METHODS FOR TREATING ACUTE CONDITIONS USING LIPID BINDING PROTEIN-BASED COMPLEXES

1. CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the priority benefit of U.S. provisional application nos. 63/011,055, filed April 16, 2020, 63/092,070, filed October 15, 2020, and 63/121,640, filed December 4, 2020, the contents of each which are incorporated herein in their entireties by reference thereto.

2. SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on April 13, 2021 is named CRN-039WO_SL.txt and is 2519 bytes in size.

3. BACKGROUND

[0003] Various acute conditions, for example, conditions that can be associated with acute inflammation such as sepsis, acute kidney injury (AKI), and cytokine release syndrome (CRS) are common and potentially life threatening. Current treatments for such conditions are oftentimes inadequate or suboptimal.

3.1. Sepsis

[0004] Sepsis is a potentially life-threatening systemic response of the immune system that arises from infection and which can cause injury to tissues and organs (Singer *et al.*, 2016, JAMA. 315(8):801–10). Common signs and symptoms of sepsis include fever, increased heart rate, increased breathing rate, and confusion. There may also be symptoms related to a specific infection, such as a cough with pneumonia, or painful urination with a kidney infection (Jui *et al.*, 2011, "Ch. 146: Septic Shock." In Tintinalli JE, *et al.* (eds.). *Tintinalli's Emergency Medicine: A Comprehensive Study Guide* (7th ed.). New York: McGraw-Hill. pp. 1003–14). Severe sepsis can be associated with poor organ function or blood flow (Dellinger *et al.*, 2013, Critical Care Medicine. 41(2):580–637). The presence of low blood pressure, high blood lactate, or low urine output may suggest poor blood flow. Sepsis can progress to septic shock, which is characterized by low blood pressure that does not improve after fluid replacement (Dellinger *et al.*, 2013, Critical Care Medicine. 41(2):580–637).

[0005] Bacterial infections are the most common cause of sepsis, but fungal, viral, and protozoan infections can also lead to sepsis (Jui *et al.*, 2011, "Ch. 146: Septic Shock." In Tintinalli JE, *et al.* (eds.). *Tintinalli's Emergency Medicine: A Comprehensive Study Guide* (7th ed.). New York: McGraw-Hill. pp. 1003–14). Common locations for the primary infection include the lungs, brain, urinary tract, skin, and abdominal organs (Jui *et al.*, 2011, "Ch. 146: Septic

Shock." In Tintinalli JE, *et al.* (eds.). *Tintinalli's Emergency Medicine: A Comprehensive Study Guide* (7th ed.). New York: McGraw-Hill. pp. 1003–14). Risk factors include being very young, older age, a weakened immune system from conditions such as cancer or diabetes, major trauma, or burns (www.cdc.gov/sepsis/what-is-sepsis.html). A sepsis diagnosis can be based on the shortened sequential organ failure assessment score (SOFA score), also known as the quick SOFA score (qSOFA), which requires at least two of the following three: increased breathing rate, change in the level of consciousness, and low blood pressure (Singer *et al.*, 2016, JAMA. 315(8):801–10).

[0006] Sepsis can require immediate treatment with intravenous fluids and antimicrobials (Rhodes *et al.*, 2017, Intensive Care Medicine. 43(3):304–377). Ongoing care often continues in an intensive care unit. If an adequate trial of fluid replacement is not enough to maintain blood pressure, then the use of medications that raise blood pressure can become necessary. Mechanical ventilation and dialysis may be needed to support the function of the lungs and kidneys, respectively. Other helpful measurements include cardiac output and superior vena cava oxygen saturation (Dellinger *et al.*, 2013, Critical Care Medicine. 41(2):580–637).

[0007] The risk of death from sepsis is as high as 30%, while for severe sepsis it is as high as 50%, and septic shock 80% (Jawad et al., 2012, J Glob Health. 2(1):010404). Early detection and treatment is essential for survival and limiting disability.

3.2. Acute kidney injury

[0008] Acute kidney injury (AKI) is a common occurrence in ICU patients, with an estimated incidence of >50% (Hoste *et al.*, 2015, Intensive Care Med; 41:1411–1423). Furthermore, increasing AKI severity is associated with increased mortality. Sepsis is the major cause of AKI, accounting for 45% to 70% of cases, and approximately 25% of sepsis is of intra-abdominal origin (Seymour *et al.*, 2016, JAMA, 315:762–774; Bagshaw *et al.*, 2007, Clin J Am Soc Nephrol, 2:431– 439). Ischemia/reperfusion injury (IRI) can cause AKI and is a common complication in subjects receiving an organ transplant, with an incidence of 50-75% after lung and heart transplantation (Gueler *et al.*, 2014, Transplantation 98:337-338. Cardiac surgery associated AKI (CSA AKI) has been reported to occur in up to 30% of subjects who undergo cardiac surgery (Rosner and Okusa, 2006, Clin J Am Soc Nephrol. 1(1):19-323). Post-surgical IL6 and IL10 levels are predictive of AKI development and outcome (Zhang *et al.*, 2015, J Am Soc Nephrol. 26(12):3123-32) and there are no good treatment options other than dialysis (Küllmar *et al.*, 2020, Crit Care Clin. 36(4):691-704.

[0009] Early diagnosis of AKI in the setting of sepsis is important in order to provide optimal treatment and avoid further kidney injury (Peerapornratana *et al.*, 2019, Kidney International 2019, 96:1083–1099). Treatment options for sepsis-related AKI are limited to supportive care. The use of blood filtration devices, including high volume hemofiltration and polymyxin B hemoperfusion, have not shown significant benefit (Joannes-Boyau *et al.*, 2013, Intensive care

medicine, 39:1535–1546; Zhang *et al.*, 2012, Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association - European Renal Association 27:967–973; Vincent *et al.*, 2005, Shock, 23:400–405; Cruz *et al.*, 2009, JAMA, 301:2445–2452; Payen *et al.*, 2015, Intensive care medicine, 41:975–98; Dellinger *et al.*, 2018, JAMA, 320:1455-463).

[0010] Experimental pharmacologic treatments are usually targeted for AKI rather than sepsis-induced AKI, with the exception of alkaline phosphatase (AP), angiotensin II (ATII), levocarnitine and reltecimod (AB103). In a recent clinical trial, recombinant AP did not reduce endogenous creatinine clearance, the primary clinical endpoint, but did improve mortality, which was a secondary endpoint (Pickkers *et al.*, 2018, JAMA, 320:1998–2009). ATII showed some benefit in a post-hoc analysis of AKI patients in a high-output shock study (ATHOS-3) and is currently being study in sepsis-related AKI in the ASK-IT trial (NCT00711789), however no updates have been given since 2011. Levocarnitine did not show organ dysfunction improvement in septic shock in the RACE study (Jones *et al.*, 2018, JAMA network open, 1:e186076) but is currently being studied as an adjunct treatment for septic shock patients with AKI in the Carnisave trial (NCT02664753). Reltecimod was being studied in a Phase 3 placebo-controlled trial in patients with sepsis- associated AKI (NCT03403751), but the study was recently terminated due to slow enrollment (clinicaltrials.gov/ct2/show/NCT03403751).

[0011] Alterations in lipid and lipoprotein metabolism have been reported to occur during infection leading to a redistribution of nutrients to cells that are important in host defense or tissue repair (Khovidhunkit *et al.*, 2004, J Lipid Res, 45(7):1169-96). In addition, lipoproteins and lipids play a key role in host defense against infection and protect the host from the toxic effects of microorganisms (Feingold and Grunfeld, 2012, J Lipid Res. 53(12):2487–248). High-density lipoprotein (HDL) is a key component of circulating blood and mainly contains phospholipids, free cholesterol, cholesteryl ester, triglycerides, apolipoproteins (Apo A-I, Apo A-II), and other proteins. It is considered an anti-inflammatory lipoprotein, which regulates vascular endothelial function and immunity (Singh *et al.*, 2007, JAMA, 298(7):786-798; Navab *et al.*, 2011, Nat Rev Cardiol 8(4):222-32). Indeed, HDL plays pivotal protective roles in all the steps of endothelial dysfunction, including suppression of inflammatory signaling in immune effector cells and direct inhibition of endothelial activation. Clinical studies have demonstrated that HDL levels drop by 40–70% during systemic inflammation and it is associated with a poor prognosis in septic subjects (van Leeuwen *et al.*, 2003, Critical care medicine, 31:1359–1366; Chien *et al.*, 2005, Critical care medicine, 33:1688–1693; Tsai *et al.*, Journal of hepatology, 50:906–915; Eggesbø *et al.*, 1996, Cytokine, 8(2):152-160; Morin *et al.*, 2015, Frontiers in Pharmacology, doi.org/10.3389/fphar.2015.00244). Moreover, low levels of HDL have been associated with increased risk of acute kidney injury (AKI) in course of sepsis (Roveran *et al.*, 2017, Journal of internal medicine, 281:518–529; Zhang *et al.*, 2009, Am J Physiol Heart Circ

Physiol 297:H866–H873). Renal function and plasma HDL are strongly related to each other as kidneys are implicated in the recycling of senescent HDL particles and their filtration function is associated with their levels and contents (Yang *et al.*, 2016, Current opinion in nephrology and hypertension, 25:174–179).

[0012] Treatments based on HDL have been proposed for sepsis-induced systemic inflammatory reaction syndrome (Morin *et al.*, 2015, Frontiers in Pharmacology, doi.org/10.3389/fphar.2015.00244; Tanaka et al., 2020, Crit Care 24:134). Several studies have suggested that the correction of dyslipoproteinemia by recombinant HDL (rHDL) may offer a strategy for the prevention and treatment of systemic inflammatory response (Morin *et al.*, 2015, Frontiers in Pharmacology, doi.org/10.3389/fphar.2015.00244; Roveran *et al.*, 2017, Journal of internal medicine, 281:518–529; Pajkrt *et al.*, 1996, Journal of Experimental Medicine, 184(5): 1601–1608; Pajkrt *et al.*, 1997, Thrombosis and Haemostasis 77(2):303-7; Guo *et al.*, 2013, J. Biol. Chem. 288(25):17947-53; Li *et al.*, 2008, European journal of pharmacology 590:417–422; McDonald *et al.*, 2003, Shock 20(6):551-7). CSL-111, a rHDL originally produced for atherosclerosis treatment (Tardif *et al.*, 2007, JAMA, 297(15):1675-82), has shown efficacy in reducing the inflammatory response during LPS-induced endotoxemia in vitro and in rabbit (Casas *et al.*,1995, The Journal of surgical research, 59:544– 552) and human models (Pajkrt *et al.*, 1996, Journal of Experimental Medicine, 184(5):1601-8; Pajkrt *et al.*, 1997, Thrombosis and Haemostasis, 77(2):303-7). In a human model, the infusion of CSL-111 has been shown to decrease the procoagulant state caused by endotoxin exposure, reduce monocyte activation and cytokine production and ameliorate clinical symptoms (Pajkrt *et al.*, 2016, Journal of Experimental Medicine, 184(5): 1601–1608; Pajkrt *et al.*, 1997, Thrombosis and Haemostasis, 77(2):303-7). ApoA1 Milano, a naturally variant of ApoA1, was widely studied in the context of cardiovascular disease (CVD) in a Phase I trial (Casas et al., 1995, The Journal of surgical research, 59:544– 552) and other further clinical studies. Recently, Zhang and colleagues demonstrated that ApoA1 was also efficacious against inflammation in an endotoxemic rat model (Zhang *et al.*, 2015, Biological Chemistry, 396(1):53-60). Among HDL mimetic peptides, L-4F has been employed in several preclinical model of sepsis and has been shown to block production of cytokines, reverse sepsis-induced hypotension, prevent organ damage, and restore renal, hepatic, and cardiac function, and increase survival rate (Zhang *et al.*, 2009, Am J Physiol Heart Circ Physiol 297: H866–H873). The altered serum lipid levels, especially cholesterol level, have been reported to occur also during infection with viruses (Meher *et al.*, 2019, J. Phys. Chem. B, 123(50):10654–10662) including human immunodeficiency virus (HIV) and hepatitis C virus (HCV). Despite the interest in HDL and HDL therapeutics, no HDL or HDL mimetic has received regulatory approval for the treatment of sepsis or AKI, including sepsis-related AKI, ischemia/reperfusion AKI and CSA AKI.

3.3. Cytokine release syndrome

[0013] Cytokine release syndrome (CRS), also called cytokine storm syndrome (CSS), is a systemic inflammatory response that can be caused by a variety of factors such as infection or treatment with some types of immunotherapy, such as monoclonal antibodies and adoptive T-cell therapies (Shimabukuro-Vornhagen, *et al.*, 2018, J. Immunotherapy Cancer, 6:56). Symptoms of CRS include fever, nausea, headache, rash, rapid heartbeat, low blood pressure, and trouble breathing. Most patients with CRS have a mild reaction, but sometimes CRS can be severe and even life threatening (NCI Dictionary of Cancer Terms (www.cancer.gov/publications/dictionaries/cancer-terms/def/cytokine-release-syndrome)).

[0014] Since late 2019, a novel coronavirus, COVID-19 (SARS-CoV-2), has been spreading around the globe. Data suggest that there are mild or severe cytokine storms in severely affected patients, accompanied by high expression of interleukin-6 (IL-6). CRS may contribute to death of these patients (Zhang *et al.*, 2020, International Journal of Antimicrobial Agents, doi.org/10.1016/j.ijantimicag.2020.105954; Mehta et al., 2020, The Lancet, 395(10229):1033-1034).

[0015] Thus, there remains a need for new treatments for acute conditions such as sepsis, AKI, including sepsis related AKI, ischemia/reperfusion AKI and CSA AKI, and CRS, for example CRS associated with immunotherapy and CRS secondary to infections such as COVID-19.

4. SUMMARY

[0016] The present disclosure provides methods for treating subjects with acute conditions, for example conditions associated with acute inflammation, with a high dose of a lipid binding protein-based complex. The high dose is typically higher than a dose that would be used to treat a chronic condition, such as familial hypercholesterolemia. The high dose is typically administered over a relatively short period of time, for example, over a period of three days to two weeks, and typically comprises multiple administrations of the lipid binding protein-based complex, for example three to 10 individual doses. The individual doses can be separated by less than one day (*e.g.*, twice daily administration), or one day or more (*e.g.*, once daily administration).

[0017] In some embodiments of the methods of the disclosure, the lipid binding protein-based complex comprises a sphingomyelin and/or a negatively charged lipid, for example CER-001. CER-001 is a negatively charged lipoprotein complex, and comprises recombinant human ApoA-I, sphingomyelin (SM), and 1, 2-dihexadecanoyl-sn-glycero-3-phospho-(1'-rac-glycerol) (Dipalmitoylphosphatidyl-glycerol; DPPG). It mimics natural, nascent discoidal pre-beta HDL, which is the form that HDL particles take prior to acquiring cholesterol. Without being bound by theory, it is believed that CER-001 therapy can reduce serum levels of inflammatory cytokines such as IL-6, thereby providing a clinical benefit to subjects having an acute condition or at risk of an acute condition, for example subjects having or at risk of an acute inflammatory condition.

[0018] In some aspects, the present disclosure provides methods for treating subjects with sepsis and methods for treating subjects with AKI or at risk for AKI with lipid binding protein-based complexes (*e.g.*, CER-001).

[0019] In one aspect, the disclosure provides a method of treating a subject with sepsis, comprising administering to the subject a lipid binding protein-based complex (*e.g.*, CER-001).

[0020] In another aspect, the disclosure provides a method of treating a subject with acute kidney injury (AKI) or at risk for AKI (*e.g.*, a subject with sepsis which has not yet caused AKI, an organ transplant recipient, or a subject who has undergone cardiac surgery, or a subject having acute or chronic liver disease and at risk of hepatorenal syndrome (HRS)), comprising administering to the subject a lipid binding protein-based complex (*e.g.*, CER-001).

[0021] In some aspects, the disclosure provides methods for treating cytokine release syndrome (CRS) and/or reducing one or more inflammatory markers in a subject in need thereof with a lipid binding protein-based complex (*e.g.*, CER-001).

[0022] In one aspect, the disclosure provides methods of treating a subject with CRS or at risk of CRS, *e.g.*, a subject with CRS secondary to COVID-19 or a subject with CRS caused by immunotherapy, comprising administering a therapeutically effective amount of a lipid binding protein-based complex (*e.g.*, CER-001) to the subject.

[0023] In another aspect, the disclosure provides methods of reducing serum levels of one or more inflammatory markers, *e.g.*, one or more markers associated with CRS such as IL-6, in a subject in need thereof. The subject can be, for example, a subject with CRS or a subject at risk of CRS, for example a subject infected with a virus such as COVID-19 or a subject receiving immunotherapy.

[0024] In some aspects, the present disclosure provides dosing regimens for lipid binding protein-based therapy (*e.g.*, CER-001 therapy) for subjects with an acute condition (*e.g.*, associated with acute inflammation), for example sepsis, AKI (*e.g.*, AKI caused by sepsis, ischemia/reperfusion, cardiac surgery, or hepatorenal syndrome), or at risk for an acute condition such as AKI (*e.g.*, a subject with sepsis which has not yet led to AKI) or CRS.

[0025] The dosing regimens of the disclosure typically entail multiple administrations of CER-001 to a subject (*e.g.*, administered daily). The CER-001 therapy can be continued for a pre-determined period, *e.g.*, for one week or a period longer than one week (*e.g.*, two weeks). Alternatively, administration of CER-001 to a subject can be continued until one or more symptoms of the acute condition (*e.g.*, acute inflammation or CRS) are reduced or continued until the serum levels of one or more inflammatory markers are reduced, for example reduced to a normal level or reduced relative to a baseline measurement taken prior to the start of CER-001 therapy. For subjects at risk of CRS or AKI due to an infection or at risk of CRS due to immunotherapy, the therapy can in some embodiments be continued until the subject has recovered from the infection or discontinues immunotherapy.

[0026] The dosing regimens of the disclosure can entail administering a lipid binding protein-based complex (*e.g.*, CER-001) to a subject according to an initial "induction" regimen, optionally followed by administering the lipid binding protein-based complex to the subject according to a "consolidation" regimen.

[0027] The induction regimen typically comprises administering multiple doses of the lipid binding protein-based complex (*e.g.*, CER-001) to the subject, for example six doses over three days.

[0028] The consolidation regimen typically comprises administering one or more doses of a lipid binding protein-based complex (*e.g.*, CER-001) to the subject following the final dose of the induction regimen, for example one or more days after the final dose of the induction regimen. In some embodiments, the first dose of the consolidation regimen is administered on the third day after the final dose of the induction regimen. For example, a dosing regimen can comprise administration of a lipid binding protein-based complex (*e.g.*, CER-001) to a subject according to an induction regimen on days 1, 2, and 3, and administration of the lipid binding protein-based complex to the subject according to a consolidation regimen on day 6. In some embodiments, the consolidation regimen comprises two doses of the lipid binding protein-based complex.

[0029] In certain embodiments, the disclosure provides methods of treating a subject having CRS, sepsis or AKI, or a subject at risk of CRS or AKI (*e.g.*, a subject with COVID-19) with a lipid binding protein-based complex (*e.g.*, CER-001) according to a dosage regimen comprising:

- 2 doses per day on days 1, 2, and 3 (induction regimen) optionally followed by
- 2 subsequent doses on day 4 or later (consolidation regimen).

In some embodiments, the regimen comprises:

- 2 doses per day on days 1, 2, and 3 (induction regimen) followed by
- 2 doses on day 6 (consolidation regimen).

[0030] In certain aspects, a lipid binding protein-based complex (*e.g.*, CER-001) is administered in combination with a standard of care therapy for sepsis such as antibiotic therapy and/or hemodynamic support.

[0031] In certain aspects, an antihistamine (*e.g.*, dexchlorpheniramine, hydroxyzine, diphenhydramine, cetirizine, fexofenadine, or loratadine) can be administered before administration of a lipid binding protein-based complex (*e.g.*, CER-001). The antihistamine can reduce the likelihood of allergic reactions.

5. BRIEF DESCRIPTION OF THE FIGURES

[0032] **FIG. 1**: shows IL-6 serum levels in a pig model of sepsis-induced AKI (Example 1).

[0033] FIG. 2: shows soluble VCAM-1 serum levels in a pig model of sepsis-induced AKI (Example 2).

[0034] FIG. 3: shows soluble ICAM-1 serum levels in a pig model of sepsis-induced AKI (Example 3).

[0035] FIG. 4: shows LPS serum levels in a pig model of sepsis-induced AKI (Example 1).

[0036] FIG. 5: shows a schematic of the clinical study of Example 2.

[0037] FIG. 6 is a flowsheet for the study of Example 3.

[0038] FIG. 7 is a flowsheet for the study of Example 4.

6. DETAILED DESCRIPTION

[0039] The present disclosure provides methods for treating subjects with acute conditions, for example, an acute condition comprising acute inflammation, with a high dose of a lipid binding protein-based complex.

[0040] In one aspect, the disclosure provides methods for treating subjects having sepsis using a lipid binding protein-based complex (*e.g.*, CER-001).

[0041] In other aspects, the disclosure provides methods for treating subjects with acute kidney injury (AKI) or at risk of AKI (*e.g.*, due to sepsis, viral infection, ischemia/reperfusion, cardiac surgery, or hepatorenal syndrome) using a lipid binding protein-based complex (*e.g.*, CER-001).

[0042] In other aspects, the disclosure provides methods of treating a subject with CRS or at risk of CRS, *e.g.*, a subject with CRS secondary to COVID-19 or a subject with CRS caused by immunotherapy.

[0043] In some embodiments, the lipid binding protein-based complex is an Apomer, a Cargomer, a HDL based complex, or a HDL mimetic based complex. In specific embodiments, the lipid binding protein-based complex is CER-001.

[0044] Exemplary features of lipid binding protein-based complexes that can be used in the methods and compositions of the disclosure are described in Section 6.1. Exemplary subject populations who can be treated by the methods of the disclosure and with the compositions of the disclosure are described in Section 6.2.

[0045] In some embodiments, methods of the disclosure comprise administering a lipid binding protein-based complex (*e.g.*, CER-001) to a subject in two phases. First, the lipid binding protein-based complex (*e.g.*, CER-001) is administered in an initial, intense “induction” regimen. The induction regimen is followed by a less intense “consolidation” regimen. Alternatively, a lipid binding protein-based complex (*e.g.*, CER-001) can be administered to a subject in a single phase, for example according to an administration regimen corresponding to the dose and administration frequency of an induction or consolidation regimen described herein.

[0046] Induction regimens that can be used in the methods of the disclosure are described in Section 6.3 and consolidation regimens that can be used in the methods of the disclosure are

described in Section 6.3.2. The dosing regimens of the disclosure comprise administering a lipid binding protein-based complex (*e.g.*, CER-001) as monotherapy or as part of a combination therapy with one or more medications, for example in combination with a standard of care therapy for sepsis such as antibiotic treatment and/or hemodynamic support. Combination therapies are described in Section 6.4.

6.1. Lipid binding protein-based complexes

6.1.1. HDL and HDL mimetic-based complexes

[0047] In one aspect, the lipid binding protein-based complexes comprise HDL or HDL mimetic-based complexes. For example, complexes can comprise a lipoprotein complex as described in U.S. Patent No. 8,206,750, PCT publication WO 2012/109162, PCT publication WO 2015/173633 A2 (*e.g.*, CER-001) or US 2004/0229794 A1, the contents of each of which are incorporated herein by reference in their entireties. The terms "lipoproteins" and "apolipoproteins" are used interchangeably herein, and unless required otherwise by context, the term "lipoprotein" encompasses lipoprotein mimetics. The terms "lipid binding protein" and "lipid binding polypeptide" are also used interchangeably herein, and unless required otherwise by context, the terms do not connote an amino acid sequence of particular length.

[0048] Lipoprotein complexes can comprise a protein fraction (*e.g.*, an apolipoprotein fraction) and a lipid fraction (*e.g.*, a phospholipid fraction). The protein fraction includes one or more lipid-binding protein molecules, such as apolipoproteins, peptides, or apolipoprotein peptide analogs or mimetics, for example one or more lipid binding protein molecules described in Section 6.1.2.

[0049] The lipid fraction typically includes one or more phospholipids which can be neutral, negatively charged, positively charged, or a combination thereof. Exemplary phospholipids and other amphipathic molecules which can be included in the lipid fraction are described in Section 6.1.3.

[0050] In certain embodiments, the lipid fraction contains at least one neutral phospholipid (*e.g.*, a sphingomyelin (SM)) and, optionally, one or more negatively charged phospholipids. In lipoprotein complexes that include both neutral and negatively charged phospholipids, the neutral and negatively charged phospholipids can have fatty acid chains with the same or different number of carbons and the same or different degree of saturation. In some instances, the neutral and negatively charged phospholipids will have the same acyl tail, for example a C16:0, or palmitoyl, acyl chain. In specific embodiments, particularly those in which egg SM is used as the neutral lipid, the weight ratio of the apolipoprotein fraction: lipid fraction ranges from about 1:2.7 to about 1:3 (*e.g.*, 1:2.7).

[0051] Any phospholipid that bears at least a partial negative charge at physiological pH can be used as the negatively charged phospholipid. Non-limiting examples include negatively charged forms, *e.g.*, salts, of phosphatidylinositol, a phosphatidylserine, a phosphatidylglycerol and a

phosphatidic acid. In a specific embodiment, the negatively charged phospholipid is 1,2-dipalmitoyl-sn-glycero-3-[phospho-rac-(1-glycerol)], or DPPG, a phosphatidylglycerol. Preferred salts include potassium and sodium salts.

[0052] In some embodiments, a lipoprotein complex used in the methods of the disclosure is a lipoprotein complex as described in U.S. Patent No. 8,206,750 or WO 2012/109162 (and its U.S. counterpart, US 2012/0232005), the contents of each of which are incorporated herein in its entirety by reference. In particular embodiments, the protein component of the lipoprotein complex is as described in Section 6.1 and preferably in Section 6.1.1 of WO 2012/109162 (and US 2012/0232005), the lipid component is as described in Section 6.2 of WO 2012/109162 (and US 2012/0232005), which can optionally be complexed together in the amounts described in Section 6.3 of WO 2012/109162 (and US 2012/0232005). The contents of each of these sections are incorporated by reference herein. In certain aspects, a lipoprotein complex of the disclosure is in a population of complexes that is at least 85%, at least 90%, at least 95%, at least 97%, or at least 99% homogeneous, as described in Section 6.4 of WO 2012/109162 (and US 2012/0232005), the contents of which are incorporated by reference herein.

[0053] In a specific embodiment, a lipoprotein complex that can be used in the methods of the disclosure comprises 2-4 ApoA-I equivalents, 2 molecules of charged phospholipid, 50-80 molecules of lecithin and 20-50 molecules of SM.

[0054] In another specific embodiment, a lipoprotein complex that can be used in the methods of the disclosure comprises 2-4 ApoA-I equivalents, 2 molecules of charged phospholipid, 50 molecules of lecithin and 50 molecules of SM.

[0055] In yet another specific embodiment, a lipoprotein complex that can be used in the methods of the disclosure comprises 2-4 ApoA-I equivalents, 2 molecules of charged phospholipid, 80 molecules of lecithin and 20 molecules of SM.

[0056] In yet another specific embodiment, a lipoprotein complex that can be used in the methods of the disclosure comprises 2-4 ApoA-I equivalents, 2 molecules of charged phospholipid, 70 molecules of lecithin and 30 molecules of SM.

[0057] In yet another specific embodiment, a lipoprotein complex that can be used in the methods of the disclosure comprises 2-4 ApoA-I equivalents, 2 molecules of charged phospholipid, 60 molecules of lecithin and 40 molecules of SM.

[0058] In a specific embodiment, a lipoprotein complex that can be used in the methods of the disclosure consists essentially of 2-4 ApoA-I equivalents, 2 molecules of charged phospholipid, 50-80 molecules of lecithin and 20-50 molecules of SM.

[0059] In another specific embodiment, a lipoprotein complex that can be used in the methods of the disclosure consists essentially of 2-4 ApoA-I equivalents, 2 molecules of charged phospholipid, 50 molecules of lecithin and 50 molecules of SM.

[0060] In yet another specific embodiment, a lipoprotein complex that can be used in the methods of the disclosure consists essentially of 2-4 ApoA-I equivalents, 2 molecules of charged phospholipid, 80 molecules of lecithin and 20 molecules of SM.

[0061] In yet another specific embodiment, a lipoprotein complex that can be used in the methods of the disclosure consists essentially of 2-4 ApoA-I equivalents, 2 molecules of charged phospholipid, 70 molecules of lecithin and 30 molecules of SM.

[0062] In yet another specific embodiment, a lipoprotein complex that can be used in the methods of the disclosure consists essentially of 2-4 ApoA-I equivalents, 2 molecules of charged phospholipid, 60 molecules of lecithin and 40 molecules of SM.

[0063] In a specific embodiment, a lipoprotein complex that can be used in the methods of the disclosure comprises a lipid component that comprises about 90 to 99.8 wt % SM and about 0.2 to 10 wt % negatively charged phospholipid, for example, about 0.2-1 wt %, 0.2-2 wt %, 0.2-3 wt %, 0.2-4 wt %, 0.2-5 wt %, 0.2-6 wt %, 0.2-7 wt %, 0.2-8 wt %, 0.2-9 wt %, or 0.2-10 wt % total negatively charged phospholipid(s). In another specific embodiment, a lipoprotein complex that can be used in the methods of the disclosure comprises about 90 to 99.8 wt % lecithin and about 0.2 to 10 wt % negatively charged phospholipid, for example, about 0.2-1 wt %, 0.2-2 wt %, 0.2-3 wt %, 0.2-4 wt %, 0.2-5 wt %, 0.2-6 wt %, 0.2-7 wt %, 0.2-8 wt %, 0.2-9 wt % or 0.2-10 wt % total negatively charged phospholipid(s).

[0064] In a specific embodiment, a lipoprotein complex that can be used in the methods of the disclosure comprises a lipid component that consists essentially of about 90 to 99.8 wt % SM and about 0.2 to 10 wt % negatively charged phospholipid, for example, about 0.2-1 wt %, 0.2-2 wt %, 0.2-3 wt %, 0.2-4 wt %, 0.2-5 wt %, 0.2-6 wt %, 0.2-7 wt %, 0.2-8 wt %, 0.2-9 wt %, or 0.2-10 wt % total negatively charged phospholipid(s). In another specific embodiment, a lipoprotein complex that can be used in the methods of the disclosure consists essentially of about 90 to 99.8 wt % lecithin and about 0.2 to 10 wt % negatively charged phospholipid, for example, about 0.2-1 wt %, 0.2-2 wt %, 0.2-3 wt %, 0.2-4 wt %, 0.2-5 wt %, 0.2-6 wt %, 0.2-7 wt %, 0.2-8 wt %, 0.2-9 wt % or 0.2-10 wt % total negatively charged phospholipid(s).

[0065] In still another specific embodiment, a lipoprotein complex that can be used in the methods of the disclosure comprises a lipid fraction that comprises about 9.8 to 90 wt % SM, about 9.8 to 90 wt % lecithin and about 0.2-10 wt % negatively charged phospholipid, for example, from about 0.2-1 wt %, 0.2-2 wt %, 0.2-3 wt %, 0.2-4 wt %, 0.2-5 wt %, 0.2-6 wt %, 0.2-7 wt %, 0.2-8 wt %, 0.2-9 wt %, to 0.2-10 wt % total negatively charged phospholipid(s).

[0066] In still another specific embodiment, a lipoprotein complex that can be used in the methods of the disclosure comprises a lipid fraction that consists essentially of about 9.8 to 90 wt % SM, about 9.8 to 90 wt % lecithin and about 0.2-10 wt % negatively charged phospholipid, for example, from about 0.2-1 wt %, 0.2-2 wt %, 0.2-3 wt %, 0.2-4 wt %, 0.2-5 wt %, 0.2-6 wt %, 0.2-7 wt %, 0.2-8 wt %, 0.2-9 wt %, to 0.2-10 wt % total negatively charged phospholipid(s).

[0067] In another specific embodiment, a lipoprotein complex that can be used in the methods of the disclosure comprises an ApoA-I apolipoprotein and a lipid fraction, wherein the lipid fraction comprises sphingomyelin and about 3 wt% of a negatively charged phospholipid, wherein the molar ratio of the lipid fraction to the ApoA-I apolipoprotein is about 2:1 to 200:1, and wherein said complex is a small or large discoidal particle containing 2-4 ApoA-I equivalents.

[0068] In another specific embodiment, a lipoprotein complex that can be used in the methods of the disclosure comprises an ApoA-I apolipoprotein and a lipid fraction, wherein the lipid fraction consists essentially of sphingomyelin and about 3 wt% of a negatively charged phospholipid, wherein the molar ratio of the lipid fraction to the ApoA-I apolipoprotein is about 2:1 to 200:1, and wherein said complex is a small or large discoidal particle containing 2-4 ApoA-I equivalents.

[0069] HDL-based or HDL mimetic-based complexes can include a single type of lipid-binding protein, or mixtures of two or more different lipid-binding proteins, which may be derived from the same or different species. Although not required, the complexes will preferably comprise lipid-binding proteins that are derived from, or correspond in amino acid sequence to, the animal species being treated, in order to avoid inducing an immune response to the therapy. Thus, for treatment of human patients, lipid-binding proteins of human origin are preferably used. The use of peptide mimetic apolipoproteins may also reduce or avoid an immune response.

[0070] In some embodiments, the lipid component includes two types of phospholipids: a sphingomyelin (SM) and a negatively charged phospholipid. Exemplary SMs and negatively charged lipids are described in Section 6.1.3.1.

[0071] Lipid components including SM can optionally include small quantities of additional lipids. Virtually any type of lipids may be used, including, but not limited to, lysophospholipids, galactocerebroside, gangliosides, cerebrosides, glycerides, triglycerides, and cholesterol and its derivatives.

[0072] When included, such optional lipids will typically comprise less than about 15 wt% of the lipid fraction, although in some instances more optional lipids could be included. In some embodiments, the optional lipids comprise less than about 10 wt%, less than about 5 wt%, or less than about 2 wt%. In some embodiments, the lipid fraction does not include optional lipids.

[0073] In a specific embodiment, the phospholipid fraction contains egg SM or palmitoyl SM or phytosphingomyelin and DPPG in a weight ratio (SM: negatively charged phospholipid) ranging from 90:10 to 99:1, more preferably ranging from 95:5 to 98:2. In one embodiment, the weight ratio is 97:3.

[0074] The molar ratio of the lipid component to the protein component of complexes of the disclosure can vary, and will depend upon, among other factors, the identity(ies) of the

apolipoprotein comprising the protein component, the identities and quantities of the lipids comprising the lipid component, and the desired size of the complex. Because the biological activity of apolipoproteins such as ApoA-I are thought to be mediated by the amphipathic helices comprising the apolipoprotein, it is convenient to express the apolipoprotein fraction of the lipid:apolipoprotein molar ratio using ApoA-I protein equivalents. It is generally accepted that ApoA-I contains 6-10 amphipathic helices, depending upon the method used to calculate the helices. Other apolipoproteins can be expressed in terms of ApoA-I equivalents based upon the number of amphipathic helices they contain. For example, ApoA-I_M, which typically exists as a disulfide-bridged dimer, can be expressed as 2 ApoA-I equivalents, because each molecule of ApoA-I_M contains twice as many amphipathic helices as a molecule of ApoA-I. Conversely, a peptide apolipoprotein that contains a single amphipathic helix can be expressed as a 1/10-1/6 ApoA-I equivalent, because each molecule contains 1/10-1/6 as many amphipathic helices as a molecule of ApoA-I. In general, the lipid:ApoA-I equivalent molar ratio of the lipoprotein complexes (defined herein as "Ri") will range from about 105:1 to 110:1. In some embodiments, the Ri is about 108:1. Ratios in weight can be obtained using a MW of approximately 650-800 for phospholipids.

[0075] In some embodiments, the molar ratio of lipid : ApoA-I equivalents ("RSM") ranges from about 80:1 to about 110:1, *e.g.*, about 80:1 to about 100:1. In a specific example, the RSM for complexes can be about 82:1.

[0076] In some embodiments, lipoprotein complexes used in the methods of the disclosure are negatively charged complexes which comprise a protein fraction which is preferably mature, full-length ApoA-I, and a lipid fraction comprising a neutral phospholipid, sphingomyelin (SM), and negatively charged phospholipid.

[0077] In a specific embodiment, the lipid component contains SM (*e.g.*, egg SM, palmitoyl SM, phytoSM, or a combination thereof) and negatively charged phospholipid (*e.g.*, DPPG) in a weight ratio (SM : negatively charged phospholipid) ranging from 90:10 to 99:1, more preferably ranging from 95:5 to 98:2, *e.g.*, 97:3.

[0078] In specific embodiments, the ratio of the protein component to lipid component can range from about 1:2.7 to about 1:3, with 1:2.7 being preferred. This corresponds to molar ratios of ApoA-I protein to lipid ranging from approximately 1:90 to 1:140. In some embodiments, the molar ratio of protein to lipid in the complex is about 1:90 to about 1:120, about 1:100 to about 1:140, or about 1:95 to about 1:125.

[0079] In particular embodiments, the complex comprises CER-001, CSL-111, CSL-112, CER-522 or ETC-216. In a preferred embodiment, the complex is CER-001.

[0080] CER-001 as used in the literature and in the Examples below refers to a complex described in Example 4 of WO 2012/109162. WO 2012/109162 refers to CER-001 as a complex having a 1:2.7 lipoprotein weight:total phospholipid weight ratio with a SM:DPPG

weight:weight ratio of 97:3. Example 4 of WO 2012/109162 also describes a method of its manufacture.

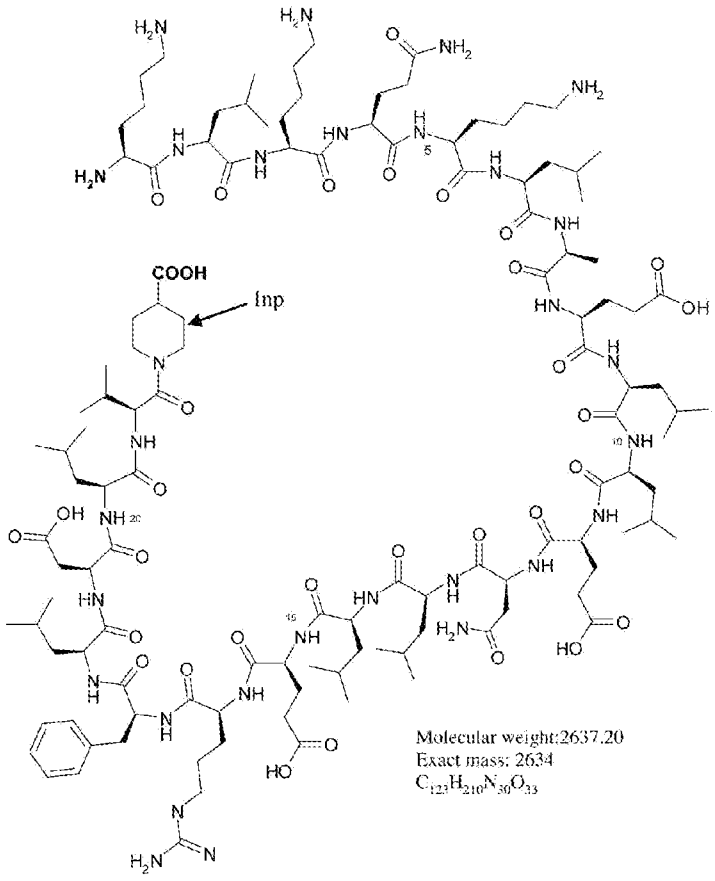
[0081] When used in the context of a method and/or CER-001 dosing regimen of the disclosure, CER-001 refers to a lipoprotein complex whose individual constituents can vary from CER-001 as described in Example 4 of WO 2012/109162 by up to 20%. In certain embodiments, the constituents of the lipoprotein complex vary from CER-001 as described in Example 4 of WO 2012/109162 by up to 10%. Preferably, the constituents of the lipoprotein complex are those described in Example 4 of WO 2012/109162 (plus/minus acceptable manufacturing tolerance variations). The SM in CER-001 can be natural or synthetic. In some embodiments, the SM is a natural SM, for example a natural SM described in WO 2012/109162, *e.g.*, chicken egg SM. In some embodiments, the SM is a synthetic SM, for example a synthetic SM described in WO 2012/109162, *e.g.*, synthetic palmitoylsphingomyelin, for example as described in WO 2012/109162. Methods for synthesizing palmitoylsphingomyelin are known in the art, for example as described in WO 2014/140787. The lipoprotein in CER-001, apolipoprotein A-I (ApoA-I), preferably has an amino acid sequence corresponding to amino acids 25 to 267 of SEQ ID NO:1 of WO 2012/109162. ApoA-I can be purified by animal sources (and in particular from human sources) or produced recombinantly. In preferred embodiments, the ApoA-I in CER-001 is recombinant ApoA-I. CER-001 used in a dosing regimen of the disclosure is preferably highly homogeneous, for example at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, at least 98%, or at least 99% homogeneous, as reflected by a single peak in gel permeation chromatography. See, *e.g.*, Section 6.4 of WO 2012/109162.

[0082] CSL-111 is a reconstituted human ApoA-I purified from plasma complexed with soybean phosphatidylcholine (SBPC) (Tardif *et al.*, 2007, JAMA 297:1675-1682).

[0083] CSL-112 is a formulation of ApoA-I purified from plasma and reconstituted to form HDL suitable for intravenous infusion (Diditchenko *et al.*, 2013, DOI 10.1161/ ATVBAHA.113.301981).

[0084] ETC-216 (also known as MDCO-216) is a lipid-depleted form of HDL containing recombinant ApoA-I_{Milano}. See Nicholls *et al.*, 2011, Expert Opin Biol Ther. 11(3):387-94. doi: 10.1517/14712598.2011.557061.

[0085] In another embodiment, a complex that can be used in the methods of the disclosure is CER-522. CER-522 is a lipoprotein complex comprising a combination of three phospholipids and a 22 amino acid peptide, CT80522:



CT80522

[0086] The phospholipid component of CER-522 consists of egg sphingomyelin,1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine (Dipalmitoylphosphatidylcholine, DPPC) and 1,2–dipalmitoyl-*sn*-glycero-3-[phospho-*rac*-(1-glycerol)] (Dipalmitoylphosphatidyl- glycerol, DPPG) in a 48.5:48.5:3 weight ratio. The ratio of peptide to total phospholipids in the CER-522 complex is 1:2.5 (w/w).

[0087] In some embodiments, the lipoprotein complex is delipidated HDL. Most HDL in plasma is cholesterol-rich. The lipids in HDL can be depleted, for example partially and/or selectively depleted, *e.g.*, to reduce its cholesterol content. In some embodiments, the delipidated HDL can resemble small α, preβ-1, and other preβ forms of HDL. A process for selective depletion of HDL is described in Sacks *et al.*, 2009, J Lipid Res. 50(5): 894–907.

[0088] In certain embodiments, a lipoprotein complex comprises a bioactive agent delivery particle as described in US 2004/0229794.

[0089] A bioactive agent delivery particle can comprise a lipid binding polypeptide (*e.g.*, an apolipoprotein as described previously in this Section or in Section 6.1.2), a lipid bilayer (*e.g.*, comprising one or more phospholipids as described previously in this Section or in Section 6.1.3.1), and a bioactive agent (*e.g.*, an anti-cancer agent), wherein the interior of the lipid bilayer comprises a hydrophobic region, and wherein the bioactive agent is associated with the

hydrophobic region of the lipid bilayer. In some embodiments, a bioactive agent delivery particle as described in US 2004/0229794.

[0090] In some embodiments, a bioactive agent delivery particle does not comprise a hydrophilic core.

[0091] In some embodiments, a bioactive agent delivery particle is disc shaped (*e.g.*, having a diameter from about 7 to about 29 nm).

[0092] Bioactive agent delivery particles include bilayer-forming lipids, for example phospholipids (*e.g.*, as described previously in this Section or in Section 6.1.3.1). In some embodiments, a bioactive agent delivery particle includes both bilayer-forming and non-bilayer-forming lipids. In some embodiments, the lipid bilayer of a bioactive agent delivery particle includes phospholipids. In one embodiment, the phospholipids incorporated into a delivery particle include dimyristoylphosphatidylcholine (DMPC) and dimyristoylphosphatidylglycerol (DMPG). In one embodiment, the lipid bilayer includes DMPC and DMPG in a 7:3 molar ratio.

[0093] In some embodiments, the lipid binding polypeptide is an apolipoprotein (*e.g.*, as described previously in this Section or in Section 6.1.2). The predominant interaction between lipid binding polypeptides, *e.g.*, apolipoprotein molecules, and the lipid bilayer is generally a hydrophobic interaction between residues on a hydrophobic face of an amphipathic structure, *e.g.*, an α-helix of the lipid binding polypeptide and fatty acyl chains of lipids on an exterior surface at the perimeter of the particle. Bioactive agent delivery particles may include exchangeable and/or non-exchangeable apolipoproteins. In one embodiment, the lipid binding polypeptide is ApoA-I.

[0094] In some embodiments, bioactive agent delivery particles include lipid binding polypeptide molecules, *e.g.*, apolipoprotein molecules, that have been modified to increase stability of the particle. In one embodiment, the modification includes introduction of cysteine residues to form intramolecular and/or intermolecular disulfide bonds.

[0095] In another embodiment, bioactive agent delivery particles include a chimeric lipid binding polypeptide molecule, *e.g.*, a chimeric apolipoprotein molecule, with one or more bound functional moieties, for example one or more targeting moieties and/or one or more moieties having a desired biological activity, *e.g.*, antimicrobial activity, which may augment or work in synergy with the activity of a bioactive agent incorporated into the delivery particle.

6.1.2. Lipid Binding Protein Molecules

[0096] Lipid binding protein molecules that can be used in the complexes described herein include apolipoproteins such as those described in Section 6.1.2.1 and apolipoprotein mimetic peptides such as those described in Section 6.1.2.2. In some embodiments, the complex comprises a mixture of lipid binding protein molecules. In some embodiments, the complex comprises a mixture of one or more lipid binding protein molecules and one or more apolipoprotein mimetic peptides.

[0097] In some embodiments, the complex comprises 1 to 8 ApoA-I equivalents (*e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 1 to 7, 1 to 6, 1 to 5, 1 to 4, 1 to 3, 1 to 2, 2 to 8, 2 to 6, 2 to 4, 4 to 6, or 4 to 8 ApoA-I equivalents). Lipid binding proteins can be expressed in terms of ApoA-I equivalents based upon the number of amphipathic helices they contain. For example, ApoA-I_M, which typically exists as a disulfide-bridged dimer, can be expressed as 2 ApoA-I equivalents, because each molecule of ApoA-I_M contains twice as many amphipathic helices as a molecule of ApoA-I. Conversely, a peptide mimetic that contains a single amphipathic helix can be expressed as a 1/10-1/6 ApoA-I equivalent, because each molecule contains 1/10-1/6 as many amphipathic helices as a molecule of ApoA-I.

6.1.2.1. Apolipoproteins

[0098] Suitable apolipoproteins that can be included in the lipid binding protein-based complexes include apolipoproteins ApoA-I, ApoA-II, ApoA-IV, ApoA-V, ApoB, ApoC-I, ApoC-II, ApoC-III, ApoD, ApoE, ApoJ, ApoH, and any combination of two or more of the foregoing. Polymorphic forms, isoforms, variants and mutants as well as truncated forms of the foregoing apolipoproteins, the most common of which are Apolipoprotein A-IMilano (ApoA-IM), Apolipoprotein A-IParis (ApoA-IP), and Apolipoprotein A-IZaragoza (ApoA-IZ), can also be used. Apolipoproteins mutants containing cysteine residues are also known, and can also be used (see, e.g., U.S. Publication No. 2003/0181372). The apolipoproteins may be in the form of monomers or dimers, which may be homodimers or heterodimers. For example, homo- and heterodimers (where feasible) of ApoA-I (Duverger et al., 1996, Arterioscler. Thromb. Vasc. Biol. 16(12):1424-29), ApoA-IM (Franceschini et al., 1985, J. Biol. Chem. 260:1632-35), ApoA-IP (Daum et al., 1999, J. Mol. Med. 77:614-22), ApoA-II (Shelness et al., 1985, J. Biol. Chem. 260(14):8637-46; Shelness et al., 1984, J. Biol. Chem. 259(15):9929-35), ApoA-IV (Duverger et al., 1991, Euro. J. Biochem. 201(2):373-83), ApoE (McLean et al., 1983, J. Biol. Chem. 258(14):8993-9000), ApoJ and ApoH may be used.

[0099] The apolipoproteins can be modified in their primary sequence to render them less susceptible to oxidations, for example, as described in U.S. Publication Nos. 2008/0234192 and 2013/0137628, and U.S. Patent Nos. 8,143,224 and 8,541,236. The apolipoproteins can include residues corresponding to elements that facilitate their isolation, such as His tags, or other elements designed for other purposes. Preferably, the apolipoprotein in the complex is soluble in a biological fluid (e.g., lymph, cerebrospinal fluid, vitreous humor, aqueous humor, blood, or a blood fraction (e.g., serum or plasma).

[0100] In some embodiments, the complex comprises covalently bound lipid-binding protein monomers, e.g., dimeric apolipoprotein A-IMilano, which is a mutated form of ApoA-I containing a cysteine. The cysteine allows the formation of a disulfide bridge which can lead to the formation of homodimers or heterodimers (e.g., ApoA-I Milano-ApoA-II).

[0101] In some embodiments, the apolipoprotein molecules comprise ApoA-I, ApoA-II, ApoA-IV, ApoA-V, ApoB, ApoC-I, ApoC-II, ApoC-III, ApoD, ApoE, ApoJ, or ApoH molecules or a combination thereof.

[0102] In some embodiments, the apolipoprotein molecules comprise or consist of ApoA-I molecules. In some embodiments, said ApoA-I molecules are human ApoA-I molecules. In some embodiments, said ApoA-I molecules are recombinant. In some embodiments, the ApoA-I molecules are not ApoA-IMilano.

[0103] In some embodiments, the ApoA-I molecules are Apolipoprotein A-IMilano (ApoA-IM), Apolipoprotein A-IParis (ApoA-IP), or Apolipoprotein A-IZaragoza (ApoA-IZ) molecules.

[0104] Apolipoproteins can be purified from animal sources (and in particular from human sources) or produced recombinantly as is well-known in the art, see, e.g., Chung et al., 1980, J. Lipid Res. 21(3):284-91; Cheung et al., 1987, J. Lipid Res. 28(8):913-29. See also U.S. Patent Nos. 5,059,528, 5,128,318, 6,617,134; U.S. Publication Nos. 2002/0156007, 2004/0067873, 2004/0077541, and 2004/0266660; and PCT Publications Nos. WO 2008/104890 and WO 2007/023476. Other methods of purification are also possible, for example as described in PCT Publication No. WO 2012/109162, the disclosure of which is incorporated herein by reference in its entirety.

[0105] The apolipoprotein can be in prepro- form, pro- form, or mature form. For example, a complex can comprise ApoA-I (e.g., human ApoA-I) in which the ApoA-I is preproApoA-I, proApoA-I, or mature ApoA-I. In some embodiments, the complex comprises ApoA-I that has at least 90% sequence identity to SEQ ID NO:1:
PPQSPWDRVKDLATVYVDVLKDSGRDYVSQFEGSALGKQLNLKLLDNWDSVTSTFSKLREQL GPVTQEFWDNLEKETEGLRQEMSKDLEEVKAKVQPYLDDFQKKWQEEMELYRQKVEPLRAE LQEGARQKLHELQEKLSPLGEEMRDRARAHVDALRTHLAPYSDELRQRLAARLEALKENGGA RLAEYHAKATEHLSTLSEKAKPALEDLRQGLLPVLESFKVSFLSALEEYTKKLNTQ (SEQ ID NO:1)

[0106] In other embodiments, the complex comprises ApoA-I that has at least 95% sequence identity to SEQ ID NO:1 of . In other embodiments, the complex comprises ApoA-I that has at least 98% sequence identity to SEQ ID NO:1. In other embodiments, the complex comprises ApoA-I that has at least 99% sequence identity to SEQ ID NO:1. In other embodiments, the complex comprises ApoA-I that has 100% sequence identity to SEQ ID NO:1.

[0107] In some embodiments, the complex comprises 1 to 8 apolipoprotein molecules (e.g., 1 to 6, 1 to 4, 1 to 2, 2 to 8, 2 to 6, 2 to 4, 4 to 8, 4 to 6, or 6 to 8 apolipoprotein molecules). In some embodiments, the complex comprises 1 apolipoprotein molecule. In some embodiments, the complex comprises 2 apolipoprotein molecules. In some embodiments, the complex comprises 3 apolipoprotein molecules. In some embodiments, the complex comprises 4 apolipoprotein molecules. In some embodiments, the complex comprises 5 apolipoprotein

molecules. In some embodiments, the complex comprises 6 apolipoprotein molecules. In some embodiments, the complex comprises 7 apolipoprotein molecules. In some embodiments, the complex comprises 8 apolipoprotein molecules.

[0108] The apolipoprotein molecule(s) can comprise a chimeric apolipoprotein comprising an apolipoprotein and one or more attached functional moieties, such as for example, one or more CRN-001 complex(es), one or more targeting moieties, a moiety having a desired biological activity, an affinity tag to assist with purification, and/or a reporter molecule for characterization or localization studies. An attached moiety with biological activity may have an activity that is capable of augmenting and/or synergizing with the biological activity of a compound incorporated into a complex of the disclosure. For example, a moiety with biological activity may have antimicrobial (for example, antifungal, antibacterial, anti-protozoal, bacteriostatic, fungistatic, or antiviral) activity. In one embodiment, an attached functional moiety of a chimeric apolipoprotein is not in contact with hydrophobic surfaces of the complex. In another embodiment, an attached functional moiety is in contact with hydrophobic surfaces of the complex. In some embodiments, a functional moiety of a chimeric apolipoprotein may be intrinsic to a natural protein. In some embodiments, a chimeric apolipoprotein includes a ligand or sequence recognized by or capable of interaction with a cell surface receptor or other cell surface moiety.

[0109] In one embodiment, a chimeric apolipoprotein includes a targeting moiety that is not intrinsic to the native apolipoprotein, such as for example, S. cerevisiae α-mating factor peptide, folic acid, transferrin, or lactoferrin. In another embodiment, a chimeric apolipoprotein includes a moiety with a desired biological activity that augments and/or synergizes with the activity of a compound incorporated into a complex of the disclosure. In one embodiment, a chimeric apolipoprotein may include a functional moiety intrinsic to an apolipoprotein. One example of an apolipoprotein intrinsic functional moiety is the intrinsic targeting moiety formed approximately by amino acids 130-150 of human ApoE, which comprises the receptor binding region recognized by members of the low density lipoprotein receptor family. Other examples of apolipoprotein intrinsic functional moieties include the region of ApoB-100 that interacts with the low density lipoprotein receptor and the region of ApoA-I that interacts with scavenger receptor type B 1. In other embodiments, a functional moiety may be added synthetically or recombinantly to produce a chimeric apolipoprotein. Another example is an apolipoprotein with the prepro or pro sequence from another preproapolipoprotein (e.g., prepro sequence from preproapoA-II substituted for the prepro sequence of preproapoA-I). Another example is an apolipoprotein for which some of the amphipathic sequence segments have been substituted by other amphipathic sequence segments from another apolipoprotein.

[0110] As used herein, "chimeric" refers to two or more molecules that are capable of existing separately and are joined together to form a single molecule having the desired functionality of

all of its constituent molecules. The constituent molecules of a chimeric molecule may be joined synthetically by chemical conjugation or, where the constituent molecules are all polypeptides or analogs thereof, polynucleotides encoding the polypeptides may be fused together recombinantly such that a single continuous polypeptide is expressed. Such a chimeric molecule is termed a fusion protein. A "fusion protein" is a chimeric molecule in which the constituent molecules are all polypeptides and are attached (fused) to each other such that the chimeric molecule forms a continuous single chain. The various constituents can be directly attached to each other or can be coupled through one or more linkers. One or more segments of various constituents can be, for example, inserted in the sequence of an apolipoprotein, or, as another example, can be added N-terminal or C-terminal to the sequence of an apolipoprotein. For example, a fusion protein can comprise an antibody light chain, an antibody fragment, a heavy-chain antibody, or a single-domain antibody.

[0111] In some embodiments, a chimeric apolipoprotein is prepared by chemically conjugating the apolipoprotein and the functional moiety to be attached. Means of chemically conjugating molecules are well known to those of skill in the art. Such means will vary according to the structure of the moiety to be attached, but will be readily ascertainable to those of skill in the art. Polypeptides typically contain a variety of functional groups, e.g., carboxylic acid (--COOH), free amino (--NH2), or sulfhydryl (--SH) groups, that are available for reaction with a suitable functional group on the functional moiety or on a linker to bind the moiety thereto. A functional moiety may be attached at the N-terminus, the C-terminus, or to a functional group on an interior residue (i.e., a residue at a position intermediate between the N- and C-termini) of an apolipoprotein molecule. Alternatively, the apolipoprotein and/or the moiety to be tagged can be derivatized to expose or attach additional reactive functional groups.

[0112] In some embodiments, fusion proteins that include a polypeptide functional moiety are synthesized using recombinant expression systems. Typically, this involves creating a nucleic acid (e.g., DNA) sequence that encodes the apolipoprotein and the functional moiety such that the two polypeptides will be in frame when expressed, placing the DNA under the control of a promoter, expressing the protein in a host cell, and isolating the expressed protein.

[0113] A nucleic acid encoding a chimeric apolipoprotein can be incorporated into a recombinant expression vector in a form suitable for expression in a host cell. As used herein, an "expression vector" is a nucleic acid which, when introduced into an appropriate host cell, can be transcribed and translated into a polypeptide. The vector may also include regulatory sequences such as promoters, enhancers, or other expression control elements (e.g., polyadenylation signals). Such regulatory sequences are known to those skilled in the art (see, e.g., Goeddel, 1990, Gene Expression Technology: Meth. Enzymol. 185, Academic Press, San Diego, Calif.; Berger and Kimmel, Guide to Molecular Cloning Techniques, Methods in Enzymology 152 Academic Press, Inc., San Diego, Calif.; Sambrook et al., 1989, Molecular

Cloning--A Laboratory Manual (2nd ed.) Vol. 1-3, Cold Spring Harbor Laboratory, Cold Spring Harbor Press, NY, etc.).

[0114] In some embodiments, an apolipoprotein has been modified such that when the apolipoprotein is incorporated into a complex of the disclosure, the modification will increase stability of the complex, confer targeting ability or increase capacity. In one embodiment, the modification includes introduction of cysteine residues into apolipoprotein molecules to permit formation of intramolecular or intermolecular disulfide bonds, e.g., by site-directed mutagenesis. In another embodiment, a chemical crosslinking agent is used to form intermolecular links between apolipoprotein molecules to enhance stability of the complex. Intermolecular crosslinking prevents or reduces dissociation of apolipoprotein molecules from the complex and/or prevents displacement by endogenous apolipoprotein molecules within an individual to whom the complexes are administered. In other embodiments, an apolipoprotein is modified either by chemical derivatization of one or more amino acid residues or by site directed mutagenesis, to confer targeting ability to or recognition by a cell surface receptor.

[0115] Complexes can be targeted to a specific cell surface receptor by engineering receptor recognition properties into an apolipoprotein. For example, complexes may be targeted to a particular cell type known to harbor a particular type of infectious agent, for example by modifying the apolipoprotein to render it capable of interacting with a receptor on the surface of the cell type being targeted. For example, complexes may be targeted to macrophages by altering the apolipoprotein to confer recognition by the macrophage endocytic class A scavenger receptor (SR-A). SR-A binding ability can be conferred to a complex by modifying the apolipoprotein by site directed mutagenesis to replace one or more positively charged amino acids with a neutral or negatively charged amino acid. SR-A recognition can also be conferred by preparing a chimeric apolipoprotein that includes an N- or C-terminal extension having a ligand recognized by SR-A or an amino acid sequence with a high concentration of negatively charged residues. Complexes comprising apoplipoproteins can also interact with apolipoprotein receptors such as, but not limited to, ABCA1 receptors, ABCG1 receptors, Megalin, Cubulin and HDL receptors such as SR-B1.

6.1.2.2. Apolipoprotein mimetics

[0116] Peptides, peptide analogs, and agonists that mimic the activity of an apolipoprotein (collectively referred to herein as “apolipoprotein peptide mimetics”) can also be used in the complexes described herein, either alone, in combination with one or more other lipid binding proteins. Non-limiting examples of peptides and peptide analogs that correspond to apolipoproteins, as well as agonists that mimic the activity of ApoA-I, ApoA-I_M, ApoA-II, ApoA-IV, and ApoE, that are suitable for inclusion in the complexes and compositions described herein are disclosed in U.S. Pat. Nos. 6,004,925, 6,037,323 and 6,046,166 (issued to Dasseux *et al.*), U.S. Pat. No. 5,840,688 (issued to Tso), U.S. Pat. No. 6,743,778 (issued to Kohno), U.S.

Publication Nos. 2004/0266671, 2004/0254120, 2003/0171277 and 2003/0045460 (to Fogelman), U.S. Publication No. 2006/0069030 (to Bachovchin), U.S. Publication No. 2003/0087819 (to Bielicki), U.S. Publication No. 2009/0081293 (to Murase *et al.*), and PCT Publication No. WO/2010/093918 (to Dasseux *et al.*), the disclosures of which are incorporated herein by reference in their entireties. These peptides and peptide analogues can be composed of L-amino acid or D-amino acids or mixture of L- and D-amino acids. They may also include one or more non-peptide or amide linkages, such as one or more well-known peptide/amide isosteres. Such apolipoprotein peptide mimetic can be synthesized or manufactured using any technique for peptide synthesis known in the art, including, *e.g.*, the techniques described in U.S. Pat. Nos. 6,004,925, 6,037,323 and 6,046,166.

[0117] In some embodiments, the lipid binding protein molecules comprise apolipoprotein peptide mimetic molecules and optionally one or more apolipoprotein molecules such as those described above.

[0118] In some embodiments, the apolipoprotein peptide mimetic molecules comprise an ApoA-I peptide mimetic, ApoA-II peptide mimetic, ApoA-IV peptide mimetic, or ApoE peptide mimetic or a combination thereof.

6.1.3. Amphipathic molecules

[0119] An amphipathic molecule is a molecule that possesses both hydrophobic (apolar) and hydrophilic (polar) elements. Amphipathic molecules that can be used in complexes described herein include lipids (*e.g.*, as described in Section 6.1.3.1), detergents (*e.g.*, as described in Section 6.1.3.2), fatty acids (*e.g.*, as described in Section 6.1.3.3), and apolar molecules and sterols covalently attached to polar molecules such as, but not limited to, sugars or nucleic acids (*e.g.*, as described in Section 6.1.3.4).

[0120] The complexes can include a single class of amphipathic molecule (*e.g.*, a single species of phospholipids or a mixture of phospholipids) or can contain a combination of classes of amphipathic molecules (*e.g.*, phospholipids and detergents). The complex can contain one species of amphipathic molecules or a combination of amphipathic molecules configured to facilitate solubilization of the lipid binding protein molecule(s).

[0121] In some embodiments, the amphipathic molecules included in comprise a phospholipid, a detergent, a fatty acid, an apolar moiety or sterol covalently attached to a sugar, or a combination thereof (*e.g.*, selected from the types of amphipathic molecules discussed above).

[0122] In some embodiments, the amphipathic molecules comprise or consist of phospholipid molecules. In some embodiments, the phospholipid molecules comprise negatively charged phospholipids, neutral phospholipids, positively charged phospholipids or a combination thereof. In some embodiments, the phospholipid molecules contribute a net charge of 1-3 per apolipoprotein molecule in the complex. In some embodiments, the net charge is a negative net charge. In some embodiments, the net charge is a positive net charge. In some embodiments,

the phospholipid molecules consist of a combination of negatively charged and neutral phospholipids. In some embodiments, the molar ratio of negatively charge phospholipid to neutral phospholipid ranges from 1:1 to 1:3. In some embodiments, the molar ratio of negatively charged phospholipid to neutral phospholipid is about 1:1 or about 1:2.

[0123] In some embodiments, the amphipathic molecules comprise neutral phospholipids and negatively charged phospholipids in a weight ratio of 95:5 to 99:1.

6.1.3.1. Lipids

[0124] Lipid binding protein-based complexes can include one or more lipids. In various embodiments, one or more lipids can be saturated and/or unsaturated, natural and/or synthetic, charged or not charged, zwitterionic or not. In some embodiments, the lipid molecules (*e.g.*, phospholipid molecules) can together contribute a net charge of 1-3 (*e.g.*, 1-3, 1-2, 2-3, 1, 2, or 3) per lipid binding protein molecule in the complex. In some embodiments, the net charge is negative. In other embodiments, the net charge is positive.

[0125] In some embodiments, the lipid comprises a phospholipid. Phospholipids can have two acyl chains that are the same or different (for example, chains having a different number of carbon atoms, a different degree of saturation between the acyl chains, different branching of the acyl chains, or a combination thereof). The lipid can also be modified to contain a fluorescent probe (*e.g.*, as described at avantilipids.com/product-category/products/fluorescent-lipids/). Preferably, the lipid comprises at least one phospholipid.

[0126] Phospholipids can have unsaturated or saturated acyl chains ranging from about 6 to about 24 carbon atoms (*e.g.*, 6-20, 6-16, 6-12, 12-24, 12-20, 12-16, 16-24, 16-20, or 20-24). In some embodiments, a phospholipid used in a complex of the disclosure has one or two acyl chains of 12, 14, 16, 18, 20, 22, or 24 carbons (*e.g.*, two acyl chains of the same length or two acyl chains of different length).

[0127] Non-limiting examples of acyl chains present in commonly occurring fatty acids that can be included in phospholipids are provided in Table 1, below:

Table 1

Length:Number of Unsaturations	Common Name
14:0	myristic acid
16:0	palmitic acid
18:0	stearic acid
18:1 cisΔ^{9}	oleic acid
18:2 cis$\Delta^{9,12}$	linoleic acid
18:3 cis$\Delta^{9,12,15}$	linonenic acid
20:4 cis$\Delta^{5,8,11,14}$	arachidonic acid
20:5 cis$\Delta^{5,8,11,14,17}$	eicosapentaenoic acid

Table 1	
Length:Number of Unsaturations	Common Name
	(an omega-3 fatty acid)

[0128] Lipids that can be present in the complexes of the disclosure include, but are not limited to, small alkyl chain phospholipids, egg phosphatidylcholine, soybean phosphatidylcholine, dipalmitoylphosphatidylcholine, dimyristoylphosphatidylcholine, distearoylphosphatidylcholine 1-myristoyl-2-palmitoylphosphatidylcholine, 1-palmitoyl-2-myristoylphosphatidylcholine, 1-palmitoyl-2-stearoylphosphatidylcholine, 1-stearoyl-2-palmitoylphosphatidylcholine, dioleoylphosphatidylcholine dioleophosphatidylethanolamine, dilauroylphosphatidylglycerol phosphatidylcholine, phosphatidylserine, phosphatidylethanolamine, phosphatidylinositol, phosphatidylglycerols, diphosphatidylglycerols such as dimyristoylphosphatidylglycerol, dipalmitoylphosphatidylglycerol, distearoylphosphatidylglycerol, dioleoylphosphatidylglycerol, dimyristoylphosphatidic acid, dipalmitoylphosphatidic acid, dimyristoylphosphatidylethanolamine, dipalmitoylphosphatidylethanolamine, dimyristoylphosphatidylserine, dipalmitoylphosphatidylserine, brain phosphatidylserine, brain sphingomyelin, palmitoylsphingomyelin, dipalmitoylsphingomyelin, egg sphingomyelin, milk sphingomyelin, phytosphingomyelin, distearoylsphingomyelin, dipalmitoylphosphatidylglycerol salt, phosphatidic acid, galactocerebroside, gangliosides, cerebrosides, dilaurylphosphatidylcholine, (1,3)-D-mannosyl-(1,3)diglyceride, aminophenylglycoside, 3-cholesteryl-6'-(glycosylthio)hexyl ether glycolipids, and cholesterol and its derivatives. Synthetic lipids, such as synthetic palmitoylsphingomyelin or N-palmitoyl-4-hydroxysphinganine-1-phosphocholine (a form of phytosphingomyelin) can be used to minimize lipid oxidation.

[0129] In some embodiments, a lipid binding protein-based complex includes two types of phospholipids: a neutral lipid, *e.g.*, lecithin and/or sphingomyelin (abbreviated SM), and a charged phospholipid (*e.g.*, a negatively charged phospholipid). A “neutral” phospholipid has a net charge of about zero at physiological pH. In many embodiments, neutral phospholipids are zwitterions, although other types of net neutral phospholipids are known and can be used. In some embodiments, the molar ratio of the charged phospholipid (*e.g.*, negatively charged phospholipid) to neutral phospholipid ranges from 1:1 to 1:3, for example, about 1:1, about 1:2, or about 1:3.

[0130] The neutral phospholipid can comprise, for example, one or both of the lecithin and/or SM, and can optionally include other neutral phospholipids. In some embodiments, the neutral phospholipid comprises lecithin, but not SM. In other embodiments, the neutral phospholipid comprises SM, but not lecithin. In still other embodiments, the neutral phospholipid comprises

both lecithin and SM. All of these specific exemplary embodiments can include neutral phospholipids in addition to the lecithin and/or SM, but in many embodiments do not include such additional neutral phospholipids.

[0131] As used herein, the expression "SM" includes sphingomyelins derived or obtained from natural sources, as well as analogs and derivatives of naturally occurring SMs that are impervious to hydrolysis by LCAT, as is naturally occurring SM. SM is a phospholipid very similar in structure to lecithin, but, unlike lecithin, it does not have a glycerol backbone, and hence does not have ester linkages attaching the acyl chains. Rather, SM has a ceramide backbone, with amide linkages connecting the acyl chains. SM can be obtained, for example, from milk, egg or brain. SM analogues or derivatives can also be used. Non-limiting examples of useful SM analogues and derivatives include, but are not limited to, palmitoylsphingomyelin, N-palmitoyl-4-hydroxysphinganine-1-phosphocholine (a form of phytosphingomyelin), palmitoylsphingomyelin, stearoylsphingomyelin, D-erythro-N-16:0-sphingomyelin and its dihydro isomer, D-erythro-N-16:0-dihydro-sphingomyelin. Synthetic SM such as synthetic palmitoylsphingomyelin or N-palmitoyl-4-hydroxysphinganine-1-phosphocholine (phytosphingomyelin) can be used in order to produce more homogeneous complexes and with fewer contaminants and/or oxidation products than sphingolipids of animal origin. Methods for synthesizing SM are described in U.S. Publication No. 2016/0075634.

[0132] Sphingomyelins isolated from natural sources can be artificially enriched in one particular saturated or unsaturated acyl chain. For example, milk sphingomyelin (Avanti Phospholipid, Alabaster, Ala.) is characterized by long saturated acyl chains (*i.e.*, acyl chains having 20 or more carbon atoms). In contrast, egg sphingomyelin is characterized by short saturated acyl chains (i.e., acyl chains having fewer than 20 carbon atoms). For example, whereas only about 20% of milk sphingomyelin comprises C16:0 (16 carbon, saturated) acyl chains, about 80% of egg sphingomyelin comprises C16:0 acyl chains. Using solvent extraction, the composition of milk sphingomyelin can be enriched to have an acyl chain composition comparable to that of egg sphingomyelin, or vice versa.

[0133] The SM can be semi-synthetic such that it has particular acyl chains. For example, milk sphingomyelin can be first purified from milk, then one particular acyl chain, *e.g.*, the C16:0 acyl chain, can be cleaved and replaced by another acyl chain. The SM can also be entirely synthesized, by *e.g.*, large-scale synthesis. See, *e.g.*, Dong *et al.*, U.S. Pat. No. 5,220,043, entitled Synthesis of D-erythro-sphingomyelins, issued Jun. 15, 1993; Weis, 1999, Chem. Phys. Lipids 102 (1-2):3-12. SM can be fully synthetic, *e.g.*, as described in U.S. Publication No. 2014/0275590.

[0134] The lengths and saturation levels of the acyl chains comprising a semi-synthetic or a synthetic SM can be selectively varied. The acyl chains can be saturated or unsaturated, and can contain from about 6 to about 24 carbon atoms. Each chain can contain the same number

of carbon atoms or, alternatively each chain can contain different numbers of carbon atoms. In some embodiments, the semi-synthetic or synthetic SM comprises mixed acyl chains such that one chain is saturated and one chain is unsaturated. In such mixed acyl chain SMs, the chain lengths can be the same or different. In other embodiments, the acyl chains of the semi-synthetic or synthetic SM are either both saturated or both unsaturated. Again, the chains can contain the same or different numbers of carbon atoms. In some embodiments, both acyl chains comprising the semi-synthetic or synthetic SM are identical. In a specific embodiment, the chains correspond to the acyl chains of a naturally-occurring fatty acid, such as for example oleic, palmitic or stearic acid. In another embodiment, SM with saturated or unsaturated functionalized chains is used. In another specific embodiment, both acyl chains are saturated and contain from 6 to 24 carbon atoms. Non-limiting examples of acyl chains present in commonly occurring fatty acids that can be included in semi-synthetic and synthetic SMs are provided in Table 1, above.

[0135] In some embodiments, the SM is palmitoyl SM, such as synthetic palmitoyl SM, which has C16:0 acyl chains, or is egg SM, which includes as a principal component palmitoyl SM.

[0136] In a specific embodiment, functionalized SM, such as phytosphingomyelin, is used.

[0137] Lecithin can be derived or isolated from natural sources, or it can be obtained synthetically. Examples of suitable lecithins isolated from natural sources include, but are not limited to, egg phosphatidylcholine and soybean phosphatidylcholine. Additional non-limiting examples of suitable lecithins include, dipalmitoylphosphatidylcholine, dimyristoylphosphatidylcholine, distearoylphosphatidylcholine 1-myristoy1-2-palmitoylphosphatidylcholine, 1-palmitoy1-2-myristoylphosphatidylcholine, 1-palmitoy1-2-stearoylphosphatidylcholine, 1-stearoy1-2-palmitoylphosphatidylcholine, 1-palmitoy1-2-oleoylphosphatidylcholine, 1-oleoy1-2-palmitylphosphatidylcholine, dioleoylphosphatidylcholine and the ether derivatives or analogs thereof.

[0138] Lecithins derived or isolated from natural sources can be enriched to include specified acyl chains. In embodiments employing semi-synthetic or synthetic lecithins, the identity(ies) of the acyl chains can be selectively varied, as discussed above in connection with SM. In some embodiments of the complexes described herein, both acyl chains on the lecithin are identical. In some embodiments of complexes that include both SM and lecithin, the acyl chains of the SM and lecithin are all identical. In a specific embodiment, the acyl chains correspond to the acyl chains of myristitic, palmitic, oleic or stearic acid.

[0139] The complexes of the disclosure can include one or more negatively charged phospholipids (*e.g.*, alone or in combination with one or more neutral phospholipids). As used herein, “negatively charged phospholipids” are phospholipids that have a net negative charge at physiological pH. The negatively charged phospholipid can comprise a single type of negatively charged phospholipid, or a mixture of two or more different, negatively charged, phospholipids.

In some embodiments, the charged phospholipids are negatively charged glycerophospholipids. Specific examples of suitable negatively charged phospholipids include, but are not limited to, a 1,2-dipalmitoyl-*sn*-glycero-3-[phospho-*rac*-(1-glycerol)], a phosphatidylglycerol, a phospatidylinositol, a phosphatidylserine, a phosphatidic acid, and salts thereof (*e.g.*, sodium salts or potassium salts). In some embodiments, the negatively charged phospholipid comprises one or more of phosphatidylinositol, phosphatidylserine, phosphatidylglycerol and/or phosphatidic acid. In a specific embodiment, the negatively charged phospholipid comprises or consists of a salt of a phosphatidylglycerol or a salt of a phosphatidylinositol. In another specific embodiment, the negatively charged phospholipid comprises or consists of 1,2-dipalmitoyl-*sn*-glycero-3-[phospho-*rac*-(1-glycerol)], or DPPG, or a salt thereof.

[0140] The negatively charged phospholipids can be obtained from natural sources or prepared by chemical synthesis. In embodiments employing synthetic negatively charged phospholipids, the identities of the acyl chains can be selectively varied, as discussed above in connection with SM. In some embodiments of the complexes of the disclosure, both acyl chains on the negatively charged phospholipids are identical. In some embodiments, the acyl chains all types of phospholipids included in a complex of the disclosure are all identical. In a specific embodiment, the complex comprises negatively charged phospholipid(s), and/or SM all having C16:0 or C16:1 acyl chains. In a specific embodiment the fatty acid moiety of the SM is predominantly C16:1 palmitoyl. In one specific embodiment, the acyl chains of the charged phospholipid(s), lecithin and/or SM correspond to the acyl chain of palmitic acid. In yet another specific embodiment, the acyl chains of the charged phospholipid(s), lecithin and/or SM correspond to the acyl chain of oleic acid.

[0141] Examples of positively charged phospholipids that can be included in the complexes of the disclosure include N1-[2-((1S)-1-[(3-aminopropyl)amino]-4-[di(3-amino-propyl)amino]butylcarboxamido)ethyl]-3,4-di[oleyloxy]-benzamide, 1,2-di-O-octadecenyl-3-trimethylammonium propane, 1,2-dimyristoleoyl-sn-glycero-3-ethylphosphocholine, 1-palmitoyl-2-oleoyl-sn-glycero-3-ethylphosphocholine, 1,2-dioleoyl-sn-glycero-3-ethylphosphocholine, 1,2-distearoyl-sn-glycero-3-ethylphosphocholine, 1,2-dipalmitoyl-sn-glycero-3-ethylphosphocholine, 1,2-dimyristoyl-sn-glycero-3-ethylphosphocholine, 1,2-dilauroyl-sn-glycero-3-ethylphosphocholine, 1,2-dilauroyl-sn-glycero-3-ethylphosphocholine, 1,2-dioleoyl-3-dimethylammonium-propane1,2-dimyristoyl-3-dimethylammonium-propane, 1,2-dipalmitoyl-3-dimethylammonium-propane, N-(4-carboxybenzyl)-N,N-dimethyl-2,3-bis(oleoyloxy)propan-1-aminium, 1,2-dioleoyl-3-trimethylammonium-propane, 1,2-dioleoyl-3-trimethylammonium-propane, 1,2-stearoyl-3-trimethylammonium-propane, 1,2-dipalmitoyl-3-trimethylammonium-propane, 1,2-dimyristoyl-3-trimethylammonium-propane, N-[1-(2,3-dimyristyloxy)propyl]-N, N-dimethyl-N-(2-hydroxyethyl) ammonium bromide, N,N,N-trimethyl-2-bis[(1-oxo-9-

octadecenyl)oxy]-(Z,Z)- 1propanaminium methyl sulfate, and salts thereof (*e.g.*, chloride or bromide salts).

[0142] The lipids used are preferably at least 95% pure, and/or have reduced levels of oxidative agents (such as but not limited to peroxides). Lipids obtained from natural sources preferably have fewer polyunsaturated fatty acid moieties and/or fatty acid moieties that are not susceptible to oxidation. The level of oxidation in a sample can be determined using an iodometric method, which provides a peroxide value, expressed in milli-equivalent number of isolated iodines per kg of sample, abbreviated meq O/kg. *See, e.g.*, Gray, 1978, Measurement of Lipid Oxidation: A Review, Journal of the American Oil Chemists Society 55:539-545; Heaton, F.W. and Ur, Improved Iodometric Methods for the Determination of Lipid Peroxides, 1958, Journal of the Science of Food and Agriculture 9:781-786. Preferably, the level of oxidation, or peroxide level, is low, *e.g.*, less than 5 meq O/kg, less than 4 meq O/kg, less than 3 meq O/kg, or less than 2 meq O/kg.

[0143] Complexes can in some embodiments include small quantities of additional lipids. Virtually any type of lipids can be used, including, but not limited to, lysophospholipids, galactocerebroside, gangliosides, cerebrosides, glycerides, triglycerides, and sterols and sterol derivatives (*e.g.*, a plant sterol, an animal sterol, such as cholesterol, or a sterol derivative, such as a cholesterol derivative). For example, a complex of the disclosure can contain cholesterol or a cholesterol derivative, *e.g.*, a cholesterol ester. The cholesterol derivative can also be a substituted cholesterol or a substituted cholesterol ester. The complexes of the disclosure can also contain an oxidized sterol such as, but not limited to, oxidized cholesterol or an oxidized sterol derivative (such as, but not limited to, an oxidized cholesterol ester). In some embodiments, the complexes do not include cholesterol and/or its derivatives (such as a cholesterol ester or an oxidized cholesterol ester).

6.1.3.2. Detergents

[0144] The complexes can contain one or more detergents. The detergent can be zwitterionic, nonionic, cationic, anionic, or a combination thereof. Exemplary zwitterionic detergents include 3-[(3-Cholamidopropyl)dimethylammonio]-1-propanesulfonate (CHAPS), 3-[(3-Cholamidopropyl)dimethylammonio]-2-hydroxy-1-propanesulfonate (CHAPSO), and N,N-dimethyldodecylamine N-oxide (LDAO). Exemplary nonionic detergents include D-(+)-trehalose 6-monooleate, N-octanoyl-N-methylglucamine, N-nonanoyl-N-methylglucamine, N-decanoyl-N-methylglucamine, 1-(7Z-hexadecenoyl)-*rac*-glycerol, 1-(8Z-hexadecenoyl)-*rac*-glycerol, 1-(8Z-heptadecenoyl)-*rac*-glycerol, 1-(9Z-hexadecenoyl)-*rac*-glycerol, 1-decanoyl-*rac*-glycerol. Exemplary cationic detergents include (S)-O-methyl-serine dodecylamide hydrochloride, dodecylammonium chloride, decyltrimethylammonium bromide, and cetyltrimethylammonium sulfate. Exemplary anionic detergents include cholesteryl hemisuccinate, cholate, alkyl sulfates, and alkyl sulfonates.

6.1.3.3. Fatty Acids

[0145] The complexes can contain one or more fatty acids. The one or more fatty acids can include short-chain fatty acids having aliphatic tails of five or fewer carbons (*e.g.* butyric acid, isobutyric acid, valeric acid, or isovaleric acid), medium-chain fatty acids having aliphatic tails of 6 to 12 carbons (*e.g.*, caproic acid, caprylic acid, capric acid, or lauric acid), long-chain fatty acids having aliphatic tails of 13 to 21 carbons (*e.g.*, myristic acid, palmitic acid, stearic acid, or arachidic acid) , very long chain fatty acids having aliphatic tails of 22 or more carbons (*e.g.*, behenic acid, lignoceric acid, or cerotic acid), or a combination thereof. The one or more fatty acids can be saturated (*e.g.*, caprylic acid, capric acid, lauric acid, myristic acid, palmitic acid, stearic acid, arachidic acid, behenic acid, lignoceric acid, or cerotic acid), unsaturated (*e.g.*, myristoleic acid, palmitoleic acid, sapienic acid, oleic acid, elaidic acid, vaccenic acid, linoleic acid, linoelaidic acid, α-linolenic acid, arachidonic acid, eicosapentaenoic acid, erucic acid, or docosahexaenoic acid) or a combination thereof. Unsaturated fatty acids can be cis or trans fatty acids. In some embodiments, unsaturated fatty acids used in the complexes of the disclosure are cis fatty acids.

6.1.3.4. Apolar molecules and sterols attached to a sugar

[0146] The complexes can contain one or more amphipathic molecules that comprise an apolar molecule or moiety (*e.g.*, a hydrocarbon chain, an acyl or diacyl chain) or a sterol (*e.g.*, cholesterol) attached to a sugar (*e.g.*, a monosaccharide such as glucose or galactose, or a disaccharide such as maltose or trehalose). The sugar can be a modified sugar or a substituted sugar. Exemplary amphipathic molecules comprising an apolar molecule attached to a sugar include dodecan-2-yloxy-ß-D-maltoside, tridecan-3-yloxy-ß-D-maltoside, tridecan-2-yloxy-ß-D-maltoside, n-dodecyl-ß-D-maltoside (DDM), n-octyl-ß-D-glucoside, n-nonyl-ß-D-glucoside, n-decyl-ß-D-maltoside, n-dodecyl-β-D-maltopyranoside, 4-n-Dodecyl-α,α-trehalose, 6-n-dodecyl-α,α-trehalose, and 3-n-dodecyl-α,α-trehalose.

[0147] In some embodiments, the apolar moiety is an acyl or a diacyl chain.

[0148] In some embodiments, the sugar is a modified sugar or a substituted sugar.

6.1.4. Formulations

[0149] Lipid binding protein-based complexes can be formulated for the intended route of administration, for example according to techniques known in the art (*e.g.*, as described in Allen *et al.*, eds., 2012, *Remington: The Science and Practice of Pharmacy*, 22nd Edition, Pharmaceutical Press, London, UK).

[0150] CER-001 intended for administration by infusion can be formulated in a phosphate buffer with sucrose and mannitol excipients, for example as described in WO 2012/109162.

6.2. Subject populations

[0151] Subjects who can be treated according to the methods described herein are preferably mammals, most preferably human.

[0152] In some aspects, the subject has an acute condition comprising acute inflammation.

[0153] In some aspects, the subject can be a subject in need of therapy for sepsis and/or AKI.

[0154] In some embodiments, the subject has sepsis (*e.g.*, associated with a gram-negative bacterial infection). The sepsis can in some embodiments be caused by an intra-abdominal cavity infection or be urosepsis. Sepsis is a risk factor for AKI. Thus, in some embodiments, the subject can be at risk for AKI, for example due to sepsis. In some embodiments, the subject has sepsis associated with a gram negative bacterial infection. In other embodiments, the subject has sepsis associated with a gram positive bacterial infection.

[0155] In some embodiments, the subject has a SOFA score of 1 to 4 before treatment with a lipid binding protein-based complex, *e.g.*, a score of 1, 2, 3, or 4 (see, Vincent *et al.* 1996, Intensive Care Med, 22:707–710).

[0156] In some embodiments, the subject has an endotoxin activity level as measured by the Endotoxin Activity Assay (EEA™) (Spectral Medical) of > 0.6 prior to administration of the lipid binding protein-based complex (see, Marshall *et al.*, 2004, J Infect Dis. 190(3):527-34).

[0157] In some embodiments, the subject has AKI or is at risk of AKI. For example, a the AKI can be sepsis-related AKI, ischemia/reperfusion AKI, CSA-AKI, or hepatorenal syndrome (HSA) AKI. In some embodiments, the AKI is sepsis-related AKI. In other embodiments, the AKI is ischemia/reperfusion AKI. In other embodiments, the AKI is CSA AKI. In other embodiments, the AKI is HRS AKI. Subjects at risk of HRS include subjects having liver disease (*e.g.*, chronic liver disease or acute liver disease). In some embodiments, the subject has chronic liver disease. In some embodiments, the subject has acute liver disease. In some embodiments, the subject has alcoholic liver disease. HRS has historically been classified as type 1 HRS, where renal function rapidly deteriorates over days to weeks, and type 2 HRS, where deterioration occurs over months. Accordingly, in some embodiments, a subject treated according to a dosage regimen of the disclosure has type 1 HRS. In other embodiments, a subject treated according to a dosage regiment of the disclosure has type 2 HRS. Newer criteria for diagnosis and classification of HRS have been developed, for example the ICA diagnostic criteria of HRS acute kidney injury (AKI). See, *e.g.*, Amin *et al.*, 2019, Seminars in Nephrology 39(1):17-30. Accordingly, in some embodiments, a subject having HRS meets the ICA diagnostic criteria of HRS AKI.

[0158] In some aspects, the subject can be any subject having CRS or at risk of CRS, and/or any subject in need of reduction in serum levels of one or more inflammatory markers such as IL-6. In some embodiments, the subject has CRS. In some embodiments, the subject has CRS secondary to an infection, for example a viral infection such as an infection with COVID-19 or

influenza. In some embodiments, the subject has CRS secondary to a COVID-19 infection. In other embodiments, the subject has CRS caused by immunotherapy, for example antibody or chimeric antigen receptor (CAR) T cell therapy. In yet other embodiments, the subject is at risk of CRS, for example due to an infection such as COVID-19 or influenza. In other embodiments, the subject is at risk of CRS due to immunotherapy.

[0159] In another aspect, the subject is a subject in need of a reduction in serum levels of one or more inflammatory markers, for example a subject with elevated levels of the one or more inflammatory markers compared to normal levels. Exemplary inflammatory cytokines include interleukin 6 (IL-6), C-reactive protein, D-dimer, ferritin, interleukin 8 (IL-8), granulocyte-macrophage colony stimulating factor (GM-CSF), monocyte chemoattractant protein (MCP) 1, and tumor necrosis factor α (TNFα). In some embodiments, the one or more cytokines comprise IL-6. In some embodiments, the one or more cytokines comprise a combination of the foregoing, for example, 2, 3, 4, 5, 6, 7, or all 8 of interleukin 6 (IL-6), C-reactive protein, D-dimer, ferritin, interleukin 8 (IL-8), granulocyte-macrophage colony stimulating factor (GM-CSF), monocyte chemoattractant protein (MCP) 1, and tumor necrosis factor α (TNFα).

6.3. Dosing Regimens

[0160] The methods of the disclosure typically entail multiple administrations of a lipid binding protein-based complex (*e.g.*, CER-001), *e.g.*, three to 10 individual doses. In some embodiments, an administration regimen can include four or more doses of a lipid binding protein-based complex (*e.g.*,CER-001), *e.g.*, five, six, seven, eight, nine, ten, eleven, twelve, or more than twelve doses.

[0161] In some embodiments, the lipid binding protein-based complex is administered according to an induction and, optionally, a consolidation regimen as described in Sections 6.3.1 and 6.3.2, respectively. In some embodiments, the lipid binding protein-based complex can be administered in a single phase, *e.g.*, according to an administration regimen described in this Section. In some embodiments, the subject is not treated with the lipid binding protein-based complex according to a maintenance regimen, *e.g.*, a regimen comprising long-term (*e.g.*, one month or longer) administration of the lipid binding protein-based complex.

[0162] The lipid binding protein-based complex (*e.g.*, CER-001) administration regimens of the disclosure can last up to one week, one week, or more than one week (*e.g.*, two weeks).

[0163] For example, a lipid binding protein-based complex (*e.g.*, CER-001) administration regimen can comprise administering:

- five doses of CER-001 over one week;
- six doses of CER-001 over one week;
- seven doses of CER-001 over one week;
- ten doses of CER-001 over two weeks;

- twelve doses of CER-001 over two weeks;
- fourteen doses of CER-001 over two weeks.

[0164] In an embodiment, the methods of the disclosure (*e.g.*, methods for treating CRS or a subject at risk of CRS) comprise administering seven doses of CER-001 over one week, *e.g.*, on days 1, 2, 3, 4, 5, 6, and 7.

[0165] In some embodiments of the methods of the disclosure, a lipid binding protein-based complex (*e.g.*, CER-001) is administered daily, *e.g.*, daily for at least 5 days, at least 6 days, at least 7 days, or more than 7 days (*e.g.*, daily for up to one week or daily for up to two weeks). In other embodiments, a lipid binding protein-based complex (*e.g.*, CER-001) is administered less frequently, *e.g.*, every other day, two times per week, three times per week, or once a week.

[0166] In practice, an administration window can be provided, for example, to accommodate slight variations to a multi-dosing per week dosing schedule. For example, a window of ± 2 days or ± 1 day around the dosage date can be used.

[0167] A lipid binding protein-based complex (*e.g.*, CER-001) can be administered in the methods of the disclosure for a pre-determined period of time, *e.g.*, for one week. Alternatively, administration of a lipid binding protein-based complex (*e.g.*, CER-001) can be continued until one or more symptoms of the acute indication (*e.g.*, CRS) are reduced or continued until the serum levels of one or more inflammatory markers are reduced, for example reduced to a normal level or reduced relative to a baseline value for the subject, *e.g.*, a baseline value measured prior to the start of lipid binding protein-based complex (*e.g.*, CER-001) therapy. Reference or "normal" levels of various inflammatory markers are known in the art. For example, the Mayo Clinic Laboratories test catalog (www.mayocliniclabs.com/test-catalog) provides the following reference values: IL-6: ≤ 1.8 pg/ml; C-reactive protein: ≤ 8.0 mg/ml; D-dimer: ≤ 500 ng/mL Fibrinogen Equivalent Units (FEU); ferritin: 24-336 mcg/L (males), 11-307 mcg/L (females); IL-8 < 57.8 pg/mL; TNF-α < 5.6 pg/mL.

[0168] When administering a lipid binding protein-based complex (*e.g.*, CER-001) to a subject who has CRS due to immunotherapy or is at risk of CRS due to immunotherapy, a lipid binding protein-based complex (*e.g.*, CER-001) can be administered before the immunotherapy begins, concurrently with the immunotherapy, after the immunotherapy ends, or a combination thereof. For example, a lipid binding protein-based complex (*e.g.*, CER-001) can be administered before the immunotherapy and currently with the immunotherapy, concurrently with the immunotherapy and after the immunotherapy, or before the immunotherapy, concurrently with the immunotherapy and after the immunotherapy. Concurrent administration is not limited to administration of the lipid binding protein-based complex (*e.g.*, CER-001) and the immunotherapy at the exact same time, and encompasses administration of one agent while a course of therapy with the other is ongoing.

[0169] The methods of the disclosure (*e.g.*, methods for treating an acute condition described herein) typically comprise administering a high dose of a lipid binding protein-based complex (*e.g.*, CER-001). The high dose can be the aggregate of multiple individual doses (*e.g.*, two, three, four, five, six, seven, eight, nine or 10 individual doses), for example administered over multiple days (*e.g.*, a period of three days, four days, five days, six days, seven days, eight days, nine days, 10 days, eleven days, 12 days, 13 days, 14 days or 15 days). The individual doses of a high dose are in some embodiments administered daily, twice daily, or two to three days apart.

[0170] In some embodiments, the high dose is an amount effective to increase the subject's HDL and/or ApoA-I blood levels and/or improve the subject's vascular endothelial function, *e.g.*, measured by circulating vascular cell adhesion molecule 1 (VCAM-1) and/or intercellular adhesion molecule 1 (ICAM-1) levels. In some embodiments, the high dose or an individual dose is an amount which increases the subject's HDL and/or ApoA-I levels by at least 25%, at least 30%, or at least 35% 2 to 4 hours after administration.

[0171] In some embodiments, the high dose is an amount effective to reduce serum levels of one or more inflammatory markers, for example, one or more of IL-6, C-reactive protein, D-dimer, ferritin, IL-8, GM-CSF, and MCP1 TNF-α. In some embodiments, the serum levels of the one or more inflammatory markers are reduced from an elevated range to a normal range, and/or reduced by at least 20%, at least 40%, or at least 60%.

[0172] The dose of a lipid binding protein-based complex (*e.g.*, CER-001) administered to a subject (*e.g.*, an individual dose which when aggregated with one or more other individual doses forms a high dose) can in some embodiments range from 4 to 40 mg/kg (*e.g.*, 10 to 40 mg/kg) on a protein weight basis (*e.g.,* 5, 10, 15, 20, 25, 30, 35, or 40 mg/kg or any range bounded by any two of the foregoing values, *e.g.*, 10 to 20 mg/kg, 15 to 25 mg/kg, 20 to 40 mg/kg, 25 to 35 mg/kg, or 30 to 40 mg/kg). As used herein, the expression "protein weight basis" means that a dose of a lipid binding protein-based complex (*e.g.*, CER-001) to be administered to a subject is calculated based upon the amount of ApoA-I in the lipid binding protein-based complex (*e.g.*, CER-001) to be administered and the weight of the subject. For example, a subject who weighs 70 kg and is to receive a 20 mg/kg dose of CER-001 would receive an amount of CER-001 that provides 1400 mg of ApoA-I (70 kg x 20 mg/kg).

[0173] In yet other aspects, a lipid binding protein-based complex (*e.g.*, CER-001) can be administered on a unit dosage basis. The unit dosage used in the methods of the disclosure can in some embodiments vary from 300 mg to 4000 mg (*e.g.*, 600 mg to 4000 mg) per administration (on a protein weight basis).

[0174] In particular embodiments, the dosage of a lipid binding protein-based complex (*e.g.*, CER-001) is 600 mg to 3000 mg, 800 mg to 3000 mg, 1000 mg to 2400 mg, or 1000 mg to 2000 mg per administration (on a protein weight basis).

[0175] In some aspects, a high dose of a lipid binding protein-based complex (*e.g.*, CER-001), *e.g.*, the aggregate of multiple individual doses, is 600 mg to 40 g (on a protein weight basis). In particular embodiments, a high dose is 3 g to 35 g or 5 g to 30 g (on a protein weight basis).

[0176] A lipid binding protein-based complex (*e.g.*, CER-001) is preferably administered as an IV infusion. For example, a stock solution of CER-001 can be diluted in normal saline such as physiological saline (0.9% NaCl) to a total volume between 125 and 250 ml. In some embodiments, subjects weighing less than 80 kg will have a total volume of 125 ml whereas subjects weighing at least 80 kg will have a total volume of 250 ml. In some embodiments, doses of CER-001 are administered in a total volume of 250 ml. A lipid binding protein-based complex (*e.g.*, CER-001) may be administered over a period ranging from one-hour to 24-hours. Depending on the needs of the subject, administration can be by slow infusion with a duration of more than one hour (*e.g.*, up to 2 hours or up to 24 hours), by rapid infusion of one hour or less, or by a single bolus injection. In an embodiment, a lipid binding protein-based complex (*e.g.*, CER-001) is administered over a one-hour period, *e.g.*, using an infusion pump at a fixed rate of 125 ml/hr or 250 ml/hr. In an embodiment, a dose of a lipid binding protein-based complex (*e.g.*, CER-001) is administered as an infusion over a 24-hour period.

6.3.1. Induction Regimen

[0177] In one embodiment, induction regimens suitable for use in the methods of the disclosure entail administering multiple doses of a lipid binding protein-based complex (*e.g.*, CER-001) over multiple consecutive days, *e.g.*, three consecutive days.

[0178] In some embodiments, induction regimens suitable for use in the methods of the disclosure entail twice daily administration of a lipid binding protein-based complex (*e.g.*, CER-001) such as twice daily administration on multiple consecutive days. Twice daily administration can comprise, for example, two doses approximately 12 hours apart or a morning dose and an evening dose (which may be more or less than 12 hours apart).

[0179] In an embodiment, the induction regimen comprises two doses of a lipid binding protein-based complex (*e.g.*, CER-001) per day for 3 consecutive days.

[0180] A therapeutic dose of a lipid binding protein-based complex (*e.g.*, CER-001) administered by infusion in the induction regimen can range from 4 to 40 mg/kg (*e.g.*, 4 to 30 mg/kg) on a protein weight basis (*e.g.*, 4, 5, 6, 7, 8, 9, 10, 12 15, 20, 25, 30 or 40 mg/kg, or any range bounded by any two of the foregoing values, *e.g.*, 5 to 15 mg/kg, 10 to 20 mg/kg, or 15 to 25 mg/kg). In some embodiments, the dose of a lipid binding protein-based complex (*e.g.*, CER-001) used in the induction regimen is 5 mg/kg. In some embodiments, the dose of a lipid binding protein-based complex (*e.g.*, CER-001) used in the induction regimen is 10 mg/kg. In some embodiments, the dose of a lipid binding protein-based complex (*e.g.*, CER-001) used in the induction regimen is 15 mg/kg. In some embodiments, the dose of a lipid binding protein-based complex (*e.g.*, CER-001) used in the induction regimen is 20 mg/kg. In some

embodiments, the induction regimen comprises six doses of a lipid binding protein-based complex (*e.g.*, CER-001) administered over three days at a dose of 5 mg/kg, 10 mg/kg, 15 mg/kg or 20 mg/kg.

[0181] In yet other aspects, a lipid binding protein-based complex (*e.g.*, CER-001) can be administered on a unit dosage basis. The unit dosage used in the induction phase can vary from 300 mg to 4000 mg (*e.g.*, 300 mg to 3000 mg) (on a protein weight basis) per administration by infusion.

[0182] In particular embodiments, the dosage of a lipid binding protein-based complex (*e.g.*, CER-001) used during the induction phase is 300 mg to 1500 mg, 400 mg to 1500 mg, 500 mg to 1200 mg, or 500 mg to 1000 mg (on a protein weight basis) per administration by infusion.

6.3.2. Consolidation Regimen

[0183] Consolidation regimens suitable for use in the methods of the disclosure entail administering one dose or multiple doses of a lipid binding protein-based complex (*e.g.*, CER-001) following an induction regimen.

[0184] In one embodiment, the consolidation regimen comprises administering two doses of a lipid binding protein-based complex (e.g., CER-001). For example, the two doses can be administered approximately 12 hours apart, or administered as a morning dose and an evening dose (which may be more or less than 12 hours apart).

[0185] The dose(s) of a lipid binding protein-based complex (e.g., CER-001) in a consolidation regimen can in some embodiments be administered on day 6 of a dosing regimen that begins with an induction regimen on day 1. The dose(s) of a lipid binding protein-based complex (e.g., CER-001) in a consolidation regimen can in some embodiments be administered on day 4 of a dosing regimen that begins with an induction regimen on day 1. The dose(s) of a lipid binding protein-based complex (e.g., CER-001) in a consolidation regimen can in some embodiments be administered on day 5 of a dosing regimen that begins with an induction regimen on day 1. The dose(s) of a lipid binding protein-based complex (e.g., CER-001) in a consolidation regimen can in some embodiments be administered on day 7 of a dosing regimen that begins with an induction regimen on day 1.

[0186] A therapeutic dose of a lipid binding protein-based complex (*e.g.*, CER-001) administered by infusion in the consolidation regimen can range from 4 mg/kg to 40 mg/kg (*e.g.*, 4 to 30 mg/kg) on a protein weight basis (*e.g.*, 4, 5, 6, 7, 8, 9, 10, 12, 15, 20, 25, 30, or 40 mg/kg, or any range bounded by any two of the foregoing values, *e.g.*, 5 to 15 mg/kg, 10 to 20 mg/kg, or 15 to 25 mg/kg). In some embodiments, the dose of a lipid binding protein-based complex (*e.g.*, CER-001) used in the consolidation regimen is 5 mg/kg. In some embodiments, the dose of a lipid binding protein-based complex (*e.g.*, CER-001) used in the consolidation regimen is 10 mg/kg. In some embodiments, the dose of a lipid binding protein-based complex (*e.g.*, CER-001) in the consolidation regimen is 15 mg/kg. In some embodiments, the dose of a

lipid binding protein-based complex (*e.g.*, CER-001) used in the consolidation regimen is 20 mg/kg. In some embodiments, the consolidation regimen comprises two doses of a lipid binding protein-based complex (*e.g.*, CER-001) administered on one day at a dose of 5 mg/kg, 10 mg/kg, 15 mg/kg or 20 mg/kg.

[0187] In yet other aspects, a lipid binding protein-based complex (*e.g.*, CER-001) can be administered on a unit dosage basis. The unit dosage used in the consolidation phase can vary from 300 mg to 4000 mg (*e.g.*, 300 mg to 3000 mg) (on a protein weight basis) per administration by infusion.

[0188] In particular embodiments, the dosage of a lipid binding protein-based complex (*e.g.*, CER-001) used during the consolidation phase is 300 mg to 1500 mg, 400 mg to 1500 mg, 500 mg to 1200 mg, or 500 mg to 1000 mg (on a protein weight basis) per administration by infusion.

[0189] The lipid binding protein-based complex (*e.g.*, CER-001) can be administered during the consolidation phase in the same manner as described in Section 6.3, *e.g.*, as an IV infusion over a one-hour period.

6.4. Combination therapies

[0190] A lipid binding protein-based complex (*e.g.*, CER-001) can be administered to a subject as described herein as a monotherapy or a part of a combination therapy regimen. For example, a combination therapy may comprise a lipid binding protein-based complex (*e.g.*, CER-001) in combination with a standard of care treatment for sepsis and/or AKI. *See, e.g.*, Rhodes *et al.*, 2017, Intensive Care Med 43:304–377; Dugar *et al.*, 2020, Cleveland Clinic Journal of Medicine 87(1):53-64.

[0191] In some embodiments, the subject is treated with a lipid binding protein-based complex (*e.g.*, CER-001) in combination with fluid replacement therapy. In some embodiments, the subject is treated with a lipid binding protein-based complex (*e.g.*, CER-001) in combination with an antimicrobial. In some embodiments, the subject is treated with a lipid binding protein-based complex (*e.g.*, CER-001) in combination with an antibiotic (*e.g.*, ceftriaxone, meropenem, ceftazidime, cefotaxime, cefepime, piperacillin and tazobactam, ampicillin and sulbactam, imipenem and cilastatin, levofloxacin, or clindamycin). In some embodiments, the subject is treated with a lipid binding protein-based complex (*e.g.*, CER-001) in combination with an antiviral. In some embodiments, the subject is treated with a lipid binding protein-based complex (*e.g.*, CER-001) in combination with a medication that raises blood pressure (*e.g.*, norepinephrine or epinephrine).

[0192] A combination therapy regimen can in some embodiments comprise one or more anti-IL-6 agents and/or one or more other agents for treating CRS such as corticosteroids (*e.g.*, methylprednisolone and/or dexamethasone). Exemplary anti-IL6 agents include tocilizumab, siltuximab, olokizumab, elsilimomab, BMS-945429, sirukumab, levilimab, and CPSI-2364. In

some embodiments, a lipid binding protein-based complex (*e.g.*, CER-001) is administered in combination with tocilizumab. Subjects who have or have had a COVID-19 infection can be treated with a lipid binding protein-based complex (*e.g.*, CER-001) in combination with one or more additional therapies such as antibodies from recovered COVID-19 patients, antibodies against the spike protein of COVID-19, one or more antiviral agents (*e.g.*, lopinavir, remdesivir, danoprevir, galidesivir, darunavir, ritonavir), chloroquine, hydroxychloroquine, azithromycin, an interferon (*e.g.*, an interferon alpha or an interferon beta, each of which can be pegylated), or a combination thereof.

[0193] In certain embodiments, an antihistamine (*e.g.*, diphenhydramine, cetirizine, fexofenadine, or loratadine) can be administered before administration of a lipid binding protein-based complex (*e.g.*, CER-001). The antihistamine can reduce the likelihood of allergic reactions.

7. EXAMPLES

7.1. Example 1: CER-001 therapy in a swine model of LPS-induced AKI

[0194] The ability of CER-001 to mitigate sepsis-related AKI was evaluated in a lipopolysaccharide (LPS)-induced swine model of AKI.

7.1.1. Materials and Methods

[0195] Pigs were randomized into three groups: LPS (endotoxemic pigs, n=3), single dose CER- 001 treated pigs (endotoxemic pigs treated with a single dose of CER-001 at 20 mg/kg; n=3), and multiple dose CER-001 treated pigs (endotoxemic pigs treated with two doses of CER-001 at 20 mg/kg; n=3).

[0196] Sepsis was induced in the pigs by intravenous infusion of a saline solution containing 300 µg/kg of LPS at T0. Single dose CER-001 treated pigs and CER-001 multiple dose treated pigs received a 20 mg/kg dose of CER-001 at T0. CER-001 multiple dose treated pigs received a second 20 mg/kg dose of CER-001 three hours later (T3). Serum IL-6, LPS, MCP-1, sVCAM-1 and sICAM-1 levels were monitored over time. Renal tissue damage and fibrosis were assessed at the end of the study period.

7.1.2. Results

[0197] An increased survival rate was observed in both CER-001 treated groups compared to LPS group (data not shown). LPS injection led to a time-dependent increase of IL-6 in endotoxemic animals (FIG. 1) compared to the basal condition (T0). CER-001 treatment was able to reverse LPS effects, as shown by reduced IL-6 levels (FIG. 1, “20 MG” and “40MG”). The second infusion of CER-001 three hours from the first dose (T3) strongly reduced IL-6 serum levels to basal level by the end of the study (T end) (FIG. 1, “40MG”). Similarly, high levels of MCP-1 in endotoxemic pigs were observed relative to the basal condition, while MCP-1 levels were lower in the pigs treated with CER-001 (data not shown).

[0198] Endothelial dysfunction was evaluated by measuring sVCAM-1 and sICAM-1 serum levels. Time-dependent increases of sVCAM-1 and sICAM-1 were observed in endotoxemic animals, while CER-001 treatment strongly decreased sVCAM-1 and sICAM-1 levels in both treated groups (FIG. 2 and FIG. 3, respectively). In line with IL-6 results, the infusion of two doses of CER-001 (FIG. 2, "40 MG") was more efficient in decreasing sVCAM-1 to basal levels. LPS levels were strongly reduced in CER-001 treated animals (FIG. 4, "20MG" and "40 MG") and the effects were more evident after the second infusion of CER-001 (FIG. 4, "40 MG").

[0199] The endotoxemic renal biopsies presented tubular vacuolization, epithelial flattening, and some apoptotic tubular cells. CER-001 treatment significantly decreased inflammatory processes and tubular damage. In endotoxemic animals, Masson's trichrome staining revealed extensive collagen deposition at the interstitial level. In both CER-001 treated groups, there were significantly fewer collagen deposits in renal parenchymal compared to the LPS group.

[0200] This preclinical data indicates that CER-001 treatment reduces systemic inflammation and endothelial dysfunction, thereby limiting renal damage in the LPS-induced swine model of AKI.

7.2. Example 2: Randomized pilot study comparing short-term CER-001 infusions at different doses to prevent sepsis-induced acute kidney injury

[0201] Currently, there are no approved treatments for sepsis-related AKI. Considering that the inflammatory response to endotoxemia is a major cause for hemodynamic destabilization and progression to AKI in septic patients, the main objective of the study is to investigate whether the use of CER-001 at different doses in combination with standard of care (SOC) treatment is safe and effective, providing a new strategy to treat septic patients, reducing the inflammatory response and preventing the progression to AKI. Without being bound by theory, the anticipated mechanism of action is two-fold, comprising both the binding of endotoxin by CER-001 and a direct anti-inflammatory effect of CER-001.

7.2.1. Study Protocol

[0202] *Study population:* This is a single-center, randomized, dose-ranging (phase II) study including patients with sepsis due to intra-abdominal cavity infection or urosepsis, admitted at the Intensive Care Unit (ICU) of the participating center. The investigators ensure that all patients meeting the following inclusion and exclusion criteria are offered enrollment in the study.

[0203] *Inclusion criteria:*

- Male or non-pregnant female adult ≥18 years of age at time of enrollment;
- Meets Sepsis 3 criteria, defined as an acute increase of at least 2 points in SOFA Score relative to the SOFA score upon admission;
- Endotoxin level (measured by Endotoxin Activity Assay (EEA™); Spectral Medical) >0.6 (see, Marshall *et al.*, 2004, J Infect Dis. 190(3):527-34);

- Signed and dated informed consent by the patient itself or by a legal representative.

[0204] *Exclusion Criteria:*

- Patients weighing more than 100 kg;
- Alanine transaminase/aspartate transaminase (ALT/AST) > 5 times the upper limit of normal;
- Stage 4 severe chronic kidney disease or requiring dialysis (i.e. estimated glomerular filtration rate (eGFR) < 30 ml /min/1.73 m^2);
- Leukocytes<2.0×10^9;
- Pregnancy or breast feeding;
- Undergone organ transplantation during the past one year;
- Anticipated transfer to another hospital, which is not a study site within 72 hours;
- Terminally ill, including metastases or hematological malignancy, with a life expectancy less than 30 days (as assessed by the attending physician) or have been classified as "Do Not Resuscitate";
- Previous history of end stage chronic organ failure(s);
- Diagnosed with HIV;
- Uncontrolled hemorrhage within the last 24 h;
- Patients who have used an investigational drug or device within 30 days of the first dose of CER-001.

[0205] *Number of subjects:* Twenty subjects are enrolled and randomized (1:1:1:1) into four experimental groups: Group A patients continue to receive conventional therapy, Group B: patients add CER-001 5 mg/kg BID for 3 days to conventional therapy, followed by 5 mg/kg BID on Day 6; Group C: patients add CER-001 10 mg/kg BID for 3 days to conventional therapy, followed by 10mg/kg BID on Day 6; Group D patients add CER-001 20 mg/kg BID for 3 days to conventional therapy, followed by 20mg/kg BID on Day 6 (FIG. 5).

[0206] *Duration of study*: This study is completed in 24 weeks (6 months). The enrolment period is approximately 20 weeks (5 months) from the first subject enrolled. The end of the study is the last visit of the last subject.

[0207] *Primary endpoint*: The primary end-point of the study is to define the safety and the optimal dose of CER-001 in combination with standard of care in patients with sepsis sustained by Gram negative bacteria.

[0208] *Secondary endpoint:* Secondary end-points are:

- Change in endotoxin and IL-6 levels from baseline to Day 3, Day 6 and Day 9.
- Baseline is defined as the last measurements taken prior to dosing on Day 1.
- Change in the SOFA score (Vincent *et al*. 1996, Intensive Care Med, 22:707–710) from baseline to Day 3, Day 6 and Day 9.

- Changes to the key inflammatory markers (CRP, D-dimer, Ferritin, IL-8, GM-CSF, MCP 1 and TNF-α) from baseline to Day 3, Day 6 and Day 9.
- Changes in AKI biomarkers and onset of AKI according to KDIGO criteria (Kidney Disease Improving Global Outcomes. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney International Supplements 2012; 2: 1–138)
- Mortality at Day 30
- An independent medical expert review outcome data during the trial.

[0209] *Intervention/exposure*: Twenty patients meeting the eligibility criteria, who sign and date an ethical committee (EC)-approved informed consent form, are randomized and assigned (1:1:1:1) ratio to conventional therapy (Group A), low dose CER-001 (Group B) or medium dose CER-001 (Group C) or high dose CER-001 (Group D). Conventional therapy is modulated according to the clinical conditions. All non-experimental treatments are allowed to be administered concomitantly during the patient's participation in this study: any medication the patient takes, other than study drugs specified per protocol, is considered a concomitant medication and is recorded in the study records.

[0210] Each patient is identified at the screening by a patient number. Once assigned to a patient, the patient number is not reused. The randomization list and the allocation assignment sequence is produced and the investigators that enroll do not have any participation in this task. The randomization list divided into blocks is adequately concealed to prevent attempts at subversion of randomization.

[0211] *Treatment group:* All patients receive conventional therapy. Treated groups receive an additional therapy with the study drugs. In particular:

- **Group A:** Conventional therapy (i.e., antibiotic treatments and hemodynamic support according to patient's conditions).
- **Group B:** Conventional therapy + CER-001 5 mg/kg BID for 3 consecutive days, followed by 5 mg/kg BID on Day 6.
- **Group C:** Conventional therapy + CER-001 10 mg/kg BID for 3 consecutive days, followed by 10 mg/kg BID on Day 6.
- **Group D:** Conventional therapy + CER-001 20 mg/kg BID for 3 consecutive days, followed by 20 mg/kg BID on Day 6.

[0212] Patients are pretreated with antihistamine prior to each CER-001 dose (*e.g.* dexchlorpheniramine 5 mg or hydroxyzine 100 mg) to avoid any potential infusion reactions. Patients may be interrupted or discontinued from study medication if any of the following occur:

[0213] Any drug-related adverse event or other reason which, in the Investigator's opinion, jeopardizes the patient's participation in the trial or the interpretation of trial data (*e.g.*, severe inter-current illness requiring additional care measures or preventing further dosing); significant tolerability issues.

[0214] At the time of study medication interruption, the study site documents the reason for drug interruption. The patient continues to be followed clinically and all attempts are made to re-institute study medication within 2 days of the study drug interruption if not otherwise contraindicated.

[0215] Reasons for withdrawal from study drug may include, but are not limited to, the following:

- Investigator's request, for safety reasons, such as severe adverse reactions;
- Investigator's request, for other reasons, such as patient non-compliance;
- Patient's request, for tolerability reasons;
- Patient's request, for other reasons, such as withdrawal of informed consent.

[0216] Discontinuation of study drug alone does not constitute discontinuation or withdrawal from the study. Patients continue to be followed as though they had completed the treatment phase. Patients who prematurely discontinue study medication (e.g., prior to completion of the 3th dose) undergo end of study evaluations whenever possible.

[0217] *Statistical analysis:* Comparison between groups is performed using the appropriate statistical tests: dichotomous variables (baseline characteristics, mortality, development of AKI) are compared by the use of Chi-square or Fisher's exact test, continuous baseline characteristics by ANOVA or Kruskall-Wallis test, t Student or Mann-Whitney U test, as appropriate. Changes in inflammatory markers are compared between groups by ANOVA and are graphically represented. Proportion of patients of AKI and mortality rate are calculated for each group. All analyses is performed using SPSS 12.0 for Windows; $p<0.05$ is considered statistically significant.

[0218] *Procedures:* The following procedures are performed during the screening visit. Following randomization, subjects initiate treatment within 2 business days.

- Informed consent
- Medical history - includes: recording past and present illnesses and collection of the subjects demographic data (birth date, sex, and race).
- Physical examination with a review of systems, height and weight, BMI and wait circumference
- Vital signs (pulse, blood pressure, and oral, auricular, axillary, or core temperature).
- Review of inclusion/exclusion criteria.
- Adverse events are recorded starting from the time informed consent is obtained.
- Prior medications are collected from 4 weeks before the first dose of test article. All current medications are recorded.
- Complete blood count (CBC) – includes white blood cell count (WBC) with differential, platelet count, red blood cell count (RBC), haemoglobin (Hb), hematocrit (Hct).

- Fasting chemistry panel/electrolytes: includes sodium, potassium, chloride, blood urea nitrogen (BUN; or urea), serum creatinine, calculated clearance creatinine (CKD-EPI), glucose, calcium, phosphorus, total protein, uric acid, AST, ALT, γ GT, ALP, total and direct bilirubine, albumin, total cholesterol, HDL, LDL, triglycerides, LDH, CPK,
- ABG (for assessing respiratory and/or metabolic disorders)
- ApoA-I (for pharmacokinetic and pharmacodynamic assessment)
- Coagulation tests – includes prothrombin time (PT) (expressed as international normalized ratio [INR]), and partial thromboplastin time (PTT).
- Urinalysis – includes specific gravity, pH, assessment of protein/albumin, glucose, ketones, and haemoglobin/blood.
- Microalbumunuria and Proteinuria g/24 h
- Serum or urine pregnancy test (for women of childbearing potential) within 7 days before randomization.
- Pharmacokinetic and pharmacodynamic assessment includes apoA-I and total cholesterol levels.
- Endotoxin levels are measured using the EAA™ kit. AKI Biomarkers (TIMP-2 and IGFBP-7) are measured using the Nephrocheck® kit. Inflammatory markers include: CRP, D-dimer, Ferritin, IL-6, IL-8, GM-CSF, MCP 1 and TNF-α.

[0219] In addition to biological samples collected for the daily routine laboratory assessments performed at the Central laboratory, biological samples for research purposes are collected, including:

- 2 tubes 5 ml of serum
- 1 tube 3ml of plasma
- urine 30ml

[0220] These samples are used to assess additional inflammatory cytokines and urinary biomolecules in order to obtain a more comprehensive characterization of patients enrolled, to better evaluate response to treatment, to provide more information in the follow-up and more importantly, to discover new potential biomarkers that could be useful for early diagnosis of sepsis-induced AKI. The analysis is performed by ELISA test and protein arrays.

[0221] *On therapy visits (Treatment period)*: Treatment period is defined as from the start of treatment. The visit is planned at Day 3, Day 6 and Day 9. A final visit is planned on Day 30. The following procedures are performed during the therapy visits:

- Recording of adverse events and concomitant medications
- Review of appropriate laboratory information
- Physical examination

- Vital signs (pulse, blood pressure and oral, auricular, axillary, or core temperature) will be assessed
- Record adverse events and concomitant medications continually
- Complete blood count (CBC) – includes white blood cell count (WBC) with differential, platelet count, red blood cell count (RBC), haemoglobin (Hb), hematocrit (Hct).
- Fasting chemistry panel/electrolytes: includes sodium, potassium, chloride, blood urea nitrogen (BUN; or urea), serum creatinine, calculated clearance creatinine (CKD-EPI),
- glucose, calcium, phosphorus, total protein, uric acid, AST, ALT, γGT, ALP, total and direct bilirubine, albumin, total cholesterol, HDL, LDL, triglycerides, LDH, CPK
- ABG (for assessing respiratory and/or metabolic disorders)
- ApoA-I (for pharmacokinetic and pharmacodynamic assessment)
- Coagulation tests – includes prothrombin time (PT) (expressed as international normalized ratio [INR]), and partial thromboplastin time (PTT).
- Urinalysis – includes specific gravity, pH, assessment of protein/albumin, glucose, ketones, and haemoglobin/blood.
- Microalbumunuria and Proteinuria g/24 h
- Serum or urine pregnancy test (for women of childbearing potential) within 7 days before randomization.
- Pharmacokinetic and pharmacodynamic assessment will include apoA-I and total cholesterol levels.
- Endotoxin levels are measured using the EAA™ kit. AKI Biomarkers (TIMP-2 and IGFBP-7) are measured using the Nephrocheck® kit. Inflammatory markers include: CRP, D-dimer, Ferritin, IL-6, IL-8, GM-CSF, MCP 1 and TNF-α.

[0222] In addition to biological samples collected for the daily routine laboratory assessments performed at the Central laboratory, biological samples for research purposes are collected, including

- 2 tubes 5 ml of serum
- 1 tube 3ml of plasma
- urine 30ml

[0223] Clinical scores include the SOFA score (Table 2) and the KDIGO criteria for AKI assessment and staging (Table 3). Individual components of each score are documented.

Table 2. The Sequential Organ Failure Assessment (SOFA) score

SOFA Score:	0	1	2	3	4
Respiration PaO_2/FIO_2 (mmHg)	≥400	<400	<300	<220 and mechanically ventilated	<100 and mechanically ventilated
Coagulation Platelets x $10^3/mm^3$	≥150	<150	<100	<50	<20
Liver Bilirubin (mg/dL)	<1.2	1.2-1.9	2.0-5.9	6.0-11.9	≥12.0
Cardiovascular[a] Hypotension	MAP≥70	MAP<70	Dopamine≤5 or dobutamine (any)	Dopamine>5 or norepinephrine≤0.1	Dopamine>15 or norepinephrine>0.1
CNS Glasgow Coma Score	15	13-14	10-12	6-9	<6
Renal Creatinine (mg/dL) or urine output (mL/day)	<1.2	1.2-1.9	2.0-3.4	3.5-4.9 or <500	>5.0 or <200

MAP = Mean arterial pressure; CNS = central nervous system; SaO_2 = peripheral arterial oxygen saturation

[a]Vasoactive medications administered for at least 1 hr (dopamine and norepinephrine μg/kg/min)

Table 3. KDIGO classification for AKI		
Stage	**Serum creatinine**	**Urine output**
1	1.5 – 1.9 times baseline OR ≥0.3 mg/dl (≥26.5µmol/l) increase	<0.5ml/kg/h for 6-12 hours
2	2.0 – 2.9 times baseline	<0.5ml/kg/h for ≥12 hours
3	3.0 times baseline OR Increase in serum creatinine to ≥4.0 mg/dl (≥353.6µmol/l) OR Initiation of renal replacement therapy OR, in patients <18 years, decrease in eGFR to <35ml/min per 1.73m^3	<0.3ml/kg/h for ≥24 hours OR Anuria for ≥12 hours

[0224] Table 4 provides a summary of the study protocol of this Example.

Table 4. Overview of study protocol										
Procedure	**Baseline**	**Treatment visits**								**Final visit Day 30**
		Day 1		**Day 2**		**Day 3**		**Day 6**	**Day 9**	
		am	**pm**	**am**	**pm**	**am**	**pm**			
CER-001 Dosing		X	X	X	X	X	X	X		
Endotoxin	X	X		X		X		X	X	X
IL-6	X	X		X		X		X	X	X
Additional Inflammatory Markers[a]	X									X
SOFA Score	X	X		X		X		X	X	X
RIFLE Score	X	X		X		X		X	X	X
apoA-I and Total Cholesterol		X[b]								

Table 4. Overview of study protocol

Procedure	Baseline	Treatment visits								Final visit Day 30
		Day 1		Day 2		Day 3		Day 6	Day 9	
		am	pm	am	pm	am	pm			
Safety Labs[c]	X									X
Optional samples	X	X		X		X		X	X	X
Concomitant Medication Monitoring	X	X		X		X		X	X	X
Adverse Event Monitoring	X	X		X		X		X	X	X

a) Includes CRP, D-dimer, Ferritin, IL-8,VCAM-1, ICAM-1, GM-CSF, MCP 1 and TNF-α.

b) On dosing days, drawn prior to and 2 hours after the start of each infusion.

c) Tested at local hospital laboratory.

[0225] ***Safety Evaluations:*** Safety evaluations are attained utilizing information collected from the following assessments: physical examination (including weight), vital signs (blood pressure, pulse, temperature), CBC with differential, platelet count, blood chemistries, and fasting lipid profiles [including HDL-cholesterol, LDL-cholesterol and Lipoprotein (a)], urea, glucose, 24 hour urine protein determination, serum creatinine and calculated creatinine clearance (CKD-EPI) and adverse events monitoring. All women of childbearing potential have a qualitative serum pregnancy test during pre-study screening/baseline evaluation and subsequently, if clinically indicated. Patients are monitored throughout the study for the occurrence of adverse events, that are recorded. Adverse events volunteered by the subject or discovered, as a result of general questioning by the investigator or by physical examination, are recorded. The duration (start and end dates), severity, cause and relationship to study medication, patient outcome, action taken, and an assessment of whether the event was serious are recorded for each reported adverse event.

[0226] Adverse events: *Definitions*

[0227] The term “adverse event,” is synonymous with the term “adverse experience,” which is used by the FDA. An adverse event (AE) is any untoward, undesired, unplanned clinical event in the form of signs, symptoms, disease, or laboratory or physiological observations occurring in a human being participating in a clinical study regardless of causal relationship. This includes the following:

- Any clinically significant worsening of a pre-existing condition.
- Any reoccurrence of a pre-existing condition.
- An AE occurring from overdose of an investigator test article whether accidental or intentional (i.e., a dose higher than that prescribed by a health care professional for clinical reasons).
- An AE occurring from abuse of an investigator test article (i.e., use for no clinical reasons).
- An AE that has been associated with the discontinuation of the use of an investigator test article.

[0228] A procedure is not an AE, but the reason for a procedure may be an AE.

[0229] A “preexisting condition” is a clinical condition (including a condition being treated) that is diagnosed before the subject signs the informed consent form and that is documented as part of the subject’s medical history. The questions concerning whether the condition existed before the start of the active phase of the study and whether it has increased in severity and/or frequency are used to determine whether an event is a treatment-emergent adverse event (TEAE). An AE is considered to be treatment emergent if (1) it was not present when the active phase of the study began and is not a chronic condition that is part of the subject’s medical history, or (2) it was present at the start of the active phase of the study or as part of the subject’s medical history, but the severity or frequency increased during the active phase. The active phase of the study begins at the time of the first dose of the drug.

[0230] A “serious adverse event” is any AE occurring at any dose that meets 1 or more of the following criteria:

- Results in death
- Is life-threatening (see below)
- Requires in subject hospitalization or prolongation of an existing hospitalization (see below)
- Results in a persistent or significant disability or incapacity (see below)
- Results in a new malignancy
- Results in a congenital anomaly or birth defect

[0231] Additionally, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based on appropriate medical

judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not require hospitalization, or development of drug dependency or drug abuse.

[0232] A "life-threatening adverse event" is any AE that places the subject at immediate risk of death from the event as it occurred. A life-threatening event does not include an event that might have caused death had it occurred in a more severe form but that did not create an immediate risk of death as it actually occurred. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening, even though drug-induced hepatitis of a more severe nature can be fatal.

[0233] Hospitalization or prolongation of a hospitalization is a criterion for considering an AE to be serious. In the absence of an AE, the participating investigator should not report hospitalization or prolongation of hospitalization on a form. This is the case in the following situations: Hospitalization or prolongation of hospitalization is needed for a procedure required by the protocol. Day or night survey visits required by the protocol are not considered serious.

[0234] *Timing for reporting serious adverse events*: Any SAE, regardless of causal relationship, is reported to medical monitor immediately (no later than 24 hours after the investigator becomes aware of the SAE) by faxing a completed serious adverse event form. Follow-up information relating to an SAE is reported to medical monitor (or designee) within 24 hours of receipt by the investigator by faxing a completed serious adverse event form. The subject is observed and monitored carefully until the condition resolves or stabilizes or its cause is identified. Any emergency is reported to medical monitor (or designee) immediately (within 24 hours) by contacting a medical monitor.

[0235] *Reportable events/information:* An AE or SAE can occur from the time that the subject signs the informed consent form to 15 days from the subject's last dose, regardless of test article or protocol relationship. This includes events that emerge during the screening and placebo run-in periods. All AEs and SAEs are recorded on source documents and recorded on CRFs. All AEs and SAEs that occur after the screening period are recorded on the CRFs.

[0236] *For SEAs:* The investigator provides all documentation pertaining to the event (*e.g.*, additional laboratory tests, consultation reports, discharge summaries, postmortem reports, etc) to the Medical monitor in a timely manner. Reports relative to the subject's subsequent course are submitted to the investigator until the event has subsided or, in case of permanent impairment, until the condition stabilizes.

[0237] The following events are recorded and reported in the same time frame and following the same process as for SAEs:

[0238] Test article abuse and overdose (i.e. use for nonclinical reasons) with or without AEs. An overdose is a dose higher than that prescribed by a health care professional for clinical reasons. It is up to the participating investigator to decide whether a dose is an overdose.

[0239] Inadvertent or accidental exposure to test article with or without an AE.

[0240] Post study test article-related SAEs.

[0241] SAEs occurring after unauthorized or accidental use in persons not participating in the study.

[0242] Abnormal biological or vital signs values that are considered clinically relevant by the participating investigator. These are reported in the same time frame and following the same process as for an AE or an SAE

[0243] *Recording and reporting*: At each required study visit, all AEs that have occurred since the previous visit are recorded in the adverse event record of the subject's CRF. The information recorded is based on the signs or symptoms detected during the physical examination and clinical evaluation of the subject. In addition to the information obtained from those sources, the subject is asked the following non specific question: "How have you been feeling since your last visit?" Signs and symptoms are recorded using standard medical terminology. The health outcomes assessment surveys administered to study subjects are intended to explore the subject's own perceptions about their quality of life. However, the investigator reviews the survey for the presence of potential AEs or SAEs and considers the subject's perceptions when determining the occurrence of an AE or SAE. The subject's assessments are not intended to be influenced by the clinical investigator. Every effort is made to maintain an unbiased assessment. The following AE information is included (when applicable): the specific condition or event and direction of change; whether the condition was pre-existing (i.e. an acute condition present at the start of the study or history of a chronic condition) and, if so, whether it has worsened (in severity and/or frequency); the dates and times of occurrence; severity; causal relationship to test article; action taken; and outcome. Any laboratory abnormality, which in the opinion of the investigator is clinically significant, is reported as an AE.

[0244] The causal relation between an AE and the test article is determined by the investigator on the basis of his or her clinical judgement and the following definitions:

- ***Definitely related***: Event can be fully explained by administration of the test article.
- ***Probably related***: Event is most likely to be explained by administration of the test article, rather than the subject's clinical state or other agents/therapies.
- ***Possibly related***: Event may be explained by administration of the test article, or by the subject's clinical state or other agents/therapies.
- ***Probably not related***: Event is most likely to be explained by the subject's clinical state or other agents/therapies, rather than the test article.

- ***Definitely not related***: Event can be fully explained by the subject's clinical state or other agents/therapies.

[0245] When assessing the relationship between administration of a test article and an AE, the following are considered:

- Temporal relationship between administration of the test article and the AE
- Biological plausibility of relationship
- Subject's underlying clinical state or concomitant agents and/or therapies

[0246] When applicable, whether the AE abates on discontinuation of the test article

[0247] When applicable, whether the AE reappears on repeat exposure to the test article SAEs that are not test article-related may nevertheless be considered by the participating investigator or the medical monitor (or designee) to be related to the conduct of the clinical study, i.e., to a subject's participation in the study. For example, a protocol-related SAE may be an event that occurs during a washout period or that is related to a procedure required by the protocol. The severity of AEs is assessed according to the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE) version 5.0. The following definitions are used for toxicities that are not defined in the NCI CTCAE:

- **Mild (Grade 1):** The AE is noticeable to the subject but does not interfere with routine activity. The AE does not require discontinuing administration or reducing the dose of the test article.
- **Moderate (Grade 2):** The AE interferes with routine activity but responds to symptomatic therapy or rest. The AE may require reducing the dose but not discontinuing administration of the test article.
- **Severe (Grade 3):** The AE significantly limits the subject's ability to perform routine activities despite symptomatic therapy. In addition, the AE leads to discontinuing administration or reducing the dose of the test article.
- **Life-Threatening (Grade 4):** The AE requires discontinuing administration of the test article. The subject is at immediate risk of death.

7.2.2. Results

[0248] Treatment with CER-001 is found to delay or prevent AKI onset in subjects having sepsis.

7.3. Example 3: CER-001 Therapy for Treating CRS Secondary to Covid-19 Infection

[0249] COVID-19 is infects host cells through binding of the viral spike protein (SARS-2-S) to the cell-surface receptor angiotensin-converting enzyme 2 (ACE2), and the HDL scavenger receptor B type 1 (SR-B1) facilitates ACE2-dependent entry of the virus. (Wei *et al.*, Nature Metabolism doi.org/10.1038/s42255-020-00324-0). Without being bound by theory, it is

believed that lipid binding protein-based complexes such as CER-001 may provide a therapeutic benefit (*e.g.*, reducing the severity and/or duration of CRS) in subjects having a COVID-19 infection through competitive binding to SR-B1, thereby limiting the virus's ability to infect additional cells.

[0250] A pilot study is conducted to investigate the safety and efficacy of seven CER-001 infusions in patients with CRS secondary to COVID-19 infection. The study consists of 9 visits:

- Pre-Dosing (Baseline) Visit: Assessment of baseline inflammatory markers and safety labs.
- Dosing Visits: Seven doses (Doses 1 through 7) are administered as a once daily infusion over a 7-day period. IL-6 is measured daily from a pre-infusion sample.
- Follow-Up Visit: Patients have their final evaluation on Day 8. Inflammatory markers and safety labs are measured.

[0251] A flowchart for the study is shown in FIG. 6.

7.3.1. Selection of Study Subjects

7.3.1.1. Inclusion Criteria

[0252] Eligible patients meeting the following criteria are enrolled into the study:

1. Male or non-pregnant female adult ≥18 years of age at time of enrollment.
2. Has laboratory-confirmed novel coronavirus (COVID-19) infection as determined by polymerase chain reaction (PCR), or other commercial or public health assay in oropharyngeal or anal specimen within 72 hours prior to hospitalization.
3. Illness of any duration, and at least one of the following:
    a. Radiographic infiltrates by imaging (chest x-ray, CT scan, etc.), OR
    b. Clinical assessment (evidence of rales/crackles on physical examination) AND SpO2 ≤93% on room air, OR
    c. Requiring mechanical ventilation and/or supplemental oxygen, OR
    d. Sustained fever in the past 24 hours and unresponsive to NSAID or steroid
4. Serum IL-6 ≥3 times the upper limit of normal
5. Females of childbearing potential that agree and commit to use an acceptable form of birth control for the entire study. Acceptable forms of birth control for this study are defined as a barrier method plus hormonal therapy (implants, injections, oral contraceptives and IUDs) or abstinence.

7.3.1.1. Exclusion Criteria

[0253] Patients meeting the following criteria are excluded from the study:

1. Patients weighing more than 100 kg

2. Alanine transaminase/aspartate transaminase (ALT/AST) > 5 times the upper limit of normal.
3. Stage 4 severe chronic kidney disease or requiring dialysis (i.e. estimated glomerular filtration rate (eGFR) < 30 ml /min/1.73 m^2)
4. Hemoglobin<80 g/L
5. Leukocytes<2.0×10^9
6. Platelets<50×10^9
7. Pregnancy or breast feeding.
8. Anticipated transfer to another hospital which is not a study site within 72 hours.
9. Expected life span does not exceed 7 days.
10. Patients who have used an investigational agent within 30 days of the first dose of CER-001.

7.3.1.2. Restrictions During the Study

[0254] There are no patient restrictions other than those outlined in the Inclusion/Exclusion criteria above.

7.3.1.3. Withdrawal Criteria

[0255] Reasons for withdrawal of a patient from study drug may include, but are not limited to, the following:

- Investigator's request, for safety reasons, such as severe adverse reactions;
- Investigator's request, for other reasons, such as patient non-compliance;
- Patient's request, for tolerability reasons;
- Patient's request, for other reasons, such as withdrawal of informed consent;

[0256] Discontinuation of study drug alone does not constitute discontinuation or withdrawal from the study. Patients continue to be followed as though they had completed the treatment phase. Patients who prematurely discontinue study medication (*e.g.*, prior to completion of the 7th dose) undergo end of study evaluations whenever possible.

7.3.2. Treatment of Patients

7.3.2.1. Investigational Product

[0257] CER-001 is provided frozen in 20 mL vials containing approximately 18 mL of product at a concentration of 8 mg/mL (ApoA-I content). CER-001 is dosed by weight. All doses are thawed and then diluted with normal saline to a volume of 250 mL.

[0258] Dosing occurs at each of the seven dosing visits. At each of these visits, patients are given a single IV infusion CER 001 (20 mg/kg) over a period of 24 hours using an infusion pump. Patients are pretreated with antihistamine prior to each CER-001 dose (*e.g.* dexchlorpheniramine 5 mg or hydroxyzine 100 mg) to avoid any potential infusion reactions.

7.3.2.2. Interruption or Discontinuation of Study Medication

[0259] Patients are interrupted or discontinued from study medication if any of the following occur:

- Any drug-related adverse event or other reason which, in the Investigator's opinion, jeopardize the patient's participation in the trial or the interpretation of trial data (*e.g.*, severe inter-current illness requiring additional care measures or preventing further dosing)
- Significant tolerability issues

[0260] At the time of study medication interruption, the study site documents the reason for drug interruption. The patient continues to be followed clinically and all attempts are made to re-institute study medication within 2 days of the study drug interruption if not otherwise contraindicated.

7.3.3. Concomitant Treatments

[0261] All non-experimental treatments are allowed to be administered concomitantly during the patient's participation in this study. Any medication the patient takes, other than study drugs specified per protocol, is considered a concomitant medication and is recorded in the study records.

7.3.4. Prohibited Medication

[0262] There are no excluded medications.

7.3.5. Monitoring Patient Compliance

[0263] CER-001 is administered in the hospital under direct observation.

7.3.6. Assessment of Efficacy

7.3.6.1. Efficacy Assessments

[0264] Inflammatory markers include: CRP, D-dimer, Ferritin, IL-6, IL-8, GM-CSF, MCP 1 and TNF-α.

7.3.6.2. Efficacy Parameters

(a) Primary Efficacy Parameters

[0265] The primary efficacy parameter is the change in IL-6 from baseline to Day 8. Baseline is defined as the average of the measurements taken at the baseline visit and prior to dosing on Day 1.

(b) Secondary Efficacy Parameters

[0266] Secondary efficacy parameters include changes to the inflammatory markers CRP, D-dimer, Ferritin, IL-8, GM-CSF, MCP 1 and TNF-α from baseline to Day 8.

7.3.7. Assessment of Safety

7.3.7.1. Safety Parameters

(a) Pregnancy Tests (if applicable)

[0267] Females of child bearing potential have a documented negative pregnancy test performed any time during hospitalization and prior to dosing.

(b) Safety Laboratory Tests

[0268] Blood samples are drawn for chemistry and hematology analyses at two time points: baseline and Day 8. The following tests are performed by the local hospital laboratory:

Chemistry Profile	Hematology
Albumin	White Blood Count
Alkaline Phosphatase	Red Blood Count
Alanine Aminotransferase (ALT/SGPT)	Hemoglobin
Aspartame Aminotransferase (AST/SGOT)	Hematocrit
Urea	Neutrophils
Calcium	Lymphocytes
Chloride	Monocytes
Bicarbonate	Eosinophils
Creatinine	Basophils
Glucose	Platelets
Potassium	
Sodium	
Total Bilirubin	
Total Protein	

7.3.8. Results

[0269] IL-6 levels are reduced from baseline to day 8. Secondary efficacy parameters are also reduced from baseline to day 8, indicating that CER-001 therapy can be used to treat CRS and reduce serum levels of inflammatory markers.

7.4. Example 4: CER-001 Therapy for Treating CRS Secondary to Covid-19 Infection - Additional Treatment Protocol

[0270] This Example is a study of CER-001 therapy in COVID-19 patients with severe cytokine release syndrome and renal injury.

7.4.1. Selection of Subjects

7.4.1.1. Inclusion Criteria

[0271] Eligible patients meet the following criteria before they are enrolled into the study:

1. Male or non-pregnant female adult 18 years of age at time of enrollment.

2. Has laboratory-confirmed novel coronavirus infection as determined by polymerase chain reaction (PCR), or other commercial or public health assay in oropharyngeal or anal specimen within 72 hours prior to hospitalization.
3. Illness of any duration, and at least one of the following:

Radiographic infiltrates by imaging (chest x-ray, CT scan, etc.), OR

Clinical assessment (evidence of rales/crackles on physical examination) AND SpO2 < 93% on room air, OR

Requiring mechanical ventilation and/or supplemental oxygen, OR

Sustained fever in the past 24 hours and unresponsive to NSAID or steroid

4. Serum IL-6 >3 times the upper limit of normal
5. Females of childbearing potential that agree and commit to use an acceptable form of birth control for the entire study. Acceptable forms of birth control for this study are defined as a barrier method plus hormonal therapy (implants, injections, oral contraceptives and IUDs) or abstinence.

7.4.1.2. Exclusion Criteria

[0272] Patients who meet any of the following criteria are excluded from this study.

1. Clinical history suggesting allergies to CER-001
2. Pregnancy or breast feeding.
3. Anticipated transfer to another hospital within 72 hours.
4. Expected life span does not exceed 7 days.
5. Patients who have used an investigational agent within 30 days of the first dose of CER-001.

7.4.2. Treatments

7.4.2.1. Treatments Administered

[0273] Patients are pretreated with antihistamine prior to each CER-001 dose (*e.g.* dexchlorpheniramine 5 mg or hydroxyzine 100 mg) to avoid any potential infusion reactions.

[0274] Patients receive IV infusion of CER-001 at the dosage of 15 mg/kg BID for 3 consecutive days. At the discretion of the investigator, patients may receive up to two additional doses.

[0275] Patients may be interrupted or discontinued from study medication if any of the following occur:

1. Any drug-related adverse event or other reason which, in the Investigator's opinion, jeopardizes the patient's participation in the trial or the interpretation of trial data (*e.g.*, severe inter-current illness requiring additional care measures or preventing further dosing);
2. Significant tolerability issues.

[0276] At the time of study medication interruption, the study site documents the reason for drug interruption. The patient continues to be followed clinically and all attempts are made to re-institute study medication within 2 days of the study drug interruption if not otherwise contraindicated.

[0277] Reasons for withdrawal from study drug may include, but are not limited to, the following:

1. Investigator's request, for safety reasons, such as severe adverse reactions
2. Investigator's request, for other reasons, such as patient non-compliance
3. Patient's request, for tolerability reasons
4. Patient's request, for other reasons, such as withdrawal of informed consent

[0278] Discontinuation of study drug alone does not constitute discontinuation or withdrawal from the study. Patients continue to be followed as though they had completed the treatment phase. Patients who prematurely discontinue study medication (*e.g.*, prior to completion of the 3th dose) undergo end of study evaluations whenever possible.

7.4.2.2. Dose Changes

[0279] In case of clinical needs defined by the main investigator, the dose of the drug may be reduced or increased

7.4.2.3. Concomitant Medications/Therapies

[0280] All non-experimental treatments are allowed to be administered concomitantly during a patient's participation in this study. Any medication the patient takes, other than study drugs specified per protocol, is considered a concomitant medication and is recorded in the study records.

7.4.3. Study Assessments

[0281] The following procedures are performed during the Baseline visit. The following tests are performed by the local hospital laboratory.

1. Informed consent
2. Medical history includes recording past and present illnesses and collection of the subject's demographic data (birth date, sex, and race).
3. Physical examination with a review of systems, height and weight, BMI and wait circumference
4. Vital signs (pulse, blood pressure, and oral, auricular, axillary, or core temperature).
5. Review of inclusion/exclusion criteria.
6. Adverse events are recorded starting from the time informed consent is obtained.
7. Prior medications are collected from 4 weeks before the first dose of test article. All current medications are recorded.

8. Complete blood count (CBC) – includes white blood cell count (WBC) with differential, platelet count, red blood cell count (RBC), haemoglobin (Hb), hematocrit (Hct).

9. Fasting chemistry panel/electrolytes: includes sodium, potassium, chloride, blood urea nitrogen (BUN; or urea), serum creatinine, calculated clearance creatinine (CKD-EPI), glucose, calcium, phosphorus, total protein, uric acid, AST, ALT, □GT, ALP, total and direct bilirubine, albumin, total cholesterol, HDL, LDL, triglycerides, LDH, CPK,

10. ABG (for assessing respiratory and/or metabolic disorders)

11. ApoA-I (for pharmacokinetic and pharmacodynamic assessment)

12. Coagulation tests – includes prothrombin time (PT) (expressed as international normalized ratio [INR]), and partial thromboplastin time (PTT).

13. Urinalysis – includes specific gravity, pH, assessment of protein/albumin, glucose, ketones, and haemoglobin/blood.

14. Microalbumunuria and Proteinuria g/24 h

15. Serum or urine pregnancy test (for women of childbearing potential) within 7 days before randomization.

16. Pharmacokinetic and pharmacodynamic assessment include apoA-I and total cholesterol levels.

17. Inflammatory markers include CRP, PCT, D-dimer, Ferritin, IL-6, IL-8, GM-CSF, MCP 1 and TNF-α.

[0282] Clinical and laboratory parameters are monitored from baseline to the Final visit at Day 8 as reported in FIG. 7 and include the following procedures:

1. Recording of adverse events and concomitant medications
2. Review of appropriate laboratory information
3. Physical examination
4. Vital signs (pulse, blood pressure and oral, auricular, axillary, or core temperature) are assessed
5. Record adverse events and concomitant medications continually
6. Complete blood count (CBC) – includes white blood cell count (WBC) with differential, platelet count, red blood cell count (RBC), haemoglobin (Hb), hematocrit (Hct).
7. Fasting chemistry panel/electrolytes: includes sodium, potassium, chloride, blood urea nitrogen (BUN; or urea), serum creatinine, calculated clearance creatinine (CKD-EPI), glucose, calcium, phosphorus, total protein, uric acid, AST, ALT, □GT, ALP, total and direct bilirubine, albumin, total cholesterol, HDL, LDL, triglycerides, LDH, CPK
8. ABG (for assessing respiratory and/or metabolic disorders)
9. ApoA-I (for pharmacokinetic and pharmacodynamic assessment)
10. Coagulation tests – includes prothrombin time (PT) (expressed as international normalized ratio [INR]), and partial thromboplastin time (PTT).

11. Urinalysis – includes specific gravity, pH, assessment of protein/albumin, glucose, ketones, and haemoglobin/blood.
12. Microalbumunuria and Proteinuria g/24 h
13. Inflammatory markers include CRP, PCT, D-dimer, Ferritin, IL-6, IL-8, GM-CSF, MCP 1 and TNF-α

7.4.4. Adverse Event (AE) Reporting

[0283] An AE is any untoward medical occurrence associated with the use of the investigational product (active or placebo drug, biologic, or device) in a clinical investigation patient, which does not necessarily have a causal relationship with the product. An AE can, therefore, be any unfavorable and unintended sign (*e.g.*, an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product.

[0284] Adverse events may include:

- Symptoms described by the patient
- Clinically significant changes in the patient's physical exam or other signs observed by the Investigator or medical staff
- Test abnormalities (laboratory tests) that reflect a change from baseline and/or that may result in changes in administration of investigational product or in an alteration in medical care (diagnostic or therapeutic)
- Conditions present at baseline that have either worsened or recurred following resolution

[0285] The patients are evaluated for new AEs and the status of existing AEs at each study visit.

7.4.5. Results

[0286] IL-6 levels and other inflammatory markers are reduced from baseline to day 8.

7.5. Example 5: CER-001 Therapy for Treating Ischemia/reperfusion AKI

[0287] This Example is a study of CER-001 therapy for treating ischemia/reperfusion AKI.

7.5.1. Materials and Methods

[0288] Pigs, with a body weight of 45-60 kg, are fasted for 24 hours before the study. All animals are premedicated with an intramuscular mixture of azaperone (8 mg kg^{-1}) and atropine (0.03 mg kg^{-1}) to reduce pharyngeal and tracheal secretions and prevent post-intubation bradycardia. After anesthesia, both kidneys are approached through a midline abdominal incision. Then, the renal arteries and vein are isolated and a vessel loop is positioned around the renal artery with a right angle clamp. Warm ischemia is induced for 60 minutes by pulling on the vessel loop. Ischemia is followed by 3 hours of reperfusion, with one half of the animals receiving CER-001 administered directly through the renal artery 5 minutes before the

beginning of reperfusion. The animals are euthanized after 24 hours by an IV administration of 1 mL/kg BW pentobarbital. Kidneys are then harvested for analysis.

7.5.2. Results

[0289] CER-001 attenuates ischemia/reperfusion AKI.

8. SPECIFIC EMBODIMENTS

8.1. Specific Embodiments: Group 1

[0290] Various aspects of the present disclosure are described in the embodiments set forth in the following numbered paragraphs, where reference to a previous numbered embodiment refers to a previous numbered embodiment in this Section 8.1.

1. A method of treating a subject with an acute condition, comprising administering to the subject in need thereof a high dose of a lipid binding protein-based complex, optionally wherein the acute condition comprises acute inflammation.

2. The method of embodiment 1, wherein the high dose is administered over a period of three days to approximately two weeks, optionally wherein the high dose is administered over a period of three days, four days, five days, six days, seven days, eight days, nine days, 10 days, eleven days, 12 days, 13 days, 14 days or 15 days.

3. The method of embodiment 1 or embodiment 2, wherein the high dose is the aggregate of two to ten individual doses, optionally wherein the high dose is an aggregate of three, four, five, six, seven, eight, nine or 10 individual doses.

4. The method of embodiment 3, wherein a plurality of individual doses are administered daily or twice daily.

5. The method of embodiment 3 or embodiment 4, wherein a plurality of individual doses are administered two to three days apart.

6. The method of any one of embodiments 3 to 5, wherein each individual dose is effective to increase the subject's HDL levels.

7. The method of embodiment 6, wherein each individual dose is effective to increase the subject's HDL levels by at least 25%, at least 30% or at least 35% 2-4 hours after administration.

8. The method of embodiment 7, wherein each individual dose is effective to increase the subject's HDL levels by at least 25%, at least 30% or at least 35% 2 hours after administration.

9. The method of embodiment 7, wherein each individual dose is effective to increase the subject's HDL levels by at least 25%, at least 30% or at least 35% 3 hours after administration.

10. The method of embodiment 7, wherein each individual dose is effective to increase the subject's HDL levels by at least 25%, at least 30% or at least 35% 4 hours after administration.

11. The method of any one of embodiments 3 to 10, wherein each individual dose is effective to increase the subject's ApoA-I levels.

12. The method of embodiment 11, wherein each individual dose is effective to increase the subject's ApoA-I levels by at least 25%, at least 30% or at least 35% 2-4 hours after administration.

13. The method of embodiment 12, wherein each individual dose is effective to increase the subject's ApoA-I levels by at least 25%, at least 30% or at least 35% 2 hours after administration.

14. The method of embodiment 12, wherein each individual dose is effective to increase the subject's ApoA-I levels by at least 25%, at least 30% or at least 35% 3 hours after administration.

15. The method of embodiment 12, wherein each individual dose is effective to increase the subject's ApoA-I levels by at least 25%, at least 30% or at least 35% 4 hours after administration.

16. The method of any one of embodiments 1 to 15, wherein the high dose is effective to improve the subject's vascular endothelial function, optionally wherein vascular endothelial function is measured by circulating VCAM-1 and/or ICAM-1.

17. The method of any one of embodiments 1 to 16, wherein the high dose is effective to reduce serum levels of one or more inflammatory markers in the subject.

18. The method of embodiment 17, wherein the high dose is effective to reduce serum levels of interleukin-6 ("IL-6").

19. The method of embodiment 17 or embodiment 18, wherein the high dose is effective to reduce serum levels of C-reactive protein.

20. The method of any one of embodiments 17 to 19, wherein the high dose is effective to reduce serum levels of D-dimer.

21. The method of any one of embodiments 17 to 20, wherein the high dose is effective to reduce serum levels of ferritin.

22. The method of any one of embodiments 17 to 21, wherein the high dose is effective to reduce serum levels of interleukin 8 (IL-8).

23. The method of any one of embodiments 17 to 22, wherein the high dose is effective to reduce serum levels of granulocyte-macrophage colony stimulating factor (GM-CSF).

24. The method of any one of embodiments 17 to 23, wherein the high dose is effective to reduce serum levels of monocyte chemoattractant protein (MCP) 1.

25. The method of any one of embodiments 17 to 24, wherein the high dose is effective to reduce serum levels of tumor necrosis factor α (TNF-α).

26. The method of any one of embodiments 17 to 25, wherein the high dose is effective to reduce serum levels of the one or more inflammatory markers from an elevated range to a normal range.

27. The method of any one of embodiments 17 to 26, wherein the high dose is effective to reduce serum levels of the one or more inflammatory markers by at least 20%, by at least 40% or by at least 60%.

28. The method of any one of embodiments 1 to 27, wherein the subject has CRS or is at risk of CRS.

29. The method of embodiment 28, wherein the subject has CRS.

30. The method of embodiment 29, wherein the subject has CRS secondary to an infection.

31. The method of embodiment 30, wherein the infection is a viral infection.

32. The method of embodiment 31, wherein the viral infection is a coronavirus infection.

33. The method of embodiment 32, wherein the coronavirus is COVID-19.

34. The method of embodiment 31, wherein the viral infection is influenza infection.

35. The method of embodiment 29, wherein the subject has CRS caused by immunotherapy.

36. The method of embodiment 35, wherein the immunotherapy comprises antibody therapy.

37. The method of embodiment 35, wherein the immunotherapy comprises chimeric antigen receptor (CAR) T cell therapy.

38. The method of any one of embodiments 35 to 37, wherein the lipid binding protein-based complex is administered before the immunotherapy begins.

39. The method of any one of embodiments 35 to 38, wherein the lipid binding protein-based complex is administered concurrently with the immunotherapy.

40. The method of any one of embodiments 35 to 39, wherein the lipid binding protein-based complex is administered after the immunotherapy ends.

41. The method of embodiment 28, wherein the subject is at risk of CRS.

42. The method of embodiment 41, wherein the subject is at risk of CRS due to an infection.

43. The method of embodiment 42, wherein the infection is a viral infection.

44. The method of embodiment 43, wherein the viral infection is a coronavirus infection.

45. The method of embodiment 44, wherein the coronavirus is COVID-19.

46. The method of embodiment 43, wherein the viral infection is influenza infection.

47. The method of embodiment 41, wherein the subject is at risk of CRS due to immunotherapy.

48. The method of embodiment 47, wherein the immunotherapy comprises antibody therapy.

49. The method of embodiment 47, wherein the immunotherapy comprises chimeric antigen receptor (CAR) T cell therapy.

50. The method of any one of embodiments 47 to 49, wherein the lipid binding protein-based complex is administered before the immunotherapy begins.

51. The method of any one of embodiments 47 to 50, wherein the lipid binding protein-based complex is administered concurrently with the immunotherapy.

52. The method of any one of embodiments 47 to 51, wherein the lipid binding protein-based complex is administered after the immunotherapy ends.

53. The method of any one of embodiments 1 to 27, wherein the subject has or is at risk of developing sepsis.

54. The method of embodiment 53, wherein the sepsis is associated with a gram-negative bacterial infection.

55. The method of embodiment 53, wherein the sepsis is associated with a gram-positive bacterial infection.

56. The method of any one of embodiments 53 to 55, wherein the subject has an intra-abdominal cavity infection.

57. The method of any one of embodiments 53 to 55, wherein the subject has urosepsis.

58. The method of any one of embodiments 53 to 57, wherein the high dose is effective to reduce the severity of the sepsis.

59. The method of any one of embodiments 1 to 58, wherein the high dose is effective to reduce the likelihood that the subject will develop acute kidney injury (AKI).

60. The method of any one of embodiments 1 to 59, wherein the high dose is effective to delay the onset of AKI.

61. The method of any one of embodiments 1 to 59, wherein the high dose is effective to prevent AKI.

62. The method of any one of embodiments 1 to 58, wherein the subject has or is at risk of developing acute kidney injury (AKI).

63. The method of embodiment 62, wherein the AKI is sepsis-related AKI.

64. The method of embodiment 62, wherein the AKI is ischemia/reperfusion AKI.

65. The method of embodiment 62, wherein the AKI is cardiac surgery-associated AKI.

66. The method of embodiment 62, wherein the AKI is hepatorenal syndrome (HRS) AKI.

67. The method of embodiment 66, wherein the HRS is type 1 HRS.

68. The method of embodiment 66, wherein the HRS is type 2 HRS.

69. The method of any one of embodiments 62 to 68, wherein the subject has AKI.

70. The method of embodiment 69, wherein the AKI is secondary to a viral infection, optionally wherein the viral infection is COVID-19.

71. The method of embodiment 69 or embodiment 70, wherein the high dose is effective to reduce the severity of the AKI.

72. The method of any one of embodiments 62 to 66, wherein the subject is at risk for AKI.

73. The method of embodiment 72, wherein the subject has sepsis.

74. The method of embodiment 73, wherein the sepsis is associated with a gram-negative bacterial infection.

75. The method of embodiment 73, wherein the sepsis is associated with a gram-positive bacterial infection.

76. The method of any one of embodiments 73 to 75, wherein the subject has an intra-abdominal cavity infection.

77. The method of any one of embodiments 73 to 75, wherein the subject has urosepsis.

78. The method of embodiment 72, wherein the subject has a viral infection, optionally wherein the viral infection is COVID-19.

79. The method of embodiment 72, wherein the subject has undergone cardiac surgery.

80. The method of embodiment 72, wherein the subject has acute liver disease.

81. The method of embodiment 72, wherein the subject has chronic liver disease.

82. The method of any one of embodiments 72 to 81, wherein the high dose is effective to reduce the likelihood that the subject will develop AKI.

83. The method of any one of embodiments 72 to 82, wherein the high dose is effective to delay the onset of AKI.

84. The method of any one of embodiments 72 to 82, wherein the high dose is effective to prevent AKI.

85. The method of any one of embodiments 72 to 83, wherein if the subject develops AKI, the high dose is effective to reduce the severity of the AKI.

86. The method of any one of embodiments 53 to 85, wherein the subject has a SOFA score of 1 to 4 prior to administration of the lipid binding protein-based complex.

87. The method of embodiment 86, wherein the subject has a SOFA score of 2 to 4 prior to administration of the lipid binding protein-based complex.

88. The method of embodiment 86, wherein the subject has a SOFA score of 1 prior to administration of the lipid binding protein-based complex.

89. The method of embodiment 86, wherein the subject has a SOFA score of 2 prior to administration of the lipid binding protein-based complex.

90. The method of embodiment 86, wherein the subject has a SOFA score of 3 prior to administration of the lipid binding protein-based complex.

91. The method of embodiment 86, wherein the subject has a SOFA score of 4 prior to administration of the lipid binding protein-based complex.

92. The method of any one of embodiments 1 to 91, wherein the subject has an endotoxin activity level of > 0.6 prior to administration of the lipid binding protein-based complex.

93. The method of any one of embodiments 1 to 92, wherein the high dose is effective to reduce the subject's endotoxin activity level.

94. The method of any one of embodiments 1 to 93, wherein the lipid binding protein-based complex is a reconstituted HDL or HDL mimetic.

95. The method of any one of embodiments 1 to 93, wherein the lipid binding protein-based complex is an Apomer or a Cargomer.

96. The method of any one of embodiments 1 to 95, wherein the lipid binding protein-based complex comprises a sphingomyelin.

97. The method of any one of embodiments 1 to 96, wherein the lipid binding protein-based complex comprises a negatively charged lipid.

98. The method of embodiment 97, wherein the negatively charged lipid is 1,2-dipalmitoyl-sn-glycero-3-[phospho-rac-(1-glycerol) (DPPG) or a salt thereof.

99. The method of embodiment 94, wherein the lipid binding protein-based complex is CER-001, CSL-111, CSL-112, CER-522 or ETC-216.

100. The method of embodiment 99, wherein the lipid binding protein-based complex is CER-001.

101. The method of any one of embodiments 1 to 100, wherein the lipid binding protein-based complex is administered systemically, optionally by infusion.

102. The method of any one of embodiments 1 to 101, wherein the lipid binding protein-based complex is administered until serum levels of one or more inflammatory markers are reduced.

103. The method of embodiment 102, wherein the lipid binding protein-based complex is administered until serum levels of one or more inflammatory markers are reduced to a normal range(s).

104. The method of embodiment 102, wherein the lipid binding protein-based complex is administered until serum levels of one or more inflammatory markers are reduced below a baseline level(s) for the one or more inflammatory markers measured prior to lipid binding protein-based complex administration.

105. The method of any one of embodiments 1 to 104, wherein each individual dose of the lipid binding protein-based complex administered is 4-40 mg/kg (on a protein weight basis).

106. The method of embodiment 105, wherein each individual dose of the lipid binding protein-based complex is 4-30 mg/kg (on a protein weight basis).

107. The method of embodiment 105, wherein each individual dose of the lipid binding protein-based complex is 15-25 mg/kg (on a protein weight basis).

108. The method of embodiment 105, wherein each individual dose of the lipid binding protein-based complex is 10-30 mg/kg (on a protein weight basis).

109. The method of embodiment 105, wherein each individual dose of the lipid binding protein-based complex is 10-20 mg/kg (on a protein weight basis).

110. The method of embodiment 105, wherein each individual dose of the lipid binding protein-based complex is 5 mg/kg (on a protein weight basis).

111. The method of embodiment 105, wherein each individual dose of the lipid binding protein-based complex is 10 mg/kg (on a protein weight basis).

112. The method of embodiment 105, wherein each individual dose of the lipid binding protein-based complex is 15 mg/kg (on a protein weight basis).

113. The method of embodiment 105, wherein each individual dose of the lipid binding protein-based complex is 20 mg/kg (on a protein weight basis).

114. The method of embodiment 105, wherein each individual dose of the lipid binding protein-based complex is 5 to 15 mg/kg (on a protein weight basis).

115. The method of embodiment 105, wherein each individual dose of the lipid binding protein-based complex is 10 to 20 mg/kg (on a protein weight basis).

116. The method of embodiment 105, wherein each individual dose of the lipid binding protein-based complex is 15 to 25 mg/kg (on a protein weight basis).

117. The method of any one of embodiments 1 to 116, wherein the high dose is administered according to an induction regimen, optionally followed by a consolidation regimen.

118. The method of embodiment 117, wherein the induction regimen comprises administering the lipid binding protein-based complex once daily or twice daily.

119. The method of embodiment 117 or embodiment 118, wherein the consolidation regimen comprises administering the lipid binding protein-based complex once daily or once every two days.

120. The method of any one of embodiments 1 to 119, wherein the subject is not treated with a maintenance regimen.

121. The method of any one of embodiments embodiment 117 to 120, wherein the consolidation regimen comprises administering one or more doses of the lipid binding protein-based complex to the subject one or more days after administration of the final dose of the induction regimen.

122. The method of embodiment 121, wherein the first dose of the lipid binding protein-based complex administered during the consolidation regimen is administered two or more days after administration of the final dose of the induction regimen.

123. The method of embodiment 121, wherein the first dose of the lipid binding protein-based complex administered during the consolidation regimen is administered three or more days after administration of the final dose of the induction regimen.

124. The method of embodiment 123, wherein the first dose of the lipid binding protein-based complex administered during the consolidation regimen is administered three days after administration of the final dose of the induction regimen.

125. The method of any one of embodiments 117 to 124, which comprises an induction regimen comprising twice daily administration of the lipid binding protein-based complex on days 1, 2, and 3 and a consolidation regimen comprising two doses of the lipid binding protein-based complex on day 6.

126. The method of any one of embodiments 117 to 125, wherein each individual dose of the lipid binding protein-based complex administered in the induction regimen is 4-40 mg/kg (on a protein weight basis).

127. The method of any one of embodiments 117 to 126, wherein each individual dose of the lipid binding protein-based complex administered in the induction regimen is 4-30 mg/kg (on a protein weight basis).

128. The method of any one of embodiments 117 to 126, wherein each individual dose of the lipid binding protein-based complex administered in the induction regimen is 15-25 mg/kg (on a protein weight basis).

129. The method of any one of embodiments 117 to 126, wherein each individual dose of the lipid binding protein-based complex administered in the induction regimen is 10-30 mg/kg (on a protein weight basis).

130. The method of any one of embodiments 117 to 126, wherein each individual dose of the lipid binding protein-based complex administered in the induction regimen is 10-20 mg/kg (on a protein weight basis).

131. The method of any one of embodiments 117 to 126, wherein each individual dose of the lipid binding protein-based complex administered in the induction regimen is 5 mg/kg (on a protein weight basis).

132. The method of any one of embodiments 117 to 126, wherein each individual dose of the lipid binding protein-based complex administered in the induction regimen is 10 mg/kg (on a protein weight basis).

133. The method of any one of embodiments 117 to 126, wherein each individual dose of the lipid binding protein-based complex administered in the induction regimen is 15 mg/kg (on a protein weight basis).

134. The method of any one of embodiments 117 to 126, wherein each individual dose of the lipid binding protein-based complex administered in the induction regimen is 20 mg/kg (on a protein weight basis).

135. The method of any one of embodiments 117 to 134, wherein the dose of the lipid binding protein-based complex administered in the consolidation regimen is 5 to 15 mg/kg (on a protein weight basis).

136. The method of any one of embodiments 117 to 134, wherein the dose of the lipid binding protein-based complex administered in the consolidation regimen is 10 to 20 mg/kg (on a protein weight basis).

137. The method of any one of embodiments 117 to 134, wherein the dose of the lipid binding protein-based complex administered in the consolidation regimen is 15 to 25 mg/kg (on a protein weight basis).

138. The method of any one of embodiments 117 to 134, wherein the dose of the lipid binding protein-based complex administered in the consolidation regimen is 5 mg/kg (on a protein weight basis).

139. The method of any one of embodiments 117 to 134, wherein the dose of the lipid binding protein-based complex administered in the consolidation regimen is 10 mg/kg (on a protein weight basis).

140. The method of any one of embodiments 117 to 134, wherein the dose of the lipid binding protein-based complex administered in the consolidation regimen is 15 mg/kg (on a protein weight basis).

141. The method of any one of embodiments 1 to 140, wherein each individual dose of the lipid binding protein-based complex administered is 300 mg to 4000 mg (on a protein weight basis).

142. The method of embodiment 141, wherein each individual dose of the lipid binding protein-based complex administered is 300 mg to 3000 mg (on a protein weight basis).

143. The method of embodiment 141, wherein each individual dose of the lipid binding protein-based complex administered is 300 mg to 1500 mg (on a protein weight basis).

144. The method of embodiment 141, wherein each individual dose of the lipid binding protein-based complex administered is 400 mg to 4000 mg (on a protein weight basis).

145. The method of embodiment 141, wherein each individual dose of the lipid binding protein-based complex administered is 400 mg to 1500 mg (on a protein weight basis).

146. The method of embodiment 141, wherein each individual dose of the lipid binding protein-based complex administered is 500 mg to 1200 mg (on a protein weight basis).

147. The method of embodiment 141, wherein each individual dose of the lipid binding protein-based complex administered is 500 mg to 1000 mg (on a protein weight basis).

148. The method of embodiment 141, wherein each individual dose of the lipid binding protein-based complex administered is 600 mg to 3000 mg (on a protein weight basis).

149. The method of embodiment 141, wherein each individual dose of the lipid binding protein-based complex administered is 800 mg to 3000 mg (on a protein weight basis).

150. The method of embodiment 141, wherein each individual dose of the lipid binding protein-based complex administered is 1000 mg to 2400 mg (on a protein weight basis).

151. The method of embodiment 141, wherein each individual dose of the lipid binding protein-based complex administered is 1000 mg to 2000 mg (on a protein weight basis).

152. The method of any one of embodiments 1 to 151, wherein the high dose of the lipid binding protein-based complex is 600 mg to 40 g (on a protein weight basis).

153. The method of any one of embodiments 1 to 151, wherein the high dose of the lipid binding protein-based complex is 3 g to 35 g (on a protein weight basis).

154. The method of any one of embodiments 1 to 151, wherein the high dose of the lipid binding protein-based complex is 5 g to 30 g (on a protein weight basis).

155. The method of any one of embodiments 1 to 154, wherein the lipid binding protein-based complex is administered by infusion.

156. The method of embodiment 155, wherein each individual dose is administered over a one to 24-hour period.

157. The method of embodiment 156, wherein each individual dose is administered over a 24-hour period.

158. The method of any one of embodiments 1 to 157, which further comprises administering an antihistamine to the subject prior to each individual dose.

159. The method of embodiment 158, wherein the antihistamine comprises dexchlorpheniramine or hydroxyzine.

160. The method of any one of embodiments 1 to 159, wherein the subject is receiving or has received one or more additional therapies and/or which further comprises administering to the subject one or more additional therapies.

161. The method of embodiment 160, wherein the one or more additional therapies comprises one or more anti-IL-6 agents.

162. The method of embodiment 161, wherein the one or more anti-IL-6 agents comprise tocilizumab, siltuximab, olokizumab, elsilimomab, BMS-945429, sirukumab, levilimab, CPSI-2364, or a combination thereof.

163. The method of embodiment 162, wherein the one or more anti-IL-6 agents comprise tocilizumab.

164. The method of any one of embodiments 160 to 163, wherein the one or more additional therapies comprise one or more corticosteroids.

165. The method of embodiment 164, wherein the one or more corticosteroids comprise methylprednisolone, dexamethasone, or a combination thereof.

166. The method of any one of embodiments 160 to 165, wherein the subject has or has had a COVID-19 infection and the one or more additional therapies comprise antibodies from recovered COVID-19 patients.

167. The method of any one of embodiments 160to 166, wherein the subject has or has had a COVID-19 infection and the one or more additional therapies comprise antibodies against the spike protein of COVID-19.

168. The method of any one of embodiments 160 to 167, wherein the subject has or has had a COVID-19 infection and the one or more additional therapies comprise one or more antiviral agents.

169. The method of embodiment 168, wherein the one or more antiviral agents comprise lopinavir.

170. The method of embodiment 168 or embodiment 169, wherein the one or more antiviral agents comprise remdesivir.

171. The method of any one of embodiments 168 to 170, wherein the one or more antiviral agents comprise danoprevir.

172. The method of any one of embodiments 168 to 171, wherein the one or more antiviral agents comprise galidesivir.

173. The method of any one of embodiments 168 to 172, wherein the one or more antiviral agents comprise darunavir.

174. The method of any one of embodiments 168 to 173, wherein the one or more antiviral agents comprise ritonavir.

175. The method of any one of embodiments 160 to 174, wherein the subject has or has had a COVID-19 infection and the one or more additional therapies comprise chloroquine or hydroxychloroquine.

176. The method of any one of embodiments 160 to 175, wherein the subject has or has had a COVID-19 infection and the one or more additional therapies comprise azithromycin.

177. The method of any one of embodiments 160 to 176, wherein the subject has or has had a COVID-19 infection and the one or more additional therapies comprise an interferon.

178. The method of embodiment 177, wherein the interferon is an interferon alpha.

179. The method of embodiment 177, wherein the interferon is an interferon beta.

180. The method of any one of embodiments 177 to 179, wherein the interferon is pegylated.

181. The method of any one of embodiments 1 to 180, wherein the lipid binding protein-based complex is CER-001.

182. The method of embodiment 181, wherein the CER-001 is a lipoprotein complex comprising ApoA-I and phospholipids in a ApoA-I weight:total phospholipid weight ratio of 1:2.7 +/- 20% and the phospholipids sphingomyelin and DPPG in a sphingomyelin:DPPG weight:weight ratio of 97:3 +/- 20%.

183. The method of embodiment 181, wherein the CER-001 is a lipoprotein complex comprising ApoA-I and phospholipids in a ApoA-I weight:total phospholipid weight ratio of 1:2.7 +/- 10% and the phospholipids sphingomyelin and DPPG in a sphingomyelin:DPPG weight:weight ratio of 97:3 +/- 10%.

184. The method of embodiment 181, wherein the CER-001 is a lipoprotein complex comprising ApoA-I and phospholipids in a ApoA-I weight:total phospholipid weight ratio of 1:2.7 and the phospholipids sphingomyelin and DPPG in a sphingomyelin:DPPG weight:weight ratio of 97:3.

185. The method of any one of embodiments 182 to 184, wherein the ApoA-I has the amino acid sequence of amino acids 25-267 of SEQ ID NO:1 of WO 2012/109162.

186. The method of any one of embodiments 182 to 185, wherein the ApoA-I is recombinantly expressed.

187. The method of any one of embodiments 182 to 186, wherein the CER-001 comprises natural sphingomyelin.

188. The method of embodiment 187, wherein the natural sphingomyelin is chicken egg sphingomyelin.

189. The method of any one of embodiments 182 to 186, wherein the CER-001 comprises synthetic sphingomyelin.

190. The method of embodiment 189, wherein the synthetic sphingomyelin is palmitoylsphingomyelin.

191. The method of any one of embodiments 181 to 190, wherein CER-001 is administered in the form of a formulation in which the CER-001 is at least 95% homogeneous.

192. The method of embodiment 191, wherein CER-001 is administered in the form of a formulation in which the CER-001 is at least 97% homogeneous.

193. The method of embodiment 191, wherein CER-001 is administered in the form of a formulation in which the CER-001 is at least 98% homogeneous.

194. The method of embodiment 191, wherein CER-001 is administered in the form of a formulation in which the CER-001 is at least 99% homogeneous.

8.2. Specific Embodiments: Group 2

[0291] Further aspects of the present disclosure are described in the embodiments set forth in the following numbered paragraphs, where reference to a previous numbered embodiment refers to a previous numbered embodiment in this Section 8.2.

1. A method of treating a subject with cytokine release syndrome (CRS) or at risk of CRS, comprising administering to the subject a therapeutically effective amount of CER-001.

2. The method of embodiment 1, which comprises administering an amount of CER-001 effective to reduce serum levels of one or more inflammatory markers in the subject.

3. A method of reducing serum levels of one or more inflammatory markers in a subject in need thereof, comprising administering to the subject an amount of CER-001 effective to reduce the serum levels of the one or more inflammatory markers.

4. The method of embodiment 3, wherein the subject has CRS or is at risk of CRS.

5. The method of any one of embodiments 1 to 4, wherein the subject has CRS.

6. The method of embodiment 5, wherein the subject has CRS secondary to an infection.

7. The method of embodiment 6, wherein the infection is a viral infection.

8. The method of embodiment 7, wherein the viral infection is a coronavirus infection.

9. The method of embodiment 8, wherein the coronavirus is COVID-19.

10. The method of embodiment 7, wherein the viral infection is influenza infection.

11. The method of embodiment 5, wherein the subject has CRS caused by immunotherapy.

12. The method of embodiment 11, wherein the immunotherapy comprises antibody therapy.

13. The method of embodiment 11, wherein the immunotherapy comprises chimeric antigen receptor (CAR) T cell therapy.

14. The method of any one of embodiments 11 to 13, wherein CER-001 is administered before the immunotherapy begins.

15. The method of any one of embodiments 11 to 14, wherein CER-001 is administered concurrently with the immunotherapy.

16. The method of any one of embodiments 11 to 15, wherein CER-001 is administered after the immunotherapy ends.

17. The method of any one of embodiments 1 to 4, wherein the subject is at risk of CRS.

18. The method of embodiment 17, wherein the subject is at risk of CRS due to an infection.

19. The method of embodiment 18, wherein the infection is a viral infection.

20. The method of embodiment 19, wherein the viral infection is a coronavirus infection.

21. The method of embodiment 20, wherein the coronavirus is COVID-19.

22. The method of embodiment 19, wherein the viral infection is influenza infection.

23. The method of embodiment 17, wherein the subject is at risk of CRS due to immunotherapy.

24. The method of embodiment 23, wherein the immunotherapy comprises antibody therapy.

25. The method of embodiment 23, wherein the immunotherapy comprises chimeric antigen receptor (CAR) T cell therapy.

26. The method of any one of embodiments 23 to 25, wherein CER-001 is administered before the immunotherapy begins.

27. The method of any one of embodiments 23 to 26, wherein CER-001 is administered concurrently with the immunotherapy.

28. The method of any one of embodiments 23 to 27, wherein CER-001 is administered after the immunotherapy ends.

29. The method of any one of embodiments 1 to 28, which comprises once daily administration of CER-001.

30. The method of any one of embodiments 1 to 29, wherein the CER-001 is administered for at least 5 days.

31. The method of any one of embodiments 1 to 29, wherein the CER-001 is administered for at least 6 days.

32. The method of any one of embodiments 1 to 29, wherein the CER-001 is administered for at least 7 days.

33. The method of embodiment 32, wherein the CER-001 is administered for 7 days.

34. The method of any one of embodiments 1 to 32, wherein the CER-001 is administered for up to 1 week.

35. The method of any one of embodiments 1 to 32, wherein the CER-001 is administered for up to 2 weeks.

36. The method of any one of embodiments 1 to 32, wherein the CER-001 is administered until one or more symptoms of CRS are reduced and/or serum levels of one or more inflammatory markers are reduced.

37. The method of embodiment 36, wherein the CER-001 is administered until serum levels of one or more inflammatory markers are reduced to a normal range(s).

38. The method of embodiment 36, wherein the CER-001 is administered until serum levels of one or more inflammatory markers are reduced below a baseline level(s) for the one or more inflammatory markers measured prior to CER-001 administration.

39. The method of any one of embodiments 1 to 38, wherein the dose of CER-001 administered is 10 to 40 mg/kg (on a protein weight basis).

40. The method of embodiment 39, wherein the dose of CER-001 administered in the induction regimen is 10-30 mg/kg (on a protein weight basis).

41. The method of embodiment 39, wherein the dose of CER-001 administered in the induction regimen is 15-25 mg/kg (on a protein weight basis).

42. The method of embodiment 39, wherein the dose of CER-001 administered in the induction regimen is 20 mg/kg (on a protein weight basis).

43. The method of any one of embodiments 1 to 42, wherein the dose of CER-001 administered at each administration is 600 mg to 4000 mg.

44. The method of embodiment 43, wherein the dose of CER-001 administered at each administration is 600 mg to 3000 mg.

45. The method of embodiment 43, wherein the dose of CER-001 administered at each administration is 800 mg to 3000 mg.

46. The method of embodiment 43, wherein the dose of CER-001 at each administration is 1000 mg to 2400 mg.

47. The method of embodiment 43, wherein the dose of CER-001 administered at each administration is 1000 mg to 2000 mg.

48. The method of any one of embodiments 1 to 47, wherein the CER-001 is administered by infusion.

49. The method of embodiment 48, wherein each dose is administered over a one to 24-hour period.

50. The method of embodiment 49, wherein each dose is administered over a 24-hour period.

51. The method of any one of embodiments 2 to 50, wherein the one or more inflammatory markers comprise interleukin 6 (IL-6).

52. The method of any one of embodiments 2 to 51, wherein the one or more inflammatory markers comprise C-reactive protein.

53. The method of any one of embodiments 2 to 52, wherein the one or more inflammatory markers comprise D-dimer.

54. The method of any one of embodiments 2 to 53, wherein the one or more inflammatory markers comprise ferritin.

55. The method of any one of embodiments 2 to 54, wherein the one or more inflammatory markers comprise interleukin 8 (IL-8).

56. The method of any one of embodiments 2 to 55, wherein the one or more inflammatory markers comprise granulocyte-macrophage colony stimulating factor (GM-CSF).

57. The method of any one of embodiments 2 to 56, wherein the one or more inflammatory markers comprise monocyte chemoattractant protein (MCP) 1.

58. The method of any one of embodiments 2 to 57, wherein the one or more inflammatory markers comprise tumor necrosis factor α (TNF-α).

59. The method of any one of embodiments 1 to 58, which further comprises administering an antihistamine to the subject prior to each CER-001 dose.

60. The method of embodiment 59, wherein the antihistamine comprises dexchlorpheniramine or hydroxyzine.

61. The method of any one of embodiments 1 to 60, wherein the subject is receiving or has received one or more additional therapies and/or which further comprises administering to the subject one or more additional therapies.

62. The method of embodiment 61, wherein the one or more additional therapies comprises one or more anti-IL-6 agents.

63. The method of embodiment 62, wherein the one or more anti-IL-6 agents comprise tocilizumab, siltuximab, olokizumab, elsilimomab, BMS-945429, sirukumab, levilimab, CPSI-2364, or a combination thereof.

64. The method of embodiment 63, wherein the one or more anti-IL-6 agents comprise tocilizumab.

65. The method of any one of embodiments 61 to 64, wherein the one or more additional therapies comprise one or more corticosteroids.

66. The method of embodiment 65, wherein the one or more corticosteroids comprise methylprednisolone, dexamethasone, or a combination thereof.

67. The method of any one of embodiments 61 to 66, wherein the subject has or has had a COVID-19 infection and the one or more additional therapies comprise antibodies from recovered COVID-19 patients.

68. The method of any one of embodiments 61 to 67, wherein the subject has or has had a COVID-19 infection and the one or more additional therapies comprise antibodies against the spike protein of COVID-19.

69. The method of any one of embodiments 61 to 68, wherein the subject has or has had a COVID-19 infection and the one or more additional therapies comprise one or more antiviral agents.

70. The method of embodiment 69, wherein the one or more antiviral agents comprise lopinavir.

71. The method of embodiment 69 or embodiment 70, wherein the one or more antiviral agents comprise remdesivir.

72. The method of any one of embodiments 69 to 71, wherein the one or more antiviral agents comprise danoprevir.

73. The method of any one of embodiments 69 to 72, wherein the one or more antiviral agents comprise galidesivir.

74. The method of any one of embodiments 69 to 73, wherein the one or more antiviral agents comprise darunavir.

75. The method of any one of embodiments 69 to 74, wherein the one or more antiviral agents comprise ritonavir.

76. The method of any one of embodiments 61 to 75, wherein the subject has or has had a COVID-19 infection and the one or more additional therapies comprise chloroquine or hydroxychloroquine.

77. The method of any one of embodiments 61 to 76, wherein the subject has or has had a COVID-19 infection and the one or more additional therapies comprise azithromycin.

78. The method of any one of embodiments 61 to 77, wherein the subject has or has had a COVID-19 infection and the one or more additional therapies comprise an interferon.

79. The method of embodiment 78, wherein the interferon is an interferon alpha.

80. The method of embodiment 78, wherein the interferon is an interferon beta.

81. The method of any one of embodiments 78 to 80, wherein the interferon is pegylated.

8.3. Specific Embodiments: Group 3

[0292] Further aspects of the present disclosure are described in the embodiments set forth in the following numbered paragraphs, where reference to a previous numbered embodiment refers to a previous numbered embodiment in this Section 8.3.

1. A method of treating a subject with sepsis, comprising administering to the subject an amount of a lipid binding protein-based complex.

2. The method of embodiment 1, wherein the sepsis is associated with a gram-negative bacterial infection.

3. The method of embodiment 1 or embodiment 2, wherein the subject has an intra-abdominal cavity infection.

4. The method of embodiment 1 or embodiment 2, wherein the subject has urosepsis.

5. The method of any one of embodiments 1 to 4, wherein the amount of the lipid binding protein-based complex is effective to reduce the severity of the sepsis.

6. The method of any one of embodiments 1 to 5, wherein the amount of the lipid binding protein-based complex is effective to reduce the likelihood that the subject will develop acute kidney injury (AKI).

7. The method of any one of embodiments 1 to 6, wherein the amount of the lipid binding protein-based complex is effective to delay the onset of AKI.

8. The method of any one of embodiments 1 to 6, wherein the amount of the lipid binding protein-based complex is effective to prevent AKI.

9. A method of treating a subject with acute kidney injury (AKI) or at risk for AKI, comprising administering to the subject an amount of a lipid binding protein-based complex.

10. The method of embodiment 9, wherein the AKI is sepsis-related AKI.

11. The method of embodiment 9 or embodiment 10, wherein the subject has AKI.

12. The method of embodiment 11, wherein the amount of the lipid binding protein-complex is effective to reduce the severity of the AKI.

13. The method of embodiment 9 or embodiment 10, wherein the subject is at risk for AKI.

14. The method of embodiment 13, wherein the subject has sepsis.

15. The method of embodiment 14, wherein the sepsis is associated with a gram-negative bacterial infection.

16. The method of embodiment 14 or embodiment 15, wherein the subject has an intra-abdominal cavity infection.

17. The method of embodiment 14 or embodiment 15, wherein the subject has urosepsis.

18. The method of any one of embodiments 13 to 17, wherein the amount of the lipid binding protein-based complex is effective to reduce the likelihood that the subject will develop AKI.

19. The method of any one of embodiments 13 to 18, wherein the amount of the lipid binding protein-based complex is effective to delay the onset of AKI.

20. The method of any one of embodiments 13 to 18, wherein the amount of the lipid binding protein-based complex is effective to prevent AKI.

21. The method of any one of embodiments 13 to 19, wherein if the subject develops AKI, the amount of the lipid binding protein-based complex is effective to reduce the severity of the AKI.

22. The method of any one of embodiments 1 to 21, wherein the subject has a SOFA score of 1 to 4 prior to administration of the lipid binding protein-based complex.

23. The method of embodiment 22, wherein the subject has a SOFA score of 2 to 4 prior to administration of the lipid binding protein-based complex.

24. The method of embodiment 22, wherein the subject has a SOFA score of 1 prior to administration of the lipid binding protein-based complex.

25. The method of embodiment 22, wherein the subject has a SOFA score of 2 prior to administration of the lipid binding protein-based complex.

26. The method of embodiment 22, wherein the subject has a SOFA score of 3 prior to administration of the lipid binding protein-based complex.

27. The method of embodiment 22, wherein the subject has a SOFA score of 4 prior to administration of the lipid binding protein-based complex.

28. The method of any one of embodiments 1 to 27, wherein the subject has an endotoxin activity level of > 0.6 prior to administration of the lipid binding protein-based complex.

29. The method of any one of embodiments 1 to 28, wherein the amount of the lipid binding protein-based complex is effective to reduce the subject's endotoxin activity level.

30. The method of any one of embodiments 1 to 29, wherein the amount of the lipid binding protein-based complex is effective to reduce the subject's serum level of IL-6.

31. The method of any one of embodiments 1 to 30, wherein the lipid binding protein-based complex is a reconstituted HDL or HDL mimetic.

32. The method of any one of embodiments 1 to 30, wherein the lipid binding protein-based complex is an Apomer or a Cargomer.

33. The method of any one of embodiments 1 to 32, wherein the lipid binding protein-based complex comprises a sphingomyelin.

34. The method of any one of embodiments 1 to 32, wherein the lipid binding protein-based complex comprises a negatively charged lipid.

35. The method of embodiment 34, wherein the negatively charged lipid is 1,2-dipalmitoyl-sn-glycero-3-[phospho-rac-(1-glycerol) (DPPG) or a salt thereof.

36. The method of embodiment 31, wherein the lipid binding protein-based complex is CER-001, CSL-111, CSL-112, CER-522 or ETC-216.

37. The method of embodiment 36, wherein the lipid binding protein-based complex is CER-001.

38. The method of any one of embodiments 1 to 37, wherein the lipid binding protein-based complex is administered systemically, optionally by infusion.

39. The method of embodiment 38, wherein the lipid binding protein-based complex is administered according to a dosing regimen which comprises:

(a) an induction regimen; and, optionally

(b) a consolidation regimen,

optionally wherein the lipid binding protein-based complex comprises CER-001.

40. The method of embodiment 39, wherein the induction regimen comprises administering the lipid binding protein-based complex on multiple consecutive days.

41. The method of embodiment 40, wherein the induction regimen comprises administering the lipid binding protein-based complex on three or more consecutive days.

42. The method of any one of embodiments 39 to 41, wherein the induction regimen comprises twice daily administration of the lipid binding protein-based complex.

43. The method of any one of embodiments 39 to 42, wherein the induction regimen comprises twice daily administration of the lipid binding protein-based complex for three consecutive days.

44. The method of any one of embodiments 39 to 43, wherein the dose of the lipid binding protein-based complex administered in the induction regimen is 4 to 30 mg/kg (on a protein weight basis).

45. The method of any one of embodiments 39 to 43, wherein the dose of the lipid binding protein-based complex administered in the induction regimen is 5 to 15 mg/kg (on a protein weight basis).

46. The method of any one of embodiments 39 to 43, wherein the dose of the lipid binding protein-based complex administered in the induction regimen is 10 to 20 mg/kg (on a protein weight basis).

47. The method of any one of embodiments 39 to 43, wherein the dose of the lipid binding protein-based complex administered in the induction regimen is 15 to 25 mg/kg (on a protein weight basis).

48. The method of any one of embodiments 39 to 43, wherein the dose of the lipid binding protein-based complex administered in the induction regimen is 5mg/kg (on a protein weight basis).

49. The method of any one of embodiments 39 to 43, wherein the dose of the lipid binding protein-based complex administered in the induction regimen is 10 mg/kg (on a protein weight basis).

50. The method of any one of embodiments 39 to 43, wherein the dose of the lipid binding protein-based complex administered in the induction regimen is 20 mg/kg (on a protein weight basis).

51. The method of any one of embodiments 39 to 43, wherein the dose of CER-001 administered in the induction regimen is 300 mg to 3000 mg.

52. The method of any one of embodiments 39 to 43, wherein the dose of CER-001 administered in the induction regimen is 300 mg to 1500 mg.

53. The method of any one of embodiments 39 to 43, wherein the dose of CER-001 administered in the induction regimen is 400 mg to 1500 mg.

54. The method of any one of embodiments 39 to 43, wherein the dose of CER-001 administered in the induction regimen is 500 mg to 1200 mg.

55. The method of any one of embodiments 39 to 43, wherein the dose of CER-001 administered in the induction regimen is 500 mg to 1000 mg.

56. The method of any one of embodiments 39 to 55, which comprises a consolidation regimen.

57. The method of embodiment 56, wherein the consolidation regimen comprises administering one or more doses of the lipid binding protein-based complex to the subject one or more days after administration of the final dose of the induction regimen.

58. The method of embodiment 57, wherein the first dose of the lipid binding protein-based complex administered during the consolidation regimen is administered two or more days after administration of the final dose of the induction regimen.

59. The method of embodiment 57, wherein the first dose of the lipid binding protein-based complex administered during the consolidation regimen is administered three or more days after administration of the final dose of the induction regimen.

60. The method of embodiment 59, wherein the first dose of the lipid binding protein-based complex administered during the consolidation regimen is administered three days after administration of the final dose of the induction regimen.

61. The method of any one of embodiments 56 to 60, wherein the consolidation regimen comprises two doses of the lipid binding protein-based complex administered on a single day.

62. The method of any one of embodiments 39 to 61, which comprises an induction regimen comprising twice daily administration of the lipid binding protein-based complex on

days 1, 2, and 3 and a consolidation regimen comprising two doses of the lipid binding protein-based complex on day 6.

63. The method of any one of embodiments 39 to 62, wherein the dose of the lipid binding protein-based complex administered in the consolidation regimen is 4 to 30 mg/kg (on a protein weight basis).

64. The method of any one of embodiments 39 to 62, wherein the dose of the lipid binding protein-based complex administered in the consolidation regimen is 5 to 15 mg/kg (on a protein weight basis).

65. The method of any one of embodiments 39 to 62, wherein the dose of the lipid binding protein-based complex administered in the consolidation regimen is 10 to 20 mg/kg (on a protein weight basis).

66. The method of any one of embodiments 39 to 62, wherein the dose of the lipid binding protein-based complex administered in the consolidation regimen is 15 to 25 mg/kg (on a protein weight basis).

67. The method of any one of embodiments 39 to 62, wherein the dose of the lipid binding protein-based complex administered in the consolidation regimen is 5 mg/kg (on a protein weight basis).

68. The method of any one of embodiments 39 to 62, wherein the dose of the lipid binding protein-based complex administered in the consolidation regimen is 10 mg/kg (on a protein weight basis).

69. The method of any one of embodiments 39 to 62, wherein the dose of the lipid binding protein-based complex administered in the consolidation regimen is 20 mg/kg (on a protein weight basis).

70. The method of any one of embodiments 39 to 62, wherein the dose of CER-001 administered in the induction regimen is 300 mg to 3000 mg.

71. The method of any one of embodiments 39 to 62, wherein the dose of CER-001 administered in the induction regimen is 300 mg to 1500 mg.

72. The method of any one of embodiments 39 to 62, wherein the dose of CER-001 administered in the induction regimen is 400 mg to 1500 mg.

73. The method of any one of embodiments v, wherein the dose of CER-001 administered in the induction regimen is 500 mg to 1200 mg.

74. The method of any one of embodiments 39 to 62, wherein the dose of CER-001 administered in the induction regimen is 500 mg to 1000 mg.

75. The method of any one of embodiments 56 to 74, wherein the dose of the lipid binding protein-based complex administered in the induction regimen and the dose of the lipid binding protein-based complex administered in the consolidation regimen are the same.

76. The method of any one of embodiments 1 to 75, wherein an antihistamine is administered prior to administration of one or more of the lipid binding protein-based complex doses.

77. The method of embodiment 76, wherein an antihistamine is administered prior to each lipid binding protein-based complex dose.

78. The method of any one of embodiments 1 to 77, wherein the subject is also treated with a standard of care therapy for sepsis.

79. The method of any one of embodiments 9 to 77, wherein the subject is also treated with a standard of care therapy for AKI.

80. The method of embodiment 78 or embodiment 79, wherein the standard of care therapy comprises an antibiotic.

81. The method of any one of embodiments 78 to 80, wherein the standard of care therapy comprises hemodynamic support.

82. The method of any one of embodiments 78 to 81, further comprising administering the standard of care therapy.

[0293] While various specific embodiments have been illustrated and described, it will be appreciated that various changes can be made without departing from the spirit and scope of the disclosure(s)

9. INCORPORATION BY REFERENCE

[0294] All publications, patents, patent applications and other documents cited in this application are hereby incorporated by reference in their entireties for all purposes to the same extent as if each individual publication, patent, patent application or other document were individually indicated to be incorporated by reference for all purposes.

[0295] Any discussion of documents, acts, materials, devices, articles or the like that has been included in this specification is solely for the purpose of providing a context for the present disclosure. It is not to be taken as an admission that any or all of these matters form part of the prior art base or were common general knowledge in the field relevant to the present disclosure as it existed anywhere before the priority date of this application.

SEQUENCE LISTING

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<120> METHODS FOR TREATING ACUTE CONDITIONS USING LIPID BINDING PROTEIN-BASED COMPLEXES

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Gln
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WHAT IS CLAIMED IS:

1. A lipid binding protein-based complex for use in a method of treating an acute condition, wherein the method comprises administering a high dose of the lipid binding protein-based complex to a subject in need thereof, optionally wherein the acute condition comprises acute inflammation.

2. The lipid binding protein-based complex for use according to claim 1, wherein in the method, the high dose is administered over a period of three days to approximately two weeks, optionally wherein the high dose is administered over a period of three days, four days, five days, six days, seven days, eight days, nine days, 10 days, eleven days, 12 days, 13 days, 14 days or 15 days.

3. The lipid binding protein-based complex for use according to claim 1 or claim 2, wherein the high dose is the aggregate of two to ten individual doses, optionally wherein the high dose is an aggregate of three, four, five, six, seven, eight, nine or 10 individual doses.

4. The lipid binding protein-based complex for use according to claim 3, wherein in the method a plurality of individual doses are administered daily or twice daily.

5. The lipid binding protein-based complex for use according to claim 3 or claim 4, wherein in the method a plurality of individual doses are administered two to three days apart.

6. The lipid binding protein-based complex for use according to any one of claims 3 to 5, wherein each individual dose is effective to increase the subject's HDL levels.

7. The lipid binding protein-based complex for use according to any one of claims 3 to 6, wherein each individual dose is effective to increase the subject's ApoA-I levels.

8. The lipid binding protein-based complex for use according to any one of claims 1 to 7, wherein the high dose is effective to improve the subject's vascular endothelial function, optionally wherein vascular endothelial function is measured by circulating VCAM-1 and/or ICAM-1.

9. The lipid binding protein-based complex for use according to any one of claims 1 to 8, wherein the high dose is effective to reduce serum levels of one or more inflammatory markers in the subject.

10. The lipid binding protein-based complex for use according to any one of claims 1 to 9, wherein the subject has CRS or is at risk of CRS.

11. The lipid binding protein-based complex for use according to claim 10, wherein the subject is at risk of CRS.

12. The lipid binding protein-based complex for use according to claim 11, wherein the subject is at risk of CRS due to an infection.

13. The lipid binding protein-based complex for use according to claim 12, wherein the infection is a viral infection.

14. The lipid binding protein-based complex for use according to claim 13, wherein the viral infection is a coronavirus infection.

15. The lipid binding protein-based complex for use according to claim 14, wherein the coronavirus is COVID-19.

16. The lipid binding protein-based complex for use according to any one of claims 1 to 9, wherein the subject has or is at risk of developing sepsis.

17. The lipid binding protein-based complex for use according to claim 16, wherein the high dose is effective to reduce the severity of the sepsis.

18. The lipid binding protein-based complex for use according to any one of claims 1 to 17, wherein the high dose is effective to reduce the likelihood that the subject will develop acute kidney injury (AKI).

19. The lipid binding protein-based complex for use according to any one of claims 1 to 18, wherein the high dose is effective to delay the onset of AKI.

20. The lipid binding protein-based complex for use according to any one of claims 1 to 18, wherein the high dose is effective to prevent AKI.

21. The lipid binding protein-based complex for use according to any one of claims 1 to 17, wherein the subject has or is at risk of developing acute kidney injury (AKI).

22. The lipid binding protein-based complex for use according to claim 21, wherein the AKI is sepsis-related AKI.

23. The lipid binding protein-based complex for use according to claim 21, wherein the AKI is ischemia/reperfusion AKI.

24. The lipid binding protein-based complex for use according to claim 21, wherein the AKI is cardiac surgery-associated (CSA) AKI.

25. The lipid binding protein-based complex for use according to claim 21, wherein the AKI is hepatorenal syndrome (HRS) AKI.

26. The lipid binding protein-based complex for use according to any one of claims 21 to 25, wherein the subject has AKI.

27. The lipid binding protein-based complex for use according to claim 26, wherein the high dose is effective to reduce the severity of the AKI.

28. The lipid binding protein-based complex for use according to any one of claims 21 to 25, wherein the subject is at risk for AKI.

29. The lipid binding protein-based complex for use according to claim 28, wherein the high dose is effective to reduce the likelihood that the subject will develop AKI.

30. The lipid binding protein-based complex for use according to claim 28 or claim 29, wherein the high dose is effective to delay the onset of AKI.

31. The lipid binding protein-based complex for use according to claim 28 or claim 29, wherein the high dose is effective to prevent AKI.

32. The lipid binding protein-based complex for use according to any one of claims 28 to 30, wherein if the subject develops AKI, the high dose is effective to reduce the severity of the AKI.

33. The lipid binding protein-based complex for use according to any one of claims 1 to 32, wherein the lipid binding protein-based complex is a reconstituted HDL or HDL mimetic.

34. The lipid binding protein-based complex for use according to any one of claims 1 to 32, wherein the lipid binding protein-based complex is an Apomer or a Cargomer.

35. The lipid binding protein-based complex for use according to any one of claims 1 to 34, wherein the lipid binding protein-based complex comprises a sphingomyelin.

36. The lipid binding protein-based complex for use according to any one of claims 1 to 35, wherein the lipid binding protein-based complex comprises a negatively charged lipid.

37. The lipid binding protein-based complex for use according to claim 36, wherein the negatively charged lipid is 1,2-dipalmitoyl-sn-glycero-3-[phospho-rac-(1-glycerol) (DPPG) or a salt thereof.

38. The lipid binding protein-based complex for use according to claim 33, wherein the lipid binding protein-based complex is CER-001, CSL-111, CSL-112, CER-522 or ETC-216.

39. The lipid binding protein-based complex for use according to claim 38, wherein the lipid binding protein-based complex is CER-001.

40. The lipid binding protein-based complex for use according to any one of claims 1 to 39, wherein in the method the lipid binding protein-based complex is administered systemically, optionally by infusion.

41. The lipid binding protein-based complex for use according to any one of claims 1 to 40, wherein each individual dose of the lipid binding protein-based complex administered is 4-40 mg/kg (on a protein weight basis).

42. The lipid binding protein-based complex for use according to any one of claims 1 to 41, wherein in the method the high dose is administered according to an induction regimen, optionally followed by a consolidation regimen.

43. The lipid binding protein-based complex for use according to claim 42, wherein the induction regimen comprises administering the lipid binding protein-based complex once daily or twice daily.

44. The lipid binding protein-based complex for use according to claim 42 or claim 43, wherein the consolidation regimen comprises administering the lipid binding protein-based complex once daily or once every two days.

45. The lipid binding protein-based complex for use according to any one of claims 1 to 44, wherein the subject is not treated with a maintenance regimen in the method.

46. The lipid binding protein-based complex for use according to any one of claims claim 42 to 45, wherein the consolidation regimen comprises administering one or more doses of the lipid binding protein-based complex to the subject one or more days after administration of the final dose of the induction regimen.

47. The lipid binding protein-based complex for use according to any one of claims 42 to 46, wherein the method comprises an induction regimen comprising twice daily administration of the lipid binding protein-based complex on days 1, 2, and 3 and a consolidation regimen comprising two doses of the lipid binding protein-based complex on day 6.

48. The lipid binding protein-based complex for use according to any one of claims 42 to 47, wherein each individual dose of the lipid binding protein-based complex administered in the induction regimen is 4-40 mg/kg (on a protein weight basis).

49. The lipid binding protein-based complex for use according to any one of claims 42 to 48, wherein the dose of the lipid binding protein-based complex administered in the consolidation regimen is 5 to 15 mg/kg (on a protein weight basis).

50. The lipid binding protein-based complex for use according to any one of claims 42 to 48, wherein the dose of the lipid binding protein-based complex administered in the consolidation regimen is 15 to 25 mg/kg (on a protein weight basis).

51. The lipid binding protein-based complex for use according to any one of claims 1 to 50, wherein the method further comprises administering an antihistamine to the subject prior to each individual dose.

52. The lipid binding protein-based complex for use according to of any one of claims 1 to 51, wherein the subject is receiving or has received one or more additional therapies and/or wherein the method further comprises administering to the subject one or more additional therapies.