



HUMAN CLINICAL ARTICLE

Benefits and obstacles to cell therapy in neonates: The INCuBAToR (Innovative Neonatal Cellular Therapy for Bronchopulmonary Dysplasia: Accelerating Translation of Research)

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Abstract

Cell-based therapies hold promise to substantially curb complications from extreme preterm birth, the main cause of death in children below the age of 5 years. Exciting preclinical studies in experimental neonatal lung injury have provided the impetus for the initiation of early phase clinical trials in extreme preterm infants at risk of developing bronchopulmonary dysplasia. Clinical translation of promising therapies, however, is slow and often fails. In the adult population, results of clinical trials so far have not matched the enticing preclinical data. The neonatal field has experienced many hard-earned lessons with the implementation of oxygen therapy or postnatal steroids. Here we briefly summarize the preclinical data that have permitted the initiation of early phase clinical trials of cell-based therapies in extreme preterm infants and describe the INCuBAToR concept (Innovative Neonatal Cellular Therapy for Bronchopulmonary Dysplasia: Accelerating Translation of Research), an evidence-based approach to mitigate the risk of translating advanced therapies into this vulnerable patient population. The INCuBAToR addresses several of the shortcomings at the preclinical and the clinical stage that usually contribute to the failure of clinical translation through (a) systematic reviews of preclinical and clinical studies, (b) integrated knowledge transfer through engaging important stakeholders early on, (c) early economic evaluation to determine if a novel therapy is viable, and (d) retrospective and prospective studies to define and test ideal eligibility criteria to optimize clinical trial design. The INCuBAToR concept can be applied to any novel therapy in order to enhance the likelihood of success of clinical translation in a timely, transparent, rigorous, and evidence-based fashion.

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KEYWORDS

clinical translation, lung injury, mesenchymal stromal cells, preterm birth, regenerative medicine

1 | MESENCHYMAL STROMAL CELLS FOR COMPLICATIONS OF PRETERM BIRTH

Bronchopulmonary dysplasia (BPD), defined as need for oxygen and/or respiratory support at 36 weeks' corrected age, is the most frequent sequela of prematurity.^{1,2} BPD contributes to lifelong respiratory and neurological impairment resulting in increased health care costs and parental burden.³ BPD occurs in neonates born during the late canalicular stage of lung development when critical components of lung vascularization and gas exchange are just being established.² BPD is a multifactorial disease in which inflammation, oxidative stress, and mechanical stretch disrupt the normal sequence of lung growth.² As a consequence, the prevention of lung injury has become increasingly more challenging with no progress over the past decade.⁴

Preclinical proof-of-concept^{5,6} and exploratory studies⁷ demonstrate that mesenchymal stromal cells (MSCs) from various sources prevent oxygen-induced lung injury in a widely used neonatal rodent model mimicking some aspects of BPD. MSCs have been ascribed pleiotropic effects (eg, anti-inflammatory, proangiogenic, antifibrotic, and antioxidative), making MSC therapy very appealing for a multifactorial disease such as BPD.⁸ Furthermore, many of the healing molecules released by MSCs, such as keratinocyte growth factor, insulin growth factor-I, and angiogenic growth factors, are known to promote lung growth, and this is of specific interest for the preterm lung. These data provide strong biological plausibility for the use of MSCs in BPD. Fueled by these promising preclinical findings, early phase clinical trials testing the safety and feasibility of MSC and other cell therapies for BPD have already been completed.⁹⁻¹¹ Many more trials are ongoing or in the planning phase, indicating the heightened recognition of the potential benefits of neonatal cell therapy for BPD and other complications of prematurity.

This current enthusiasm is reminiscent of the “Heroic” years (1950-1970) of neonatology when a “great spirit of innovation, somewhat lacking in discipline” was accompanied by the most striking care changes and errors in neonatology.¹² Avoiding errors of the past^{13,14} and overcoming obstacles to progress for cell therapy in this vulnerable patient population is the focus of the INCuBAToR (Innovative Neonatal Cellular Therapy for BPD: Accelerating Translation of Research), a multidisciplinary and evidence-based engine to ensure safe and timely translation of promising advanced therapies from the bench to the bedside. The importance of evidence-based medicine has again come to the forefront in the current pandemic and the race to find efficient treatments for COVID-19-related complications.¹⁵

Lessons learned

The INCuBAToR concept is an evidence-based approach to mitigate the risk of translating advanced therapies into vulnerable extreme preterm infants but can be applied to any population and any novel therapy. The INCuBAToR presents a unique translational research platform that offers a comprehensive infrastructure to design translational research including expertise in trial design, knowledge synthesis, economic evaluation, and knowledge translation. It aims to facilitate and enable timely and robust evaluation of promising therapeutics to help bring effective therapeutics to patients sooner.

Significance statement

Cell-based therapies offer exciting opportunities to curb complications of extreme preterm birth, the main cause of death in children aged 5 years or younger. Although early phase clinical trials have begun, the translation of promising therapies often fails. Here the INCuBAToR concept, an evidence-based approach to mitigate the risk of translating cell-based therapies into a vulnerable patient population, is introduced. The INCuBAToR concept can be applied to any novel therapy to enhance the likelihood of success of clinical translation in a timely, transparent, rigorous, and evidence-based fashion.

2 | THE INCuBAToR TO ENHANCE THE SUCCESS OF CLINICAL TRANSLATION OF MSCS FOR BPD

Translation of potentially life-saving therapies is unacceptably slow and often fails. In neonatology, it took decades to bring breakthrough therapies from discovery to approval by the U.S. Food and Drug Administration: over 30 years for surfactant¹⁶ and 20 years for inhaled nitric oxide.¹⁷ More worrisome is that less than 5% of high impact preclinical reports are being clinically translated and only 11% of those tested clinically ultimately receive licensing.¹⁸ The underlying reasons for failure are multifactorial; however, issues highlighted by others and our group include (a) lack of rigorous preclinical and clinical research methodology; (b) failure to properly synthesize current evidence to help justify and inform trial design¹⁹; (c) logistical, institutional, and regulatory obstacles at the clinical stage that add years to scientific development; and (d) failure to address concerns of ethics

boards and regulatory agencies as the result of failing to engage these stakeholders early in the translation process.²⁰ There is also failure to appreciate concerns of critical stakeholders, such as patients and their surrogates where relevant (in our case, parents) and clinicians, when establishing eligibility criteria, specifics of the intervention, and outcomes to be assessed in a clinical trial. This ultimately contributes to poor patient recruitment to trials. Moreover, eligibility criteria for trials of novel therapies are often too restrictive, resulting in failure to accrue sufficient patients within the target time. Finally, even in the case of successful therapies, the early economic consideration is often overlooked by investigators, leading to delayed commercialization of the therapy and reimbursement, which are necessary steps for clinical adoption. The INCuBAToR (Figure 1) is a novel, translational engine that can enhance speed, efficiency, rigor, and thus success for the clinical development of MSC therapy in neonatology. As outlined below, this approach was successfully applied to launch HULC-I, a phase I trial for MSC in BPD (ClinicalTrials.gov NCT04255147). A similar evidence-based approach—EPICOT (previous evidence, population to include, intervention to evaluate, comparison groups to identify, outcomes to define, and time over which the outcomes will be assessed)—has been successfully used to establish a consensus on designing efficient and consistent clinical trials for the intravenous use of MSCs for inflammatory bowel disease.²¹

2.1 | Systematic reviews of preclinical and clinical studies

Systematic reviews and meta-analyses (SRMAs) provide the most robust and evidence-based overview of the evidence on a topic and can point out knowledge gaps and thus guide future studies. Yet, their application to first-in-human trials has been limited and preclinical SRMAs for neonatal interventions were until recently nonexistent. We undertook two systematic reviews (SRs) to justify and inform our clinical trial: (a) a preclinical SR of studies testing MSCs in experimental models of neonatal lung injury and (b) a clinical SR to examine evidence for MSCs in BPD.

2.1.1 | Preclinical systematic review of evidence

Using SR methodologies described by the Cochrane Collaboration²² and modified for preclinical SRs,²³ we performed an SRMA on preclinical studies testing MSCs in experimental models of neonatal lung injury. We developed systematic strategies to search MEDLINE, Embase, BIOSIS, and Cochrane databases in collaboration with an information specialist. Validated filters were applied to improve search efficiency and strategies underwent peer review of electronic search strategy.²⁴ Two reviewers independently screened studies. Relevant data were extracted and summarized and meta-analysis performed where appropriate. The study protocol was registered through CAMARADES (www.CAMARADES.info). This SRMA included 25 studies with over 450 animals used in 33 individual experiments and

suggested the beneficial effects of MSCs on lung structure, inflammation, and other parameters.⁷ Of note, all studies used exclusively newborn rodents exposed to hyperoxia, highlighting the importance of experiments in large animal models to address important endpoints not obtainable in small rodents and additional safety data critical for regulatory agencies. Importantly, unclear risk of bias and incomplete reporting in the primary studies revealed nonadherence to reporting standards, emphasizing potential obstacles to successful clinical translation based on flawed preclinical data and the need to reinforce implementation of reporting standards such as the ARRIVE guidelines²⁵ (www.nc3rs.org.uk/arrive-guidelines). Because of the burst of preclinical MSC studies in the most recent literature and the emergence of novel cellular therapies, we updated our SR and included a network meta-analysis to compare these various cell products. Fifty-three studies assessed 15 different cell-based therapies, and 35 of those studied the effects of MSCs almost exclusively in hyperoxic rodent models of BPD.²⁶ The exploratory meta-network analysis suggested that MSCs are the most effective therapy with few head-to-head comparisons, highlighting again the relative youth of cell therapy in the neonatal arena. The unclear risk of bias still existed in most studies; however, many preclinical journals are now enforcing data transparency and reporting guidelines—at least for confirmatory research²⁷—pushing a methodology resembling norms for randomized clinical trials.²⁸ These measures should decrease waste, improve quality and rigor in the reporting of preclinical studies, and thus generate a stronger foundation on which to make sound decisions to initiate clinical trials.²⁹

2.1.2 | Clinical systematic review of evidence

A systematic review to establish the current clinical evidence for MSCs in BPD further revealed the early stage of MSC therapy in neonatology.³⁰ We used the standard search strategy of the Cochrane Neonatal review group (<https://neonatal.cochrane.org/resources-review-authors>). We also searched clinical trials databases, conference proceedings, and the reference lists of retrieved articles for randomized controlled trials and quasirandomized trials. As of 2017, there was one published phase I trial using highly expanded MSCs from *cord blood* (Pneumostem; MEDIPOST Co., Ltd., Seongnam, South-Korea) from a commercial entity.⁹ This first trial was a phase I dose-escalation trial in preterm infants with evolving BPD (5–14 days of life requiring continuous ventilatory support) to assess the safety and feasibility of cord blood MSCs. A single intratracheal injection of this allogeneic MSC product, starting with a dose of 1.0×10^7 cells/kg for the first three patients and progressing to a dose of 2.0×10^7 cells/kg for the next six patients, caused no serious adverse events or dose-limiting toxicity. Levels of proinflammatory cytokines in tracheal aspirates were reduced after MSC transplantation. When compared with historical controls, BPD severity was lower in MSC recipients, and rates of other adverse outcomes did not differ between the comparison group and MSC recipients.

Since publication of this clinical SR, the 2-year follow-up study of these nine preterm infants reported no adverse effects on growth,

respiratory, and neurodevelopmental outcomes.³¹ A second phase I dose-escalation trial using the same *cord blood-derived* MSC product (Pneumostem) and a similar trial design was published in 2019, confirming feasibility and absence of serious adverse events in 12 preterm infants.¹¹ These studies indicate feasibility and absence of short-term

toxicity in a small number of patients. As of 18 November 2020, there were 18 registered trials in ClinicalTrials.gov under the terms “bronchopulmonary dysplasia” and “mesenchymal stem cells” at various stages of development with one completed phase II trial (NCT01828957).

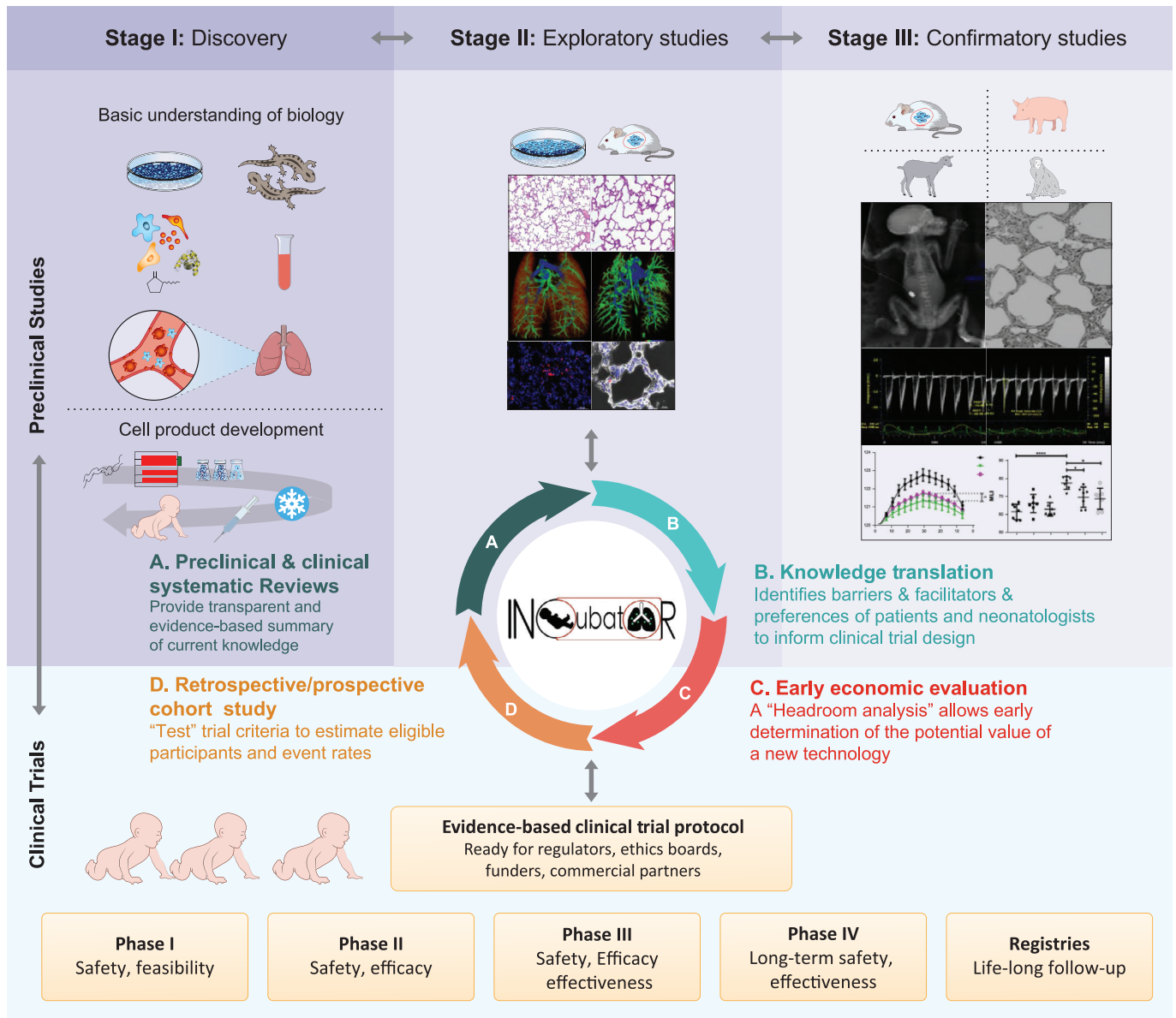


FIGURE 1 The INCuBAToR (Innovative Neonatal Cellular Therapy for BPD: Accelerating Translation of Research) for the successful clinical translation of cell-based therapies in neonates. The classical pathway to clinical translation includes the preclinical stage of discovery, exploratory, and confirmatory studies that provide the biological plausibility for the use of a novel therapy for a given disease and the rationale for initiating clinical trials. Numerous clinical trials fail because of shortcomings in the preclinical stages and/or lack of integration of critical information into clinical trial design. The INCuBAToR is designed to mitigate the risk of translating cell therapies into the clinic by providing an evidence-based approach through the following. A, Preclinical and clinical systematic reviews and meta-analyses to evaluate, synthesize, and quantitatively assess the best available evidence and identify knowledge gaps. B, Integrated knowledge translation to engage pertinent stakeholders, including patients, parents, physicians, nurses, and regulatory agencies, to identify opportunities and barriers in clinical trial implementation. C, Early economic evaluation to establish a “headroom analysis” for early determination of the potential value of the cell therapy. D, Retrospective cohort studies to estimate sample size, adverse events, and understanding of current patterns of care; this information can then be further refined by prospective observational cohort studies to provide “real world, real time” evidence to ensure feasibility and ultimately success of the clinical translation

Both the preclinical and clinical SRs provide some safety profile of MSCs and help inform trial design and potential trial participants, regulators, and research ethics boards of risks associated with MSC therapy in newborns. SRs from the adult literature further support the safety profile of MSCs from various sources.³²⁻³⁴

2.2 | Identifying barriers and enablers to conducting and participating in clinical trials of MSC therapy in preterm infants

Failure to enroll patients is a major concern to trial feasibility.¹⁸ Understanding underlying beliefs, concerns, and perspectives are crucial to directly improve processes surrounding consent, refine eligibility criteria and trial outcomes to optimize the experience of deciding to enroll their child in a trial (parents) and optimize recruitment, retention, and trial delivery practices (clinicians).³⁵ In a novel application of the theoretical domain framework³⁶ and first systematic evaluation of stakeholder beliefs prior to embarking on any cellular therapy study, semistructured interviews were used with directed content analysis to identify barriers and enablers that may influence parents' and neonatologists' participation in clinical trials of MSC for BPD.³⁷ One-on-one interviews with parents of extremely preterm infants (n = 18) and neonatologists (n = 16) revealed key barriers for parents, including lack of knowledge about clinical trials and stem cells, concerns about their risks and side effects, and preferences for who should help them make the decision. Physicians reported competing priorities, time commitment, costs, and lack of institutional support as significant barriers to their ability to recruit patients. Using this methodological approach—which is typically used to inform later phase trials—helped to identify barriers that were unanticipated and may not have otherwise been flagged. The approach allowed us to systematically identify how to better support parents and clinicians by considering their concerns in the development of this early phase clinical trial of MSC therapy. As a result, we were able to directly address issues that could have compromised recruitment. These findings led to the development of an animated information video to enhance parent education with the goal of increasing trial enrollment. This video will first be evaluated in the observational arm of our phase I clinical trial. Parent foundations such as the Canadian Premature Babies Foundation or the European Foundation for the Care of Newborn Infants provide invaluable insight and are authentic drivers in the quest for successful clinical translation of promising therapies.³⁸

Early engagement of parents and clinicians directly informs trial design, improves informed consent documents and process, and identifies feasibility issues associated with clinical adoption of MSC therapy.

2.3 | Assessing the potential value of MSC therapy for BPD

Early economic evaluation is now recognized as a tool to support product investment decision making.³⁹ Such evaluation is novel in neonatology, yet crucial to ensure that MSC therapy for BPD will be

economically viable. Given the lack of available data in the literature and the difficulty of obtaining reliable information from routinely collected databases, we developed a new, flexible tool to reliably forecast short- and long-term costs and health outcomes of BPD. The tool used an individual sample Markov model with seven health states in preterm infants born at 23-28 weeks. According to this tool, we have shown that BPD patients will incur over CAD\$700 000 in lifetime health systems costs associated with BPD and resulting complications.⁴⁰ This new model will now enable the “headroom” and the “value of information (VOI)” analyses. The headroom analysis presents the “cost-effectiveness gap” or maximum cost for which the MSC therapy can be brought to market and still be considered cost effective from the perspective of health care payers.⁴¹ The VOI analysis identifies parameters that have large impact on the cost-effectiveness profile of MSC therapy for BPD and estimates optimal sample size and follow-up period in future randomized controlled trials. The VOI analysis will also identify research areas that will have the highest impact on reimbursement decisions.⁴² As we are in the early phase of the development of MSCs for extremely preterm infants, the actual cost of MSCs is currently unknown. Unlike conventional therapeutics, there has been little published data on the cost of cell-based therapies, including MSCs. In general, biological products have higher prices in comparison with other drugs. For example, Zolgensma (onasemnogene abeparvovec-xioi; Novartis, Basel, Switzerland)—a gene therapy product for young children with spinal muscular atrophy—is priced at US \$2.1 million. Chimeric antigen receptor T-cell-based products, such as Kymriah (tisagenlecleucel; Novartis, Basel, Switzerland) and Yescarta (axicabtagene ciloleucel; Gilead Sciences, Inc, Foster City, California), cost US \$475 000 and US \$373 000, respectively, for a one-time dose. As part of INCuBAToR, we will use an early economic evaluation to estimate the potential price of MSCs at which the therapy is still considered cost effective for BPD. This estimated price will be based on early evidence on the potential impact of MSCs on health outcomes of infants with BPD.

2.4 | Retrospective and prospective observational cohort studies to ensure recruitment targets are met

Defining and “testing” optimal eligibility criteria are of particular importance in first-in-human trials as they enhance safety by excluding patients with an unacceptably high risk of treatment-related toxicity (relative to benefit) and/or insufficient expectation of efficacy. Too restrictive eligibility criteria can significantly reduce trial feasibility, as they limit patient accrual, and results may not be generalizable. Trials can also experience significant delays related to recruitment. As many as 86% of clinical trials do not reach recruitment targets within their specified time periods.⁴³ This is of particular concern in cell therapy trials, as failure to enroll patients within anticipated periods has been a major threat to trial feasibility.⁴⁴ Such an approach, paired with the abovementioned early economic evaluation, may have averted the shelving of a promising ventilation strategy for preterm infants.⁴⁵

2.4.1 | Retrospective cohort study

To provide estimates of the number of eligible patients expected during the study period, as well as the expected event rates for these patients, retrospective cohort studies are useful and increasingly facilitated by national or international repositories (eg, Canadian Neonatal Network, Vermont Oxford Network, German Neonatal Network, etc.) that gather data on antenatal characteristics, risk stratification, resource utilization, and outcomes from neonatal intensive care unit patients.

2.4.2 | Prospective cohort study

Using eligibility criteria and outcomes refined and justified by the retrospective cohort study, a prospective observational cohort study provides “real world, real time” evidence to further refine proposed criteria to ensure feasibility while balancing concerns of safety. This is a novel approach to highly refine and evidence-inform a trial protocol prior to conducting a high-stakes, resource-intensive, interventional study. Given the acuity and expected high incidence of adverse events in extreme premature infants, data from a prospective cohort of patients are needed for appropriate comparative assessment of safety in phase I/II trials. This is of particular use for investigators, data safety monitoring boards, research ethics boards, and regulators. Thus, an observational study serves a number of important purposes for phase I/II interventional trials: (a) characterize the type and incidence of serious adverse events in a population meeting eligibility criteria, (b) serve as a practical “lead-in” phase for the investigator team to gain experience enrolling patients just prior to the initiation of a phase I/II interventional study by assessing the feasibility of potential patient recruitment by gaining insights into the parents' hypothetical willingness to participate in such a trial, (c) provide prospective measures of trial conduct feasibility such as consent and data collection procedures, (d) further define current patterns of care of BPD patients against which MSCs may be tested, and (e) refine and justify sample size calculation for a definitive interventional study. This observational cohort strategy is timely as the current pandemic seems to indicate a reduction in extreme preterm birth⁴⁶ and may lead to reevaluated timelines.

In summary, the INCuBAToR provides a rational, evidence-based approach to ensure safe and successful translation of MSC therapy in a vulnerable patient population. As with any disruptive innovation, the INCuBAToR will go through several iterations to improve over time. Indeed, although it enabled the rapid launch of a phase I trial, it also uncovered—but did not address—some major obstacles to progress of MSC therapy.

3 | MAJOR OBSTACLES TO PROGRESS OF MSC THERAPY—“CLEANING UP THE MESS”

The SRMAs revealed important disparities in MSC characterization, indication, and administration strategies.³²⁻³⁴ This has also been the

experience of the Food and Drug Administration, which reported important differences in cell characterization, product bioactivity assessment, and tissue sourcing and product manufacturing in initial filings of 66 investigational new drug submissions for MSC-based therapies.⁴⁷ These inconsistencies and the stark contrast between promising results in the lab vs mitigated success in the clinic have led to major criticism regarding MSC therapy.⁴⁸ Current shortcomings, including an incomplete definition⁴⁹ and the lack of (a) potency assays to predict in vivo response, (b) standardized methods for manufacturing and use at bedside,^{50,51} and (c) complete and transparent reporting of both cell characteristics and clinical trial details,^{52,53} contribute to the controversy.⁴⁸ This lack of sufficient details concerning the cell product is highly problematic, as it significantly hinders the ability to judge the reliability of the results, interpret them, and replicate the findings. These consequences have been illustrated recently in the pandemic literature.^{54,55} Likewise, an analysis of discrepancies (defined as at least two reported facts that cannot both be true because they are logically or mathematically incompatible) in clinical studies assessing the efficacy of bone marrow-derived cells on left ventricle ejection fraction in heart disease⁵⁶ revealed that the rigor of the report was associated with the effect size: studies with no discrepancies showed no effect of MSC on left ventricle function, whereas studies with the highest number of discrepancies also reported the biggest improvement in left ventricle function. This suggests that inadequate reporting is associated with biased reports.

To better address clinical translation, reproducibility, and transparency in the field of MSC research, the scientific community needs a consensus definition of MSCs. Similarly, to improve reporting quality of clinical MSC studies, a standardized reporting guideline is needed. A query on the EQUATOR network (Enhancing the Quality and Transparency of Health Research; <https://www.equator-network.org/>) found only one published reporting guideline for studies evaluating biologics in orthopedics (platelet-rich plasma and MSCs).⁵⁷ We propose a method to establish a consensus definition of MSC and to establish relevant reporting guidelines. Our approach will directly address the pitfalls and criticisms of previous attempts to generate consensus in the MSC field by using the Delphi method, a highly studied and well-established social science approach to reach group consensus on highly contentious issues (eg, biomedical editors core competencies, defining predatory journals).^{58,59} The Delphi method allows for broader input beyond a small panel of experts, encourages independent reflection, and limits negative aspects of group decision making such as peer pressure, limited time to express point of view and reach agreement, lack of formal feedback, and nonstructured interactions and aggregation of opinion. Importantly, we will take an integrated knowledge translation approach where diverse stakeholders are part of the program from its inception,⁶⁰ which will help ensure that the definition and related reporting guidelines created are relevant to the community and ultimately are effectively adopted to improve quality, transparency, and reproducibility in basic and translational MSC research.

Nuances in the manufacturing processes can significantly influence bioactivity and functional outcomes of the MSC preparations.

The challenge here may lie in the fact that specific manufacturing processes may be proprietary and thus not disclosed particularly by commercial entities. This caveat will need to be addressed as the field matures further.

4 | CONCLUSION

MSC therapy has created much hope in neonatology with the promise to curb complications of extreme prematurity and to substantially improve the outcome of extreme preterm infants. The multidisciplinary INCuBAToR engine provides a rigorous and evidence-based approach to address the multiple obstacles to successful clinical translation of MSC and other cell therapies. The INCuBAToR has emanated from the Excelerator framework (<http://www.ohri.ca/blueprint/>) and as such can be applied to any promising novel therapy. The next iteration of this approach will include an attempt to tackle one of the remaining obstacles to progress of MSC therapy. Without stifling innovation in this still burgeoning field, the clinical translation of MSC requires an unbiased robust definition of MSCs and clinical reporting criteria. The Delphi method has previously provided solutions to contentious issues and may enable attaining this ambitious goal in order to further improve the rigor in translating promising MSC therapy into patient care.

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CONFLICT OF INTEREST

B.H. has a consultant/advisory role with Eversana Inc. The other authors declared no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

B.T.: conception/design, financial support, manuscript writing; M.L., L.R., S.v.K., J.P., K.T., K.D.C., B.H., D.M., and R.F.S.: manuscript writing; D.F.: conception/design, manuscript writing.

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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