Regenerative Medicine Therapeutic Interventions for the Treatment of Spinal Cord Injuries: A Systematic Review and Meta-Analyses based on In-Vivo Preclinical Evidence

Koby Sample[1], Mihir Somisetty [2], Neng-Hsiang Tseng[3], Chen-Ya Hung[3], Richard Chern[3], Ryan Lee[3], Xin Yi Keng [4], Max Meng-Huang Wu [3], Yen-Sheng Lin[1]
[1]University of Texas Southwestern Medical Center, Dallas, TX, USA; [2]University of Texas at Dallas, TX, USA; [3]Taipei Medical University, Taipei, Taiwan, [4]Lee Kong Chian School of Medicine, Singapore
Correspondences: yen-sheng.lin@utsouthwestern.edu & maxwutmu@gmail.com

INTRODUCTION: Spinal cord injury (SCI) is one of the devastating traumatic episodes that causes motor/sensory deficits, autonomic dysfunction, and markedly reduced quality of life.[1] Current care includes acute decompression/stabilization, hemodynamic support, and comprehensive rehabilitation.[2] However, the current standard of care ineffectively restores motor function and functional recovery.[3] Regenerative medicine offers scalable and emerging modalities that can be delivered intravenously or intrathecally to modulate the post-injury cascade and potentially improve functional outcomes.[4] The objective of this systematic review is to synthesize *in-vivo* preclinical evidence on regenerative therapies using SCI animal models to inform pragmatic early-phase clinical trials.

METHODS: Using Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline, we searched Web of Science, Scopus, PubMed, and Embase for in-vivo rat models of traumatic SCI receiving regenerative modalities versus vehicle/sham or standard-of-care controls with functional recovery outcomes (BBB/BMS), yielding 22 included studies from 734 records. The included studies did not explicitly specify the gender of the rats. Two reviewers independently extracted Basso, Beattie, Bresnahan (BBB) and Basso Mouse Sore scores (BMS) on day 28. The BBB (0–21, rats) and (BMS; 0–9, mice) are open-field locomotor ratings where 0 indicates hindlimb paralysis, higher values reflect progressively better joint function, and the top scores approximate normal gait.[5] For external benchmarking, we summarized study-level mean differences from a published meta-analysis of intravenous bone marrow–derived mesenchymal stromal cell (BMSC) therapy in rat SCI; because both datasets analyze regenerative therapies and report BBB/BMS at comparable post-injury windows, their mean differences are comparable to ours.

RESULTS SECTION: Mean difference (MD) favors experimental therapy, and no 95% CI crosses 0, which indicated a statistically significant improvement. In **Figure 1**, MDs ranged from 4 to 10 with the largest in the interventions Hyp-EVs-miR-511-3p mimic, Exo-miR-21 and GelMA+3D-Exo. Heterogeneity was significantly high (I^2=91.3%) and BBB weights were broadly shared (5.7% to 8.3% each), meaning each trial contributed a similar share of the statistical information and no single study carried enough weight to strongly steer the overall score interpretation. In **Figure 2**, MDs ranged from 2 to 6 with the largest in the interventions Gel/PRP-Exos, C-EVs-siRNA, and DSCM@EVs. Heterogeneity was considerably high (I^2=89.8%) and BMS weights were modest improvement (14% to 15%) among the treatments from RGD-CD-146+CD271+UCMSC-Exos (Xie 2023), USC-Exo (Cao 2021), C-EVs-siRNA (Rong 2023), and EGFR+NSCs-Exos (Qin 2024). Overall, the forest plots show statistically significant locomotor gains, with motor functional improvements (increased 5 to 8 BBB and increased 3 to 4 BMS).

DISCUSSION: Concentrated BMS weights suggest a pooled estimate would be pulled by a few precise trials, though these studies also provide the best variance benchmarks and designs to replicate. A similar preclinical meta-analysis of intravenous BMSC therapy in rats showed BBB MDs of ~2–4 points at 3–5 weeks which is smaller than ours but in the same direction.[6] While BBB/BMS improvements indicate better open-field locomotion, they should be paired with quantitative gait/kinematics, electrophysiology, sensory/autonomic outcomes, and histology/imaging for stronger translational inference. We prioritized BBB/BMS as primary outcomes because they are the most widely reported, validated locomotor scales in rodent SCI, providing a standardized, sensitive 28-day metric that maximizes study inclusion and enables direct comparison of study-level mean differences. Future animal studies should predefine time points, standardize lesion models/severity, and strengthen internal validity/reporting to enable comparisons across interventions. In our extracted data, despite a common 28-day endpoint, the heterogeneity for both BBB and BMS scores was substantial. Thus, we emphasize unpooled, study-level MDs with 95% CIs and weights rather than a single pooled estimate. In sum, our systematic review provided a holistic approach to support prioritizing regenerative therapeutic candidates for early-phase preclinical trials.
SIGNIFICANCE/CLINICAL RELEVANCE: This synthesis of BBB/BMS outcomes from preclinical regenerative therapies addresses a critical barrier by consolidating evidence to highlight candidates and measures with the greatest translational promise. Our work provided systematic syntheses to evaluate the regenerative therapeutic intervention to inform prospective preclinical studies before the translation to clinical application.

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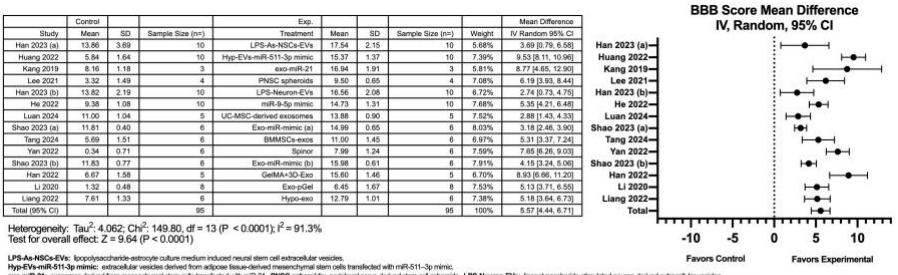
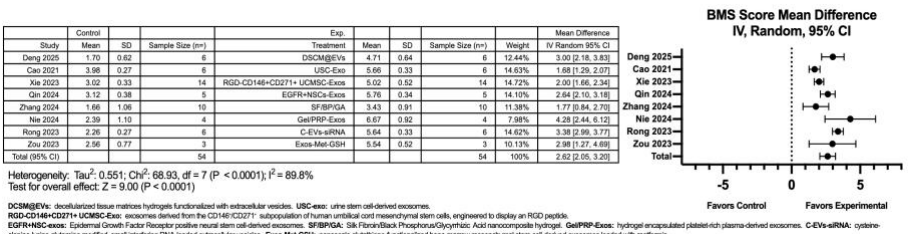


	Control			Exp.				Mean Difference
Study	Mean	SD	Sample Size (n=)	Treatment	Mean	SD	Sample Size (n=)	Weight	IV Random 95% CI
Han 2023 (a)	13.86	3.69	10	LPS-As-NSCs-EVs	17.54	2.15	10	5.68%	3.69 [0.79, 6.58]
Huang 2022	5.84	1.64	10	Hyp-EVs-miR-511-3p mimic	15.37	1.37	10	7.39%	9.53 [8.11, 10.96]
Kang 2019	8.16	1.18	3	exo-miR-21	16.94	1.91	3	5.81%	8.77 [4.65, 12.90]
Lee 2021	3.32	1.49	4	PNSC spheroids	9.50	0.65	4	7.08%	6.19 [3.93, 8.44]
Han 2023 (b)	13.82	2.19	10	LPS-Neuron-EVs	16.56	2.08	10	6.72%	2.74 [0.73, 4.75]
He 2022	9.38	1.08	10	miR-9-5p mimic	14.73	1.31	10	7.68%	5.35 [4.21, 6.48]
Luan 2024	11.00	1.04	5	UC-MSC-derived exosomes	13.88	0.90	5	7.52%	2.88 [1.43, 4.33]
Shao 2023 (a)	11.81	0.40	6	Exo-miR-mimic (a)	14.99	0.65	6	8.03%	3.18 [2.46, 3.90]
Tang 2024	5.69	1.51	6	BMMSCs-exos	11.00	1.45	6	6.97%	5.31 [3.37, 7.24]
Yan 2022	0.34	0.71	6	Spinor	7.99	1.24	6	7.59%	7.65 [6.26, 9.03]
Shao 2023 (b)	11.83	0.77	6	Exo-miR-mimic (b)	15.96	0.61	6	7.91%	4.15 [3.24, 5.06]
Han 2022	6.67	1.58	5	GelMA+3D-Exo	15.60	1.46	5	6.70%	8.93 [6.66, 11.20]
Li 2020	1.32	0.48	8	Exo-pGel	6.45	1.67	8	7.53%	5.13 [3.71, 6.55]
Liang 2022	7.61	1.33	6	Hypo-exo	12.79	1.01	6	7.38%	5.18 [3.64, 6.73]
Total (95% CI)			95				95	100%	5.57 [4.44, 6.71]

Heterogeneity: Tau^2: 4.062; Chi^2: 149.80, df = 13 (P < 0.0001); I^2 = 91.3%
Test for overall effect: Z = 9.64 (P < 0.0001)

LPS-As-NSCs-EVs: lipopolysaccharide-astrocyte culture medium induced neural stem cell extracellular vesicles.
Hyp-EVs-miR-511-3p mimic: extracellular vesicles derived from adipose tissue-derived mesenchymal stem cells transfected with miR-511–3p mimic.
exo-miR-21: exosomes derived from mesenchymal stem cells transfected with miR-21. **PNSC spheroids:** peripheral nerve-derived stem cell spheroids. **LPS-Neuron-EVs:** lipopolysaccharide-stimulated neuron-derived extracellular vesicles.
miR-9-5p mimic: exosomes derived from bone marrow mesenchymal stem cells transfected with miR-9-5p mimic. **UC-MSC-derived exosomes:** umbilical cord mesenchymal stem cell-derived exosomes. **Exo-miR-mimic (a):** exosomes derived from bone marrow mesenchymal stem cells transfected with miR-137 mimic. **BMMSCs-exos:** bone marrow mesenchymal stem cell-derived exosomes. **Spinor:** bio-assembly of dental pulp-derived mesenchymal stem cells. **Exo-miR-mimic (b):** exosomes derived from bone marrow mesenchymal stem cells transfected with miR-146a mimic. **GelMA+3D-Exo:** gelatin methacryloyl hydrogel hybrid 3D cultured mesenchymal stem cell-derived exosomes. **Exo-pGel:** human mesenchymal stem cell-derived exosomes immobilized in a peptide-modified adhesive hydrogel. **Hypo-exo:** hypoxia-conditioned adipose tissue-derived stromal cell-derived exosomes.

Figure 1. Forest Plot of BBB Score



	Control			Exp.				Mean Difference
Study	Mean	SD	Sample Size (n=)	Treatment	Mean	SD	Sample Size (n=)	Weight	IV Random 95% CI
Deng 2025	1.70	0.62	6	DSCM@EVs	4.71	0.64	6	12.44%	3.00 [2.18, 3.83]
Cao 2021	3.98	0.27	6	USC-Exo	5.66	0.33	6	14.63%	1.68 [1.29, 2.07]
Xie 2023	3.02	0.33	14	RGD-CD146+CD271+ UCMSC-Exos	5.02	0.52	14	14.72%	2.00 [1.66, 2.34]
Qin 2024	3.12	0.38	5	EGFR+NSCs-Exos	5.76	0.34	5	14.10%	2.64 [2.10, 3.18]
Zhang 2024	1.66	1.06	10	SF/BP/GA	3.43	0.91	10	11.38%	1.77 [0.84, 2.70]
Nie 2024	2.39	1.10	4	Gel/PRP-Exos	6.67	0.92	4	7.98%	4.28 [2.44, 6.12]
Rong 2023	2.26	0.27	6	C-EVs-siRNA	5.64	0.33	6	14.62%	3.38 [2.99, 3.77]
Zou 2023	2.56	0.77	3	Exos-Met-GSH	5.54	0.52	3	10.13%	2.98 [1.27, 4.69]
Total (95% CI)			54				54	100%	2.62 [2.05, 3.20]

Heterogeneity: Tau^2: 0.551; Chi^2: 68.93, df = 7 (P < 0.0001); I^2 = 89.8%
Test for overall effect: Z = 9.00 (P < 0.0001)

DCSM@EVs: decellularized tissue matrices hydrogels functionalized with extracellular vesicles. **USC-exo:** urine stem cell-derived exosomes.
RGD-CD146+CD271+ UCMSC-Exo: exosomes derived from the CD146$^+$/CD271$^+$ subpopulation of human umbilical cord mesenchymal stem cells, engineered to display an RGD peptide.
EGFR+NSC-exos: Epidermal Growth Factor Receptor positive neural stem cell-derived exosomes. **SF/BP/GA:** Silk Fibroin/Black Phosphorus/Glycyrrhizic Acid nanocomposite hydrogel. **Gel/PRP-Exos:** hydrogel encapsulated platelet-rich plasma-derived exosomes. **C-EVs-siRNA:** cysteine-alanine-lysine glutamine modified, small interfering RNA-loaded extracellular vesicles. **Exos-Met-GSH:** nanoscale glutathione-functionalized bone marrow mesenchymal stem cell-derived exosomes loaded with metformin.

Figure 2. Forest Plot of BMS Score