Claims

1. A chimeric opsin GPCR protein comprising seven transmembrane domains (TM1 to TM7) connected by extra- and intracellular loops (ELs and ILs),

wherein said chimeric opsin GPCR protein comprises a first light-sensitive opsin portion ~~of an upstream opsin~~ and a second GPCR portion (target GPCR portion),

wherein said ~~upstream~~ opsin portion comprises a chromophore pocket covalently binding a chromophore and a truncated C-terminal domain with a truncation site located at least 7 amino acids downstream of a NR(K)Q motif, and

~~wherein said chimeric opsin GPCR protein comprises a second GPCR portion (target GPCR portion) of a second GPCR protein (target GPCR protein),~~ wherein said ~~target~~ GPCR portion comprises a C-terminal domain (target-GPCR-CT) positioned downstream of the truncated C-terminal domain of the opsin portion~~;~~

~~characterized in that,~~

~~said upstream opsin portion further comprises a truncated C-terminal domain (truncated opsin CT) with a truncation site positioned at or downstream of a distal end of a proximal region of the upstream opsin CT (O-CT-proximal region),~~

~~wherein said O-CT-proximal region comprises a NR(K)Q motif and the following 7 to 13 amino acids in distal direction,~~

~~whereby said chimeric opsin GPCR protein comprises a chimeric C-terminal domain (chimeric CT); and~~

~~wherein said the target GPCR CT is positioned downstream of said truncated opsin CT~~.

2. The chimeric opsin GPCR protein according to claim 1, wherein the ~~distal end of the O-CT-proximal region~~truncation site is positioned at or downstream of ~~at a position selected from the group comprising~~:

- ~~at~~ a distal end of a helix 8 (H8); or
- ~~at~~ a palmitoylation site ~~or~~
- ~~at a position corresponding to a palmitoylation site in bovine rhodopsin~~.

3. The chimeric opsin GPCR protein according to any one of the ~~previous~~ preceding claims,
~~comprising~~ wherein the truncation site is positioned ~~of the upstream opsin CT at a distal end of a distal extension to the O-CT-proximal region~~
~~wherein the distal extension of the O-CT-proximal region comprises up to 5 or up to 10 or up to 16 or up to 22 or~~ up to ~~28, 29, 30, 31, 32,~~ 33~~, 34 or 35~~ amino acids downstream of the ~~distal end of the O-CT-proximal region or in particular downstream of the~~ palmitoylation site.

4. The chimeric opsin GPCR protein according to ~~claim 3~~any one of the preceding claims, wherein the ~~upstream~~ opsin is ~~selected from the group of~~ a melanopsin~~s~~, rhodopsin, a cone opsin, a cone opsin selected from OPN1SW, OPN1LW and OPN1MW, a jellyfish opsin, a jellyfish opsin selected from cubop and JellyOP, jumping spider rhodopsin (JSR1), Parapinopsin (PPO), Neuropsin (OPN5), or Encephalopsin (OPN3).

~~5. The chimeric opsin GPCR according to claim 3, wherein the upstream opsin is selected from a group of opsins comprising CT with a length of at least 50, 65, 80, 100, 150 or 200 amino acids.~~

~~6. The chimeric opsin GPCR according to one of the previous claims, wherein the upstream opsin portion comprises the entire upstream opsin up to the truncation site, or~~
~~wherein the upstream opsin portion comprises a continuous region of the upstream opsin from the E(DRY) motif up to the truncation site or,~~
~~wherein the upstream opsin portion comprises TM3, TM4, TM5, TM6 and TM7 and optionally the truncated opsin CT up to the truncation site.~~

~~7. The chimeric opsin GPCR according to any one of the previous claims, wherein the upstream opsin portion comprises transmembrane domains TM3 and TM7, in particular comprises transmembrane domains TM3 to TM7, TM2 to TM7 or TM1 to TM7.~~

~~8. The chimeric opsin GPCR according to one of the previous claims, wherein the upstream opsin portion comprises one or more of the extracellular domains selected from EL1, EL2, EL3 and the NT.~~

5~~9~~. The chimeric opsin GPCR protein according to any one of the ~~previous~~ preceding claims, wherein the ~~upstream~~ opsin portion is derived from two or more parent opsins~~, in particular from two parent opsins~~.

~~10. The chimeric opsin GPCR according to one of the previous claims, wherein the upstream opsin portion comprises transmembrane domains derived from a parent opsin that is a non-human opsin and wherein the upstream opsin portion further comprises one or two or three or all extracellular domains derived from a parent opsin that is a human opsin.~~

~~11. The chimeric opsin GPCR according to any one of the previous claims, wherein TM7 and the truncated opsin CT are derived from the same parent opsin.~~

~~12. The chimeric opsin GPCR according to one of the previous claims, wherein the upstream opsin portion comprises all of the extracellular domains, all of the transmembrane domains and all intracellular loops.~~

6~~13~~. The chimeric opsin GPCR protein according to any one of ~~the previous claims~~claims 1 to 4, wherein the ~~upstream~~ opsin portion comprises the entire portion of the parent ~~upstream~~ opsin ~~up~~ from the N-terminus to ~~up to~~ the truncation site ~~of the upstream opsin CT~~.

7~~14~~.- The chimeric opsin GPCR protein according to any one of the ~~previous~~ preceding claims, wherein the ~~upstream~~ opsin portion is derived from a mono-stable opsin or from a bi-stable opsin or from a tri-stable opsin, in particular from a bi-stable opsin.

~~15. The chimeric opsin GPCR according to any one of the previous claims, wherein the upstream opsin portion is derived from a parent opsin selected from the group of opsins comprising:~~

- ~~melanopsin (OPN4)~~
- ~~rhodopsin (RHO)~~
- ~~cone opsins (OPN1SW, OPN1LW and OPN1MW)~~
- ~~jellyfish opsin (cubop, JellyOP)~~
- ~~jumping spider rhodopsin (JSR1)~~
- ~~Parapinopsin (PPO)~~
- ~~Neuropsin (OPN5)~~
- ~~Encephalopsin (OPN3)~~

8~~16~~. The chimeric opsin GPCR protein according to any one of the ~~previous~~ preceding claims, wherein~~:~~ ~~comprising a target CT which~~
a) the target-GPCR-CT is a functional variant of the CT of the parent target GPCR;
b) the target-GPCR-CT ~~is a functional variant of the CT of the parent target GPCR, comprising in particular a deletion of one or more amino acids, in particular~~ comprises an N terminal deletion~~,~~ between the NPxxY motif and any amino acid position up to a palmitoylation site~~ or up to an amino acid position proximally adjacent to the palmitoylation site~~; or
c) the N-terminal end of the target-GPCR-CT is at or upstream of the target GPCR NR(K)Q motif.

9. The chimeric opsin GPCR protein according to any one of the preceding claims, wherein the target-GPCR-CT is capable of coupling light activation into the GPCR signaling pathway of the target GPCR protein.

~~17. The chimeric opsin GPCR according to claim 1, wherein the target GPCR portion is derived from a non-opsin GPCR or is derived from a second opsin termed target opsin.~~

~~18. The chimeric opsin GPCR according to any one of the previous claims, wherein the target CT portion is derived from a parent target GPCR selected from the group of GPCR proteins comprising:~~

~~Class A GPCRs, in particular selected from the group comprising:~~

- ~~cone opsins, in particular OPN1SW, OPN1MW or OPN1LW,~~
- ~~serotonin receptors, in particular 5-HT7,~~
- ~~mu opioid receptor,~~
- ~~β-adrenergic receptor, in particular beta1-adrenoceptor, beta2-adrenoceptor and beta3-adrenoceptor;~~

~~Class B GPCRs, in particular selected from the group comprising:~~

- ~~hormonal receptors, in particular *glucagon receptor*(GCGR)~~

~~Class C GPCRs, in particular selected from the group comprising:~~

- ~~$GABA_B$ receptors, in particular $GABA_{B1}$ and $GABA_{B2}$~~
- ~~metabotropic glutamate receptors, in particular the mGluR6 and mGluR5 receptors~~

~~19. The chimeric opsin GPCR protein according to one of the previous claims, wherein the target GPCR is a class A GPCR or a class B GPCR or a GPCR of another class GPCR except for a class C GPCR and wherein optionally the target GPCR portion comprises one or more intracellular loops selected from IL1, IL2 and IL3.~~

10~~20~~. The chimeric opsin GPCR protein according to ~~claim~~ any one of the ~~previous~~ preceding claims, wherein the target GPCR protein is a class C GPCR, ~~in particular~~or wherein the target GPCR protein is mGluR6~~, and wherein the class C target GPCR portion optionally comprises one or more intracellular loops selected from IL1, IL2 and IL3, with the proviso that one of the following criteria is fulfilled:~~

~~A: in the chimeric GPCR a concomitant presence of a naturally sized IL3 comprised in the upstream opsin portion and of a naturally sized IL2 of the class C GPCR at positions corresponding to their native position is excluded;~~

~~B: the upstream opsin portion comprises all of the intracellular loops IL1 to IL3;~~

~~C: the upstream opsin portion comprises IL1 and the target GPCR portion comprises both IL2 an IL3 which replace the upstream opsin IL2 and IL3 at corresponding positions~~.

11. The chimeric opsin GPCR protein according to any one of the preceding claims, wherein the opsin is a melanopsin and the target GPCR protein is mGluR6.

12~~21~~. The chimeric opsin GPCR protein according to any one of the ~~previous~~ preceding claims, wherein the CT of the chimeric opsin GPCR further comprises one or more sequence elements selected from the following group of elements:

- a Golgi export signal;
- a ~~Membrane~~ membrane trafficking sequence, or a membrane trafficking sequence which is a 1D4 tag; and
- a sequence element encoding a fluorescent protein,

and wherein the one or more selected elements are arranged independently in any order at the C-terminal end of the chimeric opsin GPCR CT.

~~22. The chimeric opsin GPCR according to any one of the previous claims, wherein the CT of the chimeric opsin GPCR comprises as a selected an export signal, in particular an endoplasmatic reticulum export signal, more particularly the endoplasmatic reticulum export signal from Kir2.1 comprising or consisting of an amino acid sequence according to SEQ ID NO 86 or in particular a Golgi export signal, more particularly the Golgi export signal from the potassium channel Kir2.1 comprising or consisting of an amino acid sequence according to SEQ ID NO 85.~~

~~23. The chimeric opsin GPCR according to any one of the previous claims, wherein the CT of the chimeric opsin GPCR comprises as a selected sequence element a membrane trafficking sequence, in particular from an opsin, more particularly from rhodopsin, most particularly comprising or consisting an amino acid sequence according to SEQ ID NO 87.~~

~~24. The chimeric opsin GPCR according to any one of the previous claims, wherein the CT of the chimeric opsin GPCR comprises a selected sequence element encoding a fluorescent protein, in particular mKate2, TurboFP635 or mScarlet,~~
~~wherein the fluorescent protein that is either directly fused to the CT of the chimeric opsin GPCR or is linked via an IRES or T2A sequence.~~

~~25. The chimeric opsin GPCR according to any one of the previous claims, wherein the target GPCR portion further comprises IL1 and wherein IL1 of the target GPCR replaces IL1 of the upstream opsin.~~

~~26. The chimeric opsin GPCR according to any one of the previous claims, wherein IL3 of the upstream opsin is replaced by IL3 of the target GPCR. ;~~
~~or~~
~~wherein IL3 of the upstream opsin is replaced by a chimeric IL3, wherein IL3 of the target GPCR replaces a variable region within the opsin IL3.~~

~~27. The chimeric opsin GPCR according one of the previous claims, in particular wherein the target GPCR is mGluR6, wherein the target CT comprises a proximal end at or upstream of the NR(K)Q motif.~~

~~28. The chimeric opsin GPCR according one of the previous claims, wherein the target GPCR is mGluR6 and wherein IL3 of mGluR6 partially replaces a variable region of the opsin IL3 thereby forming a chimeric IL3.~~

~~29. The chimeric opsin GPCR according to one of the previous claims,~~
~~wherein the target GPCR is mGluR6 and~~
~~wherein the upstream opsin portion further comprises one or more of the intracellular loops selected from IL1, IL2 and IL3,~~
~~with the proviso that a concomitant presence of a naturally sized IL3 comprised in the upstream opsin portion and a naturally sized IL2 comprised in mGluR6 portion in the upstream opsin-mGluR6 chimeric protein is excluded.~~

~~30. The chimeric opsin GPCR according to any one of the previous claims, wherein the upstream opsin portion is derived from melanopsin and comprises the NT, EL1 to EL3, TM1 to TM7, IL1 and the truncated opsin CT, and wherein the target GPCR portion is derived from mGluR6 and comprises IL2, IL3 and the CT or wherein the target GPCR portion is derived from hOPN1mw and comprises IL2, IL3 and the CT.~~

13. The chimeric opsin GPCR protein according to any one of the preceding claims comprising an amino acid sequence with at least 85%, at least 90%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity to SEQ ID NO 2, SEQ ID NO 4, SEQ ID NO 6, SEQ ID NO 8, SEQ ID NO 10 and SEQ ID NO 12, SEQ ID NO 14, SEQ ID NO 16, SEQ ID NO 18, SEQ ID NO 20, SEQ ID NO 22, SEQ ID NO 24, SEQ ID NO 26, SEQ ID NO 28, SEQ ID NO 30 and SEQ ID NO 32, SEQ ID NO 34, SEQ ID NO 36, SEQ ID NO 38, SEQ ID NO 40, SEQ ID NO 42 or SEQ ID NO 44.

14~~31~~. The chimeric opsin GPCR protein according to claim 13 comprising or consisting of an amino acid sequence selected from the group comprising SEQ ID NO 2, SEQ ID NO 4, SEQ ID NO 6, SEQ ID NO 8, SEQ ID NO 10 and SEQ ID NO 12, SEQ ID NO 14, SEQ ID NO 16, SEQ ID NO 18, SEQ ID NO 20, SEQ ID NO 22, SEQ ID NO 24, SEQ ID NO 26, SEQ ID NO 28, SEQ ID NO 30 and SEQ ID NO 32, SEQ ID NO 34, SEQ ID NO 36, SEQ ID NO 38, SEQ ID NO 40, SEQ ID NO 42 and SEQ ID NO 44.

~~32. The chimeric opsin GPCR according to claim according to claim 31 comprising or consisting of an amino acid sequence selected from the group comprising SEQ ID NO 18, SEQ ID NO 20, SEQ ID NO 22, SEQ ID NO 24, SEQ ID NO 26 and SEQ ID NO 28.~~

~~33~~15. ~~-~~The chimeric opsin GPCR protein according to claim ~~35~~14, wherein the amino acid sequence is a variant of any one of said sequences comprising one or more variations selected from:

- a conservative amino acid substitution~~,~~;
- a deletion in a range of 1 up to 3, 5, 8 or 15 amino acids~~,~~; and
- an insertion in a range of 1 up to 3, 5, 8 or 15 amino acids~~,~~; ~~and~~

and wherein the chimeric opsin-GPCR protein exhibits a light activation dependent binding of Galpha protein specific to the target GPCR.

~~34. The chimeric opsin GPCR according to claim 35 or 36 wherein the amino acid sequence is variant of any one of these sequences with at least 85%, at least 90%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% identity.~~

~~35. A peptide comprising a chimeric C-terminal domain (chimeric CT) derived from a parent opsin CT and a parent target GPCR CT, in particular comprising the chimeric C-terminal domain (chimeric CT) of the chimeric opsin GPCR protein according to anyone of the previous claims,~~
~~wherein said peptide comprises a truncated C-terminal domain of an opsin (truncated opsin-CT) including a proximal region of the CT, in particular including a helix 8 (H8) and a palmitoylation site corresponding to C322 or C323, respectively, of bovine rhodopsin) and optionally further including up to 33, 34 or 35 amino acids downstream of the palmitoylation site of the opsin,~~
~~wherein said peptide further comprises a C-terminal domain of a target GPCR (target GPCR CT) or a functional variant, in particular a functional fragment thereof, wherein the target GPCR CT is positioned downstream of the truncated opsin CT.~~

16~~36~~. A nucleic acid molecule encoding the chimeric opsin -GPCR protein ~~or the peptide~~ according to any one of the ~~previous~~ preceding claims.

~~37. The nucleic acid molecule according to claim 36 comprising a nucleic acid sequence encoding a chimeric opsin GPCR consisting of an amino acid sequence that is at least 90% or at least 95% or at least 98% identical to an amino acid sequence selected from the group comprising SEQ ID NO 2, SEQ ID NO 4, SEQ ID NO 6, SEQ ID NO 8, SEQ ID NO 10 and SEQ ID NO 12, SEQ ID~~

~~NO 14, SEQ ID NO 16, SEQ ID NO 18, SEQ ID NO 20, SEQ ID NO 22, SEQ ID NO 24, SEQ ID NO 26, SEQ ID NO 28, SEQ ID NO 30 and SEQ ID NO 32 SEQ ID NO 34, SEQ ID NO 36, SEQ ID NO 38, SEQ ID NO 40, SEQ ID NO 42 and SEQ ID NO 44.~~

~~38. The nucleic acid molecule according to claim 36 comprising a nucleic acid sequence that is at least 70% or 80% or 90% identical to a nucleic acid sequence selected from the group comprising SEQ ID NO 1, SEQ ID NO 3, SEQ ID NO 5, SEQ ID NO 7, SEQ ID NO 9 and SEQ ID NO 11, SEQ ID NO 13, SEQ ID NO 15, SEQ ID NO 17, SEQ ID NO 19, SEQ ID NO 21, SEQ ID NO 23, SEQ ID NO 25, SEQ ID NO 27, SEQ ID NO 29 and SEQ ID NO 31 SEQ ID NO 33, SEQ ID NO 35, SEQ ID NO 37, SEQ ID NO 39, SEQ ID NO 41 and SEQ ID NO 43.~~

~~39. The nucleic acid molecule according to claim 36 comprising or consisting of a nucleic acid sequence selected from the group comprising SEQ ID NO 17, SEQ ID NO 19, SEQ ID NO 21, SEQ ID NO 23, SEQ ID NO 25 and SEQ ID NO 27.~~

~~40. An AAV capsid polypeptide for use in medical therapy to deliver a nucleic acid molecule according to one of claims 35 to 39 to a target cell.~~

~~41. The AAV capsid polypeptide for the use according to claim 40, wherein the capsid protein is the capsid protein of AAV2, AAV2(7m8) or AAV8(BP2).~~

~~42. The AAV capsid polypeptide for the use according to claim 41, wherein the capsid polypeptide is an AAV2 capsid polypeptide and comprises an amino acid insert between amino acids 587 and 588 of wild type AAV2, wherein the peptide insert comprises or consists of a sequence selected from the group of peptide sequences comprising~~

- ~~SASEAST (SEQ ID NO 60)~~
- ~~TPPSITA (SEQ ID NO 61)~~
- ~~PRTPHTA (SEQ ID NO 62)~~

- NHAPNHC (SEQ ID NO 63)

43. The AAV capsid polypeptide for the use according to claim 41 or 42 wherein the AAV2 capsid comprises a polypeptide of 7 to 13 amino acids, wherein in particular the peptide insert comprises the peptide insert according to claim 42 and further comprises one or two flanking linkers,
wherein the linkers comprise up to 1, 2, 3, 4 or 5 amino acids on either side with the proviso that the total number of of amino acids in the linkers does not exceed 6 amino acids,
wherein in particular the linkers comprise 2 or 3 amino acids on either side and wherein the linkers comprise or consist of amino acids selected from i.
amino acids G and A or
ii. amino acids A, N, L, T, R, G, A, N, L and R, in particular of A, L, N, R, wherein more particularly at least one of the amino acids is selected from N and R.

44. The AAV capsid polypeptide for the use according to claim 43 comprising a peptide insert between N587 and R588 of wild type AAV2, selected from

- AAASASEASTAA (SEQ ID NO 64),
- AAATPPSITAAA (SEQ ID NO 65),
- AAAPRTPHTAAA (SEQ ID NO 66),
- NLANHAPNHCAR (SEQ ID NO 67),
- NLAPRTPHTAAR (SEQ ID NO 68).

45. An adeno-associated virus (AAV) capsid polypeptide comprising a peptide insert at a position between 587 to 592 of wild type AAV serotype 2 (AAV2), particularly between N587 and R588 of AAV serotype 2 or at a position homologous thereto in an AAV of another serotype, wherein the peptide insert is selected from the group of sequences comprising:

- NLANHAPNHCAR (SEQ ID NO 67)
- NLAPRTPHTAAR (SEQ ID NO 68)

~~46. The AAV capsid polypeptide the use according to one of claims 40 to 44, or the AAV capsid according to claim 45~~
~~wherein the capsid comprises one or more of the mutations selected from:~~

~~a. a tyrosine (Y) to phenylalanine (F) at amino acid position 252, 272, 444, 500, 700, 704 and/or 730; and/or~~

~~b. a threonine (T) to valine (V) at amino acid position 491.~~

~~47. The AAV capsid polypeptide for the use according to claim 42 or the AAV capsid according claim 45 or according to claim 45 and claim 46,~~
~~in particular comprising or consisting of the amino acid sequence according to SEQ ID NO 74.~~

~~48. A nucleic acid molecule encoding the AAV capsid according to one of claims 40 to 47.~~

~~49. The nucleic acid molecule according to claim 48, wherein the nucleic acid molecule comprises or consists of a nucleic acid sequence encoding a capsid polypeptide selected from AAV2, AAV2(7m8) or AAV8(BP2) or AAV2(NHAPNHC) or AAV2(PRTPHTA).~~

~~50. The nucleic acid molecule according to claim 48 or 49, wherein the nucleic acid molecule comprises or consists of a nucleic acid sequence encoding a capsid polypeptide comprising an amino acid sequence with a peptide insert between N587 and R588 of the AAV2 genome, selected from~~

- ~~AAASASEASTAA (SEQ ID NO 64),~~
- ~~AAATPPSITAAA (SEQ ID NO 65),~~
- ~~AAAPRTPHTAAA (SEQ ID NO 66),~~
- ~~NLANHAPNHCAR (SEQ ID NO 67),~~
- ~~NLAPRTPHTAAR (SEQ ID NO 68).~~

~~51. The nucleic acid molecule according to one of claims 48 to 50, wherein the nucleic acid molecule comprises a transgene,~~

~~wherein in particular the transgene encodes a chimeric opsin GPCR, and in particular comprises or consists of a nucleic acid sequence selected from the group comprising SEQ ID NO 1, SEQ ID NO 3, SEQ ID NO 5, SEQ ID NO 7, SEQ ID NO 9 and SEQ ID NO 11, SEQ ID NO 13, SEQ ID NO 15, SEQ ID NO 17, SEQ ID NO 19, SEQ ID NO 21, SEQ ID NO 23, SEQ ID NO 25, SEQ ID NO 27, SEQ ID NO 29 and SEQ ID NO 31 SEQ ID NO 33, SEQ ID NO 35, SEQ ID NO 37, SEQ ID NO 39, SEQ ID NO 41 and SEQ ID NO 43.~~

~~52. The nucleic acid molecule according to one of claims 48 to 51, wherein the nucleic acid molecule comprises a transgene encoding a mela(palm)-mGluR6 chimeric GPCR comprising or consisting of a nucleic acid sequence selected from the group comprising SEQ ID NO 17, SEQ ID NO 19, SEQ ID NO 21, SEQ ID NO 23, SEQ ID NO 25 and SEQ ID NO 27.~~

~~53 The nucleic acid molecule according to claim 51 or 52 and comprising a cell specific promoter,~~
~~wherein the cell specific promoter is operably linked to the transgene,~~
~~wherein the cell specific promoter is in particular an ON bipolar cell specific promoter, more particularly selected from group comprising a 200En-mGluR500P promoter, a 770En_454P(hGRM6) promoter according to SEQ ID NO 75 or a 444En_454P(hGRM6) promoter according to SEQ ID NO 76 or an endogenous mGluR6 promoter of retinal ON-bipolar cells or elements thereof.~~

~~54. A recombinant AAV vector (rAAV) comprising a sequence encoding an AAV capsid according to claim 45 or according to claim 45 and claim 46 or according to claim 45 and 47.~~

17~~55~~. A vector comprising the nucleic acid molecule according ~~one of claims 36 to 39~~to claim 16~~, in particular~~or a nucleic expression vector comprising a transgene encoding the chimeric opsin GPCR protein according to ~~one of claims 36 to 39~~any one of claims 1 to 14 operably linked to a promoter, or operably linked to a cell-specific promoter, or operably linked to a bipolar cell specific promoter.

18~~56~~. The vector according to claim ~~54 or 55~~17, wherein the vector is a recombinant adeno-associated virus (rAAV), or wherein the vector is an rAAV vector selected from a group of AAV serotypes comprising AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11 and AAV12.

~~57. The vector according to one of claims 54 to 56 selected from a group of AAV serotypes comprising AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11 and AAV12 , in particular AAV2 or AAV8.~~

~~58. The vector according to one of claims 54 to 57 further comprising a nucleic acid sequence selected from the group of sequences comprising:~~

- ~~a sequence encoding an AAV capsid protein, and/or~~
- ~~a promoter, in particular a cell-specific promoter, more particularly a bipolar cell specific promoter.~~

~~59. The vector according to one of claims 54 to 58 comprising a nucleic acid molecule encoding a chimeric opsin GPCR according to one of claims 35 to 39 is driven by an ON-bipolar cell specific promoter, selected in particular from a group of promoters comprising~~

- ~~a GRM6-sv40 promoter,~~
- ~~a 4xGRM6-sv40 promoter,~~
- ~~a 200En-mGluR500P promoter,~~
- ~~a 770En_454P(hGRM6) promoter SEQ ID NO 75,~~
- ~~a 444En_454P(hGRM6) promoter SEQ ID NO 76 and~~
- ~~an endogenous mGluR6 promoter of retinal ON-bipolar cells or elements thereof.~~

~~60. The vector according to one of claims 54 to 59, comprising a transgene encoding a chimeric melnaopsin-mGluR6 (Mela-mGluR6), in particular Mela(palm)-mGluR6 or Mela(palm+33)-mGluR6 or a chimeric OPN1mw-mGluR6 or a chimeric opsin GPCR comprising two opsins.~~

61. The vector according to claim 54 to 60 comprising a transgene, wherein the transgene encodes a chimeric Mela-mGluR6 selected from the group comprising:

- a Mela(palm)-mGluR6, in particular according to one of the sequences selected from the group comprising SEQ ID NO 17, SEQ ID NO 19, SEQ ID NO 21, SEQ ID NO 23, SEQ ID NO 25 and SEQ ID NO 27 or
- a Mela(palm+33)-mGluR6, in particular according to SEQ ID NO 15 or
- a Mela mGluR6 addtionally comprising an intracellular loop, in particular according to a sequence selected from SEQ ID NO 29 or SEQ ID NO 31.

62. The vector according to one of claims 54 to 61,
wherein the vector additionally comprises a nucleic acid sequence encoding the AAV capsid according to one of claims 40 to 47, in particular according to one of claims 43 to 47.

63. The vector according to a combination of claims 54 to 62,
wherein the vector comprises the 770En-445P(hGRM6) promoter operably linked to a transgene encoding the chimeric opsin GPCR and
wherein the vector further comprises a nucleic acid sequence encoding a capsid selected from the group comprising an AAV2(7m8), AAV8(BP2), AAV2(NHAPNHC) and AAV2(PRTPHTA),
wherein in particular the transgene encodes the chimeric opsin GPCR selected from the group comprising

- a chimeric opsin GPCR comprising melanopsin or hOPN1mw as upstream opsin and mGluR6 as target opsin or a chimeric opsin GPCR comprising two opsins,
- a chimeric opsin GPCR selected from Mela(palm)-mGluR6 or Mela(palm+33)-mGluR6
- a chimeric opsin GPCR encoded by a nucleic acid sequence selected from the group comprising SEQ ID NO 15, SEQ ID NO 17, SEQ ID NO 19, SEQ ID NO 21, SEQ ID NO 23, SEQ ID NO 25 and SEQ ID NO 27 SEQ ID NO 29 or SEQ ID NO 31.

64. The vector according to claim 54 or 55 comprising or consisting of a nucleic acid molecule with the sequence according to SEQ ID NO 79.

65. A transgenic animal, in particular a transgenic mouse, or a transgenic cell comprising the nucleic acid molecule according to one of claims 36 to 39 or comprising the vector according to one of claims 54 to 64 and/or comprising the opsin-GPCR protein according to one of the claims 1 to 35

66. The transgenic cell according to claim 60 wherein the cell is derived from a stem cell line – in particular excluding germ cell lines – or wherein the cell is derived from an organotypic cell line in particular selected from the group of cell lines comprising:

- HEK293-GIRK cells
- inner retinal neurons, in particular ON bipolar cells,
- kidney cells and
- cells expressing a G protein selected from Gs, Gq or $G_{12/13}$.

67. The transgenic animal or the transgenic cell according to claim 65 or 66 comprising a CRISPR/cas modified genome.

68. A carrier comprising
the chimeric opsin GPCR protein according to one of claims 1 to 35 or
the nucleic acid molecule according to one of claims 36 to 39 or the vector according to one of claims 54 to 64,

wherein the nucleic acid molecule or the vector comprises a transgene encoding the chimeric opsin GPCR,

wherein the carrier is suitable for a transfer of said chimeric opsin GPCR to a target cell or a human or non-human animal and
wherein optionally the carrier is selected from the group comprising a vesicle, a particle, a micro-particle, a nano- particle and a gold particle.

69. The carrier for transfer according to claim 68, wherein the carrier comprises the transgene and a CRISPR/cas cassette.

~~70. The transgenic animal or the transgenic cell according to one of claims 65 to 67 or the carrier for transfer according to one of claims 68 or 69 comprising the transgene encoding a chimeric melnaopsin-mGluR6 (Mela-mGluR6), in particular Mela(palm)-mGluR6 or Mela(palm+33)-mGluR6 or a chimeric OPN1mw-mGluR6 or a chimeric opsin GPCR comprising two opsins.~~

~~71. The transgenic animal or the transgenic cell according to one of claims 65 to 67 or the carrier for transfer according to one of claims 68 or 69, wherein the transgene encodes a chimeric Mela-mGluR6 selected from the group comprising:~~

- ~~a Mela(palm)-mGluR6, in particular according to one of the sequences selected from the group comprising SEQ ID NO 17, SEQ ID NO 19, SEQ ID NO 21, SEQ ID NO 23, SEQ ID NO 25 and SEQ ID NO 27 or~~
- ~~a Mela(palm+33)-mGluR6, in particular according to SEQ ID NO 15 or~~
- ~~a Mela-mGluR6 addtionally comprising an intracellular loop, in particular according to a sequence selected from SEQ ID NO 29 or SEQ ID NO 31.~~

~~72. A method of genetic engineering a nucleic acid molecule encoding a chimeric opsin GPCR protein or a chimeric peptide, in particular according to one of claims 1 to 35,~~

~~wherein said chimeric opsin GPCR protein or said chimeric peptide comprises a chimeric C-terminal domain (chimeric CT) comprising a truncated upstream opsin CT,~~

~~wherein said chimeric CT is derived from a parent upstream opsin CT and from a parent target GPCR CT and~~

~~wherein said method comprises the steps:~~

~~A-1 selecting a truncation site (x) in the CT of the parent upstream opsin at an amino acid position at a distal end of an O-CT-proximal region or within a distal extension to the O-CT-proximal region,~~

~~A-2 obtaining a nucleic acid molecule encoding an upstream opsin portion or a peptide with a truncated CT that is truncated at the selected truncation site;~~

B-1 selecting a cutting site (y) within a proximal region of the parent target GPCR CT, in particular at or upstream of an NR(K)Q motif or between an NPxxY and a NR(K)Q motif,

B-2 obtaining a nucleic acid molecule encoding a target GPCR CT or a functional variant thereof, in particular a functional fragment thereof; and

C-1 fusing the nucleic acid molecule encoding the truncated opsin-CT obtained in step A-2 with the nucleic acid molecule encoding the target CT or the functional variant thereof obtained in step B-2.

73. The method of genetic engineering according to claim 72, wherein in step A-1 the truncation site (x) fulfills one or more of the criteria selected from the group of criteria comprising:

- the truncation site (x) is positioned at a nucleotide located at or at least 7 or 8 or 9 or 10 or 11 or 12 or 13 amino acids downstream of the NR(K)Q motif,
- the truncation site (x) is positioned downstream of and in particular distally adjacent to a palmitoylation site or an amino acid corresponding to a palmitoylation site,
- the truncation site is positioned up to at most 45 or 47 or 49 nucleotides downstream of the NR(K)Q motif.

74. The method of genetic engineering according to claim 72, wherein in particular the upstream opsin is melanopsin and wherein in step A-1 the truncation site (x) fulfills one or more of the criteria selected from the group of criteria comprising:

- the truncation site (x) is positioned up to 30 or 31 or 32 or 33 or 34 or 35 amino acids downstream of O-CT-proximal region, in particular at a distal end of a distal extension to the O-CT-proximal region,
- the truncation site (x) is positioned up to 45 or 47 or 49 nucleotides downstream of the NR(K)Q motif,
- the truncation site is positioned at an amino acid position downstream of a conserved cluster of phosphorylation sites and in particular distally adjacent to the distal end of said cluster of conserved phosphorylation sites.

75. The method of genetic engineering according to claim 72, wherein the truncation site x in the upstream opsin selected in step A-1 and the cutting site y of the target GPCR selected in step B-1 are both positioned at their respective palmitoylation sites or at an amino acid position corresponding to a palmitoylation site or are both positioned between 7 and 13, in particular between 8 and 12, more particularly between 9 and 11 or at about 10 amino acids downstream of the NR(K)Q site.

76. The method of genetic engineering according to one of claims 72 to 75 comprising one or more additional step for replacing or partially replacing one or more intracellular loop, in particular exchanging at corresponding positions one or more intracellular loop or a partial intracellular loop of the upstream opsin by an intracellular loop of the target GPCR,
wherein in particular one or more splicing site is selected from the group comprising

- a junction a and a junction b for exchange of IL1
- a junction c and a junction d for exchange of IL2
- a junction e and a junction f for exchange of IL3
- two splicing sites within IL3 that remove a highly variable region of the upstream opsin IL3 in exchange for IL3 of the target GPCR.

77. The method of genetic engineering according to one of claims 72 to 76, additionally comprising prior to step A and or step B an identification of conserved motifs in one or both of the nucleic acid sequences encoding the parent GPCRs comprising the steps of

- aligning the amino acid sequence of the opsin or a fragment thereof with the amino acid sequence of the target GPCR or a fragment thereof optionally using a sequence alignment tool,
- determination of amino acid positions constituting a conserved motif selected from the group of conserved motifs in particular comprising
    - E(D)RY/NRI,
    - E around junction of IL3 with TM6,

- ~~NPxxY,~~
- ~~NR(K)Q,~~
- ~~palmitoylated C and~~
- ~~K for binding of the chromophore in TM7, provided the target GPCR is also an opsin;~~

~~wherein optionally the amino acid sequence of the upstream opsin is aligned with the amino acid sequence of bovine rhodopsin for identification of amino acid positions constituting a conserved motif.~~

~~78. The method of genetic engineering according to one of claims 72 to 77, additionally comprising prior to step A and/or step B an identification of conserved 3D GPCR domains or subdomains, in particular a subdomain helix 8, in one or both of the parent opsin and the parent target GPCR comprising the step of inputting the primary amino acid sequence into a program for prediction of secondary / tertiary protein structure.~~

19. A pharmaceutical composition comprising a chimeric opsin GPCR protein according to any one of claims 1 to 15, a nucleic acid molecule encoding said opsin GPCR protein according to claim 16, or a vector according to claim 17 or claim 18.

20~~79~~. Use of ~~A~~a chimeric opsin -GPCR protein according to any one of claims 1 to 15,~~35~~

or a nucleic acid molecule encoding said opsin GPCR protein according to ~~one of claims 36 to 39~~claim 16,

~~or a capsid according to one of claims 40 to 47~~

~~or a nucleic acid molecule encoding said capsid according to claim 48 to 53 or~~

or a vector according to ~~one of claims 54 zo 64~~claim 17 or claim 18,

or a pharmaceutical composition according to claim 19,~~or a carrier or a cell according to one of claims 65 to 71~~

in the manufacture of a medicament~~, in particular for gene therapy~~ for the treatment of partial or complete loss of vision due to photoreceptor degeneration.

21~~80~~. Use of ~~T~~a chimeric opsin GPCR protein according to any one of claims 1 to 15,

or ~~the~~ a nucleic acid molecule encoding said opsin GPCR according to claim 16,

~~or the capsid or the nucleic acid molecule encoding said capsid,~~

or ~~the~~ a vector ~~or the carrier or the cell~~according to claim 17 or claim 18,

or a pharmaceutical composition according to claim 19,

~~for the use~~ in the manufacture of a medicament~~ according to claim 79, wherein a purpose of the use is selected from the group comprising for improve vision,~~ for treatment of partial or complete blindness, for treatment of retinitis pigmentosa (RP), for treatment of macular degeneration, ~~and~~ or for treatment of other forms of photoreceptor degeneration.

~~81. The chimeric opsin GPCR protein,~~

~~or the nucleic acid molecule encoding said opsin GPCR,~~

~~or the capsid or the nucleic acid molecule encoding said capsid,~~

~~or the vector or the carrier or the cell~~

~~for the use according to claim 79 or 80,~~

~~wherein the chimeric opsin GPCR is selected from a chimeric opsin mGluR6 GPCR or a chimeric GPCR comprising an upstream opsin and a target opsin, wherein in particular the target opsin is a cone opsin or rhodopsin.~~

~~82. A pharmaceutical composition comprising a product selected from the group of products comprising~~

~~a chimeric opsin-GPCR protein according to one of claims 1 to 35~~

~~or a nucleic acid molecule encoding said opsin GPCR protein according to one of claims 36 to 39~~

~~or a capsid according to one of claims 40 to 47~~

~~or a nucleic acid molecule encoding said capsid according to claim 48 to 53 or~~

~~or a vector according to one of claims 54 zo 64~~

~~or a carrier or a cell according to one of claims 65 to 71,~~

~~wherein optionally the chimeric opsin GPCR is selected from a chimeric opsin mGluR6 GPCR or a chimeric GPCR comprising an upstream opsin and a target opsin, and~~

~~wherein optionally the target opsin is a cone opsin or rhodopsin.~~

~~83. A method of treating a human or non-human animal in need thereof comprising the administration of~~

~~a chimeric opsin-GPCR protein according to one of claims 1 to 35~~

~~or a nucleic acid molecule encoding said opsin GPCR protein according to one of claims 36 to 39~~

~~or a capsid according to one of claims 40 to 47~~

~~or a nucleic acid molecule encoding said capsid according to claim 48 to 53 or~~

~~or a vector according to one of claims 54 zo 64~~

~~or a carrier or a cell according to one of claims 65 to 71,~~

~~wherein optionally the chimeric opsin GPCR is selected from a chimeric opsin mGluR6 GPCR or a chimeric GPCR comprising an upstream opsin and a target opsin, and~~

~~wherein optionally the target opsin is a cone opsin or rhodopsin.~~

~~84. Use of~~

~~a chimeric opsin-GPCR protein according to one of claims 1 to 35~~

~~or a nucleic acid molecule encoding said opsin GPCR protein according to one of claims 36 to 39~~

~~or a capsid according to one of claims 40 to 47~~

~~or a nucleic acid molecule encoding said capsid according to claim 48 to 53 or~~

~~or a vector according to one of claims 54 zo 64~~

~~or a carrier or a cell according to one of claims 65 to 71,~~

~~in the manufacture of a medicament for medical therapy to improve vision, or for the treatment of partial or complete blindness, or for the treatment of retinitis pigmentosa (RP), or for the treatment of macular degeneration or for the treatment of other forms of photoreceptor degeneration,~~

~~wherein optionally the chimeric opsin GPCR is selected from a chimeric opsin mGluR6 GPCR or a chimeric GPCR comprising an upstream opsin and a target opsin, and~~

~~wherein optionally the target opsin is a cone opsin or rhodopsin.~~

~~85. A medical application according to one of claims 79 to 84 comprising a product selected from the group of products comprising~~

~~a chimeric opsin-GPCR protein according to one of claims 1 to 35~~

~~or a nucleic acid molecule encoding said opsin GPCR protein according to one of claims 36 to 39~~

~~or a capsid according to one of claims 40 to 47~~

~~or a nucleic acid molecule encoding said capsid according to claim 48 to 53~~

~~or a vector according to one of claims 54 to 64~~

~~or a carrier or a cell according to one of claims 65 to 71,~~

~~wherein the product comprises a chimeric opsin GPCR protein or comprises a nucleic acid molecule comprising a nucleic acid sequence encoding said chimeric opsin GPCR protein ,~~

~~wherein the chimeric opsin GPCR is selected from the group comprising~~

- ~~a Mela(palm)-mGluR6, in particular according to a sequence selected from the group comprising SEQ ID NO 18, SEQ ID NO 20, SEQ ID NO 22, SEQ ID NO 24, SEQ ID NO 26 and SEQ ID NO 28 or~~
- ~~a Mela(palm+33)-mGluR6, in particular according to SEQ ID NO 16 or~~
- ~~a Mela-mGluR6 addtionally comprising an intracellular loop, in particular according to a sequence selected from SEQ ID NO 30 or SEQ ID NO 32.~~