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 and a second GPCR portion (target GPCR portion),

wherein said 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 GPCR portion comprises a C-terminal domain (target-GPCR-CT) positioned downstream of the truncated C-terminal domain of the opsin portion.

2. The chimeric opsin GPCR protein according to claim 1, wherein the truncation site is positioned at or downstream of:

- a distal end of a helix 8 (H8); or
- a palmitoylation site.

3. The chimeric opsin GPCR protein according to any one of the preceding claims, wherein the truncation site is positioned up to 33 amino acids downstream of the palmitoylation site.

4. The chimeric opsin GPCR protein according to any one of the preceding claims, wherein the opsin is a melanopsin, 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 protein according to any one of the preceding claims, wherein the opsin portion is derived from two or more parent opsins.

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

7. The chimeric opsin GPCR protein according to any one of the preceding claims, wherein the 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.

8. The chimeric opsin GPCR protein according to any one of the preceding claims, wherein:
a) the target-GPCR-CT is a functional variant of the CT of the parent target GPCR;
b) the target-GPCR-CT comprises an N terminal deletion between the NPxxY motif and any amino acid position up to a 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.

10. The chimeric opsin GPCR protein according to any one of the preceding claims, wherein the target GPCR protein is a class C GPCR, or wherein the target GPCR protein is mGluR6.

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. The chimeric opsin GPCR protein according to any one of the 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 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.

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. 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.

15. The chimeric opsin GPCR protein according to claim 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 wherein the chimeric opsin-GPCR protein exhibits a light activation dependent binding of Galpha protein specific to the target GPCR.

16. A nucleic acid molecule encoding the chimeric opsin GPCR protein according to any one of the preceding claims.

17. A vector comprising the nucleic acid molecule according to claim 16 or a nucleic expression vector comprising a transgene encoding the chimeric opsin GPCR protein according to 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. The vector according to claim 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.

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

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

or a vector according to claim 17 or claim 18,

or a pharmaceutical composition according to claim 19,

in the manufacture of a medicament for the treatment of partial or complete loss of vision due to photoreceptor degeneration.

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

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

or a vector according to claim 17 or claim 18,

or a pharmaceutical composition according to claim 19,

in the manufacture of a medicament for treatment of partial or complete blindness, for treatment of retinitis pigmentosa (RP), for treatment of macular degeneration, or for treatment of other forms of photoreceptor degeneration.