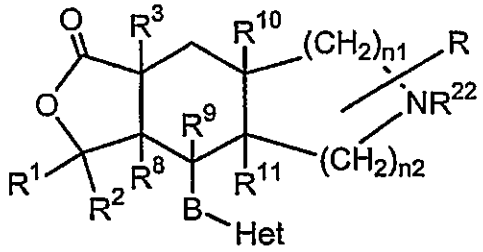
CLAIMS

What is claimed is:

1. ~~A method of treating a disease or disorder associated with the expression of at least one of transglutaminase-2 (TGM-2)~~myopia ~~comprising administering to a subject~~Use of a TG-2 inhibitor, wherein the TG-2 inhibitor is selected from the group consisting of darifenacin or an analogue thereof; 1,1-Dimethyl-4-diphenylacetoxypiperidinium iodide (4-DAMP) or an analogue thereof; a nucleic acid molecule that inhibits expression of transglutaminase-2 (TGM-2); and ~~himbacine or~~ an analogue ~~thereof~~of himbacine;

wherein the analogue of himbacine is a compound of Formula I:



(I)

or a pharmaceutically acceptable salt thereof, wherein:

R is 1 to 3 substituents independently selected from the group consisting of H, C_1-C_6 alkyl, halogen, hydroxy, amino, (C_1-C_6)alkyl-amino, (C_1-C_6)-dialkylamino, (C_1-C_6)alkoxy, -COR^{16}, -$COOR^{17}$, -SOR^{16}, -SO_2R^{16}, -$SO_2NR^{17}R^{18}$, -$NR^{17}SO_2R_{18}$, $NR^{16}COR^{16a}$, -$NR^{16}COOR^{16a}$, -$NR^{16}CONR^4R^5$, fluoro-(C_1-C_6)alkyl, difluoro(C_1-C_6)alkyl, trifluoro(C_1-C_6)alkyl, C_3-C_6cycloalkyl, aryl(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, amino-(C_1-C_6)-alkyl, aryl and thio(C_1-C_6)alkyl;

R^1 and R^2 are independently selected from the group consisting of H, C_1-C_6 alkyl, fluoro(C_1-C_6)alkyl, difluoro(C_1-C_6)alkyl, trifluoro-(C_1-C_6)alkyl, C_3-C_6cycloalkyl, C_2-C_6 alkenyl, aryl(C_1-C_6)alkyl, hydroxy-(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, aryl and thio(C_1-C_6)alkyl; or and R^1 and R^2 together form an =O group;

R^3 is H, hydroxy, C_1-C_6alkoxy, aryloxy, aryl(C_1-C_6)alkyloxy, heteroaryloxy, heteroaryl(C_1-C_6)alkyloxy, (C_3-C_6)cycloalkyloxy, -SOR^{16}, -SO_2R^{17}, -$SO_2NR^{18}R^{19}$, -SR^{18}, -SO_3H, -$C(O)OR^{17}$, -$C(O)NR^{18}R^{19}$, -$OC(O)R^{32}$, -$OC(O)NR^{33}R^{34}$, -$(CR^{33}R^{34})_nOR^{32}$, -NR^4R^5, -$NR^{33}COOR^{32}$, -$NR^{33}COR^{32}$, -$NR^{33}S(O)_2R^{32}$, -$NR^{33}CONR^{33}R^{34}$, -$NR^{33}S(O)_2NR^{33}R^{34}$, -$(CR^{33}R^{34})_nNR^4R^5$, -$(CR^{33}R^{34})_nNR^{33}COR^{32}$, -$(CR^{33}R^{34})_nNR^{33}COR^{32}$, -$(CR^{33}R^{34})_nNR^{33}S(O)_2R^{32}$, -$(CR^{33}R^{34})_nNR^{33}CONR^{33}R^{34}$, -$(CR^{33}R^{34})_nNR^{33}S(O)_2NR^{33}R^{34}$, ($C_1$-$C_6$)alkyl, halogen, C_3-C_6cycloalkyl, C_2-C_6alkenyl, -CN, aryl, heteroaryl, heterocycloalkyl, -$P(O)(OR^7)_2$ or (C_1-C_6)alkyl substituted by 1 to 3 substituents independently selected from the group consisting of halogen,-OH, -NH_2, aryl,-COOH,-SO_3H, thio and (C_1-C_6)alkylthio;

n is 1, 2, 3 or 4;

n1 and n2 are independently 0-3, provided both are not 0;

Het is a mono-, bi-or tricyclic heteroaromatic group of 5 to 14 atoms comprised of 1 to 13 carbon atoms and 1 to 4 heteroatoms independently selected from the group consisting of N, O and S, wherein a ring nitrogen can form an N-oxide or a quaternary group with a C_1-C_4 alkyl group, wherein Het is attached to B by a carbon atom ring member, and wherein the Het group is substituted by 1 to 4 substituents, W, independently selected from the group consisting of C_1-C_6alkyl; -NR^4R^5; -$NHCOR^{26}$; -$NHSO_2R^{16}$; R^{21}-aryl; aryl wherein adjacent carbons form a ring with a methylenedioxy group; and R^{21}-heteroaryl;

R^4 and R^5 are independently selected from the group consisting of H, C_1-C_6 alkyl, phenyl, benzyl and C_3-C_6 cycloalkyl, or R^4 and R^5 together are -$(CH_2)_3$-, -$(CH_2)_4$-, -$(CH_2)_5$- or -$(CH_2)_2NR^7$-$(CH_2)_2$- and form a ring with the nitrogen to which they are attached;

R^7 is H or (C_1-C_6)alkyl;

R^8, R^{10} and R^{11} are independently selected from the group consisting of R^1 and -OR^1;

R^9 is H, OH,-NR^4R^5, C_1-C_6alkoxy, halogen or halo(C_1-C_6)alkyl;

B is -$(CH_2)n_3$- or cis or trans -(CH2)n_4CR^{12}=$CR^{12a}(CH_2)n_5$, wherein n_3 is 0-5, n_4 and n_5 are independently 0-2, and R^{12} and R^{12a} are independently selected from the group consisting of H, C_1-C_6 alkyl and halogen;

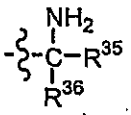
R^{16} and R^{16a} are independently selected from the group consisting of C_1-C_6 alkyl, phenyl and benzyl;

R^{17}, R^{18} and R^{19} are independently selected from the group consisting of H, C1-C_6alkyl, phenyl and benzyl;

R^{21} is 1 to 3 substituents independently selected from the group consisting of H, -CF_3, -OCF_3, halogen, -NO_2, -CN, C_1-C_6alkyl, C_1-C_6alkoxy, -NH_2, (C_1-C_6)-alkyl-amino, di-((C_1-C_6) alkyl) amino, amino(C_1-C_6)alkyl, (C_1-C_6)-alkylamino(C_1-C_6)alkyl, di-((C_1-C_6)alkyl)-amino(C_1-C_6)alkyl, hydroxy-(C_1-C_6)alkyl, -$COOR^{17}$, -COR^{17}, -$CONR^{24}R^{25}$, -$NHCOR^{16}$, -$NHSO_2R^{16}$, -$NHSO_2CH_2CF_3$, -$SO_2NR^{24}R^{25}$, -NR^{29}C(O) $NR^{24}R^{25}$, -SO_2R^{30}, -$P(O)(OR^{29})_2$, aryl, aryl(C_1-C_6)alkyl, heteroaryl, heterocycloalkyl, and -CR^{29}(=NOR^{28});

R^{22} is -COR^{23}, -$S(O)R^{31}$, -$S(O)_2R^{31}$, -$SO_2NR^{24}R^{25}$ or -$COOR^{27}$;

R^{23} is halo (C_1-C_6)alkyl; C_2-C_6alkenyl; halo (C_2-C_6)alkenyl; C_2-C_6alkynyl; C_3-C_7-cycloalkyl; (C_3-C_7)cycloalkyl(C_1-C_6) alkyl; (C_3-C_7)cycloalkyl substituted by 1 to 3 substituents selected from the group consisting of halo, (C_1-C_3)alkoxy(C_1-C_3)alkyl, hydroxy and C_1-C_6alkoxy; aryl; aryl(C_2-C_6)alkyl; heteroaryl; heterocycloalkyl; (C_1-C_6)alkyl substituted by 1-3 substituents independently selected from-COOH and –SO_3H;



or , wherein R^{35} and R^{36} are independently selected from the group consisting of H, alkyl, or R^{37}-substituted C_1-C_6alkyl, wherein R^{37} is selected from the group consisting of HO-, HS-, CH_2S-, -NH_2, phenyl, p-hydroxyphenyl and indolyl;

R^{24} and R^{25} are independently selected form the group consisting of H, C_1-C_6alkyl, halo(C_1-C_6)alkyl, C_2-C_6alkenyl, halo(C_2-C_6)alkyl, C_2-C_6alkynyl, aryl, aryl-(C_1-C_6)alkyl, C_3-C_7-cycloalkyl, halo(C_3-C_7)cycloalkyl, (C_1-C_3)alkoxy(C_1-C_3)-alkyl, hydroxy and C_1-C_6alkoxy;

R^{26} is C_3-C_7-cycloalkyl, aryl, aryl-(C_1-C_6)alkyl, heteroaryl, heteroaryl-(C_1-C_6)alkyl or (C_1-C_6)alkylamino;

R^{27} is C_1-C_6alkyl, phenyl, benzyl, (C_1-C_3)alkoxy(C_1-C_3)-alkyl, (C_3-C7)-cycloalkyl, carboxy(C_1-C_6)alkyl, sulfo(C_1-C_6)alkyl, or (C_1-C_6)alkyl substituted by $NR^{18}R^{19}$ and carboxy;

R^{28} is H, C_1-C_6alkyl, phenyl, benzyl or (C_1-C_6)alkoxy(C_1-C_3)alkyl;

R^{29} and R^{30} are independently selected from the group consisting of H and C_1-C_6alkyl;

R^{31} is (C_1-C_6)alkyl; halo(C_1-C_6)alkyl; C_2-C_6alkenyl; halo(C_2-C_6)alkyl; C_2-C_6alkynyl; C_3-C_7-cycloalkyl; (C_3-C_7)cycloalkyl substituted by 1 to 3 substituents selected from the group consisting of halo, (C_1-C_3)alkoxy(C_1-C_3)alkyl, hydroxy and C_1-C_6alkoxy; aryl; aryl (C_1-C_6)alkyl; heteroaryl; heterocycloalkyl; (C_1-C_6)alkyl substituted by 1-3 substituents independently selected from -COOH and -SO_3H; or (C_1-C_6)alkoxy;

R^{32} is R^{35}-(C_1-C_6)alkyl, R^{35}-(C_3-C_7)cycloalkyl, R^{35}-(C_2-C_6)alkenyl, R^{35}-(C_2-C_6)-alkynyl or R^{35}-aryl, wherein R^{35} is 1 or 2 substituents independently selected from the group consisting of H, -COOH, -NH_2, -SO_3H, =O and =NOR^{28}; and

R^{33} and R^{34} are independently selected from the group consisting of H, (C_1-C_6)alkyl and C_3-C_7-cycloalkyl in the preparation of a medicament for the treatment of myopia.

2. The ~~method~~ use of claim 1, wherein the TG-2 inhibitor further inhibits the expression/activity of at least one of muscarinic receptor M_2 or muscarinic receptor M_3.

3. The ~~method~~ use of claim 1 or 2, wherein the TG-2 inhibitor concentration in the medicament is ~~administered into the subject~~ in the range of about 0.01μM to about 100μM or in the range of about 0.01μM to about 1μM, or in the range of about 1 μM to about 10 μM.

4. The ~~method~~ use of any one of claims 1 to 3, wherein the medicament is for treatment of a subject that is between 3 years old to 17 years old, or 4 years old to 14 years old.

5. The ~~method~~ use of any one of claims 1 to 4, wherein the medicament is for treatment of ~~subject is~~ a mammal.

6. The ~~method~~ use of claim 5, wherein the mammal is selected from the group consisting of a Rodentia, Canis, Ungulate, Felidae, Leporidae, and Macaque.

7. The ~~method~~ use of claim 5, wherein the ~~subject~~mammal is a human.

8. The ~~method~~ use of any one of claims 1 to 7, wherein the nucleic acid molecule is RNA or DNA.

9. The ~~method~~ use of claim 8, wherein the nucleic acid molecules is an aptamer, a micro RNA (miRNA) molecule or a small interfering RNA (si-RNA) molecule.

10. The ~~method~~ use of any one of claims 1 to 9, wherein the TG-2 inhibitor is formulated into a pharmaceutical composition.

11. The ~~method~~ use of claim 10, wherein the pharmaceutical composition further comprises a pharmaceutically acceptable carrier or excipient.

12. The ~~method~~ use of claim 11, wherein the pharmaceutically acceptable carrier or excipient is selected from the group consisting of cellulose, hydroxymethylcellulose, cellulose acetate phthalate (CAP), gellan gum, polyalcohol, polyvinyl alcohol, hyaluronic acid, polyacrylic acid, carbopol polymer, poloxamer, poly(oxyethylene) and poly(oxypropylene) and block copolymers thereof, polyethylene oxide, polycarbophil, chitosan, cyclodextrin, liposome, nanoparticle, microparticle including microsphere and nanosphere, an ocular insert, ocular disc, soft contact lens, niosome, pharmacosome, collagen shield, ocular film and combinations thereof.

13. The ~~method~~ use of any one of claims 10 to 12, wherein the pharmaceutical composition is ~~administered into the subject via at~~formulated for topical, intra-ocular or systemic administration.

~~14. The method of any one of claims 1 to 13, wherein the disorder or disease associated with the expression of TGM-2 is myopia.~~

~~15~~14. The ~~method~~ use of any one of claims 1 to 13~~-14~~, wherein myopia is selected from the group consisting of axial myopia, refractive myopia, curvature myopia, index myopia, degenerative myopia, nocturnal myopia, pseudomyopia, induced myopia, form deprivation myopia, congenital myopia, youth onset myopia, school myopia, early adult onset myopia and late adult onset myopia.

~~16~~15. An ex vivo method of identifying a candidate TG-2 inhibitor comprising:

a) contacting a TGM-2 expressing cell with a solution containing a putative TG-2 inhibitor to be identified; and

b) measuring whether the expression of TGM-2 is inhibited in the cell comprising comparing the determined expression of TGM-2 with that of a control measurement which was not exposed to the putative TG-2 inhibitor,

wherein when the putative TG-2 inhibitor inhibits expression/activity of at least one of muscarinic receptor M_2 and muscarinic receptor M_3 in the cell, relative to that of a control measurement which was not exposed to the putative TG-2 inhibitor, the putative TG-2 inhibitor is identified as a candidate TG-2 inhibitor.

~~17. The method of claim 16, further comprising comparing the expression of TGM-2 obtained in step b) with that of a control measurement which was not exposed to the putative TG-2 inhibitor; and identifying the TG-2 inhibitor in the cell.~~

~~18. The method of claim 16 or 17, wherein the TG-2 inhibitor inhibits expression/activity of at least one of muscarinic receptor M_2 and muscarinic receptor M_3 in the cell, relative to that of the control measurement.~~

~~19~~16. The method of ~~any one of~~ claims ~~16 to 18~~15, wherein the cell is derived from a mammal.

~~20~~17. The method of claim ~~19~~16, wherein the mammal is selected from the group consisting of wherein the mammal is selected from the group consisting of Rodentia, Canis, Ungulate, Felidae, Leporidae, and Macaque.

~~21~~18. The method of claim ~~19~~16, wherein the cell is derived from a human.

~~22~~19. The method of any one of claims ~~16~~ 15 to ~~21~~18, wherein the cell is selected from the group consisting of an epithelial cell, a subepithelial cell, a stromal cell, a cell membrane, an endothelial cell, a fibroblast cell and combinations thereof.

~~23~~20. The method of any one of claims ~~16~~ 15 to ~~22~~19, wherein the cell is derived from a tissue or a part thereof.

~~24~~21. The method of claim ~~23~~20, wherein the tissue is an eye tissue or a part thereof.

~~25~~22. The method of claim ~~24~~21, wherein the eye tissue or part thereof is selected from the group consisting of sclera, cornea, retina pigment epithelium (RPE), choroid, conjunctiva and combinations thereof.