Claims

1. ~~Chimeric~~ Composition comprising: (i) a chimeric GPCR having the structure:

[N-terminal sequence]-[TM1]-[IC1]-[TM2]-[EC1]-[TM3]-[IC2]-[TM4]-[EC2]-[TM5]-[IC3]-[TM6]-[EC3]-[TM7]-[C-terminal sequence]

in which the extracellular loops and TM's form a functional ligand binding site and the extracellular loops and TM's are derived from a first GPCR and the intracellular loops that are derived from a second GPCR (different from the first) and (ii) an immunoglobulin single variable domain that can bind to at least one of the intracellular loops that are derived from said second GPCR.

~~2. Chimeric GCPR according to claim 1, in which the extracellular binding domain of said chimeric GPCR is derived from said first GPCR.~~

~~3. Chimeric GCPR according to claim 1 or 2, in which the TMs are derived from said first GPCR.~~

4~~2~~. ~~Chimeric GCPR~~Composition according to ~~any of claims 1 to 3~~claim 1, in which the first GPCR and the second GPCR both belong to class A.

~~5. Composition comprising a chimeric GPCR according to any of claims 1 to 4 and a binding domain or binding unit that can bind to at least one of the intracellular loops that are derived from said second GPCR.~~

6~~3~~. Composition according to claim 5~~2~~, in which said immunoglobulin single variable domain~~binding domain or binding unit is ligand~~ is capable of stabilizing and/or inducing a functional and/or active conformational state of the chimeric GPCR upon binding to the chimeric GPCR.

~~7. Composition according to claim 5 or 6, in which said binding domain or binding unit is an immunoglobulin single variable domain.~~

~~8~~4. Composition according to any of claims ~~4 to 6~~1 to 3, which is a cellular composition.

5. Composition according to any of claims 1 to 4, further comprising a compound or ligand that is capable of binding to an extracellular binding site (as defined herein) on said chimeric GPCR.

~~9~~6. Method of forming a complex of a chimeric GPCR, an immunoglobulin single variable domain~~a binding domain or binding unit~~, and a compound or ligand that is capable of binding to an extracellular binding site (as defined herein) on said chimeric GPCR, said method comprising the steps of:

a) providing a composition according to any of claims ~~6 to 8~~1 to 4; and
b) contacting said composition with one or more test compounds or ligands under conditions that (i) allow said immunoglobulin single variable domain~~binding domain or binding unit~~ to bind to said binding site on the chimeric GPCR that comprises at least one of said intracellular loops; and (ii) allow said test compounds to bind to the extracellular binding site of said chimeric GPCR.

~~10~~7. Method of identifying and/or generating compounds or ligands that are capable of binding to an extracellular binding site (as defined herein) of a GPCR, said method comprising the steps of:

a) providing a composition according to any of claims ~~6 to 8~~1 to 4~~, in which the chimeric GPCR comprises at least the extracellular loops of said GPCR~~;
b) contacting said composition with one or more test compounds or ligands under conditions that (i) allow the immunoglobulin single variable domain ~~said binding domain or binding unit~~ to bind to said binding site on the chimeric GPCR that comprises at least one of said intracellular loops; and (ii) allow said test compounds to bind to the extracellular binding site of said chimeric GPCR;
c) evaluating whether each of the test compounds or ligands (and/or which of said test compounds or ligands) binds to the chimeric GPCR; in said composition; and optionally
d) selecting the test compounds or ligands that bind to the chimeric GPCR in said composition.

~~11~~8. Method of identifying and/or generating compounds or ligands that are capable of binding to an active conformation of a GPCR, said method comprising the steps of:

a) providing a composition according to any of claims ~~6 to 8~~1 to 4, in which the chimeric GPCR comprises ~~at least~~ the extracellular loops and TMs of said GPCR and in which the immunoglobulin single variable domain ~~binding domain or binding unit~~ is ligand is capable of stabilizing and/or inducing an active conformational state of the chimeric GPCR upon binding to the chimeric GPCR.;

b) contacting said composition with one or more test compounds or ligands under conditions that (i) allow said immunoglobulin single variable domain ~~binding domain or binding unit~~ to bind to said binding site on the chimeric GPCR that comprises at least one of said intracellular loops; and (ii) allow said test compounds to bind to the extracellular binding site of said chimeric GPCR;

c) evaluating whether each of the test compounds or ligands (and/or which of said test compounds or ligands) binds to the chimeric GPCR; in said composition; and optionally

d) selecting the test compounds or ligands that bind to the chimeric GPCR in said composition.

9. Method according to claim 7 or 8, in which said immunoglobulin single variable domain is capable of stabilizing and/or inducing a functional and/or active conformational state of the chimeric GPCR upon binding to the chimeric GPCR.

~~12~~10. Arrangement that comprises at least the following elements:

– a boundary layer that separates a first environment from a second environment;

– a chimeric GPCR having the structure:

[N-terminal sequence]-[TM1]-[IC1]-[TM2]-[EC1]-[TM3]-[IC2]-[TM4]-[EC2]-[TM5]-[IC3]-[TM6]-[EC3]-[TM7]-[C-terminal sequence]

in which the extracellular loops and TM's form a functional ligand binding site and the extracellular loops and TM's are derived from a first GPCR and the intracellular loops that are derived from a second GPCR (different from the first);

– ~~a chimeric GPCR according to any of claims 1 to 4~~;

- a ~~first~~ ligand for the chimeric GPCR that is present in the first environment;
- an immunoglobulin single variable domain that is present in the second environment and that can bind to at least one of the intracellular loops that are derived from said second GPCR;~~a second ligand for the chimeric GPCR that is present in the second environment, which second ligand is a binding domain or binding unit that can bind to at least one of the intracellular loops on said chimeric GPCR~~; and
- a binding pair that consists of at least a first binding member and a second binding member, which binding pair is capable of generating a detectable signal.

~~13~~11. Arrangement according to claim ~~12~~10, in which the chimeric GPCR is fused or linked, either directly or via a suitable spacer or linker, to the first binding member of said binding pair and in which the immunoglobulin single variable domain ~~the second ligand~~ is fused or linked, either directly or via a suitable spacer or linker, to the first binding member of said binding pair.

12. Arrangement according to claim 10 or 11, in which said immunoglobulin single variable domain is capable of stabilizing and/or inducing a functional and/or active conformational state of the chimeric GPCR upon binding to the chimeric GPCR.

~~14. Fusion protein comprising a chimeric GPCR according to any of claims 1 to 4 that is fused or linked, either directly or via a suitable spacer or linker, to a binding domain or binding unit that can bind to at least one of the intracellular loops of said chimeric GPCR.~~

~~15. Fusion protein according to claim 14, in which said binding domain or binding unit is ligand is capable of stabilizing and/or inducing a functional and/or active conformational state of the chimeric GPCR upon binding to the chimeric GPCR.~~