an HDL Therapeutic is receiving a therapeutically effective or optimal dose while optimizing the safety.

[0070] The methods as described herein can be employed wherein the subject is being treated for a Condition (as defined in Section 6.1 below) with an HDL Therapeutic, or to identify or optimize a dosing schedule for an HDL Therapeutic to treat a subject suffering from a Condition.

[0071] Also provided herein is a method of predicting the likelihood of response of a subject to treatment with an HDL Therapeutic.

[0072] In certain embodiments, the present disclosure relates to methods of treating a subject suffering from a Condition with an HDL Therapeutic, identifying a suitable dose of an HDL Therapeutic for treating a Condition, mobilizing cholesterol in a subject suffering from a Condition, or monitoring the efficacy of an HDL Therapeutic in a subject. The methods typically comprise administering an HDL Therapeutic to a subject (one or more times, for example in accordance with a dosing regimen) and monitoring changes in gene expression of at least one, in some embodiments two or three or more, HDL Markers in a test sample from the individual. Any changes can be as compared to the subject's own baseline, the subject's prior measurements, and/or a control obtained from measuring the one or more HDL Markers in a population of individuals. The population of individuals can be any appropriate population, *e.g.*, healthy individuals, individuals suffering from a Condition, genetically matched individuals, *etc.* Following measurement, the dose, frequency of dosing or both, can be adjusted if the HDL Therapeutic down regulates components of the cholesterol efflux pathway to a degree such that therapeutic efficacy is attenuated. In some embodiments, a dose is identified that does not alter or even increases the expression levels of one or more HDL Markers in the subject's circulating monocytes, macrophages or mononuclear cells.

[0073] In some embodiments, the methods comprise the steps of: (a) obtaining a first test sample from the subject or a population of subjects; (b) measuring expression levels of one or more HDL Markers (as defined in Section 6.1 below) in the test sample; (c) administering a dose (or a series of doses) of an HDL Therapeutic to the subject or a population of subjects; (d) obtaining a second test sample from the subject or the population of subjects; and (e) measuring expression levels of the one or more HDL Markers in the second test sample. In some embodiments, the first sample is obtained prior to treatment with the HDL Therapeutic. In other embodiments, the first sample is

expression of an HDL Marker (*e.g.*, primers and/or probes for detection of an HDL Marker in the case of a nucleic acid assay and at least one anti-HDL Marker antibody (polyclonal or monoclonal) in the case of a protein assay). In another embodiment, HDL markers are determined with the help of a cell sorter or a FACS instrument used to separate cells from a biological sample (for instance blood or lymph).

[0077] Also presented herein are methods of treating a subject suffering from familial hypoalphalipoproteinemia, *e.g.*, an ABCA1 deficiency, with an HDL Therapeutic. Preferably, the therapy is given in two phases, an initial, more intense "induction" phase and a subsequent, less intense "maintenance" phase. Optionally, the therapy is given according to a dosing schedule identified using the methods described herein.

[0077a] In one aspect, there is provided use of an HDL Therapeutic, which is optionally CER-001, in the manufacture of a medicament for treating a subject with an ABCA1 deficiency, optionally wherein the subject is heterozygous for an ABCA1 mutation or homozygous for an ABCA1 mutation. In another aspect, there is provided use of an HDL Therapeutic, which is optionally CER-001, in the manufacture of a medicament for treating a subject suffering from familial primary hypoalphalipoproteinemia, wherein the medicament is to be administered according to: (a) an induction regimen; and, subsequently (b) a maintenance regimen, optionally wherein the medicament is to be administered at a lower dose, a lower frequency, or both.

[0078] Also presented herein are methods of treating a subject suffering from an LCAT deficiency (homozygote or heterozygote) with an HDL Therapeutic, optionally using a dosing schedule identified using the methods described herein.

[0079] Also presented herein are methods of treating a subject suffering from an ApoA-I deficiency (homozygote or heterozygote) with an HDL Therapeutic, optionally using a dosing schedule identified using the methods described herein.

[0080] Also presented herein are methods of treating a subject suffering from an low HDL levels (below 40 mg/dl of HDL-chol in men or below 50mg/dl of HDL-chol in women) with an HDL Therapeutic, optionally using a dosing schedule identified using the methods described herein.

[0081] In certain embodiments, the disclosure provides a method of identifying a dose of an HDL Therapeutic effective to mobilize cholesterol in a subject. In some embodiments, the method comprises: (a) administering a first dose of an HDL Therapeutic to a subject, (b) following administering said first dose, measuring expression levels of one or more HDL Markers in said subject's circulating monocytes, macrophages or mononuclear cells to evaluate the effect of said first dose on said expression levels; and (c) (i) if the subject's expression levels of one or more HDL Markers are reduced by more than a cutoff amount, administering a second dose of said HDL Therapeutic, wherein the second dose of said HDL Therapeutic is lower than the first dose; or (ii) if the subject's expression levels of one or more HDL Markers are not reduced by more than the cutoff amount, treating the subject with the first dose of said HDL Therapeutic.

[0081a] In another aspect, there is provided a method of identifying a dose of an HDL Therapeutic effective to mobilize cholesterol in a sample to be obtained from a subject, wherein the subject has been administered a first dose of the HDL Therapeutic, the method comprising:

(a) measuring expression levels of one or more HDL Markers in said subject's circulating monocytes, macrophages or mononuclear cells to evaluate the effect of said first dose on said expression levels; and

(b) (i) if the subject's expression levels of one or more HDL Markers are below a cutoff amount, a second dose of said HDL Therapeutic is to be administered, wherein the second dose of said HDL Therapeutic is lower than the first dose; or

(ii) if the subject's expression levels of one or more HDL Markers are not below the cutoff amount, the first dose of said HDL Therapeutic is to be administered;

wherein the cutoff amount is (i) determined from a dose response curve for the HDL Therapeutic or (ii) is relative to a reference expression level for the one or more HDL Markers.

[0082] In certain embodiments, the disclosure provides a method for monitoring the efficacy of an HDL Therapeutic in a subject. In some embodiments, the method comprises: (a) treating a subject with an HDL Therapeutic according to a first dosing schedule, (b) measuring expression levels of one or more HDL Markers in said subject's circulating monocytes, macrophages or mononuclear cells to evaluate the effect of said first dosing schedule on said expression levels; and (c) (i) if the subject's expression levels of one or more HDL Markers are reduced by more than an upper cutoff amount, treating the subject with the HDL Therapeutic according to a second dosing schedule, wherein the second dosing schedule comprises one or more of: administering a lower dose of the HDL Therapeutic, infusing the HDL Therapeutic into the subject over a longer period of time, and administering the HDL Therapeutic to the subject on a less frequent basis; (ii) if the subject's expression levels of one or more HDL Markers are not reduced by more than a lower cutoff amount, treating the subject with the HDL Therapeutic according to a second dosing schedule, wherein the second dosing schedule comprises one or more of: administering a higher dose of the HDL Therapeutic, infusing the HDL Therapeutic into the subject over a shorter period of time, and administering the HDL Therapeutic to the subject on a more frequent basis; or (iii) if the subject's expression levels of one or more HDL Markers are reduced by an amount

between the upper and lower cutoff amounts, continuing to treat the subject according to the first dosing schedule.

[0082a] In another aspect, there is provided a method for monitoring the efficacy of an HDL Therapeutic in a sample to be obtained from a subject, wherein the subject has been administered with the HDL Therapeutic according to a first dosing schedule, the method comprising:

(a) measuring expression levels of one or more HDL Markers in said subject's circulating monocytes, macrophages or mononuclear cells to evaluate the effect of said first dosing schedule on said expression levels; and

(b) (i) if the subject's expression levels of one or more HDL Markers are below a lower cutoff amount, the HDL Therapeutic is to be administered according to a second dosing schedule, wherein the second dosing schedule comprises one or more of: a lower dose of the HDL Therapeutic which to be administered, the HDL Therapeutic which to be infused into the subject over a longer period of time, and the HDL Therapeutic which is to be administered to the subject on a less frequent basis;

(ii) if the subject's expression levels of one or more HDL Markers are above an upper cutoff amount, the HDL Therapeutic is to be administered according to a second dosing schedule, wherein the second dosing schedule comprises one or more of: a higher dose of the HDL Therapeutic which is to be administered, the HDL Therapeutic which is to be infused into the subject over a shorter period of time, and the HDL Therapeutic which is to be administered to the subject on a more frequent basis; or

(iii) if the subject's expression levels of one or more HDL Markers are between the upper and lower cutoff amounts, the HDL therapeutic is continued to be administered to the subject according to the first dosing schedule;

wherein the upper cutoff amount and lower cutoff amount are (i) determined from a dose response curve for the HDL Therapeutic or (ii) are relative to a reference expression level for the one or more HDL Markers.

[0083] The cutoff amount may be relative to the subject's own baseline prior to said administration or the cutoff amount may be relative to a control amount such as a population average from *e.g.*, healthy subjects or a population with the same disease

condition as the subject or a population sharing one more disease risk genes with the subject.

[0084] In certain embodiments, the disclosure provides a method of identifying a dose of an HDL Therapeutic effective to mobilize cholesterol. In some embodiments, the method comprises: (a) administering a first dose of an HDL Therapeutic to a population of subjects; (b) following administering said first dose, measuring expression levels of one or more HDL Markers in said subjects' circulating monocytes, macrophages or mononuclear cells to evaluate the effect of said first dose on said expression levels; (c) administering a second dose of said HDL Therapeutic, wherein the second dose of said HDL Therapeutic is greater or lower than the first dose; (d) following administering said second dose, measuring expression levels of one or more HDL Markers in said subjects'

WHAT IS CLAIMED IS:

1. A method of identifying a dose of an HDL Therapeutic effective to mobilize cholesterol in a sample to be obtained from a subject, wherein the subject has been administered a first dose of the HDL Therapeutic, the method comprising:

(a) measuring expression levels of one or more HDL Markers in said subject's circulating monocytes, macrophages or mononuclear cells to evaluate the effect of said first dose on said expression levels; and

(b) (i) if the subject's expression levels of one or more HDL Markers are below a cutoff amount, a second dose of said HDL Therapeutic is to be administered, wherein the second dose of said HDL Therapeutic is lower than the first dose; or

(ii) if the subject's expression levels of one or more HDL Markers are not below the cutoff amount, the first dose of said HDL Therapeutic is to be administered;

wherein the cutoff amount is (i) determined from a dose response curve for the HDL Therapeutic or (ii) is relative to a reference expression level for the one or more HDL Markers.

2. The method according to claim 1, wherein the cutoff amount is relative to a reference expression level for the one or more HDL Markers, optionally wherein:

(a) the reference expression level is (i) the subject's own baseline prior to said administration or (ii) a control amount, which is optionally a population average, which is optionally from healthy subjects or from a population with the same disease condition as the subject, and/or

(b) the cutoff amount is 10%-80%, 20%-80%, 30%-70%, 40%-60%, 10%-50%, 10%-40%, or 20%-50% of the reference expression level.

3. The method according to claim 1 wherein the cutoff amount is determined from a dose response curve for the HDL Therapeutic, optionally wherein the cutoff amount

is 25% - 75% or 40%-60% of the expression level of the one or more HDL Markers at an inflection point in the dose response curve.

4. The method according to any one of claims 1 to 3, wherein the method further comprises, following administration of said second dose, measuring expression levels of one or more HDL Markers in said subject's circulating monocytes, macrophages or mononuclear cells to evaluate the effect of said second dose on said expression levels, and optionally wherein if the subject's expression levels of one or more HDL Markers are below the cutoff amount, a third dose of said HDL Therapeutic is to be administered, wherein the third dose of said HDL Therapeutic is lower than the second dose.

5. The method according to any one of claims 1 to 4, wherein

(a) at least one of the HDL Markers is ABCA1, optionally wherein ABCA1 mRNA expression levels or ABCA1 protein expression levels are measured, and optionally wherein ABCA1 expression levels are measured 2-12 hours, 4-10 hours, 2-8 hours, 2-6 hours, 4-6 hours or 4-8 hours after administration of the HDL Therapeutic;

(b) at least one of the HDL Markers is ABCG1, optionally wherein ABCG1 mRNA expression levels or ABCG1 protein expression levels are measured, and optionally wherein ABCG1 expression levels are measured 2-12 hours, 4-10 hours, 2-8 hours, 2-6 hours, 4-6 hours or 4-8 hours after administration of the HDL Therapeutic;

(c) at least one of the HDL Markers is SREBP-1, optionally wherein SREBP-1 mRNA expression levels or SREBP-1 protein expression levels are measured, and optionally wherein SREBP-1 expression levels are measured 2-12 hours, 4-10 hours, 2-8 hours, 2-6 hours, 4-6 hours or 4-8 hours after administration of the HDL Therapeutic; or

(d) any combination of (a)-(c).

6. A method for monitoring the efficacy of an HDL Therapeutic in a sample to be obtained from a subject, wherein the subject has been administered with the HDL Therapeutic according to a first dosing schedule, the method comprising:

(a) measuring expression levels of one or more HDL Markers in said subject's circulating monocytes, macrophages or mononuclear cells to evaluate the effect of said first dosing schedule on said expression levels; and

(b) (i) if the subject's expression levels of one or more HDL Markers are below a lower cutoff amount, the HDL Therapeutic is to be administered according to a second dosing schedule, wherein the second dosing schedule comprises one or more of: a lower dose of the HDL Therapeutic which to be administered, the HDL Therapeutic which to be infused into the subject over a longer period of time, and the HDL Therapeutic which is to be administered to the subject on a less frequent basis;

(ii) if the subject's expression levels of one or more HDL Markers are above an upper cutoff amount, the HDL Therapeutic is to be administered according to a second dosing schedule, wherein the second dosing schedule comprises one or more of: a higher dose of the HDL Therapeutic which is to be administered, the HDL Therapeutic which is to be infused into the subject over a shorter period of time, and the HDL Therapeutic which is to be administered to the subject on a more frequent basis; or

(iii) if the subject's expression levels of one or more HDL Markers are between the upper and lower cutoff amounts, the HDL therapeutic is continued to be administered to the subject according to the first dosing schedule;

wherein the upper cutoff amount and lower cutoff amount are (i) determined from a dose response curve for the HDL Therapeutic or (ii) are relative to a reference expression level for the one or more HDL Markers.

7. The method according to claim 6, wherein

(a) at least one of the HDL Markers is ABCA1, optionally wherein ABCA1 mRNA expression levels or ABCA1 protein expression levels are measured, and optionally wherein ABCA1 expression levels are

measured 2-12 hours, 4-10 hours, 2-8 hours, 2-6 hours, 4-6 hours or 4-8 hours after administration of the HDL Therapeutic;

(b) at least one of the HDL Markers is ABCG1, optionally wherein ABCG1 mRNA expression levels or ABCG1 protein expression levels are measured, and optionally wherein ABCG1 expression levels are measured 2-12 hours, 4-10 hours, 2-8 hours, 2-6 hours, 4-6 hours or 4-8 hours after administration of the HDL Therapeutic;

(c) at least one of the HDL Markers is SREBP-1, optionally wherein SREBP-1 mRNA expression levels or SREBP-1 protein expression levels are measured, and optionally wherein SREBP-1 expression levels are measured 2-12 hours, 4-10 hours, 2-8 hours, 2-6 hours, 4-6 hours or 4-8 hours after administration of the HDL Therapeutic; or

(d) any combination of (a)-(c).

8. The method according to any one of claims 1 to 7, wherein the subject is human or a non-human animal, optionally wherein the non-human animal is a mouse.

9. The method according to any one of claims 1 to 8, wherein the subject has an ABCA1 deficiency, optionally wherein the subject is homozygous for an ABCA1 mutation or is heterozygous for an ABCA1 mutation.

10. The method according to any one of claims 1 to 9, wherein the HDL Therapeutic is

(a) a lipoprotein complex, optionally wherein lipoprotein complex:

(i) comprises an apolipoprotein, which is optionally ApoA-I, ApoA-II, ApoA-IV, ApoE or a combination thereof;

(ii) comprises an apolipoprotein peptide mimic, which is optionally an ApoA-I, ApoA-II, ApoA-IV, or ApoE peptide mimic or a combination thereof; or

(iii) is CER-001, CSL-111, CSL-112, or ETC-216;

or

(b) a small molecule, optionally wherein the small molecule:

(i) is a CETP inhibitor; or

(ii) is a pantothenic acid derivative.

11. Use of an HDL Therapeutic, which is optionally CER-001, in the manufacture of a medicament for treating a subject with an ABCA1 deficiency, optionally wherein the subject is heterozygous for an ABCA1 mutation or homozygous for an ABCA1 mutation.

12. Use of an HDL Therapeutic, which is optionally CER-001, in the manufacture of a medicament for treating a subject suffering from familial primary hypoalphalipoproteinemia, wherein the medicament is to be administered according to:

(a) an induction regimen; and, subsequently

(b) a maintenance regimen, optionally wherein the medicament is to be administered at a lower dose, a lower frequency, or both.

13. The use according to claim 12, wherein the subject is:

(a) heterozygous or homozygous for an ABCA1 mutation;

(b) homozygous or heterozygous for an LCAT mutation;

(c) homozygous or heterozygous for an ApoA-I mutation;

(d) homozygous or heterozygous for an ABCG1 mutation;

(e) one which has been treated with a lipid control medication, which is optionally is atorvastatin, ezetimibe, niacin, rosuvastatin, simvastatin, aspirin, fluvastatin, lovastatin, pravastatin or a combination thereof; or

(f) any combination of (a)-(e).

14. The use according to claim 12 or claim 13, wherein the medicament comprises CER-001 and optionally wherein:

(a) the induction regimen is of a duration of 4 weeks;

(b) the induction regimen comprises CER-001 which is to be administered three times a week;

(c) the dose to be administered in the induction regimen is 8-15 mg/kg (on a protein weight basis), which is optionally 8 mg/kg, 12 mg/kg or 15 mg/kg;

(d) the maintenance regimen comprises CER-001 which is to be administered for at least one month, at least two months, at least three months, at least six months, at least a year, at least 18 months, at least two years, or indefinitely;

(e) the maintenance regimen comprises CER-001 which is to be administered twice a week;

(f) the dose to be administered in the maintenance regimen is 1-6 mg/kg (on a protein weight basis), which is optionally 1 mg/kg, 3 mg/kg or 6 mg/kg.

15. The use according to any one of claims 12 to 14, wherein:

(a) the induction regimen utilizes a dose that reduces expression levels of one or more HDL Markers by 20%-80% or 40%-60%, as compared to the subject's baseline amount and/or a population average; and/or

(b) the maintenance regimen utilizes a dose that does not reduce expression levels of one or more HDL Markers by more than 20% or more than 10% as compared to the subject's baseline amount and/or a population average, optionally wherein the maintenance regimen utilizes a dose that does not reduce expression levels of one or more HDL Markers.