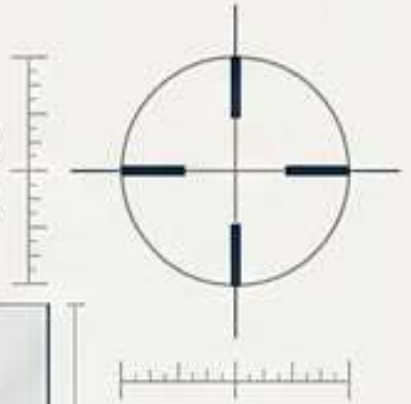
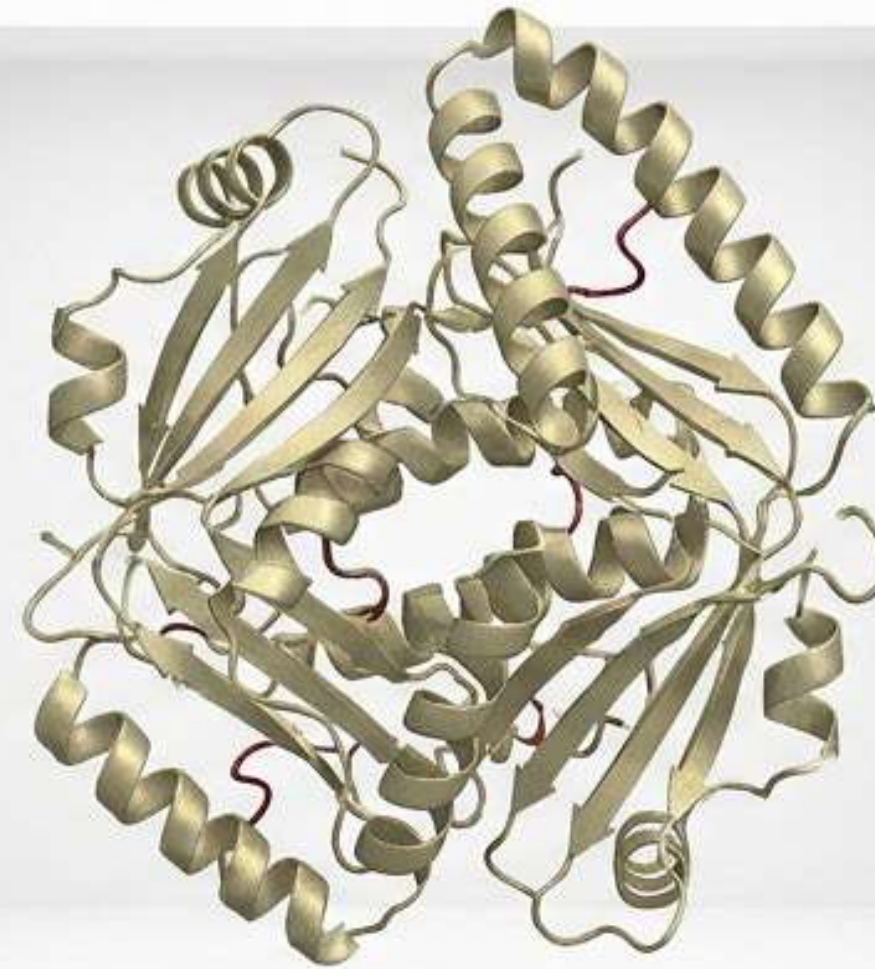


SCALE: SYSTEMIC
TO MOLECULAR



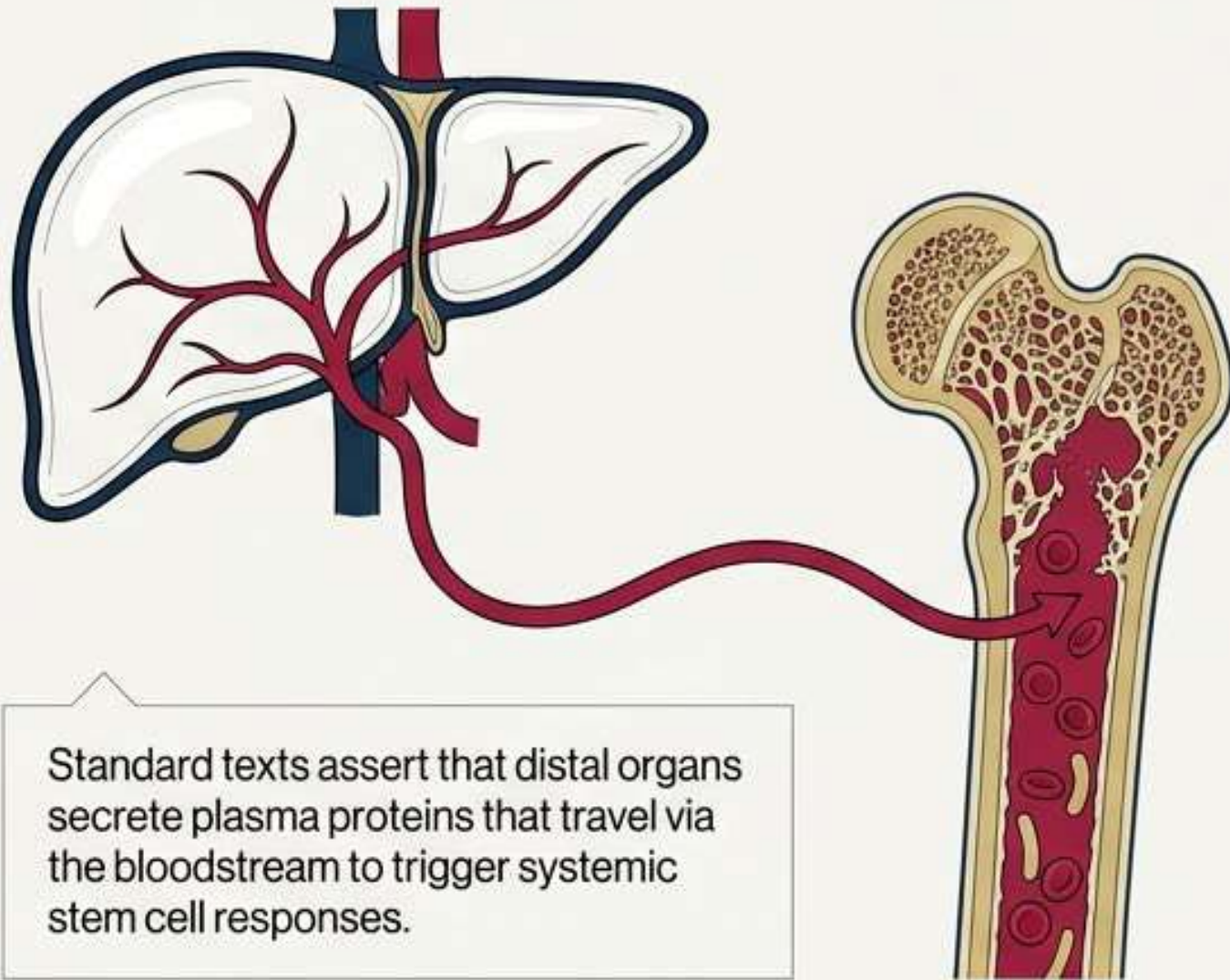
The Picogram Paradox

How Micro-Dose
Plasma Proteins Drive
Macro-Physiology

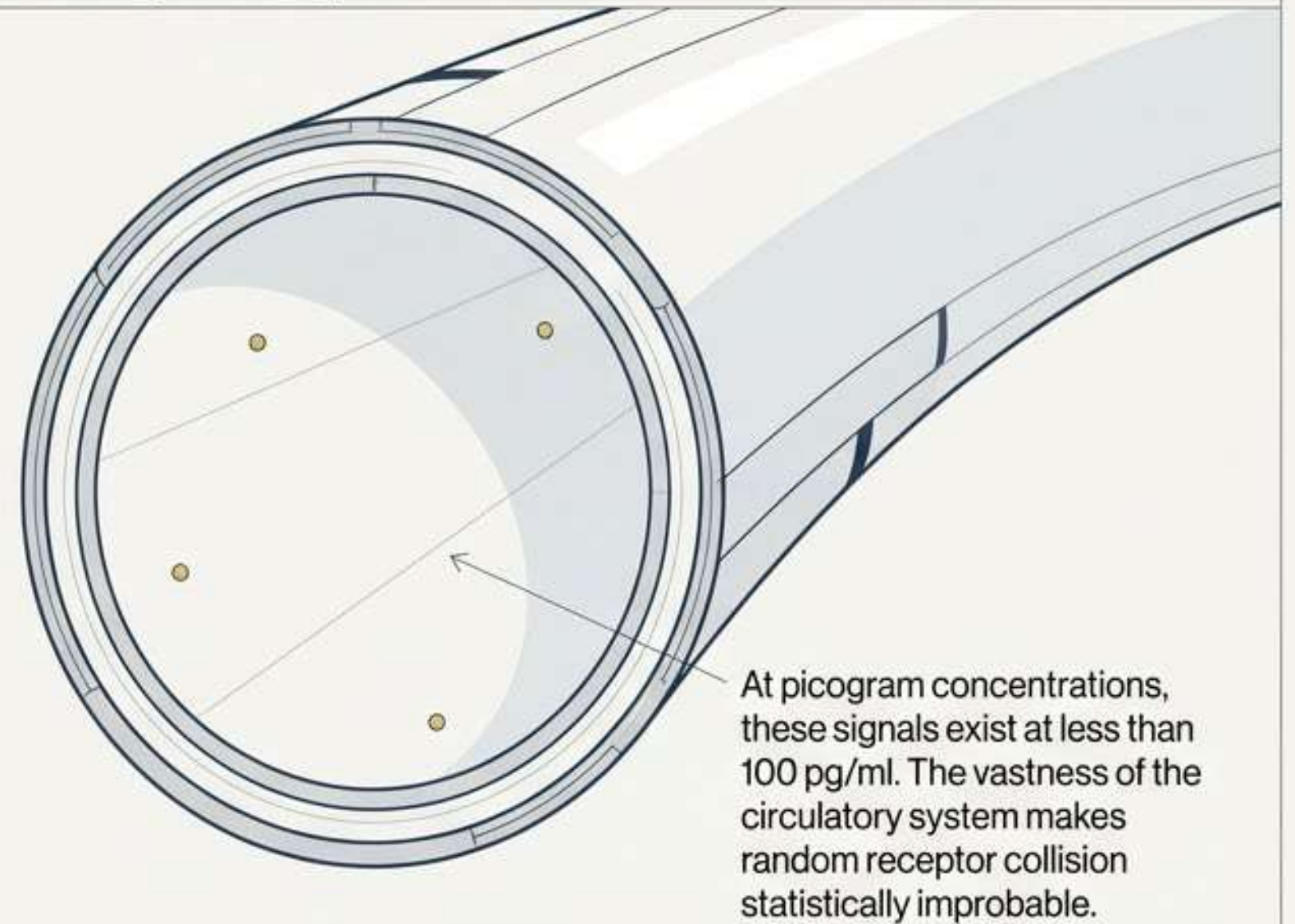


The accepted model of distal endocrine signaling contains a hidden mathematical impossibility.

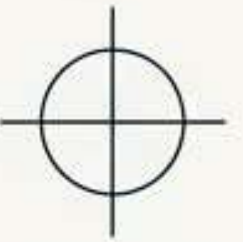
The Biological Postulate



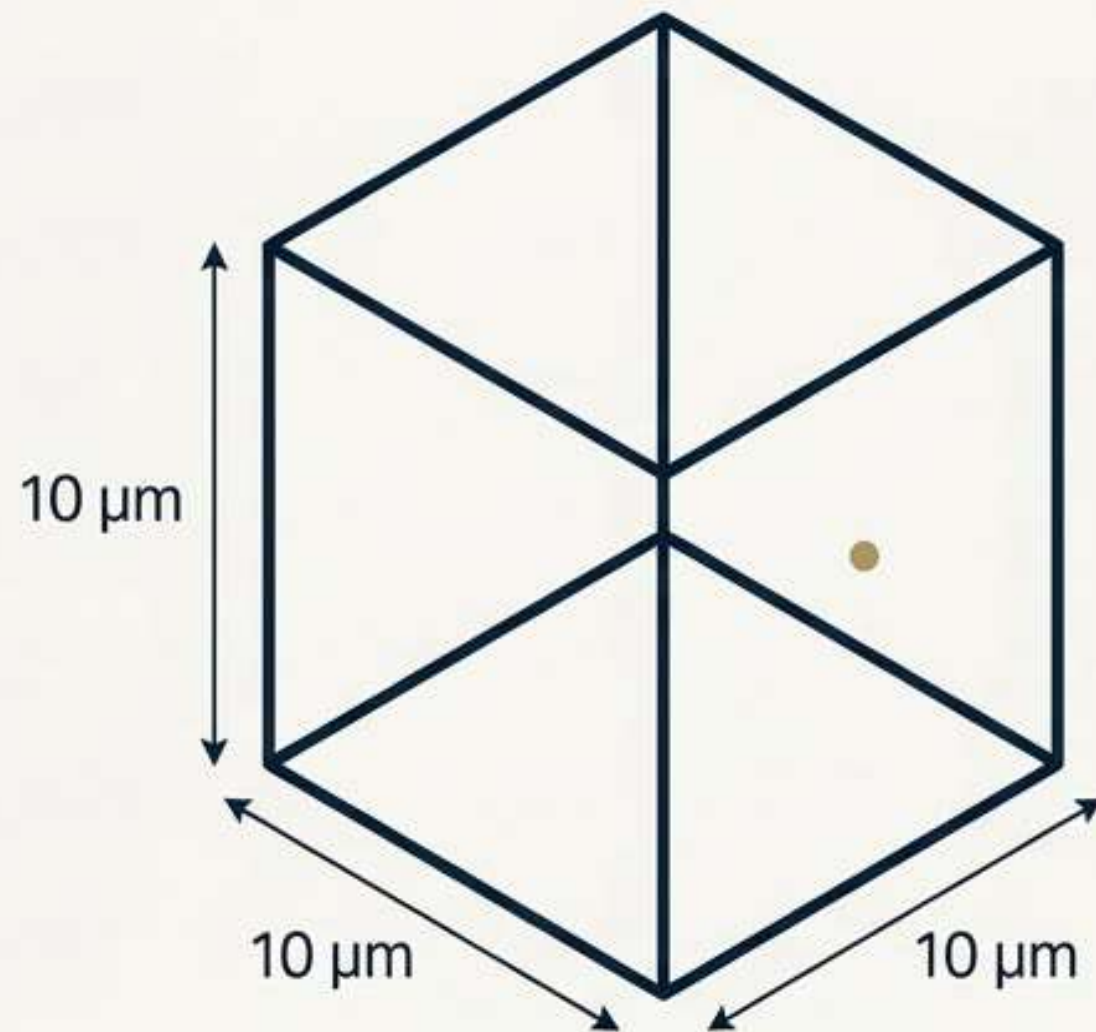
The Physical Reality



At picogram concentrations, the probability of a random receptor collision rounds to zero.



SCALE: MICRO
(10-MICROMETER CAPILLARY)



Volume = 10^{-15} cubic meters

Concentration = Picogram Range

Avogadro's Constant = 6.02×10^{23}

Molecular Weight = 20kD

**0.03 molecules exist
per cubic micrometer.**

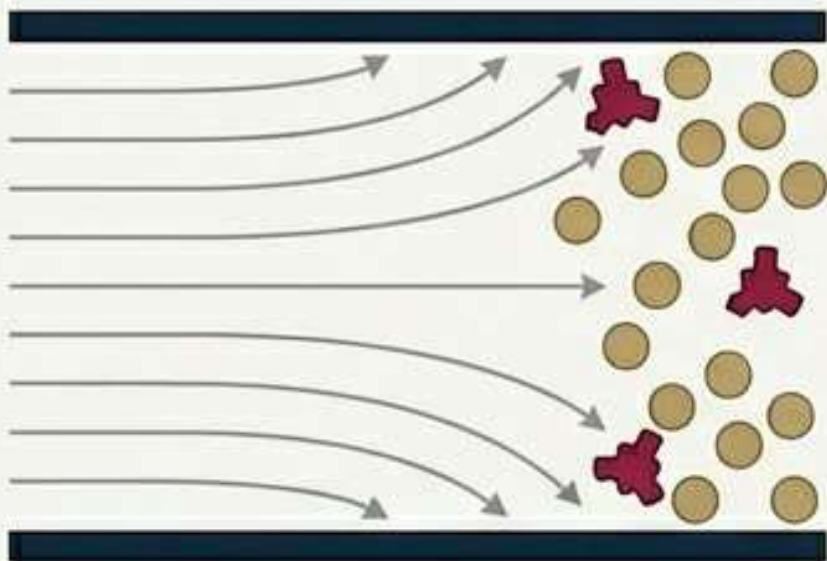
In a standard 100 μ m segment of a capillary, there are roughly 3 target molecules floating in a rushing river of blood. **Physics** demands a non-random targeting mechanism.

Nature solves the collision paradox through a three-stage biophysical funnel.



SCALE: MULTISCALE
SEQUENCE

Stage 1: Spatial Concentration (Physics)



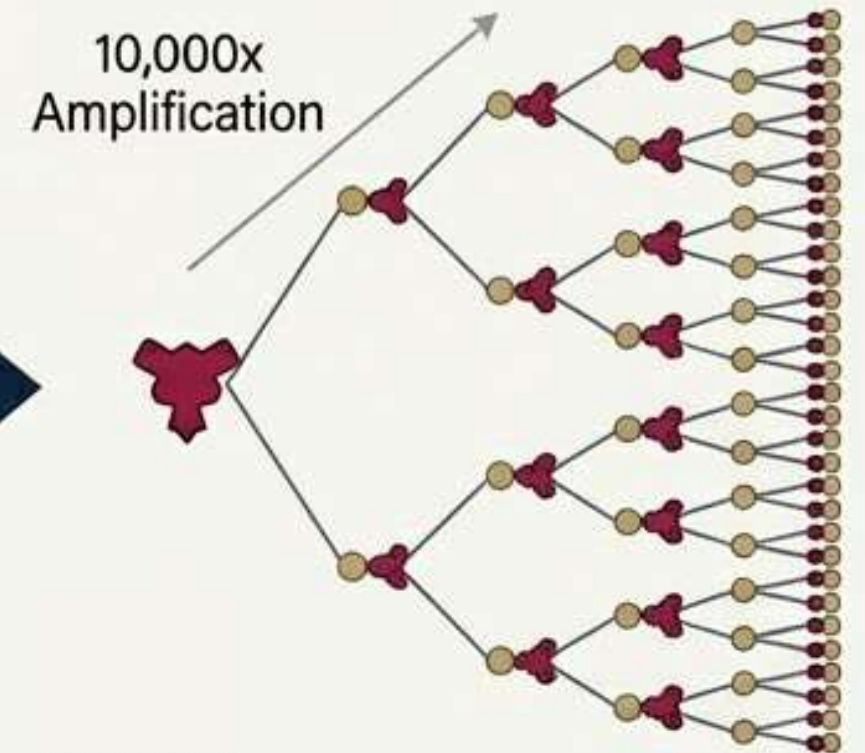
Hemodynamics and electrostatics force rare molecules to the capillary walls.

Stage 2: Structural Stabilization (Chemistry)



Specific co-receptors bridge and lock the isolated molecules, preventing signal loss.

Stage 3: Intracellular Ignition (Biology)

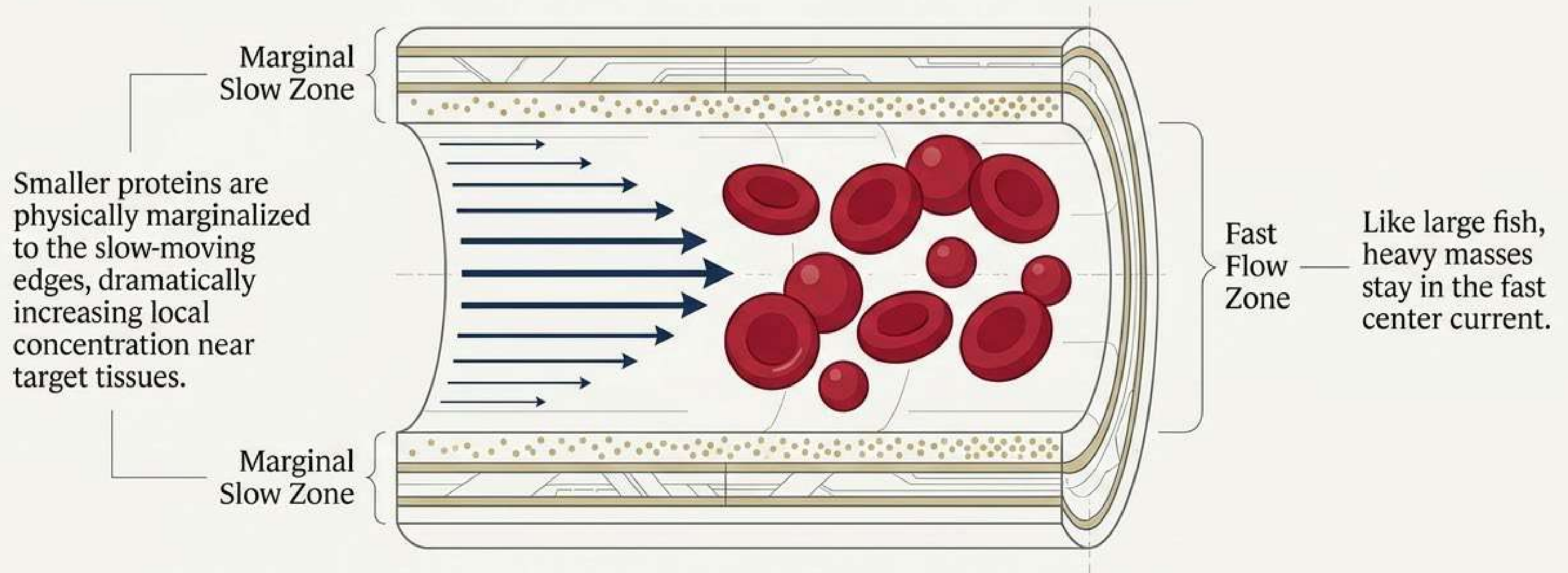


A single stabilized binding event triggers a 10,000x downstream amplification cascade.



SCALE: MICRO (VESSEL FLOW)

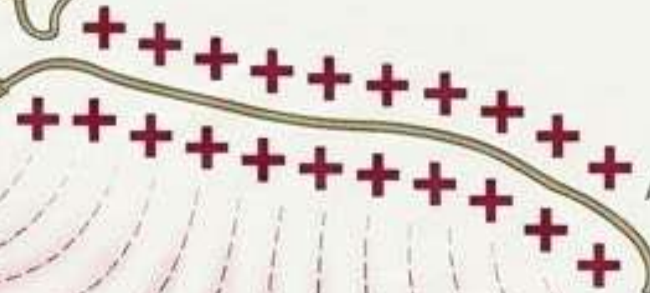
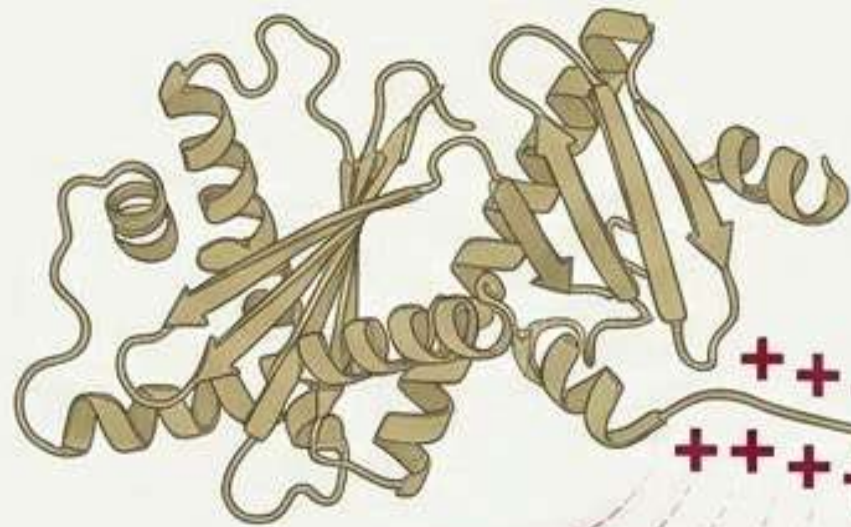
Laminar flow hemodynamics passively sort and localize micro-molecules.



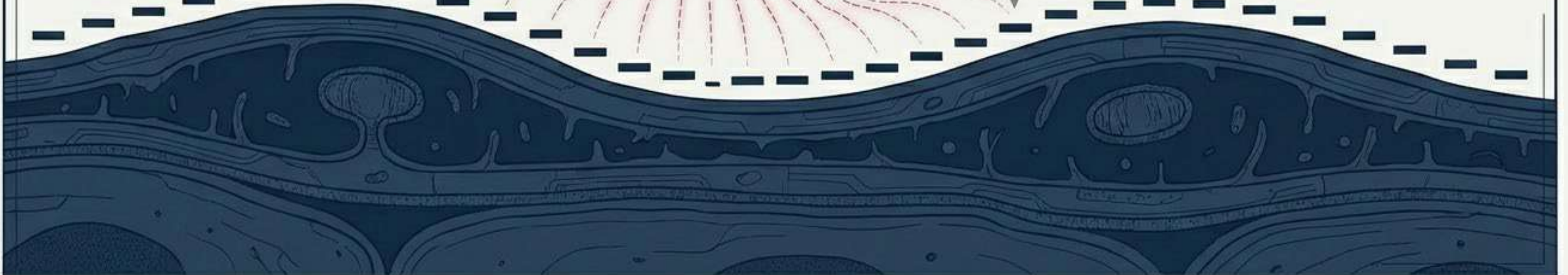


SCALE: NANO (CELL SURFACE INTERFACE)

Electrostatic gradients act as a velcro net to capture marginalized proteins.

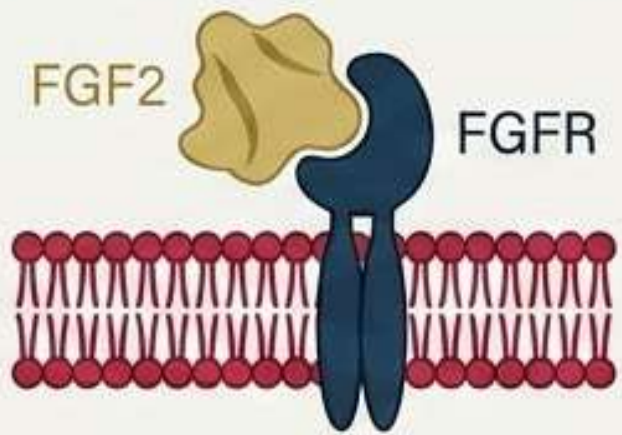


Extreme macro-zoom section
Free-floating soluble proteins are snagged by opposing electrostatic charges on the capillary wall, halting their momentum and positioning them directly adjacent to cellular receptors.



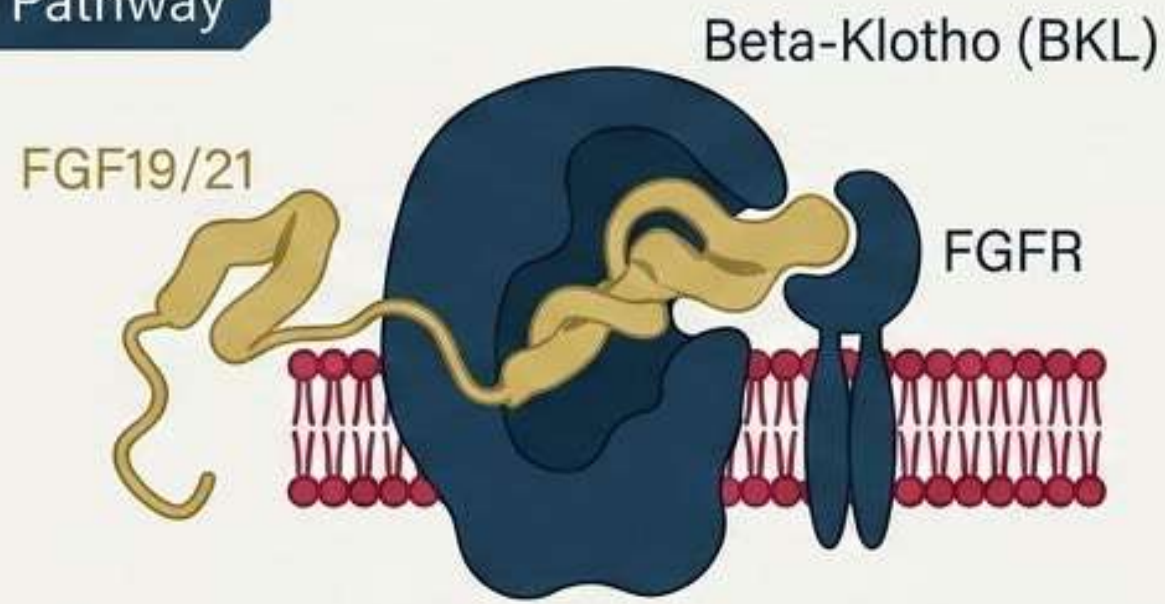
Co-receptors mechanically twist and bridge molecules to guarantee signal transduction.

FGF2 Pathway



Background signaling: requires no co-factor.

FGF19/21 Pathway



The rare FGF molecule is caught, twisted, and physically bridged to the receptor by Beta-Klotho.

Data Callout: Knocking out the BKL mRNA abolishes the signal entirely, regardless of FGF dosage. The co-receptor is structurally mandatory to stabilize the rare picogram signal.



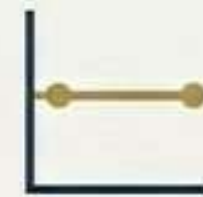
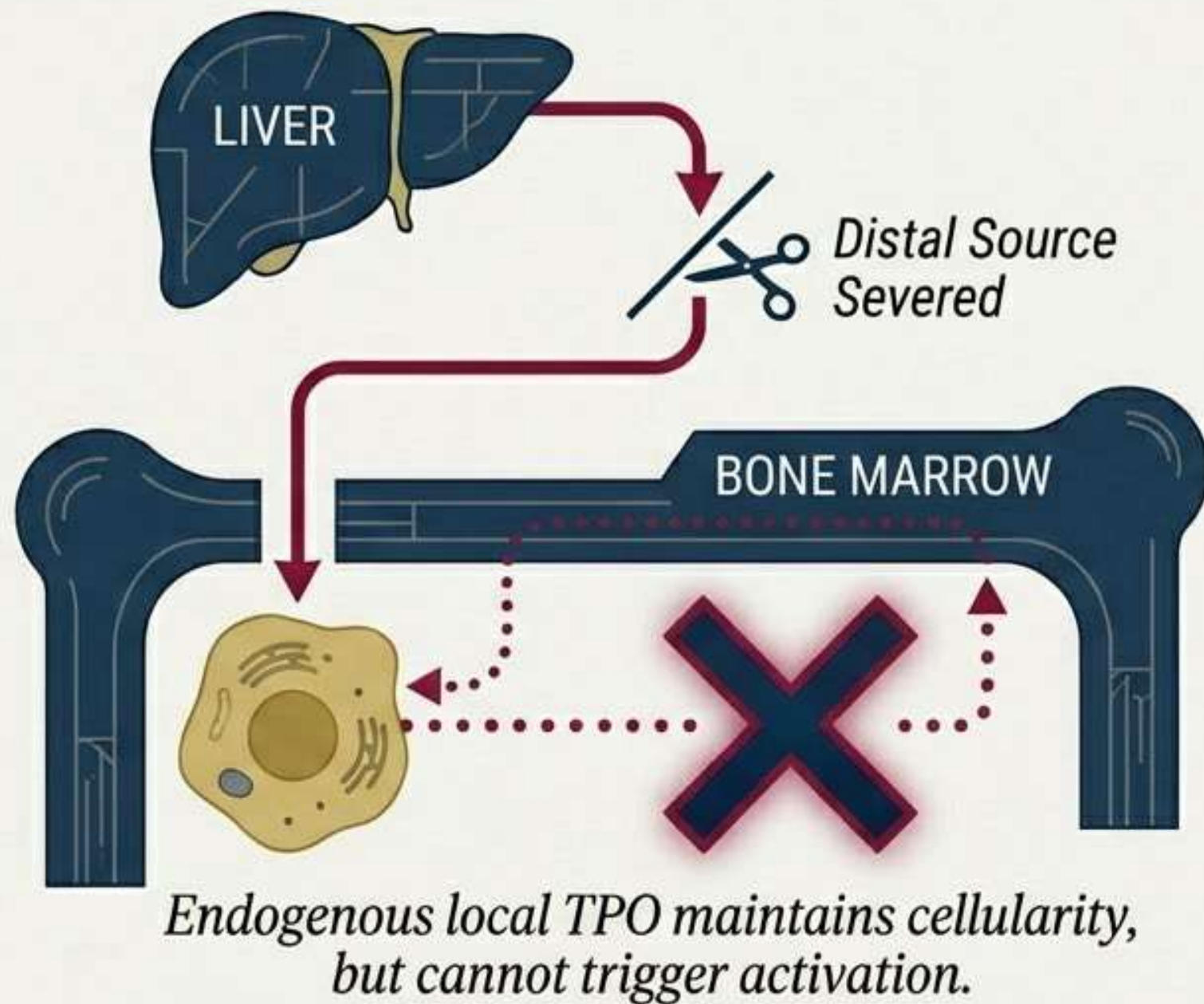
Precision receptor mechanics remain consistent across divergent distal systems.

		FGF19/21 Pathway	TPO (Thrombopoietin) Pathway
1	Systemic Origin	Various	Liver-derived
2	Target Tissue	Metabolic	Bone Marrow (HSCs)
3	Signal Concentration	Picogram range	Exceptionably low background (~39 pg/ml)
4	Receptor Mechanism	FGFR complex	MPL receptor (Expressed on strictly ~10% of Stage 1-4 stem cells)
5	Stabilization Required	BKL affinity bridging	High-affinity niche localization

Both systems pair exceptionally low systemic volume with highly restrictive, localized receptor complexes.



Severing the distal source collapses the system,
proving macroscopic dependency.



When distal liver-derived TPO is severed, overall cell count remains stable, but HSC activation frequency plummets.

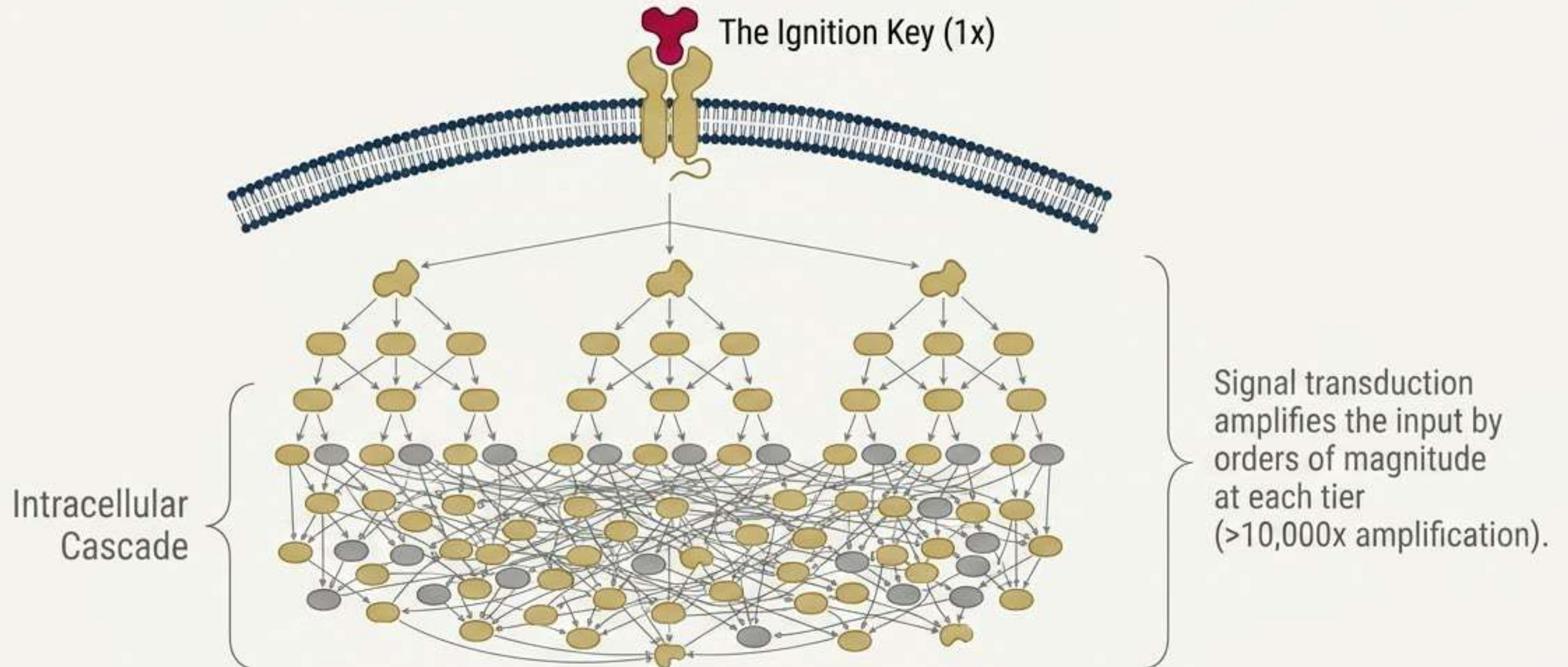


The downstream production of platelets and blood cells collapses.



Conclusion: Distal picogram signaling is an absolute physiological requirement, not a redundancy.

A single stabilized receptor event triggers a massive, exponential ignition cascade.

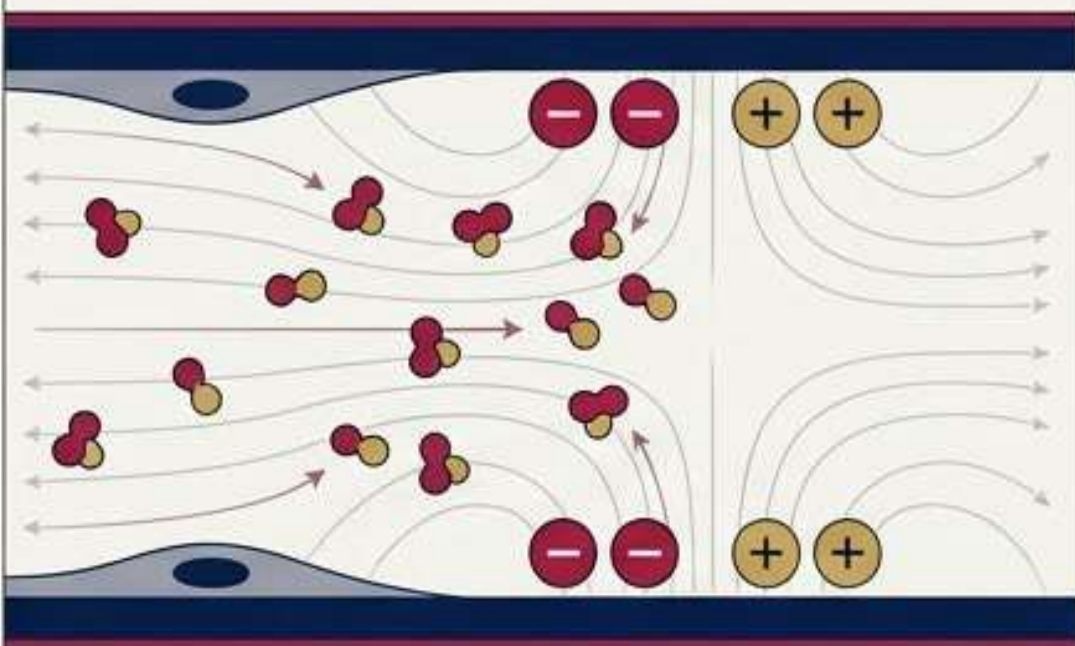


Like turning a key to start a massive engine, the picogram protein does not provide the energy for the cellular response; it merely releases the engineered constraints of the local biological network.



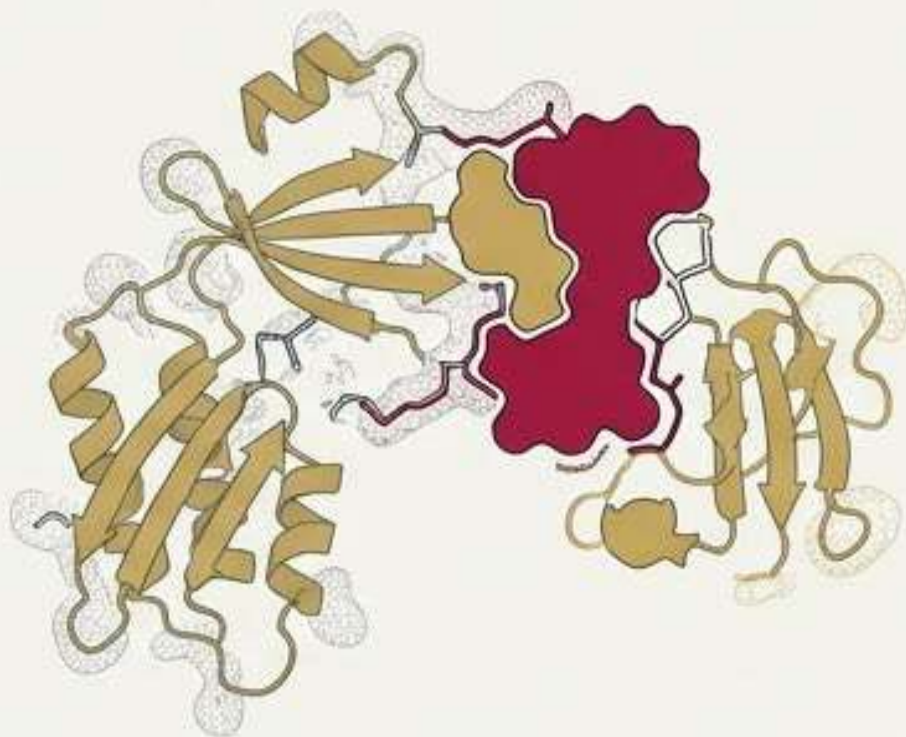
The Biophysical Blueprint for Distal Therapy

1. Physics



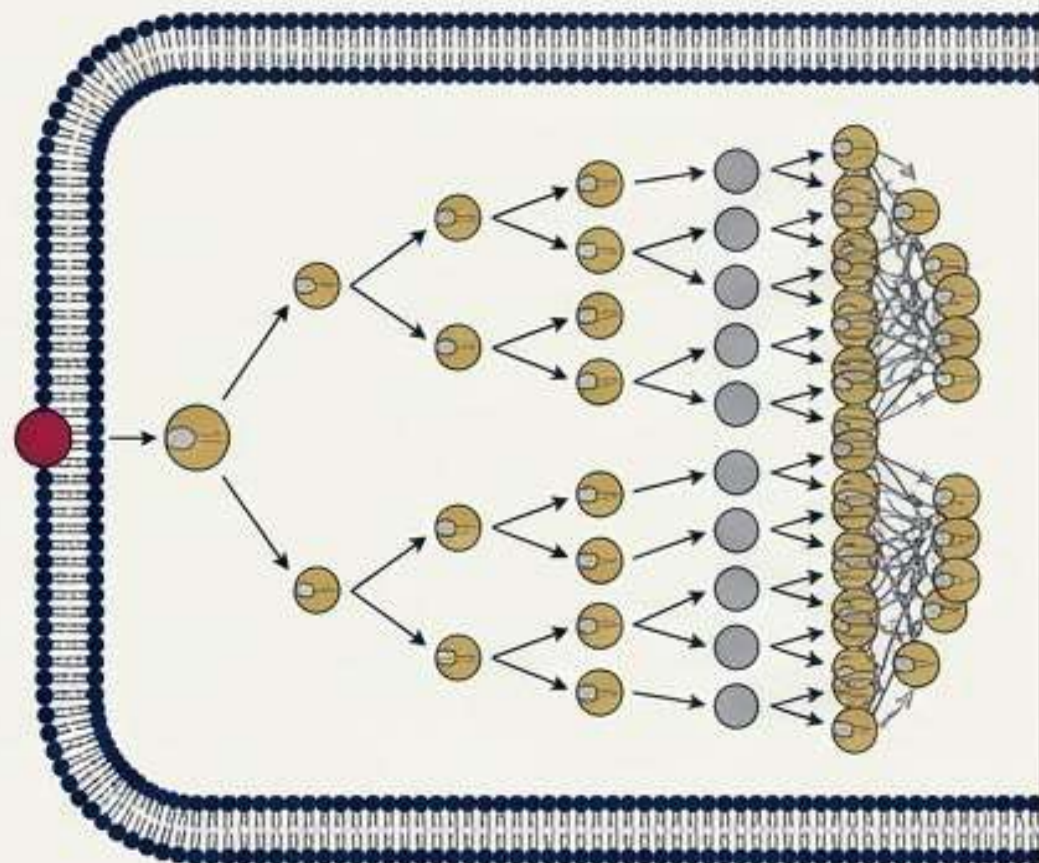
Hemodynamics & Charge Localization

2. Chemistry



Structural Affinity Bridging

3. Biology



10^4 Intracellular Amplification

Distal signaling at picogram concentrations is **not** a random chemical mixing problem. It is a **highly engineered** sequence of **fluid dynamics, electrostatics, structural chemistry, and biological amplification**. Understanding this blueprint is the key to engineering next-generation targeted therapeutics.