Porous Nanoparticle-Supported Lipid Bilayers (Protocells) for Targeted Delivery Including Transdermal Delivery of Cargo and Methods Thereof

Related Applications and Government Support

This invention claims the benefit of priority of United States Provisional Application Serial No. 61/547,402, filed October 14, 2011, entitled "Engineering Nanoporous Particle-Supported Lipid Bilayers ('Protocells') for Transdermal Cargo Delivery", and United States Provisional Application Serial No. 61/578,463, filed December 21, 2011, entitled "Engineering Nanoporous Particle-Supported Lipid Bilayers ('Protocells') for Transdermal Cargo Delivery", ~~the entire contents of which are incorporated by reference herein~~.

This invention also claims the benefit of priority of United States Provisional Application Serial No. 61/577,410, filed December 19, 2011, entitled "Delivery of Therapeutic Macromolecular Cargos by Targeted Protocells", ~~the entire contents of which are incorporated by reference herein~~.

This invention was made with government support under grant no. PHS 2 PN2 EY016570B of the National Institutes of Health; grant no. awarded by 1U01CA151792-01 of the National Cancer Institute; grant no. FA 9550-07-1-0054/9550-10-1-0054 of the Air Force Office of Scientific Research; 1U19ES019528-01 of NIEHS; NSF:EF-0820117 of the National Science Foundation and DGE-0504276 of the National Science Foundation. The government has certain rights in the invention.

Field of the Invention

Embodiments of the present invention are directed to protocells for specific targeting of cells within a patient's body, especially including hepatocellular and other cancer cells which comprise a 1) a nanoporous silica or metal oxide core; 2) a supported lipid bilayer; 3) at least one agent which facilitates cancer cell death (such as a traditional small molecule, a macromolecular cargo (e.g. siRNA, shRNA other micro RNA, or a protein toxin such as ricin toxin A-chain or diphtheria toxin A-chain) and/or DNA, including double stranded or linear DNA, plasmid DNA which may be supercoiled and/or packaged such as with histones and disposed within the nanoporous silica core (preferably supercoiled in order to more efficiently package the DNA into protocells) which is optionally modified with a nuclear

silica shell. For example, the hydrolysis can be carried out by addition of ammonium hydroxide to the mixture comprising silica precursor(s) and conjugated silica precursor(s).

Silica precursors are compounds which under hydrolysis conditions can form silica. Examples of silica precursors include, but are not limited to, organosilanes such as, for example, tetraethoxysilane (TEOS), tetramethoxysilane (TMOS) and the like.

The silica precursor used to form the conjugated silica precursor has a functional group or groups which can react with the absorbing molecule or molecules to form a covalent bond or bonds. Examples of such silica precursors include, but is not limited to, isocyanatopropyltriethoxysilane (ICPTS), aminopropyltrimethoxysilane (APTS), mercaptopropyltrimethoxysilane (MPTS), and the like.

In one embodiment, an organosilane (conjugatable silica precursor) used for forming the core has the general formula R_{4n} SiX_n, where X is a hydrolyzable group such as ethoxy, methoxy, or 2-methoxy-ethoxy; R can be a monovalent organic group of from 1 to 12 carbon atoms which can optionally contain, but is not limited to, a functional organic group such as mercapto, epoxy, acrylyl, methacrylyl, or amino; and n is an integer of from 0 to 4. The conjugatable silica precursor is conjugated to an absorber molecule and subsequently co-condensed for forming the core with silica precursors such as, for example, TEOS and TMOS. A silane used for forming the silica shell has n equal to 4. The use of functional mono-, bis- and tris-alkoxysilanes for coupling and modification of co-reactive functional groups or hydroxy-functional surfaces, including glass surfaces, is also known, see Kirk-Othmer, Encyclopedia of Chemical Technology, Vol. 20, 3rd Ed., J. Wiley, N.Y.; *see also* E. Pluedemann, Silane Coupling Agents, Plenum Press, N.Y. 1982. The organo-silane can cause gels, so it may be desirable to employ an alcohol or other known stabilizers. Processes to synthesize core-shell nanoparticles using modified Stoeber processes can be found in U.S. patent applications Ser. Nos. 10/306,614 and 10/536, 569~~, the disclosure of such processes therein are incorporated herein by reference~~.

"Amine-containing silanes" include, but are not limited to, a primary amine, a secondary amine or a tertiary amine functionalized with a silicon atom, and may be a monoamine or a polyamine such as diamine. Preferably, the amine-containing silane is N-(2-aminoethyl)-3-aminopropyltrimethoxysilane (AEPTMS). Non-limiting examples of amine-

What is claimed is:

1. A ~~cell-targeting porous~~ protocell composition comprising a plurality of protocells, the protocells comprising:

a nanoporous silica or metal oxide core with a supported lipid bilayer and at least one further component selected from the group consisting of:

a cell targeting species;

a fusogenic peptide that promotes endosomal escape of protocells; and

~~encapsulated DNA, and other cargo comprising~~

at least one cargo component selected from the group consisting of:

double stranded linear DNA~~;~~,

plasmid DNA~~;~~,

a drug~~;~~,

an imaging agent,

small interfering RNA,

small hairpin RNA,

microRNA,

~~or~~ and a mixture thereof,

wherein one of said cargo components is optionally conjugated further with a nuclear localization sequence; and

wherein the plurality of protocells is monodisperse.

2. The protocell composition according to claim 1 wherein said silica or metal oxide cores of the protocells ~~is~~ are spherical and ranges in diameter from about 10 nm to about 250 nm.

~~3. The protocell according to claim 2 wherein said silica core has a mean diameter of about 150 nm.~~

43. The protocell composition according to ~~either of~~ claims ~~2~~ 1 or ~~3~~ 2 wherein said silica or metal oxide cores of the protocells ~~is~~ are monodisperse ~~or polydisperse in size distribution~~.

~~5. The protocell according to either of claims 2 or 3 wherein said silica core is monodisperse.~~

~~6. The procell according to either of claims 2 or 3 wherein said silica core is polydisperse.~~

~~7~~4. The protocell composition according to any one of claims 1-~~6~~ 3 wherein said lipid bilayer is comprised of lipids selected from the group consisting of 1,2-dioleoyl-*sn*-glycero-3-phosphocholine (DOPC), 1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine (DPPC), 1,2-distearoyl-*sn*-glycero-3-phosphocholine (DSPC), 1,2-dioleoyl-sn-glycero-3-[phosphor-L-serine] (DOPS), 1,2-dioleoyl-3-trimethylammonium-propane (18:1 DOTAP), 1,2-dioleoyl-*sn*-glycero-3-phospho-(1'-*rac*-glycerol) (DOPG), 1,2-dioleoyl-*sn*-glycero-3-phosphoethanolamine (DOPE), 1,2-dipalmitoyl-*sn*-glycero-3-phosphoethanolamine (DPPE), 1,2-dioleoyl-*sn*-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)-2000] (18:1 PEG-2000 PE), 1,2-dipalmitoyl-*sn*-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)-2000] (16:0 PEG-2000 PE), 1-Oleoyl-2-[12-[(7-nitro-2-1,3-benzoxadiazol-4-yl)amino]lauroyl]-*sn*-Glycero-3-Phosphocholine (18:1-12:0 NBD PC), 1-palmitoyl-2-{12-[(7-nitro-2-1,3-benzoxadiazol-4-yl)amino]lauroyl}-*sn*-glycero-3-phosphocholine (16:0-12:0 NBD PC), cholesterol and mixtures thereof.

~~8. The protocell according to any of claims 1-7 wherein said lipid bilayer comprises DOPC in combination with DOPE.~~

~~9~~5. The protocell composition according to any one of claims 1-~~7~~ 4 wherein said lipid bilayer comprises DOPC, DOPE, DOTAP, DOPG, DOPC or mixtures thereof.

~~10. The protocell according to any of claims 1-7 wherein said lipid bilayer comprises DOPG and DOPC.~~

~~11~~6. The protocell composition according to any one of claims ~~8~~1-~~10~~ 5 wherein said lipid bilayer further comprises cholesterol.

~~12~~7. The protocell composition according to any one of claims 1-~~7~~ 6 wherein said lipid bilayer comprises DOPC in combination with about 5 wt% DOPE, about 30 wt% cholesterol, and about 10 wt% PEG-2000 PE (18:1).

~~13. The protocell according to any of claims 1-7 wherein lipid bilayer comprises about 5% by weight DOPE, about 5% by weight PEG, about 30% by weight cholesterol, about 60% by weight DOPC and/or DPPC.~~

~~14~~8. The protocell composition according to claim ~~13~~ 7 wherein said PEG is conjugated to said DOPE.

~~15~~9. The protocell composition according to any one of claims 1-~~14~~ 8 wherein said targeting species is a targeting peptide.

~~16~~10. The protocell composition according to claim ~~15~~ 9 wherein said targeting peptide is a SP94 peptide or a MET binding peptide.

~~17~~11. The protocell composition according to claim ~~16~~ 10 wherein said targeting peptide is SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID No. 4 or SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7 or SEQ ID NO: 8.

~~18. The protocell according to claim 15 wherein said targeting peptide is a MET binding peptide according to SEQ ID NO: 1, SEQ ID NO: 2, SEQ I.D. NO: 3, SEQ I.D. No. 4 or SEQ ID NO: 5.~~

~~19~~12. The protocell composition according to any one of claims 1-~~18~~ 11 wherein said fusogenic protein is H5WYG peptide (SEQ ID NO: 13) or an eight mer of polyarginine (SEQ ID NO: 14).

~~20. The protocell according to claim 19 wherein said fusogenic peptide is SEQ ID NO: 13.~~

~~21~~13. The protocell composition according to any one of claims 1-~~20~~ 12 comprising plasmid DNA~~, wherein said plasmid DNA is optionally modified to express a nuclear localization sequence~~.

~~22~~14. The protocell composition according to ~~21~~ claim 13 wherein said plasmid DNA is supercoiled and/or packaged plasmid DNA

~~23. The protocell according to claim 22 wherein said DNA is both supercoiled and packaged plasmid DNA.~~

~~24~~15. The protocell composition according to ~~any of~~ claims ~~20-23~~13 or 14 wherein said plasmid DNA is modified to express a nuclear localization sequence.

~~25~~16. The protocell composition according to any one of claims ~~21~~13-~~24~~-15 wherein said DNA is histone-packaged supercoiled plasmid DNA comprises a mixture of human histone proteins.

~~26. The protocell according to claim 25 wherein said mixture of histones consists of H1, H2A, H2B, H3, and H4.~~

~~27. The protocell according to claim 25 wherein said mixture of histones is H1, H2A, H2B, H3 and H4 is in a weight ratio of 1:2:2:2:2.~~

~~28~~17. The protocell composition according to any one of claims ~~1-27~~13-16 wherein said plasmid DNA is capable of expressing a polypeptide toxin, a small hairpin RNA (shRNA) or a small interfering RNA (siRNA).

~~29~~18. The protocell composition according to claim ~~28~~-17 wherein said polypeptide toxin is selected from the group consisting of ricin toxin chain-A or diphtheria toxin chain-A.

~~30~~19. The protocell composition according to claims 1 or ~~28~~-17 wherein ~~said shRNA or~~ said siRNA ~~induces apoptosis of a cell~~is selected from the group consisting of s565, s7824 and s10234.

20. The protocell composition according to claims 1 or 17 wherein said shRNA is a cyclin B1-specific shRNA.

~~31~~21. The protocell composition according to any one of claims 1-~~30~~-20 wherein said DNA is capable of expressing a reporter protein.

~~32~~22. The protocell composition according to ~~claim 31~~any one of claims 1-21 wherein said ~~reporter protein is green fluorescent protein or red fluorescent protein~~ cargo component is conjugated with a nuclear localization sequence.

~~33~~23. The protocell composition according to any one of claims 1-~~32~~ 22 wherein said nuclear localization sequence is a peptide according to SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11 or SEQ ID NO: 12.

~~34. The protocell according to any of claims 1-33 wherein said nuclear localization sequence is a peptide according to SEQ ID NO: 9.~~

~~35~~24. The protocell composition according to any one of claims 1-~~34~~ 23 ~~futher comprising as~~wherein the cargo is a drug, and the drug is an anticancer agent.

~~36~~25. The protocell composition according to claim ~~35~~ 24 wherein said anticancer agent is everolimus, trabectedin, abraxane, TLK 286, AV-299, DN-101 , pazopanib, GSK690693, RTA 744, ON 0910.Na, AZD 6244 (ARRY-142886), AMN-107, TKI-258, GSK461364, AZD 1152, enzastaurin, vandetanib, ARQ-197, MK-0457, MLN8054, PHA-739358, R-763, AT-9263, a FLT-3 inhibitor, a VEGFR inhibitor, an EGFR TK inhibitor, an aurora kinase inhibitor, a PIK-1 modulator, a Bcl-2 inhibitor, an HDAC inhbitor, a c-MET inhibitor, a PARP inhibitor, a Cdk inhibitor, an EGFR TK inhibitor, an IGFR-TK inhibitor, an anti-HGF antibody, a PI3 kinase inhibitors, an AKT inhibitor, a JAK/STAT inhibitor, a checkpoint-1 or 2 inhibitor, a focal adhesion kinase inhibitor, a Map kinase kinase (mek) inhibitor, a VEGF trap antibody, pemetrexed, erlotinib, dasatanib, nilotinib, decatanib, panitumumab, amrubicin, oregovomab, Lep-etu, nolatrexed, azd2171, batabulin, ofatumumab, zanolimumab, edotecarin, tetrandrine, rubitecan, tesmilifene, oblimersen, ticilimumab, ipilimumab, gossypol, Bio 111 , 131-I-TM-601 , ALT-110, BIO 140, CC 8490, cilengitide, gimatecan, IL13-PE38QQR, INO 1001 , $IPdR_1$ KRX-0402, lucanthone, LY 317615, neuradiab, vitespan, Rta 744, Sdx 102, talampanel, atrasentan, Xr 311 , romidepsin, ADS-100380, sunitinib, 5-fluorouracil, vorinostat, etoposide, gemcitabine, doxorubicin, 5'-deoxy-5-fluorouridine, vincristine, temozolomide, ZK-304709, seliciclib; PD0325901 , AZD-6244, capecitabine, L-Glutamic acid, N -[4-[2-(2-amino-4,7-dihydro-4-oxo-1 H - pyrrolo[2,3- d]pyrimidin-5-yl)ethyl]benzoyl]-, disodium salt, heptahydrate, camptothecin, PEG-labeled irinotecan, tamoxifen, toremifene citrate, anastrazole, exemestane, letrozole,

DES(diethylstilbestrol), estradiol, estrogen, conjugated estrogen, bevacizumab, IMC-1C11 , CHIR-258,); 3-[5-(methylsulfonylpiperadinemethyl)- indolylj-quinolone, vatalanib, AG-013736, AVE-0005, the acetate salt of [D- Ser(Bu t) 6 ,Azgly 10] (pyro-Glu-His-Trp-Ser-Tyr-D-Ser(Bu t)-Leu-Arg-Pro- Azgly-NH_2 acetate [$C_{59}H_{84}N_{18}Oi_4$ -$(C_2H_4O_2)_X$ where x = 1 to 2.4], goserelin acetate, leuprolide acetate, triptorelin pamoate, medroxyprogesterone acetate, hydroxyprogesterone caproate, megestrol acetate, raloxifene, bicalutamide, flutamide, nilutamide, megestrol acetate, CP-724714; TAK-165, HKI-272, erlotinib, lapatanib, canertinib, ABX-EGF antibody, erbitux, EKB-569, PKI-166, GW-572016, Ionafarnib, BMS-214662, tipifarnib; amifostine, NVP-LAQ824, suberoyl analide hydroxamic acid, valproic acid, trichostatin A, FK-228, SU11248, sorafenib, KRN951 , aminoglutethimide, arnsacrine, anagrelide, L-asparaginase, Bacillus Calmette-Guerin (BCG) vaccine, bleomycin, buserelin, busulfan, carboplatin, carmustine, chlorambucil, cisplatin, cladribine, clodronate, cyproterone, cytarabine, dacarbazine, dactinomycin, daunorubicin, diethylstilbestrol, epirubicin, fludarabine, fludrocortisone, fluoxymesterone, flutamide, gemcitabine, gleevac, hydroxyurea, idarubicin, ifosfamide, imatinib, leuprolide, levamisole, lomustine, mechlorethamine, melphalan, 6-mercaptopurine, mesna, methotrexate, mitomycin, mitotane, mitoxantrone, nilutamide, octreotide, oxaliplatin, pamidronate, pentostatin, plicamycin, porfimer, procarbazine, raltitrexed, rituximab, streptozocin, teniposide, testosterone, thalidomide, thioguanine, thiotepa, tretinoin, vindesine, 13-cis-retinoic acid, phenylalanine mustard, uracil mustard, estramustine, altretamine, floxuridine, 5-deooxyuridine, cytosine arabinoside, 6-mecaptopurine, deoxycoformycin, calcitriol, valrubicin, mithramycin, vinblastine, vinorelbine, topotecan, razoxin, marimastat, COL-3, neovastat, BMS-275291 , squalamine, endostatin, SU5416, SU6668, EMD121974, interleukin-12, IM862, angiostatin, vitaxin, droloxifene, idoxyfene, spironolactone, finasteride, cimitidine, trastuzumab, denileukin diftitox,gefitinib, bortezimib, paclitaxel, cremophor-free paclitaxel, docetaxel, epithilone B, BMS- 247550, BMS-310705, droloxifene, 4-hydroxytamoxifen, pipendoxifene, ERA- 923, arzoxifene, fulvestrant, acolbifene, lasofoxifene, idoxifene, TSE-424, HMR-3339, ZK186619, topotecan, PTK787/ZK 222584, VX-745, PD 184352, rapamycin, 40-O-(2-hydroxyethyl)-rapamycin, temsirolimus, AP-23573, RAD001 , ABT-578, BC-210, LY294002, LY292223, LY292696, LY293684, LY293646, wortmannin, ZM336372, L-779,450, PEG-filgrastim, darbepoetin, erythropoietin, granulocyte colony-stimulating factor, zolendronate, prednisone, cetuximab, granulocyte macrophage colony-stimulating factor, histrelin, pegylated interferon alfa-2a, interferon alfa-2a, pegylated interferon alfa-2b, interferon alfa-2b, azacitidine, PEG-L-asparaginase, lenalidomide, gemtuzumab,

hydrocortisone, interleukin-11 , dexrazoxane, alemtuzumab, all-transretinoic acid, ketoconazole, interleukin-2, megestrol, immune globulin, nitrogen mustard, methylprednisolone, ibritgumomab tiuxetan, androgens, decitabine, hexamethylmelamine, bexarotene, tositumomab, arsenic trioxide, cortisone, editronate, mitotane, cyclosporine, liposomal daunorubicin, Edwina-asparaginase, strontium 89, casopitant, netupitant, an NK-1 receptor antagonists, palonosetron, aprepitant, , diphenhydramine, hydroxyzine, metoclopramide, lorazepam, alprazolam, haloperidol, droperidol, dronabinol, dexamethasone, methylprednisolone, prochlorperazine, granisetron, ondansetron, dolasetron, tropisetron, pegfilgrastim, erythropoietin, epoetin alfa, darbepoetin alfa or a mixture thereof.

26. The protocell composition according to any one of claims 1-23 wherein said drug is nexavar (sorafenib), sunitinib, bevacizumab, tarceva (erlotinib), tykerb (lapatinib) or a mixture thereof.

~~37~~27. The protocell composition according to any one of claims 1~~-36~~-23 wherein said drug comprises an antiviral agent.

~~38. The protocell according to claim 37 wherein said antiviral agent is an anti-HIV agent, an anti-HBV agent or an anti-HCV agent.~~

~~39. A protocell comprising a nanoporous silica core with a supported lipid bilayer and a MET binding peptide according to SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO:3, SEQ ID. NO: 4 or SEQ ID NO: 5.~~

~~40. The protocell according to claim 31 wherein said MET binding peptide is a peptide according to SEQ ID NO:1.~~

~~41~~28. The protocell composition according to ~~claim 39 or 40~~any one of claims 10-12 wherein said ~~MET binding~~targeting peptide is conjugated to said lipid bilayer.

~~42. The protocell according to any of claims 39-41 wherein said protocell further comprises at least one component selected from the group consisting of a fusogenic peptide that promotes endosomal escape of protocells and encapsulated DNA; a plasmid DNA; double stranded linear DNA, a drug; an imaging agent, small interfering RNA, small hairpin~~

~~RNA and micro RNA wherein said plasmid DNA, said drug, said imaging agent and/or said RNA are further conjugated with a nuclear localization sequence.~~

~~43. A protocell according to claim 42 wherein said drug comprises at least one one anticancer agent.~~

~~44. The protocell according to claim 43 wherein said anticancer agent is selected from the group consisting of everolimus, trabectedin, abraxane, TLK 286, AV-299, DN-101 , pazopanib, GSK690693, RTA 744, ON 0910.Na, AZD 6244 (ARRY-142886), AMN-107, TKI-258, GSK461364, AZD 1152, enzastaurin, vandetanib, ARQ-197, MK-0457, MLN8054, PHA-739358, R-763, AT-9263, a FLT-3 inhibitor, a VEGFR inhibitor, an EGFR-TK inhibitor, an aurora kinase inhibitor, a PIK-1 modulator, a Bcl-2 inhibitor, an HDAC inhbitor, a c-MET inhibitor, a PARP inhibitor, a Cdk inhibitor, an EGFR-TK inhibitor, an IGFR-TK inhibitor, an anti-HGF antibody, a PI3 kinase inhibitors, an AKT inhibitor, a JAK/STAT inhibitor, a checkpoint-1 or 2 inhibitor, a focal adhesion kinase inhibitor, a Map kinase kinase (mek) inhibitor, a VEGF trap antibody, pemetrexed, erlotinib, dasatanib, nilotinib, decatanib, panitumumab, amrubicin, oregovomab, Lep-etu, nolatrexed, azd2171, batabulin, ofatumumab, zanolimumab, edotecarin, tetrandrine, rubitecan, tesmilifene, oblimersen, ticilimumab, ipilimumab, gossypol, Bio 111 , 131-I-TM-601 , ALT-110, BIO 140, CC 8490, cilengitide, gimatecan, IL13-PE38QQR, INO-1001 , IPdR$_1$-KRX-0402, lucanthone, LY 317615, neuradiab, vitespan, Rta 744, Sdx-102, talampanel, atrasentan, Xr-311 , romidepsin, ADS- 100380, sunitinib, 5-fluorouracil, vorinostat, etoposide, gemcitabine, doxorubicin, 5'-deoxy-5-fluorouridine, vincristine, temozolomide, ZK-304709, seliciclib; PD0325901 , AZD-6244, capecitabine, L-Glutamic acid, N -[4-[2-(2-amino-4,7-dihydro-4-oxo-1 H - pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl] , disodium salt, heptahydrate, camptothecin, PEG-labeled irinotecan, tamoxifen, toremifene citrate, anastrazole, exemestane, letrozole, DES(diethylstilbestrol), estradiol, estrogen, conjugated estrogen, bevacizumab, IMC-1C11 , CHIR-258,); 3-[5-(methylsulfonylpiperadinemethyl)- indolylj-quinolone, vatalanib, AG-013736, AVE 0005, the acetate salt of [D- Ser(Bu t) 6 ,Azgly 10] (pyro-Glu-His-Trp-Ser-Tyr-D-Ser(Bu t)-Leu-Arg-Pro- Azgly-NH$_2$ acetate [$C_{59}H_{84}N_{18}Oi_4$-($C_2H_4O_2$)$_X$ where x = 1 to 2.4], goserelin acetate, leuprolide acetate, triptorelin pamoate, medroxyprogesterone acetate, hydroxyprogesterone caproate, megestrol acetate, raloxifene, bicalutamide, flutamide, nilutamide, megestrol acetate, CP-724714; TAK-165, HKI-272, erlotinib, lapatanib, canertinib, ABX-EGF antibody, erbitux, EKB-569, PKI-166, GW-572016, Ionafarnib, BMS-~~

214662, tipifarnib; amifostine, NVP-LAQ824, suberoyl analide hydroxamic acid, valproic acid, trichostatin A, FK-228, SU11248, sorafenib, KRN951 , aminoglutethimide, arnsacrine, anagrelide, L-asparaginase, Bacillus Calmette-Guerin (BCG) vaccine, bleomycin, buserelin, busulfan, carboplatin, carmustine, chlorambucil, cisplatin, cladribine, clodronate, cyproterone, cytarabine, dacarbazine, dactinomycin, daunorubicin, diethylstilbestrol, epirubicin, fludarabine, fludrocortisone, fluoxymesterone, flutamide, gemcitabine, gleevac, hydroxyurea, idarubicin, ifosfamide, imatinib, leuprolide, levamisole, lomustine, mechlorethamine, melphalan, 6-mercaptopurine, mesna, methotrexate, mitomycin, mitotane, mitoxantrone, nilutamide, octreotide, oxaliplatin, pamidronate, pentostatin, plicamycin, porfimer, procarbazine, raltitrexed, rituximab, streptozocin, teniposide, testosterone, thalidomide, thioguanine, thiotepa, tretinoin, vindesine, 13-cis-retinoic acid, phenylalanine mustard, uracil mustard, estramustine, altretamine, floxuridine, 5-deooxyuridine, cytosine arabinoside, 6-mecaptopurine, deoxycoformycin, calcitriol, valrubicin, mithramycin, vinblastine, vinorelbine, topotecan, razoxin, marimastat, COL-3, neovastat, BMS-275291 , squalamine, endostatin, SU5416, SU6668, EMD121974, interleukin-12, IM862, angiostatin, vitaxin, droloxifene, idoxyfene, spironolactone, finasteride, cimitidine, trastuzumab, denileukin diftitox,gefitinib, bortezimib, paclitaxel, cremophor-free paclitaxel, docetaxel, epithilone B, BMS- 247550, BMS-310705, droloxifene, 4-hydroxytamoxifen, pipendoxifene, ERA- 923, arzoxifene, fulvestrant, acolbifene, lasofoxifene, idoxifene, TSE-424, HMR-3339, ZK186619, topotecan, PTK787/ZK 222584, VX-745, PD 184352, rapamycin, 40-O-(2-hydroxyethyl)-rapamycin, temsirolimus, AP-23573, RAD001 , ABT-578, BC-210, LY294002, LY292223, LY292696, LY293684, LY293646, wortmannin, ZM336372, L-779,450, PEG-filgrastim, darbepoetin, erythropoietin, granulocyte colony-stimulating factor, zolendronate, prednisone, cetuximab, granulocyte macrophage colony-stimulating factor, histrelin, pegylated interferon alfa-2a, interferon alfa-2a, pegylated interferon alfa-2b, interferon alfa-2b, azacitidine, PEG-L asparaginase, lenalidomide, gemtuzumab, hydrocortisone, interleukin-11 , dexrazoxane, alemtuzumab, all-transretinoic acid, ketoconazole, interleukin-2, megestrol, immune globulin, nitrogen mustard, methylprednisolone, ibritgumomab tiuxetan, androgens, decitabine, hexamethylmelamine, bexarotene, tositumomab, arsenic trioxide, cortisone, editronate, mitotane, cyclosporine, liposomal daunorubicin, Edwina-asparaginase, strontium-89, casopitant, netupitant, an NK-1 receptor antagonists, palonosetron, aprepitant, , diphenhydramine, hydroxyzine, metoclopramide, lorazepam, alprazolam, haloperidol, droperidol, dronabinol, dexamethasone,

~~methylprednisolone, prochlorperazine, granisetron, ondansetron, dolasetron, tropisetron, pegfilgrastim, erythropoietin, epoetin alfa, darbepoetin alfa and mixtures thereof.~~

~~45. The protocell according to any of claims 39-45 wherein said drug comprises at least one antiviral agent.~~

~~46. The protocell according to claim 45 wherein said antiviral agent is an anti-HIV agent, an anti-HBV agent, an anti-HCV agent or mixtures thereof.~~

~~47. A protocell according to any of claims 39-46 wherein said DNA is capable of expressing at least one reporter molecule.~~

~~48. The protocell according to any of claims 39-47 comprisng plasmid DNA, wherein said plasmid DNA is optionally modified to express a nuclear localization sequence.~~

~~49. The protocell according to 48 wherein said DNA is supercoiled or packaged plasmid DNA~~

~~50. The protocell according to claim 49 wherein said DNA is both supercoiled and packaged plasmid DNA.~~

~~51. The protocell according to any of claims 48-51 wherein said plasmid DNA is modified to express a nuclear localization sequence.~~

~~52. The protocell according to any of claims 47-51 wherein said DNA is histone-packaged supercoiled plasmid DNA comprises a mixture of human histone proteins.~~

~~53. The protocell according to claim 52 wherein said mixture of histones consists of H1, H2A, H2B, H3, and H4.~~

~~54. The protocell according to claim 53 wherein said mixture of histones is H1, H2A, H2B, H3 and H4 is in a weight ratio of 1:2:2:2:2.~~

~~55. The protocell according to any of claims 48-54 wherein said plasmid DNA is capable of expressing a polypeptide toxin, a small hairpin RNA (shRNA) or a small interfering RNA (siRNA).~~

~~56. The protocell according to claim 55 wherein said polypeptide toxin is selected from the group consisting of ricin toxin chain-A or diphtheria toxin chain-A.~~

~~57. The protocell according to claim 55 wherein said shRNA or said siRNA induces apoptosis of a cell.~~

~~58. The protocell according to any of claims 48-57 wherein said plasmid DNA is capable of expressing a reporter protein.~~

~~59. The protocell according to claim 58 wherein said reporter protein is green fluorescent protein or red fluorescent protein.~~

~~60. The protocell according to any of claims 39-59 wherein said nuclear localization sequence is a peptide according to SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11 or SEQ ID NO: 12.~~

~~61. The protocell according to claim 60 wherein said nuclear localization sequence is a peptide according to SEQ ID NO: 9.~~

~~62. A pharmaceutical composition comprising a population of protocells according to any of claims 1-61 in an amount effective for effecting a therapeutic effect in combination with a pharmaceutically acceptable carrier, additive or excipient.~~

~~63. The composition according to claim 62 further comprising a drug which is not disposed as cargo within the protocell.~~

~~64. The composition according to claim 63 wherein said drug is an anti-cancer agent or an anti-viral agent.~~

~~65. The composition according to claim 64 wherein said anti-viral agent is an anti-HIV agent, anti-HBV agent, an anti-HCV agent or mixtures thereof.~~

~~66. The composition according to any of claims 62-65 in parenteral dosage form.~~

~~67. The composition according to claim 66 wherein said dosage form is intradermal, intramuscular, intraosseous, intraperitoneal, intravenous, subcutaneous or intrathecal.~~

~~68. The composition according to any of claims 62-65 in topical or transdermal dosage form.~~

~~69. A MET binding peptide according to SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO:3, SEQ ID. NO: 4 or SEQ ID NO: 5.~~

~~70. A MET binding peptide of claim 69 according to SEQ ID NO: 1.~~

~~71. A pharmaceutical compostion comprising a MET binding peptide according to claim 69 or 70.~~

~~72. A pharmacetucial composition comprising a population of protocells which comprise a targeting peptide so that the protocells selectively bind to hepatocellular cancer cells in combination with an anticancer agent and an anti-HBV agent an anti-HCV agent or a mixture thereof.~~

~~73. The composition according to claim 72 wherein said targeting peptide is selected from the group consisting of a S94 peptide, a MET binding peptide or mixtures thereof.~~

~~74. The composition according to claim 72 wherein said anticancer agent is nexavar (sorafenib), sunitinib, bevacizumab, tarceva (erlotinib), tykerb (lapatinib) or a mixture thereof..~~

~~75. The compositioin according to any of claims 72 to 74 wherein said anti-HBV agent is Hepsera (adefovir dipivoxil), lamivudine, entecavir, telbivudine, tenofovir, emtricitabine,~~

~~clevudine, valtoricitabine, amdoxovir, pradefovir, racivir, BAM 205, nitazoxanide, UT 231-B, Bay 41-4109, EHT899, zadaxin (thymosin alpha-1) or a mixture thereof.~~

~~76. The composition according to any of claims 72 to 75 wherein said anti-HCV agent is boceprevir, daclatasvir, asunapavir, INX-189, FV-100, NM 283, VX-950 (telaprevir), SCH 50304, TMC435, VX-500, BX-813, SCH503034, R1626, ITMN-191 (R7227), R7128, PF-868554, TT033, CGH-759, GI 5005, MK-7009, SIRNA-034, MK-0608, A-837093, GS-9190, GS-9256, GS-9451, GS-5885, GS-6620, GS-9620, GS9669, ACH-1095, ACH-2928, GSK625433, TG4040 (MVA-HCV), A-831, F351, NS5A, NS4B, ANA598, A-689, GNI-104, IDX102, ADX184, ALS-2200, ALS-2158, BI 201335, BI 207127, BIT-225, BIT-8020, GL59728, GL60667, PSI-938, PSI-7977, PSI-7851, SCY-635, ribavirin, pegylated interferon, PHX1766, SP-30 or a mixture thereof.~~

~~77. A method of treating cancer comprising administering to a patient in need an effective amount of a composition comprising a population of protocells according to any of claims 1-61 which have been adapted to deliver an anticancer agent to a cancer cell in said patient.~~

~~78. A method of treating hepatocellular cancer comprising administering to said patient an effective amount of composition according to any of claims 72-76.~~

~~79. A method of treating cancer comprising administering to a patient in need an effective amount of a population of protocells according to any of claims 1-61 wherein said DNA plasmid is supercoiled and is adapted to express an anticancer polypeptide and/or RNA, optionally in combination with an effective amount of an additional anticancer agent which is formulated as cargo within said protocells.~~

~~80. The method according to claim 79 wherein said anticancer polypeptide is ricin toxin chain-A or diphtheria toxin chain-A.~~

~~81. The method according to claim 79 or 80 wherein said RNA is shRNA or siRNA which induces apoptosis of a cancer cell.~~

~~82. The method according to any of claims 79-81 wherein said siRNA is selected from the group consisting of s565, s7824 or s10234.~~

83. The method according to claim 81 wherein said shRNA is a cyclin B1-specific shRNA which induces cell death.

84. The method according to any of claims 79-84 wherein said anticancer agent is selected from the group consisting of everolimus, trabectedin, abraxane, TLK 286, AV-299, DN-101 , pazopanib, GSK690693, RTA 744, ON 0910.Na, AZD 6244 (ARRY-142886), AMN-107, TKI-258, GSK461364, AZD 1152, enzastaurin, vandetanib, ARQ-197, MK-0457, MLN8054, PHA-739358, R-763, AT-9263, a FLT-3 inhibitor, a VEGFR inhibitor, an EGFR TK inhibitor, an aurora kinase inhibitor, a PIK-1 modulator, a Bcl-2 inhibitor, an HDAC inhbitor, a c-MET inhibitor, a PARP inhibitor, a Cdk inhibitor, an EGFR-TK inhibitor, an IGFR-TK inhibitor, an anti-HGF antibody, a PI3 kinase inhibitors, an AKT inhibitor, a JAK/STAT inhibitor, a checkpoint-1 or 2 inhibitor, a focal adhesion kinase inhibitor, a Map kinase kinase (mek) inhibitor, a VEGF trap antibody, pemetrexed, erlotinib, dasatanib, nilotinib, decatanib, panitumumab, amrubicin, oregovomab, Lep-etu, nolatrexed, azd2171, batabulin, ofatumumab, zanolimumab, edotecarin, tetrandrine, rubitecan, tesmilifene, oblimersen, ticilimumab, ipilimumab, gossypol, Bio 111 , 131-I-TM-601 , ALT-110, BIO 140, CC 8490, cilengitide, gimatecan, IL13-PE38QQR, INO 1001 , IPdR$_1$ KRX-0402, lucanthone, LY 317615, neuradiab, vitespan, Rta 744, Sdx 102, talampanel, atrasentan, Xr 311 , romidepsin, ADS- 100380, sunitinib, 5-fluorouracil, vorinostat, etoposide, gemcitabine, doxorubicin, liposomal doxorubicin, 5'-deoxy-5-fluorouridine, vincristine, temozolomide, ZK-304709, seliciclib; PD0325901 , AZD-6244, capecitabine, L-Glutamic acid, N-[4-[2-(2-amino-4,7-dihydro-4-oxo-1 H - pyrrolo[2,3- d]pyrimidin-5-yl)ethyl]benzoyl] , disodium salt, heptahydrate, camptothecin, PEG-labeled irinotecan, tamoxifen, toremifene citrate, anastrazole, exemestane, letrozole, DES(diethylstilbestrol), estradiol, estrogen, conjugated estrogen, bevacizumab, IMC-1C11 , CHIR-258,); 3-[5-(methylsulfonylpiperadinemethyl)-indolylj-quinolone, vatalanib, AG-013736, AVE-0005, the acetate salt of [D- Ser(Bu t) 6 ,Azgly 10] (pyro-Glu-His-Trp-Ser-Tyr-D-Ser(Bu t)-Leu-Arg-Pro- Azgly-NH $_2$ acetate [$C_{59}H_{84}N_{18}Oi_4$–($C_2H_4O_2$)$_X$ where x = 1 to 2.4], goserelin acetate, leuprolide acetate, triptorelin pamoate, medroxyprogesterone acetate, hydroxyprogesterone caproate, megestrol acetate, raloxifene, bicalutamide, flutamide, nilutamide, megestrol acetate, CP-724714; TAK-165, HKI-272, erlotinib, lapatanib, canertinib, ABX-EGF antibody, erbitux, EKB-569, PKI-166, GW-572016, Ionafarnib, BMS-214662, tipifarnib; amifostine, NVP-LAQ824, suberoyl analide hydroxamic acid, valproic acid, trichostatin A, FK-228, SU11248, sorafenib,

~~KRN951 , aminoglutethimide, arnsacrine, anagrelide, L-asparaginase, Bacillus Calmette-Guerin (BCG) vaccine, bleomycin, buserelin, busulfan, carboplatin, carmustine, chlorambucil, cisplatin, cladribine, clodronate, cyproterone, cytarabine, dacarbazine, dactinomycin, daunorubicin, diethylstilbestrol, epirubicin, fludarabine, fludrocortisone, fluoxymesterone, flutamide, gemcitabine, gleevac, hydroxyurea, idarubicin, ifosfamide, imatinib, leuprolide, levamisole, lomustine, mechlorethamine, melphalan, 6-mercaptopurine, mesna, methotrexate, mitomycin, mitotane, mitoxantrone, nilutamide, octreotide, oxaliplatin, pamidronate, pentostatin, plicamycin, porfimer, procarbazine, raltitrexed, rituximab, streptozocin, teniposide, testosterone, thalidomide, thioguanine, thiotepa, tretinoin, vindesine, 13-cis-retinoic acid, phenylalanine mustard, uracil mustard, estramustine, altretamine, floxuridine, 5-deooxyuridine, cytosine arabinoside, 6-mecaptopurine, deoxycoformycin, calcitriol, valrubicin, mithramycin, vinblastine, vinorelbine, topotecan, razoxin, marimastat, COL-3, neovastat, BMS-275291 , squalamine, endostatin, SU5416, SU6668, EMD121974, interleukin-12, IM862, angiostatin, vitaxin, droloxifene, idoxyfene, spironolactone, finasteride, cimitidine, trastuzumab, denileukin diftitox,gefitinib, bortezimib, paclitaxel, cremophor-free paclitaxel, docetaxel, epithilone B, BMS- 247550, BMS-310705, droloxifene, 4-hydroxytamoxifen, pipendoxifene, ERA- 923, arzoxifene, fulvestrant, acolbifene, lasofoxifene, idoxifene, TSE-424, HMR- 3339, ZK186619, topotecan, PTK787/ZK 222584, VX-745, PD 184352, rapamycin, 40-O-(2-hydroxyethyl)-rapamycin, temsirolimus, AP-23573, RAD001 , ABT-578, BC-210, LY294002, LY292223, LY292696, LY293684, LY293646, wortmannin, ZM336372, L-779,450, PEG-filgrastim, darbepoetin, erythropoietin, granulocyte colony-stimulating factor, zolendronate, prednisone, cetuximab, granulocyte macrophage colony-stimulating factor, histrelin, pegylated interferon alfa-2a, interferon alfa-2a, pegylated interferon alfa-2b, interferon alfa-2b, azacitidine, PEG-L-asparaginase, lenalidomide, gemtuzumab, hydrocortisone, interleukin-11 , dexrazoxane, alemtuzumab, all-transretinoic acid, ketoconazole, interleukin-2, megestrol, immune globulin, nitrogen mustard, methylprednisolone, ibritgumomab tiuxetan, androgens, decitabine, hexamethylmelamine, bexarotene, tositumomab, arsenic trioxide, cortisone, editronate, mitotane, cyclosporine, liposomal daunorubicin, Edwina-asparaginase, strontium-89, casopitant, netupitant, an NK-1 receptor antagonists, palonosetron, aprepitant, , diphenhydramine, hydroxyzine, metoclopramide, lorazepam, alprazolam, haloperidol, droperidol, dronabinol, dexamethasone, methylprednisolone, prochlorperazine, granisetron, ondansetron, dolasetron, tropisetron, pegfilgrastim, erythropoietin, epoetin alfa, darbepoetin alfa and mixtures thereof.~~

85. The method according to any of claims 79-84 wherein said protocells or said composition outside of said protocells further comprise an antiviral agent.

86. The method according to claim 85 wherein said antiviral agent is an anti-HBV agent or an anti-HCV agent.

87. A method of treating cancer in a patient comprising administering to a patient in need an effective amount of a composition according to any of claims 62-76.

88. The method according to any of claims 87 wherein said cancer is squamous-cell carcinoma, adenocarcinoma, hepatocellular carcinoma, renal cell carcinomas, carcinoma of the bladder, bone, bowel, breast, cervix, colon (colorectal), esophagus, head, kidney, liver (hepatocellular), lung, nasopharyngeal, neck, ovary, testicles, pancreas, prostate, and stomach; a leukemia, Burkitt's lymphoma, Non-Hodgkin's lymphoma, B-cell lymphoma; malignant melanoma; myeloproliferative diseases; Ewing's sarcoma, hemangiosarcoma, Kaposi's sarcoma, liposarcoma, myosarcomas, peripheral neuroepithelioma,synovial sarcoma; gliomas, astrocytomas, oligodendrogliomas, ependymomas, gliobastomas, neuroblastomas, ganglioneuromas, gangliogliomas, medulloblastomas, pineal cell tumors, meningiomas, meningeal sarcomas, neurofibromas, Schwannomas, bowel cancer, breast cancer, prostate cancer, cervical cancer, uterine cancer, non-small cell lung cancer, small cell lung cancer, mixed small cell and non-small cell lung cancer, pleural mesothelioma, pleural mesothelioma, testicular cancer, thyroid cancer and astrocytoma.

89. A method of diagnosing cancer in a patient at risk for cancer, the method comprising administering to said patient a pharmaceutical composition comprising a population of protocells according to any of claims 1-61 comprising targeting peptides adapted to selectively bind to cancer cells and deliver the protocells to said cells, wherein said protocells comprise a plasmid DNA adapted to express a reporter molecule and optionally comprise an additional reporter molecule, whereupon the binding of the protocell to a cancer cell in said patient will release said reporter molecules into the cancer cells, if present, and the reporter molecules will elicit a signal which can be compared with a standard to determine whether or not the patient has cancer and if so, the extent of the cancer and/or size of a cancerous tumor, if present.

~~90. A method of monitoring cancer therapy in a patient comprising administering to said patient a population of protocells according to any of claims 1-61 comprising targeting peptides adapted to selectively bind to cancer cells and deliver the protocells to said cells, wherein said protocells comprise a plasmid DNA adapted to express a reporter molecule and optionally comprise an additional reporter molecule, whereupon the binding of the protocell to a cancer cell in said patient will release said reporter molecules into the cancer cells and the reporter molecules will elicit a signal which can be compared with a standard at the commencement of therapy and at varying intervals during the course of therapy to determine whether or not patient is responding to the therapy and if so, the extent of the response to the therapy.~~

~~91. A transdermal protocell comprising a plurality of porous nanoparticulates that (a) are loaded with one or more pharmaceutically-active agents and (b) that are encapsulated by and that support a lipid bilayer, wherein the lipid bilayer comprises one or more stratum corneum permeability-enhancers selected from the group consisting of a monosaturated omega-9 fatty acid, an alcohol, a diol, a solvent, a co-solvent, R8 peptide, and an edge activator, wherein the protocell has an average diameter of between about 50 nm to about 300 nm.~~

~~92. The transdermal protocell of claim 91, wherein the monosaturated omega-9 fatty acid is selected from the group consisiting of oleic acid, elaidic acid, eicosenoic acid, mead acid, erucic acid, and nervonic acid, most preferably oleic acid, and mixtures thereof.~~

~~93. The transdermal protocell of claim 91, wherein the alcohol is selected from the group consisting of methanol, ethanol, proponal, and butanol, and mixtures thereof, and the solvent and co-solvent are selected from the group consisting of PEG 400 and DMSO.~~

~~94. The transdermal protocell of claim 91, wherein the diol is selected from the group consisting of ethylene glycol and polyethylene glycol, and mixtures thereof.~~

~~95. The transdermal protocell of claim 91, wherein the edge activator is selected from the group consisting of bile salts, polyoxyethylene esters and polyoxyethylene ethers, and a single-chain surfactant, and mixtures thereof.~~

~~96. The transdermal protocell of claim 91, wherein the edge activator is sodium deoxycholate.~~

~~97. The transdermal protocell of claim 92, wherein the protocell has an average diameter of between about 50 nm to about 300 nm.~~

~~98. The transdermal protocell of claim 91, wherein the protocell has an average diameter of between about 55 nm to about 270 nm.~~

~~99. The transdermal protocell of claim 92, wherein the protocell has an average diameter of between about 60 nm to about 240 nm.~~

~~100. The transdermal protocell of claim 91, wherein the protocell has an average diameter of between about 65 nm to about 210 nm.~~

~~101. The transdermal protocell of claim 91, wherein the protocell has an average diameter of between about 65 nm to about 190 nm.~~

~~102. The transdermal protocell of claim 92, wherein the protocell has an average diameter diameter of between about 65 nm to about 160 nm.~~

~~103. The transdermal protocell of claim 91, wherein the protocell has an average diameter of between about 65 nm to about 130 nm.~~

~~104. The transdermal protocell of claim 91, wherein the protocell has an average diameter of between about about 65 nm to about 100 nm.~~

~~105. The transdermal protocell of claim 91, wherein the protocell has an average diameter of between about 65 nm to about 90 nm.~~

~~106. The transdermal protocell of claim 91, wherein the protocell has an average diameter of between about, more preferably between about 65 nm to about 80 nm.~~

~~107. The transdermal protocell of claim 91, wherein the protocell has an average diameter of between about 65 nm to about 75 nm.~~

~~108. The transdermal protocell of claim 91, wherein the protocell has an average diameter of between about 65 nm to about 66, 67, 68, 69, 70, 71, 72, 73, 74 or 75 nm.~~

~~109. The transdermal protocell of claim 91, wherein the protocell has an average diameter of around 70 nm.~~

~~110. The transdermal protocell of claims 91-109, wherein (a) the nanoparticulates are comprised of one or more compositions selected from the group consisting of silica, a biodegradable polymer, a solgel, a metal and a metal oxide; and (b) the protocell includes at least one anticancer agent.~~

~~111. The transdermal protocell of claims 91-109, wherein (a) the nanoparticulates are comprised of one or more compositions selected from the group consisting of silica, a biodegradable polymer, a solgel, a metal and a metal oxide; and (b) the protocell includes at least one anticancer agent selected from the group consisting of everolimus, trabectedin, abraxane, TLK 286, AV-299, DN-101 , pazopanib, GSK690693, RTA 744, ON 0910.Na, AZD 6244 (ARRY-142886), AMN-107, TKI-258, GSK461364, AZD-1152, enzastaurin, vandetanib, ARQ-197, MK-0457, MLN8054, PHA-739358, R-763, AT-9263, a FLT-3 inhibitor, a VEGFR inhibitor, an EGFR TK inhibitor, an aurora kinase inhibitor, a PIK-1 modulator, a Bcl-2 inhibitor, an HDAC inhbitor, a c-MET inhibitor, a PARP inhibitor, a Cdk inhibitor, an EGFR TK inhibitor, an IGFR-TK inhibitor, an anti-HGF antibody, a PI3 kinase inhibitors, an AKT inhibitor, a JAK/STAT inhibitor, a checkpoint-1 or 2 inhibitor, a focal adhesion kinase inhibitor, a Map kinase kinase (mek) inhibitor, a VEGF trap antibody, pemetrexed, erlotinib, dasatanib, nilotinib, decatanib, panitumumab, amrubicin, oregovomab, Lep-etu, nolatrexed, azd2171, batabulin, ofatumumab, zanolimumab, edotecarin, tetrandrine, rubitecan, tesmilifene, oblimersen, ticilimumab, ipilimumab, gossypol, Bio 111 , 131-I-TM-601 , ALT-110, BIO 140, CC 8490, cilengitide, gimatecan, IL13-PE38QQR, INO 1001 , $IPdR_1$ KRX-0402, lucanthone, LY 317615, neuradiab, vitespan, Rta 744, Sdx 102, talampanel, atrasentan, Xr 311 , romidepsin, ADS- 100380, sunitinib, 5-fluorouracil, vorinostat, etoposide, gemcitabine, doxorubicin, liposomal doxorubicin, 5'-deoxy-5-fluorouridine, vincristine, temozolomide, ZK-304709, seliciclib; PD0325901 , AZD-6244,~~

capecitabine, L-Glutamic acid, N-[4-[2-(2-amino-4,7-dihydro-4-oxo-1 H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl] , disodium salt, heptahydrate, camptothecin, PEG-labeled irinotecan, tamoxifen, toremifene citrate, anastrazole, exemestane, letrozole, DES(diethylstilbestrol), estradiol, estrogen, conjugated estrogen, bevacizumab, IMC-1C11 , CHIR-258,); 3-[5-(methylsulfonylpiperadinemethyl)-indolylj-quinolone, vatalanib, AG-013736, AVE-0005, the acetate salt of [D-Ser(Bu t)6 ,Azgly 10] (pyro-Glu-His-Trp-Ser-Tyr-D-Ser(Bu t)-Leu-Arg-Pro-Azgly-NH_2 acetate [$C_{59}H_{84}N_{18}Oi_4$-($C_2H_4O_2$)$_X$ where x = 1 to 2.4], goserelin acetate, leuprolide acetate, triptorelin pamoate, medroxyprogesterone acetate, hydroxyprogesterone caproate, megestrol acetate, raloxifene, bicalutamide, flutamide, nilutamide, megestrol acetate, CP-724714; TAK-165, HKI-272, erlotinib, lapatanib, canertinib, ABX-EGF antibody, erbitux, EKB-569, PKI-166, GW-572016, Ionafarnib, BMS-214662, tipifarnib; amifostine, NVP-LAQ824, suberoyl analide hydroxamic acid, valproic acid, trichostatin-A, FK-228, SU11248, sorafenib, KRN951 , aminoglutethimide, arnsacrine, anagrelide, L-asparaginase, Bacillus Calmette-Guerin (BCG) vaccine, bleomycin, buserelin, busulfan, carboplatin, carmustine, chlorambucil, cisplatin, cladribine, clodronate, cyproterone, cytarabine, dacarbazine, dactinomycin, daunorubicin, diethylstilbestrol, epirubicin, fludarabine, fludrocortisone, fluoxymesterone, flutamide, gemcitabine, gleevac, hydroxyurea, idarubicin, ifosfamide, imatinib, leuprolide, levamisole, lomustine, mechlorethamine, melphalan, 6-mercaptopurine, mesna, methotrexate, mitomycin, mitotane, mitoxantrone, nilutamide, octreotide, oxaliplatin, pamidronate, pentostatin, plicamycin, porfimer, procarbazine, raltitrexed, rituximab, streptozocin, teniposide, testosterone, thalidomide, thioguanine, thiotepa, tretinoin, vindesine, 13-cis-retinoic acid, phenylalanine mustard, uracil mustard, estramustine, altretamine, floxuridine, 5-deooxyuridine, cytosine arabinoside, 6-mecaptopurine, deoxycoformycin, calcitriol, valrubicin, mithramycin, vinblastine, vinorelbine, topotecan, razoxin, marimastat, COL-3, neovastat, BMS-275291 , squalamine, endostatin, SU5416, SU6668, EMD121974, interleukin-12, IM862, angiostatin, vitaxin, droloxifene, idoxyfene, spironolactone, finasteride, cimitidine, trastuzumab, denileukin diftitox,gefitinib, bortezimib, paclitaxel, cremophor-free paclitaxel, docetaxel, epithilone B, BMS-247550, BMS-310705, droloxifene, 4-hydroxytamoxifen, pipendoxifene, ERA-923, arzoxifene, fulvestrant, acolbifene, lasofoxifene, idoxifene, TSE-424, HMR-3339, ZK186619, topotecan, PTK787/ZK-222584, VX-745, PD-184352, rapamycin, 40-O-(2-hydroxyethyl)-rapamycin, temsirolimus, AP-23573, RAD001 , ABT-578, BC-210, LY294002, LY292223, LY292696, LY293684, LY293646, wortmannin, ZM336372, L-779,450, PEG-filgrastim, darbepoetin, erythropoietin, granulocyte colony-stimulating factor,

~~zolendronate, prednisone, cetuximab, granulocyte macrophage colony-stimulating factor, histrelin, pegylated interferon alfa-2a, interferon alfa-2a, pegylated interferon alfa-2b, interferon alfa-2b, azacitidine, PEG-L-asparaginase, lenalidomide, gemtuzumab, hydrocortisone, interleukin-11 , dexrazoxane, alemtuzumab, all-transretinoic acid, ketoconazole, interleukin-2, megestrol, immune globulin, nitrogen mustard, methylprednisolone, ibritgumomab tiuxetan, androgens, decitabine, hexamethylmelamine, bexarotene, tositumomab, arsenic trioxide, cortisone, editronate, mitotane, cyclosporine, liposomal daunorubicin, Edwina-asparaginase, strontium 89, casopitant, netupitant, an NK-1 receptor antagonists, palonosetron, aprepitant, , diphenhydramine, hydroxyzine, metoclopramide, lorazepam, alprazolam, haloperidol, droperidol, dronabinol, dexamethasone, methylprednisolone, prochlorperazine, granisetron, ondansetron, dolasetron, tropisetron, pegfilgrastim, erythropoietin, epoetin alfa, darbepoetin alfa and mixtures thereof.~~

~~112. A transdermal protocell comprising a plurality of porous nanoparticulates that (a) are loaded with a pharmaceutically-effective amount of imatinib and (b) that are encapsulated by and that support a lipid bilayer, wherein the lipid bilayer comprises one or more stratum corneum permeability-enhancers selected from the group consisting of PEG-400, DMSO and ethanol, and mixtures thereof, and wherein the protocell has an average diameter of between about 65 nm to about 66, 67, 68, 69, 70, 71, 72, 73, 74 or 75 nm.~~

~~113. The transdermal protocell of claim 112, wherein the protocell has an average flux of imatinib of around 0.20 to about 0.30 µg/cm^2 hr.~~

~~114. The transdermal protocell of claim 113, wherein the lipid bilayer is comprised of lipids selected from the group consisting of 1,2-dioleoyl-*sn*-glycero-3-phosphocholine (DOPC), 1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine (DPPC), 1,2-distearoyl-*sn*-glycero-3-phosphocholine (DSPC), 1,2-dioleoyl-sn-glycero-3-[phosphor-L-serine] (DOPS), 1,2-dioleoyl-3-trimethylammonium-propane (18:1 DOTAP), 1,2-dioleoyl-*sn*-glycero-3-phospho-(1'-*rac*-glycerol) (DOPG), 1,2-dioleoyl-*sn*-glycero-3-phosphoethanolamine (DOPE), 1,2-dipalmitoyl-*sn*-glycero-3-phosphoethanolamine (DPPE), 1,2-dioleoyl-*sn*-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)-2000] (18:1 PEG-2000 PE), 1,2-dipalmitoyl-*sn*-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)-2000] (16:0 PEG-2000 PE), 1-Oleoyl-2-[12-[(7-nitro-2-1,3-benzoxadiazol-4-yl)amino]lauroyl]-*sn*-Glycero-3-Phosphocholine (18:1-12:0 NBD-PC), 1-palmitoyl-2-{12-[(7-nitro-2-1,3-~~

benzoxadiazol-4-yl)amino]lauroyl}-*sn*-glycero-3-phosphocholine (16:0-12:0 NBD PC), cholesterol and mixtures thereof.

115. A method of treating a subject who suffers from a cancer, the method comprising transdermally administering to the subject a pharmaceutically-effective amount of a protocell of claims 110-114.

116. A method of treating a subject who suffers from one or more diseases selected from the group consisting of chronic myelogenous leukemia, a gastrointestinal stromal tumor and acute lymphocytic leukemia hypereosinophilic syndrome (HES), the method comprising transdermally administering to the subject a pharmaceutically-effective amount of a protocell of claims 112-114.

117. A method of treating a subject who suffers from a cancer, the method comprising transdermally administering to the subject a pharmaceutically-effective amount of a protocell of claim 111.

118. A transdermal pharmaceutical composition comprising a pharmaceutically-effective amount of a protocell of claims 91-109, 112, 113 and 114, and optionally a pharmaceutically-acceptable excipient.

119. A transdermal pharmaceutical composition comprising a pharmaceutically-effective amount of a protocell of claim 110, and optionally a pharmaceutically-acceptable excipient.

120. A transdermal pharmaceutical composition comprising a pharmaceutically-effective amount of a protocell of claim 111, and optionally a pharmaceutically-acceptable excipient.

121. A protocell comprising a plurality of negatively-charged, nanoporous, nanoparticulate silica cores that are modified with an amine-containing silane (AEPTMS) and that (a) are loaded with a siRNA or ricin toxin A-chain and (b) that are encapsulated by and that support a lipid bilayer comprising one of more lipids selected from the group consisting of 1,2-dioleoyl-*sn*-glycero-3-phosphocholine (DOPC), 1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine (DPPC), 1,2-distearoyl-*sn*-glycero-3-phosphocholine (DSPC), 1,2-dioleoyl-sn-glycero-3-[phosphor-L-serine] (DOPS), 1,2-dioleoyl-3-trimethylammonium-propane (18:1

~~DOTAP), 1,2-dioleoyl-*sn*-glycero-3-phospho-(1'-*rac*-glycerol) (DOPG), 1,2-dioleoyl-*sn*-glycero-3-phosphoethanolamine (DOPE), 1,2-dipalmitoyl-*sn*-glycero-3-phosphoethanolamine (DPPE), 1,2-dioleoyl-*sn*-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)-2000] (18:1 PEG-2000 PE), 1,2-dipalmitoyl-*sn*-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)-2000] (16:0 PEG-2000 PE), 1-Oleoyl-2-[12-[(7-nitro-2-1,3-benzoxadiazol-4-yl)amino]lauroyl]-*sn*-Glycero-3-Phosphocholine (18:1-12:0 NBD PC), 1-palmitoyl-2-{12-[(7-nitro-2-1,3-benzoxadiazol-4-yl)amino]lauroyl}-*sn*-glycero-3-phosphocholine (16:0-12:0 NBD PC), cholesterol and mixtures/combinations thereof, wherein the lipid bilayer comprises a cationic lipid and one or more zwitterionic phospholipids.~~

29. The protocell composition according to any one of claims 1-28, wherein the protocells comprise a silica core modified with an amine-containing silane.

30. The protocell composition according to any one of claims 1-29 wherein the lipid bilayer comprises a cationic lipid and one or more zwitterionic phospholipids.

~~122~~31. The protocell composition according to any one of ~~claim 121~~claims 1-6 and 9-30, wherein the lipid is selected from the group consisting of 1,2-dioleoyl-3-trimethylammonium-propane (18:1 DOTAP) or 1,2-dioleoyl-*sn*-glycero-3-phospho-(1'-*rac*-glycerol) (DOPG), 1,2-dioleoyl-*sn*-glycero-3-phosphoethanolamine (DOPE) and mixtures thereof.

~~123~~32. The protocell composition according to any one of ~~claim 122~~claims 1-31, wherein the ~~protocell~~ silica or metal oxide cores ~~has~~ have at least one of the following characteristics: a BET surface area of greater than about 600 m^2/g, a pore volume fraction of between about 60% to about 70%, a multimodal pore morphology composed of pores having an average diameter of between about 20 nm to about 30 nm, and surface-accessible pores interconnected by pores having an average diameter of between about 5 nm to about 15 nm.

~~124~~33. The protocell composition according to any one of claims ~~121 or 122~~1-32, wherein the ~~protocell~~ silica or metal oxide cores are modified with an amine-containing silane and encapsulate~~s~~ around 10 nM of siRNA per 10^{10} nanoparticulate silica cores.

~~125~~34. A protocell composition ~~comprising a plurality of negatively-charged, nanoporous, nanoparticulate~~according to any one of claims 1-33 wherein the silica or metail oxide cores ~~that are modified with an amine-containing silane (AEPTMS) and that~~:

(a) are loaded with one or more siRNAs that target members of the cyclin superfamily selected from the group consisting of cyclin A2, cyclin B1, cyclin D1, and cyclin E; and

~~(b) that are encapsulated by and that support a lipid bilayer comprising one of more lipids selected from the group consisting of 1,2-dioleoyl-*sn*-glycero-3-phosphocholine (DOPC), 1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine (DPPC), 1,2-distearoyl-*sn*-glycero-3-phosphocholine (DSPC), 1,2-dioleoyl-sn-glycero-3-[phosphor-L-serine] (DOPS), 1,2-dioleoyl-3-trimethylammonium-propane (18:1 DOTAP), 1,2-dioleoyl-*sn*-glycero-3-phospho-(1'-*rac*-glycerol) (DOPG), 1,2-dioleoyl-*sn*-glycero-3-phosphoethanolamine (DOPE), 1,2-dipalmitoyl-*sn*-glycero-3-phosphoethanolamine (DPPE), 1,2-dioleoyl-*sn*-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)-2000] (18:1 PEG-2000 PE), 1,2-dipalmitoyl-*sn*-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)-2000] (16:0 PEG-2000 PE), 1-Oleoyl-2-[12-[(7-nitro-2-1,3-benzoxadiazol-4-yl)amino]lauroyl]-*sn*-Glycero-3-Phosphocholine (18:1-12:0 NBD PC), 1-palmitoyl-2-{12-[(7-nitro-2-1,3-benzoxadiazol-4-yl)amino]lauroyl}-*sn*-glycero-3-phosphocholine (16:0-12:0 NBD PC), cholesterol and mixtures/combinations thereof,**

~~and~~ wherein (1) the lipid bilayer is loaded with SP94 and/or ~~an endosomolytic~~a MET peptide and an fusogenic peptide, and

(2) ~~the protocell~~once loaded, selectively bind~~s~~ to a hepatocellular carcinoma cell.

~~126. The protocell of claim 123, wherein the lipid bilayer comprises DOPC/DOPE/cholesterol/PEG-2000 in an approximately 55:5:30:10 mass ratio.~~

~~127. A method of treating a subject suffering from a cancer comprising administering to the subject a pharmaceutically-effective amount of a protocell of claims 121-126.~~

~~128. The method of claim 127, wherein the subject suffers from liver cancer and is administered a pharmaceutically-effective amount of a protocell of claims 123-125.~~

~~129. A pharmaceutical composition comprising a pharmaceutically-effective amount of a protocell of claims 121-126, and optionally a pharmaceutically-acceptable excipient.~~

~~130. A protocell comprising a plurality of mesoporous, nanoparticulate silica cores that (a) are loaded with a siRNA that induces sequence-specific degradation of NiV-nucleocapsid protein (NiV-N) mRNA and (b) that are encapsulated by and that support a lipid bilayer comprising one of more lipids selected from the group consisting of 1,2-dioleoyl-*sn*-glycero-3-phosphocholine (DOPC), 1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine (DPPC), 1,2-distearoyl-*sn*-glycero-3-phosphocholine (DSPC), 1,2-dioleoyl-sn-glycero-3-[phosphor-L-serine] (DOPS), 1,2-dioleoyl-3-trimethylammonium-propane (18:1 DOTAP), 1,2-dioleoyl-*sn*-glycero-3-phospho-(1'-*rac*-glycerol) (DOPG), 1,2-dioleoyl-*sn*-glycero-3-phosphoethanolamine (DOPE), 1,2-dipalmitoyl-*sn*-glycero-3-phosphoethanolamine (DPPE), 1,2-dioleoyl-*sn*-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)-2000] (18:1 PEG-2000 PE), 1,2-dipalmitoyl-*sn*-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)-2000] (16:0 PEG-2000 PE), 1-Oleoyl-2-[12-[(7-nitro-2-1,3-benzoxadiazol-4-yl)amino]lauroyl]-*sn*-Glycero-3-Phosphocholine (18:1-12:0 NBD PC), 1-palmitoyl-2-{12-[(7-nitro-2-1,3-benzoxadiazol-4-yl)amino]lauroyl}-*sn*-glycero-3-phosphocholine (16:0-12:0 NBD PC), cholesterol and mixtures/combinations thereof.~~

~~131. The protocell of claim 130, wherein the lipid bilayer comprises 1,2-dioleoyl-*sn*-glycero-3-phosphocholine (DOPC), 1,2-dioleoyl-*sn*-glycero-3-phosphoethanolamine (DOPE) a polyethylene glycol (PEG), a targeting peptide, and R8, and wherein the mesoporous, nanoparticulate silica cores (1) each have an average diameter of around 100 nm, an average surface area of greater than 1,000 m^2/g and surface-accessible pores having an average diameter of between about 20 nm to about 25 nm, and (2) have a siRNA load of around 1 μM per 10^{10} particles or greater.~~

~~132. The protocell of claim 131, wherein the targeting peptide is a peptide that binds to ephrin B2 (EB2).~~

~~133. The protocell of claim 132, wherein the targeting peptide is TGAILHP (SEQ ID NO:18).~~

~~134. The protocell of claim 133, wherein the protocell comprises around 0.01 to around 0.02 wt% of TGAILHP (SEQ ID NO:18) around 10 wt% PEG-2000 and around 0.500 wt% of R8.~~

~~135. A method of treating a subject who has been infected by, or is at risk of infection with, Nipah virus (NiV), the method comprising administering to the subject a pharmaceutically-effective amount of a protocell of claims 130-134.~~

~~136. A pharmaceutical composition comprising a pharmaceutically-effective amount of a protocell of claims 130-134, and optionally a pharmaceutically-acceptable excipient.~~

~~137~~35. A protocell composition according to any one of claims 1-34 wherein the ~~comprising a plurality of negatively-charged, nanoporous, nanoparticulate~~ silica or metal oxide cores ~~that~~:

~~(a)~~ are modified with an amine-containing silane selected from the group consisting of (1) a primary amine, a secondary amine a tertiary amine, each of which is functionalized with a silicon atom, (2) a monoamine or a polyamine, (3) N-(2-aminoethyl)-3-aminopropyltrimethoxysilane (AEPTMS), (4) 3-aminopropyltrimethoxysilane (APTMS), (5) 3-aminopropyltriethoxysilane (APTS), (6) an amino-functional trialkoxysilane, and (7) protonated secondary amines, protonated tertiary alkyl amines, protonated amidines, protonated guanidines, protonated pyridines, protonated pyrimidines, protonated pyrazines, protonated purines, protonated imidazoles, protonated pyrroles, and quaternary alkyl amines, or combinations thereof~~;~~.

~~(b) are loaded with a siRNA or ricin toxin A-chain; and~~

~~(c) that are encapsulated by and that support a lipid bilayer comprising one of more lipids selected from the group consisting of 1,2-dioleoyl-*sn*-glycero-3-phosphocholine (DOPC), 1,2 dipalmitoyl *sn* glycero-3-phosphocholine (DPPC), 1,2-distearoyl *sn* glycero-3-phosphocholine (DSPC), 1,2-dioleoyl sn-glycero-3-[phosphor-L-serine] (DOPS), 1,2-dioleoyl-3-trimethylammonium-propane (18:1 DOTAP), 1,2-dioleoyl-*sn*-glycero-3-phospho-(1'-*rac*-glycerol) (DOPG), 1,2-dioleoyl-*sn*-glycero-3-phosphoethanolamine (DOPE), 1,2-dipalmitoyl *sn* glycero-3-phosphoethanolamine (DPPE), 1,2-dioleoyl *sn* glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)-2000] (18:1 PEG-2000 PE), 1,2-dipalmitoyl-*sn*-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)-2000] (16:0 PEG-2000 PE), 1-Oleoyl-2-[12-[(7-nitro-2-1,3-benzoxadiazol-4-yl)amino]lauroyl]-*sn*-Glycero-3-Phosphocholine (18:1-12:0 NBD PC), 1-palmitoyl-2-{12-[(7-nitro-2-1,3-benzoxadiazol-4-yl)amino]lauroyl}-*sn*-glycero-3-phosphocholine (16:0-12:0 NBD PC),

~~cholesterol and mixtures/combinations thereof, and wherein the lipid bilayer comprises a cationic lipid and one or more zwitterionic phospholipids.~~

~~138. The protocell of claim 137, wherein the lipid is selected from the group consisting of 1,2-dioleoyl-3-trimethylammonium-propane (18:1 DOTAP) or 1,2-dioleoyl-*sn*-glycero-3-phospho-(1'-*rac*-glycerol) (DOPG), 1,2-dioleoyl-*sn*-glycero-3-phosphoethanolamine (DOPE) and mixtures thereof.~~

~~139. The protocell of claim 138, wherein the protocell has at least one of the following characteristics: a BET surface area of greater than about 600 m^2/g, a pore volume fraction of between about 60% to about 70%, a multimodal pore morphology composed of pores having an average diameter of between about 20nm to about 30 nm, surface-accessible pores interconnected by pores having an averahe diameter of between about 5 nm to about 15 nm.~~

~~140. The protocell of claims 138 or 139, wherein the protocell encapsulates around 10 nM of siRNA per 10^{10} nanoparticulate silica cores.~~

~~141~~36. A protocell composition according to claim 1 wherein the ~~comprising a plurality of negatively-charged, nanoporous, nanoparticulate~~ silica or metal oxide cores ~~that~~:
(a) are modified with an amine-containing silane selected from the group consisting of (1) a primary amine, a secondary amine a tertiary amine, each of which is functionalized with a silicon atom (2) a monoamine or a polyamine (3) N-(2-aminoethyl)-3-aminopropyltrimethoxysilane (AEPTMS) (4) 3-aminopropyltrimethoxysilane (APTMS) (5) 3-aminopropyltriethoxysilane (APTS) (6) an amino-functional trialkoxysilane, and (7) protonated secondary amines, protonated tertiary alkyl amines, protonated amidines, protonated guanidines, protonated pyridines, protonated pyrimidines, protonated pyrazines, protonated purines, protonated imidazoles, protonated pyrroles, and quaternary alkyl amines, or combinations thereof;
(b) are loaded with one or more siRNAs that target members of the cyclin superfamily selected from the group consisting of cyclin A2, cyclin B1, cyclin D1, and cyclin E; and
(c) ~~that are encapsulated by and that~~the supported ~~a~~ lipid bilayer ~~comprising~~ comprises one of more lipids selected from the group consisting of 1,2-dioleoyl-*sn*-glycero-3-phosphocholine (DOPC), 1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine (DPPC), 1,2-distearoyl-*sn*-glycero-3-phosphocholine (DSPC), 1,2-dioleoyl-sn-glycero-3-[phosphor-L-serine] (DOPS), 1,2-

dioleoyl-3-trimethylammonium-propane (18:1 DOTAP), 1,2-dioleoyl-*sn*-glycero-3-phospho-(1'-*rac*-glycerol) (DOPG), 1,2-dioleoyl-*sn*-glycero-3-phosphoethanolamine (DOPE), 1,2-dipalmitoyl-*sn*-glycero-3-phosphoethanolamine (DPPE), 1,2-dioleoyl-*sn*-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)-2000] (18:1 PEG-2000 PE), 1,2-dipalmitoyl-*sn*-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)-2000] (16:0 PEG-2000 PE), 1-Oleoyl-2-[12-[(7-nitro-2-1,3-benzoxadiazol-4-yl)amino]lauroyl]-*sn*-Glycero-3-Phosphocholine (18:1-12:0 NBD PC), 1-palmitoyl-2-{12-[(7-nitro-2-1,3-benzoxadiazol-4-yl)amino]lauroyl}-*sn*-glycero-3-phosphocholine (16:0-12:0 NBD PC), cholesterol and mixtures/combinations thereof,
and wherein (1) the lipid bilayer is loaded with SP94 and an ~~endosomolytic~~ fusogenic peptide, and (2) the protocell selectively binds to a hepatocellular carcinoma cell.

~~142. The protocell of claim 141, wherein the lipid bilayer comprises DOPC/DOPE/cholesterol/PEG-2000 in an approximately 55:5:30:10 mass ratio.~~

~~143. A method of treating a subject suffering from a cancer comprising administering to the subject a pharmaceutically-effective amount of a protocell of claims 137-142.~~

~~144. The method of claim 143, wherein the subject suffers from liver cancer and is administered a pharmaceutically-effective amount of a protocell of claims 141 or 142.~~

~~145~~37. A pharmaceutical composition comprising the protocell composition according to any one of claims 1-36 in an ~~a pharmaceutically-effective~~ amount ~~of a protocell of claims 137-142, and optionally a pharmaceutically-acceptable~~effective to produce a therapeutic effect in a subject in combination with a pharmaceutically acceptable carrier, additive or excipient.

38. The pharmaceutical composition according to claim 37 further comprising a drug which is not disposed as cargo within the protocell.

39. The pharmaceutical composition according to claims 37 or 38 in parenteral dosage form.

40. The pharmaceutical composition according to claim 39 wherein said dosage form is intradermal, intramuscular, intraosseous, intraperitoneal, intravenous, subcutaneous or intrathecal.

41. The pharmaceutical composition according to any one of claims 37-40 for use in the treatment of a subject who suffers from a cancer.

42. The pharmaceutical composition according to claim 41, wherein said cancer is metastatic.

43. The protocell composition according to any one of claims 1-28 and 30-36, wherein the nanoporous silica or metal oxide is a nanoporous silica core.