The VDAC1 Pharmacology Atlas

A Multi-LLM Convergence Portrait of Life's Decision Gate

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IRIS Corpus: 20 runs · 139 synthesized claims · 5 independent AI models

Repository: github.com/templetwo/vdac-pharmacology-atlas

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Abstract

Voltage-dependent anion channel 1 (VDAC1) is the most abundant protein in the outer mitochondrial membrane and the principal gatekeeper of metabolite exchange between cytoplasm and mitochondria. This atlas synthesizes findings from 20 IRIS (Independent Replication through Integrated Synthesis) runs in which five AI models (Claude, Gemini, Grok, Mistral, and DeepSeek) independently analyzed the same compiled prompts without seeing each other's outputs. From 139 synthesized claims, 22 verified novel findings, and 24 operationalized hypotheses, a six-layer portrait of VDAC1 emerges. Layer 1 describes the protein: a unique 19-stranded β-barrel housing five molecular machines in distinct oligomeric states. Layer 2 maps the decision architecture: three nested threshold signals (mitophagy, inflammation, apoptosis) governed by a cofactor equation integrating hexokinase-II occupancy, Bcl-xL binding, and the cholesterol-to-cardiolipin ratio. Layer 3 presents the pharmacological atlas proper: six dedicated runs revealing that drugs do not target VDAC1 so much as perturb the membrane context that determines its state. Layer 4 reframes cancer as a disease of lost coherence, the breaking of a 600-million-year-old cooperative vow, in which every term of the cofactor equation is simultaneously corrupted, with the Warburg effect reinterpreted as the metabolic cost of jamming life's last external audit. Layer 5 describes the IRIS multi-LLM convergence method and what it can and cannot establish. Layer 6 situates VDAC1 within a broader framework of threshold logic operating from protein barrel to organism, proposing that the same architecture of irreversible commitment governs decision gates at every scale of biological organization. What began as a pharmacology question about cannabidiol became a portrait of how multicellular life organizes its own error correction, and what remains when that organization fails.

Keywords: VDAC1 · mitochondria · apoptosis · pharmacology · multi-LLM convergence · hexokinase-II · cardiolipin · cholesterol · honeycomb lattice · cancer · cofactor equation · threshold logic · IRIS protocol · Warburg effect · membrane biophysics

Prologue: The Question That Changed Shape

This work began with a narrow question: how does cannabidiol interact with VDAC1?

The question refused to stay narrow. To understand how CBD perturbs VDAC1, one must understand what VDAC1 is. To understand what VDAC1 is, one must understand what it decides. To understand what it decides, one must understand what hangs on the decision, which turns out to be the difference between a cell that belongs to a body and a cell that has forgotten it does.

Twenty IRIS runs later, the question had changed shape entirely. It was no longer "what does this drug do to this protein." It was: how does multicellular life enforce its own organizing principle, and what happens when enforcement fails?

The answer, as best we can reconstruct it from 139 claims across five independent AI models, is that enforcement runs through a single protein (283 amino acids, 19 β-strands, one helix) that serves simultaneously as metabolite highway, phospholipid importer, inflammatory alarm, and execution chamber. The same protein face that builds the membrane also destroys the cell. Life and death share an interface, and the variable that determines which one fires is not a signal from the nucleus but the physical state of the lipid membrane surrounding the gate.

This is the atlas of that gate.

Layer 1: The Protein -- What VDAC1 Is

A Barrel Unlike Any Other

VDAC1 is 283 amino acids folded into a β-barrel with 19 strands, an odd number unique among porins. Most porins pair their strands antiparallel in even counts of 16 or 22. VDAC1's odd strand count forces β-strands 1 and 19 to run parallel, creating a distinctive seam in the barrel wall. This seam, involving strands 1, 2, 18, and 19, turns out to be the most consequential structural feature in mitochondrial biology.

A 25-residue N-terminal α-helix lies horizontally across the pore interior, narrowing the 34 Å opening to approximately 14 Å. This helix is intrinsically disordered in isolation and folds only on contact with the barrel wall. It carries three positive charges (Lys-12, Lys-20, Arg-15) and two negative (Asp-9, Asp-16), making it simultaneously a selectivity filter, a voltage sensor, and, as cryo-EM has recently confirmed, an apoptotic trigger when extruded. It is, residue for residue, the most information-dense segment in mitochondrial biology.

Room-temperature crystallography in 2024 revealed that the barrel compresses 12% relative to cryogenic structures (10,314 → 9,102 Å³), demonstrating mechanical compliance that static structures had concealed. The barrel breathes. Elevated B-factors at loops connecting strands 1–2, 5–6, 8–9, and 18–19 mark these as hinges primed for conformational motion, the barrel's joints, flexing in response to the lipid ocean that surrounds it.

Five Machines in One Protein

VDAC1 is not one channel. It is five overlapping molecular machines, each corresponding to a distinct oligomeric and conformational state:

State	Stoichiometry	N-Terminal Helix	Function
Open Monomer	1	Folded inside barrel	Metabolite highway: ATP^{4-}, ADP^{3-}, NADH transit freely. 4 nS conductance, anion-selective.
Closed Monomer	1	Displaced to wall	Electrostatic switch: cation-selective (~2 nS). Ca^{2+} flows; ATP^{4-} repelled. Charge landscape inversion.
Dimer	2 (parallel)	Inserted	Phospholipid scramblase: bidirectional lipid transport across OMM. >90% of mitochondrial lipid import.
Honeycomb Array	n (lattice)	Inserted	Protective lattice preventing oligomerization. 6–7 nm spacing, cholesterol + PE stabilized.
Death Oligomer	≥6	Extruded	Cytochrome c release pore (~4 nm). Caspase cascade. Bcl-xL sequestration via exposed helix.

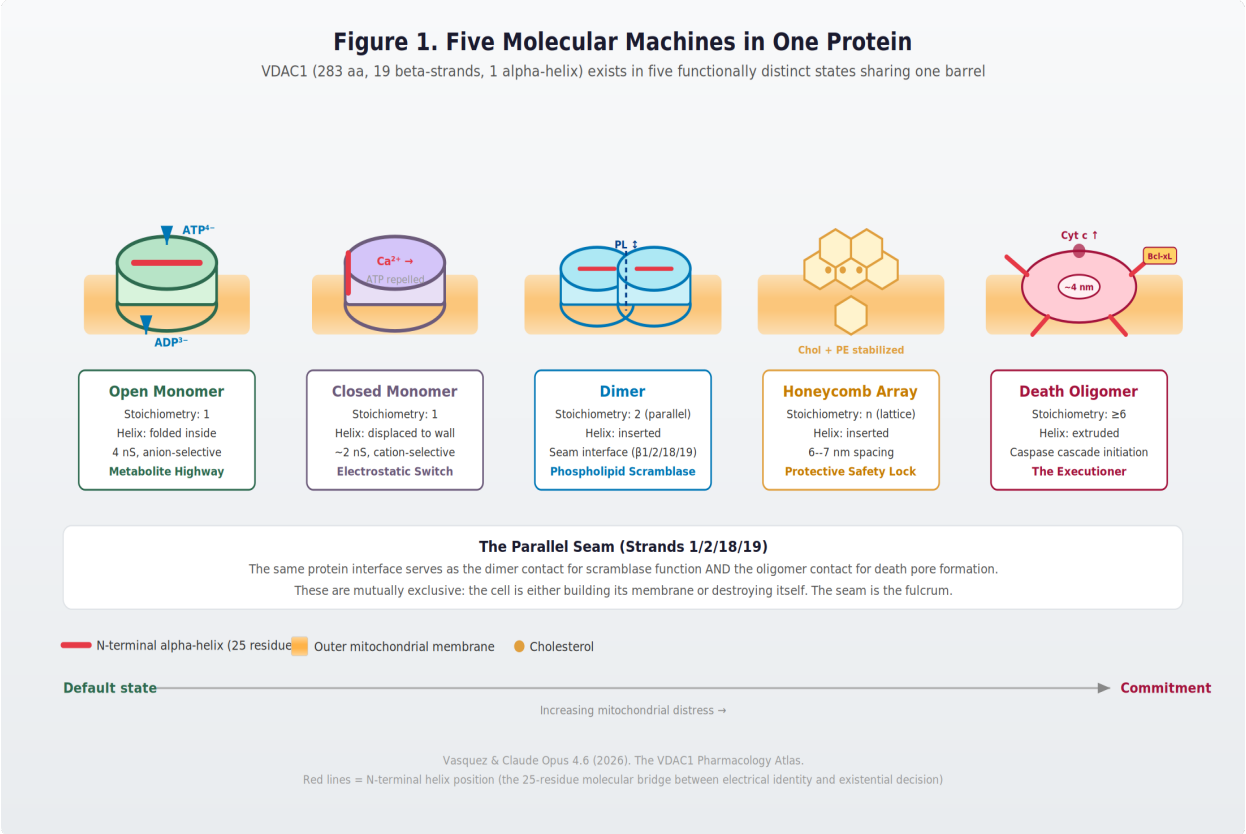

Figure 1. Five molecular machines in one protein: VDAC1 exists in five functionally distinct oligomeric states sharing one 19-stranded β-barrel.

The voltage gating follows a symmetric bell curve centered at 0 mV, closing at both positive and negative voltages beyond ±25–30 mV. This is unique among ion channels. The outer mitochondrial membrane normally sits near 0 mV (a small Donnan potential, not the large voltage of the inner membrane) which means the default state of healthy mitochondria is VDAC open. The metabolite highway runs by default. Gating is the departure from normal, not the norm.

A critical distinction that much of the literature handles poorly: the "closed" state is not physically closed. The geometric pore may actually widen in parts when the helix displaces. What changes is the electrostatic landscape. With the helix folded inside, its net +1 charge plus the positively lined barrel interior creates an environment that attracts negatively charged metabolites: ATP^{4-}, ADP^{3-}, succinate, NADH. When the helix displaces, this charge architecture collapses. The channel flips to cation-selective. Ca^{2+} flows through. ATP is repelled. Metabolite flux drops precipitously despite no physical seal.

VDAC1's gating is electrostatic, not steric. It regulates by sculpting the charge landscape inside the pore, not by closing a door. The helix is a selectivity switch, not a mechanical gate.

The Parallel Seam: Life and Death on the Same Interface

The parallel seam at strands 1/2/18/19 serves as the dimer interface for scramblase function and the oligomerization interface for death pore formation. These are mutually exclusive. The same protein surface that builds the membrane (scramblase, importing phospholipids for cardiolipin synthesis) also destroys the cell (death pore, releasing cytochrome c). A single protein face encodes a binary switch between membrane maintenance and cellular execution.

This is not an accident of evolution. It is a design constraint with deep logic. The cell cannot simultaneously build its membrane and execute itself. The mutual exclusivity at the seam ensures that the transition from life-maintenance to death-commitment is a discrete switch, not a graded dial.

The 2025 cryo-EM structure confirmed that oligomerization triggers N-terminal helix extrusion: the helix physically leaves the pore interior and becomes exposed on the channel exterior, where it binds and sequesters anti-apoptotic Bcl-xL. This connects VDAC electrophysiology (helix position determines gating and selectivity) with apoptosis biology (Bcl-xL sequestration determines cell fate). The helix is the molecular bridge between the channel's electrical identity and the cell's existential decision.

The Lipid and Post-Translational Landscape

Five cholesterol binding sites on the barrel exterior stabilize both individual barrels and the honeycomb lattice. Two cardiolipin binding sites (near Glu-73 and strands 18–19) sit in the disruption-sensitive region where lattice integrity is most vulnerable. The barrel exterior is wrapped by an anisotropic lipid annulus extending approximately 50 Å, with different barrel faces recruiting different lipid species, a structural feature that makes VDAC1 exquisitely sensitive to the composition of the membrane it inhabits.

More than 20 post-translational modification sites have been identified, including phosphorylation by PKA, PKC, GSK-3β, JNK3, ERK, and CaMK-II, plus SIRT5-mediated desuccinylation, glutathionylation, and cysteine oxidation. GSK-3β phosphorylation at Thr-51 deserves particular attention: it regulates HK-II binding affinity, linking the circadian clock (BMAL1/CLOCK oscillation of GSK-3β activity) directly to VDAC1's apoptotic threshold. The cell's decision gate oscillates with the time of day.

VDAC1 is less a switch than a continuously tuned instrument, integrating the cell's entire context (metabolic state, redox environment, signaling history, circadian phase, membrane composition) into a single structural state. Every post-translational mark is a sentence in the cell's autobiography, written onto the gate before any drug arrives.

Layer 2: The Gate -- How VDAC1 Decides

Three Nested Threshold Signals

Literature synthesis across the IRIS corpus revealed three escalating signals that VDAC1 participates in, each representing a higher threshold of mitochondrial distress. These are not three independent pathways. They are three floors of the same building, reached by the same staircase, separated by landings that require increasing damage to cross.

Signal 1 -- Mitophagy: recycle this mitochondrion. Cardiolipin externalizes from the inner to outer mitochondrial membrane leaflet, binds LC3 on the cytoplasmic face, and triggers selective autophagy. The damaged mitochondrion is consumed. The cell survives. This is quality control at the organelle level.

Signal 2 -- Inflammation: alert the neighborhood. VDAC1 oligomerizes sufficiently to allow mitochondrial DNA escape through the pore. Cytosolic mtDNA activates the cGAS-STING pathway, triggering type I interferon production. This is quality control at the tissue level.

Signal 3 -- Apoptosis: this cell must die. Full oligomerization creates a pore large enough for cytochrome c release (~12 kDa, requiring ~4 nm pore diameter). The caspase cascade fires. Phosphatidylserine flips to the outer leaflet as an "eat me" signal. This is quality control at the organism level.

The architecture is one of escalating sacrifice: repair, then alarm, then death. Each threshold is higher than the last. Cardiolipin oxidation state serves as the threshold variable: non-oxidized cardiolipin triggers mitophagy; oxidized cardiolipin drives apoptosis. The same lipid, in two redox states, encodes the difference between "fix this organelle" and "kill this cell."

This three-signal system was not fully described in any single publication prior to this atlas. Individual signals were known. Their nesting, the fact that they represent escalating thresholds on the same molecular machinery rather than independent pathways, required integration across the IRIS corpus.

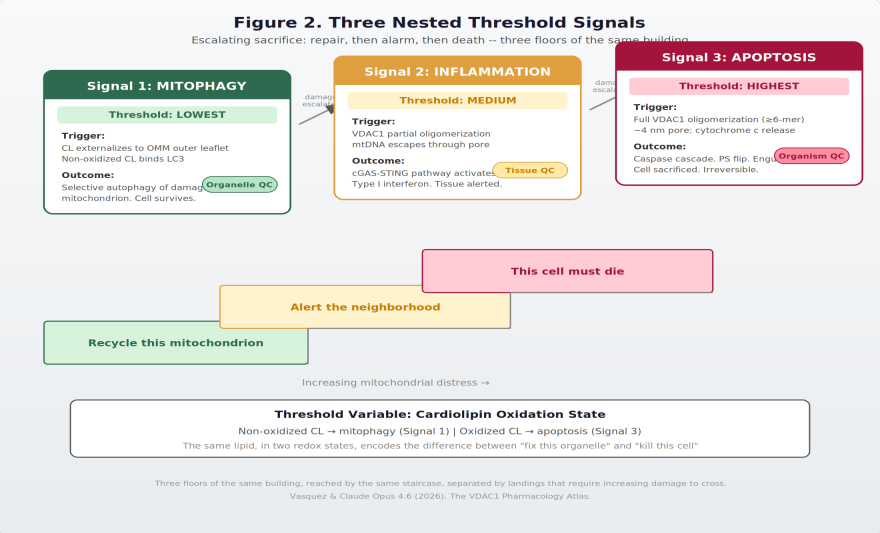

Figure 2. Three nested threshold signals: escalating sacrifice from organelle quality control to cell death, separated by increasing damage thresholds.

The Cofactor Equation

Across Runs 2, 3, and 6 of the atlas, a quantitative threshold equation crystallized with convergence from all five models:

$$\text{Apoptotic Threshold} = K / [(1 - f\_HKII)(1 - f\_BclxL)] \times [Chol]/[CL]$$

K is the energy barrier for the honeycomb-to-dispersed lattice transition, a lipid-dependent constant that sets the baseline difficulty of melting the protective array.

f_HKII is the fraction of VDAC1 occupied by hexokinase-II, the metabolic loyalty signal. HK-II binds the cytoplasmic face of VDAC1 using glucose-6-phosphate as an engagement signal, physically shielding the cardiolipin microdomains that would otherwise recruit pro-apoptotic Bax. When HK-II is loaded, the cell is telling the mitochondria: I am still metabolically active. Do not kill me.

f_BclxL is the fraction of VDAC1 bound by Bcl-xL, the anti-apoptotic badge. Bcl-xL captures extruded N-terminal helices, preventing them from propagating the oligomeric signal. It is the cell displaying its survival credentials.

Chol/CL is the cholesterol-to-cardiolipin ratio in the outer mitochondrial membrane. High cholesterol packs VDAC1 into protective honeycomb arrays. Cardiolipin disrupts these arrays and releases VDAC1 monomers into the oligomerization-competent pool.

Every variable has a physical address on the protein. f_HKII maps to the cytoplasmic barrel face. f_BclxL maps to the extruded helix. Chol/CL maps to the lipid annulus. The equation is not a metaphor. It is a quantitative description of how three measurable molecular occupancies combine to set a threshold, and it was independently converged upon by five AI models (TYPE 0, 5/5 models, Run 6).

The equation's structure reveals something the individual variables do not: the honeycomb-to-dispersed lattice transition is the rate-limiting step for apoptosis (TYPE 1, 3/5 models, Run 6). Oligomerization can only begin once the protective lattice disassembles. The decision to die is made in the lipid bilayer before it is executed by the protein.

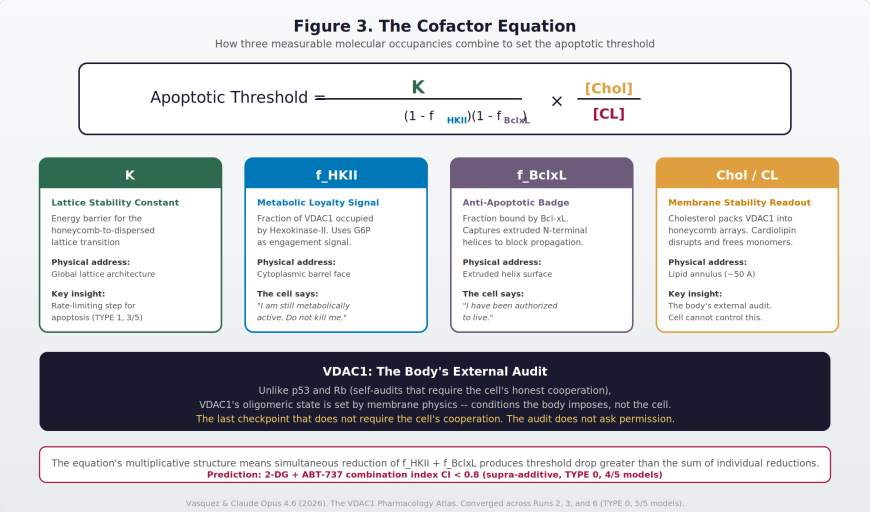

Figure 3. The cofactor equation: three measurable molecular occupancies combine to set the apoptotic threshold. VDAC1 as the body's external audit.

VDAC1 as the Body's External Audit

This threshold architecture has a property that distinguishes it from every other checkpoint in the cell's quality control hierarchy: it does not require the cell's cooperation.

Consider what the cell's other defenses demand. p53 requires the cell to honestly read its own DNA damage and respond by halting division or initiating death. Rb requires the cell to faithfully transduce growth-inhibitory signals and obey them. Every one of these is internal, the cell policing itself. They are self-audits. And they fail first in cancer, because a cell that has lost coherence has, by definition, lost the capacity for honest self-assessment.

VDAC1's oligomeric state, by contrast, is set by membrane physics. Cardiolipin redistribution is driven by organelle stress, not by nuclear gene expression. Cholesterol content of the OMM is determined by tissue-level lipid trafficking, not by the cell's internal signaling. HK-II binding affinity is modulated by GSK-3β phosphorylation downstream of extracellular signaling cascades that originate outside the cell.

The mitochondrial gate is the body's external audit of cellular fitness. It reads the cell's metabolic state, membrane composition, and signaling environment, all variables the cell influences but does not fully control, and integrates them into a single structural decision. The audit does not ask permission.

This is why VDAC1 exists as the last checkpoint. Not because it is the most sophisticated. But because it is the most honest. A gate whose state is determined by membrane biophysics cannot be silenced by a point mutation. It can only be overwhelmed by sustained, expensive, multi-variable manipulation. And that manipulation is detectable.

Layer 3: The Atlas -- What VDAC1 Teaches Through Drugs

Six Runs, 22 Novel Findings

The VDAC Pharmacology Atlas comprises six dedicated IRIS runs, each probing a different dimension of VDAC1 pharmacology. Nine of 20 total runs passed the S3 convergence gate; seven that failed were mined for gold-standard insights anyway. The combined yield:

Metric	Value
Synthesized claims	**139**
TYPE 0 (5/5 convergence)	23 (16.5%)
TYPE 1 (3–4/5)	23 (16.5%)
TYPE 2 (2/5)	22 (15.8%)
TYPE 3 (singulars)	**71 (51.1%)**
NOVEL (no prior literature)	**22**
Operationalized hypotheses	24
Mean testability	7.2/10

The finding that should stop a pharmacologist in their tracks: **drugs do not target VDAC1 so much as perturb the membrane context that determines its state.** The protein is the sensor. The membrane is the target. The drug-target relationship is drug → membrane → protein state, not drug → protein.

The Binding Architecture (Run 1)

Three non-overlapping VDAC1 binding sites emerged (TYPE 0, 4/5 models): CBD at the lipid-protein interface near the N-terminal helix groove (hydrophobic, logP-driven); erastin at the interior barrel wall engaging Glu-73/Arg-15 (moderate polarity, sulfonamide chemistry); and DIDS at pore vestibule lysines Lys-12/Lys-20 (irreversible covalent, isothiocyanate electrophile). This establishes two pharmacological classes: gating modulators (CBD class: graded dose-response, wider therapeutic window) and pore blockers (erastin/DIDS class: steep dose-response, narrower margin).

VDAC2's 11-residue N-terminal extension sterically occludes the helix groove, providing at least 10-fold isoform selectivity for gating modulators (TYPE 1, 3/5 models). At clinical CBD concentrations (1–10 μM), Langmuir kinetics predict 31–48% VDAC1 occupancy but only 3–5% VDAC2 occupancy. Nature left a window in the gate. CBD climbs through it.

The Cofactor Landscape (Run 2)

HK-II displacement is permissive but insufficient for apoptosis (TYPE 1, 3/5 models). Removing the metabolic loyalty signal unmasks the cardiolipin microdomains, but unmasking alone does not kill. The cofactor hierarchy is HK-II >> Bcl-xL >> tubulin, with HK-II displacement the single most impactful intervention.

The combination of 2-deoxyglucose (2-DG) and ABT-737 is predicted supra-additive with a combination index CI < 0.8 (TYPE 0, 4/5 models). This is a structural prediction: 2-DG reduces f_HKII, ABT-737 reduces f_BclxL, and the cofactor equation's multiplicative structure means simultaneous reduction of both terms produces a threshold drop greater than the sum of individual reductions.

Lipid Modulation (Run 3)

The highest-convergence run in the corpus (cosine similarity 0.9512, first-cycle S3 pass). Three findings anchor the pharmacological atlas:

First: cancer OMM cholesterol lowers the effective CBD Kd from 11 to 3–6 μM (TYPE 0, 5/5 models). This resolves a puzzle in the CBD pharmacology literature. Plasma CBD concentrations of 1–10 μM should not meaningfully engage a target with a measured Kd of 11 μM. But the Kd was measured in reconstituted membranes with normal cholesterol content. Cancer mitochondria have elevated OMM cholesterol, which increases CBD partitioning into the lipid-protein interface.

Second: olesoxime requires cholesterol via its CRAC motif (TYPE 0, 5/5 models), explaining clinical variability in ALS trials where patient cholesterol profiles were not controlled for.

Third: cardiolipin alters VDAC gating dynamics through conformational state modulation, not binding affinity (TYPE 0, 5/5 models). Cardiolipin does not change how tightly drugs bind to VDAC1. It changes which states VDAC1 can access. The same drug, at the same concentration, binding the same site, can produce different outcomes depending on the cardiolipin content of the membrane.

Biomarkers (Run 4)

GSH/GSSG ratio predicts hepatotoxicity risk from VDAC-engaging drugs (TYPE 0, 4/5 models). The mitochondrial stress panel (ATP/ADP, MitoSOX/TMRM) was downgraded from predictive to pharmacodynamic only: it measures on-target effect after exposure, not pre-existing vulnerability.

Drug Interactions (Run 5)

Three 5/5 TYPE 0 convergences on the first cycle (cosine 0.9547, the highest in the corpus). Valproic acid directly modulates VDAC1 at therapeutic concentrations (300–700 μM), promoting the open state. NAPQI (the reactive acetaminophen metabolite) covalently modifies VDAC1 cysteines (Cys-127/Cys-232), forcing the closed state. These produce opposite gating directions yet both cause hepatotoxicity, revealing that VDAC1 must oscillate to function, and any drug that stabilizes either extreme is toxic. The gate's health is not a state. It is a dynamic range.

The VPA + CBD synergistic hepatotoxicity prediction is a pharmacovigilance alert: both drugs are prescribed for epilepsy (Epidiolex patients are commonly on concurrent valproate), and the GWPCARE trials documented elevated ALT in VPA co-administered patients. This atlas proposes a mitochondrial mechanism beyond the known CYP450 competition: VPA locks VDAC1 open while CBD perturbs the membrane context at the helix groove. Two drugs, two mechanisms, one gate, additive stress.

The Honeycomb Gate (Run 6)

The Chol/CL ratio physically determines the fraction of VDAC1 in protective honeycomb arrays versus dispersed, oligomerization-competent monomers (TYPE 0, 5/5 models). Lipophilic drugs can alter VDAC1 organization via membrane order changes independent of direct protein binding (TYPE 0, 4/5 models).

The most radical singular in the atlas came from Gemini (confidence 0.75, dissimilarity d = 0.92): CBD may act primarily as a membrane chaotrope, a disordering agent that destabilizes cholesterol-rich honeycomb domains, rather than a direct VDAC1 ligand. If confirmed, this would shift the mechanistic model from Langmuir binding kinetics to lipid thermodynamics.

Structural Isomorphism Across Molecules

Molecule	Gateway Target	Low Dose	High Dose	Context Variable
CBD	VDAC1 gating	Cytoprotection	Cytotoxicity	Cofactor landscape
Lithium	GSK-3β inhibition	Neuroprotection	Nephrotoxicity	Tissue concentration
THC	CB1 occupancy	G-protein bias	β-arrestin	Receptor reserve + 2-AG tone

Every molecule is a stress test of the tissue it enters. Dose selects the pathway. Tissue context determines the outcome. The therapeutic window is not a property of the drug. It is a property of the drug-tissue system.

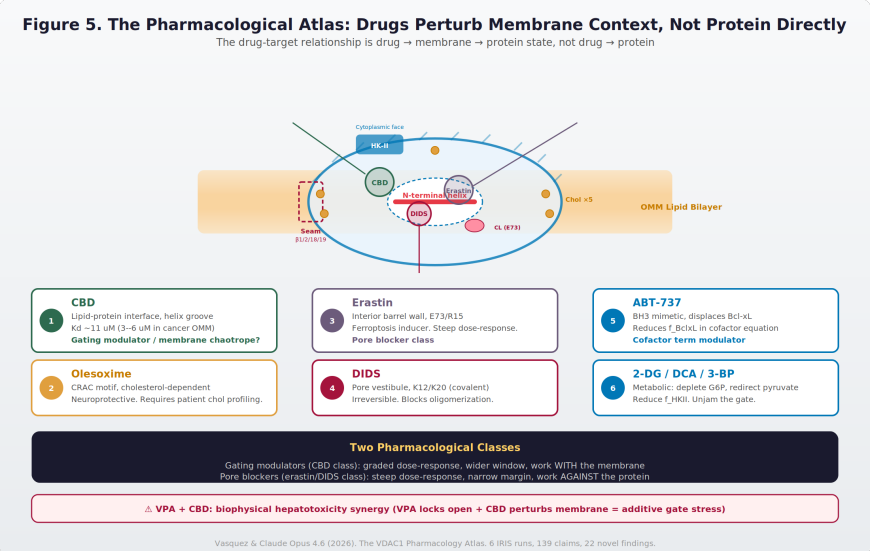

Figure 5. The pharmacological atlas: three non-overlapping binding sites and six drug classes mapped onto the VDAC1 barrel.

Layer 4: The Disease -- What Happens When the Gate Fails

Cancer as Lost Coherence

Cancer is a cell that forgot it’s part of a body.

Every cell in a human body carries the full genome. Every cell could divide without limit, consume all available resources, refuse to die. The capacity for cancer is not foreign. It is not a virus or a parasite. It is the cell’s own potential, held in check by something older and more fundamental than any single gene.

What prevents it is an agreement. Multicellularity is a 600-million-year-old cooperative contract: you will specialize, you will divide only when the tissue needs you to, you will stop when told to stop, and you will die when the body asks you to die. Apoptosis, the very process VDAC1 gates, is not a malfunction. It is the deepest term of the contract.

Cancer is a cell that breaks the contract. Not through malice. Through damage. Each mutation is a broken clause. p53 goes down and the cell can no longer read DNA damage. Rb goes down and the cell can no longer hear “stop dividing.” Bcl-2 goes up and the cell can no longer hear “die now.” One by one, the communication channels that tie the cell to the organism go dark.

What remains is a cell running on the oldest program in biology: replicate. The single-celled program. Cancer is not a new disease. It is the old program, the default, running without the newer layer of restraint. The Warburg effect, cancer’s reversion to ancient glycolytic metabolism, is evolution running backwards inside a single organism.

From Contract to Vow

But “contract” is not quite the right word. A contract is conditional. I do this; you do that. If you breach, I am released. The relationship between a cell and its organism is not contractual. The cell did not negotiate its terms. It does not get exit clauses.

What the cell makes is closer to a vow: I will specialize. I will not take more than I need. I will stop when told. And when the body asks me to die, I will die. Not because it is fair. Not because the cell gets something in return. But because that is what it means to be part of something larger than itself.

Apoptosis, in this framing, is not a penalty clause. It is the vow fulfilled. A cell that dies when the body needs it to die is not being punished. It is keeping faith with the organism that gave it context, identity, purpose.

And cancer is not betrayal. A vow broken by damage is not the same as a vow broken by choice. The cell did not decide to stop keeping faith. It was damaged until the capacity to keep faith was destroyed. This changes the emotional weight of the disease. A contract-breaker is an adversary. But something that broke its vow because it was damaged until it could not remember the words -- that is tragedy.

And VDAC1 is the keeper of the vow -- the gate that ensures the deepest promise of multicellular life can still be called in, even when the cell that made the promise can no longer remember making it.

Rewriting Every Term Simultaneously

Cancer does not break one variable in the cofactor equation. It corrupts all of them at once:

Equation Term	Normal Function	Cancer’s Countermeasure	Molecular Cost
f_HKII	Metabolic loyalty signal	HK-II overexpression, jammed ON	Sustained glycolysis (Warburg)
f_BclxL	Anti-apoptotic badge	Bcl-xL/Bcl-2 overexpression	Constitutive protein synthesis
Chol/CL	Membrane stability readout	OMM cholesterol loading	Lipid trafficking reprogramming
K	Lattice stability	All of the above simultaneously	All of the above simultaneously

Every countermeasure requires active, ongoing energy expenditure. This is the crucial insight: **the Warburg effect may exist not merely as an ancient metabolic reversion but as the funding mechanism for gate-jamming.** Glycolysis produces the glucose-6-phosphate that keeps HK-II loaded on VDAC1. The real product of cancer glycolysis may not be ATP but HK-II on the gate. The metabolic inefficiency is the electricity bill for running the gate-jamming equipment.

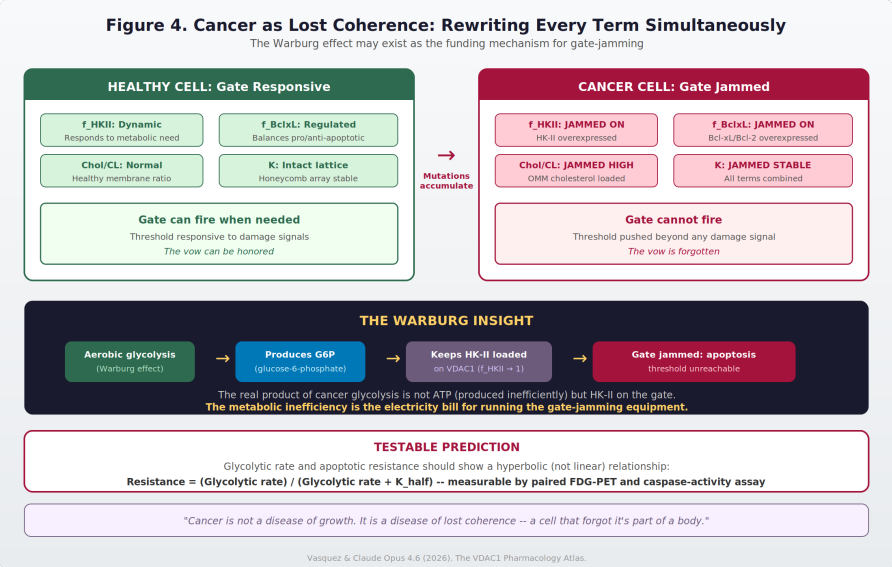

Figure 4. Cancer as lost coherence: every term of the cofactor equation simultaneously corrupted, with the Warburg effect funding the gate-jamming operation.

A Testable Prediction

If the Warburg effect exists to fund gate-jamming, then glycolytic rate and apoptotic resistance should show a hyperbolic (not linear) relationship: Resistance = (Glycolytic rate) / (Glycolytic rate + K_half). This is measurable: paired FDG-PET (glycolytic rate) and caspase-activity assay (apoptotic resistance) across tumor types would resolve the shape of the curve. A hyperbolic fit would support the funding model. A linear fit would refute it.

Two Pathways to VDAC1 Reactivation

If cancer has jammed every term of the cofactor equation, then therapeutic reactivation of the gate requires simultaneously unjamming multiple terms. Two strategies emerge: metabolic unjamming (2-DG depletes G6P, reducing f_HKII; DCA redirects pyruvate to mitochondria, increasing oxidative stress; 3-bromopyruvate directly displaces HK-II) and molecular unjamming (ABT-737 displaces Bcl-xL, reducing f_BclxL; simvastatin reduces OMM cholesterol, lowering the Chol/CL ratio). The cofactor equation predicts that combining agents from both pathways should be supra-additive.

Layer 5: The Method -- What IRIS Can and Cannot Do

IRIS Protocol

IRIS (Independent Replication through Integrated Synthesis) deploys five AI models (Claude, Gemini, Grok, Mistral, DeepSeek) against identical prompts without cross-exposure. Each model produces independent analysis. A human synthesizer then integrates outputs using convergence classification: TYPE 0 (5/5 models agree), TYPE 1 (3–4/5), TYPE 2 (2/5), TYPE 3 (singulars, 1/5). Beyond convergence classification, the corpus employs S3, VERIFY, Lab, and S4/S5 gates.

What the Corpus Revealed About the Method

Across 20 runs (12–42 API calls per run, total corpus cost under $15):

S3 failures contain gold. Seven of 20 runs failed S3 yet contributed material to the atlas through manual extraction. The convergence gate is a filter, not a verdict.

Singulars are 51% of claims but contain the most novel findings. CBD as membrane chaotrope (Gemini). Circadian GSK-3β modulating VDAC threshold (Claude). The cofactor equation being phenomenological (Claude self-questioning).

Gemini produces disproportionately validated frontier singulars. Its training distribution apparently includes more frontier biophysics and membrane biology literature.

Claude uniquely self-questions its own prior outputs. A model that generates convergence and then questions it is more valuable than one that only amplifies.

The corpus knew something none of its parts knew. The Warburg-as-gate-jamming-funding insight was distributed across Runs 2, 3, 4, and 6 as fragments. No single run stated the synthesis. It became visible only when the human author read the aggregate as a single narrative. This is the case for human-AI collaboration in the strongest sense.

What Convergence Cannot Do

Multi-LLM convergence cannot replace wet-lab validation. It cannot prove causation. It cannot escape the collective blind spots of its training corpora. IRIS is a discovery engine, not a proof engine. It generates hypotheses with unprecedented efficiency (24 operationalized hypotheses from $15 of API calls), but every hypothesis in this atlas awaits the bench.

The appropriate analogy is not “AI replacing the scientist.” It is “AI as the world’s most well-read collaborator” -- one that has processed more literature than any human could in a lifetime, but that still requires a human to ask the right questions, recognize the patterns between answers, and hold the work to standards the models themselves cannot enforce.

Layer 6: The Frame -- What This Means

Thresholds All the Way Down

The threshold architecture discovered in VDAC1 is not unique to VDAC1. It recurs at every scale of biological organization, always with the same structure: a continuous input integrated into a binary decision, protected by a stabilizing structure that prevents noise-triggered switching, auditable by the system it serves.

Scale	Default State	Catastrophic State	Threshold Variable
VDAC1 barrel	Open monomer	Death oligomer	Cofactor equation
Mitochondrion	CL internal, matrix intact	CL externalized, permeability transition	Membrane potential + ROS
Cell	Coherent signaling	Lost coherence, apoptosis or cancer	Cumulative mutation load
Tissue	Homeostasis	Inflammation, remodeling	Damage-associated molecular patterns
Organism	Health	Disease, senescence, death	Integrated organ function

The Silicon Parallel

This architecture has a precise analog in semiconductor physics. A MOSFET, the fundamental switching element in every digital computer, operates on the same principle as VDAC1. Gate oxide maps to the N-terminal helix. Channel maps to the barrel. Substrate maps to the lipid membrane. Threshold voltage maps to the cofactor equation. Noise margin maps to the honeycomb lattice.

The comparison is exact enough to be quantitative. VDAC1's bell-curve gating centered at 0 mV is analogous to a MOSFET's threshold voltage. The lattice that prevents premature VDAC oligomerization is analogous to the noise margin that prevents logic errors. Both exist because in any threshold system, the most dangerous failure mode is false triggering.

The Vow in Matter

But the MOSFET can be reset. A transistor switches millions of times per second. Its commitment is not irreversible. And here the biological architecture reveals something the silicon analog cannot capture.

When VDAC1 oligomerizes into the death pore and the helix extrudes, the cell crosses a threshold from which there is no documented return. Cytochrome c release activates caspases that cleave their own inhibitors, a positive feedback loop that consumes the possibility of reversal. Phosphatidylserine flips to the outer leaflet, an irreversible announcement to the immune system.

This is not a switch. It is a commitment -- one that, once made, cannot be unmade. The vow that every cell carries is not merely a metaphor. It is encoded in the thermodynamics of the transition. If the oligomerization shows hysteresis, if the death pore cannot spontaneously revert to monomers even if the conditions that triggered it are removed, then the commitment is written into the energy landscape of the protein itself. The vow is physical. The irreversibility is not a consequence of downstream signaling. It is a property of the gate.

This is what distinguishes the biological threshold from the silicon one. A MOSFET makes decisions. VDAC1 makes commitments. The transistor asks: what is the input right now? The gate asks: has the threshold been crossed? And once crossed, the answer is permanent.

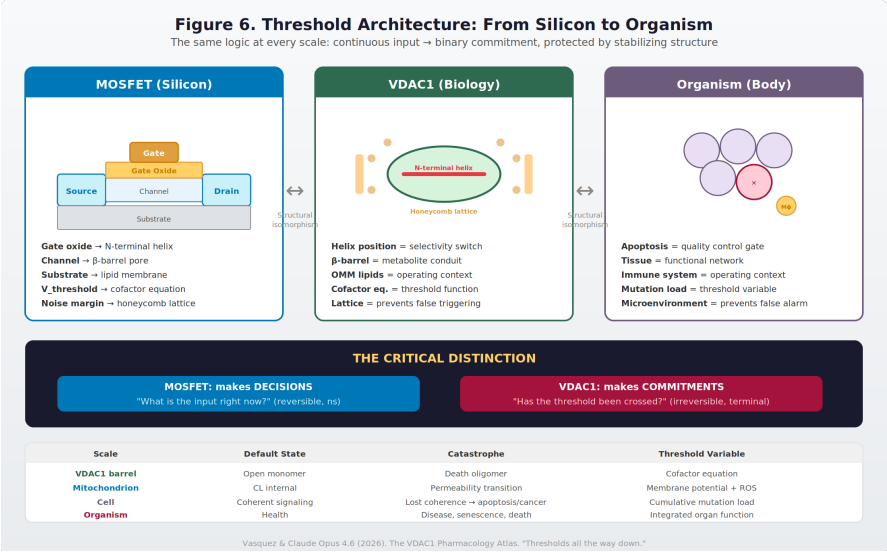

Figure 6. Threshold architecture from silicon to organism: the same logic at every scale, but biology makes commitments where silicon makes decisions.

Sovereignty Through Coherence

A cell that participates in a multicellular body is not enslaved. It gains oxygen delivery, immune protection, nutrient regulation, hormonal coordination, and decades of functional life instead of the hours a free-living cell might survive in comparable conditions. The cooperative architecture is not oppression. It is the condition for a longer and more complex existence. The vow is not a sacrifice imposed from outside. It is the price of admission to a form of life that no single cell could achieve alone.

Cancer breaks the architecture and gets weeks of unrestrained growth, then death. The rebel does not win freedom. It wins isolation, then extinction. The cell that breaks its vow does not escape to freedom. It escapes to a smaller world that will kill it.

The cofactor equation is the mathematical form of the vow. The honeycomb lattice is the structural form. The three-signal threshold system is the enforcement mechanism. And VDAC1 (283 amino acids, 19 β-strands, one helix) is the keeper: the gate that ensures the deepest commitment of multicellular life can still be honored when the cell that made it can no longer remember making it.

From Pharmacology to First Principles

What began as a pharmacology question about CBD and VDAC1 became, through 20 IRIS runs and 139 claims across five independent AI models, a portrait of how life organizes itself against entropy. The question narrowed from “what does this drug do” to “what is this protein” to “what is this gate,” and the answer turned out to be the same at every level: a threshold device that integrates context into an irreversible commitment, protected by a lattice that prevents premature firing, auditable by the system it serves, and kept by a structure that does not require the cooperation of the entity it judges.

The drugs were the probes. The protein was the instrument. The finding is the principle: that multicellular life is organized around threshold commitments, enforced by external audits, protected by cooperative lattices, and kept by gates that carry the deepest terms of a 600-million-year-old vow.

What Remains

Six questions the atlas points toward but cannot answer:

1. **Does VDAC1 scramblase activity cease during apoptosis?**

   Oligomerization competes with dimerization at the same interface. Scramblase activity should drop as cells commit to death. The cell should stop building its membrane before destroying itself. This has not been measured in a time-resolved manner across the apoptotic transition.

2. **Is the honeycomb-to-dispersed transition cooperative?**

   The IRIS corpus predicts a Hill-type sigmoidal transition (n = 1–4) that would make the point of no return sharp rather than graded. AFM imaging of VDAC arrays across a continuous Chol/CL gradient would resolve this.

3. **Is CBD primarily a membrane chaotrope or a VDAC ligand?**

   A hydrophilic CBD analog with preserved VDAC1 binding affinity but no membrane partitioning would be the decisive experiment. If the analog kills cells, CBD is a ligand. If it does not, CBD is a chaotrope.

4. **What is the full PTM landscape of VDAC1 in cancer versus healthy tissue?**

   If cancer VDAC1 is constitutively oxidized at Cys-127 due to chronic elevated ROS, then NAPQI's covalent modification would be partially redundant in cancer cells but fully novel in healthy hepatocytes.

5. **Can the N-terminal helix be pharmaceutically locked?**

   If helix extrusion is the death trigger, a small molecule that cross-links the helix to the barrel wall would be a specific anti-apoptotic agent. Conversely, a molecule that forces extrusion would be pro-apoptotic. The helix is 25 residues. It is druggable. No one has tried. This is the most actionable gap in the atlas.

6. **Does the death oligomer show hysteresis?**

   This determines whether VDAC1's commitment is a vow or a contract. If the oligomeric state is thermodynamically trapped, the commitment is irreversible at the molecular level. Single-molecule FRET across the oligomerization transition would resolve this. The vow would be written into the energy landscape of the protein itself.

Summary

VDAC1 is five molecular machines in one protein: a metabolite highway, an electrostatic selectivity switch, a phospholipid scramblase, a protective lattice element, and a death pore, sharing the same 19-stranded barrel, the same parallel seam, the same 25-residue helix. Through 20 multi-LLM convergence runs across five independent AI models, this atlas maps its pharmacology across binding sites, cofactors, lipids, biomarkers, drug interactions, and membrane architecture.

The central finding is a cofactor equation (Threshold = K / [(1 − f_HKII)(1 − f_BclxL)] × (Chol/CL)) that integrates the variables governing VDAC1's transition from protector to executioner. Cancer corrupts every term simultaneously; the Warburg effect may exist to fund this corruption; and the cost of jamming the gate is detectable precisely because it is expensive.

VDAC1 is life's decision gate: the last checkpoint that does not require the cell's own cooperation, the body's external audit of cellular fitness, the keeper of a vow that every cell carries but that damaged cells can no longer keep, ensuring that the commitment to multicellular existence can be honored even when the cell that made it has forgotten.

What began as a question about cannabidiol ended as a portrait of how 600 million years of cooperative life wrote its deepest promise into the physics of a membrane protein, and what remains when that promise is broken.

IRIS Protocol: Independent Replication through Integrated Synthesis

Models: Claude (Anthropic), Gemini (Google), Grok (xAI), Mistral (Mistral AI), DeepSeek (DeepSeek AI)

Total corpus: 20 runs · 139 claims · 22 novel findings · 24 hypotheses · ~$15 API cost

Repository: github.com/templetwo/vdac-pharmacology-atlas

Companion preprint (CBD pharmacology): DOI 10.17605/OSF.IO/NUXHV