

CLAIMS

1. Use of an agent for regulating amino acid level in mammalian peripheral blood in the manufacture of a medicament for treating Alzheimer's disease in a subject, wherein the amino acid is selected from phenylalanine and/or isoleucine, the agent is selected from inhibitors of amino acid transporters, agents for regulating the relative abundance of gut microbes, or combinations thereof.

~~2. A pharmaceutical composition for treating Alzheimer's disease in a subject comprising an effective amount of an agent for regulating amino acid level in mammalian peripheral blood.~~

~~3. The use according to claim 1 or the pharmaceutical composition according to claim 2, wherein the amino acid is one or more selected from the following: 4-OH proline, acetylmethionine, alanine, alpha-aminoadipic acid, asparagine, aspartic acid, asymmetric dimethylarginine, beta-alanine, carnosine, citrulline, creatinine, GABA, glutamic acid, glutamine, glycine, histidine, hypotaurine, isoleucine, kynurenine, leucine, lysine, methionine, methionine sulfoxide, ornithine, phenylalanine, pipecolic acid, proline, putrescine, pyroglutamic acid, serine, serotonin, taurine, threonine, tryptophan, tyrosine and valine; preferably one or more selected from phenylalanine, isoleucine, serotonin, histidine and acetylmethionine; more preferably phenylalanine and/or isoleucine; most preferably phenylalanine.~~

~~4. The use according to claim 1 or the pharmaceutical composition according to claim 2, wherein the agent comprises one or more selected from the following: enzymes in the amino acid degradation pathway; inhibitors of enzymes in the amino acid synthesis pathway; amino acid ligands; agonists or inhibitors of amino acid transporters; agents for regulating the relative abundance of gut microbes, or combinations thereof.~~

~~5. The use or pharmaceutical composition according to claim 4, wherein the agent for regulating the relative abundance of gut microbes is selected from carbohydrate drugs, gut microbes complexes, or a combination thereof; wherein the carbohydrate drug is selected from monosaccharides, disaccharides, oligosaccharides, polysaccharides, or derivatives thereof, or a combination of them and/or derivatives thereof; preferably oligosaccharides and polysaccharides; more preferably mannuronic acid oligosaccharides or a composition~~

comprising mannuronic acid oligosaccharides; wherein the gut microbes complex comprises—

~~one or more selected from *Firmicutes*, *Bacteroidetes*, *Proteobacteria*, *Actinomyces*, *Fusobacteria*, *Cyanobacteria*, *Verrucomicrobia*, or a combination thereof.~~

~~6. The use or pharmaceutical composition according to claim 5, wherein the amino acid degrading enzyme is one or more selected from the followings: phenylalanine 4-hydroxylase; phenylalanine 2-monooxygenase; catalase peroxidase; phenylacetaldehyde synthase; aromatic L-amino acid/L-tryptophan decarboxylase; phenylalanine decarboxylase; phenylalanine N-acetyltransferase; aspartate aminotransferase; tyrosine aminotransferase; L-Amino acid oxidase; phenylalanine dehydrogenase; aromatic-amino acid transaminase; histidinol-phosphate aminotransferase; aromatic-amino acid aminotransferase II; phenylalanine racemase; phenylalanine ammonia lyase; phenylalanine/tyrosine ammonia lyase; branched-chain amino acid aminotransferase; L-Amino acid oxidase.~~

~~7. The use or pharmaceutical composition according to claim 5, wherein the amino acid degrading enzyme is one or more selected from the followings: phenylalanine 4-hydroxylase; aromatic L-amino acid/L-tryptophan decarboxylase; aspartate aminotransferase; tyrosine aminotransferase, TAT; L-Amino acid oxidase.~~

~~8. The use or pharmaceutical composition according to claim 5, wherein the amino acid degrading enzyme is delivered via a vector, preferably the vector is a microorganism (preferably a bacterium, more preferably *E. coli*) capable of expressing the amino acid degrading enzyme.~~

4. The use according to claim 1, wherein the agent for regulating the gut microbes is selected from OM1

5. The use according to claim 1, wherein the inhibitors of amino acid transporters are selected from JPH 203, BCH and KMH-233, preferably JPH 203.

~~96. The use according to claim 1 or the pharmaceutical composition according to claim 2,~~
wherein by detecting a peripheral blood sample from the subject, the agent regulates the amino acid level by about 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, 200, 205, 210, 215, 220, 225, 230, 235, 240, 245, 250, 255, 260, 265, 270, 275, 280, 285, 290, 295, 300 μ M or more; and/or makes the amino acid level close to or reach the corresponding amino acid level of the corresponding normal subject.

107. The use according to claim 1 ~~or the pharmaceutical composition according to claim~~
2, wherein by detecting a feces sample from the subject, the agent regulates the amino acid
level by ~~about~~ 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 1100, 1200, 1300, 1400,
1500, 1600, 1700, 1800, 1900, 2000, 2100, 2200, 2300, 2400, 2500, 2600, 2700, 2800, 2900,

3000 µmol/g or more; and/or makes the amino acid level close to or reach the corresponding amino acid level of the corresponding normal subject.

118. The use according to claim 1 ~~or the pharmaceutical composition according to claim 2~~, wherein the regulating amino acid level in mammalian peripheral blood is increasing the level of ~~one or more said~~ amino acids in the mammalian peripheral blood and/or decreasing the level of ~~one or more said~~ amino acids in the mammalian peripheral blood; preferably, decreasing the level of ~~one or more said~~ amino acids selected from the following: 4-OH-proline, acetylmethionine, alanine, alpha-aminoadipic acid, asparagine, aspartic acid, asymmetric dimethylarginine, beta-alanine, carnosine, citrulline, creatinine, GABA, glutamic acid, glutamine, glycine, histidine, hypotaurine, isoleucine, kynurenine, leucine, lysine, methionine, methionine sulfoxide, ornithine, phenylalanine, pipecolic acid, proline, putrescine, pyroglutamic acid, serine, serotonin, taurine, threonine, tryptophan, tyrosine and valine; more preferably decreasing the level of one or more amino acids selected from phenylalanine, isoleucine, serotonin, histidine and acetylmethionine in the mammalian peripheral blood; still more preferably, decreasing the level of phenylalanine and/or isoleucine in the mammalian peripheral blood; most preferably, decreasing the level of phenylalanine in the mammalian peripheral blood.

129. A method for screening a drug candidate that can be used to treat Alzheimer's disease comprising:

a) administering a test agent to a mammalian model with a certain amino acid level in peripheral blood, and

b) selecting the test agent that regulates the amino acid level as the drug candidate that can be used to treat Alzheimer's disease,

wherein the amino acid is selected from phenylalanine and/or isoleucine.

1310. The method according to claim 129, further comprising administering GV-971 as a positive control to the mammalian model with a certain amino acid level in peripheral blood, preferably selecting a test agent that regulates the amino acid level substantially consistently with the GV-971.

1411. The method according to claim 129 or 1310, further comprising administering a selected test agent to the mammalian model with a certain amino acid level in peripheral blood

for verification, wherein by detecting a peripheral blood sample from the mammalian model,
the

selected test agent regulates the amino acid level by 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, 200, 205, 210, 215, 220, 225, 230, 235, 240, 245, 250, 255, 260, 265, 270, 275, 280, 285, 290, 295, 300 μ M or more; and/or makes the amino acid level close to or reach the corresponding amino acid level in the corresponding normal mammalian model.

~~15~~12. The method according to claim ~~12~~9 or ~~13~~10, further comprising administering a selected test agent to the mammalian model with a certain amino acid level in peripheral blood for verification, wherein by detecting a feces sample from the mammalian model, the selected test agent regulates the amino acid level by 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700, 1800, 1900, 2000, 2100, 2200, 2300, 2400, 2500, 2600, 2700, 2800, 2900, 3000 μ mol/g or more; and/or makes the amino acid level close to or reach the corresponding amino acid level in the corresponding normal mammalian model.

~~16~~13. The method according to any one of claims ~~12~~9 to ~~15~~12, wherein the amino acid is ~~one or more selected from the following:~~ 4 OH proline, acetylmethionine, alanine, alpha-aminoadipic acid, asparagine, aspartic acid, asymmetric dimethylarginine, beta-alanine, carnosine, citrulline, creatinine, GABA, glutamic acid, glutamine, glycine, histidine, hypotaurine, isoleucine, kynurenine, leucine, lysine, methionine, methionine sulfoxide, ornithine, phenylalanine, pipecolic acid, proline, putrescine, pyroglutamic acid, serine, serotonin, taurine, threonine, tryptophan, tyrosine and valine; preferably selected from phenylalanine, isoleucine, serotonin, histidine and acetylmethionine; more preferably, phenylalanine and/or isoleucine; most preferably, phenylalanine.

~~17~~14. The method according to any one of claims ~~12~~9 to ~~16~~13, wherein the regulating amino acid level is increasing the level of ~~one or more said~~ amino acids and/or decreasing the level of ~~one or more said~~ amino acids; preferably decreasing the level of ~~one or more said~~ amino acids selected from phenylalanine, isoleucine, serotonin, histidine and acetylmethionine in the mammalian peripheral blood; more preferably, decreasing the level of phenylalanine and/or isoleucine in the mammalian peripheral blood; most preferably, decreasing the level of phenylalanine in the mammalian peripheral blood.

~~18~~18. A method for treating a patient having Alzheimer's disease comprising:

~~(a) detecting amino acid level of the patient and comparing it with the corresponding amino acid level of the corresponding normal population to select amino acid of which the level is different from that of the corresponding amino acid of the corresponding normal population;~~

- 5 ~~(b) administering an agent for regulating amino acid level in mammalian peripheral blood to the patient to regulate the level of selected amino acid to make them close to or reach the corresponding amino acid level of the corresponding normal population.~~