a) providing purified iron binding protein;

b) covalently or non-covalently linking a drug to and/or encapsulating a drug in an iron binding protein;

c) providing a CD45+ leukocyte cell; and

d) incubating the CD45+ leukocyte cell in the presence of the iron binding protein produced in step b) until the CD45+ leukocyte cell is at least partially loaded with the iron binding protein produced in step b).

In yet another aspect, the present invention refers to a pharmaceutical composition comprising the isolated targeted delivery system of the present invention and a pharmaceutically acceptable carrier and/or suitable excipient(s).

In yet another aspect, the present invention refers to the use of an isolated targeted delivery system of the present invention in the manufacture of a medicament for preventing/treating tumours, preferably a solid tumour, preferably breast cancer, pancreatic cancer, bladder cancer, lung cancer, colon cancer, or a tumour having hypoxic areas, inflammatory disease or ischemic areas in skin wounds or after organ infarctus (heart) or ischemic retina.

In a first example the present disclosure relates to an isolated targeted delivery system comprising a $CD45^+$ leukocyte cell, which is preferably capable of internalizing an iron binding protein comprising within said cell a complex of one or more iron binding proteins and one or more active ingredients.

Claims

1. An isolated targeted delivery system comprising a $CD45^+$ leukocyte cell comprising within said cell a complex of one or more iron binding proteins and a drug.

2. The isolated targeted delivery system according to claim 1, wherein the isolated targeted delivery system is capable of specifically delivering the drug into diseased cells in tissues that attract CD45+ leukocytes.

3. The isolated targeted delivery system according to claim 1 or 2, wherein the leukocyte cell is producible from a $CD34^+$ hematopoietic precursor cell.

4. The isolated targeted delivery system according to claim 1 to 3, wherein the leukocyte is selected from the group consisting of a monocyte, a differentiated monocyte which preferably is a macrophage, lymphocyte and a granulocyte.

5. The isolated targeted delivery system according to claim 4, wherein

(i) the monocyte is a $CD11b^+$ monocyte, preferably selected from the group consisting of a $CD11b^+$ $CD14^+$ monocyte, a $CD11b^+$ $CD16^+$ monocyte, a $CD11b^+$ $CD14^+$ $CD16^+$ monocyte, a $CD11b^+$ $CD14^+$ $MHCII^+$ monocyte, a $CD11b^+$ $CD14^+$ $CD115^+$ monocyte, $CD11b^+$ $CD114^+$ monocyte, $CD11b^+$ $CD116^+$ monocyte, $CD11b^+$ $CCR1^+$ monocyte, $CD11b^+$ $CCR2^+$ monocyte, $CD11b^+$ $CX3CR^+$ monocyte, $CD11b^+$ $CXR4^+$ monocyte, $CD11b^+$ $CXR6^+$ monocyte and a $CD11b^+$ $CD14^+$ $CD33^+$ monocyte;

(ii) the differentiated monocyte is selected from the group consisting of a macrophage, an activated macrophage, preferably a $CD11b^+$ macrophage, more preferably a $CD11b^+$ $CD16^+$ macrophage, $CD11b^+$ $CD32^+$ macrophage, $CD11b^+$ $CD64^+$ macrophage, $CD11b^+$ $CD68^+$ macrophage, preferably a $CD11b^+$ $CD86^+$ M1 macrophage, preferably producing iNOS and/or secreting interleukin 12 (IL-12) or preferably $CD11b^+$ $CCR2^+$ M2 macrophage, $CD11b^+$ $CD204^+$ M2 macrophage, $CD11b^+$ $CD206^+$ M2 macrophage, $CD11b^+$ $CD204^+$ $CD206^+$ M2 macrophage, $CD11b^+$ Mayor Histocompatibility Complex II^+ ($MHCII^+$) (low or hi expression) M2 macrophage, $CD11b^+$ $CD200R^+$ M2 macrophage, $CD11b^+$ $CD163^+$ M2 macrophage or activated macrophage producing arginase and/or secreting

interleukin 10 (IL-10); or a dendritic cell, preferably with expression of CD11b CD11c, CD11b CD80, CD11c CD80, CD11c CD86, CD11c MHCII and CD11c CD123, preferably the differentiated monocyte is not a Lox1+, CXCR7+ and NRF2+ foam cell;

(iii) monocyte or activated monocyte expressing of at least one chemokine receptor, preferably selected from the group consisting of CCR1, CCR2$^+$, CXR4$^+$, and CXR6$^+$, or at least one growth factor receptor, preferably selected from the group consisting of macrophage colony stimulating factor Receptor (CD115), granulocyte colony stimulating factor Receptor (CD114), and granulocyte-macrophage colony stimulating factor Receptor (consisting of CD116 and CD131); monocytes of these characteristics are particular suitable to treat inflammatory conditions and cancer;

(iv) the lymphocyte is selected from the group consisting of a CD3$^+$ and CD4$^+$ or CD8$^+$ T lymphocyte, or a CD19$^+$, CD20$^+$, CD21$^+$, CD19$^+$ CD20$^+$, CD19$^+$ CD21$^+$, CD20$^+$ CD21$^+$, or CD19$^+$ CD20$^+$ CD21$^+$ B lymphocyte; or

(v) the granulocyte is selected from the group consisting of a neutrophil, preferably a CD66b$^+$ neutrophil, an eosinophil and a basophil, preferably a CD193$^+$ eosinophil.

6. The isolated targeted delivery system of claim 5, wherein the activated macrophage:

(i) is producible by *in vitro* incubation of a monocyte or macrophage with a factor capable of altering expression markers on macrophages, preferably

(a) with at least one M1 inducer,

(b) with at least one M2 inducer,

(c) or with a factor capable of altering the macrophages ability to secrete cytokines, preferably IL-10 and IL-12, chemokines and/or to produce iNOS, arginase or other immunomodulating enzymes;

(ii) is characterized by expression of at least one of following antigens: CD64, CD86, CD16, CD32, high expression of MHCII, and/or production of iNOS and/or IL-12;

(iii) is producible by *in vitro* incubation of a monocyte or macrophage with a factor capable of inducing the ability of the macrophage to phagocytose;

(iv) is characterized by expression of at least one of following antigens: CD204, CD206, CD200R; CCR2, transferrin receptor (TfR), CXC-motive chemokine receptor 4 (CXCR4), CD163, and/or T cell immunoglobulin-domain and mucin-domain 2 (TIM-2), and/or show low expression of MHCII;

(v) has the ability to phagocytose; and/or

(vi) is capable of cytokine secretion, preferably of IL-12, or IL-10, or production of inducible nitric oxide synthetase (iNOS) (or other pro-inflammatory compounds), arginase or other immunosuppressive/anti-inflammatory compounds.

7. The targeted delivery system according to claim 6, wherein:

(i) the M1 inducer is selected from the group consisting of LPS, INF-γ, GM-CSF and viral and bacterial infection; or

(ii) the M2 inducer is selected from the group consisting of IL-4, IL-10, IL-13, immune complex of an antigen and antibody, IgG, heat activated gamma-globulin, glucocorticosteroid, TGF-β, IL-1R, CCL-2, IL-6, M-CSF, PPARγ agonist, Leukocyte inhibitory factor, adenosine, helminth and fungal infection.

8. The isolated targeted delivery system of claim 5, wherein the monocyte:

(i) is producible from a $CD34^+$ hematopoietic precursor cell;

(ii) is producible by *in vitro* incubation of monocytes with at least one inducer, preferably M1 or M2 inducer, more preferably at least one M2 inducer;

(iii) is characterized by expression of at least one of the following antigens: TfR^+, $CD163^+$, $TIM\text{-}2^+$, $CD14^+$, $CD16^+$, $CD33^+$, and/or $CD115^+$;

(iv) is characterized by expression of at least one of the following antigens: TfR^+, $CD163^+$, $TIM\text{-}2^+$, $CXCR4^+$, $CD14^+$, and/or $CD16^+$; and/or

(v) has the ability to phagocytose.

9. The targeted delivery system according to claim 8, wherein:

(i) the M1 inducer is selected from the group consisting of LPS, INF-γ, GM-CSF or viral or bacterial infection;

(ii) the M2 inducer is selected from the group consisting of IL-4, IL-10, IL-13, immune complex of an antigen and antibody, IgG, heat activated gamma-globulins, Glucocorticosteroids, TGF-β, IL-1R, CCL-2, IL-6, M-CSF, PPARγ agonist, Leukocyte inhibitory factor, cancer-conditioned medium, cancer cells, adenosine and helminth or fungal infection.

10. The isolated targeted delivery system of claim 5, wherein the lymphocyte:

(i) is obtainable from blood, spleen, or bone marrow or is producible from a $CD34^+$ precursor cell;

(ii) is an immunologically competent lymphocyte;

(iii) expresses antigen specific T cell receptors; and/or

(iv) is characterized by expression of at least one of the following antigens: (a) $CD3^+$ and $CD4^+$ or $CD8^+$ or (b): $CD19^+$, $CD20^+$, $CD21^+$, $CD19^+$ $CD20^+$, $CD19^+$ $CD21^+$, $CD20^+$ $CD21^+$, or $CD19^+$ $CD20^+$ $CD21^+$ antigen, and is preferably capable of producing immunoglobulins.

11. The isolated targeted delivery system of claim 5, wherein the granulocyte:

(i) is obtainable from blood, spleen or bone marrow or producible from a $CD34^+$ precursor cell;

(ii) is characterized by expression of at least one of the following $CD66b^+$ and/or $CD193^+$;

(iii) is a polymorphonuclear leukocyte characterized by the presence of granules in their cytoplasm; and/or

(iii) is characterized by expression of at least one of the following: TfR^+, $CD163^+$, TIM-2^+, and/or $CXCR4^+$.

12. The isolated targeted delivery system of any of claims 1 to 11, wherein the iron binding protein is selected from the group consisting of ferritin, preferably heavy (H) type ferritin, light (L) ferritin and/or mitochondrial ferritin; haemoglobin, preferably haemoglobin A, haemoglobin AS, haemoglobin SC, haemoglobin C, haemoglobin D, haemoglobin E, haemoglobin F, haemoglobin H; haemoglobin-haptoglobin complex, hemopexin, transferrin; and lactoferrin.

13. The isolated targeted delivery system according to any of claims 1 to 12, wherein the drug is selected from the group consisting of a protein, a nucleic acid a chemical non-protein non-nucleic acid compound with a molecular weight of less than 1 kD, preferably an anticancer drug, in particular a cytostatic drug, cytotoxic drug and prodrugs thereof; an anti arteriosclerotic drug; and anti-inflammatory drug; and photosensitizing compound; a virus, in particular oncolytic virus; and a α or ß radiation emitting radioisotope, which also emit a cell damaging amount of γ radiation, preferably selected from the group consisting of lutetium-177, ytterbium-90, iodine-

131, samarium-153, phosphorus-32, caesium-131, palladium-103, radium-233, iodine-125, and boron-10 or a cell damaging amount of α radiation, preferably selected from the group consisting of actinium-225, bismuth-213, lead-212, and polonium-212.

14. The isolated targeted delivery system according to claim 13, wherein the anticancer drug is selected from the group consisting of an apoptosis-inducing drug, an alkylating substance, anti-metabolites, antibiotics, epothilones, nuclear receptor agonists and antagonists, an anti-androgene, an anti-estrogen, a platinum compound, a hormone, a antihormone, an interferon, an inhibitor of cell cycle-dependent protein kinases (CDKs), an inhibitor of cyclooxygenases and/or lipoxygenases, a biogeneic fatty acid, a biogenic fatty acid derivative, including prostanoids and leukotrienes, an inhibitor of protein kinases, an inhibitor of protein phosphatases, an inhibitor of lipid kinases, a platinum coordination complex, an ethyleneimine, a methylmelamine, a triazine, a vinca alkaloid, a pyrimidine analog, a purine analog, an alkylsulfonate, a folic acid analog, an anthracendione, a substituted urea, and a methylhydrazin derivative, an ene-diyne antibiotic, a maytansinoid an auristatine derivate, immune check-point inhibitor, and an inhibitor of tumour-specific protein or marker, preferably a Rho-GDP-dissociation inhibitor, more preferably Grp94.

15. The isolated targeted delivery system according to claim 13, wherein the anticancer drug is a acediasulfone, aclarubicine, ambazone, aminoglutethimide, L-asparaginase, azathioprine, banoxantrone, bendamustine, bleomycin, busulfan, calcium folinate, carboplatin, carpecitabine, carmustine, celecoxib, chlorambucil, cis-platin, cladribine, cyclophosphamide, cytarabine, dacarbazine, dactinomycin dapsone, daunorubicin, dibrompropamidine, diethylstilbestrole, docetaxel, doxorubicin, enediynes, epirubicin, epothilone B, epothilone D, estramucin phosphate, estrogen, ethinylestradiole, etoposide, flavopiridol, floxuridine, fludarabine, fluorouracil, fluoxymesterone, flutamide fosfestrol, furazolidone, gemcitabine, gonadotropin releasing hormone analog, hexamethylmelamine, hydroxycarbamide, hydroxymethylnitrofurantoin, hydroxyprogesteronecaproat, hydroxyurea, idarubicin, idoxuridine, ifosfamide, interferon α, irinotecan, leuprolide, lomustine, lurtotecan, mafenide sulfate olamide, mechlorethamine, medroxyprogesterone acetate, megastrolacetate, melphalan, mepacrine, mercaptopurine, methotrexate, metronidazole, mitomycin C, mitopodozide, mitotane, mitoxantrone, mithramycin, nalidixic acid, nifuratel, nifuroxazide,

nifuralazine, nifurtimox, nimustine, ninorazole, nitrofurantoin, nitrogen mustards, oleomucin, oxolinic acid, pentamidine, pentostatin, phenazopyridine, phthalylsulfathiazole, pipobroman, prednimustine, prednisone, preussin, procarbazine, pyrimethamine, raltitrexed, rapamycin, rofecoxib, rosiglitazone, salazosulfapyridine, scriflavinium chloride, semustine streptozocine, sulfacarbamide, sulfacetamide, sulfachlopyridazine, sulfadiazine, sulfadicramide, sulfadimethoxine, sulfaethidole, sulfafurazole, sulfaguanidine, sulfaguanole, sulfamethizole, sulfamethoxazole, co-trimoxazole, sulfamethoxydiazine, sulfamethoxypyridazine, sulfamoxole, sulfanilamide, sulfaperin, sulfaphenazole, sulfathiazole, sulfisomidine, staurosporin, tamoxifen, taxol, teniposide, tertiposide, testolactone, testosteronpropionate, thioguanine, thiotepa, tinidazole, topotecan, triaziquone, treosulfan, trimethoprim, trofosfamide, UCN-01, vinblastine, vincristine, vindesine, vinblastine, vinorelbine, and zorubicin, preferably selected from the group consisting of auristatin, banoxantrone, bendamustine, chlorambucil, chaliceamycin, dynemycin A, maytansine, melphalan, mertansine, and neocazinostatin; or

wherein the anticancer drug is a proliferation inhibiting protein, preferably a cell cycle inhibitor or an antibody or antibody like binding protein that specifically binds to a proliferation promoting protein or a nucleic acid, preferably encoding a proliferation inhibiting protein or an antibody or antibody like binding protein that specifically binds to a proliferation promoting protein or a siRNA or DNAzyme.

16. The isolated targeted delivery system according to any of claim 1 to 13, wherein the drug is a hypoxia–activated prodrug, preferably selected from the group consisting of benzotriazine N-oxides, apaziquone (EO9), tirapazamine (TPN), SN30000, PR-104A, TH-302, TH-4000, AQ4N.

17. The isolated targeted delivery system according to any of claims 1 to 16, wherein:

(i) bond(s) between the iron binding protein(s) and the drug comprised in the complex are covalent and/or non-covalent; and/or

(ii) the drug comprised in the complex is entrapped/encapsulated by the iron binding protein or multimers thereof.

18. Method of preparation of the isolated targeted delivery system of claims 1 to 17 comprising steps of
    a) providing purified iron binding protein;
    b) covalently or non-covalently linking a drug to and/or encapsulating a drug in an iron binding protein;
    c) providing a $CD45^+$ leukocyte cell; and
    d) incubating the $CD45^+$ leukocyte cell in the presence of the iron binding protein produced in step b) until the $CD45^+$ leukocyte cell is at least partially loaded with the iron binding protein produced in step b).

19. The isolated targeted delivery system of any of claims 1-17 for use as a medicament.

20. A pharmaceutical composition comprising the isolated targeted delivery system of any of claims 1-17 and a pharmaceutically acceptable carrier and/or suitable excipient(s).

21. Use of an isolated targeted delivery system of any of claims 1-17 in the manufacture of a medicament for preventing/treating tumours, preferably a solid tumour, preferably breast cancer, pancreatic cancer, bladder cancer, lung cancer, colon cancer, or a tumour having hypoxic areas, inflammatory disease or ischemic areas in skin wounds or after organ infarctus (heart) or ischemic retina.