GHR106-CAR-T

Novel CAR-T Therapy for Multiple Malignancies Expressing GnRH Receptor

Overview

Drug Name	GHR106-CAR-T
Description	GHR106-CAR-T is a chimeric antigen receptor (CAR) T cell technology developed on a patented monoclonal antibody, GHR106, which targets specifically at the extracellular domain of human gonadotropin releasing hormone (GnRH) receptor. GnRH receptor is abundantly expressed on the surface of most cancer cells, and has been demonstrated to be a potent target for anti-cancer treatment. Over years of R&D work, GHR106 was successfully engineered and constructed into a novel chimeric antigen receptor (CAR), which enrolled efficacy and safety proved co-stimulatory elements and a co-expressed recombinant cytokine which is important for T cell regulation. GHR106-CAR is able to target GnRH via scFv of humanized GHR106, activate T cells via intracellular signaling domains, and regulate T cell response via cytokine element. In preclinical studies, GHR106-CAR T cells display strong anti-cancer effects in various types of cancer cells, indicating therapeutic potential for treatment of a wide variety of cancers, especially cancers of the ovary, prostate and pancreas.
Indication	Cancer
Target	Gonadotropin-releasing hormone receptor (GnRHR)
Product Category	CAR-T; Immunotherapy
Mechanism of Action	Targeting tumor cells that express GnRHR through the CAR of GHR106 activates T cells to exert immune effects and kill tumor cells.
Status	Pre-clinical
Patent	In addition to the 10 patents granted for hGHR106 monoclonal antibody worldwide, CAR constructs of hGHR106 have been patented in the United States and China.

Cooperation Seeking

Protheragen Inc. is interested in partnering with companies to further develop hGHR106 pipeline, either in the form of a strategic alliance, licensing, or marketing agreement.

Look forward to cooperating with you in the near future.

Phone: 1-516-765-9461 Fax: 1-516-927-0118
Email: info@protheragen.com www.protheragen.com
2200 Smithtown Avenue, Room 1, Ronkonkoma, NY 11779-7329, USA

Target

Gonadotropin-Releasing Hormone Receptor (GnRHR)

Introduction	This gene encodes the receptor for type 1 gonadotropin-releasing hormone. This receptor is a member of the seven-transmembrane, 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 that activate a phosphatidylinositol-calcium second messenger system. Activation of 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, it has been identified that more than 18 transcription initiation sites were 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

Phone: 1-516-765-9461 Fax: 1-516-927-0118
Email: info@protheragen.com www.protheragen.com
2200 Smithtown Avenue, Room 1, Ronkonkoma, NY 11779-7329, USA

Clinical Resources

Gene Function	The growth of sex hormone-dependent tumors is inhibited by analogs of GnRH. GnRH agonists for treatment of prostatic and breast cancer is based on suppression of pituitary-gonadal function to lead a state of sex-steroid deficiency. In addition, GnRH agonists and antagonists exert a direct effect on these tumors that probably is mediated by specific high-affinity GnRH receptors found on these cells. GnRH agonists and antagonists also suppress the growth of experimental 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 immunohistochemical studies show that an antibody to the GnRH receptor reacted with sites 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, and 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;

Phone: 1-516-765-9461 Fax: 1-516-927-0118
Email: info@protheragen.com www.protheragen.com
2200 Smithtown Avenue, Room 1, Ronkonkoma, NY 11779-7329, USA

Indication

Cancers Expressing GnRHR

GnRHR expressed primarily on cancer cells can serve as targets for a selective destruction of malignant tumors. As shown in the table below, GnRHR were found on about 80% of human ovarian and endometrial cancers, 86% of human prostatic carcinoma and 52% of human breast cancers specimens, *etc.*, so GHR106-CAR-T is expected to be a potential drug for these cancers.

Cancer type	**Incidence of GnRHR expression as determined by**			
	Binding assay (%)	Reference	RT-PCR analysis (%)	Reference
Prostate	19 of 22 (86)	Qayum et al (1990)		
	69 of 80 (86)	Halmos et al (2000)	19 of 22 (86)	Halmos et al (2000)
	13 of 13 (100)	Tieva et al (2001)		
	16 of 16 (100)	Straub et al (2001)		
Endometrial	24 of 31 (77)	Srkalovic et al (1990)		
	5 of 6 (83)	Völker et al (2002)	5 of 6 (83)	Völker et al (2002)
	12 of 12 (100)	Pahwa et al (1991)		
Ovarian	32 of 40 (80)	Emons et al (1989)		
	29 of 37 (78)	Srkalovic et al (1989)		
	14 of 20 (70)	Völker et al (2002)	14 of 20 (70)	Völker et al (2002)
Kidney	4 of 5 (80)	Sion-Vardi et al (1992)		
Pancreatic	3 of 3 (100)	Fekete et al (1989)		
	13 of 23 (57)	Friess et al (1991)		
Breast	260 of 500 (52)	Fekete et al (1989)		
	121 of 235 (51.5)	Baumann et al (1993)		
Brain	9 of 21 (43)	van Groeninghen et al (2002)		

Prostate Cancer	Globally, prostate cancer contributes the second highest morbidity and mortality rates following lung cancer in men. In 2018, it was estimated that there would be 1,276,106 new cases of prostate cancer, accounting for 7.1% of the total number of new cancer patients, and the death toll may reach 358,989. The 5-year survival rate in the developed states is high. For prostate cancer, common treatments include surgery, radiation therapy, hormone therapy, vaccine, and chemotherapy.
Endometrial Cancer	Endometrial cancer (EC) originates in the endometrium, the inner lining of the body of the uterus (corpus uteri), and is classified into type I or type II. EC is the fifth most common cancer in women worldwide, and continues to increase in both incidence (by 1-2% yearly) as well as prevalence. Although the prevalence of endometrial cancer is high, the mortality-to-incidence ratio is lower than that of other gynecological malignancies. Most patients do well with surgery alone. Five-year survival rates for women with FIGO stage I-II endometrial cancer range from 74% to 91%.

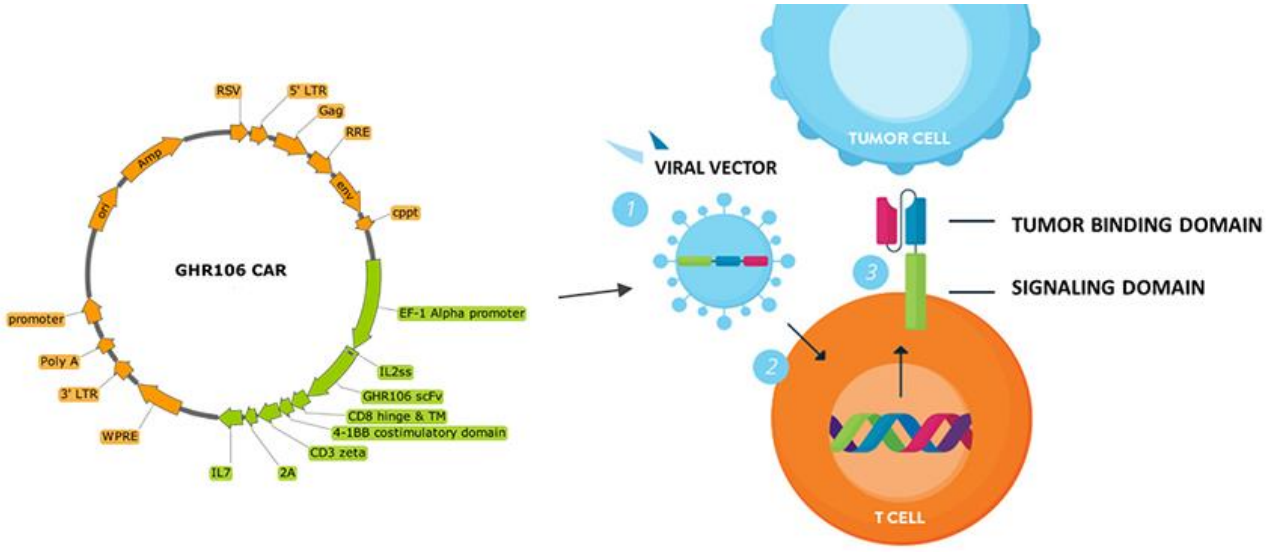
Phone: 1-516-765-9461 Fax: 1-516-927-0118
Email: info@protheragen.com www.protheragen.com
2200 Smithtown Avenue, Room 1, Ronkonkoma, NY 11779-7329, USA

Ovarian Cancer	Ovarian cancer typically spreads via local shedding into the peritoneal cavity, followed by the implantation of high-grade papillary serous tumors on the peritoneum and local invasion of the bowel and bladder. The cancer spreading to pelvic lymph nodes is also common and it increases with the stages of disease. According to Globocan data for 2018, the global incidence of ovarian cancer would be 295,414. Worldwide, the five-year survival rate in average is 30-40%. The principal reason why ovarian cancer is so lethal is the lack of clinically specific symptoms leading to detection at early, more successfully treatable stages.
Kidney Cancer	Kidney cancer is an umbrella term for cancer which forms in the kidney tubules. The main forms of kidney cancer are renal cell carcinoma, transitional cell carcinoma, renal sarcoma, and Wilm's tumor. Renal cell carcinoma (RCC) accounts for 90% of all kidney cancers. According to the Globocan data for 2018 by the International Agency for Research on Cancer (IARC), the global incidence of kidney cancer was 403,262 and the five-year global prevalence was 1,025,730.
Pancreatic Cancer	The pancreas is a dual-function gland, having both endocrine and exocrine components. Tumors can arise in either part, although the vast majority arise in the exocrine glands and ducts, which together account for more than 95% of the cells in the pancreas. Because the location of the pancreas is deep within the abdominal cavity, tumors are not palpable and may not be symptomatic until the neighboring organs are affected. According to the Globocan data for 2018, the global incidence of pancreatic cancer was 458,918. Pancreatic cancer is highly prone to both local invasion and distant metastases with a corresponding negative impact on survival.
Breast Cancer	Breast cancer is the most common invasive cancer in women. In 2018, it was estimated that about 2,088,849 people worldwide suffered from breast cancer and the death toll was about 626,679. The survival rate of breast cancer in the developed countries is high and most of patients survive at least 5 years. Depending on the specific situation of the cancer, appropriate treatment options can be used, including chemotherapy, hormonal therapy and targeted therapy.

Mechanism of Action

Targeting Tumor Cells via CAR of GHR106 Activates T Cells to Kill Tumor Cells.

GHR106 ScFv gene was packaged in the vector in the form of chimeric antigen receptor (CAR) and transfected into T cells from a patient *in vitro* to become GHR106-CAR-T. After injected back into the patient, GHR106-CAR-T cells effectively identify and bind GnRHR-expressing tumor cells to be activated. Then perforin and granulocase B are released to kill tumor cells directly, and also endogenous immune cells are recruited to kill tumor cells by releasing cytokines. Moreover, specific long-term anti-tumor mechanism can be obtained by forming immune memory T cells.



Status

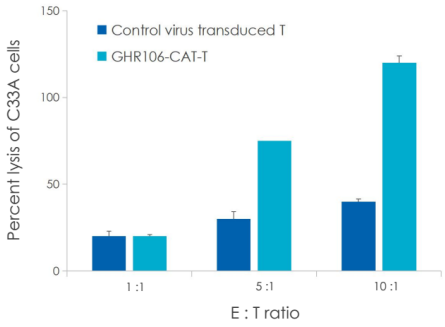
The Patent Situation of GHR106-CAR-T

In addition to the 10 patents granted for hGHR106 monoclonal antibody worldwide, CAR constructs of hGHR106 monoclonal antibody have been patented in the United States and China.

	Discovery/Optimization	Pre-clinical	Phase I	PhaseII	PhaseIII	IND Field
GHR106-CAR-T						

Phone: 1-516-765-9461 Fax: 1-516-927-0118
Email: info@protheragen.com www.protheragen.com
2200 Smithtown Avenue, Room 1, Ronkonkoma, NY 11779-7329, USA

Data

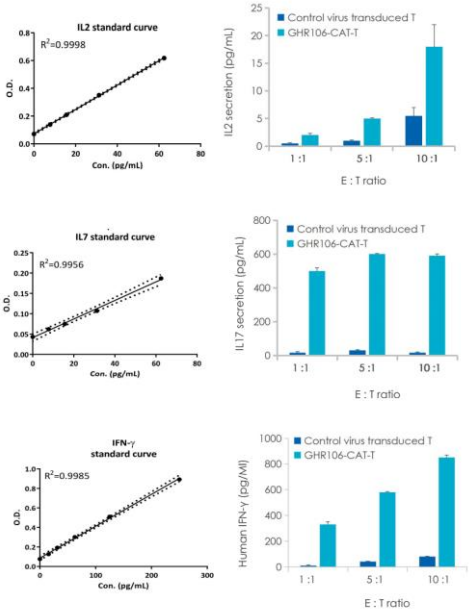


In vitro Cytotoxicity of GHR106-CAR-T

C33A cancer cells (T) were co-cultured with GHR106- CAR-T cells (E) or with control virus transduced T cells at three different E/T (Effect/Target) ratios for 6 hours. The percentage of tumor cells lysis was measured by lactate dehydrogenase (LDH) levels.

In the E/T ratio of 5:1 and 10:1, GHR106-CAR-T could significantly increase the cell lysis, indicating that GHR106-CAR-T had the ability to kill tumor cells.

Cytokine Assays (ELISA)



After C33A cancer cells (T) co-cultured with GHR106- CAR-T cells (E) or with control cells, the release levels of three cytokines involved in the immune response were measured by ELISA.

IL-2 plays an important role in key functions, tolerance and immunity of the immune system, mainly through its direct effects on T cells. IL-7 is important for proliferation during certain stages of B-cell maturation, T and NK cell survival, development and homeostasis. And IFN-γ is a cytokine critical for innate and adaptive immunity against viral, bacterial and infections.

As shown in the figures, GHR106-CAR-T cells significantly increased the release levels of three cytokines compared with control cells, especially in the E/T ratio of 5:1 to 10:1.

Phone: 1-516-765-9461
Fax: 1-516-927-0118
Email: info@protheragen.com
www.protheragen.com
2200 Smithtown Avenue, Room 1,
Ronkonkoma, NY 11779-7329, USA