CLAIMS

1. An adjuvant composition comprising:

(a) an immunogenically effective amount of intact, bacterially derived minicells or killed bacterial cells that encapsulate a CD1d-restricted invariant Natural Killer T (iNKT) cell antigen;

(b) intact, bacterially derived minicells or killed bacterial cells that encapsulate an antineoplastic agent, and

(~~b~~c) at least one pharmaceutically acceptable carrier,

wherein: (i) the intact bacterially-derived minicells comprising an CD1d-restricted iNKT cell antigen do not comprise a targeting agent, and (ii) the intact bacterially-derived minicells comprising an antineoplastic agent comprise a targeting agent.

2. The adjuvant composition of claim ~~0~~1, wherein:

(a) the encapsulated CD1d-restricted iNKT cell antigen is capable of uptake by a phagocytic cell; and/or

(b) the encapsulated CD1d-restricted iNKT cell antigen is capable of uptake by a phagocytic cell and wherein the phagocytic cell is a dendritic cell or a macrophage.

3. The adjuvant composition of claim 1 or 2, wherein the CD1d-restricted iNKT cell antigen:

(a) induces a Th1 cytokine response by an iNKT cell that recognizes the antigen presented by CD1d; and/or

(b) is a glycosphingolipid; and/or

(c) is a glycosphingolipid which is selected from the group consisting of α-galactosylceramide (α-GalCer), C-glycosidific form of α-galactosylceramide (α-C-GalCer), 12 carbon acyl form of galactosylceramide (β-GalCer), β-D-glucopyranosylceramide (β-GlcCer), l,2-Diacyl-3-O-galactosyl-sn-glycerol (BbGL-II), diacylglycerol containing glycolipids (Glc-DAG-s2), ganglioside (GD3), gangliotriaosylceramide (Gg3Cer), glycosylphosphatidylinositol

(GPI), α-glucuronosylceramide (GSL-1 or GSL-4), isoglobotrihexosylceramide (iGb3), lipophosphoglycan(LPG), lyosphosphatidylcholine (LPC), α-galactosylceramide analog (OCH), threitolceramide, and a derivative of any thereof; and/or

(d) is a glycosphingolipid which is α-GalCer; and/or

(e) is a glycosphingolipid which is a synthetic α-GalCer analog; and/or

(f) is a glycosphingolipid which is a synthetic α-GalCer analog, wherein the synthetic α-GalCer analog is selected from the group consisting of 6′-deoxy-6′-acetamide α-GalCer (PBS57), naphtylurea α-GalCer (NU-α-GC), NC-α-GalCer, 4ClPhC-α-GalCer, PyrC-α-GalCer, α-carba-GalCer, carba-α-D-galactose α-GalCer analog (RCAI-56), 1-deoxy-neo-inositol α-GalCer analog (RCAI-59), 1-O-methylated α-GalCer analog (RCAI-92), and HS44 aminocyclitol ceramide; and/or

(g) is derived from a bacterial antigen, a fungal antigen, or a protozoan antigen.

~~4. The adjuvant composition of any one of claims 1-3, further comprising at least one antineoplastic agent.~~

~~5~~4. The adjuvant composition of claim ~~4~~1, wherein the antineoplastic agent is:

(a) is selected from the group consisting of a radionuclide, a chemotherapy drug, a functional nucleic acid, and a polynucleotide from which a functional nucleic acid can be transcribed; and/or

(b) a cytotoxin; and/or

(c) selected from the group consisting of morpholinyl anthracycline, a maytansinoid, duocarmycin, auristatins, calicheamicins (DNA damaging agents), α-amanitin (RNA polymerase II inhibitor), centanamycin, pyrrolobenzodiazepine, streptonigtin, nitrogen mustards, nitrosorueas, alkane sulfonates, pyrimidine analogs, purine analogs, antimetabolites, folate analogs, anthracyclines, taxanes, vinca alkaloids, topoisomerase inhibitors, hormonal agents, and a combination thereof; and/or

(d) a morpholinyl anthracycline selected from the group consisting of nemorubicin, PNU-159682, idarubicin, daunorubicin, caminomycin, and doxorubicin; and/or

(e) a functional nucleic acid selected from the group consisting of a siRNA, a miRNA, a shRNA, a lincRNA, an antisense RNA, and a ribozyme, and optionally wherein the functional nucleic acid inhibits a gene that promotes tumor cell proliferation, angiogenesis or resistance to chemotherapy and/or that inhibits apoptosis or cell cycle arrest.

~~6. The adjuvant composition of claim 4 or 5, wherein:~~

~~(a) the antineoplastic agent is comprised in an intact bacterially-derived minicell or killed bacterial cell; and/or~~

~~(b) the antineoplastic agent is comprised in an intact bacterially-derived minicell or killed bacterial cell, and wherein the intact bacterially-derived minicell comprising the antineoplastic agent further comprises a targeting agent.~~

~~7~~5. The adjuvant composition of claim ~~6~~1, wherein:

(a) the targeting agent is a bispecific ligand; and/or

(b) the targeting agent is a bispecific ligand and the bispecific ligand comprises a first arm that carries specificity for a minicell surface structure and a second arm that carries specificity for a non-phagocytotic mammalian cell surface receptor; and/or

(c) the targeting agent is a bispecific ligand and the bispecific ligand comprises a first arm that carries specificity for a minicell surface structure and a second arm that carries specificity for a non-phagocytotic mammalian cell surface receptor, wherein the minicell surface structure is an O-polysaccharide component of a lipopolysaccharide on the minicell surface; and/or

(d) the non-phagocytotic mammalian cell surface receptor of (b) or (c) is capable of activating macropinocytosis of the minicell or killed bacterial cell.

~~8~~6. The adjuvant composition of claim ~~7~~5, wherein:

(a) the bispecific ligand comprises a bispecific antibody or antibody fragment; and/or

(b) the bispecific ligand comprises a bispecific antibody or antibody fragment and wherein the antibody or antibody fragment comprises a first multivalent arm that carries specificity for a bacterially derived minicell surface structure and a second multivalent arm that

carries specificity for a cancer cell surface receptor, wherein the cancer cell surface receptor is capable of activating macropinocytosis of the minicell.

~~9~~7. Use of:

(a) an immunogenically effective amount of intact, bacterially derived minicells or killed bacterial cells that encapsulate a CD1d-restricted invariant Natural Killer T (iNKT) cell antigen; and

(b) intact, bacterially derived minicells comprising an antineoplastic agent that induces the death of neoplastic cells in a subject~~,~~

in the preparation of a medicament for combination therapy for treating a neoplastic disease in ~~a~~the subject,

wherein: (i) the intact bacterially-derived minicells comprising an CD1d-restricted iNKT cell antigen do not comprise a targeting agent, and (ii) the intact bacterially-derived minicells comprising an antineoplastic agent comprises a targeting agent.

~~10~~8. The use of claim ~~9~~7, wherein:

(a) the encapsulated CD1d-restricted iNKT cell antigen is capable of uptake by a phagocytic cell; and/or

(b) the encapsulated CD1d-restricted iNKT cell antigen is capable of uptake by a phagocytic cell, wherein the phagocytic cell is a dendritic cell or a macrophage; and/or

(c) the CD1d-restricted iNKT cell antigen induces a Th1 cytokine response by an iNKT cell that recognizes the antigen presented by CD1d; and/or

(d) the CD1d-restricted iNKT cell antigen is a glycosphingolipid; and/or

(e) the CD1d-restricted iNKT cell antigen is a glycosphingolipid and the glycosphingolipid is selected from the group consisting of α-galactosylceramide (α-GalCer), C-glycosidific form of α-galactosylceramide (α-C-GalCer), 12 carbon acyl form of galactosylceramide (β-GalCer), β-D-glucopyranosylceramide (β-GlcCer), l,2-Diacyl-3-O-galactosyl-sn-glycerol (BbGL-II), diacylglycerol containing glycolipids (Glc-DAG-s2), ganglioside (GD3), gangliotriaosylceramide (Gg3Cer), glycosylphosphatidylinositol (GPI), α-

glucuronosylceramide (GSL-1 or GSL-4), isoglobotrihexosylceramide (iGb3), lipophosphoglycan(LPG), lyosphosphatidylcholine (LPC), α-galactosylceramide analog (OCH), threitolceramide and a derivative of any thereof; and/or

(f) the CD1d-restricted iNKT cell antigen is a glycosphingolipid and the glycosphingolipid is α-GalCer; and/or

(g) the CD1d-restricted iNKT cell antigen is a glycosphingolipid and the glycosphingolipid is a synthetic α-GalCer analog; and/or

(h) the CD1d-restricted iNKT cell antigen is a glycosphingolipid and the glycosphingolipid is a synthetic α-GalCer analog which is selected from among 6′-deoxy-6′-acetamide α-GalCer (PBS57), naphtylurea α-GalCer (NU-α-GC), NC-α-GalCer, 4ClPhC-α-GalCer, PyrC-α-GalCer, α-carba-GalCer, carba-α-D-galactose α-GalCer analog (RCAI-56), 1-deoxy-neo-inositol α-GalCer analog (RCAI-59), 1-O-methylated α-GalCer analog (RCAI-92), and HS44 aminocyclitol ceramide; and/or

(i) the CD1d-restricted iNKT cell antigen is derived from a bacterial antigen, a fungal antigen, or a protozoan antigen.

~~11~~9. The use of claim ~~9~~7 or ~~10~~8, wherein:

(a) the antineoplastic agent is selected from the group consisting of a radionuclide, a chemotherapy drug, a functional nucleic acid, and a polynucleotide from which a functional nucleic acid can be transcribed; and/or

(b) the antineoplastic agent is:

(i) a cytotoxin; or

(ii) selected from the group consisting of morpholinyl anthracycline, a maytansinoid, duocarmycin, auristatins, calicheamicins (DNA damaging agents), α-amanitin (RNA polymerase II inhibitor), centanamycin, pyrrolobenzodiazepine, streptonigtin, nitrogen mustards, nitrosorueas, alkane sulfonates, pyrimidine analogs, purine analogs, antimetabolites, folate analogs, anthracyclines, taxanes, vinca alkaloids, topoisomerase inhibitors, hormonal agents, and a combination thereof; or

(iii) a morpholinyl anthracycline selected from the group consisting of

nemorubicin, PNU-159682, idarubicin, daunorubicin, caminomycin, and doxorubicin; or

(iv) a functional nucleic acid selected from the group consisting of a siRNA, a miRNA, a shRNA, a lincRNA, an antisense RNA, and a ribozyme, and optionally wherein the functional nucleic acid inhibits a gene that promotes tumor cell proliferation, angiogenesis or resistance to chemotherapy and/or that inhibits apoptosis or cell cycle arrest.

~~12. The use of claim 11, wherein:~~

~~(a) the chemotherapeutic drug is contained in an intact bacterially-derived minicell; and/or~~

~~(b) the chemotherapeutic drug is contained in an intact bacterially-derived minicell and wherein the intact bacterially-derived minicell comprising the chemotherapeutic drug further comprises a targeting agent.~~

1~~3~~0. The use of any one of claims ~~1~~27-9, wherein:

(a) the targeting agent is a bispecific ligand; and/or

(b) the targeting agent is a bispecific ligand and wherein the bispecific ligand comprises a first arm that carries specificity for a minicell surface structure and a second arm that carries specificity for a non-phagocytotic mammalian cell surface receptor;

(c) the targeting agent is a bispecific ligand and wherein the bispecific ligand comprises a first arm that carries specificity for a minicell surface structure and a second arm that carries specificity for a non-phagocytotic mammalian cell surface receptor, wherein the minicell surface structure is an O-polysaccharide component of a lipopolysaccharide on the minicell surface; and/or

(d) the non-phagocytotic mammalian cell surface receptor of (b) or (c) is capable of activating macropinocytosis of the minicell; and/or

(e) the targeting agent is a bispecific ligand and the bispecific ligand comprises a bispecific antibody or antibody fragment; and/or

(f) the targeting agent is a bispecific ligand and the bispecific ligand comprises a bispecific antibody or antibody fragment, wherein the antibody or antibody fragment comprises a first multivalent arm that carries specificity for a bacterially derived minicell surface structure

and a second multivalent arm that carries specificity for a cancer cell surface receptor, wherein the cancer cell surface receptor is capable of activating macropinocytosis of the minicell.

141. The use of any one of claims ~~97~~-1~~3~~0, wherein:

(a) the encapsulated CD1d-restricted iNKT cell antigen and the antineoplastic agent that induces the death of neoplastic cells are to be administered simultaneously; and/or

(b) wherein the encapsulated CD1d-restricted iNKT cell antigen and the antineoplastic agent that induces the death of neoplastic cells are to be administered sequentially; and/or

(c) the encapsulated CD1d-restricted iNKT cell antigen and the antineoplastic agent that induces the death of neoplastic cells are to be administered in the same composition; and/or

(d) the encapsulated CD1d-restricted iNKT cell antigen and the antineoplastic agent that induces the death of neoplastic cells are to be administered in separate compositions.

152. The use of any one of claims ~~97~~-141, wherein the subject is a mammal, a human, a non-human primate, a dog, a cat, a cow, a sheep, a horse, a rabbit, a mouse, or a rat.

163. The use of any one of claims ~~97~~-1~~5~~2, wherein:

(a) the neoplastic disease is cancer;

(b) the neoplastic disease is cancer and wherein the cancer is selected from the group consisting of lung cancer, breast cancer, brain cancer, liver cancer, colon cancer, pancreatic cancer, and bladder cancer;

(c) the neoplastic disease is cancer and wherein the cancer selected from the group consisting of an acute lymphoblastic leukemia; acute myeloid leukemia; adrenocortical carcinoma; AIDS-related cancers; AIDS-related lymphoma; anal cancer; appendix cancer; astrocytomas; atypical teratoid/rhabdoid tumor; basal cell carcinoma; bladder cancer; brain stem glioma; brain tumor; breast cancer; bronchial tumors; Burkitt lymphoma; cancer of unknown primary site; carcinoid tumor; carcinoma of unknown primary site; central nervous system atypical teratoid/rhabdoid tumor; central nervous system embryonal tumors; cervical cancer; childhood cancers; chordoma; chronic lymphocytic leukemia; chronic myelogenous leukemia;

chronic myeloproliferative disorders; colon cancer; colorectal cancer; craniopharyngioma; cutaneous T-cell lymphoma; endocrine pancreas islet cell tumors; endometrial cancer; ependymoblastoma; ependymoma; esophageal cancer; esthesioneuroblastoma; Ewing sarcoma; extracranial germ cell tumor; extragonadal germ cell tumor; extrahepatic bile duct cancer; gallbladder cancer; gastric (stomach) cancer; gastrointestinal carcinoid tumor; gastrointestinal stromal cell tumor; gastrointestinal stromal tumor (GIST); gestational trophoblastic tumor; glioma; hairy cell leukemia; head and neck cancer; heart cancer; Hodgkin lymphoma; hypopharyngeal cancer; intraocular melanoma; islet cell tumors; Kaposi sarcoma; kidney cancer; Langerhans cell histiocytosis; laryngeal cancer; lip cancer; liver cancer; malignant fibrous histiocytoma bone cancer; medulloblastoma; medulloepithelioma; melanoma; Merkel cell carcinoma; Merkel cell skin carcinoma; mesothelioma; metastatic squamous neck cancer with occult primary; mouth cancer; multiple endocrine neoplasia syndromes; multiple myeloma; multiple myeloma/plasma cell neoplasm; mycosis fungoides; myelodysplastic syndromes; myeloproliferative neoplasms; nasal cavity cancer; nasopharyngeal cancer; neuroblastoma; Non-Hodgkin lymphoma; nonmelanoma skin cancer; non-small cell lung cancer; oral cancer; oral cavity cancer; oropharyngeal cancer; osteosarcoma; other brain and spinal cord tumors; ovarian cancer; ovarian epithelial cancer; ovarian germ cell tumor; ovarian low malignant potential tumor; pancreatic cancer; papillomatosis; paranasal sinus cancer; parathyroid cancer; pelvic cancer; penile cancer; pharyngeal cancer; pineal parenchymal tumors of intermediate differentiation; pineoblastoma; pituitary tumor; plasma cell neoplasm/multiple myeloma; pleuropulmonaryblastoma; primary central nervous system (CNS) lymphoma; primary hepatocellular liver cancer; prostate cancer; rectal cancer; renal cancer; renal cell (kidney) cancer; renal cell cancer; respiratory tract cancer; retinoblastoma; rhabdomyosarcoma; salivary gland cancer; Sezary syndrome; small cell lung cancer; small intestine cancer; soft tissue sarcoma; squamous cell carcinoma; squamous neck cancer; stomach (gastric) cancer; supratentorial primitive neuroectodermal tumors; T-cell lymphoma; testicular cancer; throat cancer; thymiccarcinoma; thymoma; thyroid cancer; transitional cell cancer; transitional cell cancer of the renal pelvis and ureter; trophoblastic tumor; ureter cancer; urethral cancer; uterine cancer; uterine sarcoma; vaginal cancer; vulvar cancer; Waldenström macroglobulinemia; and

Wilms' tumor; and/or

(d) the neoplastic disease is cancer and wherein the cancer is malignant; and/or

(e) the neoplastic disease is cancer and wherein the cancer is a recurrent or relapsed cancer.

174. The use of any one of claims 97-163, wherein:

(a) the encapsulated CD1d-restricted iNKT cell antigen and/or the antineoplastic agent that induces the death of neoplastic cells is/are to be administered multiple times; and/or

(b) the encapsulated CD1d-restricted iNKT cell antigen and/or the antineoplastic agent that induces the death of neoplastic cells is/are to be administered at least once a week over the course of several weeks; and/or

(c) the encapsulated CD1d-restricted iNKT cell antigen and/or the antineoplastic agent that induces the death of neoplastic cells is/are to be administered at least once a week over several weeks to several months; and/or

(d) the encapsulated CD1d-restricted iNKT cell antigen and/or the antineoplastic agent that induces the death of neoplastic cells is/are to be administered at least once a week for about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, about 15, about 16, about 17, about 18, about 19 or about 20 weeks or more; and/or

(e) the encapsulated CD1d-restricted iNKT cell antigen and/or the antineoplastic agent that induces the death of neoplastic cells is/are to be administered about twice every week; and/or

(f) the encapsulated CD1d-restricted iNKT cell antigen and/or the antineoplastic agent that induces the death of neoplastic cells is/are to be administered twice a week for about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, about 15, about 16, about 17, about 18, about 19 or about 20 weeks or more.

185. Use of an adjuvant composition according to any one of claims 1- 86 for the preparation of a medicament for the treatment of a neoplastic disease.

196. The use of claim 185, wherein:

(a) the neoplastic disease is cancer;

(b) the neoplastic disease is cancer and wherein the cancer is selected from the group consisting of lung cancer, breast cancer, brain cancer, liver cancer, colon cancer, pancreatic cancer, and bladder cancer;

(c) the neoplastic disease is cancer and wherein the cancer selected from the group consisting of an acute lymphoblastic leukemia; acute myeloid leukemia; adrenocortical carcinoma; AIDS-related cancers; AIDS-related lymphoma; anal cancer; appendix cancer; astrocytomas; atypical teratoid/rhabdoid tumor; basal cell carcinoma; bladder cancer; brain stem glioma; brain tumor; breast cancer; bronchial tumors; Burkitt lymphoma; cancer of unknown primary site; carcinoid tumor; carcinoma of unknown primary site; central nervous system atypical teratoid/rhabdoid tumor; central nervous system embryonal tumors; cervical cancer; childhood cancers; chordoma; chronic lymphocytic leukemia; chronic myelogenous leukemia; chronic myeloproliferative disorders; colon cancer; colorectal cancer; craniopharyngioma; cutaneous T-cell lymphoma; endocrine pancreas islet cell tumors; endometrial cancer; ependymoblastoma; ependymoma; esophageal cancer; esthesioneuroblastoma; Ewing sarcoma; extracranial germ cell tumor; extragonadal germ cell tumor; extrahepatic bile duct cancer; gallbladder cancer; gastric (stomach) cancer; gastrointestinal carcinoid tumor; gastrointestinal stromal cell tumor; gastrointestinal stromal tumor (GIST); gestational trophoblastic tumor; glioma; hairy cell leukemia; head and neck cancer; heart cancer; Hodgkin lymphoma; hypopharyngeal cancer; intraocular melanoma; islet cell tumors; Kaposi sarcoma; kidney cancer; Langerhans cell histiocytosis; laryngeal cancer; lip cancer; liver cancer; malignant fibrous histiocytoma bone cancer; medulloblastoma; medulloepithelioma; melanoma; Merkel cell carcinoma; Merkel cell skin carcinoma; mesothelioma; metastatic squamous neck cancer with occult primary; mouth cancer; multiple endocrine neoplasia syndromes; multiple myeloma; multiple myeloma/plasma cell neoplasm; mycosis fungoides; myelodysplastic syndromes; myeloproliferative neoplasms; nasal cavity cancer; nasopharyngeal cancer; neuroblastoma; Non-Hodgkin lymphoma; nonmelanoma skin cancer; non-small cell lung cancer; oral cancer; oral cavity cancer; oropharyngeal cancer; osteosarcoma; other brain and spinal cord tumors; ovarian cancer; ovarian

epithelial cancer; ovarian germ cell tumor; ovarian low malignant potential tumor; pancreatic cancer; papillomatosis; paranasal sinus cancer; parathyroid cancer; pelvic cancer; penile cancer; pharyngeal cancer; pineal parenchymal tumors of intermediate differentiation; pineoblastoma; pituitary tumor; plasma cell neoplasm/multiple myeloma; pleuropulmonaryblastoma; primary central nervous system (CNS) lymphoma; primary hepatocellular liver cancer; prostate cancer; rectal cancer; renal cancer; renal cell (kidney) cancer; renal cell cancer; respiratory tract cancer; retinoblastoma; rhabdomyosarcoma; salivary gland cancer; Sezary syndrome; small cell lung cancer; small intestine cancer; soft tissue sarcoma; squamous cell carcinoma; squamous neck cancer; stomach (gastric) cancer; supratentorial primitive neuroectodermal tumors; T-cell lymphoma; testicular cancer; throat cancer; thymiccarcinoma; thymoma; thyroid cancer; transitional cell cancer; transitional cell cancer of the renal pelvis and ureter; trophoblastic tumor; ureter cancer; urethral cancer; uterine cancer; uterine sarcoma; vaginal cancer; vulvar cancer; Waldenström macroglobulinemia; and Wilms' tumor; and/or

(d) the neoplastic disease is cancer and wherein the cancer is malignant; and/or

(e) the neoplastic disease is cancer and wherein the cancer is a recurrent or relapsed.