

5 unexpectedly” that human LAG3 or derivatives thereof when inoculated into patients with highly malignant tumors induced a potent immunity which is monocyte dependent. The induced immunity manifests itself by a significant increase in blood monocyte counts. Despite the use of hLAG3 as a vaccine adjuvant to boost T-cell counts in known cancer patients, no one has yet been motivated to peremptorily screen for a LAG3 deficiency marker
10 and, if found, ameliorate the consequent risk by treating prospective patients with recombinant human LAG3 by periodic administration of at different time points. The present inventor does this by pre-screening patients at risk for cardiovascular disease, other chronic inflammatory diseases, cardiovascular and/or non-cardiovascular morbidity and mortality using specific 2-point expression profiles (combinations of mutations and/or non-genetic
15 causes , e.g., SCARB1 rs10846744 mutation and/or LAG-3 rs870849 or other genetic or non-genetic causes and a mutation), followed by a tailored therapeutic regimen using recombinant human lymphocyte activation gene-3 as a companion therapeutic.

SUMMARY OF THE INVENTION

20 It is, therefore, an object of the present innovation to provide a novel strategy for assessing patients at risk for cardiovascular disease, other chronic inflammatory diseases, cardiovascular and/or non-cardiovascular morbidity and mortality based on lymphocyte activation gene 3 (LAG3) protein deficiency, and for mediating said risk with a tailored therapeutic regimen including use of recombinant human lymphocyte activation gene-3 as a
25 companion therapeutic.

In one aspect, the present invention provides for the use of soluble lymphocyte activation gene 3 (sLAG3) as an adjuvant with at least one agent in the manufacture of a medicament for combination therapy of chronic inflammatory and cardiovascular disease in a human adult

5 subject, wherein a qualitative pre-screen of said subject's medical or family history or
symptoms to detect a predisposition to cardiovascular or chronic inflammatory disease; a
quantitative test on said subject if said qualitative pre-screen indicates a predisposition to
cardiovascular or chronic inflammatory disease, that a blood sample is to be obtained from
said human adult subject and genotyping to detect the presence of the SCARB I rs10846744
10 and the LAG3 rs870849 mutations; a LAG3 expression profile is to be compiled from
combined results of said qualitative prescreen and said quantitative test indicating risk that
the subject has a deficiency in LAG3 expression; and the medicament is to be administered to
the subject when said LAG3 expression profile indicates that the subject is at risk of a
deficiency in LAG3 expression in form of a therapeutic regimen of sLAG3 in combination
15 with one or more agents from a group including an anti-inflammatory agent, an anti-
atherosclerotic agent, a statin, an anti-hyperlipidemic agent, and a PCSK9 inhibitor.

In one example, the method comprises a first step of qualitatively pre-screening a
subject for one or more risk factors for developing cardiovascular disease, a second step of
quantitatively detecting a LAG3 protein deficiency in a sample from the subject, and a third

- 5 I claim:
1. Use of soluble lymphocyte activation gene 3 (sLAG3) as an adjuvant with at least one agent in the manufacture of a medicament for combination therapy of chronic inflammatory and cardiovascular disease in a human adult subject, wherein
- 10 a qualitative pre-screen of said subject's medical or family history or symptoms to detect a predisposition to cardiovascular or chronic inflammatory disease;
- a quantitative test on said subject if said qualitative pre-screen indicates a predisposition to cardiovascular or chronic inflammatory disease, that a blood sample is to be obtained from said human adult subject and genotyping to detect the presence of the SCARB
- 15 I rs10846744 and the LAG3 rs870849 mutations;
- a LAG3 expression profile is to be compiled from combined results of said qualitative pre-screen and said quantitative test indicating risk that the subject has a deficiency in LAG3 expression; and
- the medicament is to be administered to the subject when said LAG3 expression
- 20 profile indicates that the subject is at risk of a deficiency in LAG3 expression in form of a therapeutic regimen of sLAG3 in combination with one or more agents from a group including an anti-inflammatory agent, an anti-atherosclerotic agent, a statin, an anti-hyperlipidemic agent, , and a PCSK9 inhibitor.
- 25 2. The use of claim 1, wherein said qualitative pre-screen of said subject comprises pre-screening a medical record.

- 5 3. The use of claim 1, wherein said qualitative pre-screen of said subject comprises pre-screening a family history.
4. The use of claim 1, wherein said quantitative test comprises that a quantitative test is to be administered on a blood sample from said subject to confirm said LAG3 protein deficiency.
- 10 5. The use of claim 1, wherein said quantitative test comprises both a genetic test and an assay of a plasma sample from said subject for presence of low level expression of LAG3 below 3400 pg/ml.
6. The use of claim 1, wherein said quantitative genetic test is configured to detect a polymorphism in the coding sequence of the *SCARB1* or *LAG3* genes.
- 15 7. The use of claim 6, wherein said quantitative test on said blood sample includes amplifying at least a portion of a *SCARB1* or *LAG3* gene prior to identifying an allelic variant.
8. The use of claim 1, wherein the therapeutic regimen comprises that recombinant human LAG3 is to be administered periodically.
- 20 9. The use of claim 8, wherein the anti-hyperlipidemic agent is probucol.
10. The use of claim 9, wherein probucol is to be administered periodically within a range of from three to four months.
11. The use of claim 9, wherein probucol is to be administered periodically for a remainder of said subject's lifetime.
- 25 12. The use of claim 1, further comprising that the said subject is monitored during said administration to determine effect on LDL oxidation and plasma-HDL cholesterol and plasma/serum cytokines.

- 5 13. The use of claim 12, wherein said monitoring comprises monthly safety labs with comprehensive profiles and EKGs.