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Cell Therapy for Lung Diseases

Report from an NIH–NHLBI Workshop, November 13–14, 2012

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The National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health convened the Cell Therapy for Lung Disease Working Group on November 13–14, 2012, to review and formulate recommendations for future research directions. The workshop brought together investigators studying basic mechanisms and the roles of cell therapy in preclinical models of lung injury and pulmonary vascular disease, with clinical trial experts in cell therapy for cardiovascular diseases and experts from the NHLBI Production Assistance for Cell Therapy program. The purpose of the workshop was to discuss the current status of basic investigations in lung cell therapy, to identify some of the scientific gaps in current knowledge regarding the potential roles and mechanisms of cell therapy in the treatment of lung diseases, and to develop recommendations to the NHLBI and the research community on scientific priorities and practical steps that would lead to first-in-human trials of lung cell therapy.

Keywords: mesenchymal stromal (stem) cells; epithelial and endothelial progenitor cells; lung stem cells

Among the leading causes of morbidity, mortality, and high health care expenditures, acute and chronic lung diseases are in urgent need of innovative approaches and new therapies. Because of limited opportunities to participate in clinical studies of stem cells here in the United States, patients who suffer from chronic lung diseases are seeking stem cell therapies outside the country. In many cases these are unproven, unregulated, and potentially dangerous studies or therapies. The current National Heart, Lung, and Blood Institute (NHLBI) portfolio focuses on basic research to build fundamental knowledge of the role of stem/progenitor cells in lung disease and injury/repair. The slower progress being made in the potential clinical application of cell therapies for lung diseases not only represents a gap in knowledge and a lost opportunity for catalyzing further progress, but also underscores the particular challenge of cell therapy for lung disease posed by the unique structural and cellular complexity of the lung. An executive summary of this workshop was previously posted on the web at http://www.nhlbi.nih.gov/meetings/workshops/cell-therapy.htm.

LUNG STEM AND PROGENITOR CELLS

Lung stem/progenitor cells are difficult to identify because the lung is typically quiescent in steady state, with low cell turnover. Inhaled environmental exposures cause injury to the lung epithelium and activate reparative mechanisms, which may be variable depending on the severity and persistence of the exposure. Preclinical cell therapy studies suggest three fundamental strategies to facilitate repair: (*1*) reprogramming endogenous stem/progenitor cells *in situ*, (*2*) delivering exogenous stem/progenitor cells to diseased lung, and (*3*) reseeding bioengineered scaffolds with pluripotent or multipotent stem/progenitor cells.

Several candidate multipotent lung epithelial cells capable of self-renewal and differentiation have been proposed: a bronchioalveolar stem cell (BASC) that resides at the bronchioalveolar duct junctions in mice (1), a c-Kit–positive subpopulation interspersed in airways and parenchyma (2), integrins $\alpha_6\beta_4^+$/SP-C$^-$/CC10$^-$ distal airway and alveolar epithelial cells in mice (3), and basal cells or basal-like cells that are widely distributed in the airways (4–6). Progenitor cell populations have the ability to differentiate and repopulate injured lung epithelia, and appear to have some regional specificity from proximal (subpopulations of club [Clara], basal, and submucosal gland cells) to distal (bronchoalveolar duct junction and alveolar type II cells) lung (7, 8). Additional preclinical studies are needed to define the signaling events that determine the

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Other participants in the workshop may be found before the beginning of the REFERENCES.

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regenerative activity of the lung after injury so as to stimulate therapeutic reprogramming of stem/progenitor cells in the context of disease. There is a need to better define human epithelial stem/progenitor cells to identify an expandable population e*x vivo* and to assess the influence of cell-based or other therapeutics on stem/progenitor cell functions.

CELL-BASED THERAPIES

The cells with the most immediate potential to provide new therapeutic options in the treatment of lung diseases are mesenchymal stromal (or stem) cells (MSCs), although other types of stem/progenitor cells (e.g., endothelial progenitor cells [EPCs]) also show promise. This is due to a more advanced level of knowledge concerning the isolation, *ex vivo* expansion, and transplantation effects *in vivo* of MSCs compared with lung resident stem/progenitor cells and their use in ongoing clinical studies. Infusion of MSCs derived from bone marrow (BM-MSCs), adipose, cord blood, or placental tissues, or the conditioned media from MSC cultures, has resulted in promising effects in animal models of acute and chronic lung injuries. Paracrine modulating factors secreted by the MSCs seem to confer this effect rather than MSC engraftment. Evidence suggests that in addition to the release of soluble antiinflammatory factors, the MSC transfers mitochondria, protein, and microRNA via microvesicles and/or exosomes to other cells, including the alveolar epithelium (9–12). How MSCs modulate innate and adaptive immune cells, as well as lung resident cells including the endothelium and the epithelium, is incompletely understood and deserves further study. There is no consensus on the source of MSCs that might prove therapeutically beneficial in different lung diseases. Specific disease-targeted preclinical models should be used to help clarify the targets and biological end points for cell therapy to increase the likelihood of well-designed clinical trials. In spite of the progress in understanding MSC biology, much still needs to be learned regarding the role of endogenous MSCs in the bone marrow, the lung, and other organs, as well as their potential as a therapeutic in human disease (13).

Bone marrow–derived or umbilical cord–derived MSCs and conditioned media from MSCs inhibit inflammation and promote normal alveolar development and lung function (14–17), in hyperoxia-induced neonatal lung injury models of bronchopulmonary dysplasia. This therapeutic benefit persists after 6 months without adverse effects on lung structure or tumor formation (18). Preconditioning of MSCs with hyperoxia may enhance the beneficial effect of the MSC conditioned media (19). Little is known about the safety and/or efficacy of these potential therapies in larger animal models of bronchopulmonary dysplasia. No clinical trial in human infants has been conducted in the United States, although a trial in South Korea was just completed.

The granulocyte-macrophage colony-stimulating factor (GM-CSF) receptor β knockout mouse closely recapitulates hereditary pulmonary alveolar proteinosis, a devastating rare genetic disorder of impaired surfactant clearance. Intratracheal administration of normal bone marrow–derived macrophages to this GM-CSF knockout normalized bronchoalveolar lavage fluid turbidity and cellular content, lung histology, and GM-CSF levels for up to 1 year (20). Children and adults with pulmonary alveolar proteinosis have high serum levels of GM-CSF antibodies, raising the opportunity for testing gene correction.

Lung MSCs, isolated from human lung biopsies, were shown to have multilineage potential to synthesize basement membrane (collagen IV, laminin) and to promote proliferation of epithelial progenitor cells. Comparable to BM-MSCs, lung MSCs produce substantial healing of elastase-induced injury, a preclinical model of chronic obstructive pulmonary disease. Compared with BM-MSCs, lung MSCs exhibit greater survival, avoidance of phagocytosis, and retention in the lung after intravenous transplantation in mice (21). When combined with "bioscaffolds" (fibrinogen, fibronectin, and poly-L-lysine) to enhance survival and engraftment *in vivo*, endobronchially delivered lung MSCs improved tissue mass and vascular perfusion in elastase-injured regions of sheep lung (22). MSCs of various origins (marrow, adipose, placental tissue, and others), various sources (autologous, allogeneic), and various routes of administration (intravenous, intratracheal) have been tested in numerous preclinical models of lung disease (23). Also, genetically modified EPCs have been tested in preclinical models of pulmonary hypertension and some are in clinical trials (24).

Lung tissue regeneration is a potential strategy for addressing the significant shortage of available donor lungs for transplantation in end-stage lung disease recipients. Decellularized human lung provides a native scaffold for recellularization with stem/progenitor cells (25); however, the optimal characteristics of the decellularization process have not been determined. In addition, to support gas exchange and barrier functions of the endothelial and alveolar compartments, numerous parameters need to be optimized including the cell source, the environment for cell engraftment, control of cell fate, and determination of optimal cell numbers for repopulating the lung. The isolated perfused lung model provides opportunities as a model for cell therapy, long-term organ culture, and *ex vivo* lung perfusion.

PATHWAYS TO FIRST-IN-HUMAN LUNG CELL THERAPY TRIALS

The safety of cell-based therapy has been shown in several trials of patients with acute myocardial infarction (26, 27), heart failure (28), and some noncardiac disorders (29). Although the efficacy of cell therapy for cardiac indications is not yet established, NHLBI Cardiovascular Cell Therapy Research Network investigators have addressed several issues including cell source (autologous or allogeneic BM-MSCs), methods of cell expansion in culture, optimal dosing, methods of delivery of cell-based therapy (intracoronary and transendocardial delivery via catheter-based technologies), short- and long-term safety, and primary outcomes that could be used for larger efficacy trials (30). The biology of MSCs in preclinical and clinical trials suggests that MSCs are antiinflammatory and possibly antifibrotic, and may enhance recruitment and lineage commitment of putative cardiac stem cells (c-Kit$^+$) (31). This has consequences not only in the heart but also perhaps in the lung, given the observation that the human lung harbors a c-Kit$^+$ stem cell (2). However, the pathogeneses of lung diseases and the potential mechanisms of MSC actions in lung compared with cardiac diseases are different and must be considered in the design of cell therapy trials in lung diseases. Cardiac stem cells have been used as another source for cell therapy. Autologous human cardiac stem cells have been isolated and expanded, and their safety and therapeutic efficacy were tested in patients with chronic heart failure (32).

An industry-sponsored placebo-controlled trial of allogeneic BM-MSCs for myocardial infarction showed an increase in FEV_1, a prespecified lung function safety end point. This led to an Osiris Therapeutics Inc.–sponsored multicenter trial to evaluate the effects of systemic administration of allogeneic BM-MSCs versus vehicle control in patients with moderate-to-severe chronic obstructive pulmonary disease (33). The primary end point was safety, and there was no evidence of short or longer term toxicity. The trial was not powered for efficacy, but did not reveal any differences in pulmonary function. *Post hoc* analysis showed an early decrease in a circulating inflammatory mediator

(C-reactive protein) in a subgroup of patients with elevated C-reactive protein at baseline in those who received MSCs compared with placebo. There is also some interest in the possibility that MSCs might have therapeutic value for idiopathic pulmonary fibrosis (34), and one group in the United States is planning a phase 1 safety trial after receiving approval of an Investigational New Drug application (IND).

An NHLBI-supported program to test MSCs for the treatment of adult respiratory distress syndrome has developed from promising preclinical studies and moved through U.S. Food and Drug Administration (FDA) regulatory requirements. The details are included in a case study that outlines the timeline and steps that were needed to obtain approval of an IND for this clinical trial (*see* case study and Figure E1 in the online supplement).

STEM CELL AND TISSUE–ENGINEERED PRODUCTS: PATHWAYS TO IND APPROVAL

Cell therapy products from sources such as bone marrow, mobilized peripheral blood, and umbilical cord blood have been used in clinical practice for decades. Increasing awareness of the potential of cell therapeutics for modifying acute and chronic diseases now emphasizes the need to understand product development of cell therapeutics, which is complex. With cell therapy products, complete characterization of the end product is not as possible as it is for drug development, and therefore control over the manufacturing process is even more critical to ensure product consistency, quality, identity, purity, and potency. Product development benefits from a team approach to coordinate technology transfer, cell processing, and assay development. Good manufacturing practice (GMP) compliance issues include donor eligibility requirements, development of manufacturing batch records, development of quality control test methods (including appropriate potency assays), and validation of aseptic processing for the full manufacturing process. Issues to consider in the manufacturing process include variability of human donors, use of animal-derived raw materials (fetal bovine serum, growth factors), and scalability of cell expansion, including passage number of cultured cells.

For quality control, testing should be conducted to characterize the quality, identity, purity, and potency of the product. Some of the standard testing for cultured products includes donor infectious disease markers, cell count, viability, cytogenetics (e.g., karyotype), cell identity (e.g., immunophenotype and genotype), microbial contamination, and bacterial endotoxins. In addition, an appropriate potency assay must be developed (Table 1), and should be fully validated by the time of phase 3 trials. Once established, the potency assay can be used to test the impact of donor variability, fetal bovine serum, or alternative growth medium lots, and supplemental growth factors, passage number, and effects of storage, including freeze–thawing, on potency and product functionality. The potency assay will also be a critical component of the stability testing program.

To ensure that preclinical studies support the initial IND filing, the investigator should design animal experiments that simulate the protocol design for the human safety study, and discussions should be undertaken with the FDA to clarify the requirements for the IND filing. Although there is no standard animal model defined to support an IND filing, the investigator should select the most appropriate animal model(s) that best reflect the human disease and stage of disease targeted for first-in-human studies. It is advisable to discuss proposed models with the FDA *before* initiating studies (pre-IND meeting). The cell product should be comparable to the cells to be used in human clinical trials and follow GMP processes. Considerations include cell formulation and packaging, storage and shipment conditions, and short-term (e.g., postthaw) and long-term (e.g., cryopreservation) stability and potency. In preclinical studies, the cell administration, including the process of thawing and reconstitution (e.g., dilution or wash), should mimic the planned human dosing schedule. If intravenous infusion occurs over an extended period, there may be issues with cell settling and survival during administration. Animal safety testing to support INDs must follow Good Laboratory Practice (GLP) regulations.

TABLE 1. ESTABLISHING A CELL THERAPEUTIC POTENCY ASSAY

- Development timeline
  - Establish early in program based on hypothesized mode of action
  - Correlate assay data with in vivo performance
  - Goal of establishing assay and validating by phase 3 clinical trials
- Reference standard
  - Create reference standard before initiating assay development
  - Use to establish assay characteristics—accuracy, precision
  - Monitor stability of standard
- Considerations for process development
  - Impact of donor variability on product quality
  - Screening of raw materials (e.g., fetal bovine serum)
  - Evaluation of process changes and scale-up on product quality

Another challenge to consider is the complementary path for cell-based products that are combined with bioscaffolds and/or delivery devices. Although the cell product development process can be lengthy, additional discussions will be needed with the FDA for such combination products. Several lessons have been learned from cardiovascular experiences with cell therapeutics and bioscaffolds, which may be helpful for other fields. In general, investigators and their teams are encouraged to seek advice along the way, particularly from those with regulatory expertise (35). A framework for facilitating protocol development of cell therapy trials is presented in Table 2.

CHALLENGES TO OBTAINING IND APPROVAL

The pathway to obtaining IND approval for cell-based therapy in acute or chronic lung diseases involves several steps and challenges. Some of the most important issues that can delay the translational goal include (*1*) a reliable, high-quality source of the cell therapy that will meet the FDA criteria as described previously, whether the source is from private industry or a National Institutes of Health (NIH, Bethesda, MD)–supported program, such as Production Assistance for Cellular Therapies (PACT); (*2*) adequate evidence in preclinical models of lung diseases, a challenge when the data are derived almost exclusively from small-animal models such as rodents; (*3*) the need for large-animal studies to test lung and systemic physiological and pathological effects, as well as clinically relevant safety issues; (*4*) institutional support for the process of preparing an IND including expertise in GMP and GLP along with the required formatting and regulatory issues in submitting an IND to the FDA; (*5*) funding for small- and large-animal studies; and (*6*) the labor-intensive process of preparing and submitting an IND. It is possible for a university investigator to partner with industry, but this approach requires an explicit contract between the industry partner and the university. Details on how to allocate intellectual property rights in joint university and industry projects need to be worked out as well. For institutions with Clinical Translational Science Awards from the NIH, regulatory support group that can assist with the IND process should be available.

CONCLUSIONS

Cell-based therapeutics hold promise and have capabilities that differ from small molecules and biologicals, perhaps offering a new "pillar" of drug development (36). To advance clinical testing of cell therapies in acute and chronic pediatric and adult

TABLE 2. FRAMEWORK FOR FACILITATING PROTOCOL DEVELOPMENT OF CELL THERAPY TRIALS

1. Define cell therapy product (categorical)
   a. Source
   b. Cell isolation/processing
   c. Cell culture/expansion/passage number
   d. Identity/cell characteristics
   e. Purity
   f. Key biotherapeutic components
   g. Stability in storage and at bedside
   h. Potency
2. Define manufacturing processes
   a. Scale-up process validation
   b. Quality assessment
   c. Quality control
3. Define delivery approach
   a. Route: intratracheal, intravenous
   b. Device
4. Predelivery preparation (e.g., scaffolding)
5. Preclinical safety data
   a. Model(s): Small and large animal, human ex vivo lung model
   b. Dose and timing
   c. Duration—acute, chronic
   d. Number of species needed
   e. Defining the types of safety data needed
   f. Biomarkers of safety—biological and other
6. Define preclinical efficacy outcomes
   a. Model
   b. Pharmacokinetics
   c. Mechanism of action
   d. Biomarkers of biological activity
   e. Biomarkers of therapeutic efficacy
   f. Biomarkers of persistence
7. Pre-IND discussions are important to initiate with FDA before preclinical studies are initiated

Definition of abbreviations: FDA = U.S. Food and Drug Administration; IND = Investigational New Drug application.

lung diseases, and to help ensure the high likelihood that this approach will facilitate bench-to-bedside and bedside-to-bench discoveries, parallel paths of basic and clinical research are needed. Resources to conduct preclinical cell therapy studies to evaluate safety and efficacy end points in large-animal models are crucial. Typically these studies are proof-of-concept studies, and, although they may not be favorably peer reviewed, they are crucial for demonstrating safety and outcomes relevant for a clinical trial. GMP-compliant facilities capable of isolating, expanding, and processing cells are needed. Clinical trials of cell therapies in lung diseases should include parallel mechanistic assessments to further our understanding of cell actions in various lung diseases, which will lead to improvements in study design and implementation.

SCIENTIFIC PRIORITIES FOR RESEARCH TO ADVANCE LUNG CELL THERAPY

While establishing the framework to facilitate protocol development for cell therapy trials, it is critical to prioritize scientific investigation in the biology and the mechanisms of cell therapy. Several areas of research need further development as outlined here:

1. What are the mechanisms by which MSCs and other progenitor cells exert biological activity in lung repair and regeneration *in vivo* in both the mature and the immature lung?
   - What are the critical components that comprise the biological activity of MSCs, EPCs, and other stem/progenitor cell preparations in preclinical models of lung disease and in early cell therapy trials?
   - Are conditioned media, or even microvesicles or exosomes, or the conditioned medium preparations from MSCs viable alternatives to MSCs as therapeutics in adult and pediatric populations?
   - Do mitochondria derived from MSCs play an important therapeutic role in lung diseases?
   - Do MSCs and/or EPCs form gap junctions with target cells in the lung epithelium and pulmonary vasculature to exert their therapeutic effect?
2. What are the cellular targets of administered MSCs and other cell-based preparations?
   - Are pathways of altered inflammation or immune mechanisms the most consistent finding and likely workable end point for clinical studies of MSCs and other cell types?
   - What is the effect of factors secreted by MSCs and other potential cell types on lung endothelial, epithelial, and interstitial cell functions?
   - How are MSCs/exosomes distributed after transplantation, and what is their fate?
3. Are there improved methods of isolation of endogenous lung epithelial and endothelial stem/progenitor cells in both the mouse and particularly the human lung that will clarify the potential influence of MSCs and other cell therapy preparations on lung stem/progenitor cell functions? This approach will better enable preclinical studies in replicated *ex vivo* or *in vivo* models.
4. What are the goals of MSC- and other cell-based therapies for specific pediatric and adult lung diseases: prevention, reversal, or arrest of disease?
   - In specific acute and chronic lung diseases, what biological and clinical end points should be monitored for safety and efficacy?
   - What are the broad characteristics of the disease, and at what stage of the disease should cell therapy intervention be considered potentially efficacious, safe, and feasible?
   - Which preclinical models are most predictive of efficacy of cell therapies in humans?
   - What small- and large-animal models are the most appropriate for prediction of safety in human trials?
   - Can xenograft models help fill the gap from bench science with human cells and transplantation of these cells into humans?
5. Is there an optimal preparation of MSCs or their derivatives such as conditioned media, exosomes, or microvesicles that will have efficacy in clinical lung diseases?
   - Comparisons of bone marrow, adipose, cord blood, and placental sources in relevant preclinical models should be assessed.
   - In addition to source, what biological characteristics should be characterized: pluripotency, differentiation and self-renewal capacity, lineage commitment, paracrine profile, exosomal profile?
   - What are the advantages/disadvantages of autologous versus allogeneic MSCs for a given disease?
   - What variability of effect is due to the donor characteristics?

6. What are the optimal modes and strategies for delivery of MSCs and other cell-based therapeutic products in terms of efficacy and safety? Do these differ for specific lung diseases? Is there an optimal dose for use in different lung diseases? Is repeat cell therapy administration safe and efficacious?
7. What is the potential for scalability of MSC- and other cell-based therapeutic preparations for sufficient expansion for large clinical trials?
8. What are appropriate measures of safety and efficacy of the critical components of cell therapy products:
   - What are the methods used to ensure acceptability of the cell products, including residual materials from cell production/expansion such as fetal bovine serum, actin, dimethyl sulfoxide, detergents, microbes, secretome?
   - What are the appropriate lot release criteria for MSCs and other cell-based products?
   - What are the stability and potency of the cell products in storage and after thawing?
   - Can imaging tools be developed to track the fate of the cells?
   - What is the toxicity/immunogenicity/long-term tumorigenic potential?
9. What assays are needed to adequately define which cell characteristics are related to cell potency and to develop minimal criteria that should be reported in clinical trials (Table 1)?
   - An assay should quantify active components and include a measure of bioactivity.
   - High-throughput assays might be developed for measuring potency.
   - Screening rapid-throughput systems as a bioactivity readout might be developed in decellularized–recellularized lung tissue.

RESOURCES AND OPPORTUNITIES

- The NHLBI-supported Production Assistance for Cellular Therapies (PACT) program has been a resource for the scientific community to leverage regulatory and cell-processing expertise that can lead to successful IND submissions for first-in-human clinical trials. In some cases, PACT can supply the clinical-grade cell therapy for a clinical trial and for relevant preclinical studies (*see* http://www.pactgroup.net).
- Organ procurement organizations in the United States discard approximately 70–80% of lungs, which are deemed not viable for transplantation. This wasted resource of human lungs could be ideal for the cell therapy research community to use for preclinical cell therapy studies.
- Food and Drug Administration Pre–Investigational New Drug (IND) discussions are valuable and should be encouraged. For a comprehensive summary regarding the preclinical assessment of cell and gene therapy products, *see* the OCTGT Learn video tutorials, at http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm.
- Resources from clinical and translational science institutes should be used to understand regulatory requirements for cell therapy.
- Take advantage of FDA orphan market opportunities.
- Leverage other existing clinical trials for information relevant to lung diseases. For example, addition of pulmonary function tests and chest radiographs as an outcome of cell-based therapy trials designed for other organ diseases will provide valuable information about potential effects on the lung.

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