SUMMARY

In one aspect of the present disclosure, there is provided a composition comprising two or more cytidine diphosphate (CDP)-conjugated precursors selected from the group consisting of CDP-choline, CDP-ethanolamine, and CDP-diacylglycerol (CDP-DAG), in a pharmaceutically acceptable carrier.

In another aspect of the current disclosure, there is provided use of a composition comprising one or more cytidine diphosphate (CDP)-conjugated precursors selected from the group consisting of CDP-choline, CDP-ethanolamine, CDP-diacylglycerol (CDP-DAG), and combinations thereof in the manufacture of a medicament for treating an acute respiratory distress syndrome (ARDS) in a subject.

In a further aspect of the present disclosure, there is provided a composition comprising one or more cytidine diphosphate (CDP)-conjugated precursors selected from the group consisting of CDP-choline, CDP-ethanolamine, CDP-diacylglycerol (CDP-DAG), and combinations thereof for use in treating an acute respiratory distress syndrome (ARDS) in a subject.

Development of influenza-induced ARDS is shown herein to result from reduced levels of phospholipids and cytidine diphosphate (CDP)-conjugated liponucleotide precursors for phospholipid synthesis in ATII cells. This is accompanied by reduced BALF surfactant phospholipid content. The disclosed data indicate that influenza infection results in decreased synthesis of CDP-conjugated liponucleotide precursors for phospholipid synthesis by ATII cells. This may occur directly as a result of influenza viral infection of and/or replication in said cell, or indirectly as a result of the effect of host factors currently known or to be discovered in the future that are induced in other cells in response to viral infection acting on said cell. Therefore, as disclosed herein, supplementation with the liponucleotides CDP-choline, CDP-ethanolamine, CDP-diacylglycerol (CDP-DAG), or any combination thereof, either prior to or after onset of injury or disease has occurred can bypass the block(s) in phospholipid synthesis resulting from reduced liponucleotide synthesis and thereby improve ATII cell phospholipid synthesis in a cell being susceptible to an injury which causes normal phospholipid production of said cell to become retarded and/or completely inhibited. This supplementation can result in increased ATII cell and surfactant phospholipid levels, thereby promoting improved ATII cell and lung function. This will prevent or retard development of ARDS in influenza-infected

subjects, or will reduce severity of ongoing ARDS and will thereby increase influenza survival rates and reduce incidence and severity of long-term clinical sequelae associated with ARDS and mechanical ventilation. These include, but are not limited to, reduced lung function, pulmonary fibrosis, depression, post-traumatic stress disorder, and others known to those skilled in the art. Because similar decreases in BALF surfactant levels have been described for ARDS caused by other insults, this therapy could have general patient outcome benefits in various delivery modalities and the wide applicability for ARDS.

An additional reason for the focus on these lipids is that they are vital to many other aspects of cellular and organellar metabolism and function. ATII cells have high metabolic activity and are therefore heavily dependent on mitochondrial (Mi) function for energy production. Mi function is also important for other lung cells. Mi membranes contain large amounts of phospholipids, which play an important role in maintaining normal Mi structure and function. Hence, alterations in phospholipid synthesis may also impair Mi viability, function and generation of ATP. This will have consequences for ATII cell function. A change in Mi phospholipid composition could also promote mitophagy, Mi-dependent ATII cell apoptosis, and release of Mi DNA,

cases, the subject has a PaO_2/FiO_2 ratio of less than 300 mmHg, less than 200 mmHg, or less than 100 mmHg. These 3 categories correspond to mild, moderate and severe ARDS, as currently defined clinically by the Berlin criteria. In other cases, the subject may have a PaO_2/FiO_2 ratio of about 300 - 550 mmHg (≤ 73.3 kPa), which would be considered moderately abnormal clinically. Alternatively, the subject has an arterial O_2 saturation of less than 92%. In other cases, the subject has a reduced lung compliance or evidence of non-cardiogenic pulmonary edema by radiography, CT scan, magnetic resonance imaging, or other imaging modalities present and future. The subject may exhibit alterations in other measures that may have been or will be found to be associated with ARDS presence and severity in either clinical or experimental situations, including, but not limited to, impaired alveolar fluid clearance, elevated pro-inflammatory cytokines, chemokines, and other inflammatory mediators in lung and/or blood, decreased anti-inflammatory cytokines, chemokines, and other inflammatory mediators in lung and/or blood, increased leukocytes in lung and/or blood, and increased cell death in lung tissue.

The disclosed composition can be administered, for example, intravenously, orally, intramuscular, intraperitoneally, by intrapulmonary instillation, or by inhalation (e.g., aerosolized dry powder or nebulized droplet). Compositions delivered by different routes may contain different formulations.

In some embodiments, the method further involves treating the subject with surfactant therapy. In some embodiments, the method further involves treating the subject with tracheal intubation, tracheotomy, tracheostomy, mechanical ventilation, with or without positive end-expiratory pressure (PEEP), prone or supine positioning, supplemental oxygen, nitric oxide, extracorporeal membrane oxygenation, beta-adrenergic agonists or antagonists, corticosteroids and other anti-inflammatory agents, antibiotics, antiviral drugs, antifungal drugs, cytokines, stem cells from any source, intravenous fluids, whole blood or blood components, parenteral or enteral nutritional formulations, vasodilators, vasoconstrictors, diuretics, insulin or other synthetic or natural hormones, or any combination thereof, or any other treatments found to be beneficial in future experimental and/or clinical situations.

The details of one or more embodiments of the present disclosure are set forth in the accompanying drawings and the description below. Other features, objects, and advantages of the present disclosure will be apparent from the description and drawings, and from the claims.

WHAT IS CLAIMED IS:

1. A composition comprising two or more cytidine diphosphate (CDP)-conjugated precursors selected from the group consisting of CDP-choline, CDP-ethanolamine, and CDP-diacylglycerol (CDP-DAG), in a pharmaceutically acceptable carrier.

2. The composition of claim 1, comprising CDP-choline and CDP-DAG in a pharmaceutically acceptable carrier.

3. The composition of claim 1, consisting essentially of CDP-choline and CDP-DAG in a pharmaceutically acceptable carrier.

4. The composition of claim 2 or 3, wherein the CDP-choline and CDP-DAG are present in equal concentrations.

5. The composition of claim 1, comprising CDP-choline, CDP-ethanolamine, and CDP-DAG in a pharmaceutically acceptable carrier.

6. The composition of claim 5, wherein the CDP-choline, CDP-ethanolamine, and CDP-DAG are present in equal concentrations.

7. The composition of any one of claims 1 to 6, wherein the CDP-conjugated precursors are collectively present at a concentration of at least 0.1 ng per kg of body weight.

8. The composition of any one of claims 1 to 7, wherein the CDP-conjugated precursors comprise one or more chemical modification selected from the group consisting of methylation, esterification, amidation, nitration, nitrosylation, oxidation, sulfation, acetylation, alcoholysis, acidolysis, biotinylation, and fluorophore conjugation.

9. Use of a composition comprising one or more cytidine diphosphate (CDP)-conjugated precursors selected from the group consisting of CDP-choline, CDP-ethanolamine, CDP-diacylglycerol (CDP-DAG), and combinations thereof in the manufacture of a medicament for treating an acute respiratory distress syndrome (ARDS) in a subject.

10. The use of claim 9, wherein the medicament comprises the composition of any one of claim 1 to 8.

11. The use of claim 9 or 10, wherein the medicament is to be administered intravenously, orally, or by inhalation.

12. The use of any one of claims 9 to 11, wherein the ARDS is caused by a direct lung insult.

13. The use of claim 12, wherein the direct lung insult is selected from the group consisting of a viral, bacterial, or fungal infection; toxic gas inhalation; a lung cancer; chemotherapy; acid aspiration; and chest trauma.

14. The use of claim 13, wherein the infection comprises influenza.

15. The use of any one of claims 9 to 14, wherein the ARDS is caused by an indirect result of trauma to other body regions.

16. The use of claim 15, wherein the trauma is selected from the group consisting of sepsis, ischemia/reperfusion, and surgery.

17. The use of any one of claims 9 to 16, wherein the subject is to be further treated with surfactant therapy.

18. The use of any one of claims 9 to 17, wherein the medicament is to be administered to the subject prior to infection with one or more influenza virus strains.

19. The use of any one of claims 9 to 17, wherein the medicament is to be administered after the subject has been infected with one or more influenza virus strains but before said subject has developed ARDS.

20. The use of any one of claims 9 to 17, wherein the medicament is to be administered after the subject has developed ARDS.

21. A composition comprising one or more cytidine diphosphate (CDP)-conjugated precursors selected from the group consisting of CDP-choline, CDP-ethanolamine, CDP-diacylglycerol (CDP-DAG), and combinations thereof for use in treating an acute respiratory distress syndrome (ARDS) in a subject.