GPNMB-targeted Antibody-drug Conjugate for Cancer Treatment

First-in-class ADC Optimized by New Conjugation Strategy

Overview

Drug Name	A1801
Description	A1801 is an in-licensed and optimized antibody-drug conjugate consisting of a potent cellular toxin and a fully human monoclonal antibody against glycoprotein nonmetastatic melanoma protein B (GPNMB) highly expressed in melanoma and breast cancer.
Target	Transmembrane glycoprotein GPNMB
Drug Modality	Antibody-drug conjugate (ADC)
Indication	Triple-negative breast cancer; melanoma
Product Category	Cancer immunotherapy
Mechanism of Action	Delivering cytotoxins specifically into tumor cells
Status	Preclinical
Patent	Granted

Collaboration Opportunity

Protheragen Inc. is actively seeking partnership for A1801. Potential collaboration can be strategic alliance, licensing, or marketing agreement.
We look forward to hearing from you.

Target

Glycoprotein Nonmetastatic Melanoma Protein B (GPNMB)

Introduction	GPNMB is a type 1 transmembrane protein that is expressed in a wide array of tumors and has both anti- and pro-tumorigenic properties. GPNMB is expressed at

	a higher level in numerous malignant cancers than in normal tissues, and is associated with reduced disease-free and overall survival. GPNMB expression often correlates with increased proliferation, migration, invasion, and decreased apoptosis of tumor cell in cancers including melanoma, triple-negative breast cancer, gliomas, prostate cancer, and lung cancer.
Approved Name	Glycoprotein nmb
Official Symbol	GPNMB
Gene Type	Protein coding
Synonyms	NMB; HGFIN; PLCA3
Ensembl	ENSG00000136235
Gene ID	10457
mRNA Refseq	NM_001005340.2; NM_002510.3
Protein Refseq	NP_001005340.1; NP_002501.1
OMIM	604368
UniProt ID	Q14956
Chromosome Location	7p15.3

Clinical Resources

Gene Function	The 560 and 572 amino acid proteins encoded by the two *GPNMB* mRNA isoforms show homology to the pMEL17 precursor, a melanocyte-specific protein. Both isoforms consist of a large ectodomain, a single pass transmembrane domain, and a shorter cytoplasmic tail. GPNMB may be involved in growth delay and reduction of metastatic potential.
Pathway	GPNMB can interact with some receptors, proteins, and other molecules in the cell membrane. Some of these interactions activate intracellular pathways, such as FAK/Src pathway, ERK/MEK pathway, and AKT/PI3K pathway.
Major Conditions	Melanoma; Breast Cancer; Glioma

Drug Modality

Antibody-drug Conjugate (ADC)

To realize the potential utility of GPNMB as a target for cancer therapy, a first-in-class ADC consisting of a fully human monoclonal antibody and a cytotoxic agent monomethyl auristatin E (MMAE) was developed. Through innovative technology optimization, A1801 contains more active ingredients, less chemical residue, and the main cause of adverse reactions has been removed.

Indication

Triple-negative Breast Cancer

Breast cancer is a pathological condition that occurs in the breast tissue. Immunopathologically, four subtypes of breast cancer have been distinguished based on expression of hormone receptors including estrogen receptors (ER), progesterone receptors (PR) and the proto-oncogene HER2/neu. Triple-negative breast cancer (TNBC, ER-/PR-/HER2-) is an aggressive subtype of breast cancer that lack expression of these three hormone receptors.

Breast Cancer was the most commonly diagnosed malignancy in women (24.5% of all cancers) and the number one cause of cancer death (15.5% of cancer deaths) for females worldwide in 2020, according to the International Agency for Research on Cancer (IARC). TNBC accounts for 15 - 25% of all breast cancers and has the worst prognosis among breast cancers. Unlike other breast cancer subtypes, there are no approved targeted treatments available, although immunotherapy is available for those with advanced TNBC that expresses programmed cell death ligand 1 (PD-L1).

Melanoma

Melanoma is a highly aggressive, therapy-resistant malignant tumor that originates in melanocytes, a specialized class of melanin-producing cells found primarily in the skin. The normal role of melanin is to protect the deeper layers of the skin from the harmful effects caused by ultraviolet radiation. Melanoma develops when melanocytes are injured and transformed.

IARC's data showed that approximately 325,000 incident cases of skin melanoma cases were diagnosed globally in 2020. Moreover, if 2020 rates continue, the burden from melanoma could increase to 510,000 new cases by 2040. Nearly 75% of all skin cancer deaths are attributable to metastatic melanoma, and the principal cause of death from melanoma is metastasis that is resistant to conventional therapies. Treatment of the

patient diagnosed with thin primary cutaneous melanoma consists of relatively easy surgical excision and is associated with a high cure rate. When the disease is more advanced, metastatic, or vertical growth stage, however, therapeutic options are limited and the failure rate continues to be high. Therefore, there is a need to develop therapeutic agents that can overcome potential resistance and achieve optimal clinical outcomes.

Mechanism of Action

Delivering Cytotoxins Specifically into Tumor Cells

Antibody-drug conjugate (ADC) is a valuable emerging therapeutic strategy for selectively targeting tumor cells. GPNMB enriched on the cell surface of melanoma and triple-negative breast cancer is an attractive therapeutic target, because it plays an important role in driving cancer progression and enhances cell surface localization on cancer cells, whereas in normal cells it is primarily intracellular localization.
A1801 is an optimized ADC that consists of a fully human anti-GPNMB monoclonal antibody conjugated to the potent microtubule inhibitor MMAE via a cathepsin cleavable dipeptide linker. The linkage is stable in the bloodstream. Once the antibody in A1801 specifically binds to GPNMB expressed on the tumor cell surface, A1801 is endocytosed by the tumor cell. Within cellular endosomes, the linker is cleaved by protease and the released MMAE toxin inhibits tumor cell mitosis, resulting in the target cell death due to impaired microtubule structure.

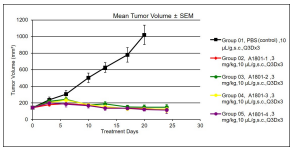
Status

The Status of A1801

Patents have been licensed or granted, and pre-testing of A1801 *in vivo* has been completed. The preclinical studies are expected to be completed next year.

	Discovery/Optimization	Preclinical	Phase I	PhaseII	PhaseIII
A1801					

Data



Inhibitory effect of A1801 on tumor growth

The results of *in vivo* experiments showed that A1801 (3 mg/kg) with different drug-to-antibody ratio (DAR) had a good inhibitory effect on tumor growth.

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