CLAIMS

1. A method for manufacture of a medicament to improve the efficacy and/or reduce the side effects of the administration of a substituted hexitol derivative for treatment of GBM or medulloblastoma comprising the steps of:

(a) identifying at least one factor or parameter associated with the efficacy and/or occurrence of side effects of the administration of the substituted hexitol derivative for treatment of GBM or medulloblastoma; and

(b) modifying the factor or parameter to improve the efficacy and/or reduce the side effects of the administration of the substituted hexitol derivative for treatment of GBM or medulloblastoma for production of a medicament to treat GBM or medulloblastoma, wherein the substituted hexitol derivative is selected from the group consisting of dianhydrogalactitol, derivatives of dianhydrogalactitol, diacetyldianhydrogalactitol, derivatives of diacetyldianhydrogalactitol, dibromodulcitol, and derivatives of dibromodulcitol.

2. The method of claim 1 wherein the substituted hexitol derivative is dianhydrogalactitol.

3. The method of claim 1 wherein the factor or parameter is selected from the group consisting of:

(a) dose modification;
(b) route of administration;
(c) schedule of administration;
(d) indications for use;
(e) selection of disease stage;
(f) other indications;
(g) patient selection;
(h) patient/disease phenotype;
(i) patient/disease genotype;
(j) pre/post-treatment preparation

(k) toxicity management;

(l) pharmacokinetic/pharmacodynamic monitoring;

(m) drug combinations;

(n) chemosensitization;

(o) chemopotentiation;

(p) post-treatment patient management;

(q) alternative medicine/therapeutic support;

(r) bulk drug product improvements;

(s) diluent systems;

(t) solvent systems;

(u) excipients;

(v) dosage forms;

(w) dosage kits and packaging;

(x) drug delivery systems;

(y) drug conjugate forms;

(z) compound analogs;

(aa) prodrugs;

(ab) multiple drug systems;

(ac) biotherapeutic enhancement;

(ad) biotherapeutic resistance modulation;

(ae) radiation therapy enhancement;

(af) novel mechanisms of action; and

(ag) selective target cell population therapeutics.

4. The method of claim 1 wherein the improvement is made by patient selection and wherein the patient selection is at least one patient selection carried out by a criterion selected from the group consisting of:

(i) selecting patients with a disease condition characterized by a high level of a metabolic enzyme selected from the group consisting of histone deacetylase and ornithine decarboxylase;

(ii) selecting patients with a low or high susceptibility to a condition selected from the group consisting of thrombocytopenia and neutropenia;

(iii) selecting patients intolerant of GI toxicities;

(iv) selecting patients characterized by over- or under-expression of a gene selected from the group consisting of c-Jun, a GPCR, a signal transduction protein, VEGF, a prostate-specific gene, and a protein kinase.

(v) selecting patients characterized by carrying extra copies of the EGFR gene for GBM;

(vi) selecting patients characterized by mutations in at least one gene selected from the group consisting of TP53, PDGFRA, IDH1, and NF1 for GBM;

(vii) selecting patients characterized by methylation or lack of methylation of the promoter of the MGMT gene;

(viii) selecting patients characterized by one or more deletions of the distal part of chromosome 17, distal to the p53 gene for medulloblastoma; and

(ix) selecting patients characterized by a particular cytogenic subgroup selected from the group consisting of: (i) a gain of 6q or amplification of MYC or MYCN; (ii) gain of 17q or an i(17q) without gain of 6q or amplification of MYC or MYCN; and (iii) 6q and 17q balanced or 6q deletion for medulloblastoma;

(x) selecting patients characterized by the existence of an IDH1 mutation;

(xi) selecting patients characterized by the presence of IDH1 wild-type gene;

(xii) selecting patients characterized by the presence of 1p/19q co-deletion;

(xiii) selecting patients characterized by the absence of an 1p/19q co-deletion;

(xiv) selecting patients characterized by an unmethylated promoter region of MGMT (O^6-methylguanine methyltransferase);

(xv) selecting patients characterized by a methylated promoter region of MGMT;

(xvi) selecting patients characterized by a high expression of MGMT;

(xvii) selecting patients characterized by a low expression of MGMT; and

(xviii) selecting patients characterized by a mutation in EGFR.

5. The method of claim 1 wherein the improvement is made by analysis of patient or disease genotype and the analysis of patient or disease genotype is a method of analysis of patient or disease genotype carried out by a method selected from the group consisting of:

(i) use of a diagnostic tool, a diagnostic technique, a diagnostic kit, or a diagnostic assay to confirm a patient's particular genotype;

(ii) use of a gene chip;

(iii) use of gene expression analysis;

(iv) use of single nucleotide polymorphism (SNP) analysis;

(v) measurement of the level of a metabolite or a metabolic enzyme;

(vi) determination of mutation of PDGFRA gene;

(vii) determination of mutation of IDH1 gene;

(viii) determination of mutation of NF1 gene;

(ix) determination of copy number of the EGFR gene;

(x) determination of status of methylation of promoter of MGMT gene;

(xi) determination of cytogenic subgroup classification (for medulloblastoma);

(xii) determination of the existence of an IDH1 mutation;

(xiii) determination of the existence of IDH1 wild-type;

(xiv) determination of the existence of a 1p/19q co-deletion;

(xv) determination of the absence of a 1p/19q co-deletion;

(xvi) determination of the existence of an unmethylated promoter region of the MGMT gene;

(xvii) determination of the existence of a methylated promoter region of the MGMT gene;

(xviii) determination of the existence of high expression of MGMT; and

(xix) determination of the existence of low expression of MGMT.

6. A composition to improve the efficacy and/or reduce the side effects of suboptimally administered drug therapy employing a substituted hexitol derivative for the treatment of GBM or medulloblastoma comprising an alternative selected from the group consisting of:

(a) a therapeutically effective quantity of a modified substituted hexitol derivative or a derivative, analog, or prodrug of a substituted hexitol derivative or a modified substituted hexitol derivative, wherein the modified substituted hexitol derivative or the derivative, analog or prodrug of the substituted hexitol derivative or modified substituted hexitol derivative possesses increased therapeutic efficacy or reduced side effects for treatment of GBM or medulloblastoma as compared with an unmodified substituted hexitol derivative;

(b) a composition comprising:

(i) a therapeutically effective quantity of a substituted hexitol derivative, a modified substituted hexitol derivative, or a derivative, analog, or prodrug of a substituted hexitol derivative or a modified substituted hexitol derivative; and

(ii) at least one additional therapeutic agent, therapeutic agent subject to chemosensitization, therapeutic agent subject to chemopotentiation, diluent, excipient, solvent system, or drug delivery system, wherein the composition possesses increased therapeutic efficacy or reduced side effects for treatment of GBM or medulloblastoma as compared with an unmodified substituted hexitol derivative;

(c) a therapeutically effective quantity of a substituted hexitol derivative, a modified substituted hexitol derivative or a derivative, analog, or prodrug of a substituted hexitol derivative or a modified substituted hexitol derivative that is incorporated into a dosage form, wherein the substituted hexitol derivative, the modified substituted hexitol derivative or the derivative, analog, or prodrug of a substituted hexitol

derivative or a modified substituted hexitol derivative incorporated into the dosage form possesses increased therapeutic efficacy or reduced side effects for treatment of GBM or medulloblastoma as compared with an unmodified substituted hexitol derivative;

(d) a therapeutically effective quantity of a substituted hexitol derivative, a modified substituted hexitol derivative or a derivative, analog, or prodrug of a substituted hexitol derivative or a modified substituted hexitol derivative that is incorporated into a dosage kit and packaging, wherein the substituted hexitol derivative, the modified substituted hexitol derivative or the derivative, analog, or prodrug of a substituted hexitol derivative or a modified substituted hexitol derivative incorporated into the dosage kit and packaging possesses increased therapeutic efficacy or reduced side effects for treatment of GBM or medulloblastoma as compared with an unmodified substituted hexitol derivative; and

(e) a therapeutically effective quantity of a substituted hexitol derivative, a modified substituted hexitol derivative or a derivative, analog, or prodrug of a substituted hexitol derivative or a modified substituted hexitol derivative that is subjected to a bulk drug product improvement, wherein substituted hexitol derivative, a modified substituted hexitol derivative or a derivative, analog, or prodrug of a substituted hexitol derivative or a modified substituted hexitol derivative subjected to the bulk drug product improvement possesses increased therapeutic efficacy or reduced side effects for treatment of GBM or medulloblastoma as compared with an unmodified substituted hexitol derivative.

7. The composition of claim 6 wherein the unmodified substituted hexitol derivative is selected from the group consisting of dianhydrogalactitol, derivatives of dianhydrogalactitol, diacetyldianhydrogalactitol, derivatives of diacetyldianhydrogalactitol, dibromodulcitol, and derivatives of dibromodulcitol.

8. The composition of claim 7 wherein the unmodified substituted hexitol derivative is dianhydrogalactitol.

9. The composition of claim 6 wherein the composition comprises a drug combination comprising:

(a) a substituted hexitol derivative; and

(b) an additional therapeutic agent selected from the group consisting of:

(i) topoisomerase inhibitors;

(ii) fraudulent nucleosides;

(iii) fraudulent nucleotides;

(iv) thymidylate synthetase inhibitors;

(v) signal transduction inhibitors;

(vi) cisplatin or platinum analogs;

(vii) alkylating agents;

(viii) anti-tubulin agents;

(ix) antimetabolites;

(x) berberine;

(xi) apigenin;

(xii) amonafide;

(xiii) vinca alkaloids;

(xiv) 5-fluorouracil;

(xv) curcumin;

(xvi) NF-κB inhibitors;

(xvii) rosmarinic acid;

(xviii) mitoguazone;

(xix) tetrandrine;

(xx) tyrosine kinase inhibitors;

(xxi) epidermal growth factor inhibitors; and

(xxii) inhibitors of poly-ADP ribose polymerase (PARP).

10. The composition of claim 6 wherein the composition comprises:

(a) a substituted hexitol derivative; and

(b) a therapeutic agent subject to chemosensitization selected from the group consisting of:

(i) topoisomerase inhibitors;
(ii) fraudulent nucleosides;
(iii) fraudulent nucleotides;
(iv) thymidylate synthetase inhibitors;
(v) signal transduction inhibitors;
(vi) cisplatin or platinum analogs;
(vii) alkylating agents;
(viii) anti-tubulin agents;
(ix) antimetabolites;
(x) berberine;
(xi) apigenin;
(xii) amonafide;
(xiii) vinca alkaloids;
(xiv) 5-fluorouracil;
(xv) curcumin;
(xvi) NF-κB inhibitors;
(xvii) rosmarinic acid;
(xviii) mitoguazone; and
(xix) tetrandrine;
(xx) tyrosine kinase inhibitors;
(xxi) epidermal growth factor inhibitors; and
(xxii) inhibitors of poly-ADP ribose polymerase (PARP);

wherein the substituted hexitol derivative acts as a chemosensitizer.

11. The composition of claim 6 wherein the composition comprises:

(a) a substituted hexitol derivative; and

(b) a therapeutic agent subject to chemopotentiation selected from the group consisting of:

(i) topoisomerase inhibitors;

(ii) fraudulent nucleosides;
(iii) fraudulent nucleotides;
(iv) thymidylate synthetase inhibitors;
(v) signal transduction inhibitors;
(vi) cisplatin or platinum analogs;
(vii) alkylating agents;
(viii) anti-tubulin agents;
(ix) antimetabolites;
(x) berberine;
(xi) apigenin;
(xii) amonafide;
(xiii) vinca alkaloids;
(xiv) 5-fluorouracil;
(xv) curcumin;
(xvi) NF-κB inhibitors;
(xvii) rosmarinic acid;
(xviii) mitoguazone;
(xix) tetrandrine;
(xx) biotherapeutics;
(xxi) a tyrosine kinase inhibitor;
(xxii) an inhibitor of EGFR; and
(xxiii) an inhibitor of PARP;

wherein the substituted hexitol derivative acts as a chemopotentiator.

12. The composition of claim 6 wherein the substituted hexitol derivative is subjected to a bulk drug product improvement, wherein the bulk drug product improvement is selected from the group consisting of:

(i) salt formation;
(ii) preparation as a homogeneous crystal structure;
(iii) preparation as a pure isomer;
(iv) increased purity;

(v) preparation with lower residual solvent content; and

(vi) preparation with lower residual heavy metal content.

13. The composition of claim 6 wherein the composition comprises a substituted hexitol derivative and a diluent, wherein the diluent is selected from the group consisting of:

(i) an emulsion;

(ii) dimethylsulfoxide (DMSO);

(iii) N-methylformamide (NMF)

(iv) DMF;

(v) ethanol;

(vi) benzyl alcohol;

(vii) dextrose-containing water for injection;

(viii) Cremophor;

(ix) cyclodextrin; and

(x) PEG.

14. The composition of claim 6 wherein the composition comprises a substituted hexitol derivative and a solvent system, wherein the solvent system is selected from the group consisting of:

(i) an emulsion;

(ii) dimethylsulfoxide (DMSO);

(iii) N-methylformamide (NMF)

(iv) DMF;

(v) ethanol;

(vi) benzyl alcohol;

(vii) dextrose-containing water for injection;

(viii) Cremophor;

(ix) cyclodextrin; and

(x) PEG.

15. The composition of claim 6 wherein the composition comprises a substituted hexitol derivative and an excipient, wherein the excipient is selected from the group consisting of:

(i) mannitol;
(ii) albumin;
(iii) EDTA;
(iv) sodium bisulfite;
(v) benzyl alcohol;
(vi) a carbonate buffer; and
(vii) a phosphate buffer.

16. The composition of claim 6 wherein the substituted hexitol derivative is incorporated into a dosage form selected from the group consisting of:

(i) tablets;
(ii) capsules;
(iii) topical gels;
(iv) topical creams;
(v) patches;
(vi) suppositories; and
(vii) lyophilized dosage fills.

17. The composition of claim 6 wherein the composition comprises a substituted hexitol derivative and a drug delivery system selected from the group consisting of:

(i) nanocrystals;
(ii) bioerodible polymers;
(iii) liposomes;
(iv) slow release injectable gels; and
(v) microspheres.

18. The composition of claim 6 wherein the substituted hexitol derivative is present in the composition in a drug conjugate form selected from the group consisting of:

(i) a polymer system;

(ii) polylactides;

(iii) polyglycolides;

(iv) amino acids;

(v) peptides; and

(vi) multivalent linkers.

19. The composition of claim 6 wherein the therapeutic agent is a modified substituted hexitol derivative and the modification is selected from the group consisting of:

(i) alteration of side chains to increase or decrease lipophilicity;

(ii) addition of an additional chemical functionality to alter a property selected from the group consisting of reactivity, electron affinity, and binding capacity; and

(iii) alteration of salt form.

20. The composition of claim 6 wherein the composition comprises a substituted hexitol derivative and at least one additional therapeutic agent to form a multiple drug system, wherein the at least one additional therapeutic agent is selected from the group consisting of:

(i) an inhibitor of multi-drug resistance;

(ii) a specific drug resistance inhibitor;

(iii) a specific inhibitor of a selective enzyme;

(iv) a signal transduction inhibitor;

(v) an inhibitor of a repair enzyme; and

(vi) a topoisomerase inhibitor with non-overlapping side effects.

21. A method for the preparation of a medicament for treating a malignancy selected from the group consisting of glioblastoma multiforme and medulloblastoma wherein the medicament comprises a therapeutically effective quantity of a substituted hexitol derivative for administration to a patient suffering from the malignancy.

22. The method of claim 21 wherein the substituted hexitol derivative is selected from the group consisting of galactitols, substituted galacitols, dulcitols, and substituted dulcitols.

23. The method of claim 22 wherein the substituted hexitol derivative is selected from the group consisting of dianhydrogalactitol, derivatives of dianhydrogalactitol, diacetyldianhydrogalactitol, derivatives of diacetyldianhydrogalactitol, dibromodulcitol and derivatives of dibromodulcitol.

24. The method of claim 23 wherein the substituted hexitol derivative is dianhydrogalactitol.

25. The method of claim 21 wherein the malignancy is glioblastoma multiforme.

26. The method of claim 21 wherein the malignancy is medulloblastoma.

27. The method of claim 24 wherein the therapeutically effective quantity of dianhydrogalactitol is a quantity of dianhydrogalactitol that results in a dosage of from about 1 mg/m^2 to about 40 mg/m^2.

28. The method of claim 27 wherein the therapeutically effective quantity of dianhydrogalactitol is a quantity of dianhydrogalactitol that results in a dosage of from about 5 mg/m^2 to about 25 mg/m^2.

29. The method of claim 21 wherein the substituted hexitol derivative is administered by a route selected from the group consisting of intravenous and oral.

30. The method of claim 29 wherein the substituted hexitol derivative is dianhydrogalactitol.

31. The method of claim 29 wherein the substituted hexitol derivative is administered intravenously.

32. The method of claim 21 wherein the medicament is to be administered together with a therapeutically effective dose of ionizing radiation.

33. The method of claim 21 wherein the medicament is to be administered together with a therapeutically effective quantity of temozolomide.

34. The method of claim 21 wherein the medicament is to be administered together with a therapeutically effective quantity of bevacizumab.

35. The method of claim 21 wherein the medicament is to be administered together with a therapeutically effective quantity of a corticosteroid.

36. The method of claim 21 wherein the medicament is to be administered together with at least one chemotherapeutic agent selected from the group consisting of lomustine, cisplatin, carboplatin, vincristine, and cyclophosphamide.

37. The method of claim 21 wherein the dianhydrogalactitol substantially suppresses the growth of cancer stem cells (CSCs).

38. The method of claim 37 wherein the suppression of the growth of cancer stem cells is at least 50%.

39. The method of claim 38 where the suppression of the growth of cancer stem cells is at least 99%.

40. The method of claim 24 wherein the dianhydrogalactitol is effective in suppressing the growth of cancer cells possessing O^6-methylguanine-DNA methyltransferase (MGMT)-driven drug resistance.

41. The method of claim 24 wherein the dianhydrogalactitol is effective in suppressing the growth of cancer cells resistant to temozolomide.

42. The method of claim 21 wherein the medicament is to be administered together with a therapeutically effective quantity of a tyrosine kinase inhibitor.

43. The method of claim 21 wherein the medicament is to be administered together with a therapeutically effective quantity of an EGFR inhibitor.

44. The method of claim 43 wherein the EGFR inhibitor affects wild-type binding sites.

45. The method of claim 43 wherein the EGFR inhibitor affects mutated binding sites.

46. The method of claim 43 wherein the EGFR inhibitor affects EGFR Variant III.

Claims

1. Use of a hexitol derivative selected from the group consisting of dianhydrogalactitol, diacetyldianhydrogalactitol, and dibromodulcitol for manufacture of a medicament to improve the efficacy and/or reduce the side effects of the administration of dianhydrogalactitol for treatment of GBM or medulloblastoma comprising the steps of:

(a) identifying at least one factor or parameter associated with the efficacy and/or occurrence of side effects of the administration of the hexitol derivative selected from the group consisting of dianhydrogalactitol, diacetyldianhydrogalactitol, and dibromodulcitol for treatment of GBM or medulloblastoma; and

(b) modifying the factor or parameter to improve the efficacy and/or reduce the side effects of the administration of the hexitol derivative selected from the group consisting of dianhydrogalactitol, diacetyldianhydrogalactitol, and dibromodulcitol for treatment of GBM or medulloblastoma.

2. The use of claim 1 wherein the factor or parameter is selected from the group consisting of:

(a) dose modification;
(b) route of administration;
(c) schedule of administration;
(d) indications for use;
(e) selection of disease stage;
(f) other indications;
(g) patient selection;
(h) patient/disease phenotype;
(i) patient/disease genotype;
(j) pre/post-treatment preparation
(k) toxicity management;
(l) pharmacokinetic/pharmacodynamic monitoring;
(m) drug combinations;
(n) chemosensitization;
(o) chemopotentiation;
(p) post-treatment patient management;
(q) alternative medicine/therapeutic support;
(r) bulk drug product improvements;
(s) diluent systems;
(t) solvent systems;
(u) excipients;
(v) dosage forms;
(w) dosage kits and packaging;
(x) drug delivery systems;
(y) drug conjugate forms;
(z) compound analogs;
(aa) prodrugs;
(ab) multiple drug systems;
(ac) biotherapeutic enhancement;

(ad) biotherapeutic resistance modulation;
(ae) radiation therapy enhancement;
(af) novel mechanisms of action; and
(ag) selective target cell population therapeutics.

3. The use of claim 1 wherein the hexitol derivative is dianhydrogalactitol.

4. The use of claim 1 wherein the improvement is made by patient selection and wherein the patient selection is at least one patient selection carried out by a criterion selected from the group consisting of:

(i) selecting patients with a disease condition characterized by a high level of a metabolic enzyme selected from the group consisting of histone deacetylase and ornithine decarboxylase;

(ii) selecting patients with a low or high susceptibility to a condition selected from the group consisting of thrombocytopenia and neutropenia;

(iii) selecting patients intolerant of GI toxicities;

(iv) selecting patients characterized by over- or under-expression of a gene selected from the group consisting of c-Jun, a GPCR, a signal transduction protein, VEGF, a prostate-specific gene, and a protein kinase.

(v) selecting patients characterized by carrying extra copies of the EGFR gene for GBM;

(vi) selecting patients characterized by mutations in at least one gene selected from the group consisting of TP53, PDGFRA, IDH1, and NF1 for GBM;

(vii) selecting patients characterized by methylation or lack of methylation of the promoter of the MGMT gene;

(viii) selecting patients characterized by one or more deletions of the distal part of chromosome 17, distal to the p53 gene for medulloblastoma; and

(ix) selecting patients characterized by a particular cytogenic subgroup selected from the group consisting of: (i) a gain of 6q or amplification of MYC or MYCN; (ii) gain of 17q or an i(17q) without gain of 6q or amplification of MYC or MYCN; and (iii) 6q and 17q balanced or 6q deletion for medulloblastoma;

(x) selecting patients characterized by the existence of an IDH1 mutation;

(xi) selecting patients characterized by the presence of IDH1 wild-type gene;

(xii) selecting patients characterized by the presence of 1p/19q co-deletion;

(xiii) selecting patients characterized by the absence of an 1p/19q co-deletion;

(xiv) selecting patients characterized by an unmethylated promoter region of MGMT (O^6-methylguanine methyltransferase);

(xv) selecting patients characterized by a methylated promoter region of MGMT;

(xvi) selecting patients characterized by a high expression of MGMT;

(xvii) selecting patients characterized by a low expression of MGMT; and

(xviii) selecting patients characterized by a mutation in EGFR.

5. The use of claim 1 wherein the improvement is made by analysis of patient or disease genotype and the analysis of patient or disease genotype is a method of analysis of patient or disease genotype carried out by a method selected from the group consisting of:

(i) use of a diagnostic tool, a diagnostic technique, a diagnostic kit, or a diagnostic assay to confirm a patient's particular genotype;

(ii) use of a gene chip;

(iii) use of gene expression analysis;

(iv) use of single nucleotide polymorphism (SNP) analysis;

(v) measurement of the level of a metabolite or a metabolic enzyme;

(vi) determination of mutation of PDGFRA gene;

(vii) determination of mutation of IDH1 gene;

(viii) determination of mutation of NF1 gene;

(ix) determination of copy number of the EGFR gene;

(x) determination of status of methylation of promoter of MGMT gene;

(xi) determination of cytogenic subgroup classification (for medulloblastoma);

(xii) determination of the existence of an IDH1 mutation;

(xiii) determination of the existence of IDH1 wild-type;

(xiv) determination of the existence of a 1p/19q co-deletion;

(xv) determination of the absence of a 1p/19q co-deletion;

(xvi) determination of the existence of an unmethylated promoter region of the MGMT gene;

(xvii) determination of the existence of a methylated promoter region of the MGMT gene;

(xviii) determination of the existence of high expression of MGMT; and

(xix) determination of the existence of low expression of MGMT.

6. A composition to improve the efficacy and/or reduce the side effects of suboptimally administered drug therapy employing a hexitol derivative selected from the group consisting of dianhydrogalactitol, diacetyldianhydrogalactitol, and dibromodulcitol for the treatment of GBM or medulloblastoma comprising an alternative selected from the group consisting of:

(a) a therapeutically effective quantity of dianhydrogalactitol, a prodrug of dianhydrogalactitol, diacetyldianhydrogalactitol, a prodrug of diacetyldianhydrogalactitol, dibromodulcitol, or a prodrug of dibromodulcitol, wherein the dianhydrogalactitol, the prodrug of dianhydrogalactitol, the diacetyldianhydrogalactitol, the prodrug of diacetyldianhydrogalactitol, the dibromodulcitol, the a prodrug of dibromodulcitol possesses increased therapeutic efficacy or reduced side effects for treatment of GBM or medulloblastoma;

(b) a composition comprising:

(i) a therapeutically effective quantity of dianhydrogalactitol, a prodrug of dianhydrogalactitol, a prodrug of dianhydrogalactitol, diacetyldianhydrogalactitol, a prodrug of diacetyldianhydrogalactitol, dibromodulcitol, or a prodrug of dibromodulcitol; and

(ii) at least one additional therapeutic agent, therapeutic agent subject to chemosensitization, therapeutic agent subject to chemopotentiation, diluent, excipient, solvent system, or drug delivery system, wherein the composition possesses increased therapeutic efficacy or reduced side effects for treatment of GBM or medulloblastoma;

(c) a therapeutically effective quantity of dianhydrogalactitol, a prodrug of dianhydrogalactitol, a prodrug of dianhydrogalactitol, diacetyldianhydrogalactitol, a prodrug of diacetyldianhydrogalactitol, dibromodulcitol, or a prodrug of dibromodulcitol that is incorporated into a dosage form, wherein the dianhydrogalactitol, the prodrug of dianhydrogalactitol, the diacetyldianhydrogalactitol, the prodrug of diacetyldianhydrogalactitol, the dibromodulcitol, or the prodrug of dibromodulcitol incorporated into the dosage form possesses increased therapeutic efficacy or reduced side effects for treatment of GBM or medulloblastoma;
and

(d) a therapeutically effective quantity of dianhydrogalactitol, a prodrug of dianhydrogalactitol, a prodrug of dianhydrogalactitol, diacetyldianhydrogalactitol, a prodrug of diacetyldianhydrogalactitol, dibromodulcitol, or a prodrug of dibromodulcitol that is subjected to a bulk drug product improvement, wherein the dianhydrogalactitol, the prodrug of dianhydrogalactitol, the diacetyldianhydrogalactitol, the prodrug of diacetyldianhydrogalactitol, the dibromodulcitol, or the prodrug of dibromodulcitol subjected to the bulk drug product improvement possesses increased therapeutic efficacy or reduced side effects for treatment of GBM or medulloblastoma.

7. The composition of claim 6 wherein the composition comprises a drug combination comprising:

(a) dianhydrogalactitol; and

(b) an additional therapeutic agent selected from the group consisting of:

(i) topoisomerase inhibitors;
(ii) fraudulent nucleosides;
(iii) fraudulent nucleotides;
(iv) thymidylate synthetase inhibitors;
(v) signal transduction inhibitors;
(vi) cisplatin or platinum analogs;
(vii) alkylating agents;
(viii) anti-tubulin agents;
(ix) antimetabolites;
(x) berberine;
(xi) apigenin;
(xii) amonafide;
(xiii) vinca alkaloids;
(xiv) 5-fluorouracil;
(xv) curcumin;
(xvi) NF-κB inhibitors;

(xvii) rosmarinic acid;
(xviii) mitoguazone;
(xix) tetrandrine;
(xx) tyrosine kinase inhibitors;
(xxi) epidermal growth factor inhibitors; and
(xxii) inhibitors of poly-ADP ribose polymerase (PARP).

8. The composition of claim 6 wherein the composition comprises:
(a) dianhydrogalactitol; and
(b) a therapeutic agent subject to chemosensitization selected from the group consisting of:
(i) topoisomerase inhibitors;
(ii) fraudulent nucleosides;
(iii) fraudulent nucleotides;
(iv) thymidylate synthetase inhibitors;
(v) signal transduction inhibitors;
(vi) cisplatin or platinum analogs;
(vii) alkylating agents;
(viii) anti-tubulin agents;
(ix) antimetabolites;
(x) berberine;
(xi) apigenin;
(xii) amonafide;
(xiii) vinca alkaloids;
(xiv) 5-fluorouracil;
(xv) curcumin;
(xvi) NF-κB inhibitors;
(xvii) rosmarinic acid;
(xviii) mitoguazone; and
(xix) tetrandrine;
(xx) tyrosine kinase inhibitors;
(xxi) epidermal growth factor inhibitors; and
(xxii) inhibitors of poly-ADP ribose polymerase (PARP);
wherein the dianhydrogalactitol acts as a chemosensitizer.

9. The composition of claim 6 wherein the composition comprises:
(a) dianhydrogalactitol; and
(b) a therapeutic agent subject to chemopotentiation selected from the group consisting of:
(i) topoisomerase inhibitors;
(ii) fraudulent nucleosides;
(iii) fraudulent nucleotides;
(iv) thymidylate synthetase inhibitors;
(v) signal transduction inhibitors;
(vi) cisplatin or platinum analogs;
(vii) alkylating agents;
(viii) anti-tubulin agents;

(ix) antimetabolites;
(x) berberine;
(xi) apigenin;
(xii) amonafide;
(xiii) vinca alkaloids;
(xiv) 5-fluorouracil;
(xv) curcumin;
(xvi) NF-κB inhibitors;
(xvii) rosmarinic acid;
(xviii) mitoguazone;
(xix) tetrandrine;
(xx) biotherapeutics;
(xxi) a tyrosine kinase inhibitor;
(xxii) an inhibitor of EGFR; and
(xxiii) an inhibitor of PARP;

wherein the dianhydrogalactitol acts as a chemopotentiator.

10. The composition of claim 6 wherein the composition comprises dianhydrogalactitol and the dianhydrogalactitol is subjected to a bulk drug product improvement, wherein the bulk drug product improvement is selected from the group consisting of:

(i) salt formation;
(ii) preparation as a homogeneous crystal structure;
(iii) preparation as a pure isomer;
(iv) increased purity;
(v) preparation with lower residual solvent content; and
(vi) preparation with lower residual heavy metal content.

11. The composition of claim 6 wherein the composition comprises dianhydrogalactitol and a diluent, wherein the diluent is selected from the group consisting of:

(i) an emulsion;
(ii) dimethylsulfoxide (DMSO);
(iii) N-methylformamide (NMF)
(iv) DMF;
(v) ethanol;
(vi) benzyl alcohol;
(vii) dextrose-containing water for injection;
(viii) Cremophor;
(ix) cyclodextrin; and
(x) PEG.

12. The composition of claim 6 wherein the composition comprises dianhydrogalactitol and a solvent system, wherein the solvent system is selected from the group consisting of:

(i) an emulsion;
(ii) dimethylsulfoxide (DMSO);

(iii) N-methylformamide (NMF)
(iv) DMF;
(v) ethanol;
(vi) benzyl alcohol;
(vii) dextrose-containing water for injection;
(viii) Cremophor;
(ix) cyclodextrin; and
(x) PEG.

13. The composition of claim 6 wherein the composition comprises dianhydrogalactitol and an excipient, wherein the excipient is selected from the group consisting of:

(i) mannitol;
(ii) albumin;
(iii) EDTA;
(iv) sodium bisulfite;
(v) benzyl alcohol;
(vi) a carbonate buffer; and
(vii) a phosphate buffer.

14. The composition of claim 6 wherein the composition comprises dianhydrogalactitol and the dianhydrogalactitol is incorporated into a dosage form selected from the group consisting of:

(i) tablets;
(ii) capsules;
(iii) topical gels;
(iv) topical creams;
(v) patches;
(vi) suppositories; and
(vii) lyophilized dosage fills.

15. The composition of claim 6 wherein the composition comprises dianhydrogalactitol and a drug delivery system selected from the group consisting of:

(i) nanocrystals;
(ii) bioerodible polymers;
(iii) liposomes;
(iv) slow release injectable gels; and
(v) microspheres.

16. The composition of claim 6 wherein the composition comprises dianhydrogalactitol and the dianhydrogalactitol is present in the composition in a drug conjugate form selected from the group consisting of:

(i) a polymer system;
(ii) polylactides;
(iii) polyglycolides;
(iv) amino acids;
(v) peptides; and

(vi) multivalent linkers.

17. The composition of claim 6 wherein the composition comprises dianhydrogalactitol and at least one additional therapeutic agent to form a multiple drug system, wherein the at least one additional therapeutic agent is selected from the group consisting of:

(i) an inhibitor of multi-drug resistance;
(ii) a specific drug resistance inhibitor;
(iii) a specific inhibitor of a selective enzyme;
(iv) a signal transduction inhibitor;
(v) an inhibitor of a repair enzyme; and
(vi) a topoisomerase inhibitor with non-overlapping side effects.

18. Use of a hexitol derivative selected from the group consisting of dianhydrogalactitol, a prodrug of dianhydrogalactitol, diacetyldianhydrogalactitol, a prodrug of diacetyldianhydrogalactitol, dibromodulcitol, and a prodrug of dibromodulcitol for the preparation of a medicament for treating a malignancy selected from the group consisting of glioblastoma multiforme and medulloblastoma wherein the medicament comprises a therapeutically effective quantity of the hexitol derivative selected from the group consisting of dianhydrogalactitol, a prodrug of dianhydrogalactitol, diacetyldianhydrogalactitol, a prodrug of diacetyldianhydrogalactitol, dibromodulcitol, and a prodrug of dibromodulcitol for administration to a patient suffering from the malignancy.

19. The use of claim 18 wherein the hexitol derivative is selected from the group consisting of dianhydrogalactitol, diacetyldianhydrogalactitol, and dibromodulcitol.

20. The use of claim 19 wherein the hexitol derivative is dianhydrogalactitol.

21. The use of claim 18 wherein the malignancy is glioblastoma multiforme.

22. The use of claim 18 wherein the malignancy is medulloblastoma.

23. The use of claim 20 wherein the therapeutically effective quantity of dianhydrogalactitol is a quantity of dianhydrogalactitol that results in a dosage of from about 1 mg/m^2 to about 40 mg/m^2.

24. The use of claim 23 wherein the therapeutically effective quantity of dianhydrogalactitol is a quantity of dianhydrogalactitol that results in a dosage of from about 5 mg/m^2 to about 25 mg/m^2.

25. The use of claim 20 wherein the dianhydrogalactitol is administered by a route selected from the group consisting of intravenous and oral.

26. The use of claim 25 wherein the dianhydrogalactitol is administered intravenously.

27. The use of claim 18 wherein the medicament is to be administered together with a therapeutically effective dose of ionizing radiation.

28. The use of claim 18 wherein the medicament is to be administered together with a therapeutically effective quantity of temozolomide.

29. The use of claim 18 wherein the medicament is to be administered together with a therapeutically effective quantity of bevacizumab.

30. The use of claim 18 wherein the medicament is to be administered together with a therapeutically effective quantity of a corticosteroid.

31. The use of claim 18 wherein the medicament is to be administered together with a therapeutically effective quantity of at least one chemotherapeutic agent selected from the group consisting of lomustine, cisplatin, carboplatin, vincristine, and cyclophosphamide.

32. The use of claim 18 wherein the dianhydrogalactitol substantially suppresses the growth of cancer stem cells (CSCs).

33. The use of claim 32 wherein the suppression of the growth of cancer stem cells is at least 50%.

34. The use of claim 33 wherein the suppression of the growth of cancer stem cells is at least 99%.

35. The use of claim 20 wherein the dianhydrogalactitol is effective in suppressing the growth of cancer cells possessing O^6-methylguanine-DNA methyltransferase (MGMT)-driven drug resistance.

36. The use of claim 20 wherein the dianhydrogalactitol is effective in suppressing the growth of cancer cells resistant to temozolomide.

37. The use of claim 18 wherein the medicament is to be administered together with a therapeutically effective quantity of a tyrosine kinase inhibitor.

38. The use of claim 18 wherein the medicament is to be administered together with a therapeutically effective quantity of an EGFR inhibitor.

39. The use of claim 38 wherein the EGFR inhibitor affects wild-type binding sites.

40. The use of claim 38 wherein the EGFR inhibitor affects mutated binding sites.

41. The use of claim 40 wherein the EGFR inhibitor affects EGFR Variant III.