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de Sauvage et al.

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(54) **GFR α 3 POLYPEPTIDES**

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See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,709,858 A 1/1998 Godowski et al. 424/143.1
6,677,135 B1 1/2004 Sanicola-Nadel et al. .. 435/69.1

FOREIGN PATENT DOCUMENTS

EP 307247 3/1989
EP 846764 6/1998
WO WO 93/06116 4/1993
WO WO 97/33912 9/1997
WO WO 97/44356 11/1997
WO WO 98/53069 11/1998
WO WO 98/54213 12/1998

OTHER PUBLICATIONS

*Arenas et al., "GDNF Prevents Degeneration and Promotes the Phenotype of Brain Noradrenergic Neurons in Vivo" *Neuron* 15:1465-1473 (1995).

*Baloh et al., "Artemin, A Novel Member of the GDNF Ligand Family, Supports Peripheral and Central Neurons and Signals through the GFR α 3-RET Receptor Complex", *Neuron* 21(6):1291-1302 (Dec. 1998).

*Beck et al., "Mesencephalic Dopaminergic Neurons Protected by GDNF from Axotomy-Induced Degeneration in the Adult Brain" *Nature* 373:339-341 (1995).

*Berkemeier et al., "Neurotrophin-5: A Novel Neurotrophic Factor That Activates trk and trkB" *Neuron* 7:857-866 (Nov. 1991).

*Bolivar et al., "Construction and Characterization of New Cloning Vehicles. II. A Multipurpose Cloning System" *Gene* 2:95-113 (1977).

*Buj-Bello et al., "GDNF is an Age-Specific Survival Factor for Sensory and Autonomic Neuron" *Neuron* 15:821-828 (1995).

*Cash et al., "Parkinson's Disease and Dementia: Norepinephrine and Dopamine in Locus Coeruleus" *Neurology* 37:42-46 (1987).

*Chan-Palay et al., "Alterations in Catecholamine Neurons of the Locus Coeruleus in Senile Dementia of the Alzheimer Type and in Parkinson's Disease with and Without Dementia and Depression" *The Journal of Comparative Neurology* 287:373-392 (1989).

*Durbec et al., "GDNF Signalling Through the Ret Receptor Tyrosine Kinase" *Nature* 381:789-793 (1996).

*Hefti, F., "Nerve Growth Factor Promotes Survival of Septal Cholinergic Neurons After Fimbrial Transections" *J. of Neuroscience* 6(8):2155-2162 (Aug. 1986).

*Henderson et al., "GDNF: A Potent Survival Factor for Motoneurons Present in Peripheral Nerve and Muscle" *Science* 266:1062-1064 (1994).

*Heumann, R., "Regulation of the Synthesis of Nerve Growth Factor" *J. Exp. Biol.* 132:133-150 (1987).

*Hirano, A., "Cytopathology of Amyotrophic Lateral Sclerosis" *Advances in Neurology: Amyotrophic Lateral Sclerosis and Other Motor Neuron Diseases*, Lewis P. Rowland, Raven Press, Ltd., Chapter 8, vol. 56:91-101 (1991).

*Hirsch et al., "Melanized dopaminergic neurons are differentially susceptible to degeneration in Parkinson's disease" *Nature* 334:345-348 (1988).

*Holmes et al., "Structure and Functional Expression of a Human Interleukin-8 Receptor" *Science* 253 (5025):1278-1280 (Sep. 13, 1991).

*Hornykiewicz, O., "Neurochemical Pathology and the Etiology of Parkinson's Disease: Basic Facts and Hypothetical Possibilities" *Mt. Sinai J. Med.* 55:11-20 (1988).

*Jing et al., "GDNF-Induced Activation of the Ret Protein Tyrosine Kinase Is Mediated by GDNFR- Ψ , a Novel Receptor for GDNF" *Cell* 85:1113-1124 (1996).

*Kaisho et al., "Cloning and expression of a cDNA encoding a novel human neurotrophic factor" *FEBS Letters* 266 (1,2):187-191 (Jun. 1990).

*Kearns et al., "GDNF protects nigral dopamine neurons against 6-hydroxydopamine in vivo" *Brain Research* 672:104-111 (1995).

*Kotzbauer et al., "Neurturin, a relative of glial-cell-line-derived neurotrophic factor" *Nature* 384:467-470 (1996).

*Leibrock et al., "Molecular Cloning and Expression of Brain-derived Neurotrophic Factor" *Nature* 341:149-152 (Sep. 14, 1989).

(Continued)

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(57) **ABSTRACT**

The present invention relates to nucleotide sequences, including expressed sequence tags (ESTs), oligonucleotide probes, polypeptides, vectors and host cells expressing, and immunoadhesions and antibodies to mammalian GFR α 3, a novel α -subunit receptor of the GDNF (i.e. GFR) receptor family. It further relates to an assay for measuring activation of an α -subunit receptor by detecting tyrosine kinase receptor activation (i.e., autophosphorylation) or other activities related to ligand-induced α -subunit receptor homo-dimerization or homo-oligomerization.