

Anti-Scg3 Therapeutic Antibody

A Selective Angiogenesis Blocker to Treat Multiple Angiogenesis-Dependent Diseases

Overview

Drug Name	Anti-Scg3 antibody
Description	Anti-Scg3 antibody aims at the target secretogranin III (Scg3). It alleviates disease vascular leakage with high efficacy and no side-effects. In addition to curing diabetic retinopathy, anti-Scg3 antibody has the utility to treat other angiogenesis-dependent diseases such as retinopathy of prematurity, choroidal neovascularization, and tumor growth and metastasis. Data implicates that Scg3 has minimal binding and angiogenic activity in normal vessels but it markedly increases the binding and angiogenic activity in disease conditions. Different from vascular endothelial growth factor (VEGF), anti-Scg3 antibody can selectively bind and inhibit angiogenic activity in disease micro-environment, thus avoiding the damage to normal vasculature. In this case, anti-Scg3 antibody has great potentials to be widely applied in the treatment of various angiogenesis-dependent diseases with high safety. All the research results have been patented.
Indication	Diabetic retinopathy (DR); Cancers; Retinopathy of prematurity (ROP); Diabetic macula edema (DME); Choroidal neovascularization (CNV)
Target	Scg3
Product Category	Humanized monoclonal antibody; Cancer immunotherapy; Fertility regulation
Mechanism of Action	Antibody; Anti-angiogenesis
Status	Pre-clinical
Patent	Two patents have been filed.

* This program was developed by Protheragen's partner Everglades Biopharma.

Cooperation Seeking

Protheragen Inc. is interested in partnering with companies to further develop anti-Scg3 antibody pipeline, either in the form of a strategic alliance, licensing, or marketing agreement.

Look forward to cooperating with you in the near future.

Target

Secretogranin III (Scg3)

Introduction

The protein encoded by this gene is a member of the chromogranin/secretogranin family of neuroendocrine secretory proteins. Granins can be used as precursors of bioactive peptides and some of them function as helper proteins in sorting and proteolytic processing of prohormones. Two transcript variants encoding different isoforms for this gene have been found.

Approved Name	Secretogranin III [Homo sapiens (human)]
Official Symbol	SCG3
Gene Type	Protein coding
Synonyms	SGIII
Ensembl	ENSG00000104112
Gene ID	29106
mRNA Refseq	NM_013243.4 ; NM_001165257.1
Protein Refseq	NP_037375.2 ; NP_001158729.1
OMIM	611796
UniProt ID	Q8WXD2
Chromosome Location	15q21.2

Clinical Resources

A yeast 2-hybrid assay showed that rat Scg3 interacts with chromogranin A (CgA). These 2 proteins colocalized in pituitary and pancreatic endocrine cells. Deletion of the Scg3-binding domain in CgA resulted in missorting of CgA to the constitutive secretory pathway, whereas deletion of the CgA-binding domain in Scg3 did not affect the sorting of Scg3 in mouse pituitary corticotrophs.

Gene Function

A research showed that Scg3 localized to the secretory granule membrane fraction in a rat insulinoma-derived cell line. Depletion of cholesterol from secretory granule membranes resulted in impaired Scg3 binding to the membranes. Scg3 strongly bound to the secretory granule membrane-type liposomes in intragranular conditions, but CgA bound to the liposomes only in the presence of Scg3. Scg3 binds directly to cholesterol components of the secretory granule membrane and targets CgA to secretory granules in pituitary and pancreatic endocrine cells.

An analysis in mice showed that Scg3 protein coexisted with orexin, melanin-concentrating hormone, neuropeptide Y, and proopiomelanocortin. Scg3 formed a granule-like structure together with these neuropeptides. A conclusion is drawn that genetic variations in Scg3 gene may influence the risk of obesity through possible regulation of hypothalamic neuropeptide secretion.

Pathway

Scg3 promotes angiogenesis through MEK/ERK signaling pathway.

Major Conditions

Diabetic retinopathy;
Breast cancer.

Indication

Abnormal angiogenesis in various tissues or organs of the body can lead to a variety of diseases, including diabetic retinopathy, retinopathy of premature infants, choroidal neovascularization, and tumor growth and metastasis. The newly developed anti-Scg3 antibody has shown excellent efficacy in corresponding animal models of above diseases. The targeting vascular endothelial growth factor (VEGF) drugs on the market have many insurmountable side effects. Therefore, anti-Scg3 with high safety may have great potential in the market for the treatment of these diseases.

Diabetic Retinopathy (DR)

Diabetic retinopathy (DR), also called diabetic eye disease, is a disease that causes damage to the retina due to diabetes. Hyperglycemia leads to microangiopathy in various tissues of the whole body, selective loss of capillary pericytes, formation of microhemangioma, thickening of capillary basement membrane, destruction of integrity of tight junctions, and dysfunction of blood-retinal barrier. In this process, oxidative stress injury, VEGF and inflammatory changes are involved, resulting in capillary occlusion and non-perfusion areas, neovascularization fiber proliferation. The subsequently occurring of diabetic macular edema (DME) and proliferative diabetic retinopathy (PDR) leads to the decrease of visual acuity of patients.

DR affects 80% of diabetic patients with a history of more than 20 years. With appropriate treatment and eye monitoring, at least 90% of new cases can be reduced. In the United States, approximately 7.7 million Americans have diabetic retinopathy, and of those about 0.75 million also have DME.

There are three major treatments for diabetic retinopathy, i.e. laser surgery, injection of corticosteroids or anti-VEGF agents into the eye, and vitrectomy. Although these treatments have been proved successful, they cannot cure diabetic retinopathy. Laser surgery can lead to the loss of retinal tissue, and one should be more cautious with the injection of triamcinolone acetonide or anti-VEGF drugs, which are usually associated with systemic adverse events and devastating ocular complications.

Retinopathy of Prematurity (ROP)

Retinopathy of prematurity (ROP) is a potentially blinding eye disorder that primarily affects premature infants. It is thought to be caused by disorganized growth of retinal blood vessels, which may lead to scarring and retinal detachment. The smaller the baby at birth, the more likely it is to develop ROP, usually in both eyes, making it one of the most common causes of visual loss in children. There are about 14,000-16,000 of infants who weigh 2.75 pounds or less are affected by some degree of ROP. In developing countries, the prevalence of ROP is as high as 30%.

Peripheral retinal ablation is the main method of ROP treatment. Scleral buckling and / or vitrectomy may be considered for stage 4 and 5 ROP, with progression to retinal detachment. Intravitreal injection of Bevacizumab (Avastin) is reported as a supportive measure in aggressive posterior ROP. However, the safety of the new treatment has not yet been determined in terms of ocular and systemic complications, because the active components of Bevacizumab can not only block the development of abnormal blood vessels in the eye, but also prevent the normal development of other organs such as lung and kidney.

Choroidal Neovascularization (CNV)

Choroidal neovascularization (CNV) is the formation of choroidal neovascularization in the eye. It can occur rapidly in individuals with defects in Bruch's membrane, the innermost layer of the choroid. It is also associated with excess VEGF. CNV is a common cause of neovascular degenerative macular disease, which is often aggravated by high myopia, malignant myopia degeneration or age-related development.

Intravitreal injection of angiogenesis inhibitors is usually used to control neovascularization and reduce the liquid area under retinal pigment epithelium in CNV. In addition, CNV can also be treated with photodynamic therapy in combination with a photosensitive drug.

Cancers

Cancer is a group of diseases involving uncontrolled cell growth and may invade or spread to other parts of the body. Global cancer statistics estimated that 18.1 million new cases of cancer and 9.6 million deaths occurred globally in 2018, and about 20% of males and 17% of females would get cancer. Angiogenesis plays a key role in the development of cancer because blood and oxygen are supplied to ensure the growth of tumor volume. Tumors can actually stimulate angiogenesis by releasing chemical signals, as well as stimulating nearby normal cells to produce angiogenesis signaling molecules.

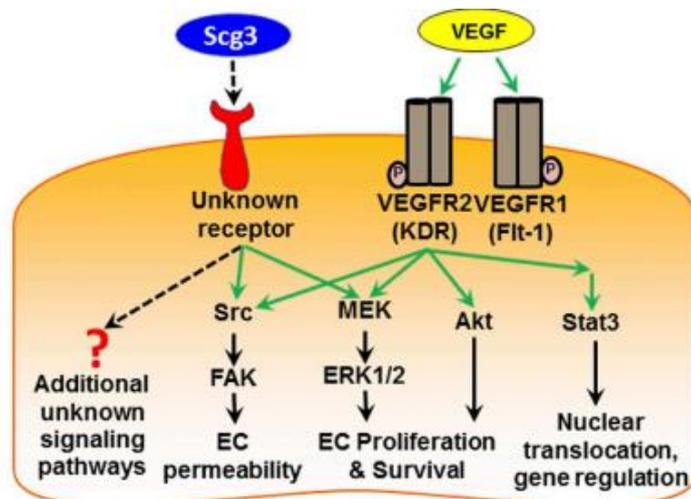
New blood vessels supply the oxygen and nutrients needed for tumor growth, allowing the tumor to expand and metastasize. As a result, angiogenesis inhibitors were developed to prevent tumor angiogenesis. FDA has approved a number of angiogenesis inhibitors, most of which are targeted therapies being developed specifically to target VEGF or related molecules involved in angiogenesis. Treatment with VEGF targeted angiogenesis inhibitors can lead to a range of side effects, including bleeding, arterial thrombosis, hypertension, impaired wound healing, and *etc.*

Mechanism of Action

Anti-Scg3 Antibody Inhibits Angiogenesis by Blocking Scg3

As a bona fide endothelial ligand, Scg3 has a capability of activating intracellular signaling cascades. Different from VEGF, Scg3 activates ERK and Src pathways, but not Akt and Stat3, to regulate angiogenesis and vascular leakage. MEK/ERK is critical to Scg3-induced pro-angiogenic intracellular signaling. ERK1 and ERK2 are serine/threonine protein kinases, which are critically involved in regulation of many biological processes, including cell adhesion, cell differentiation, transcription, metabolism, cell survival, migration and proliferation. At the same time, inhibition of MEK/ERK could suppress VEGF-induced endothelial proliferation.

Scg3 is the first highly disease-restricted angiogenic factor with undetectable binding and angiogenic activity in normal vessels. Anti-Scg3 antibody alleviates the leakage and inhibits angiogenesis by blocking Scg3 binding to its receptor without affecting the physiological activity of normal blood vessels.



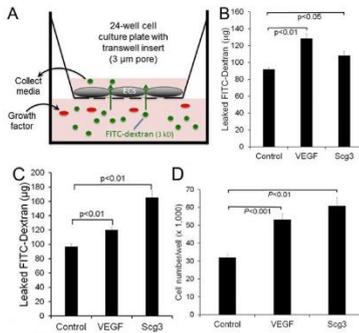
Status

The Patent Situation of Anti-Scg3 Antibody

Anti-Scg3 antibody has been through completed function identification, therapeutic effect study on four diseases models (DR, PDR, ROP and cancer) and the toxicology study. All the research results which prove anti-Scg3 antibody is both safe and efficient have been patented.

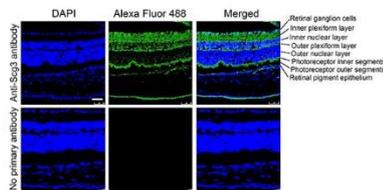
	Antibody Discovery	Pharmacodynamic Studies	Pharmacokinetic Studies	Toxicology & Safety Studies	CMC	IND Field
Anti-Scg3 Antibody						

Data



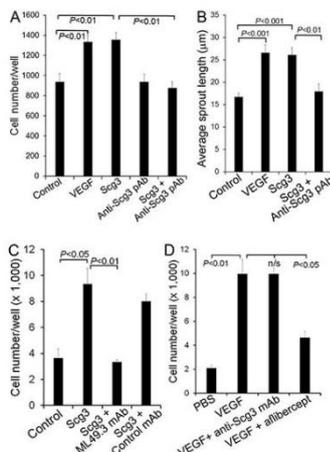
Scg3 Promotes Endothelial Permeability

Permeability assay with transwell inserts is illustrated in (A). 1 µg/ml Scg3, 100 ng/ml VEGF, or PBS was added to the bottom (B) or upper (C) chamber. After 24 hrs, the media were collected from the top chamber and quantified for leaked FITC-dextran. (D) Endothelial proliferation assay with human umbilical vein endothelial cells (HUVECs) in 48-well plates. Cell number in each well was quantified at 48 h. Scg3, 1 µg/ml; VEGF, 50 ng/ml.



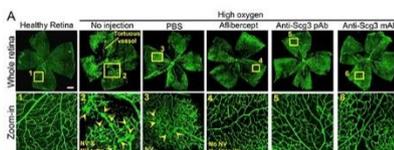
Scg3 Expression in the Retina

By immunohistochemical analysis, Scg3 is expressed in the retinal ganglion cell layer, inner and outer plexiform layer, photoreceptor inner segments, and retinal pigment epithelial cells. Few Scg3 signals were detected in the inner and outer nuclear layer and photoreceptor outer segments.



Anti-Scg3 Therapy of Diabetic Retinopathy (DR)

(A) Affinity-purified anti-Scg3 polyclonal antibody (pAb) blocks Scg3-induced proliferation of human retinal microvascular endothelial cells (HRMVECs). VEGF, 100 ng/ml; Scg3, 1 µg/ml; anti-Scg3 pAb, 2 µg/ml. (B) Anti-Scg3 pAb inhibits Scg3-induced spheroid sprouting of HRMVECs. VEGF, 2.5 ng/ml; Scg3, 15 ng/ml; anti-Scg3 pAb, 30 ng/ml. (C) Anti-Scg3 ML49.3 monoclonal antibody (mAb) inhibits Scg3-induced HRMVEC proliferation. Concentrations are as in A. (D) Anti-Scg3 mAb cannot neutralize VEGF-induced proliferation of HRMVECs.



Anti-Scg3 Therapy of Oxygen-Induced Retinopathy (OIR)

Arrowheads indicate neovascularization (NV) and neovascularization tufts. Anti-Scg3 pAb, ML49.3 mAb (0.36 µg/1 µl/eye), aflibercept (2 µg/1 µl/eye), or PBS was intravitreally injected.