

LIPID BINDING PROTEIN MOLECULE THERAPY**1. CROSS-REFERENCE TO RELATED APPLICATIONS**

[0001] This application claims the priority benefit of U.S. provisional application no. 63/594,669, filed October 31, 2023, the contents of which are incorporated herein in their entireties by reference thereto.

2. SUMMARY

[0002] The instant application contains a Sequence Listing which has been submitted electronically in XML format and is hereby incorporated by reference in its entirety. Said XML Sequence Listing, created on October 21, 2024, is named CRN-053WO_SL and is 3223 bytes in size.

3. TECHNICAL FIELD

[0003] The present application relates to personalized approaches for treating patients suffering from and at risk of conditions treatable with lipid binding molecule therapy.

4. SUMMARY

[0004] The present disclosure provides methods of treating various conditions with lipid binding protein molecules, for example conditions associated with inflammation such as sepsis. In some embodiments, the methods of the disclosure can be performed in a critical care setting, for example in connection with treatment of a subject being treated a hospital (e.g., in the intensive care unit) for a condition described herein.

[0005] In one aspect, the disclosure provides a method of treating a subject having or at risk of a condition treatable with a lipid binding protein molecule comprising measuring an ApoA-I level or an HDL level (e.g., an HDL-cholesterol (HDL-C) level) of the subject, and administering one or more doses of the lipid binding protein molecule to the subject if the measured ApoA-I level is below a target ApoA-I level or a target ApoA-I range or if the measured HDL level is below a target HDL level.

[0006] The ApoA-I or HDL measurement can be performed before the lipid binding protein molecule is first administered to the subject. A pre-treatment measurement can be used, for example, in the selection of a starting dose and/or administration frequency. Alternatively, or in addition, the subject's ApoA-I or HDL level can be measured after the subject receives one or more doses of the lipid binding protein molecule.

[0007] In some embodiments, the lipid binding protein molecule is a component of a lipid binding protein-based complex. Lipid binding protein-based complexes can comprise amphipathic molecules such as lipids, for example a sphingomyelin and/or a negatively charged lipid. An exemplary lipid binding protein-based complex that can be used in the methods of the disclosure is 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).

[0008] In certain aspects, a lipid binding protein molecule (e.g., ApoA-I) is administered in combination with a standard of care therapy for the subject's disease or condition. For example, subjects having sepsis can be administered an antibiotic and/or receive hemodynamic support.

[0009] In certain aspects, an antihistamine (e.g., dexchlorpheniramine, hydroxyzine, diphenhydramine, cetirizine, fexofenadine, or loratadine) can be administered before administration of a lipid binding protein molecule (e.g., ApoA-I). The antihistamine can reduce the likelihood of allergic reactions.

[0010] Further features of exemplary lipid binding protein molecules and lipid binding-protein based complexes that can be used in methods of the disclosure are described in Section 6.1 and specific embodiments 239 to 267, *infra*.

[0011] Further features of exemplary conditions and subject populations who can be treated according to the methods of the disclosure are described in Section 6.2 and specific embodiments 158 to 238 and 405 to 427, *infra*.

[0012] Exemplary target ApoA-I levels, target ApoA-I ranges, target HDL ranges, and methods for measuring ApoA-I levels and HDL levels are described in further detail in Section 6.3 and specific embodiments 54 to 147, *infra*.

[0013] Further features of exemplary dosing regimens are described in Section 6.4 and specific embodiments 1 to 53, 148 to 157, 268 to 388, and 428, *infra*.

[0014] Further features of exemplary combination therapies are described in Section 6.5 and specific embodiments 389 to 404, *infra*.

5. BRIEF DESCRIPTION OF THE FIGURES

[0015] FIG. 1 shows a schematic of the clinical study of Example 1.

[0016] FIGS. 2A-2F show: lipopolysaccharide (LPS) changes from baseline for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) (FIG. 2A); LPS changes from baseline for each of Groups A-D (FIG. 2B); LPS changes as a percentage of peak for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) (FIG. 2C); LPS changes as a percentage of peak for the SOC group (Group A) and the three experimental groups (Groups B-D), broken out by whether the subject was enrolled from the ICU or the nephrology department of the center (FIG. 2D); LPS changes from baseline for each subject in the SOC group and the three experimental groups (FIG. 2E); and LPS changes from baseline for each subject in the SOC group and each of the three experimental groups (FIG. 2F), in the clinical study of Example 1.

[0017] FIGS. 3A-3E show endotoxin activity assay (EAA) changes: from baseline for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) (FIG. 3A); from baseline for each of Groups A-D (FIG. 3B); as a percentage of peak for the SOC group (Group A) and the three experimental groups (Groups B-D) (FIG. 3C); as a percentage of peak for the SOC group (Group A) and the three experimental groups (Groups B-D), broken out by whether the subject was enrolled from the ICU or the nephrology department of the center (FIG. 3D); and changes from baseline for the SOC group (Group A) and the three experimental groups (Groups B-D) (FIG. 3E), in the clinical study of Example 1.

[0018] FIGS. 4A-4F show TNF-alpha changes: from baseline for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) (FIG. 4A); from baseline for each of Groups A-D (FIG. 4B); as a percentage of peak for the SOC group (Group A) and the three experimental groups

(Groups B-D) (FIG. 4C); as a percentage of peak for the SOC group (Group A) and the three experimental groups (Groups B-D), broken out by whether the subject was enrolled from the ICU or the nephrology department of the center (FIG. 4D); from baseline for each subject in the SOC group (Group A) and the three experimental groups (Groups B-D) (FIG. 4E); and from baseline for each subject in each of the SOC group (Group A) and the three experimental groups (Groups B-D) (FIG. 4F), in the clinical study of Example 1.

[0019] FIGS. 5A-5F show: MCP-1 changes: from baseline for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) (FIG. 5A); from baseline for each of Groups A-D (FIG. 5B); as a percentage of peak for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) (FIG. 5C); as a percentage of peak for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D), broken out by whether the subject was enrolled from the ICU or the nephrology department of the center, (FIG. 5D); from baseline for each subject in the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) (FIG. 5E); and from baseline for each subject in each of the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) (FIG. 5F), in the clinical study of Example 1.

[0020] FIGS. 6A-6F show IL-6 changes: from baseline for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) (FIG. 6A); from baseline for each of Groups A-D (FIG. 6B); as a percentage of peak for the SOC group (Group A) and the three experimental groups (Groups B-D) (FIG. 6C); as a percentage of peak for the SOC group (Group A) and the three experimental groups (Groups B-D), broken out by whether the subject was enrolled from the ICU or the nephrology department of the center (FIG. 6D); from baseline for each subject in the SOC group (Group A) and the three experimental groups (Groups B-D) (FIG. 6E); and from baseline for each subject in each of the SOC group (Group A) and the three experimental groups (Groups B-D) (FIG. 6F), in the clinical study of Example 1.

[0021] FIGS. 7A-7F show IL-8 changes: from baseline for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) (FIG. 7A); from baseline for each of Groups A-D (FIG. 7B); as a percentage of peak for the SOC group (Group A) and the three experimental groups (Groups B-D) (FIG. 7C); as a percentage of peak for the SOC group (Group A) and the three experimental groups (Groups B-D), broken out by whether the subject was enrolled from the ICU or the nephrology department of the center, (FIG. 7D); from baseline for the SOC group (Group A) and the three experimental groups (Groups B-D) (FIG. 7E); and from baseline for the SOC group (Group A) and each of the three experimental groups (Groups B-D) (FIG. 7F), in the clinical study of Example 1.

[0022] FIGS. 8A-8D show IL-10 changes: from baseline for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) (FIG. 8A); baseline for each of Groups A-D (FIG. 8B); as a percentage of peak for the SOC group (Group A) and the three experimental groups (Groups B-D) (FIG. 8C); and as a percentage of peak for the SOC group (Group A) and the three experimental groups (Groups B-D), broken out by whether the subject was enrolled from the ICU or the nephrology department of the center (FIG. 8D), in the clinical study of Example 1.

[0023] FIGS. 9A-9F show s-TREM-1 changes: from baseline for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) (FIG. 9A); from baseline for each of Groups A-D (FIG. 9B); as a percentage of peak for the SOC group (Group A) and the three experimental groups (Groups B-D) (FIG. 9C); as a percentage of peak for the SOC group (Group A) and the three

experimental groups (Groups B-D), broken out by whether the subject was enrolled from the ICU or the nephrology department of the center (FIG. 9D); from baseline for each subject in the SOC group (Group A) and the three experimental groups (Groups B-D) (FIG. 9E); from baseline for each subject in each of the SOC group (Group A) and the three experimental groups (Groups B-D) (FIG. 9F), in the clinical study of Example 1.

[0024] FIGS. 10A-10F show s-VCAM changes: from baseline for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) (FIG. 10A); baseline for each of Groups A-D (FIG. 10B); as a percentage of peak for the SOC group (Group A) and the three experimental groups (Groups B-D) (FIG. 10C); as a percentage of peak for the SOC group (Group A) and the three experimental groups (Groups B-D), broken out by whether the subject was enrolled from the ICU or the nephrology department of the center (FIG. 10D) from baseline for each subject in the SOC group (Group A) and the three experimental groups (Groups B-D) (FIG. 10E); and from baseline for each subject in each of the SOC group (Group A) and the three experimental groups (Groups B-D) (FIG. 10F), in the clinical study of Example 1.

[0025] FIGS. 11A-11F show s-ICAM changes from: baseline for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) (FIG. 11A); baseline for each of Groups A-D (FIG. 11B); as a percentage of peak for the SOC group (Group A) and the three experimental groups (Groups B-D) (FIG. 11C); as a percentage of peak for the SOC group (Group A) and the three experimental groups (Groups B-D), broken out by whether the subject was enrolled from the ICU or the nephrology department of the center (FIG. 11D); from baseline for each subject in the SOC group (Group A) and the three experimental groups (Groups B-D) (FIG. 11E); and from baseline for each subject in each of the SOC group (Group A) and the three experimental groups (Groups B-D) (FIG. 11F), in the clinical study of Example 1.

[0026] FIGS. 12A-12D show ferritin changes: from baseline for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) (FIG. 12A); from baseline for each of Groups A-D (FIG. 12B); as a percentage of peak for the SOC group (Group A) and the three experimental groups (Groups B-D) (FIG. 12C); and as a percentage of peak for the SOC group (Group A) and the three experimental groups (Groups B-D), broken out by whether the subject was enrolled from the ICU or the nephrology department of the center (FIG. 12D), in the clinical study of Example 1.

[0027] FIGS. 13A-13D show white blood cell count changes: from baseline for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) (FIG. 13A); from baseline for each of Groups A-D (FIG. 13B); as a percentage of peak for the SOC group (Group A) and the three experimental groups (Groups B-D) (FIG. 13C); and as a percentage of peak for the SOC group (Group A) and the three experimental groups (Groups B-D), broken out by whether the subject was enrolled from the ICU or the nephrology department of the center (FIG. 13D), in the clinical study of Example 1.

[0028] FIGS. 14A-14F show C-reactive protein (CRP) changes: from baseline for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) (FIG. 14A); from baseline for each of Groups A-D (FIG. 14B); as a percentage of peak for the SOC group (Group A) and the three experimental groups (Groups B-D) (FIG. 14C); as a percentage of peak for the SOC group (Group A) and the three experimental groups (Groups B-D), broken out by whether the subject was enrolled from the ICU or the nephrology department of the center, (FIG. 14D); from baseline for each subject in SOC group (Group A) and the three experimental groups (Groups B-D) (FIG. 14E); and from baseline for each

subject in the SOC group (Group A) and each of the three experimental groups (Groups B-D) (FIG. 14F), in the clinical study of Example 1.

[0029] FIGS. 15A-15D show KIM-1 changes: from baseline for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) (FIG. 15A); from baseline for each of Groups A-D (FIG. 15B); as a percentage of peak for the SOC group (Group A) and the three experimental groups (Groups B-D) (FIG. 15C); and as a percentage of peak for the SOC group (Group A) and the three experimental groups (Groups B-D), broken out by whether the subject was enrolled from the ICU or the nephrology department of the center (FIG. 15D), in the clinical study of Example 1.

[0030] FIGS. 16A-16E show serum albumin changes: from baseline for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) (FIG. 16A); from baseline for each of Groups A-D (FIG. 16B); as a percentage of peak for the SOC group (Group A) and the three experimental groups (Groups B-D) (FIG. 16C); as a percentage of peak for the SOC group (Group A) and the three experimental groups (Groups B-D), broken out by whether the subject was enrolled from the ICU or the nephrology department of the center (FIG. 16D); and from baseline for each subject in the SOC group (Group A) and the three experimental groups (Groups B-D) (FIG. 16E), in the clinical study of Example 1.

[0031] FIGS. 17A-17F show serum creatinine changes from baseline for the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) (FIG. 17A); serum creatinine changes from baseline for each of Groups A-D (FIG. 17B); serum creatinine changes as a percentage of peak for the SOC group (Group A) and the three experimental groups (Groups B-D) (FIG. 17C); serum creatinine changes as a percentage of peak for the SOC group (Group A) and the three experimental groups (Groups B-D), broken out by whether the subject was enrolled from the ICU or the nephrology department of the center (FIG. 17D); the AUC for serum creatinine (mean $\pm$ SEM) for the SOC group (Group A) and the three experimental groups (Groups B-D) (FIG. 17E); and the AUC for serum creatinine (95% confidence interval) for the SOC group (Group A) and the three experimental groups (Groups B-D) (FIG. 17F), in the clinical study of Example 1.

[0032] FIGS. 18A-18F show estimated glomerular filtration rate (eGFR) changes: from baseline for all subjects in the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) (FIG. 18A); from baseline for all subjects in each of Groups A-D (FIG. 18B); from baseline only for subjects in the SOC group (Group A) and the three experimental groups (Groups B-D) who entered the clinical study of Example 2 with AKI (FIG. 18C); from baseline for the same subjects as in FIG. 18C (FIG. 18D); as a percentage of peak for all subjects in the SOC group (Group A) and aggregated Groups B-D (FIG. 18E); and as a percentage of peak only for subjects entering the study with AKI, in the SOC group (Group A) and aggregated Groups B-D (FIG. 18F), in the clinical study of Example 1.

[0033] FIG. 19 shows P/F changes from baseline for all subjects in the standard of care (SOC) group (Group A) and the three experimental groups (Groups B-D) in the clinical study of Example 1.

[0034] FIG. 20 shows survival proportions for all subjects after days in ICU for the standard of care group (Group A, "SOC") and aggregated Groups B-D ("CER-001") in the clinical study of Example 1.

[0035] FIGS. 21A-22B show survival proportions over 30 days for all subjects: for the standard of care group (Group A, "SOC") and aggregated Groups B-D ("CER-001") (FIG. 21A); and who entered the study from the center's ICU, for the standard of care group (Group A, "SOC") and aggregated Groups B-D ("CER-001") (FIG. 21B).

[0036] FIGS. 22A-22B show the evolution of AKI staging: for the standard of care group (Group A, "SOC") (FIG. 22A); and for aggregated Groups B-D ("CER-001") (FIG. 22B), in the clinical study of Example 1.

[0037] FIG. 23 shows days on mechanical ventilation for all subjects who entered the study from the center's ICU, for the standard of care group (Group A, "SOC") and aggregated Groups B-D ("CER-001") in the clinical study of Example 1.

[0038] FIG. 24 shows days on vasopressor therapy for all subjects who entered the study from the center's ICU, for the standard of care group (Group A, "SOC") and aggregated Groups B-D ("CER-001") in the clinical study of Example 1.

[0039] FIGS. 25A-25B show days on dialysis for all subjects: who entered the study from the center's ICU, for the standard of care group (Group A, "SOC") and aggregated Groups B-D ("CER-001") (FIG. 25A); and who entered the study for the standard of care group (Group A, "SOC") and aggregated Groups B-D ("CER-001") (FIG. 25B), in the clinical study of Example 1.

[0040] FIG. 26 shows days alive without organ support for all subjects who entered the study from the center's ICU, for the standard of care group (Group A, "SOC") and aggregated Groups B-D ("CER-001") in the clinical study of Example 1.

[0041] FIGS. 27A-27B show changes in daily average mean arterial pressure (MAP) for: all subjects who entered the study from the center's ICU, for the standard of care group (Group A, "SOC") and aggregated Groups B-D ("CER-001") (FIG. 27A); and each subject who entered the study from the center's ICU, for the standard of care group (Group A, "SOC") and aggregated Groups B-D ("CER-001") (FIG. 27B), in the clinical study of Example 1.

[0042] FIG. 28 shows change in daily average heart rate (HR) for all subjects who entered the study from the center's ICU, for the standard of care group (Group A, "SOC") and aggregated Groups B-D ("CER-001") in the clinical study of Example 1.

[0043] FIG. 29 shows change in daily average P/F ratio for all subjects who entered the study from the center's ICU, for the standard of care group (Group A, "SOC") and aggregated Groups B-D ("CER-001") in the clinical study of Example 1.

[0044] FIGS. 30A-30D show mean ApoA-I levels for the control group and the aggregated study groups (FIG. 30A); ApoA-I levels for each subject broken out by study group (FIG. 30B); changes from baseline of ApoA-I levels for each subject (FIG. 30C); and changes from baseline of ApoA-I levels for each subject broken out by study group (FIG. 30D), in the clinical study of Example 1.

[0045] FIGS. 31A-31B show changes from baseline of aspartate transaminase (AST) levels for each subject (FIG. 31A); and changes from baseline of alanine transaminase (ALT) levels for each subject (FIG. 31B), in the clinical study of Example 1.

[0046] FIG. 32 shows days until ICU discharge for all subjects who entered the study from the center's ICU, for the standard of care group (Group A, "SOC") and aggregated Groups B-D ("CER-001") in the clinical study of Example 1.

[0047] FIG. 33 shows changes from baseline for triglycerides between the standard of care group (Group A, "SOC") and the experimental groups (Groups B-D, "CER-001") in the clinical study of Example 1.

[0048] FIGS. 34A-34D illustrate four exemplary courses of administration of a lipid binding protein molecule. Doses A-E each represent a dose of the lipid binding protein molecule; arrows represent the

days on which administration(s) of the lipid binding protein molecule occur(s); asterisks represent measurements of ApoA-I levels and/or HDL levels; arrows with dashed outlines represent administrations performed only if a measured ApoA-I level is below a target ApoA-I level or ApoA-I range or if a measured HDL level is below a target level. **FIG. 34A:** after a three-day induction regimen in which doses A, B, and C are administered, an ApoA-I or HDL level is measured on Day 4, and doses D and E are administered on Days 5 and 6 if the measured ApoA-I level is below a target level or target range or if the measured HDL level is below a target level. **FIG. 34B:** after administering doses A, B, and C on Days 1-3, an ApoA-I or HDL level is measured on Day 5, and doses D and E are administered on Days 5 and 6 if the measured ApoA-I level is below a target level or target range or if the measured HDL level is below a target level. **FIG. 34C:** an ApoA-I level or HDL level is measured on Day 1, after which the dose administered on Days 2 and 3 is double a reference or standard dose (2x A, 2x B, which can correspond to two administrations of the reference or standard dose in the same day, or a single administration of double the reference or standard dose) if the measured ApoA-I level is below a target ApoA-I level or target ApoA-I range or if the measured HDL level is below a target HDL level. Dose C is administered on Day 4, an ApoA-I or HDL level is measured on Day 5, and doses D and E are administered on Days 6 and 7 if the ApoA-I level measured on Day 5 is below a target ApoA-I level or target range or if the HDL level measured on Day 5 is below a target HDL level. In another embodiment of the regimen illustrated in FIG. 34C, a reference or standard dose is administered on Days 2 and 3 if measured ApoA-I level is at or above a target ApoA-I level, within a target ApoA-I range or if the measured HDL level is at or above a target HDL level (alternative embodiment not shown). **FIG. 34D:** after administering doses A, B, C, and D on Days 1-4, an ApoA-I or HDL level is measured on Day 5, and doses E and F are administered on Days 6 and 7 if the measured ApoA-I level is below a target level or target range or if the measured HDL level is below a target level.

6. DETAILED DESCRIPTION

[0049] The present disclosure provides methods for treating subjects having or at risk of various conditions, for example sepsis (e.g., septic shock) with lipid binding protein molecules. In some embodiments, the condition is an acute condition, e.g., associated with inflammation. In some embodiments, the subject is being treated in a critical care setting. The methods typically comprise measuring an ApoA-I level or HDL level of the subject and administering one or more doses of the lipid binding protein molecule to the subject if the measured ApoA-I level is below a target ApoA-I level or a target ApoA-I range or if the measured HDL level is below a target HDL level. Measurement of ApoA-I level or HDL level can optionally be preceded by administration of one or more doses of a lipid binding protein molecule. The target ApoA-I level can be, for example, a normal ApoA-I level in healthy subjects and/or the target ApoA-I range can be a normal ApoA-I range in healthy subjects. The target HDL level can be, for example, a normal HDL-C level in healthy subjects. ApoA-I or HDL measurement and subsequent administration steps can be repeated one or more times, for example, until the subject's ApoA-I level is at or above the target level or within the target range or until the subject's HDL level is at or above the target level.

[0050] If the measured ApoA-I value is at or above the target level or within the target range or if the measured HDL value is at or above the target level, administration of the lipid binding protein molecule

can be discontinued (if the subject previously received the lipid binding protein molecule) or not initiated (if the subject had not previously received the lipid binding protein molecule). Alternatively, if the subject had previously received the lipid binding protein molecule, the subject can be administered one or more doses of the lipid binding protein molecule at a dose and/or frequency that is lower than the dose and/or frequency of the prior administration(s). The subject's ApoA-I level or HDL level can subsequently be measured again, and the administration regimen can be restarted or adjusted (as the case may be) if the subject's ApoA-I level falls below the target ApoA-I level or target ApoA-I range or if the subject's HDL level falls below the target HDL level.

[0051] In various aspects, the condition is sepsis (e.g., septic shock, e.g. septic shock following trauma, for example abdominal trauma, or septic shock not following trauma, e.g., post-operative sepsis), sepsis with risk (e.g., high risk) of developing acute kidney injury, a bacterial infection (e.g. a gram-positive bacterial infection or a gram-negative bacterial infection), optionally with an antibiotic-resistant bacterium (e.g., MRSA), a urinary tract infection, a blood infection, a post-surgical infection, gastrointestinal perforation, a perforated duodenal ulcer, a perforated bowel, pneumonia, e.g., hospital acquired pneumonia, a pancreatitis, e.g., necrotizing pancreatitis, a viral infection (e.g., a SARS-CoV-2 (COVID-19) infection or an influenza virus infection), acute myocardial infarction (AMI), cytokine release syndrome (CRS), ischemia reperfusion-induced tissue injury, post-operative inflammation, sepsis-induced acute kidney injury (AKI), hypoalbuminemia (e.g., hypoalbuminemia associated with a vitamin deficiency, hypoalbuminemia associated with inflammatory bowel disease (IBD), hypoalbuminemia associated with kidney disease, hypoalbuminemia associated with an infection, optionally wherein the infection is a gram-positive bacterial infection, a gram-negative bacterial infection, or a viral infection such as a SARS-CoV-2 (COVID-19) infection or influenza infection, hypoalbuminemia associated with stress, hypoalbuminemia associated with thyroid disease, hypoalbuminemia associated with diabetes, hypoalbuminemia associated with nephrotic syndrome, hypoalbuminemia associated with lupus, hypoalbuminemia associated with cirrhosis, hypoalbuminemia associated with liver disease, hypoalbuminemia associated with heart failure, or hypoalbuminemia associated with malnutrition, cytokine release syndrome (CRS; cytokine storm), risk of CRS, acute kidney injury (AKI), or risk of developing AKI. In some aspects, the subject has had a recent surgery. For example, a recent surgery can be a surgery that was performed within the previous month. As another example, a recent surgery can be a surgery that was performed within the previous two weeks. In yet another example, a recent surgery can be a surgery that was performed within the previous week. In some aspects, the subject is a candidate for a surgery (e.g., a surgery to be performed for within one week, two weeks, or one month). In some embodiments, the surgery is to be performed within one week. In some embodiments, the surgery is to be performed within two weeks. In some embodiments, the surgery is to be performed within one month.

[0052] In some embodiments, the lipid binding protein molecule is provided as a component of a lipid binding protein-based complex. In some embodiments, the lipid binding protein-based complex is an Apomer (e.g., as described in WO 2019/030575), a Cargomer (e.g., as described in WO 2019/030574), a HDL based complex, or a HDL mimetic based complex. In specific embodiments, the lipid binding protein-based complex is CER-001.

[0053] Exemplary features of lipid binding protein molecules and lipid binding protein-based complexes comprising the lipid binding protein molecules 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.

[0054] In some embodiments, methods of the disclosure comprise administering a lipid binding protein molecule (e.g., ApoA-I) to a subject in an initial “induction” regimen. In some embodiments, an ApoA-I level of the subject is measured following the induction regimen. In some embodiments, the induction regimen is followed by a “consolidation” regimen, for example if the subject’s ApoA-I level is below a target value or below a target range or if the subject’s HDL level is below a target value following the induction regimen. Alternatively, a lipid binding protein molecule (e.g., ApoA-I) 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. For example, a subject’s ApoA-I level can be measured before the lipid binding protein molecule is administered and, if the measured ApoA-I level is below the target value or below the target range, treatment with the lipid binding protein molecule can be initiated. As another example, a subject’s HDL level can be measured before the lipid binding protein molecule is administered and, if the measured HDL level is below the target value, treatment with the lipid binding protein molecule can be initiated.

[0055] Induction regimens that can be used in the methods of the disclosure are described in Section 6.4.1 and consolidation regimens that can be used in the methods of the disclosure are described in Section 6.4.2. The dosing regimens of the disclosure comprise administering a lipid binding protein molecule (e.g., ApoA-I) 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 the subject’s disease or condition. Combination therapies are described in Section 6.5.

6.1. Lipid binding protein molecules and lipid binding protein-based complexes

6.1.1. Lipid Binding Protein Molecules

[0056] Lipid binding protein molecules that can be used, either directly or in a lipid binding protein-based complexes described herein, include apolipoproteins such as those described in Section 6.1.1.1 and apolipoprotein mimetic peptides such as those described in Section 6.1.1.2. In some embodiments, a mixture of lipid binding protein molecules can be used, optionally as members of a complex. In some embodiments, the mixture of lipid binding protein molecules can comprise one or more apolipoproteins. In some embodiments, the mixture of lipid binding protein molecules can comprise one or more apolipoprotein mimetic peptides. In some embodiments, the mixture of lipid binding protein molecules can comprise one or more apolipoproteins and one or more apolipoprotein mimetic peptides.

6.1.1.1. Apolipoproteins

[0057] Suitable apolipoproteins from which the lipid binding protein molecule can be chosen, and that can be included in lipid binding protein-based complexes disclosed herein, 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-I_{Milano} (ApoA-I_M), Apolipoprotein A-I_{Paris} (ApoA-I_P), and Apolipoprotein A-I_{Zaragoza} (ApoA-I_Z), 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.

[0058] 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 or apolipoprotein containing 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)).

[0059] In some embodiments, the lipid binding protein molecule 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-IMilano-ApoA-II).

[0060] 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.

[0061] 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.

[0062] 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.

[0063] 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.

[0064] In particular embodiments, the ApoA-I is recombinant ApoA-I produced by a mammalian host cell. The host cell can be from any mammalian cell line. Polynucleotides encoding the ApoA-I can be codon optimized for expression in recombinant host cells. In some embodiments, host cells are mammalian host cells, including, but not limited to, Chinese hamster ovary cells (e.g. CHO-K1; ATCC No. CCL 61; CHO-S (e.g., GIBCO Life Technologies Inc., Rockville, MD, Catalog #11619012)), VERO cells, BHK (ATCC No. CRL 1632), BHK 570 (ATCC No. CRL 10314), HeLa cells, COS-1 (ATCC No. CRL 1650), COS-7 (ATCC No. CRL 1651), MDCK cells, 293 cells (ATCC No. CRL 1573; Graham *et al.*, *J. Gen. Virol.* 36:59-72, 1977), 3T3 cells, myeloma cells (especially murine), PC12 cells and W138 cells. In certain embodiments, the mammalian cells, such as CHO-S cells, are adapted for growth in serum-free

medium. Additional suitable cell lines are known in the art and available from public depositories such as the American Type Culture Collection, Manassas, Va.

[0065] In some embodiments, the recombinant ApoA-I is produced by a CHO cell, for example a CHO-S cell. As the person of ordinary skill in the art will be aware, recombinant polypeptides (e.g., recombinant ApoA-I) expressed by a mammalian host cell, such as a CHO cell, may undergo post-translational processing (e.g., glycosylation, etc.). The resulting recombinant ApoA-I can have one or more structural features (e.g., glycosylation pattern) that are different from ApoA-I purified from human plasma.

[0066] The apolipoprotein can be in prepro- form, pro- form, or mature form. For example, the apolipoprotein 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 ApoA-I has at least 90% sequence identity to SEQ ID NO:1:

PPQSPWDRVKDLATVYVDVLKDSGRDYVSQFEGSALGKQLNLKLLDNWDSVTSTFSKLREQLGPVTQE
FWDNLEKETEGRLQEMSKDLEEVKAKVQPYLDDFQKKWQEE MELYRQKVEPLRAELQEGARQKLHEL
QEKLSPLGEEMRDRARAHVDALRTHLAPYSDELQRRLAARLEALKENG GARLA EYHAKATEHLSTLSEK
AKPALEDLRQGLLPVLESFKVSFLSALEEYTKKLNTQ (SEQ ID NO:1)

[0067] In other embodiments, the ApoA-I has at least 95% sequence identity to SEQ ID NO:1. In other embodiments, the ApoA-I has at least 98% sequence identity to SEQ ID NO:1. In other embodiments, the ApoA-I has at least 99% sequence identity to SEQ ID NO:1. In other embodiments, the ApoA-I has 100% sequence identity to SEQ ID NO:1.

[0068] In some embodiments, the ApoA-I comprises a sequence having at least 90% sequence identity to amino acids 25 to 267 of SEQ ID NO:2:

MKAAVLTAVLFLTGSQARHFWQQDEPPQSPWDRVKDLATVYVDVLKDSGRDYVSQFEGSALGKQLNL
KLLDNWDSVTSTFSKLREQLGPVTQEFWDNLEKETEGRLQEMSKDLEEVKAKVQPYLDDFQKKWQEE
MELYRQKVEPLRAELQEGARQKLHELQEKLSPLGEEMRDRARAHVDALRTHLAPYSDELQRRLAARLE
ALKENG GARLA EYHAKATEHLSTLSEKAKPALEDLRQGLLPVLESFKVSFLSALEEYTKKLNTQ (SEQ ID
NO:2).

[0069] In other embodiments, the complex comprises ApoA-I that has at least 95% sequence identity to amino acids 25 to 267 of SEQ ID NO:2. In other embodiments, the complex comprises ApoA-I that has at least 98% sequence identity to amino acids 25 to 267 of SEQ ID NO:2. In other embodiments, the complex comprises ApoA-I that has at least 99% sequence identity to amino acids 25 to 267 of SEQ ID NO:2. In other embodiments, the complex comprises ApoA-I that has 100% sequence identity to amino acids 25 to 267 of SEQ ID NO:2.

[0070] In particular embodiments, the ApoA-I is recombinant ApoA-I produced by a mammalian host cell. The host cell can be from any mammalian cell line. The polynucleotides encoding the ApoA-I can be codon optimized for expression in recombinant host cells. Preferred host cells are mammalian host cells, including, but not limited, Chinese hamster ovary cells (e.g. CHO-K1; ATCC No. CCL 61; CHO-S (GIBCO Life Technologies Inc., Rockville, MD, Catalog #11619012)), VERO cells, BHK (ATCC No. CRL 1632), BHK 570 (ATCC No. CRL 10314), HeLa cells, COS-1 (ATCC No. CRL 1650), COS-7 (ATCC No. CRL 1651), MDCK cells, 293 cells (ATCC No. CRL 1573; Graham *et al.*, J. Gen. Virol. 36:59-72, 1977), 3T3 cells, myeloma cells (especially murine), PC12 cells and W138 cells. In certain embodiments, the mammalian cells, such as CHO-S cells (Invitrogen™, Carlsbad CA), are adapted for growth in serum-free

medium. Additional suitable cell lines are known in the art and available from public depositories such as the American Type Culture Collection, Manassas, Va.

[0071] In a particular embodiment, the recombinant ApoA-I is produced by a CHO cell. As the person of ordinary skill in the art will be aware, expression by a mammalian host cell, such as a CHO cell, may undergo post-translational processing (e.g., glycosylation, etc.). The resulting recombinant ApoA-I population can have one or more characteristics (e.g., homogeneity, glycosylation pattern) that are distinct from ApoA-I purified from human plasma.

[0072] In certain embodiments, a nucleotide sequence encodes the amino acid sequence of a mature ApoA-I protein, preferably operably linked to a signal sequence for secretion of the ApoA-I from the host cell and/or a proprotein sequence. In some embodiments, the nucleotide sequence encodes the amino acid sequence of SEQ ID NO:2 (human prepro-ApoA-I), which comprises a signal sequence (amino acids 1-18) and a propeptide sequence (amino acids 19-24). Other signal sequences suitable for directed secretion of ApoA-I can be either heterologous to ApoA-I, e.g., a human albumin signal peptide or a human IL-2 signal peptide, or homologous to ApoA-I.

[0073] In some embodiments, ApoA-I is produced by a CHO cell (e.g., CHO-S cell) engineered to express the amino acid sequence of SEQ ID NO:2. The engineered cell can comprise a nucleotide sequence encoding SEQ ID NO:2 operably linked to a promoter, for example a constitutive promoter. In some embodiments, the engineered cell comprises a nucleotide sequence encoding SEQ ID NO:2 operably linked to a simian cytomegalovirus immediate early promoter.

[0074] In some embodiments, recombinant ApoA-I can be produced by culturing any of the mammalian host cells described herein under conditions in which ApoA-I is expressed and secreted. The ApoA-I can be recovered from the supernatant of a cultured mammalian host cell, and optionally purified to yield mature, biologically active ApoA-I.

[0075] Further methods for recombinant expression and purification of ApoA-I are described in detail in WO 2012/109162, the contents of which are incorporated herein by reference in their entirety. See, for example, Sections 6.1.2-6.1.4 and Examples 1-2 of PCT Publication No. WO 2012/109162, the contents of which are incorporated herein by reference in their entirety.

[0076] In some embodiments, a lipid binding protein-based 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.

[0077] 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 CER-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.

[0078] 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.

[0079] 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.

[0080] 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 ($-\text{COOH}$), free amino ($-\text{NH}_2$), or sulfhydryl ($-\text{SH}$) 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.

[0081] 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.

[0082] 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.).

[0083] 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.

[0084] Lipid binding protein molecules and complexes comprising lipid binding protein molecules can be targeted to a specific cell surface receptor by engineering receptor recognition properties into an apolipoprotein. For example, lipid binding protein molecules or complexes may be targeted to a particular cell type known to harbor a particular type of infectious agent, for example by modifying a apolipoprotein of other lipid binding protein molecule to render it capable of interacting with a receptor on the surface of the cell type being targeted. For example, lipid binding protein molecules or complexes may be targeted to macrophages by altering a apolipoprotein or other lipid binding protein molecule to confer recognition by the macrophage endocytic class A scavenger receptor (SR-A). SR-A binding ability can be conferred to a lipid binding protein molecule or complex by modifying a apolipoprotein or other lipid binding protein molecule 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. Lipid binding protein molecules and complexes comprising lipid binding protein molecules (e.g., apolipoproteins) 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.

6.1.1.2. Apolipoprotein mimetics

[0085] Peptides, peptide analogs, and agonists that mimic the activity of an apolipoprotein (collectively referred to herein as “apolipoprotein peptide mimetics”) can also be used as the lipid binding protein molecule or 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-_{IM}, ApoA-II, ApoA-IV, and ApoE, that are useful as lipid binding protein molecules and/or 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.

[0086] 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.

[0087] 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.

6.1.2. Lipid binding protein-based complexes

[0088] In some aspects, a lipid binding protein is a component of a lipid binding protein-based complex, for example complexed with one or more amphipathic molecules such as lipids. Lipid binding protein-based complexes that can be used include HDL and HDL mimetic-based complexes.

[0089] In some aspects, lipid binding protein-based 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.

[0090] 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 6.1.1.

[0091] 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.

[0092] 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).

[0093] 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.

[0094] 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 lipid binding protein molecule 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.

[0095] 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.

[0096] 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.

[0097] 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.

[0098] 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.

[0099] 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.

[0100] 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.

[0101] 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.

[0102] 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.

[0103] 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.

[0104] 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.

[0105] 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.

[0106] 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).

[0107] 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).

[0108] 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).

[0109] 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).

[0110] 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.

[0111] 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.

[0112] 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.

[0113] 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.

[0114] 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, cerebroside, glycerides, triglycerides, and cholesterol and its derivatives.

[0115] 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.

[0116] 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.

[0117] 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-IM, which typically exists as a disulfide-bridged dimer, can be expressed as 2 ApoA-I equivalents, because each molecule of ApoA-IM 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.

[0118] 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.

[0119] 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.

[0120] 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.

[0121] 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.

[0122] In particular embodiments, the complex comprises CER-001, CSL-111, CSL-112, CER-522, ETC-216, or ETC-642. In a preferred embodiment, the complex is CER-001.

[0123] 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.

[0124] 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 or plant 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 and WO 2024/003612, the contents of which are incorporated herein by reference in their entireties. 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:2. 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.

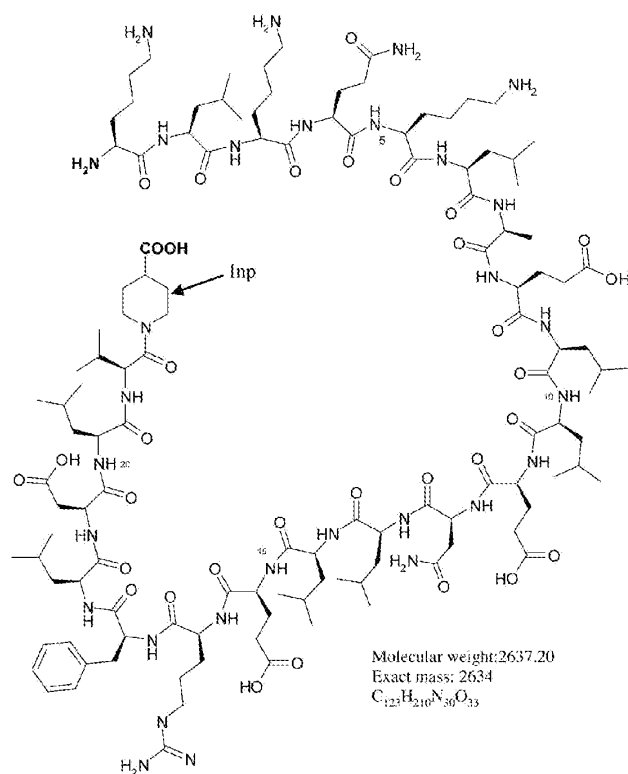
[0125] CSL-111 is a reconstituted human ApoA-I purified from plasma complexed with soybean phosphatidylcholine (SBPC) (Tardif *et al.*, 2007, JAMA 297:1675-1682).

[0126] 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).

[0127] ETC-216 (also known as MDCO-216) is a lipid-depleted form of HDL containing recombinant ApoA-I^{Milano} (Nicholls *et al.*, 2011, Expert Opin Biol Ther. 11(3):387-94. doi: 10.1517/14712598.2011.557061).

[0128] ETC-642 is complex of a 22-amino acid amphipathic peptide (ESP-2418) complexed with sphingomyelin and 1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine (Dipalmitoylphosphatidylcholine, DPPC) (Di Bartolo *et al.*, 2011, Atherosclerosis 217:395-400).

[0129] 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

[0130] 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).

[0131] 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 , pre β -1, and other pre β forms of HDL. A process for selective depletion of HDL is described in Sacks *et al.*, 2009, J Lipid Res. 50(5): 894–907.

[0132] In certain embodiments, a lipoprotein complex comprises a bioactive agent delivery particle as described in US 2004/0229794.

[0133] A bioactive agent delivery particle can comprise a lipid binding polypeptide (*e.g.*, an apolipoprotein as described previously in this Section or in Section 6.1.1), 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.

[0134] In some embodiments, a bioactive agent delivery particle does not comprise a hydrophilic core.

[0135] In some embodiments, a bioactive agent delivery particle is disc shaped (*e.g.*, having a diameter from about 7 to about 29 nm).

[0136] 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.

[0137] In some embodiments, the lipid binding polypeptide is an apolipoprotein (*e.g.*, as described previously in this Section or in Section 6.1.1). 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.

[0138] 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.

[0139] 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.

[0140] In some embodiments of the methods described herein, a lipid binding protein-based complex (*e.g.*, CER-001) can be used as a carrier to deliver one or more active agents to a subject's body or portion thereof. In some embodiments, the one or more active agents can be considered cargo moieties, and can be complexed to a lipid binding protein-based complex (*e.g.*, CER-001) either non-covalently or covalently to a component of the complex (*e.g.*, via an anchor or linker). In some embodiments, the one or more active agents are not covalently linked to the complex. One or more active agents can be added to a pre-formed complex, *e.g.*, pre-formed CER-001, to make a complex which further comprises the one or more active agents. Lipid binding protein-based complexes having active agents and processes for their production are described in WO 2012/109162, WO 2019/030574, and WO 2022/069942.

6.1.3. Amphipathic molecules

[0141] 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).

[0142] 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).

[0143] 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).

[0144] 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.

[0145] 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

[0146] 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.

[0147] 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.

[0148] 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).

[0149] 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 Unsaturation	Common Name
14:0	myristic acid
16:0	palmitic acid
18:0	stearic acid
18:1 cis Δ^9	oleic acid
18:2 cis $\Delta^{9,12}$	linoleic acid
18:3 cis $\Delta^{9,12,15}$	linolenic acid
20:4 cis $\Delta^{5,8,11,14}$	arachidonic acid
20:5 cis $\Delta^{5,8,11,14,17}$	eicosapentaenoic acid (an omega-3 fatty acid)

[0150] 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, cerebroside, 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.

[0151] 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.

[0152] 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.

[0153] 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, stearyl sphingomyelin, 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.

[0154] 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.

[0155] 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.

[0156] 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.

[0157] 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.

[0158] In a specific embodiment, functionalized SM, such as phytosphingomyelin, is used.

[0159] 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-myristoyl-2-palmitoylphosphatidylcholine, 1-palmitoyl-2-myristoylphosphatidylcholine, 1-palmitoyl-2-stearoylphosphatidylcholine, 1-stearoyl-2-palmitoylphosphatidylcholine, 1-palmitoyl-2-oleoylphosphatidylcholine, 1-oleoyl-2-palmitoylphosphatidylcholine, dioleoylphosphatidylcholine and the ether derivatives or analogs thereof.

[0160] 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 myristic, palmitic, oleic or stearic acid.

[0161] 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 phosphatidylinositol, 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.

[0162] 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.

[0163] 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[oleoyloxy]-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-propane, 1,2-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).

[0164] 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, , *Journal of the American Oil Chemists Society* 55:539-545; Heaton *et al.*, , 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.

[0165] 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, cerebroside, 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

[0166] 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

[0167] 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

[0168] 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- β -D-maltoside, tridecan-3-yloxy- β -D-maltoside, tridecan-2-yloxy- β -D-maltoside, n-dodecyl- β -D-maltoside (DDM), n-octyl- β -D-glucoside, n-nonyl- β -D-glucoside, n-decyl- β -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.

[0169] In some embodiments, the apolar moiety is an acyl or a diacyl chain.

[0170] In some embodiments, the sugar is a modified sugar or a substituted sugar.

6.1.4. Formulations

[0171] Lipid binding protein molecules and lipid binding protein-based complexes comprising a lipid binding protein molecule 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).

[0172] 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

[0173] Subjects who can be treated according to the methods described herein are preferably mammals, most preferably human.

[0174] In some aspects, the subject has or is at risk of sepsis (e.g., septic shock, e.g. septic shock following trauma, for example abdominal trauma, or septic shock not following trauma, e.g., post-operative sepsis), sepsis-induced cognitive deficiency, sepsis with risk (e.g., high risk) of developing acute kidney injury, a bacterial infection (e.g. a gram-positive bacterial infection or a gram-negative bacterial infection), optionally with an antibiotic-resistant bacterium (e.g., MRSA), a urinary tract infection, a blood infection, a post-surgical infection, gastrointestinal perforation, a perforated duodenal ulcer, a perforated bowel, pneumonia, e.g., hospital acquired pneumonia, a pancreatitis, e.g., necrotizing pancreatitis, a viral infection (e.g., a SARS-CoV-2 (COVID-19) infection or an influenza virus infection), acute myocardial infarction (AMI), cytokine release syndrome (CRS), ischemia reperfusion-induced tissue injury, post-operative inflammation, sepsis-induced acute kidney injury (AKI), hypoalbuminemia (e.g., hypoalbuminemia associated with a vitamin deficiency, hypoalbuminemia associated with inflammatory bowel disease (IBD), hypoalbuminemia associated with kidney disease, hypoalbuminemia associated with an infection, optionally wherein the infection is a gram-positive bacterial infection, a gram-negative bacterial infection, or a viral infection such as a SARS-CoV-2 (COVID-19) infection or influenza infection, hypoalbuminemia associated with stress, hypoalbuminemia associated with thyroid disease, hypoalbuminemia associated with diabetes, hypoalbuminemia associated with nephrotic syndrome, hypoalbuminemia associated with lupus, hypoalbuminemia associated with cirrhosis, hypoalbuminemia associated with liver disease, hypoalbuminemia associated with heart failure, or hypoalbuminemia associated with malnutrition, cytokine release syndrome (CRS; cytokine storm), risk of CRS, acute kidney injury (AKI), risk of developing AKI, acute respiratory distress syndrome (ARDS), or risk of developing ARDS.

[0175] In some aspects, the subject has or is at risk of graft-versus-host-disease (GVHD). A subject having or at risk of GVHD can be a subject who has received a stem cell transplant, bone marrow transplant, or organ transplant.

[0176] In some aspects, the subject has asthma, e.g., acute severe asthma.

[0177] In some aspects, the subject has or is at risk of a bacterial infection. Examples of bacteria that commonly cause infection and sepsis (e.g., septic shock) include *Staphylococcus aureus*, *Escherichia coli*, *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* (GBD 2019 Antimicrobial Resistance Collaborators, 2023, *Lancet* 400(10369):2221-2248), *Acinetobacter baumannii*, *Bacteroides fragilis*, and *Proteus mirabilis*.

[0178] In some aspects, the subject has or is at risk of cytokine release syndrome (CRS, cytokine storm). In some embodiments, CRS is secondary to an infection, such as a bacterial infection or a viral infection.

[0179] In some embodiments, the subject has a SOFA score of 1 to 24 before treatment with a lipid binding protein molecule, *e.g.*, a score of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24 (see, Vincent *et al.* 1996, Intensive Care Med, 22:707–710).

[0180] In some embodiments, the subject has a SOFA score of 2 to 24, such as 2 to 16, before treatment with a lipid binding protein molecule (*e.g.*, ApoA-I), *e.g.*, a SOFA score of 2 to 3, 2 to 4, 3 to 4, 2 to 5, 3 to 5, 4 to 5, 2 to 6, 3 to 6, 4 to 6, 5 to 6, 2 to 7, 3 to 7, 4 to 7, 5 to 7, 6 to 7, 2 to 8, 3 to 8, 4 to 8, 5 to 8, 6 to 8, 7 to 8, 2 to 9, 3 to 9, 4 to 9, 5 to 9, 6 to 9, 7 to 9, 8 to 9, 2 to 10, 3 to 10, 4 to 10, 5 to 10, 6 to 10, 7 to 10, 8 to 10, 9 to 10, 2 to 11, 3 to 11, 4 to 11, 5 to 11, 6 to 11, 7 to 11, 8 to 11, 9 to 11, 10 to 11, 2 to 12, 3 to 12, 4 to 12, 5 to 12, 6 to 12, 7 to 12, 8 to 12, 9 to 12, 10 to 12, 11 to 12, 2 to 13, 3 to 13, 4 to 13, 5 to 13, 6 to 13, 7 to 13, 8 to 13, 9 to 13, 10 to 13, 11 to 13, 12 to 13, 2 to 14, 3 to 14, 4 to 14, 5 to 14, 6 to 14, 7 to 14, 8 to 14, 9 to 14, 10 to 14, 11 to 14, 12 to 14, 13 to 14, 2 to 15, 3 to 15, 4 to 15, 5 to 15, 6 to 15, 7 to 15, 8 to 15, 9 to 15, 10 to 15, 11 to 15, 12 to 15, 13 to 15, 14 to 15, 2 to 16, 3 to 16, 4 to 16, 5 to 16, 6 to 16, 7 to 16, 8 to 16, 9 to 16, 10 to 16, 11 to 16, 12 to 16, 13 to 16, 14 to 16, or 15 to 16.

[0181] In one aspect, the disclosure provides a method of increasing the probability of survival of a subject with a SOFA score of 2 to 24, such as 2 to 16 or any of the subranges thereof set forth in the preceding paragraph, comprising administering to the subject a lipid binding protein molecule (*e.g.*, ApoA-I), the increased probability of survival relative to subjects of the same or similar age, underlying medical conditions, and SOFA score who receive the standard of care and to whom the lipid binding protein molecule (*e.g.*, ApoA-I) is not administered. Increased survival can be determined over a period of 30 days to 1 year (*e.g.*, 30 days, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, or 12 months) from the date of first administration of the lipid binding protein molecule (*e.g.*, ApoA-I). In some embodiments, increased survival is determined over 30 days (*i.e.*, is 30-day survival).

6.3. Measurement Assays and Target Levels

6.3.1. ApoA-I Measurement

[0182] ApoA-I levels can be measured in serum, plasma, or other blood samples from a subject. In some embodiments, the blood sample is a serum sample. ApoA-I levels can be measured, for example, by enzyme-linked immunoassay (ELISA), immunoturbidometry, or immunonephelometry making use of anti-ApoA-I antibodies. An exemplary ELISA kit for measuring ApoA-I levels in blood samples is available from R&D Systems, Minneapolis MN, USA (catalog no. DAPA10). Commercial blood testing laboratories routinely perform immunoturbidometric and immunonephelometric testing for ApoA-I (*e.g.*, Quest Diagnostics test code 5223; Labcorp test code 016873), and such tests can be used. Blood samples used for testing can be serum samples, plasma samples, and whole blood samples. In some embodiments, serum samples are used.

[0183] A target ApoA-I level or range can be defined with reference to healthy subjects. A normal ApoA-I level or range in healthy subjects can vary between males and females. Generally, a normal ApoA-I level or the bounds of a normal ApoA-I range are roughly 0.1 g/L higher for females than for males. In

some embodiments, a target ApoA-I level or range is a serum ApoA-I level or range, for example a normal ApoA-I level or range in healthy subjects.

[0184] In some embodiments, a level of 0.8 g/L is used as a cutoff for normal (such that a level of > 0.8 g/L is considered normal). In other embodiments, a level of 0.9 g/L is used as a cutoff for normal. In other embodiments, a cutoff of 1.0 g/L is used as a cutoff for normal. In other embodiments, a cutoff of 1.1 g/L is used as a cutoff for normal. In other embodiments, a cutoff of 1.2 g/L is used as a cutoff for normal. In other embodiments, a cutoff of 1.3 g/L is used as a cutoff for normal. In some embodiments, 1.8 g/L is used as an upper cutoff for a normal level. In other embodiments, 1.9 g/L is used as an upper cutoff for a normal level. In some embodiments, 2.0 g/L is used as an upper cutoff for a normal level. In some embodiments, 2.1 g/L is used as an upper cutoff for a normal level.

[0185] In some embodiments, a target ApoA-I level is an ApoA-I level (e.g., serum level) of 1.0 g/L or 1.1 g/L.

[0186] In some embodiments, a target ApoA-I level (e.g., serum level) is between 1.0 g/L and 2.0 g/L, such as from 1.0 g/L to 1.1 g/L, from 1.0 g/L to 1.2 g/L, from 1.1 g/L to 1.2 g/L, from 1.0 g/L to 1.3 g/L, from 1.1 g/L to 1.3 g/L, from 1.2 g/L to 1.3 g/L, from 1.0 g/L to 1.4 g/L, from 1.1 g/L to 1.4 g/L, from 1.2 g/L to 1.4 g/L, from 1.3 g/L to 1.4 g/L, from 1.0 g/L to 1.5 g/L, from 1.1 g/L to 1.5 g/L, from 1.2 g/L to 1.5 g/L, from 1.3 g/L to 1.5 g/L, from 1.4 g/L to 1.5 g/L, from 1.0 g/L to 1.6 g/L, from 1.1 g/L to 1.6 g/L, from 1.2 g/L to 1.6 g/L, from 1.3 g/L to 1.6 g/L, from 1.4 g/L to 1.6 g/L, from 1.5 g/L to 1.6 g/L, from 1.0 g/L to 1.7 g/L, from 1.1 g/L to 1.7 g/L, from 1.2 g/L to 1.7 g/L, from 1.3 g/L to 1.7 g/L, from 1.4 g/L to 1.7 g/L, from 1.5 g/L to 1.7 g/L, from 1.6 g/L to 1.7 g/L, from 1.0 g/L to 1.8 g/L, from 1.1 g/L to 1.8 g/L, from 1.2 g/L to 1.8 g/L, from 1.3 g/L to 1.8 g/L, from 1.4 g/L to 1.8 g/L, from 1.5 g/L to 1.8 g/L, from 1.6 g/L to 1.8 g/L, from 1.7 g/L to 1.8 g/L, from 1.0 g/L to 1.9 g/L, from 1.1 g/L to 1.9 g/L, from 1.2 g/L to 1.9 g/L, from 1.3 g/L to 1.9 g/L, from 1.4 g/L to 1.9 g/L, from 1.5 g/L to 1.9 g/L, from 1.6 g/L to 1.9 g/L, from 1.7 g/L to 1.9 g/L, from 1.8 g/L to 1.9 g/L, from 1.0 g/L to 2.0 g/L, from 1.1 g/L to 2.0 g/L, from 1.2 g/L to 2.0 g/L, from 1.3 g/L to 2.0 g/L, from 1.4 g/L to 2.0 g/L, from 1.5 g/L to 2.0 g/L, from 1.6 g/L to 2.0 g/L, from 1.7 g/L to 2.0 g/L, from 1.8 g/L to 2.0 g/L, from 1.9 g/L to 2.0 g/L, from 1.1 g/L to 2.1 g/L, from 1.2 g/L to 2.1 g/L, from 1.3 g/L to 2.1 g/L, from 1.4 g/L to 2.1 g/L, from 1.5 g/L to 2.1 g/L, from 1.6 g/L to 2.1 g/L, from 1.7 g/L to 2.1 g/L, from 1.8 g/L to 2.1 g/L, from 1.9 g/L to 2.1 g/L, or from 2.0 g/L to 2.1 g/L. Each of the foregoing ranges can be used as a target ApoA-I (e.g., target serum ApoA-I) range.

[0187] In some embodiments, a target ApoA-I range is a serum ApoA-I level of 1.0 g/L to 2.0 g/L, 1.1 g/L to 1.7 g/L, 1.2 g/L to 1.8 g/L, 1.0 g/L to 1.8 g/L, 1.1 g/L to 1.8 g/L, or 1.1 g/L to 2.1 g/L.

6.3.2. HDL Measurement

[0188] HDL levels can be measured in serum, plasma, or other blood samples from a subject. In some embodiments, the blood sample is a serum sample. HDL levels can be measured as HDL cholesterol (HDL-C) or HDL particle number (HDL-P), with HDL-C being more common. HDL-C levels can be measured, for example, by enzymatic assays, e.g., enzymatic colorimetric assays. Common HDL-C (HDL cholesterol) tests react HDL-C with the enzymes cholesterol oxidase (CHOD) and cholesterol esterase (CHER) after making non-HDL lipoproteins such as LDL, VLDL, and chylomicron (CM) inaccessible to the enzymes with polyanions and detergent (e.g., polyvinyl sulfonic acid (PVS) and polyethylene-glycol-methyl ether (PEGME)). HDL-C reacts with the enzymes to form hydrogen peroxide which can be detected and quantified photometrically through a Trinder reaction. Commercially available

laboratory tests can be used to determine HDL-C levels (e.g., Quest Diagnostics test code 608; Labcorp test code 001925). HDL-C testing meters, which require a minimal amount of blood and provide a fast result, are commercially available and can be also used. HDL-C testing meters typically have a test strip and provide a result based on a reading of light reflected off a test strip that has changed color after blood is applied. Exemplary HDL-C testing meters include the CardioChek® PA test system (PTS Diagnostics) and Cholestech LDX™ analyzer (Abbott). HDL-P can be measured by nuclear magnetic resonance (NMR). Commercially available laboratory tests can be used to determine HDL-P levels (e.g., Labcorp test code 818542).

[0189] HDL-C levels below 40 mg/dL (male) or below 50 mg/dL (female) are considered to be low according to the guidelines published by the United States National Institutes of Health National Library of Medicine (medlineplus.gov/cholesterollevelswhatyouneedtoknow.html). In some embodiments, a target HDL-C level is 50 mg/dL, 45 mg/dL, 40 mg/dL, or 35 mg/dL. A target HDL-C level can be set the same for male and female subjects, or the target HDL-C level can be different for male and female subjects, for example 40 mg/dL for male subjects and 50 mg/dL for female subjects.

6.4. Dosing Regimens

[0190] In some aspects, the methods of the disclosure relate to personalized medicine approaches, in which a subject's ApoA-I level is measured (e.g., before and/or during a course of treatment) and dosing of lipid binding protein molecules such as ApoA-I (including in the form of an ApoA-I based complex such as CER-001) is performed to increase and/or maintain ApoA-I level at or above a target value (e.g., a target corresponding to a normal ApoA-I level in healthy subjects as described in Section 6.3.1) and/or within a target range (e.g., a target corresponding to a normal ApoA-I range in healthy subjects as described in Section 6.3.1).

[0191] As an alternative to measuring a subject's ApoA-I level (or in addition to measuring a subject's ApoA-I level), a subject's high density lipoprotein (HDL) level (e.g., HDL-C) can be measured (e.g., as described in Section 6.3.2). Low HDL levels generally indicate that a subject's ApoA-I level is low. Thus, measuring a subject's HDL level can be useful, for example, if an ApoA-I test is unavailable or if a more rapid result can be obtained for an HDL test compared to an ApoA-I test. When HDL levels are measured and are found to be below a target HDL level (e.g., a target HDL level corresponding to a normal HDL level), the subject can be administered one or more doses of the lipid binding protein molecule. It is believed that normal or high HDL levels do not necessarily indicate that a subject's ApoA-I level is normal or high, as it is believed that in some cases a subject can have ApoA-I poor HDL. Thus, if a measured HDL level is at or above a target HDL level, a follow-up ApoA-I test can optionally be performed to determine if the subject's ApoA-I level is in fact low. In some embodiments, treatment is administered based on the results of the HDL test without waiting for the results of a follow-up ApoA-I test. Once the results of the ApoA-I test are obtained, treatment can be continued or modified based on the results of the ApoA-I test, e.g., if the subject's ApoA-I level measured in the follow-up test is below a target ApoA-I level or within a target ApoA-I range treatment can be continued, and if the ApoA-I level measured in the follow-up test is at or above the target ApoA-I level treatment can be discontinued or otherwise modified.

[0192] The subject can be as described in Section 6.2. ApoA-I or HDL levels can be measured and compared to target levels or ranges as described in Section 6.3.

[0193] The subject's ApoA-I level or HDL level can be measured before a course of treatment. This information can be used to assess a suitable dosing regimen, *e.g.*, an induction regimen as described in Section 6.4.1.

[0194] Alternatively, or in addition, the subject's ApoA-I level or HDL level can be measured during a course of treatment. This can be informative as to how the subject is responding to the treatment, *e.g.*, whether the subject is clearing HDL cholesterol and/or ApoA-I at a higher rate than in a normal subject (*e.g.*, in subjects suffering from acute indications such as sepsis, a higher rate of ApoA-I clearance is believed to reflect increased toxin clearance), and can be used to assess whether to continue administering the lipid binding protein molecule and/or to adjust the frequency and/or dose administered.

[0195] For example, a subject's ApoA-I level (*e.g.*, serum level) or HDL level can be measured before a lipid-binding protein (*e.g.*, ApoA-I, *e.g.*, in an ApoA-I based complex such as CER-001) is administered for the first time and, if the measured value is below the target value or range, the subject can be administered one or more doses of the lipid-binding protein molecule. As another example, a subject's ApoA-I level or HDL level can be measured after a lipid-binding protein (*e.g.*, ApoA-I, *e.g.*, in an ApoA-I based complex such as CER-001) is administered and, if the subject's serum ApoA-I level is below a target level or below a target range and/or the subject's HDL level is below a target level, additional doses of the lipid-binding protein molecule can be administered to the subject to increase the subject's ApoA-I level or HDL level. When an ApoA-I level or HDL level is measured during the course of a treatment and low levels of ApoA-I or HDL level are observed, the course of treatment can be adjusted to increase the subject's ApoA-I level or HDL level, for example, by increasing the dose and/or dose frequency and/or duration of treatment (*e.g.*, extending an initial three-day course of treatment beyond three days). As another example, if a subject has completed an initial course of treatment with a lipid binding protein molecule such as ApoA-I (*e.g.*, CER-001), an ApoA-I level or HDL level can be measured in the subject following the initial course of treatment (*e.g.*, at the end of the treatment or after a period of time, for example one week), and if the measured ApoA-I level or HDL level is below a target level or below a target range, the subject can be retreated with the lipid binding protein molecule. Without being bound by theory, such personalized medicine approaches are believed to be particularly useful in treating acute conditions such as sepsis with a lipid-binding protein (*e.g.*, ApoA-I, *e.g.*, in an ApoA-I based complex such as CER-001), as the clearance rates of a lipid-binding protein are believed to generally be more variable between subjects with sepsis than subjects with other, non-acute conditions. In some embodiments, the methods of the disclosure are performed in a critical care context, for example in an intensive care unit of a hospital.

[0196] In some aspects, the methods of the disclosure comprise administering a lipid binding protein molecule such as ApoA-I (*e.g.*, in an ApoA-I based complex such as CER-001) to a subject according to an initial treatment regimen followed by measurement of ApoA-I level at the conclusion of the initial treatment regimen. For example, the initial regimen can be for three days or more (*e.g.*, four days or five days). If the measured ApoA-I level is below a target level or below a target range, treatment with the lipid binding protein molecule can be continued by administered one or more additional doses (*e.g.*, over one, two, or more than two days). If the measured ApoA-I level is above a target value or within a target range, treatment with ApoA-I can be discontinued. Alternatively, if the measured ApoA-I level is above a target value or within a target range the subject can be administered the lipid binding protein molecule at

a lower dose and/or frequency than in the initial treatment regimen. Further exemplary courses of treatment are illustrated in FIGS. 34A-34D.

[0197] In some aspects, methods of the disclosure can comprise administering ApoA-I to a subject in an amount sufficient to elevate a subject's ApoA-I level to a normal level (e.g., a serum level greater than 1.1 g/L) or range (e.g., 1.1 g/L to 1.7 g/L, 1.2 g/L to 1.8 g/L, 1.0 g/L to 1.8 g/L, or 1.1 g/L to 1.8 g/L). In some embodiments, the amount of administered ApoA-I is sufficient to increase a subject's ApoA-I level to and/or maintain a normal ApoA-I level or range until the subject's condition improves and/or for a predetermined period of time (e.g., 3, days, 4 days, 5 days, or more than 5 days). Preferably, the amount and/or frequency of ApoA-I administration is sufficient to maintain normal ApoA-I levels or ranges during treatment.

[0198] In the methods of the disclosure, individual doses of the lipid binding protein molecule are typically administered daily or more frequently than once per day (e.g., twice daily administration). Alternatively, for example in a critical care context (e.g., for a subject in a hospital's intensive care unit), a lipid binding protein molecule can be administered by continuous infusion rather than individual doses.

[0199] In some aspects, methods of the disclosure entail optionally administering one or more doses of a lipid binding protein molecule to a subject; measuring the subject's ApoA-I level (typically serum ApoA-I levels, although other blood samples can also be used, for example whole blood or plasma), and administering one dose or multiple doses of a lipid binding protein molecule (e.g., ApoA-I) if the measured ApoA-I level is below a target ApoA-I level or a target ApoA-I range. Alternatively (or in addition) to measuring a subject's ApoA-I level, a subject's HDL level can be measured (e.g., a serum, plasma, or whole blood HDL level), and one dose or multiple doses of a lipid binding protein molecule (e.g., ApoA-I) can be administered if the measured HDL level is below a target HDL level.

[0200] When one or more doses of the lipid binding protein molecule are administered to the subject prior to measuring the subject's ApoA-I level or HDL level, the subject's ApoA-I level or HDL level can be measured, for example, 0.5 day to one week after the most recent administration of the lipid binding protein molecule. In some embodiments, the subject's ApoA-I or HDL level is measured 0.5 day to 1 day after the most recent administration of the lipid binding protein molecule, one day after the most recent administration of the lipid binding protein molecule, two days after the most recent administration of the lipid binding protein molecule, three days after the most recent administration of the lipid binding protein molecule, or more than three days after the most recent administration of the lipid binding protein molecule (e.g., four days, five days, six days, or one week). In some embodiments, a subject's ApoA-I or HDL level is measured after a final administration of the lipid binding protein molecule during an induction regimen.

[0201] In some embodiments, the subject has completed a course of treatment with the lipid binding protein molecule (e.g., for sepsis) and is to undergo a subsequent surgical procedure. The subject's ApoA-I or HDL level can be measured before or after surgery, and the subject can be retreated with the lipid binding protein molecule (with the same or different regimen of lipid binding protein molecule) if the subject's ApoA-I level is below a target value or range (e.g., below a normal value or range) or if the subject's HDL level is below a target value.

[0202] In some embodiments, one or more doses of the lipid binding protein molecule are administered (e.g., following an HDL test result that is below an HDL target value) while awaiting results of an ApoA-I test. Administration of one or more doses of the lipid binding protein before the result of an ApoA-I test is

known can be used, for example, in situations in which the ApoA-I test will take a significant amount of time or is otherwise delayed.

[0203] ApoA-I or HDL levels can be measured at any desired frequency, such as twice daily, once daily, every other day, or every third day. In some embodiments, the time period between measurements can be constant or essentially constant (e.g., can vary by a few minutes or hours according to standard procedures in a hospital or other clinical setting). In some embodiments, the time period between measurements can be chosen to vary according to the judgement of a clinician (e.g., to coincide with the timing of other clinical measurements as part of a subject's treatment).

[0204] In some embodiments, the time period between measurements can be increased if the subject's ApoA-I or HDL levels have been above a target (e.g., normal) level for one measurement, two consecutive measurements, or three consecutive measurements, among other possibilities that will be apparent to persons of ordinary skill in the art having the benefit of the present disclosure. Additionally or alternatively, the time period between measurements can be increased if the subject's ApoA-I or HDL levels increased over one interval between measurements, two consecutive intervals between measurements, or three consecutive measurements, among other possibilities.

[0205] In some embodiments, the time period between measurements can be decreased if the subject's ApoA-I or HDL levels have been below a target level for one measurement, two consecutive measurements, or three consecutive measurements, among other possibilities. Additionally or alternatively, the time period between measurements can be decreased if the subject's ApoA-I or HDL levels decreased over one interval between measurements, two consecutive intervals between measurements, or three consecutive measurements, among other possibilities that will be apparent to persons of ordinary skill in the art having the benefit of the present disclosure.

[0206] When a measured ApoA-I level is below a target level or below a target range, the subject can be administered an amount of a lipid binding protein effective to increase the subject's ApoA-I level to or above the target value or within the target range.

[0207] When a measured HDL level is below a target level, the subject can be administered an amount of a lipid binding protein effective to increase the subject's HDL level to or above the target value.

[0208] Measuring a subject's ApoA-I or HDL level can be performed, for example, before the first administration of the lipid binding protein molecule to the subject; simultaneously therewith, one day after the first administration, two days after the first administration, three days after the first administration, or after the final administration of an induction regimen, among other possibilities.

[0209] In some embodiments, the time period between administrations of a lipid binding protein molecule (e.g., ApoA-I) can be increased if the subject's ApoA-I levels have been above a normal level or range for one measurement, two consecutive measurements, or three consecutive measurements, among other possibilities that will be apparent to persons of ordinary skill in the art having the benefit of the present disclosure. Additionally or alternatively, the time period between administrations of a lipid binding protein molecule (e.g., ApoA-I) can be increased if the subject's ApoA-I levels increased over one interval between measurements, two consecutive intervals between measurements, or three consecutive measurements, among other possibilities. The time period between administrations can be similarly adjusted when HDL levels rather than ApoA-I levels are used.

[0210] In some embodiments, the time period between administrations of a lipid binding protein molecule (e.g., ApoA-I) can be decreased if the subject's ApoA-I levels have been below a normal level

or range for one measurement, two consecutive measurements, or three consecutive measurements, among other possibilities. Additionally or alternatively, the time period between administrations of a lipid binding protein molecule (e.g., ApoA-I) can be decreased if the subject's ApoA-I levels decreased over one interval between measurements, two consecutive intervals between measurements, or three consecutive measurements, among other possibilities that will be apparent to persons of ordinary skill in the art having the benefit of the present disclosure. The time period between administrations can be similarly adjusted when HDL rather than ApoA-I levels are used.

[0211] The administering of lipid binding protein molecules can be performed at doses, dose frequencies, and routes of administration as described herein. In some embodiments, if measuring indicates that a subject's ApoA-I level is below a target (e.g., normal) level or range or that a subject's HDL level is below a target level, the subject receives a first dosage amount of the lipid binding protein molecule; if measuring indicates that the subject's ApoA-I level is at or above the target level or within the target range or that the subject's HDL level is at or above the target level, the subject receives a second dosage amount of the lipid binding protein molecule which is less than the first dosage amount.

[0212] In some embodiments, the first dosage is 5 mg/kg, 10 mg/kg, or 20 mg/kg on a weight lipid binding protein molecule to body weight basis, and the second dosage is 5 mg/kg, or 10 mg/kg, provided the second dosage is less than the first.

[0213] In some embodiments, if measuring indicates that a subject's ApoA-I level is below a target level or range, the subject receives a first dosage amount of the lipid binding protein molecule; if measuring indicates that the subject's ApoA-I level is at or above the target level or within the target range, the subject receives a second dosage amount of the lipid binding protein molecule which is less than the first dosage amount.

[0214] In some embodiments, if measuring indicates that a subject's ApoA-I level is below a target level or range, the subject receives one or more doses of the lipid binding protein molecule at a first frequency; if measuring indicates that the subject's ApoA-I level is at or above the target level or within the target range, the subject receives one or more doses of the lipid binding protein molecule at a second frequency less than the first frequency.

[0215] Measurement of the subject's ApoA-I level and thereafter administering one or more doses of the lipid binding protein molecule can be repeated, for example until the subject's condition has improved (e.g., a subject in the ICU is well enough to be discharged from the ICU), or until the subject's ApoA-I level is above the target value or within the target range.

[0216] In one embodiment, the subject is administered the lipid binding protein molecule at least once per day (e.g., once or twice per day) on days 1, 2, and 3 of a treatment regimen, and the ApoA-I level is measured on day 4.

[0217] In one embodiment, the subject is administered the lipid binding protein molecule at least once per day (e.g., once or twice per day) on days 1, 2, 3, and 4 of a treatment regimen, and the ApoA-I level is measured on day 5.

[0218] In one embodiment, the subject is administered the lipid binding protein molecule at least once per day (e.g., once or twice per day) on days 1, 2, 3, 4, and 5 of a treatment regimen, and the ApoA-I level is measured on day 6.

[0219] In one embodiment, the subject is administered the lipid binding protein molecule at least once per day (e.g., once or twice per day) on days 1, 2, 3, 4, 5, and 6 of a treatment regimen, and the ApoA-I level is measured on day 7.

[0220] In one embodiment, the subject is administered the lipid binding protein molecule at least once per day (e.g., once or twice per day) on days 1, 2, 3, 4, 5, 6, and 7 of a treatment regimen, and the ApoA-I level is measured on day 8.

[0221] In one embodiment, the subject is administered the lipid binding protein molecule at least once per day (e.g., once or twice per day) on days 1, 2, 3, and 6 of a treatment regimen, and the ApoA-I level is measured on day 4 and/or day 7.

[0222] In some embodiments, subjects can be identified as having a high ApoA-I clearance rate. The identification can comprise evaluating the subject's ApoA-I level after administering an amount of ApoA-I (e.g., as a single dose or multiple doses) and comparing the measured ApoA-I level to a standard value (e.g., generated from a population having the same condition as the subject). If the measured value is lower than the standard value, the subject can be identified as having a high ApoA-I clearance rate.

[0223] Identifying subjects as having a high ApoA-I clearance rate can provide useful information to a clinician. In some embodiments, the dosage of the lipid binding protein molecule per administration and/or the frequency of administration is selected in response to the subject being identified as having a high ApoA-I clearance rate. For example, if a subject is identified as having a high ApoA-I clearance rate, a higher dose and/or administration frequency can be selected as compared to a subject not identified as having a high ApoA-I clearance rate.

[0224] In some embodiments, the amount of lipid binding protein molecule delivered by each dose (e.g., administered prior to an ApoA-I measurement and/or subsequent to an ApoA-I measurement) can be from 5 mg/kg to 40 mg/kg on a protein weight basis. In some embodiments, the amount of lipid binding protein molecule delivered by each dose can be from 5 mg/kg to 10 mg/kg on a protein weight basis. In some embodiments, the amount of lipid binding protein molecule delivered by each dose can be from 5 mg/kg to 20 mg/kg on a protein weight basis. In some embodiments, the amount of lipid binding protein molecule delivered by each dose can be from 10 mg/kg to 30 mg/kg on a protein weight basis. In some embodiments, the amount of lipid binding protein molecule delivered by each dose can be from 10 mg/kg to 20 mg/kg on a protein weight basis. In some embodiments, a dose is 5 mg/kg on a protein weight basis. In some embodiments, a dose is 6 mg/kg on a protein weight basis. In some embodiments, a dose is 7 mg/kg on a protein weight basis. In some embodiments, a dose is 8 mg/kg on a protein weight basis. In some embodiments, a dose is 9 mg/kg on a protein weight basis. In some embodiments, a dose is 10 mg/kg on a protein weight basis. In some embodiments, a dose is 11 mg/kg on a protein weight basis. In some embodiments, a dose is 12 mg/kg on a protein weight basis. In some embodiments, a dose is 13 mg/kg on a protein weight basis. In some embodiments, a dose is 14 mg/kg on a protein weight basis. In some embodiments, a dose is 15 mg/kg on a protein weight basis. In some embodiments, a dose is 16 mg/kg on a protein weight basis. In some embodiments, a dose is 17 mg/kg on a protein weight basis. In some embodiments, a dose is 18 mg/kg on a protein weight basis. In some embodiments, a dose is 19 mg/kg on a protein weight basis. In some embodiments, a dose is 20 mg/kg on a protein weight basis. In some embodiments, a dose is 21 mg/kg on a protein weight basis. In some embodiments, a dose is 22 mg/kg on a protein weight basis. In some embodiments, a dose is 23 mg/kg on a protein weight basis. In some embodiments, a dose is 24 mg/kg on a protein weight basis. In some embodiments, a dose is 25

mg/kg on a protein weight basis. In some embodiments, a dose is 26 mg/kg on a protein weight basis. In some embodiments, a dose is 27 mg/kg on a protein weight basis. In some embodiments, a dose is 28 mg/kg on a protein weight basis. In some embodiments, a dose is 29 mg/kg on a protein weight basis. In some embodiments, a dose is 30 mg/kg on a protein weight basis. In some embodiments, a dose is 31 mg/kg on a protein weight basis. In some embodiments, a dose is 32 mg/kg on a protein weight basis. In some embodiments, a dose is 33 mg/kg on a protein weight basis. In some embodiments, a dose is 34 mg/kg on a protein weight basis. In some embodiments, a dose is 35 mg/kg on a protein weight basis. In some embodiments, a dose is 36 mg/kg on a protein weight basis. In some embodiments, a dose is 37 mg/kg on a protein weight basis. In some embodiments, a dose is 38 mg/kg on a protein weight basis. In some embodiments, a dose is 39 mg/kg on a protein weight basis. In some embodiments, a dose is 40 mg/kg on a protein weight basis.

[0225] In some embodiments, the lipid binding protein molecule is administered according to an induction and, optionally, a consolidation regimen as described in Sections 6.4.1 and 6.4.2, respectively. For example, an ApoA-I level can be measured after an induction regimen and, if the measured ApoA-I level is below a target level or below a target range the subject can be administered a consolidation regimen.

[0226] In some embodiments, the lipid binding protein molecule can be administered in a single phase, for example following an ApoA-I measurement performed prior to any administration of the lipid binding protein molecule.

[0227] In some embodiments, the subject is not treated with the lipid binding protein molecule according to a maintenance regimen, *e.g.*, a regimen comprising long-term (*e.g.*, one month or longer) administration of the lipid binding protein molecule.

[0228] The lipid binding protein molecule (*e.g.*, ApoA-I) administration regimens of the disclosure can last up to one week, one week, or more than one week (*e.g.*, two weeks or three weeks).

[0229] The dose of a lipid binding protein molecule (*e.g.*, ApoA-I) administered to a subject 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 molecule (*e.g.*, ApoA-I) to be administered to a subject is calculated based upon the amount of the lipid binding protein molecule (*e.g.*, ApoA-I) 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).

[0230] The same amount of lipid binding protein can be administered for each individual dose. Alternatively, the amount of lipid binding protein can vary between individual doses. For example, one or more individual doses can be administered at a first dose amount and, subsequently, one or more individual doses can be administered at a different, second dose amount. For example, a first dose amount can be 5 mg/kg (on a protein weight basis) and the second dose amount can be a higher amount, for example 10 mg/kg (on a protein weight basis). As another example, a first dose amount can be 10 mg/kg (on a protein weight basis) and the second dose amount can be a higher amount, for example 15 mg/kg (on a protein weight basis). As another example, a first dose amount can be 10 mg/kg (on a protein weight basis) and the second dose amount can be a higher amount, for example 20 mg/kg

(on a protein weight basis). As another example, a first dose amount can be 15 mg/kg (on a protein weight basis) and the second dose amount can be a higher amount, for example 20 mg/kg (on a protein weight basis). As another example, a first dose amount can be 20 mg/kg (on a protein weight basis) and the second dose amount can be a lower amount, for example 10 mg/kg (on a protein weight basis). As another example, a first dose amount can be 20 mg/kg (on a protein weight basis) and the second dose amount can be a lower amount, for example 5 mg/kg (on a protein weight basis). As another example, a first dose amount can be 10 mg/kg (on a protein weight basis) and the second dose amount can be a lower amount, for example 5 mg/kg (on a protein weight basis). Different dose amounts can be selected, for example, following measurement of a subject's ApoA-I level. If a measured ApoA-I level following administration of a first dose amount is below a target level or below a target range, a second, higher dose amount can be selected for subsequent administration. Conversely, if the measured ApoA-I level following administration of a first dose amount is above the target level or above the target range, a second, lower dose amount can be selected for subsequent administration.

[0231] In some aspects, a lipid binding protein molecule (e.g., ApoA-I) 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).

[0232] In particular embodiments, the dosage of a lipid binding protein molecule (e.g., ApoA-I) is 300 mg to 400 mg, 300 mg to 500 mg, 300 mg to 600 mg, 300 mg to 800 mg, 300 mg to 1000 mg, 300 mg to 1200 mg, 300 mg to 1500 mg, 300 mg to 2000 mg, 300 mg to 2400 mg, 300 mg to 3000 mg, 400 mg to 500 mg, 400 mg to 600 mg, 400 mg to 800 mg, 400 mg to 1000 mg, 400 mg to 1200 mg, 400 mg to 1500 mg, 400 mg to 2000 mg, 400 mg to 2400 mg, 400 mg to 3000 mg, 400 mg to 4000 mg, 500 mg to 600 mg, 500 mg to 800 mg, 500 mg to 1000 mg, 500 mg to 1200 mg, 500 mg to 1500 mg, 500 mg to 2000 mg, 500 mg to 2400 mg, 500 mg to 3000 mg, 500 mg to 4000 mg, 600 mg to 800 mg, 600 mg to 1000 mg, 600 mg to 1200 mg, 600 mg to 1500 mg, 600 mg to 2000 mg, 600 mg to 2400 mg, 600 mg to 3000 mg, 600 mg to 4000 mg, 800 mg to 1000 mg, 800 mg to 1200 mg, 800 mg to 1500 mg, 800 mg to 2000 mg, 800 mg to 2400 mg, 800 mg to 3000 mg, 800 mg to 4000 mg, 1000 mg to 1200 mg, 1000 mg to 1500 mg, 1000 mg to 2000 mg, 1000 mg to 2400 mg, 1000 mg to 3000 mg, 1000 mg to 4000 mg, 1200 mg to 1500 mg, 1200 mg to 2000 mg, 1200 mg to 2400 mg, 1200 mg to 3000 mg, 1200 mg to 4000 mg, 1500 mg to 2000 mg, 1500 mg to 2400 mg, 1500 mg to 3000 mg, 1500 mg to 4000 mg, 2000 mg to 2400 mg, 2000 mg to 3000 mg, 2000 mg to 4000 mg, 2400 mg to 3000 mg, 2400 mg to 4000 mg, or 3000 mg to 4000 mg per administration (on a protein weight basis).

[0233] A lipid binding protein molecule (e.g., ApoA-I) 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 ml and 1L, such as between 125 ml and 250 ml, between 250 ml and 500 ml, or between 500 ml and 1L. In some embodiments, the total volume is 125 ml, 250 ml, 500 ml, or 1000 ml. A total volume can be readily selected based on the total dose of lipid binding protein molecule to be administered. 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 molecule (e.g., ApoA-I) can 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 (e.g., over a period of one-

half hour to one hour), or by a single bolus injection. In an embodiment, a lipid binding protein molecule (e.g., ApoA-I) 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 molecule (e.g., ApoA-I) is administered as an infusion over a 24-hour period.

6.4.1. Induction Regimen

[0234] Induction regimens suitable for use in the methods of the disclosure typically entail administering multiple doses of a lipid binding protein molecule (e.g., ApoA-I) over multiple consecutive days, e.g., three consecutive days, four consecutive days, five consecutive days, six consecutive days, or seven consecutive days. In some embodiments, lipid binding protein molecule (e.g., ApoA-I) is administered for three consecutive days. In some embodiments, lipid binding protein molecule (e.g., ApoA-I) is administered for four consecutive days. In some embodiments, lipid binding protein molecule (e.g., ApoA-I) is administered for five consecutive days.

[0235] In some embodiments, induction regimens suitable for use in the methods of the disclosure entail administering multiple doses of a lipid binding protein molecule (e.g., ApoA-I) over more than six consecutive days. In some embodiments, lipid binding protein molecule (e.g., ApoA-I) is administered for seven consecutive days. In some embodiments, lipid binding protein molecule (e.g., ApoA-I) is administered for eight consecutive days. In some embodiments, lipid binding protein molecule (e.g., ApoA-I) is administered for nine consecutive days. In some embodiments, lipid binding protein molecule (e.g., ApoA-I) is administered for ten consecutive days. In some embodiments, lipid binding protein molecule (e.g., ApoA-I) is administered for eleven consecutive days. In some embodiments, lipid binding protein molecule (e.g., ApoA-I) is administered for twelve consecutive days. In some embodiments, lipid binding protein molecule (e.g., ApoA-I) is administered for thirteen consecutive days. In some embodiments, lipid binding protein molecule (e.g., ApoA-I) is administered for fourteen consecutive days.

[0236] In some embodiments, a subject's ApoA-I level or HDL level is measured following an induction regimen (e.g., 0.5 day to one week following the final dose of the induction regimen).

[0237] In some embodiments, induction regimens suitable for use in the methods of the disclosure entail twice daily administration of a lipid binding protein molecule (e.g., ApoA-I) 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).

[0238] In an embodiment, the induction regimen comprises two doses of a lipid binding protein molecule (e.g., ApoA-I) per day for three consecutive days. In an embodiment, the induction regimen comprises two doses of a lipid binding protein molecule (e.g., ApoA-I) per day for four consecutive days. In an embodiment, the induction regimen comprises two doses of a lipid binding protein molecule (e.g., ApoA-I) per day for five consecutive days. In an embodiment, the induction regimen comprises two doses of a lipid binding protein molecule (e.g., ApoA-I) per day for six consecutive days.

[0239] In some embodiments, the induction regimen comprises two doses of a lipid binding protein molecule (e.g., ApoA-I) per day for more than six consecutive days. In some embodiments, two doses of a lipid binding protein molecule (e.g., ApoA-I) are administered per day for seven consecutive days. In some embodiments, two doses of a lipid binding protein molecule (e.g., ApoA-I) are administered per day for eight consecutive days. In some embodiments, two doses of a lipid binding protein molecule (e.g.,

ApoA-I) are administered per day for nine consecutive days. In some embodiments, two doses of a lipid binding protein molecule (e.g., ApoA-I) are administered per day for ten consecutive days. In some embodiments, two doses of a lipid binding protein molecule (e.g., ApoA-I) are administered per day for eleven consecutive days. In some embodiments, two doses of a lipid binding protein molecule (e.g., ApoA-I) are administered per day for twelve consecutive days. In some embodiments, two doses of a lipid binding protein molecule (e.g., ApoA-I) are administered per day for thirteen consecutive days. In some embodiments, two doses of a lipid binding protein molecule (e.g., ApoA-I) are administered per day for fourteen consecutive days.

[0240] A therapeutic dose of a lipid binding protein molecule (e.g., ApoA-I) 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 molecule (e.g., ApoA-I) used in the induction regimen is 5 mg/kg. In some embodiments, the dose of a lipid binding protein molecule (e.g., ApoA-I) used in the induction regimen is 10 mg/kg. In some embodiments, the dose of a lipid binding protein molecule (e.g., ApoA-I) used in the induction regimen is 15 mg/kg. In some embodiments, the dose of a lipid binding protein molecule (e.g., ApoA-I) used in the induction regimen is 20 mg/kg. In some embodiments, the induction regimen comprises six doses of a lipid binding protein molecule (e.g., ApoA-I) administered over three days at a dose of 5 mg/kg, 10 mg/kg, 15 mg/kg or 20 mg/kg. In some embodiments, the induction regimen comprises eight doses of a lipid binding protein molecule (e.g., ApoA-I) administered over four days at a dose of 5 mg/kg, 10 mg/kg, 15 mg/kg or 20 mg/kg. In some embodiments, the induction regimen comprises ten doses of a lipid binding protein molecule (e.g., ApoA-I) administered over five days at a dose of 5 mg/kg, 10 mg/kg, 15 mg/kg or 20 mg/kg. In some embodiments, the induction regimen comprises twelve doses of a lipid binding protein molecule (e.g., ApoA-I) administered over six days at a dose of 5 mg/kg, 10 mg/kg, 15 mg/kg or 20 mg/kg.

[0241] In yet other aspects, a lipid binding protein molecule (e.g., ApoA-I) 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.

[0242] In particular embodiments, the dosage of a lipid binding protein molecule (e.g., ApoA-I) 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. In particular embodiments, the dosage of a lipid binding protein molecule (e.g., ApoA-I) is 300 mg to 400 mg, 300 mg to 500 mg, 300 mg to 600 mg, 300 mg to 800 mg, 300 mg to 1000 mg, 300 mg to 1200 mg, 300 mg to 1500 mg, 300 mg to 2000 mg, 300 mg to 2400 mg, 300 mg to 3000 mg, 400 mg to 500 mg, 400 mg to 600 mg, 400 mg to 800 mg, 400 mg to 1000 mg, 400 mg to 1200 mg, 400 mg to 1500 mg, 400 mg to 2000 mg, 400 mg to 2400 mg, 400 mg to 3000 mg, 400 mg to 4000 mg, 500 mg to 600 mg, 500 mg to 800 mg, 500 mg to 1000 mg, 500 mg to 1200 mg, 500 mg to 1500 mg, 500 mg to 2000 mg, 500 mg to 2400 mg, 500 mg to 3000 mg, 500 mg to 4000 mg, 600 mg to 800 mg, 600 mg to 1000 mg, 600 mg to 1200 mg, 600 mg to 1500 mg, 600 mg to 2000 mg, 600 mg to 2400 mg, 600 mg to 3000 mg, 600 mg to 4000 mg, 800 mg to 1000 mg, 800 mg to 1200 mg, 800 mg to 1500 mg, 800 mg to 2000 mg, 800 mg to 2400 mg, 800 mg to 3000 mg, 800 mg to 4000 mg, 1000 mg to 1200 mg, 1000 mg to 1500 mg, 1000 mg to 2000 mg, 1000 mg to 2400 mg, 1000 mg to 3000 mg, 1000 mg to 4000 mg, 1200 mg to 1500 mg, 1200 mg to 2000 mg, 1200 mg to

2400 mg, 1200 mg to 3000 mg, 1200 mg to 4000 mg, 1500 mg to 2000 mg, 1500 mg to 2400 mg, 1500 mg to 3000 mg, 1500 mg to 4000 mg, 2000 mg to 2400 mg, 2000 mg to 3000 mg, 2000 mg to 4000 mg, 2400 mg to 3000 mg, 2400 mg to 4000 mg, or 3000 mg to 4000 mg per administration (on a protein weight basis).

6.4.2. Consolidation Regimen

[0243] Consolidation regimens suitable for use in the methods of the disclosure typically entail administering one dose or multiple doses of a lipid binding protein molecule (e.g., ApoA-I) following an induction regimen. A consolidation regimen can be preceded by an ApoA-I level measurement. For example, a consolidation regimen can be administered if a subject's ApoA-I level is below a target ApoA-I level or below a target ApoA-I range or if a subject's HDL level is below a target HDL level. The ApoA-I measurement preceding a consolidation regimen can also be used, for example, to guide the parameters of the consolidation regimen. For example, a relatively high dose and/or administration frequency can be selected if the ApoA-I or HDL measurement is relatively low, while a relatively low dose and/or administration frequency can be selected if the ApoA-I measurement or HDL measurement is relatively high.

[0244] In one embodiment, the consolidation regimen comprises administering two doses of a lipid binding protein molecule (e.g., ApoA-I). 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).

[0245] The dose(s) of a lipid binding protein molecule (e.g., ApoA-I) 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 molecule (e.g., ApoA-I) 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 molecule (e.g., ApoA-I) 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 molecule (e.g., ApoA-I) 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. In some embodiments, the dose(s) of a lipid binding protein molecule (e.g., ApoA-I) in a consolidation regimen can be administered on day 8 of a dosing regimen that begins with an induction regimen on day 1. In some embodiments, the dose(s) of a lipid binding protein molecule (e.g., ApoA-I) in a consolidation regimen can be administered on day 9 of a dosing regimen that begins with an induction regimen on day 1. In some embodiments, the dose(s) of a lipid binding protein molecule (e.g., ApoA-I) in a consolidation regimen can be administered on day 10 of a dosing regimen that begins with an induction regimen on day 1. In some embodiments, the dose(s) of a lipid binding protein molecule (e.g., ApoA-I) in a consolidation regimen can be administered on day 11 of a dosing regimen that begins with an induction regimen on day 1. In some embodiments, the dose(s) of a lipid binding protein molecule (e.g., ApoA-I) in a consolidation regimen can be administered on day 12 of a dosing regimen that begins with an induction regimen on day 1. In some embodiments, the dose(s) of a lipid binding protein molecule (e.g., ApoA-I) in a consolidation regimen can be administered on day 13 of a dosing regimen that begins with an induction regimen on day 1. In some embodiments, the dose(s) of a lipid binding protein molecule (e.g., ApoA-I) in a consolidation regimen can be administered on day 14 of a dosing regimen that begins with an induction

regimen on day 1. In some embodiments, the dose(s) of a lipid binding protein molecule (e.g., ApoA-I) in a consolidation regimen can be administered on day 15 of a dosing regimen that begins with an induction regimen on day 1.

[0246] In some embodiments, a consolidation regimen comprises once daily administration of a lipid binding protein molecule (e.g., ApoA-I) following an induction regimen that comprises twice daily administration of the lipid binding protein molecule (e.g., ApoA-I). In other embodiments, a consolidation regimen comprises twice daily administration of a lipid binding protein molecule (e.g., ApoA-I) following an induction regimen that comprises twice daily administration of the lipid binding protein molecule (e.g., ApoA-I). Each individual dose of the consolidation regimen can be the same, higher, or lower than each individual dose of the induction regimen.

[0247] A therapeutic dose of a lipid binding protein molecule (e.g., ApoA-I) 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 molecule (e.g., ApoA-I) used in the consolidation regimen is 5 mg/kg. In some embodiments, the dose of a lipid binding protein molecule (e.g., ApoA-I) used in the consolidation regimen is 10 mg/kg. In some embodiments, the dose of a lipid binding protein molecule (e.g., ApoA-I) used in the consolidation regimen is 15 mg/kg. In some embodiments, the dose of a lipid binding protein molecule (e.g., ApoA-I) used in the consolidation regimen is 20 mg/kg. In some embodiments, the consolidation regimen comprises two doses of a lipid binding protein molecule (e.g., ApoA-I) administered on one day at a dose of 5 mg/kg, 10 mg/kg, 15 mg/kg or 20 mg/kg.

[0248] In yet other aspects, a lipid binding protein molecule (e.g., ApoA-I) 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.

[0249] In particular embodiments, the dosage of a lipid binding protein molecule (e.g., ApoA-I) 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. In particular embodiments, the dosage of a lipid binding protein molecule (e.g., ApoA-I) is 300 mg to 400 mg, 300 mg to 500 mg, 300 mg to 600 mg, 300 mg to 800 mg, 300 mg to 1000 mg, 300 mg to 1200 mg, 300 mg to 1500 mg, 300 mg to 2000 mg, 300 mg to 2400 mg, 300 mg to 3000 mg, 400 mg to 500 mg, 400 mg to 600 mg, 400 mg to 800 mg, 400 mg to 1000 mg, 400 mg to 1200 mg, 400 mg to 1500 mg, 400 mg to 2000 mg, 400 mg to 2400 mg, 400 mg to 3000 mg, 400 mg to 4000 mg, 500 mg to 600 mg, 500 mg to 800 mg, 500 mg to 1000 mg, 500 mg to 1200 mg, 500 mg to 1500 mg, 500 mg to 2000 mg, 500 mg to 2400 mg, 500 mg to 3000 mg, 500 mg to 4000 mg, 600 mg to 800 mg, 600 mg to 1000 mg, 600 mg to 1200 mg, 600 mg to 1500 mg, 600 mg to 2000 mg, 600 mg to 2400 mg, 600 mg to 3000 mg, 600 mg to 4000 mg, 800 mg to 1000 mg, 800 mg to 1200 mg, 800 mg to 1500 mg, 800 mg to 2000 mg, 800 mg to 2400 mg, 800 mg to 3000 mg, 800 mg to 4000 mg, 1000 mg to 1200 mg, 1000 mg to 1500 mg, 1000 mg to 2000 mg, 1000 mg to 2400 mg, 1000 mg to 3000 mg, 1000 mg to 4000 mg, 1200 mg to 1500 mg, 1200 mg to 2000 mg, 1200 mg to 2400 mg, 1200 mg to 3000 mg, 1200 mg to 4000 mg, 1500 mg to 2000 mg, 1500 mg to 2400 mg, 1500 mg to 3000 mg, 1500 mg to 4000 mg, 2000 mg to 2400 mg, 2000 mg to 3000 mg, 2000 mg to 4000 mg, 2400 mg to 3000 mg, 2400 mg to 4000 mg, or 3000 mg to 4000 mg per administration (on a protein weight basis).

[0250] The lipid binding protein molecule (e.g., ApoA-I) can be administered during the consolidation phase in the same manner as described in Section 6.4, e.g., as an IV infusion over a one-hour period.

6.5. Combination therapies

[0251] A lipid binding protein molecule (e.g., ApoA-I) 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 can comprise a lipid binding protein molecule (e.g., ApoA-I) in combination with a standard of care treatment for the condition from which the subject suffers or is at risk of suffering, e.g., sepsis (e.g., septic shock) 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.

[0252] In some embodiments, for example for subjects having sepsis (e.g., septic shock), the subject is treated with a lipid binding protein molecule (e.g., ApoA-I) in combination with fluid replacement therapy. In some embodiments, for example for subjects having sepsis, the subject is treated with a lipid binding protein molecule (e.g., ApoA-I) in combination with an antimicrobial. In some embodiments, for example for subjects having sepsis, the subject is treated with a lipid binding protein molecule (e.g., ApoA-I) in combination with an antibiotic (e.g., ceftriaxone, meropenem, ceftazidime, cefotaxime, cefepime, piperacillin and tazobactam, ampicillin and sulbactam, imipenem and cilastatin, levofloxacin, or clindamycin).

[0253] In some embodiments, the subject is mechanically ventilated when the lipid binding protein molecule is administered for the first time.

[0254] In some embodiments, the subject is not mechanically ventilated when the lipid binding protein molecule is administered for the first time.

[0255] In some embodiments, the subject is receiving vasopressor therapy when the lipid binding protein molecule is administered for the first time.

[0256] In some embodiments, the subject is not receiving vasopressor therapy when the lipid binding protein molecule is administered for the first time.

[0257] In some embodiments, the subject has a blood lactate level of 0.4 mmol/L to 12 mmol/L (e.g., 0.4 mmol/L to 5 mmol/L, 1 mmol/L to 5 mmol/L, or 1 mmol/L to 4 mmol/L) when the lipid binding protein molecule is administered for the first time.

[0258] In some embodiments, the subject has a P/F ratio (PaO₂ (arterial oxygen partial pressure obtained from an arterial blood gas) to the FiO₂ (fraction of inspired oxygen) ratio) of 90 to 550 (e.g., 90 to 250, 150 to 400, or 300 to 510) when the lipid binding protein molecule is administered for the first time.

[0259] In some embodiments, the subject has a serum creatinine level of 0.5 mg/dL to 6 mg/dL (e.g., 0.5 mg/dL to 3 mg/dL or 3 mg/dL to 6 mg/dL) when the lipid binding protein molecule is administered for the first time.

[0260] In some embodiments, the subject is in an intensive care unit (ICU) when the lipid binding protein molecule is administered for the first time. Administering the lipid binding protein molecule may reduce the number of days the subject is in the ICU compared to the standard of care.

[0261] In some embodiments, the subject is not in an intensive care unit (ICU) when the lipid binding protein molecule is administered for the first time.

[0262] In some embodiments, the subject has sepsis and the method increases 30-day survival compared to the standard of care.

[0263] In some embodiments, for example for subjects having a viral infection, the subject is treated with a lipid binding protein molecule (e.g., ApoA-I) in combination with an antiviral. In some embodiments, the subject is treated with a lipid binding protein molecule (e.g., ApoA-I) in combination with a medication that raises blood pressure (e.g., norepinephrine or epinephrine). In some embodiments, the subject is treated with a lipid binding protein molecule (e.g., ApoA-I) in combination with an immunosuppressant such as tacrolimus or everolimus.

[0264] 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 molecule (e.g., ApoA-I) is administered in combination with tocilizumab.

[0265] In certain embodiments, an antihistamine (e.g., diphenhydramine, cetirizine, fexofenadine, or loratadine) can be administered before administration of a lipid binding protein molecule (e.g., ApoA-I). The antihistamine can reduce the likelihood of allergic reactions.

7. SPECIFIC EMBODIMENTS

[0266] The present disclosure is exemplified by the numbered embodiments set forth below.

[0267] In the embodiments below and throughout the specification, unless indicated otherwise, an “or” conjunction is intended to be used in its correct sense as a Boolean logical operator, encompassing both the selection of features in the alternative (A or B, where the selection of A is mutually exclusive from B) and the selection of features in conjunction (A and B, where both A and B are selected). In some places in the text, the term “and/or” is used for the same purpose, which shall not be construed to imply that “or” is used with reference to mutually exclusive alternatives.

1. A method of treating a subject having or at risk of a condition treatable with a lipid binding protein molecule, which is optionally sepsis (e.g., septic shock), comprising:
 - (a) optionally, administering one or more doses of a lipid binding protein molecule to the subject;
 - (b) measuring an ApoA-I level or an HDL level of the subject; and
 - (c) administering one or more doses of the lipid binding protein molecule to the subject if the measured ApoA-I level is below a target ApoA-I level or a target ApoA-I range or if the measured HDL level is below a target HDL level.
2. The method of embodiment 1, which comprises administering one or more doses of the lipid binding protein molecule to the subject prior to step (b).
3. The method of embodiment 2, wherein step (b) comprises measuring the ApoA-I level or HDL level 0.5 day to one week after the most recent administration of the lipid binding protein molecule.
4. The method of embodiment 2 or embodiment 3, wherein step (b) comprises measuring the ApoA-I level or HDL level on the day following the most recent administration of the lipid binding protein molecule.

5. The method of embodiment 2 or embodiment 3, wherein step (b) comprises measuring the ApoA-I level or HDL level 0.5 day to 1 day after the most recent administration of the lipid binding protein molecule.
6. The method of any embodiment 2 or embodiment 3, wherein step (b) comprises measuring the ApoA-I level or HDL level 0.5 day after the most recent administration of the lipid binding protein molecule.
7. The method of embodiment 2 or embodiment 3, wherein step (b) comprises measuring the ApoA-I level or HDL level 1 day after the most recent administration of the lipid binding protein molecule.
8. The method of embodiment 2 or embodiment 3, wherein step (b) comprises measuring the ApoA-I level or HDL level one day after the most recent administration of the lipid binding protein molecule.
9. The method of embodiment 2 or embodiment 3, wherein step (b) comprises measuring the ApoA-I level or HDL level two days after the most recent administration of the lipid binding protein molecule.
10. The method of embodiment 2 or embodiment 3, wherein step (b) comprises measuring the ApoA-I level or HDL level three days after the most recent administration of the lipid binding protein molecule.
11. The method of embodiment 2 or embodiment 3, wherein step (b) comprises measuring the ApoA-I level or HDL level four days after the most recent administration of the lipid binding protein molecule.
12. The method of embodiment 2 or embodiment 3, wherein step (b) comprises measuring the ApoA-I level or HDL level five days after the most recent administration of the lipid binding protein molecule.
13. The method of embodiment 2 or embodiment 3, wherein step (b) comprises measuring the ApoA-I level or HDL level six days after the most recent administration of the lipid binding protein molecule.
14. The method of embodiment 2 or embodiment 3, wherein step (b) comprises measuring the ApoA-I level or HDL level seven days after the most recent administration of the lipid binding protein molecule.
15. The method of any one of embodiments 2 to 14, wherein step (a) comprises administering the lipid binding protein molecule according to an induction regimen.
16. The method of embodiment 15, wherein the induction regimen comprises one or more doses of the lipid binding protein molecule administered over three days.
17. The method of embodiment 15, wherein the induction regimen comprises one or more doses of the lipid binding protein molecule administered over four days.
18. The method of embodiment 15, wherein the induction regimen comprises one or more doses of the lipid binding protein molecule administered over five days.
19. The method of embodiment 15, wherein the induction regimen comprises one or more doses of the lipid binding protein molecule administered over six days.
20. The method of embodiment 15, wherein the induction regimen comprises one or more doses of the lipid binding protein molecule administered over seven days.

21. The method of any one of embodiments 15 to 20, wherein the induction regimen comprises once daily administration of the lipid binding protein molecule.
22. The method of any one of embodiments 15 to 20, wherein the induction regimen comprises twice daily administration of the lipid binding protein molecule.
23. The method of embodiment 1, wherein the subject is administered the lipid binding protein molecule at least once per day on days 1, 2, and 3 of a treatment regimen, and the ApoA-I level or HDL level is measured on day 4.
24. The method of embodiment 23, wherein the subject is administered the lipid binding protein molecule twice per day on days 1, 2, and 3.
25. The method of embodiment 1, wherein the subject is administered the lipid binding protein molecule at least once per day on days 1, 2, 3, and 4 of a treatment regimen, and the ApoA-I level or HDL level is measured on day 5.
26. The method of embodiment 25, wherein the subject is administered the lipid binding protein molecule twice per day on days 1, 2, 3, and 4.
27. The method of embodiment 1, wherein the subject is administered the lipid binding protein molecule at least once per day on days 1, 2, 3, 4, and 5 of a treatment regimen, and the ApoA-I level or HDL level is measured on day 6.
28. The method of embodiment 27, wherein the subject is administered the lipid binding protein molecule twice per day on days 1, 2, 3, 4, and 5.
29. The method of embodiment 1, wherein the subject is administered the lipid binding protein molecule at least once per day on days 1, 2, 3, 4, 5, and 6 of a treatment regimen, and the ApoA-I level or HDL level is measured on day 7.
30. The method of embodiment 29, wherein the subject is administered the lipid binding protein molecule twice per day on days 1, 2, 3, 4, 5, and 6.
31. The method of embodiment 1, wherein the subject is administered the lipid binding protein molecule at least once per day on days 1, 2, 3, 4, 5, 6, and 7 of a treatment regimen, and the ApoA-I level or HDL level is measured on day 8.
32. The method of embodiment 31, wherein the subject is administered the lipid binding protein molecule twice per day on days 1, 2, 3, 4, 5, 6, and 7.
33. The method of any one of embodiments 1 to 32, which comprises administering multiple doses of the lipid binding protein molecule to the subject prior to step (b).
34. The method of embodiment 33, wherein step (c) comprises administering multiple doses of the lipid binding protein molecule at a greater frequency than the multiple doses of the lipid binding protein molecule administered in step (a).
35. The method of embodiment 33, wherein step (c) comprises administering multiple doses of the lipid binding protein molecule at a lower frequency than the multiple doses of the lipid binding protein molecule administered in step (a).
36. The method of any one of embodiments 1 to 35, which comprises step (a), and wherein the dose of the lipid binding protein molecule administered in step (c) is the same as the dose administered in step (a).

37. The method of any one of embodiments 1 to 35, which comprises step (a), and wherein the dose of the lipid binding protein molecule administered in step (c) is greater than the dose administered in step (a).
38. The method of any one of embodiments 1 to 37, further comprising repeating steps (b) and (c) one or more times.
39. The method of embodiment 38, wherein the ApoA-I level or HDL level is measured daily.
40. The method of embodiment 38, wherein the ApoA-I level or HDL level is measured twice daily.
41. The method of embodiment 38, wherein the ApoA-I level or HDL level is measured every other day.
42. The method of embodiment 38, wherein the ApoA-I level or HDL level is measured every third day.
43. The method of embodiment 38, wherein the time period between ApoA-I or HDL measurements is increased if the most recent measured ApoA-I level or HDL level is higher than the previous measured ApoA-I level or HDL level.
44. The method of embodiment 38, wherein the time period between ApoA-I or HDL measurements is decreased if the most recent measured ApoA-I level or HDL level is lower than the previous measured ApoA-I level or HDL level.
45. The method of any one of embodiments 38 to 44, wherein steps (b) and (c) are repeated until the measured ApoA-I level is at or above the target ApoA-I level or within the target ApoA-I range or until the measured HDL level is at or above the target HDL level.
46. The method of any one of embodiments 38 to 45, wherein when step (b) comprises measuring an ApoA-I level, steps (b) and (c) are repeated until the measured ApoA-I level is at or above the target ApoA-I level.
47. The method of any one of embodiments 38 to 45, wherein when step (b) comprises measuring an ApoA-I level, steps (b) and (c) are repeated until the measured ApoA-I level is within the target ApoA-I range.
48. The method of any one of embodiments 38 to 45, wherein when step (b) comprises measuring an HDL level, steps (b) and (c) are repeated until the measured HDL level is at or above the target HDL level.
49. The method of any one of embodiments 1 to 48, which comprises step (a) and further comprising:
- (d) administering one or more doses of the lipid binding protein molecule to the subject at a lower dose and/or frequency than in step (a) if the measured ApoA-I level or HDL level is at or above the target ApoA-I level, within the target ApoA-I range, or at or above the target HDL level.
50. The method of embodiment 49, further comprising repeating (i) step (b) and (ii) step (c) or step (d).
51. The method of embodiment 49 or embodiment 50, wherein step (d) comprises administering one or more doses of the lipid binding protein molecule to the subject at a lower dose than in step (a).

52. The method of embodiment 49 or embodiment 50, wherein step (d) comprises administering one or more doses of the lipid binding protein molecule to the subject at a lower frequency than in step (a).
53. The method of embodiment 49 or embodiment 50, wherein step (d) comprises administering one or more doses of the lipid binding protein molecule to the subject at a lower dose and lower frequency than in step (a).
54. The method of any one of embodiments 1 to 53, wherein the ApoA-I level is a serum ApoA-I level.
55. The method of any one of embodiments 1 to 53, wherein the ApoA-I level is a plasma ApoA-I level.
56. The method of any one of embodiments 1 to 53, wherein the ApoA-I level is a whole blood ApoA-I level.
57. The method of any one of embodiments 1 to 56, wherein the target ApoA-I level is a normal ApoA-I level in healthy subjects.
58. The method of any one of embodiments 1 to 56, wherein the target ApoA-I level is an ApoA-I level of 1.0 g/L.
59. The method of any one of embodiments 1 to 56, wherein the target ApoA-I level is an ApoA-I level of 1.1 g/L.
60. The method of any one of embodiments 1 to 59, wherein the target ApoA-I range is a normal ApoA-I range in healthy subjects.
61. The method of any one of embodiments 1 to 60, wherein the target ApoA-I range is from 1.0 g/L to 1.1 g/L.
62. The method of any one of embodiments 1 to 60, wherein the target ApoA-I range is from 1.0 g/L to 1.2 g/L.
63. The method of any one of embodiments 1 to 60, wherein the target ApoA-I range is from 1.0 g/L to 1.3 g/L.
64. The method of any one of embodiments 1 to 60, wherein the target ApoA-I range is from 1.0 g/L to 1.4 g/L.
65. The method of any one of embodiments 1 to 60, wherein the target ApoA-I range is from 1.0 g/L to 1.5 g/L.
66. The method of any one of embodiments 1 to 60, wherein the target ApoA-I range is from 1.0 g/L to 1.6 g/L.
67. The method of any one of embodiments 1 to 60, wherein the target ApoA-I range is from 1.0 g/L to 1.7 g/L.
68. The method of any one of embodiments 1 to 60, wherein the target ApoA-I range is from 1.0 g/L to 1.8 g/L.
69. The method of any one of embodiments 1 to 60, wherein the target ApoA-I range is from 1.0 g/L to 1.9 g/L.
70. The method of any one of embodiments 1 to 60, wherein the target ApoA-I range is from 1.0 g/L to 2.0 g/L.
71. The method of any one of embodiments 1 to 60, wherein the target ApoA-I range is from 1.0 g/L to 2.1 g/L.

72. The method of any one of embodiments 1 to 60, wherein the target ApoA-I range is from 1.1 g/L to 1.2 g/L.
73. The method of any one of embodiments 1 to 60, wherein the target ApoA-I range is from 1.1 g/L to 1.3 g/L.
74. The method of any one of embodiments 1 to 60, wherein the target ApoA-I range is from 1.1 g/L to 1.4 g/L.
75. The method of any one of embodiments 1 to 60, wherein the target ApoA-I range is from 1.1 g/L to 1.5 g/L.
76. The method of any one of embodiments 1 to 60, wherein the target ApoA-I range is from 1.1 g/L to 1.6 g/L.
77. The method of any one of embodiments 1 to 60, wherein the target ApoA-I range is from 1.1 g/L to 1.7 g/L.
78. The method of any one of embodiments 1 to 60, wherein the target ApoA-I range is from 1.1 g/L to 1.8 g/L.
79. The method of any one of embodiments 1 to 60, wherein the target ApoA-I range is from 1.1 g/L to 1.9 g/L.
80. The method of any one of embodiments 1 to 60, wherein the target ApoA-I range is from 1.1 g/L to 2.0 g/L.
81. The method of any one of embodiments 1 to 60, wherein the target ApoA-I range is from 1.1 g/L to 2.1 g/L.
82. The method of any one of embodiments 1 to 60, wherein the target ApoA-I range is from 1.2 g/L to 1.3 g/L.
83. The method of any one of embodiments 1 to 60, wherein the target ApoA-I range is from 1.2 g/L to 1.4 g/L.
84. The method of any one of embodiments 1 to 60, wherein the target ApoA-I range is from 1.2 g/L to 1.5 g/L.
85. The method of any one of embodiments 1 to 60, wherein the target ApoA-I range is from 1.2 g/L to 1.6 g/L.
86. The method of any one of embodiments 1 to 60, wherein the target ApoA-I range is from 1.2 g/L to 1.7 g/L.
87. The method of any one of embodiments 1 to 60, wherein the target ApoA-I range is from 1.2 g/L to 1.8 g/L.
88. The method of any one of embodiments 1 to 60, wherein the target ApoA-I range is from 1.2 g/L to 1.9 g/L.
89. The method of any one of embodiments 1 to 60, wherein the target ApoA-I range is from 1.2 g/L to 2.0 g/L.
90. The method of any one of embodiments 1 to 60, wherein the target ApoA-I range is from 1.2 g/L to 2.1 g/L.
91. The method of any one of embodiments 1 to 60, wherein the target ApoA-I range is from 1.3 g/L to 1.4 g/L.
92. The method of any one of embodiments 1 to 60, wherein the target ApoA-I range is from 1.3 g/L to 1.5 g/L.

93. The method of any one of embodiments 1 to 60, wherein the target ApoA-I range is from 1.3 g/L to 1.6 g/L.
94. The method of any one of embodiments 1 to 60, wherein the target ApoA-I range is from 1.3 g/L to 1.7 g/L.
95. The method of any one of embodiments 1 to 60, wherein the target ApoA-I range is from 1.3 g/L to 1.8 g/L.
96. The method of any one of embodiments 1 to 60, wherein the target ApoA-I range is from 1.3 g/L to 1.9 g/L.
97. The method of any one of embodiments 1 to 60, wherein the target ApoA-I range is from 1.3 g/L to 2.0 g/L.
98. The method of any one of embodiments 1 to 60, wherein the target ApoA-I range is from 1.3 g/L to 2.1 g/L.
99. The method of any one of embodiments 1 to 60, wherein the target ApoA-I range is from 1.4 g/L to 1.5 g/L.
100. The method of any one of embodiments 1 to 60, wherein the target ApoA-I range is from 1.4 g/L to 1.6 g/L.
101. The method of any one of embodiments 1 to 60, wherein the target ApoA-I range is from 1.4 g/L to 1.7 g/L.
102. The method of any one of embodiments 1 to 60, wherein the target ApoA-I range is from 1.4 g/L to 1.8 g/L.
103. The method of any one of embodiments 1 to 60, wherein the target ApoA-I range is from 1.4 g/L to 1.9 g/L.
104. The method of any one of embodiments 1 to 60, wherein the target ApoA-I range is from 1.4 g/L to 2.0 g/L.
105. The method of any one of embodiments 1 to 60, wherein the target ApoA-I range is from 1.4 g/L to 2.1 g/L.
106. The method of any one of embodiments 1 to 60, wherein the target ApoA-I range is from 1.5 g/L to 1.6 g/L.
107. The method of any one of embodiments 1 to 60, wherein the target ApoA-I range is from 1.5 g/L to 1.7 g/L.
108. The method of any one of embodiments 1 to 60, wherein the target ApoA-I range is from 1.5 g/L to 1.8 g/L.
109. The method of any one of embodiments 1 to 60, wherein the target ApoA-I range is from 1.5 g/L to 1.9 g/L.
110. The method of any one of embodiments 1 to 60, wherein the target ApoA-I range is from 1.5 g/L to 2.0 g/L.
111. The method of any one of embodiments 1 to 60, wherein the target ApoA-I range is from 1.5 g/L to 2.1 g/L.
112. The method of any one of embodiments 1 to 60, wherein the target ApoA-I range is from 1.6 g/L to 1.7 g/L.
113. The method of any one of embodiments 1 to 60, wherein the target ApoA-I range is from 1.6 g/L to 1.8 g/L.

114. The method of any one of embodiments 1 to 60, wherein the target ApoA-I range is from 1.6 g/L to 1.9 g/L.
115. The method of any one of embodiments 1 to 60, wherein the target ApoA-I range is from 1.6 g/L to 2.0 g/L.
116. The method of any one of embodiments 1 to 60, wherein the target ApoA-I range is from 1.6 g/L to 2.1 g/L.
117. The method of any one of embodiments 1 to 60, wherein the target ApoA-I range is from 1.7 g/L to 1.8 g/L.
118. The method of any one of embodiments 1 to 60, wherein the target ApoA-I range is from 1.7 g/L to 1.9 g/L.
119. The method of any one of embodiments 1 to 60, wherein the target ApoA-I range is from 1.7 g/L to 2.0 g/L.
120. The method of any one of embodiments 1 to 60, wherein the target ApoA-I range is from 1.7 g/L to 2.1 g/L.
121. The method of any one of embodiments 1 to 60, wherein the target ApoA-I range is from 1.8 g/L to 1.9 g/L.
122. The method of any one of embodiments 1 to 60, wherein the target ApoA-I range is from 1.8 g/L to 2.0 g/L.
123. The method of any one of embodiments 1 to 60, wherein the target ApoA-I range is from 1.8 g/L to 2.1 g/L.
124. The method of any one of embodiments 1 to 60, wherein the target ApoA-I range is from 1.9 g/L to 2.0 g/L.
125. The method of any one of embodiments 1 to 60, wherein the target ApoA-I range is from 1.9 g/L to 2.1 g/L.
126. The method of any one of embodiments 1 to 60, wherein the target ApoA-I range is from 2.0 g/L to 2.1 g/L.
127. The method of any one of embodiments 1 to 126, wherein the HDL level is a serum HDL level.
128. The method of any one of embodiments 1 to 126, wherein the HDL level is a plasma HDL level.
129. The method of any one of embodiments 1 to 126, wherein the HDL level is a whole blood HDL level.
130. The method of any one of embodiments 1 to 129, wherein the HDL level is an HDL-cholesterol (HDL-C) level.
131. The method of any one of embodiments 1 to 129, wherein the target HDL level is a normal HDL level in healthy subjects.
132. The method of any one of embodiments 1 to 129, wherein the target HDL level is an HDL-C level of 50 mg/dL.
133. The method of any one of embodiments 1 to 129, wherein the target HDL level is an HDL-C level of 45 mg/dL.
134. The method of any one of embodiments 1 to 129, wherein the target HDL level is an HDL-C level of 40 mg/dL.

135. The method of any one of embodiments 1 to 129, wherein the target HDL level is an HDL-C level of 35 mg/dL.
136. The method of any one of embodiments 1 to 129, wherein the target HDL level is an HDL-C level of 50 mg/dL for a female subject.
137. The method of any one of embodiments 1 to 129, wherein the target HDL level is an HDL-C level of 45 mg/dL for a female subject.
138. The method of any one of embodiments 1 to 129, wherein the target HDL level is an HDL-C level of 40 mg/dL for a female subject.
139. The method of any one of embodiments 1 to 129, wherein the target HDL level is an HDL-C level of 35 mg/dL for a female subject.
140. The method of any one of embodiments 1 to 129, wherein the target HDL level is an HDL-C level of 50 mg/dL for a male subject.
141. The method of any one of embodiments 1 to 129, wherein the target HDL level is an HDL-C level of 45 mg/dL for a male subject.
142. The method of any one of embodiments 1 to 129, wherein the target HDL level is an HDL-C level of 40 mg/dL for a male subject.
143. The method of any one of embodiments 1 to 129, wherein the target HDL level is an HDL-C level of 35 mg/dL for a male subject.
144. The method of any one of embodiments 1 to 143, wherein the ApoA-I level is an ApoA-I level as measured by enzyme-linked immunoassay (ELISA).
145. The method of any one of embodiments 1 to 143, wherein the ApoA-I level is an ApoA-I level as measured by immunoturbidimetry.
146. The method of any one of embodiments 1 to 143, wherein the ApoA-I level is an ApoA-I level as measured by immunonephelometry.
147. The method of any one of embodiments 1 to 146, wherein the HDL level is an HDL-C level as measured by a cholesterol oxidase (CHOD) and cholesterol esterase (CHER) enzymatic assay.
148. The method of any one of embodiments 1 to 147, wherein the amount of the lipid binding protein molecule administered to the subject in step (c) is effective to increase the subject's ApoA-I level to or above the target ApoA-I level.
149. The method of any one of embodiments 1 to 148, wherein the amount of the lipid binding protein molecule administered to the subject in step (c) is effective to increase the subject's ApoA-I level to a level within the target ApoA-I range.
150. The method of any one of embodiments 1 to 149, wherein the amount of the lipid binding protein molecule administered to the subject in step (c) is effective to increase the subject's HDL level to a level at or above the target HDL level.
151. The method of any one of embodiments 1 to 150, wherein step (b) comprises measuring an ApoA-I level.
152. The method of embodiment 151, wherein step (c) comprises administering one or more doses of the lipid binding protein molecule to the subject if the measured ApoA-I level is below the target ApoA-I level.

153. The method of embodiment 151, wherein step (c) comprises administering one or more doses of the lipid binding protein molecule to the subject if the measured ApoA-I level is below the target ApoA-I range.
154. The method any one of embodiments 1 to 153, wherein step (b) comprises measuring an HDL level.
155. The method of embodiment 154, wherein step (c) comprises administering one or more doses of the lipid binding protein molecule to the subject if the measured HDL level is below the target HDL level.
156. The method of embodiment 154, further comprising measuring an ApoA-I level if the measured HDL level is at or above the target HDL level.
157. The method of embodiment 156, further comprising administering one or more doses of the lipid binding protein molecule to the subject if the measured ApoA-I level is below the target ApoA-I level or the target ApoA-I range.
158. The method of any one of embodiments 1 to 157, wherein the condition is associated with inflammation.
159. The method of any one of embodiments 1 to 158, wherein the condition is an acute condition.
160. The method of any one of embodiments 1 to 159, wherein the condition is sepsis.
161. The method of any one of embodiments 1 to 159, wherein the condition is sepsis-induced cognitive deficiency.
162. The method of embodiment 160 or embodiment 161, wherein the subject is at risk of sepsis (e.g., at risk of sepsis due to surgery).
163. The method of embodiment 160 or embodiment 161, wherein the subject has sepsis.
164. The method of embodiment 163, wherein the subject has septic shock.
165. The method of embodiment 164, wherein the subject has septic shock following trauma (e.g., abdominal trauma).
166. The method of embodiment 164, wherein the subject has septic shock not following trauma.
167. The method of any one of embodiments 163 to 166, wherein the subject is at risk (e.g., high risk) of developing acute kidney injury.
168. The method of any one of embodiments 1 to 167, wherein the subject has a bacterial infection, optionally with an antibiotic-resistant bacterium (e.g., MRSA).
169. The method of any one of embodiments 1 to 168, wherein the subject has a *Staphylococcus aureus* infection.
170. The method of any one of embodiments 1 to 168, wherein the subject has an *Escherichia coli* infection.
171. The method of any one of embodiments 1 to 168, wherein the subject has a *Streptococcus pneumoniae* infection.
172. The method of any one of embodiments 1 to 168, wherein the subject has a *Klebsiella pneumoniae* infection.
173. The method of any one of embodiments 1 to 168, wherein the subject has a *Pseudomonas aeruginosa* infection.

174. The method of any one of embodiments 1 to 168, wherein the subject has an *Acinetobacter baumannii* infection.
175. The method of any one of embodiments 1 to 168, wherein the subject has a *Bacteroides fragilis* infection.
176. The method of any one of embodiments 1 to 168, wherein the subject has a *Proteus mirabilis* infection.
177. The method of any one of embodiments 1 to 168, wherein the subject has a gram-positive bacterial infection.
178. The method of any one of embodiments 1 to 168, wherein the subject has a gram-negative bacterial infection.
179. The method of any one of embodiments 1 to 178, wherein the subject has a urinary tract infection.
180. The method of any one of embodiments 1 to 178, wherein the subject has an intra-abdominal cavity infection.
181. The method of any one of embodiments 1 to 178, wherein the subject has a blood infection.
182. The method of any one of embodiments 1 to 178, wherein the subject has a post-surgical infection.
183. The method of any one of embodiments 1 to 178, wherein the subject has gastrointestinal perforation.
184. The method of any one of embodiments 1 to 178, wherein the subject has a perforated duodenal ulcer.
185. The method of any one of embodiments 1 to 178, wherein the subject has a perforated bowel.
186. The method of any one of embodiments 1 to 178, wherein the subject has pneumonia, e.g., hospital acquired pneumonia.
187. The method of any one of embodiments 1 to 178, wherein the subject has a pancreatitis, e.g., necrotizing pancreatitis.
188. The method of any one of embodiments 1 to 167, wherein the subject has a viral infection.
189. The method of embodiment 188, wherein the viral infection is a SARS-CoV-2 (COVID-19) infection.
190. The method of embodiment 188, wherein the viral infection is an influenza virus infection.
191. The method of any one of embodiments 1 to 159, wherein the condition is acute myocardial infarction (AMI).
192. The method of any one of embodiments 1 to 159, wherein the condition is cytokine release syndrome (CRS).
193. The method of any one of embodiments 1 to 159, wherein the condition is ischemia reperfusion-induced tissue injury.
194. The method of any one of embodiments 1 to 159, wherein the condition is post-operative inflammation.

195. The method of any one of embodiments 1 to 159, wherein the condition is sepsis-induced acute kidney injury (AKI).
196. The method of any one of embodiments 1 to 159, wherein the condition is hypoalbuminemia.
197. The method of embodiment 196, wherein the condition is hypoalbuminemia associated with a vitamin deficiency.
198. The method of embodiment 196, wherein the condition is hypoalbuminemia associated with inflammatory bowel disease (IBD).
199. The method of embodiment 196, wherein the condition is hypoalbuminemia associated with kidney disease.
200. The method of embodiment 196, wherein the condition is hypoalbuminemia associated with an infection, optionally wherein the infection is a gram-positive bacterial infection, a gram-negative bacterial infection, or a viral infection such as a SARS-CoV-2 (COVID-19) infection or influenza infection.
201. The method of embodiment 196, wherein the condition is hypoalbuminemia associated with stress.
202. The method of embodiment 196, wherein the condition is hypoalbuminemia associated with thyroid disease.
203. The method of embodiment 196, wherein the condition is hypoalbuminemia associated with diabetes.
204. The method of embodiment 196, wherein the condition is hypoalbuminemia associated with nephrotic syndrome.
205. The method of embodiment 196, wherein the condition is hypoalbuminemia associated with lupus.
206. The method of embodiment 196, wherein the condition is hypoalbuminemia associated with cirrhosis.
207. The method of embodiment 196, wherein the condition is hypoalbuminemia associated with liver disease.
208. The method of embodiment 196, wherein the condition is hypoalbuminemia associated with heart failure.
209. The method of embodiment 196, wherein the condition is hypoalbuminemia associated with malnutrition.
210. The method of any one of embodiments 1 to 159, wherein the condition is asthma, e.g., acute severe asthma.
211. The method of any one of embodiments 1 to 159, wherein the condition is graft versus host disease (GVHD), optionally wherein the subject has received a stem cell transplant, bone marrow transplant, or organ transplant.
212. The method of any one of embodiments 1 to 211, wherein the subject has CRS or is at risk of CRS.
213. The method of embodiment 212, wherein the subject has CRS.
214. The method of embodiment 212, wherein the subject is at risk of CRS.
215. The method of any one of embodiments 1 to 214, wherein the subject has or is at risk of developing acute kidney injury (AKI).

216. The method of embodiment 215, wherein the subject has AKI.
217. The method of embodiment 215, wherein the subject is at risk for AKI.
218. The method of any one of embodiments 1 to 217, wherein the subject has acute respiratory distress syndrome (ARDS).
219. The method of any one of embodiments 1 to 217, wherein the subject is at risk for ARDS.
220. The method of any one of embodiments 1 to 219, wherein the subject has had a recent surgery or is a candidate for surgery.
221. The method of any one of embodiments 1 to 220, wherein the subject has a SOFA score of 1 to 24 prior to the first administration of the lipid binding protein molecule.
222. The method of any one of embodiments 1 to 220, wherein the subject has a SOFA score of 5 to 24 prior to the first administration of the lipid binding protein molecule.
223. The method of any one of embodiments 1 to 220, wherein the subject has a SOFA score of 10 to 24 prior to the first administration of the lipid binding protein molecule.
224. The method of any one of embodiments 1 to 220, wherein the subject has a SOFA score of 15 to 24 prior to the first administration of the lipid binding protein molecule.
225. The method of any one of embodiments 1 to 220, wherein the subject has a SOFA score of 1 to 20 prior to the first administration of the lipid binding protein molecule.
226. The method of any one of embodiments 1 to 220, wherein the subject has a SOFA score of 5 to 20 prior to the first administration of the lipid binding protein molecule.
227. The method of any one of embodiments 1 to 220, wherein the subject has a SOFA score of 10 to 20 prior to the first administration of the lipid binding protein molecule.
228. The method of any one of embodiments 1 to 220, wherein the subject has a SOFA score of 10 to 15 prior to the first administration of the lipid binding protein molecule.
229. The method of any one of embodiments 1 to 220, wherein the subject has a SOFA score of 1 to 10 prior to the first administration of the lipid binding protein molecule.
230. The method of any one of embodiments 1 to 220, wherein the subject has a SOFA score of 2 to 10 prior to the first administration of the lipid binding protein molecule.
231. The method of any one of embodiments 1 to 220, wherein the subject has a SOFA score of 2 to 5 prior to the first administration of the lipid binding protein molecule.
232. The method of any one of embodiments 1 to 220, wherein the subject has a SOFA score of 5 to 10 prior to the first administration of the lipid binding protein molecule.
233. The method of any one of embodiments 1 to 232, wherein the subject is hospitalized and the subject's SOFA score has increased by at least 2 points during the hospitalization and prior to the first administration of the lipid binding protein molecule.
234. The method of any one of embodiments 1 to 233, wherein the subject has, prior to the first administration of the lipid binding protein molecule, two or more of:
- (d) a body temperature greater than 38°C (100.4°F) or less than 36°C (96.8°F);
 - (e) a respiratory rate greater than 20 breaths per minute;
 - (f) a heart rate greater than 90 beats per minute;
 - (g) a white blood cell count greater than 12,000 cells/μl or less than 4,000 cells/μl; or
 - (h) a pCO₂ value less than 32 mm Hg (4.27 kPa).

235. The method of any one of embodiments 1 to 234, wherein the subject has a mean arterial pressure below 65 mm Hg and/or a serum lactate level greater than 2 mmol/L (18 mg/dL) prior to the first administration of the lipid binding protein molecule.
236. The method of any one of embodiments 1 to 235, wherein the subject has an Endotoxin Activity Assay level greater than 0.6 prior to the first administration of the lipid binding protein molecule.
237. The method of any one of embodiments 1 to 236, wherein the subject is being treated in a hospital.
238. The method of embodiment 237, wherein the subject is being treated in an intensive care unit (ICU).
239. The method of any one of embodiments 1 to 238, wherein the lipid binding protein molecule is an apolipoprotein.
240. The method of embodiment 239, wherein the apolipoprotein is ApoA-I.
241. The method of embodiment 240, wherein the ApoA-I has the amino acid sequence of amino acids 25-267 of SEQ ID NO:2.
242. The method of embodiment 240 or embodiment 241, wherein the ApoA-I is a recombinant ApoA-I.
243. The method of embodiment 242, wherein the ApoA-I is produced by a mammalian host cell.
244. The method of embodiment 243, wherein the mammalian host cell is a Chinese hamster ovary (CHO) cell.
245. The method of embodiment 244, wherein the CHO cell is a CHO-S cell.
246. The method of any one of embodiments 242 to 245, wherein the ApoA-I has undergone post-translational processing (e.g., glycosylation) such that the ApoA-I has one or more structural features (e.g., glycosylation pattern) that are different from human ApoA-I purified from human plasma.
247. The method of any one of embodiments 1 to 238, wherein the lipid binding protein molecule is an apolipoprotein mimetic.
248. The method of any one of embodiments 1 to 247, wherein the lipid binding protein molecule is a component of a lipid binding protein-based complex, optionally wherein the lipid binding protein-based complex is a reconstituted HDL or HDL mimetic.
249. The method of any one of embodiments 1 to 248, wherein the lipid binding protein molecule is a component of a lipid binding protein-based complex, and the lipid binding protein-based complex is an Apomer or a Cargomer.
250. The method of any one of embodiments 1 to 249, wherein the lipid binding protein molecule is a component of a lipid binding protein-based complex, and the lipid binding protein-based complex comprises a sphingomyelin.
251. The method of embodiment 250, wherein the lipid binding protein-based complex comprises 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%.
252. The method of embodiment 251, wherein the lipid binding protein-based complex comprises 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%.

253. The method of embodiment 252, wherein lipid binding protein-based complex comprises 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.

254. The method of any one of embodiments 250 to 253, wherein the lipid binding protein-based complex comprises natural sphingomyelin.

255. The method of embodiment 254, wherein the natural sphingomyelin is chicken egg sphingomyelin.

256. The method of embodiment 254, wherein the natural sphingomyelin is milk sphingomyelin.

257. The method of any one of embodiments 250 to 253, wherein the lipid binding protein-based complex comprises synthetic sphingomyelin.

258. The method of embodiment 257, wherein the sphingomyelin comprises palmitoylsphingomyelin.

259. The method of any one of embodiments 1 to 258, wherein the lipid binding protein molecule is a component of a lipid binding protein-based complex, and the lipid binding protein-based complex comprises a negatively charged lipid.

260. The method of embodiment 259, wherein the negatively charged lipid is 1,2-dipalmitoyl-sn-glycero-3-[phospho-rac-(1-glycerol) (DPPG) or a salt thereof.

261. The method of embodiment 248, wherein the lipid binding protein-based complex is CER-001, CSL-111, CSL-112, CER-522 ETC-216, or ETC-642.

262. The method of embodiment 261, wherein the lipid binding protein-based complex is CER-001.

263. The method of embodiment 262, wherein CER-001 is administered in the form of a formulation in which the CER-001 is at least 95% homogeneous.

264. The method of embodiment 263, wherein CER-001 is administered in the form of a formulation in which the CER-001 is at least 97% homogeneous.

265. The method of embodiment 264, wherein CER-001 is administered in the form of a formulation in which the CER-001 is at least 98% homogeneous.

266. The method of embodiment 265, wherein CER-001 is administered in the form of a formulation in which the CER-001 is at least 99% homogeneous.

267. The method of any one of embodiments 248 to 266, wherein the lipid binding protein based complex is a carrier for an active agent.

268. The method of any one of embodiments 1 to 267, wherein the lipid binding protein molecule is administered systemically, optionally by infusion.

269. The method of any one of embodiments 1 to 268, wherein each individual dose of the lipid binding protein molecule administered in step (c) is 4 mg/kg to 40 mg/kg (on a protein-weight basis).

270. The method of embodiment 269, wherein each individual dose of the lipid binding protein molecule administered in step (c) is 5 mg/kg, 10 mg/kg, or 20 mg/kg (on a protein-weight basis).

271. The method of embodiment 269, wherein each individual dose of the lipid binding protein molecule administered in step (c) is 5 mg/kg (on a protein-weight basis).

356. The method of embodiment 310, wherein each dose of the lipid binding protein molecule administered in step (c) is 1000 mg to 1500 mg on a protein weight basis.
357. The method of embodiment 310, wherein each dose of the lipid binding protein molecule administered in step (c) is 1000 mg to 2000 mg on a protein weight basis.
358. The method of embodiment 310, wherein each dose of the lipid binding protein molecule administered in step (c) is 1000 mg to 2400 mg on a protein weight basis.
359. The method of embodiment 310, wherein each dose of the lipid binding protein molecule administered in step (c) is 1000 mg to 3000 mg on a protein weight basis.
360. The method of embodiment 310, wherein each dose of the lipid binding protein molecule administered in step (c) is 1000 mg to 4000 mg on a protein weight basis.
361. The method of embodiment 310, wherein each dose of the lipid binding protein molecule administered in step (c) is 1200 mg to 1500 mg on a protein weight basis.
362. The method of embodiment 310, wherein each dose of the lipid binding protein molecule administered in step (c) is 1200 mg to 2000 mg on a protein weight basis.
363. The method of embodiment 310, wherein each dose of the lipid binding protein molecule administered in step (c) is 1200 mg to 2400 mg on a protein weight basis.
364. The method of embodiment 310, wherein each dose of the lipid binding protein molecule administered in step (c) is 1200 mg to 3000 mg on a protein weight basis.
365. The method of embodiment 310, wherein each dose of the lipid binding protein molecule administered in step (c) is 1200 mg to 4000 mg on a protein weight basis.
366. The method of embodiment 310, wherein each dose of the lipid binding protein molecule administered in step (c) is 1500 mg to 2000 mg on a protein weight basis.
367. The method of embodiment 310, wherein each dose of the lipid binding protein molecule administered in step (c) is 1500 mg to 2400 mg on a protein weight basis.
368. The method of embodiment 310, wherein each dose of the lipid binding protein molecule administered in step (c) is 1500 mg to 3000 mg on a protein weight basis.
369. The method of embodiment 310, wherein each dose of the lipid binding protein molecule administered in step (c) is 1500 mg to 4000 mg on a protein weight basis.
370. The method of embodiment 310, wherein each dose of the lipid binding protein molecule administered in step (c) is 2000 mg to 2400 mg on a protein weight basis.
371. The method of embodiment 310, wherein each dose of the lipid binding protein molecule administered in step (c) is 2000 mg to 3000 mg on a protein weight basis.
372. The method of embodiment 310, wherein each dose of the lipid binding protein molecule administered in step (c) is 2000 mg to 4000 mg on a protein weight basis.
373. The method of embodiment 310, wherein each dose of the lipid binding protein molecule administered in step (c) is 2400 mg to 3000 mg on a protein weight basis.
374. The method of embodiment 310, wherein each dose of the lipid binding protein molecule administered in step (c) is 2400 mg to 4000 mg on a protein weight basis.
375. The method of embodiment 310, wherein each dose of the lipid binding protein molecule administered in step (c) is 3000 mg to 4000 mg on a protein weight basis.
376. The method of any one of embodiments 1 to 375, wherein the lipid binding protein molecule is administered in step (a), when performed, and/or step (c) by infusion.

377. The method of embodiment 376, wherein each individual dose of the lipid binding protein molecule is administered by continuous infusion, e.g., for a predetermined time period.
378. The method of embodiment 377, wherein the continuous infusion is over 1 day.
379. The method of embodiment 377, wherein the continuous infusion is over 2 days.
380. The method of embodiment 377, wherein the continuous infusion is over 3 days.
381. The method of embodiment 377, wherein the continuous infusion is over 4 days.
382. The method of embodiment 377, wherein the continuous infusion is over 5 days.
383. The method of embodiment 377, wherein the continuous infusion is over 6 days.
384. The method of embodiment 377, wherein the continuous infusion is over 7 days.
385. The method of embodiment 376, wherein each individual dose is administered over a one to 24-hour period.
386. The method of embodiment 377, wherein each individual dose is administered over a 24-hour period.
387. The method of embodiment 376, wherein each individual dose is administered over a period of one hour or less.
388. The method of embodiment 376, wherein each individual dose is administered over a period of one-half hour to one hour.
389. The method of any one of embodiments 1 to 388, which further comprises administering an antihistamine to the subject prior to each dose of the lipid binding protein molecule.
390. The method of embodiment 389, wherein the antihistamine comprises dexchlorpheniramine, hydroxyzine, diphenhydramine, cetirizine, fexofenadine, or loratadine.
391. The method of embodiment 390, wherein the antihistamine comprises dexchlorpheniramine.
392. The method of embodiment 390, wherein the antihistamine comprises hydroxyzine.
393. The method of embodiment 390, wherein the antihistamine comprises diphenhydramine.
394. The method of embodiment 390, wherein the antihistamine comprises cetirizine.
395. The method of embodiment 390, wherein the antihistamine comprises fexofenadine.
396. The method of embodiment 390, wherein the antihistamine comprises loratadine.
397. The method of any one of embodiments 1 to 396, 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.
398. The method of embodiment 397, wherein the one or more additional therapies comprises one or more anti-IL-6 agents.
399. The method of embodiment 398, wherein the one or more anti-IL-6 agents comprise tocilizumab, siltuximab, olokizumab, elsilimomab, BMS-945429, sirukumab, levilimab, CPSI-2364, or a combination thereof.
400. The method of embodiment 399, wherein the one or more anti-IL-6 agents comprise tocilizumab.
401. The method of any one of embodiments 397 to 400, wherein the one or more additional therapies comprise one or more corticosteroids.
402. The method of embodiment 401, wherein the one or more corticosteroids comprise methylprednisolone, dexamethasone, or a combination thereof.

403. The method of any one of embodiments 397 to 402, wherein the one or more additional therapies comprise one or more standard of care therapies for the condition.
404. The method of embodiment 403, wherein the one or more standard of care therapies for a subject having sepsis comprise antibiotic therapy and/or hemodynamic support.
405. The method of any one of embodiments 1 to 404, wherein the subject is a human.
406. The method of any one of embodiments 1 to 405, wherein the subject is not mechanically ventilated when the lipid binding protein molecule is administered for the first time.
407. The method of any one of embodiments 1 to 405, wherein the subject is mechanically ventilated when the lipid binding protein molecule is administered for the first time.
408. The method of any one of embodiments 1 to 407, wherein the subject is receiving vasopressor therapy when the lipid binding protein molecule is administered for the first time.
409. The method of any one of embodiments 1 to 407, wherein the subject is not receiving vasopressor therapy when the lipid binding protein molecule is administered for the first time.
410. The method of any one of embodiments 1 to 409, wherein the subject has a blood lactate level of 0.4 mmol/L to 12 mmol/L when the lipid binding protein molecule is administered for the first time.
411. The method of any one of embodiments 1 to 409, wherein the subject has a blood lactate level of 0.4 mmol/L to 5 mmol/L when the lipid binding protein molecule is administered for the first time.
412. The method of any one of embodiments 1 to 409, wherein the subject has a blood lactate level of 1 mmol/L to 5 mmol/L when the lipid binding protein molecule is administered for the first time.
413. The method of any one of embodiments 1 to 409, wherein the subject has a blood lactate level of 1 mmol/L to 4 mmol/L when the lipid binding protein molecule is administered for the first time.
414. The method of any one of embodiments 1 to 413, wherein the subject has a P/F ratio (PaO₂ (arterial oxygen partial pressure obtained from an arterial blood gas) to the FiO₂ (fraction of inspired oxygen) ratio) of 90 to 550 when the lipid binding protein molecule is administered for the first time.
415. The method of any one of embodiments 1 to 413, wherein the subject has a P/F ratio of 90 to 250 when the lipid binding protein molecule is administered for the first time.
416. The method of any one of embodiments 1 to 413, wherein the subject has a P/F ratio of 150 to 400 when the lipid binding protein molecule is administered for the first time.
417. The method of any one of embodiments 1 to 413, wherein the subject has a P/F ratio of 300 to 510 when the lipid binding protein molecule is administered for the first time.
418. The method of any one of embodiments 1 to 417, wherein the subject has a serum creatinine level of 0.5 mg/dL to 6 mg/dL when the lipid binding protein molecule is administered for the first time.
419. The method of any one of embodiments 1 to 417, wherein the subject has a serum creatinine level of 0.5 mg/dL to 3 mg/dL when the lipid binding protein molecule is administered for the first time.

420. The method of any one of embodiments 1 to 417, wherein the subject has a serum creatinine level of 3 mg/dL to 6 mg/dL when the lipid binding protein molecule is administered for the first time.

421. The method of any one of embodiments 1 to 420, wherein the subject is in an intensive care unit (ICU) when the lipid binding protein molecule is administered for the first time.

422. The method of embodiment 421, which reduces the number of days the subject is in the ICU compared to the standard of care.

423. The method of any one of embodiments 1 to 420, wherein the subject is not in an intensive care unit (ICU) when the lipid binding protein molecule is administered for the first time.

424. The method of any one of embodiments 1 to 423, wherein the subject has sepsis and wherein the method increases 30-day survival compared to the standard of care.

425. The method of any one of the preceding embodiments, wherein step (a) comprises an induction regimen as described in 6.4.1.

426. A method of treating a subject having asthma (e.g., acute severe asthma), comprising administering to the subject one or more doses of a lipid binding protein molecule.

427. A method of treating a subject having or at risk of graft versus host disease (GVHD) (e.g., a subject who has received a stem cell transplant, bone marrow transplant, or organ transplant) comprising administering to the subject one or more doses of a lipid binding protein molecule

428. The method of embodiment 425 or embodiment 427, wherein the lipid binding protein molecule is a lipid binding protein molecule described in any of the preceding embodiments.

8. EXAMPLES

8.1. Example 1: Randomized pilot study comparing short-term CER-001 infusions at different doses to prevent sepsis-induced acute kidney injury

[0268] 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 was to investigate whether the use of CER-001 at different doses in combination with standard of care (SOC) treatment was 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.

[0269] The study reported in this example included 20 patients with gram-negative sepsis who were at high risk for acute kidney injury due to high levels of endotoxin activity and decline in function of one or more organ systems. Patients received either standard of care treatment alone, or in combination with one of three dosage regimens of CER-001 (five patients per group), to investigate whether the use of CER-001 at different doses, in combination with standard of care (SOC) treatment, was safe and effective, providing a potential new strategy to treat septic patients, reducing the inflammatory response to endotoxin and preventing the progression to AKI according to KDIGO (Kidney Disease: Improving

Global Outcomes) criteria, as well as safety and tolerability of the dosage regimens in order to select the optimal dose of CER-001.

[0270] One of the metabolic characteristics of bacterial (like sepsis) or virus infections (like SARS-CoV-2) is the strong decrease of circulating lipoprotein and particularly the High-Density Lipoprotein (HDL) with its main containing protein apolipoprotein A-I (ApoA-I). As an example, ApoA-I level was recently described as the biomarker predictive of long-term mortality after surgical sepsis.

[0271] One aim of the study was to restore, using CER-001, the ApoA-I levels to reestablish all the functionality of this individualized biomarker, leading to benefit in sepsis pathology.

8.1.1. Study Protocol

[0272] Study population: This was 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 ensured that all patients meeting the following inclusion and exclusion criteria were offered enrollment in the study.

[0273] 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 (EAA™); 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.

[0274] 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 m²);
- Leukocytes $< 2.0 \times 10^9$;
- Pregnancy or breast feeding;
- Undergone organ transplantation during the past one year;
- Anticipated transfer to another hospital, which was 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 had 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.

[0275] Number of subjects: Twenty subjects were enrolled and randomized (1:1:1:1) into four experimental groups, Groups A-D, defined below. Baseline characteristics of the subjects are summarized in the following table:

Sub.	Sex/ Age	Underlying Condition	SOFA Score	Organ Systems Affected	Mech. Ventilation	Vaso- pressors	Lactate	P/F Ratio	Creatinine
1	M/53	Perforated duodenal ulcer	6	Respiratory, Coagulation, Cardiovascular	Yes	Yes	3.8	99	0.82
2	M/82	Urinary tract infection	5	Cardiovascular, Renal	No	No	0.6	510	5.69
3	F/34	Urinary tract infection	2	Renal	No	No	0.8	443	2.34
4	M/67	Urinary tract infection	3	Respiratory, Coagulation, Renal	No	No	1	300	1.72
5	F/22	Urinary tract infection	2	Respiratory	No	No	1.1	243	0.7
6	F/41	Urinary tract infection	2	Renal	No	No	0.9	414	1.79
7	M/25	Septic shock following abdominal trauma with gastric bleeding	7	Respiratory, Cardiovascular	Yes	Yes	0.9	222	0.61
8	M/79	Post-surgical infection	10	Respiratory, Cardiovascular, CNS, Renal	Yes	Yes	3.5	190	1.43
9	M/74	Urinary tract infection	3	Respiratory, Renal	No	No	0.8	338	3.45
10	M/66	Urinary tract infection	2	Respiratory, Cardiovascular	No	No	0.6	371	0.6
11	M/53	Pseudomonas + blood cultures (Post- apheresis)	2	Respiratory, Coagulation	No	No	1.4	331	0.9
12	M/63	Urinary tract infection	13	Respiratory, Hepatic, Cardiovascular, CNS, Renal	Yes	Yes	11.3	133	3
13	M/60	Septic shock following colon surgery	10	Respiratory, Cardiovascular, CNS, Renal	Yes	Yes	3.2	240	2.23
14	F/59	Urinary tract infection	6	Respiratory, Coagulation, Renal	No	No	0.4	333	3.6
15	F/61	Nosocomial lung, urinary and blood infections following brain hemorrhage	15	Respiratory, Coagulation, Hepatic, CNS, Renal	Yes	Yes	0.8	304	1.27
16	F/63	Urinary tract infection	3	Renal	No	No	0.6	367	4.8

Sub.	Sex/ Age	Underlying Condition	SOFA Score	Organ Systems Affected	Mech. Ventilation	Vaso- pressors	Lactate	P/F Ratio	Creatinine
17	M/59	Sepsis with history of renal graft	6	Respiratory, Coagulation, Renal	Yes	No	2.6	277	3.83
18	F/61	Prolonged nosocomial urinary tract and blood infections	6	Respiratory, Coagulation	No	No	0.7	223	0.8
19	M/71	Septic shock with positive blood cultures	14	Respiratory, Coagulation, Hepatic, Neurologic, Renal	Yes	No	4.1	130	3.6
20	M/45	Necrotizing pancreatitis	16	Coagulation, Hepatic, Cardiovascular, Neurologic, Renal	Yes	Yes	2.3	447	2.15

[0276] The subject populations had the following baseline clinical and demographic characteristics.

Intervention	SOC group n=5	CER-001 group n=15	p-value
Age (years), mean (SD)	59 (10.29)	56.6 (18.63)	0.789
Male gender, n (%)	2 (40%)	4 (26.4%)	0.573
Site of infection/sepsis, n(%)			
Urine	4 (80%)	7 (46.7%)	
Intra-abdominal	0	6 (40%)	0.238
Other	1 (20%)	2 (13.3%)	
Hospital Unit, n(%)			
Intensive Care Unit	2 (40%)	7 (46.7%)	0.795
Nephrology	3 (60%)	8 (53.3%)	
SOFA score, mean (SD)	6.6 (6.07)	6.07 (4.62)	0.830
Arterial pressure, mean (SD)	85.8 (9.73)	81 (14.22)	0.495
Vasopressors use, n(%)	1 (20%)	5 (33.3%)	0.573
Mechanical Ventilation, n(%)	2 (40%)	6 (40%)	1
Acute Kidney Injury (AKI), n(%)	3 (60%)	8 (53.3%)	0.795
Renal Replacement Therapy (RRT), n(%)	1 (20%)	2 (13.3%)	0.717

[0277] Duration of study: This study was completed in 24 weeks (6 months). The enrolment period was approximately 20 weeks (5 months) from the first subject enrolled. The end of the study was the last visit of the last subject.

[0278] Primary endpoint: The co-primary endpoints of the study were (1) 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, (2) to determine the onset of AKI according to KDIGO criteria, and (3) to determine the severity of AKI according to KDIGO criteria.

[0279] Secondary endpoint: Secondary endpoints were:

- 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

[0280] Intervention/exposure: Twenty patients meeting the eligibility criteria, who signed and dated an ethical committee (EC)-approved informed consent form, were randomized and assigned (1:1:1:1) ratio to conventional therapy (Group A), low dose CER-001 (Group B), medium dose CER-001 (Group C), or high dose CER-001 (Group D). Conventional therapy was modulated according to the clinical conditions. All non-experimental treatments were allowed to be administered concomitantly during the patient's participation in this study: any medication the patient took, other than study drugs specified per protocol, was considered a concomitant medication and was recorded in the study records.

[0281] Each patient was identified at the screening by a patient number. Once assigned to a patient, the patient number was not reused. The investigators that enrolled patients did not participate in randomization and allocation assignment. The randomization list divided into blocks was adequately concealed to prevent attempts at subversion of randomization.

[0282] Treatment group: All patients received conventional therapy. Treated groups received 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.

[0283] FIG. 1 summarizes the study regimen.

[0284] Patients were pretreated with antihistamine prior to each CER-001 dose (*e.g.* dexchlorpheniramine 5 mg or hydroxyzine 100 mg) to avoid any potential infusion reactions.

[0285] Statistical analysis: Comparison between groups was performed using the appropriate statistical tests: dichotomous variables (baseline characteristics, mortality, development of AKI) were compared by the use of Chi-square or Fisher's exact test, continuous baseline characteristics by ANOVA or Kruskal-Wallis test, t Student or Mann-Whitney U test, as appropriate. Changes in inflammatory markers were compared between groups by ANOVA and were graphically represented. Proportion of patients of AKI and mortality rate were calculated for each group. All analyses were performed using SPSS 12.0 for Windows; $p < 0.05$ was considered statistically significant.

[0286] Procedures: The following procedures were performed during the screening visit. Following randomization, subjects initiated treatment within 2 business days.

- Informed consent
- Medical history - included: recording past and present illnesses and collection of the subject's demographic data (birth date, sex, and race).
- Physical examination with a review of systems, height and weight, BMI and waist circumference
- Vital signs (pulse, blood pressure, and oral, auricular, axillary, or core temperature).
- Review of inclusion/exclusion criteria.
- Adverse events were recorded starting from the time informed consent is obtained.
- Prior medications were collected from 4 weeks before the first dose of test article. All current medications were recorded.
- Complete blood count (CBC) – included white blood cell count (WBC) with differential, platelet count, red blood cell count (RBC), hemoglobin (Hb), hematocrit (Hct).
- Fasting chemistry panel/electrolytes: included 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 bilirubin, 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 – included prothrombin time (PT) (expressed as international normalized ratio [INR]), and partial thromboplastin time (PTT).
- Urinalysis – included specific gravity, pH, assessment of protein/albumin, glucose, ketones, and hemoglobin/blood.
- Microalbuminuria and Proteinuria g/24 h
- Serum or urine pregnancy test (for women of childbearing potential) within 7 days before randomization.
- Pharmacokinetic and pharmacodynamic assessment included ApoA-I and total cholesterol levels.

- Endotoxin levels were 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.

[0287] In addition to biological samples collected for the daily routine laboratory assessments performed at the Central laboratory, biological samples for research purposes were collected, including:

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

[0288] These samples were 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 was performed by ELISA test and protein arrays.

[0289] *On therapy visits (Treatment period):* Treatment period was defined as from the start of treatment. The visit was planned at Day 3, Day 6 and Day 9. A final visit was planned on Day 30. The following procedures were 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) were assessed
- Record adverse events and concomitant medications continually
- Complete blood count (CBC) – included white blood cell count (WBC) with differential, platelet count, red blood cell count (RBC), hemoglobin (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, □GT, ALP, total and direct bilirubin, albumin, total cholesterol, HDL, LDL, triglycerides, LDH, CPK
- ABG (for assessing respiratory and/or metabolic disorders)
- ApoA-I (for pharmacokinetic and pharmacodynamic assessment).
 - o Specifically, serum ApoA-I levels were assessed at day 1, day 3, day 6, and day 9. For subjects in the treatment groups, serum ApoA-I assessment took place before CER-001 administration. Specifically, the day 1 values were determined prior to any dosing, the day 3 values were determined about 12 hours after the fourth dose, the day 6 values were determined 60 hours after the sixth dose, and the day 9 values were determined 60 hours after the last dose.
- Coagulation tests – included prothrombin time (PT) (expressed as international normalized ratio [INR]), and partial thromboplastin time (PTT).
- Urinalysis – included specific gravity, pH, assessment of protein/albumin, glucose, ketones, and hemoglobin/blood.

- Microalbuminuria and Proteinuria g/24 h
 - Serum or urine pregnancy test (for women of childbearing potential) within 7 days before randomization.
 - Pharmacokinetic and pharmacodynamic assessment included ApoA-I and total cholesterol levels.
 - Endotoxin levels were measured using the EAA™ kit. AKI Biomarkers (TIMP-2 and IGFBP-7) were measured using the Nephrocheck® kit. Inflammatory markers included: CRP, D-dimer, Ferritin, IL-6, IL-8, GM-CSF, MCP 1 and TNF-α.
- [0290]** In addition to biological samples collected for the daily routine laboratory assessments performed at the Central laboratory, biological samples for research purposes were collected, including
- 2 tubes 5 ml of serum
 - 1 tube 3ml of plasma
 - urine 30ml
- [0291]** Clinical scores included the SOFA score (Table 2) and the KDIGO criteria for AKI assessment and staging (Table 3). Individual components of each score were documented.

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

SOFA Score:	0	1	2	3	4
Respiration					
PaO ₂ /FIO ₂ (mmHg) (P/F ratio)	≥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

[0292] 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									
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,s-VCAM-1, s-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.										

[0293] Safety Evaluations: Safety evaluations were 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 had a qualitative serum pregnancy test during pre-study screening/baseline evaluation and subsequently, if clinically indicated. Patients were monitored throughout the study for the occurrence of adverse events, that were recorded. Adverse events volunteered by the subject or discovered as a result of general questioning by the investigator or by physical examination were 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 were recorded for each reported adverse event.

[0294] Across all subjects, liver enzymes changed by anywhere from about 0.2-fold to about 4-fold of baseline levels after 9 days (**FIGS. 31A-31B**). Subjects receiving CER-001 had comparable changes to liver enzyme levels as the group receiving standard of care only.

[0295] Adverse events: Of the 20 subjects, 9 experienced adverse events, of which 7 were definitely not related to the test article (*i.e.*, the adverse event could be fully explained by the subject's clinical state or other agents/therapies), and 2 were probably not related to the test article (*i.e.*, the adverse event could most likely to be explained by the subject's clinical state or other agents/therapies, rather than the test article).

8.1.2. Results

[0296] In Sections 8.1.2.1 to 8.1.2.25, the following abbreviations are used: n.d., not determined; NS, not significant; NT, not tested.

8.1.2.1. Serum ApoA-I

[0297] FIGS. 30A-30D show mean ApoA-I levels for the control group and the aggregated study groups (**FIG. 30A**); shows mean ApoA-I levels for the control group and the aggregated study group, **FIG. 30B** shows mean ApoA-I levels for the control group and each study group, **FIG. 30C** shows ApoA-I changes for each subject in the standard of care group (SOC) and the experimental groups (CER-001), and **FIG. 30D** shows changes from baseline of ApoA-I levels for each subject broken out by study group, as measured by ELISA. Serum ApoA-I levels rapidly increased in the first 3 days of treatment in patients receiving CER-001, while the increase in the SOC group was delayed. Statistically significant differences were assessed by using a mixed model ANOVA (ns: $p > 0.05$).

[0298] The following table reports serum ApoA-I levels assessed on day 1, day 3, day 6, and day 9 for subjects in the CER-001 treatment groups.

ApoA-I by ELISA (g/L)					
Subject	CER-001 Tx Group	Day 1	Day 3	Day 6	Day 9
1	5 mg/kg BID	0.37	0.75	0.69	1.03
2	5 mg/kg BID	0.46	0.73	0.60	0.54
3	5 mg/kg BID	0.98	1.09	1.03	1.27
4	5 mg/kg BID	1.06	1.06	1.11	0.93

ApoA-I by ELISA (g/L)					
Subject	CER-001 Tx Group	Day 1	Day 3	Day 6	Day 9
5	5 mg/kg BID	0.315	0.4962	0.4284	0.39
6	10 mg/kg BID	1.15	1.43	1.03	1.66
7	10 mg/kg BID	0.61	0.13	0.72	0.82
8	10 mg/kg BID	1.03	1.48	1.01	1.35
9	10 mg/kg BID	0.41	0.75	0.88	0.51
10	10 mg/kg BID	0.64	0.97	0.76	0.87
11	20 mg/kg BID	1.18	1.67	1.23	1.46
12	20 mg/kg BID	0.56	1.03	1.40	n.d.
13	20 mg/kg BID	1.02	1.25	1.34	1.47
14	20 mg/kg BID	0.56	1.39	0.62	0.81
15	20 mg/kg BID	1.55	2.28	1.42	3.12

[0299] The results indicated that subjects in the treated groups had a wide range of ApoA-I levels at day 1 prior to CER-001 treatment (0.32 g/L to 1.55 g/L). The results also indicated that some but not all (2/8) subjects with day 1 ApoA-I levels below 1.0 g/L had ApoA-I levels of 1.0 g/L or higher on day 9. Further, most but not all (5/6) subjects with day 1 ApoA-I levels above 1.0 g/L had ApoA-I levels of 1.0 g/L or higher on day 9.

8.1.2.2. Lipopolysaccharides (LPS)

[0300] FIGS. 2A-2F show lipopolysaccharide (LPS) changes for the standard of care group (Group A) and the experimental groups (Groups B-D). FIG. 2A: LPS changes from baseline for Group A and aggregated Groups B-D. FIG. 2B: LPS changes from baseline for Group A, Group B, Group C, and Group D. FIG. 2C: LPS changes, reported as a percentage relative to peak LPS levels (peak = 100%), for Group A and aggregated Groups B-D. The treatment x study day effect relative to peak was $p < 0.0005$. FIG. 2D: LPS changes for Group A and aggregated Groups B-D, broken out by whether the subject was enrolled from the ICU or the nephrology department of the center. FIG. 2E: LPS changes from baseline for each subject in Group A and aggregated Groups B-D. FIG. 2F: LPS changes from baseline for each subject in each of Groups A-D. LPS levels were measured by ELISA. Statistically significant differences were assessed by using a mixed model ANOVA (ns: $p > 0.05$).

[0301] Generally, treatment regimens providing 5 mg/kg, 10 mg/kg, or 20 mg/kg CER-001 in addition to the SOC reduced LPS more than the SOC alone. Significant or near-significant results are summarized in the following table:

Treatment Effect	Overall	Day 3	Day 6	Day 9
CER-001 vs SOC	$p=0.0011$	$p=0.0494$	$p=0.0473$	$p=0.0039$
Treatment Groups	$p=0.0124$			
SOC vs 5		$p=0.0567$	NS	$p=0.0405$
SOC vs 10		$p=0.0401$	$p=0.0757$	$p=0.0329$
SOC vs 20		$p=0.0790$	$p=0.0126$	$p=0.0070$
5 vs 10		NS	NS	NS
5 vs 20		NS	$p=0.0363$	NS

Treatment Effect	Overall	Day 3	Day 6	Day 9
10 vs 20		NS	NS	NS

[0302] Consistent with animal data and the observed ApoA-I increase, treatment with CER-001 significantly decreased LPS bloodstream concentrations compared to SOC subjects (**FIG. 2E**). This observation reinforces the hypothesis of a positive impact of decreasing LPS on clinical outcomes. However, other studies highlighted the need to extend such a hypothesis beyond simply LPS removal (Monard *et al.*, 2023, *Critical Care* 27(1):36; Cavaillon *et al.*, 2020, *EMBO Molecular Medicine* 12(4)). Indeed, a pleiotropic effect including LPS decrease/inactivation and inhibition of cytokine storm cascade and/or endothelial dysfunction could have strong biochemical and clinical impacts. Without being bound by theory, it is believed that CER-001 not only decreases LPS level in animals and humans, but also has a direct interaction with the immune system through ApoA-I and also provides endothelial protection.

8.1.2.3. Endotoxin Activity Assay (EAA)

[0303] **FIGS. 3A-3E** show endotoxin activity assay (EAA) changes for the standard of care group (Group A) and the experimental groups (Groups B-D). **FIG. 3A**: EAA changes from baseline for Group A and aggregated Groups B-D. **FIG. 3B**: EAA changes from baseline for Group A, Group B, Group C, and Group D. **FIG. 3C**: EAA changes, reported as a percentage relative to peak EAA levels (peak = 100%), for Group A and aggregated Groups B-D. The treatment x study day effect relative to peak was $p < 0.1769$. **FIG. 3D**: EAA changes for Group A and aggregated Groups B-D, broken out by whether the subject was enrolled from the ICU or the nephrology department of the center. **FIG. 3E**: EAA changes from baseline for Group A and aggregated Groups B-D. EAA was performed at each timepoint using commercial kits (Spectral Medical, Toronto, Canada). Statistically significant differences were assessed by using a mixed model ANOVA (ns: $p > 0.05$).

[0304] Generally, treatment regimens providing 10 mg/kg CER-001 in addition to the SOC reduced EAA more than the SOC alone. Significant or near-significant results are summarized in the following table:

Treatment Effect	Overall	Day 3	Day 6	Day 9
CER-001 vs SOC	NS	NS	$p = 0.0590$	NS
Treatment Groups	NS			
SOC vs 5		NS	NS	NS
SOC vs 10		NS	$p = 0.0468$	NS
SOC vs 20		NS	NS	NT
5 vs 10		NS	NS	NS
5 vs 20		NS	NS	NT
10 vs 20		NS	NS	NT

8.1.2.4. TNF- α

[0305] **FIGS. 4A-4F** show TNF- α changes for the standard of care group (Group A) and the experimental groups (Groups B-D) measured by ELISA. Statistically significant differences were assessed by using a mixed model ANOVA (ns: $p > 0.05$). **FIG. 4A**: TNF- α changes from baseline for

Group A and aggregated Groups B-D. **FIG. 4B:** TNF- α changes from baseline for Group A, Group B, Group C, and Group D. **FIG. 4C:** TNF- α changes, reported as a percentage relative to peak TNF- α levels (peak = 100%), for Group A and aggregated Groups B-D. The treatment x study day effect relative to peak was $p < 0.0004$. **FIG. 4D:** TNF- α changes for Group A and aggregated Groups B-D, broken out by whether the subject was enrolled from the ICU or the nephrology department of the center. **FIG. 4E:** TNF- α changes from baseline for each subject in Group A and aggregated Groups B-D. **FIG. 4F:** TNF- α changes from baseline for each subject in each of Groups A-D.

[0306] Generally, treatment regimens providing 10 mg/kg CER-001 in addition to the SOC reduced TNF- α more than the SOC alone.

8.1.2.5. MCP-1

[0307] **FIGS. 5A-5F** show MCP-1 changes for the standard of care group (Group A) and the experimental groups (Groups B-D) measured by ELISA. Statistically significant differences were assessed by using a mixed model ANOVA (ns: $p > 0.05$). **FIG. 5A:** MCP-1 changes from baseline for Group A and aggregated Groups B-D. **FIG. 5B:** MCP-1 changes from baseline for Group A, Group B, Group C, and Group D. **FIG. 5C:** MCP-1 changes, reported as a percentage relative to peak MCP-1 levels (peak = 100%), for Group A and aggregated Groups B-D. The treatment x study day effect relative to peak was $p < 0.0090$. **FIG. 5D:** MCP-1 changes for Group A and aggregated Groups B-D, broken out by whether the subject was enrolled from the ICU or the nephrology department of the center. **FIG. 5E:** MCP-1 changes from baseline for Group A and aggregated Groups B-D. **FIG. 5F:** MCP-1 changes from baseline for each subject in each of Groups A-D.

8.1.2.6. Interleukin-6 (IL-6)

[0308] **FIGS. 6A-6F** show IL-6 changes for the standard of care group (Group A) and the experimental groups (Groups B-D) measured by ELISA. Statistically significant differences were assessed by using a mixed model ANOVA (ns: $p > 0.05$). **FIG. 6A:** IL-6 changes from baseline for Group A and aggregated Groups B-D. **FIG. 6B:** IL-6 changes from baseline for Group A, Group B, Group C, and Group D. **FIG. 6C:** IL-6 changes, reported as a percentage relative to peak IL-6 levels (peak = 100%), for Group A and aggregated Groups B-D. The treatment x study day effect relative to peak was $p < 0.0037$. **FIG. 6D:** IL-6 changes for Group A and aggregated Groups B-D, broken out by whether the subject was enrolled from the ICU or the nephrology department of the center. **FIG. 6E:** IL-6 changes from baseline for each subject in Group A and aggregated Groups B-D. **FIG. 6F:** IL-6 changes from baseline for each subject in each of Groups A-D.

[0309] Generally, treatment regimens providing CER-001 in addition to the SOC, and particular CER-001 at 10 mg/kg, reduced IL-6 more than the SOC alone. Significant or near-significant results are summarized in the following table:

Treatment Effect	Overall	Day 3	Day 6	Day 9
CER-001 vs SOC	$p = 0.0309$	$p = 0.0329$	NS	$p = 0.0290$
Treatment Groups	NS			
SOC vs 5		NS	NS	NS

Treatment Effect	Overall	Day 3	Day 6	Day 9
SOC vs 10		p=0.0304	NS	NS
SOC vs 20		NS	NS	NS
5 vs 10		NS	NS	NS
5 vs 20		NS	NS	NS
10 vs 20		NS	NS	NS

8.1.2.7. Interleukin-8 (IL-8)

[0310] FIGS. 7A-7F show IL-8 changes for the standard of care group (Group A) and the experimental groups (Groups B-D). **FIG. 7A:** IL-8 changes from baseline for Group A and aggregated Groups B-D measured by ELISA. Statistically significant differences were assessed by using a mixed model ANOVA (ns: $p > 0.05$). **FIG. 7B:** IL-8 changes from baseline for Group A, Group B, Group C, and Group D. **FIG. 7C:** IL-8 changes, reported as a percentage relative to peak IL-8 levels (peak = 100%), for Group A and aggregated Groups B-D. The treatment x study day effect relative to peak was $p < 0.0001$. **FIG. 7D:** IL-8 changes for Group A and aggregated Groups B-D, broken out by whether the subject was enrolled from the ICU or the nephrology department of the center. **FIG. 7E:** IL-8 changes from baseline for each subject in Group A and aggregated Groups B-D. **FIG. 7F:** IL-8 changes from baseline for each subject in each of Groups A-D.

[0311] Generally, treatment regimens providing CER-001 in addition to the SOC reduced IL-8 more than the SOC alone. Significant or near-significant results are summarized in the following table:

Treatment Effect	Overall	Day 3	Day 6	Day 9
CER-001 vs SOC	p=0.0453	p=0.0523	p=0.0040	p=0.0305
Treatment Groups	p=0.0681			
SOC vs 5		p=0.0525	p=0.0671	
SOC vs 10		p=0.0594	p=0.0197	p=0.0851
SOC vs 20			p=0.0476	p=0.0488
5 vs 10		NS	NS	NS
5 vs 20		NS	NS	NS
10 vs 20		NS	NS	NS

8.1.2.8. Interleukin-10 (IL-10)

[0312] FIGS. 8A-8D show IL-10 changes for the standard of care group (Group A) and the experimental groups (Groups B-D) measured by ELISA. Statistically significant differences were assessed by using a mixed model ANOVA (ns: $p > 0.05$). **FIG. 8A:** IL-10 changes from baseline for Group A and aggregated Groups B-D. **FIG. 8B:** IL-10 changes from baseline for Group A, Group B, Group C, and Group D. **FIG. 8C:** IL-10 changes, reported as a percentage relative to peak IL-10 levels (peak = 100%), for Group A and aggregated Groups B-D. The treatment x study day effect relative to peak was $p < 0.3780$. **FIG. 8D:**

IL-10 changes for Group A and aggregated Groups B-D, broken out by whether the subject was enrolled from the ICU or the nephrology department of the center.

8.1.2.9. s-TREM-1

[0313] **FIGS. 9A-9F** show s-TREM-1 changes for the standard of care group (Group A) and the experimental groups (Groups B-D) measured by ELISA. Statistically significant differences were assessed by using a mixed model ANOVA (ns: $p > 0.05$). **FIG. 9A**: s-TREM-1 changes from baseline for Group A and aggregated Groups B-D. **FIG. 9B**: s-TREM-1 changes from baseline for Group A, Group B, Group C, and Group D. **FIG. 9C**: s-TREM-1 changes, reported as a percentage relative to peak s-TREM-1 levels (peak = 100%), for Group A and aggregated Groups B-D. The treatment x study day effect relative to peak was $p < 0.0003$. **FIG. 9D**: s-TREM-1 changes for Group A and aggregated Groups B-D, broken out by whether the subject was enrolled from the ICU or the nephrology department of the center. **FIG. 9E**: s-TREM-1 changes from baseline for each subject in Group A and aggregated Groups B-D. **FIG. 9F**: s-TREM-1 changes from baseline for each subject in each of Groups A-D.

[0314] Generally, treatment regimens providing CER-001 in addition to the SOC reduced s-TREM-1 more than the SOC alone. Significant or near-significant results are summarized in the following table:

Treatment Effect	Overall	Day 3	Day 6	Day 9	Day 30
CER-001 vs SOC	$p=0.0103$	$p=0.0218$	$p=0.0382$	$p=0.0001$	$p=0.0005$
Treatment Groups	$p=0.0903$				
SOC vs 5		$p=0.0229$	$p=0.0600$	$p=0.0199$	$p=0.0199$
SOC vs 10		$p=0.0653$	NS	$p=0.0831$	$p=0.0831$
SOC vs 20		NS	NS	$p=0.0357$	$p=0.0357$
5 vs 10		NS	NS	NS	NS
5 vs 20		NS	NS	NS	NS
10 vs 20		NS	NS	NS	NS

8.1.2.10. s-VCAM and s-ICAM

[0315] **FIGS. 10A-10F** show s-VCAM changes for the standard of care group (Group A) and the experimental groups (Groups B-D) measured by ELISA. Statistically significant differences were assessed by using a mixed model ANOVA (ns: $p > 0.05$). **FIG. 10A**: s-VCAM changes from baseline for Group A and aggregated Groups B-D. **FIG. 10B**: s-VCAM changes from baseline for Group A, Group B, Group C, and Group D. **FIG. 10C**: s-VCAM changes, reported as a percentage relative to peak s-VCAM levels (peak = 100%), for Group A and aggregated Groups B-D. The treatment x study day effect relative to peak was $p < 0.0001$. **FIG. 10D**: s-VCAM changes for Group A and aggregated Groups B-D, broken out by whether the subject was enrolled from the ICU or the nephrology department of the center. **FIG. 10E**: s-VCAM changes from baseline for each subject in Group A and aggregated Groups B-D. **FIG. 10F**: s-VCAM changes from baseline for each subject in each of Groups A-D.

[0316] Generally, treatment regimens providing CER-001 in addition to the SOC reduced s-VCAM more than the SOC alone. Significant or near-significant results are summarized in the following table:

Treatment Effect	Overall	Day 3	Day 6	Day 9
CER-001 vs SOC	p=0.0090	NS	p=0.0520	p=0.0510
Treatment Groups	p=0.0870			
SOC vs 5		NS	p=0.0687	p=0.0805
SOC vs 10		NS	p=0.0556	p=0.0558
SOC vs 20		NS	p=0.0646	NS
5 vs 10		NS	NS	NS
5 vs 20		NS	NS	NS
10 vs 20		NS	NS	NS

[0317] FIGS. 11A-11F show s-ICAM changes for the standard of care group (Group A) and the experimental groups (Groups B-D) measured by ELISA. Statistically significant differences were assessed by using a mixed model ANOVA (ns: $p > 0.05$). **FIG. 11A:** s-ICAM changes from baseline for Group A and aggregated Groups B-D. **FIG. 11B:** s-ICAM changes from baseline for Group A, Group B, Group C, and Group D. **FIG. 11C:** s-ICAM changes, reported as a percentage relative to peak s-ICAM levels (peak = 100%), for Group A and aggregated Groups B-D. The treatment x study day effect relative to peak was $p < 0.0001$. **FIG. 11D:** s-ICAM changes for Group A and aggregated Groups B-D, broken out by whether the subject was enrolled from the ICU or the nephrology department of the center. **FIG. 11E:** s-ICAM changes from baseline for each subject in Group A and aggregated Groups B-D. **FIG. 11F:** s-ICAM changes from baseline for each subject in each of Groups A-D.

[0318] Generally, treatment regimens providing CER-001 in addition to the SOC reduced s-ICAM more than the SOC alone. Significant or near-significant results are summarized in the following table:

Treatment Effect	Overall	Day 3	Day 6	Day 9
CER-001 vs SOC	p=0.0015	NS	p=0.0020	p=0.0003
Treatment Groups	p=0.0127			
SOC vs 5		p=0.0552	p=0.0056	p=0.0454
SOC vs 10		NS	p=0.0213	p=0.0329
SOC vs 20		p=0.0831	p=0.0087	p=0.0023
5 vs 10		NS	NS	NS
5 vs 20		NS	NS	NS
10 vs 20		NS	NS	NS

8.1.2.11. Ferritin

[0319] FIGS. 12A-12D show ferritin changes for the standard of care group (Group A) and the experimental groups (Groups B-D). **FIG. 12A:** ferritin changes from baseline for Group A and aggregated Groups B-D. **FIG. 12B:** ferritin changes from baseline for Group A, Group B, Group C, and Group D. **FIG.**

12C: ferritin changes, reported as a percentage relative to peak ferritin levels (peak = 100%), for Group A and aggregated Groups B-D. The treatment x study day effect relative to peak was $p < 0.0962$. **FIG. 12D:** ferritin changes for Group A and aggregated Groups B-D, broken out by whether the subject was enrolled from the ICU or the nephrology department of the center.

8.1.2.12. White Blood Cells

[0320] FIGS. 13A-13D show white blood cell count changes for the standard of care group (Group A) and the experimental groups (Groups B-D). **FIG. 13A:** white blood cell count changes from baseline for Group A and aggregated Groups B-D. **FIG. 13B:** white blood cell count changes from baseline for Group A, Group B, Group C, and Group D. **FIG. 13C:** white blood cell count changes, reported as a percentage relative to peak white blood cell counts (peak = 100%), for Group A and aggregated Groups B-D. The treatment x study day effect relative to peak was $p = 0.5492$. **FIG. 13D:** white blood cell count changes for Group A and aggregated Groups B-D, broken out by whether the subject was enrolled from the ICU or the nephrology department of the center.

8.1.2.13. C-Reactive Protein

[0321] FIGS. 14A-14F show CRP changes for the standard of care group (Group A) and the experimental groups (Groups B-D). Statistically significant differences were assessed by using a mixed model ANOVA (ns: $p > 0.05$). **FIG. 14A:** CRP changes from baseline for Group A and aggregated Groups B-D. **FIG. 14B:** CRP changes from baseline for Group A, Group B, Group C, and Group D. **FIG. 14C:** CRP changes, reported as a percentage relative to peak CRP levels (peak = 100%), for Group A and aggregated Groups B-D. The treatment x study day effect relative to peak was $p < 0.6446$. **FIG. 14D:** CRP changes for Group A and aggregated Groups B-D, broken out by whether the subject was enrolled from the ICU or the nephrology department of the center. **FIG. 14E:** CRP changes from baseline for each subject in Group A and aggregated Groups B-D. **FIG. 14F:** CRP changes from baseline for each subject in each of Groups A-D.

8.1.2.14. KIM-1

[0322] FIGS. 15A-15D show KIM-1 changes for the standard of care group (Group A) and the experimental groups (Groups B-D). **FIG. 15A:** KIM-1 changes from baseline for Group A and aggregated Groups B-D. **FIG. 15B:** KIM-1 changes from baseline for Group A, Group B, Group C, and Group D. **FIG. 15C:** KIM-1 changes, reported as a percentage relative to peak KIM-1 levels (peak = 100%), for Group A and aggregated Groups B-D. The treatment x study day effect relative to peak was $p < 0.0001$. **FIG. 15D:** KIM-1 changes for Group A and aggregated Groups B-D, broken out by whether the subject was enrolled from the ICU or the nephrology department of the center.

8.1.2.15. Serum Albumin

[0323] FIGS. 16A-16E show serum albumin changes for the standard of care group (Group A) and the experimental groups (Groups B-D). **FIG. 16A:** serum albumin changes from baseline for Group A and aggregated Groups B-D. **FIG. 16B:** serum albumin changes from baseline for Group A, Group B, Group C, and Group D. **FIG. 16C:** serum albumin changes, reported as a percentage relative to peak serum albumin levels (peak = 100%), for Group A and aggregated Groups B-D. The treatment x study day effect

relative to peak was $p=0.1595$. **FIG. 16D**: serum albumin changes for Group A and aggregated Groups B-D, broken out by whether the subject was enrolled from the ICU or the nephrology department of the center. **FIG. 16E**: serum albumin changes from baseline for each subject in Group A and aggregated Groups B-D.

[0324] Generally, treatment regimens providing CER-001 in addition to the SOC raised serum albumin more than the SOC alone.

[0325] Significant or near-significant results are summarized in the following table:

Treatment Effect	Overall	Day 3	Day 6	Day9
CER-001 vs SOC	NS	NS	$p=0.0603$	NS
Treatment Groups	NS			
SOC vs 5		NS	NS	NS
SOC vs 10		NS	NS	NS
SOC vs 20		NS	NS	NS
5 vs 10		NS	NS	NS
5 vs 20		NS	NS	NS
10 vs 20		NS	NS	NS

8.1.2.16. Triglycerides

[0326] **FIG. 33** shows changes from baseline for triglycerides between the standard of care group (Group A) and the experimental groups (Groups B-D). Generally, treatment regimens providing CER-001 in addition to the SOC had slightly higher triglycerides than the SOC alone.

8.1.2.17. Serum Creatinine

[0327] **FIGS. 17A-17F** show serum creatinine changes for the standard of care group (Group A) and the experimental groups (Groups B-D). **FIG. 17A**: serum creatinine changes from baseline for Group A and aggregated Groups B-D. **FIG. 17B**: serum creatinine changes from baseline for Group A, Group B, Group C, and Group D. **FIG. 17C**: serum creatinine changes, reported as a percentage relative to peak serum creatinine levels (peak = 100%), for Group A and aggregated Groups B-D. The treatment x study day effect relative to peak was $p=0.1630$. **FIG. 17D**: serum creatinine changes for Group A and aggregated Groups B-D, broken out by whether the subject was enrolled from the ICU or the nephrology department of the center. **FIG. 17E**: area under the curve (AUC) (mean $\pm$ SEM) for serum creatinine for Group A and aggregated Groups B-D for all subjects, and subject populations from ICU and nephrology intake routes. **FIG. 17F**: AUC (95% confidence interval) for serum creatinine for Group A and aggregated Groups B-D, and subject populations from ICU and nephrology intake routes.

8.1.2.18. Estimated Glomerular Filtration Rate (eGFR)

[0328] **FIGS. 18A, 18B, and 18E** show eGFR changes for all subjects in the standard of care group (Group A) and the experimental groups (Groups B-D). Estimated GFR was determined by CKD-EPI. **FIG. 18A**: eGFR changes from baseline for Group A and aggregated Groups B-D. **FIG. 18B**: eGFR changes from baseline for Group A, Group B, Group C, and Group D. **FIG. 18E** shows eGFR changes, reported

as a percentage relative to peak levels (peak = 100%), for Group A and aggregated Groups B-D, for all subjects. The treatment x study day effect relative to peak was $p=0.5666$.

[0329] FIGS. 18C, 18D, and 18F show eGFR changes for subjects entering the study with AKI. **FIG. 18C:** eGFR changes from baseline for Group A and aggregated Groups B-D. **FIG. 18D:** eGFR changes for Group A, Group B, Group C, and Group D. **FIG. 18F** shows eGFR changes, reported as a percentage relative to peak levels (peak = 100%), for Group A and aggregated Groups B-D, for subjects entering the study with AKI. The treatment x study day effect relative to peak was $p=0.2406$.

[0330] Significant or near-significant results from - are summarized in the following table:

Treatment Effect	Overall	Day 3	Day 6	Day 9
CER-001 vs SOC	NS	NS	NS	NS
Treatment Groups	NS			
SOC vs 5		NS	NS	0.0525
SOC vs 10		NS	NS	NS
SOC vs 20		NT	NT	NT
5 vs 10		NS	NS	NS
5 vs 20		NT	NT	NT
10 vs 20		NT	NT	NT

8.1.2.19. P/F Ratio

[0331] FIG. 19 shows changes in the P/F ratio for all subjects in the standard of care group (Group A) and aggregated Groups B-D.

8.1.2.20. Days in ICU

[0332] FIG. 20 shows survival proportions for all subjects after days in ICU for the standard of care group (Group A, "SOC") and aggregated Groups B-D ("CER-001").

8.1.2.21. Thirty Day Survival

[0333] FIG. 21A shows 30-day survival proportions for all subjects for the standard of care group (Group A, "SOC") and aggregated Groups B-D ("CER-001").

[0334] FIG. 21B shows 30-day survival proportions for all subjects who entered the study from the center's ICU, for the standard of care group (Group A, "SOC") and aggregated Groups B-D ("CER-001").

8.1.2.22. AKI Staging

[0335] FIG. 22A shows the evolution of AKI, as assessed by KDIGO staging criteria, for all subjects in the standard of care group (Group A, "SOC"). AKI stages: 0, serum creatinine < 1.5x baseline or increased by less than 0.3 mg/dl within 48 hours, and urine volume > 0.5 ml/kg/h for 6-12 hours; 1, serum creatinine from 1.5 to 1.9x baseline or increased by more than 0.3 mg/dl, or urine volume < 0.5 ml/kg/h for 6-12 hours; 2, serum creatinine from 2.0 to 2.9x baseline or urine volume < 0.5 ml/kg/h for more than 12 hours; 3, serum creatinine 3.0x baseline or more or 4.0 mg/dl or more, or urine output < 0.3 ml/kg/h

for more than 24 hours or ≈ 0 for more than 12 hours. About 40% of SOC subjects were at AKI 0 (least severe) and the remainder were at AKI 2-3 (more to most severe) from Day 1 to Day 6.

[0336] **FIG. 22B** shows the evolution of AKI, as assessed by KDIGO staging criteria, for all subjects in aggregated Groups B-D ("CER-001"). About 60% of CER-001 subjects were at AKI 0 and 20% were at AKI 3 at Day 6.

8.1.2.23. Days on Mechanical Ventilation and Vasopressor

[0337] **FIG. 23** shows the number of days on mechanical ventilation for all subjects who entered into the study while in the center's ICU, for the standard of care group (Group A, SOC) and aggregated Groups B-D (CER-001). CER-001 reduced the number of days on mechanical ventilation relative to SOC for 5/7 subject.

[0338] **FIG. 24** shows the number of days on vasopressor for all subjects who entered into the study while in the center's ICU, for the standard of care group (Group A, SOC) and aggregated Groups B-D (CER-001).

8.1.2.24. Days on Dialysis

[0339] **FIG. 25A** shows the number of days on dialysis for all subjects who entered into the study while in the center's ICU, for the standard of care group (Group A) and aggregated Groups B-D. **FIG. 25B** shows this result for all subjects. Both intermittent and continuous modalities were considered. A reduction in the number of days of dialysis is indicative of improved kidney function.

8.1.2.25. Days Alive Without Organ Support, Days Until ICU

Discharge, and Changes in Hemodynamics

[0340] **FIG. 26** shows the number of days alive without organ support for all subjects who entered into the study while in the center's ICU, for the standard of care group (SOC) and aggregated Groups B-D (CER-001). Any use of vasopressors, mechanical ventilation, and/or renal support was considered organ support.

[0341] **FIG. 32** shows days until ICU discharge for all subjects who entered the study from the center's ICU, for the standard of care group (SOC) and aggregated Groups B-D (CER-001).

[0342] **FIGS. 27A-27B** show changes in daily average mean arterial pressure (MAP) for all subjects who entered into the study while in the center's ICU, for the standard of care group (SOC) and aggregated Groups B-D (CER-001). Decreases in MAP are generally desirable for ICU subjects.

[0343] **FIG. 28** shows the change in daily average heart rate (HR) for all subjects who entered into the study while in the center's ICU, for the standard of care group (SOC) and aggregated Groups B-D (CER-001). Decreases in MAP are generally desirable for ICU subjects.

[0344] **FIG. 29** shows the change in daily average P/F ratio for all subjects who entered into the study while in the center's ICU, for the standard of care group (SOC) and aggregated Groups B-D (CER-001). Increases in P/F ratio are generally desirable for ICU subjects.

8.1.3. Conclusions

[0345] Generally, coadministration of CER-001 with the standard of care led to improved scavenging of endotoxins (as shown by the LPS and EAA data), modulation of CRS (most pronounced for IL-6, IL-8,

and s-TREM-1), vascular endothelial protection (as shown by the s-VCAM and s-ICAM data), without increasing inflammation or negatively impacting AKI biomarkers or hemodynamics.

[0346] Notably, the trend of endothelial dysfunction markers s-VCAM and s-ICAM showed a different trend than ApoA-I among study participants, as their values increased in patients in the SOC group, while they significantly decreased with CER-001 treatment (**FIGS. 10A-10F, FIGS. 11A-11F**), suggesting an increased vascular protection as these mediators contribute to enhance tubular apoptosis and irreversible mechanisms of renal damage.

[0347] Recently the anti-inflammatory capacity of CER-001 was highlighted in a severe COVID-19 patient in ICU where assessment of serum amyloid A-1, inflammatory markers, and cytokines showed predominantly significant decreases during CER-001 infusion (Begue, *et al.*, 2021, *Sci Rep* **11**, 2291). Similarly, the data of this Example showed that CER-001 treatment induced a significant reduction of serum levels of MCP-1, TNF- α , IL-6 and IL-8 in treated-patients compared to SOC group (**FIG. 5E, FIG. 4E, FIG. 6E, and FIG. 7E**), suggesting the immunomodulatory and anti-inflammatory effects of CER-001 treatment and its ability to modulate the cytokine storm. Consistent with modulating the cytokine storm, a more pronounced reduction in C-reactive protein (CRP) in the first 9 days in the treated group compared to the SOC group was shown (**FIG. 14E**).

[0348] Soluble triggering receptor expressed on myeloid cells-1 (s-TREM-1) has been suggested as a strong predictor for poor prognosis and poor survival in septic patients. Persistently high s-TREM-1 levels during the first days following ICU admission are associated with mortality in human septic shock (Jolly, *et al.*, 2021, *Cell Mol Immunol* **18**, 2054-2056). The results of this Example suggest that s-TREM-1 rapidly decreases with CER-001 treatment within the first 3 days and remains low and stable through at least 30 days (**FIG. 9E**). More importantly, this decrease is accompanied by an amelioration of clinical signs and symptoms. All together, these observations confirm the potential anti-inflammatory effect of the ApoA-I complexes independent of LPS removal. Knowing that HDL and ApoA-I can directly interact with monocytes/macrophages through either receptor interactions such as SR-BI or transporters like ABCA-1 and/or ABCG-1, or by blocking contact-mediated activation of monocytes/macrophages by T lymphocytes as evidenced by TNF- α decrease (**FIG. 4E**) one can hypothesize a direct cellular effect of HDL and thus CER-001 on such cells leading to a global decrease of cytokine production by a yet unknown mechanism.

[0349] The potential impact of the cytokine cascade and endothelial dysfunction on clinical outcomes was evaluated given the strong effect of CER-001 observed.

[0350] The effects on organ dysfunction were analyzed with the hypothesis that the immunomodulatory effects of CER-001 treatment may limit renal dysfunction. For this purpose, renal function among study participants was analyzed and AKI onset and severity was classified according to KDIGO criteria based on both creatinine and urine output criteria. Overall, a low risk for the onset and/or progression to moderate to severe AKI (AKI stage 2-3) up to day 6 among CER-001 treated patients (26.6%) as compared to SOC group was observed, in which about 60% of patients presented such conditions (**FIG. 22A-22B**). These results are consistent with the laboratory and histological data reported in the animal model and confirmed the protective effects of the treatment.

[0351] In addition, the effects of the study drug on liver function were analyzed. As shown in **FIG. 31A-31B**, significant alteration of liver enzymes (AST, ALT) among CER-001 subjects were not observed; only 2 patients in the treated group presented a slight and no clinically significant increase in AST and ALT.

Conversely, an increase of albumin levels in the CER-001 treated group compared to SOC group was observed (**FIG. 16E**). Overall, these results supported the safety of CER-001 and the possibility that the early and sustained effects of the treatment on the inflammatory status may improve liver function and increase albumin production.

[0352] A subset of critically ill patients enrolled in the ICU were focused on to analyze the main clinical outcomes. Although the small sample size (7 treated patients; 2 SOC subjects) limits statistical evaluation, a reduced length of ICU stay among patients in the treatment group was observed (mean days of ICU stay 23.2 vs 29) (**FIG. 32**). In addition, the daily average mean arterial pressure (MAP) during the study period improved after the second day of treatment as compared to SOC subjects with an overall lower days on vasopressors (mean days 6.5 vs 8 in the SOC group) (**FIGS. 27A-27B, FIG. 24**). Similarly, days on mechanical ventilation (mean days 16.7 vs 26.5) were lower among CER-001 treated patients (**FIG. 23**). Both SOC subjects required dialysis during the study period, while only 3 of 7 CER-001 treated patients did (**FIGS. 25A-25B**).

[0353] Finally, the need for any form of organ support (a composite endpoint including mechanical ventilation, dialysis and/or use of vasopressors) was lower in the treated subjects (mean days alive and without organ support 5.8 vs 2) (**FIG. 26**). Overall, these results suggested a more rapid improvement of clinical conditions among patients who received CER-001 treatment.

[0354] In particular, the results demonstrate:

- Direct and significant effect of CER-001 on endotoxin removal and consequent reduction in the inflammatory cascade or “cytokine storm”
- Significant protective effect of CER-001 on endothelial functionality
- Trends towards fewer ICU days for patients treated, lower requirement for organ support, and improved 30-day survival
- Reinforcement of the well-established safety profile of CER-001

8.2. Example 2. CER-001 administration in view of measured per-subject ApoA-I levels

[0355] Serum ApoA-I levels are determined by ELISA for subjects having sepsis. Subjects with an ApoA-I level below a normal value (“low ApoA-I level”) receive CER-001 twice per day until the next determination. Serum ApoA-I levels are assessed at day 1, day 3, day 6, and day 9, in each case before CER-001 administration. Specifically, the day 1 values are determined prior to any dosing, the day 3 values are determined about 12 hours after a fourth dose is administered to any subject with a low Apo-I level on day 1, the day 6 values are determined 60 hours after a sixth dose is administered to any subject with a low Apo-I level on day 3, and the day 9 values are determined 60 hours after the last dose is administered to any subject with a low Apo-I level on day 6.

[0356] Subjects having sepsis have a range of ApoA-I levels at day 1 prior to CER-001 treatment. Subjects whose ApoA-I levels are restored to normal levels have better clinical outcomes compared to subjects whose ApoA-I levels are not restored to normal levels.

8.3. Discussion of Examples

[0357] Current treatment guidelines for septic patients are based on hemodynamic resuscitation, supportive therapy and adequate antibiotic therapy. However, in most critically ill patients, these measures are not enough to prevent sepsis-related organ dysfunction and the onset of AKI. The findings described in the Examples demonstrate, in a pilot clinical study testing the safety and efficacy of CER-001 in the treatment of a heterogeneous cohort of septic patients, the ability of CER-001 treatment to enhance LPS removal, to modulate the inflammatory response secondary to sepsis and to prevent endothelial and organ dysfunction was confirmed.

[0358] In the clinical study of Example 1, CER-001 was administered twice per day for three days, followed by two doses on day 6. A trend of increased serum ApoA-I levels in subjects administered CER-001 versus standard of care was observed at day 3, but sub-normal ApoA-I levels were observed in some subjects at day 6 (see, e.g., FIG. 30A-30B) even in some subjects administered relatively high amounts of exogenous ApoA-I as part of CER-001. Without being bound by theory, it is believed that this observation is due to increased ApoA-I clearance in some subjects, which may be exacerbated by impaired production of ApoA-I in some subjects in a critical care setting. It is further believed that ApoA-I levels correlate with clinical benefit, and that an improved therapeutic benefit in subjects having sepsis and other conditions (e.g., an acute condition described herein) can be achieved by administering lipid binding protein molecules such as ApoA-I in a dosing regimen that increases a sub-normal ApoA-I level to at least a normal level and/or maintains an ApoA-I level that is at least a normal level (e.g., > 1.1 g/L).

[0359] In summary, the present disclosure provides new treatment methods for conditions (e.g., acute conditions such as sepsis) using lipid binding protein molecules such as ApoA-I, including in lipid binding protein molecule-based complexes such as CER-001.

[0360] 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

[0361] 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.

[0362] 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.

WHAT IS CLAIMED IS:

1. A method of treating a subject having or at risk of a condition treatable with a lipid binding protein molecule, which is optionally sepsis (e.g., septic shock), comprising:
 - (a) optionally, administering one or more doses of a lipid binding protein molecule to the subject;
 - (b) measuring an ApoA-I level or an HDL level of the subject; and
 - (c) administering one or more doses of the lipid binding protein molecule to the subject if the measured ApoA-I level is below a target ApoA-I level or a target ApoA-I range or if the measured HDL level is below a target HDL level.
2. The method of claim 1, which comprises administering one or more doses of the lipid binding protein molecule to the subject prior to step (b).
3. The method of claim 2, wherein step (b) comprises measuring the ApoA-I level or HDL level 0.5 day to one week after the most recent administration of the lipid binding protein molecule.
4. The method of claim 2 or claim 3, wherein step (b) comprises measuring the ApoA-I level or HDL level on the day following the most recent administration of the lipid binding protein molecule.
5. The method of any one of claims 1 to 4, further comprising repeating steps (b) and (c) one or more times.
6. The method of claim 5, wherein steps (b) and (c) are repeated until the measured ApoA-I level is at or above the target ApoA-I level or within the target ApoA-I range or until the measured HDL level is at or above the target HDL level.
7. The method of any one of claims 1 to 6, which comprises step (a) and further comprising:
 - (d) administering one or more doses of the lipid binding protein molecule to the subject at a lower dose and/or frequency than in step (a) if the measured ApoA-I level or HDL level is at or above the target ApoA-I level, within the target ApoA-I range, or at or above the target HDL level.
8. The method of any one of claims 1 to 7, wherein the ApoA-I level is a serum, plasma, or whole blood ApoA-I level.
9. The method of any one of claims 1 to 8, wherein the target ApoA-I level is a normal ApoA-I level in healthy subjects.
10. The method of any one of claims 1 to 9, wherein the target ApoA-I range is a normal ApoA-I range in healthy subjects.
11. The method of any one of claims 1 to 10, wherein the HDL level is a serum, plasma, or whole blood HDL level.

12. The method of any one of claims 1 to 11, wherein the HDL level is an HDL-cholesterol (HDL-C) level.
13. The method of any one of claims 1 to 12, wherein the target HDL level is a normal HDL level in healthy subjects.
14. The method of any one of claims 1 to 13, wherein the ApoA-I level is an ApoA-I level as measured by enzyme-linked immunoassay (ELISA), immunoturbidimetry, or immunonephelometry.
15. The method of any one of claims 1 to 14, wherein the HDL level is an HDL-C level as measured by a cholesterol oxidase (CHOD) and cholesterol esterase (CHER) enzymatic assay.
16. The method of any one of claims 1 to 15, wherein the condition is an acute condition.
17. The method of any one of claims 1 to 16, wherein the condition is sepsis.
18. The method of any one of claims 1 to 16, wherein the condition is sepsis-induced cognitive deficiency.
19. The method of claim 17 or claim 18, wherein the subject has sepsis.
20. The method of claim 19, wherein the subject has septic shock.
21. The method of claim 19 or claim 20, wherein the subject is at risk (e.g., high risk) of developing acute kidney injury.
22. The method of any one of claims 1 to 21, wherein the subject has a bacterial infection, optionally with an antibiotic-resistant bacterium (e.g., MRSA).
23. The method of any one of claims 1 to 21, wherein the subject has a viral infection.
24. The method of any one of claims 1 to 16, wherein the condition is acute myocardial infarction (AMI), cytokine release syndrome (CRS), ischemia reperfusion-induced tissue injury, post-operative inflammation, sepsis-induced acute kidney injury (AKI), or hypoalbuminemia.
25. The method of any one of claims 1 to 16, wherein the condition is asthma, e.g., acute severe asthma.
26. The method of any one of claims 1 to 16, wherein the condition is graft versus host disease (GVHD), optionally wherein the subject has received a stem cell transplant, bone marrow transplant, or organ transplant.
27. The method of any one of claims 1 to 26, wherein the subject has CRS or is at risk of CRS.
28. The method of any one of claims 1 to 27, wherein the subject has or is at risk of developing acute kidney injury (AKI).

29. The method of any one of claims 1 to 28, wherein the subject has or at risk of acute respiratory distress syndrome (ARDS).
30. The method of any one of claims 1 to 29, wherein the lipid binding protein molecule is an apolipoprotein.
31. The method of claim 30, wherein the apolipoprotein is ApoA-I.
32. The method of claim 31, wherein the ApoA-I has the amino acid sequence of amino acids 25-267 of SEQ ID NO:2.
33. The method of claim 31 or claim 32, wherein the ApoA-I is a recombinant ApoA-I.
34. The method of claim 33, wherein the ApoA-I is produced by a mammalian host cell.
35. The method of claim 34, wherein the mammalian host cell is a Chinese hamster ovary (CHO) cell.
36. The method of claim 35, wherein the CHO cell is a CHO-S cell.
37. The method of any one of claims 1 to 36, wherein the lipid binding protein molecule is a component of a lipid binding protein-based complex, optionally wherein the lipid binding protein-based complex is a reconstituted HDL or HDL mimetic.
38. The method of claim 37, wherein the lipid binding protein-based complex is CER-001.
39. The method of any one of claims 1 to 38, wherein the lipid binding protein molecule is administered systemically, optionally by infusion.
40. The method of any one of claims 1 to 39, wherein each individual dose of the lipid binding protein molecule administered in step (c) is 4 mg/kg to 40 mg/kg (on a protein-weight basis).
41. The method of any one of claims 1 to 39, wherein each dose of the lipid binding protein molecule administered in step (c) is 300 mg to 4000 mg (on a protein weight basis).
42. The method of any one of claims 1 to 41, 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.
43. The method of claim 42, wherein the one or more additional therapies comprise one or more standard of care therapies for the condition.