CELL & GENE THERAPIES FOR MUSCULOSKELETAL CONDITIONS

MHSRS 2026

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DISCLOSURE OF RELEVANT FINANCIAL RELATIONSHIP(S) WITH INELIGIBLE COMPANIES

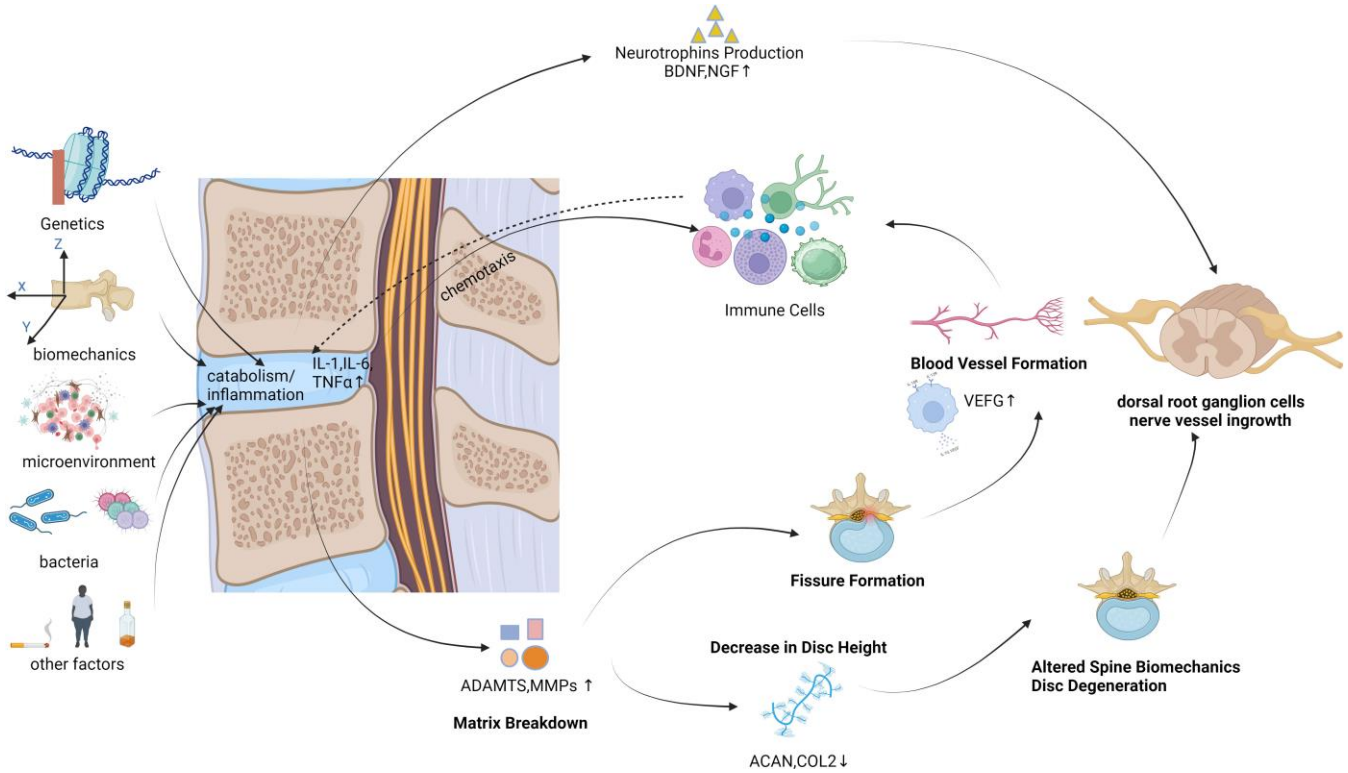
Engineered Mesenchymal Stem Cell-derived Extracellular Vesicles Deliver Complementary IL-1Ra And GH-1 Bioactive Cargos To Enable Disc Regeneration

- Provisional Patent

LEARNING OBJECTIVES

- Understand The Immune-degeneration Feedback Loop In Disc Disease
- Learn How Engineered MSC Evs Can Deliver Protective Biologics
- Appreciate Why Dual Cargo (Il-1Ra + GH-1) Is Required For Structural Preservation

Inflammation Drives A Self-reinforcing Degenerative Loop In Intervertebral Discs



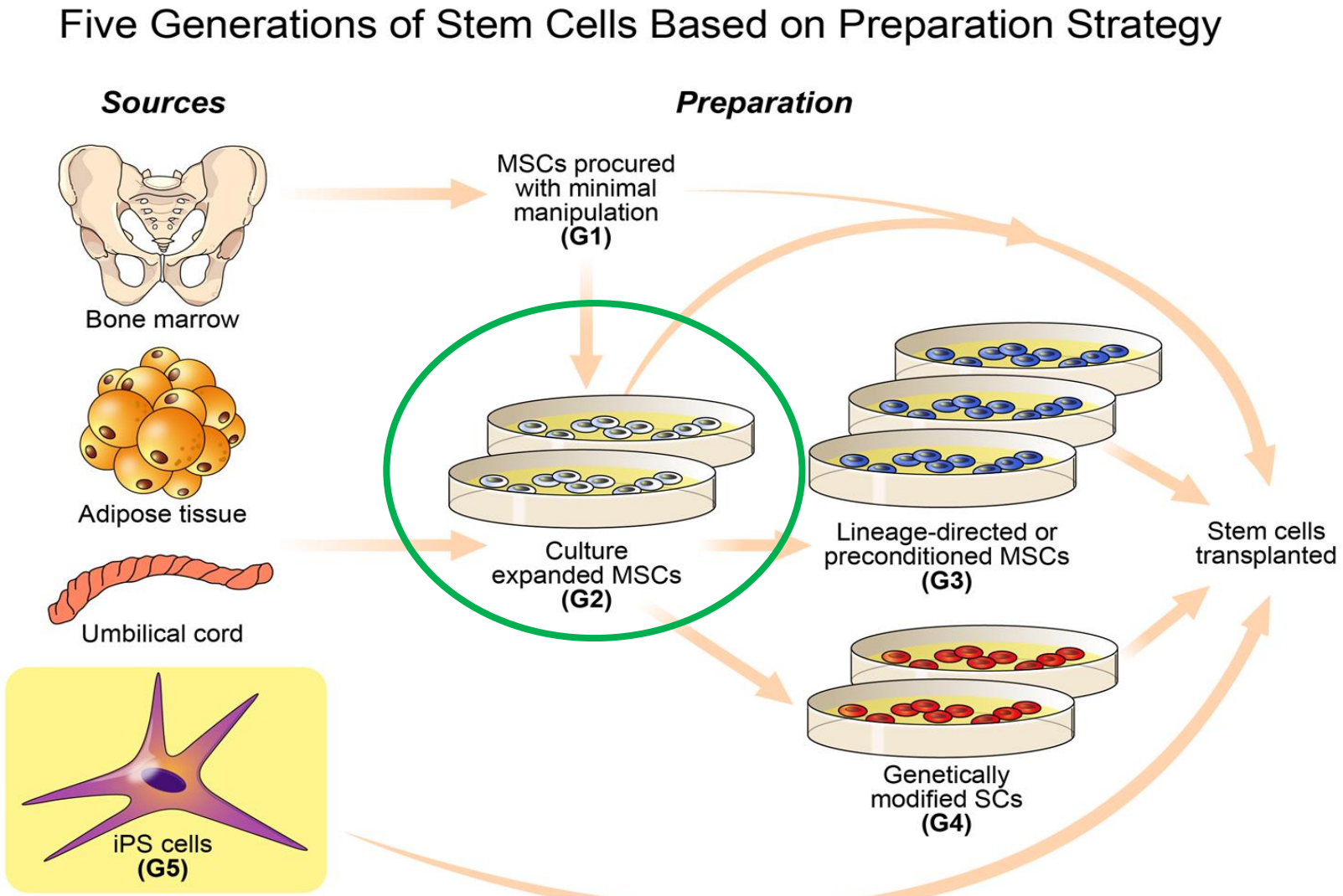
The Problem: Disc degeneration is inflammation-locked

- IL-1-driven inflammation sustains matrix breakdown
- Protease-rich disc environment limits biologic durability
- Regeneration fails without immune reset

Front. Cell. Infect. Microbiol., 29 January 2024
Intervertebral disc inflammation and degeneration: immune mechanisms and pathological consequences.
doi:10.3389/fcimb.2024.1303645

MAYO CLINIC

Historical Progress of Cell & Gene Therapy



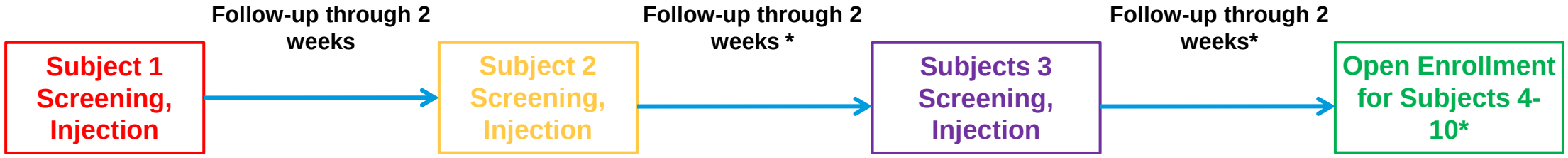
Qu et al, Journal of the American Academy of Regenerative Medicine 1:1 (2

CellKine 1: Facet-Mediated Low Back Pain

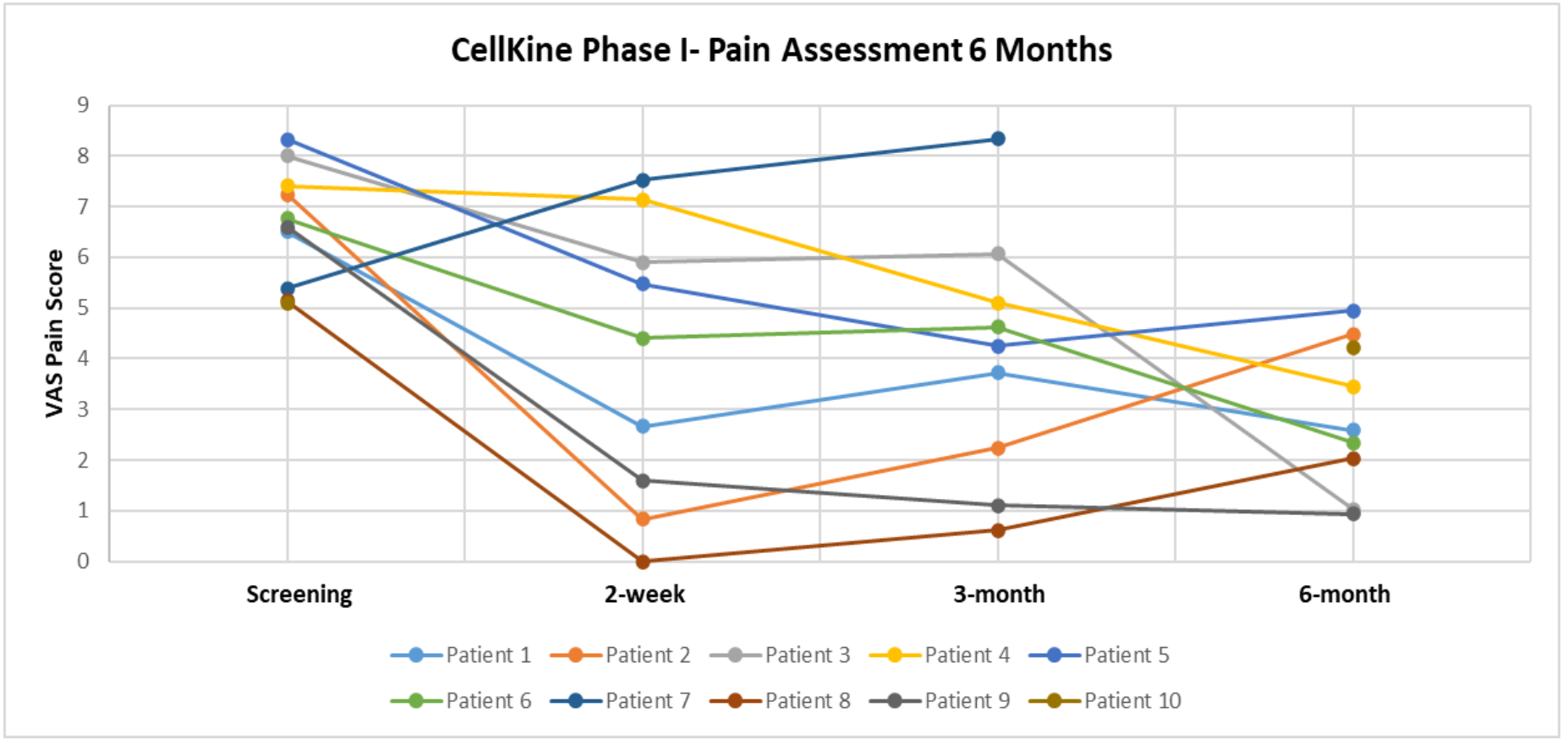
- **Sponsor**: Gerstner Family Foundation
- **Study Information**
  - **Title:** Cellkine: Phase I study evaluating the safety and feasibility of allogeneic, culture-expanded bone marrow-derived mesenchymal stem cells in subjects with painful lumbar facet joint arthropathies
  - **IRB** # 20-000330
    - Approval: 28-April-2020
  - **PI:** W. Qu
  - **IND # 19593**
  - **Study Drug Description**
    - Clinical grade, allogeneic, culture expanded BM-MSCs produced by the Mayo Clinic Human Cellular Therapy Laboratory in FL, Jacksonville using cGMPs and previously established standard operating procedures (SOPs).

CellKine 1: Facet-Mediated Low Back Pain

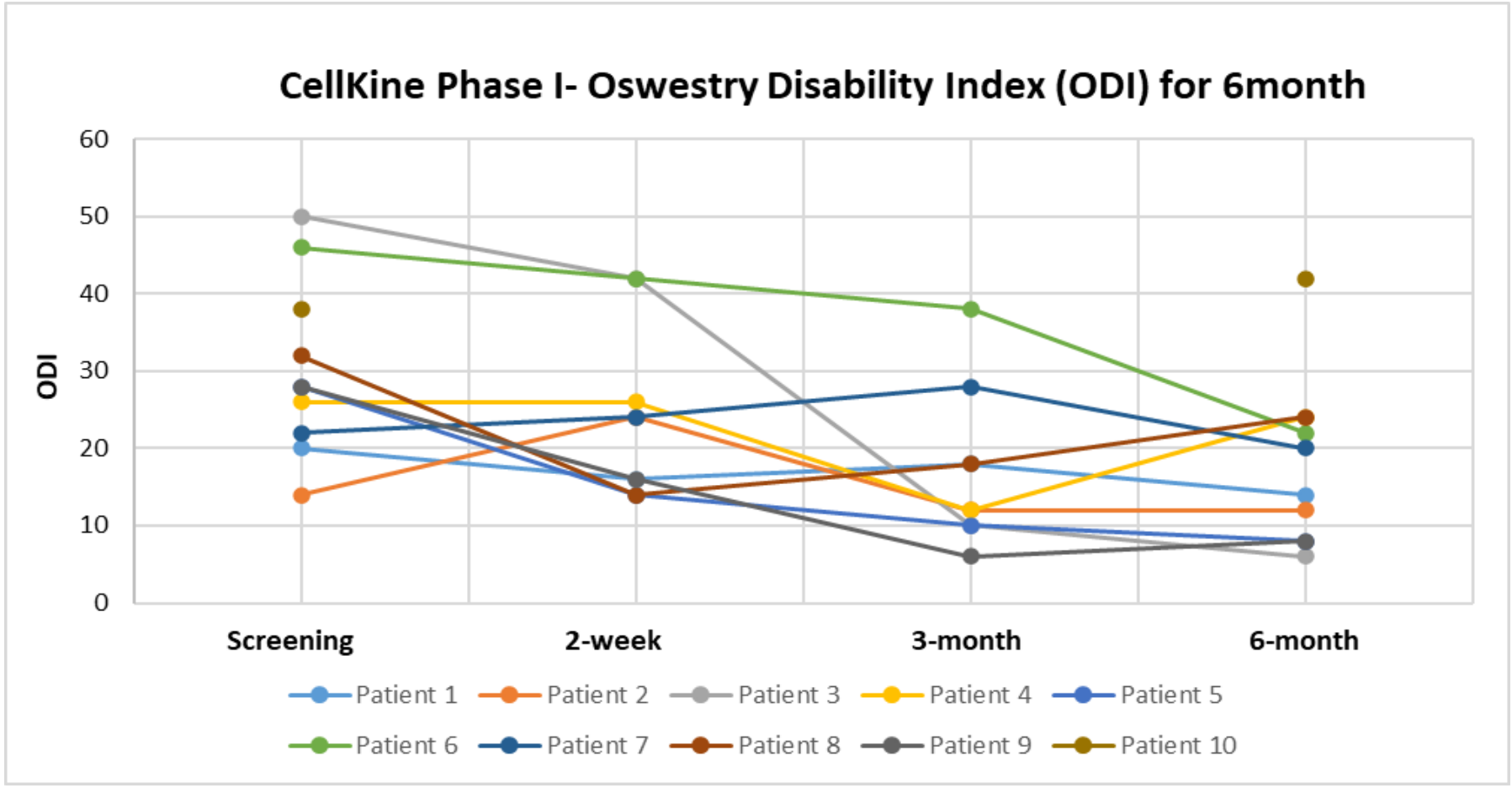
- **Study Design**
  - **Prospective Phase I Safety Study**
    - 10 patients (non-blinded); Allogenic BM-MSC 10 mil/joint x2
  - **Primary Objective**
    - Nature, incidence and severity of Adverse Events (AEs)
  - **Secondary Objectives**
    - Pain score
    - Functional status
    - Radiological and laboratory assessments
  - **Staggered Enrollment Plan**



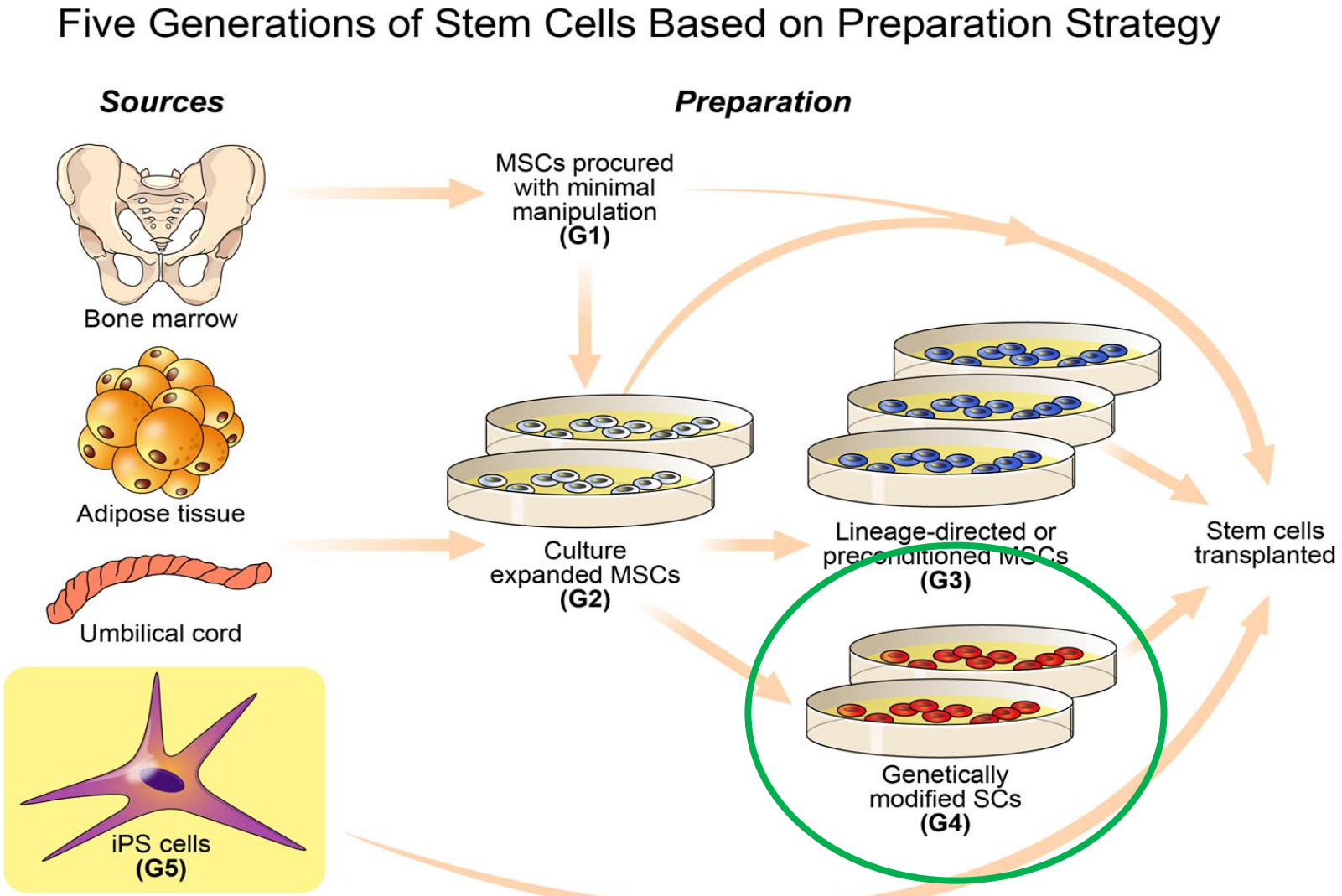
CellKine 1:Facet-Mediated Low Back Pain (VAS)



CellKine 1:Facet-Mediated Low Back Pain



Historical Progress of Cell & Gene Therapy



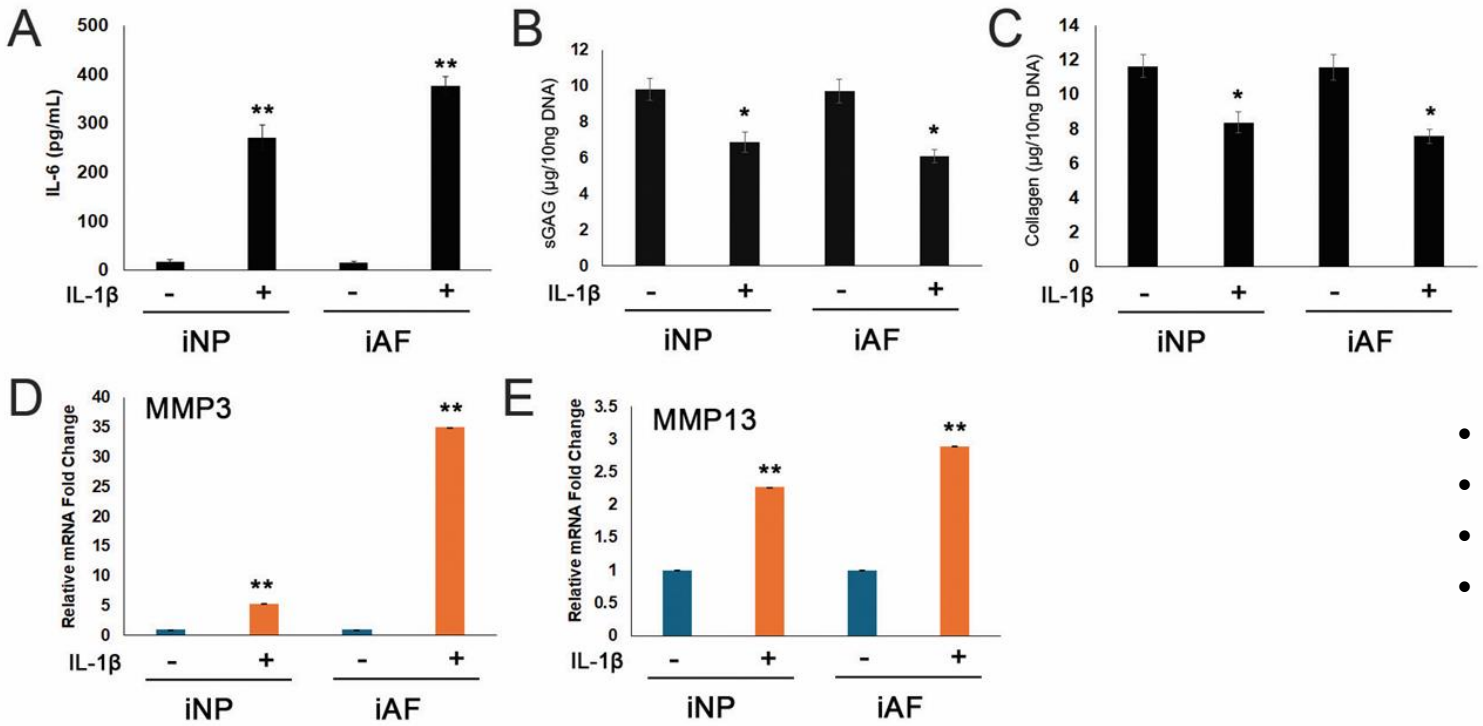
Qu et al, Journal of the American Academy of Regenerative Medicine 1.1 (2

A Combined Stem Cell and Gene Therapy for Degenerative Disc Disease

- **Study Title:** IL-1Ra and GH-1 Transduced BM-MSCs using mRNA Technology for the Treatment of Degenerative Disc Disease

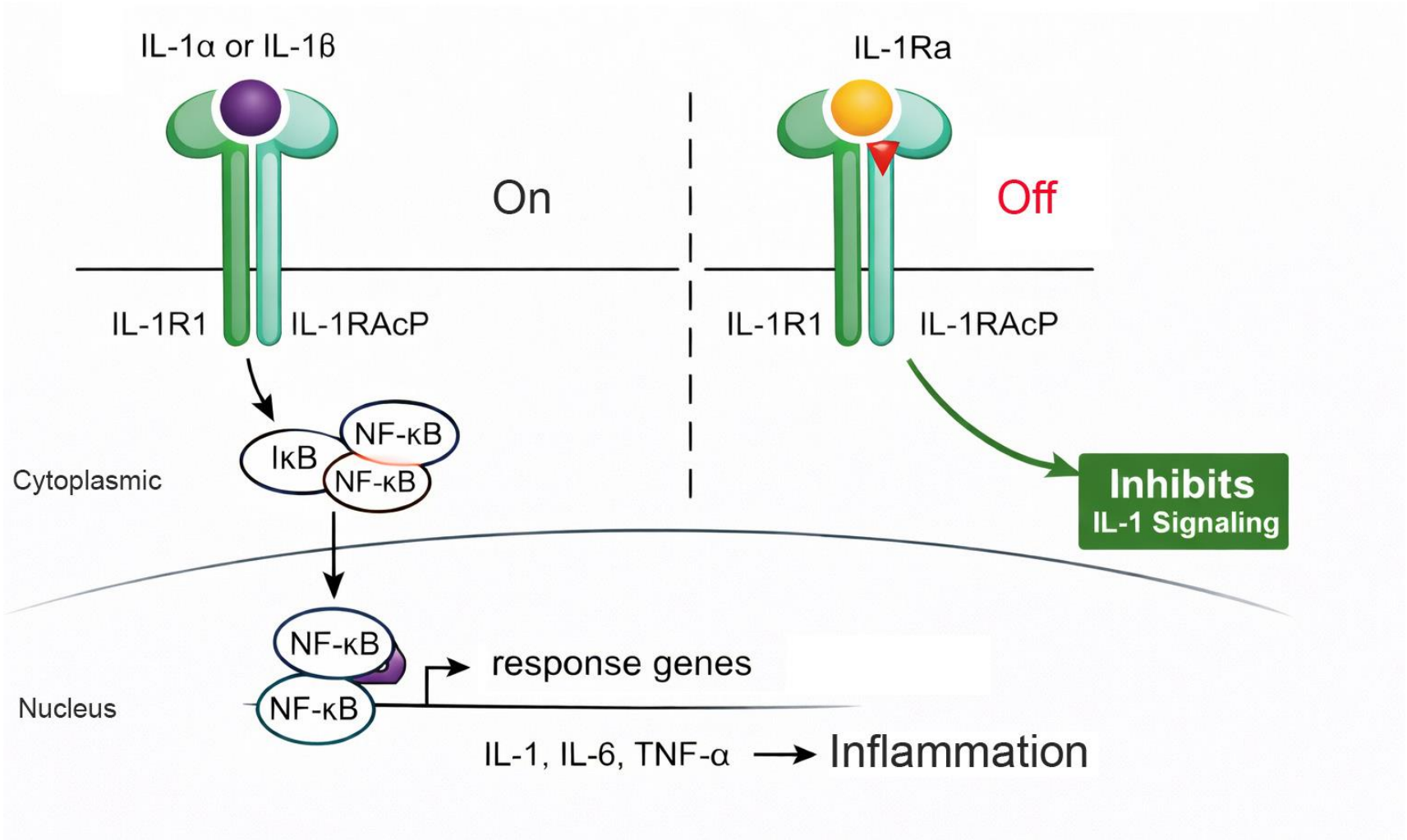
  - Genetically modified MSCs producing specific proteins targeting core molecules to interrupt pathophysiological processes – IL1Ra and GH-1
  - IL-1Ra: Added effect to MSC's immunomodulatory functions
  - GH-1: Added effects to matrix protection

IL-1β drives degenerative signaling in NP/AF spheroids

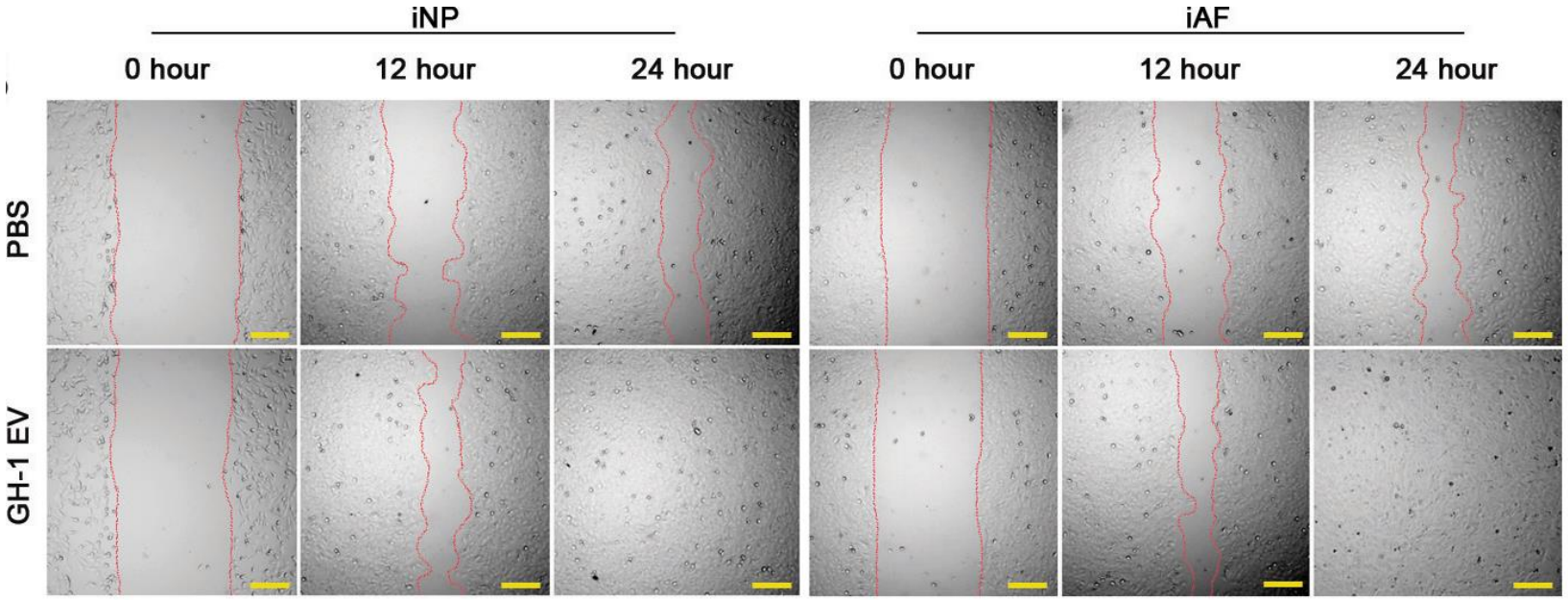


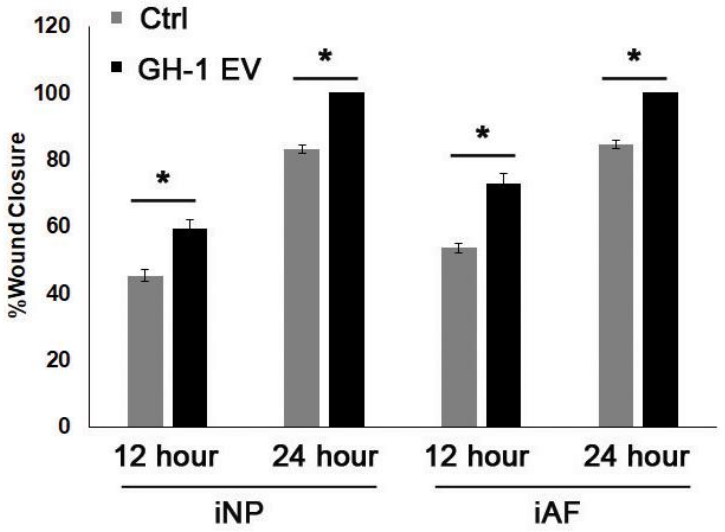
- Upregulation of catabolic enzymes
- Promotes ECM degradation
- Phenocopies degeneration
- Matrix Metalloproteinases upregulation

IL-1 signaling drives inflammatory degeneration and is competitively inhibited by IL-1Ra

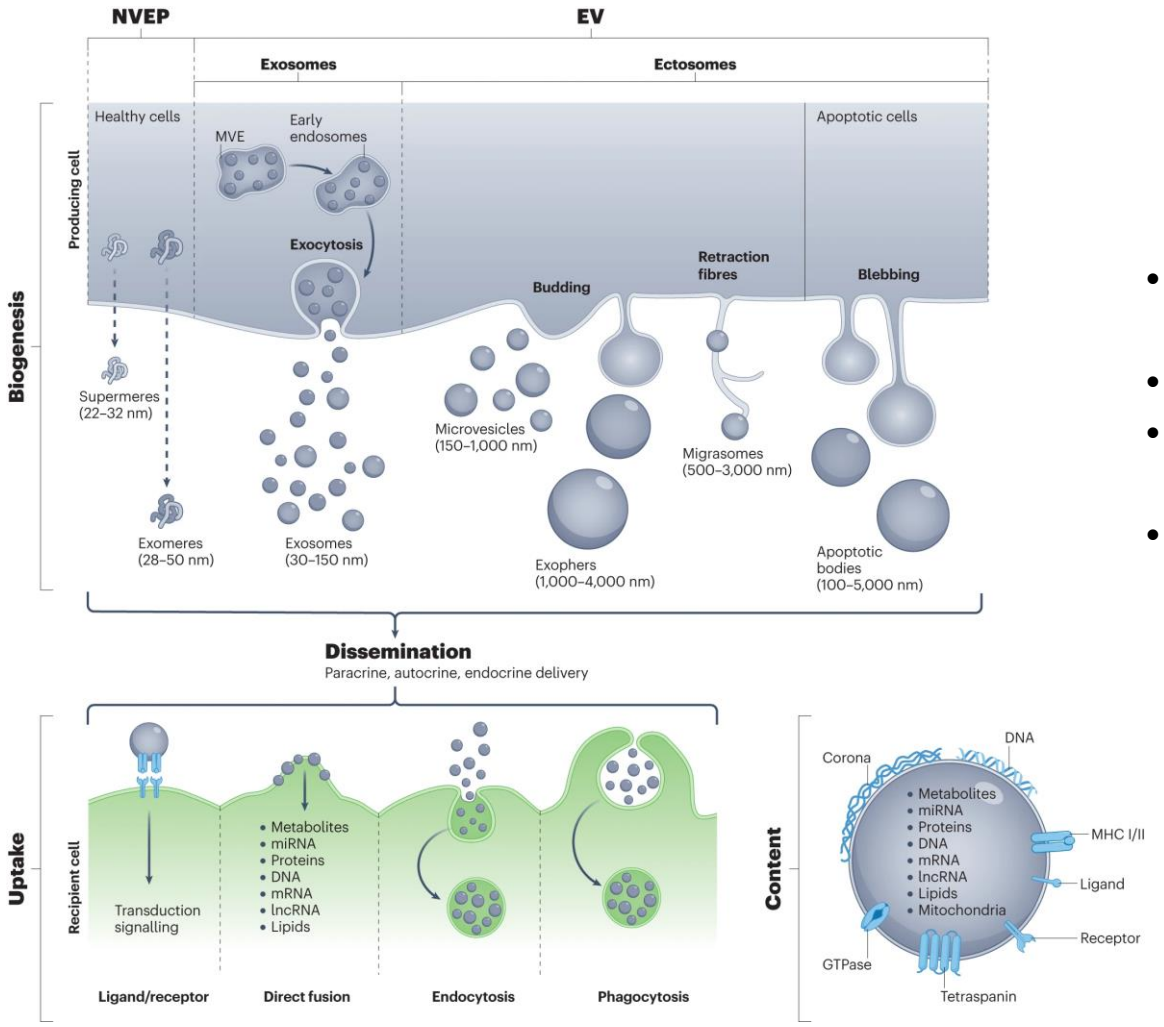


GH-1-enriched MSC-EVs enhance disc cell motility and wound closure





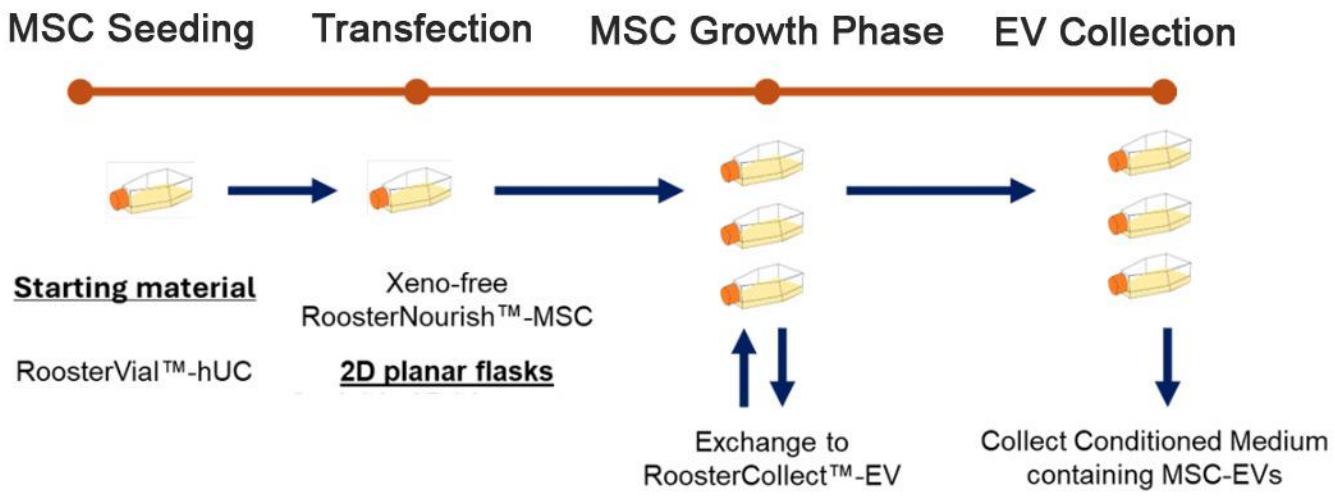
Extracellular Vesicles (EVs)/Exosomes from MSCs are promising preclinical therapeutics: Engineering enhances precision and potency



- MSC-derived EVs are natural mediators of paracrine signaling
- EVs carry bioactive proteins, RNAs, and lipids
- EVs carry key anti-inflammatory and regenerative effects of MSCs
- Engineering enables defined, potent, and reproducible cargo delivery

Nature Reviews Rheumatology (Nat Rev Rheumatol) ISSN 1759-4804

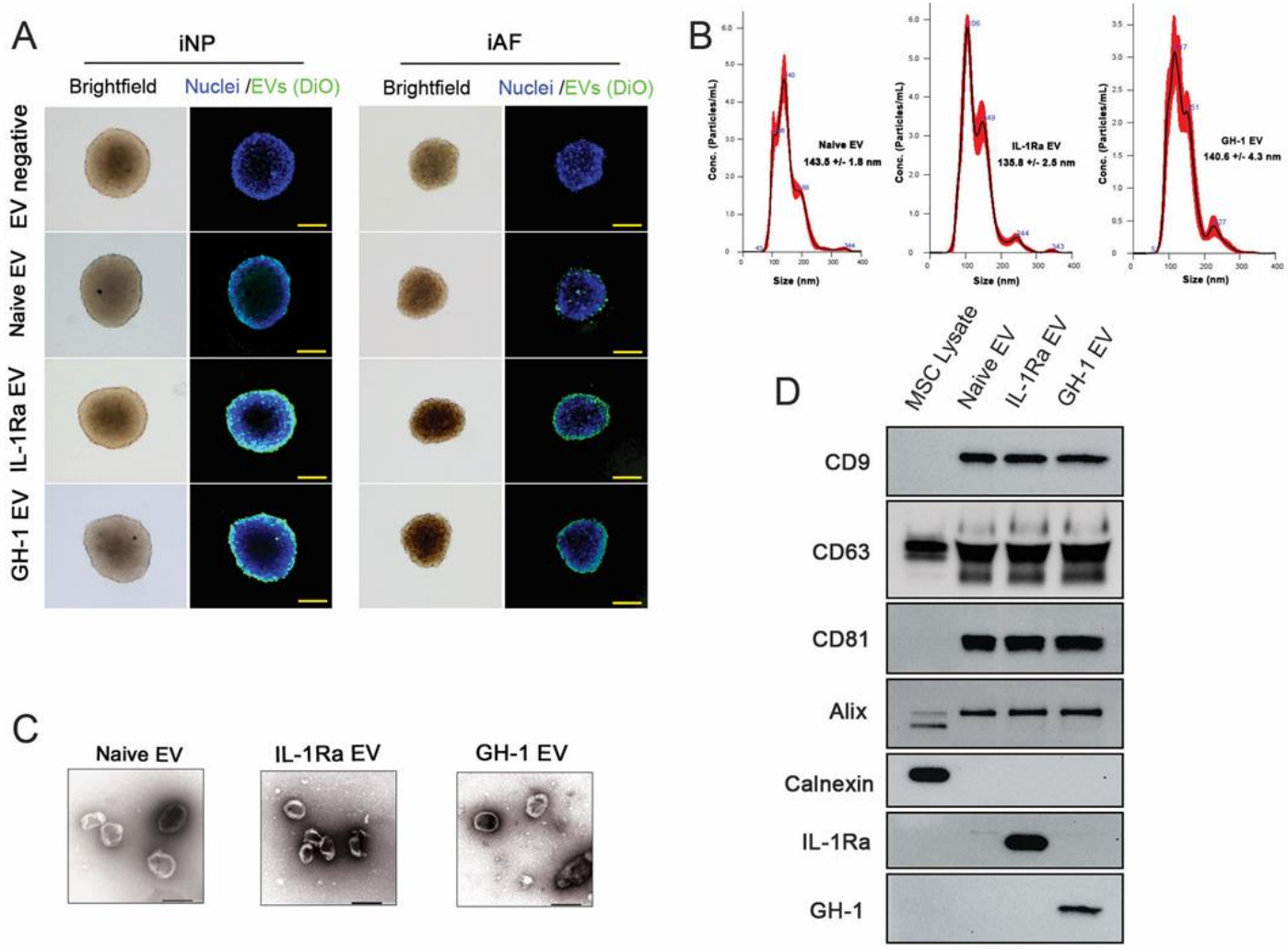
Engineering MSCs To Generate Cargo-enriched Extracellular Vesicles



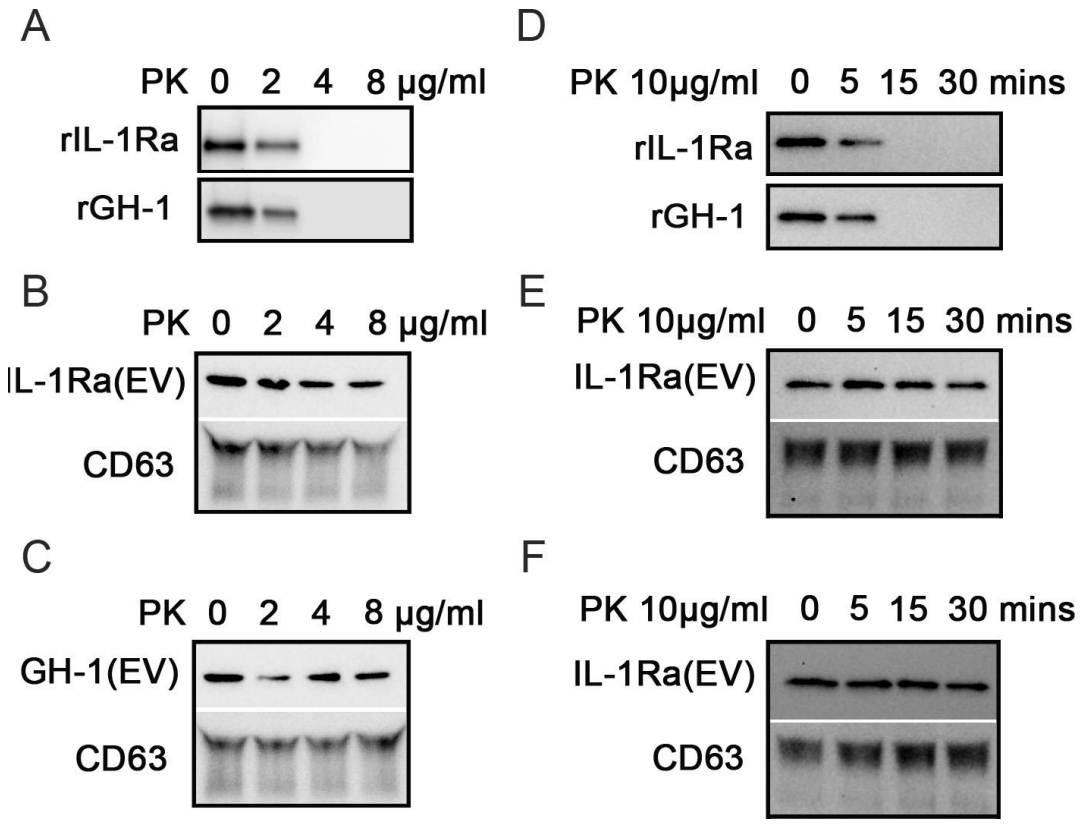
- MSCs are engineered at the cell level, not post-isolation
- Standardized, xeno-free culture supports reproducible EV production
- Conditioned media serves as the source of engineered MSC-EVs

Engineered MSC-EVs Retain Characteristic Features And Are Efficiently Taken Up By Disc Cells

- Engineered EVs maintain canonical EV size and morphology
- IL-1Ra and GH-1 are successfully enriched in EV cargo
- MSC-EVs are efficiently internalized by NP and AF spheroids

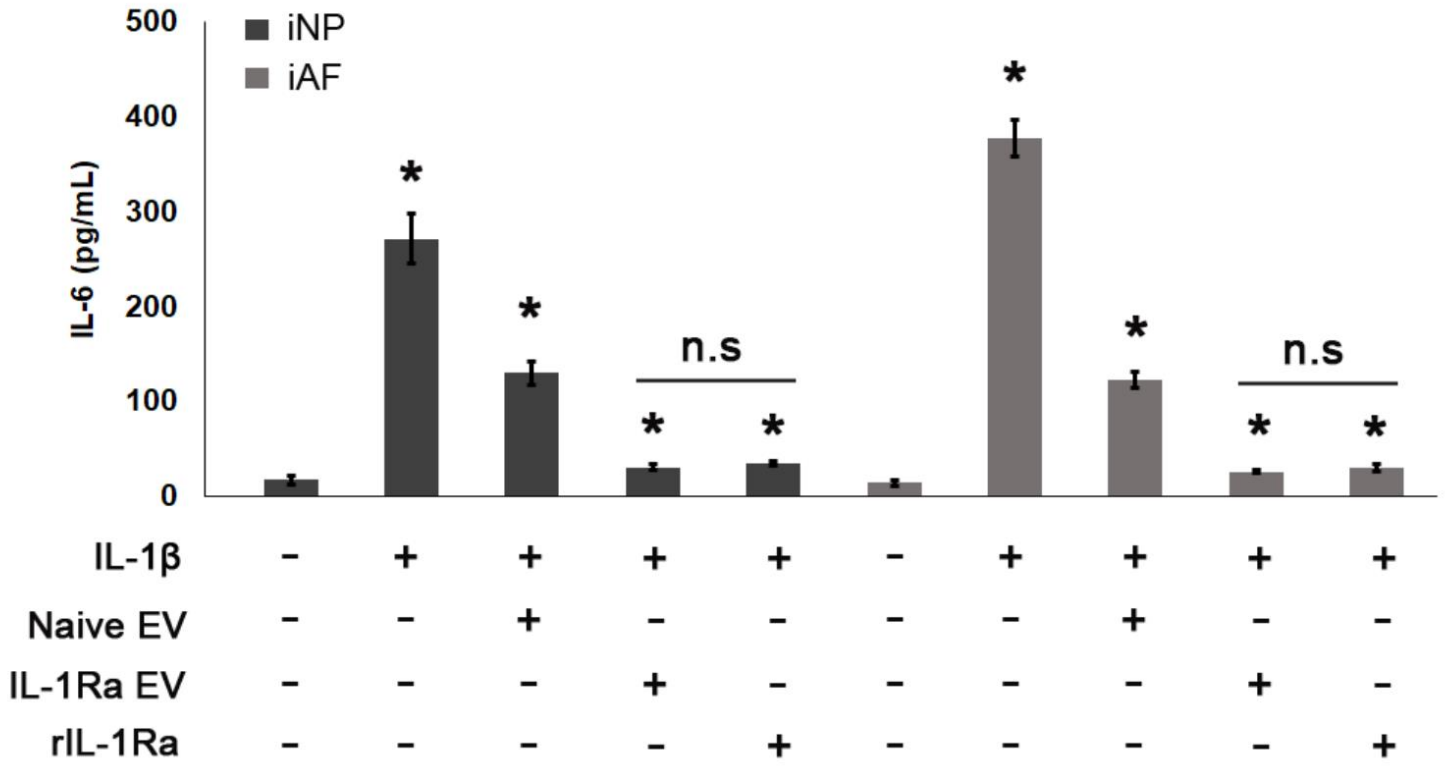


MSC-EV encapsulation preserves IL-1Ra and GH-1 stability under proteolytic stress

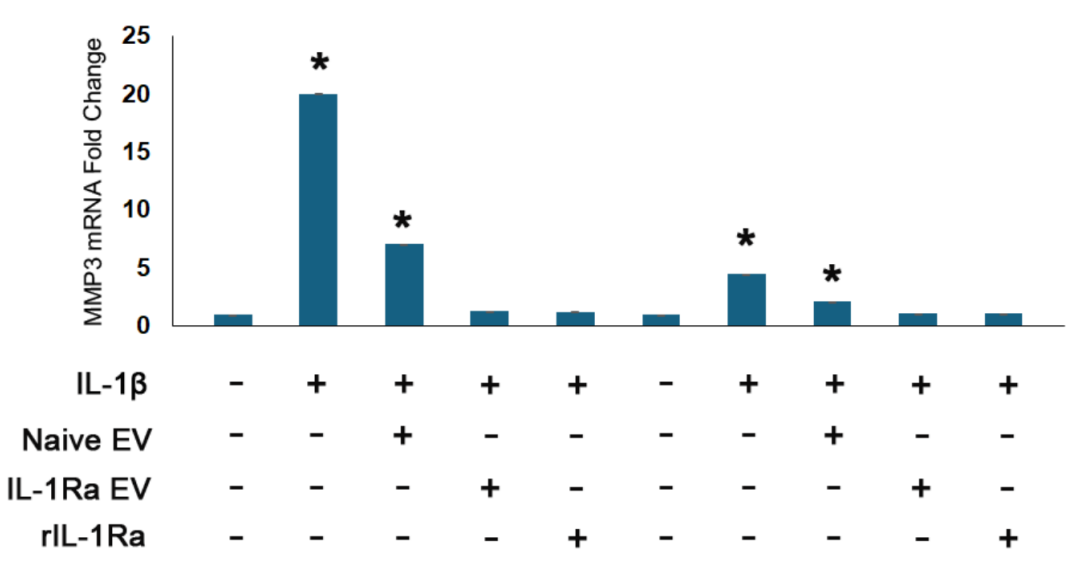


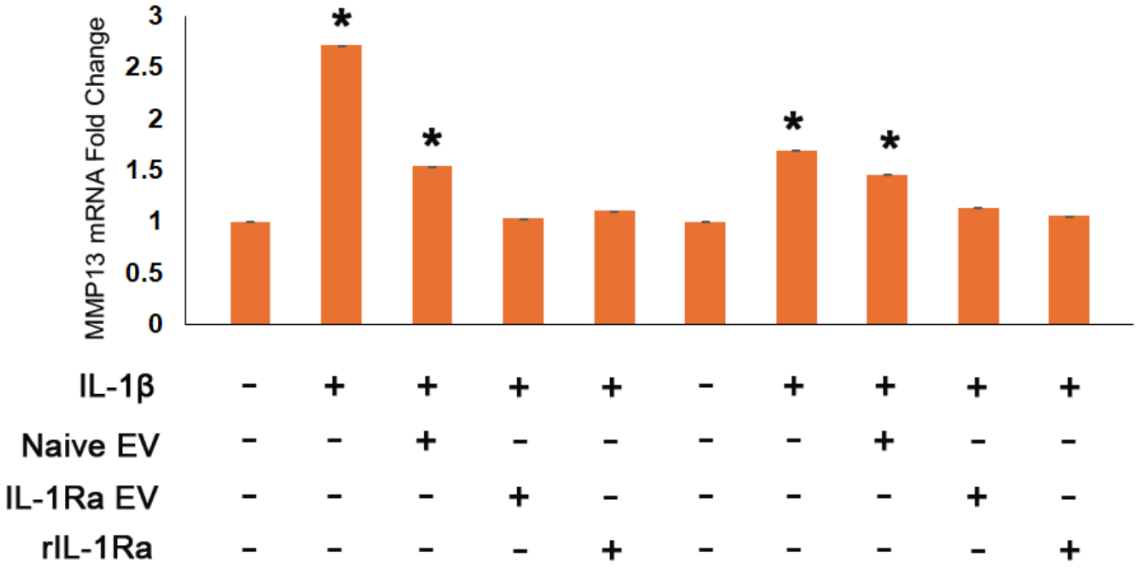
- Free IL-1Ra and GH-1 are rapidly degraded by protease treatment
- EV-encapsulated IL-1Ra and GH-1 are protected over dose and time

IL-1Ra-enriched MSC-EVs suppress IL-1β-induced inflammatory signaling in disc cells

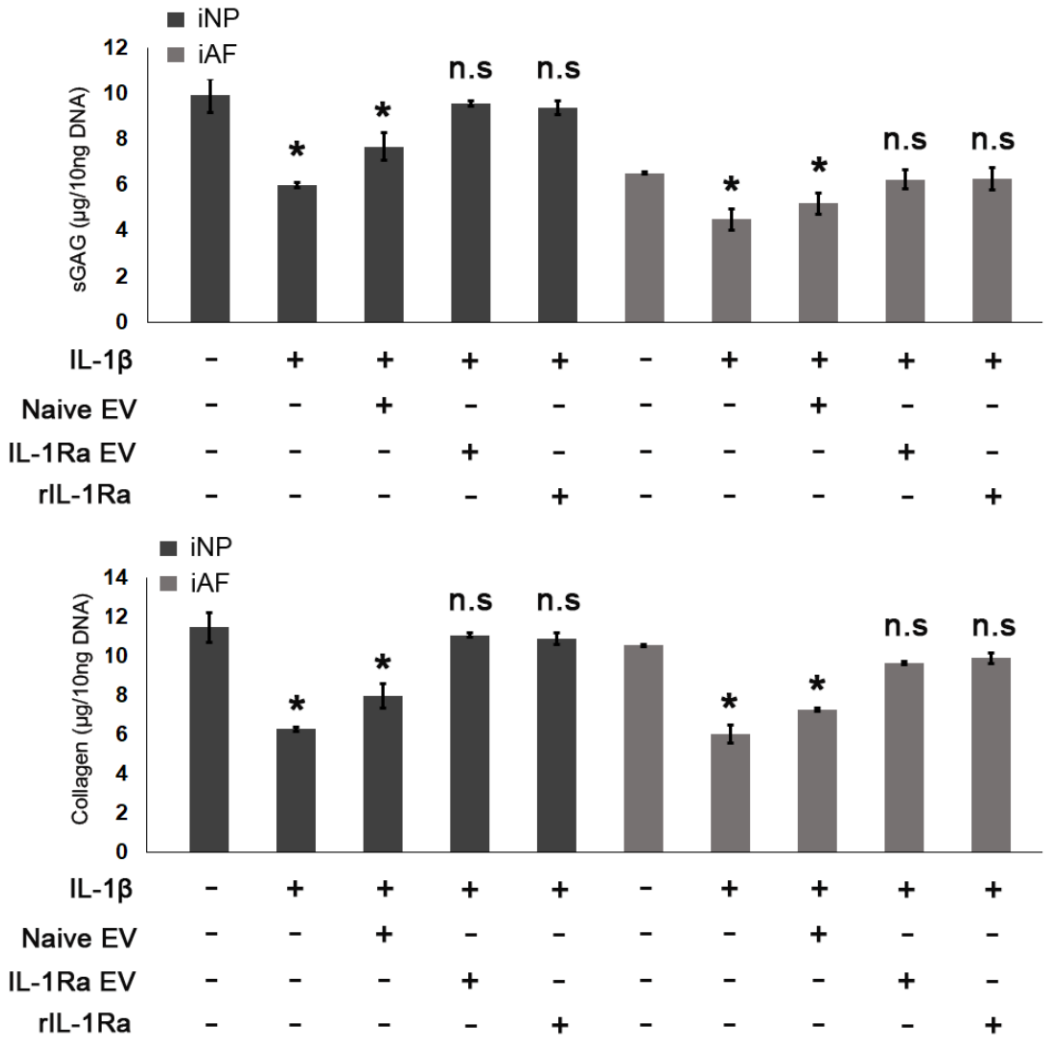


IL-1Ra-enriched MSC-EVs suppress IL-1β-induced catabolic enzyme expression

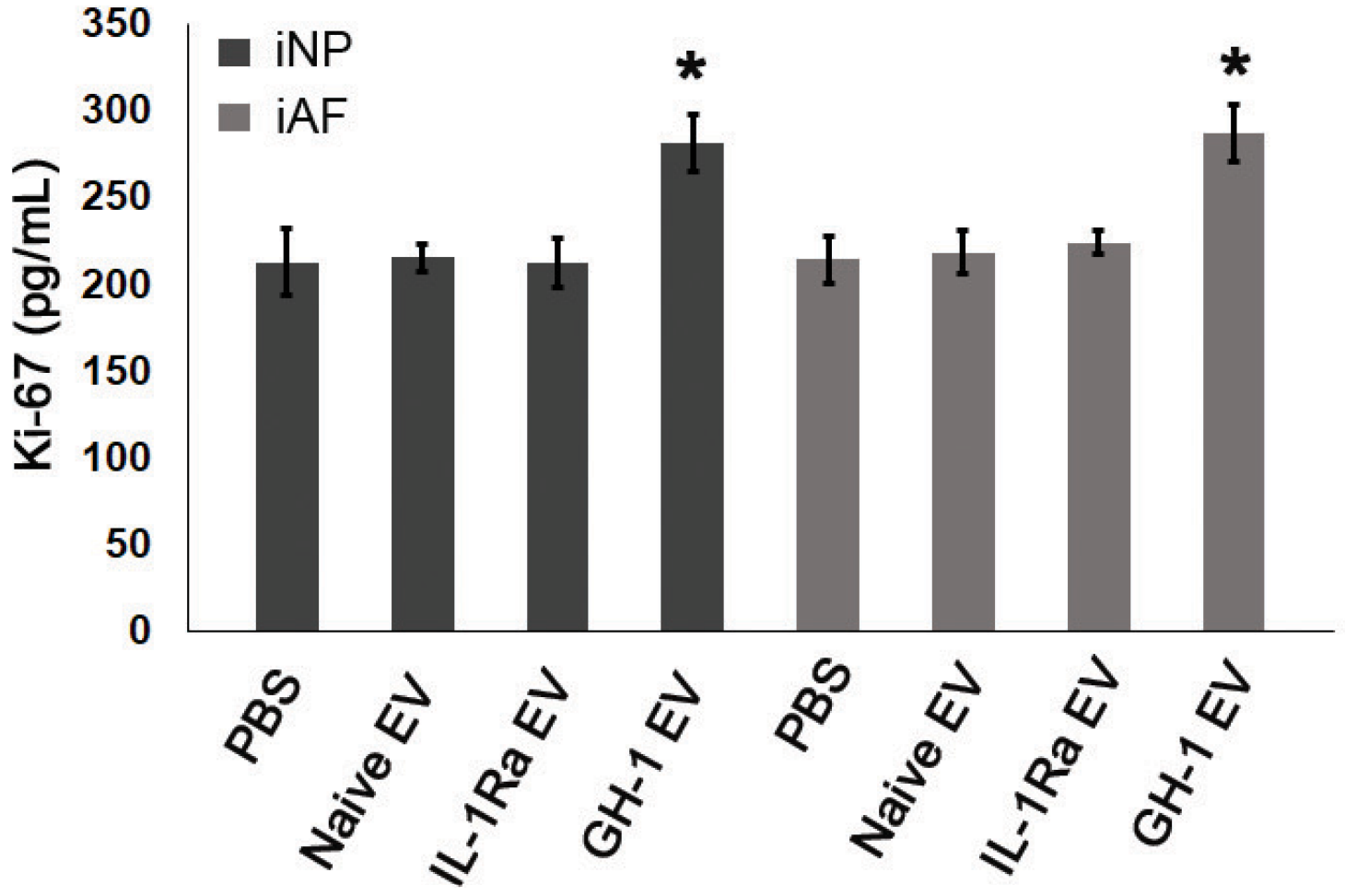




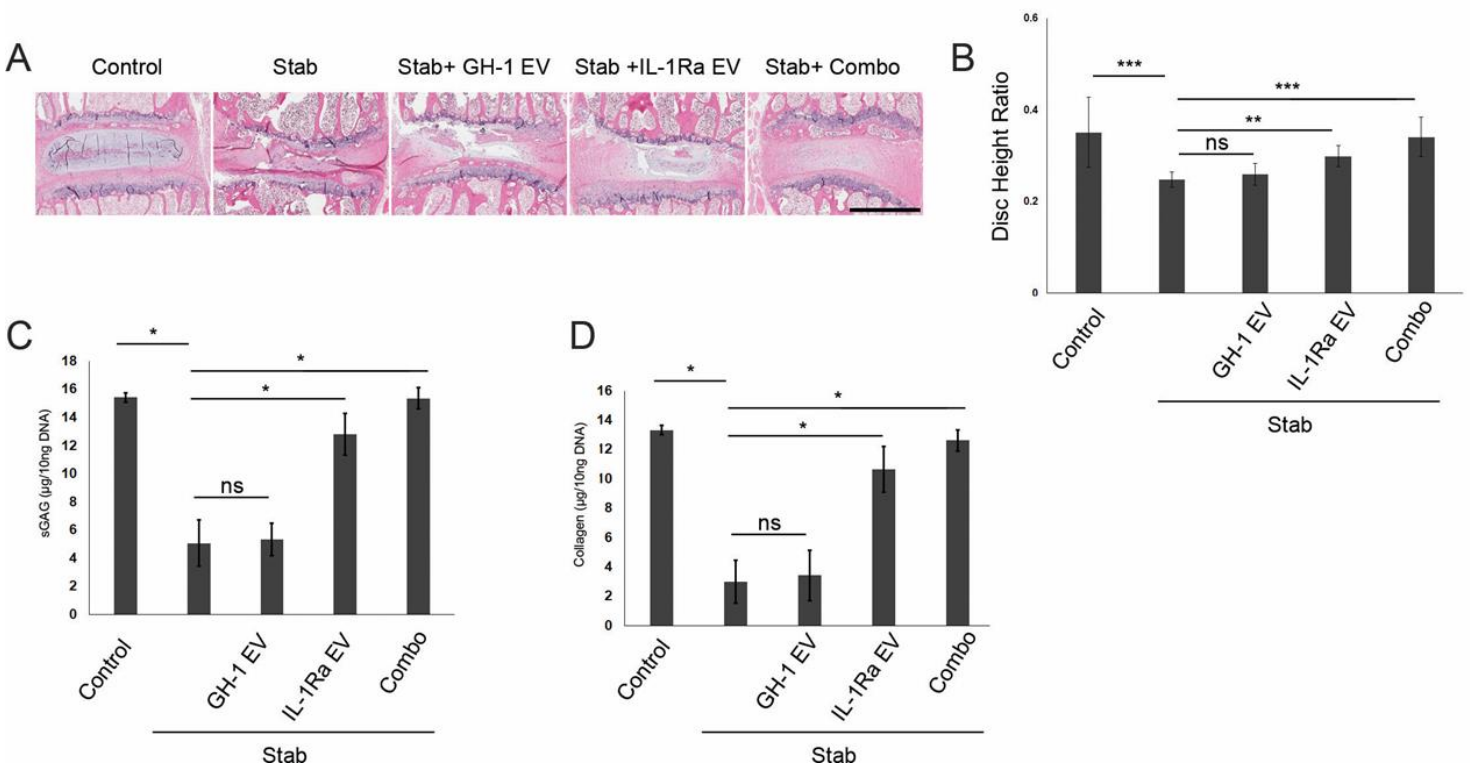
IL-1Ra–enriched MSC-EVs preserve extracellular matrix under inflammatory stress



GH-1-enriched MSC-EVs promote proliferative responses in disc cells



Combined IL-1Ra and GH-1 MSC-EV therapy restores disc structure and matrix composition ex vivo



- Combination EV therapy improves disc height and tissue architecture
- IL-1Ra or GH-1 alone provides partial benefit
- Dual-cargo EVs synergistically restore matrix composition

SUMMARY

Engineered dual-cargo MSC-EVs coordinately suppress degeneration and activate regeneration in disc disease

- Disc degeneration is driven by inflammatory dominance and loss of regenerative programs
- IL-1 signaling promotes catabolism and matrix degradation
- Regenerative capacity declines across degeneration stages
- MSC-derived EVs serve as biologically active delivery platforms
- EV encapsulation protects cargo stability
- IL-1Ra cargo suppresses inflammatory and catabolic signaling
- GH-1 cargo promotes proliferative and reparative cell behaviors
- Dual-cargo EVs restore disc structure and matrix in ex vivo FSU model

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QUESTIONS & ANSWERS