CLAIMS

1. Use of a hexitol derivative selected from the group consisting of dianhydrogalactitol and diacetyldianhydrogalactitol for manufacture of a medicament to improve the efficacy and/or reduce the side effects of the administration of dianhydrogalactitol or diacetyldianhydrogalactitol 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 dianhydrogalactitol or diacetyldianhydrogalactitol 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 dianhydrogalactitol or diacetyldianhydrogalactitol 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;

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(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 (O6-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;

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(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 and diacetyldianhydrogalactitol 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 selected from the group consisting of a prodrug with an enzyme sensitive ester, a dimer prodrug, a prodrug with a Schiff base, a prodrug with a pyridoxal complex, and a prodrug with a caffeine complex, diacetyldianhydrogalactitol, and a prodrug of diacetyldianhydrogalactitol selected from the group consisting of a prodrug with an enzyme sensitive ester, a dimer prodrug, a prodrug with a Schiff base, a prodrug with a pyridoxal complex, and a prodrug with a caffeine complex, wherein the dianhydrogalactitol, the prodrug of dianhydrogalactitol, the diacetyldianhydrogalactitol, or the prodrug of diacetyldianhydrogalactitol 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 selected from the group consisting of a prodrug with an enzyme sensitive ester, a dimer prodrug, a prodrug with a Schiff base, a prodrug with a pyridoxal complex, and a prodrug with a caffeine complex, diacetyldianhydrogalactitol, and a prodrug of diacetyldianhydrogalactitol selected from the group consisting of a prodrug with an enzyme sensitive ester, a dimer prodrug, a prodrug with a Schiff base, a prodrug with a pyridoxal complex, and a prodrug with a caffeine complex; 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 selected from the group consisting of a prodrug with an enzyme sensitive ester, a dimer prodrug, a prodrug with a Schiff base, a prodrug with a pyridoxal complex, and a prodrug with a caffeine complex, diacetyldianhydrogalactitol, and a prodrug of diacetyldianhydrogalactitol selected from the group consisting of a prodrug with an enzyme sensitive ester, a dimer prodrug, a prodrug with a Schiff base, a prodrug with a pyridoxal complex, and a prodrug with a caffeine complex that is incorporated into a dosage form, wherein the dianhydrogalactitol, the prodrug of dianhydrogalactitol, the diacetyldianhydrogalactitol, or the prodrug of diacetyldianhydrogalactitol 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 selected from the group consisting of a prodrug with an enzyme sensitive ester, a dimer prodrug, a prodrug with a Schiff base, a prodrug with a pyridoxal complex, and a prodrug with a caffeine complex, diacetyldianhydrogalactitol, or a prodrug of diacetyldianhydrogalactitol selected from the group consisting of a prodrug with an enzyme sensitive ester, a dimer prodrug, a prodrug with a Schiff base, a prodrug with a pyridoxal complex, and a prodrug with a caffeine complex that is subjected to a bulk drug product improvement, wherein the dianhydrogalactitol, the prodrug of dianhydrogalactitol, the diacetyldianhydrogalactitol, or the prodrug of diacetyldianhydrogalactitol 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-□B inhibitors;

(xvii) rosmarinic acid;

(xviii) mitoguazone;

(xix) tetrandrine;

(xx) tyrosine kinase inhibitors;

(xxi) epidermal growth factor inhibitors; and

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(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-□B 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

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(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-□B 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 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;

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(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;

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(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 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 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

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(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 selected from the group consisting of a prodrug with an enzyme sensitive ester, a dimer prodrug, a prodrug with a Schiff base, a prodrug with a pyridoxal complex, and a prodrug with a caffeine complex, diacetyldianhydrogalactitol, and a prodrug of diacetyldianhydrogalactitol selected from the group consisting of a prodrug with an enzyme sensitive ester, a dimer prodrug, a prodrug with a Schiff base, a prodrug with a pyridoxal complex, and a prodrug with a caffeine complex 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, and a prodrug of diacetyldianhydrogalactitol 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 and diacetyldianhydrogalactitol.

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/m2 to about 40 mg/m2.

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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/m2 to about 25 mg/m2.

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 .

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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.

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