We claim:

1. A pharmaceutical formulation comprising

a composition comprising hydroxyl-terminated dendrimers complexed, covalently conjugated or intra-molecularly dispersed or encapsulated with one or more receptor tyrosine kinase inhibitors,

and one or more pharmaceutically acceptable excipients suitable for systemic administration,

wherein the composition is in an amount effective to treat or alleviate one or more symptoms associated with one or more diseases and/or disorders of the eye.

2. The formulation of claim 1, wherein the dendrimers are complexed, covalently conjugated or intra-molecularly dispersed or encapsulated with one or more additional therapeutic, prophylactic and/or diagnostic agents.

3. The formulation of claim 1 or 2, wherein the receptor tyrosine kinase inhibitor is a receptor tyrosine kinase inhibitor of vascular endothelial growth factor receptors (VEGFR).

4. The formulation of any one of claims 1-3, wherein the VEGFR inhibitor is selected from the group consisting of sunitinib, sorafenib, pazopanib, vandetanib, axitinib, cediranib, vatalanib, dasatinib, nintedanib, motesanib, and analogues thereof.

5. The formulation of any one of claims 1-4, wherein the VEGFR inhibitor is sunitinib or an analogue thereof.

6. The formulation of any one of claims 2-5, wherein the diagnostic agent is selected from the group consisting of dyes, fluorescent dyes, Near infra-red dyes, SPECT imaging agents, PET imaging agents and radioisotopes.

7. The formulation of claim 6, wherein the fluorescent dye is selected from the group consisting of indocyanine green, fluorescein isothiocynate, boron-dipyrromethene, rhodamine, rose Bengal, and a combination thereof.

8. The formulation of claim 7, wherein the diagnostic agent is indocyanine green.

9. The formulation of any one of claims 1-8, wherein the dendrimers are generation 4, generation 5, generation 6, generation 7, generation 8, generation 9, or generation 10 poly(amidoamine) (PAMAM) hydroxyl-terminated dendrimers.

10. The formulation of any one of claims 1-9, wherein the one or more receptor tyrosine kinase inhibitors are covalently conjugated to the dendrimers.

11. The formulation of any one of claims 1-10, wherein the one or more receptor tyrosine kinase inhibitors are at a concentration by weight of the dendrimer conjugate between about 0.01% w/w and about 30% w/w, between about 1% w/w and about 25% w/w, between about 5% w/w and about 20% w/w, ~~and~~ or between about 10% w/w and about 15% w/w.

12. The formulation of any one of claims 1-11, wherein the one or more diseases and/or disorders of the eye are inflammatory and/or angiogenic diseases of the eye.

13. The formulation of any one of claims 1-12, wherein the one or more diseases and/or disorders of the eye are selected from the group consisting of age-related macular degeneration (AMD), retinitis pigmentosa, optic neuritis, uveitis, retinal detachment, temporal arteritis, retinal ischemia, arteriosclerotic retinopathy, hypertensive retinopathy, retinal artery blockage, retinal vein blockage, diabetic retinopathy, macular edema, retinal neovascularization, and choroidal neovascularization.

14. ~~A method of treating and/or diagnosing one or more one or more diseases and/or disorders of the eye comprising administering to a subject in need thereof~~ Use of the formulation of any one of claims 1-13 in the manufacture of a medicament for treating and/or diagnosing one or more diseases and/or disorders of the eye in a subject in need thereof, wherein the formulation is to be administered to the subject.

15. The ~~method~~ use of claim 14, wherein the one or more ~~one or more~~ diseases and/or disorders of the eye are inflammatory and/or angiogenic diseases of the eye.

16. The use ~~method~~ of claim 14 or claim 15, wherein the one or more diseases and/or disorders of the eye are selected from the group consisting of age-related macular degeneration (AMD), retinitis pigmentosa, optic neuritis, uveitis, retinal detachment, temporal arteritis, retinal ischemia, arteriosclerotic retinopathy, hypertensive retinopathy, retinal artery blockage, retinal vein blockage, diabetic retinopathy, macular edema, retinal neovascularization, and choroidal neovascularization.

17. The use ~~method~~ of any one of claims 14-16, wherein the one or more diseases and/or disorders of the eye are diseases and/or disorders associated with activated microglia, activated macrophages, and/or retinal pigment epithelial (RPE) cells in the eye.

18. The use ~~method~~ of any one of claims 14-17, wherein the composition is in an amount effective to target to the activated microglia, activated macrophages, and/or RPE cells in the one or more diseases and/or disorders of the eye.

19. The use ~~method~~ of any one of claims 14-18, wherein the composition is in an amount effective to reduce the number and/or activity of the activated microglia and/or activated macrophages in the eye.

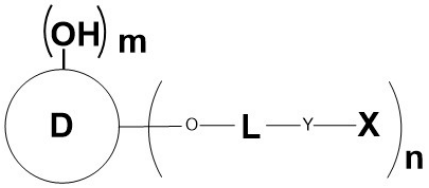
20. The use ~~method~~ of any one of claims 14-19, wherein the composition is in an amount effective to alleviate one or more symptoms of the one or more ~~one or more~~ diseases and/or disorders of the eye.

21. The use ~~method~~ of any one of claims 14-20, wherein the composition is administered via systemic administration.

22. The use ~~method~~ of any one of claims 14-21, wherein the composition is administered intravenously, subcutaneously, or orally.

23. The use ~~method~~ of any one of claims 14-22, wherein the composition is administered to the subject in a time period selected from the group consisting of daily, weekly, biweekly, monthly, and bimonthly.

24. A dendrimer of formula (I):



Formula (I)

~~,~~wherein~~,~~:

D is a poly(amidoamine) (PAMAM) dendrimer selected from generation 2, generation 3, generation 4, generation 5, generation 6, generation 7, generation 8, generation 9, and generation 10~~,~~;

L is one or more linking moieties or spacers~~,~~;

X is an active agent or a derivative, analog or prodrug thereof~~,~~;

n is an integer from 1 to 100~~,~~;

m is an integer from 16 to 4096~~,~~; and

Y is a linker selected from secondary amides (-CONH-), tertiary amides (-CONR-), sulfonamide (-S(O)2-NR-), secondary carbamates (-OCONH-; -NHCOO-), tertiary carbamates (-OCONR-; -NRCOO-), carbonate (-O-C(O)-O-), ureas (-NHCONH-; -NRCONH-; -NHCONR-, -NRCONR-), carbinols (-CHOH-, -CROH-), disulfide groups, hydrazones, hydrazides, and ethers (-O-), wherein R is an alkyl group, an aryl group, or a heterocyclic group.

25. The dendrimer of claim 24,

~~W~~wherein~~,~~:

D is a poly(amidoamine) (PAMAM) dendrimer selected from generation 4, generation 5, generation 6, generation 7, and generation 8~~,~~;

L is one or more linking or spacer moieties~~,~~;

X is an inhibitor of vascular endothelial growth factor receptor (VEGFR), or an inhibitor of TIE2 receptor tyrosine kinases~~,~~;

n is an integer from 1 to 100~~,~~;

m is an integer from 16 to 4096; and

Y is a bond or linkage that is minimally cleavable *in vivo*.

26. The dendrimer of claim 24, wherein:

D is a G4 PAMAM dendrimer~~,~~;

L is one or more linking or spacer moieties;

X is sunitinib, or a derivative, analog or prodrug thereof;

Y is a secondary amide (-CONH-);

n is an integer from 5 to 15;

m is an integer from 49 to 59; and

n+m=64.

27. The dendrimer of claim 24, wherein:

D is a G4 PAMAM dendrimer;

L is polyethylene glycol with a triazole linker;

X is *N, N*-didesethyl sunitinib, or a derivative, analog or prodrug thereof;

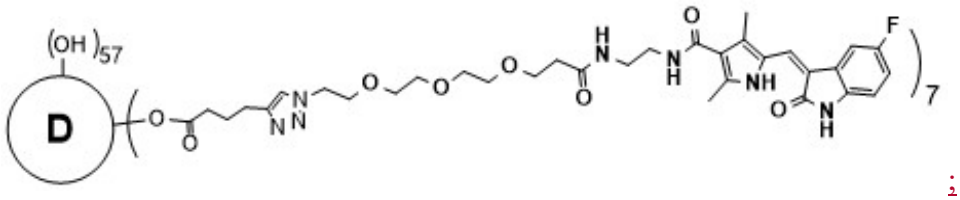
Y is a secondary amide (-CONH-);

n is an integer from 5 to 15;

m is an integer from 49 to 59; and

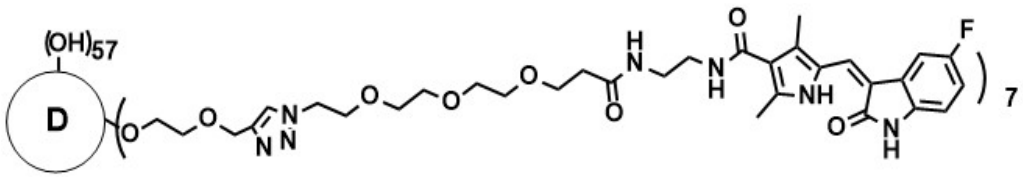
n+m=64.

28. The dendrimer of claim 24, wherein Ff formula (I) has the following structure:

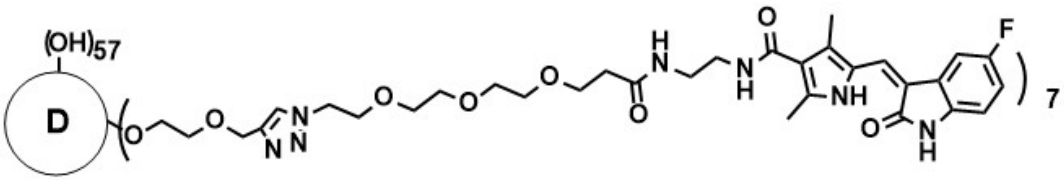


;

or



29. The dendrimer of claim 28, wherein Ff formula (I) has the following structure:



30. The dendrimer of any one of claims 24-29, wherein the dendrimer has a diameter of from about 1 nm to about 20 nm.

31. The dendrimer of any one of claims 24-30, wherein the dendrimer has a diameter of from about 2 nm to about 10 nm.

32. The dendrimer of any one of claims 24-31, wherein the dendrimer has a surface charge between -20 mV and 20 mV, between -10 mV and 10 mV, between -10 mV and 5 mV, between -5 mV and 5 mV, or between -2 mV and 2 mV, inclusive.

33. The dendrimer of any one of claims 24-32, wherein about 0.1% to about 40% of the total surface groups of the dendrimer are covalently linked to active agent or an analog thereof.

34. The pharmaceutical formulation of any one of claims 1-13 for use as a medicament.