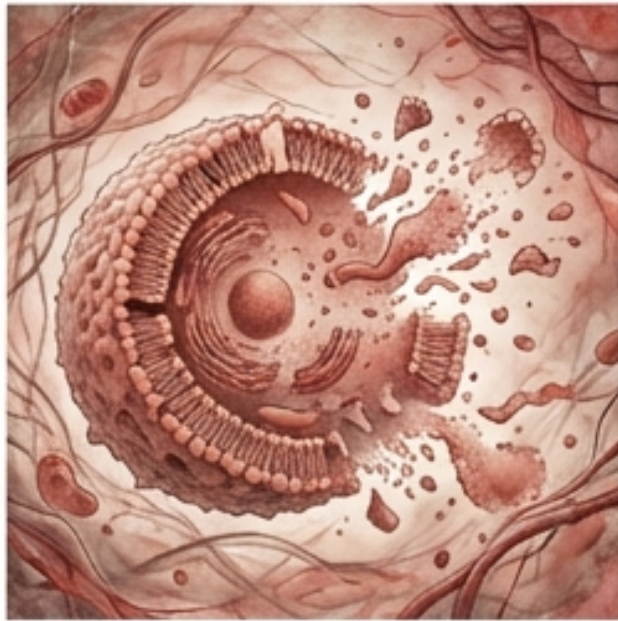


The Evolution of Regenerative Signaling

Moving Past the Cellular Vehicle:
The Clinical Emergence of
Regenerative Signaling Factors (RSF)

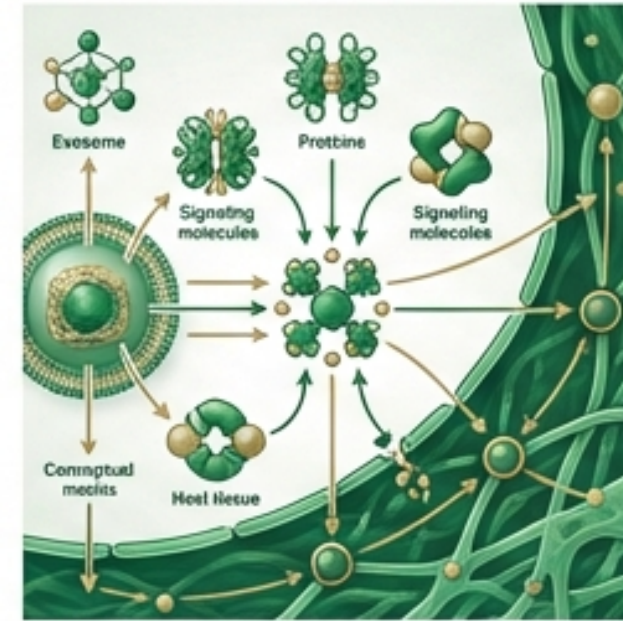


The Paradigm Shift: From Seed to Paracrine Reality



The Biological Myth of the Seed

- Legacy theory assumed injected live stem cells engrafted and grew like seeds in a garden.
- Reality: The cell is merely a temporary factory that quickly perishes in the host.



The Pure Signaling Era

- Regenerative medicine has moved past the vehicle (the cell).
- Focus has entirely shifted to the Instructional Payload: Regenerative Signaling Factors (RSF).

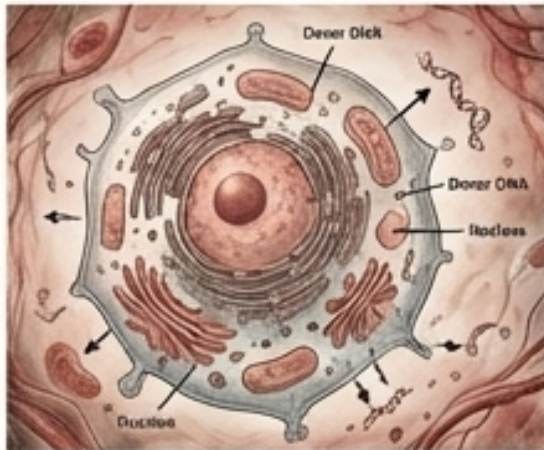
Stem Cells Translational Medicine, Caplan A.I. (2017)
'Mesenchymal Stem Cells: Time to Change the Name!'

Technology Evolution: The Path to Pure Signaling

v2.0: MSCs

Live Cellular Therapy

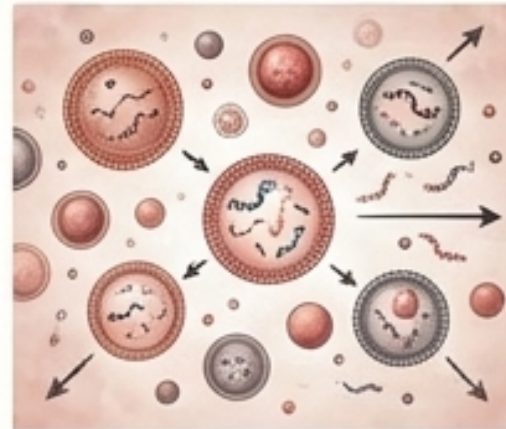
Cumbersome live cells carrying foreign donor DNA. High biological noise.



v3.0: Exosomes

Acellular Vesicles

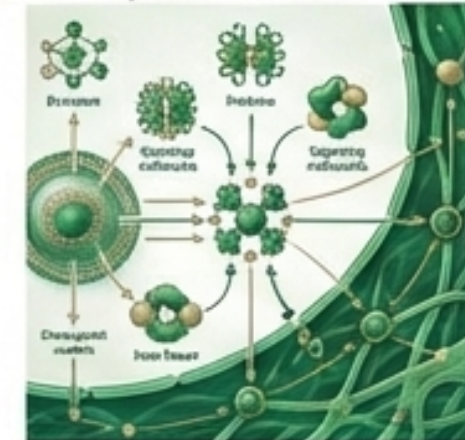
Nanoparticles carrying inconsistent, volatile foreign RNA payloads. Subject to rapid washout.



v4.0: RSF

Pure Signaling Matrix

The first DNA/RNA-free signaling matrix. A pure software update of proteins, growth factors, and chemokines.



RSF delivers regenerative instructions without the risk of genetic factory resets or tumor growth.

The Vehicle Problem: Genetic Baggage & Biological Noise



Legacy Vulnerabilities

MSCs (Version 2.0): Derived from only 1 of 6 placental regions. Introduction of foreign donor DNA carries a documented 5-10% risk of Graft-Versus-Host Disease (GVHD) and immune rejection.

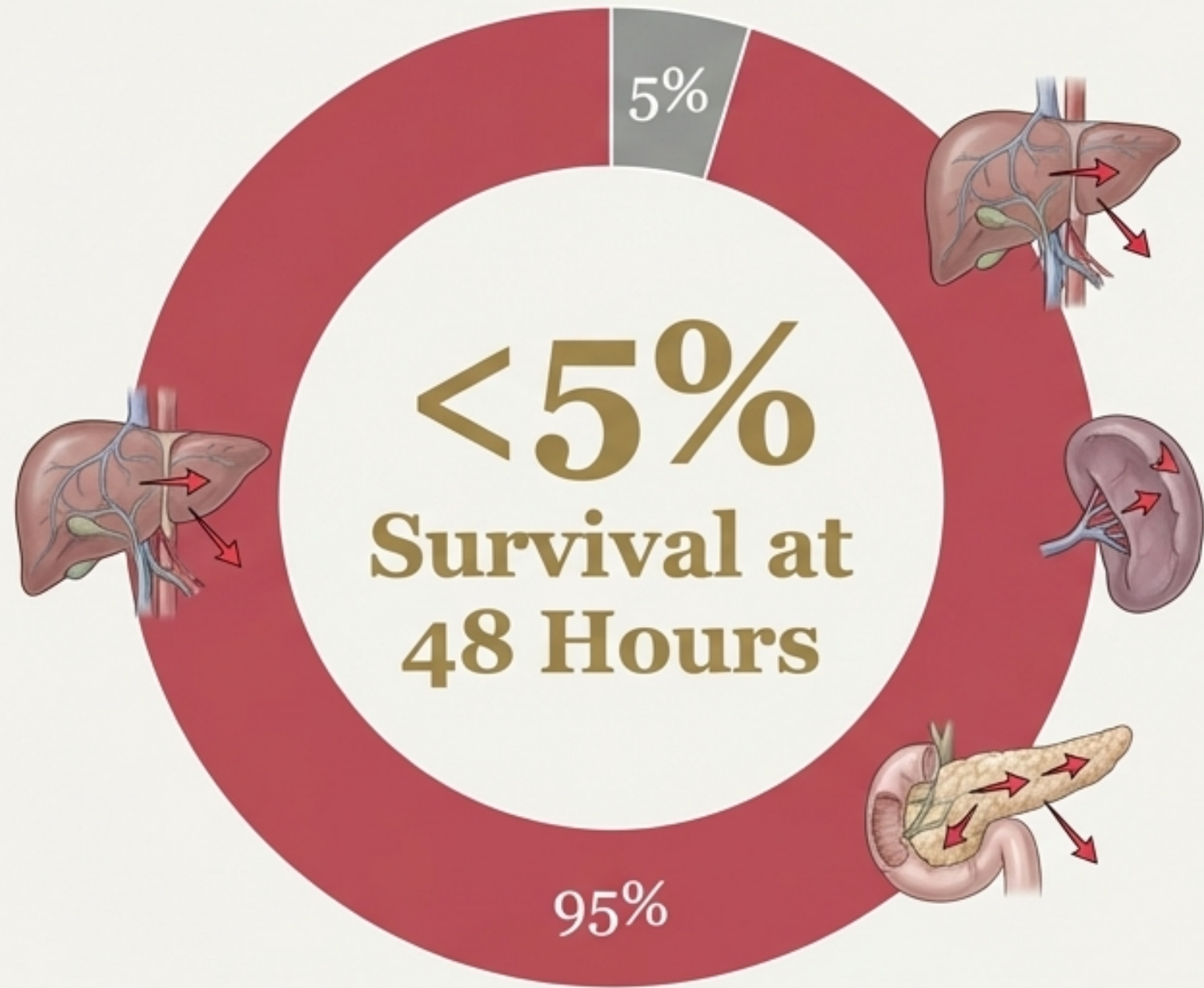
Exosomes (Version 3.0): Regulated biologics containing volatile, inconsistent foreign RNA from a single tissue source.



The RSF Solution

RSF (Version 4.0): 100% DNA and RNA-free. Delivers a highly concentrated payload of regenerative proteins, peptides, and cytokines **with zero genetic interference or oncogenic risk.**

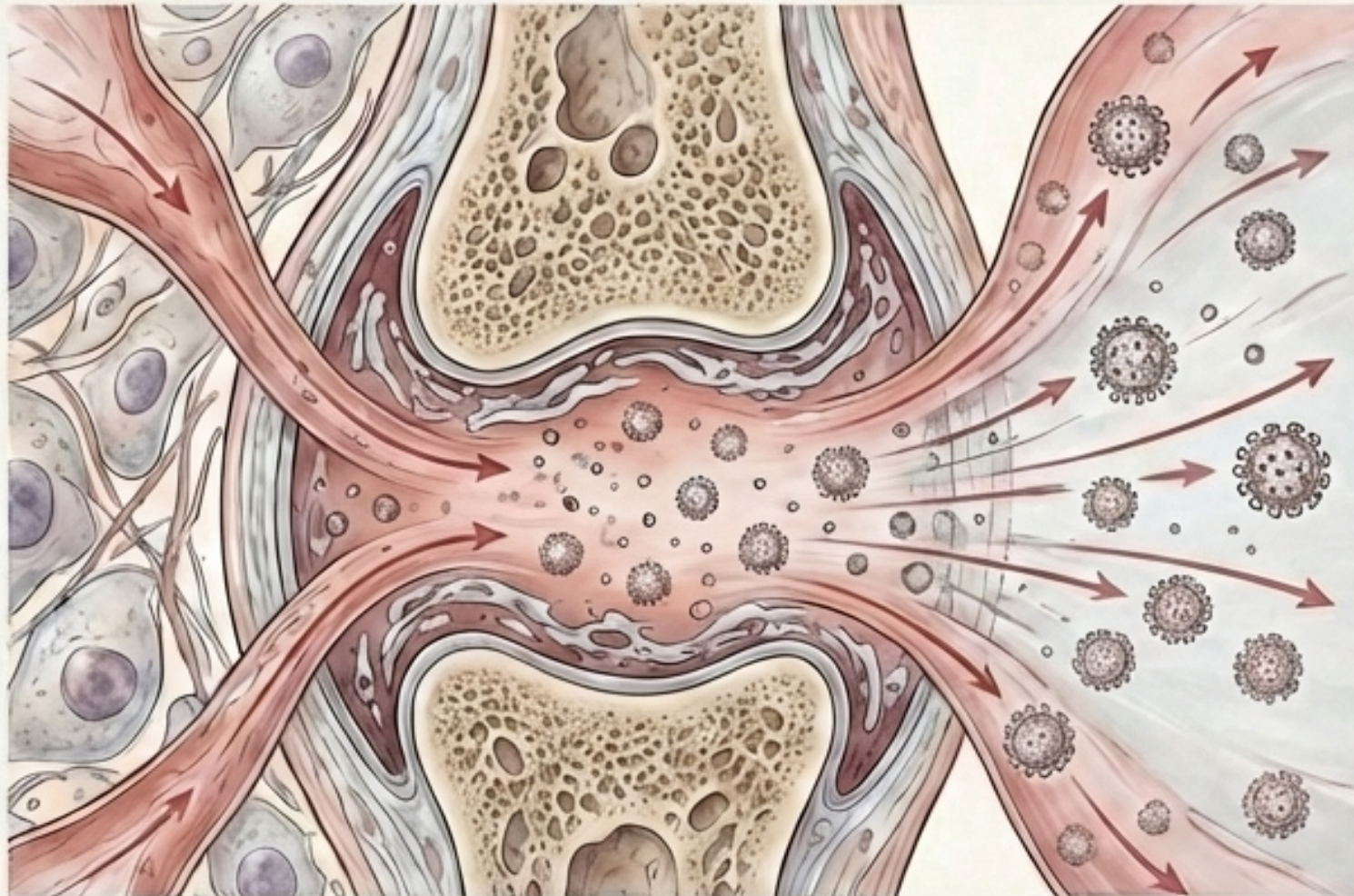
The Hostile Microenvironment: The Survival Gap



- **The Inflammatory Inferno:** Injected MSCs face immediate destruction in inflamed host tissue. The environment destroys the biological factory before signaling begins.
- **Systemic Trapping:** The >95% of cells that perish do not simply disappear; they are pharmacokinetically trapped and filtered by the liver, spleen, and pancreas.
- **Conclusion:** Live cells are structurally incompatible with highly inflamed, degenerative microenvironments.

The Washout Phenomenon: Pharmacokinetic Failure

**The fatal flaw of legacy biologics is simple:
they do not stay where you put them.**



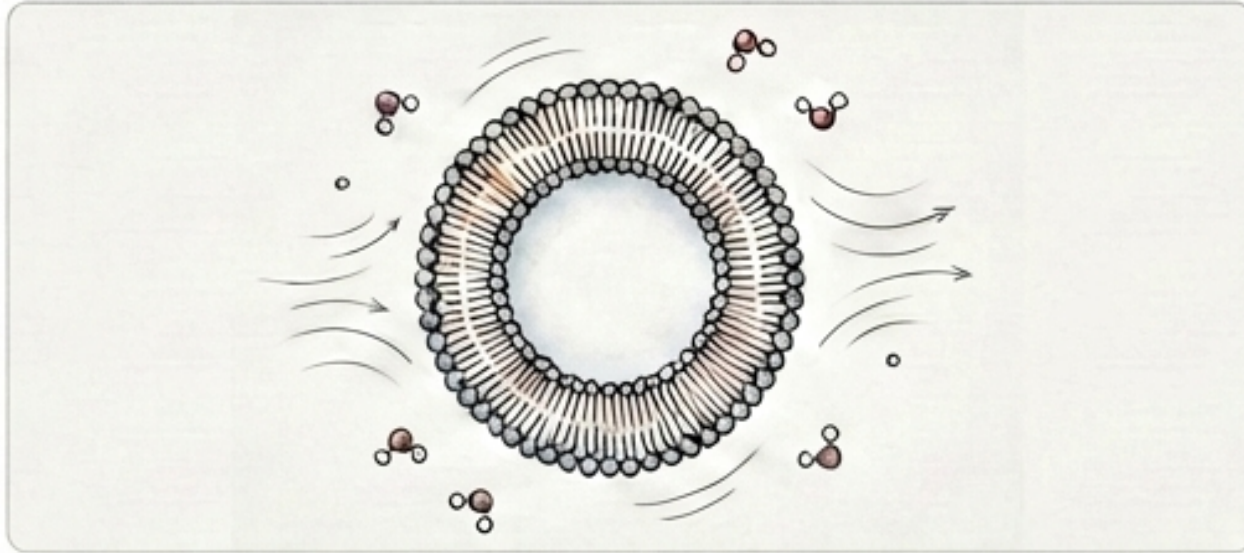
Legacy Biologics (MSC and Exosomes): lack the structural ability to attach themselves to host tissue.

Rapid Clearance: Unbound MSC and Exosomes are rapidly metabolized and washed out of the local injection site within days.

Therapeutic Gap: This results in transient, short-lived signaling that fails to overcome chronic degenerative inertia.

Mechanical Anchoring vs. Washout

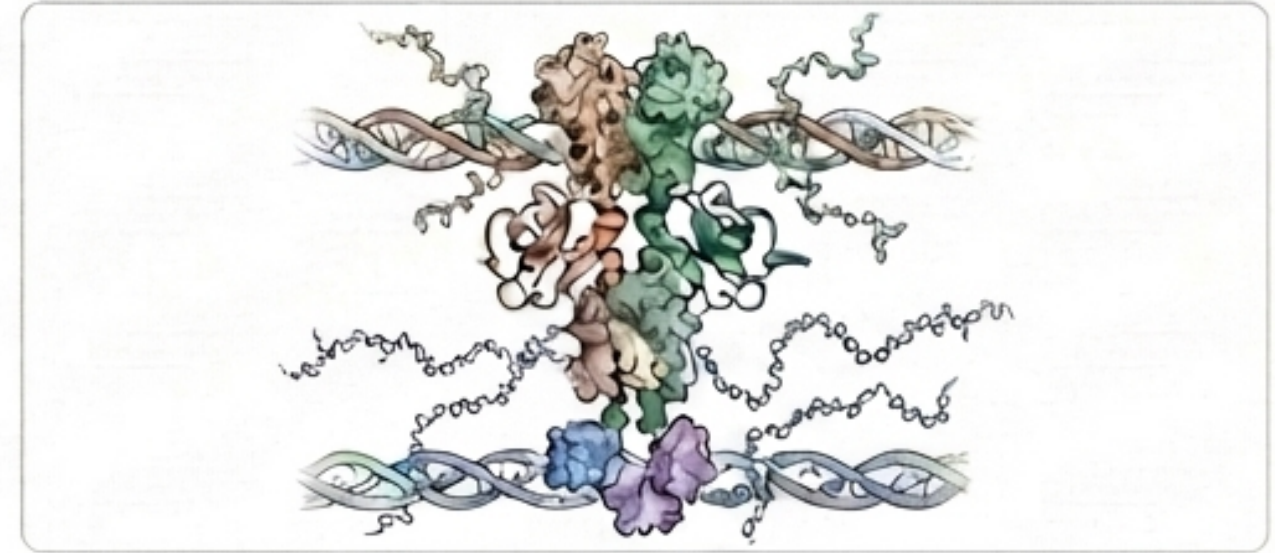
MSC/ Exosomes



Mechanism: No ECM binding mechanism.

- **Retention:** Wash-out in 3-7 days.
- **Result:** Transient, incomplete signaling phase.

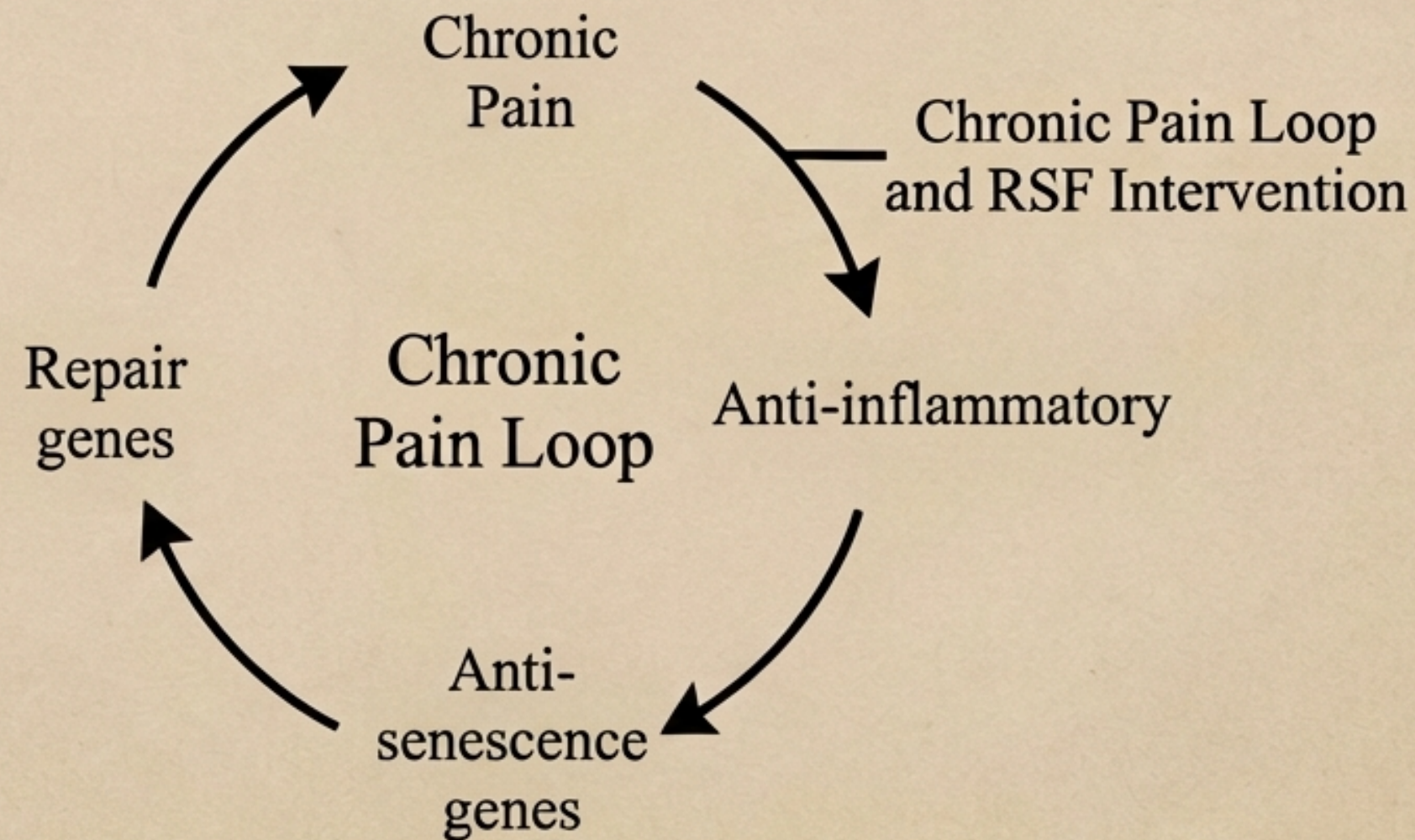
Ultra RSF / Version 4.0



Mechanism: Extracellular Matrix (ECM) Anchoring. Protein complex binds directly to host collagen and hyaluronic acid.

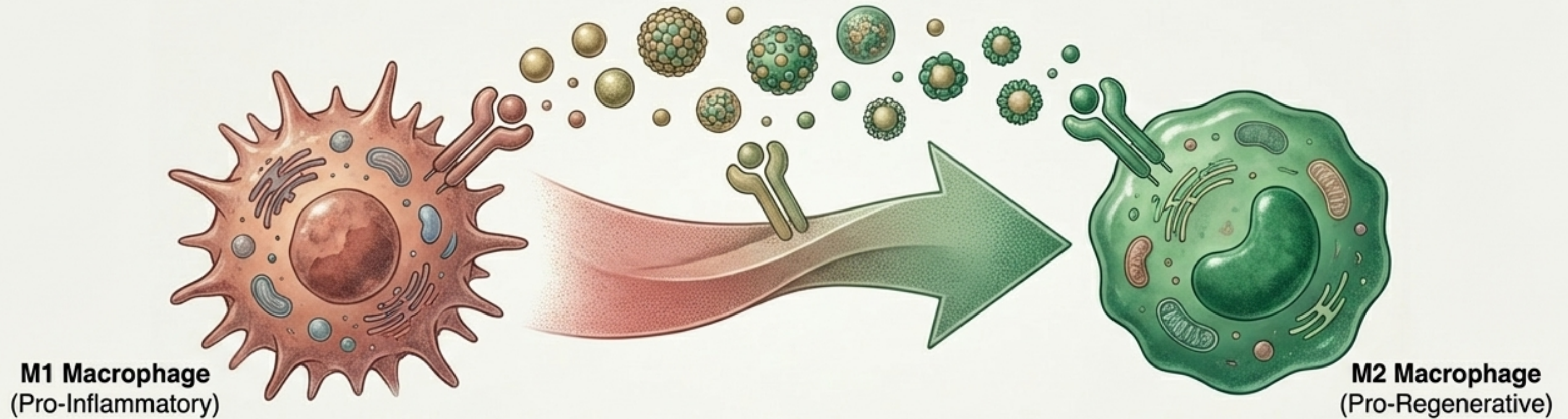
- **Retention:** Approaches > 90% local retention.
- **Result:** Creates a persistent broadcast station providing sustained, full-spectrum regenerative signaling for up to 4 weeks.

Epigenetic Reprogramming: Overcoming Maladaptive Down-Regulation



Epigenetic silencing of repair/anti-inflammatory/anti-senescence genes . (Gurven et al. 2017+)

Macrophage Polarization Cascade



Action: RSF forces local immune cells to undergo rapid phenotypic shifting from the M1 (Pro-Inflammatory) phase to the M2 (Pro-Regenerative) phase within hours.

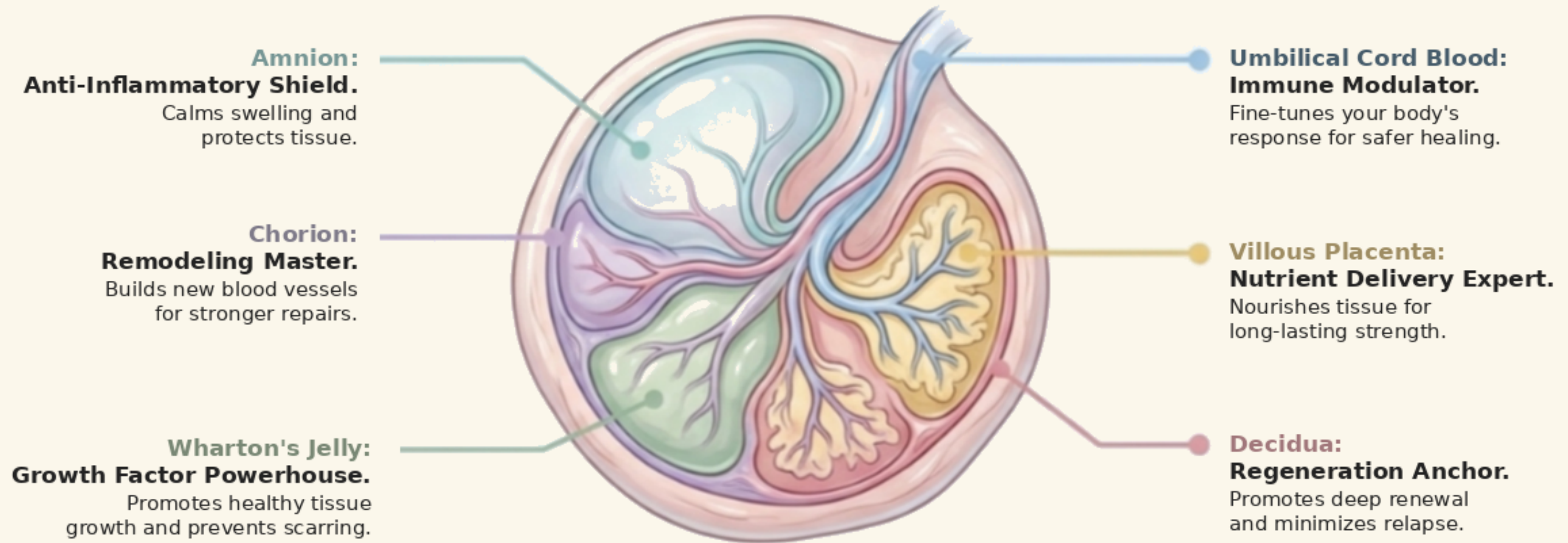
Pathway Specifics: Driven by concentrated PGE2 and TSG-6 pathway activation within the RSF matrix.

Clinical Outcome: Noticeable, rapid suppression of localized pain and acute inflammation.

Frontiers in Immunology (2019)
"Macrophage Polarization in
Tissue Repair and Remodeling"

The Six Geographies of the Placental Matrix

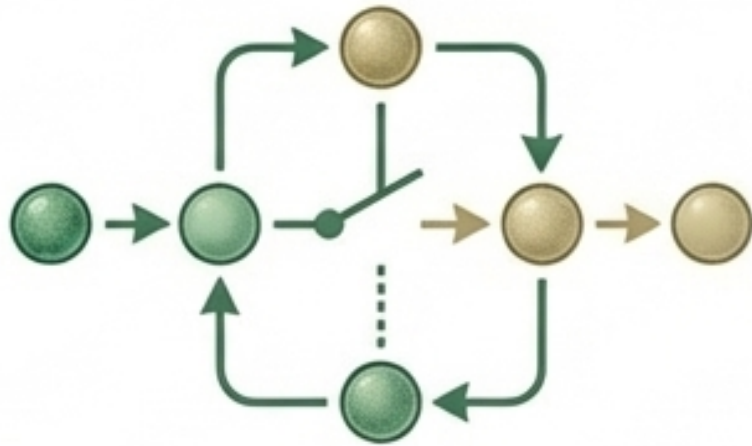
RSF is derived from the full secretome of the placenta, utilizing all six distinct geographies. This holistic approach contrasts with limited-source MSCs or exosomes that deliver only a fraction of the necessary signals.



Combating Senescence: GDF11 and TIMP2 Youth Factors

Ultra RSF actively combats cellular senescence through the targeted delivery of isolated youth factors.

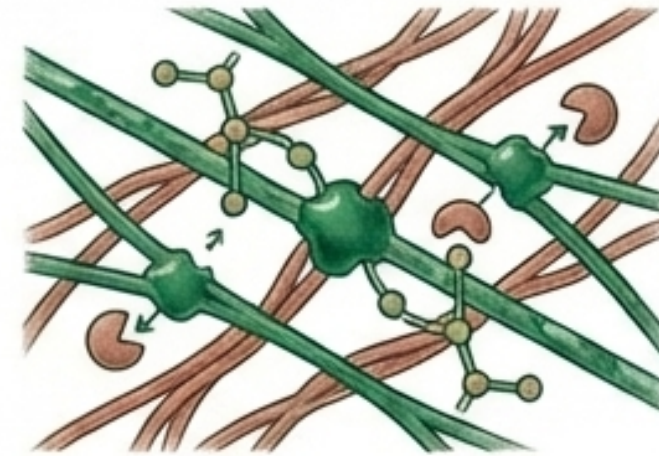
GDF11 (Growth Differentiation Factor 11)



- Reverses age-related hypertrophy and restores tissue elasticity.
- **Pathway:** Modulates the **Smad2/p21 signaling pathway** to rejuvenate stem cell populations.

Nature Communications: 'GDF11 Rejuvenates Aging Tissues'

TIMP2 (Tissue Inhibitor of Metalloproteinases 2)



- Revitalizes aged neurogenic capabilities and halts extracellular matrix degradation.

Heliyon: 'TIMP2 as a Systemic Youth Factor'

At-Home Delivery & Patient Empowerment



Subcutaneous Simplicity.



Targeted Home Utility.



Intra-Nasal Delivery.



At-Home: Room-temp stable (24 months). No thawing. No “bio-baggage.”



In-Office Administration



IV Infusion Therapy.



Intra-Articular Injection with Ultrasound.

➤ **In-Office:** Physician-supervised IV & injection protocols.



From Live Cells to Acellular Signals: A Safer, Smarter Approach

Placental-derived Regenerative Signaling Factors (RSF) represent a paradigm shift in treating CNS disorders. This cell-free secretome bypasses the risks of live cell therapy and the physical barrier of the brain.



The Challenge

Traditional CNS therapies are blocked by the Blood-Brain Barrier (BBB). Live cell therapies introduce risks of immunogenicity, malignant transformation, and complex logistics.



The Solution

An acellular, off-the-shelf secretome—a cocktail of proteins, growth factors, and extracellular vesicles—that circumvents the challenges of live cell transplantation.



The Breakthrough

A non-invasive intranasal delivery route provides direct access to the brain, while the therapy leverages the injury's own microenvironment for precise, passive targeting.

Intranasal Administration: A Direct, Non-Invasive Pathway to the Brain

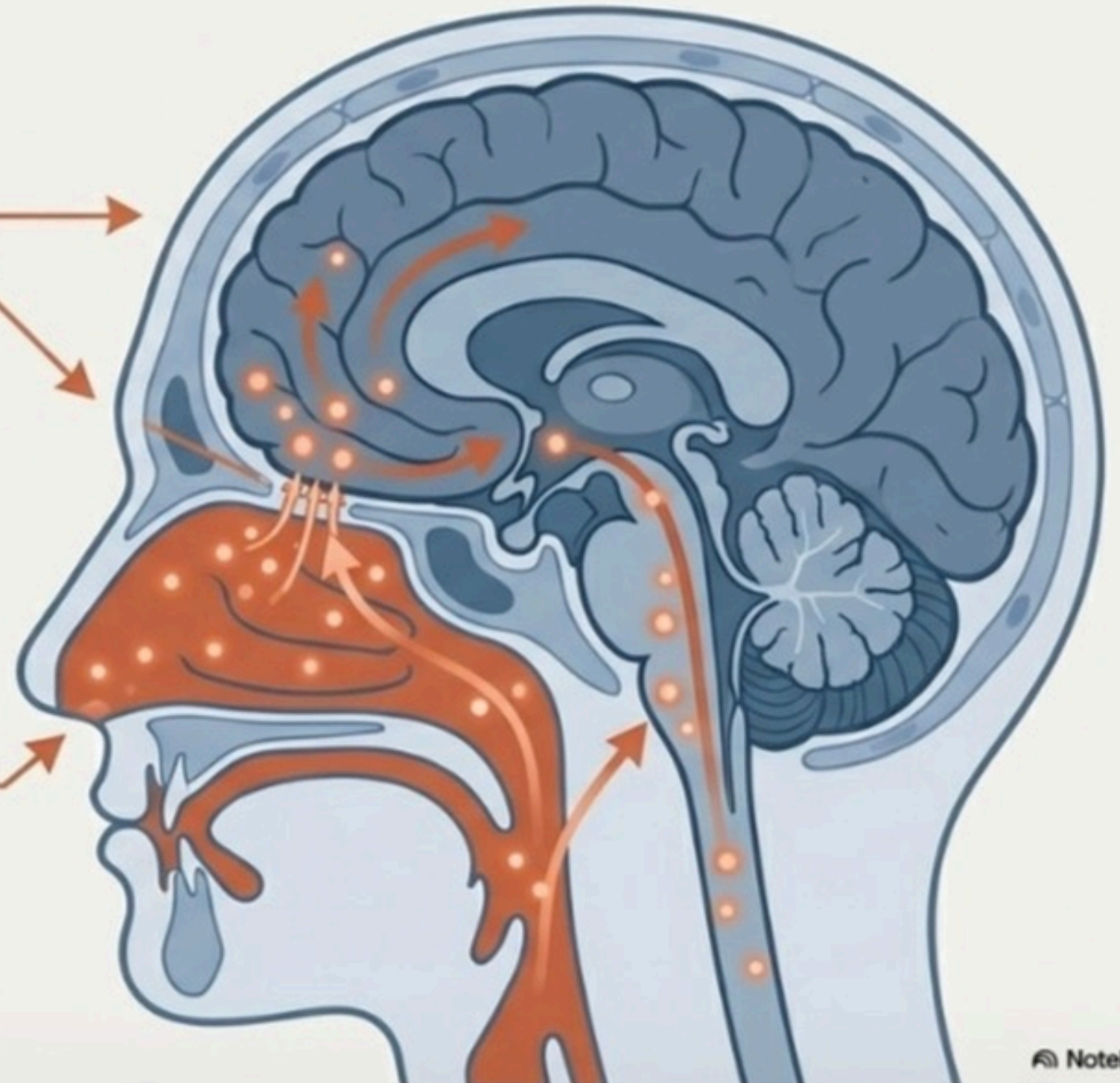
The nasal cavity's unique anatomy provides a direct connection to the CNS, allowing therapeutics to bypass the Blood-Brain Barrier entirely.

Olfactory Nerve Pathway:

Direct transport along olfactory neurons, moving from the nasal mucosa through the cribriform plate to the olfactory bulb and rostral brain regions.

Trigeminal Nerve Pathway:

Transport along trigeminal nerve bundles, providing access to the brainstem and more caudal brain regions.



Acellular Regulatory Compliance

Section 351 vs. Section 361 HCT/P Classification

Section 351

DRUGS / BIOLOGICS

- ✗ **Requires full FDA premarket approval**
(BLA / IND pathway)
- ✗ **Includes cell therapies, gene therapies,**
and cell-based biologics
- ✗ **Clinical trials required**
Lengthy review, significant cost
- ✗ **Eligible for RMAT designation**
(cell/gene therapies for serious conditions)

Section 361

TISSUE PRODUCTS

- ✓ **Exempt from premarket review**
Regulated under 21 CFR Part 1271
- ✓ **Structural tissue scaffold**
(acellular HCT/P classification)
- ✓ **No BLA / IND required**
Faster, compliant market access
- ✓ **Not a drug or biologic**
Functional re-training of tissue, not cell replacement

Why Ultra RSF Qualifies as Section 361

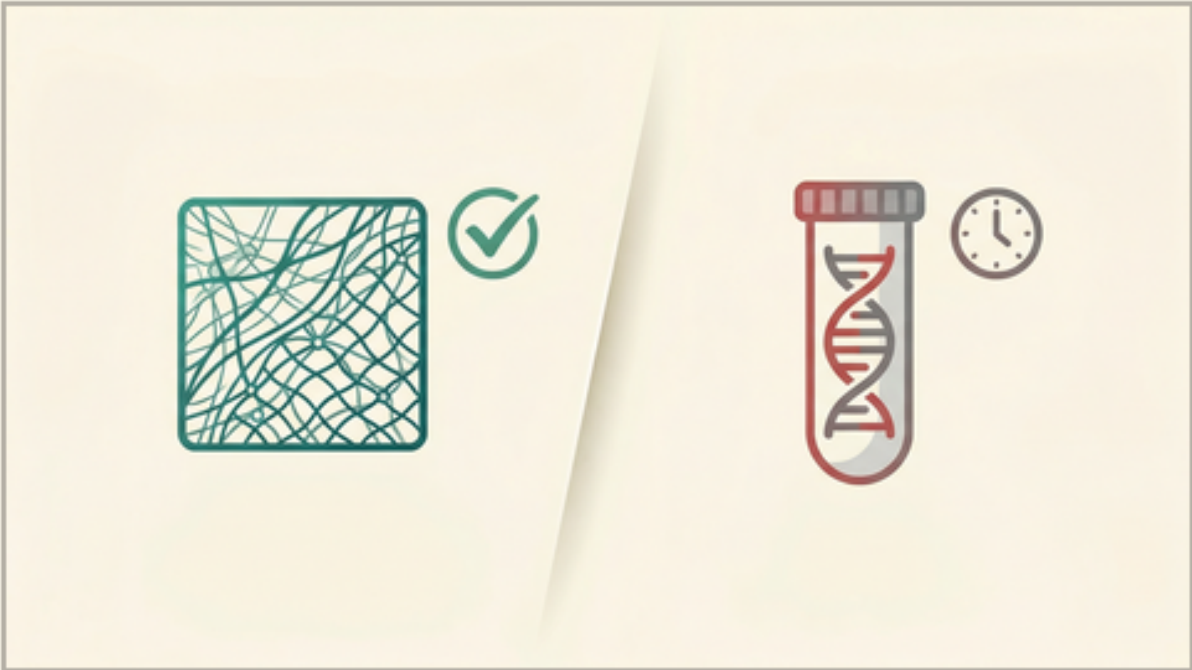
- ✓ **Minimal Manipulation**
Decellularization preserves native ECM
- ✓ **Not Combined**
No added drugs, devices, or biologics
- ✓ **Homologous Use**
Structural scaffold for tissue repair
- ✓ **No Systemic Effect**
Acellular — structural, not metabolic

RMAT designation is reserved for cell/gene therapies (351). Ultra RSF is a 361 tissue product — already compliant.



Regulatory Clarity: HCT/P 361 vs. RMAT 351

Why Ultra RSF Is Available for Immediate Clinical Integration



What Is RMAT?

Regenerative Medicine Advanced Therapy

- An FDA fast-track designation for cell & gene therapies
- Reserved for 351 biologic drugs (BLA required)
- Applies to: stem cells, gene therapies, CAR-T, tissue engineering
- Must treat serious or life-threatening conditions

✓ Ultra RSF Does Not Need RMAT

RMAT is a fast-track for drugs not yet on the market.
Ultra RSF is a naturally processed tissue —
it is already at the finish line.

Section 361 — Tissue
Ready for Clinical Use

Section 351 — Drug
Years of Clinical Trials

FEATURE	Ultra RSF (Section 361)	RMAT Products (Section 351)
Classification	Human Cell & Tissue Product (HCT/P)	Biologic Drug
Regulation	21 CFR 1271.10(a)	BLA / IND Required
Clinical Trials	Not Required	Years of FDA-Monitored Trials
Availability	Immediate Clinical Use	Pending FDA Approval
Function	Structural / Mechanical Scaffold	Cell or Gene Replacement Therapy

- **Ultra RSF:** Regulated as Tissue (Scaffold). No IND/BLA required.
- **RMAT:** Regulated as a Drug. Requires years of FDA-monitored trials.

Broad Provider Eligibility & Compliance

Section 361 Compliant

Classified as a **structural tissue scaffold** — No BLA/IND. Exempt from premarket review.

- ✓ Minimal Manipulation
- ✓ Homologous Use
- ✓ Non-Combined
- ✓ No Systemic Effect

Multi-Disciplinary Integration

Accessible to a broad range of licensed healthcare professionals:

MDs & DOs

Physicians &
Osteopathic Physicians

NMDs & NDs

Naturopathic Medical
Doctors & NDs

DCs

Doctors of
Chiropractic

PAAs & NPs

Physician Assistants
& Nurse Practitioners

Why This Matters: RSF Is Not a Drug or Biologic

- Ultra RSF is a **structural tissue scaffold** — not a cell or gene therapy
- RMA designation **does not apply** — reserved for 351 cell/gene biologics
- Function is **tissue re-training & repair**, not cellular replacement

⚠ **Important:** Utilization subject to individual State Board regulations and scope of practice.

Clinical Modality Comparison

ELEMENTS	MSCs (v2.0)	Exosomes (v3.0)	Ultra RSF (v4.0)
DNA/RNA Baggage	Yes (Foreign DNA) X	Yes (Volatile RNA) X	ZERO (100% Acellular) ✓
GVHD / Immune Risk	5-10% Risk X	Moderate X	None ✓
Local Retention Time	3-7 Days X	1-3 Days X	Up to 28 Days (ECM Anchoring) ✓
Storage Requirements	Cryofreezing (-80°C)	Cryofreezing (-80°C)	Room Temperature (2 Years) ✓
Tissue Source	1 Placental Region X	1 Placental Region X	All 6 Placental Geographies ✓

Ultra RSF vs. MSCs (Stem Cells) — Why RSF Wins

MSCs (v2.0)

Local Retention Time

3-7 Days ✗

Tissue Source

1 Placental Region ✗

DNA/RNA Baggage

Yes (Foreign DNA) ✗

GVHD / Immune Risk

5-10% Risk ✗

Storage Requirements

Cryofreezing (−80°C) ✗

Ultra RSF (v4.0)

Local Retention Time

21-28 Days (ECM Anchoring) ✓

Tissue Source

All 6 Placental Geographies ✓

DNA/RNA Baggage

ZERO (100% Acellular) ✓

GVHD / Immune Risk

None ✓

Storage Requirements

Room Temp (2-Year Shelf Life) ✓

4x

6x

4x Retention × 6x Tissue Diversity = 24x Signal Potency



MSCs



Cryofreezing (−80°C)



Ultra RSF

Ultra RSF vs. Exosomes — Why RSF Wins

Exosomes (v3.0)

Local Retention Time

1-3 Days ✗

10x

Tissue Source

1 Placental Region ✗

6x

DNA/RNA Baggage

Yes (Volatile RNA) ✗

GVHD / Immune Risk

Moderate ✗

Storage Requirements

Cryofreezing (−80°C) ✗

Ultra RSF (v4.0)

Local Retention Time

21-28 Days (ECM Anchoring) ✓

Tissue Source

All 6 Placental Geographies ✓

DNA/RNA Baggage

ZERO (100% Acellular) ✓

GVHD / Immune Risk

None ✓

Storage Requirements

Room Temp (2-Year Shelf Life) ✓

10x Retention × 6x Tissue Diversity = 60x Signal Potency



Exosomes



Cryofreezing (−80°C)



Ultra RSF



The Bottom Line

Ultra RSF makes Legacy Biologics – like MSC's and Exosomes obsolete

- Strips away volatile DNA/RNA vehicles and genetic baggage
- Solves the pharmacokinetic washout problem via direct ECM anchoring
- Delivers a full-spectrum, 6-geography placental protein matrix directly to degenerated tissue

RSF has definitively established itself as the most prolific, stable, and powerful tool in modern regenerative medicine.