

A TARGETING CONJUGATE WITH A HYDROPHILIC POLYMER BONDED TO A FLAVONOID

BACKGROUND OF THE INVENTION

5

1. Field of the invention

The present invention generally relates to pharmaceuticals, more specifically, to targeted therapeutic formulations and ligands thereof.

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2. Description of the prior art

Tumor incidence is rising in recent years. Chemotherapy is one of the main treatment of tumors, but limited by poor water solubility and high side effects in clinical application.

15 Flavonoids, especially catechins, for cancer treatment have been studied in recent years. Among tea catechins, (-)-epigallallocatechin-3-gallate (EGCG) is the most abundant and has been regarded to play a major role in the beneficial effects of green tea. Numerous studies have demonstrated that EGCG possesses antioxidant, antidiabetic, antibacterial, anti-inflammatory and hypocholesterolemic effects. Moreover, it has been shown to effectively inhibit
20 tumor growth and metastasis by targeting multiple signal transduction pathways essential for cancer cell survival.

WO2015171079 discloses a micellar nanocomplexes comprising a micelle

and an agent encapsulated within said micelle, said micelle comprising a polymer-flavonoid conjugate to achieve a desired EGCG plasma concentration for therapeutic effect.

WO9515979 discloses a method of increasing highly toxic active agent
5 localization at a target cell site, which method based on the administration of a first conjugate comprising the specific target molecule conjugated with a ligand or an anti-ligand followed by the administration of a second conjugate consisting of the toxic agent bound to an anti-ligand or to the ligand.

WO9913329 discloses a method of identifying a tumor homing molecule
10 that homes to angiogenic vasculature by contacting a substantially purified NGR receptor, where the presence of specific binding identifies the molecule as a tumor homing molecule that homes to angiogenic vasculature.

Target therapy for cancer cells or their associated biomarkers can be used to treat different types of cancer. There is therefore a need to provide a targeting
15 flavonoid conjugate to be drug or to manufacture drug delivery system, especially molecular targeted intervention and nanocarrier drug delivery, which overcomes or at least ameliorates, one or more of the disadvantages described above.

SUMMARY OF THE INVENTION

20 According to one aspect of the present invention there is provided a targeting conjugate comprising: (1) tumor targeting moiety (TTM), (2) hydrophilic polymer linked to said tumor targeting molecular through a first linker,

and (3) flavonoid linked to said hydrophilic polymer through a second linker or said TTM through a third linker.

According to the invention, wherein said TTM contains nucleic acid, peptide, glycoprotein, small molecule, carbohydrate, or lipid.

5 According to the invention, wherein said TTM contains NGR, RGD, RGE, DGEA, EILDV, GPRP, KQAGDV, or QKRLDGS motif, HIV-tat, Annexin V, Osteopontin, Fibronectin, Collagen Type I or IV , Hyaluronate, Ephrin, or is a binding partner to oncofetal fibronectin; or a fragment thereof.

According to the invention, wherein said TTM is targeted to Act R11,
 10 ActRIIB, ActRI, ActRIB, CD44, aminopeptidase A, aminopeptidase N (CD13), BAG-1, CA 125, CD31, CD13, c-Kit, c-Met, CTLA-4, CXCR4, CCR7, EGFR, endothelin-A, EP-CAM, ErbB, FGF-1, 2, 3, or 4, folate, Her-2 / neu, HER-3, HER-4, H-ferritin, ICAM 1, 2 or 3, integrin, Selectin, IL-1R, EPHR, metastin, MMP, NG2, oncofetal fibronectin, PD-ECGFR, PDGFR , PECAM-1, PPAR-delta,
 15 PSMA, tenascin, TNFR, VCAM-1, VEGFR , and receptor such as somatostatin receptors, vasoactive intestinal peptide receptors, integrin receptors, fibroblast growth factor receptors, hepatocyte growth factor receptors, epidermal growth factor receptors, insulin-like growth factor receptors, nerve growth factor receptors, vascular endothelial growth factor receptors, platelet-derived growth
 20 factor receptors, or transforming growth factor receptors.

According to the invention, wherein said hydrophilic polymer comprises a monomer comprising acrylamide, alkyl, oxazoline, alkenyl, imine, acrylic acid,

methacrylate, diol, oxirane, alcohol, amine, anhydride, ester, lactone, carbonate, carboxylic acid, acrylate, hydroxyl, phosphate, terephthalate, amide or ether.

According to the invention, wherein said hydrophilic polymer contains polyacrylamide, poly(N-isopropylacrylamide), poly(oxazoline), polyethylenimine, 5 poly(acrylic acid), polymethacrylate, poly(ethylene glycol), poly(ethylene oxide), poly(vinyl alcohol), poly(vinylpyrrolidinone), polyethers, poly(allylamine), polyanhydrides, poly(β -amino ester), poly(butylene succinate), polycaprolactone, polycarbonate, polydioxanone, poly(glycerol), polyglycolic acid, poly(3-hydroxypropionic acid), poly(2-hydroxyethyl methacrylate), 10 poly(*N*-(2-hydroxypropyl)methacrylamide), polylactic acid, poly(lactic-*co*-glycolic acid), poly(ortho esters), poly(2-oxazoline), poly(sebacic acid), poly(terephthalate-*co*-phosphate) or copolymers thereof.

According to the invention, wherein said hydrophilic polymer is polysaccharide contains hyaluronic acid, dextran, pullulan, chitosan, cellulose, 15 amylose, starch, gelatin, carrageenan, cyclodextrin, dextran sulfate, Ficoll, gellan, guar gum, pectin, polysucrose, pullulan, scleroglucan, xanthan, xyloglucan or alginate.

According to the invention, wherein said flavonoid contains flavone, isoflavone, flavan, proanthocyanidin and anthocyanidin.

20 According to the invention, wherein said flavonoid can be an oligomer

According to the invention, wherein said flavan contains (-)-epicatechin, (+)-epicatechin, (-)-catechin, (+)-catechin, epicatechin gallate, epigallocatechin,

epigallocatechin gallate, Fisetinidol, Gallocatechin, Gallocatechin gallate, Mesquitol and Robinetinidol, ellagitannin, gallotannin, oolongtheanin, phlorotannin, tannin, theacitrin, theadibenzotropolone, theaflavin, theanaphthoquinone, thearubigins, theasinensin or mixtures thereof.

5 According to the invention, wherein said first linker is any chemical group that may link the TTM and the hydrophilic polymer.

 According to the invention, wherein said second linker contains thioether, imine, amine, azo, or 1,2,3-triazole group.

 According to the invention, wherein said third linker is any chemical group
10 that may link the TTM and the flavonoid.

 According to the invention, wherein said peptide contains oligopeptides, polypeptide, or antibody.

 According to another aspect of the present invention there is provided a method of treating a cancer comprising the step of administering the targeting
15 conjugate of preceding description to a cancer patient.

 According to the invention, wherein said cancer patient is suffering from a cancer comprising adrenocortical carcinoma, AIDS-related lymphoma, anal cancer, appendix cancer, grade I (anaplastic) astrocytoma, grade II astrocytoma, grade III astrocytoma, grade IV astrocytoma, atypical teratoid/rhabdoid tumor of
20 the central nervous system, basal cell carcinoma, bladder cancer, bronchial cancer, bronchioalveolar carcinoma, Burkitt lymphoma, cervical cancer, colon cancer, colorectal cancer, craniopharyngioma, cutaneous T-cell lymphoma, endometrial

- cancer, endometrial uterine cancer, ependymblastoma, ependymoma, esophageal cancer, esthesioneuroblastoma, Ewing's sarcoma, extracranial germ cell tumor, extragonadal germ cell tumor, extrahepatic bile duct cancer, fibrous histiocytoma, gallbladder cancer, gastric cancer, gastrointestinal carcinoid tumor,
- 5 gastrointestinal stromal tumor, gestational trophoblastic tumor, gestational trophoblastic tumor, glioma, head and neck cancer, heart cancer, hepatocellular cancer, Hilar cholangiocarcinoma, Hodgkin's lymphoma, hypopharyngeal cancer, intraocular melanoma, islet cell tumor, Kaposi sarcoma, Langerhans cell histiocytosis, laryngeal cancer, lip cancer, lymphoma, macroglobulinemia,
- 10 malignant fibrous histiocytoma, medulloblastoma, medulloepithelioma, melanoma, Merkel cell carcinoma, mesothelioma, endocrine neoplasia, multiple myeloma, mycosis fungoides, myelodysplasia, myelodysplastic/myeloproliferative neoplasms, myeloproliferative disorders, nasal cavity cancer, nasopharyngeal cancer, neuroblastoma, non-Hodgkin's lymphoma, oral cancer, oropharyngeal
- 15 cancer, osteosarcoma, ovarian clear cell carcinoma, ovarian epithelial cancer, ovarian germ cell tumor, papillomatosis, paranasal sinus cancer, parathyroid cancer, penile cancer, pharyngeal cancer, pineal parenchymal tumor, pineoblastoma, pituitary tumor, plasma cell neoplasm, plasma cell neoplasm, pleuropulmonary blastoma, primary central nervous system lymphoma, prostate
- 20 cancer, rectal cancer, renal cell cancer, respiratory tract cancer with chromosome 15 changes, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, Sezary syndrome, small intestine cancer, soft tissue sarcoma, squamous cell carcinoma,

squamous neck cancer, supratentorial primitive neuroectodermal tumor, supratentorial primitive neuroectodermal tumor, testicular cancer, throat cancer, thymic carcinoma, thymoma, thyroid cancer, cancer of the renal pelvis, urethral cancer, uterine sarcoma, vaginal cancer, vulvar cancer, Waldenstrom

5 macroglobulinemia, and Wilms tumor.

According to another aspect of the present invention there is provided a therapeutic nanocomplex comprising a targeting conjugate in proceeding claims and an agent encapsulated, said targeting conjugate comprising a hydrophilic polymer-flavonoid-TTM conjugate, wherein at least one of said flavonoid is
10 bonded to said hydrophilic polymer via a linker via the A or B or C ring of said flavonoid.

According to the invention, wherein said therapeutic nanocomplex is monolayer or liposome.

According to the invention, wherein said agent is a therapeutic agent
15 comprising antibodies, nucleic acids or small molecular drug.

According to the invention, wherein said therapeutic agents comprise topoisomerase I and II inhibitor, angiogenesis inhibitor, DNA-transcribing enzyme inhibitor, camptothecin and analogue, antibiotics, antiparasitics, antineoplastics, anti-inflammatory agent, antimetabolite, antimetabolic agent,
20 antitumor agent that react or bind with DNA, immune-modifying agent, oligonucleotide and polynucleotide, chemical radiation sensitizer and protector, or photochemically active anticancer agent.

A method of treating a cancer comprising the step of administering the therapeutic agents of preceding description to a cancer patient.

According to the invention, wherein said cancer patient is suffering from a cancer comprising adrenocortical carcinoma, AIDS-related lymphoma, anal
 5 cancer, appendix cancer, grade I (anaplastic) astrocytoma, grade II astrocytoma, grade III astrocytoma, grade IV astrocytoma, atypical teratoid/rhabdoid tumor of the central nervous system, basal cell carcinoma, bladder cancer, bronchial cancer, bronchioalveolar carcinoma, Burkitt lymphoma, cervical cancer, colon cancer, colorectal cancer, craniopharyngioma, cutaneous T-cell lymphoma, endometrial
 10 cancer, endometrial uterine cancer, ependymblastoma, ependymoma, esophageal cancer, esthesioneuroblastoma, Ewing's sarcoma, extracranial germ cell tumor, extragonadal germ cell tumor, extrahepatic bile duct cancer, fibrous histiocytoma, gallbladder cancer, gastric cancer, gastrointestinal carcinoid tumor, gastrointestinal stromal tumor, gestational trophoblastic tumor, gestational
 15 trophoblastic tumor, glioma, head and neck cancer, heart cancer, hepatocellular cancer, Hilar cholangiocarcinoma, Hodgkin's lymphoma, hypopharyngeal cancer, intraocular melanoma, islet cell tumor, Kaposi sarcoma, Langerhans cell histiocytosis, laryngeal cancer, lip cancer, lymphoma, macroglobulinemia, malignant fibrous histiocytoma, medulloblastoma, medulloepithelioma, melanoma,
 20 Merkel cell carcinoma, mesothelioma, endocrine neoplasia, multiple myeloma, mycosis fungoides, myelodysplasia, myelodysplastic/myeloproliferative neoplasms, myeloproliferative disorders, nasal cavity cancer, nasopharyngeal

cancer, neuroblastoma, non-Hodgkin's lymphoma, oral cancer, oropharyngeal cancer, osteosarcoma, ovarian clear cell carcinoma, ovarian epithelial cancer, ovarian germ cell tumor, papillomatosis, paranasal sinus cancer, parathyroid cancer, penile cancer, pharyngeal cancer, pineal parenchymal tumor,

5 pineoblastoma, pituitary tumor, plasma cell neoplasm, plasma cell neoplasm, pleuropulmonary blastoma, primary central nervous system lymphoma, prostate cancer, rectal cancer, renal cell cancer, respiratory tract cancer with chromosome 15 changes, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, Sezary syndrome, small intestine cancer, soft tissue sarcoma, squamous cell carcinoma,

10 squamous neck cancer, supratentorial primitive neuroectodermal tumor, supratentorial primitive neuroectodermal tumor, testicular cancer, throat cancer, thymic carcinoma, thymoma, thyroid cancer, cancer of the renal pelvis, urethral cancer, uterine sarcoma, vaginal cancer, vulvar cancer, Waldenstrom macroglobulinemia, and Wilms tumor.

15

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a conceptual diagram for explaining a structure of the targeting conjugate of present invention.

Figure 2 shows a preparation process for targeting drug delivery system.

20 Figure 3 shows a preparation process for targeting drug delivery system.

【 Description of major components' symbols 】

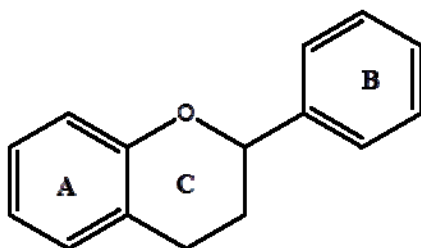
- 1 Targeting drug delivery
 system
- 10 targeting conjugate
- 101 tumor targeting moiety (TTM)
- 102 hydrophilic polymer
- 103 flavonoid
- 104 drug
- 2 Non-targeting drug delivery
 system

Definitions

The following words and terms used herein shall have the meaning indicated:

The “B ring” of a flavonoid refers to an optionally substituted phenyl that is bonded to a bicyclic structure (the bicyclic structure made up of a benzene ring (A) condensed with a six membered ring (C)). The optionally substituted phenyl is bonded to the 2-position or 3-position of the C ring. For the purposes of this disclosure, one of the examples of the rings are labelled as follows:

[Chem. 1]



The term “epigallocatechin gallate” refers to an ester of epigallocatechin and gallic acid, and may be used interchangeably with “epigallocatechin-3-gallate” or EGCG.

For the purposes of this application, the phrase “PEG-EGCG conjugates” refer to both PEG-mEGCG conjugates (monomeric EGCG) and PEG-dEGCG (dimeric EGCG) conjugates, unless specified.

The word “substantially” does not exclude “completely” e.g. a composition which is “substantially free” from Y may be completely free from Y. Where necessary, the word “substantially” may be omitted from the definition of the

invention.

Unless specified otherwise, the terms "comprising" and "comprise", and grammatical variants thereof, are intended to represent "open" or "inclusive" language such that they include recited elements but also permit inclusion of additional, unrecited elements.

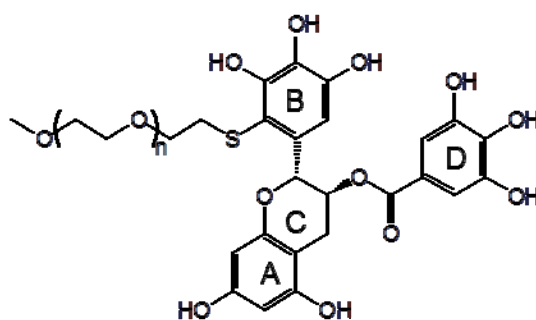
As used herein, the term "about", in the context of concentrations of components of the formulations, typically means $\pm 5\%$ of the stated value, more typically $\pm 4\%$ of the stated value, more typically $\pm 3\%$ of the stated value, more typically, $\pm 2\%$ of the stated value, even more typically $\pm 1\%$ of the stated value, and even more typically $\pm 0.5\%$ of the stated value.

Throughout this disclosure, certain embodiments may be disclosed in a range format. It should be understood that the description in range format is merely for convenience and brevity and should not be construed as an inflexible limitation on the scope of the disclosed ranges. Accordingly, the description of a range should be considered to have specifically disclosed all the possible sub-ranges as well as individual numerical values within that range. For example, description of a range such as from 1 to 6 should be considered to have specifically disclosed sub-ranges such as from 1 to 3, from 1 to 4, from 1 to 5, from 2 to 4, from 2 to 6, from 3 to 6 etc., as well as individual numbers within that range, for example, 1, 2, 3, 4, 5, and 6. This applies regardless of the breadth of the range.

Certain embodiments may also be described broadly and generically herein. Each of the narrower species and subgeneric groupings falling within the generic disclosure also form part of the disclosure. This includes the generic description of the embodiments with a proviso or negative limitation removing any subject
 5 matter from the genus, regardless of whether or not the excised material is specifically recited herein.

The polymer-flavonoid may have the following formula

[Chem. 2]



10 wherein n is in the range of 20 to 910.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

The present invention is illustrated by the embodiments below. However, the present invention is not limited by the embodiments below.

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EXAMPLE 1

TTM conjugate

As shown in FIG. 1, a targeting conjugate (10) according to an embodiment of the present invention has a tumor targeting moiety (TTM) (101), a hydrophilic

polymer (102), and a flavonoid. The hydrophilic polymer (102) linked to the TTM (101) through a first linker. The flavonoid (103) linked to said hydrophilic polymer (102) through a second linker or said TTM (101) through a third linker.

A tumor targeting moiety (TTM) may be a nucleic acid, peptide, glycoprotein, small molecule, carbohydrate, lipid etc. The peptide comprises oligopeptide, polypeptide, and antibody.

In some embodiments, a target may be a marker that is exclusively or primarily associated with one or a few tissue types, with one or a few cell types, with one or a few diseases, and/or with one or a few developmental stages. In some embodiments, a target can comprise a, a carbohydrate, a lipid, and/or a nucleic acid.

In one embodiment the TTM is a tumor vasculature targeting molecule (TVTM).

In another embodiment the TVTM is a binding partner of a tumor vasculature receptor, marker or other extracellular component.

In another embodiment the TTM is a binding partner of a tumor receptor, marker or other extracellular component.

In another embodiment the TTM contains ligands, antibodies, antigens, glycoproteins. The antibody is monoclonal antibody or polyclonal antibody.

In another embodiment the TTM contains the NGR, RGD, RGE, DGEA, EILDV, GPRP, KQAGDV, or QKRLDGS motif, HIV-tat, Annexin V, Osteopontin, Fibronectin, Collagen Type I or IV, Hyaluronate, Ephrin, or is a

binding partner to oncofetal fibronectin; or a fragment thereof.

In another embodiment the TTM is targeted to Act R11, ActRIIB, ActRI, ActRIB, CD44, aminopeptidase A, aminopeptidase N (CD13), BAG-1, CA 125, CD31, CD13, c-Kit, c-Met, CTLA-4, CXCR4, CCR7, EGFR, endothelin-A, EP-CAM, ErbB, FGF-1, 2, 3, or 4, folate, Her-2 / neu, HER-3, HER-4, H-ferritin, ICAM 1, 2 or 3, integrin, Selectin, IL-1R, Ephr, metastin, MMP, NG2, oncofetal fibronectin, PD-ECGFR, PDGFR, PECAM-1, PPAR-delta, PSMA, tenascin, TNFR, VCAM-1, VEGF, or receptor such as somatostatin receptors, vasoactive intestinal peptide receptors, integrin receptors, fibroblast growth factor receptors, hepatocyte growth factor receptors, epidermal growth factor receptors, insulin-like growth factor receptors, nerve growth factor receptors, vascular endothelial growth factor receptors, platelet-derived growth factor receptors, or transforming growth factor receptors.

In one embodiment the hydrophilic polymer comprises monomers comprising acrylamides, alkyls, oxazolines, alkenyls, imines, acrylic acids, methacrylates, diols, oxiranes, alcohols, amines, anhydrides, esters, lactones, carbonates, carboxylic acids, acrylates, hydroxyls, phosphates, terephthalate, amides or ethers.

The hydrophilic polymer comprises polyacrylamide, poly(N-isopropylacrylamide), poly(oxazoline), polyethylenimine, poly(acrylic acid), polymethacrylate, poly(ethylene glycol), poly(ethylene oxide), poly(vinyl alcohol), poly(vinylpyrrolidinone), polyethers, poly(allylamine), polyanhydrides,

poly(β -amino ester), poly(butylene succinate), polycaprolactone, polycarbonate, polydioxanone, poly(glycerol), polyglycolic acid, poly(3-hydroxypropionic acid), poly(2-hydroxyethyl methacrylate), poly(*N*-(2-hydroxypropyl)methacrylamide), polylactic acid, poly(lactic-*co*-glycolic acid), poly(ortho esters),

5 poly(2-oxazoline), poly(sebacic acid), poly(terephthalate-*co*-phosphate) and copolymers thereof.

The hydrophilic polymer may be a polysaccharide. The polymer comprises hyaluronic acid, dextran, pullulan, chitosan, cellulose, amylose, starch, gelatin, carrageenan, cyclodextrin, dextran sulfate, Ficoll, gellan, guar gum, pectin,

10 polysucrose, pullulan, scleroglucan, xanthan, xyloglucan and alginate.

The hydrophilic polymer may be polyethylene glycol (PEG). PEG is a synthetic polymer that has been used in biomedical applications because of its hydrophilic, flexible and biocompatible nature. Specifically, PEG has been utilized to modify the surface of polymeric micelles and nanoparticles to produce

15 anti-fouling surfaces.

Advantageously, polyethylene glycol (PEG) was selected as the polymer to be conjugated to the flavonoid. The conjugation was accomplished by nucleophilic addition of a thiol group of PEG at the C2' position of the B ring of the flavonoid under controlled pH conditions.

20 In one embodiment the flavonoid contains flavones, isoflavones, flavans, proanthocyanidins and anthocyanidins.

In another embodiment the flavonoid can be an oligomer.

In one embodiment the flavans contains (-)-epicatechin, (+)-epicatechin, (-)-catechin, (+)-catechin, epicatechin gallate, epigallocatechin, epigallocatechin gallate, Fisetinidol, Gallocatechin, Gallocatechin gallate, Mesquitol and Robinetinidol, ellagitannin, gallotannin, oolongtheanin, phlorotannin, tannin, theacitrin, theadibenzotropolone, theaflavin, theanaphthoquinone, thearubigins, theasinensin and mixtures thereof.

The first linker may be any chemical group that may link the TTM and the hydrophilic polymer.

The second linker may be any chemical group that may link the hydrophilic polymer and the flavonoid. In one embodiment the second linker contains thioether, imine, amine, azo, or 1,2,3-triazole group.

The third linker may be any chemical group that may link the TTM and the flavonoid.

EXAMPLE 2

The TTM conjugates for treating cancer

In an embodiment of the method of treating a cancer comprising the step of administering the TTM conjugate to a cancer patient.

In one embodiment, the cancer patient is suffering from a cancer comprising adrenocortical carcinoma, AIDS-related lymphoma, anal cancer, appendix cancer, grade I (anaplastic) astrocytoma, grade II astrocytoma, grade III astrocytoma, grade IV astrocytoma, atypical teratoid/rhabdoid tumor of the central nervous system, basal cell carcinoma, bladder cancer, bronchial cancer,

bronchioalveolar carcinoma, Burkitt lymphoma, cervical cancer, colon cancer,
 colorectal cancer, craniopharyngioma, cutaneous T-cell lymphoma, endometrial
 cancer, endometrial uterine cancer, ependymblastoma, ependymoma, esophageal
 cancer, esthesioneuroblastoma, Ewing's sarcoma, extracranial germ cell tumor,
 5 extragonadal germ cell tumor, extrahepatic bile duct cancer, fibrous histiocytoma,
 gallbladder cancer, gastric cancer, gastrointestinal carcinoid tumor,
 gastrointestinal stromal tumor, gestational trophoblastic tumor, gestational
 trophoblastic tumor, glioma, head and neck cancer, heart cancer, hepatocellular
 cancer, Hilar cholangiocarcinoma, Hodgkin's lymphoma, hypopharyngeal cancer,
 10 intraocular melanoma, islet cell tumor, Kaposi sarcoma, Langerhans cell
 histiocytosis, laryngeal cancer, lip cancer, lymphoma, macroglobulinemia,
 malignant fibrous histiocytoma, medulloblastoma, medulloepithelioma,
 melanoma, Merkel cell carcinoma, mesothelioma, endocrine neoplasia, multiple
 myeloma, mycosis fungoides, myelodysplasia,
 15 myelodysplastic/myeloproliferative neoplasms, myeloproliferative disorders,
 nasal cavity cancer, nasopharyngeal cancer, neuroblastoma, non-Hodgkin's
 lymphoma, oral cancer, oropharyngeal cancer, osteosarcoma, ovarian clear cell
 carcinoma, ovarian epithelial cancer, ovarian germ cell tumor, papillomatosis,
 paranasal sinus cancer, parathyroid cancer, penile cancer, pharyngeal cancer,
 20 pineal parenchymal tumor, pineoblastoma, pituitary tumor, plasma cell neoplasm,
 plasma cell neoplasm, pleuropulmonary blastoma, primary central nervous system
 lymphoma, prostate cancer, rectal cancer, renal cell cancer, respiratory tract

cancer with chromosome 15 changes, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, Sezary syndrome, small intestine cancer, soft tissue sarcoma, squamous cell carcinoma, squamous neck cancer, supratentorial primitive neuroectodermal tumor, supratentorial primitive neuroectodermal tumor, 5 testicular cancer, throat cancer, thymic carcinoma, thymoma, thyroid cancer, cancer of the renal pelvis, urethral cancer, uterine sarcoma, vaginal cancer, vulvar cancer, Waldenstrom macroglobulinemia, and Wilms tumor.

EXAMPLE 3

The TTM-PEG-EGCG conjugates

10 In an embodiment, the hydrophilic polymer is PEG, and the flavonoid is EGCG. In this study, two types of PEG-EGCG conjugates were used to form micellar nanocomplexes, PEG-mEGCG and PEG-dEGCG, which have one and two EGCG moieties at one end of the PEG, respectively.

Synthesis of PEG-mEGCG conjugate

15 PEG-mEGCG conjugate was synthesized by conjugating EGCG to PEG containing a thiol end terminal.

It is noteworthy that the conjugation reaction proceeded in the presence of dimethyl sulfoxide (DMSO). In addition, sodium pyruvate was used as a scavenger for H_2O_2 generated during the autoxidation of EGCG and increase the 20 number of PEG-SH molecules available for a conjugation reaction with EGCG.

The PEG-mEGCG conjugate obtained was purified by dialysis under a nitrogen atmosphere and then lyophilized to obtain a white powder.

Synthesis of TTM-PEG-mEGCG conjugate

In an embodiment, the TTM is added to PEG-mEGCG to synthesis of
 5 TTM-PEG-mEGCG conjugate. TTM can be covalently linked to the PEG of the PEG-mEGCG or the mEGCG of the PEG-mEGCG. TTM is linked to hydrophilic polymer through a first linker. The TTM is linked to flavonoid through a third linker.

Synthesis of PEG-dEGCG conjugate

10 PEG-dEGCG conjugates were synthesized by conjugating EGCG to PEG with an aldehyde end group (PEG-CHO).

Synthesis of TTM-PEG-dEGCG conjugate

In a preferred embodiment, the TTM is added to PEG-dEGCG to synthesis
 of TTM-PEG-mEGCG conjugate. TTM can be covalently linked to the PEG of
 15 the PEG-dEGCG or the dEGCG of the PEG-dEGCG. TTM is linked to hydrophilic polymer through a first linker. The TTM is linked to flavonoid through a third linker.

EXAMPLE 4

Drug delivery system (I)

For cancer therapy applications, the targeting conjugates, which can be, were designed to form a targeting drug delivery system, micellar carrier, monolayer carrier or liposome carrier, capable of carrying a large number of anticancer drugs in the interior. As shown in FIG. 2, drugs (104), especially anticancer drugs, is encapsulated by targeting conjugates (10) to form a targeting drug delivery system (1). It is envisioned that targeting drug delivery system can minimize such adverse side effects by stably encapsulating drug molecules in their interior and releasing them in a sustained manner.

In one embodiment the therapeutic nanocomplex comprising a targeting conjugate in proceeding claims and an agent encapsulated, said targeting conjugate comprising a hydrophilic polymer-flavonoid-TTM conjugate, wherein at least one of said flavonoid is bonded to said hydrophilic polymer via a linker via the B or C ring of said flavonoid. The therapeutic nanocomplex is monolayer or liposome. The agent is therapeutic agents comprising antibodies, or small drugs.

In one embodiment the therapeutic agent is a therapeutic agent comprises alkylating agents, anthracyclines, cytoskeletal disruptors, epothilones, histone deacetylase inhibitors, topoisomerase I inhibitors, topoisomerase II inhibitors, kinase inhibitors, monoclonal antibodies, antibody-drug conjugates, nucleotide analogs, precursor analogs, peptide antibiotics, platinum-based agents, retinoids,

vinca alkaloids , cytokines , anti-metabolites, or vinca alkaloids derivatives, and other cytotoxics.

In an embodiment the therapeutic agent is a therapeutic agent comprising alkylating agents, anthracyclines, cytoskeletal disruptors, epothilones, histone
 5 deacetylase inhibitors, topoisomerase I inhibitors, topoisomerase II inhibitors, kinase inhibitors, monoclonal antibodies, antibody-drug conjugates, nucleotide analogs, precursor analogs, peptide antibiotics, platinum-based agents, retinoids, vinca alkaloids , cytokines , anti-metabolites, or vinca alkaloids derivatives, or other cytotoxics.

10

EXAMPLE 5

15 **Drug delivery system (II)**

For cancer therapy applications, the targeting conjugates were designed to form a targeting drug delivery system, micellar carrier, monolayer carrier or liposome carrier, capable of carrying a large number of anticancer drugs in the interior. As shown in FIG. 3, drugs, especially anticancer drugs, is encapsulated
 20 by non-targeting conjugates to form a non-targeting drug delivery system (2). TTM is added to non-targeting drug delivery system (2) and form a targeting drug delivery system (1). It is envisioned that targeting drug delivery system can

minimize such adverse side effects by stably encapsulating drug molecules in their interior and releasing them in a sustained manner.

In one embodiment the therapeutic nanocomplex comprising a targeting conjugate in proceeding claims and an agent encapsulated, said targeting
 5 conjugate comprising a hydrophilic polymer-flavonoid-TTM conjugate, wherein at least one of said flavonoid is bonded to said hydrophilic polymer via a linker via the B or C ring of said flavonoid. The therapeutic nanocomplex is monolayer or liposome. The agent is therapeutic agents comprising antibodies, or small drugs.

10 In one embodiment the therapeutic agent is a therapeutic agent comprises alkylating agents, anthracyclines, cytoskeletal disruptors, epothilones, histone deacetylase inhibitors, topoisomerase I inhibitors, topoisomerase II inhibitors, kinase inhibitors, monoclonal antibodies, antibody-drug conjugates, nucleotide analogs, precursor analogs, peptide antibiotics, platinum-based agents, retinoids,
 15 vinca alkaloids , cytokines , anti-metabolites, or vinca alkaloids derivatives, and other cytotoxics.

In an embodiment the therapeutic agent is a therapeutic agent comprising alkylating agents, anthracyclines, cytoskeletal disruptors, epothilones, histone
 20 deacetylase inhibitors, topoisomerase I inhibitors, topoisomerase II inhibitors,

kinase inhibitors, monoclonal antibodies, antibody-drug conjugates, nucleotide analogs, precursor analogs, peptide antibiotics, platinum-based agents, retinoids, vinca alkaloids, cytokines, anti-metabolites, or vinca alkaloids derivatives, or other cytotoxics.

5

EXAMPLE 6

The TTM nanocomplex for treating cancer

In an embodiment the method of treating a cancer comprising the step of administering the micellar nanocomplex.

In an embodiment the cancer patient is suffering from a cancer comprising

10 adrenocortical carcinoma, AIDS-related lymphoma, anal cancer, appendix cancer, grade I (anaplastic) astrocytoma, grade II astrocytoma, grade III astrocytoma, grade IV astrocytoma, atypical teratoid/rhabdoid tumor of the central nervous system, basal cell carcinoma, bladder cancer, bronchial cancer, bronchioalveolar carcinoma, Burkitt lymphoma, cervical cancer, colon cancer, colorectal cancer,

15 craniopharyngioma, cutaneous T-cell lymphoma, endometrial cancer, endometrial uterine cancer, ependymoblastoma, ependymoma, esophageal cancer, esthesioneuroblastoma, Ewing's sarcoma, extracranial germ cell tumor, extragonadal germ cell tumor, extrahepatic bile duct cancer, fibrous histiocytoma, gallbladder cancer, gastric cancer, gastrointestinal carcinoid tumor,

20 gastrointestinal stromal tumor, gestational trophoblastic tumor, gestational trophoblastic tumor, glioma, head and neck cancer, heart cancer, hepatocellular

cancer, Hilar cholangiocarcinoma, Hodgkin's lymphoma, hypopharyngeal cancer, intraocular melanoma, islet cell tumor, Kaposi sarcoma, Langerhans cell histiocytosis, laryngeal cancer, lip cancer, lymphoma, macroglobulinemia, malignant fibrous histiocytoma, medulloblastoma, medulloepithelioma, melanoma,

5 Merkel cell carcinoma, mesothelioma, endocrine neoplasia, multiple myeloma, mycosis fungoides, myelodysplasia, myelodysplastic/myeloproliferative neoplasms, myeloproliferative disorders, nasal cavity cancer, nasopharyngeal cancer, neuroblastoma, non-Hodgkin's lymphoma, oral cancer, oropharyngeal cancer, osteosarcoma, ovarian clear cell carcinoma, ovarian epithelial cancer,

10 ovarian germ cell tumor, papillomatosis, paranasal sinus cancer, parathyroid cancer, penile cancer, pharyngeal cancer, pineal parenchymal tumor, pineoblastoma, pituitary tumor, plasma cell neoplasm, plasma cell neoplasm, pleuropulmonary blastoma, primary central nervous system lymphoma, prostate cancer, rectal cancer, renal cell cancer, respiratory tract cancer with chromosome

15 15 changes, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, Sezary syndrome, small intestine cancer, soft tissue sarcoma, squamous cell carcinoma, squamous neck cancer, supratentorial primitive neuroectodermal tumor, supratentorial primitive neuroectodermal tumor, testicular cancer, throat cancer, thymic carcinoma, thymoma, thyroid cancer, cancer of the renal pelvis, urethral

20 cancer, uterine sarcoma, vaginal cancer, vulvar cancer, Waldenstrom macroglobulinemia, and Wilms tumor.

The above elaboration is embodiments of feasible examples of the present invention. However, those examples are not meant to limit the scopes of the present invention. Equivalents or alternations without departing from the spirit of the present invention should be contained in the scopes of the present invention.

- 5 The above-mentioned multiple effects relate to fully satisfying the statutory patentability elements of novelty and inventiveness. An application is filed according to laws, and please grant the present invention patent application, to encourage invention.

What is claimed is:

1. A targeting conjugate comprising:
 - (1) tumor targeting moiety (TTM),
 - (2) hydrophilic polymer linked to said tumor targeting molecular through a
5 first linker, and
 - (3) flavonoid linked to said hydrophilic polymer through a second linker or
said TTM through a third linker.
2. The targeting conjugate according to claim 1, wherein said TTM contains
nucleic acid, peptide, glycoprotein, small molecule, carbohydrate, or lipid.
- 10 3. A targeting conjugate according to claim 1, wherein said TTM contains
NGR, RGD, RGE, DGEA, EILDV, GPRP, KQAGDV, or QKRLDGS motif,
HIV-tat, Annexin V, Osteopontin, Fibronectin, Collagen Type I or IV,
Hyaluronate, Ephrin, or is a binding partner to oncofetal fibronectin; or a
fragment thereof.
- 15 4. The targeting conjugate according to claim 1, wherein said TTM is targeted
to Act R11, ActRIIB, ActRI, ActRIB, CD44, aminopeptidase A,
aminopeptidase N (CD13), BAG-1, CA 125, CD31, CD13, c-Kit, c-Met,
CTLA-4, CXCR4, CCR7, EGFR, endothelin-A, EP-CAM, ErbB, FGF-1, 2, 3,
or 4, folate, Her-2 / neu, HER-3, HER-4, H-ferritin, ICAM 1, 2 or 3, integrin,
20 Selectin, IL-1R, Ephr, metastin, MMP, NG2, oncofetal fibronectin,
PD-ECGFR, PDGFR, PECAM-1, PPAR-delta, PSMA, tenascin, TNFR,
VCAM-1, VEGFR, and receptor such as somatostatin receptors, vasoactive

intestinal peptide receptors, integrin receptors, fibroblast growth factor
 receptors, hepatocyte growth factor receptors, epidermal growth factor
 receptors, insulin-like growth factor receptors, nerve growth factor receptors,
 vascular endothelial growth factor receptors, platelet-derived growth factor
 5 receptors, or transforming growth factor receptors.

5. The targeting conjugate according to claim 1, wherein said hydrophilic
 polymer comprises monomers comprising acrylamides, alkyls, oxazolines,
 alkenyls, imines, acrylic acids, methacrylates, diols, oxiranes, alcohols, amines,
 anhydrides, esters, lactones, carbonates, carboxylic acids, acrylates, hydroxyls,
 10 phosphates, terephthalate, amides or ethers.

6. The targeting conjugate according to claim 1, wherein said hydrophilic
 polymer contains polyacrylamide, poly(N-isopropylacrylamide),
 poly(oxazoline), polyethylenimine, poly(acrylic acid), polymethacrylate,
 poly(ethylene glycol), poly(ethylene oxide), poly(vinyl alcohol),
 15 poly(vinylpyrrolidinone), polyethers, poly(allylamine), polyanhydrides,
 poly(β -amino ester), poly(butylene succinate), polycaprolactone,
 polycarbonate, polydioxanone, poly(glycerol), polyglycolic acid,
 poly(3-hydroxypropionic acid), poly(2-hydroxyethyl methacrylate),
 poly(*N*-(2-hydroxypropyl)methacrylamide), polylactic acid,
 20 poly(lactic-*co*-glycolic acid), poly(ortho esters), poly(2-oxazoline),
 poly(sebacic acid), poly(terephthalate-*co*-phosphate) or copolymers thereof.

7. The targeting conjugate according to claim 1, wherein said hydrophilic

polymer is polysaccharide contains hyaluronic acid, dextran, pullulan, chitosan, cellulose, amylose, starch, gelatin, carrageenan, cyclodextrin, dextran sulfate, Ficoll, gellan, guar gum, pectin, polysucrose, pullulan, scleroglucan, xanthan, xyloglucan or alginate.

- 5 8. The targeting conjugate according to claim 1, wherein said flavonoid containing flavone, isoflavone, flavan, proanthocyanidin and anthocyanidin.
9. A targeting conjugate according to claim 1, wherein said flavonoid can be an oligomer.
10. The targeting conjugate according to claim 9, wherein said flavan contains
10 (-)-epicatechin, (+)-epicatechin, (-)-catechin, (+)-catechin, epicatechin gallate, epigallocatechin, epigallocatechin gallate, Fisetinidol, Gallocatechin, Gallocatechin gallate, Mesquitol and Robinetinidol, ellagitannin, gallotannin, oolongtheanin, phlorotannin, tannin, theacitrin, theadibenzotropolone, theaflavin, theanaphthoquinone, thearubigins, theasinensin or mixtures
15 thereof.
11. The targeting conjugate according to claim 1, wherein said first linker is any chemical group that may link the TTM and the hydrophilic polymer.
12. The targeting conjugate according to claim 1, wherein said second linker contains thioether, imine, amine, azo, or 1,2,3-triazole group.
- 20 13. The targeting conjugate according to claim 1, wherein said first linker is any chemical group that may link the TTM and the flavonoid.
14. The targeting conjugate according to claim 1, wherein said peptide

comprises oligopeptide, polypeptide, or antibody.

15. A method of treating a cancer comprising the step of administering the targeting conjugate of any one of claims 1 to 14 to a cancer patient.

16. The method of any one of claims 15, wherein said cancer patient is

5 suffering from a cancer selected from the group consisting of adrenocortical carcinoma, AIDS-related lymphoma, anal cancer, appendix cancer, grade I (anaplastic) astrocytoma, grade II astrocytoma, grade III astrocytoma, grade IV astrocytoma, atypical teratoid/rhabdoid tumor of the central nervous system, basal cell carcinoma, bladder cancer, bronchial cancer,
 10 bronchioalveolar carcinoma, Burkitt lymphoma, cervical cancer, colon cancer, colorectal cancer, craniopharyngioma, cutaneous T-cell lymphoma, endometrial cancer, endometrial uterine cancer, ependymblastoma, ependymoma, esophageal cancer, esthesioneuroblastoma, Ewing's sarcoma, extracranial germ cell tumor, extragonadal germ cell tumor, extrahepatic bile
 15 duct cancer, fibrous histiocytoma, gallbladder cancer, gastric cancer, gastrointestinal carcinoid tumor, gastrointestinal stromal tumor, gestational trophoblastic tumor, gestational trophoblastic tumor, glioma, head and neck cancer, heart cancer, hepatocellular cancer, Hilar cholangiocarcinoma, Hodgkin's lymphoma, hypopharyngeal cancer, intraocular melanoma, islet cell
 20 tumor, Kaposi sarcoma, Langerhans cell histiocytosis, laryngeal cancer, lip cancer, lymphoma, macroglobulinemia, malignant fibrous histiocytoma, medulloblastoma, medulloepithelioma, melanoma, Merkel cell carcinoma,

- mesothelioma, endocrine neoplasia, multiple myeloma, mycosis fungoides, myelodysplasia, myelodysplastic/myeloproliferative neoplasms, myeloproliferative disorders, nasal cavity cancer, nasopharyngeal cancer, neuroblastoma, non-Hodgkin's lymphoma, oral cancer, oropharyngeal cancer, osteosarcoma, ovarian clear cell carcinoma, ovarian epithelial cancer, ovarian germ cell tumor, papillomatosis, paranasal sinus cancer, parathyroid cancer, penile cancer, pharyngeal cancer, pineal parenchymal tumor, pineoblastoma, pituitary tumor, plasma cell neoplasm, plasma cell neoplasm, pleuropulmonary blastoma, primary central nervous system lymphoma, prostate cancer, rectal cancer, renal cell cancer, respiratory tract cancer with chromosome 15 changes, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, Sezary syndrome, small intestine cancer, soft tissue sarcoma, squamous cell carcinoma, squamous neck cancer, supratentorial primitive neuroectodermal tumor, supratentorial primitive neuroectodermal tumor, testicular cancer, throat cancer, thymic carcinoma, thymoma, thyroid cancer, cancer of the renal pelvis, urethral cancer, uterine sarcoma, vaginal cancer, vulvar cancer, Waldenstrom macroglobulinemia, and Wilms tumor.
17. A therapeutic nanocomplex comprising a targeting conjugate in any one of claims 1 to 14 and an agent encapsulated, said targeting conjugate comprising a hydrophilic polymer-flavonoid-TTM conjugate, wherein at least one of said flavonoid is bonded to said hydrophilic polymer via a linker via the A or B or C ring of said flavonoid.

18. The therapeutic nanocomplex according to claim 15, wherein said therapeutic nanocomplex is monolayer or liposome.
19. The therapeutic nanocomplex according to claim 15, wherein said agent is a therapeutic agent comprising antibodies, nucleic acids or small molecular drugs.
20. The therapeutic nanocomplex according to claim 15, wherein said therapeutic agent comprises topoisomerase I and II inhibitor, angiogenesis inhibitor, DNA-transcribing enzyme inhibitor, camptothecin and analogue, antibiotics, antiparasitics, antineoplastics, anti-inflammatory agent, antimetabolite, antimitotic agent, antitumor agent that react or bind with DNA, immune-modifying agent, oligonucleotide and polynucleotide, chemical radiation sensitizer and protector, or photochemically active anticancer agent.
21. A method of treating a cancer comprising the step of administering the micellar nanocomplex of any one of claims 17 to 20 to a cancer patient.
22. The method of any one of claims 21, wherein said cancer patient is suffering from a cancer comprising adrenocortical carcinoma, AIDS-related lymphoma, anal cancer, appendix cancer, grade I (anaplastic) astrocytoma, grade II astrocytoma, grade III astrocytoma, grade IV astrocytoma, atypical teratoid/rhabdoid tumor of the central nervous system, basal cell carcinoma, bladder cancer, bronchial cancer, bronchioalveolar carcinoma, Burkitt lymphoma, cervical cancer, colon cancer, colorectal cancer, craniopharyngioma, cutaneous T-cell lymphoma, endometrial cancer,

endometrial uterine cancer, ependymblastoma, ependymoma, esophageal
 cancer, esthesioneuroblastoma, Ewing's sarcoma, extracranial germ cell tumor,
 extragonadal germ cell tumor, extrahepatic bile duct cancer, fibrous
 histiocytoma, gallbladder cancer, gastric cancer, gastrointestinal carcinoid
 5 tumor, gastrointestinal stromal tumor, gestational trophoblastic tumor,
 gestational trophoblastic tumor, glioma, head and neck cancer, heart cancer,
 hepatocellular cancer, Hilar cholangiocarcinoma, Hodgkin's lymphoma,
 hypopharyngeal cancer, intraocular melanoma, islet cell tumor, Kaposi
 sarcoma, Langerhans cell histiocytosis, laryngeal cancer, lip cancer,
 10 lymphoma, macroglobulinemia, malignant fibrous histiocytoma,
 medulloblastoma, medulloepithelioma, melanoma, Merkel cell carcinoma,
 mesothelioma, endocrine neoplasia, multiple myeloma, mycosis fungoides,
 myelodysplasia, myelodysplastic/myeloproliferative neoplasms,
 myeloproliferative disorders, nasal cavity cancer, nasopharyngeal cancer,
 15 neuroblastoma, non-Hodgkin's lymphoma, oral cancer, oropharyngeal cancer,
 osteosarcoma, ovarian clear cell carcinoma, ovarian epithelial cancer, ovarian
 germ cell tumor, papillomatosis, paranasal sinus cancer, parathyroid cancer,
 penile cancer, pharyngeal cancer, pineal parenchymal tumor, pineoblastoma,
 pituitary tumor, plasma cell neoplasm, plasma cell neoplasm,
 20 pleuropulmonary blastoma, primary central nervous system lymphoma,
 prostate cancer, rectal cancer, renal cell cancer, respiratory tract cancer with
 chromosome 15 changes, retinoblastoma, rhabdomyosarcoma, salivary gland

cancer, Sezary syndrome, small intestine cancer, soft tissue sarcoma,
squamous cell carcinoma, squamous neck cancer, supratentorial primitive
neuroectodermal tumor, supratentorial primitive neuroectodermal tumor,
testicular cancer, throat cancer, thymic carcinoma, thymoma, thyroid cancer,
5 cancer of the renal pelvis, urethral cancer, uterine sarcoma, vaginal cancer,
vulvar cancer, Waldenstrom macroglobulinemia, and Wilms tumor.