Tissue-Engineered Scaffolds for Spinal Cord Regeneration

A Systematic Review of Preclinical Animal Studies

Sabaa Husnaa Majid

LAIDLAW SCHOLARS
University of St Andrews

Acknowledgements
I would like to sincerely thank Professor Gareth Miles for his supervision, guidance, and for recognising my passion for this area of research. I am also grateful to the Laidlaw Foundation for funding and supporting this research.

Introduction

Spinal cord injury (SCI) causes persistent motor, sensory and autonomic impairment, with limited spontaneous regeneration. Secondary inflammation, glial scarring, extracellular matrix changes and tissue loss further restrict axonal regeneration and functional repair [1,2,4–9].

Tissue-engineered scaffolds aim to overcome these barriers by bridging the lesion, supporting cellular interactions and promoting axonal growth, vascularisation and tissue integration. They can also deliver cells, growth factors, drugs and other therapeutic components to modify the injured environment [3,10–12].

However, preclinical evidence is highly heterogeneous, with scaffold composition and architecture, animal species, injury models, treatment timing and outcome measures varying substantially [12–14]. Behavioural, histological, molecular and electrophysiological outcomes therefore capture different aspects of recovery.

Aim: To evaluate the effectiveness of tissue-engineered scaffolds for spinal cord regeneration in preclinical animal models by synthesising behavioural, histological, molecular and electrophysiological outcomes, while assessing methodological quality and translational potential.

Summary

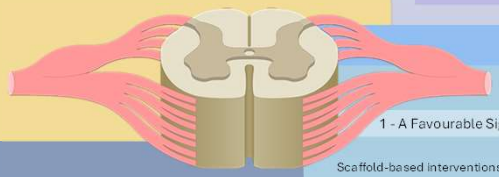
1. SCI is difficult to repair.
Spinal cord injury causes lasting neurological impairment, while damaged spinal tissue has limited regenerative capacity.

2. Scaffolds aim to support repair.
They can bridge the injury, support cells and axons, and deliver cells, drugs or growth factors.

3. 622 animal studies were analysed.
The review assessed experimental efficacy, scaffold design features and readiness for clinical translation.

4. Efficacy was favourable, but no clear material winner emerged.
Differences between materials, architectures and combination therapies were difficult to isolate because studies often changed several features simultaneously.

5. The major gap is translation.
The literature shows that scaffolds can improve experimental outcomes, but provides much less evidence on which features drive recovery, whether findings are reproducible, and whether benefits will persist under clinical conditions.



Methods

1. Design
Systematic review of preclinical animal studies, designed and reported according to PRISMA 2020 [15].

2. Search Strategy
MEDLINE (Ovid), Embase and Web of Science were searched from database inception to 10 July 2026, with no publication-date restriction. Searches combined controlled vocabulary and free-text terms relating to SCI and tissue engineering/scaffolds. English-language studies were eligible, and reference lists of relevant studies were screened.

3. Eligibility
Animal models with experimentally induced SCI receiving a biomaterial scaffold, either alone or combined with cells, growth factors, drugs or other therapeutic components. Cell-, drug- or growth-factor-only interventions were excluded. Eligible comparators included untreated SCI, sham, vehicle or standard-treatment controls.

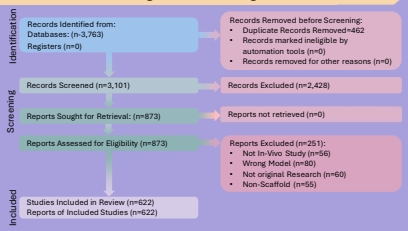
4. Screening and Extraction
Duplicates were removed in Zotero. Titles/abstracts and full texts were screened against predefined criteria. Data were extracted into a standardised Excel form covering animal/injury characteristics, scaffold composition and architecture, therapeutic components and outcomes.

5. Synthesis
Due to substantial heterogeneity, quantitative meta-analysis was not performed. Predefined functional, histological/molecular and electrophysiological regeneration scores were calculated and combined into an overall regeneration score where sufficient data were available.

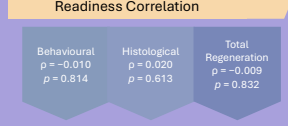
6. Quality & Translation
Risk of bias was assessed using SYRCLE [16]. Translational potential was assessed using a predefined Translational Readiness Index (TRI).

Results

PRISMA 2020 Flow Diagram – Screening Results



Outcome to Translational Readiness Correlation



SYRCLE Results By Domain

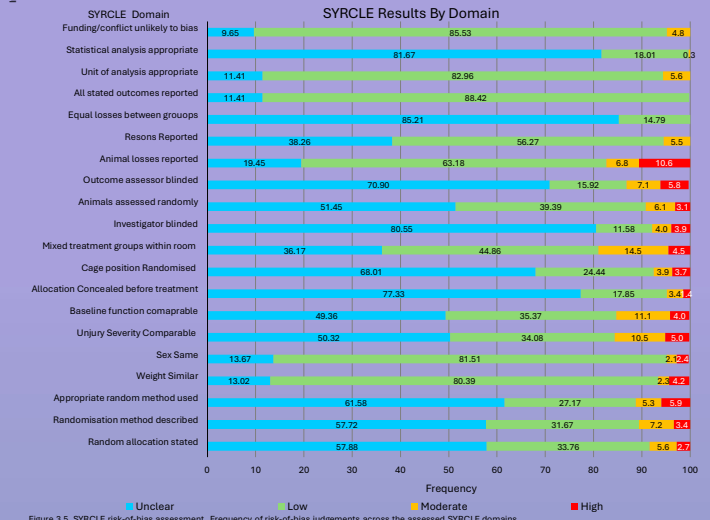


Figure 3.5. SYRCLE risk-of-bias assessment. Frequency of risk-of-bias judgements across the assessed SYRCLE domains.

3.6.1 Average Outcomes By Scaffold Class

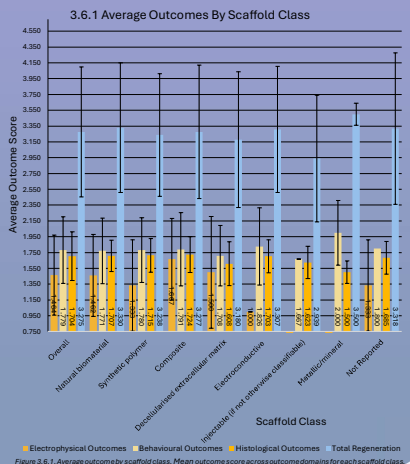
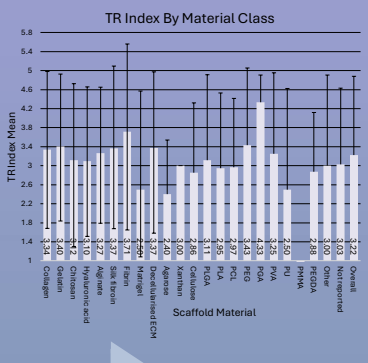
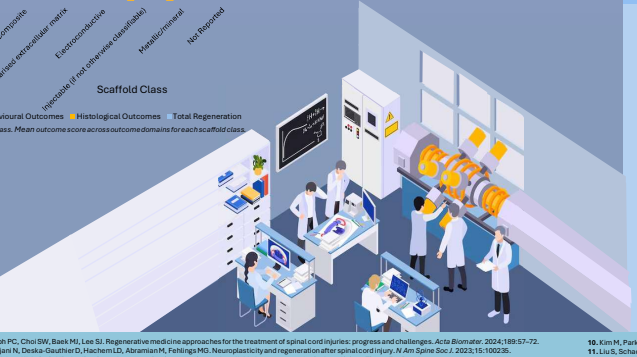


Figure 3.6.1. Average outcome by scaffold class. Mean outcome score across outcome domains for each scaffold class.

TR Index By Material Class

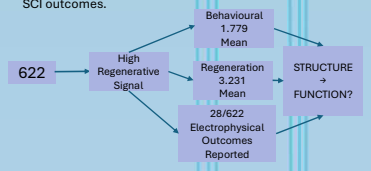




Discussion

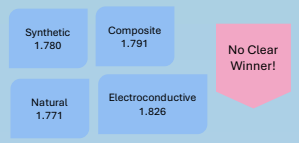
1 - A Favourable Signal, But Not the Whole Story

Scaffold-based interventions consistently improve experimental SCI outcomes.



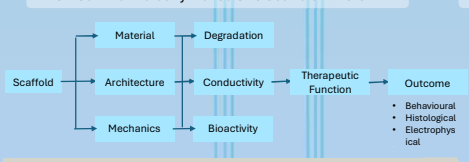
Across 622 studies, behavioural and histological outcomes were predominantly favourable, supporting an experimental efficacy signal. However, only 4.5% reported electrophysiological outcomes, so anatomical recovery cannot be assumed to represent restored neural conduction. Categorical scoring captures the direction of findings rather than treatment-effect magnitude.

2 -There is no obvious "best" material



No significant differences were found between broad scaffold classes, suggesting that labels such as natural, synthetic or composite are too coarse to predict recovery. Properties including architecture, stiffness, degradation and therapeutic loading can vary substantially within each class.

3 – So What Actually Makes One Scaffold Different



Same material → different architecture → potentially different biological behaviour

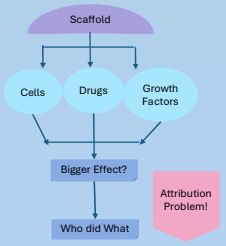
PLGA, gelatine and hyaluronic acid all showed favourable descriptive scores, but these do not establish superiority. Scaffold architecture and functional properties may be more informative than material identity alone, however studies rarely isolate these variables sufficiently for direct comparison.

Descriptive values ≠ proof of superiority

"What is it made from?" may be the wrong first question.

Same material. Different scaffold. Different biology.

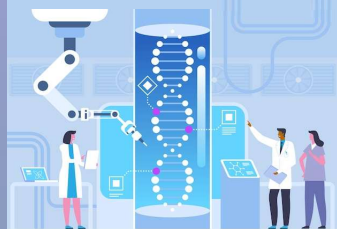
4 - More components ≠ clearer evidence



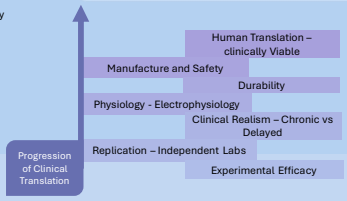
Combination therapies may target multiple barriers to repair, but their added benefit is difficult to establish when scaffold-only, cell-only and combination controls are absent. More controlled comparisons are needed to distinguish additive effects from genuine synergy.

5 - The Translational Drop-Off

The literature is much stronger at demonstrating experimental recovery than at testing durability, safety, reproducibility and clinical feasibility. Low translational-readiness scores therefore reveal a substantial gap between *proof that scaffolds can work* and *evidence that they can translate*.



6 – Steps to Translation?



Future studies should prioritise independent replication, clinically realistic treatment timing, long-term follow-up, physiological validation, broader animal populations, dose–response and safety testing, and reproducible manufacture. Controlled comparisons of architecture, mechanics and therapeutic components could then identify which features actually drive recovery.

Conclusions

622 preclinical studies show a broadly favourable experimental efficacy signal for scaffold-based SCI therapies.

No broad scaffold class clearly outperformed another, suggesting that material labels alone are poor predictors of recovery.

Translation remains the major weakness: only 4.5% of studies assessed electrophysiological outcomes and 10.5% reported independent laboratory validation.

The field should shift from creating increasingly complex scaffolds towards validating which design features actually drive durable, reproducible and clinically relevant recovery.

Full Report

References

1. Ralph PC, Choi SW, Baek MJ, Lee SJ. Regenerative medicine approaches for the treatment of spinal cord injuries: progress and challenges. *Acta Biomater.* 2024;189:57–72.
2. Punjani N, Deska-Gauthier D, Hachem LD, Abramian M, Fehlings MG. Neuroplasticity and regeneration after spinal cord injury. *N Am Spine Soc J.* 2023;15:100235.
3. Bradshaw KJ, Leipzig ND. Applications of regenerative tissue-engineered scaffolds for treatment of spinal cord injury. *Tissue Eng Part A.* 2025;31:108–25.
4. Tran AP, Warren PM, Silver J. The biology of regeneration failure and success after spinal cord injury. *Physiol Rev.* 2018;98:881–917.
5. Alizadeh A, Dyck SM, Karimi-Abdolrezaee S. Traumatic spinal cord injury: an overview of pathophysiology, models and acute injury mechanisms. *Front Neurol.* 2019;10:282.
6. Gao Y, Wang Y, Wu Y, Liu S. Biomaterials targeting the microenvironment for spinal cord injury repair: progression and perspectives. *Front Cell Neurosci.* 2024;18:1362494.
7. Gaudet AD, Fonken LK. Glial cells shape pathology and repair after spinal cord injury. *Neurotherapeutics.* 2018;15:554–77.
8. Hagg T, Oudega M. Degenerative and spontaneous regenerative processes after spinal cord injury. *J Neurotrauma.* 2006;23:264–80.
9. Elmaky MI, Alvarez-Bolado G, Younis A, Skutella T. Axonal regeneration after spinal cord injury: molecular mechanisms, regulatory pathways, and novel strategies. *Biology.* 2024;13:703.
10. Kim M, Park SR, Choi BH. Biomaterial scaffolds used for the regeneration of spinal cord injury. *Histol Histopathol.* 2014;29:1395–408.
11. Liu S, Schackel T, Weidner N, Puttagunta R. Biomaterial-supported cell transplantation treatments for spinal cord injury: challenges and perspectives. *Front Cell Neurosci.* 2017;11:430.
12. Zhu S, Diao S, Liu X, Zhang Z, Liu F, Chen W, et al. Biomaterial-based strategies: a new era in spinal cord injury treatment. *Neural Regen Res.* 2025;20:3476–500.
13. Khavandegar A, Safari Dehnavi N, Ganau M, Ramezani Z, Khodadoust E, Hassan Zadeh Tabatabaei MS, et al. Neuroregenerative and neuroprotective effects of bioengineered scaffolds in spinal cord injury. *Spinal Cord.* 2025;63:451–69.
14. Verstappen K, Aquarius R, Klymov A, Wever KE, Damveld L, Leeuwenburgh SCG, et al. Systematic evaluation of spinal cord injury animal models in the field of biomaterials. *Tissue Eng Part B Rev.* 2022;28:1169–79.
15. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *J Clin Epidemiol.* 2021;134:178–89.
16. Hooijmans CR, Rovers MM, de Vries RBM, Leenaars M, Ritskes-Hoitinga M, Langendam MW. SYRCLE's risk of bias tool for animal studies. *BMC Med Res Methodol.* 2014;14:43.