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(54) **BIO PROTAC PROTEIN HAVING INTRACELLULAR DELIVERY FUNCTION, AND PHARMACEUTICAL COMPOSITION COMPRISING SAME**

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(57) **ABSTRACT**

The present invention relates to a proteolysis targeting chimera (PROTAC) protein having an intracellular delivery function, and a pharmaceutical composition comprising same. The PROTAC protein according to the present invention has higher solubility than a PROTAC prepared by a conventional method and efficiently degrades intrinsic disease proteins when applied to cells, and thus is effective in the treatment of cancer or inflammatory diseases.

Specification includes a Sequence Listing.

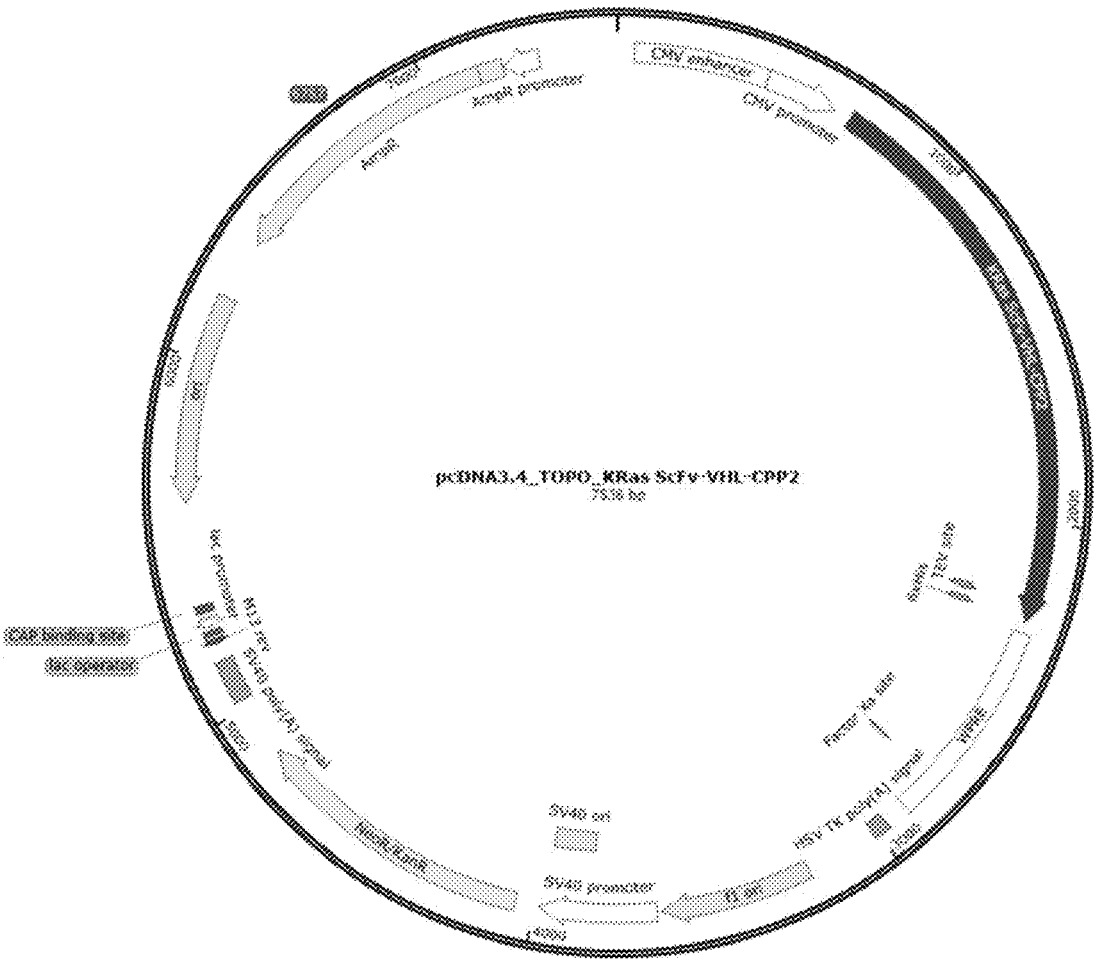


FIG. 1

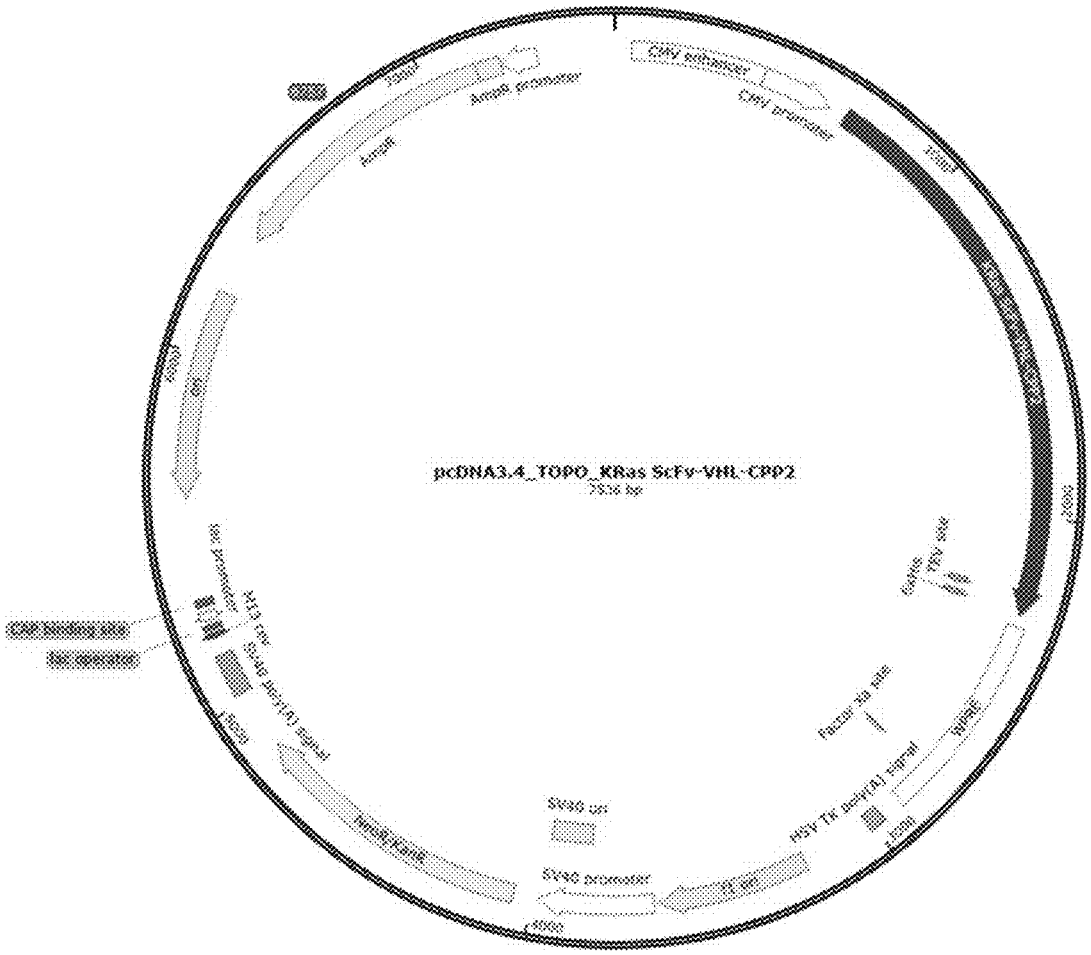

pcDNA3.4_TOPO_KRas ScFv-VHL-CPP2
7530 bp
CMV enhancer
CMV promoter
Ampicillin promoter
Ampicillin
pUC ori
f1 ori
SV40 ori
SV40 promoter
SV40 poly(A) signal
HSV TK poly(A) signal
bGH poly(A) signal
EM7 promoter
M13 rev
pUC/M13 Reverse Sequencing Primer
pUC/M13 Forward Sequencing Primer
T7 promoter/priming site
BGH reverse priming site

FIG. 2

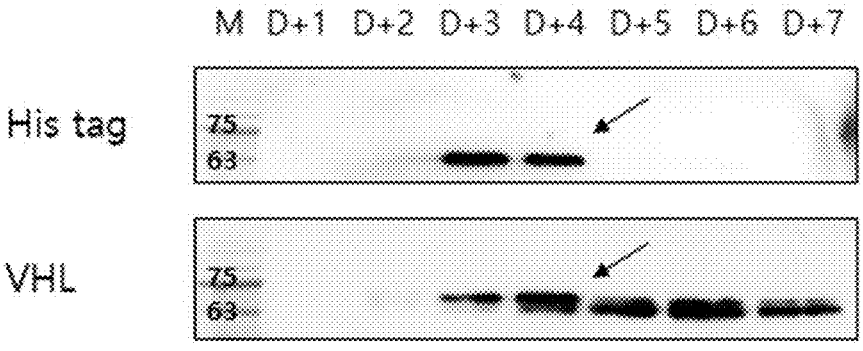

M D+1 D+2 D+3 D+4 D+5 D+6 D+7
His tag
75
63
VHL
75
63

FIG. 3

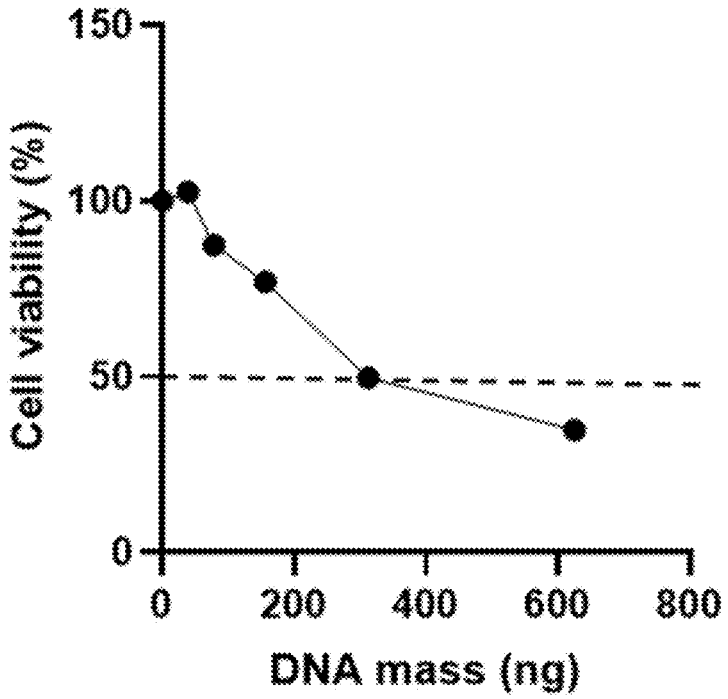

150
100
50
0
Cell viability (%)
0
200
400
600
800
DNA mass (ng)

FIG. 4

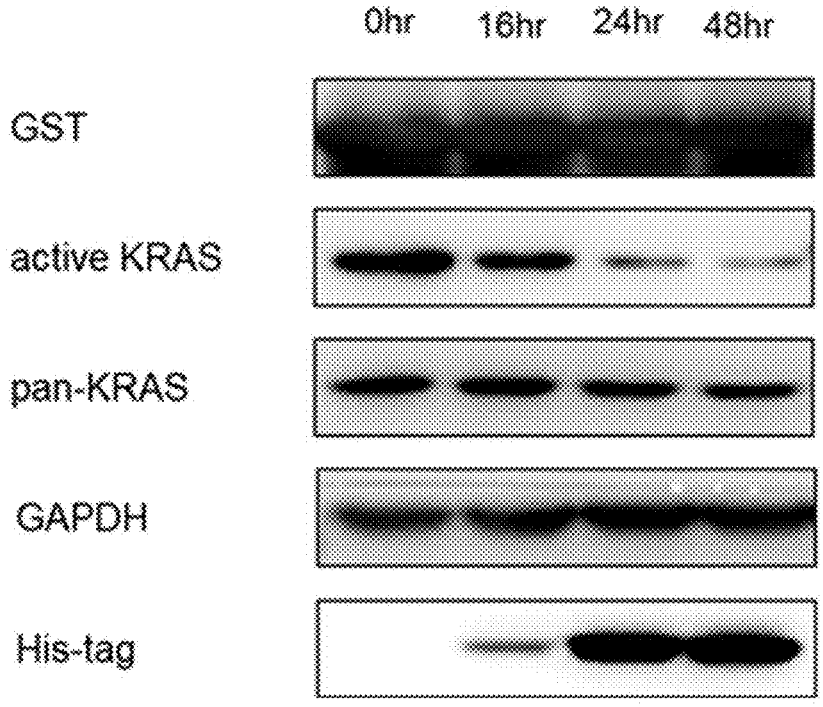
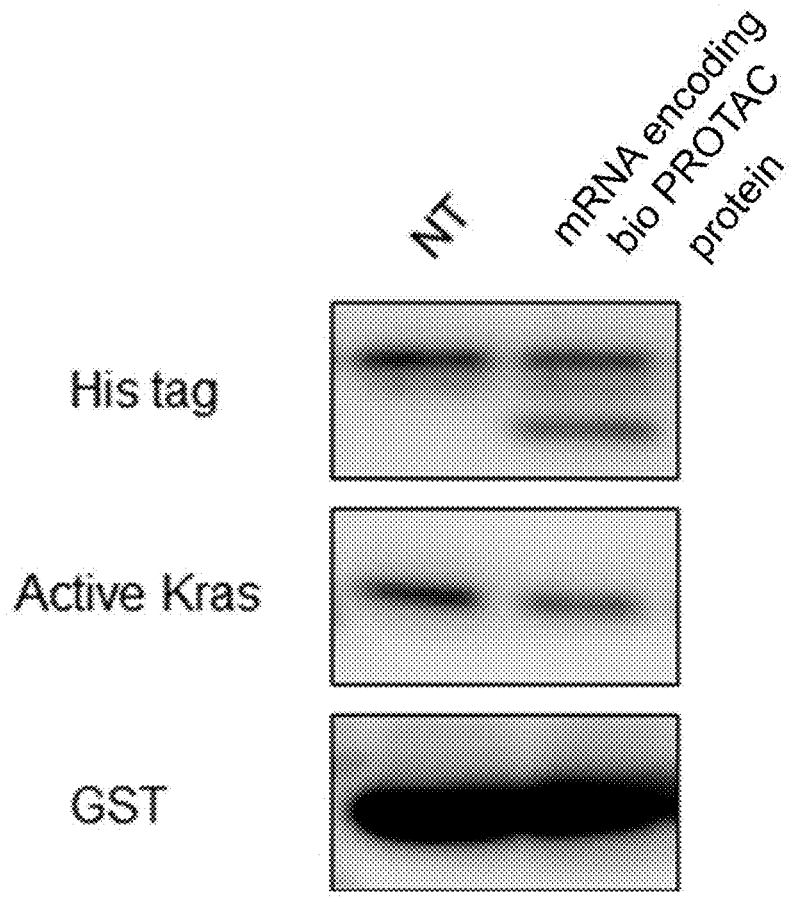

0hr
16hr
24hr
48hr
GST
active KRAS
pan-KRAS
GAPDH
His-tag

FIG. 5



BIO PROTAC PROTEIN HAVING INTRACELLULAR DELIVERY FUNCTION, AND PHARMACEUTICAL COMPOSITION COMPRISING SAME

TECHNICAL FIELD

[0001] The present invention relates to a proteolysis targeting chimera (PROTAC) protein having an intracellular delivery function and a pharmaceutical composition comprising the same.

BACKGROUND ART

[0002] Proteolysis targeting chimera (PROTAC) is a double-headed molecule that binds to a disease-causing protein, inducing the proteasome to degrade the protein, resulting in selective proteolysis. PROTAC is composed of two protein-binding molecules, one for binding to an E3 ubiquitin ligase and the remaining one for binding to a target protein. By binding to both proteins, PROTAC delivers the target protein to the E3 ligase and causes tagging, namely ubiquitination, of the target protein for subsequent degradation by the proteasome.

[0003] Ubiquitination involves three steps: activation, conjugation, and ligation performed by ubiquitin-activating enzymes (E1), ubiquitin-conjugating enzymes (E2), and ubiquitin ligases (E3). As a result of this sequential cascade, ubiquitin is covalently attached to the target protein. The ubiquitinated protein is eventually degraded by the proteasome.

[0004] PROTAC technology was first reported in 2001 (Sakamoto et al., Proceedings of the National Academy of Sciences of the United States of America. 98: 8554, 2001). Since then, this technology has been used in various drug designs: pVHL, MDM2, beta-TrCP1, cereblon, and c-IAP1. PROTAC drugs have been developed mostly from small-molecule compounds. Various types of small-molecule compounds derived from the thalidomide family have the advantage of being able to simultaneously conjugate a target protein and an E3 ligase structurally. These known PROTAC drugs are very useful, but measures are needed to address concerns about the low solubility of small-molecule compounds, the decreased intrinsic protein degradation efficiency due to low intracellular penetration, and safety, and a need for PROTAC drugs that overcome these problems is required.

[0005] Therefore, the present inventors have made great efforts to develop a PROTAC protein with high target protein degradation efficiency and intracellular delivery function, rather than using a small-molecule compound, and ascertained that a target protein binding sequence linked via a linker composed of five glycines to a von Hippel-Lindau (VHL) protein sequence as a substrate recognition unit capable of transferring, to a target protein, an E3 ligase, which is an important target in cancer, inflammatory diseases, and infection, may be constructed, and an antibody or a cell-penetrating peptide may be attached to the end of this chimeric protein using a linker, so the target protein of the underlying disease may be actually degraded through intracellular delivery, thus culminating in the present invention.

[0006] The above information described in the background section is only for improving the understanding of the background of the present invention, and it does not include information forming the prior art known to those of ordinary skill in the art to which the present invention pertains.

SUMMARY OF THE INVENTION

[0007] It is one object of the present invention to provide a PROTAC protein having high target protein degradation efficiency and intracellular delivery function.

[0008] It is another object of the present invention to provide a nucleic acid encoding the PROTAC protein.

[0009] It is still another object of the present invention to provide a pharmaceutical composition comprising the PROTAC protein or the nucleic acid encoding the same as an active ingredient.

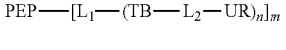
[0010] It is yet another object of the present invention to provide a method of preventing or treating a disease comprising administering the PROTAC protein or the nucleic acid encoding the same.

[0011] It is still yet another object of the present invention to provide the use of the PROTAC protein or the nucleic acid encoding the same for the prevention or treatment of a disease.

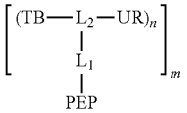
[0012] It is even yet another object of the present invention to provide the use of the PROTAC protein or the nucleic acid encoding the same in the manufacture of a medicament for preventing or treating a disease.

[0013] In order to accomplish the above objects, the present invention provides a PROTAC protein having the structure of Chemical Formula 1 or Chemical Formula 2 below:

[Chemical Formula 1]



[Chemical Formula 2]



[0014] in Chemical Formula 1 or Chemical Formula 2,

[0015] (i) PEP is an antibody or an antibody fragment, or a cell-penetrating peptide,

[0016] (ii) L_1 and L_2 are linkers, L_1 and L_2 may be the same as or different from each other, and L_1 binds to TB or L_2,

[0017] (iii) TB is a binder or conjugate that binds to a target protein,

[0018] (iv) UR is a ligand binding to a ubiquitin ligase, and

[0019] (v) n and m are each independently an integer of 1 to 10.

[0020] In addition, the present invention provides a nucleic acid encoding the PROTAC protein.

[0021] In addition, the present invention provides a pharmaceutical composition comprising the PROTAC protein or the nucleic acid encoding the same as an active ingredient.

[0022] In addition, the present invention provides a method of preventing or treating a disease comprising administering the PROTAC protein or the nucleic acid encoding the same.

[0023] In addition, the present invention provides the use of the PROTAC protein or the nucleic acid encoding the same for the prevention or treatment of a disease.

[0024] In addition, the present invention provides the use of the PROTAC protein or the nucleic acid encoding the same in the manufacture of a medicament for preventing or treating a disease.

BRIEF DESCRIPTION OF DRAWINGS

[0025] FIG. **1** schematically shows an expression vector of a PROTAC protein with cell-penetrating activity.

[0026] FIG. **2** shows results of Western blotting of the PROTAC protein expressed on a plasmid introduced into cells.

[0027] FIG. **3** shows results of cancer cell viability by the PROTAC protein expressed on the plasmid introduced into cells.

[0028] FIG. **4** shows results of Western blotting confirming inhibition of expression of active KRAS by the PROTAC protein expressed on the plasmid introduced into cells.

[0029] FIG. **5** shows results of Western blotting confirming expression of the PROTAC protein and inhibition of expression of active KRAS in cells after introduction of mRNA encoding the PROTAC protein into the cells.

DETAILED DESCRIPTION AND PREFERRED EMBODIMENTS OF THE INVENTION

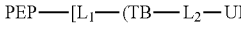
[0030] Unless otherwise defined, all technical and scientific terms used herein have the same meanings as typically understood by those skilled in the art to which the present invention belongs. In general, the nomenclature used herein and experimental methods described below are well known in the art and are typical.

[0031] The present invention is based on the discovery that a ubiquitin pathway protein ubiquitinates any target protein when the ubiquitin pathway protein and the target protein are in proximity to a chimeric construct that binds to the ubiquitin pathway protein and the target protein.

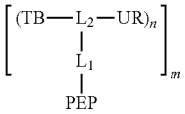
[0032] The present invention is mainly intended to overcome limitations of conventional PROTAC technology in that PROTAC has low solubility or does not efficiently degrade intrinsic disease proteins when applied to cells.

[0033] In one aspect, the present invention is directed to a PROTAC protein having the structure of Chemical Formula 1 or Chemical Formula 2 below:

[Chemical Formula 1]



[Chemical Formula 2]



[0034] in Chemical Formula 1 or Chemical Formula 2,

[0035] (i) PEP is an antibody or an antibody fragment, or a cell-penetrating peptide,

[0036] (ii) L_1 and L_2 are linkers, L_1 and L_2 may be the same as or different from each other, and L_1 binds to TB or L_2,

[0037] (iii) TB is a binder or conjugate that binds to a target protein,

[0038] (iv) UR is a ligand binding to a ubiquitin ligase, and

[0039] (v) n and m are each independently an integer of 1 to 10.

[0040] As used herein, the term "PROTAC" is an abbreviation of proteolysis targeting chimera, refers to a bifunctional small molecule composed of two active domains and a linker, and is capable of removing a specific unwanted protein. In the present specification, "PROTAC protein" may be used interchangeably with "bio PROTAC protein" and "chimeric protein".

[0041] The PROTAC protein according to the present invention is capable of inducing ubiquitination of a selected target protein, and is designed to be linked via a linker to include a target protein binding site and a ubiquitin ligase binding site.

[0042] In the present invention, the PROTAC protein includes a ubiquitin ligase binding ligand at one end and a target protein binding site at the remaining end, and a cell-penetrating domain is included in the end of the protein binding to the target protein or in the linker that connects the ubiquitin ligase binding ligand and the target protein binding site to each other. Thereby, when the PROTAC protein is introduced into cells, it is located close to the target protein, making it possible to induce degradation of the protein, and is present in high concentration in the cells depending on the numerical values of n and m, inducing effective target protein degradation.

[0043] In the present invention, the PROTAC protein may be represented by the amino acid sequences of SEQ ID NOs: 1 to 6, but is not limited thereto.

SEQ ID NO: 1:
EVQLLESGGGLVQPGGSLRLSCAASGFTFSTESMNWVRQAPGKGLEWVSYI

SRTSKTIYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARGRFFDYWGQGT

LVTVSSGGSEGKSSGSGSESKSTGGSDIQMTQSPSSLSASVGDRVTITCRASQSISSY

LNWYQQKPGEAPKLLIYSASVLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQ

SVMIPMTFGQGTKVEIKGSGGGGSMPRRAENWDEAEVGAEEAGVEEYGPEEDGGEESG

AEESGPEESGPEELGAEEEMEAGRPRPVLRSVNSREPSQVIFCNRSPRVVLPVWLNED

GEPQPYPTLPPGTGRRIHSYRGHLWLFRDAGTHDGLLVNQTELFVPSLNVDGQPIFAN

ITLPVYTLKERCLQVVRSLVKPENYRRLDIVRSLYEDLEDHPNVQKDLERLTQERIAH

QRMGDENLYFQGGSGGSGGSHHHHHHH

-continued

SEQ ID NO: 2:
MAWVWTLLFLMAAAQSIQAVSRRRRRRGGRRRRGGGGSEVQLLESGGGLVQ

PGGSLRLSCAASGFTFSTFSMNWVRQAPGKGLEWVSYISRTSKTIYYADSVKGRFTIS

RDNSKNTLYLQMNSLRAEDTAVYYCARGRFFDYWGQGTLVTVSSGGSEGKSSGSGSES

KSTGGSDIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGEAPKLLIYSAS

VLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSVMIPMTFGQGTKVEIKGSG

GGGSMPRRAENWDEAEVGAEEAGVEEYGPEEDGGEESGAEESGPEESGPEELGAEEEM

EAGRPRPVLRSVNSREPSQVIFCNRSPRVVLPVWLNEDGEPQPYPTLPPGTGRRIHSY

RGHLWLFRDAGTHDGLLVNQTELFVPSLNVDGQPIFANITLPVYTLKERCLQVVRSLV

KPENYRRLDIVRSLYEDLEDHPNVQKDLERLTQERIAHQRMGDENLYFQGGSGGSGGS

HHHHHHHH

SEQ ID NO: 3:
MAWVWTLLELMAAAQSIQAEVQLLESGGGLVQPGGSLRLSCAASGETESTE

SMNWVRQAPGKGLEWVSYISRISKTIYYADSVKGRFTISRDNSKNTLYLQMNSLRAED

TAVYYCARGRFFDYWGQGTLVTVSSGGSEGKSSGSGSESKSTGGSDIQMTQSPSSLSA

SVGDRVTITCRASQSISSYLNWYQQKPGEAPKLLIYSASVLQSGVPSRFSGSGSGTDE

TLTISSLQPEDFATYYCQQSVMIPMTFGQGTKVEIKGSGGGGSMPRRAENWDEAEVGA

EEAGVEEYGPEEDGGEESGAEESGPEESGPEELGAEEEMEAGRPRPVLRSVNSREPSQ

VIFCNRSPRVVLPVWLNEDGEPQPYPTLPPGTGRRIHSYRGHLWLFRDAGTHDGLLVN

QTELFVPSLNVDGQPIFANITLPVYTLKERCLQVVRSLVKPENYRRLDIVRSLYEDLE

DHPNVQKDLERLTQERIAHQRMGDGGGGSVSRRRRRRGGRRRRENLYFQGGSGGSGGS

HHHHHHHH

SEQ ID NO: 4:
EVQLLESGGGLVQPGGSLRLSCAASGFTFSTESMNWVRQAPGKGLEWVSYI

SRTSKTIYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARGREEDYWGQGT

LVTVSSGGSEGKSSGSGSESKSTGGSDIQMTQSPSSLSASVGDRVTITCRASQSISSY

LNWYQQKPGEAPKLLIYSASVLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQ

SVMIPMTFGQGTKVEIKGSGGGGSMENRWQVMIVWQVDRMRIRTWKSLVKHHMYVSGK

ARGWFYRHHYESPHPRISSEVHIPLGDARLVITTYWGLHTGERDWHLGQGVSIEWRKK

RYSTQVDPELADQLIHLYYFDCESDSAIRKALLGHIVSPRCEYQAGHNKVGSLQYLAL

AALITPKKIKPPLPSVTKLTEDRWNKPQKTKGHRGSHTMNGHENLYFQGGSGGSGGSH

HHHHHHH

SEQ ID NO: 5:
MAWVWILLFLMAAAQSIQAVSRRRRRRGGRRRRGGGGSEVQLLESGGGLVQ

PGGSLRLSCAASGFTFSTFSMNWVRQAPGKGLEWVSYISRTSKTIYYADSVKGRFTIS

RDNSKNTLYLQMNSLRAEDTAVYYCARGRFFDYWGQGTLVTVSSGGSEGKSSGSGSES

KSTGGSDIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGEAPKLLIYSAS

VLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSVMIPMTFGQGTKVEIKGSG

GGGSMENRWQVMIVWQVDRMRIRTWKSLVKHHMYVSGKARGWFYRHHYESPHPRISSE

-continued

VHIPLGDARLVITTYWGLHTGERDWHLGQGVSIEWRKKRYSTQVDPELADQLIHLYYF

DCFSDSAIRKALLGHIVSPRCEYQAGHNKVGSLQYLALAALITPKKIKPPLPSVTKLT

EDRWNKPQKTKGHRGSHTMNGHENLYFQGGSGGSGGSHHHHHHHH

SEQ ID NO: 6:
MAWVWTLLFLMAAAQSIQAEVQLLESGGGLVQPGGSLRLSCAASGFTFSTF

SMNWVRQAPGKGLEWVSYISRISKTIYYADSVKGRFTISRDNSKNTLYLQMNSLRAED

TAVYYCARGRFFDYWGQGTLVTVSSGGSEGKSSGSGSESKSTGGSDIQMTQSPSSLSA

SVGDRVTITCRASQSISSYLNWYQQKPGEAPKLLIYSASVLQSGVPSRFSGSGSGTDF

TLTISSLQPEDFATYYCQQSVMIPMTFGQGTKVEIKGSGGGGSMENRWQVMIVWQVDR

MRIRTWKSLVKHHMYVSGKARGWFYRHHYESPHPRISSEVHIPLGDARLVITTYWGLH

TGERDWHLGQGVSIEWRKKRYSTQVDPELADQLIHLYYFDCFSDSAIRKALLGHIVSP

RCEYQAGHNKVGSLQYLALAALITPKKIKPPLPSVTKLTEDRWNKPQKTKGHRGSHTM

NGHGGGGSVSRRRRRGGRRRRENLYFQGGSGGSGGSHHHHHHHH

[0044] The binder or conjugate that binds to the target protein, named TB in the present invention, may be selected from a library. TB is designed to be coupled via a linker with a ubiquitin pathway protein binding site, such as a VHL protein. The ubiquitin pathway protein recognizes the E3 ubiquitin ligase.

[0045] In the present invention, the target protein of the PROTAC protein may include, but is not limited to, a mutated RAS superfamily, a kinase, a transcription factor, and a phosphatase.

[0046] In the present invention, the RAS superfamily may be selected from the group consisting of KRAS, HRAS, and NRAS.

[0047] In the present invention, TB may be selected from the group consisting of a mutated RAS superfamily inhibitor, a kinase inhibitor, a phosphatase inhibitor, a heat shock protein 90 (HSP90) inhibitor, an MDM2 (mouse double minute 2 homolog) inhibitor, an HDAC (histone deacetylase) inhibitor, a human lysine methyltransferase inhibitor, an angiogenesis inhibitor, an immunosuppressive compound, a compound targeting human BET (bromodomain and extraterminal domain) bromodomain-containing protein, a compound targeting aryl hydrocarbon receptor (AHR), a compound targeting EGF (epithelial growth factor) receptor kinase, a compound targeting FKBP (FK506 binding protein), a compound targeting androgen receptor (AR), a compound targeting estrogen receptor (ER), a compound targeting thyroid hormone receptor, a compound targeting HIV protease, a compound targeting HIV integrase, a compound targeting HCV protease, a compound targeting acyl-protein thioesterase-1 (APT1), and a compound targeting acyl-protein thioesterase-2 (APT2), but is not limited thereto.

[0048] In the present invention, TB may be a peptide comprising any one amino acid selected from SEQ ID NO: 7 to SEQ ID NO: 14, but is not limited thereto.

SEQ ID NO: 7:
LTPHKHHKHLHA

SEQ ID NO: 8:
WPGKHHNHYLRS

SEQ ID NO: 9:
HDGYWWHSMTMW

SEQ ID NO: 10:
LIHPMTVKHVHL

SEQ ID NO: 11:
GSHWHEPKHQQQ

SEQ ID NO: 12:
GSHWHFPKHQQH

SEQ ID NO: 13:
WPGKHHHHYLRR

SEQ ID NO: 14:
EVQLLESGGGLVQPGGSLRLSCAASGFTFSTFSMNWVRQAPGKGLEWVS

YISRTSKTIYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR

GRFFDYWGQGTLVTVSSGGSEGKSSGSGSESKSTGGSDIQMTQSPSSLS

ASVGDRVTITCRASQSISSYLNWYQQKPGEAPKLLIYSASVLQSGVPSR

FSGSGSGTDFTLTISSLQPEDFATYYCQQSVMIPMTFGQGTKVEIK

[0049] In the present invention, UR is a ligand binding to a ubiquitin ligase, and may be a ligand binding to an E3 ligase selected from the group consisting of XIAP (X-linked inhibitor of apoptosis protein), VHL (von Hippel-Lindau) protein, IAPB (inhibitor of apoptosis proteins), cereblon, and MDM2 (mouse double minute 2 homolog), but is not limited thereto.

[0050] In the present invention, PEP may be an antibody or an antibody fragment, or a cell-penetrating peptide.

[0051] In the present invention, the cell-penetrating peptide is a peptide having specific ability to penetrate target disease cells, and examples of the usable cell-penetrating peptide sequence are shown in Table 1 below, but are not limited thereto.

TABLE 1

Sequence of cancer cell-penetrating peptide				
Type and location of spacer	Cancer cell-penetrating peptide (CCPP)	Amino acid sequence of spacer and cancer cell-penetrating peptide	SEQ ID NO:	Protein connection site
N term of (CCPPGGGGS)o*	H4K	GGGGS-HRRCNKNNKKR	15	C term
	H4P	GGGGS-HRRCNPNNKKR	16	C term
	LMWP	GGGGS-VSRRRRRRGGRRRR	17	C term
	hBD3-3	GGGGS-GKCSTRGRKCCRRKK	18	C term
	NRP	GGGGS-NRPDSAQFWLHHRR	19	
C term of (CCPPGGGGS)o*	H4K	HRRCNKNNKKR-GGGGS	20	N term
	H4P	HRRCNPNNKKR-GGGGS	21	N term
	LMWP	VSRRRRRRGGRRRR-GGGGS	22	N term
	hBD3-3	GKCSTRGRKCCRRKK-GGGGS	23	N term
	NRP	NRPDSAQFWLHHRRR-GGGGS	24	

(*: o is defined as 1-5 and determines the length of the spacer)

[0052] In the present invention, the antibody may bind to at least one polypeptide selected from the group consisting of EGFR, DLL3, EDAR, CLL1, BMPR1B, E16, STEAP1, 0772P, MPF, NaPi2b, Sema 5b, PSCA hlg, ETBR, MSG783, STEAP2, TrpM4, CRIPTO, CD21, CD79b, FcRH2, B7-H4, HER2, NCA, MDP, IL2ORct, brevican, EphB2R, ASLG659, PSCA, GEDA, BAFF-R, CD22, CD79a, CXCRS, HLA-DOB, P2X5, CD72, LY64, FcRH1, IRTA2, TENB2, PMEL17, TMEFF1, GDNF-Ral, Ly6E, TMEM46, Ly6G6D, LGR5, RET, LY6K, GPR19, GPR54, ASPHD1, tyrosinase, TMEM118, GPR172A, MUC16, and CD33, but the present invention is not limited thereto.

[0053] In the present invention, the antibody may be a monoclonal antibody or a variant thereof, and the monoclonal antibody may be selected from the group consisting of trastuzumab, cetuximab, rituximab, brentuximab, gemtuzumab, inotuzumab, sacituzumab, alemtuzumab, and nimotuzumab, but is not limited thereto.

[0054] In another aspect, the present invention is directed to a nucleic acid encoding the PROTAC protein.

[0055] In the present invention, the nucleic acid may be DNA, mRNA, plasmid DNA, etc., and the gene encoding the PROTAC protein, such as plasmid DNA or mRNA derived therefrom, may be delivered into cells by a cell-penetrating nanocarrier, thus exhibiting the same target protein degradation efficacy.

[0056] In the present invention, the nucleic acid may be used along with various carriers such as lipid nanoparticles (LNPs), liposomes, etc., which are known to effectively deliver oligonucleotides into cells, but the present invention is not limited thereto.

[0057] In still another aspect, the present invention is directed to a pharmaceutical composition comprising the PROTAC protein or the nucleic acid encoding the PROTAC protein.

[0058] The present invention is directed to degradation of the target protein and thus provides a wide range of pharmaceutical compositions related to the PROTAC protein according to the present invention.

[0059] In the present invention, the pharmaceutical composition may be used for the treatment or prevention of cancer or an inflammatory disease, particularly a disease selected from the group consisting of cancer, asthma, autoimmune disease, rheumatoid arthritis, multiple sclerosis, ciliary disease, cleft palate, diabetes, heart disease, hypertension, inflammatory bowel disease, mental retardation, mood disorder, obesity, refractive error, infertility, Engelman syndrome, Canavan disease, chronic digestive disorder, Charcot-Marie-Tooth disease, cystic fibrosis, Duchenne muscular dystrophy, hemochromatosis, hemophilia, Klinefelter syndrome, neurofibromatosis, phenylketonuria, autosomal dominant polycystic neoplasm (PKD1 or PKD2), Prader-Willi syndrome, sickle cell anemia, Tay-Sachs disease, Turner syndrome, HIV-infected disease, and HCV-infected disease.

[0060] In the present invention, the cancer may be selected from the group consisting of squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, hepatocellular carcinoma, renal cell carcinoma, bladder cancer, bowel cancer, breast cancer, cervical cancer, uterine cancer, colon cancer, esophageal cancer, head cancer, kidney cancer, liver cancer, lung cancer, ovary cancer, pancreatic cancer, prostate cancer, gastric cancer, leukemia, benign and malignant lymphoma, especially Burkitt lymphoma and non-Hodgkin lymphoma, benign and malignant melanoma, myeloproliferative disease, sarcoma including Ewing sarcoma, angiosarcoma, Kaposi sarcoma, liposarcoma, myoma, neuroepithelial sarcoma, synovial sarcoma, neurosarcoma, astrocytoma, oligodendrogliocytoma, ependymoma, glioblastoma, neuroblastoma, gangliocytoma, ganglioglioma, medulloblastoma, pineocytoma, meningioma, meningeal sarcoma, neurofibroma, and schwannoma, testicular cancer, thyroid cancer, carcinosarcoma, Hodgkin disease, Wilms tumor, and teratocalcinomas.

[0061] In the present invention, the inflammatory disease may be selected from the group consisting of arthritis, autoimmune disease, Parkinson's disease, dementia, hepatitis, and viral infection.

[0062] The pharmaceutical composition of the present invention may be administered via oral, parenteral, inhalation spray, topical, rectal, nasal, or implanted reservoir routes, and may be administered using nanoparticles or liposomes as a carrier upon oral or parenteral administration.

[0063] In an embodiment of the present invention, a single dose of the PROTAC protein may be 1 ng/kg to 100 mg/kg, preferably 5 ng/kg to 50 mg/kg, and administration may be performed once a day or 1-3 times a week. However, the dose and interval of administration are not limited thereto.

[0064] In yet another aspect, the present invention is directed to a method of preventing or treating a disease comprising administering the PROTAC protein or the nucleic acid encoding the PROTAC protein.

[0065] In still yet another aspect, the present invention is directed to the use of the PROTAC protein or the nucleic acid encoding the PROTAC protein for the prevention or treatment of a disease.

[0066] In even yet another aspect, the present invention is directed to the use of the PROTAC protein or the nucleic acid encoding the PROTAC protein in the manufacture of a medicament for preventing or treating a disease.

[0067] In the present invention, the disease may be cancer or an inflammatory disease, but is not limited thereto.

[0068] In the present invention, the method and use comprise the PROTAC protein or the nucleic acid encoding the same according to the present invention, and relate to the pharmaceutical composition comprising the PROTAC protein or the nucleic acid encoding the same, so a redundant description of the PROTAC protein or the nucleic acid encoding the same and the pharmaceutical composition is omitted.

[0069] A better understanding of the present invention may be obtained through the following examples. These examples are merely set forth to illustrate the present invention, and are not to be construed as limiting the scope of the present invention, as will be apparent to those of ordinary skill in the art.

Example 1: Expression of PROTAC protein with cell-penetrating Activity in animal cells (mammalian cells)

[0070] The present inventors designed an expression vector of a PROTAC protein that degrades a target protein as described below. A monoclonal antibody targeting an activated protein (KRASc 22 c) in which the 12th glycine of human KRAS is mutated to cysteine, a VHL protein binding to an E3 ligase, and cDNA including a kozak sequence that binds to ribosome and helps transcription were inserted into a pcDNA3.4 vector, cloned, and identified by DNA sequencing. To the resulting plasmid DNA sequence, a signal peptide, a linker, and a PEP sequence were added. The signal peptide was located at the N-terminus, and the monoclonal antibody targeting mutant human KRAS G12C, VHL, and PEP linked by linkers of various lengths were cloned in various locations. A CHO-S cell line was transfected with the plasmid thus constructed (FIG. **1**), followed by culture for 7 days with addition of an enhancer.

[0071] The expressed PROTAC protein was measured by Western blotting using anti-His tag antibody (Abcam, ab18184) and anti-VHL antibody (Invitrogen, MA5-13940), and the results of Western blotting are shown in FIG. **2**. The theoretical protein size is 56 kDa, and the PROTAC protein began to appear from the 3rd day of culture. His tag did not appear after 5 days of culture, indicating that it was cleaved from the protein.

Example 2: Confirmation of cancer cell growth inhibitory effect by PROTAC protein

[0072] Cancer cells were transfected with a plasmid encoding PROTAC, and an MTT assay was performed to evaluate the anticancer effect of the PROTAC protein expressed by the plasmid. 5×10^3 H358 cells (ATCC, CRL-5807), non-small cell lung cancer cells having the phenotype of human $KRAS^{G12C}$, were transfected with various amounts of plasmid using Lipofectamine 3000 (Invitrogen, L3000001), and after 72 hours, cell viability was evaluated through MTT assay (FIG. **3**). H358 cell viability decreased with an increase in the concentration of the treated plasmid. Therefore, it was confirmed that the PROTAC protein was expressed by the plasmid introduced into the cells and thus acted.

Example 3: Confirmation of KRAS signaling inhibitory effect by PROTAC protein

[0073] In order to confirm degradation of the target protein by the PROTAC protein expressed in cells, H358 cells (ATCC, CRL-5807), non-small cell lung cancer cells having the phenotype of human $KRAS^{G12C}$, were transfected with the plasmid DNA constructed in Example 1 using Lipofectamine 3000 (Invitrogen, L3000001). After transfection, the cells were lysed at 16, 24, and 48 hours to obtain cell lysates.

[0074] In order to isolate active KRAS, 80 μg of GST-Rafl-RBD was added using an active GTPase kit (Cell Signaling, 11860S), and 500 μg of protein was dispensed into a spin cup. After reaction at 4° C. for 1 hour and then centrifugation at 6000× g for 15 seconds, the column was transferred to a new tube, and 400 μl of **1**× lysis buffer was added thereto. After centrifugation at 6000× g for 15 seconds, the column was transferred to a new tube, and 50 μl of 2× SDS buffer (a mixture of 200 μl of 5× SDS sample loading dye and 300 μl of water) was dispensed and then allowed to react for 2 minutes. After centrifugation at 6000× g for 2 minutes, heating was performed at 100° C. for 7 minutes. Proteins (protein loading volume: 20 μl/lane) were electrophoretically separated by 11% SDS-PAGE and transferred to a nitrocellulose membrane. In order to measure ERK½ corresponding to a subsignal of KRAS, 30 μg of protein was electrophoresed by 11% SDS-PAGE and transferred to a nitrocellulose membrane. Blocking was performed for 1 hour with 5% skim milk dissolved in T-TBS, and the primary antibody was diluted 1:1000 in T-TBS and allowed to react overnight while inverting at 4° C. After washing with T-TBS three times for 10 minutes, the secondary antibody was diluted 1:3000 in T-TBS and allowed to react for 1 hour while inverting at room temperature. After washing with T-TBS three times for 10 minutes, chemiluminescence was performed with an ECL substrate (Thermo, 34580) and confirmed with Amersham Imager 680 (GE). Information on the antibodies used is shown in Table 2 below.

TABLE 2

Antibody information used

	Antibody name	Company	Catalog number
1	GST	Abcam	ab19256
2	Active KRAS	Santa cruz	SC-30
3	pan RAS(E4K9L)	Cell signaling	3965S
4	anti-His tag antibody	abcam	ab18184
5	GAPDH	Santa cruz	sc-47724
6	Goat anti-Rabbit IgG	BETHYL	A120-101P
7	Goat anti-Mouse IgG	BETHYL	A90-116P

[0075] Using immunoblotting, the PROTAC protein was identified with anti-His tag antibody, and pan KRAS or active KRAS in the cells were identified (FIG. **4**). As the PROTAC protein was expressed, the expression level of active KRAS decreased, but pan KRAS did not change. Therefore, it was confirmed that the PROTAC protein selectively degraded only active KRAS and did not degrade normal pan KRAS.

Example 4: Introduction of mRNA encoding PROTAC protein into cells

[0076] In order to express a PROTAC protein in cells, mRNA was constructed instead of the plasmid. Stability of mRNA was increased by adding 5' capping and 3' poly A tail. Transfection was performed using Lipofectamine MessengerMAX (Invitrogen, LMRNA003). 24 hours after transfection, the cells were lysed to obtain cell lysate. Active KRAS was screened in the same manner as in the method described in Example 3. Using immunoblotting, the PROTAC protein expressed by mRNA introduced into the cells was identified with anti-His tag antibody (Abcam). It was confirmed that the expression level of active KRAS decreased as the PROTAC protein was expressed (FIG. **5**). The PROTAC protein introduced in the form of mRNA was expressed and thus active KRAS, which is the target protein, was degraded.

INDUSTRIAL APPLICABILITY

[0077] According to the present invention, a PROTAC protein has high solubility compared to PROTAC constructed by conventional methods, and can efficiently degrade intrinsic disease protein when applied to cells, and is thus effective for the treatment of cancer or an inflammatory disease.

[0078] Having described specific parts of the present invention in detail above, it will be obvious to those skilled in the art that these specific descriptions are only preferred embodiments, and the scope of the present invention is not limited thereby. Accordingly, the substantial scope of the present invention will be defined by the appended claims and equivalents thereto.

SEQUENCE LIST FREE TEXT

[0079] An electronic file is attached.

SEQUENCE LISTING

<160> NUMBER OF SEQ ID NOS: 24

<210> SEQ ID NO 1
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<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: chimera protein

<400> SEQUENCE: 1

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Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Thr Phe
            20                  25                  30

Ser Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Tyr Ile Ser Arg Thr Ser Lys Thr Ile Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Gly Arg Phe Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
            100                 105                 110

Val Ser Ser Gly Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu
        115                 120                 125

Ser Lys Ser Thr Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser
    130                 135                 140
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Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala
145                 150                 155                 160

Ser Gln Ser Ile Ser Ser Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly
                165                 170                 175

Glu Ala Pro Lys Leu Leu Ile Tyr Ser Ala Ser Val Leu Gln Ser Gly
            180                 185                 190

Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu
        195                 200                 205

Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln
    210                 215                 220

Gln Ser Val Met Ile Pro Met Thr Phe Gly Gln Gly Thr Lys Val Glu
225                 230                 235                 240

Ile Lys Gly Ser Gly Gly Gly Gly Ser Met Pro Arg Arg Ala Glu Asn
                245                 250                 255

Trp Asp Glu Ala Glu Val Gly Ala Glu Glu Ala Gly Val Glu Glu Tyr
            260                 265                 270

Gly Pro Glu Glu Asp Gly Gly Glu Glu Ser Gly Ala Glu Glu Ser Gly
        275                 280                 285

Pro Glu Glu Ser Gly Pro Glu Glu Leu Gly Ala Glu Glu Glu Met Glu
    290                 295                 300

Ala Gly Arg Pro Arg Pro Val Leu Arg Ser Val Asn Ser Arg Glu Pro
305                 310                 315                 320

Ser Gln Val Ile Phe Cys Asn Arg Ser Pro Arg Val Val Leu Pro Val
                325                 330                 335

Trp Leu Asn Phe Asp Gly Glu Pro Gln Pro Tyr Pro Thr Leu Pro Pro
            340                 345                 350

Gly Thr Gly Arg Arg Ile His Ser Tyr Arg Gly His Leu Trp Leu Phe
        355                 360                 365

Arg Asp Ala Gly Thr His Asp Gly Leu Leu Val Asn Gln Thr Glu Leu
    370                 375                 380

Phe Val Pro Ser Leu Asn Val Asp Gly Gln Pro Ile Phe Ala Asn Ile
385                 390                 395                 400

Thr Leu Pro Val Tyr Thr Leu Lys Glu Arg Cys Leu Gln Val Val Arg
                405                 410                 415

Ser Leu Val Lys Pro Glu Asn Tyr Arg Arg Leu Asp Ile Val Arg Ser
            420                 425                 430

Leu Tyr Glu Asp Leu Glu Asp His Pro Asn Val Gln Lys Asp Leu Glu
        435                 440                 445

Arg Leu Thr Gln Glu Arg Ile Ala His Gln Arg Met Gly Asp Glu Asn
    450                 455                 460

Leu Tyr Phe Gln Gly Gly Ser Gly Gly Ser Gly Gly Ser His His His
465                 470                 475                 480

His His His His His
                485


<210> SEQ ID NO 2
<211> LENGTH: 523
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: chimera protein

<400> SEQUENCE: 2
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Ile Gln Ala Val Ser Arg Arg Arg Arg Arg Arg Gly Gly Arg Arg Arg
            20                  25                  30

Arg Gly Gly Gly Gly Ser Glu Val Gln Leu Leu Glu Ser Gly Gly Gly
        35                  40                  45

Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly
    50                  55                  60

Phe Thr Phe Ser Thr Phe Ser Met Asn Trp Val Arg Gln Ala Pro Gly
65                  70                  75                  80

Lys Gly Leu Glu Trp Val Ser Tyr Ile Ser Arg Thr Ser Lys Thr Ile
                85                  90                  95

Tyr Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn
            100                 105                 110

Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
        115                 120                 125

Thr Ala Val Tyr Tyr Cys Ala Arg Gly Arg Phe Phe Asp Tyr Trp Gly
    130                 135                 140

Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Ser Glu Gly Lys Ser
145                 150                 155                 160

Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Gly Gly Ser Asp Ile Gln
                165                 170                 175

Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val
            180                 185                 190

Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr Leu Asn Trp
        195                 200                 205

Tyr Gln Gln Lys Pro Gly Glu Ala Pro Lys Leu Leu Ile Tyr Ser Ala
    210                 215                 220

Ser Val Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser
225                 230                 235                 240

Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe
                245                 250                 255

Ala Thr Tyr Tyr Cys Gln Gln Ser Val Met Ile Pro Met Thr Phe Gly
            260                 265                 270

Gln Gly Thr Lys Val Glu Ile Lys Gly Ser Gly Gly Gly Gly Ser Met
        275                 280                 285

Pro Arg Arg Ala Glu Asn Trp Asp Glu Ala Glu Val Gly Ala Glu Glu
    290                 295                 300

Ala Gly Val Glu Glu Tyr Gly Pro Glu Glu Asp Gly Gly Glu Glu Ser
305                 310                 315                 320

Gly Ala Glu Glu Ser Gly Pro Glu Glu Ser Gly Pro Glu Glu Leu Gly
                325                 330                 335

Ala Glu Glu Glu Met Glu Ala Gly Arg Pro Arg Pro Val Leu Arg Ser
            340                 345                 350

Val Asn Ser Arg Glu Pro Ser Gln Val Ile Phe Cys Asn Arg Ser Pro
        355                 360                 365

Arg Val Val Leu Pro Val Trp Leu Asn Phe Asp Gly Glu Pro Gln Pro
    370                 375                 380

Tyr Pro Thr Leu Pro Pro Gly Thr Gly Arg Arg Ile His Ser Tyr Arg
385                 390                 395                 400

Gly His Leu Trp Leu Phe Arg Asp Ala Gly Thr His Asp Gly Leu Leu
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                405                 410                 415

Val Asn Gln Thr Glu Leu Phe Val Pro Ser Leu Asn Val Asp Gly Gln
            420                 425                 430

Pro Ile Phe Ala Asn Ile Thr Leu Pro Val Tyr Thr Leu Lys Glu Arg
        435                 440                 445

Cys Leu Gln Val Val Arg Ser Leu Val Lys Pro Glu Asn Tyr Arg Arg
    450                 455                 460

Leu Asp Ile Val Arg Ser Leu Tyr Glu Asp Leu Glu Asp His Pro Asn
465                 470                 475                 480

Val Gln Lys Asp Leu Glu Arg Leu Thr Gln Glu Arg Ile Ala His Gln
                485                 490                 495

Arg Met Gly Asp Glu Asn Leu Tyr Phe Gln Gly Gly Ser Gly Gly Ser
            500                 505                 510

Gly Gly Ser His His His His His His His His
        515                 520


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<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: chimera protein

<400> SEQUENCE: 3

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1               5                   10                  15

Ile Gln Ala Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln
            20                  25                  30

Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
        35                  40                  45

Ser Thr Phe Ser Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
    50                  55                  60

Glu Trp Val Ser Tyr Ile Ser Arg Thr Ser Lys Thr Ile Tyr Tyr Ala
65                  70                  75                  80

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn
                85                  90                  95

Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
            100                 105                 110

Tyr Tyr Cys Ala Arg Gly Arg Phe Phe Asp Tyr Trp Gly Gln Gly Thr
        115                 120                 125

Leu Val Thr Val Ser Ser Gly Gly Ser Glu Gly Lys Ser Ser Gly Ser
    130                 135                 140

Gly Ser Glu Ser Lys Ser Thr Gly Gly Ser Asp Ile Gln Met Thr Gln
145                 150                 155                 160

Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr
                165                 170                 175

Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr Leu Asn Trp Tyr Gln Gln
            180                 185                 190

Lys Pro Gly Glu Ala Pro Lys Leu Leu Ile Tyr Ser Ala Ser Val Leu
        195                 200                 205

Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp
    210                 215                 220

Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr
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225                 230                 235                 240

Tyr Cys Gln Gln Ser Val Met Ile Pro Met Thr Phe Gly Gln Gly Thr
                245                 250                 255

Lys Val Glu Ile Lys Gly Ser Gly Gly Gly Gly Ser Met Pro Arg Arg
            260                 265                 270

Ala Glu Asn Trp Asp Glu Ala Glu Val Gly Ala Glu Glu Ala Gly Val
        275                 280                 285

Glu Glu Tyr Gly Pro Glu Glu Asp Gly Gly Glu Glu Ser Gly Ala Glu
    290                 295                 300

Glu Ser Gly Pro Glu Glu Ser Gly Pro Glu Glu Leu Gly Ala Glu Glu
305                 310                 315                 320

Glu Met Glu Ala Gly Arg Pro Arg Pro Val Leu Arg Ser Val Asn Ser
                325                 330                 335

Arg Glu Pro Ser Gln Val Ile Phe Cys Asn Arg Ser Pro Arg Val Val
            340                 345                 350

Leu Pro Val Trp Leu Asn Phe Asp Gly Glu Pro Gln Pro Tyr Pro Thr
        355                 360                 365

Leu Pro Pro Gly Thr Gly Arg Arg Ile His Ser Tyr Arg Gly His Leu
    370                 375                 380

Trp Leu Phe Arg Asp Ala Gly Thr His Asp Gly Leu Leu Val Asn Gln
385                 390                 395                 400

Thr Glu Leu Phe Val Pro Ser Leu Asn Val Asp Gly Gln Pro Ile Phe
                405                 410                 415

Ala Asn Ile Thr Leu Pro Val Tyr Thr Leu Lys Glu Arg Cys Leu Gln
            420                 425                 430

Val Val Arg Ser Leu Val Lys Pro Glu Asn Tyr Arg Arg Leu Asp Ile
        435                 440                 445

Val Arg Ser Leu Tyr Glu Asp Leu Glu Asp His Pro Asn Val Gln Lys
    450                 455                 460

Asp Leu Glu Arg Leu Thr Gln Glu Arg Ile Ala His Gln Arg Met Gly
465                 470                 475                 480

Asp Gly Gly Gly Gly Ser Val Ser Arg Arg Arg Arg Arg Arg Gly Gly
                485                 490                 495

Arg Arg Arg Arg Glu Asn Leu Tyr Phe Gln Gly Gly Ser Gly Gly Ser
            500                 505                 510

Gly Gly Ser His His His His His His His His
        515                 520


<210> SEQ ID NO 4
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: chimera protein

<400> SEQUENCE: 4

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Thr Phe
            20                  25                  30

Ser Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Tyr Ile Ser Arg Thr Ser Lys Thr Ile Tyr Tyr Ala Asp Ser Val
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    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Gly Arg Phe Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
            100                 105                 110

Val Ser Ser Gly Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu
        115                 120                 125

Ser Lys Ser Thr Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser
    130                 135                 140

Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala
145                 150                 155                 160

Ser Gln Ser Ile Ser Ser Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly
                165                 170                 175

Glu Ala Pro Lys Leu Leu Ile Tyr Ser Ala Ser Val Leu Gln Ser Gly
            180                 185                 190

Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu
        195                 200                 205

Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln
    210                 215                 220

Gln Ser Val Met Ile Pro Met Thr Phe Gly Gln Gly Thr Lys Val Glu
225                 230                 235                 240

Ile Lys Gly Ser Gly Gly Gly Gly Ser Met Glu Asn Arg Trp Gln Val
                245                 250                 255

Met Ile Val Trp Gln Val Asp Arg Met Arg Ile Arg Thr Trp Lys Ser
            260                 265                 270

Leu Val Lys His His Met Tyr Val Ser Gly Lys Ala Arg Gly Trp Phe
        275                 280                 285

Tyr Arg His His Tyr Glu Ser Pro His Pro Arg Ile Ser Ser Glu Val
    290                 295                 300

His Ile Pro Leu Gly Asp Ala Arg Leu Val Ile Thr Thr Tyr Trp Gly
305                 310                 315                 320

Leu His Thr Gly Glu Arg Asp Trp His Leu Gly Gln Gly Val Ser Ile
                325                 330                 335

Glu Trp Arg Lys Lys Arg Tyr Ser Thr Gln Val Asp Pro Glu Leu Ala
            340                 345                 350

Asp Gln Leu Ile His Leu Tyr Tyr Phe Asp Cys Phe Ser Asp Ser Ala
        355                 360                 365

Ile Arg Lys Ala Leu Leu Gly His Ile Val Ser Pro Arg Cys Glu Tyr
    370                 375                 380

Gln Ala Gly His Asn Lys Val Gly Ser Leu Gln Tyr Leu Ala Leu Ala
385                 390                 395                 400

Ala Leu Ile Thr Pro Lys Lys Ile Lys Pro Pro Leu Pro Ser Val Thr
                405                 410                 415

Lys Leu Thr Glu Asp Arg Trp Asn Lys Pro Gln Lys Thr Lys Gly His
            420                 425                 430

Arg Gly Ser His Thr Met Asn Gly His Glu Asn Leu Tyr Phe Gln Gly
        435                 440                 445

Gly Ser Gly Gly Ser Gly Gly Ser His His His His His His His His
    450                 455                 460
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<210> SEQ ID NO 5
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<212> TYPE: PRT
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<220> FEATURE:
<223> OTHER INFORMATION: chimera protein

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Ile Gln Ala Val Ser Arg Arg Arg Arg Arg Arg Arg Gly Gly Arg Arg Arg
20 25 30

Arg Gly Gly Gly Gly Ser Glu Val Gln Leu Leu Glu Ser Gly Gly Gly
35 40 45

Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly
50 55 60

Phe Thr Phe Ser Thr Phe Ser Met Asn Trp Val Arg Gln Ala Pro Gly
65 70 75 80

Lys Gly Leu Glu Trp Val Ser Tyr Ile Ser Arg Thr Ser Lys Thr Ile
85 90 95

Tyr Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn
100 105 110

Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
115 120 125

Thr Ala Val Tyr Tyr Cys Ala Arg Gly Arg Phe Phe Asp Tyr Trp Gly
130 135 140

Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Ser Glu Gly Lys Ser
145 150 155 160

Ser Gly Ser Gly Ser Glu Ser Lys Ser Thr Gly Gly Ser Asp Ile Gln
165 170 175

Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val
180 185 190

Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr Leu Asn Trp
195 200 205

Tyr Gln Gln Lys Pro Gly Glu Ala Pro Lys Leu Leu Ile Tyr Ser Ala
210 215 220

Ser Val Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser
225 230 235 240

Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe
245 250 255

Ala Thr Tyr Tyr Cys Gln Gln Ser Val Met Ile Pro Met Thr Phe Gly
260 265 270

Gln Gly Thr Lys Val Glu Ile Lys Gly Ser Gly Gly Gly Gly Ser Met
275 280 285

Glu Asn Arg Trp Gln Val Met Ile Val Trp Gln Val Asp Arg Met Arg
290 295 300

Ile Arg Thr Trp Lys Ser Leu Val Lys His His Met Tyr Val Ser Gly
305 310 315 320

Lys Ala Arg Gly Trp Phe Tyr Arg His His Tyr Glu Ser Pro His Pro
325 330 335

Arg Ile Ser Ser Glu Val His Ile Pro Leu Gly Asp Ala Arg Leu Val
340 345 350

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Ile Thr Thr Tyr Trp Gly Leu His Thr Gly Glu Arg Asp Trp His Leu
        355                 360                 365

Gly Gln Gly Val Ser Ile Glu Trp Arg Lys Lys Arg Tyr Ser Thr Gln
    370                 375                 380

Val Asp Pro Glu Leu Ala Asp Gln Leu Ile His Leu Tyr Tyr Phe Asp
385                 390                 395                 400

Cys Phe Ser Asp Ser Ala Ile Arg Lys Ala Leu Leu Gly His Ile Val
                405                 410                 415

Ser Pro Arg Cys Glu Tyr Gln Ala Gly His Asn Lys Val Gly Ser Leu
            420                 425                 430

Gln Tyr Leu Ala Leu Ala Ala Leu Ile Thr Pro Lys Lys Ile Lys Pro
        435                 440                 445

Pro Leu Pro Ser Val Thr Lys Leu Thr Glu Asp Arg Trp Asn Lys Pro
    450                 455                 460

Gln Lys Thr Lys Gly His Arg Gly Ser His Thr Met Asn Gly His Glu
465                 470                 475                 480

Asn Leu Tyr Phe Gln Gly Gly Ser Gly Gly Ser Gly Gly Ser His His
                485                 490                 495

His His His His His His
            500


<210> SEQ ID NO 6
<211> LENGTH: 502
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: chimera protein

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Ile Gln Ala Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln
            20                  25                  30

Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
        35                  40                  45

Ser Thr Phe Ser Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
    50                  55                  60

Glu Trp Val Ser Tyr Ile Ser Arg Thr Ser Lys Thr Ile Tyr Tyr Ala
65                  70                  75                  80

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn
                85                  90                  95

Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
            100                 105                 110

Tyr Tyr Cys Ala Arg Gly Arg Phe Phe Asp Tyr Trp Gly Gln Gly Thr
        115                 120                 125

Leu Val Thr Val Ser Ser Gly Gly Ser Glu Gly Lys Ser Ser Gly Ser
    130                 135                 140

Gly Ser Glu Ser Lys Ser Thr Gly Gly Ser Asp Ile Gln Met Thr Gln
145                 150                 155                 160

Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr
                165                 170                 175

Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr Leu Asn Trp Tyr Gln Gln
            180                 185                 190
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Lys Pro Gly Glu Ala Pro Lys Leu Leu Ile Tyr Ser Ala Ser Val Leu
        195                 200                 205

Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp
    210                 215                 220

Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr
225                 230                 235                 240

Tyr Cys Gln Gln Ser Val Met Ile Pro Met Thr Phe Gly Gln Gly Thr
                245                 250                 255

Lys Val Glu Ile Lys Gly Ser Gly Gly Gly Gly Ser Met Glu Asn Arg
            260                 265                 270

Trp Gln Val Met Ile Val Trp Gln Val Asp Arg Met Arg Ile Arg Thr
        275                 280                 285

Trp Lys Ser Leu Val Lys His His Met Tyr Val Ser Gly Lys Ala Arg
    290                 295                 300

Gly Trp Phe Tyr Arg His His Tyr Glu Ser Pro His Pro Arg Ile Ser
305                 310                 315                 320

Ser Glu Val His Ile Pro Leu Gly Asp Ala Arg Leu Val Ile Thr Thr
                325                 330                 335

Tyr Trp Gly Leu His Thr Gly Glu Arg Asp Trp His Leu Gly Gln Gly
            340                 345                 350

Val Ser Ile Glu Trp Arg Lys Lys Arg Tyr Ser Thr Gln Val Asp Pro
        355                 360                 365

Glu Leu Ala Asp Gln Leu Ile His Leu Tyr Tyr Phe Asp Cys Phe Ser
    370                 375                 380

Asp Ser Ala Ile Arg Lys Ala Leu Leu Gly His Ile Val Ser Pro Arg
385                 390                 395                 400

Cys Glu Tyr Gln Ala Gly His Asn Lys Val Gly Ser Leu Gln Tyr Leu
                405                 410                 415

Ala Leu Ala Ala Leu Ile Thr Pro Lys Lys Ile Lys Pro Pro Leu Pro
            420                 425                 430

Ser Val Thr Lys Leu Thr Glu Asp Arg Trp Asn Lys Pro Gln Lys Thr
        435                 440                 445

Lys Gly His Arg Gly Ser His Thr Met Asn Gly His Gly Gly Gly Gly
    450                 455                 460

Ser Val Ser Arg Arg Arg Arg Arg Arg Arg Gly Gly Arg Arg Arg Arg Glu
465                 470                 475                 480

Asn Leu Tyr Phe Gln Gly Gly Ser Gly Gly Ser Gly Gly Ser His His
                485                 490                 495

His His His His His His
            500


<210> SEQ ID NO 7
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: binder that binds to the RAS superfamily

<400> SEQUENCE: 7

Leu Thr Pro His Lys His His Lys His Leu His Ala
1               5                   10


<210> SEQ ID NO 8
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<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: binder that binds to the RAS superfamily

<400> SEQUENCE: 8

Trp Pro Gly Lys His His Asn His Tyr Leu Arg Ser
1 5 10

<210> SEQ ID NO 9
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: binder that binds to the RAS superfamily

<400> SEQUENCE: 9

His Asp Gly Tyr Trp Trp His Ser Met Thr Met Trp
1 5 10

<210> SEQ ID NO 10
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: binder that binds to the RAS superfamily

<400> SEQUENCE: 10

Leu Ile His Pro Met Thr Val Lys His Val His Leu
1 5 10

<210> SEQ ID NO 11
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: binder that binds to the RAS superfamily

<400> SEQUENCE: 11

Gly Ser His Trp His Phe Pro Lys His Gln Gln Gln
1 5 10

<210> SEQ ID NO 12
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: binder that binds to the RAS superfamily

<400> SEQUENCE: 12

Gly Ser His Trp His Phe Pro Lys His Gln Gln His
1 5 10

<210> SEQ ID NO 13
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: binder that binds to the RAS superfamily

<400> SEQUENCE: 13

Trp Pro Gly Lys His His His His Tyr Leu Arg Arg
1 5 10

-continued

<210> SEQ ID NO 14
<211> LENGTH: 242
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: binder that binds to the RAS superfamily

<400> SEQUENCE: 14

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Thr Phe
20 25 30

Ser Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Tyr Ile Ser Arg Thr Ser Lys Thr Ile Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Arg Phe Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser Gly Gly Ser Glu Gly Lys Ser Ser Gly Ser Gly Ser Glu
115 120 125

Ser Lys Ser Thr Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser
130 135 140

Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala
145 150 155 160

Ser Gln Ser Ile Ser Ser Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly
165 170 175

Glu Ala Pro Lys Leu Leu Ile Tyr Ser Ala Ser Val Leu Gln Ser Gly
180 185 190

Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu
195 200 205

Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln
210 215 220

Gln Ser Val Met Ile Pro Met Thr Phe Gly Gln Gly Thr Lys Val Glu
225 230 235 240

Ile Lys

<210> SEQ ID NO 15
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Cancer Cell-penetrating functional peptide

<400> SEQUENCE: 15

Gly Gly Gly Gly Ser His Arg Arg Cys Asn Lys Asn Asn Lys Lys Arg
1 5 10 15

<210> SEQ ID NO 16
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: Cancer Cell-penetrating functional peptide

<400> SEQUENCE: 16

Gly Gly Gly Gly Ser His Arg Arg Cys Asn Pro Asn Asn Lys Lys Arg
1 5 10 15

<210> SEQ ID NO 17
<211> LENGTH: 19
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Cancer Cell-penetrating functional peptide

<400> SEQUENCE: 17

Gly Gly Gly Gly Ser Val Ser Arg Arg Arg Arg Arg Arg Gly Gly Arg
1 5 10 15

Arg Arg Arg

<210> SEQ ID NO 18
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Cancer Cell-penetrating functional peptide

<400> SEQUENCE: 18

Gly Gly Gly Gly Ser Gly Lys Cys Ser Thr Arg Gly Arg Lys Cys Cys
1 5 10 15

Arg Arg Lys Lys
20

<210> SEQ ID NO 19
<211> LENGTH: 19
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Cancer Cell-penetrating functional peptide

<400> SEQUENCE: 19

Gly Gly Gly Gly Ser Asn Arg Pro Asp Ser Ala Gln Phe Trp Leu His
1 5 10 15

His Arg Arg

<210> SEQ ID NO 20
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Cancer Cell-penetrating functional peptide

<400> SEQUENCE: 20

His Arg Arg Cys Asn Lys Asn Asn Lys Lys Arg Gly Gly Gly Gly Ser
1 5 10 15

<210> SEQ ID NO 21
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Cancer Cell-penetrating functional peptide

<400> SEQUENCE: 21

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His Arg Arg Cys Asn Pro Asn Asn Lys Lys Arg Gly Gly Gly Gly Ser
1               5                   10                  15


<210> SEQ ID NO 22
<211> LENGTH: 19
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Cancer Cell-penetrating functional peptide

<400> SEQUENCE: 22

Val Ser Arg Arg Arg Arg Arg Arg Gly Gly Arg Arg Arg Arg Gly Gly
1               5                   10                  15

Gly Gly Ser


<210> SEQ ID NO 23
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Cancer Cell-penetrating functional peptide

<400> SEQUENCE: 23

Gly Lys Cys Ser Thr Arg Gly Arg Lys Cys Cys Arg Arg Lys Lys Gly
1               5                   10                  15

Gly Gly Gly Ser
            20


<210> SEQ ID NO 24
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Cancer Cell-penetrating functional peptide

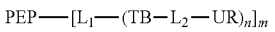
<400> SEQUENCE: 24

Asn Arg Pro Asp Ser Ala Gln Phe Trp Leu His His Arg Arg Arg Gly
1               5                   10                  15

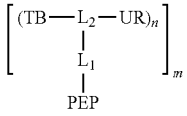
Gly Gly Gly Ser
            20
```

1. A PROTAC protein having a structure of Chemical Formula 1 or Chemical Formula 2 below:

[Chemical Formula 1]



[Chemical Formula 2]



in Chemical Formula 1 or Chemical Formula 2,

(i) PEP is an antibody or an antibody fragment, or a cell-penetrating peptide,

(ii) L_1 and L_2 are linkers, L_1 and L_2 are same as or different from each other, and L_1 binds to TB or L_2,

(iii) TB is a binder or conjugate that binds to a target protein,

(iv) UR is a ligand binding to a ubiquitin ligase, and

(v) n and m are each independently an integer of 1 to 10.

2. The PROTAC protein according to claim **1**, wherein the target protein is selected from the group consisting of a mutated RAS superfamily, a kinase, a transcription factor, and a phosphatase.

3. The PROTAC protein according to claim **2**, wherein the RAS superfamily is selected from the group consisting of KRAS, HRAS, and NRAS.

4. The PROTAC protein according to claim **1**, wherein the TB is selected from the group consisting of a mutated RAS superfamily inhibitor, a kinase inhibitor, a phosphatase inhibitor, a heat shock protein 90 inhibitor, an MDM2 inhibitor, an HDAC inhibitor, a human lysine methyltransferase inhibitor, an angiogenesis inhibitor, an immunosuppressive compound, a compound targeting human BET bromodomain-containing protein, a compound targeting aryl hydrocarbon receptor, a compound targeting EGF (epithelial growth factor) receptor kinase, a compound targeting FKBP, a compound targeting androgen receptor, a compound targeting estrogen receptor, a compound targeting thyroid hormone receptor, a compound targeting HIV protease, a compound targeting HIV integrase, a compound targeting

HCV protease, a compound targeting acyl-protein thioesterase-1, and a compound targeting acyl-protein thioesterase-2.

5. The PROTAC protein according to claim **1**, wherein the TB is a peptide comprising any one amino acid selected from SEQ ID NO: 7 to SEQ ID NO: 14.

6. The PROTAC protein according to claim **1**, wherein the UR is a ligand binding to an E3 ligase selected from the group consisting of XIAP, VHL protein, IAPB, cereblon, and MDM2.

7. The PROTAC protein according to claim **1**, wherein the antibody is an antibody or a fragment thereof binding to at least one polypeptide selected from the group consisting of EGFR, DLL3, EDAR, CLL1, BMPR1B, E16, STEAP1, 0772P, MPF, NaPi2b, Sema 5b, PSCA hlg, ETBR, MSG783, STEAP2, TrpM4, CRIPTO, CD21, CD79b, FcRH2, B7-H4, HER2, NCA, MDP, IL20Rct, brevican, EphB2R, ASLG659, PSCA, GEDA, BAFF-R, CD22, CD79a, CXCRS, HLA-DOB, P2X5, CD72, LY64, FcRH1, IRTA2, TENB2, PMEL17, TMEFF1, GDNF-Ral, Ly6E, TMEM46, Ly6G6D, LGRS, RET, LY6K, GPR19, GPR54, ASPHD1, tyrosinase, TMEM118, GPR172A, MUC16, and CD33.

8. The PROTAC protein according to claim **7**, wherein the antibody is a monoclonal antibody or a variant thereof

9. The PROTAC protein according to claim **8**, wherein the monoclonal antibody is selected from the group consisting of trastuzumab, cetuximab, rituximab, brentuximab, gemtuzumab, inotuzumab, sacituzumab, alemtuzumab, and nimotuzumab.

10. A nucleic acid encoding the PROTAC protein according to claim **1**.

11. A pharmaceutical composition comprising the PROTAC protein according to claim **1**.

12. The pharmaceutical composition according to claim **11**, in which used to treat or prevent cancer or an inflammatory disease.

13. The pharmaceutical composition according to claim **12**, in which used to treat or prevent a disease selected from the group consisting of cancer, asthma, autoimmune disease, rheumatoid arthritis, multiple sclerosis, ciliary disease, cleft palate, diabetes, heart disease, hypertension, inflammatory bowel disease, mental retardation, mood disorder, obesity, refractive error, infertility, Engelman syndrome, Canavan disease, chronic digestive disorder, Charcot-Marie-Tooth disease, cystic fibrosis, Duchenne muscular dystrophy, hemochromatosis, hemophilia, Klinefelter syndrome, neurofibromatosis, phenylketonuria, autosomal dominant polycystic neoplasm (PKD1 or PKD2), Prader-Willi syndrome, sickle cell anemia, Tay-Sachs disease, Turner syndrome, HIV-infected disease, and HCV-infected disease.

14. The pharmaceutical composition according to claim **12**, wherein the cancer is selected from the group consisting of squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, hepatocellular carcinoma, renal cell carcinoma, bladder cancer, bowel cancer, breast cancer, cervical cancer, uterine cancer, colon cancer, esophageal cancer, head cancer, kidney cancer, liver cancer, lung cancer, ovary cancer, pancreatic cancer, prostate cancer, gastric cancer, leukemia, benign and malignant lymphoma, benign and malignant melanoma, myeloproliferative disease, sarcoma including Ewing sarcoma, angiosarcoma, Kaposi sarcoma, liposarcoma, myoma, neuroepithelial sarcoma, synovial sarcoma, neurosarcoma, astrocytoma, oligodendrogliocytoma, ependymoma, glioblastoma, neuroblastoma, gangliocytoma, ganglioglioma, medulloblastoma, pineocytoma, meningioma, meningeal sarcoma, neurofibroma, and schwannoma, testicular cancer, thyroid cancer, carcinosarcoma, Hodgkin disease, Wilms tumor, and teratocalcinomas.

15. The pharmaceutical composition according to claim **12**, wherein the inflammatory disease is selected from the group consisting of arthritis, autoimmune disease, Parkinson's disease, dementia, hepatitis, and viral infection.

16. The pharmaceutical composition according to claim **12**, in which administered via oral, parenteral, inhalation spray, topical, rectal, nasal, or implanted reservoir routes.

17. The pharmaceutical composition according to claim **16**, in which administered using nanoparticles or liposomes as a carrier upon oral or parenteral administration.

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