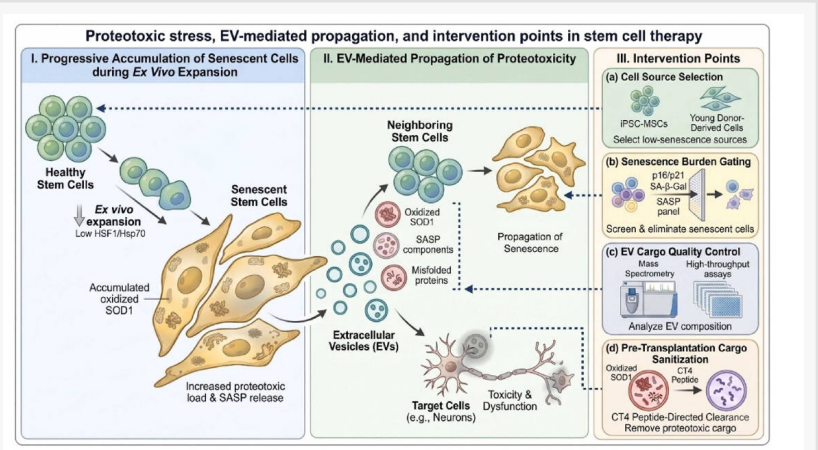
Cleaning up stem cell therapy: removing oxidized SOD1 restores youth and safety

GA, GA, UNITED STATES, August 18, 2026 /EINPresswire.com/ -- As stem cell therapies move from experimental trials into routine clinical practice, researchers are raising a critical alarm: current manufacturing standards may be missing a key factor that determines whether these treatments actually work. The protein quality control systems of donor cells—their capacity to maintain healthy proteins under stress—deteriorate as cells age during laboratory expansion, and this decline can turn therapeutic cells into sources of toxicity rather than repair. A new review argues that without assessing this "proteostatic fitness," even rigorously manufactured cell products could fail in patients.



From sick cells to sick neighbours: how senescent stem cells spread proteotoxicity via EVs – and how to stop it.

Stem cell therapies have expanded rapidly, with more than 115 clinical trials involving over 1,200 patients approved by late 2024. The U.S. Food and Drug Administration (FDA) recently approved Ryoncil (remestemcel‑L) for children with steroid‑refractory acute graft‑versus‑host disease, signalling a major shift toward routine clinical use. Yet current Good Manufacturing Practice (GMP) standards primarily evaluate identity, viability, sterility, and genetic stability—checks that researchers say are necessary but insufficient. These standards provide little insight into how cells will cope with the oxidative and inflammatory stress encountered after transplantation. Given these challenges, a deeper investigation into the role of donor cell protein homeostasis in therapeutic outcomes is urgently needed.

A team from the University of Manitoba (Canada) and Zhujiang Hospital of Southern Medical University (China) published (DOI: 10.1016/j.rerere.2026.06.004) their analysis in 2026 in the journal Regenesis Repair Rehabilitation. The review synthesises evidence from neural stem cell (NSC) research to propose that proteostatic fitness—the ability of cells to preserve protein balance under stress—should become a standard quality attribute in cell and extracellular vesicle (EV) manufacturing pipelines.

The core problem begins during ex vivo expansion, the laboratory process in which stem cells are multiplied before patient administration. As cells divide repeatedly, a subset becomes senescent—aged and dysfunctional. Senescent cells are marked by increased p16/p21 expression, senescence‑associated β‑galactosidase (SA‑β‑Gal) activity, and a pro‑inflammatory senescence‑associated secretory phenotype (SASP) rich in cytokines. More troubling, their protein quality control systems break down. In healthy mesenchymal stromal cells (MSCs), heat shock factor 1 (HSF1) triggers protective heat shock proteins like Hsp70 in response to stress. But in senescent cells this response is impaired due to declining HSF1 activity. The team's previous work in NSCs revealed a specific culprit: oxidised superoxide dismutase 1 (SOD1) protein accumulates during senescence and is packaged into EVs. These EVs then propagate neuronal toxicity and secondary senescence to recipient cells. Importantly, SOD1 is ubiquitously expressed—not just in neural cells—raising concerns that this proteotoxic transfer could extend beyond neurodegeneration, including amyotrophic lateral sclerosis (ALS). The review proposes four intervention points: selecting low‑senescence cell sources like induced pluripotent stem cell (iPSC)‑derived MSCs or young donor cells; establishing quantitative senescence thresholds (e.g., SA‑β‑Gal‑positive fraction below 10–15%) as batch release criteria; implementing proteomic profiling of EV cargo; and developing targeted pre‑transplantation "cargo sanitisation" strategies, such as the CT4 peptide that reduced spinal cord SOD1 burden by more than 50% in mouse models.

"The manufacturing standards we currently use tell us if cells are alive, pure, and genetically stable—but they don't tell us if those cells are actually fit to do their job once they're inside a patient," the authors said. "A cell therapy product could pass every existing quality check and still fail clinically because its protein quality control machinery can't handle the stress of the transplant environment. We need to start thinking of proteostatic fitness as a non‑negotiable quality attribute, not an optional extra."

The implications span multiple clinical applications. The recent FDA approval of Ryoncil for paediatric graft‑versus‑host disease highlights the urgent need to address batch‑to‑batch variability and the absence of standardised potency testing. In cardiac repair, MSC‑derived EVs have shown anti‑apoptotic and pro‑angiogenic effects, yet standard release criteria lack functional bioassays to detect donor‑dependent variation. For neurological conditions, intranasal administration of healthy MSC‑derived EVs has extended survival in SOD1‑G93A mouse models of ALS and shown benefit in a recent case report—but neither study characterised the proteostatic state of the parent cells. Adopting multi‑parameter senescence assessment, proteome‑informed EV cargo profiling, and targeted clearance of pathogenic proteins could bridge the gap between current GMP standards and the functional demands of the post‑transplantation environment. The authors emphasise that while the mechanistic foundation rests predominantly on NSC data, direct validation in MSC and iPSC‑derived systems remains a priority before universal thresholds can be established.

References

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Lucy Wang
BioDesign Research
email us here