Humanized Anti-GnRH Receptor Monoclonal Antibody

Overview

Drug Name	ANTIGN-109
Description	The humanized monoclonal antibody ANTIGN-109 was developed against the extracellular domain (N1-29) of the gonadotropin-releasing hormone (GnRH) receptor. It belongs to a new class of bioequivalent long-acting GnRH analogs, and can serve as an alternative to the current GnRH decapeptide antagonists for cancer immunotherapy and fertility regulation. ANTIGN-109 has shown to act in a similar manner to the decapeptide Antide (a GnRH decapeptide antagonist), in inducing the apoptosis of cultured cancer cells from various tissue origins. As a monoclonal antibody, ANTIGN-109 demonstrates a remarkably longer circulating half-life than GnRH peptide analogs. Furthermore, ANTIGN-109 was found to induce complement-dependent cytotoxicity (CDC) reaction to cancer cells, an immune property which is not shared by decapeptide GnRH analogs.
Target	Gonadotropin-releasing hormone receptor (GnRHR)
Drug Modality	Monoclonal antibody
Indication	Cancers; Reproductive diseases
Product Category	Cancer immunotherapy; Fertility regulation
Mechanism of Action	By binding to GnRHR in multiple tumor cells, ANTIGN-109 induces cellular apoptosis and cytolysis.
Status	Preclinical
Patent	Granted

Collaboration Opportunity

Protheragen Inc. is actively seeking partnership to further develop ANTIGN-109. Potential collaboration can be strategic alliance, licensing, or marketing agreement.
We look forward to hearing from you.

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Target

Gonadotropin-Releasing Hormone Receptor (GnRHR)

Introduction	This gene encodes the receptor for type 1 gonadotropin-releasing hormone. GnRHR is a member of the seven-transmembrane receptors, belonging to G-protein coupled receptor (GPCR) family. GnRHR is expressed on the surface of pituitary gonadotrope cells as well as breast, ovary, lymphocytes and prostate cells. After binding to gonadotropin-releasing hormone, the receptor associates with G-proteins to activate a phosphatidylinositol-calcium second messenger system. Activation of the GnRHR ultimately causes the release of gonadotropic luteinizing hormone (LH) and follicle stimulating hormone (FSH). The lack of this gene can lead to hypogonadotropic hypogonadism (HH). Alternative splicing causes multiple transcript variants to encode different isoforms. For this gene, more than 18 transcription initiation sites were identified in the 5′ region and multiple polyA signals were in the 3′ region.
Approved Name	Gonadotropin releasing hormone receptor [Homo sapiens (human)]
Official Symbol	GnRHR
Gene Type	Protein coding
Synonyms	HH7; GRHR; LRHR; LHRHR; GnRHR1
Ensembl	ENSG00000109163
Gene ID	4421
mRNA Refseq	NM_000406.2; NM_001012763.1
Protein Refseq	NP_000397.1; NP_001012781.1
OMIM	138850
UniProt ID	P30968
Chromosome Location	4q13.2

Clinical Resources

Gene Function	The growth of sex hormone-dependent tumors is inhibited by analogs of GnRH. GnRH agonists suppress the pituitary-gonadal function, which results in the deficiency of sex-steroid in order to treat prostatic and breast cancers. In addition,

	GnRH agonists and antagonists exert a direct effect on these tumors that is mediated by specific high-affinity GnRH receptors found on these cells. GnRH agonists and antagonists also suppress the growth of pancreatic cancers. Szende et al. (1991) demonstrated that pancreatic tumor cells exhibit high-affinity binding sites for GnRH, but only in their nuclei; low-affinity sites are associated with the cell membranes. These binding sites appear to be GnRH receptors since electron microscopic immunohistochemistry showed that the antibody against GnRH receptor reacted in the nucleus of pancreatic tumor cells. Maji et al. (2009) found that peptide and protein hormones, including GnRH, in secretory granules of the endocrine system are stored in an amyloid-like cross-beta-sheet-rich conformation. They concluded that functional amyloids in the pituitary and other organs can contribute to normal cell and tissue physiology.
Pathway	G-protein-coupled receptor signaling pathways
Major Conditions	Pain; Disorders of sexual function, breast and reproduction; Neurological disorders; AIDS; Genitourinary disorders; Endocrine disorders; Congenital defects; Cancer;

Drug Modality

Monoclonal Antibody

To facilitate the therapeutic applications in humans, ANTIGN-109 was structurally modified into humanized antibody against the GnRH receptor. The biological properties, binding affinity and specificity of the ANTIGN-109 to GnRH receptor were found to be bioequivalent to Antide, but the circulation half-life of hGHR106 was much longer.

Indication

As a GnRH antagonist, ANTIGN-109 is developed to 1). treat reproductive diseases and 2). use in cancer therapy.

Cancer

Among various human cancer expressed GnRHR, lung, breast, and prostate cancers are the top 3 cancer types worldwide.

Lung Cancer	According to the global cancer statistics for 2018, the incidence for lung cancer was 2,093,867, including 11.6% of new cancer cases. Non-small cell lung cancer and small cell lung cancer are two main types of lung cancer. 5 types of standard treatment for lung cancer are surgery, chemotherapy, radiation therapy, immunotherapy, and laser therapy. Moreover, endoscopic stent placement can be used to open a blocked airway by small cell lung cancer. For treating non-small cell lung cancer, targeted therapy, photodynamic therapy (PDT), cryosurgery and electrocautery are also the options.
Breast Cancer	In 2018, about 2,088,849 people worldwide suffered from breast cancer and the death toll was about 626,679. Survival rates of breast cancer in the developed countries are high and most of the patients would survive for at least 5 years. Depending on the specifics, appropriate treatment options can be used, including chemotherapy, hormonal therapy and targeted therapy.
Prostate Cancer	Globally, prostate cancer is the second highest morbidity and mortality rate following lung cancer in men. In 2018, there were 1,276,106 new cases of prostate cancer, accounting for 7.1% of the total number of new cancer patients, with death toll reached 358,989. The 5-year survival rate in the developed countries is high. For prostate cancer, the common treatments include surgery, radiation therapy, hormone therapy, vaccine or chemotherapy.

Reproductive Diseases

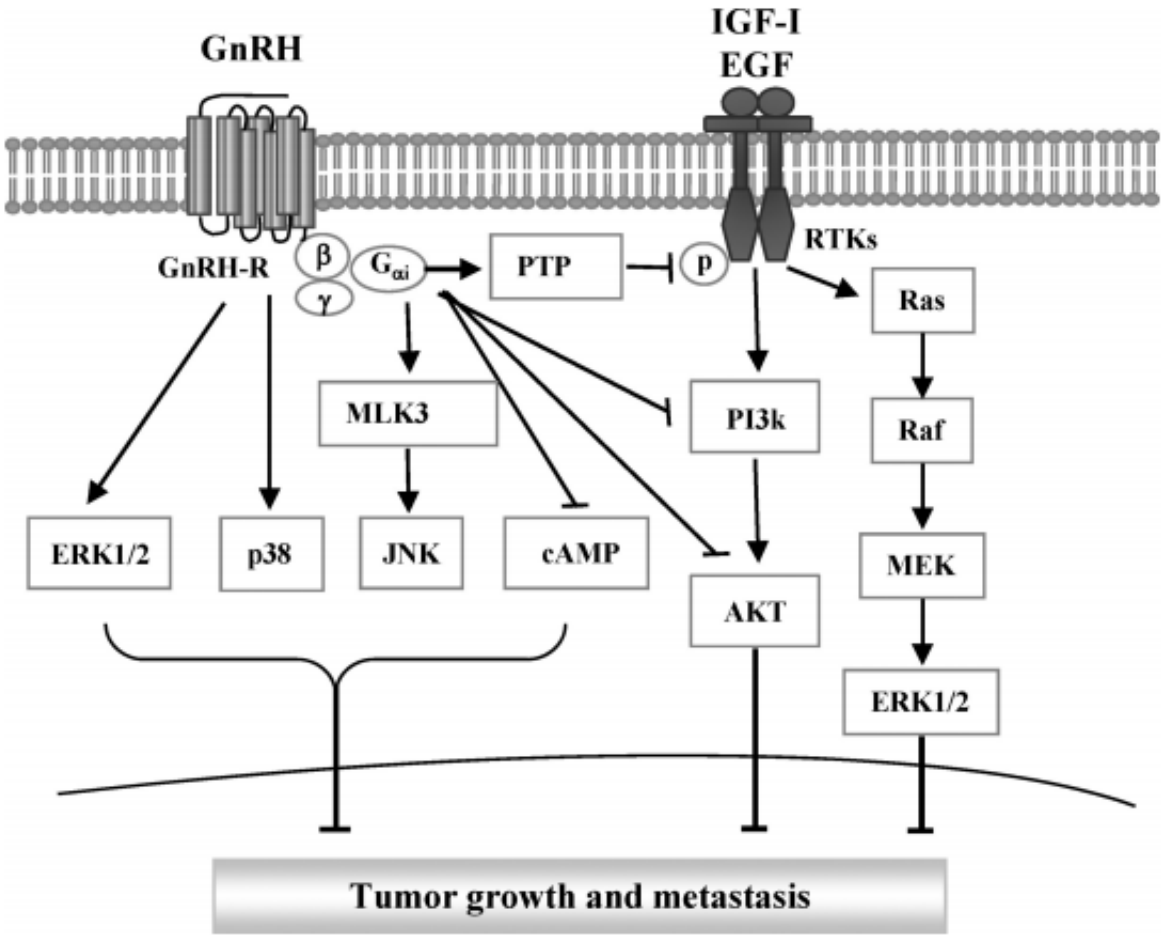
Infertility by Chemotherapy	In women, chemotherapy drugs can stop the ovaries from working properly and releasing eggs (ovulation). The damaged ovaries and loss of healthy eggs can lead to early menopause, which may be temporary or permanent. In order to protect the

	fertility of female cancer patients, it is an ideal method to prevent the maturation of eggs in female ovaries. Some research studies show that using GnRH drugs during chemotherapy may help protect a woman's ovaries and fertility.
In vitro Fertilization for Infertility	IVF is a type of assisted reproductive technology applied for infertility treatment and gestational surrogacy. In 2018, 8 million infants had been born through IVF and other assisted reproductive ways. During IVF, suppression of spontaneous ovulation can be used for generating multiple eggs, for which either a GnRH agonist protocol or a GnRH antagonist protocol is available.
Endometriosis	Endometriosis is a disease that the endometrial tissues are located outside of the uterus. Incidences of endometriosis occur mostly in postmenopausal women, rarely seen in younger adults before reaching the menarche. The rate of recurrence is estimated to be 40-50% for female over a 5-year period. Pelvic pain and infertility are the main results of endometriosis. For endometriosis, there is no cure but some treatments for pelvic pain, such as pain relievers, hormone therapy, and surgical treatments for severe pain. In hormone therapy, GnRH antagonists can reduce estrogen levels to relieve pain caused by endometriosis.

Mechanism of Action

Antitumor Activity Stimulated Through Receptor Binding

ANTIGN-109 binds to GnRHR and competitively blocks the activation. At the pituitary level, it causes a rapid and sustained inhibition of the pituitary–gonadal functions without inducing the suppressive flare effect.
By targeting GnRHR in multiple tumor cells, ANTIGN-109 induces cellular apoptosis and cytolysis to achieve antitumor activity. In cancer cells, Gαi is the major G protein coupled with GnRHR, mediating antitumor effects through the inhibition of cAMP accumulation. Coupling of the GnRHR to Gαi is followed by the activation of intracellular MAPK signaling cascades, a downstream mediator of the antiproliferative/proapoptotic activity.



Endocrine Reviews, October 2012, 33(5):784–811

Status

The Status of ANTIGN-109

Patents on ANTIGN-109 have been granted worldwide and multi-level patent protection barriers will be built completely.

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Data

Please feel free to contact us for non-confidential data.

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