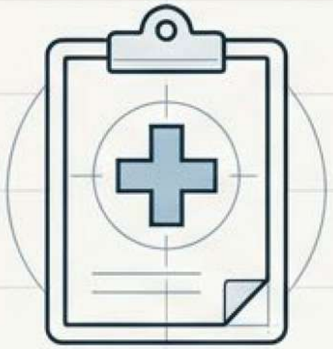
Mesenchymal Stem Cells for Chronic Kidney Disease

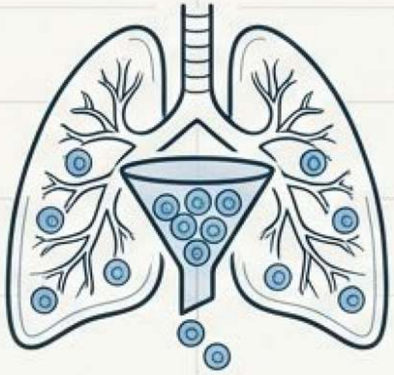
Clinical Realities, Delivery Paradoxes, and Next-Generation Paracrine Strategies

Executive Synthesis: The Paradox to Paradigm



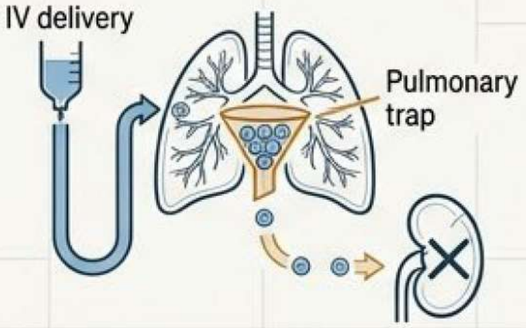
Clinical Validation

18 completed Phase 1/2 trials prove baseline safety and demonstrate early efficacy markers for Chronic Kidney Disease (CKD).



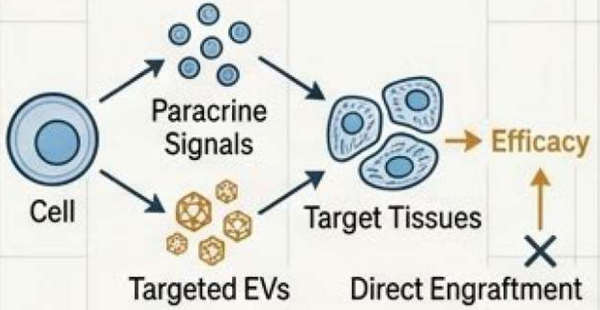
The Biological Paradox

Intravenous (IV) delivery physically traps the vast majority of cells in the pulmonary system, disproving direct renal engraftment.



The Secretome Paradigm

Efficacy is primarily driven by paracrine signaling, immunomodulation, and targeted Extracellular Vesicles (EVs), not the cells themselves.



The MSC Arsenal: Clinical Parameters & Variables

Cellular Sources	Therapeutic Modality	GMP Imperatives
 Umbilical Cord (UC)	Autologous (Patient-derived)	Identity (Positive/negative surface markers)
 Adipose Tissue (ADSCs)	Allogeneic (Donor-derived)	Potency (Functional assay validation)
 Bone Marrow (BM)		Sterility (Safety baseline)

Key Insight: Efficacy in CKD is highly variable and depends intrinsically on the specific cell source and in-vitro processing protocols prior to infusion.

Current Clinical Landscape

18

Completed Phase 1/2 Trials evaluating safety and primary efficacy

10^6 to 10^8

Cells/kg standard systemic IV infusion dosage

Primary Indications

Systemic Lupus Erythematosus (Lupus Nephritis) and Ischemic CKD

Post-Infusion Follow-up Window

Clinical improvements track consistently across this entire timeframe.

The Safety Profile: Signal vs. Noise

The Noise: Common Adverse Events

Minor respiratory infections
Infusion-site reactions
Transient fevers

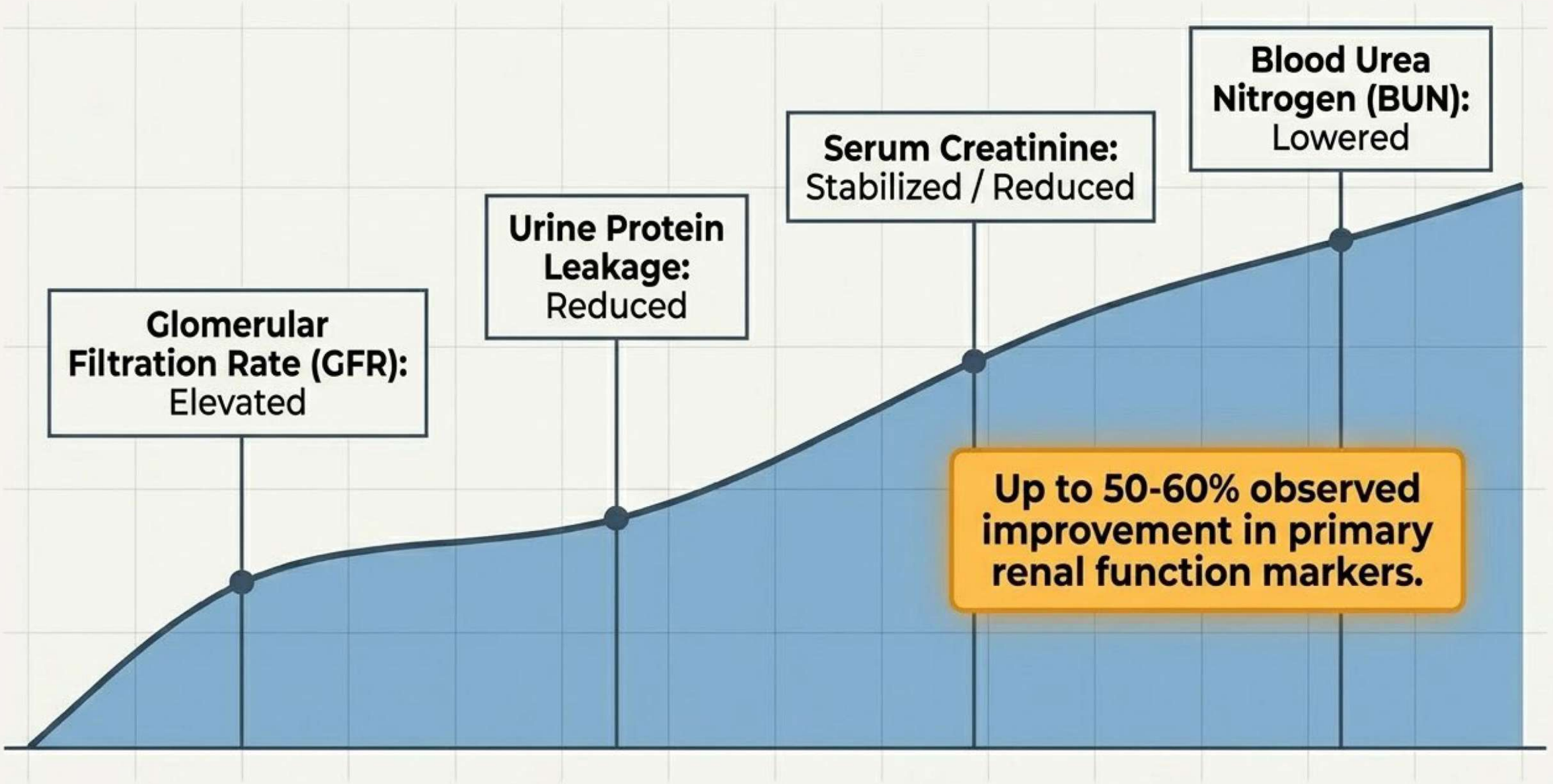
The Signal: Cell-Linked Toxicity

0%

Rigorous tracking shows zero statistical correlation between common AEs and the MSC product itself.

Conclusion: Intravenous MSC infusion is fundamentally safe, with no severe systemic toxicity observed across the Phase 1/2 landscape.

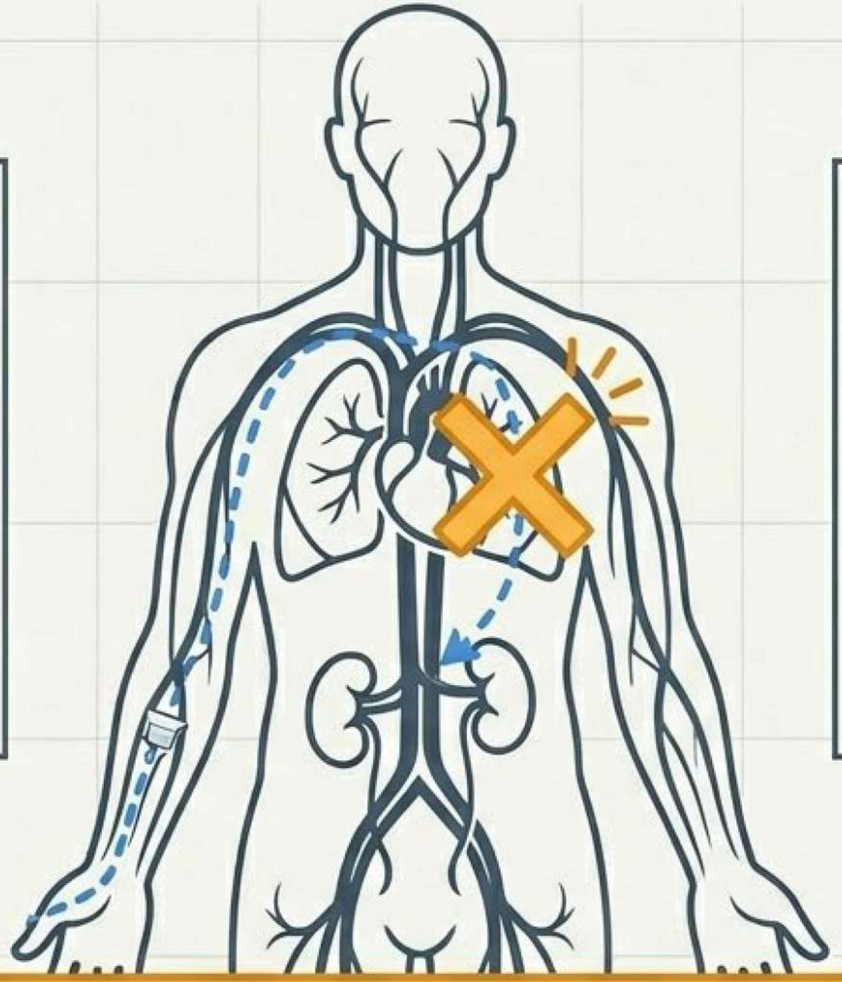
Efficacy Signals in Renal Function Recovery



The Core Delivery Paradox

The Engraftment Hypothesis

Intravenously injected MSCs travel systemically, locate the damaged renal tissue, engraft, and physically repair the kidney.



The Clinical Reality

Cells do not reach the kidney in meaningful numbers. High adhesion molecules and physical cell size cause systemic bottlenecks early in circulation.

Central Question: If the cells don’t reach the target, why does the kidney heal?

The Pulmonary First-Pass Effect: The Lung Trap

Intravenous Infusion

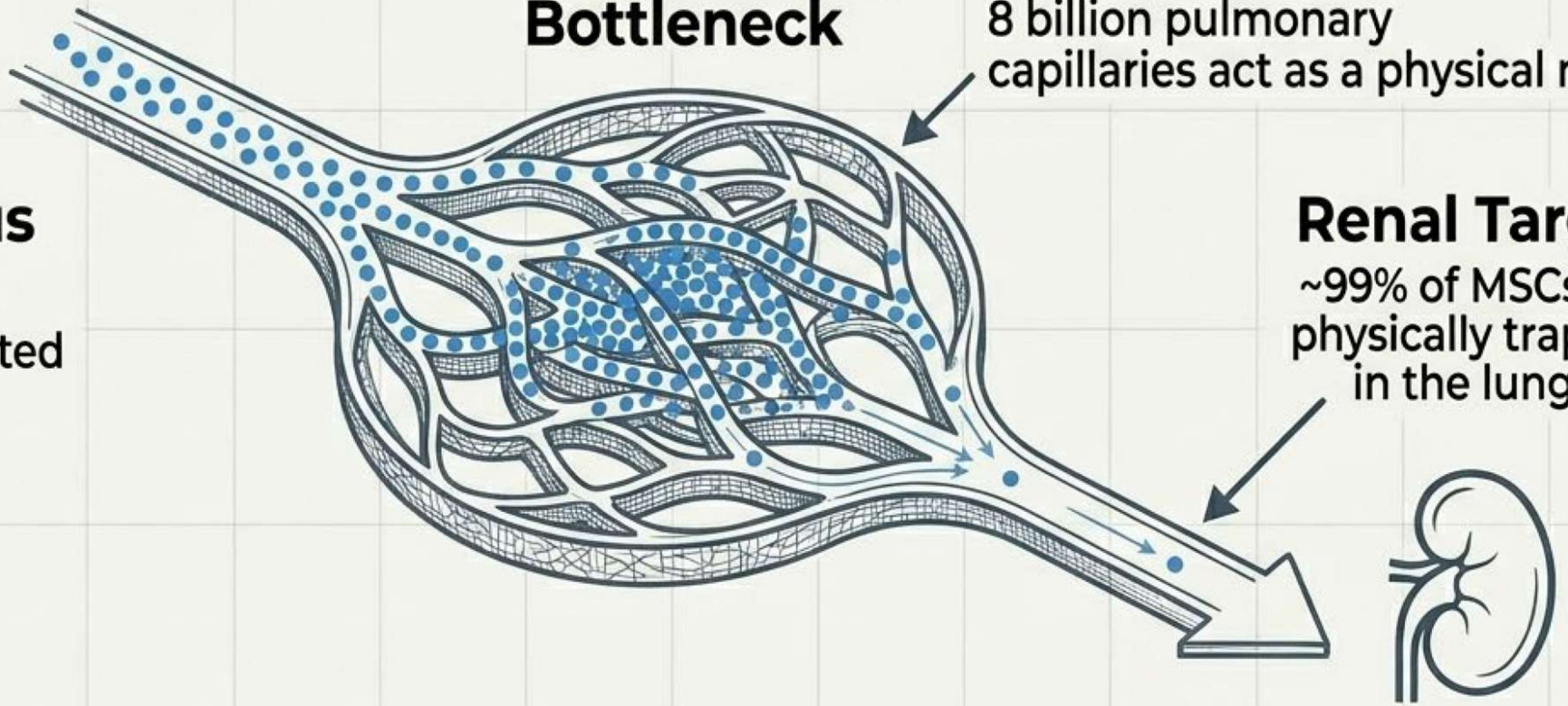
10^8 MSCs injected

The Pulmonary Bottleneck

8 billion pulmonary capillaries act as a physical net.

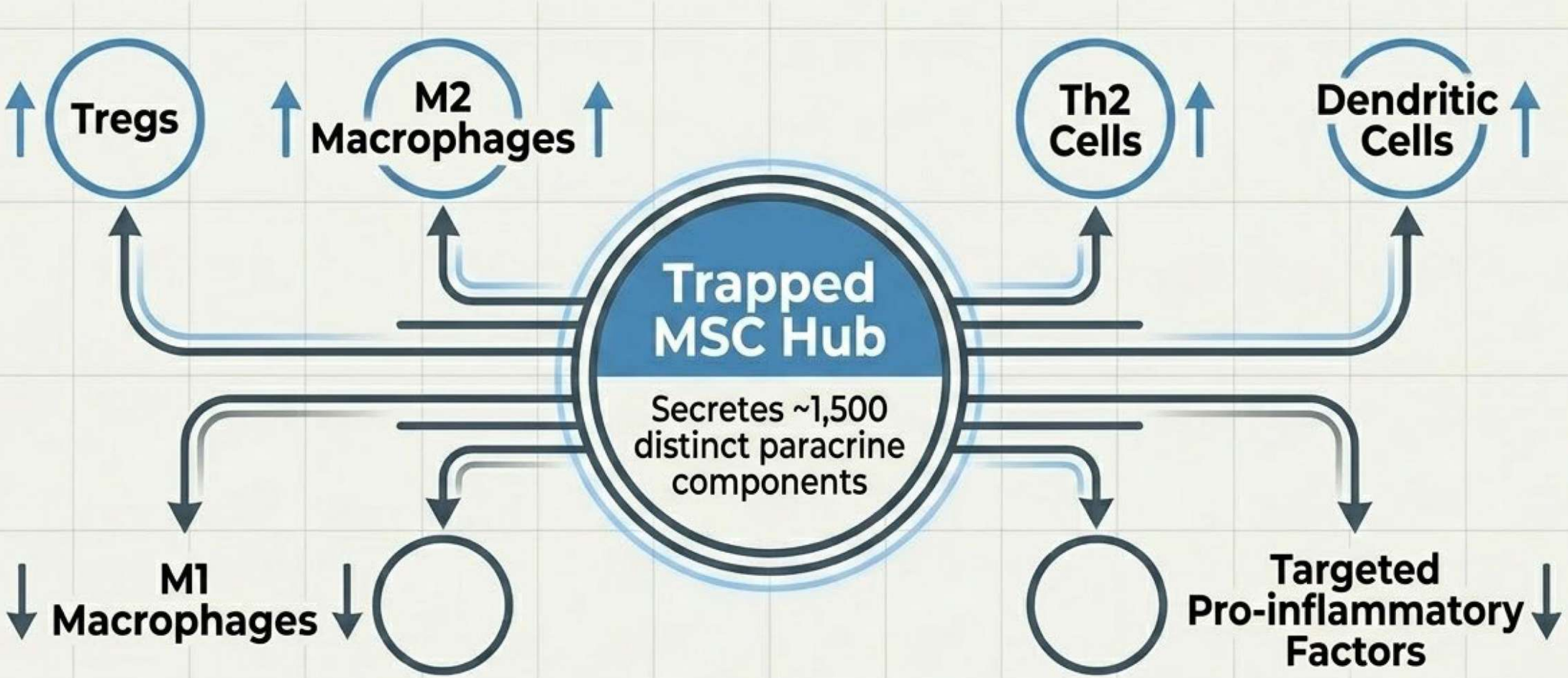
Renal Target

~99% of MSCs are physically trapped in the lungs.



Insight: With only a microscopic fraction of cells reaching the renal target, direct tissue engraftment is mathematically impossible as the primary mechanism of action.

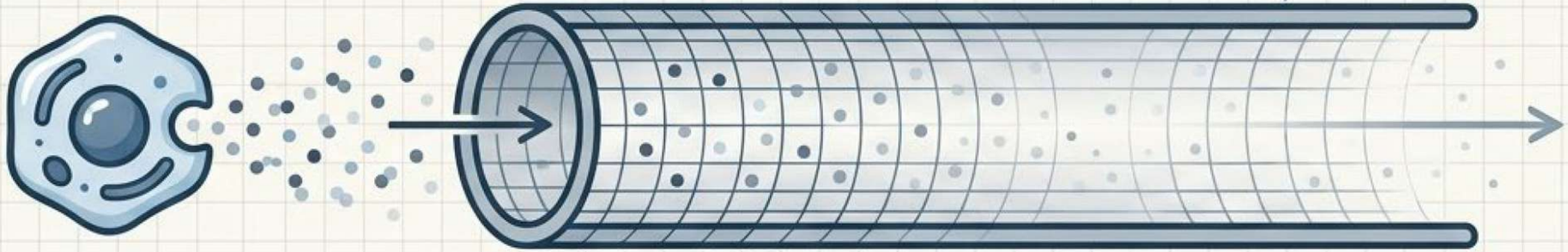
Mechanism 1: The Paracrine Signaling Factory



The MSC fundamentally alters the systemic and renal microenvironment remotely, acting as an immunomodulatory factory.

Mechanism 2: Targeted Extracellular Vesicles (EVs)

Path A: Soluble Proteins



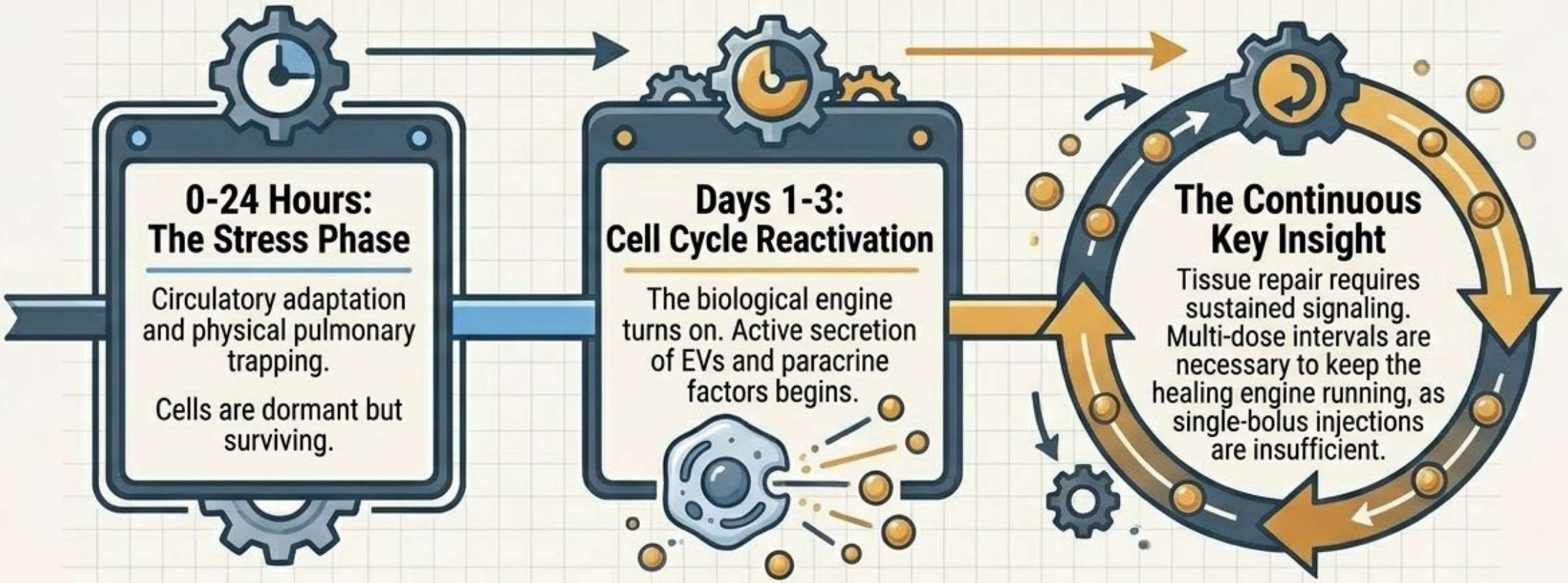
Rapid dilution in 5-6 liters of blood plasma (10^{-6} dilution rate).

Path B: Enveloped Delivery (EVs / Exosomes)

Lipid envelopes protect mRNA and proteins, surviving the circulatory journey with organ-specific targeting.

Conclusion: Extracellular Vesicles provide stable, mechanical delivery of the secretome to the renal microenvironment, bypassing the lung trap.

Temporal Reality: The Activation Timeline



Days 1-3: Cell Cycle Reactivation

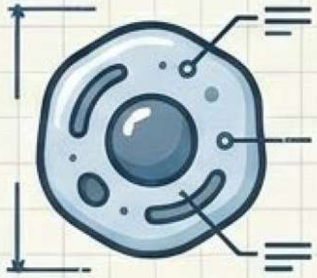
The biological engine turns on. Active secretion of EVs and paracrine factors begins.

The Continuous Key Insight

Tissue repair requires sustained signaling. Multi-dose intervals are necessary to keep the healing engine running, as single-bolus bolus injections are insufficient.

Strategic Pivot: Cells vs. Conditioned Medium

Path A: Cell Therapy (Current)



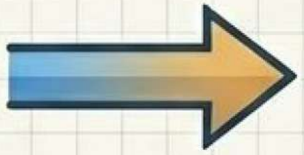
- Relies on live cellular engines

- Variable in-vivo survival rates

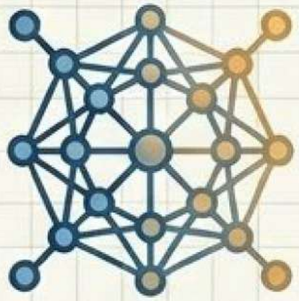
- Constrained by IV bottlenecks and the Lung Trap

Path B: Conditioned Medium (Future)

- Acellular therapy (Plasma proteins & EVs)



- Direct systemic delivery of the secretome



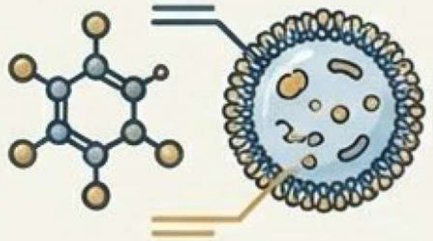
- Highly scalable and bypasses physical trapping

Strategic Question: If the secretome is the cure, do we actually need the cell?

Future Horizons & Strategic Action Plan

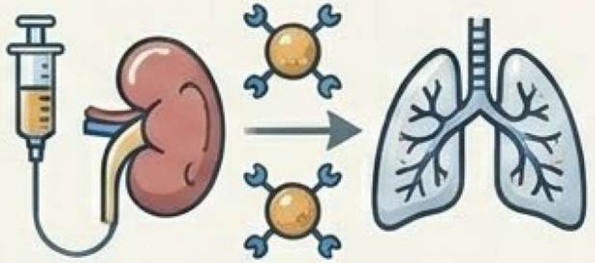
Refine the Secretome

Map, stabilize, and standardize the specific **plasma proteins** and **Extracellular Vesicles** within Conditioned Medium therapeutics.



Evolve Delivery Mechanisms

Investigate local infusion (renal arterial perfusion) to bypass pulmonary trapping entirely, alongside systemic EV targeting.



Innovate Cell Sources

Explore iPSC-derived solutions to create mass-producible allogeneic therapeutics that maximize secretome output while minimizing immunogenicity.