CONCISE REVIEW

Are all stem cells equal? Systematic review, evidence map, and meta-analyses of preclinical stem cell-based therapies for bronchopulmonary dysplasia

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Abstract

Regenerative stem cell-based therapies for bronchopulmonary dysplasia (BPD), the most common preterm birth complication, demonstrate promise in animals. Failure to objectively appraise available preclinical data and identify knowledge gaps could jeopardize clinical translation. We performed a systematic review and network meta-analysis (NMA) of preclinical studies testing cell-based therapies in experimental neonatal lung injury. Fifty-three studies assessing 15 different cell-based therapies were identified: 35 studied the effects of mesenchymal stromal cells (MSCs) almost exclusively in hyperoxic rodent models of BPD. Exploratory NMAs, for select outcomes, suggest that MSCs are the most effective therapy. Although a broad range of promising cell-based therapies has been assessed, few head-to-head comparisons and unclear risk of bias exists. Successful clinical translation of cell-based therapies demands robust preclinical experimental design with appropriately blinded, randomized, and statistically powered studies, based on biological plausibility for a given cell product, in standardized models and endpoints with transparent reporting.

KEYWORDS

animal model, bronchopulmonary dysplasia, cell-based therapy, lung injury, network meta-analysis, preclinical, preterm birth, stem cells, systematic review, translation

1 | INTRODUCTION

Preterm birth complications have now surpassed infectious diseases as a leading cause of death in children below the age of 5 years.[1,2] Bronchopulmonary dysplasia (BPD), a chronic lung disease defined as oxygen requirement at 36 weeks' postmenstrual age, is the most common sequela of preterm birth affecting up to 40% of survivors.[3,4] BPD is strongly associated with late death or disability, and adds considerable economic burden to the health care system.[5,6] BPD is a multifactorial disease: prematurity, perinatal lung inflammation, growth restriction, mechanical ventilation, and oxygenation[7] lead to interrupted lung alveolar and vascular growth, often complicated by pulmonary hypertension.[8] None of the existing therapies have made any perceptible impact in reducing the burden of BPD among survivors.[9]

Stem cells are unique in their capacity to self-renew and differentiate into specialized cell types thereby promoting organogenesis, tissue regeneration, maintenance, and repair.[10] Therefore, regenerative cell-based therapy for BPD has received singular interest, with manifold preclinical studies testing assorted cell products for their feasibility, safety, and efficacy.[11] Although the fundamental mechanism of action of many of these therapies continues to be unraveled, mesenchymal stromal cells (MSCs), by virtue of their pleotropic effects, a

postulated paracrine-mediated action and apparent safety, have been extensively studied and already spawned numerous clinical trials (NCT03378063, NCT02443961, NCT01207869, NCT02381366, NCT01297205, NCT01828957, NCT01897987, NCT01632475, NCT03392467, and NCT02023788). Over the past 5 years, additional candidate cell therapies have proliferated, often without clear biological plausibility. The plethora of cell therapies warranted a systematic review to assess the extent of current evidence regarding preclinical safety and efficacy of available cell-based therapies in experimental BPD.

Systematic reviews can help assess the methodological quality of existing studies and assess their totality of findings, both of which can help inform the design of new experiments, provide evidence-based choice of animal models, and facilitate evidence-based translation from bench to bedside.[12] A meta-analysis, while being more robust than single animal studies, provides a comprehensive knowledge of treatment or efficacy by quantitatively combining study outcome data across experiments, thereby often resulting in more reliable conclusions [13,14] In many cases, new knowledge can be obtained by evaluation of heterogeneity between studies, which may affect the design of future animal or clinical experiments.[15] Failing to consider weaknesses of past evidence has historically resulted in failure of translation of promising therapies to the clinic. [16,17] Undeterred by the widespread heterogeneity in preclinical studies, stem cell therapy in cardiac repair advanced to clinical trials more than a decade ago, where it was found to be safe yet with inconsistent or conflicting benefit and today it is far from being an approved tool in the management of adult cardiac disease and is not much closer to becoming a clinical reality.[18,19] Even more telling is the translation failure in preclinical stroke research, given that of the over 500 interventions deemed beneficial only one was found to be effective in a clinical trial.[20]

The purpose of this systematic scoping review was to draw an evidence map of existing primary studies of cell-based therapies for BPD that have been studied in the preclinical setting, an approach that will further the research community's understanding and awareness regarding the current distribution of evidence in the field of interest.[21,22]

2 | METHODS

This mapping exercise was carried out to address the following broadly framed research question of interest: "In controlled preclinical studies of BPD, do cell-based therapies reduce the severity of lung injury?" The protocol, developed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)-P checklist,[23] was prospectively registered and is available on the Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies website (CAMARADES).[24] We followed the PRISMA guidelines[25] in preparing this manuscript.

Please refer to the Online Supplement for detailed description of methods including search strategy, process of study selection, study eligibility criteria, data collection, risk of bias assessment, evidence summaries, exploratory meta-analyses, post hoc amendments to

Significance statement

Bronchopulmonary dysplasia (BPD), a chronic lung disease that follows ventilator and oxygen therapy for acute respiratory failure after premature birth, is the most frequent complication of extreme prematurity. BPD is associated with long-term respiratory and neurological consequences reaching into adulthood and currently lacks effective therapy. Regenerative cell-based therapy, demonstrating therapeutic benefit in experimental neonatal lung injury, has now spawned clinical trials. Yet there has been no systematic review to assess the extent of current evidence regarding safety and efficacy of cell-based therapies in preclinical BPD and identify gaps that could jeopardize successful clinical translation.

exploratory network meta-analysis (NMA), and details of the NMA model.

3 | RESULTS

3.1 | Extent of literature identified

A flow diagram of the study selection process is presented in Figure 1. A total of 2464 unique abstracts remained for screening following removal of duplicates across databases. Based on relevancy screening, a total of 87 remained for the full text evaluation. A total of 53 of these articles were retained for final inclusion;[26–78] reasons for exclusion at full text screening are provided in Figure 1. Supplemental Table S1 presents an overview of the set of included studies, the characteristics of which are described in the subsequent sections below.

3.2 | Overview of study characteristics and study populations

The majority of included studies were published during the last decade, with a median year of publication of 2013 (range 2007-2017) (Supplemental Table S1). Although often unreported, the median sample size among studies (where available) was 56 (range 15-166). Rodents were used to model BPD in nearly all studies, with the lamb model being the solitary exception.[36,45,64] Induction of the BPD model, for the most part, was by hyperoxia where the O_2 concentrations ranged from 60% to 95% and the duration of exposure ranged from 3.5 to 28 days. Alternate models included bleomycin,[60] prenatal LPS in combination with postnatal hyperoxia,[29] prenatal LPS,[64] mechanical ventilation (2-12 hours),[36] and hypoxia followed by hyperoxia.[47]

3.3 | Overview of interventions assessed

The range of cell therapy interventions identified across studies is outlined in Table 1. "Cell-containing" therapies represented the majority of the interventions tested in preclinical BPD. These included MSC (n = 35
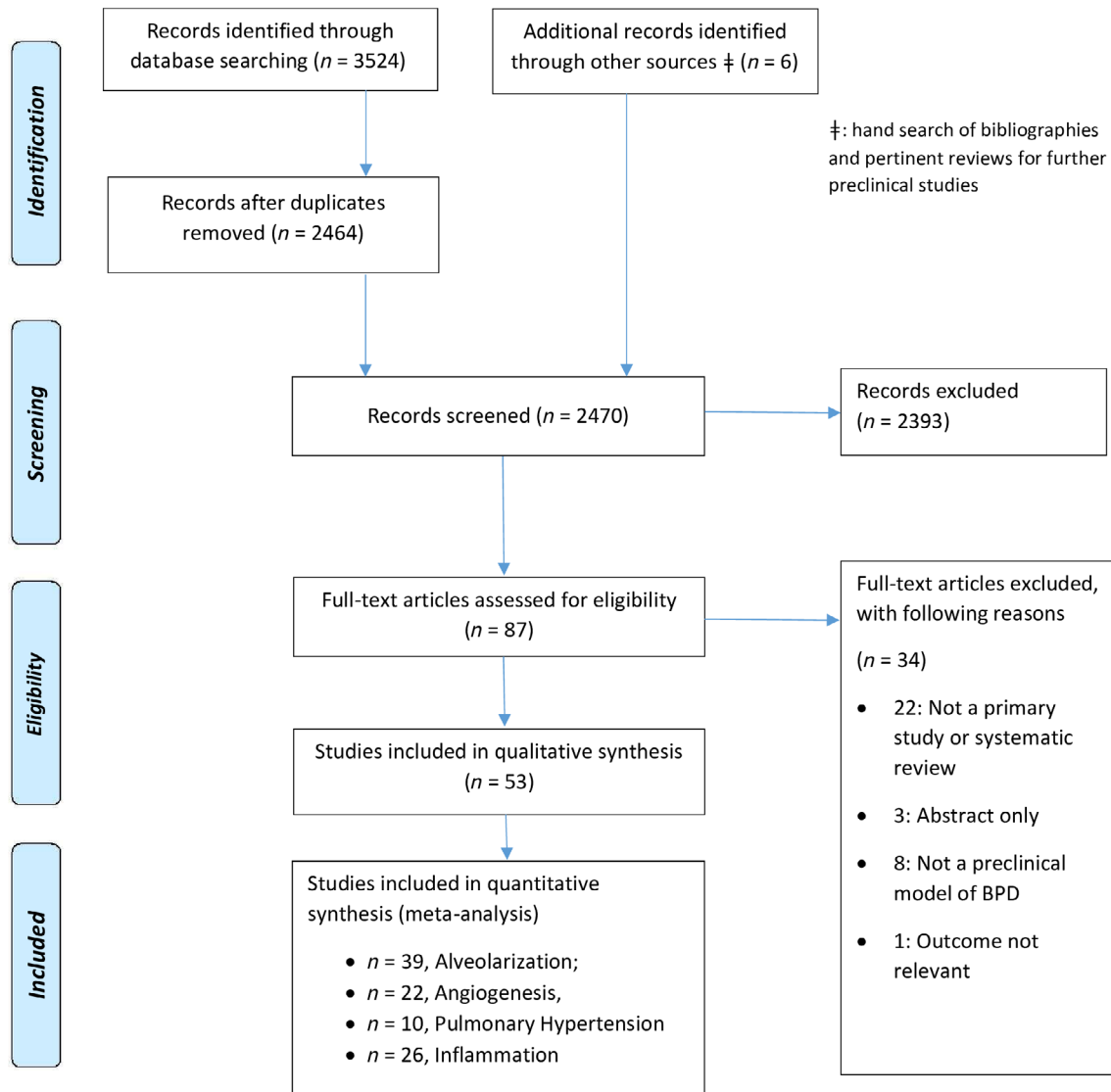
FIGURE 1 PRISMA 2009 flow diagram. "Other sources" refer to hand search of bibliographies of included studies and pertinent reviews for further preclinical studies

studies),[26–29,32,34,35,37,39,40,42,43,48,49,51–53,55–59,61–63,66,68–70,72,73,75–78] human amniotic epithelial cells (hAEC, n = 4),[36,64,65,74] mononuclear CD34 + (n = 4),[27,30,46,47] endothelial colony forming cells (ECFC, n = 3),[46,64,70] endothelial progenitor cells (EPCs, n = 3),[31,41,71] bone marrow derived angiogenic cells (BMDAC, n = 1),[71] bone marrow derived (BM) ckit+ cells (n = 1),[50] cord blood CD34 + (n = 1),[44] human amniotic fluid stem cells (hAFSC, n = 1),[33] human-induced pluripotent stem cells (hiPSC)-derived lung progenitor cells (LPC, n = 1),[53] hiPSC-derived alveolar epithelial cells (AEC, n = 1),[53] and undifferentiated hiPSC (n = 1).[53] In contrast, fewer "Cell-free" therapies were investigated, and these included MSC-derived conditioned media (CdM, n = 6),[34,35,48,49,56,66] ECFC-Conditioned media (CdM, n = 2),[38,60] or MSC-derived exosomes (n = 1).[67] The control groups were most often treated with saline (n = 32)[26–32,34,37,40,44,46,47,49,51,52,56–59,61,62,64,65,68–72,74,77] or with a control cell/ cell-free media (n = 12).[33,35,46,48–50,53,60,63,66,67,78] Rarely, the control would receive no treatment (sham control) (n = 2).[36,39]

3.4 | Overview of outcomes

The range of clinical outcomes assessed across the set of included studies is outlined in Supplemental Table S2. We systematically collected a listing of all outcome measures reported from studies meeting our eligibility criteria to establish an understanding of the information available from these studies. For the purposes of the current review, overviews and syntheses were focused on four measures: alveolarization, lung angiogenesis, pulmonary hypertension, and lung inflammation.

Alveolarization was examined as an outcome in 47 of the 53 studies.[26–44,46–53,55–58,60,62–67,69,71–78] Lung angiogenesis was investigated as an outcome in 24 primary studies,[26,27,29,31,35,38,39,41–43,48,51,52,54–56,60,63,67,70,71,73–75] pulmonary hypertension in 13 studies,[35,38,48–52,56,60,63,66,67,74] and lung inflammation was tested using 32 biomarkers of inflammation (among which we focused on IL-1a, IL-1b, IL-6, TNF-α, TGF-β1, or their mRNA, macrophages, and neutrophils).[26–29,36,37,39,42,45,49,51,52,55–59,61,62,64,65,69,70,72–78]

TABLE 1 Interventions for bronchopulmonary dysplasia (BPD) investigated in preclinical studies

| Intervention category/class	# studies (with references)
Cell-based therapy	
1. Mesenchymal stromal cell (MSC)	35[26–29,32,34,35,37,39,40,42,43,48,49,51–53,55–59,61–63,66,68–70,72,73,75–78]
2. Human amnion epithelial cells (hAEC)	4[36,64,65,74]
3. Mononuclear CD34+	4[27,30,46,47]
4. Endothelial colony forming cells (ECFC)	3[46,64,70]
5. Endothelial progenitor cells (EPCs)	3[31,41,71]
6. Bone marrow derived angiogenic cells (BMDAC)	1[71]
7. Human amniotic fluid stem cells (hAFSC)	1[33]
8. Cord blood (CB) CD34+	1[44]
9. Bone marrow (BM) derived ckit+ cells	1[50]
10. Undifferentiated human-induced pluripotent stem cells (hiPSC)	1[53]
11. hiPSC-derived LPSCs	1[53]
12. hiPSC-derived AECs	1[53]
Cell-free therapy	
1. MSC conditioned media	6[34,35,48,49,56,66]
2. MSC exosome	1[67]
3. ECFC-conditioned media	2[38,60]

TABLE 2A Risk of bias
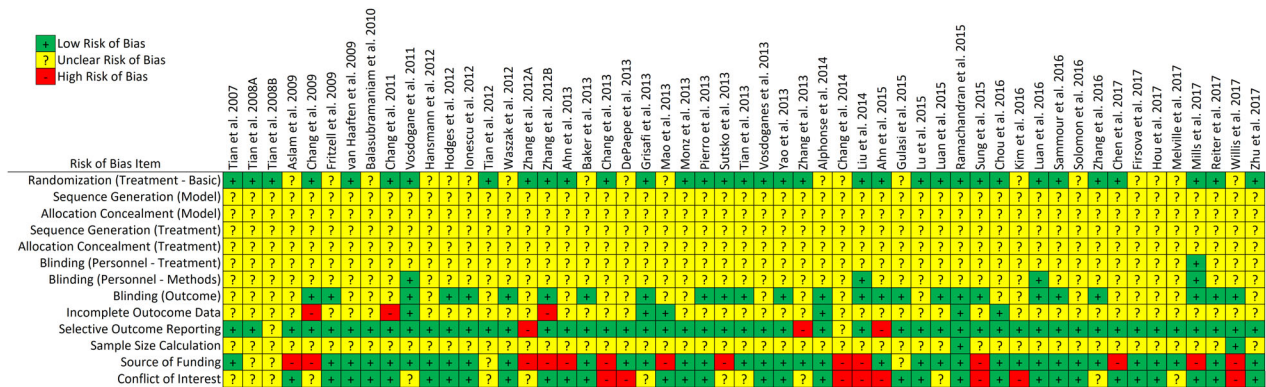
TABLE 2B Risk of bias
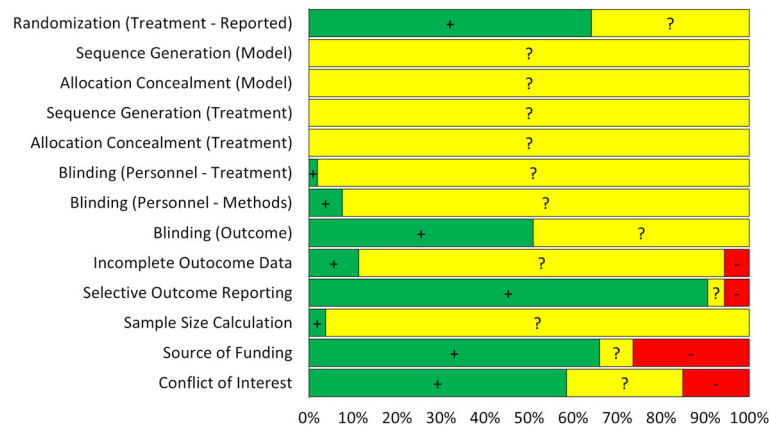
3.5 | Risk of bias evaluations

The risk of bias assessment from the 53 studies is presented in Table 2A (individual studies) and Table 2B (overall). Although 34 of the studies (66%, Table 2B) reported randomizing animals to treatment, none described the method of randomization (ie, sequence generation). None of the included studies described their methods of allocation concealment. Blinding was reported rarely and inconsistently depending on where in the experimental process the blinding occurred (Table 2B), with blinding of outcome assessment being the most frequent (51%, Table 2B). Although only six studies (11%) reported that no animals were lost due to dropouts (attrition bias), 100% reported the outcome in both the methods and results of the study. Two studies (4%) reported how the sample size was calculated, whereas the remaining studies were unclear (Table 2B). The source of funding was always reported in sufficient detail to assess risk of bias. In total, 35 (66%) studies reported a nonindustry source of funding that was a low risk of bias, with 14 (27%) reporting industry funding that presented a risk of bias (Table 2B). Finally, 31 (59%) studies

reported no conflicts of interest, 8 (15%) reported a conflict, and 14 (26%) were rated as unclear for not reporting whether conflicts of interest existed or not (Table 2B).

3.6 | Summary of authors' conclusions regarding interventions

Supplemental Table S1 presents the individual categorizations of author interpretations drawn, whereas Supplemental Table S4 provides an overview of these interpretations categorized by the strength of conclusion. In considering findings observed across all outcome measures, the appraisal of the effects of cell-based therapies, overall, concluded benefit. "Beneficial" therapies included MSC,[26–29,34,35,37,39,40,42,43,48,49,51–53,55–59,61–63,66,68–70,72,73,75–78] ECFC,[38] EPC,[31,41] BMDAC,[71] hAEC,[36,74] hAFSC,[33] hiPSC-derived LPC,[53] and hiPSC-derived AEC.[53] Different from this were "probably beneficial" therapies which included ECFC,[60] hAEC,[60,64,65] CB CD 34+,[44] Mononuclear CD 34+,[46,47] and BM Ckit+.[50] Furthermore, two studies with Mononuclear cells (MNC) (different animal species,
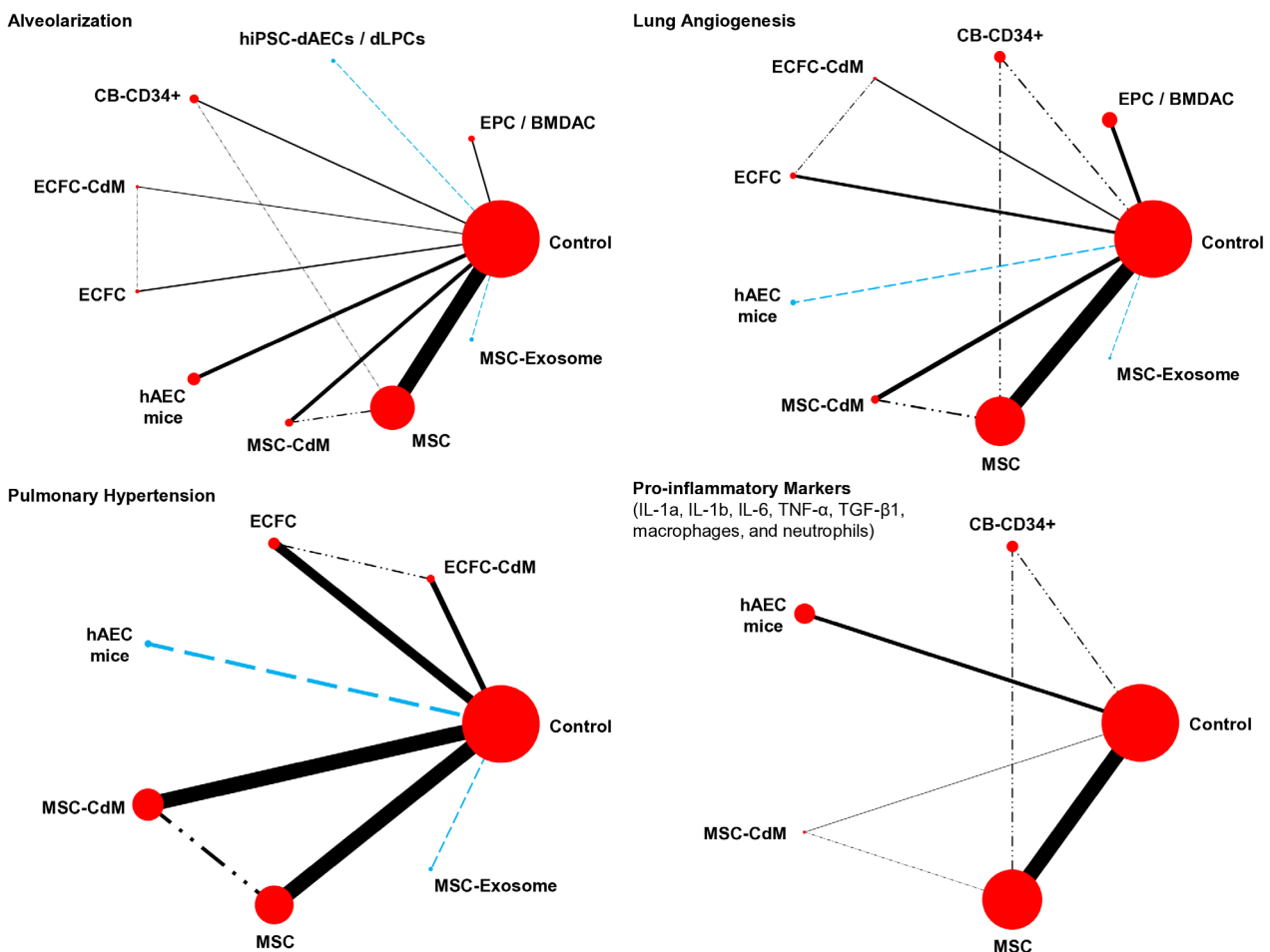
FIGURE 2 Network diagrams underlying exploratory network meta-analyses (NMAs). The blue-colored dashed lines represent comparisons between interventions which were assessed in a single study vs bronchopulmonary dysplasia (BPD)-only control. The dash-dotted lines represent comparisons that were assessed in a single study but involved intervention(s) other than control. Nodes are proportionately sized to reflect the numbers of animals studied with each intervention. Edge width reflects the number of experiments or metrics for each comparison

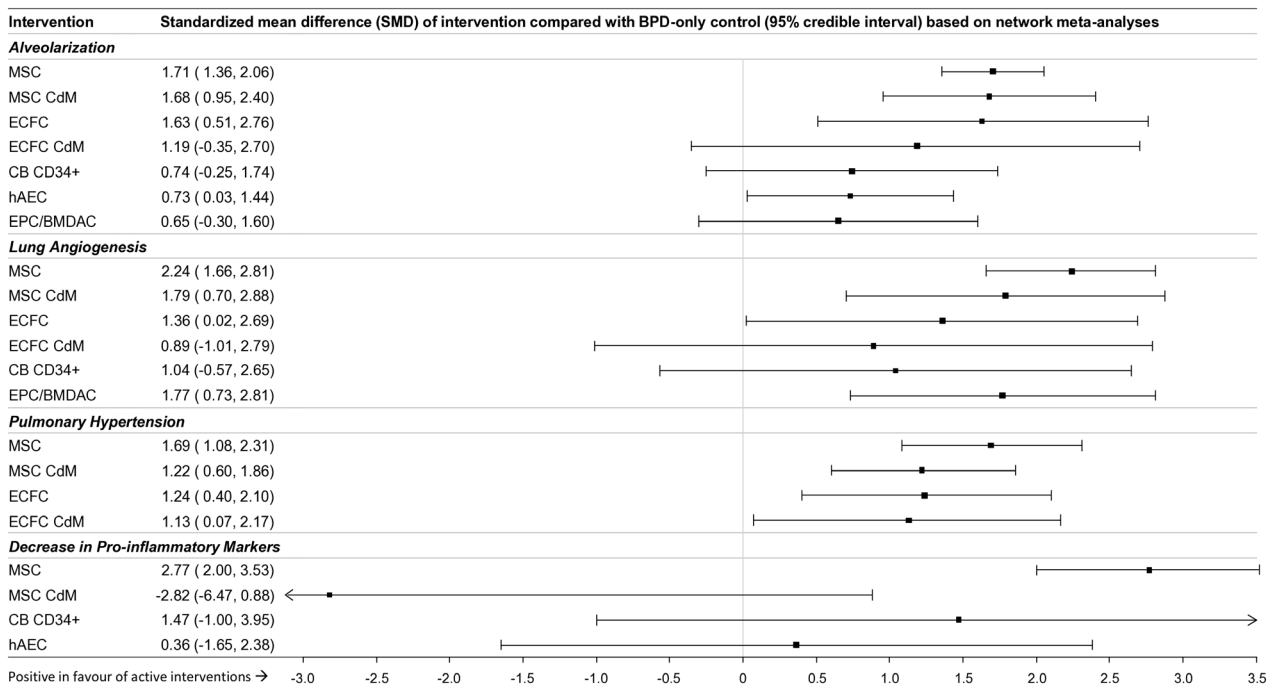| Intervention	Standardized mean difference (SMD) of intervention compared with BPD-only control (95% credible interval) based on network meta-analyses
Alveolarization	
MSC	1.71 (1.36, 2.06)
MSC CdM	1.68 (0.95, 2.40)
ECFC	1.63 (0.51, 2.76)
ECFC CdM	1.19 (-0.35, 2.70)
CB CD34+	0.74 (-0.25, 1.74)
hAEC	0.73 (0.03, 1.44)
EPC/BMDAC	0.65 (-0.30, 1.60)
Lung Angiogenesis	
MSC	2.24 (1.66, 2.81)
MSC CdM	1.79 (0.70, 2.88)
ECFC	1.36 (0.02, 2.69)
ECFC CdM	0.89 (-1.01, 2.79)
CB CD34+	1.04 (-0.57, 2.65)
EPC/BMDAC	1.77 (0.73, 2.81)
Pulmonary Hypertension	
MSC	1.69 (1.08, 2.31)
MSC CdM	1.22 (0.60, 1.86)
ECFC	1.24 (0.40, 2.10)
ECFC CdM	1.13 (0.07, 2.17)
Decrease in Pro-inflammatory Markers	
MSC	2.77 (2.00, 3.53)
MSC CdM	-2.82 (-6.47, 0.88)
CB CD34+	1.47 (-1.00, 3.95)
hAEC	0.36 (-1.65, 2.38)

Positive in favour of active interventions → -3.0 -2.5 -2.0 -1.5 -1.0 -0.5 0 0.5 1.0 1.5 2.0 2.5 3.0 3.5

FIGURE 3 Forest plots of the estimated standardized mean differences (SMDs) compared to bronchopulmonary dysplasia (BPD)-only control for each outcome. The SMDs (with 95% credible intervals) were estimated from the random-effects consistency model. A, Alveolarization; B, lung angiogenesis; C, pulmonary hypertension; D, lung inflammation: pro-inflammatory markers

route, hyperoxia duration and the dose of MNCs),[27,30] one study with MSCs (intranasal route)[32] and one with embryonic EPC,[71] concluded that these therapies were not effective. Conversely, four therapies, EPC Cultured (aberrant tissue formation in lungs and inflammation),[31] miPSC (cystic teratomas),[53] mESC (fibrosarcomas),[53] and hiPSC (lung teratomas and perivascular infiltration of the lungs, liver, heart, and kidneys)[53] were found to be harmful, although the translational potential of these therapies remains circumspect, as the rationale behind the use of these cells in the primary studies remains unclear. Although these negative effects were anticipated with iPSCs and ESC, the finding with cultured EPCs was unexpected and warrants further studies.

Following the criteria of interventions for NMA described in the Methods section, a total of 39, 22, 10, and 26 studies remained for each of the outcomes of alveolarization,[27–32,35,37–44,46,48,49,51–53,55–58,60,62,63,65,66,69,71–78] lung angiogenesis,[26,27,29,31,35,38,39,41–43,48,51,52,54–56,60,63,70,71,73,75] pulmonary hypertension,[35,38,48,49,51,52,56,60,63,66] and inflammation (seven pro-inflammatory markers: IL-1α, IL-1β, IL-6, TNF-α, TGF-β1, or their mRNA, and macrophages, neutrophils),[26–29,37,39,43,45,51,52,55–59,61,62,64,65,69,72,74–78] respectively. Network diagrams describing the evidence base for each of the four outcomes are presented in Figure 2.

Figure 3 presents forest plots of findings for all four outcomes with estimated standardized mean differences (SMDs) of interventions compared with BPD-only control, whereas Supplemental Table S5 and Online Appendix 4 present a summary of secondary measures (including SUCRA and treatment rankings). Online Appendix

5 presents the league tables of posterior median pairwise SMDs with 95% credible intervals in the lower triangle of the league tables, and the pairwise probabilities that an intervention is better than another in the upper triangle.

4 | DISCUSSION

Our exploratory NMAs represent the first and most expansive synthesis of data on cell-based therapies in preclinical BPD. We found 15 distinct cell-derived therapies, largely tested in the hyperoxic rodent model of BPD. MSCs appear as the most effective cell-based therapy for all the four clinically relevant outcomes of alveolarization, lung angiogenesis, pulmonary hypertension, and lung inflammation. The second-ranked therapy was contingent on the outcome: MSC-CdM for alveolarization and lung angiogenesis, ECFC for pulmonary hypertension, and CB CD34+ for lung inflammation. Although a broad range of promising cell-based therapies has been assessed, few head-to-head comparisons and unclear risk of bias exist.

4.1 | External validity and implications for preclinical research

4.1.1 | Replicative or duplicative research: When too much is too little and small is not enough

MSCs and MSC-derived conditioned media made up for the biggest share (84%) of cell-based therapies investigated in experimental BPD over the last decade, from 2007 to as recent as 2017. Conspicuously,

this therapy was investigated solely in the hyperoxic rodent model of BPD. Although a well-established model, other animal models do exist.[80,81,88] Replicability and reproducibility is key in preclinical research, as single experiments must be repeated (replicability) and research hypotheses constantly reexamined by independent observers to confirm and corroborate one another's findings (reproducibility), thereby conferring confidence to conclusions drawn from them. We found that 34 of 35 studies (97.1%) on MSCs concluded a beneficial therapeutic effect in ameliorating neonatal lung injury in the select hyperoxic rodent model, and that this research finding is well endorsed in this model. Therefore, one could argue, repeating confirmatory experiments in the same model no longer adds to the knowledge base and, in fact, risks becoming duplicative. This duplication is intrinsically wasteful and should be guarded against.[91,92] One means by which to avoid such waste is by investigating this promising therapy in diverse and larger animal models such as the fetal lamb model[80] or the nonhuman primate model,[88] recreating the clinical setting of preterm birth and respiratory failure demanding extended invasive mechanical ventilation with oxygen-rich gas and reproducing the evolving pathophysiology of human neonatal BPD. Such a complementary approach, an important attribute in research, could potentially fast track (or reconsider) the successful translation of such therapies into the clinic while addressing regulatory concerns.[79] MSCs have advanced to Phases I and II clinical trials without undergoing testing in larger animal models.

Alternate therapies to the widely used MSCs have been investigated, although these are few and far between. EPCs were found to be beneficial in two out of three studies, whereas ECFC (one of two) and hAEC (two of four) were found to be beneficial in half the studies they were investigated in Supplemental Table S4. Of note is the spread of ECFC and hAEC in both "beneficial" and "probably beneficial" categories. This could be attributed to the use of a diverse induction (Bleomycin[60]) or animal model (fetal lamb[64]). Authors investigating mononuclear cells speculated on their probable benefit, whereas others determined that these cells had no effect (Supplemental Table S4). At this juncture, the unambiguous benefits of these alternate therapies require further compelling evidence as they await further replication and continuing complementary research. Refreshingly, hAEC were explored not only in the ubiquitous rodent model, but also in a larger animal model (fetal lamb)[36,64] with the use of diverse modes of injury induction.

4.1.2 | Isolated exploratory research: A research waste?

In contrast, we identified a number of isolated therapies that were investigated in single exploratory experiments (BMDAC, hAFSC, and BM-derived Ckit+).[33,50,71] The rationale for testing these novel therapies ranged from speculative role for a bone marrow-derived cell population in the maintenance of adult lung structure exposed to hyperoxia (BMDAC), likeness to MSC (hAFSC) or promise demonstrated in adult cardiac repair (Ckit+), although the research integrity of the latter has been recently brought into question.[93] Exploratory studies are precisely articulated hypothesis-generating research based

on sound scientific rationale and may involve demonstrating a dose-response relationship. These studies are further tested in confirmatory studies which are akin to clinical trials in terms to rigor and quality, confirming or rejecting the hypothesis in terms of safety and efficacy.[79] Despite being described as beneficial in studies dating back to between 2010 and 2015, the findings for these exploratory interventions have not been reproduced or replicated to date. Robust, reproducible research is the cornerstone on which scientific discoveries are made. Irreproducibility remains a challenge in preclinical research when upward of 50% findings fail replication resulting in over $28 billion US/y in preclinical research waste.[89] Reasons for irreproducibility could be observer bias or confirmation bias. Other opportunities for improvement include: following through with promising cell products, use of bona fide controls, validation of reagents, and the use of appropriate statistical tests.[82]

4.1.3 | Interstudy standardization of experimental design

Poorly connected network

Since head-to-head preclinical trials ascertaining the comparative efficacy of every single cell-based intervention may not be feasible, NMA, which allows for the synthesis of direct and indirect evidence, is a useful alternative.[90] Although MSCs were found to be the most heavily investigated cell therapy in our mapping of the evidence base, remarkably, there were only two direct comparisons between this preferred therapy and alternate therapies, such as MSC-Cdm and CB-CD34+. The reliance on extensive indirect comparisons in our meta-analysis resulted in poorly connected networks, as illustrated by the network diagram for all four outcomes (Figure 2). Findings from meta-analyses based upon such networks may be less reliable than those from networks wherein most therapies have been directly compared.[83] For this reason, there is a need to rethink current experimental modeling strategies and promote collaboration and reciprocity between independent research teams in designing experiments which directly compare, where indicated, some of these interventions. Remaining evidence gaps could potentially be filled by a NMA, thereby allowing evidence-based choice of therapies which are not only the most efficacious in the animal model but also have the highest chance of translational success.

Standardization of metrics measuring identical outcomes

We observed an array of measurements being used to assess identical outcomes. For instance, 32 different biomarkers were used across 31 included primary studies to assess lung inflammation alone. Furthermore, many of these biomarkers were measured using assorted techniques (eg, mRNA vs protein), precluding interstudy comparison, synthesis, and subsequent translatability to clinic trials. Although exploratory studies may justify the use of novel measurements of common outcomes, there is a need to collaboratively develop an essential minimal set of measurements for outcomes in exploratory and confirmatory studies and promote minimal a priori reporting standards for these outcome data which are not only coherent but also

verifiable and comparable.[84] Specifically, investigation of lung morphometry by adopting state of the art and unbiased stereological methods and guidelines will improve the validity and uniformity of structural assessment in lung biology.[85]

Preclinical alliance for successful translation

Given the preceding contentious issues, there is a need to promote a preclinical network where independent laboratories with expertise in well-endorsed animal models can transparently share standardized models and protocols: collaborate on multicenter, randomized, blinded, and well-powered preclinical studies with a priori outcomes, sample size, and exclusion criteria.[86]

4.2 | Implications for clinical trial design and successful translation

Please see Online Supplement for discussion on candidate therapy for clinical trials manufacturing challenges, trial design, optimal route of administration, dose, and dose frequency.

4.3 | Strengths and limitations

The strengths of our systematic review include a rigorous peer-reviewed search strategy and use of international guidance and standards to conduct our systematic review and NMA (Online Appendix 8).[87] However, our review was limited by the fact that a large number of published data were available only in the form of figures and not in an easily extractable numerical form. Almost all the data were extracted from the figures in the published article using an open source program that can work with a variety of plot types and images. Minor distortion of data is possible, but all groups would be equally affected. Also, incorrectly reported SDs/SEMs could have potentially impacted SMD estimates. Additionally, to facilitate data synthesis, we made several post hoc variations (Online Appendix 9). Furthermore, the risk of bias assessment for the primary studies was hampered by poor reporting quality of important domains such as randomization, blinding, and sample size calculation. Finally, high prevalence of publication bias in animal research and bloated effect sizes causing potentially biased conclusions is a cause for concern.[94]

5 | CONCLUSION

In this systematic review incorporating exploratory NMAs on cell-based therapies in preclinical BPD, MSCs appeared as the most efficacious among all interventions, although exclusively investigated in the rodent hyperoxic model of BPD. Numerous limitations point toward the need for more robust experimental design and reporting in preclinical studies including due consideration of the biological plausibility for a given cell product, use of standardized models and endpoints appropriately powered for statistics, blinding, and randomization. Adoption of these considerations may enhance the successful translation of cell-based therapies into the clinic.

AUTHOR CONTRIBUTIONS

S.A.: conception and design, collection and/or assembly of data, manuscript writing, final approval of manuscript; W.C.: collection and/or assembly of data, manuscript writing, final approval of manuscript, design, data analysis and interpretation; M.T.A.: collection and/or assembly of data, final approval of manuscript, design; M.L.C., S.M.C. L.: collection and/or assembly of data, final approval of manuscript; B. H.: final approval of manuscript, critical revisions to the manuscript; B. T.: conception and design, manuscript writing, final approval of manuscript, financial support.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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