

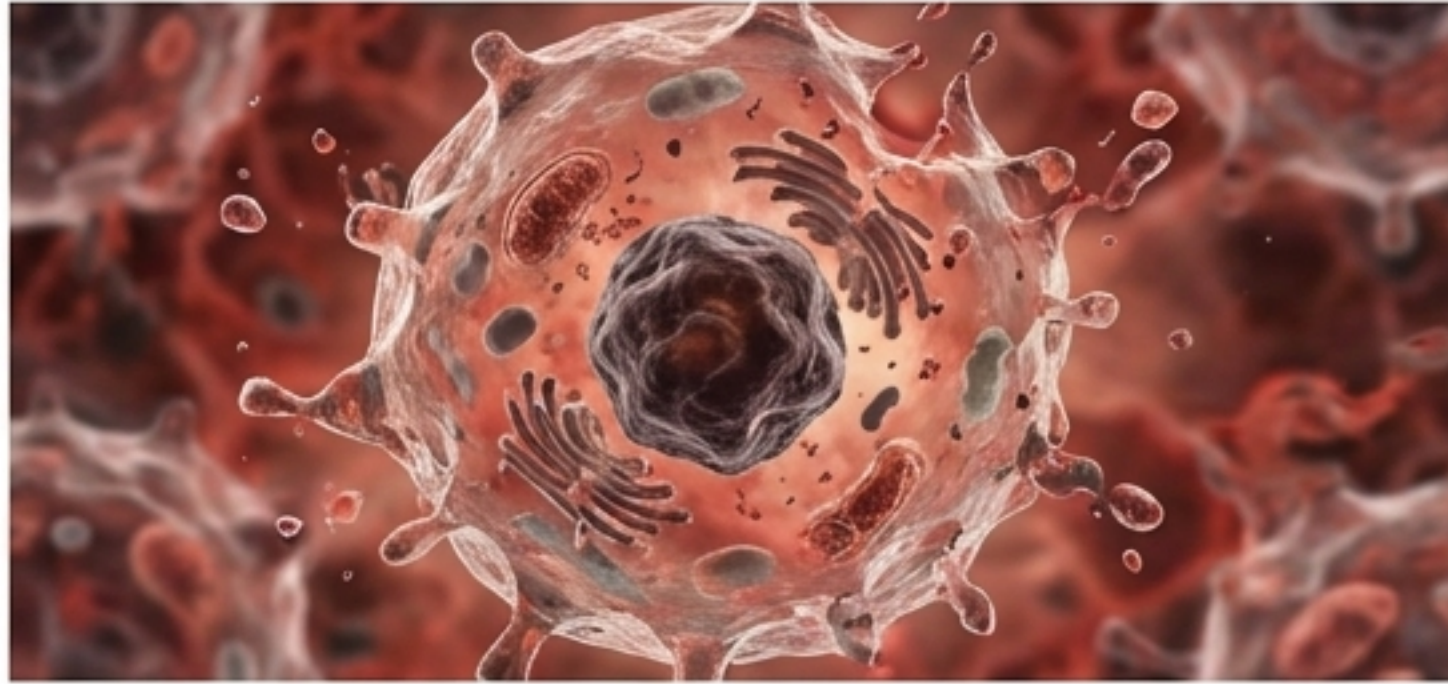
Peer-Reviewed Clinical Slidedoc

The Evolution of Regenerative Signaling

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

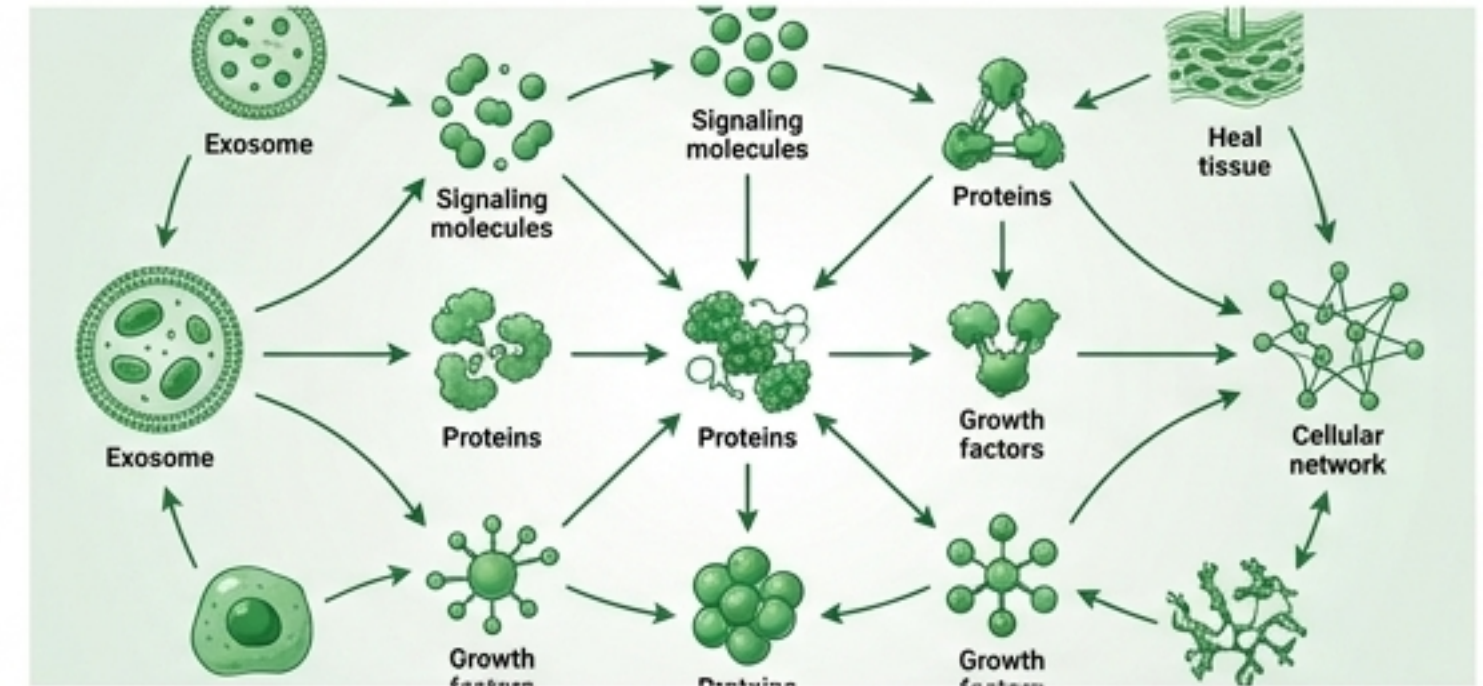


The Paradigm Shift: From Seed to Paracrine Reality



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

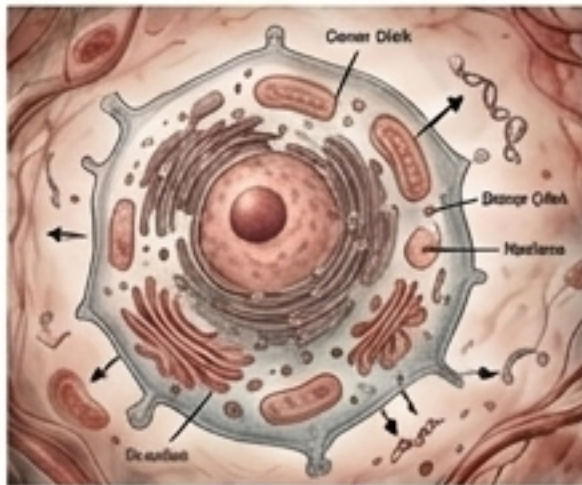
- Regenerative medicine has moved past the vehicle (the cell).
- Focus has entirely shifted to the Instructional Payload: Regenerative Signaling Factors (RSF).

Technology Evolution: The Path to Pure Signaling

v2.0: MSCs

Live Cellular Therapy

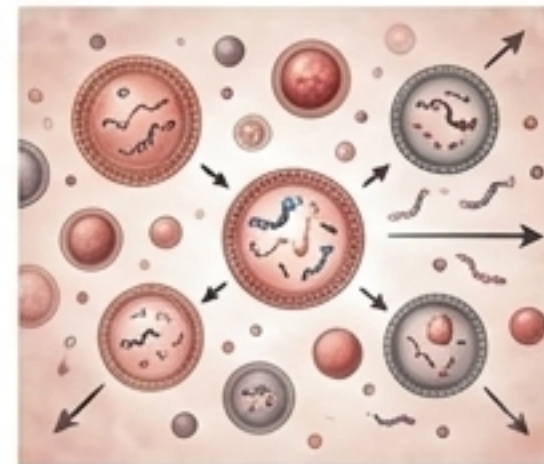
- Cumbersome live cells carrying foreign donor DNA.
- High biological noise.
- 5-10% GVHD risk.



v3.0: Exosomes

Acellular Vesicles

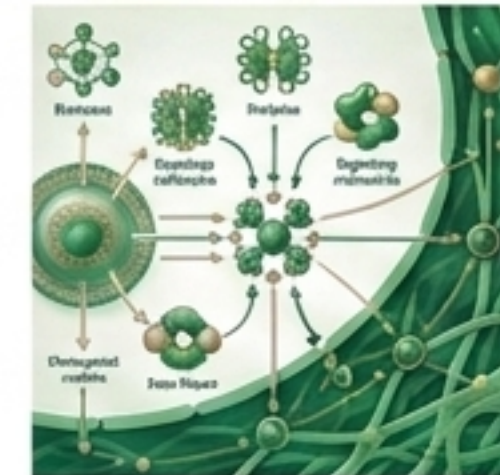
- Nanoparticles carrying inconsistent, volatile foreign RNA payloads.
- Subject to rapid washout.
- Single tissue source.



v4.0: RSF

Pure Signaling Matrix

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



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



LUNGS: First-pass pulmonary capillary trapping. MSCs (15-20 μ m) physically lodge in the pulmonary microvasculature (5-10 μ m diameter).



LIVER (12-22%): Kupffer cell-mediated phagocytosis. Hepatic sinusoidal filtration captures and destroys circulating foreign cells.



SPLEEN (5-12%): Reticuloendothelial filtration. The splenic red pulp filters damaged, apoptotic, and foreign cells from circulation.

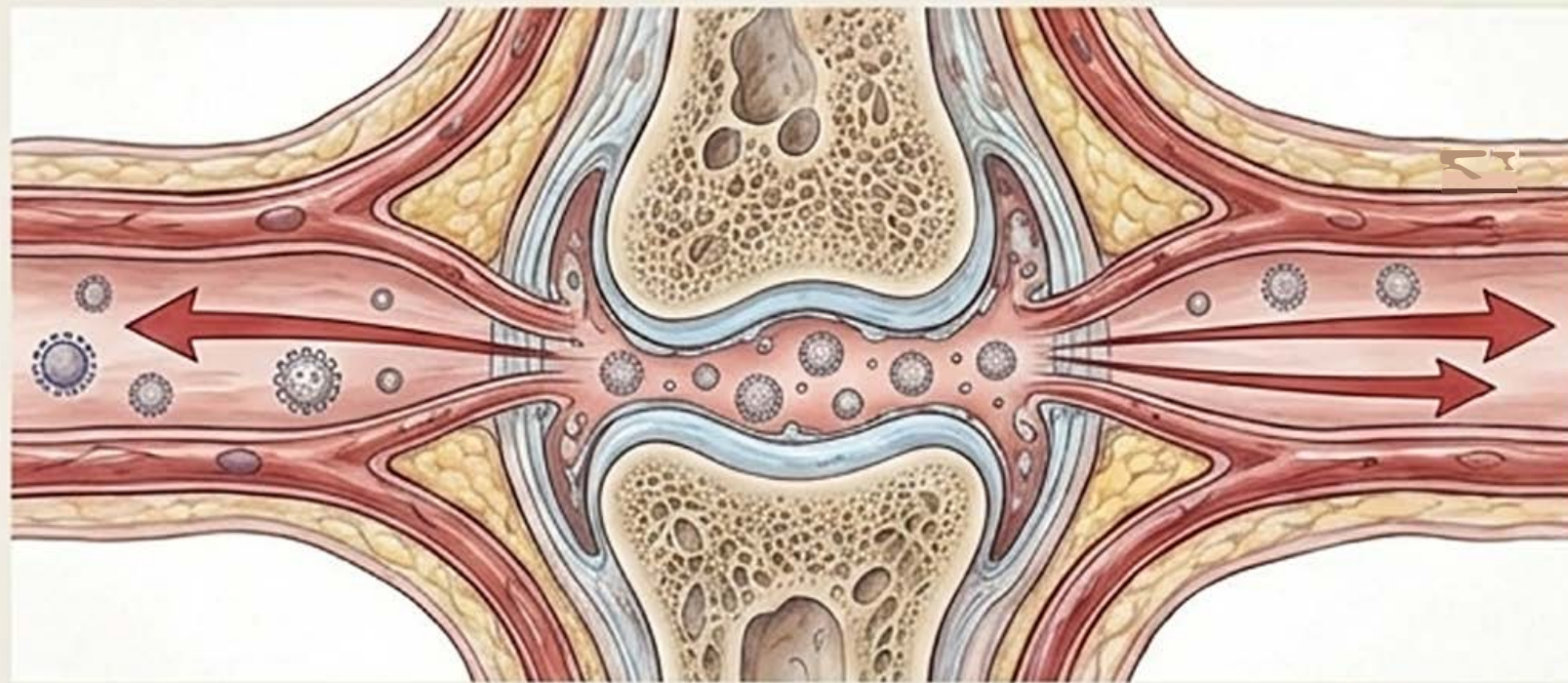


KIDNEYS (3-8%): Glomerular filtration barrier traps cellular debris and fragments, completing the systemic clearance cascade.

Conclusion: Live cells are structurally incompatible with highly inflamed, degenerative microenvironments.

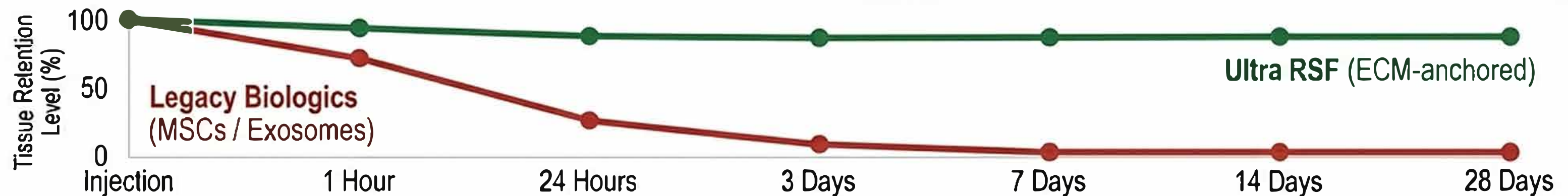
The Washout Phenomenon: Pharmacokinetic Failure

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



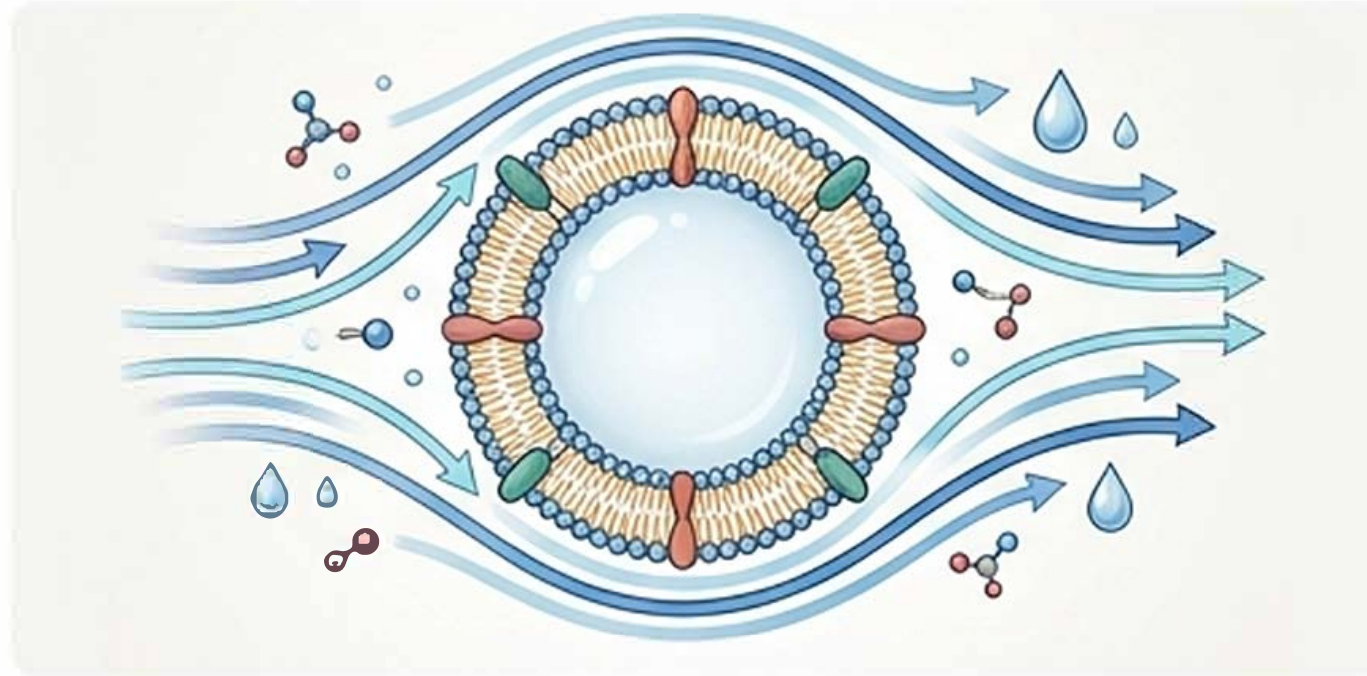
Legacy Biologics: MSCs and Exosomes
lack the structural ability to attach
themselves to host tissue.

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



Mechanical Anchoring vs. Washout

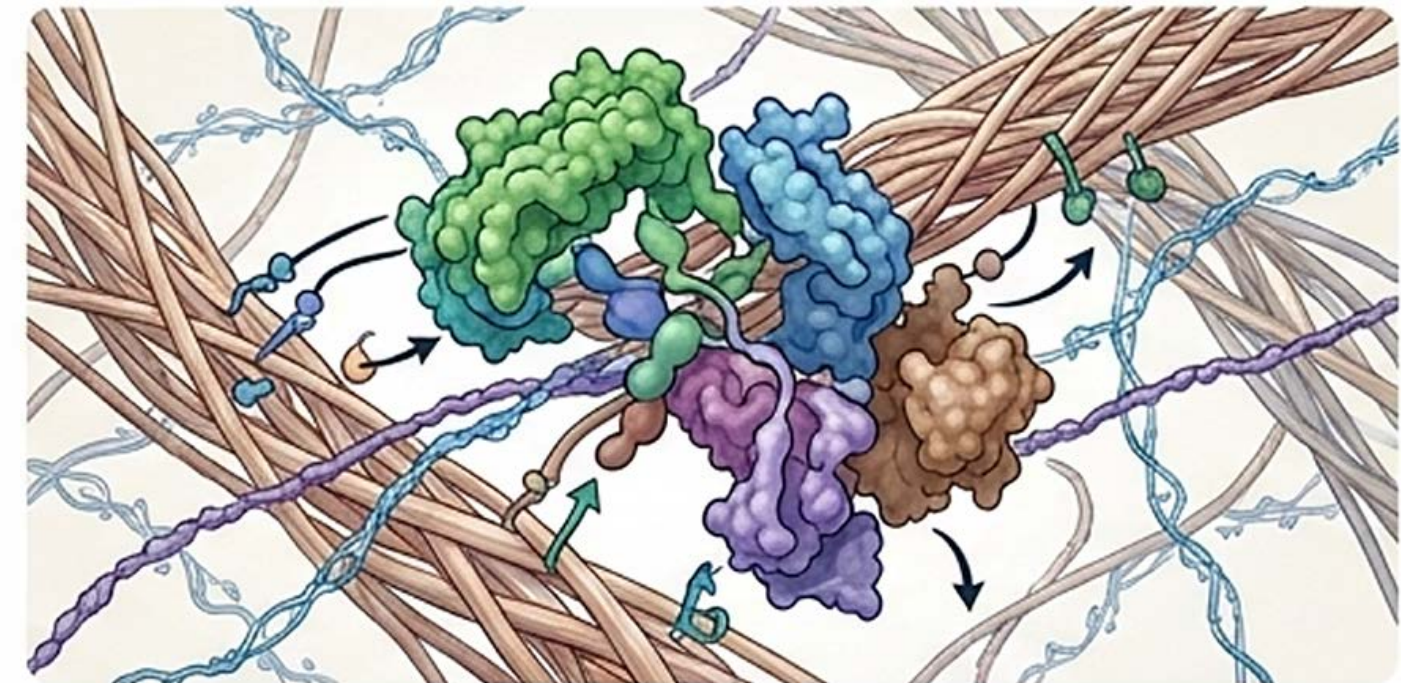
MSC / Exosomes



Mechanism: No ECM binding mechanism.

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

Ultra RSF / Version 4.0



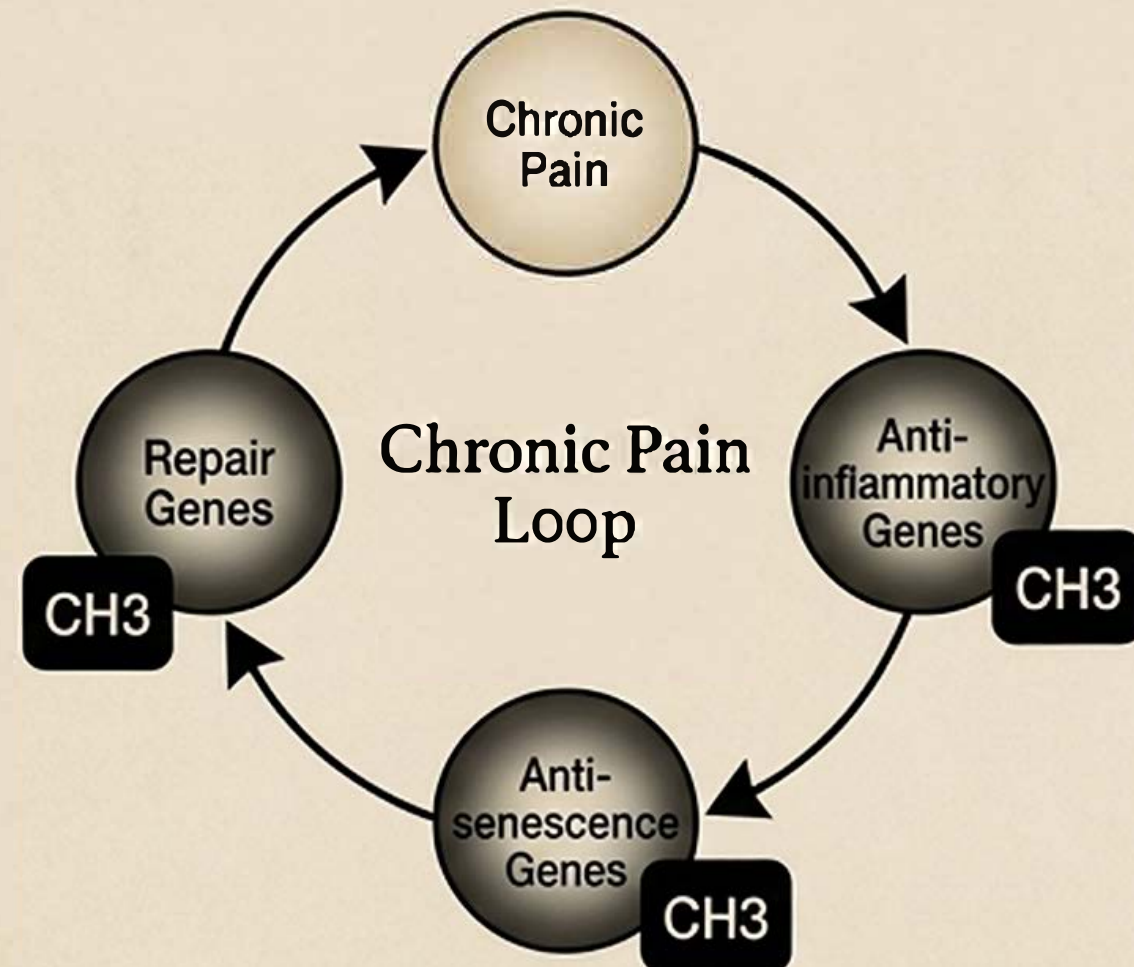
Mechanism: ECM Anchoring. Protein complex binds directly to host collagen and hyaluronic acid.

- **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

THE PROBLEM:

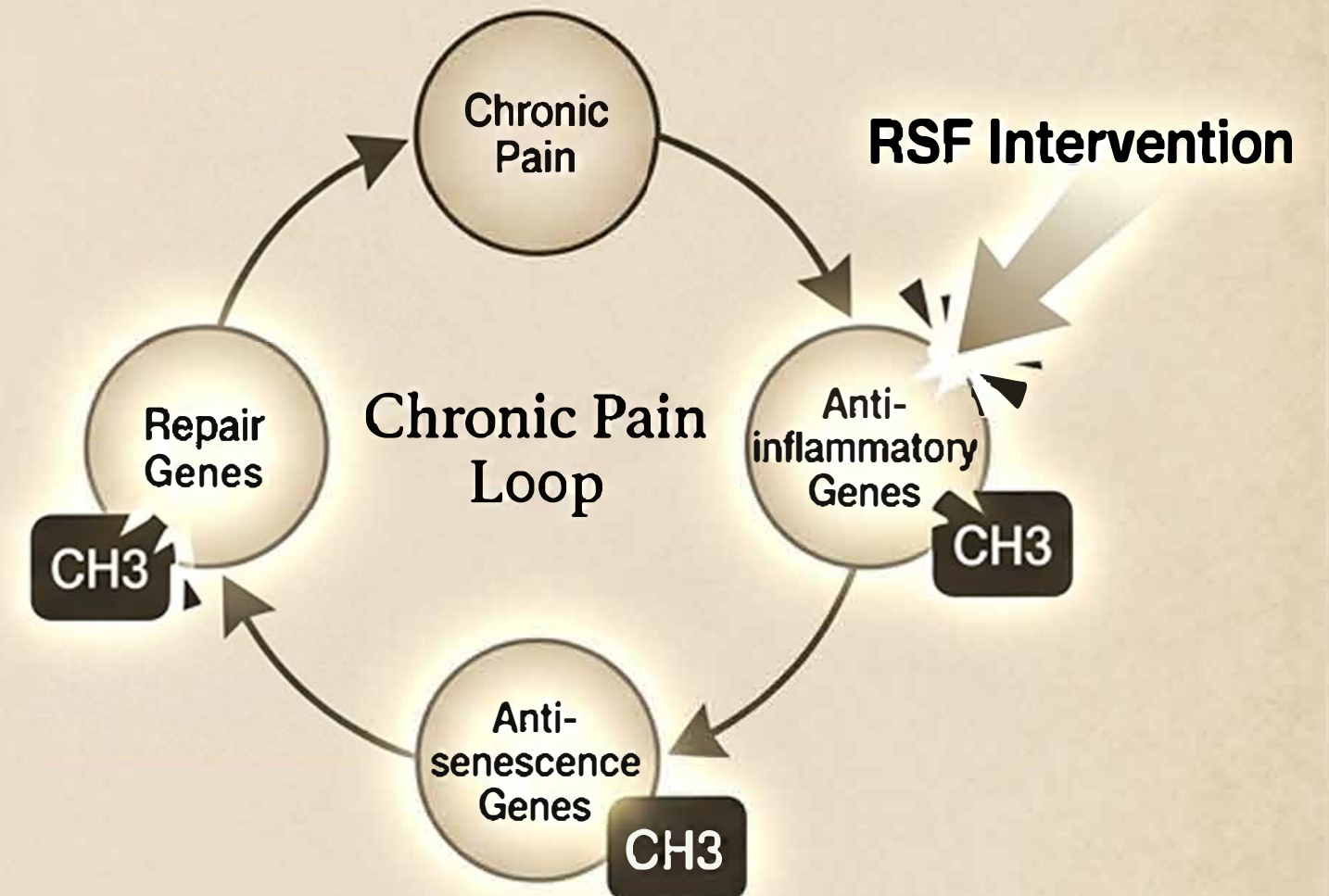
Chronic inflammation silences repair genes



Epigenetic methylation silences repair/anti-inflammatory/anti-senescence genes, creating a self-reinforcing degenerative cycle.

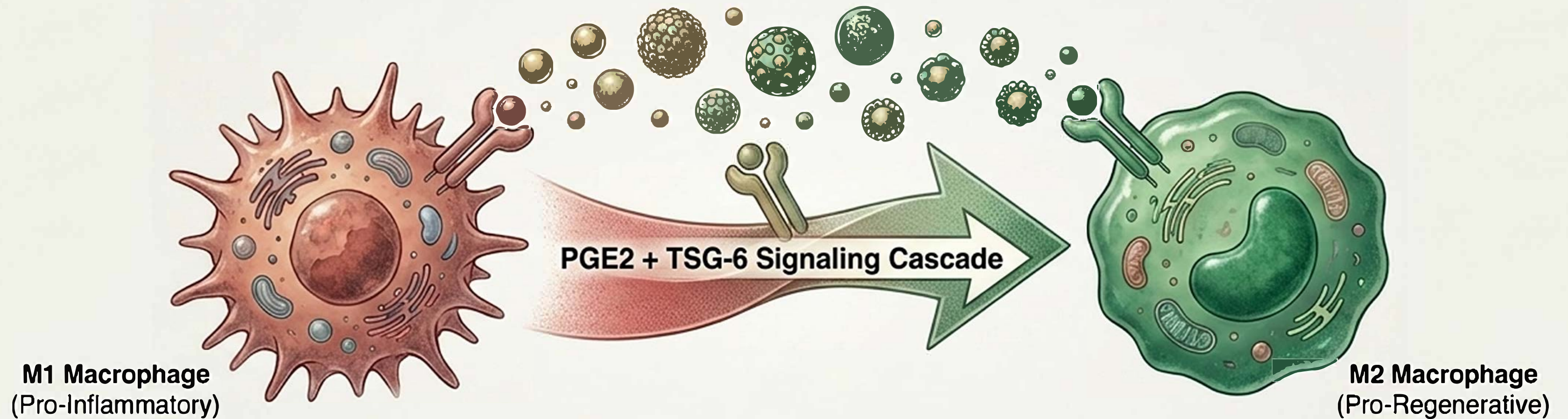
THE SOLUTION:

RSF reactivates silenced repair pathways



Concentrated signaling factors override methylation patterns, reactivating dormant regenerative gene expression. Outcome: Restoration of the body's native repair cascade.

Macrophage Polarization Cascade: M1 to M2 Phase Shift



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

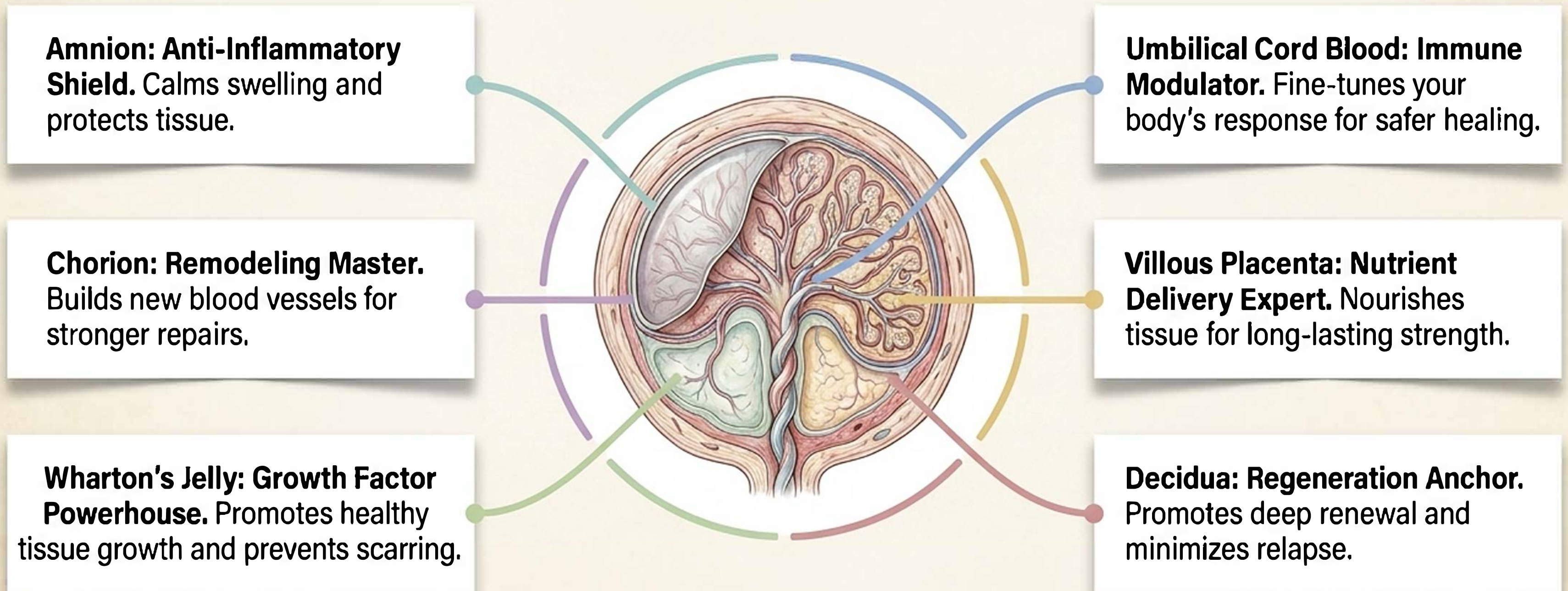
Pathway Specifics: Driven by concentrated PGE2 and TSG-6 pathway activation within the RSF matrix.
Placental Geography Source: AMNION (Primary). Umbilical cord amnion = 66% of PGE2 output.
TSG-6 constitutively expressed in amnion (unique: no TNF stimulation required).

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

Frontiers in Immunology (2019)
I McCoshen et al. *AJOG* (1989)

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.

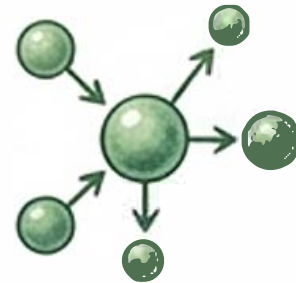


Amnion: The Anti-Inflammatory Command Center

Primary source of immunomodulatory analytes driving M1 to M2 macrophage conversion

PGE2 (Prostaglandin E2)

AMNION - Primary Source

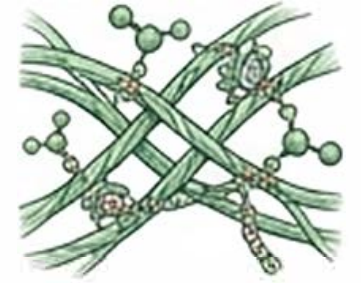


- AMNION (including amnion covering UC) = 66% of total PGE2 output before labor
- AM-MSCs produce highest PGE2 among all placental MSC populations
- EP2/EP4 receptor binding on macrophages converts M1 to M2 phenotype
- T-cell suppression via cAMP-PKA signaling
- Upregulates VEGF expression for angiogenesis via COX-2 pathway

McCoshen et al. AJOG 1989; Wu et al. Sci Rep 2018

TSG-6 (TNFAIP6)

AMNION - Constitutive Expression



- Unique: Constitutively expressed by amnion epithelial and stromal cells — no TNF stimulation required
- Only known extrahepatic tissue producing both Ial and TSG-6 for endogenous HC-HA complex formation
- NF-κB suppression via CD44 binding on resident macrophages
- Inhibits neutrophil extracellular trap (NET) formation
- ECM remodeling: binds hyaluronan, chondroitin sulfate, aggrecan

Zhang et al. J Biol Chem 2012; Rodas-Junco et al. Sci Rep 2017

Amnion PGE2 + TSG-6 = Primary M1 to M2 Conversion Pathway in RSF

Cord Blood & Wharton's Jelly: Youth Factor Reservoirs

Primary sources of anti-senescence and neuroregenerative factors

GDF11 (Growth Differentiation Factor 11)

CORD BLOOD MSCs - Primary

- **UCB-MSCs express GDF11 at >100x higher levels than bone marrow or adipose MSCs**
- **Reverses age-related hypertrophy — restores tissue elasticity in cardiac, skeletal muscle, and neural systems**
- Stimulates ECM synthesis: collagen I/III, fibronectin, elastin production while suppressing MMP-1
- Enhances angiogenesis via VEGF/HGF upregulation through PI3K/Akt signaling
- Smad2/3 pathway modulation rejuvenates stem cell populations

Kim et al. Biochem Biophys Res 2018; Zhao et al. Stem Cell Res Ther 2021

TIMP2 (Tissue Inhibitor of MMPs 2)

CORD BLOOD Plasma & **Wharton's Jelly**

- Markedly enriched in cord blood plasma vs. adult plasma — recognized as a principal 'youth-associated' factor
- **WJ contains ~8,664 pg/mL TIMP2 — one of the highest-concentration cytokines in WJ formulations**
- Revitalizes hippocampal function in aged mice — restores dendritic spine plasticity and adult neurogenesis
- Inhibits MMP-1, -2, -3, -7, -8, -9, -13, -14 — prevents premature ECM degradation
- Anti-angiogenic activity independent of MMPs via integrin signaling

Castellano et al. Nature 2017; Farberg et al. J Orthop Surg Res 2020

GDF11 + TIMP2 = Anti-Senescence & Neuroregenerative Core of RSF

Chemotaxis, DAMP Signaling & Major Analyte Networks

How the placental secretome orchestrates immune cell recruitment, danger sensing, and tissue remodeling

Chemotaxis

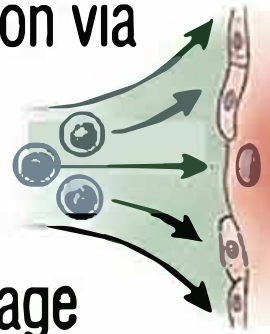
Stem Cell Homing & Immune Recruitment

SDF-1 / CXCL12 (Chorionic Villi)

- Creates chemotactic gradient recruiting CXCR4+ MSCs to injury sites
- Promotes trophoblast invasion via RhoA/Rock pathway

MCP-1 / CCL2 (Decidua)

- Primary monocyte/macrophage chemoattractant
- Supports M1 to M2 transition in wound healing



Kim et al. Biochem Biophys Res 2018

DAMP Signaling

Danger Sensing & Alarm Response

HMGB1 (Amnion + WJ)

- Alarmin signaling via RAGE and TLR2/TLR4 receptors
- Activates NF- κ B and MMP-9 for tissue remodeling
- Recruits repair cells to damage sites



Annexin A1 (Villous Placenta)

- Anti-inflammatory DAMP modulator
- Suppresses PGE2 overproduction via cPLA2 inhibition
- FPR-mediated inflammation resolution

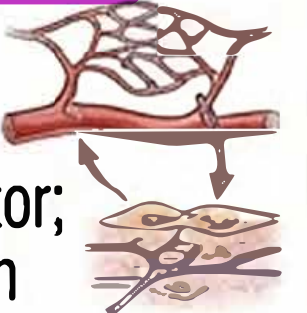
Zhao et al. Villous Sell Cell Res 2018

Growth & Repair

Angiogenesis & ECM Homeostasis

VEGF & HGF (Decidua/Chorion)

- Drives angiogenesis and neovascularization
- Tissue repair via MET receptor; promotes Treg differentiation



TGF- β 1 & IL-10 (Amnion/Decidua)

- Master anti-inflammatory signals
- ECM protection; Treg induction; anti-scar signaling
- M2 macrophage polarization

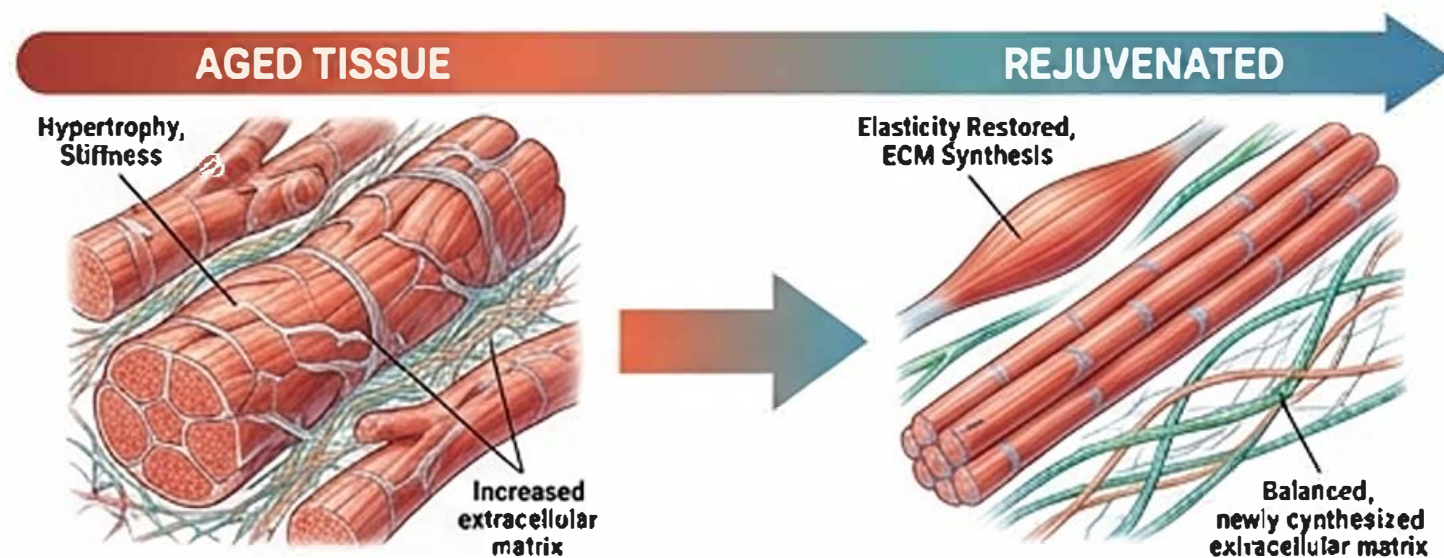
Zhang et al. J Biol Chem 2017; J Jorthop Res 2020

Placental Secretome = Integrated Network for Immune Modulation & Tissue Regeneration in RSF

Combating Senescence: GDF11 and TIMP2 Youth Factors

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

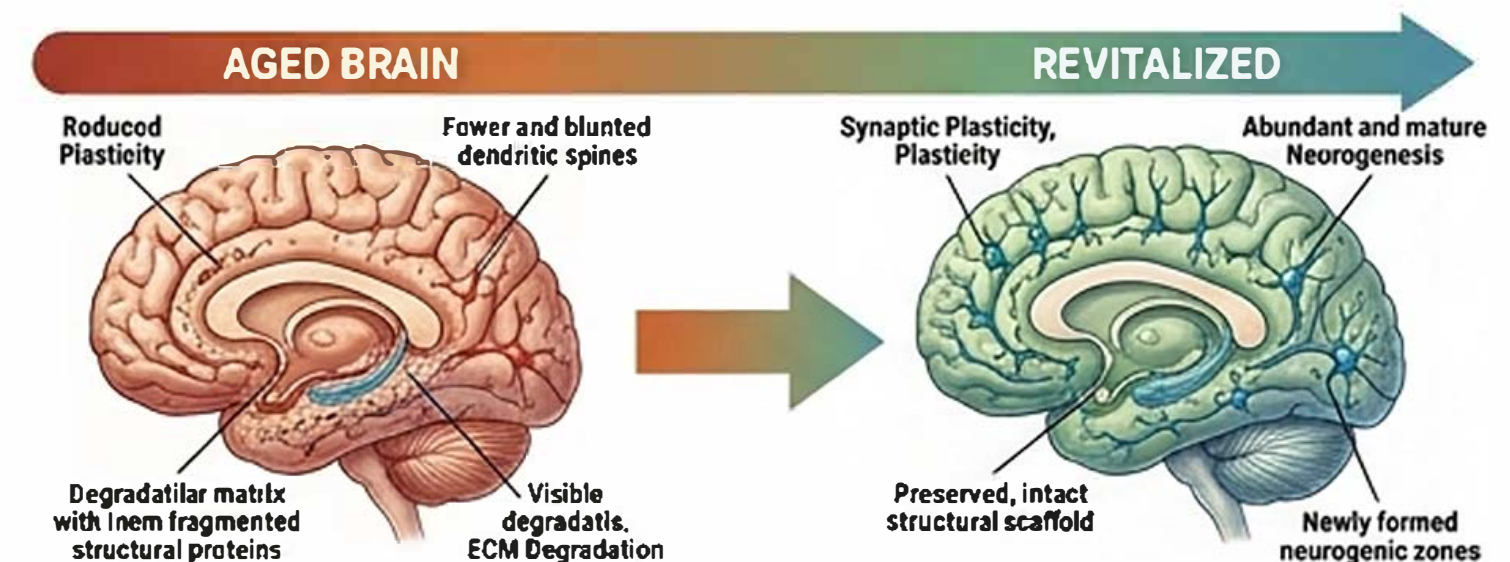
GDF11 (Growth Differentiation Factor 11)



- Reverses age-related hypertrophy and restores tissue elasticity.
- Pathway: Modulates the Smad2/p21 signaling pathway to rejuvenate stem cell populations.
- Stimulates collagen I/III and elastin synthesis while suppressing MMP-1.

Nature Communications: "GDF11 Rejuvenates Aging Tissues"

TIMP2 (Tissue Inhibitor of MMPs 2)

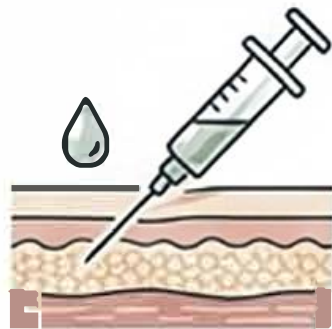


- Revitalizes aged neurogenic capabilities and halts extracellular matrix degradation.
- Restores hippocampal dendritic spine plasticity and adult neurogenesis (dentate gyrus).
- Inhibits MMP-mediated ECM breakdown, preserving structural scaffold for regeneration.

Castellano et al. *Nature* 2017: "TIMP2 as a Systemic Youth Factor"

Administration Modalities

At-Home Delivery & Patient Empowerment



Subcutaneous: Self-administered abdominal injection. Simple, painless, 30-second protocol.

Targeted Home Utility: Upper arm and specific site injections for localized therapy.



Intra-Nasal Delivery: Non-invasive nasal administration for CNS-targeted signaling.

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

In-Office Administration



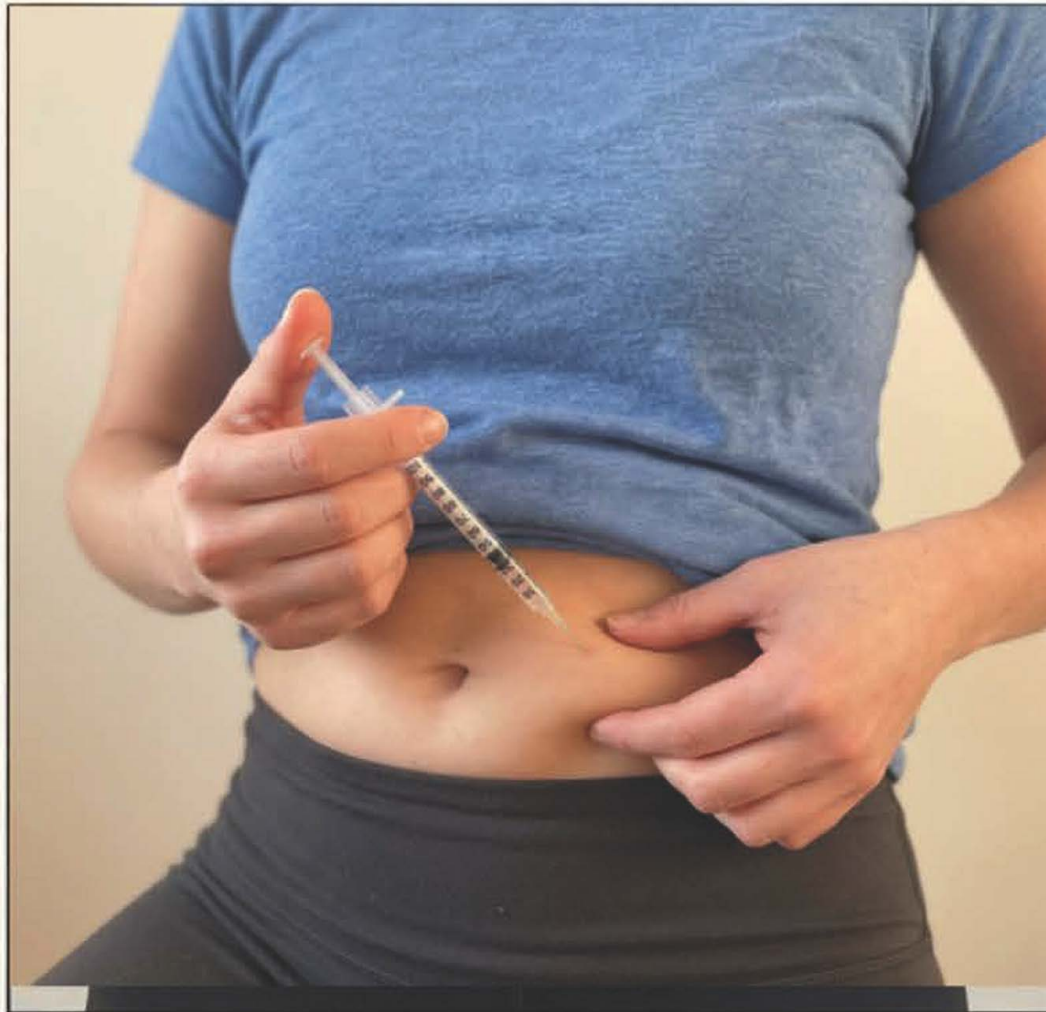
IV Infusion Therapy: Physician-supervised intravenous delivery for systemic regenerative signaling. Ideal for whole-body anti-aging, neurological support, and multi-system conditions.



Intra-Articular with Ultrasound: Ultrasound-guided precision injection directly into joint capsules. ECM anchoring ensures signals remain at the target tissue for up to 4 weeks.

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

At-Home Delivery & Patient Empowerment



Subcutaneous Simplicity.



Targeted Home Utility.



Intra-Nasal Delivery.

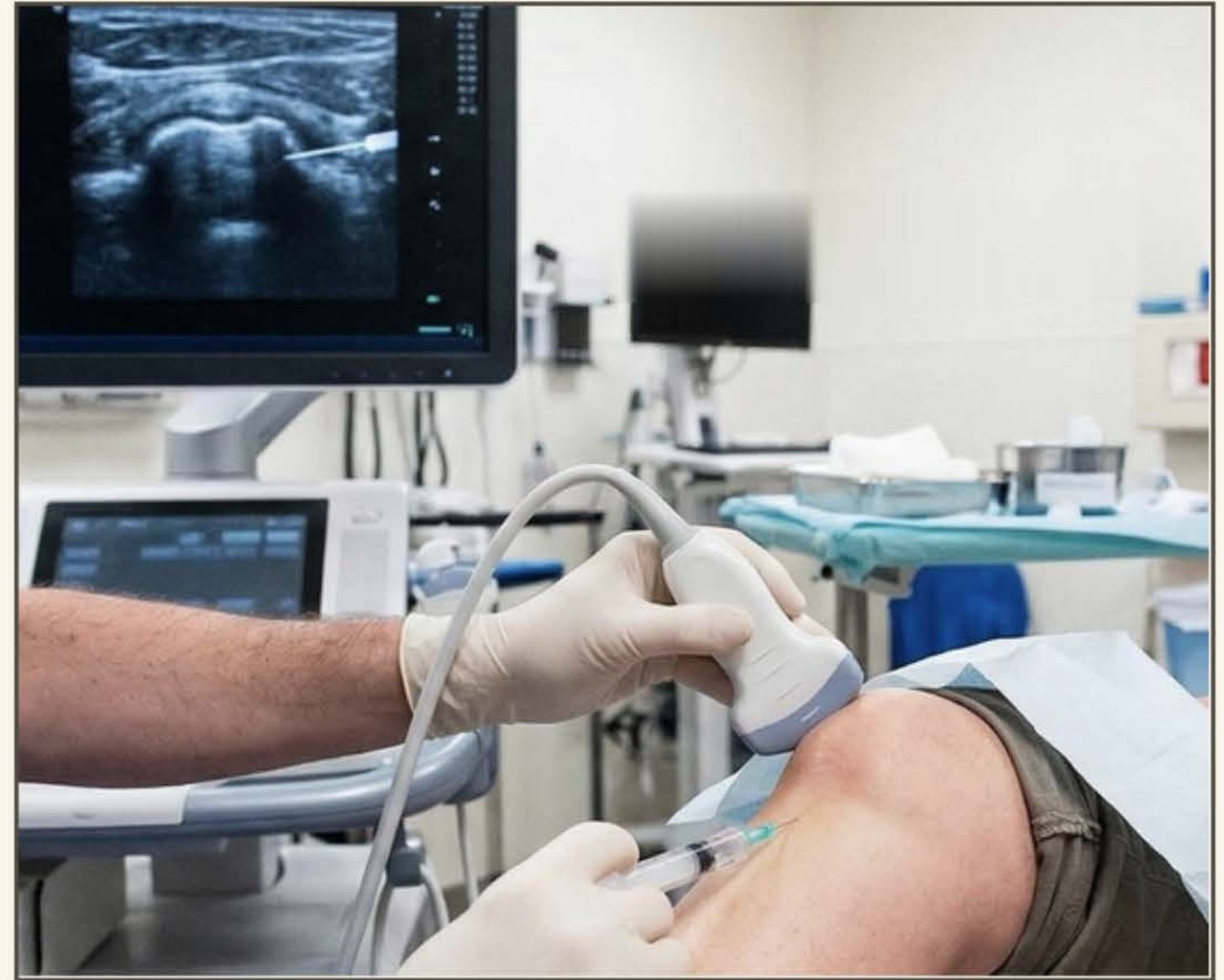


At-Home: Room-temp stable (24 months). No thawing. No “bio-baggage.”

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

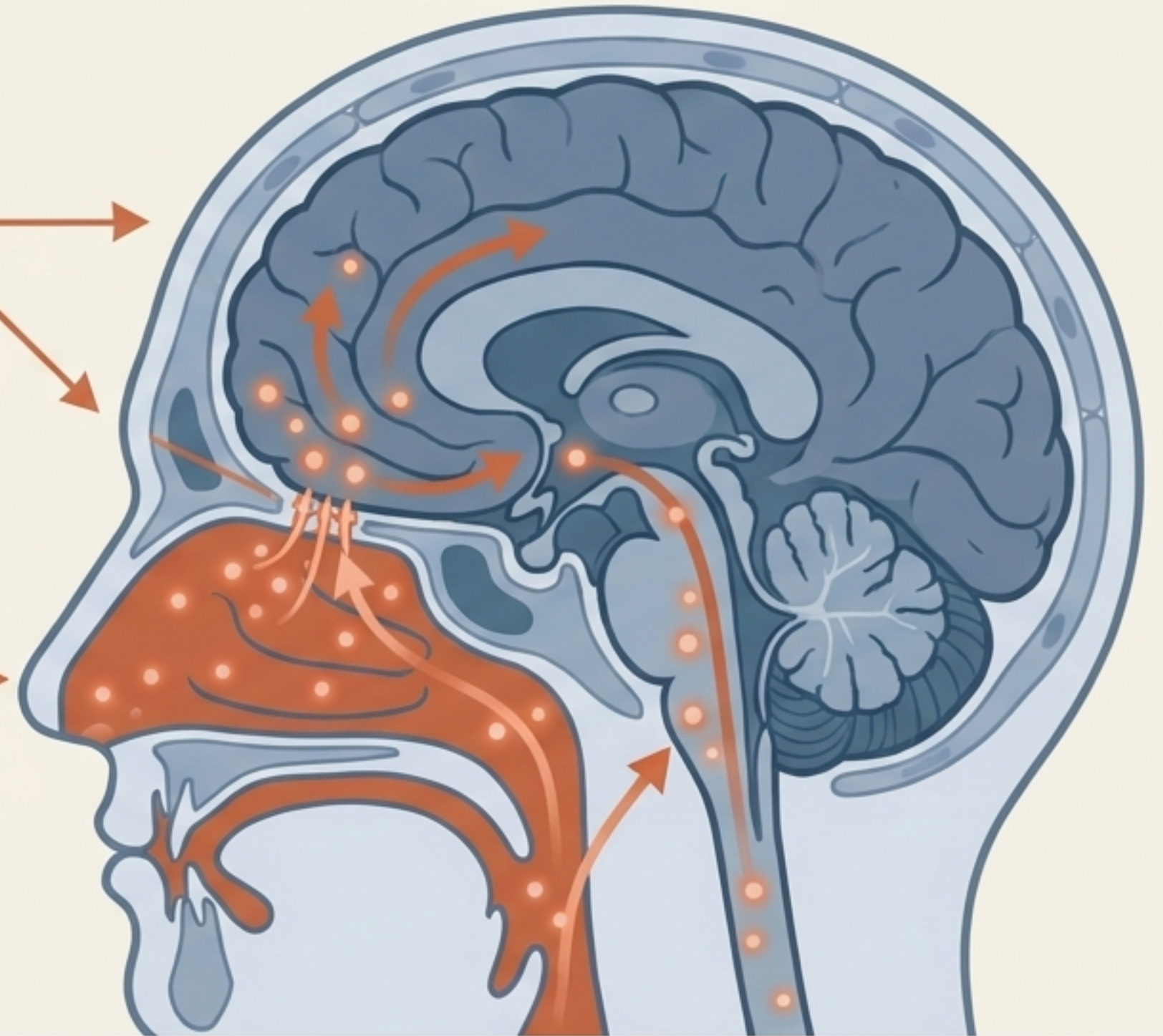
The nasal cavity's unique anatomy provides a direct connection to the CNS, bypassing the Blood-Brain Barrier.

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. This pathway enables proteins and growth factors to reach the hippocampus and cortical regions within hours of administration.

Trigeminal Nerve Pathway

Transport along trigeminal nerve bundles, providing access to the brainstem and more caudal brain regions. This secondary route ensures broad CNS distribution and complements the olfactory pathway for comprehensive



Intranasal RSF: Non-invasive, BBB-bypassing delivery for neurodegenerative conditions

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

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

Why Ultra RSF Qualifies as Section 361

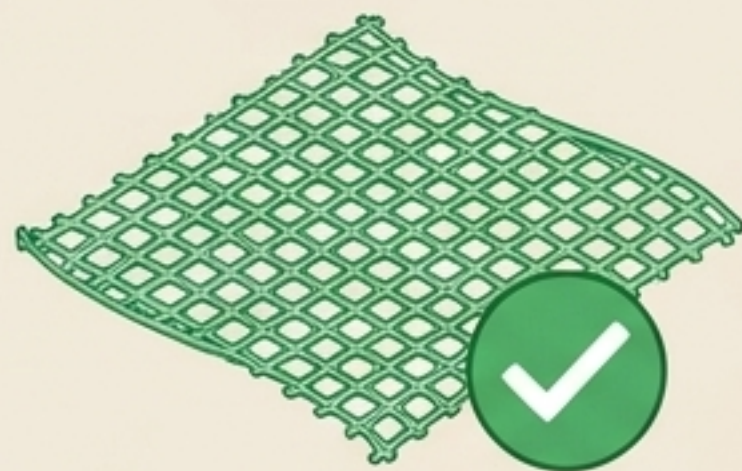
- ✓ Minimal Manipulation
- ✓ Homologous Use
- ✓ Not Combined
- ✓ No Systemic Effect

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



Section 361 — Tissue.
Ready for Clinical Use



Section 351 — Drug.
Years of Clinical Trials

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.

FEATURE		Ultra RSF (Section 361)	RMAT Products (Section 351)
1	Classification	Human Cell & Tissue Product (HCT/P)	Biologic Drug
2	Regulation	21 CFR 1271.10(a)	BLA / IND Required
3	Clinical Trials	Not Required	Years of FDA-Monitored Trials
4	Availability	Immediate Clinical Use	Pending FDA Approval
5	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

PAs & 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
- RMAT 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) ✖	Yes (Volatile RNA) ✖	ZERO (100% Acellular) ✔
GVHD / Immune Risk	5-10% Risk ✖	Moderate ✖	None ✔
Local Retention Time	3-7 Days ✖	1-3 Days ✖	Up to 28 Days (ECM Anchoring) ✔
Storage Requirements	Cryofreezing (-80°C)	Cryofreezing (-80°C)	Room Temperature (2 Years) ✔
Tissue Source	1 Placental Region ✖	1 Placental Region ✖	All 6 Placental Geographies ✔

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

MSCs (v2.0)

Local Retention Time:
3-7 Days **X**

X

4x

Tissue Source:
1 Placental Region **X**

X

6x

DNA/RNA Baggage:
Yes (Foreign DNA) **X**

X

GVHD / Immune Risk:
5-10% Risk **X**

X

Storage Requirements:
Cryofreezing (-80°C) **X**

X

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 Retention x 6x Tissue Diversity = 24x Signal Potency



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 x 6x Tissue Diversity = 60x Signal Potency





The Bottom Line

Ultra RSF makes Legacy Biologics — like MSCs 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
- Traceable analyte geography: each signaling factor mapped to its placental origin

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