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(54) **METHODS OF PREVENTING, TREATING, AND DIAGNOSING DISORDERS OF PROTEIN AGGREGATION**

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(57) **ABSTRACT**

Disclosed are methods of preventing, treating, or diagnosing in a subject a disorder in protein folding or aggregation, or amyloid formation, deposition, accumulation, or persistence consisting of administering to said subject a pharmaceutically effective amount of inositol stereoisomers, enantiomers or derivatives thereof.

7 Claims, 17 Drawing Sheets

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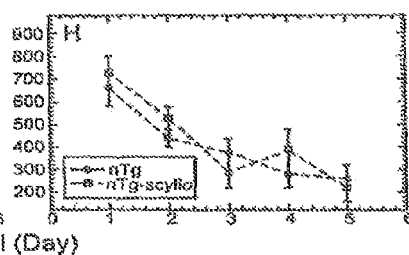
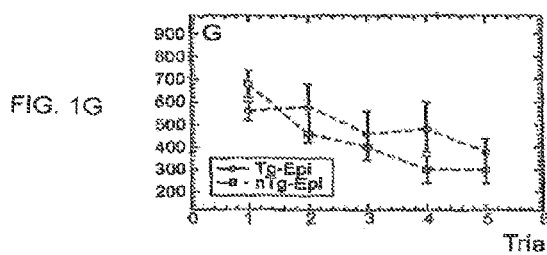
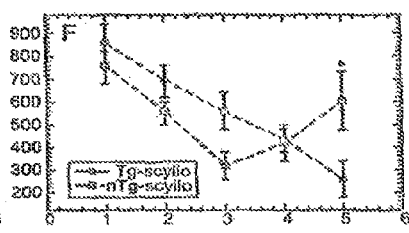
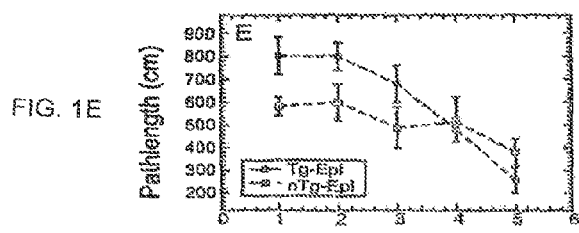
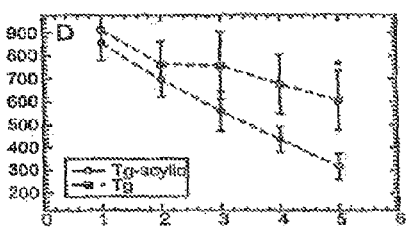
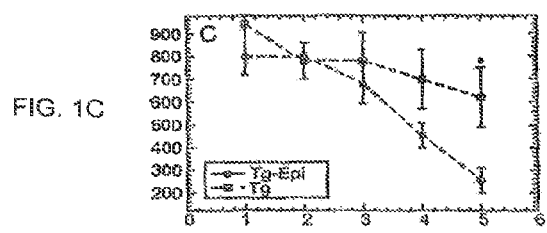
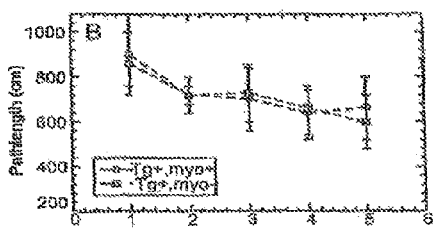
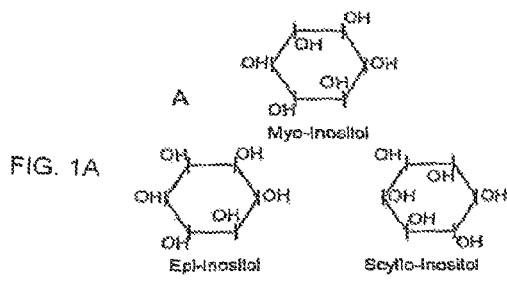
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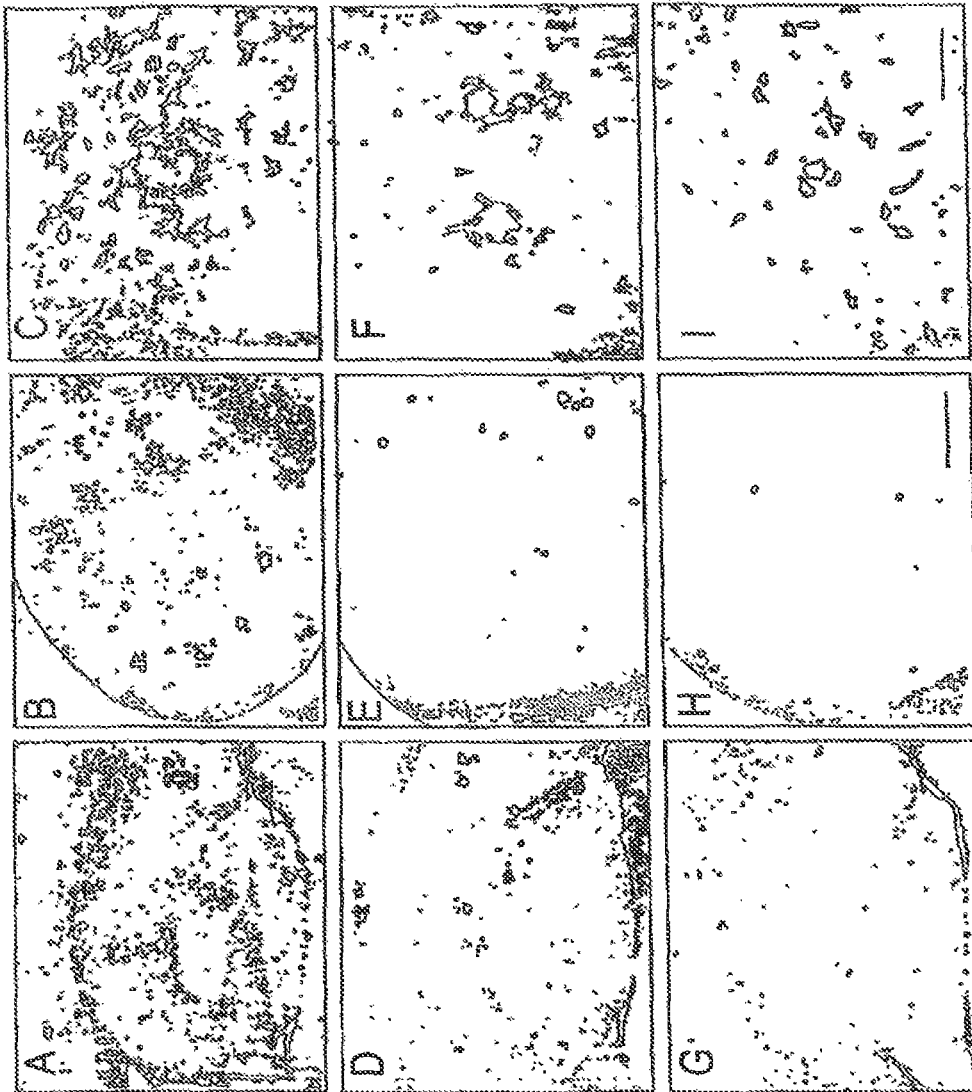
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FIGS. 2A, 2B & 2C

FIGS. 2D, 2E & 2F

FIGS. 2G, 2H & 2I

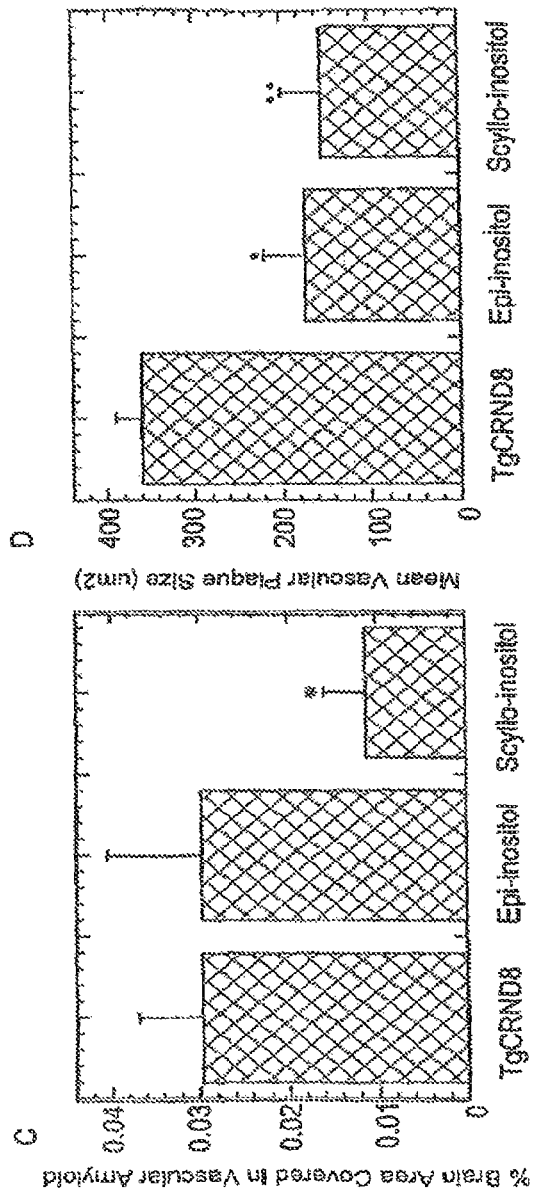
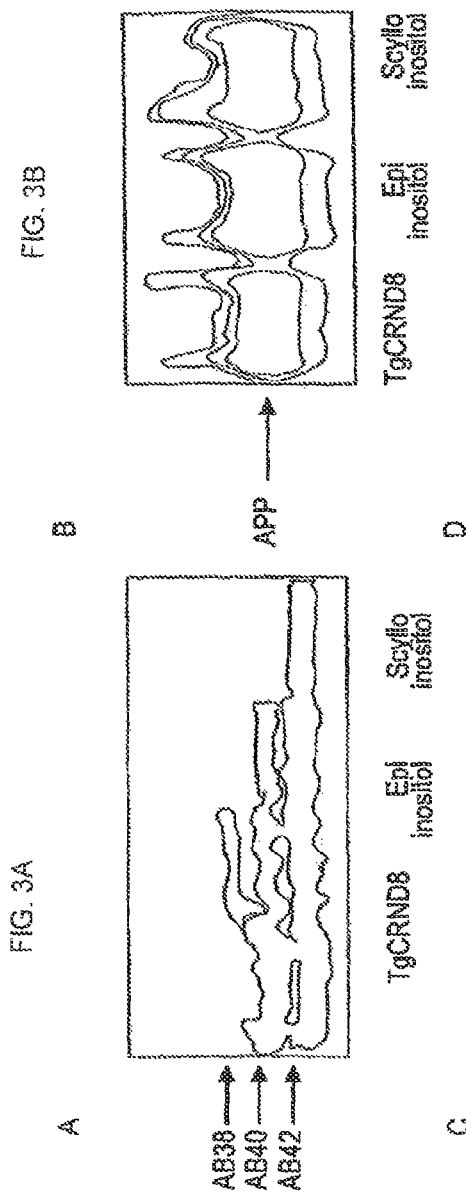


FIG. 3C

FIG. 3D

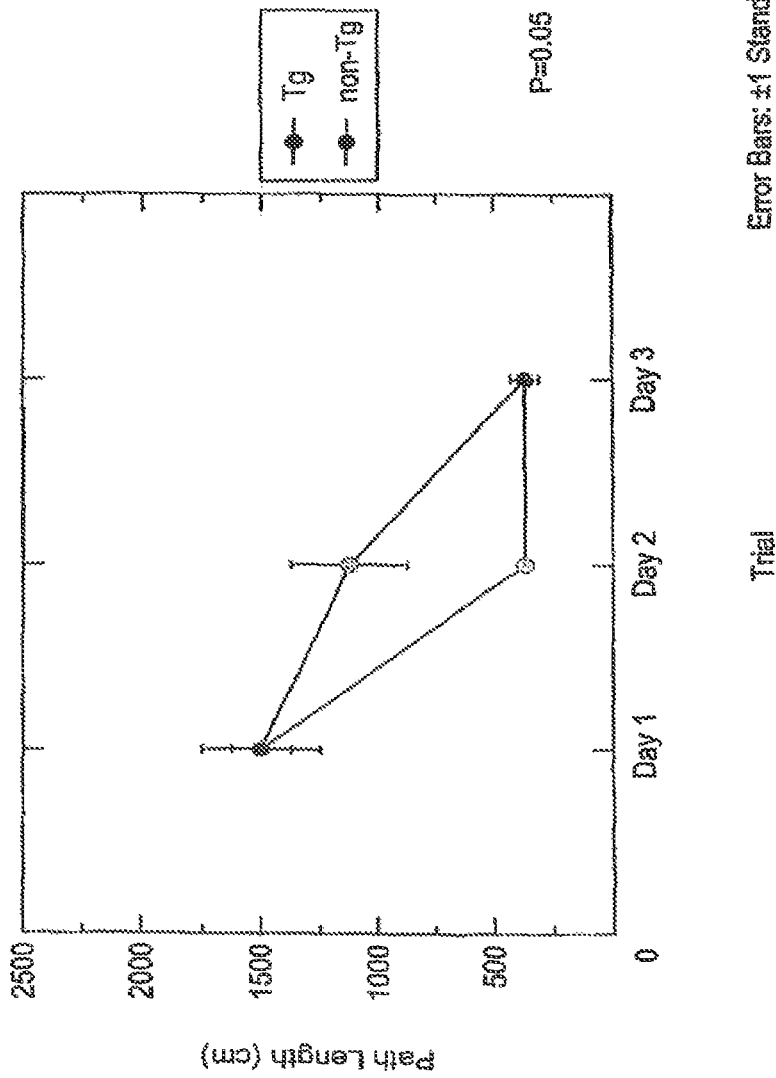


FIG. 4

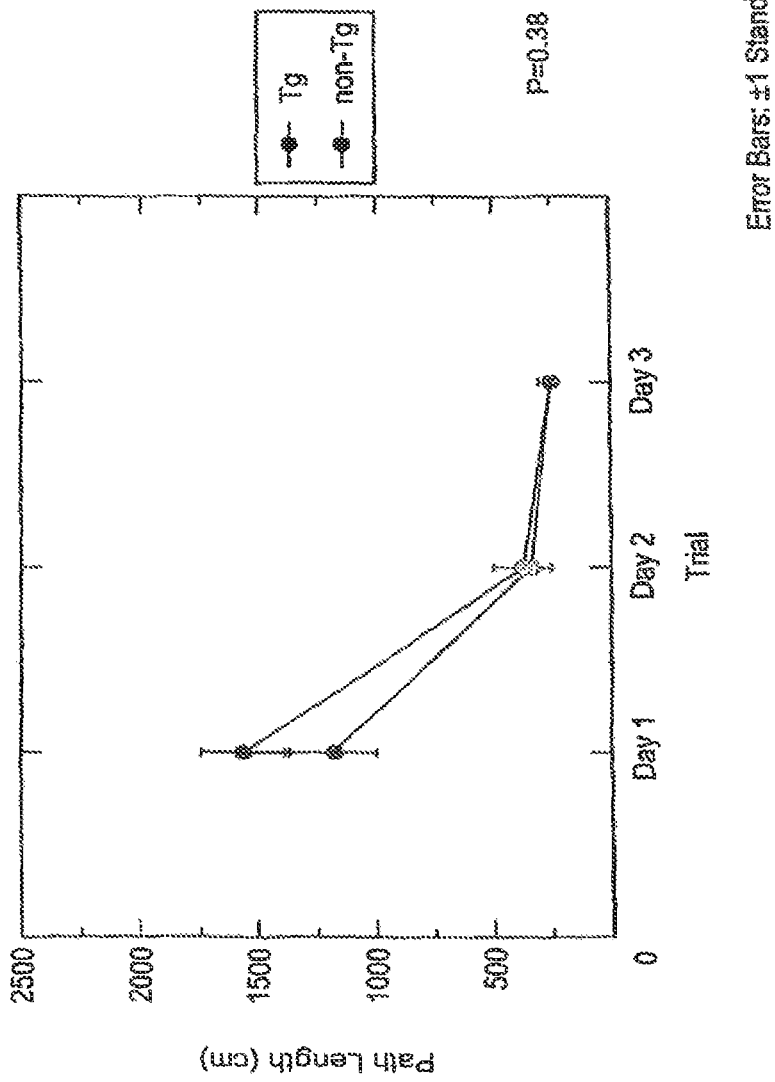


FIG. 5

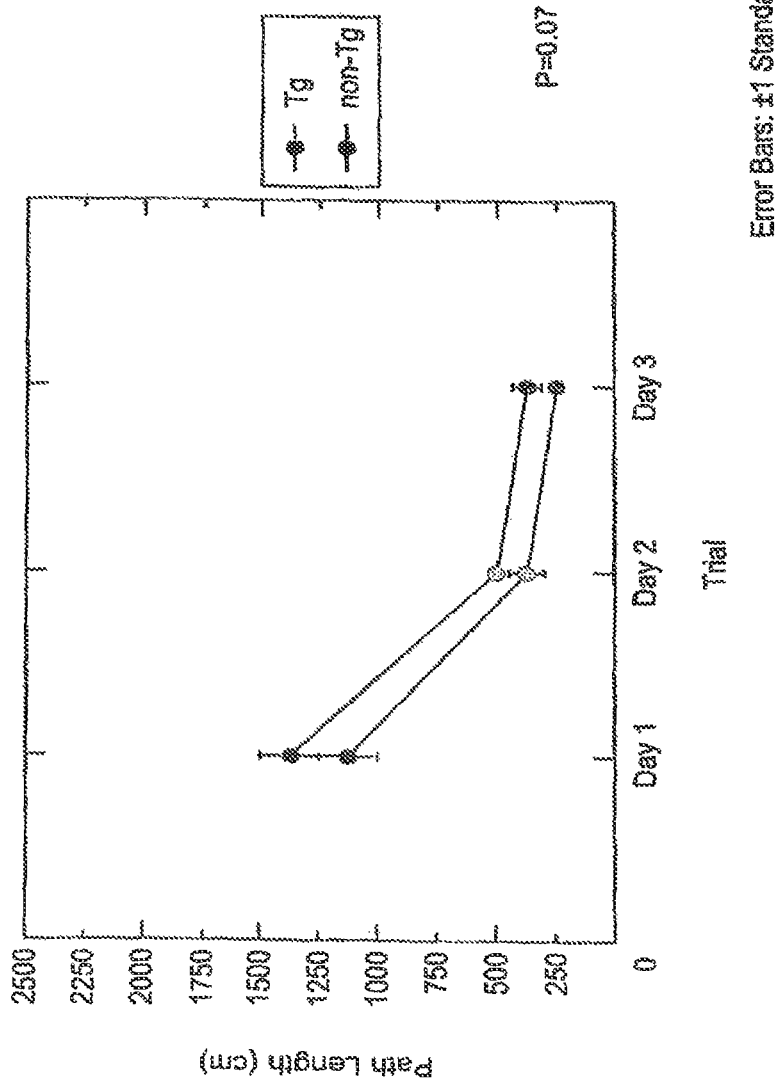


FIG. 6

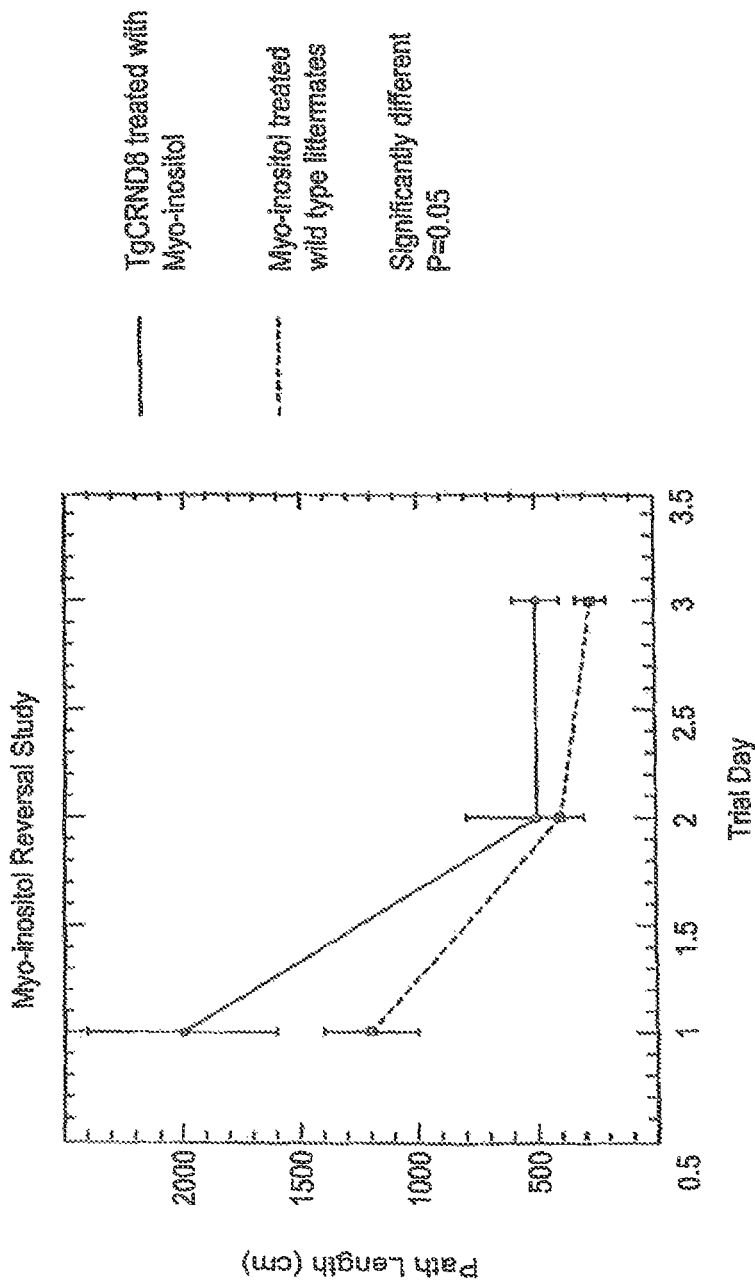


FIG. 7

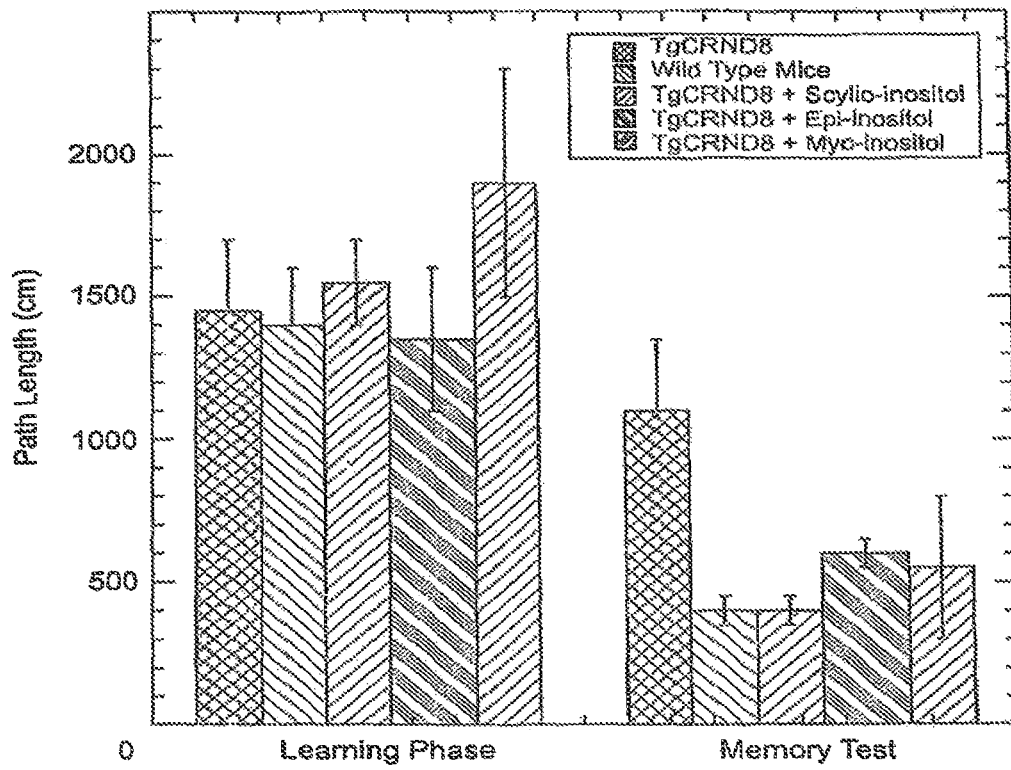


FIG. 8

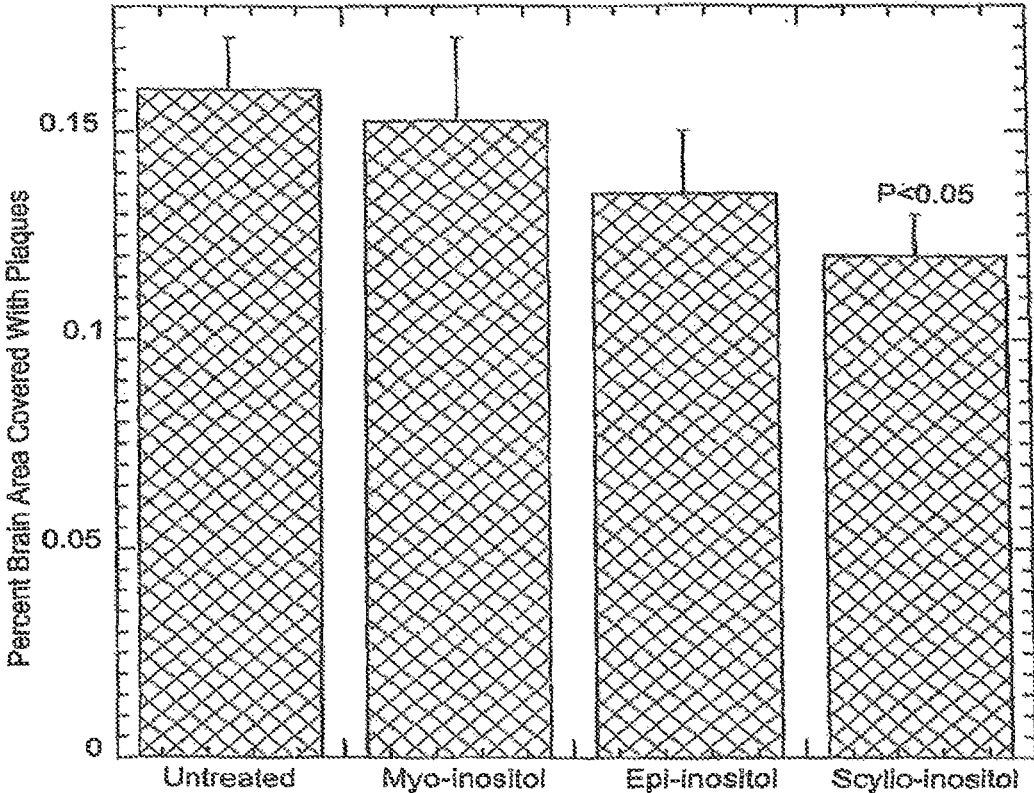


FIG. 9

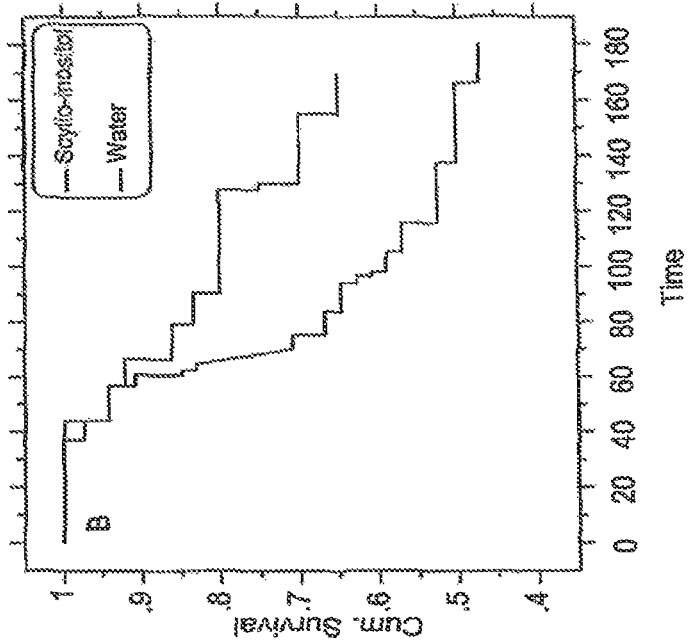


FIG. 10A

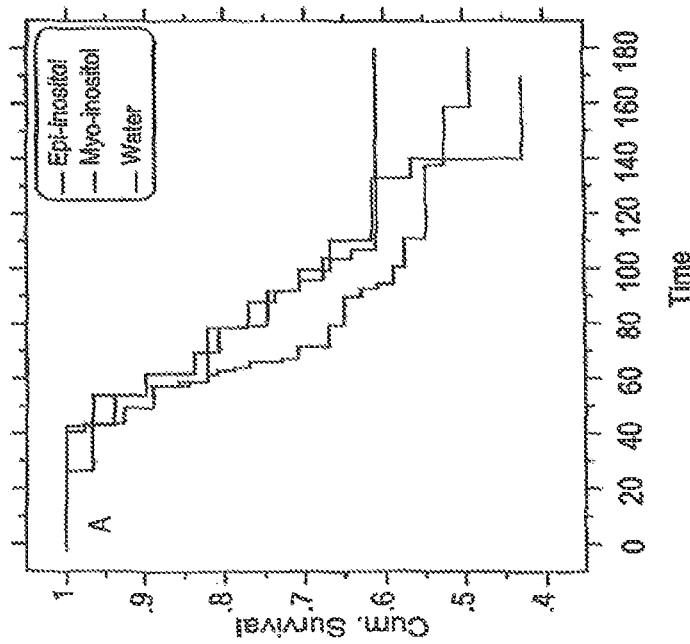


FIG. 10B

FIG. 11A

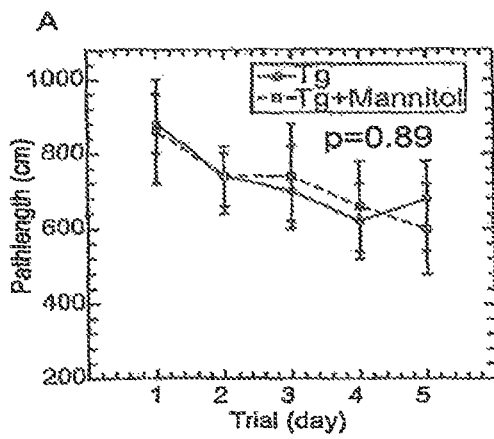


FIG. 11B

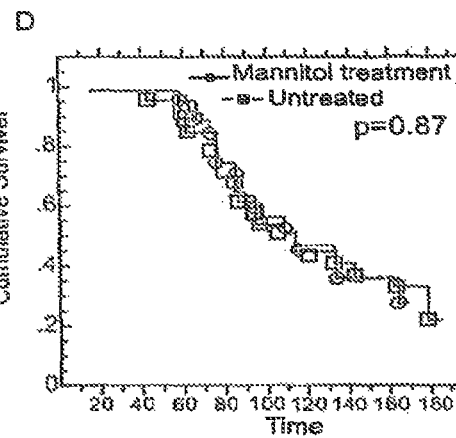
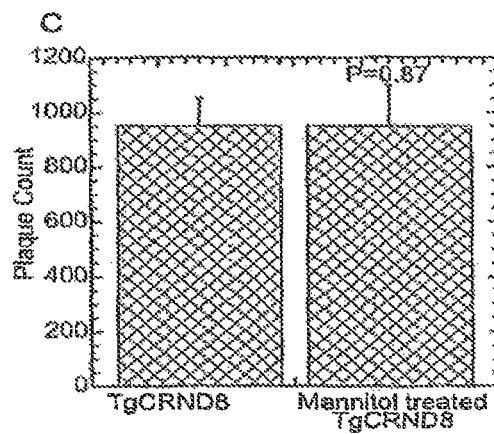
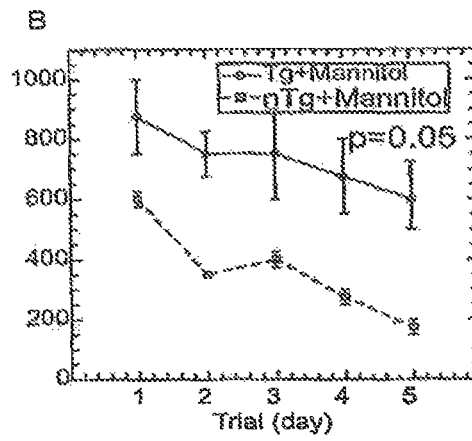


FIG. 11C

FIG. 11D

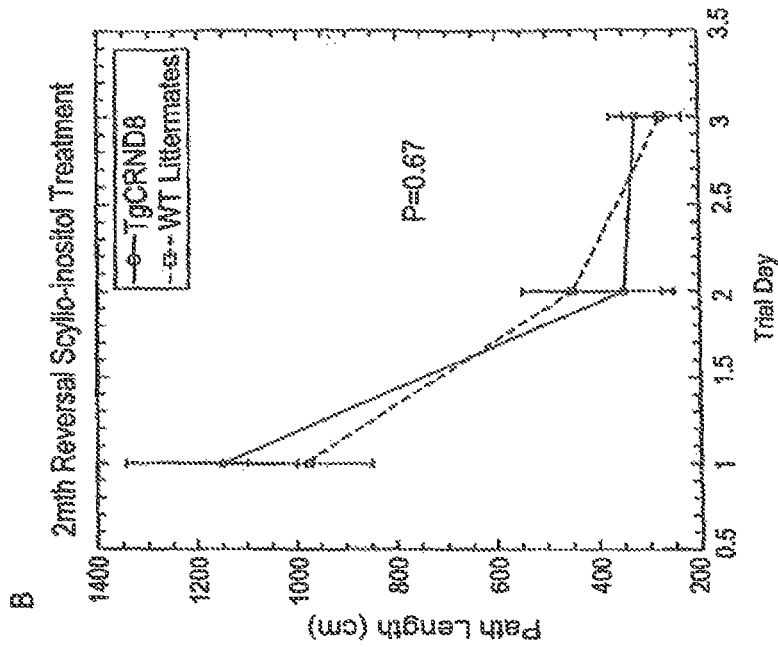


FIG. 12B

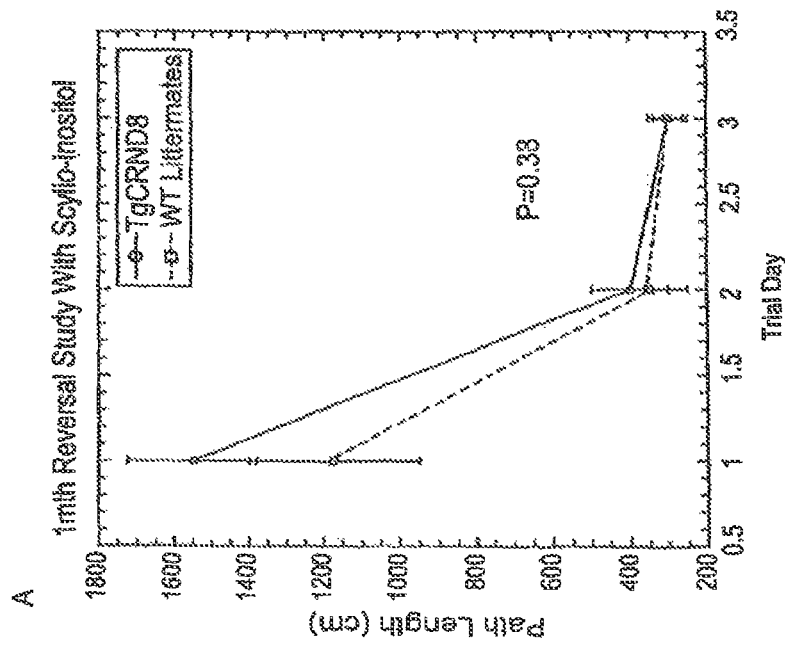


FIG. 12A

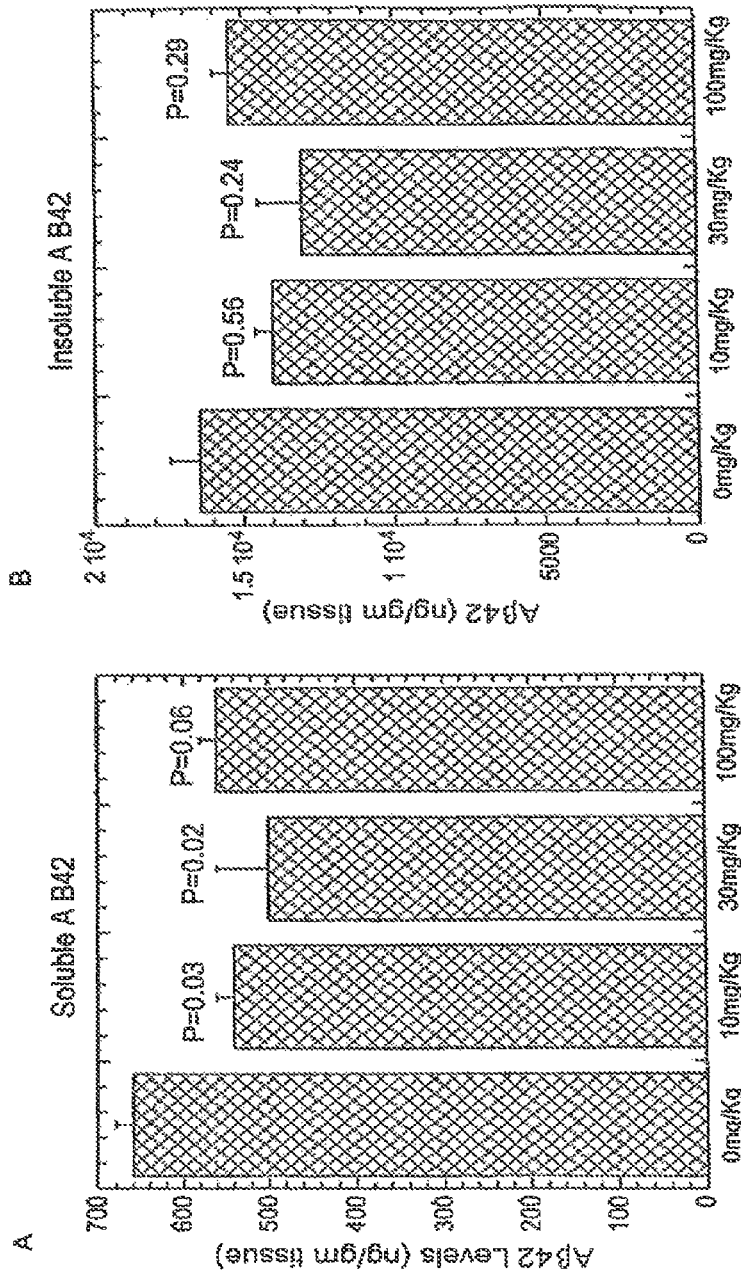


FIG. 13B

FIG. 13A

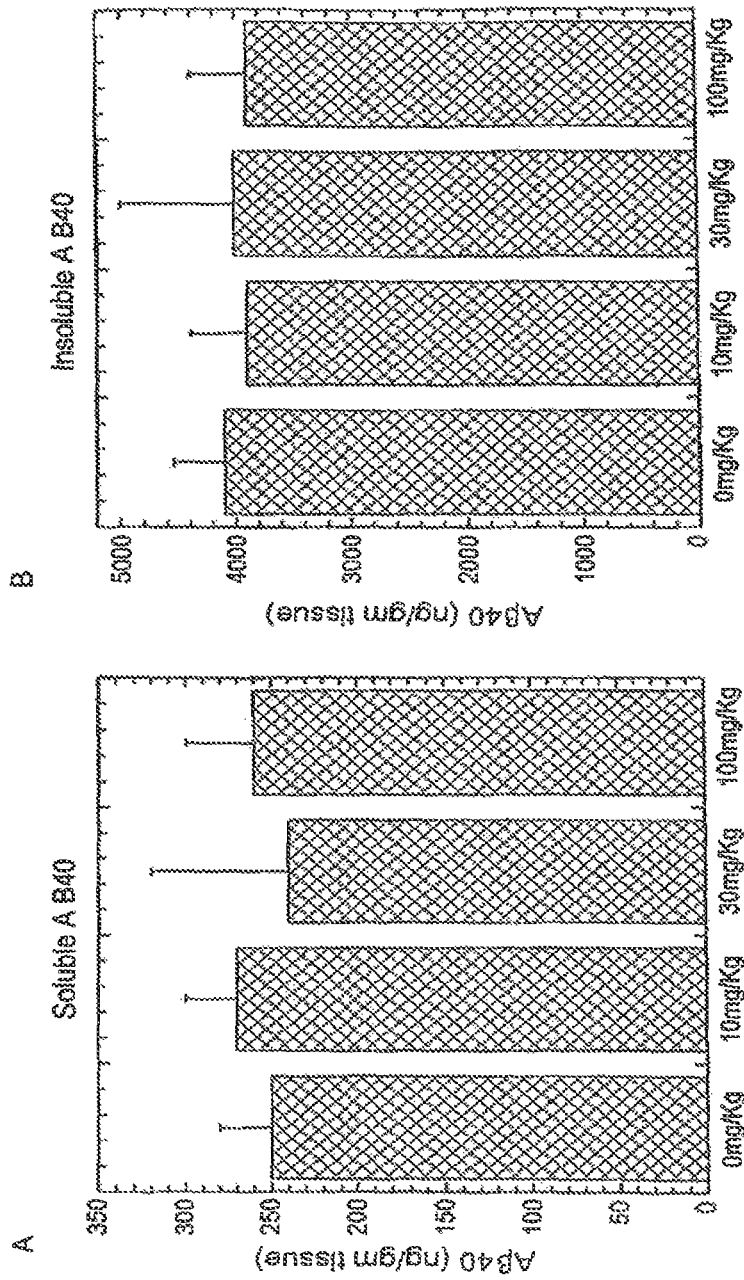


FIG. 14A

FIG. 14B

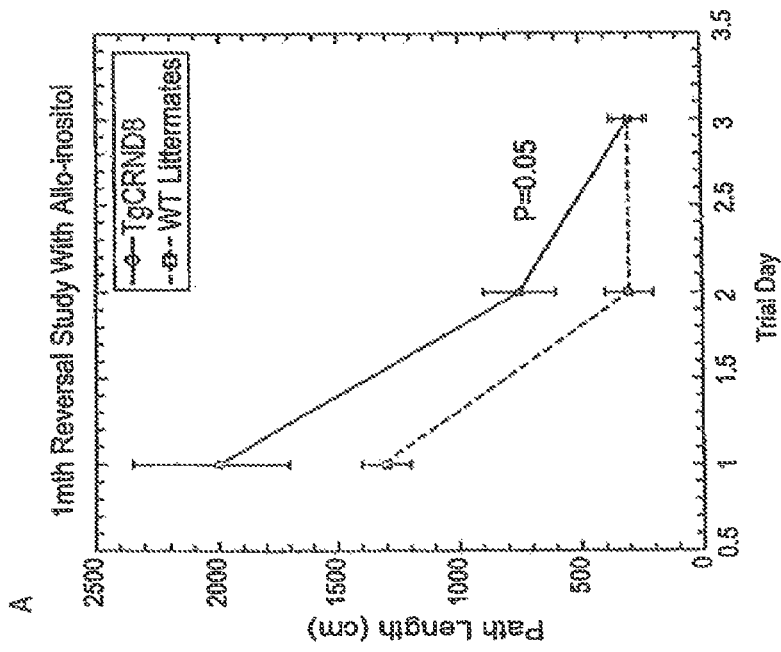


FIG. 15

FIG. 16B

FIG. 16D

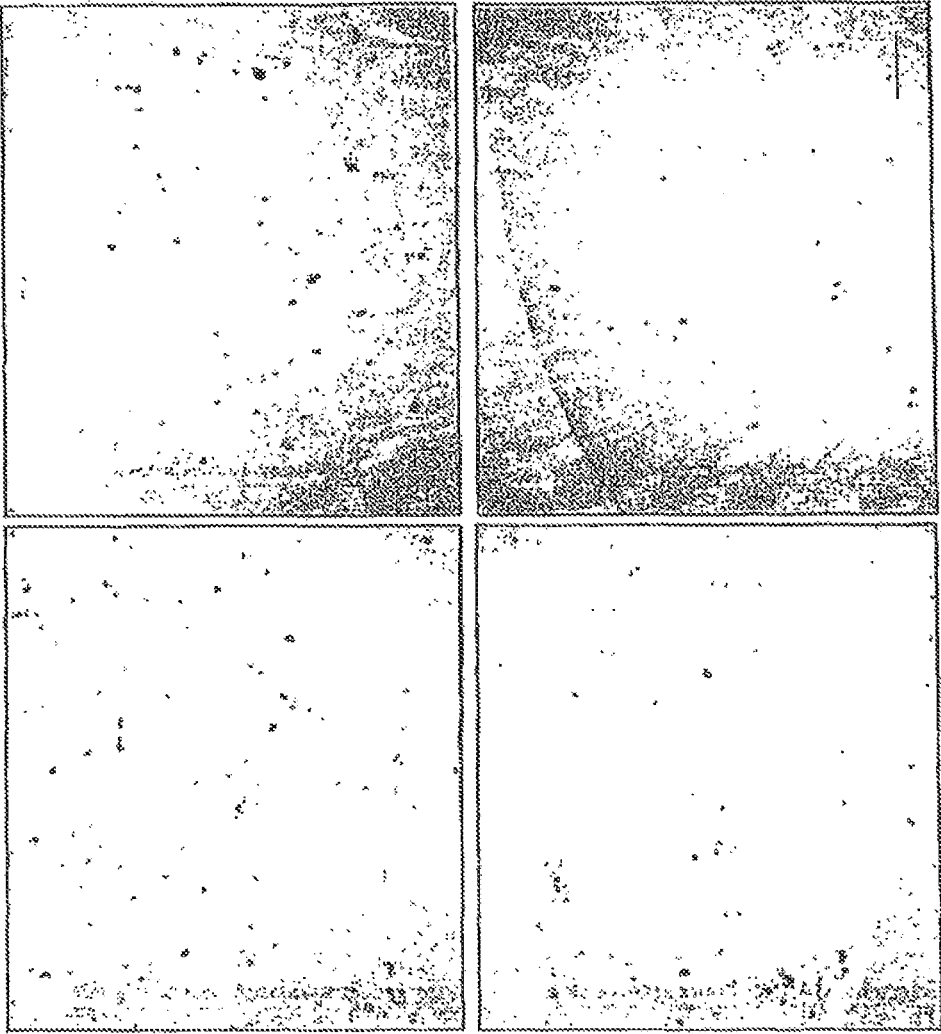


FIG. 16A

FIG. 16C

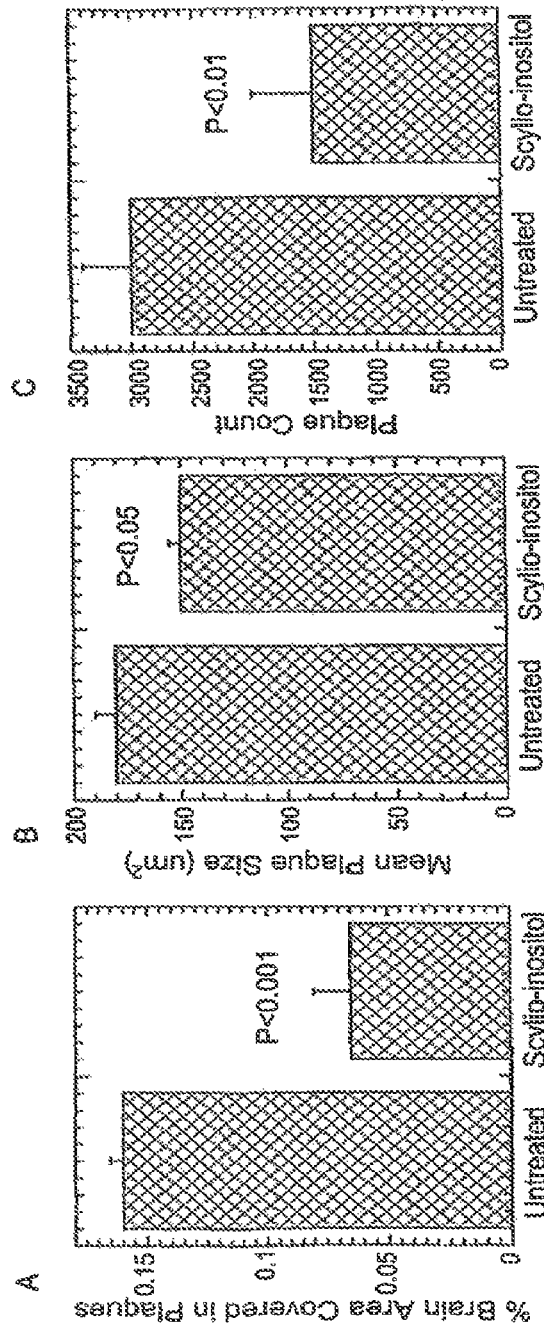


FIG. 17C

FIG. 17B

FIG. 17A

1

METHODS OF PREVENTING, TREATING, AND DIAGNOSING DISORDERS OF PROTEIN AGGREGATION

RELATED APPLICATIONS

This application claims the priority of U.S. Provisional Application Ser. Nos. 60/451,363, 60/520,958 and 60/523,534, filed Feb. 27, 2003, Nov. 17, 2003 and Nov. 19, 2003, respectively.

FIELD OF THE INVENTION

The invention relates to methods for treating Alzheimer's Disease and other amyloidoses; more particularly, it relates to methods for inhibiting and reducing amyloid fibril formation in therapeutic intervention in Alzheimer's disease and other amyloidoses.

DESCRIPTION OF THE RELATED ART

Alzheimer's disease is characterized neuropathologically by amyloid deposits, neurofibrillary tangles, and selective neuronal loss. The major component of the amyloid deposits is amyloid- β (A β), a 39-43 residue peptide. Soluble forms of A β generated from cleavage of amyloid precursor protein are normal products of metabolism. The importance of residues 1-42 (A β 42) in Alzheimer's disease was highlighted in the discovery that mutations in codon 717 of the amyloid precursor protein gene, presenilin 1 and presenilin 2 genes result in an increased production of A β 42 over A β 1-40. These results in conjunction with the presence of A β 42 in both mature plaques and diffuse amyloid lead to the hypothesis that this more amyloidogenic species may be the critical element in plaque formation. This hypothesis was supported by the fact that A β 42 deposition precedes that of A β 40 in Down's syndrome in PS1 mutations and in hereditary cerebral hemorrhage with amyloidosis.

Many in vitro studies have demonstrated that A β can be neurotoxic or enhance the susceptibility of neurons to excitotoxic, metabolic, or oxidative insults. Initially it was thought that only the fibrillar form of A was toxic to neurons but more thorough characterization of A β structures demonstrated that dimers and small aggregates of A β are also neurotoxic. These data suggested that prevention of A β oligomerization would be a likely strategy to prevent AD-related neurodegeneration. Several studies have demonstrated that in vitro A β -induced neurotoxicity can be ablated by compounds that can increase neuronal resistance by targeting cellular pathways involved in apoptosis, block downstream pathways after A β induction of destructive routes, or block A β oligomerization and ultimately fibril formation. The site at which A β acts to induce neurotoxicity has yet to be elucidated but its toxic effects have been blocked by a variety of disparate agents.

Docking of A β -fibrils to neuronal and glial cell membranes may be an early and intervenable step during the progression of AD. Formation of amyloid plaques, as well as neurotoxicity and inflammation may be direct or indirect consequences of the interaction of A with molecules containing sugar moieties. Previous studies have demonstrated that A β interaction with glycosaminoglycans results in aggregation of A β possibly adding to their insolubility and plaque persistence. Glycosaminoglycans have also been implicated in neuronal toxicity and microglial activation. Alternatively, interaction with glycolipids such as gangliosides results in the stabilization and prevention of Ab fibril

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formation, as well as, the site of A β production. The family of phosphatidylinositols, on the other hand, results in acceleration of fibril formation. The headgroup of phosphatidylinositol is myo-inositol, a naturally occurring simple sugar involved in lipid biosynthesis, signal transduction, and osmolarity control.

It is also noteworthy that a variety of other human diseases also demonstrate amyloid deposition and usually involve systemic organs (i.e. organs or tissues lying outside the central nervous system), with the amyloid accumulation leading to organ dysfunction or failure. In Alzheimer's disease and "systemic" amyloid diseases, there is currently no cure or effective treatment, and the patient usually dies within 3 to 10 years from disease onset.

U.S. Pat. No. 4,847,082 discloses the use of phytic acid, a phytate salt, an isomer or hydrolysate of phytic acid for the treatment of Alzheimer's disease. It also discloses that isomers of phytic acid or phytate salt comprise the hexakisphosphate myo-inositol, hexakisphosphate scyllo-inositol, hexakisphosphate D-chiro-inositol, hexakisphosphate L-chiro-inositol, hexakisphosphate neo-inositol and hexakisphosphate muco-inositol conformations. Phytic acid is inositol-hexakisphosphate (IP6).

U.S. Pat. No. 5,112,814 discloses the use of phytic acid and isomers thereof for the treatment of Parkinson's disease. As is the case with U.S. Pat. No. 4,847,082, the phytic acid isomers disclosed in this patent retain the six phosphate groups on the six-carbon inositol sugar.

It is noteworthy that in subsequent publications, the ability of inositol-monophosphate, inositol-1,4-bisphosphate and inositol-1,4,5-triphosphate to inhibit amyloid-beta peptide fibrillogenesis were investigated and found not to be effective (*J. Mol. Biol.* 278:183-194, 1998).

Barak et al. disclose the use of inositol for the treatment of Alzheimer's Disease (AD). (*Prog Neuro-psychopharmacol & Biol Psychiat.* 20:729-735, 2000). However, this reference does not disclose the use of inositol isomers. Patients treated with inositol did not show any significant differences in overall cognitive function scores (CAMCOG index) between inositol and placebo (dextrose) in AD patients while two specific subscales of the CAMCOG index did show significant improvement (orientation and language).

Levine J, reviews the above Barak et al. paper and specifically states that inositol treatment is not beneficial in AD or ECT-induced cognitive impairment (*Eur Neuropsychopharm.* 1997; 7,147-155, 1997).

Colodny L, et al. suggests further studies for the usefulness of inositol in Alzheimer's disease by referring to the above Barak et al. paper and therefore does not disclose or suggest such use for inositol isomers (*Altern Med Rev* 3(6):432-47, 1998).

McLaurin et al. disclosed that myo-inositol stabilizes a small micelle of A β 42 (*J. Mol. Biol.* 278, 183-194, 1998). In addition, McLaurin et al. disclose that epi- and scyllo-but not chiro-inositol were able to induce a structural transition from random to β -structure in A β 42 (*J Biol Chem.* June 16; 275(24):18495-502, 2000; and *J Struct Biol* 130:259-270, 2000). Alternatively, none of the stereoisomers were able to induce a structural transition in A β 40. Electron microscopy showed that inositol stabilizes small aggregates of A β 42. These references also disclose that inositol-A β interactions result in a complex that is non-toxic to nerve growth factor-differentiated PC-12 cells and primary human neuronal cultures.

Much work in Alzheimer's disease has been accomplished, but little is conventionally known about compounds or agents for therapeutic regimes to arrest or reverse amyloid

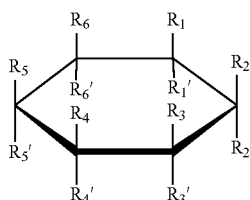
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formation, deposition, accumulation and/or persistence that occurs in Alzheimer's disease and other amyloidoses.

New compounds or agents for therapeutic regimes to arrest or reverse amyloid formation, deposition, accumulation and/or persistence that occurs in Alzheimer's disease and other amyloidoses are therefore desperately needed.

SUMMARY OF THE INVENTION

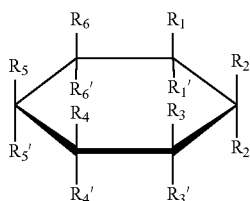
The present invention provides a method of treating or preventing in a subject a condition of the central or peripheral nervous system or systemic organ associated with a disorder in protein folding or aggregation, or amyloid formation, deposition, accumulation, or persistence comprising administering to said subject a pharmaceutically effective amount of compound selected having the following structure:



wherein each of $R_1, R_1', R_2, R_2', R_3, R_3', R_4, R_4', R_5, R_5', R_6,$ and R_6' is independently selected from the group of:

- (a) hydrogen atom;
- (b) NHR_7 , wherein said R_7 is selected from the group of hydrogen; $\text{C}_2\text{-C}_{10}$ acyl and $\text{C}_1\text{-C}_{10}$ alkyl;
- (c) NR_8R_9 , wherein said R_8 is $\text{C}_2\text{-C}_{10}$ acyl or $\text{C}_1\text{-C}_{10}$ alkyl and said R_9 is $\text{C}_2\text{-C}_{10}$ acyl or $\text{C}_1\text{-C}_{10}$ alkyl;
- (d) OR_{10} , wherein said R_{10} is selected from the group of no group, hydrogen, $\text{C}_2\text{-C}_{10}$ acyl, $\text{C}_1\text{-C}_{10}$ alkyl and SO_3H ;
- (e) $\text{C}_5\text{-C}_7$ glycosyl;
- (f) $\text{C}_3\text{-C}_8$ cycloalkyl optionally substituted with a substituent selected from the group of hydrogen, OH, NH_2 , SH, OSO_3H and OPO_3H_2 ;
- (g) SR_{11} wherein R_{11} is selected from the group of hydrogen, $\text{C}_1\text{-C}_{10}$ alkyl and O_3H ;
- (h) $\text{C}_1\text{-C}_{10}$ alkyl optionally substituted with a substituent selected from the group of hydrogen, OR_{10} , NHR_7 , NR_8R_9 , and SR_{11} ; and
- (i) $\text{C}_3\text{-C}_8$ cycloalkyl optionally substituted with a substituent selected from the group of hydrogen, OR_{10} , NHR_7 , NR_8R_9 and SR_{11} , providing that the compound is not myo-inositol.

The present invention also provides a method of preventing abnormal protein folding, abnormal protein aggregation, amyloid formation, deposition, accumulation, or persistence, or amyloid lipid interactions in a subject comprising administering to said subject a pharmaceutically effective amount of a compound having the following structure:

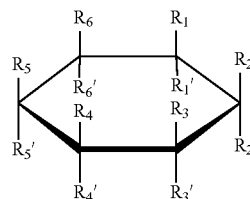


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wherein each of $R_1, R_1', R_2, R_2', R_3, R_3', R_4, R_4', R_5, R_5', R_6,$ and R_6' is independently selected from the group of:

- (a) hydrogen atom;
- (b) NHR_7 , wherein said R_7 is selected from the group of hydrogen; $\text{C}_2\text{-C}_{10}$ acyl and $\text{C}_1\text{-C}_{10}$ alkyl;
- (c) NR_8R_9 , wherein said R_8 is $\text{C}_2\text{-C}_{10}$ acyl or $\text{C}_1\text{-C}_{10}$ alkyl and said R_9 is $\text{C}_2\text{-C}_{10}$ acyl or $\text{C}_1\text{-C}_{10}$ alkyl;
- (d) OR_{10} , wherein said R_{10} is selected from the group of no group, hydrogen, $\text{C}_2\text{-C}_{10}$ acyl, $\text{C}_1\text{-C}_{10}$ alkyl and SO_3H ;
- (e) $\text{C}_5\text{-C}_7$ glycosyl;
- (f) $\text{C}_3\text{-C}_8$ cycloalkyl optionally substituted with a substituent selected from the group of hydrogen, OH, NH_2 , SH, OSO_3H and OPO_3H_2 ;
- (g) SR_{11} wherein R_{11} is selected from the group of hydrogen, $\text{C}_1\text{-C}_{10}$ alkyl and O_3H ;
- (h) $\text{C}_1\text{-C}_{10}$ alkyl optionally substituted with a substituent selected from the group of hydrogen, OR_{10} , NHR_7 , NR_8R_9 and SR_{11} ; and
- (i) $\text{C}_3\text{-C}_8$ cycloalkyl optionally substituted with a substituent selected from the group of hydrogen, OR_{10} , NHR_7 , NR_8R_9 and SR_{11} , providing that the compound is not myo-inositol.

The present invention further provides a method of causing the dissociation of abnormally aggregated proteins and/or dissolving or disrupting pre-formed or pre-deposited amyloid fibril or amyloid in a subject comprising administering to said subject a pharmaceutically effective amount of a compound having the following structure:

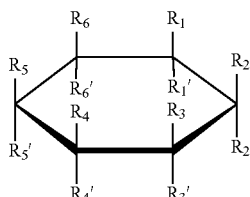


wherein each of $R_1, R_1', R_2, R_2', R_3, R_3', R_4, R_4', R_5, R_5', R_6,$ and R_6' is independently selected from the group of:

- (a) hydrogen atom;
- (b) NHR_7 , wherein said R_7 is selected from the group of hydrogen; $\text{C}_2\text{-C}_{10}$ acyl and $\text{C}_1\text{-C}_{10}$ alkyl;
- (c) NR_8R_9 , wherein said R_8 is $\text{C}_2\text{-C}_{10}$ acyl or $\text{C}_1\text{-C}_{10}$ alkyl and said R_9 is $\text{C}_2\text{-C}_{10}$ acyl or $\text{C}_1\text{-C}_{10}$ alkyl;
- (d) OR_{10} , wherein said R_{10} is selected from the group of no group, hydrogen, $\text{C}_2\text{-C}_{10}$ acyl, $\text{C}_1\text{-C}_{10}$ alkyl and SO_3H ;
- (e) $\text{C}_5\text{-C}_7$ glycosyl;
- (f) $\text{C}_3\text{-C}_8$ cycloalkyl optionally substituted with a substituent selected from the group of hydrogen, OH, NH_2 , SH, OSO_3H and OPO_3H_2 ;
- (g) SR_{11} , wherein R_{11} is selected from the group of hydrogen, $\text{C}_1\text{-C}_{10}$ alkyl and O_3H ;
- (h) $\text{C}_1\text{-C}_{10}$ alkyl optionally substituted with a substituent selected from the group of hydrogen, OR_{10} , NHR_7 , NR_8R_9 and SR_{11} ; and
- (i) $\text{C}_3\text{-C}_8$ cycloalkyl optionally substituted with a substituent selected from the group of hydrogen, OR_{10} , NHR_7 , NR_8R_9 and SR_{11} , providing that the compound is not myo-inositol.

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The present invention also provides a method of diagnosing the presence of abnormally folded or aggregated protein and/or amyloid fibril or amyloid in a subject comprising: (a) administering to said subject a radioactive compound or compound tagged with a substance that emits a detectable signal in a quantity sufficient and under conditions to allow for the binding of said compound to the abnormally folded or aggregated protein and/or fibrils or amyloid, if present; and (b) detecting the radioactivity or the signal from the compound bound to the abnormally folded or aggregated protein and/or fibrils or amyloid, thus diagnosing the presence of abnormally folded or aggregated protein and/or amyloid fibril or amyloid in said subject, wherein said compound has the following structure:



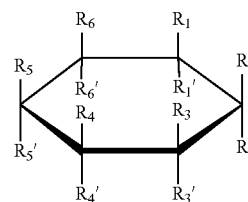
wherein each of $R_1, R_1', R_2, R_2', R_3, R_3', R_4, R_4', R_5, R_5', R_6,$ and R_6' , is independently selected from the group of:

- (a) hydrogen atom;
- (b) NHR_7 , wherein said R_7 is selected from the group of hydrogen; $\text{C}_2\text{-C}_{10}$ acyl and $\text{C}_1\text{-C}_{10}$ alkyl;
- (c) NR_8R_9 , wherein said R_8 is $\text{C}_2\text{-C}_{10}$ acyl or $\text{C}_1\text{-C}_{10}$ alkyl and said R_9 is $\text{C}_2\text{-C}_{10}$ acyl or $\text{C}_1\text{-C}_{10}$ alkyl;
- (d) OR_{10} , wherein said R_{10} is selected from the group of no group, hydrogen, $\text{C}_2\text{-C}_{10}$ acyl, $\text{C}_1\text{-C}_{10}$ alkyl and SO_3H ;
- (e) $\text{C}_5\text{-C}_7$ glycosyl;
- (f) $\text{C}_3\text{-C}_8$ cycloalkyl optionally substituted with a substituent selected from the group of hydrogen, OH, NH_2 , SH, OSO_3H and OPO_3H_2 ;
- (g) SR_{11} , wherein R_{11} is selected from the group of hydrogen, $\text{C}_1\text{-C}_{10}$ alkyl and O_3H ;
- (h) $\text{C}_1\text{-C}_{10}$ alkyl optionally substituted with a substituent selected from the group of hydrogen, OR_{10} , NHR_7 , NR_8R_9 and SR_{11} ; and
- (i) $\text{C}_3\text{-C}_8$ cycloalkyl optionally substituted with a substituent selected from the group of hydrogen, OR_{10} , NHR_7 , NR_8R_9 and SR_{11} ,

providing that the compound is not myo-inositol.

The present invention further provides a method of diagnosing the presence of abnormally folded or aggregated protein and/or amyloid fibril or amyloid in a subject comprising: (a) collecting a sample from said subject; (b) contacting said sample with a radioactive compound or compound tagged with a substance that emits a detectable signal under conditions to allow the binding of said compound to the abnormally folded or aggregated protein and/or amyloid fibril or amyloid if present; and (c) detecting the radioactivity or the signal from the compound bound to the abnormally folded or aggregated protein and/or fibrils or amyloid, thus diagnosing the presence of abnormally folded or aggregated protein and/or amyloid fibril or amyloid in said subject, wherein said compound has the following structure:

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wherein each of $R_1, R_1', R_2, R_2', R_3, R_3', R_4, R_4', R_5, R_5', R_6,$ and R_6' , is independently selected from the group of;

- (a) hydrogen atom;
 - (b) NHR_7 , wherein said R_7 is selected from the group of hydrogen, $\text{C}_2\text{-C}_{10}$ acyl and $\text{C}_1\text{-C}_{10}$ alkyl;
 - (c) NR_8R_9 , wherein said R_8 is $\text{C}_2\text{-C}_{10}$ acyl or $\text{C}_1\text{-C}_{10}$ alkyl and said R_9 is $\text{C}_2\text{-C}_{10}$ acyl or $\text{C}_1\text{-C}_{10}$ alkyl;
 - (d) OR_{10} , wherein said R_{10} is selected from the group of no group, hydrogen, $\text{C}_2\text{-C}_{10}$ acyl, $\text{C}_1\text{-C}_{10}$ alkyl and SO_3H ;
 - (e) $\text{C}_5\text{-C}_7$ glycosyl;
 - (f) $\text{C}_3\text{-C}_8$ cycloalkyl optionally substituted with a substituent selected from the group of hydrogen, OH, NH_2 , SH, OSO_3H and OPO_3H_2 ;
 - (g) SR_{11} , wherein R_{11} is selected from the group of hydrogen, $\text{C}_1\text{-C}_{10}$ alkyl and O_3H ;
 - (h) $\text{C}_1\text{-C}_{10}$ alkyl optionally substituted with a substituent selected from the group of hydrogen, OR_{10} , NHR_7 , NR_8R_9 and SR_{11} ; and
 - (i) $\text{C}_3\text{-C}_8$ cycloalkyl optionally substituted with a substituent selected from the group of hydrogen, OR_{10} , NHR_7 , NR_8R_9 and SR_{11} ,
- providing that the compound is not myo-inositol.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1A shows the structure of myo-, epi- and scyllo-inositol while FIGS. 1B-1H show the spatial reference memory version of the Morris water maze test in TgCRND8 mice. Myo-inositol treatment did not alter cognitive function (1B). At 6 months of age, non-treated TgCRND8 ($n=10$) show cognitive impairment relative to non-Tg controls and epi- (1C) and scyllo-inositol (1D) treated mice ($n=10$ per group, $p<0.02$ untreated vs. treated). The performance of epi-inositol treated TgCRND8 mice remained impaired with respect to non-Tg littermates (1E) whereas the performance of scyllo-inositol TgCRND8 approached that of non-Tg littermates (1F). Non-Tg littermate behavior was not effected by either epi- (1G) or scyllo-inositol (1H) treatment. Vertical bars represent S.E.M.

FIGS. 2A-2I show at 6 months of age, the plaque burden and astrogliosis in TgCRND8 treated with epi- and scyllo-inositol treated mice. Control animals have a high plaque load and astrogliosis in the hippocampus (2A) and cerebral cortex (2B). Higher magnification demonstrates that astrocytic activation is not only associated with plaque load (2C). Epi-inositol treatment has a modest effect on amyloid burden with a decrease in astrogliosis (2D, 2E and 2F). Scyllo-inositol treatment significantly decreased amyloid burden and gliosis (2G, 2H, and 2I). Higher magnification illustrates the smaller mean plaque size in scyllo-inositol treated mice (2I). Astrocytes were labeled using anti-GFAP antibody and plaque burden was identified using anti-A β antibody. Scale Bar 450 microns (A,B,D,E,G,H) and 94 microns (C,F,I).

FIGS. 3A-3D show that the A β species, 1-42, 1-40 and 1-38, in control and treated TgCRND8 mice was indistinguishable (3A) as was the extent of APP processing (3B).

Vascular amyloid burden was quantitated on serial sagittal sections in treated and untreated TgCRND8 mice. TgCRND8 mice have a significant vascular amyloid burden that is associated with small and medium sized vessels, the load is decreased in scyllo-inositol treated TgCRND8 mice (3A). Scyllo-inositol treatment significantly decreased the total vascular load in comparison to untreated and epi-inositol treated TgCRND8 mice (3C). Scyllo-inositol decreases plaque deposition as illustrated by the significant decrease in mean plaque size (3D).

FIG. 4 shows the effect of water on the cognitive function of TgCRND8 and non-Tg mice using the spatial reference memory version of the Morris Water Maze in a three day trial paradigm.

FIG. 5 shows the effect of scyllo-inositol on the cognitive function of TgCRND8 and non-Tg mice using the spatial reference memory version of the Morris Water Maze in a three day trial paradigm.

FIG. 6 shows the effect of epi-inositol on the cognitive function of TgCRND8 and non-Tg mice using the spatial reference memory version of the Morris Water Maze in a three day trial paradigm.

FIG. 7 shows the effect of myo-inositol on the cognitive function of TgCRND8 and non-Tg mice using the spatial reference memory version of the Morris Water Maze in a three day trial paradigm.

FIG. 8 shows the effect of scyllo-inositol, epi-inositol and myo-inositol on the cognitive function of TgCRND8 (learning phase and memory test) and compared with wild type mice using the spatial reference memory version of the Morris Water Maze in a three-day trial paradigm.

FIG. 9 shows the percentage of brain area covered with plaques in untreated TgCRND8 mice versus mice treated with scyllo-inositol, epi-inositol or myo-inositol.

FIGS. 10A and 10B show the survival rates of TgCRND8 mice treated with water versus epi-inositol or myo-inositol (10A) or versus scyllo-inositol (10B).

FIGS. 11 A-D show the results of spatial reference memory version of the Morris Water Maze test in 6-month old TgCRND8 mice non-treated or treated with mannitol (A,B). Mannitol treated TgCRND8 mice were not significantly different from untreated TgCRND8 mice ($p=0.89$; A). The performance of mannitol treated TgCRND8 mice was significantly different from mannitol treated non-Tg littermates ($p=0.05$; B). Plaque burden was analyzed at 6 months of age using quantitative image analyses (C). Mannitol treated TgCRND8 mice were indistinguishable from untreated TgCRND8 mice when plaque count was used as a measure of total plaque burden ($p=0.87$). Vertical bars represent S.E.M. Kaplan-Meier Cumulative survival plots for TgCRND8 mice treated and untreated with mannitol (D). The two cohorts of animals, $n=35$ per group, were not significantly different as determined by the Tarone-Ware statistical test, $p=0.87$.

FIGS. 12A and B show the results of a spatial reference memory test in the treatment studies when performed in a 3-day trial paradigm. The performance of scyllo-inositol treated TgCRND8 mice was comparable to scyllo-inositol treated non-Tg littermates ($p=0.38$; A). In agreement, scyllo-inositol treated TgCRND8 mice remained indistinguishable from non-Tg littermates after two months of treatment ($p=0.67$; B).

FIGS. 13A and B show A β levels within the CNS after administration of various doses of scyllo-inositol were administered once daily for one month to five month old TgCRND8 mice. Soluble A β 42 levels were decreased at all doses and were significantly different from untreated con-

trols (A). In contrast, insoluble A β 42 was not significantly different under all conditions (B). Vertical bars represent S.E.M.

FIGS. 14A and B. TgCRND8 mice administered various doses of scyllo-inositol once daily for one month were analyzed for levels of brain A β 40. No difference was detected in soluble (A) and insoluble (B) levels of A β 40 of untreated and scyllo-inositol treated TgCRND8 mice at all doses examined.

FIG. 15 shows the cognitive performance of 6-month old allo-inositol-treated TgCRND8 mice compared with that of their non-transgenic littermates.

FIGS. 16A-D show that at 2 months of age, the plaque burden in TgPS1 \times APP mice is decreased in scyllo-inositol treated mice. Control animals have a high plaque load in the hippocampus (A) and cerebral cortex (B). Scyllo-inositol treatment significantly decreased amyloid burden (C, D). Plaque burden identified using anti-A β antibody (brown). Scale Bar 300 μ m.

FIGS. 17A-C show the quantification of the plaque burden in TgPS1 \times APP mice after scyllo-inositol treatment. The percent brain area covered in plaques (A), mean plaque size (B) and plaque count (C) were significantly reduced. Vertical bars are S.E.M.

DETAILED DESCRIPTION OF THE INVENTION

The present invention discloses novel, unpredictable and unexpected properties of certain inositol stereoisomers in relation to the treatment of amyloid-related disorders such as Alzheimer's Disease.

It has been surprisingly discovered that certain stereoisomers of inositol and related compounds block A β -induced progressive cognitive decline and cerebral amyloid plaque pathology, and improve survival when given to a transgenic mouse model of human Alzheimer Disease during the nascent phase of A β deposition.

As disclosed above, previous data suggested that some, but not all, inositol stereoisomers might have an effect on amyloid aggregation in cultured neuronal cells in vitro (McLaurin et al., *J. Biol. Chem.* 275(24): 18495-18502 (2000)). Those observations did not provide any method to predict which, if any, of the studied stereoisomers (myo-, epi-, scyllo- and chiro-inositols) would have such effects, nor whether any other stereoisomers would have such effects. Also, those studies could not predict if any inositol stereoisomers would have effects on amyloid deposition, cognitive defects or lifespan in vivo. The present invention describes the unpredictable results that only certain inositol stereoisomers, in particular scyllo- and allo-inositols reduce amyloid plaque burden, improve cognition and increase lifespan in animal models of amyloid-related disorders, whereas others studied did not have such effects.

Previous studies also suggested only that certain inositol stereoisomers (e.g. epi- and scyllo-inositols) might inhibit de novo amyloid aggregation in vitro. The present invention describes the unexpected results that scyllo-inositol inhibits already established cerebral amyloid deposition, and does so in the living brain. This is not implied by the previously published in vitro data which considered only certain neuronal cell types in culture, not the complex tissues of the living brain, and only suggested that inositols might inhibit de novo aggregation, thereby having no relevance to established disease.

Previous in vitro data also suggested that epi- and scyllo-inositol administration affects amyloid A β 40 levels as well

as A β 42 levels. The *in vivo* dosing study of the present invention revealed the unpredictable result that administration of allo- or scyllo-inositol specifically reduced A β 42 levels, whereas insoluble A β 42 and either soluble or insoluble A β 40 levels were unaffected.

The observation of the present invention showing changes in glial activity and inflammation is novel and surprising, and could not have been predicted by the *in vitro* data previously published.

The observation of the present invention demonstrating that scyllo-inositol improves lifespan in transgenic model animals is also novel and surprising, since no drug for Alzheimer's Disease has previously been shown to increase survival and extend lifespan *in vivo*.

Preferably, the compounds of the present invention are 1,2,3,4,5,6-cyclo-hexanhexols, more preferably selected from the group of cis-, epi-, allo-, muco-, neo-, scyllo-, D-chiro- and L-chiro-inositols.

Also preferably, these compounds are 1,2,3,4,5-cyclohexanepentols (quercitols), more preferably selected from the group of epi-, vibo-, scyllo-, allo-, talo-, gala-, cis-, muco-, neo-, proto-quercitols and enantiomers thereof.

Also preferably, these compounds are selected from the group of a cyclohexanetetrol, a cyclohexanetriol, stereoisomer of cyclohexanetetrol, stereoisomer of cyclohexanetriol, enantiomer of cyclohexanetetrol, and enantiomer of cyclohexanetriol.

These compounds may also be compound is pentahydroxycyclohexanones or stereoisomers or enantiomers thereof.

Yet again preferably, these compounds are inosose compounds selected from the group of scyllo-inosose, L-chiro-inosose-1 and L-epi-inosose.

Also preferably, these compounds are trihydroxycyclohexanones, or stereoisomers or enantiomers thereof. More preferably, (-)-1-deoxy-scyllo-inosose.

Also preferably, these compounds are pentahydroxycyclohexanones (inosose), or stereoisomers or enantiomers thereof, more preferably selected from the group of scyllo-inosose, L-chiro-inosose-1 and L-epi-inosose.

Optionally, these compounds are trihydroxycyclohexanones or stereoisomers or enantiomers thereof such as (-)-1-deoxy-scyllo-inosose.

Also preferably, these compounds are O-monomethylcyclohexanhexols or stereoisomers or enantiomers thereof; more preferably selected from the group of D-pinitol, L-quebrachitol and D-bornesitol.

Again, these compounds may be selected from the group of monoaminocyclohexanepentols (inosamines), diaminocyclohexanetetrols (inosdiamines), diaminocyclohexanetriols, stereoisomers thereof; and enantiomers thereof, and pharmaceutically acceptable salts thereof such as L-neo-inosamine, D,L-epi-inosamine-2, streptamine and deoxystreptamine.

Yet again preferably, these compounds are monomercapto-cyclohexanepentols or stereoisomers or enantiomers thereof, more preferably 1L-1-deoxy-1-mercapto-8-O-methyl-chiro-inositol.

The most preferred compounds of the present invention are allo-inositol and scyllo-inositol, with scyllo-inositol being the most preferred. As indicated above, the inositol stereoisomers of the present invention exclude myo-inositol and may also exclude epi-inositol.

Even when given after the amyloid pathology has been well established for several months, these compounds effectively reverse cerebral A β accumulation and amyloid pathology.

Accordingly, these compounds are found to be useful in treating or preventing in a subject a condition of the central or peripheral nervous system or systemic organ associated with a disorder in protein folding or aggregation, or amyloid formation, deposition, accumulation, or persistence. These compounds are also found to be useful in preventing abnormal protein folding, abnormal protein aggregation, amyloid formation, deposition, accumulation, or persistence, or amyloid lipid interactions as well as causing the dissociation of abnormally aggregated proteins and/or dissolving or disrupting pre-formed or pre-deposited amyloid fibril or amyloid in a subject.

Preferably, the condition of the central or peripheral nervous system or systemic organ results in the deposition of proteins, protein fragments and peptides in beta-pleated sheets and/or fibrils and/or aggregates. More preferably, the condition of the central or peripheral nervous system or systemic organ is selected from the group of: Alzheimer's disease, presenile and senile forms; amyloid angiopathy; mild cognitive impairment; Alzheimer's disease-related dementia; tauopathy; α -synucleinopathy; Parkinson's disease; Amyotrophic Lateral Sclerosis; motor neuron Disease; Spastic paraplegia; Huntington's Disease, spinocerebellar ataxia, Freidrich's Ataxia; neurodegenerative diseases associated with intracellular and/or intraneuronal aggregates of proteins with polyglutamine, polyalanine or other repeats arising from pathological expansions of tri- or tetra-nucleotide elements within corresponding genes; cerebrovascular diseases; Down's syndrome; head trauma with post-traumatic accumulation of amyloid beta peptide; Prion related disease; Familial British Dementia; Familial Danish Dementia; Presenile Dementia with Spastic Ataxia; Cerebral Amyloid Angiopathy, British Type; Presenile Dementia With Spastic Ataxia Cerebral Amyloid Angiopathy, Danish Type; Familial encephalopathy with neuroserpin inclusion bodies (FENIB); Amyloid Polyneuropathy; Inclusion Body myositis due to amyloid beta peptide; Familial and Finnish Type Amyloidosis; Systemic amyloidosis associated with multiple myeloma; Familial Mediterranean Fever; chronic infections and inflammations; and Type II Diabetes Mellitus associate with islet amyloid polypeptide (IAPP).

Also preferably, the Alzheimer's disease-related dementias are vascular or Alzheimer dementia and tauopathy selected from the group of argyrophilic grain dementia, corticobasal degeneration, dementia pugilistica, diffuse neurofibrillary tangles with calcification, frontotemporal dementia with parkinsonism, Prion-related disease, Hallervorden-Spatz disease, myotonic dystrophy, Niemann-Pick disease type C, non-Guamanian Motor Neuron disease with neurofibrillary tangles, Pick's disease, postencephalitic parkinsonism, prion protein cerebral amyloid angiopathy, progressive subcortical gliosis, progressive supranuclear palsy, subacute sclerosing panencephalitis, and tangle only dementia.

Also preferably, the α -synucleinopathy is selected from the group of dementia with Lewy bodies, multiple system atrophy with glial cytoplasmic inclusions, Shy-Drager syndrome, striatonigral degeneration, olivopontocerebellar atrophy, neurodegeneration with brain iron accumulation type I, olfactory dysfunction, and amyotrophic lateral sclerosis.

Again preferably, the Motor Neuron Disease is associated with filaments and aggregates of neurofilament and/or superoxide dismutase proteins, the Spastic paraplegia is associated with defective function of chaperones and/or triple A proteins and the spinocerebellar ataxia is DRPLA or Machado-Joseph Disease.

Also preferably, the Prion related disease is selected from the group of Creutzfeldt-Jakob disease, Gerstmann-Straussler-Scheinker disease, and variant Creutzfeldt-Jakob disease and the Amyloid Polyneuropathy is Senile amyloid polyneuropathy or Systemic Amyloidosis.

More preferably, the condition of the central or peripheral nervous system or systemic organ is Parkinson's disease including familial and non-familial types. Most preferably, said condition of the central or peripheral nervous system or systemic organ is Alzheimer's disease.

Preferably, the compound is administered to the subject at a dose of about 1 mg to about 1 g per kg, preferably 1 mg to about 200 mg per kg, more preferably about 10 mg to about 100 mg per kg and most preferably about 30 mg to 70 mg per kg of the weight of said subject. The administration can be accomplished by a variety of ways such as orally (oral pill, oral liquid or suspension), intravenously, intramuscularly, intraperitoneally, intradermally, transcutaneously, subcutaneously, intranasally, sublingually, by rectal suppository or inhalation, with the oral administration being the most preferred. The administration of the compounds of the present invention can be undertaken at various intervals such as once a day, twice per day, once per week, once a month or continuously.

Preferably, the compounds of the present invention are administered in combination with other treatments such as beta-secretase inhibitors, gamma-secretase inhibitors (APP-specific or non-specific), epsilon-secretase inhibitors (APP-specific or non-specific), other inhibitors of beta-sheet aggregation/fibrillogenesis/ADDL formation (e.g. Alzhemed), NMDA antagonists (e.g. memantine), non-steroidal anti-inflammatory compounds (e.g. Ibuprofen, Celebrex), anti-oxidants (e.g. Vitamin E), hormones (e.g. estrogens), nutrients and food supplements (e.g. *Gingko biloba*); acetylcholinesterase inhibitors (e.g. donepezil), muscarinic agonists (e.g. AF102B (Cevimeline, EVOXAC), AF150(S), and AF267B), anti-psychotics (e.g. haloperidol, clozapine, olanzapine); anti-depressants including tricyclics and serotonin reuptake inhibitors (e.g. Sertraline and Citalopram Hbr), gene therapy and/or drug based approaches to upregulate neprilysin (an enzyme which degrades A β); gene therapy and/or drug based approaches to upregulate insulin degrading enzyme (an enzyme which degrades A β), vaccines, immunotherapeutics and antibodies to A β (e.g. ELAN AN-1792), statins and other cholesterol lowering drugs (e.g. Lovastatin and Simvastatin), stem cell and other cell-based therapies, inhibitors of kinases (CDK5, GSK3 α , GSK3 β) that phosphorylate TAU protein (e.g. Lithium chloride), or inhibitors of kinases that modulate AR production (GSK3 α , GSK3 β , Rho/ROCK kinases) (e.g. lithium Chloride and Ibuprofen).

It is believed that these other therapies act via a different mechanism and may have additive/synergistic effects with the present invention. In addition, many of these other therapies will have mechanism-based and/or other side effects which limit the dose or duration at which they can be administered alone.

Because of their ability to bind amyloids in vivo as discussed hereinbelow in more detail, the compounds of the present invention are also useful in diagnosing the presence of abnormally folded or aggregated protein and/or amyloid fibril or amyloid in a subject using a method that comprises administering to said subject a radioactive compound or compound tagged with a substance that emits a detectable signal in a quantity sufficient and under conditions to allow for the binding of said compound to the abnormally folded or aggregated protein and/or fibrils or amyloid, if present;

and detecting the radioactivity or the signal from the compound bound to the abnormally folded or aggregated protein and/or fibrils or amyloid, thus diagnosing the presence of abnormally folded or aggregated protein and/or amyloid fibril or amyloid.

Alternatively, a sample suspected of containing abnormally folded or aggregated protein and/or amyloid fibril or amyloid is collected from a subject and is contacted with a radioactive compound or compound tagged with a substance that emits a detectable signal under conditions to allow the binding of said compound to the abnormally folded or aggregated protein and/or amyloid fibril or amyloid if present; and thereafter detect the radioactivity or the signal from the compound bound to the abnormally folded or aggregated protein and/or fibrils or amyloid, thus diagnosing the presence of abnormally folded or aggregated protein and/or amyloid fibril or amyloid in said subject.

Preferably, said detectable signal is a fluorescent or an enzyme-linked immunosorbent assay signal and said sample is whole blood (including all cellular constituents) or plasma.

As shown hereinbelow, the compounds of the present invention can abrogate the cerebral accumulation of A β , the deposition of cerebral amyloid plaques, and cognitive decline in a transgenic mouse model of Alzheimer Disease when given during the "late presymptomatic" phase, prior to the onset of overt cognitive deficits and amyloid neuropathology in these mice. Furthermore, even when these compounds are given after the onset of cognitive deficits and amyloid plaque neuropathology, they can effectively reverse the amyloid deposition and neuropathology. Importantly, the mechanism of action of these compounds follows a rational design based upon their capacity to modulate the assembly of A β monomers into neurotoxic oligomers and/or protofibrils.

Other advantages of the compounds of the present invention include the fact that they are transported into the CNS by both known transporters and by passive diffusion, and therefore provide ready CNS bioavailability. Second, these compounds are catabolized to glucose. Third, as a class, these compounds generally have low toxicity profiles, and some of them have previously been given to humans albeit for a different purpose.

Example 1—Development of Alzheimer's Mouse Model and Methods of Administering Compounds of the Present Invention

TgCRND8 mice are a robust murine model of Alzheimer's disease as described by Janus et al. (*Nature* 408:979-982 (2000)). They express a human amyloid precursor protein (APP695) transgene under the regulation of the Syrian hamster prion promoter on a C3H/B6 outbred background. The human APP695 transgene bears two mutations that cause AD in humans (K670N/M671 L and V717F). Beginning at about 3 months of age, TgCRND8 mice have progressive spatial learning deficits that are accompanied by rising cerebral A β levels and by increasing number of cerebral extracellular amyloid plaques that are similar to those seen in the brains of humans with AD (C. Janus et al., *Nature* 408:979-982 (2000)).

Age and sex-matched cohorts of TgCRND8 mice and non-transgenic littermates (n=35 in each cohort) were either untreated, or were given a compound of the present invention as indicated below at 30 mg/day/mouse beginning at age of about 6 weeks. The mice were followed for outcome

measures cognitive function, brain A β levels, brain pathology, and survival at 4 months and 6 months of age.

Prevention Studies Methods

Mice—

Experimental groups of TgCRND8 mice were fed myo-, epi- and scyllo-inositol at 30 mg/mouse/day. Two cohorts entered the study at 6 weeks of age and outcomes were analyzed at 4- and 6-months of age. The body weight, coat characteristics and in cage behavior was monitored. All experiments were performed according to the Canadian Council on Animal Care guidelines.

Behavioral Tests—

After non-spatial pre-training, mice underwent place discrimination training for 5 days with 4 trials per day. Behavioral data was analyzed using a mixed model of factorial analysis of variance (ANOVA) with drug or genotype and training sessions as repeated measure factors.

Cerebral Amyloid Burden—

Brains were removed and one hemisphere was fixed in 4% paraformaldehyde and embedded in paraffin wax in the mid saggital plane. To generate sets of systematic uniform random sections, 5 μ m serial sections were collected across the entire hemisphere. Sets of sections at 50 μ m intervals were used for analyses (10-14 sections/set). Plaques were identified after antigen retrieval with formic acid, and incubated with primary anti-A β antibody (Dako M-0872), followed by secondary antibody (Dako StreptABCcomplex/horseradish kit). End products were visualized with DAB counter-stained with hematoxylin. Amyloid plaque burden was assessed using Leco IA-3001 image analysis software interfaced with Leica microscope and Hitachi KP-M1U CCD video camera. Vascular burden was analyzed similarly and a dissector was used to measure the diameter of affected vessels.

Plasma and Cerebral AD Content—

Hemi-brain samples were homogenized in a buffered sucrose solution, followed by either 0.4% diethylamine/100 mM NaCl for soluble A β levels or cold formic acid for the isolation of total A β . After neutralization the samples were diluted and analyzed for A β 40 and A β 42 using commercially available kits (BIOSOURCE International). Each hemisphere was analyzed in triplicate with the mean \pm SEM reported. Western blot analyses were performed on all fractions using urea gels for A β species analyses. A β was detected using 6E10 (BIOSOURCE International) and Enhanced Chemiluminescence (Amersham).

Analysis of APP in Brain—

Mouse hemi-brain samples were homogenized in 20 mM Tris pH7.4, 0.25M sucrose, 1 mM EDTA and 1 mM EGTA, and a protease inhibitor cocktail, mixed with 0.4% DEA (diethylamine)/100 mM NaCl and spun at 109,000 \times g. The supernatants were analysed for APPs levels by Western blotting using mAb 22C11, while the pellets were analysed for APP holoprotein using mAb C1/6.1.

Gliososis Quantitation—

Five randomly selected, evenly spaced, sagittal sections were collected from paraformaldehyde-fixed and frozen hemispheres of treated and control mice. Sections were immunolabelled for astrocytes with anti-rat GFAP IgG2a (Dako; diluted 1:50) and for microglia with anti-rat CD68 IgG2b (Dako; 1:50). Digital images were captured using a Coolsnap digital camera (Photometrics, Tucson, Ariz.) mounted to a Zeiss Axioscope 2 Plus microscope. Images were analysed using Openlab 3.08 imaging software (Improvision, Lexington Mass.).

Survival Census—

The probability of survival was assessed by the Kaplan-Meier technique, computing the probability of survival at every occurrence of death, thus making it suitable for small sample sizes. For the analyses of survival, 35 mice were used for each treatment group. The comparison between treatments was reported using the Tarone-Ware test.

Example 2—Prevention of Cognitive Deficits

The cognitive function of TgCRND8 mice was assessed using the spatial reference memory version of the Morris Water Maze using a five-day trial paradigm (FIGS. 1C-1H). Data from treated and non-treated TgCRND8 mice, and from treated and non-treated non-Tg littermates (n=10 for all combinations) were analyzed using a mixed model of analysis of variance (ANOVA) with treatment (untreated, epi- or scyllo-inositol) and genotype (TgCRND8 versus non-Tg) as 'between-subject' factors. TgCRND8 mice treated with either epi- or scyllo-inositol performed significantly better than untreated TgCRND8 mice (p<0.02; FIGS. 1C and D). When compared to treated or non-treated non-Tg littermates, epi-inositol treated TgCRND8 mice had a slightly slower learning curve during the first three days of training. However, after 4 days of training, epi-inositol treated TgCRND8 mice were not statistically different from their non-Tg littermates (FIG. 2E). In contrast, scyllo-inositol treated TgCRND8 mice were indistinguishable from non-Tg littermates on all days. Thus both stereoisomers inhibited the development of cognitive deficits, and scyllo-inositol actually prevented the deficits to such a degree that the scyllo-inositol treated TgCRND8 mice were indistinguishable from normal mice. This improved performance was not due to a non-specific effect on behavioral, motoric, or perceptual systems because epi- and scyllo-inositol treatment had no effect on the performance of non-Tg mice (FIGS. 2G and 2H). The improved performance was also not due to nutritional or caloric effects because body weight, activity, and coat condition were not different between treated and untreated cohorts. Furthermore, treatment with mannitol (a sugar of similar molecular weight) had no effect on behavior. Gender effects were not significant between any treatment group (p=0.85).

Example 3—Reduction of Cerebral A β Burden and Amyloid Neuropathology

At four months of age, untreated TgCRND8 mice have a robust expression of both A β 40 and A β 42 (Table 1). Epi-inositol treatment as described in Example 1 reduced both A β 40 (43 \pm 12% reduction in both soluble and insoluble pools; p0.0.05) and A β 42 levels (69% reduction in soluble pool, p=0.005; 28% reduction in insoluble pool, p=0.02) at 4-months of age. However, these improvements were not sustained, and by 6 months of age, brain A β levels rose to levels similar to those observed in untreated TgCRND8 mice (Table 1).

In contrast, at four months of age, scyllo-inositol treatment decreased total brain A β 40 by 62% (p=0.0002) and total brain A β 42 by 22% (p=0.0096; Table 1). At 6 months of age, scyllo-inositol treatment caused a 32% reduction in A β 40 levels (p=0.04) and 20% reduction in A β 42 (p=0.02) compared to untreated TgCRND8 mice.

Because the decreased A β concentrations detected after inositol treatment could have resulted from altered efflux of A β into the plasma, A β - β levels in the plasma were examined at 4- and 6-months of age (Table 1). TgCRND8 mice

have high plasma A β concentrations at 4-months of age and remain constant at 6 months of age even though CNS plaque load is still rising at 6-months of age (Table 1). Neither epi-inositol nor scyllo-inositol treatment had any effect on plasma A β levels in comparison to untreated TgCRND8 mice (p=0.89). The most parsimonious explanation for this observation is that the inositols have selectively altered the fibrillization of A β in the CNS, but have not affected β - or γ -secretase activity, or the normal mechanisms for clearance of A β into plasma. Nevertheless, this observation is significant for two reasons. First, a drop in plasma and CSF A β levels is usually detected as the clinical course progresses in untreated A β patients (Mayeux, et al., *Ann. Neurol* 46, 412,

that at modest A β levels, epi-inositol prevents A β oligomerization but once initiated at higher A β concentrations, epi-inositol is unable to inhibit fibrillogenesis. Scyllo-inositol treatment decreased the mean plaque size from $136\pm 15 \mu\text{m}^2$ to $103\pm 4 \mu\text{m}^2$ (p=0.01) at 4 months of age. In scyllo-inositol treated TgCRND8 mice at 6 months of age, the decrease in A β peptide levels was accompanied by a 20% reduction in plaque number (p=0.005), a 35% decrease in brain area covered with plaques (p=0.015) and a decreased mean plaque size (339 ± 10 vs. $423\pm 21 \mu\text{m}^2$, p=0.009). These results demonstrate that by every measure there was a reduction in plaque burden after scyllo-inositol treatment.

TABLE 1

Inositol treatment decreases A β 40 and A β 42 Levels								
	A β 40 (ng/gm wet brain \pm sem)		A β 42 (ng/gm wet brain \pm sem)		Total A β	Plaque Count	Plaque Area (μm^2)	Total Plaque Area/Total Brain Area (%)
	Soluble	Insoluble	Soluble	Insoluble				
4 month prevention								
Control	75 \pm 6	1163 \pm 9	273 \pm 18	5658 \pm 248	7169 \pm 284	696 \pm 25	100766 \pm 7564	0.026 \pm 0.004
Epi-Inositol	43 \pm 7*	615 \pm 32†	85 \pm 7†	4059 \pm 179*	4802 \pm 176	678 \pm 64	65042 \pm 5199	0.020 \pm 0.001
Scyllo-Inositol	37 \pm 5*	437 \pm 80†	206 \pm 8*	4409 \pm 135*	5089 \pm 173	598 \pm 19*	63847 \pm 2895	0.015 \pm 0.001*
6 month prevention								
Control	187 \pm 29	3576 \pm 172	626 \pm 87	15802 \pm 237	20191 \pm 211	960 \pm 44	411288 \pm 11912	0.120 \pm 0.001
Epi-Inositol	188 \pm 24	3668 \pm 149	665 \pm 39	13943 \pm 277†	18464 \pm 229	979 \pm 32	380456 \pm 13498	0.096 \pm 0.04
Scyllo-Inositol	105 \pm 8*	2453 \pm 251*†	475 \pm 26*	12588 \pm 82†	15621 \pm 151	774 \pm 10*†	262379 \pm 5373†	0.079 \pm 0.013†
Plasma A β Levels (pg/ml)								
4 month prevention								
Control				1018 \pm 27				
Epi-Inositol				1082 \pm 164				
Scyllo-Inositol				952 \pm 49				
6 month prevention								
Control				915 \pm 59				
Epi-Inositol				952 \pm 56				
Scyllo-Inositol				905 \pm 55				

Anova with Fisher's PLSD,

†p < 0.001 and

*p < 0.05

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2001). Secondly, patients in the AN1792 immunization study who developed a strong antibody response and an apparent clinical response did not have altered plasma A β - β levels (Hock et al., *Neuron* 38, 547 2003). Therefore, these results indicate that it is not necessary to change plasma A β levels to obtain an effective therapeutic outcome.

To confirm that inositol stereoisomers had no effect on either the expression or proteolytic processing of APP, the levels of APP holo-protein, sAPP- α , and various A β species were examined within the brain of inositol-treated and untreated TgCRND8 mice. Consistent with our previously reported data (McLaurin, et al., *Nat. Med.* 8, 1263, 2002), A β 42, A β 40 and A β 38 are the predominant species in the brain of TgCRND8 mice (FIG. 3A), and the CNS levels of immature and mature glycolyslated APP (FIG. 3B), and of sAPP- α were indistinguishable regardless of treatment. In combination, these results indicate that epi- and scyllo-inositol have a direct and selective effect on A β oligomerization and not the processing of APP.

The changes in A β - β peptide load were accompanied by a significant decrease in plaque burden (Table 1; FIGS. 2A-2I). In epi-inositol treated TgCRND8 mice, there was a significant decrease in the mean plaque size at 4- but not 6-months of age compared with untreated TgCRND8 mice ($95\pm 4.3 \mu\text{m}^2$ versus $136\pm 15 \mu\text{m}^2$, p=0.04; $370\pm 9 \mu\text{m}^2$ versus $423\pm 221 \mu\text{m}^2$, p=0.06, respectively). These results indicate

Example 4—Reduction of Glial Reactivity and Inflammation

Astroglial and microglial reactions are neuropathological features both of human AD and of all amyloid mouse models (Irizarry et al., *J Neuropathol Exp Neurol.* 56, 965, 1997; K. D. Bornemann et al. *Ann N Y Acad Sci.* 908, 260, 2000). Therefore, the effect of epi- and scyllo-inositol treatment was investigated on astrogliosis and microgliosis in the brains of TgCRND8 mice (FIGS. 3A-3D). Serial sagittal sections were stained with the astrocytic marker glial fibrillary acidic protein (GFAP) and quantitated for percent brain area covered by astrogliosis. TgCRND8 mice have a high basal astrogliosis at 4-months of age ($0.459\pm 0.048\%$), which increases slightly by 6-months of age ($0.584\pm 0.089\%$), and which is not restricted to plaque areas (FIGS. 2A-C). Epi-inositol decreased the astroglial response to $0.388\pm 0.039\%$ at 6-months of age (p=0.04; FIG. 2D-F). Scyllo-inositol, on the other hand, decreased astrogliosis much more efficiently to $0.269\pm 0.028\%$ at 6-months of age, (p=0.006) (FIG. 2G-I). Microglial activation was also significantly attenuated in scyllo-inositol treated TgCRND8 mice ($0.20\pm 0.008\%$ brain area) when compared to age- and sex-matched untreated TgCRND8 mice ($0.31\pm 0.01\%$; p<0.001). However, epi-inositol treated mice demonstrated no significant reduction in microglial activation at 6 months

(0.248±0.02%; p=NS). Taken together these data indicate that scyllo-inositol treatment decreases the A β -induced inflammatory response within the CNS.

Example 5—Reduction of Vascular Amyloid Load

Alzheimer's disease is characterized by the presence of both parenchymal and vascular amyloid deposits. In untreated 6 month old TgCRND8 mice approximately 0.03% of the brain area is associated with vascular amyloid. No difference could be detected in the vascular amyloid burden after epi-inositol treatment at 6 months of age (FIG. 3C). In contrast, scyllo-inositol treatment significantly decreased the vascular amyloid burden (p=0.05) (FIG. 3C), and the amyloid deposition was predominantly localized to smaller vessels, <25 μ m in diameter (56±2% versus 70±8% in small vessels in untreated TgCRND8 mice). The mean size of cerebrovascular plaques was significantly decreased in the scyllo-inositol treated mice in comparison to untreated mice (154.416 vs. 363±34, p=0.008; FIG. 3D).

Example 6—Survival Improvement

TgCRND8 mice have a 50% survival at 175 days, which after treatment was improved to 72% with scyllo-inositol (n=35 per group, p<0.02 for scyllo-inositol vs. control, FIG. 10B). Treatment with myo-inositol did not affect overall survival significantly (FIG. 10A). Control experiments confirmed that the enhanced survival of scyllo-inositol treated mice was not an indirect effect of increased caloric intake. Thus, treatment of wild type mice with scyllo-inositol had no effect either on survival or on other parameters such as weight, fur condition or cage behavior. Furthermore, the weight, fur condition and home-cage behavior of the inositol-treated TgCRND8 mice did not vary from untreated TgCRND8 mice. Simultaneous experiments with mannitol, a simple sugar of similar molecular weight, also had no effect on survival of TgCRND8 mice.

Example 7—Treatment and Reversal of Amyloid Deposition

Taken together, the prevention studies demonstrate that scyllo-inositol inhibits both parenchymal and cerebrovascular amyloid deposition and results in improved survival and cognitive function in the TgCRND8 mouse model of Alzheimer disease. However, most Alzheimer's disease patients will likely seek treatment only once symptomatic, and when A β oligomerization, deposition, toxicity and plaque formation are already well advanced within the CNS. A pilot study was therefore initiated on 5 month old TgCRND8 mice. These mice have significant A β and plaque burdens that are comparable to those in the brain of humans with AD.

Treatment Study Methods

Mice—

Experimental groups of TgCRND8 mice were fed myo-, epi- and scyllo-inositol at 30 mg/mouse/day. A cohort entered the study at 5 months of age and outcomes were analyzed at 6-months of age. The body weight, coat characteristics and in cage behavior was monitored. All experiments were performed according to the Canadian Council on Animal Care guidelines.

Survival Census—

The probability of survival was assessed by the Kaplan-Meier technique, computing the probability of survival at every occurrence of death, thus making it suitable for small

sample sizes. For the analyses of survival, 35 mice were used for each treatment group. The comparison between treatments was reported using the Tarone-Ware test.

Behavioral Test—

Reversal Study—Mice entered the Morris water maze test with a hidden platform on day one without pretraining. Mice were tested for 3 days with six trials per day. On the fourth day, the platform was removed from the pool and each mouse received one 30-s swim probe trial. On the last day the animals underwent a cue test in order to evaluate swimming ability, eye sight and general cognition. The cue test is composed at the platform being placed in a different quadrant than that used for testing and is tagged with a flag. Animals are allowed 60 s to find the platform. Animals that do not find the platform are not used in the final analyses of spatial memory. Behavioural data was analysed using a mixed model of factorial analysis of variance (ANOVA) with drug or genotype and training sessions as repeated measure factors.

Cerebral Amyloid Burden—

Brains were removed and one hemisphere was fixed in 4% paraformaldehyde and embedded in paraffin wax in the mid saggital plane. To generate sets of systematic uniform random sections, 5 μ m serial sections were collected across the entire hemisphere. Sets of sections at 50 μ m intervals were used for analyses (10-14 sections/set). Plaque were identified after antigen retrieval with formic acid, and incubated with primary anti-A β antibody (Dako M-0872), followed by secondary antibody (Dako StreptABCcomplex/horseradish kit). End products were visualized with DAB counter-stained with hematoxylin. Amyloid plaque burden was assessed using Leco IA-3001 image analysis software interfaced with Leica microscope and Hitachi KP-M1U CCD video camera.

Plasma and Cerebral A β Content—

Hemi-brain samples were homogenized in a buffered sucrose solution, followed by either 0.4% diethylamine/100 mM NaCl for soluble A β levels or cold formic acid for the isolation of total A β . After neutralization the samples were diluted and analyzed for A β 40 and A β 42 using commercially available kits (BIOSOURCE International). Each hemisphere was analyzed in triplicate with the mean±SEM reported.

Results and Significance—

All animals that entered the reversal study survived and did not display outward signs of distress or toxicity. The cognitive function of TgCRND8 mice was assessed using the spatial reference memory version of the Morris Water Maze using a three day trial paradigm (FIGS. 4-8). Data from treated and non-treated TgCRND8 mice, and from treated and non-treated non-Tg littermates (n=10 for all combinations) were analyzed using a mixed model of analysis of variance (ANOVA) with treatment (untreated, myo-, epi- or scyllo-inositol) and genotype (TgCRND8 versus non-Tg) as 'between-subject' factors. In this paradigm TgCRND8 mice were significantly impaired in comparison to wild type littermates (FIG. 4). In contrast, scyllo-inositol treated TgCRND8 mice were indistinguishable from non-Tg littermates on all days. (p=0.38; FIG. 5). When compared to treated non-Tg littermates, epi-inositol treated TgCRND8 mice were almost significantly different (p=0.07; FIG. 6). Similarly, myo-inositol treated TgCRND8 mice were significantly different from treated non-Tg littermates (p=0.05. FIG. 7). When the learning phase of the Morris water maze test is compared between treatments, all mice behaved similarly (FIG. 8). In contrast, only scyllo-inositol was indistinguishable from non-Tg littermates (FIG. 8). Thus,

scyllo-inositol actually reversed the cognitive deficits to such a degree that the scyllo-inositol treated TgCRND8 mice were indistinguishable from normal mice. This improved performance was not due to a non-specific effect on behavioral, motoric, or perceptual systems because epi- and scyllo-inositol treatment had no effect on the performance of non-Tg mice. The improved performance was also not due to nutritional or caloric effects because body weight, activity, and coat condition were not different between treated and untreated cohorts.

In order to determine if the improved cognition was associated with decreased plaque burden and A β load, brain tissue was examined post-mortem. The changes in cognition were accompanied by a corresponding change in plaque burden and A β load (FIG. 9 and Table 2). Myo-inositol treatment did not affect the plaque burden or A β load (FIG. 9 and Table 2). In epi-inositol treated TgCRND8 mice, there was not a significant decrease in the mean plaque size compared with untreated TgCRND8 mice (FIG. 9), yet the A β load was significantly decreased (Table 2). These results suggest that at modest A β levels, epi-inositol prevents A β oligomerization but at higher A β concentrations, epi-inositol is unable to inhibit fibrillogenesis completely. Scyllo-inositol treatment significantly decreased the plaque burden and the A β load. These results demonstrate that by every measure there was a reduction in plaque burden after scyllo-inositol treatment. These results are comparable in effect size to the 6-month prophylactic studies, and further support the potential for scyllo-inositol.

Because the decreased A β concentrations detected after inositol treatment could have resulted from altered efflux of

A β into the plasma, we examined A β levels in the plasma (Table 2). TgCRND8 mice have high plasma A β concentrations at 6 months of age. Neither myo-inositol, epi-inositol nor scyllo-inositol treatment had any effect on plasma A β levels in comparison to untreated TgCRND8 mice ($p=0.89$). The most parsimonious explanation for this observation is that the inositols have selectively altered the fibrillization of A β in the CNS, but have not affected β - or γ -secretase activity, or the normal mechanisms for clearance of A β into plasma. Nevertheless, this observation is significant for two reasons. First, a drop in plasma and CSF A β levels is usually detected as the clinical course progresses in untreated AD patients. Secondly, patients in the AN1792 immunization study who developed a strong antibody response and an apparent clinical response did not have altered plasma A β levels. Therefore, these results further indicate that it is not necessary to change plasma A β levels to obtain an effective therapeutic outcome.

Taken together, these data reveal that selected scyllo-inositol can abrogate the cerebral accumulation of A β , the deposition of cerebral amyloid plaques, and cognitive decline in a transgenic mouse model of Alzheimer Disease when given during the "late presymptomatic" phase, prior to the onset of overt cognitive deficits and amyloid neuropathology in these mice. Furthermore, even when scyllo-inositol is given after the onset of cognitive deficits and amyloid plaque neuropathology, these compounds can effectively reverse the amyloid deposition, neuropathology and cognitive deficits. Therefore, these results indicate that scyllo-inositol is effective at both prevention of disease and in the treatment of existing disease in patients already diagnosed with AD.

TABLE 2

Inositol treatment decreases A β 40 and A β 42 Levels								
	A β 40 (ng/gm wet brain \pm sem)		A β 42 (ng/gm wet brain \pm sem)		Total A β	Plaque Count	Plaque Area (μ m ²)	Total Plaque Area/Total Brain Area (%)
	Soluble	Insoluble	Soluble	Insoluble				
4 month prevention								
Control	75 \pm 6	1163 \pm 9	273 \pm 18	5658 \pm 248	7169 \pm 284	696 \pm 25	100766 \pm 7564	0.026 \pm 0.004
Myo-Inositol	42 \pm 6	485 \pm 143	174 \pm 9	4268 \pm 308	4969 \pm 434	649 \pm 50	91902 \pm 7453	0.023 \pm 0.004
Epi-Inositol	43 \pm 7*	615 \pm 32†	85 \pm 7†	4059 \pm 179*	4802 \pm 176	678 \pm 64	65042 \pm 5199	0.020 \pm 0.001
Scyllo-Inositol	37 \pm 5*	437 \pm 80†	206 \pm 8*	4409 \pm 135*	5089 \pm 173	598 \pm 19*	63847 \pm 2895	0.015 \pm 0.001*
6 month prevention								
Control	187 \pm 29	3576 \pm 172	626 \pm 87	15802 \pm 237	20191 \pm 211	960 \pm 44	411288 \pm 11912	0.120 \pm 0.001
Myo-Inositol	221 \pm 19	3436 \pm 189	543 \pm 71	13219 \pm 535	17489 \pm 354	927 \pm 78	400013 \pm 19638	0.100 \pm 0.005
Epi-Inositol	188 \pm 24	3668 \pm 149	665 \pm 39	13943 \pm 277†	18464 \pm 229	979 \pm 32	380456 \pm 13498	0.096 \pm 0.04
Scyllo-Inositol	105 \pm 8*	2453 \pm 251*†	475 \pm 26*	12588 \pm 82†	15621 \pm 151	774 \pm 10*†	262379 \pm 5373†	0.079 \pm 0.013†
1 month treatment								
Control	207 \pm 16	4965 \pm 457	426 \pm 14	14503 \pm 1071	20101 \pm 854	1441 \pm 29	486002 \pm 16156	0.159 \pm 0.014
Myo-Inositol	194 \pm 12	4187 \pm 226	487 \pm 25	15622 \pm 675	20490 \pm 526	1324 \pm 69	469968 \pm 35664	0.153 \pm 0.088
Epi-Inositol	264 \pm 11	3637 \pm 113	540 \pm 14	12830 \pm 330	17271 \pm 415	1342 \pm 114	459706 \pm 49966	0.134 \pm 0.017
Scyllo-Inositol	178 \pm 11	3527 \pm 241	374 \pm 23	11115 \pm 647	15194 \pm 579	1260 \pm 27*	420027 \pm 14986*	0.119 \pm 0.010*
Plasma A β Levels (pg/ml)								
4 month prevention								
Control	1018 \pm 27			915 \pm 59			2287 \pm 151	
Myo-Inositol	942 \pm 30			969 \pm 67			2110 \pm 174	
Epi-Inositol	1082 \pm 164			952 \pm 56			2158 \pm 157	
Scyllo-Inositol	952 \pm 49			905 \pm 55			1980 \pm 146	
6 month prevention								
Control	1018 \pm 27			915 \pm 59			2287 \pm 151	
Myo-Inositol	942 \pm 30			969 \pm 67			2110 \pm 174	
Epi-Inositol	1082 \pm 164			952 \pm 56			2158 \pm 157	
Scyllo-Inositol	952 \pm 49			905 \pm 55			1980 \pm 146	
1 month treatment								
Control	1018 \pm 27			915 \pm 59			2287 \pm 151	
Myo-Inositol	942 \pm 30			969 \pm 67			2110 \pm 174	
Epi-Inositol	1082 \pm 164			952 \pm 56			2158 \pm 157	
Scyllo-Inositol	952 \pm 49			905 \pm 55			1980 \pm 146	

Anova with Fisher's PLSD,

† $p < 0.001$ and

* $p < 0.05$; IP = in progress.

Example 8—Two-Month Treatment Study with Scyllo-Inositol

In order to determine longer efficacy ranges of scyllo-inositol for the treatment of disease, 5-month old TgCRND8 mice were fed scyllo-inositol or untreated for two months (n=10 per group). The cognitive function of 7-month old TgCRND8 mice treated with scyllo-inositol was compared to untreated TgCRND8 and treated non-Tg littermates in the three-day paradigm of the Morris Water Maze. Behavioural data was analysed using a mixed model of factorial analysis of variance (ANOVA) with drug and genotype as between subject variables and training sessions as within subject variable. As was seen with the 1-month treatment of scyllo-inositol (FIG. 12A), TgCRND8 mice treated for two months with scyllo-inositol were indistinguishable from scyllo-inositol treated non-Tg littermates (FIG. 12B). In order to correlate the improved cognition with pathology, A β 40 and A β 42 levels were analysed in the brain (Table 3). Both insoluble A β 40 and A β 42 levels were decreased 20% after scyllo-inositol treatment. These results demonstrate that scyllo-inositol effects persist during disease progression.

TABLE 3

	Inositol treatment decreases A β 40 and A β 42 Levels					
	Brain A β 40 (ng/gm wet brain \pm sem)		Brain A β 42 (ng/gm wet brain \pm sem)		Plasma A β Levels (pg/ml)	
	Soluble	Insoluble	Soluble	Insoluble	A β 40	A β 42
	2 month treatment					
Control	487 \pm 14	6924 \pm 287	764 \pm 51	25827 \pm 1238	5212 \pm 219	3455 \pm 331
Scyllo-inositol	395 \pm 60	5703 \pm 612*	688 \pm 28	20818 \pm 1404*	4507 \pm 207	3035 \pm 236

ANOVA with Fisher's PLSD,
*p < 0.05.

Example 9—Effect of Dose on Pathological Outcome in Disease Bearing TgCRND8 Mice

5-month old TgCRND8 mice were gavaged once daily with scyllo-inositol in water at doses of 10 mg/Kg, 30 mg/Kg, 100 mg/Kg or untreated. Animals were sacrificed after one month of treatment and analysed for pathological outcomes. Analysis of the levels of A β within the brain of all the cohorts demonstrates that all drug doses were effective to the same extent on lowering soluble A β 42 levels in comparison to untreated TgCRND8 mice (20% reduction, $F_{3,15}=3.1$, p=0.07; FIG. 13A). Analyses of individual doses demonstrate that 10 mg/Kg and 30 mg/Kg doses were significantly different from untreated controls (p=0.03 and p=0.02, respectively). None of the doses chosen were significantly different from each other ($F_{2,11}=0.6$, p=0.57; FIG. 13A). Gavage dosing had no significant effect on insoluble A β 42 ($F_{3,15}=0.69$, p=0.58; FIG. 13B) or soluble and insoluble A β 40 ($F_{3,15}=0.04$, p=0.99 and $F_{3,15}=0.36$, p=0.79, respectively; FIGS. 14A and 14B).

Example 10—Efficacy of Allo-Inositol for the Treatment of Disease Bearing TgCRND8 Mice

To assess whether allo-inositol might also be effective in preventing further progression and/or might partially reverse a well-established AD-like phenotype, the start of treatment of the TgCRND8 mice was delayed until 5 months of age. Cohorts of TgCRND8 and non-transgenic littermates were either treated for 28 days with allo-inositol, or were untreated. In these experiments, the dosage and oral administration of compounds, and the behavioral and neurochemical assays were the same as those employed in the above treatment experiments.

The cohort of 6-month old allo-inositol-treated TgCRND8 mice performed significantly better than untreated TgCRND8 mice ($F_{1,13}=0.45$, p=0.05; data not shown). The cognitive performance of 6-month old allo-inositol-treated TgCRND8 mice was still significantly different from that of their non-transgenic littermates

($F_{1,13}=5.9$, p=0.05; FIG. 15). The beneficial effect of inositol treatment was not due to non-specific effects on behavioral, motor, or perceptual systems because inositol treatment had no effect on the cognitive performance of non-Tg mice ($F_{1,12}=0.98$; p=0.49). Cerebral A β levels were analyzed for treatment versus untreated TgCRND8 mice to determine whether improved behavior could be correlated with changes in A β (Table 4). Allo-inositol treatment reduced soluble A β 42 (20% reduction, p<0.05) an effect similar to that seen for scyllo-inositol. Allo-inositol did not significantly alter insoluble A β 42 or A β 40 (soluble and insoluble pools). One possible explanation for the decrease in A β 42 is clearance of A β 42 in the periphery with a subsequent increase in plasma A β 42. The levels of A β 42 in plasma after allo-inositol treatment were indistinguishable from untreated TgCRND8 plasma levels (Table 5). In agreement with the other inositol stereoisomers, these results demonstrate that plasma A β levels are unaffected by allo-inositol treatment.

TABLE 4

	Allo-Inositol treatment decreases A β 42 levels				
	Brain A β 40 (ng/gm wet brain \pm sem)		Brain A β 42 (ng/gm wet brain \pm sem)		Plasma A β Levels
	Soluble	Insoluble	Soluble	Insoluble	(pg/ml)
	1 month treatment				
Control	252 \pm 48	4105 \pm 851	666 \pm 39	16448 \pm 2120	2359 \pm 147
Allo-inositol	281 \pm 21	3787 \pm 342	547 \pm 47*	16336 \pm 910	2458 \pm 95

ANOVA with Fisher's PLSD,
*p < 0.05.

TABLE 5

Blood Biochemistry - scyllo-inositol Dose Study					
	Untreated n = 4	100 mg/Kg n = 4	30 mg/Kg n = 3	10 mg/Kg n = 5	Reference Levels (Vita-Tech & CCAC)
Biochemistry					
Total protein	46 ± 2 g/L	49 ± 2	50 ± 2.6	50 ± 3	35-72
Albumin	35 ± 0 g/L	31 ± 1	33 ± 2	33 ± 4	25-48
Globulin	12 ± 1 g/L	19 ± 2	17 ± 1	17 ± 2	18-82
Bilirubin	2.4 ± 1 umol/L	1.9 ± 0	2.0 ± 1	1.9 ± 0.6	2-15
ALP	81 ± 10 U/L	76 ± 11	81 ± 10	73 ± 22	28-94
ALT	42 ± 4 U/L	38 ± 4	42 ± 4	51 ± 20	28-184
Glucose	11 ± 2 mmol/L	11 ± 2	12 ± 2	7 ± 2	9.7-18.6
Urea	9 ± 3 mmol/L	7.4 ± 1	9 ± 3	10 ± 2	12.1-20.6
Creatinine	36 ± 5 umol/L	31 ± 4	35 ± 5	40 ± 5	26-88
Hemolysis	Normal	Normal	Normal	Normal	
Icteria	Normal	Normal	Normal	Normal	
Lipemia	Normal	Normal	Normal	Normal	

Example 11—Inositol Treatment does not Affect Blood Chemistry

In order to rule out any deleterious effects of inositol treatment on blood chemistry and organ function, blood was analyzed after one month treatment with both scyllo- and allo-inositol (Table 5,6). The total protein, albumin, globulin, bilirubin, alkaline phosphatase, glucose, urea and creatinine were not significantly different between treatment groups or from untreated TgCRND8 mice. All levels fell within the normal range as determined for non-transgenic wild type mice. In addition hemolysis, ictericia and lipemia were all normal. These results suggest that allo- and scyllo-inositol do not exhibit obvious deleterious effects on blood chemistry or organ function.

TABLE 6

Blood Biochemistry - 1 Month Treatment Study			
	Untreated n = 4	Allo-Inositol n = 4	Reference Levels (Vita-Tech & CCAC)
Biochemistry			
Total protein	46 ± 2 g/L	48 ± 2	35-72
Albumin	35 ± 0 g/L	32 ± 2	25-48
Globulin	12 ± 1 g/L	17 ± 3	18-82
Bilirubin	2.4 ± 1 umol/L	2.9 ± 3	2-15
ALP	81 ± 10 U/L	95 ± 16	28-94
ALT	42 ± 4 U/L	44 ± 4	28-184
Glucose	11 ± 2 mmol/L	10 ± 3	9.7-18.6
Urea	9 ± 3 mmol/L	18.6 ± 13	12.1-20.6
Creatinine	36 ± 5 umol/L	69 ± 64	26-88
Hemolysis	Normal	Normal	
Icteria	Normal	Normal	
Lipemia	Normal	Normal	

Example 12—Efficacy of Scyllo-Inositol in Preventing AD-Like Pathology in a Double Transgenic Mouse Model of Alzheimer's Disease, PS1×APP

Tg PS1×APP mice are an enhanced model of Alzheimer's disease which express a mutant human PS1 transgene encoding two familial mutations (M46L and L286V) in conjunction with the human APP transgene encoding the Indiana and Swedish familial mutations. These animals develop robust expression of cerebral A β levels and amyloid deposition by 30-45 days of age. In a prophylactic trial,

TgPS1×APP mice were treated with scyllo-inositol from weaning and were assessed for effects on neuropathology at 2 months of age (FIGS. 16 and 17). Compared with untreated TgPS1×APP mice, scyllo-inositol treated TgPS1×APP mice displayed a significant decrease in all measures of plaque burden at 2 months of age (% brain area covered in plaques=0.157±0.007 vs. 0.065±0.016, p<0.001; mean plaque size=177±8 μ m² vs. 149±5 μ m², p<0.05; plaque count 3054±324 vs. 1514±510, p<0.01; (FIG. 17). These results demonstrate that scyllo-inositol prevents amyloid deposition in two robust models of Alzheimer's disease.

Example 13—Effect of Increased Caloric Intake on TgCRND8 Mice

In order to rule out the contribution of increased caloric intake or non-specific effects, TgCRND8 mice were treated with a simple sugar of similar molecular weight, mannitol. At 6 months of age, mannitol treated TgCRND8 mice were indistinguishable from untreated TgCRND8 mice (FIG. 11A) and were significantly different from mannitol treated non-Tg littermates (FIG. 11B). Mannitol had no effect on the behaviour of non-Tg mice, since mannitol treated non-Tg mice were indistinguishable from untreated non-Tg mice. These results correlate with the pathological studies that indicate mannitol did not alter the plaque load in TgCRND8 mice (FIG. 11C). Simultaneous monitoring of survival demonstrated that mannitol had no effect on the survival of TgCRND8 mice (FIG. 11D).

Although the present invention has been described in relation to particular embodiments thereof, many other variations and modifications and other uses will become apparent to those skilled in the art. The present invention therefore is not limited by the specific disclosure herein, but only by the appended claims.

What is claimed is:

1. A method of treating Alzheimer's symptoms in a subject having Down's syndrome comprising administering to said subject about 1 to about 70 mg/kg/day of scyllo-inositol.

2. The method of claim 1 wherein said amount is about 1 to about 10 mg/kg/day.

3. The method of claim 2 wherein the administration is orally.

4. The method of claim 3 wherein the administration is once or twice a day.

5. The method of claim 2 comprising administering scyllo-inositol in a pharmaceutical composition.

6. The method of claim 2 wherein scyllo-inositol is administered in an oral pill, liquid or suspension.

7. The method of claim 2 further comprising administering a second agent which is an anti-depressant.

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