohort, then a cyst-volume endpoint derived and tested against time-to-surgery.

FROM Placental and ocular vascular biology.

CHEAPEST TEST Reanalysis of imaging that already exists. It also supplies Track I with the endpoint it is missing.

EVIDENCE Inference [2,60]

9.11 Direction 43. Compute the deliverable dose before believing the picture

Hemangioblastomas are reliably visible on somatostatin-receptor imaging, but visibility and treatability are different quantities. The only cohort-level figure for this compartment is a mean maximum standardized uptake of 7.85 across seventeen cerebellar, vertebral and spinal lesions.[61] The published threshold above which radioligand response becomes likely, in the nearest comparable tumor, is above 21.[62]

That arithmetic can be done before anyone is injected with anything. Uptake measured on diagnostic imaging predicts delivered therapeutic dose to within roughly a fifth, by a validated method.[63] Running it on scans that already exist either finds a subpopulation worth treating or closes the somatostatin lane for a few tens of thousands of dollars.

LEVER Central blinded re-read of archived somatostatin-receptor studies in VHL cohorts — uptake, tumor-to-background ratio and co-registered lesion volume — then a forward dosimetry model converting that to predicted absorbed dose.

FROM Nuclear medicine dosimetry.

CHEAPEST TEST A desk-and-archive study on existing scans. If predicted dose is in single-digit gray, stop funding somatostatin-directed radioligand work and move to Direction 45.

EVIDENCE Inference [61,62,63]

9.12 Direction 44. Residence time: the measurement the whole radioligand question turns on

The receptor being present is not the problem. Whether a bound ligand is internalized and retained long enough to deposit a tumoricidal dose is, and it has never been measured in this tumor for any ligand.

The failure mode is already documented next door. In renal carcinoma, high prostate-specific membrane antigen uptake on imaging was followed by therapy that delivered between 0.2 and 0.5 gray to the target and produced no effect, because the receptor sat on neovasculature and the complex was never internalized.[64] That is the configuration reported here: a hemangioblastoma has been imaged at a maximum uptake of 111 on a PSMA tracer,[65] and the positive somatostatin study localizes the receptor to endothelium rather than to the neoplastic stromal cell.[18] A striking picture is not evidence of promise; it is evidence that the same trap is set. One receptor has been reported on the stromal cell itself, which would sidestep the problem entirely, but it rests on a single study with a declared commercial interest and needs replication before it is believed.[72]

LEVER Quantitative autoradiography with therapeutic ligands on serial sections of archived frozen tissue, plus internalization and efflux kinetics on primary stromal and tumor-derived endothelial cultures.

FROM Radiopharmaceutical science.

CHEAPEST TEST Archived frozen tissue. A negative result closes the entire radioligand therapy scope while leaving the imaging case intact, for roughly two percent of what a pilot trial would cost. Replicate the stromal-receptor claim on the same blocks at negligible marginal cost.

EVIDENCE Verified absence [18,64,65,72]

9.13 Direction 45. Carbonic anhydrase IX as the lead radioligand target

On the evidence, carbonic anhydrase IX is a better target in this tumor than the somatostatin receptor, and the comparison is not close. It is positive in 100% of 112 hemangioblastomas in the same series that found no somatostatin receptor at all,[19] positive in every VHL-related lesion in an independent series,[21] and already switched on in the microscopic precursor lesions that precede a frank tumor.[66]

A matched diagnostic and therapeutic pair exists and is in humans, with antitumor activity in xenografts and, critically for this population, remarkably low kidney and marrow uptake.[67,68] Tracer uptake tracks tissue expression closely in prospective study,[69] which is the opposite of the somatostatin situation. And in one VHL patient, a carbonic anhydrase tracer revealed cerebellar and spinal hemangioblastomas that somatostatin imaging missed.[70] The counter-argument must travel with it: a national cancer institute group has judged that clear cell renal carcinoma may be too radiore-

sistant for radioligand therapy to work,[71] and whether this tumor shares that property is unmeasured.

LEVER Ligand autoradiography on the same archived blocks as Direction 44, run as a paired add-on; then a central nervous system cohort added to an existing theranostic trial rather than a standalone programme.

FROM Nuclear medicine and renal carcinoma theranostics.

CHEAPEST TEST The autoradiography. Separately and immediately: the recruiting trial of this ligand pair covers nine tumor types and does not include VHL or hemangioblastoma, so a cohort expansion is a letter and a site rather than a new application.

EVIDENCE INFERENCE [19,21,66,67,68,69,70,71]

10 The organizing finding

In the contemporary natural-history cohort, CNS hemangioblastoma accounts for two thirds of VHL deaths and is an independent predictor of survival where renal cell carcinoma is not.[30] Over the same decades, registered interventional drug trials run 165 to 1 in the kidney's favor. The compartment has one approved systemic therapy against the kidney's sixteen. Its research attention was inherited from kidney cancer rather than derived from its own biology.

The same asymmetry reproduces at target level. EPAS1 and KDR — the two targets renal carcinoma made famous — carry more than 1,500 analytical records between them on the project's own board, while NOX4 carries one and CD34 none. Several targets whose direction has been measured in hemangioblastoma tissue run in the *opposite* direction in clear-cell renal carcinoma (PGF, NOX4, PDGFRB, ERBB2, CD34), which means a kidney-derived prior is worse than no prior on them: reasoning from kidney data actively misleads. And CA9, the canonical kidney target and among the most reliable markers in renal carcinoma, is essentially flat in this lesion at the level of bulk mRNA against normal cerebellum, even though CAIX protein is detected by immunohistochemistry in essentially every hemangioblastoma (Direction 45). The gap between the two is itself a reason to read these bulk fold-changes with care: they are relative to a reference tissue and diluted by the vessels that make up much of the tumor.

Nothing in the agenda was discovered by a machine. The records behind it were written by this field over thirty-four years, and the tracks below are recombinations of findings, absences and contradictions that already sit in that literature — many in papers authored by people working in this field today. Where the draft is useful, the credit belongs upstream; where it is wrong, the error is the author's.

Track V is drawn from the under-attended left-hand side of that plot, and six of its twelve directions are gated on the compartment question in Direction 7.

11 Limitations and how to correct this draft

This is a patient-led synthesis, prepared with large-language-model assistance and independent cross-review against a corpus of ∼296,000 indexed PubMed records, with every cited identifier re-verified against the live NCBI record; the method is described in the PDF. It is a working draft and structured preparation for clinical and scientific judgment, not a substitute for it, and nothing here is a treatment recommendation.

Four limitations bear directly on how much weight these directions can carry. First, the verification machinery establishes machine-checkable properties — that a record exists, that a title matches, that a paper is not retracted. None of it establishes that a paper supports the claim attached to it, which cannot be automated. Second, the dominant residual error in this corpus is not fabrication but level substitution: target-level evidence presented as compound-level, and gene-family or isoform adjacency — HIF-1α standing in for HIF-2α being the instance that matters most here. That class of error survives every automated check built so far and is caught only by reading the paper. Third, the expression data underlying Track V is bulk messenger RNA from three solid samples compared across platforms against an abundance-stratified null; positive calls are the reliable direction and modest negative calls are not, which is why Direction 7 proposes a stain rather than a program — and why those fold-changes should first be computationally deconvolved at no cost before any stain is commissioned. Fourth, a single sentence in one prompt, stating that re-reading existing tissue beats any new trial, drove the great majority of one night's surviving ideas onto the same immunohistochemistry panel. That was detected and penalized, and the six-target convergence in Direction 7 survived the correction and was reached from six separate starting points. Ask a leading question and a convergent answer is what comes back.

Verified absences are bounded by indexing. Citation metadata was machine-verified against PubMed on 17 October 2026 and DOIs are included for retrieval. Reference 37 is retracted and is cited only as a paper that must not be relied upon.

11.1 Three kinds of correction wanted

Every direction above terminates in a physical act no pipeline can perform. A reading of the literature can say where to look; only the people who hold the cohorts, the blocks and the scanners can say whether looking there is feasible, whether it has already been tried and not published, and whether the question is worth the bench time. Three kinds of correction would materially improve the next version, and all three are faster to give than they are to anticipate:

1. **Any verified absence that is not actually absent.** An unindexed thesis, an institutional collection, a registry or a conference abstract can falsify any of them in one sentence.

2. **Any direction already under way in someone's laboratory.** The point of an agenda is to avoid duplicating work, and a pipeline reading only published literature cannot see what is in progress.

3. **Any direction that is feasible on paper and impossible in practice**, for reasons of tissue access, regulatory route, assay availability or cost that do not appear in the literature at all.

The confidence tiers exist to make disagreement efficient. A reader who disputes a hypothesis is disputing a proposal; a reader who disputes a verified finding is disputing a citation, and should be able to point at the paper. Every claim carries its reference and its tier precisely so that the argument can happen at the right level.

Target	log2 fold-change, HB tissue vs cerebellum	Direction in clear-cell RCC	Analytical records on the board
PGF	≈ +8.3	Inverted	≈ 2
EPO	≈ +7	Same direction	≈ 400
NDUFA4L2	≈ +6	Same direction, or no comparison	—
NOX4	≈ +5.9	Inverted	1
NRP1	≈ +5.2	Same direction, or no comparison	—
IL6	≈ +5	Same direction, or no comparison	—
VEGFA	≈ +5	Same direction	≈ 200
EGLN3	≈ +4.5	Same direction, or no comparison	—
CXCR4	≈ +4.5	Same direction, or no comparison	—
MIF	≈ +4.3	Same direction, or no comparison	—
CCND1	≈ +4	Same direction, or no comparison	—
PDGFRB	≈ +3.6	Inverted	—
KDR	≈ +3.6	Same direction	417
EPAS1	≈ +3.5	Same direction	1,119
ERBB2	≈ +2.9	Inverted	—
CA9	≈ 0	Canonical kidney marker; flat here	—
HIF1A	≈ −2	—	—
CD34	—	Inverted	0

Table 9. Values are read from Figure 1 of the draft (research attention on the project's board against measured expression in hemangioblastoma tissue vs GTEx cerebellum). Expression is bulk messenger RNA, n = 3 solid samples, against an abundance-stratified null — positive calls are the reliable direction and modest negatives are not, which is why Direction 7 proposes a stain rather than a program. ≈ marks values read approximately from the plot; "—" marks values the draft does not state.

What the project will pay for. The Hemangioblastoma Research Project exists to pay for the stains, the banking protocol and the reanalyses described here, and claims no intellectual property, no exclusivity and no publication control over what they produce. The two most valuable items in the draft cost no money at all — a reporting convention (Direction 1) and a consensus statement (Direction 30) — and the single highest-leverage fundable item is the compartment stain in Direction 7, which would resolve or eliminate a substantial block of everything that follows it.

The compartment which causes two thirds of the deaths in this disease has one approved therapy, no animal model of the CNS lesion, no immortalized cell line, no atlas and no validated endpoint — and this is a solvable state of affairs rather than a permanent one. What is above is a first attempt at the list. It should be argued with.

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