

a method for producing an inhibitory effect against the accumulation of abnormal protein aggregates in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

5 **[0040]** Furthermore, the compounds of this invention are useful in the treatment, control and management of diseases characterized by accumulation of abnormal protein aggregates, especially in the brain – for example, diseases such as Alzheimer’s disease, progressive supranuclear palsy, Down Syndrome, memory and cognitive disorders, dementia, amyloid neuropathies, brain inflammation, nerve and brain trauma, vascular amyloidosis, cerebral hemorrhage with amyloidosis, Parkinson’s disease, Huntington’s disease, prion disease and/or vascular, neurological, and/or neurodegenerative disorders related to the abnormal expression or accumulation of tau or amyloid proteins such as A β . Such abnormal protein aggregates include, for example, i) amyloid plaques and neurofibrillary tangles, and

10 ii) precipitates of tau or amyloid proteins such as A β .

15 **[0041]** Accordingly, the present invention provides methods of treatment of Alzheimer’s disease, progressive supranuclear palsy, Down Syndrome, memory and cognitive disorders, dementia, amyloid neuropathies, brain inflammation, nerve and brain trauma, vascular amyloidosis, cerebral hemorrhage with amyloidosis, Parkinson’s disease, Huntington’s disease, prion disease and/or vascular, neurological, and/or neurodegenerative disorders related to the abnormal expression or accumulation of tau or amyloid proteins such as A β , comprising administering an effective amount of a compound to inhibit gSAP activity.

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[0042] Compounds useful to inhibit gSAP activity include known small molecules, e.g.

- 25 a. Imatinib and other compounds as disclosed in International Patent Publication No. WO 03/057165 and in U.S. Patent No. 5,521,184, ~~the contents of which are incorporated herein by reference;~~
- 30 b. Compounds as described in WO 05/072826; J. Zimmermann et al., Bioorganic & Medicinal Chem. Lett., 7(2): 187- 192; EP 1 533 304; WO 04/005281; WO 05/039586; U.S. Patent No. 5,521,184; and WO 04/110452, ~~the contents of which are incorporated herein by reference;~~ and
- c. Compounds as disclosed in WO/2008/153974, WO/2008/153959, and WO/2008/057599, ~~the contents of which are incorporated herein by reference.~~

CLAIMS

1. A gSAP peptide selected from the following:

- ~~a. A peptide at least 60% similar to a sequence selected from the sequences depicted in Figure 1, wherein similarity is measured by a BLAST algorithm;~~
- ~~b. a peptide having residues corresponding to the conserved residues in bold in Figure 1,~~
- c. a peptide comprising the sequence Seq ID No. 7 (LWDHPMSSNIISR) and/or Seq ID No. 8 (NHVTRLLQNYKK),
- ~~d. any of the peptides of Seq ID Nos. 1-6 as depicted in Figure 1,~~
- e. gSAP from any mammalian species, for example mouse, rat or monkey,
- f. a fragment of gSAP capable of forming a complex with gamma secretase,
- ~~g. a fragment of approximately 16 kDa from the C-terminal of any of Seq ID Nos. 1-6 as depicted in Figure 1,~~

wherein the gSAP peptide is isolated or separated from its natural environment.

- 2. A gSAP peptide according to claim 1 which is produced by a recombinant cell, e.g., selected from a bacterial cell, a baculovirus or a mammalian cell.
- 3. A vector comprising a gene for encoding a gSAP peptide according to claim 1 operably linked to a heterologous promoter.
- 4. A transgenic cell containing a heterologous gene which expresses a gSAP peptide according to claim 1.
- 5. A nucleic acid which is or which expresses a RNA construct capable of inhibiting gSAP-expression of a gSAP peptide according to claim 1 in a mammalian cell.
- 6. An antibody to a gSAP according to claim 1.
- 7. A vaccine comprising an immunogenic fragment of a gSAP peptide according to claim 1 in combination with a suitable adjuvant and/or carrier.
- 8. A non-human gSAP knockout mammal, wherein its gene for gSAP is disrupted, and wherein said gSAP is a gSAP peptide according to claim 1.
- 9. Use of a gSAP peptide according to claim 1 in an assay to identify compounds which inhibit A β -deposition
- 10. A method of identifying a compound inhibiting A β -deposition, comprising measuring binding of a test compounds to a gSAP peptide according to claim 1.

11. A derivative of imatinib wherein the methylpiperiziny moiety of imatinib is substituted or modified with a labeling group.
12. The derivative of claim 11 selected from photolabeled derivatives, radiolabeled derivatives and biotinylated derivatives.
13. A method of identifying persons at risk of developing Alzheimer's disease comprising checking for elevated expression levels and/or mutations in gSAP relative to normal values as identified using a control population.
14. A method for inhibiting the accumulation of abnormal protein aggregates in a warm-blooded animal in need of such inhibition which comprises administering to said animal an effective amount of a compound to inhibit ~~gSAP~~the activity of a gSAP peptide according to claim 1 administered to said animal.
15. An effective amount of a compound to inhibit the activity of a gSAP peptide according to claim 1 for use in the treatment~~method of treating~~ Alzheimer's disease, progressive supranuclear palsy, Down Syndrome, memory and cognitive disorders, dementia, amyloid neuropathies, brain inflammation, nerve and brain trauma, vascular amyloidosis, cerebral hemorrhage with amyloidosis, Parkinson's disease, Huntington's disease, prion disease and/or vascular, neurological, and/or neurodegenerative disorders related to the abnormal expression or accumulation of tau or amyloid proteins such as A β , ~~comprising administering an effective amount of a compound to inhibit gSAP activity.~~
16. The method of claim 14 or 15 wherein the compound to inhibit gSAP activity is selected from small molecules, inhibitory RNA molecules, vectors and cells producing inhibitory RNA molecules, antibodies to gSAP, and vaccines for gSAP.
17. A gSAP peptide according to claim 1 which has been labeled.
- ~~18. Use of gSAP derivatives in biochemical or genetic screening systems to identify further proteins in the gSAP macromolecular complex that could function as alternative targets for disease intervention.~~
- ~~19.~~18. A method of identifying a candidate for treatment with gSAP-targeted therapy, comprising measuring gSAP expression of the gSAP according to claim 1, using antibodies to gSAP or quantitative PCR for gSAP expression, wherein elevated expression is seen in candidates for treatment with gSAP targeted therapy.
- ~~20.~~19. A method of identifying a candidate for treatment with gSAP-targeted therapy, comprising identifying patients having mutations or genetic variations affecting gSAP or gSAP expression or gSAP activity of the gSAP according to claim 1, wherein patients having such mutations or haplotypes are candidates for treatment with gSAP targeted therapy.

~~21.~~20. The method of claim ~~20~~19 wherein the variant is a haplotype selected from the following groups of SNPs:

- a) rs6976567|rs1468682|rs1819814,
- b) rs1468682|rs1819814|rs4729535,
- c) rs1819814|rs4729535|rs4729540,
- d) rs7781642|rs6955503|rs7776973

~~22.~~21. The method of claim ~~20~~19 wherein the variant is a variant of the sequence encoding the juxtamembrane region of APP-CTF.