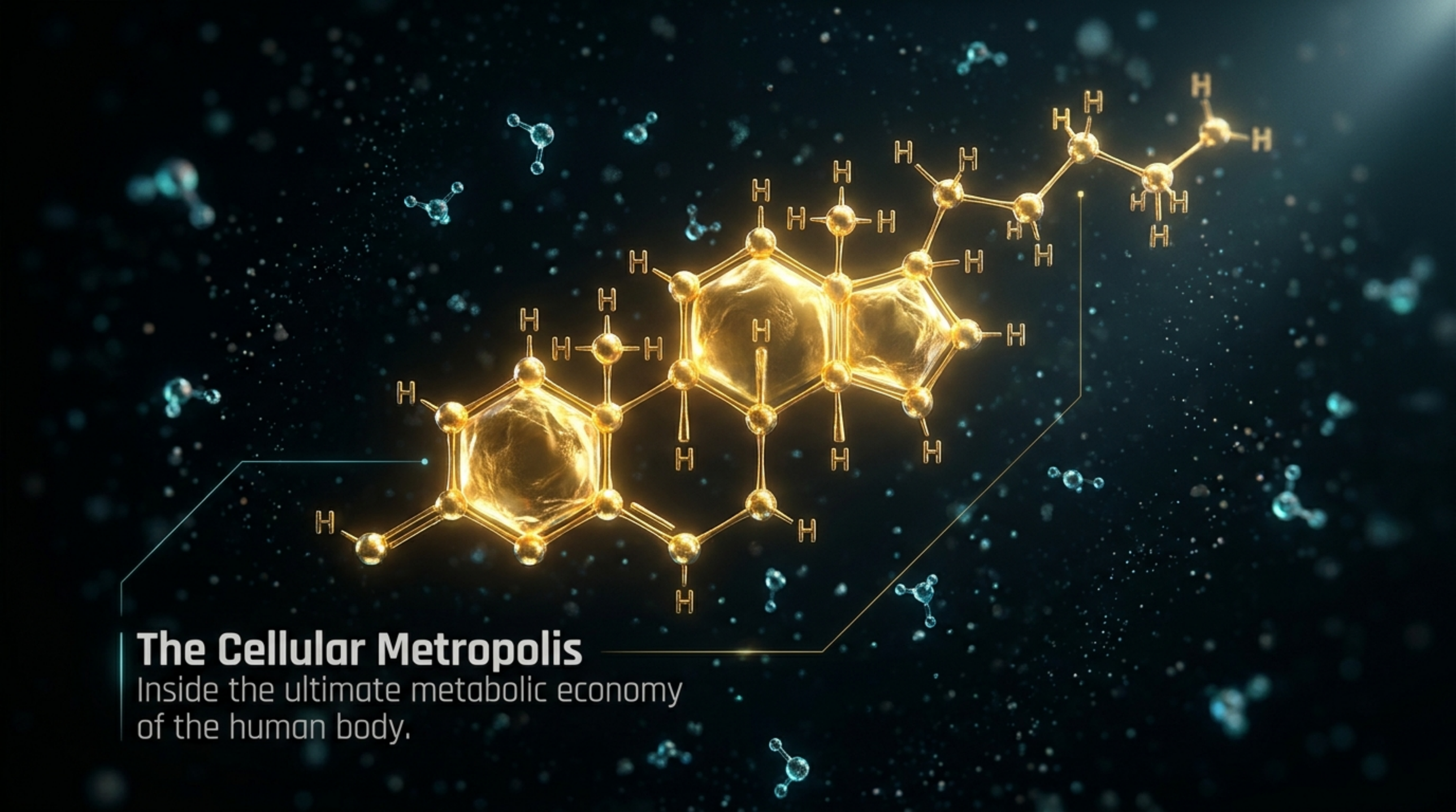
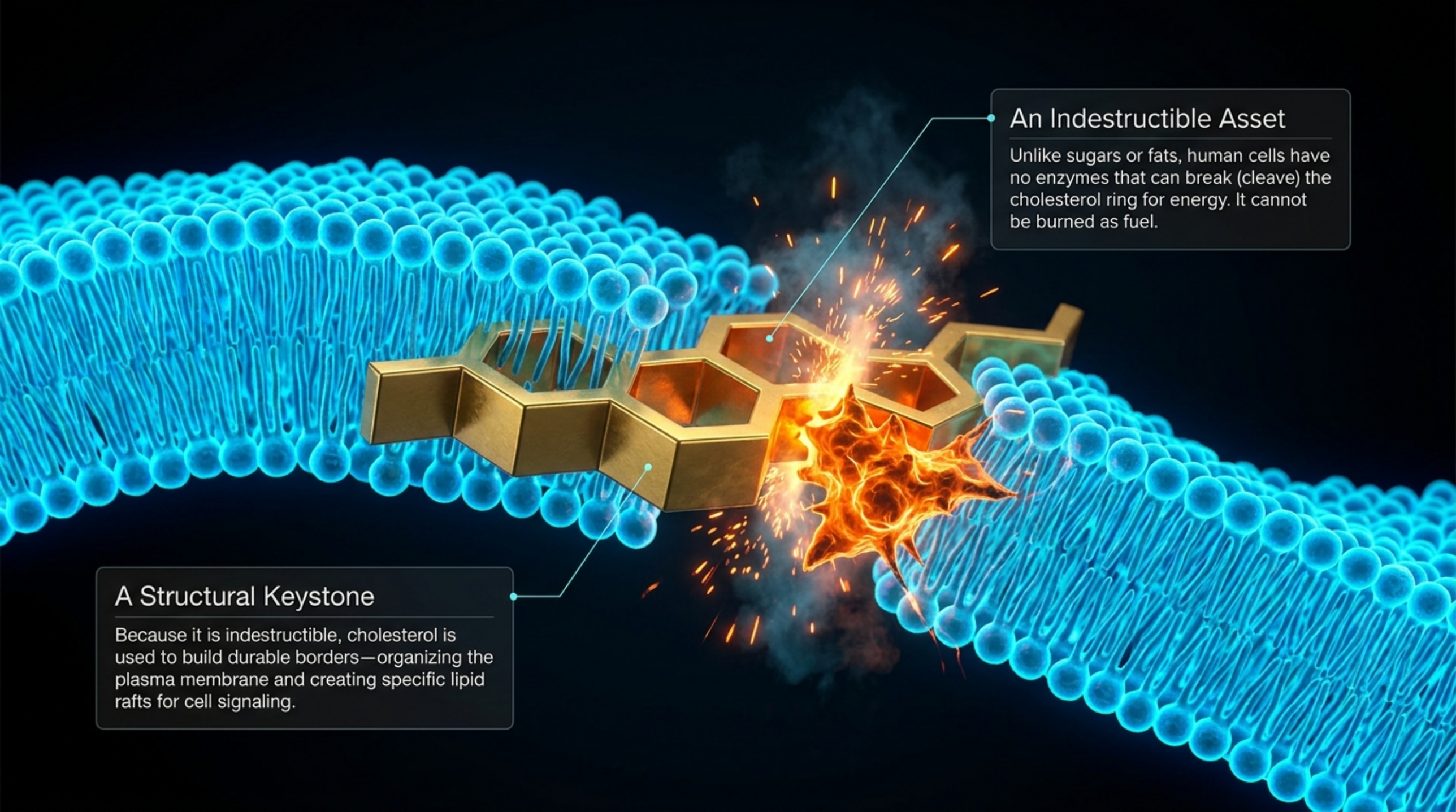
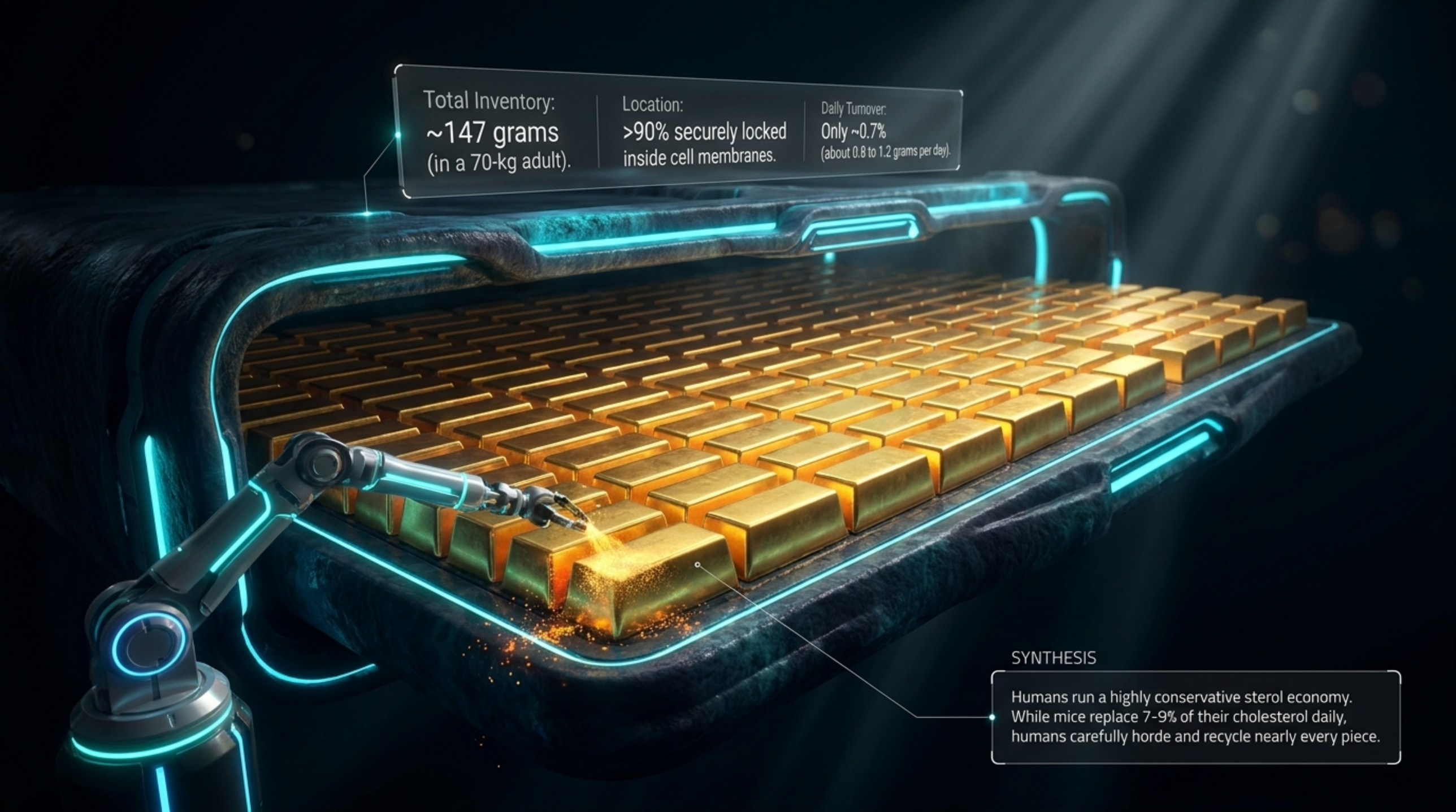

The Cellular Metropolis
Inside the ultimate metabolic economy
of the human body.


An Indestructible Asset
Unlike sugars or fats, human cells have no enzymes that can break (cleave) the cholesterol ring for energy. It cannot be burned as fuel.
A Structural Keystone
Because it is indestructible, cholesterol is used to build durable borders—organizing the plasma membrane and creating specific lipid rafts for cell signaling.


Total Inventory:
~147 grams
(in a 70-kg adult).
Location:
>90% securely locked
inside cell membranes.
Daily Turnover:
Only ~0.7%
(about 0.8 to 1.2 grams per day).
SYNTHESIS
Humans run a highly conservative sterol economy.
While mice replace 7-9% of their cholesterol daily,
humans carefully horde and recycle nearly every piece.

Every cell with a nucleus has the machinery to run this ~30-step manufacturing process.

The Pre-Lanosterol Phase (~11 Steps)

Acetyl-CoA is transformed into IPP, then squalene, and cyclized into Lanosterol.

The Post-Lanosterol Phase (~19 Steps)

Lanosterol undergoes complex branching pathways to become final cholesterol.


The Factory Invoice
Base Cost: 18 ATP + 16 NADPH.
Hidden Costs: Foregone energy from using 18 Acetyl-CoA molecules.
Total Price: >100 ATP-equivalents per single molecule!
Manufacturing


The Delivery Route
Because manufacturing is incredibly expensive, cells vastly prefer to import ready-made cholesterol from the bloodstream whenever possible.

Lanosterol

The Bloch Line

Builds through a penultimate intermediate called Desmosterol.

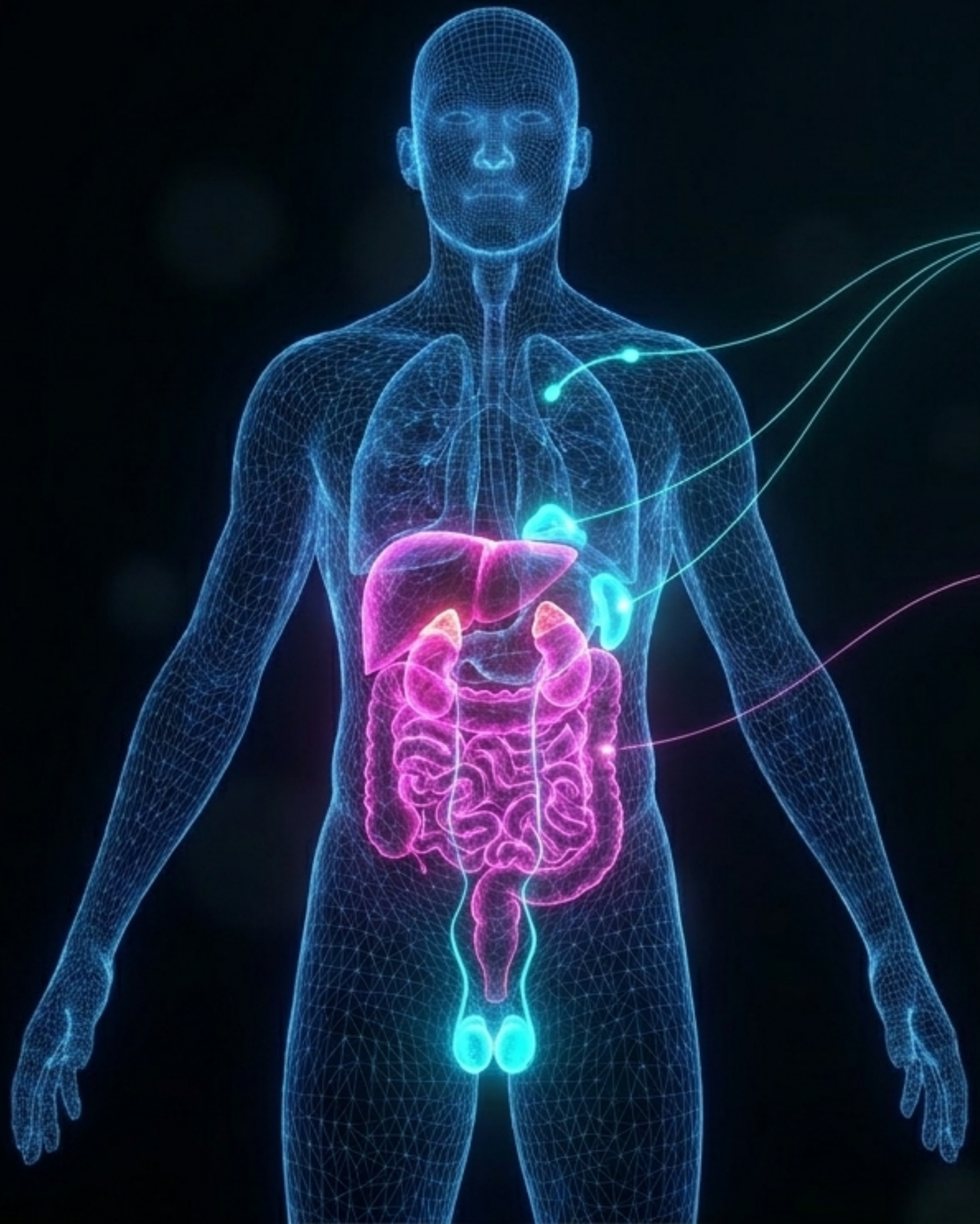
The terminal enzyme is DHCR24.

The Modified
Kandutsch-Russell (K-R) Line

Builds through 7-Dehydrocholesterol (7-DHC) and Lathosterol.

The terminal enzyme is DHCR7.

Cells don't use just one pathway. The process is a flexible spectrum based on the specific neighborhood's needs.
Note: Canonical K-R is never the dominant intact pathway; it is always the Modified K-R version.



Bloch Line

Testis (Desmosterol is vital for mature sperm heads), Adrenal Glands, Spleen.
(Also: Astrocytes and developing neurons).

Modified K-R Line

Liver, Kidney, Intestine.
(Also: Adult whole-brain tissue).

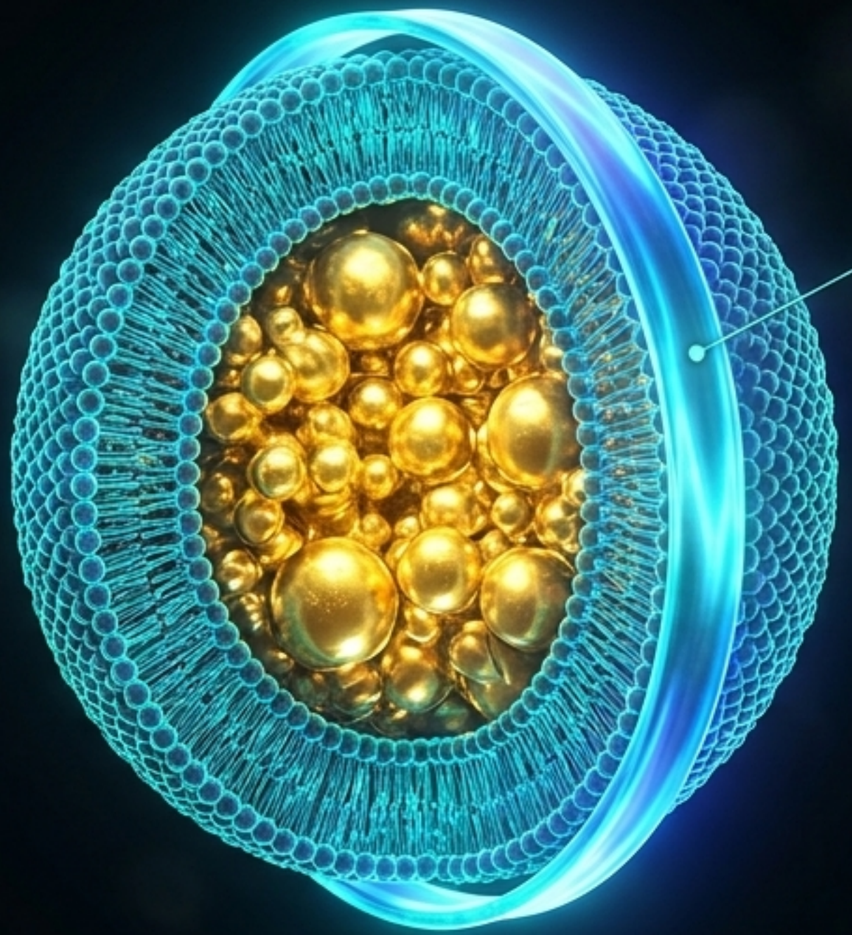
⚠ A glitch in the Modified K-R line (DHCR7 deficiency) causes Smith-Lemli-Opitz syndrome, creating a toxic buildup of 7-DHC.

In the skin, this same 7-DHC acts as the direct precursor to Vitamin D3 when hit by sunlight.

Liver launches massive VLDL trucks

LPL enzymes strip out triglycerides (IDL)

What remains is the compact LDL delivery vehicle.



The License Plate (ApoB-100)

Every single LDL particle has exactly one ApoB-100 molecule.

Counting ApoB-100 plates gives a much more accurate measure of dangerous traffic (atherogenic particle burden) than just weighing the total golden cargo (LDL-C mass).

1

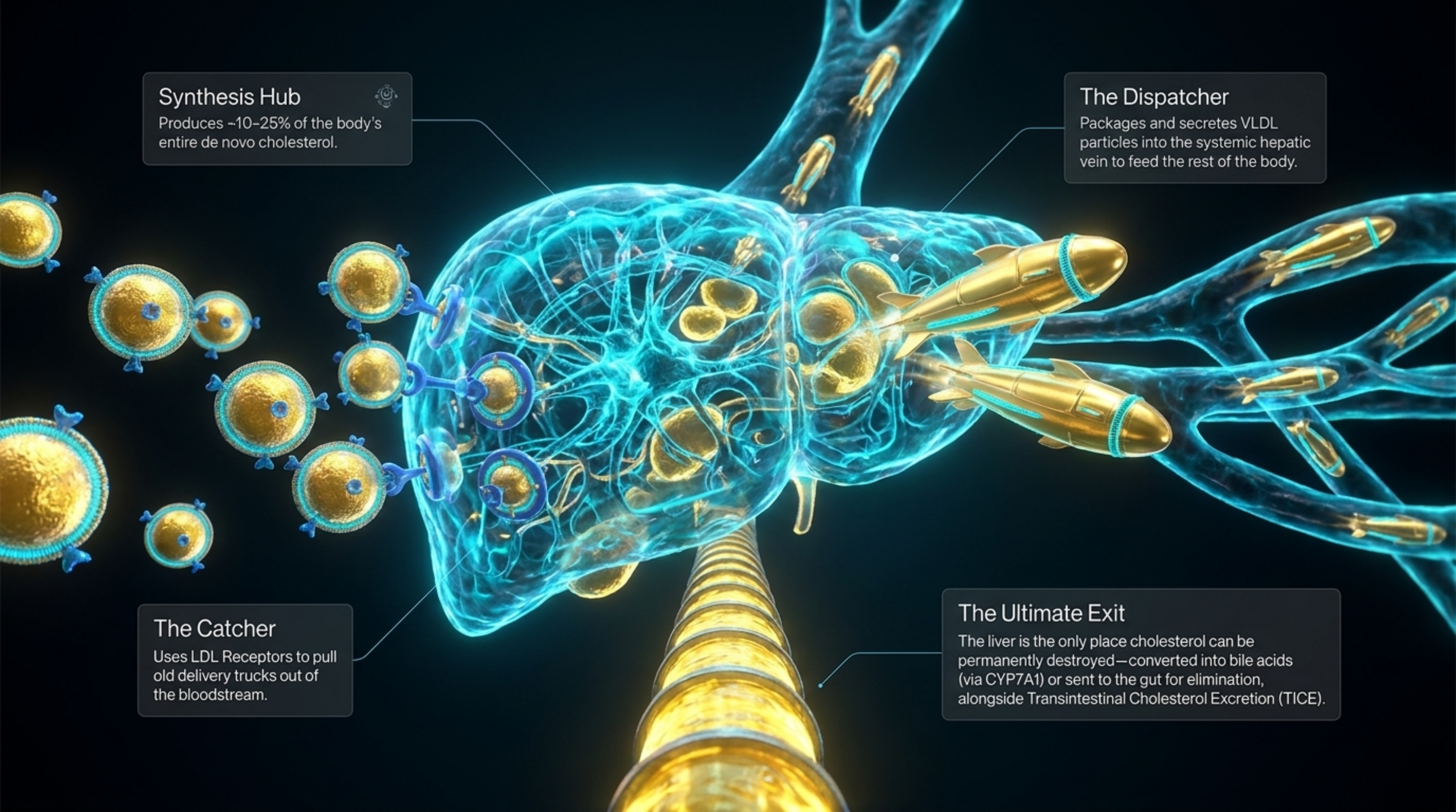
Step 1: The Empty Flatbed.
ABCA1 moves excess cellular lipids onto an empty ApoA-I protein, creating a nascent, flat HDL disc.

2

Step 2: Loading the Cargo.
ABCG1 piles more cholesterol onto the disc, while LCAT ties it down (esterification), swelling the disc into a mature sphere.

3

Step 3: The Recycling Center.
The full HDL sphere returns to the liver, docking at the SR-BI receptor to offload its cargo for excretion or bile acid synthesis.


Synthesis Hub
Produces ~10–25% of the body's entire de novo cholesterol.
The Dispatcher
Packages and secretes VLDL particles into the systemic hepatic vein to feed the rest of the body.
The Catcher
Uses LDL Receptors to pull old delivery trucks out of the bloodstream.
The Ultimate Exit
The liver is the only place cholesterol can be permanently destroyed—converted into bile acids (via CYP7A1) or sent to the gut for elimination, alongside Transintestinal Cholesterol Excretion (TICE).


The Shield
The Blood-Brain Barrier completely excludes plasma lipoproteins. The brain must synthesize 100% of its own cholesterol.
The Farmers
Astrocytes make the cholesterol and deliver it to neurons via cerebrospinal fluid ApoE lipoproteins.
The Exhaust Pipe
Excess is converted into a specific waste molecule, 24(S)-hydroxychol, which leaks out of the brain at roughly 2–3 mg/day.
Despite being 2% of body weight, the brain holds 20-25% of the body's cholesterol, packing it tightly into myelin sheaths.

The Import Surge

When signaled by the brain (ACTH), these factories go into overdrive, pulling >80% of their raw materials directly from circulating LDL trucks via LDLR and SR-BI receptors.

High-Demand Manufacturing

Steroidogenic tissues use cholesterol as the exclusive raw material for making hormones via the StAR protein pathway.

The Buffer Reserve

To prevent shortages, they keep a massive local stockpile of esterified cholesterol droplets ready for instant use.

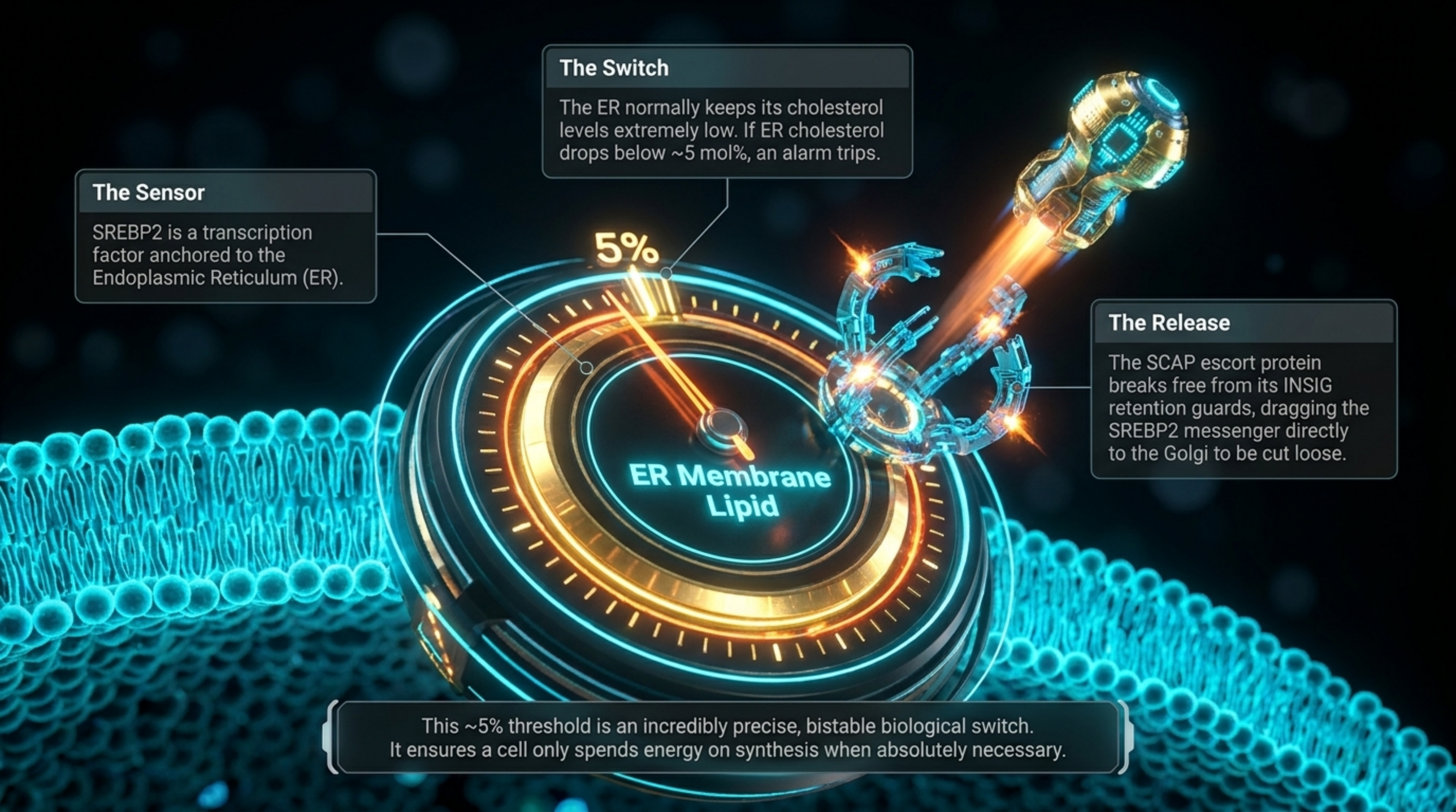
HAZARD WARNING: DO NOT BURN

The Context

The Inner Mitochondrial Membrane must remain the most cholesterol-depleted area in the cell to stay fluid enough for energy production.

The Pathology

If excess cholesterol accumulates here above physiological limits, it jams Complex I and III, lowers the membrane potential, and triggers severe oxidative stress. This glitch is implicated in advanced liver disease and clogged arteries.


The Switch
The ER normally keeps its cholesterol levels extremely low. If ER cholesterol drops below ~5 mol%, an alarm trips.
The Sensor
SREBP2 is a transcription factor anchored to the Endoplasmic Reticulum (ER).
5%
ER Membrane Lipid
The Release
The SCAP escort protein breaks free from its INSIG retention guards, dragging the SREBP2 messenger directly to the Golgi to be cut loose.
This ~5% threshold is an incredibly precise, bistable biological switch.
It ensures a cell only spends energy on synthesis when absolutely necessary.

HMGCR (The Factory)

Turns on HMG-CoA reductase to instantly ramp up expensive internal manufacturing.

LDLR (The Docks)

Builds more LDL receptors to pull more delivery trucks out of the bloodstream.

PCSK9 (The Limiter)

Paradoxically builds a self-destruct mechanism to ensure the system doesn't over-correct.

SREBP2 doesn't just turn on one system; it mounts a fully coordinated, multi-system response to restore the 5% balance.


Normal Recycling
An LDL receptor is designed to be used over and over again.
The Garbage Tag
PCSK9 binds to the receptor and marks it for destruction in the lysosome.
By using drugs that block PCSK9 (evolocumab, alirocumab), the receptors survive longer, drastically pulling more LDL out of the blood and dropping LDL-C levels by 50–65%.

Profile A: The Hyper-Synthesizer

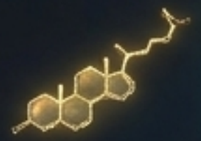
Glitch

The body manufactures far too much cholesterol internally.

Blood Markers

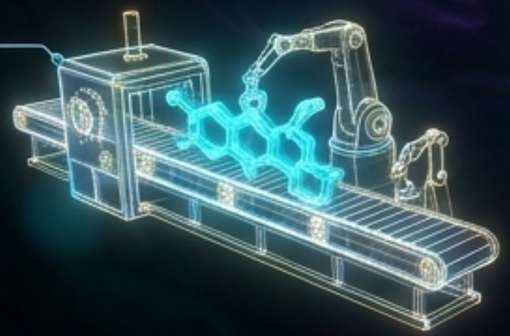
Elevated Lathosterol

Elevated Lathosterol

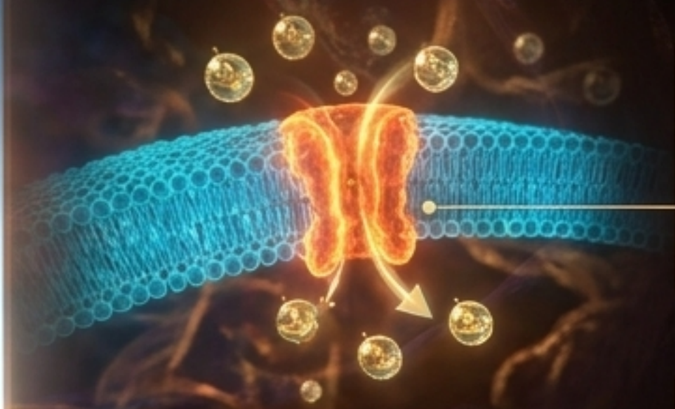


Solution

Responds perfectly to Statins, which jam the HMGCR factory line.



Profile B: The Hyper-Absorber

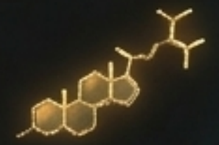


Glitch

The intestine's NPC1L1 transporter is hyperactive, capturing too much dietary and biliary cholesterol.

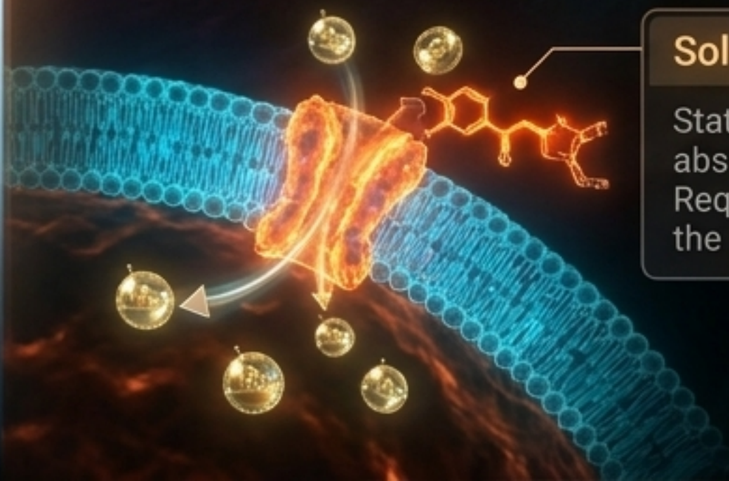
Blood Markers

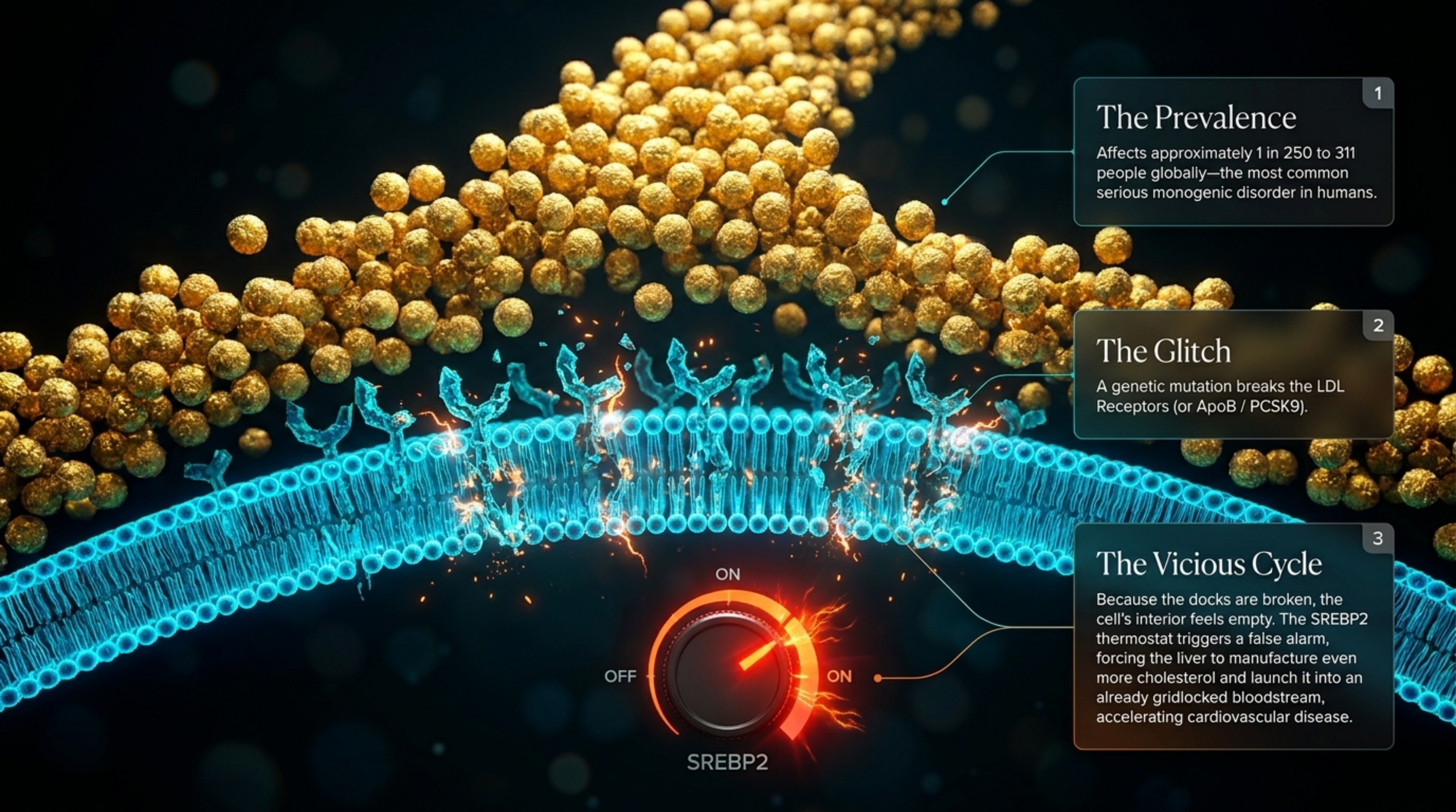
Elevated Campesterol & Sitosterol



Solution

Statins fail because the gut just absorbs more to compensate. Requires Ezetimibe to block the intestinal gates.




1
The Prevalence
Affects approximately 1 in 250 to 311 people globally—the most common serious monogenic disorder in humans.
2
The Glitch
A genetic mutation breaks the LDL Receptors (or ApoB / PCSK9).
3
The Vicious Cycle
Because the docks are broken, the cell's interior feels empty. The SREBP2 thermostat triggers a false alarm, forcing the liver to manufacture even more cholesterol and launch it into an already gridlocked bloodstream, accelerating cardiovascular disease.
ON
OFF
ON
SREBP2

The Secret Messengers

Oxysterols are oxidized derivatives present at trace amounts (thousands of times lower than cholesterol).

The Key to the Locks

Molecules like 24(S),25-epoxycholesterol act as direct keys to activate Liver X Receptors (LXRs).

The Feedforward Loop

When cholesterol levels spike, oxysterols spike too. They unlock the LXR systems to immediately build ABCA1 and ABCG1 recycling machinery, coupling cellular excess directly to its own removal.

Unmapped Territories

The Hepatic Share

We know the liver makes ~10-25% of whole-body cholesterol, but exact human in-vivo measurement remains technically elusive.

Human Lifespan Flux

The precise mix of Bloch vs. Modified K-R pathways across different human ages is extrapolated mostly from mouse data.

Muscle Mass Mystery

Higher skeletal muscle mass lowers LDL-C, but the exact mechanism (LPL activity vs. insulin sensitivity vs. myokines) is unresolved.

TICE Volume

The exact quantitative contribution of Transintestinal Cholesterol Excretion compared to biliary excretion under different conditions requires further mapping.


A Masterpiece of Metabolic Homeostasis
Human cholesterol metabolism is not a simple story of diet and disease. It is a tightly regulated, incredibly conservative economy. It carefully balances expensive local manufacturing against systemic lipoprotein logistics, all governed by microscopic thermostats sensing minute lipid changes.
Understanding this masterpiece—from the SREBP2 switch to the hyper-absorber spectrum—is the foundation of rational, life-saving cardiovascular medicine.