METHOD FOR PREVENTING AND/OR TREATING A DISEASE, CONDITION OR STATE ASSOCIATED WITH REDUCED DOPAMINERGIC NEURON FUNCTION

The present invention relates to a method of preventing and/or treating a disease, condition or state associated with reduced dopaminergic neuron function in a subject. The method includes the step of administering to the subject an effective amount of a substance P receptor antagonist. The present invention also relates to the administration of a substance P receptor antagonist to a subject in methods for inhibiting progression of a disease, condition or state associated with reduced dopaminergic neuron function in the subject, or for alleviating one or more complications in the subject which are associated with administration of a dopaminergic agent. Pharmaceutical compositions and combination products which include a substance P receptor antagonist are also described.
METHOD FOR PREVENTING AND/OR TREATING A DISEASE, CONDITION OR STATE ASSOCIATED WITH REDUCED DOPAMINERGIC NEURON FUNCTION

Priority Claim

This international patent application claims priority to Australian provisional patent application 2008901050 filed on 4 March 2008, the content of which is herein incorporated by reference.

Field of the Invention

The present invention relates to a method of preventing and/or treating a disease, condition or state associated with reduced dopaminergic neuron function.

Background of the Invention

Neurodegenerative diseases, such as Parkinson's disease place a huge burden on society, both socially and economically. Many of these diseases have a significant impact on the affected individual and ultimately require medical intervention.

Moreover, as the population ages and the average individual lives longer, the prevalence of neurodegenerative diseases is likely to increase.

Many neurodegenerative diseases involve the loss of dopaminergic neurons, which are neurons that release dopamine from its synapses. Such diseases may result not only in the loss of motor skills, but also in the development of a number of other non-motor symptoms, such as mood disturbances and cognitive disturbances.

For example, Parkinson's disease is characterised by a loss of dopaminergic neurons from the substantia nigra. These dopaminergic neurons release dopamine within the striatum, the area of the brain that regulates smooth execution of movement. As such, motor symptoms such as resting tremor and bradykinesia, a slowness in movement, predominate as the disease progresses. Fortunately, the loss of dopaminergic neurons progresses slowly, and surviving neurons can compensate for this loss by increasing
dopamine synthesis and release. This is reasonably effective until approximately 50% of neurons have been lost, at which point the clinical symptoms present.

Once diagnosed, there is some time for therapeutic intervention that will slow down or stop the progression of the disease, since the continued loss of dopaminergic neurons does not occur at a faster rate after the presentation of clinical symptoms. However, to date no effective neuroprotective therapy has been developed. This is because the cause of death of the dopaminergic neurons is unknown, despite a number of factors having been implicated, including oxidative stress, glutamate excitotoxicity and mitochondrial dysfunction.

To counteract motor symptoms, patients diagnosed with Parkinson's disease are currently treated with the dopaminergic agent levodopa (an intermediate in dopamine biosynthesis) to increase the amount of dopamine in the central nervous system (CNS). Administration of dopamine itself is inefficient, as it is unable to cross the blood brain barrier. Levodopa is able to cross the blood brain barrier and is metabolized to dopamine by aromatic L-amino acid decarboxylases.

However, administration of levodopa can in itself cause significant side effects including drowsiness, dizziness, headache, loss of appetite, stomach upset, nausea, vision changes, or trembling of the hands. In addition as metabolism of levodopa is not exclusive to the CNS and may also occur in peripheral tissues, further adverse side-effects may result. Peripheral metabolism of levodopa and associated side effects may be minimized by treatment with carbidopa or benserazide, which inhibit the conversion of levodopa to dopamine and which are not able to cross the blood brain barrier. Nevertheless, despite the beneficial effects of carbidopa and benserazide, side effects are still commonly associated with levodopa administration.

In addition, while levodopa can be beneficial in improving motor symptoms and quality of life, it is unable to stop the progression of the disease. There are also symptoms of Parkinson's disease that are unresponsive to levodopa. Furthermore, after prolonged use of levodopa almost all patients will develop additional motor complications such as dyskinesia and motor fluctuations, and also experience "wearing off" effects or shorter
periods in which levodopa gives a symptomatic response. They may also experience pain, nausea and hypotension. Depression is also seen in up to 40% of patients, as well as stress and anxiety, speech and swallowing difficulties, sexual dysfunction and cognitive decline. Indeed, the levodopa-related effects are often more disabling than the initial motor symptoms associated with Parkinson's disease.

Other diseases or conditions associated with reduced dopaminergic neuron function include reverse schizophrenia and attention deficit hyperactivity disorder (ADHD). Treatment of these diseases and conditions can also involve the administration of levodopa to increase the dopamine levels in the CNS.

Accordingly, there is a need for new therapeutic interventions to prevent and/or treat diseases, conditions or states associated with reduced dopaminergic neuron function. The present invention relates to the use of substance P receptor antagonists to prevent and/or treat such diseases, conditions or states.

A reference herein to a patent document or other matter which is given as prior art is not to be taken as an admission that that document or matter was known or that the information it contains was part of the common general knowledge as at the priority date of any of the claims.

**Summary of the Invention**

The present invention arises from studies into the association of substance P with diseases, conditions or states associated with reduced dopaminergic neuron function.

In particular, it has been found that the level of substance P is significantly increased in patients with early dopaminergic cell loss, such as early stage Parkinson's disease. Furthermore, using experimental models it has been demonstrated that substance P exacerbates the onset and symptoms of Parkinson's disease, and that substance P receptor antagonists are effective in reducing the progression of Parkinson's disease and reducing symptoms.
Accordingly, the present invention provides a method of preventing and/or treating a disease, condition or state associated with reduced dopaminergic neuron function in a subject, the method including administering to the subject an effective amount of a substance P receptor antagonist.

The present invention also provides use of a substance P receptor antagonist in the preparation of a medicament for preventing and/or treating a disease, condition or state associated with reduced dopaminergic neuron function in a subject.

The present invention also provides a pharmaceutical composition when used to treat a disease, condition or state associated with reduced dopaminergic function, the composition including a substance P receptor antagonist.

The present invention also provides a pharmaceutical composition including a substance P receptor antagonist and a dopaminergic agent.

The present invention also provides a combination product including the following components:

- a substance P receptor antagonist; and
- a dopaminergic agent;

wherein the components are provided in a form for separate administration to a subject, or in a form for co-administration to a subject.

The present invention also provides a method of alleviating one or more complications in a subject associated with administration of a dopaminergic agent, the method including administering to the subject an effective amount of a substance P receptor antagonist.

The present invention also provides use of a substance P receptor antagonist in the preparation of a medicament for alleviating one or more complications in a subject associated with administration of a dopaminergic agent.
The present invention also provides a method of inhibiting progression of a disease, condition or state associated with reduced dopaminergic neuron function in a subject, the method including administering to the subject an effective amount of a substance P receptor antagonist.

The present invention also provides use of a substance P receptor antagonist in the preparation of a medicament for inhibiting progression of a disease, condition or state associated with reduced dopaminergic neuron function in a subject.

Various terms that will be used throughout the specification have meanings that will be well understood by a skilled addressee. However, for ease of reference, some of these terms will now be defined.

The term "dopaminergic neuron" as used throughout the specification is a neuron that releases dopamine from its synapses. Examples of dopaminergic neurons include dopaminergic neurons present in the ventral tegmental area of the midbrain, substantia nigra pars compacta, and arcuate nucleus of the hypothalamus.

The term "dopaminergic neuron function" as used throughout the specification is to be understood to mean one or more activities of a dopaminergic neuron. Dopaminergic neuron function includes, for example, the stimulation of a dopaminergic neuron, the transmission of an electrical impulse along a dopaminergic neuron, release of dopamine as a result of the electrical impulse, binding of released dopamine to dopamine receptors, and dopamine receptor signalling.

In this regard, a disease condition or state associated with reduced dopaminergic function is a disease, condition or state associated with one or more of a loss of dopaminergic neuron function, a loss of dopaminergic neurons, and dopaminergic neuron dysfunction.

The term "dopaminergic agent" as used throughout the specification is to be understood to mean an agent that increases one or more of the level and/or activity of dopamine, an agent that increases dopaminergic neuron function, an agent that binds to and activates a
dopamine receptor, and an agent that increases the responsiveness of the central nervous system to dopamine.

The term "substance P receptor antagonist" as used throughout the specification is to be understood to mean an agent that directly or indirectly inhibits the binding of substance P to one of its receptors. In this regard, it will be appreciated that a substance P receptor antagonist includes a derivative, a variant, an analogue, a pharmaceutically acceptable salt, a tautomer or a pro-drug of a substance P receptor antagonist.

In this regard, substance P is an excitatory neurotransmitter and is a peptide having the structure RPKPEFFGLM-NH₂. Methods for determining the ability of an agent to act as a substance P receptor antagonist are known in the art.

The term "variant" as used throughout the specification is to be understood to mean an amino acid sequence of a polypeptide or protein that is altered by one or more amino acids. The variant may have "conservative" changes, wherein a substituted amino acid has similar structural or chemical properties to the replaced amino acid (e.g., replacement of leucine with isoleucine). A variant may also have "non-conservative" changes (e.g., replacement of a glycine with a tryptophan) or a deletion and/or insertion of one or more amino acids. The term also includes within its scope any insertions/deletions of amino acids for a particular polypeptide or protein. A "functional variant" will be understood to mean a variant that retains the functional capacity of a reference protein or polypeptide.

Conservative substitutions typically include substitutions within the following groups: glycine and alanine; valine, isoleucine, and leucine; aspartic acid and glutamic acid; asparagine and glutamine; serine and threonine; lysine and arginine; and phenylalanine and tyrosine. Under some circumstances, substitutions within the aliphatic group alanine, valine, leucine and isoleucine are also considered as conservative. Sometimes substitution of glycine for one of these can also be considered conservative. Other conservative interchanges include those within the aliphatic group aspartate and glutamate; within the amide group asparagine and glutamine; within the hydroxyl group serine and threonine; within the aromatic group phenylalanine, tyrosine and tryptophan;
within the basic group lysine, arginine and histidine; and within the sulfur-containing group methionine and cysteine. Sometimes substitution within the group methionine and leucine can also be considered conservative. Substitutions as described above are contemplated within the scope of the present invention.

The term "prevent" as used throughout the specification is to be understood to mean an intervention that prevents or delays the onset of a disease, condition or state in a subject.

The term "treat" as used throughout the specification is to be understood to mean an intervention that improves the prognosis and/or state of a subject with respect to a disease, condition or state.

The term "subject" as used throughout the specification is to be understood to mean a human or animal subject.

In this regard, it will be understood that the present invention also includes within its scope veterinary applications. For example, the animal subject may be a mammal, a primate, a livestock animal (eg. a horse, a cow, a sheep, a pig, or a goat), a companion animal (eg. a dog, a cat), a laboratory test animal (eg. a mouse, a rat, a guinea pig, a bird, a rabbit), an animal of veterinary significance, or an animal of economic significance.

**Brief Description of the Figures**

Figure 1 shows immunohistology using an anti-substance P receptor antibody of sections of human substantia nigra from a normal subject (left panel), a subject with early stage Parkinson's disease (centre panel) and a subject with late stage Parkinson's disease (right panel).

Figure 2 shows Rotarod results for rodents with 6-OHDA-induced Parkinson's disease (closed squares), rodents with 6-OHDA-induced Parkinson's disease and treated with substance P (open bold triangles), rodents with 6-OHDA-induced Parkinson's disease and treated with a substance P receptor antagonist (N-acetyl-L-tryptophan) (open
triangles) and control rodents (open squares). Decreased time on the Rotarod is indicative of the induction of Parkinson's disease and increased motor deficits.

Figure 3 shows Rotarod results for rodents with 6-OHDA-induced Parkinson's disease (closed triangles), rodents with 6-OHDA-induced Parkinson's disease and treated with an alternative substance P receptor antagonist (L,733-060) (closed squares) and control rodents (open squares). Decreased time on the Rotarod is indicative of the induction of Parkinson's disease and increased motor deficits.

Figure 4 shows day 7 and day 14 Rotameter results for rodents with 6-OHDA-induced Parkinson's disease, rodents with 6-OHDA-induced Parkinson's disease and treated with substance P, rodents with 6-OHDA-induced Parkinson's disease and treated with a substance P receptor antagonist (N-acetyl-L-tryptophan) and control rodents. Increased ipsilateral turns per minute are indicative of increased lesion size in experimental Parkinson's disease.

Figure 5 shows the amount of dopaminergic cell loss in the substantia nigra in normal rodents (column 1), rodents with 6-OHDA-induced Parkinson's disease (column 2), rodents with 6-OHDA-induced Parkinson's disease and treated with substance P (column 3), rodents with 6-OHDA-induced Parkinson's disease and treated with a substance P receptor antagonist (N-acetyl-L-tryptophan; column 4) and rodents with 6-OHDA-induced Parkinson's disease and treated with an alternative substance P receptor antagonist (L,733-060; column 5). Decreased cell death is indicative of an attenuation of Parkinson's disease.

**General Description of the Invention**

As described above, in one embodiment the present invention provides a method of preventing and/or treating a disease, condition or state associated with reduced dopaminergic neuron function in a subject, the method including administering to the subject an effective amount of a substance P receptor antagonist.
This embodiment of the present invention is directed to preventing and/or treating a disease, condition or state associated with reduced dopaminergic neuron function by administering to a subject one or more substance P receptor antagonists.

Dopaminergic neuron function may be reduced for a variety of reasons, including for example a loss of dopaminergic neurons and/or a dysfunction of dopaminergic neurons. In this regard, a reduction in dopaminergic neuron function in a subject may be associated, for example, with either or both of a reduction in dopaminergic function over time as measured within the one subject, or may be a reduction in dopaminergic function of one subject in relation to the average dopaminergic function in a population. Diseases, conditions or states associated with low or reduced dopaminergic neuron function in a subject in the various embodiments of the present invention include Parkinson's disease and related movement disorders, attention-deficit hyperactivity disorder (ADHD), Lesch-Nyhan syndrome and negative schizophrenia.

Parkinson's disease is normally classified as a disease associated with loss of dopaminergic neurons from the substantia nigra. There is currently no blood or laboratory test that is accurate for the diagnosis of Parkinson's disease and as such a number of clinical criteria are usually evaluated before a diagnosis is made. In this regard, the Unified Parkinson's Disease Rating Scale (Fahn S, et al. (1987), Recent Developments in Parkinson's Disease, Vol 2. Florham Park, NJ. Macmillan Health Care Information, pp 15 3-163, 293-304) is commonly used to assess a number of parameters to provide an indication of the presence and severity of Parkinson's disease in a subject. Nuclear medical imaging, including Positron Emission Tomography (PET), may also be used to assess the presence and severity of Parkinson's disease. Methods of assessing Parkinson's disease in a subject using PET include for example Sossi et al. (1998) J. Nucl. Med. 39: 1714-1719 and Suzuki et al. (2006) Parkinsonism and Related Disorders. 12: S90.

Attention-deficit hyperactivity disorder (ADHD) is typically characterised by a chronic pattern of inattention and/or hyperactivity in addition to forgetfulness, poor impulse control or impulsivity, and distractibility. ADHD is also associated with reduced

Lesch-Nyhan syndrome (LNS) is a rare, inherited disorder caused by a deficiency of the enzyme hypoxanthine-guanine phosphoribosyltransferase (HPRT). The deficiency in HRPT has also been shown to cause a reduction in brain dopamine levels. The result is a build-up of uric acid in all body fluids, and development of symptoms such as severe gout, poor muscle control, and moderate retardation, which appear in the first year of life. Neurological symptoms include facial grimacing, involuntary writhing, and repetitive movements of the arms and legs. A striking feature of LNS is self-mutilating behaviors - characterized by lip and finger biting - that begin in the second year of life. Assaying levels of HPRT enzyme in red blood cells or cultured fibroblasts is used to make the definitive diagnosis.

Negative schizophrenia, or type II schizophrenia, typically manifests in patients as social withdrawal and psychomotor retardation, including lack of emotional response, poverty of speech, and absence of volition or will. Symptoms and methods of diagnosing negative schizophrenia are provided, for example, by American Psychiatric Association (2000) Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR), 4th Ed. American Psychiatric Publishing Inc, Arlington, VA 22209.

In one specific embodiment, the disease, condition or state associated with reduced dopaminergic neuron function is Parkinson's disease.

The substance P receptor antagonist in the various embodiments of the present invention is an agent that directly or indirectly inhibits the binding of substance P to one of its receptors. It will be also appreciated that the substance P receptor antagonist also includes a derivative, a variant, an analogue, a pharmaceutically acceptable salt, tautomer or pro-drug of a substance P receptor antagonist.
In this regard, substance P is an excitatory neurotransmitter and is peptide a having the structure RPKPEFFGLM-NH2. Substance P binds to a number of receptors including the NK1 receptor (neurokinin 1 receptor), the NK2 receptor and the NK3 receptor. Substance P antagonists inhibit the binding of substance P to any one of its receptors. It will be appreciated that the term "substance P" includes within its scope various variants, truncated forms or analogues of the peptide, for example as described in US patent 4,481,139.

The identification of a substance as a substance P receptor antagonist may be determined by a method known in the art, for example as described in US patents 5,990,125, 6,482,829; and 5,972,938; and US patent application 20030083345.

Examples of substance P receptor antagonists are shown in Tables 1 to 3.

<table>
<thead>
<tr>
<th>Chemical Code</th>
<th>Chemical Name</th>
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<tbody>
<tr>
<td>CGP49823</td>
<td>(2R,4S)-2-benzy1-1-(3,5-dimethylbenzoyl)-N-[[4-(quinolinyl)methyl]-4-piperine]amide dihydrochloride</td>
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<tr>
<td>CP-96,345</td>
<td>2S,3S)-cis-[[2-(phenylmethyl)N-[2-(methoxyphenyl)methyl]-1-azacyclo[2.2.2]octan-3-amne</td>
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<tr>
<td>CP-99,994</td>
<td>(2S,3S)-cis-3-(2-methoxybenzylamino)-2-phenyl-piperidine dihydrochloride</td>
</tr>
<tr>
<td>CP-122,721</td>
<td>(+)-2S,3S)-3-(2-methoxy-5-trifluoromethoxybenzyl)amino-2-phenyl-piperidine</td>
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<tr>
<td>FK 888</td>
<td>(N2-[4R]-4-hydroxy-1-(1-methyl-1H-indol-3-yl)carbonyl-L-propyl-N-methyl-N-phenylmethyl-L-3-(2-naphthyl)alaninamide</td>
</tr>
<tr>
<td>GR203040</td>
<td>(2S,3S and 2R,3R)-2-methoxy-5-tetrazol-1-yl-benzyl-(2-phenylpiperidin-3-yl)-amne</td>
</tr>
<tr>
<td>GR-205171</td>
<td>3-Piperidinamme,N-[2-methoxy-5-[5-(trifluoromethyl)-1H-tetrasol-1-yl]phenyl[methyl]-2-phenyl-, (2S-cis)-</td>
</tr>
<tr>
<td>GR 82334</td>
<td>[D-Pro9,spiro-gamma-lactam)].eu10, Tip11 physalaemus-(1-11)</td>
</tr>
<tr>
<td>GR 94800</td>
<td>PhCO-Ala-Ala-DTrp-Phe-DPro-Pro-Nle-NH2</td>
</tr>
<tr>
<td>HSP-117</td>
<td>3-Piperidinamme, N-[2,3-di-hydro-5-(1-methylthyl)-7-benzofuranylmethyl]-2-phenyl-dihydrochloride, (2S-cis)-</td>
</tr>
<tr>
<td>L 703,606</td>
<td>1-Azabicyclo[2.2.2]octan-3-amne, 2-(diphenylmethyl)-N-[2-(2-phenylethyl)methyl]-, (2S-cis)-, oxalate</td>
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<tr>
<td>L 732,138</td>
<td>N-acetyl-L-trytophan</td>
</tr>
<tr>
<td>L 733,060</td>
<td>(2S,3S)-3-(5-bromo-2-trifluoromethylphenoxy)methyl)oxyl)-2-phenyl piperidine</td>
</tr>
<tr>
<td>L 742,094</td>
<td>(2S)-3,3-bis[trifluoromethyl]benzyloxy)-3-(S)-phenyl-4-(5-(3-oxo-1,2,4-triazol)methyl)morpholine</td>
</tr>
<tr>
<td>L 754,030</td>
<td>2-(R)-(1-R)-3, 5-bis(trifluoromethylphenoxylthoxy)-3(S)-(4-fluorophenyl-4-(3-oxo-1,2,4-triazol-5-yl)methyl)morpholine</td>
</tr>
<tr>
<td>LY 303241</td>
<td>1-Piperazinacetamide, N-[2-acetyl]-2-methoxyphenylmethylamino]-1-(1H-indol-3-ylmethyl)ethyl]-4-phenyl-, (R)-</td>
</tr>
<tr>
<td>LY 303870</td>
<td>(R)-1-[N-[2-methoxybenzyl]acetamidom]-3-(1H-indol-3-yl)-2-[N-[2-(4-piperidiny]piperidin-1-yl]acetyl]amino]propane</td>
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<tr>
<td>LY 306740</td>
<td>1-Piperazinacetamide, N-[2-acetyl]-2-methoxyphenylmethylamino]-1-(1H-indol-3-ylmethyl)ethyl]-4-cyclohexyl, (R)-</td>
</tr>
<tr>
<td>MEN 11149</td>
<td>2-(2-naphthyl)-1-N-[1R,2S]-2-N-[1H-indol-3-ylcarbonyl]ammoniocyclohexanecarboxy]-N-[2-ethyl-N-4-(4-fluorophenylacetyl)]diaminoethane</td>
</tr>
</tbody>
</table>
| MK-869        | 3H-1,2,4-Triazo[3,1-e]-5,1-[2]-3,5-bis(trifluoromethyl)]phenyl[ethoxy]-3-(4-fluorophenyl)-4-morpholino[methyl]-1, 2-di hydro-[2R-[2a(R)]-
| PD 154075     | (2-benzoxuran)-CH2OOC)-(R)-alpha-MeTrp-(S)-NHCH(Ch3)Ph |
| R-544         | Ac-Thr-D-Trp(FOR)-Phe-N-MeBzl |
### Table 1 (cont.)

<table>
<thead>
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<tr>
<td>RP-67580</td>
<td>(3αR, 7αa)-7,7-diphenyl-2-[l-imino-2-(2-methoxyphenyl)-(ethyl)]++perhydroisoindol-4-one hydrochloride</td>
</tr>
<tr>
<td>RPR 100893</td>
<td>(3αS, 7αa)-7,7-diphenyl-4-(2-methoxyphenyl)-2-[(S)-2-(2-methoxyphenyl)proprionyl]perhydroisoindol-4-ol</td>
</tr>
<tr>
<td>Spendide</td>
<td>Tyr-D-Phe-D-Heu-Met-NH2</td>
</tr>
<tr>
<td>Spantide II</td>
<td>D-NicLys, 3-Pal3, D-C12Phe5, Asn6, D-Tp 7.0, Nle 11-substance P</td>
</tr>
<tr>
<td>Spantide III</td>
<td>L-Norleucinamide, N6-(3-pyridinylcarbonyl)-D-lysyl-L-prolyl-3-(3-pyridinyl)-L-alanyl-L-prolyl-3,4-dichloro-D-phenylalanyl-L-asparaginyl-D-tryptophyl-L-phenylalanyl-3-(3-pyridinyl)-D-alanyl-L-leucyl-</td>
</tr>
<tr>
<td>SR140333</td>
<td>(S)-l-[2-[(3-iso-propoxyphenylacetyl)pinacin-3-yl]ethyl]-4-phenyl-lazaniabicyclo[2.2.2]octane</td>
</tr>
<tr>
<td>WIN-41,708</td>
<td>(1‘beta-hydroxy-17alpha-ethynyl-5alpha-androstano[3,2-b]imidazo[1,2-a]benzimidazole</td>
</tr>
<tr>
<td>WIN-62,577</td>
<td>1H-Benzimidazo[2,1-b]cyclopenta[5,6]naptha[1,2-g]quinazolin-1,6-ol, L-ethynyl-2,3,3a,3b,4,5,15,15a,15b,17,17a-dodecahydro-15a,17a-dimethyl-</td>
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</tbody>
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### Table 2 - NK2 Receptor Antagonists

<table>
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<tr>
<th>Chemical Code</th>
<th>Chemical Name</th>
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<tbody>
<tr>
<td>SR-48,968</td>
<td>(S)-N-methyl-N-[4-(4-acetylamino-4-[phenylpipridin]-2)]-(3,4-dichlorophenyl)-butyl]benzamide</td>
</tr>
<tr>
<td>L-659,877</td>
<td>Cyclo[Gin,Trp,Phg,N(Me)-Bzl]</td>
</tr>
<tr>
<td>MEN 10627</td>
<td>Cyclo[Met-Asp-Tp -Phe-Dap-Leu)cyclo(2beta-5beta)-</td>
</tr>
<tr>
<td>SR 144190</td>
<td>(R)-3-1-[2-(4-benzoyl-2-(3,4-difluorophenyl)morpholin-2-yl)-ethyl]-4-phenylpipridin-3-yl]-ethyl]-4-phenylpipridin-3-yl]1-dimethylurea</td>
</tr>
<tr>
<td>GR 94800</td>
<td>PhCO-Ala-Ala-D-Tp -Phe-D-Pro-Pro-Nle-NH2</td>
</tr>
</tbody>
</table>

### Table 3 - NK3 Receptor Antagonists

<table>
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<th>Chemical Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>SR-142,801</td>
<td>(S)-N-methyl-N-[4-(4-acetylamino-4-[phenylpipridin]-3-yl)]-butyl]benzamide</td>
</tr>
<tr>
<td>R820</td>
<td>3-Indolcarbonyl-Hyp-Phe(N(Me)-Bzl</td>
</tr>
<tr>
<td>R486</td>
<td>H-Asp-Ser-Phe-Tp -beta-Ala-Leu-Met-NH2</td>
</tr>
<tr>
<td>SB 222200</td>
<td>(S)-N-(a-ethylbenzyl)-3-methyl-2-phenylquinoline-4-carboximide</td>
</tr>
<tr>
<td>L 758,298</td>
<td>Phosphonic acid, [3-1-[3-(3,5-bis(trfluormethyl)phenyl)ethoxy]-3-(4-fluorophenyl)-4-mo -Phe(2R)-proline]-, 2R-[2a(R*)], 3a]</td>
</tr>
<tr>
<td>NK-608</td>
<td>(2R,4S)-N-[l-[3,5-bis(trfluormethyl)benzoyl]-2-(4-chloro-benzyl)-4-piperidinyl]-quinoline-4-carboximide</td>
</tr>
</tbody>
</table>

Other examples of substance P receptor antagonists are as described in US patents 4,481,139 and 5,977,104. Examples of NK1 receptor antagonists are as described in US patent 5,990,125.

Tachykinin antagonists (as described in US patent 4,981,744) may also be used as substance P antagonists. Other examples of substance P receptor antagonists include piperdine and morpholine derivatives (as described in US 4,985,896), piperazino (as described in US 5,981,52), piperidinyl compounds as NK1 or NK2 antagonists (as described in US 5,998,444), N-benzyl-4-tolylnicotinic acids and related compounds as NK1 receptor antagonists (as described in European patent application EP-A-1035 115), phenyl and pyridine derivatives as NK1 receptor antagonists (as described in
international patent application WO 0050398), and 3-phenylpyridines, biphenyl derivatives, 5-phenyl-pyrimidine derivatives and 4-phenyl-pyrimidine derivatives (as described in international patent applications WO 0050401, WO 0053572, WO 0073278 and WO 0073279).

In one embodiment, the substance P receptor antagonist is one or more of a NK1 receptor antagonist, a NK2 receptor antagonist, and a NK3 receptor antagonist.

In one embodiment, the NK1 receptor antagonist is selected from one or more of the group consisting of CGP49823, CP-96,345, CP99,994, CP-122,721, FK88, GR203040, GR205171, GR82334, GR94800, HSP-1 17, L-703,606 oxalate, L-732,138 (N-acetyl-L-tryptophan), L-733060, L-742,694, L-745,030, L-668,169, LY-303241, LY-303870, LY306740, MEN-1 1149, MK-869, PD-154075, R-544, RP-67580, RPR100893, Sendide, Spantide II, Spantide III, SR140333, WIN-41,7098, WIN-62,577, or a derivative, a variant, an analogue, a pharmaceutically acceptable salt, tautomer or pro-drug thereof.

In another embodiment, the NK2 receptor antagonist is selected from one or more of the group consisting of SR-48968, L-659877, GR103537, MGN-10627, SR144190 and GR94800, or a derivative, a variant, an analogue, a pharmaceutically acceptable salt, tautomer or pro-drug thereof.

In another embodiment, the NK3 receptor antagonist is selected from one or more of the group consisting of SR-143,801, R820, R486, SB222200, L758,298 and NKP608, or a derivative, a variant, an analogue, a pharmaceutically acceptable salt, tautomer or pro-drug thereof.

In one embodiment, the substance P receptor antagonist is L-732,138, namely N-acetyl-L-tryptophan, or a derivative, analogue, pharmaceutically acceptable salt, tautomer or pro-drug thereof. Examples include lipid soluble analogues, N-acetyl-L-tryptophan 3,5-bis(trifluoromethyl)benzyl ester and N-acetyl tryptophan methyl ester.
One or more substance P receptor antagonists may also be used in the preparation of a medicament for preventing and/or treating a disease, condition or state associated with reduced dopaminergic function.

Accordingly, in another embodiment the present invention provides use of a substance P receptor antagonist in the preparation of a medicament for preventing and/or treating a disease, condition or state associated with reduced dopaminergic function.

One or more substance P receptor antagonists may also be used in a pharmaceutical composition, to prevent and/or treat a disease, condition or state associated with reduced dopaminergic function.

Accordingly, in another embodiment the present invention provides a pharmaceutical composition when used to prevent and/or treat a disease, condition or state associated with reduced dopaminergic function, the composition including a substance P receptor antagonist.

The administration of one or more substance P receptor antagonists may also be used to inhibit progression of the disease, condition or state associated with reduced dopaminergic neuron in the subject.

Accordingly, in another embodiment the present invention provides a method of inhibiting progression of a disease, condition or state associated with reduced dopaminergic neuron in a subject, the method including administering to the subject an effective amount of a substance P receptor antagonist.

The effective amount of a substance P receptor antagonist to be delivered in the various embodiments of the present invention is not particularly limited, so long as it is within such an amount and in such a form that generally exhibits a useful or therapeutic effect.

The term "effective amount" is the quantity which when delivered, improves the prognosis of the subject. The amount to be delivered will depend on the particular characteristics of the condition being treated, the mode of delivery, and the
characteristics of the subject, such as general health, other diseases, age, sex, genotype, body weight and tolerance to drugs.

Accordingly, a suitable dosage of the substance P receptor antagonist for delivery to the desired site of action in the various embodiments of the present invention may be selected.

In one embodiment, the dosage of the substance P receptor antagonist administered to a subject in the various embodiments of the present is in the range from 0.1 mg/kg to 100 mg/kg.

In a specific embodiment, the substance P receptor antagonist is administered to the subject at a dose of 0.25 mg/kg to 25 mg/kg. For example, a suitable dose of N-acetyl-tryptophan is 2.5 mg/kg.

Generally, the dosage of the substance P receptor antagonist in a pharmaceutical composition may be in the range from 10-5,000 mg per subject, and typically will be in the range of 50-2,000 mg per subject.

Suitable dosages are generally as described in US patents 4,990,125 and US 5,977,104.

Examples of formulations are described in US patent 5,990,125.


The prevention and/or treatment of a disease, condition or state associated with reduced dopaminergic neuron function may further include administering to the subject one or more agents selected from the group consisting of a dopaminergic agent (eg levodopa), an anticholinergic, Amantadine, a monoamine oxidase (MAO) inhibitor, and a COMT inhibitor.
Thus, the present invention also provides use of one or more of the above agents for preventing and/or treating a disease, condition or state associated with reduced dopaminergic function, the use of one or more of the above agents in the preparation of a medicament with a substance P receptor antagonist, and the use of one or more of the above agents in a pharmaceutical composition including a substance P receptor antagonist.

A suitable dose of one or more of the above agents may be selected.

In one specific embodiment, the prevention and/or treatment of a disease, condition or state associated with reduced dopaminergic function further includes administration to the subject of a dopaminergic agent.

Dopaminergic agents include, for example, levodopa, phenylalanine, theanine, tyrosine, vitamin C, vitamin B6, amantadine, yohimbe (IVα-hydroxy-yohimban-l βα-carboxylic acid methyl ester), monoamine oxidase inhibitors, buproprion and dopamine agonists. Dopamine agonists include bromocriptine, cabergoline, pergolide, pramipexole, ropinirole and apomorphine.

In one specific embodiment, the dopaminergic agent is levodopa.

Levodopa has a chemical formula of 3,4-dihydroxy-L-phenylalanine and is available commercially.

In the case of levodopa, a suitable dose for administration to a subject may be chosen. For example, a subject being treated for Parkinson's disease may generally receive an initial levodopa dose of 100 mg to 1 g daily, usually in 250 mg increments four times a day. The levodopa dose can be increased in increments of 100 to 750 mg/day at 3 to 7 day intervals, until a daily maintenance dose of 2.5 to 6 g/day is reached. Generally, no more than 8 g/day levodopa is administered.

Levodopa is most commonly administered orally in tablet form, however other routes of administration may be used including intravenous, intraperitoneal, subcutaneous,
intramuscular or topical routes or by direct injection. Under some circumstances, levodopa may be delivered by oral sustained release administration.

Further, to restrict the metabolism of levodopa to dopamine outside the CNS, levodopa may also be administered with carbidopa or benserazide. Carbidopa or benserazide inhibit the conversion of levodopa to dopamine, and like dopamine, neither is able to cross the blood brain barrier. Accordingly, another embodiment includes the administration of carbidopa or benserazide in conjunction with levodopa.

In another embodiment, administration of a substance P receptor antagonist delays and/or prevents the "wearing off" effects of levodopa. In this regard, the effects of the levodopa in many patients begin to last for shorter periods of time, also known as "wearing off," forcing an increase in the dosage required. This can result in dyskinesia, which is an inability to control muscles.

In another embodiment, the administration of the substance P receptor antagonist reduces the amount and/or frequency of the dopaminergic agent administered to the subject.

In another embodiment, the administration of the substance P receptor antagonist reduces one or more complications (side-effects) in the subject associated with administration of the dopaminergic agent.

Examples of such complications include drowsiness, dizziness, headache, loss of appetite, stomach upset, nausea, vision changes, trembling of the hands, dyskinesia, pain, nausea, hypotension, depression, stress and anxiety, speech and swallowing difficulties, sexual dysfunction and cognitive decline, seizures, vomiting or diarrhea, gastrointestinal bleeding, insomnia, confusion, nightmares, muscle twitches, loss of appetite, change in sense of taste, decreased attention span, memory loss, nervousness, weakness, increased sweating, fatigue, unusual or uncontrolled movements of the mouth, tongue, face, head, neck, arms, and legs, difficulty walking, back and neck muscle spasms, fast, irregular, or pounding heartbeat and eye pain.
For example, the administration of levodopa can cause significant side effects including drowsiness, dizziness, headache, loss of appetite, stomach upset, nausea, vision changes, or trembling of the hands. In addition as metabolism of levodopa is not exclusive to the CNS and may also occur in peripheral tissues, further adverse side-effects may result.

Amantadine has side-effects including nervousness, anxiety, agitation, insomnia, difficulty in concentrating, and exacerbations of pre-existing seizure disorders and psychiatric symptoms.

Bupropion has side-effects including seizures, delusions, hallucinations, psychosis, concentration disturbance, paranoia, and confusion, dry mouth, nausea, insomnia, tremor, excessive sweating and tinnitus.

Bromocriptine has side-effects including dizziness, upset stomach, headache, fatigue, vomiting, constipation, swelling of the feet or ankles, fast, irregular, or pounding heartbeat, confusion and watery discharge from nose.

Carbegoline has side-effects including depression, dyskinesia, hallucinations, sleep disturbances, vertigo, nausea, obstipation, dry mouth, gastric irritation, vomiting, dyspepsia, hypotension, peripheral edema, non-specific edema, arrhythmias and angina pectoris.

Pergolide has side-effects including associative learning difficulties, cardiac fibrosis and valvular damage.

Pramipexole has side-effects including dizziness, lightheadedness, or fainting, hallucinations weight gain, weight loss, nausea, insomnia twitching, twisting, or other unusual body movements or unusual tiredness or weakness.

Ropinirole has side-effects including nausea, hallucinations, drowsiness, vomiting and dizziness.
Apomorphine has side-effects include confusion, hallucinations, tremor (uncontrolled shaking, nausea or vomiting that continues after taking an anti-nausea medication, light-headedness, falling or passing out, chest pain or heavy feeling, pain spreading to the arm or shoulder, sweating, general ill feeling, restless muscle movements in your eyes, tongue, jaw, or neck, and penis erection that is painful or lasts 4 hours or longer.

Accordingly, in another embodiment the present invention provides a method of alleviating one or more complications in a subject associated with administration of a dopaminergic agent, the method including administering to the subject an effective amount of a substance P receptor antagonist.

One or more substance P receptor antagonists and one or more dopaminergic agents may also be used in a pharmaceutical composition.

Accordingly, in another embodiment the present invention provides a pharmaceutical composition including a substance P receptor antagonist and a dopaminergic agent.


Examples of substance P receptor antagonists and dopaminergic agents are as previously discussed herein.

In one embodiment, the dopaminergic agent is levadopa.

An example of a formulation of a substance P receptor antagonist and levodopa is a 50/100 mg (substance P receptor antagonist/levodopa) tablet formulation. Levodopa may be wet granulated together with maize starch, mannitol, croscarmellose sodium and povidone in a conventional high shear mixer. The substance P receptor antagonist may be wet granulated separately with maize starch, mannitol, croscarmellose sodium and povidone in a high shear mixer. The dry levodopa-granules, the dry substance P
receptor granules, croscarmellose sodium, mannitol and magnesium stearate may be
mixed together and the mass obtained compressed to tablets and coated with HPMC-
coating containing a color pigment.

The present invention also provides a combination product including one or more
substance P receptor antagonists and one or more dopaminergic agents.

Accordingly, in another embodiment the present invention provides a combination
product including the following components:

- a substance P receptor antagonist; and
- a dopaminergic agent;

wherein the components are provided in a form for separate administration to a subject,
or in a form for co-administration to a subject.

The subject may be suffering from, or susceptible to, one or more of the various
diseases, conditions or states associated with reduced dopaminergic neuron function, as
previously described herein.

The components of the combination product may packaged separately or together in
suitably sterilized containers such as ampoules, bottles, or vials, either in multi-dose or
in unit dosage forms. The containers are typically hermetically sealed. Methods are
known in the art for the packaging of the components.

The effective amount of the substance P receptor antagonist, and/or one or more of the
other agents of the present invention, to be administered to the subject in the various
embodiments of the present invention is not particularly limited, so long as it is within
such an amount and in such a form that generally exhibits a useful or therapeutic effect.

The term "therapeutically effective amount" is the quantity which, when administered to
a subject in need of treatment, improves the prognosis and/or state of the subject. The
amount to be administered to a subject will depend on the particular characteristics of
the disease, condition or state in the subject, the mode of administration, and the
characteristics of the subject, such as general health, other diseases, age, sex, genotype, body weight and tolerance to drugs.

As discussed previously herein, administration and delivery of the compositions may be for example by the intravenous, intraperitoneal, subcutaneous, intramuscular, oral, or topical route, or by direct injection. The mode and route of administration in most cases will depend on the type of disease, condition or state being treated.

The dosage form, frequency and will depend on the mode and route of administration.

As described above, the administration of the substance P receptor antagonist and other agents may also include the use of one or more pharmaceutically acceptable additives, including pharmaceutically acceptable salts, amino acids, polypeptides, polymers, solvents, buffers, excipients, preservatives and bulking agents, taking into consideration the particular physical, microbiological and chemical characteristics of the agents to be administered.

For example, the substance P receptor antagonist and/or the other agents can be prepared into a variety of pharmaceutically acceptable compositions in the form of, e.g., an aqueous solution, an oily preparation, a fatty emulsion, an emulsion, a lyophilised powder for reconstitution, etc. and can be administered as a sterile and pyrogen free intramuscular or subcutaneous injection or as injection to an organ, or as an embedded preparation or as a transmucosal preparation through nasal cavity, rectum, uterus, vagina, lung, etc. The composition may be administered in the form of oral preparations (for example solid preparations such as tablets, caplets, capsules, granules or powders; liquid preparations such as syrup, emulsions, dispersions or suspensions).

Compositions containing the substance P receptor antagonist and/or the other agents may also contain one or more pharmaceutically acceptable preservatives, buffering agents, diluents, stabilisers, chelating agents, viscosity enhancing agents, dispersing agents, pH controllers, or isotonic agents.
Examples of suitable preservatives are benzoic acid esters of para-hydroxybenzoic acid, propylene glycol, phenols, phenylethyl alcohol or benzyl alcohol. Examples of suitable buffers are sodium phosphate salts, citric acid, tartaric acid and the like. Examples of suitable stabilisers are, antioxidants such as alpha-tocopherol acetate, alpha-thioglycerin, sodium metabisulphite, ascorbic acid, acetylcysteine, 8-hydroxyquinoline, chelating agents such as disodium edetate. Examples of suitable viscosity enhancing agents, suspending or dispersing agents are substituted cellulose ethers, substituted cellulose esters, polyvinyl alcohol, polyvinylpyrrolidone, polyethylene glycols, carbomer, polyoxypropylene glycols, sorbitan monooleate, sorbitan sesquioleate, polyoxyethylene hydrogenated castor oil 60.

Examples of suitable pH controllers include hydrochloric acid, sodium hydroxide and the like. Examples of suitable isotonic agents are glucose, D-sorbitol or D-mannitol, sodium chloride.

The administration of a substance P receptor antagonist and/or the other agents in the various embodiments of the present invention may also be in the form of a composition containing a pharmaceutically acceptable carrier, diluent, excipient, suspending agent, lubricating agent, adjuvant, vehicle, delivery system, emulsifier, disintegrant, absorbent, preservative, surfactant, colorant, glidant, anti-adherant, binder, flavorant or sweetener, taking into account the physical, chemical and microbiological properties of the agents being administered.

For these purposes, the composition may be administered orally, parenterally, by inhalation spray, adsorption, absorption, topically, rectally, nasally, mucosally, transdermally, buccally, vaginally, intraventricularly, via an implanted reservoir in dosage formulations containing conventional non-toxic pharmaceutically-acceptable carriers, or by any other convenient dosage form. The term parenteral as used herein includes subcutaneous, intravenous, intramuscular, intraperitoneal, intrathecal, intraventricular, intrasternal, and intracranial injection or infusion techniques.

When administered parenterally, the compositions will normally be in a unit dosage, sterile, pyrogen free injectable form (solution, suspension or emulsion, which may have
been reconstituted prior to use) which is generally isotonic with the blood of the recipient with a pharmaceutically acceptable carrier. Examples of such sterile injectable forms are sterile injectable aqueous or oleaginous suspensions. These suspensions may be formulated according to techniques known in the art using suitable vehicles, dispersing or wetting agents and suspending agents. The sterile injectable forms may also be sterile injectable solutions or suspensions in non-toxic parenterally acceptable diluents or solvents, for example, as solutions in 1,3-butanediol. Among the pharmaceutically acceptable vehicles and solvents that may be employed are water, ethanol, glycerol, saline, Ringer's solution, dextrose solution, isotonic sodium chloride solution, and Hanks' solution. In addition, sterile, fixed oils are conventionally employed as solvents or suspending mediums. For this purpose, any bland fixed oil may be employed including synthetic mono- or di-glycerides, corn, cottonseed, peanut, and sesame oil. Fatty acids such as ethyl oleate, isopropyl myristate, and oleic acid and its glyceride derivatives, including olive oil and castor oil, especially in their polyoxyethylated versions, are useful in the preparation of injectables. These oil solutions or suspensions may also contain long-chain alcohol diluents or dispersants.

The carrier may contain minor amounts of additives, such as substances that enhance solubility, isotonicity, and chemical stability, for example anti-oxidants, buffers and preservatives.

In addition, the compositions may be in a form to be reconstituted prior to administration. Examples include lyophilisation, spray drying and the like to produce a suitable solid form for reconstitution with a pharmaceutically acceptable solvent prior to administration.

Compositions may include one or more buffers, bulking agents, isotonic agents and cryoprotectants and lyoprotectants. Examples of excipients include, phosphate salts, citric acid, non-reducing such as sucrose or trehalose, polyhydroxy alcohols, amino acids, methylamines, and lyotropic salts which are usually used instead of reducing sugars such as maltose or lactose.
When administered orally, the substance P receptor antagonist and/or the other agents will usually be formulated into unit dosage forms such as tablets, caplets, cachets, powder, granules, beads, chewable lozenges, capsules, liquids, aqueous suspensions or solutions, or similar dosage forms, using conventional equipment and techniques known in the art. Such formulations typically include a solid, semisolid, or liquid carrier. Exemplary carriers include excipients such as lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, mineral oil, cocoa butter, oil of theobroma, alginates, tragacanth, gelatin, syrup, substituted cellulose ethers, polyoxyethylene sorbitan monolaurate, methyl hydroxybenzoate, propyl hydroxybenzoate, talc, magnesium stearate, and the like.

A tablet may be made by compressing or molding the agent optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active, or dispersing agent. Moulded tablets may be made by moulding in a suitable machine, a mixture of the powdered active ingredient and a suitable carrier moistened with an inert liquid diluent.

The administration of the substance P receptor antagonist and/or the other agents may also utilize controlled release technology.

The substance P receptor antagonist and/or the other agents may also be administered as a sustained-release pharmaceutical composition. To further increase the sustained release effect, the agent may be formulated with additional components such as vegetable oil (for example soybean oil, sesame oil, camellia oil, castor oil, peanut oil, rape seed oil); middle fatty acid triglycerides; fatty acid esters such as ethyl oleate; polysiloxane derivatives; alternatively, water-soluble high molecular weight compounds such as hyaluronic acid or salts thereof, carboxymethylcellulose sodium hydroxypropylcellulose ether, collagen polyethylene glycol polyethylene oxide, hydroxypropymethylcellulosemethylcellulose, polyvinyl alcohol, polyvinylpyrrolidone.
Alternatively, the substance P receptor antagonist and/or the other agents may be incorporated into a hydrophobic polymer matrix for controlled release over a period of days. The agent may then be moulded into a solid implant, or externally applied patch, suitable for providing efficacious concentrations of the agents over a prolonged period of time without the need for frequent re-dosing. Such controlled release films are well known to the art. Other examples of polymers commonly employed for this purpose that may be used include nondegradable ethylene-vinyl acetate copolymer a degradable lactic acid-glycolic acid copolymers, which may be used externally or internally. Certain hydrogels such as poly(hydroxyethylmethacrylate) or poly(vinylalcohol) also may be useful, but for shorter release cycles than the other polymer release systems, such as those mentioned above.

The carrier may also be a solid biodegradable polymer or mixture of biodegradable polymers with appropriate time-release characteristics and release kinetics. The agent may then be moulded into a solid implant suitable for providing efficacious concentrations of the agents over a prolonged period of time without the need for frequent re-dosing. The agent can be incorporated into the biodegradable polymer or polymer mixture in any suitable manner known to one of ordinary skill in the art and may form a homogeneous matrix with the biodegradable polymer, or may be encapsulated in some way within the polymer, or may be moulded into a solid implant.

For topical administration, the substance P receptor antagonist and/or the other agents may be in the form of a solution, spray, lotion, cream (for example a non-ionic cream), gel, paste or ointment. Alternatively, the composition may be delivered via a liposome, nanosome, rivosome, or nutri-diffuser vehicle.

It will be appreciated that other forms of administration of agents are also contemplated, including the use of a nucleic acid encoding a polypeptide for delivering of such agents.
**Description of Specific Embodiments**

Reference will now be made to experiments that embody the above general principles of the present invention. However, it is to be understood that the following description is not to limit the generality of the above description.

**Example 1**

*Substance P concentration increases in dopaminergic neurons in early state Parkinson's disease.*

Previous studies have shown that there is a decline in substance P associated with loss of dopaminergic neurons within the substantia nigra in the later stages of Parkinson's disease (see Sivam SP, 1991, Neuropeptides 18:201-207; Fernandez A et al, 1994, Neuroscience 61:73-79).

We investigated whether there were any changes in substance P expression in the early stages of Parkinson's disease, and compared this to end stage Parkinson's disease and to a normal individual.

For this study, sections of human substantia nigra obtained from post-mortem samples were assessed for substance P immunostaining by a neuropathologist. Substance P antibody (1:2000 goat anti-substance P antibody from Santa Cruz) was used on paraffin embedded sections using a hemotoxylin counterstain and DAB for visualization. Based on dopaminergic cell numbers in the substantia nigra, samples were either classified as normal, or early or late stage Parkinson's disease where an essentially normal dopamine cell count in the substantia nigra was considered as normal, severe (>80%) reduction in dopamine cell count in the substantia nigra together with clinical signs of Parkinsonism in the medical record was considered as late stage, and moderate reduction (<80%) in dopamine cell count in the substantia nigra together with an absence of clinical signs of Parkinsonism in the medical record was considered as early stage. Stained sections were viewed under a light microscope. From the substance P immunoreactivity in these sections, it could clearly be seen that early Parkinson's disease (Figure 1, centre panel)
had a greater intensity of "brown" substance P staining within the dopamine neurons than either the normal (Figure 1, left panel) or late stage Parkinson's disease (Figure 1, right panel). This confirms the increased substance P concentration in dopaminergic neurons at this stage of the disease. The similarity in background staining between the normal and early sections of Parkinson's disease also confirms that there was no loss of substance P at this early stage, as opposed to the clear decrease in background and dopaminergic neuron substance P staining in late Parkinson's disease.

Example 2

Changes in substance P concentration is associated with an increased rate of onset of Parkinson's disease

Having established that substance P is increased in the early stages of human Parkinson's disease, we used an animal model of Parkinson's disease to investigate whether changes in substance P are associated with rate of onset of the disease. We chose to use the well-characterised rodent 6-hydroxydopamine (6-OHDA) model of Parkinson's disease to replicate the disease progression (Lee CS et al, 1996, Neuroscience 72:641-653), and subsequently determine the effects of substance P or a substance P receptor (NK1) antagonist on this progression. Intrastriatal injection of the 6-OHDA neurotoxin (20 μg dissolved in saline containing 0.01% ascorbic acid) results in Parkinson's disease, and particularly motor symptoms of Parkinson's disease, as assessed by the Rotarod test (Hamm RJ et al., 1994, J. Neurotrauma 11:197-196) (Figure 2). In contrast, animals injected with the 6-OHDA vehicle (normal controls) did not develop any such deficits, and had no indication of Parkinson's disease. When substance P (3mM; intracerebroventricular) was administered simultaneously with the intrastriatal neurotoxin, these animals had a more rapid onset of the disease as assessed by the greater motor deficit on the Rotarod than the 6-OHDA untreated animals, and this occurred at every assessment day post-lesion. Finally, we assessed the effects of a substance P receptor (NK1) antagonist on outcome. A number of commercially synthesised substance P receptor (NK1) antagonists are currently available from standard scientific chemical suppliers. We chose to use the compound N-acetyl-L-tryptophan, which has been successfully used in our earlier work in traumatic brain
injury and stroke. Simultaneous administration of N-acetyl-L-tryptophan (50nM; intracerebroventricular) with the intrastriatal 6-OHDA neurotoxin significantly attenuated the onset of the disease, as assessed by the Rotarod test of motor function, when compared to the 6-OHDA untreated animals (Figure 2). Indeed, animals treated with the NK1 antagonist did not have significant motor dysfunction when compared to normal animals at any day post-lesion. This confirmed that substance P played an integral role in onset of Parkinson's disease and its associated motor deficits.

Example 3

The attenuation of motor deficits by an NK1 receptor antagonist is a class effect

Having established that the substance P antagonist N-acetyl-tryptophan significantly attenuated the onset of Parkinson's disease, as assessed by the Rotarod test of motor function, we repeated the experiment using an alternative NK1 antagonist, L,733-060. We again chose to use the well-characterised rodent 6-hydroxydopamine (6-OHDA) model of Parkinson's disease to replicate the disease progression (Lee CS et al, 1996, Neuroscience 72:641-653), and subsequently determine the effects of substance P or a substance P receptor (NK1) antagonist on this progression. Intrastriatal injection of the 6-OHDA neurotoxin (20 µg dissolved in saline containing 0.01% ascorbic acid) results in Parkinson's disease, and particularly motor symptoms of Parkinson's disease, as assessed by the Rotarod test (Hamm RJ et al., 1994, J. Neurotrauma 11:197-196) (Figure 3). In contrast, animals injected with the 6-OHDA vehicle (normal controls) did not develop any such deficits, and had no indication of Parkinson's disease. Finally, we assessed the effects of an alternative substance P receptor (NK1) antagonist on outcome. A number of commercially synthesised substance P receptor (NK1) antagonists are currently available from standard scientific chemical suppliers. We chose to use the compound L,733-060, which has been successfully used in our earlier work in traumatic brain injury and stroke. Simultaneous administration of L,733-060 (100nM; intracerebroventricular) with the intrastriatal 6-OHDA neurotoxin significantly attenuated the onset of the disease, as assessed by the Rotarod test of motor function, when compared to the 6-OHDA untreated animals (Figure 3). Indeed, animals treated with the NK1 antagonist did not have significant motor dysfunction when compared to
normal animals at any day post-lesion. This confirmed that substance P played an integral role in onset of Parkinson's disease and its associated motor deficits.

Example 4

Administration of a substance P receptor antagonist in an animal model of lesion formation in Parkinson’s disease

Having established the effects of substance P and NKI antagonists on motor function in Parkinson's disease, we chose to characterise the effects of these compounds on disease lesion size. A test routinely used to estimate lesion size in experimental Parkinson's disease is the rotometer test (Ungerstedt U and Arbuthnott GW, 1970, Brain Res. 24:485-493). In this test, a greater number of circular rotations per minute in response to injection of a stimulant is a reflection of a larger lesion in the affected (neurotoxin treated) hemisphere. We used the stimulant amphetamine (Sigma) dissolved in saline and administered subcutaneously at a dose of 5 mg/kg 10 min prior to the start of the test. Figure 4 shows that an animal that is administered saline vehicle but no neurotoxin (normal) shows few rotations over a 14 day assessment period. In contrast, an animal that has induced Parkinson's disease (6-OHDA) has an increased number of rotations per minute relative to controls, indicative of lesion formation in the substantia nigra. Simultaneous administration of substance P with the neurotoxin resulted in a significantly greater number of rotations, and a greater lesion size, in the affected hemisphere than in those animals treated with the neurotoxin alone. As opposed to the increase in lesion size shown with substance P co-administration, simultaneous administration of the NKI antagonist reduced the lesion size in the affected hemisphere. Thus, substance P played an integral role in the death of dopamine neurons in the substantia nigra, and the development of Parkinson's disease lesions.

Example 5

Administration of a substance P receptor antagonist in an animal model of dopaminergic cell loss in Parkinson’s disease
Having established the effects of substance P and NKI antagonists on motor function and lesion size in Parkinson's disease, we chose to characterise the effects of these compounds on early dopaminergic cell loss in the substantia nigra (SN) in this animal model of Parkinson's disease. Dopaminergic cell loss can be assessed using an antibody for tyrosine hydroxylase (TH), an enzyme involved in dopamine metabolism that is only localized to dopaminergic neurons. As shown in Figure 5, intrastriatal injection of the 6-OHDA neurotoxin (20 μg dissolved in saline containing 0.01% ascorbic acid) results in death of dopaminergic neurons in the substantia nigra. Sham (normal) animals displayed no loss of dopaminergic (TH immunoreactive) neurons in their ipsilateral SN compared to their contralateral SN (column 1). In contrast at day 21 following 6-OHDA administration, animals had lost a significant percentage of their ipsilateral dopaminergic neurons compared to control animals (column 2). SP treatment in lesioned animals increased the loss of dopaminergic neurons (column 3), whereas treatment with the NKI antagonist, N-acetyl-tryptophan (NAT; 5OnM; intracerebroventricular) in 6-OHDA lesioned animals protected dopaminergic neurons from 6-OHDA induced cell loss (column 4). Simultaneous administration of the alternative NKI antagonist, L,733-060 (10OnM; intracerebroventricular) with the intrastriatal 6-OHDA neurotoxin also significantly reduced death of dopaminergic neurons in the ipsilateral substantia nigra (column 5). These results clearly demonstrate that even in the early stages of dopaminergic cell death, substance P exacerbates neuronal cell death whereas an NKI antagonist attenuates cell death.

These experimental results indicate that substance P receptor (NKI) antagonists are able to reduce motor deficits, lesion size, and attenuate disease progression in Parkinson's disease.

Since levodopa administration increases substance P levels, and our data shows that increased substance P is associated with neuronal cell death and onset of Parkinson's symptoms, our data supports the claim that substance P receptor (NKI) antagonists represent an effective treatment for Parkinson's disease, either alone or in combination with levodopa thereby reducing mortality, morbidity and the disease progression.
Finally, it will be appreciated that various modifications and variations of the described methods and compositions of the invention will be apparent to those skilled in the art without departing from the scope and spirit of the invention. Although the invention has been described in connection with specific embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying out the invention which are apparent to those skilled in the art are intended to be within the scope of the present invention.

Future patent applications may be filed in Australia or overseas on the basis of or claiming priority from the present application. It is to be understood that the following provisional claims are provided by way of example only, and are not intended to limit the scope of what may be claimed in any such future application. Features may be added to or omitted from the provisional claims at a later date so as to further define or redefine the invention or inventions.
Claims

1. A method of preventing and/or treating a disease, condition or state associated with reduced dopaminergic neuron function in a subject, the method including administering to the subject an effective amount of a substance P receptor antagonist.

2. A method according to claim 1, wherein the disease, condition or state associated with reduced dopaminergic neuron function is Parkinson's disease.

3. A method according to claims 1 or 2, wherein the substance P receptor antagonist is a NK1 receptor antagonist, a NK2 receptor antagonist, or a NK3 receptor antagonist.

4. A method according to claim 3, wherein the NK1 receptor antagonist is selected from one or more of the group consisting of CGP49823, CP-96, 345, CP99, 994, CP-122, 721, FK88, GR203040, GR205171, GR82334, GR94800, HSP-1 17, L-703, 606 oxalate, L-732, 138, L-733060, L-742, 694, L-745, 030, L-668, 169, LY-303241, LY-303870, LY306740, MEN-1 1149, MK-869, PD-154075, R-544, RP-67580, RPR100893, Sendide, Spantide II, Spantide III, SR140333, WIN-41, 7098, WIN-62, 577, or a derivative, a variant, an analogue, a pharmaceutically acceptable salt, a tautomer or a pro-drug thereof.

5. A method according to claim 3, wherein the NK2 receptor antagonist is selected from one or more of the group consisting of SR-48968, L-659877, GR103537, MGN-10627, SR144190 and GR94800, or a derivative, a variant, an analogue, a pharmaceutically acceptable salt, a tautomer or a pro-drug thereof.

6. A method according to claim 3, wherein the NK3 receptor antagonist is selected from one or more of the group consisting of SR-143, 801, R820, R486, SB222200, L758, 298 and NKP608, or a derivative, a variant, an analogue, a pharmaceutically acceptable salt, a tautomer or a pro-drug thereof.
7. A method according to any one of claims 1 to 6, wherein the substance P receptor antagonist is administered to the subject at a dose of 0.25 mg/kg to 25 mg/kg.

8. A method according to any one of claims 1 to 7 wherein the method further includes administration to the subject of a dopaminergic agent.

9. A method according to claim 8, wherein the dopaminergic agent is levodopa.

10. A method according to claims 8 or 9, wherein administration of the substance P receptor antagonist reduces the amount and/or frequency of the dopaminergic agent administered to the subject.

11. A method according to any one of claims 8 to 10, wherein administration of the substance P receptor antagonist reduces one or more complications in the subject associated with administration of the dopaminergic agent.

12. A method according to any one of claims 1 to 11, wherein the method reduces progression of the disease, condition or state associated with reduced dopaminergic neuron function in the subject.

13. Use of a substance P receptor antagonist in the preparation of a medicament for preventing and/or treating a disease, condition or state associated with reduced dopaminergic neuron function in a subject.

14. A pharmaceutical composition when used to prevent and/or treat a disease, condition or state associated with reduced dopaminergic function, the composition including a substance P receptor antagonist.

15. A pharmaceutical composition according to claim 14, wherein the composition further includes a dopaminergic agent.

16. A pharmaceutical composition including a substance P receptor antagonist and a dopaminergic agent.
17. A pharmaceutical composition according to claim 16, wherein the substance P receptor antagonist is a NK1 receptor antagonist, a NK2 receptor antagonist, or a NK3 receptor antagonist.

18. A pharmaceutical composition according to claim 17, wherein the NK1 receptor antagonist is selected from one or more of the group consisting of CGP49823, CP-96,345, CP99,994, CP-122,721, FK88, GR203040, GR205171, GR82334, GR94800, HSP-117, L-703,606 oxalate, L-732,138, L-733060, L-742,694, L-745,030, L-668,169, LY-303241, LY-303870, LY306740, MEN-11149, MK-869, PD-154075, R-544, RP-67580, RPR100893, Sendide, Spantide II, Spantide III, SR140333, WIN-41,7098, WIN-62,577, or a derivative, a variant, an analogue, a pharmaceutically acceptable salt, a tautomer or a pro-drug thereof.

19. A pharmaceutical composition according to claim 17, wherein the NK2 receptor antagonist is selected from one or more of the group consisting of SR-48968, L-659877, GR103537, MGN-10627, SR144190 and GR94800, or a derivative, a variant, an analogue, a pharmaceutically acceptable salt, a tautomer or a pro-drug thereof.

20. A pharmaceutical composition according to claim 17, wherein the NK3 receptor antagonist is selected from one or more of the group consisting of SR-143,801, R820, R486, SB222200, L758,298 and NKP608, or a derivative, a variant, an analogue, a pharmaceutically acceptable salt, a tautomer or a pro-drug thereof.

21. A pharmaceutical composition according to any one of claims 16 to 20, wherein the dopaminergic agent is levodopa.

22. A pharmaceutical composition according to any one of claims 16 to 21, wherein the pharmaceutical composition is used for either or both of:

i) preventing and/or treating a disease, condition or state associated with reduced dopaminergic neuron function, including Parkinson's disease;

ii) inhibiting progression of a disease, condition or state associated with reduced dopaminergic neuron function, including Parkinson's disease.
23. A combination product including the following components:
   a substance P receptor antagonist; and
   a dopaminergic agent;
wherein the components are provided in a form for separate administration to a subject, or in a form for co-administration to a subject.

24. A combination product according to claim 23, wherein the subject is susceptible to, or suffering from, a disease, condition or state associated with reduced dopaminergic neuron function.

25. A combination product according to claim 24, wherein the disease, condition or state associated with reduced dopaminergic neuron function is Parkinson's disease.

26. A combination product according to any one of claims 23 to 25, wherein the substance P receptor antagonist is a NK1 receptor antagonist, a NK2 receptor antagonist, or a NK3 receptor antagonist, or a derivative, a variant, an analogue, a pharmaceutically acceptable salt, a tautomer or a pro-drug thereof.

27. A combination product according to claim 26, wherein the NK1 receptor antagonist is selected from one or more of the group consisting of CGP49823, CP-96,345, CP99,994, CP-122,721, FK88, GR203040, GR205171, GR82334, GR94800, HSP-117, L-703,606 oxalate, L-732,138, L-733060, L-742,694, L-745,030, L-668,169, LY-303241, LY-303870, LY306740, MEN-1 1149, MK-869, PD-154075, R-544, RP-67580, RPR100893, Sendide, Spantide II, Spantide III, SR140333, WIN-41,7098, WIN-62,577, or a derivative, a variant, an analogue, a pharmaceutically acceptable salt, a tautomer or a pro-drug thereof.

28. A combination product according to claim 26, wherein the NK2 receptor antagonist is selected from one or more of the group consisting of SR-48968, L-659877, GR103537, MGN-10627, SR144190 and GR94800 or a derivative, a variant, an analogue, a pharmaceutically acceptable salt, a tautomer or a pro-drug thereof.
29. A combination product according to claim 26, wherein the NK3 receptor antagonist is selected from one or more of the group consisting of SR-143,801, R820, R486, SB222200, L758,298 and NKP608, or a derivative, a variant, an analogue, a pharmaceutically acceptable salt, a tautomer or a pro-drug thereof.

30. A method of alleviating one or more complications in a subject associated with administration of a dopaminergic agent, the method including administering to the subject an effective amount of a substance P receptor antagonist.

31. A method according to claim 30, wherein the subject is suffering from, or susceptible to, a disease, condition or state associated with reduced dopaminergic neuron function.

32. A method according to claim 31, wherein the disease, condition or state associated with reduced dopaminergic neuron function is Parkinson's disease.

33. A method according to any one of claims 30 to 32, wherein the one or more complications are selected from the group consisting of a motor complication, a motor fluctuation, cognitive decline, pain, nausea, dizziness, hallucinations, confusion, agitation, hypotension, depression, stress, anxiety, speech difficulty, swallowing difficulty, and sexual dysfunction.

34. A method according to any one of claims 30 to 33, wherein the dopaminergic agent is levodopa.

35. A method according to any one of claims 30 to 34, wherein the substance P receptor antagonist is a NK1 receptor antagonist, a NK2 receptor antagonist, or a NK3 receptor antagonist.

36. A method according to claim 35, wherein the NK1 receptor antagonist is selected from one or more of the group consisting of CGP49823, CP-96,345, CP99,994, CP-122,721, FK88, GR203040, GR205171, GR82334, GR94800, HSP-117, L-703,606 oxalate, L-732,138, L-733060, L-742,694, L-745,030, L-668,169, LY-303241, LY-
303870, LY306740, MEN-1149, MK-869, PD-154075, R-544, RP-67580, RPR100893, Sendide, Spantide II, Spantide III, SR140333, WIN-41,7098, WIN-62,577, or a derivative, a variant, an analogue, a pharmaceutically acceptable salt, a tautomer or a pro-drug thereof.

37. A method according to claim 35, wherein the NK2 receptor antagonist is selected from one or more of the group consisting of SR-48968, L-659877, GR103537, MGN-10627, SR144190 and GR94800, or a derivative, a variant, an analogue, a pharmaceutically acceptable salt, a tautomer or a pro-drug thereof.

38. A method according to claim 35, wherein the NK3 receptor antagonist is selected from one or more of the group consisting of SR-143,801, R820, R486, SB222200, L758,298 and NKP608, or a derivative, a variant, an analogue, a pharmaceutically acceptable salt, a tautomer or a pro-drug thereof.

39. A method according to any one of claims 30 to 38, wherein the substance P receptor antagonist is administered to the subject at a dose of 0.25 mg/kg to 25 mg/kg.

40. Use of a substance P receptor antagonist in the preparation of a medicament for alleviating one or more complications in a subject associated with administration of a dopaminergic agent.

41. A use according to claim 40, wherein the subject is suffering from, or susceptible to, a disease, condition or state associated with reduced dopaminergic neuron function.

42. A use according to claim 41, wherein the disease, condition or state associated with reduced dopaminergic neuron function is Parkinson's disease.

43. A use according to any one of claims 40 to 42, wherein the dopaminergic agent is levodopa.
44. A method of inhibiting progression of a disease, condition or state associated with reduced dopaminergic neuron function in a subject, the method including administering to the subject an effective amount of a substance P receptor antagonist.

45. A method according to claim 44, wherein the disease, condition or state associated with reduced dopaminergic neuron function is Parkinson's disease.

46. A method according to claims 44 or 45, wherein the substance P receptor antagonist is a NK1 receptor antagonist, a NK2 receptor antagonist, or a NK3 receptor antagonist.

47. A method according to claim 46, wherein the NK1 receptor antagonist is selected from one or more of the group consisting of CGP49823, CP-96,345, CP99,994, CP-122,721, FK88, GR203040, GR205171, GR82334, GR94800, HSP-1 17, L-703,606 oxalate, L-732,138, L-733060, L-742,694, L-745,030, L-668,169, LY-303241, LY-303870, LY306740, MEN-1 1149, MK-869, PD-154075, R-544, RP-67580, RPR100893, Sendide, Spantide II, Spantide III, SR140333, WIN-41,7098, WIN-62,577, or a derivative, a variant, an analogue, a pharmaceutically acceptable salt, a tautomer or a pro-drug thereof.

48. A method according to claim 46, wherein the NK2 receptor antagonist is selected from one or more of the group consisting of SR-48968, L-659877, GR103537, MGN-10627, SR144190 and GR94800, or a derivative, a variant, an analogue, a pharmaceutically acceptable salt, a tautomer or a pro-drug thereof.

49. A method according to claim 46, wherein the NK3 receptor antagonist is selected from one or more of the group consisting of SR-143,801, R820, R486, SB222200, L758,298 and NKP608, or a derivative, a variant, an analogue, a pharmaceutically acceptable salt, a tautomer or a pro-drug thereof.

50. A method according to any one of claims 44 to 49, wherein the substance P receptor antagonist is administered to the subject at a dose of 0.25 mg/kg to 25 mg/kg.
51. A method according to any one of claims 44 to 50, wherein the method further includes administration to the subject of a dopaminergic agent.

52. A method according to claim 51, wherein the dopaminergic agent is levodopa.

53. Use of a substance P receptor antagonist in the preparation of a medicament for inhibiting progression of a disease, condition or state associated with reduced dopaminergic neuron function in a subject.

54. A use according to claim 53, wherein the disease, condition or state associated with reduced dopaminergic neuron function is Parkinson's disease.
Figure 1
**Figure 2**

*Rotarod*

- **6-OHDA**
- **6-OHDA + SP**
- **6-OHDA + NAT**
- **Normal**

*Time (secs)*

*Day Post-Lesion*
Figure 3

Rotarod

Time (secs)

Day Post-Lesion

- Normal
- 6-OHDA
- 6-OHDA + L-733,060

* * *
Figure 4

Rotometer

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<td>6-OHDA + SP</td>
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<tr>
<td>Normal</td>
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Ipsilateral turns/min

Day Post-Lesion

* p < 0.05
** p < 0.01
Figure 5

TH Immunoreactive Cell Death
Within the Ipsilateral SN

% TH+ Cell loss in RSN compared to LSN

1. Normal
2. 6-OHDA
3. 6-OHDA + SP
4. 6-OHDA + NAT
5. 6-OHDA + L-733,060
A. CLASSIFICATION OF SUBJECT MATTER

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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPIDS, EPODOC, MEDLINE, GOOGLE; Key words: Substance P receptor antagonist, NK (I, II, III) receptor antagonist, Parkinson's Disease, Schizophrenia, ADHD, LNS, Dopaminergic agent, Levopopa and like terms.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<td>WO 2007/100775 A2 (MICHALOW, A.) 7 September 2007 Paragraphs 0083, 00271, 0085, 0074; claims 361 and17.</td>
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Further documents are listed in the continuation of Box C [X] See Patent family annex

Date of the actual completion of the international search 20 March 2009

Name and mailing address of the ISA/AU

AUSTRALIAN PATENT OFFICE
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Date of mailing of the international search report 1 MAY 2009

Authorized officer

JAMES SUNG

AUSTRALIAN PATENT OFFICE
(ISO 9001 Quality Certified Service)
Telephone No +61 2 6283 2747
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<td>WO 1999/064010 A1 (MERCK SHARP &amp; DOHME LIMITED) 16 December 1999 Claims &amp; examples; page 20 lines 8-14 &amp; page 9 line 26- page 10 line 13</td>
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<td>WO 2000/068224 A1 (PFIZER PRODUCTS INC.) 16 November 2000 Claims, page 1 line 7 and page 2 lines 3-8 and see page 18 line 11</td>
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**INTERNATIONAL SEARCH REPORT**

**Box No. II  Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. □ Claims Nos.:
   - because they relate to subject matter not required to be searched by this Authority, namely:

2. □ Claims Nos.:
   - because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. □ Claims Nos.:
   - because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

**Box No. HI  Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

Invention 1: Claims 1-3, 7-17, 21-26, 30-35, 39-46 and 50-54 are directed to substance P antagonists and their methods of use in treating, preventing and/or inhibiting progression of a disease, condition or state related to reduced dopaminergic neuron function or their method of use in treating, preventing and/or inhibiting complications associated with the administration of a dopaminergic agent.

Other inventions include: claims 4-6, 18-20, 27-29, 36-38 and 47-49 that appear to relate to 47 different inventions pertaining to each NK1, 2 or 3 antagonist. It is not clear whether there are any structural features common to any of the 47 substance P receptor antagonists.

1. □ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. □ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. □ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. □ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

- □ The additional search fees were accompanied by the applicant’s protest and, where applicable, the payment of a protest fee.

- □ The additional search fees were accompanied by the applicant’s protest but the applicable protest fee was not paid within the time limit specified in the invitation.

- □ No protest accompanied the payment of additional search fees.

Form PCT/ISA/2 10 (continuation of first sheet (2)) (July 2008)
This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.