(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 December 2016 (15.12.2016)

WIPO | PCT

(10) International Publication Number
WO 2016/201152 A1

(51) International Patent Classification:
C07K 14/72 (2006.01)

(21) International Application Number:
PCT/US2016/036776

(22) International Filing Date:
9 June 2016 (09.06.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/173,762 10 June 2015 (10.06.2015) US

(71) Applicant: **FIRMENICH SA** [CH/CH]; 1, route des Jeunes, PO Box 239, 1211 Geneva 8 (CH).

(72) Inventors; and
(71) Applicants *(for US only)*: **PFISTER, Patrick** [US/US]; 85 Ave. A, Apt. 5D, New York, New York 10009 (US). **ROGERS, Matthew** [US/US]; 535 West 110th St., Apt. 6D, New York, New York 10025 (US).

(74) Agents: **FANUCCI, Allan, A.** et al.; Winston & Strawn LLP, Patent Department, 1700 K Street, N.W., Washington, District of Columbia 20006-3817 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

[Continued on next page]

(54) Title: METHOD OF IDENTIFYING MUSK COMPOUNDS

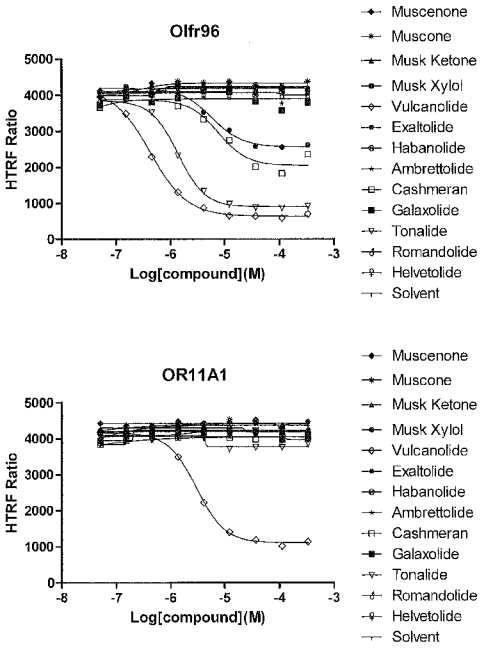


FIGURE 3

(57) Abstract: Provided herein are polypeptides that bind to Musk compounds. Also provided are nucleic acid sequences that encode for the polypeptides. Further provided herein is a method for identifying a compound that activates, mimics, blocks, inhibits, modulates, and/or enhances the activity of an olfactory receptor that is activated by a polycyclic Musk or a nitro Musk wherein the receptor is a polypeptide having an amino acid sequence that is at least 75% identical to Olfr96 or OR11A1 wherein the method includes a) contacting the receptor, or a chimera or fragment thereof with a compound and b) determining whether the compound has an effect on the activity of the receptor.

WO 2016/201152 A1

Published:

— *with international search report (Art. 21(3))*

— *with sequence listing part of description (Rule 5.2(a))*

METHOD OF IDENTIFYING MUSK COMPOUNDS

Field

The technical field is directed to odorant and aroma receptors and assays that can be used to identify odorant and/or aroma compounds and more specifically enhancers of Musk compounds.

Background

Olfaction is one of the most complex and poorly understood of human sensory systems. From olfactory receptor (OR) activation to perception, there are many steps that still require further investigation. Musk compounds are part of a structurally diverse group of chemicals comprising macrocyclic Musks, polycyclic Musks, alicyclic Musks and nitro Musks. These Musk compounds are used in perfumery, and form the base notes in many commercial formulations. Hence, there is a need to identify new Musk compounds and compounds that enhance the perception of Musk in perfumes.

SUMMARY

Provided herein is a host cell transformed to express a polypeptide having an amino acid sequence that is at least 75% identical to SEQ ID NO: 2 or SEQ ID NO: 4.

Further provided herein is an expression vector comprising a nucleic acid that encodes for a polypeptide having an amino acid sequence that is at least 75% identical to SEQ ID NO: 2 or SEQ ID NO: 4.

Also provided herein is an expression vector having a nucleic acid wherein the nucleic acid comprises a nucleotide sequence that is at least 75% identical to SEQ ID NO: 1 or SEQ ID NO: 3.

Further provided herein is a method for identifying a compound that blocks, inhibits, modulates, and/or enhances the activity of an olfactory receptor that is activated by a polycyclic musk or a nitro musk wherein the receptor is a polypeptide having an amino acid sequence that is at least 75% identical to SEQ ID NO: 2 or SEQ ID NO: 4 wherein the method comprises:

a) contacting the receptor, or a chimera or fragment thereof with a compound;

b) determining whether the compound has an effect on the activity of the receptor.

Still yet further provided is a cell that is recombinantly modified to express a polypeptide described above.

DETAILED DESCRIPTION OF THE DRAWINGS

Figure 1 displays Ca^{2+} imaging traces of olfactory sensory neurons that responded to mixtures of musk compounds (Figure 1A) and the subsequent identification of mouse receptors Olfr96 and Olfr235 (Figure 1 B).

Figure 2 shows Musk dose response curves of Olfr96 with polycyclic musk compounds vulcanolide and tonalide.

Figure 3 shows Musk dose response curves of Olfr96 and OR11A1 with polycyclic musk compounds vulcanolide, tonalide and cashmeran, and nitro musk compound Musk X.

DETAILED DESCRIPTION

For the descriptions herein and the appended claims, the use of "or" means "and/or" unless stated otherwise. Similarly, "comprise," "comprises," "comprising" "include," "includes," and "including" are interchangeable and not intended to be limiting.

It is to be further understood that where descriptions of various embodiments use the term "comprising," those skilled in the art would understand that in some specific instances, an embodiment can be alternatively described using language "consisting essentially of" or "consisting of."

In one embodiment, a host cell is transformed to express a polypeptide wherein the polypeptide comprises an amino acid sequence is at least 75%, 80%, 85%, 90%, 95%, 98% or 99% identical to SEQ ID NO: 2.

In one embodiment, a host cell is transformed to express a polypeptide wherein the polypeptide comprises an amino acid sequence is at least 80%, 85%, 90%, 95%, 98% or 99% identical to SEQ ID NO: 2.

In one embodiment, a host cell is transformed to express a polypeptide wherein the polypeptide comprises an amino acid sequence is at least 85%, 90%, 95%, 98% or 99% identical to SEQ ID NO: 2.

In one embodiment, a host cell is transformed to express a polypeptide wherein the polypeptide comprises an amino acid sequence is at least 90%, 95%, 98% or 99% identical to SEQ ID NO: 2.

In one embodiment, a host cell is transformed to express a polypeptide wherein the polypeptide comprises an amino acid sequence is at least 95%, 98% or 99% identical to SEQ ID NO: 2.

In one embodiment, a host cell is transformed to express a polypeptide wherein the polypeptide comprises an amino acid sequence is at least 98% or 99% identical to SEQ ID NO: 2.

In one embodiment, a host cell is transformed to express a polypeptide wherein the polypeptide comprises an amino acid sequence is at least 99% identical to SEQ ID NO: 2.

In one embodiment, a host cell is transformed to express a polypeptide wherein the polypeptide comprises an amino acid sequence is at least 75%, 80%, 85%, 90%, 95%, 98% or 99% identical to SEQ ID NO: 4.

In one embodiment, a host cell is transformed to express a polypeptide wherein the polypeptide comprises an amino acid sequence is at least 80%, 85%, 90%, 95%, 98% or 99% identical to SEQ ID NO: 4.

In one embodiment, a host cell is transformed to express a polypeptide wherein the polypeptide comprises an amino acid sequence is at least 85%, 90%, 95%, 98% or 99% identical to SEQ ID NO: 4.

In one embodiment, a host cell is transformed to express a polypeptide wherein the polypeptide comprises an amino acid sequence is at least 90%, 95%, 98% or 99% identical to SEQ ID NO: 4.

In one embodiment, a host cell is transformed to express a polypeptide wherein the polypeptide comprises an amino acid sequence is at least 95%, 98% or 99% identical to SEQ ID NO: 4.

In one embodiment, a host cell is transformed to express a polypeptide wherein the polypeptide comprises an amino acid sequence is at least 98% or 99% identical to SEQ ID NO: 4.

In one embodiment, a host cell is transformed to express a polypeptide wherein the polypeptide comprises an amino acid sequence is at least 99% identical to SEQ ID NO: 4.

In one embodiment, a host cell is transformed to express a having an amino acid sequence that is identical to SEQ ID NO: 2 or SEQ ID NO: 4; more particularly an amino acid sequence that is identical to SEQ ID NO: 2; even more particularly an amino acid sequence that is identical to SEQ ID NO.: 4.

Further provided herein is an expression vector comprising a nucleic acid that encodes for a polypeptide having an amino acid sequence that is at least 75%, 80%, 85%, 90%, 95%, 98% or 99% identical to SEQ ID NO: 2.

Further provided herein is an expression vector comprising a nucleic acid that encodes for a polypeptide having an amino acid sequence that is at least 80%, 85%, 90%, 95%, 98% or 99% identical to SEQ ID NO: 2.

Further provided herein is an expression vector comprising a nucleic acid that encodes for a polypeptide having an amino acid sequence that is at least 85%, 90%, 95%, 98% or 99% identical to SEQ ID NO: 2.

Further provided herein is an expression vector comprising a nucleic acid that encodes for a polypeptide having an amino acid sequence that is at least 90%, 95%, 98% or 99% identical to SEQ ID NO: 2.

Further provided herein is an expression vector comprising a nucleic acid that encodes for a polypeptide having an amino acid sequence that is at least 95%, 98% or 99% identical to SEQ ID NO: 2.

Further provided herein is an expression vector comprising a nucleic acid that encodes for a polypeptide having an amino acid sequence that is at least 98% or 99% identical to SEQ ID NO: 2.

Further provided herein is an expression vector comprising a nucleic acid that encodes for a polypeptide having an amino acid sequence that is at least 99% identical to SEQ ID NO: 2.

Further provided herein is an expression vector comprising a nucleic acid that encodes for a polypeptide having an amino acid sequence that is at least 75%, 80%, 85%, 90%, 95%, 98% or 99% identical to SEQ ID NO: 4.

Further provided herein is an expression vector comprising a nucleic acid that encodes for a polypeptide having an amino acid sequence that is at least 80%, 85%, 90%, 95%, 98% or 99% identical to SEQ ID NO: 4.

Further provided herein is an expression vector comprising a nucleic acid that encodes for a polypeptide having an amino acid sequence that is at least 85%, 90%, 95%, 98% or 99% identical to SEQ ID NO: 4.

Further provided herein is an expression vector comprising a nucleic acid that encodes for a polypeptide having an amino acid sequence that is at least 90%, 95%, 98% or 99% identical to SEQ ID NO: 4.

Further provided herein is an expression vector comprising a nucleic acid that encodes for a polypeptide having an amino acid sequence that is at least 95%, 98% or 99% identical to SEQ ID NO: 4.

Further provided herein is an expression vector comprising a nucleic acid that encodes for a polypeptide having an amino acid sequence that is at least 98% or 99% identical to SEQ ID NO: 4.

Further provided herein is an expression vector comprising a nucleic acid that encodes for a polypeptide having an amino acid sequence that is at least 99% identical to SEQ ID NO: 4.

Further provided herein is an expression vector comprising a nucleic acid that encodes for a polypeptide having an amino acid sequence that is identical to SEQ ID NO: 2 or SEQ ID NO: 4; more particularly an amino acid sequence that is identical to SEQ ID NO: 2; even more particularly an amino acid sequence that is identical to SEQ ID NO: 4.

Also provided herein is an expression vector having a nucleic acid wherein the nucleic acid comprises a nucleotide sequence that is at least 75%, 80%, 85%, 90%, 95%, 98% or 99% identical to SEQ ID NO: 1.

Also provided herein is an expression vector having a nucleic acid wherein the nucleic acid comprises a nucleotide sequence that is at least 80%, 85%, 90%, 95%, 98% or 99% identical to SEQ ID NO: 1.

Also provided herein is an expression vector having a nucleic acid wherein the nucleic acid comprises a nucleotide sequence that is at least 85%, 90%, 95%, 98% or 99% identical to SEQ ID NO: 1.

Also provided herein is an expression vector having a nucleic acid wherein the nucleic acid comprises a nucleotide sequence that is at least 90%, 95%, 98% or 99% identical to SEQ ID NO: 1.

Also provided herein is an expression vector having a nucleic acid wherein the nucleic acid comprises a nucleotide sequence that is at least 95%, 98% or 99% identical to SEQ ID NO: 1.

Also provided herein is an expression vector having a nucleic acid wherein the nucleic acid comprises a nucleotide sequence that is at least 98% or 99% identical to SEQ ID NO: 1.

Also provided herein is an expression vector having a nucleic acid wherein the nucleic acid comprises a nucleotide sequence that is at least 99% identical to SEQ ID NO: 1.

Also provided herein is an expression vector having a nucleic acid wherein the nucleic acid comprises a nucleotide sequence that is at least 75%, 80%, 85%, 90%, 95%, 98% or 99% identical to SEQ ID NO: 3.

Also provided herein is an expression vector having a nucleic acid wherein the nucleic acid comprises a nucleotide sequence that is at least 80%, 85%, 90%, 95%, 98% or 99% identical to SEQ ID NO: 3.

Also provided herein is an expression vector having a nucleic acid wherein the nucleic acid comprises a nucleotide sequence that is at least 85%, 90%, 95%, 98% or 99% identical to SEQ ID NO: 3.

Also provided herein is an expression vector having a nucleic acid wherein the nucleic acid comprises a nucleotide sequence that is at least 90%, 95%, 98% or 99% identical to SEQ ID NO: 3.

Also provided herein is an expression vector having a nucleic acid wherein the nucleic acid comprises a nucleotide sequence that is at least 95%, 98% or 99% identical to SEQ ID NO: 3.

Also provided herein is an expression vector having a nucleic acid wherein the nucleic acid comprises a nucleotide sequence that is at least 98% or 99% identical to SEQ ID NO: 3.

Also provided herein is an expression vector having a nucleic acid wherein the nucleic acid comprises a nucleotide sequence that is at least 99% identical to SEQ ID NO: 3.

Also provided herein is an expression vector having a nucleic acid wherein the nucleic acid comprises a nucleotide sequence that is identical to SEQ ID NO: 1.

Also provided herein is an expression vector having a nucleic acid wherein the nucleic acid comprises a nucleotide sequence that is identical to SEQ ID NO: 3.

In one embodiment provided herein is a cell that is recombinantly modified to express a polypeptide having an amino acid sequence that is at least 75% identical to SEQ ID NO: 2 or SEQ ID NO: 4.

Further provided herein is a method for identifying a compound that blocks, inhibits, modulates, and/or enhances the activity of an olfactory receptor that is activated by a polycyclic musk wherein the receptor is a polypeptide having an amino acid sequence that is at least 75% identical to SEQ ID NO: 2 or SEQ ID NO: 4 wherein the method comprises:

a) contacting the receptor, or a chimera or fragment thereof with a compound;

b) determining whether the compound has an effect on the activity of the receptor.

Further provided herein is a method for identifying a compound that blocks, inhibits, modulates, and/or enhances the activity of an olfactory receptor that is activated by a polycyclic musk wherein the receptor is a polypeptide having an amino acid sequence that is

at least 75%, 80%, 85%, 90%, 95%, 98% and 99% identical to SEQ ID NO: 2 wherein the method comprises:

c) contacting the receptor, or a chimera or fragment thereof with a compound;

d) determining whether the compound has an effect on the activity of the receptor.

Further provided herein is a method for identifying a compound that blocks, inhibits, modulates, and/or enhances the activity of an olfactory receptor that is activated by a polycyclic musk wherein the receptor is a polypeptide having an amino acid sequence that is at least 80%, 85%, 90%, 95%, 98% and 99% identical to SEQ ID NO: 2 wherein the method comprises:

a) contacting the receptor, or a chimera or fragment thereof with a compound;

b) determining whether the compound has an effect on the activity of the receptor.

Further provided herein is a method for identifying a compound that blocks, inhibits, modulates, and/or enhances the activity of an olfactory receptor that is activated by a polycyclic musk wherein the receptor is a polypeptide having an amino acid sequence that is at least 85%, 90%, 95%, 98% and 99% identical to SEQ ID NO: 2 wherein the method comprises:

a) contacting the receptor, or a chimera or fragment thereof with a compound;

b) determining whether the compound has an effect on the activity of the receptor.

Further provided herein is a method for identifying a compound that blocks, inhibits, modulates, and/or enhances the activity of an olfactory receptor that is activated by a polycyclic musk wherein the receptor is a polypeptide having an amino acid sequence that is at least 90%, 95%, 98% and 99% identical to SEQ ID NO: 2 wherein the method comprises:

a) contacting the receptor, or a chimera or fragment thereof with a compound;

b) determining whether the compound has an effect on the activity of the receptor.

Further provided herein is a method for identifying a compound that blocks, inhibits, modulates, and/or enhances the activity of an olfactory receptor that is activated by a polycyclic musk wherein the receptor is a polypeptide having an amino acid sequence that is at least 95%, 98% and 99% identical to SEQ ID NO: 2 wherein the method comprises:

a) contacting the receptor, or a chimera or fragment thereof with a compound;

b) determining whether the compound has an effect on the activity of the receptor.

Further provided herein is a method for identifying a compound that blocks, inhibits, modulates, and/or enhances the activity of an olfactory receptor that is activated by a

polycyclic musk wherein the receptor is a polypeptide having an amino acid sequence that is at least 98% and 99% identical to SEQ ID NO: 2 wherein the method comprises:

a) contacting the receptor, or a chimera or fragment thereof with a compound;

b) determining whether the compound has an effect on the activity of the receptor.

Further provided herein is a method for identifying a compound that blocks, inhibits, modulates, and/or enhances the activity of an olfactory receptor that is activated by a polycyclic musk wherein the receptor is a polypeptide having an amino acid sequence that is at least 99% identical to SEQ ID NO: 2 wherein the method comprises:

a) contacting the receptor, or a chimera or fragment thereof with a compound;

b) determining whether the compound has an effect on the activity of the receptor.

Further provided herein is a method for identifying a compound that blocks, inhibits, modulates, and/or enhances the activity of an olfactory receptor that is activated by a polycyclic musk wherein the receptor is a polypeptide having an amino acid sequence that is at least 75%, 80%, 85%, 90%, 95%, 98% and 99% identical to SEQ ID NO: 4 wherein the method comprises:

a) contacting the receptor, or a chimera or fragment thereof with a compound;

b) determining whether the compound has an effect on the activity of the receptor.

Further provided herein is a method for identifying a compound that blocks, inhibits, modulates, and/or enhances the activity of an olfactory receptor that is activated by a polycyclic musk wherein the receptor is a polypeptide having an amino acid sequence that is at least 80%, 85%, 90%, 95%, 98% and 99% identical to SEQ ID NO: 4 wherein the method comprises:

a) contacting the receptor, or a chimera or fragment thereof with a compound;

b) determining whether the compound has an effect on the activity of the receptor.

Further provided herein is a method for identifying a compound that blocks, inhibits, modulates, and/or enhances the activity of an olfactory receptor that is activated by a polycyclic musk wherein the receptor is a polypeptide having an amino acid sequence that is at least 85%, 90%, 95%, 98% and 99% identical to SEQ ID NO: 4 wherein the method comprises:

a) contacting the receptor, or a chimera or fragment thereof with a compound;

b) determining whether the compound has an effect on the activity of the receptor.

Further provided herein is a method for identifying a compound that blocks, inhibits, modulates, and/or enhances the activity of an olfactory receptor that is activated by a

polycyclic musk wherein the receptor is a polypeptide having an amino acid sequence that is at least 90%, 95%, 98% and 99% identical to SEQ ID NO: 4 wherein the method comprises:

a) contacting the receptor, or a chimera or fragment thereof with a compound;

b) determining whether the compound has an effect on the activity of the receptor.

Further provided herein is a method for identifying a compound that blocks, inhibits, modulates, and/or enhances the activity of an olfactory receptor that is activated by a polycyclic musk wherein the receptor is a polypeptide having an amino acid sequence that is at least 95%, 98% and 99% identical to SEQ ID NO: 4 wherein the method comprises:

a) contacting the receptor, or a chimera or fragment thereof with a compound;

b) determining whether the compound has an effect on the activity of the receptor.

Further provided herein is a method for identifying a compound that blocks, inhibits, modulates, and/or enhances the activity of an olfactory receptor that is activated by a polycyclic musk wherein the receptor is a polypeptide having an amino acid sequence that is at least 98% and 99% identical to SEQ ID NO: 4 wherein the method comprises:

a) contacting the receptor, or a chimera or fragment thereof with a compound;

b) determining whether the compound has an effect on the activity of the receptor.

Further provided herein is a method for identifying a compound that blocks, inhibits, modulates, and/or enhances the activity of an olfactory receptor that is activated by a polycyclic musk wherein the receptor is a polypeptide having an amino acid sequence that is at least 99% identical to SEQ ID NO: 4 wherein the method comprises:

a) contacting the receptor, or a chimera or fragment thereof with a compound;

b) determining whether the compound has an effect on the activity of the receptor.

Further provided herein is a method for identifying a compound that blocks, inhibits, modulates, and/or enhances the activity of an olfactory receptor that is activated by a polycyclic musk wherein the receptor is a polypeptide having an amino acid sequence that is identical to SEQ ID NO: 4 wherein the method comprises:

a) contacting the receptor, or a chimera or fragment thereof with a compound;

b) determining whether the compound has an effect on the activity of the receptor.

Further provided herein is a method for identifying a compound that blocks, inhibits, modulates, and/or enhances the activity of an olfactory receptor that is activated by a polycyclic musk wherein the receptor is a polypeptide having an amino acid sequence that is identical to SEQ ID NO: 2 wherein the method comprises:

a) contacting the receptor, or a chimera or fragment thereof with a compound;

b) determining whether the compound has an effect on the activity of the receptor.

Further provided herein is a method for identifying a compound that blocks, inhibits, modulates, and/or enhances the activity of an olfactory receptor that is activated by a nitro musk wherein the receptor is a polypeptide having an amino acid sequence that is at least 75% identical to SEQ ID NO: 2 or SEQ ID NO: 4 wherein the method comprises:

a) contacting the receptor, or a chimera or fragment thereof with a compound;

b) determining whether the compound has an effect on the activity of the receptor.

Further provided herein is a method for identifying a compound that blocks, inhibits, modulates, and/or enhances the activity of an olfactory receptor that is activated by a nitro musk wherein the receptor is a polypeptide having an amino acid sequence that is at least 75%, 80%, 85%, 90%, 95%, 98% and 99% identical to SEQ ID NO: 2 wherein the method comprises:

a) contacting the receptor, or a chimera or fragment thereof with a compound;

b) determining whether the compound has an effect on the activity of the receptor.

Further provided herein is a method for identifying a compound that blocks, inhibits, modulates, and/or enhances the activity of an olfactory receptor that is activated by a nitro musk wherein the receptor is a polypeptide having an amino acid sequence that is at least 80%, 85%, 90%, 95%, 98% and 99% identical to SEQ ID NO: 2 wherein the method comprises:

a) contacting the receptor, or a chimera or fragment thereof with a compound;

b) determining whether the compound has an effect on the activity of the receptor.

Further provided herein is a method for identifying a compound that blocks, inhibits, modulates, and/or enhances the activity of an olfactory receptor that is activated by a nitro musk wherein the receptor is a polypeptide having an amino acid sequence that is at least 85%, 90%, 95%, 98% and 99% identical to SEQ ID NO: 2 wherein the method comprises:

a) contacting the receptor, or a chimera or fragment thereof with a compound;

b) determining whether the compound has an effect on the activity of the receptor.

Further provided herein is a method for identifying a compound that blocks, inhibits, modulates, and/or enhances the activity of an olfactory receptor that is activated by a nitro musk wherein the receptor is a polypeptide having an amino acid sequence that is at least 90%, 95%, 98% and 99% identical to SEQ ID NO: 2 wherein the method comprises:

a) contacting the receptor, or a chimera or fragment thereof with a compound;

b) determining whether the compound has an effect on the activity of the receptor.

Further provided herein is a method for identifying a compound that blocks, inhibits, modulates, and/or enhances the activity of an olfactory receptor that is activated by a nitro musk wherein the receptor is a polypeptide having an amino acid sequence that is at least 95%, 98% and 99% identical to SEQ ID NO: 2 wherein the method comprises:

a) contacting the receptor, or a chimera or fragment thereof with a compound;

b) determining whether the compound has an effect on the activity of the receptor.

Further provided herein is a method for identifying a compound that blocks, inhibits, modulates, and/or enhances the activity of an olfactory receptor that is activated by a nitro musk wherein the receptor is a polypeptide having an amino acid sequence that is at least 98% and 99% identical to SEQ ID NO: 2 wherein the method comprises:

a) contacting the receptor, or a chimera or fragment thereof with a compound;

b) determining whether the compound has an effect on the activity of the receptor.

Further provided herein is a method for identifying a compound that blocks, inhibits, modulates, and/or enhances the activity of an olfactory receptor that is activated by a nitro musk wherein the receptor is a polypeptide having an amino acid sequence that is at least 99% identical to SEQ ID NO: 2 wherein the method comprises:

a) contacting the receptor, or a chimera or fragment thereof with a compound;

b) determining whether the compound has an effect on the activity of the receptor.

Further provided herein is a method for identifying a compound that blocks, inhibits, modulates, and/or enhances the activity of an olfactory receptor that is activated by a nitro musk wherein the receptor is a polypeptide having an amino acid sequence that is at least 75%, 80%, 85%, 90%, 95%, 98% and 99% identical to SEQ ID NO: 4 wherein the method comprises:

a) contacting the receptor, or a chimera or fragment thereof with a compound;

b) determining whether the compound has an effect on the activity of the receptor.

Further provided herein is a method for identifying a compound that blocks, inhibits, modulates, and/or enhances the activity of an olfactory receptor that is activated by a nitro musk wherein the receptor is a polypeptide having an amino acid sequence that is at least 80%, 85%, 90%, 95%, 98% and 99% identical to SEQ ID NO: 4 wherein the method comprises:

a) contacting the receptor, or a chimera or fragment thereof with a compound;

b) determining whether the compound has an effect on the activity of the receptor.

Further provided herein is a method for identifying a compound that blocks, inhibits, modulates, and/or enhances the activity of an olfactory receptor that is activated by a nitro musk wherein the receptor is a polypeptide having an amino acid sequence that is at least 85%, 90%, 95%, 98% and 99% identical to SEQ ID NO: 4 wherein the method comprises:

a) contacting the receptor, or a chimera or fragment thereof with a compound;

b) determining whether the compound has an effect on the activity of the receptor.

Further provided herein is a method for identifying a compound that blocks, inhibits, modulates, and/or enhances the activity of an olfactory receptor that is activated by a nitro musk wherein the receptor is a polypeptide having an amino acid sequence that is at least 90%, 95%, 98% and 99% identical to SEQ ID NO: 4 wherein the method comprises:

a) contacting the receptor, or a chimera or fragment thereof with a compound;

b) determining whether the compound has an effect on the activity of the receptor.

Further provided herein is a method for identifying a compound that blocks, inhibits, modulates, and/or enhances the activity of an olfactory receptor that is activated by a nitro musk wherein the receptor is a polypeptide having an amino acid sequence that is at least 95%, 98% and 99% identical to SEQ ID NO: 4 wherein the method comprises:

a) contacting the receptor, or a chimera or fragment thereof with a compound;

b) determining whether the compound has an effect on the activity of the receptor.

Further provided herein is a method for identifying a compound that blocks, inhibits, modulates, and/or enhances the activity of an olfactory receptor that is activated by a nitro musk wherein the receptor is a polypeptide having an amino acid sequence that is at least 98% and 99% identical to SEQ ID NO: 4 wherein the method comprises:

a) contacting the receptor, or a chimera or fragment thereof with a compound;

b) determining whether the compound has an effect on the activity of the receptor.

Further provided herein is a method for identifying a compound that blocks, inhibits, modulates, and/or enhances the activity of an olfactory receptor that is activated by a nitro musk wherein the receptor is a polypeptide having an amino acid sequence that is at least 99% identical to SEQ ID NO: 4 wherein the method comprises:

a) contacting the receptor, or a chimera or fragment thereof with a compound;

b) determining whether the compound has an effect on the activity of the receptor.

Further provided herein is a method for identifying a compound that blocks, inhibits, modulates, and/or enhances the activity of an olfactory receptor that is activated by a nitro

musk wherein the receptor is a polypeptide having an amino acid sequence that is identical to SEQ ID NO: 4 wherein the method comprises:

a) contacting the receptor, or a chimera or fragment thereof with a compound;

b) determining whether the compound has an effect on the activity of the receptor.

Further provided herein is a method for identifying a compound that blocks, inhibits, modulates, and/or enhances the activity of an olfactory receptor that is activated by a nitro musk wherein the receptor is a polypeptide having an amino acid sequence that is identical to SEQ ID NO: 2 wherein the method comprises:

a) contacting the receptor, or a chimera or fragment thereof with a compound;

b) determining whether the compound has an effect on the activity of the receptor.

Further provided is any one of a number of musk compounds that activates, mimics, blocks, inhibits, modulates, and/or enhances the activity of an olfactory receptor and that is identified by the methods disclosed herein.

Another embodiment of the invention relates the use of a polypeptide having an amino acid sequence that is at least 75% identical to SEQ ID NO: 2 or SEQ ID NO: 4 for identifying a musk compound that activates, mimics, blocks, inhibits, modulates, and/or enhances the activity of an olfactory receptor.

Still yet further provided is a cell that is recombinantly modified to express a polypeptide described above.

In one embodiment, provided herein is a non-human cell transformed to express a polypeptide having an amino acid sequence that is identical to SEQ ID NO: 2 or SEQ ID NO: 4; more particularly an amino acid sequence that is identical to SEQ ID NO: 2; even more particularly an amino acid sequence that is identical to SEQ ID NO: 4.

Further provided herein is an expression vector comprising a nucleic acid that encodes for a polypeptide having an amino acid sequence that is identical to SEQ ID NO: 2 or SEQ ID NO: 4; more particularly an amino acid sequence that is identical to SEQ ID NO: 2; even more particularly an amino acid sequence that is identical to SEQ ID NO: 4.

In one embodiment provided herein is a cell that is recombinantly modified to express a polypeptide having an amino acid sequence that is at least 75% identical to SEQ ID NO: 2 or SEQ ID NO: 4.

In one embodiment provided herein is a cell that is recombinantly modified to express a polypeptide having an amino acid sequence that is identical to SEQ ID NO: 2 or SEQ ID

NO: 4; more particularly an amino acid sequence that is identical to SEQ ID NO: 2; even more particularly an amino acid sequence that is identical to SEQ ID NO: 4.

Further provided herein is a method for identifying a compound that blocks, inhibits, modulates, and/or enhances the activity of an olfactory receptor that is activated by a polycyclic musk wherein the receptor is a polypeptide having an amino acid sequence that is identical to SEQ ID NO: 2 or SEQ ID NO: 4, more particularly an amino acid sequence that is identical to SEQ ID NO: 2; even more particularly an amino acid sequence that is identical to SEQ ID NO: 4.wherein the method comprises:

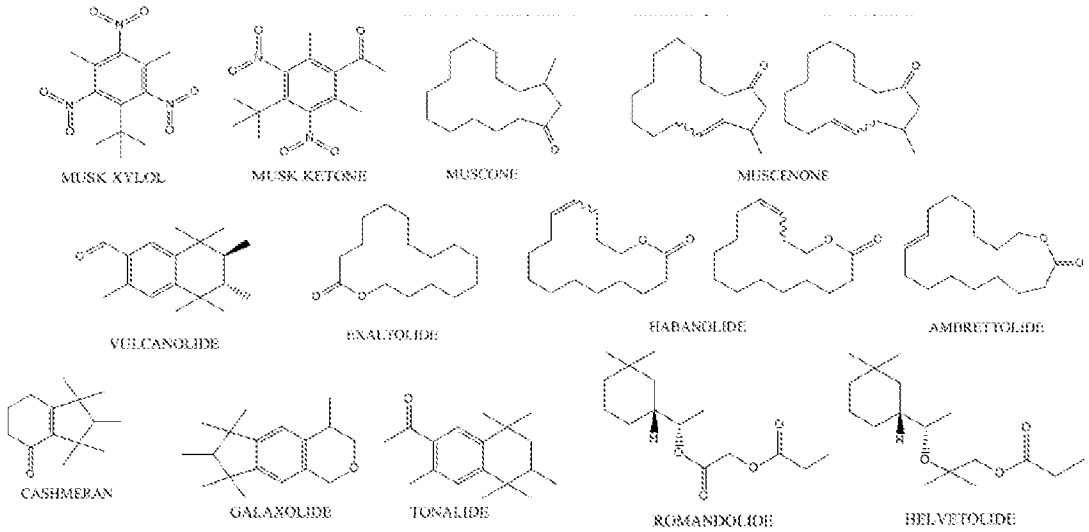
a) contacting the receptor, or a chimera or fragment thereof with a compound; and

b) determining whether the compound has an effect on the activity of the receptor.

In one embodiment provided herein is a cell wherein the cell is a prokaryotic cell. In another embodiment the cell provided herein is a eukaryotic cell. In a particular embodiment, the cell provided herein is selected from a group consisting of a yeast cell and a plant cell. In a more particular embodiment provided herein the cell is selected from the group consisting of HEK293, CHO, Xenopus oocytes, COS, yeast, bacteria and cells derived from the olfactory placode.

In order to identify unknown musk-specific receptors, representative mixtures of musks are used to screen dissociated olfactory sensory neurons (OSNs). Individual musk compounds can be further used for cell-based dose-response experiments performed on specific musk receptors to assess both specificity and sensitivity of the receptors.

For example, Musk compounds are part of a structurally diverse group of chemicals comprising macrocyclic musks, polycyclic musks, alicyclic musks and nitro musks as set forth below.



In one aspect, provided herein are methods to identify mammalian odorant receptors for musk perfume compounds and the use of the receptor for screening, particularly for high throughput screening (HTS) of Musk modulators (e.g. enhancers) and new Musk compounds. In particular provided herein are mouse receptors, for example Olfr96 (SEQ ID NO: 2) and its human counterpart OR11A1 (SEQ ID NO: 4) as receptors for Musk compounds comprising Vulcanolide, Cashmeran, Tonalide, and Musk X.

While not wishing to be bound to any theory, mouse receptor Olfr235 is a paralog of receptor Olfr1440 and an ortholog of human receptor OR5AN1. These receptors were previously identified as muscone- and muscenone-sensitive receptors (WO2015/020158; Shirasu et al., Neuron (2013)).

In a further embodiment, indicators for monitoring the activity of olfactory receptors are selected from a fluorescent calcium indicator dye, a calcium indicator protein, a fluorescent cAMP indicator, a cAMP response element (CRE) mediated reporter protein, a biochemical cAMP HTRF assay, a beta-arrestin assay, or an electrophysiological recording. Particularly, a calcium indicator dye is selected that can be used to monitor the activity of olfactory receptors expressed on the membrane of the olfactory neurons (e.g., Fura-2 AM).

In a particular embodiment, compounds are screened sequentially and the odorant-dependent changes in calcium dye fluorescence are measured using a fluorescent microscope or fluorescent-activated cell sorter (FACS).

In a further embodiment, molecular 3D receptor modeling of olfactory receptors is used to assess the binding potential *in silico* and identify compounds that may activate, mimic, block, inhibit, modulate, and/or enhance the activity of an olfactory receptor.

As an example, olfactory neurons are isolated by one or more Musk compounds using either a glass microelectrode attached to a micromanipulator or a FACS machine. Mouse olfactory sensory neurons are screened by Ca^{2+} imaging similar to procedures previously described (Malnic *et al.*, 1999; Areneda *et al.*, 2004; WO2014/210585). Particularly, a motorized movable microscope stage is used to increase the number of cells that can be screened to at least 1,500 per experiment. Since there are approximately 1,200 different olfactory receptors in the mouse and each olfactory sensory neurons expresses only 1 of 1,200 olfactory receptor genes, this screening capacity will cover virtually the entire mouse odorant receptor repertoire. In other words, the combination of calcium imaging for high-throughput olfactory sensory neuron screening leads to the identification of nearly all of the odorant receptors that respond to a particular profile of odorants. In a particular aspect, odorant receptors that respond to Musk compounds can be isolated. For example, at least one neuron is isolated.

For calcium imaging of olfactory neurons, the main olfactory epithelium may be dissected from a mouse before neuronal dissociation. Dissected olfactory epithelium may then be transferred to a dissociation buffer for mechanical and enzymatic dissociation. Dissociated neurons may then be seeded onto a coverslip allowing the screening of thousands of cells by fluorescence microscopy and the cells may be loaded with a calcium sensitive dye (Fura-2 AM) for example for about 30 minutes at 31 °C and transferred onto the microscope ready for screening. Cells are stimulated by perfusing diluted solutions of odorants (in physiological saline) over the dissociated olfactory neurons. The rare cells that respond to the malodor compound are identified by for example stimulating the receptors with 50 μm of the Musk compounds and then by monitoring the intracellular Ca^{2+} flux indicated by changes in Fura-2 fluorescence. After analysis, responding cells may be retrieved from a glass coverslip with a suction micropipette. Isolated cells are then pooled into one sample for subsequent identification of the odorant receptor genes expressed as mRNA in the responding cells.

In a particular embodiment, the mRNA of olfactory neurons are purified and amplified according to the method generally described in Marko, N. F., *et al.*, (2005) A robust method for the amplification of RNA in the sense orientation. *BMC genomics*, *6*, 27; doi:10.1186/1471-2164-6-27 (Eberwine method). At least a portion of the transcriptome (up to including the entire transcriptome) is sequenced using Next-Generation Sequencing (NGS) or hybridized to known genes using Microarray technologies. NGS is generally discussed and described in Metzker, M. L. (2010). Sequencing technologies - the next generation. *Nature*

reviews. Genetics, *11*(1), 31–46; doi:10.1038/nrg262. In a particular embodiment, a minimum of 5 neurons presenting the same response profile are pooled. The mRNA is released by cell lysis immediately after picking; no DNAse and no purification steps are carried out. The mRNA are amplified by two consecutive rounds of in vitro transcription (IVT). The amplification may be done according to MesageAmpII aRNA kit (Ambion, AMA1751) with the following parameters: two rounds of consecutive 14 hour long IVT.

In a further embodiment, the identity of a group or gene family of Musk olfactory receptors is determined (e.g., up to as many as the number of neurons picked) by comparing the results of the NGS reads obtained from the isolated activated olfactory sensory neurons to a reference genome sequence of the same species. Particularly, the putative Musk receptors will be the most highly abundant mRNA in the olfactory neuron-derived NGS sample or present in more than one independent biological replicate. Because of the combinatorial nature of the olfactory code (one compound activates many ORs and one OR can be activated by many compounds), pooling several neurons activated by given compounds allows the retrieval of virtually all of the receptors responsible for the perception of these molecules in a single NGS experiment. Pooling functionally similar neurons thus greatly improves the deorphanization throughput and speed.

Standard bioinformatics tools are then used to identify the most closely related human odorant receptor(s) to other putative mammalian (non-human) Musk receptor(s) under the assumption that homologous sequence receptors retain similar function. Adipietro *et al.* (2012) Functional Evolution of Mammalian Odorant Receptors. PLoS Genet 8(7): e1002821. doi:10.1371/ journal.pgen.1002821. Default parameters of BLASTP and/or BLASTN algorithm may be used.

The human or non-human mammalian Musk receptors may be adapted to a functional assay that can be used to identify compounds that activate, mimic, block, modulate, and/or enhance the activity of a Musk compound. In particular, the assay may be a cell-based assay or a binding assay and the method for identifying compounds may be a high-throughput screening assay. More particularly, provided herein are receptor-based assays adaptable for high-throughput screening of receptors with compound libraries for the discovery of modulating compounds (e.g., blocking, enhancing and masking).

In a particular embodiment, musk receptor gene sequences are identified from Musk compounds-sensitive cells as follows: Pooled neurons are heated to 75°C for 10 minutes to break the cell membrane and render their mRNA available for amplification. This

amplification step is important when applying NGS technologies with limited amount of starting material, typically between 5 to 15 cells. A linear amplification according to the Eberwine method (IVT) ensures the maintenance of the relative transcription levels of expressed genes. Two consecutive overnight (14h) rounds of in vitro transcription are used to yield sufficient amounts of cRNA; Amplified cRNA is then used to generate an Illumina HiSeq cDNA library. The resulting short sequences of typically 150 base pairs (commonly referred to as "reads") are aligned against the reference genome of the mouse (such as UCSC version mm9 or mm10) in order to build the full transcriptome of these cells. Quantitative analysis of the transcriptome data yields a list of transcribed odorant receptor genes and their respective expression levels. Odorant receptor genes that show the most abundant levels of mRNA (most abundant "reads") or are present in more than one replicate experiment are considered putative Musk compounds receptors.

The predicted mouse OR genes are then used to mine the latest versions of both the mouse and human genome databases in order to identify the most closely related receptors (i.e. highest sequence similarity) in mouse (paralogous genes) and in human (orthologous genes). This process may be performed using the BLAST search algorithm (publically available at the NCBI website), a sequence similarity search tool, where every putative gene sequence previously obtained from the initial transcriptome analysis is used as a query sequence. The newly identified genes identified from this data mining process are also considered as potential Musk receptors under the assumption that paralogous and orthologous genes are highly likely to possess similar activities. In a particular embodiment, pairwise comparison of sequence homology is carried out to identify closely related receptors in mouse and humans using the following iterative scheme:

Step	Query sequence	BLASTN/BLASTP Result
1.	Mouse candidate 1 →	Mouse paralog 1 and human ortholog 1
2.	Mouse paralog 1→	Human ortholog 2
3.	Human ortholog 1→	Human paralog 2
4.	Human ortholog 2→	Human paralog 3

Paralog = homolog in same species Ortholog = homolog in other species

Paralogous genes are then aligned using a multiple alignment tool in order to generate a phylogenetic tree. Functional in vitro data can be interpreted in the light of such a

phylogenetic relationship between closely related but distinct receptors. This step is essential in the identification of complete OR gene families that respond, to varying degrees, to the test compounds, for example vulcanolide.

This approach has several major advantages over previously established single cell RT-PCR methods. First, by pooling multiple neurons sharing similar binding properties, a unique mRNA sequencing experiment (NGS) identifies virtually all the receptors that are activated by the target Musk compounds. Therefore the throughput is higher than what was previously achieved. Second, because multiple cells can be pooled into one sample, this approach allows for the selection of genes through a comprehensive comparison of replicate samples across experiments. Third, NGS does not require the use of PCR primers specific to an OR. NGS also does not require the use of degenerate primers specific to ORs, which are problematic and often lead to false positives due to non-linear or non-specific PCR amplification. In particular, since OR coding sequences lie within a single exon, sample contamination with genomic DNA can easily lead to aspecific amplification of OR gene sequences. Fourth, RT-PCR analysis is difficult to perform on pooled samples because of the inherent false positive rate. Single cell mRNA hybridization experiments have been performed using of high-density DNA microarray chips. However, this approach is generally less sensitive than NGS and is further restricted to known genes for which corresponding DNA probes need to be synthesized. Hence, the use of NGS is significantly advantageous to rapidly identify OR and ultimately results in a more accurate selection of candidate receptors compared to the standard (e.g. RT-PCR and microarray) approaches. While the NGS approach is preferred, other approaches may be used such as RT-PCR and microarray approaches.

In a further embodiment, to complete the deorphanization process, the candidate OR genes are further expressed *in vitro* for confirmation of activity against the compounds used to isolate the olfactory sensory neurons and other structurally-related compounds of interest. The mouse receptors identified from isolated olfactory neurons that respond to both Musk compounds are modified at their N-terminus with short polypeptide sequences (e.g., Flag (SEQ ID NO: 6), Rho (SEQ ID NO: 8; 20 first amino acids of the bovine rhodopsin receptor), or Lucy (SEQ ID NO: 10) tags), transiently expressed in HEK 293T cells, and stimulated separately with Musk compounds to confirm their identity as bona fide Musk compound receptors. Co-expression of the human G alpha subunit $G\alpha_{olf}$ in this cell-based assay activates the Gs transduction pathway that leads to an internal cAMP increase upon binding to the

appropriate ligand. Alternatively, co-expression of the human G alpha subunit $G\alpha_{15}$ in the cell based assay activates the Gq transduction pathway that leads to an internal Ca^{2+} increase upon binding to the appropriate ligand. The above process and the results obtained so far serve to validate the process for rapid and reliable identification of mammalian odorant receptors for Musk compounds.

Definitions

The following terms have the meanings ascribed to them unless specified otherwise.

"OR" refers to one or more members of a family of G protein-coupled receptors that are expressed in olfactory cells. Olfactory receptor cells can also be identified on the basis of morphology or by the expression of proteins specifically expressed in olfactory cells. OR family members may have the ability to act as receptors for olfactory transduction.

"OR" nucleic acids encode a family of GPCRs with seven transmembrane regions that have "G protein-coupled receptor activity," e.g., they may bind to G proteins in response to extracellular stimuli and promote production of second messengers such as IP3, cAMP, cGMP, and Ca^{2+} via stimulation of enzymes such as phospholipase C and adenylate cyclase.

The "N terminal domain" region starts at the N-terminus and extends to a region close to the start of the first transmembrane region. "Transmembrane domain," which comprises the seven "transmembrane regions," refers to the domain of OR polypeptides that lies within the plasma membrane, and may also include the corresponding cytoplasmic (intracellular) and extracellular loops. The seven transmembrane regions and extracellular and cytoplasmic loops can be identified using standard methods, as described in Kyte & Doolittle, J. Mol. Biol., 157:105-32 (1982), or in Stryer. The general secondary and tertiary structure of transmembrane domains, in particular the seven transmembrane domains of G protein-coupled receptors such as olfactory receptors, are known in the art. Thus, primary structure sequence can be designed or predicted based on known transmembrane domain sequences, as described in detail below. These transmembrane domains are useful for in vitro ligand-binding assays, both soluble and solid phase.

The phrase "functional effects" in the context of assays for testing compounds that modulate OR family member mediated olfactory transduction includes the determination of any parameter that is indirectly or directly under the influence of the receptor, e.g., functional, physical and chemical effects. It includes ligand binding, changes in ion flux, membrane potential, current flow, transcription, G protein binding, GPCR phosphorylation or

dephosphorylation, signal transduction receptor-ligand interactions, second messenger concentrations (e.g., cAMP, cGMP IP3, or intracellular Ca. $^{2+}$), in vitro, in vivo, and ex vivo and also includes other physiologic effects such increases or decreases of neurotransmitter or hormone release.

By "determining the functional effect" or “confirming the activity” in the context of assays is meant assays for a compound that increases or decreases a parameter that is indirectly or directly under the influence of an OR family member, e.g., functional, physical and chemical effects. Such functional effects can be measured by any means known to those skilled in the art, e.g., changes in spectroscopic characteristics (e.g., fluorescence, absorbance, refractive index), hydrodynamic (e.g., shape), chromatographic, or solubility properties, patch clamping, voltage-sensitive dyes, whole cell currents, radioisotope efflux, inducible markers, oocyte OR gene expression; tissue culture cell OR expression; transcriptional activation of OR genes; ligand-binding assays; voltage, membrane potential and conductance changes; ion flux assays; changes in intracellular second messengers such as cAMP, cGMP, and inositol triphosphate (IP3); changes in intracellular calcium levels; neurotransmitter release, and the like.

"Inhibitors," "activators," “counteractants” and "modulators" of OR genes or proteins are used interchangeably to refer to inhibitory, activating, or modulating molecules identified using in vivo, in vitro and in vivo assays for olfactory transduction, e.g., ligands, agonists, antagonists, enhancers, and their homologs and mimetics. Inhibitors are compounds that, e.g., bind to, partially or totally block stimulation, decrease, prevent, delay activation, inactivate, desensitize, or down regulate olfactory transduction, e.g., antagonists. Activators are compounds that, e.g., bind to, stimulate, increase, open activate, facilitate, enhance activation, sensitize, or up regulate olfactory transduction, e.g., agonists. Modulators include compounds that, e.g., alter the interaction of a receptor with: extracellular proteins that bind activators or inhibitor (e.g., odorant-binding proteins, ebnerin and other members of the hydrophobic carrier family); G proteins; kinases (e.g., homologs of rhodopsin kinase and beta adrenergic receptor kinases that are involved in deactivation and desensitization of a receptor); and arrestins, which also deactivate and desensitize receptors. Modulators can include genetically modified versions of OR family members, e.g., with altered activity, as well as naturally occurring and synthetic ligands, antagonists, agonists, small chemical molecules and the like. Such assays for inhibitors and activators include, e.g., expressing OR family members in cells or cell membranes, applying putative modulator compounds, in the presence or absence of

flavor or fragrance molecules, e.g. Musks , and then determining the functional effects on olfactory transduction, as described above. Samples or assays comprising OR family members that are treated with a potential activator, inhibitor, or modulator are compared to control samples without the inhibitor, activator, or modulator to examine the extent of modulation. Control samples (untreated with modulators) are assigned a relative OR activity value of 100%. Inhibition of an OR is achieved when the OR activity value relative to the control is about 80%, optionally 50% or 25-0%. Activation of an OR is achieved when the OR activity value relative to the control is 110%, optionally 150%, optionally 200-500%, or 1000-3000% higher.

The terms "purified," "substantially purified," and "isolated" as used herein refer to the state of being free of other, dissimilar compounds with which the compound of the invention is normally associated in its natural state, so that the "purified," "substantially purified," and "isolated" subject comprises at least 0.5%, 1%, 5%, 10%, or 20%, and most preferably at least 50% or 75% of the mass, by weight, of a given sample. In one preferred embodiment, these terms refer to the compound of the invention comprising at least 95% of the mass, by weight, of a given sample. As used herein, the terms "purified," "substantially purified," and "isolated" "isolated," when referring to a nucleic acid or protein, of nucleic acids or proteins, also refers to a state of purification or concentration different than that which occurs naturally in the mammalian, especially human, body. Any degree of purification or concentration greater than that which occurs naturally in the mammalian, especially human, body, including (1) the purification from other associated structures or compounds or (2) the association with structures or compounds to which it is not normally associated in the mammalian, especially human, body, are within the meaning of "isolated." The nucleic acid or protein or classes of nucleic acids or proteins, described herein, may be isolated, or otherwise associated with structures or compounds to which they are not normally associated in nature, according to a variety of methods and processes known to those of skill in the art.

As used herein, the term "isolated," when referring to a nucleic acid or polypeptide refers to a state of purification or concentration different than that which occurs naturally in the mammalian, especially human, body. Any degree of purification or concentration greater than that which occurs naturally in the body, including (1) the purification from other naturally-occurring associated structures or compounds, or (2) the association with structures or compounds to which it is not normally associated in the body are within the meaning of "isolated" as used herein The nucleic acids or polypeptides described herein may be isolated

or otherwise associated with structures or compounds to which they are not normally associated in nature, according to a variety of methods and processed known to those of skill in the art.

As used herein, the terms "amplifying" and "amplification" refer to the use of any suitable amplification methodology for generating or detecting recombinant of naturally expressed nucleic acid, as described in detail, below. For example, the invention provides methods and reagents (e.g., specific degenerate oligonucleotide primer pairs) for amplifying (e.g., by polymerase chain reaction, PCR) naturally expressed (e.g., genomic DNA or mRNA) or recombinant (e.g., cDNA) nucleic acids of the invention in vivo or in vitro.

The term "7-transmembrane receptor" means a polypeptide belonging to a superfamily of transmembrane proteins that have seven domains that span the plasma membrane seven times (thus, the seven domains are called "transmembrane" or "TM" domains TM I to TM VII). The families of olfactory and certain taste receptors each belong to this super-family. 7-transmembrane receptor polypeptides have similar and characteristic primary, secondary and tertiary structures, as discussed in further detail below.

The term "nucleic acid" or "nucleic acid sequence" refers to a deoxy-ribonucleotide or ribonucleotide oligonucleotide in either single- or double-stranded form. The term encompasses nucleic acids, i.e., oligonucleotides, containing known analogs of natural nucleotides. The term also encompasses nucleic-acid-like structures with synthetic backbones. Unless otherwise indicated, a particular nucleic acid sequence also implicitly encompasses conservatively modified variants thereof (e.g., degenerate codon substitutions) and complementary sequences, as well as the sequence explicitly indicated. Specifically, degenerate codon substitutions may be achieved by generating, e.g., sequences in which the third position of one or more selected codons is substituted with mixed-base and/or deoxyinosine residues.

The terms "polypeptide," "peptide" and "protein" are used interchangeably herein to refer to a polymer of amino acid residues. The terms apply to amino acid polymers in which one or more amino acid residue is an artificial chemical mimetic of a corresponding naturally occurring amino acid, as well as to naturally occurring amino acid polymers and non-naturally occurring amino acid polymer. The term "heterologous" when used with reference to portions of a nucleic acid indicates that the nucleic acid comprises two or more subsequences that are not found in the same relationship to each other in nature. For instance, the nucleic acid is typically recombinantly produced, having two or more sequences from unrelated genes

arranged to make a new functional nucleic acid, e.g., a promoter from one source and a coding region from another source. Similarly, a heterologous protein indicates that the protein comprises two or more subsequences that are not found in the same relationship to each other in nature (e.g., a fusion protein).

A "promoter" is defined as an array of nucleic acid sequences that direct transcription of a nucleic acid. As used herein, a promoter includes necessary nucleic acid sequences near the start site of transcription, such as, in the case of a polymerase II type promoter, a TATA element. A promoter also optionally includes distal enhancer or repressor elements, which can be located as much as several thousand base pairs from the start site of transcription. A "constitutive" promoter is a promoter that is active under most environmental and developmental conditions. An "inducible" promoter is a promoter that is active under environmental or developmental regulation. The term "operably linked" refers to a functional linkage between a nucleic acid expression control sequence (such as a promoter, or array of transcription factor binding sites) and a second nucleic acid sequence, wherein the expression control sequence directs transcription of the nucleic acid corresponding to the second sequence.

As used herein, "recombinant" refers to a polynucleotide synthesized or otherwise manipulated in vitro (e.g., "recombinant polynucleotide"), to methods of using recombinant polynucleotides to produce gene products in cells or other biological systems, or to a polypeptide ("recombinant protein") encoded by a recombinant polynucleotide. "Recombinant" means also the ligation of nucleic acids having various coding regions or domains or promoter sequences from different sources into an expression cassette or vector for expression of, e.g., inducible or constitutive expression of a fusion protein comprising a translocation domain of the invention and a nucleic acid sequence amplified using a primer of the invention. "Recombinant" means also modifications obtained by genome editing techniques, such as CRISPR/Cas9, of a cell that leads to stable or transient expression of endogenous genes such as the receptor gene referred to herein.

The term "expression vector" refers to any recombinant expression system for the purpose of expressing a nucleic acid sequence of the invention in vitro or in vivo, constitutively or inducibly, in any cell, including prokaryotic, yeast, fungal, plan insect or mammalian cell. The term includes linear or circular expression systems. The term includes expression systems that remain episomal or integrate into the host cell genome. The expression systems can have the ability to self-replicate or not, i.e., drive only transient

expression in a cell. The term includes recombinant expression "cassettes which contain only the minimum elements needed for transcription of the recombinant nucleic acid.

By "host cell" is meant a cell that contains an expression vector and supports the replication or expression of the expression vector. Host cells may be prokaryotic cells such as E. coli, or eukaryotic cells such as yeast, insect, amphibian, or mammalian cells such as CHO, HeLa, HEK-293, and the like, e.g., cultured cells, explants, and cells in vivo.

Nucleic acid and amino acid sequences identified and/or used herein are listed below:

Mouse Olfr96 (SEQ ID NO: 1 DNA; SEQ ID NO: 2 PROTEIN)

SEQ ID NO: 1

atgggaatcctttccacaggaaatcaaactgtcactgagtttgtacttcttggtttccatgaagtccctgggctg
cacctcctgtttttttctgtgttcaccatcctctatgcctccatcatcacagggaacatgctcattgcagtggtg
gtggtgagctcccagaggcttcacacacccatgtatttctttctggtgaatctgtccttcatagagattgtctat
acctccacagtggtgcccaaaatgctggaaggcttcttacaggaggccaccatatctgtggctggctgcttgctc
cagttctttgtttttggctctctggccacagatgagtgttttctgctggctgtgatggcatatgatcgatatctc
gcaatttgtcaccctctacgatacccacacctcatggggcctcaatggtgcctggggttggtgctcacagtctgg
ctgtctggcttcatggtagatggactagttgttgctctgatggcccagttgagattctgtggccccaacttagtt
gatcacttttactgtgatttttcacctttgatggtcctggcttgctcagatacccaagtggcccaggtgactaca
tttgttctctctgtggtcttcctgactgtccccttgggctggttctgatctcctatgctcagattgtagtgact
gtgctgagagttccttctgggaccagaagaaccaaggccttctccacatgctcctctcacctggctgtggtgtcc
acgttctatggaacactcatggtattgtacattgtgccctctgctgttcattctcagctcctctccaaggtcatt
gccctgctctacacagtggtcactcccatcttcaaccctgtcatctacaccttgaggaaccaggaggtgcagcag
gcactaagaaggcttctctactgcaaaccaactgaaatgtga

SEQ ID NO: 2

mgilstgnqtvtefvllgfhevpglhllffsvftilyasiitgnmliavvvvssqrlhtpmyfflvnlsfieivy
tstvvpkmlegflqeatisvagcllqffvfgslatdecfllavmaydrylaichplryphlmgpqwclglvltvw
lsgfmvdglvvalmaqlrfcgpnlvdhfycdfsplmvlacsdtqvaqvttfvlsvvfltvpfglvlisyaqivvt
vlrvpsgtrrtkafstcsshlavvstfygtlmvlyivpsavhsqllskviallytvvtpifnpviytlrnqevqq
alrrllyckptem

Human OR11A1 (SEQ ID NO: 3 DNA; SEQ ID NO: 4 PROTEIN)

SEQ ID NO: 3

atggaaattgtctccacaggaaacgaaactattactgaatttgtcctccttggcttctatgacatccctgaactg
catttcttgtttttattgtattcactgctgtctatgtcttcatcatcatagggaatatgctgattattgtagca
gtggttagctcccagaggctccacaaacccatgtatattttcttggcgaatctgtccttcctggatattctctac
acctccgcagtgatgccaaaaatgctggagggcttcctgcaagaagcaactatctctgtggctggttgcttgctc
cagttctttatcttcggctctctagccacagctgaatgcttactgctggctgtcatggcatatgaccgctacctg
gcaatttgctacccactccactacccactcctgatggggcccagacggtacatggggctggtggtcacaacctgg
ctctctggatttgtggtagatggactggttgtggccctggtggcccagctgaggttctgtggccccaaccacatt
gaccagttttactgtgactttatgcttttcgtgggcctggcttgctcggatcccagagtggctcaggtgacaact
ctcattctgtctgtgttctgcctcactattccttttggactgattctgacatcttatgccagaattgtggtggca
gtgctgagagttcctgctggggcaagcaggagaagggctttctccacatgctcctcccacctagctgtagtgacc
acattctatggaacgctcatgatcttttatgttgcaccctctgctgtccattcccagctcctctccaaggtcttc
tccctgctctacactgtggtcacccctctcttcaatcctgtgatctataccatgaggaacaaggaggtgcatcag
gcacttcggaagattctctgtatcaaacaaactgaaacacttgattga

SEQ ID NO: 4

meivstgnetitefvllgfydipelhflffivftavyvfiiignmliivavvssqrlhkpmyiflanlsfldily
tsavmpkmlegflqeatisvagcllqffifgslataeclllavmaydrylaicyplhypllmgprrymglvvttw
lsgfvvdglvvalvaqlrfcgpnhidqfycdfmlfvglacsdprvaqvttlilsvfcltipfgliltsyarivva
vlrvpagasrrrafstcsshlavvttfygtlmifyvapsavhsqllskvfsllytvvtplfnpviytmrnkevhq
alrkilcikqtetld

Flag tag (SEQ ID NO: 5 DNA; SEQ ID NO: 6 PROTEIN)

SEQ ID NO: 5

gattacaaggacgacgacgataag

SEQ ID NO: 6

dykddddk

Rho tag (SEQ ID NO: 7 DNA; SEQ ID NO: 8 PROTEIN)

SEQ ID NO: 7

atgaacgggaccgagggcccaaacttctacgtgcctttctccaacaagacgggcgtggtg

SEQ ID NO: 8

mngtegpnfyvpfsnktgvv

Lucy tag (SEQ ID NO: 9 DNA; SEQ ID NO: 10 PROTEIN)

SEQ ID NO: 9

atgagaccccagatcctgctgctcctggccctgctgaccctaggcctggct

SEQ ID NO: 10

mrpqillllalltlgla

The following examples are illustrative only and are not meant to limit the scope of invention as set forth in the Summary, Description or in the Claims.

EXAMPLES

Example 1

The identification of polycyclic Musk receptors mouse Olfr96 and human OR11A1.

Musk responsive cells were isolated and further processed for Next Generation Sequencing (NGS) based transcriptome analysis. A mixture of Cashmeran, Tonalide and Galaxolide was prepared (Mix A). A mixture of Muscone, Muscenone and Habanolide was also prepared (Mix B). Each individual Musk was blended at a final concentration of 50 μM. Ca^{2+} imaging traces were recorded for distinct Olfactory Sensory Neurons (OSNs) that were activated by mix A and/or mix B. The Y axis of Figure 1A shows the average intensity of the relative fluorescent unit as a result of a ratiometric 340/380 nm Ca^{2+} imaging recording. The X axis of Figure 1A shows the time frames (8s/frame). Responding cells were pooled for RNA extraction and subsequent Next-Generation-Sequencing experiment (i.e. RNAseq). All expression levels were further normalized to olfactory marker protein (OMP). The analysis of the resulting transcriptome analysis revealed the most highly expressed odorant receptors (i.e.

most abundant read counts, normalized by FPKM): Olfr235 and Olfr96 (Figure 1B). They correspond to the following human orthologous genes: OR5AN1 and OR11A1, respectively.

Example 2

Functional characterization of mouse Olfr96 and human OR11A1 Musk receptors

Functional dose-response experiments were performed to evaluate the level of functional activity of the modified cell line. Using a cell-based assay, mouse Olfr96 was tested in an HEK293T cell line wherein the endogenous RTP1 gene has been activated and the odorant receptor chaperone was expressed. Flag-Rho-tagged receptor genes were co-transfected with the olfactory canonical G-protein G_{olf} gene and were exposed to increasing concentrations of the Musk odorants Tonalide, Vulcanolide, and Muscone. Odorant-induced activity was detected by measuring the cAMP increase in the cytosol using an HTRF based kit (CisBio, cAMP dynamic 2 kit, 62AM4PEJ). A dose-dependent increase of Olfr96 receptor activity is observed for the 2 polycyclic Musks (Tonalide and Vulcanolide), but not the macrocyclic Musk, Muscone (Figure 2). In an additional repeat experiment using the same conditions, mouse Olfr96 and corresponding human ortholog OR11A1 were tested side by side in duplicate with a musk diversity set for specificity assessment. Lucy-Flag-Rho-tagged receptor genes were co-transfected with the olfactory canonical G-protein G_{olf} gene and were exposed to increasing concentrations of the macrocyclic Musk odorants Muscenone, Muscone, Habanolide and Exaltolide; the polycyclic Musk odorants Tonalide, Vulcanolide, Cashmeran, Galaxolide; the alicycyclic Musk odorants Helvetolide, Ambretolide and Romandolide; and the nitro Musk odorants Musk C and Musk X. A dose-dependent increase of Olfr96 receptor activity is observed for 3 polycyclic Musks (Tonalide, Cashmeran and Vulcanolide) and a nitro Musk (Musk X), but not Musk C, Galaxolide, the macrocyclic Musks or the alicyclic Musks (Figure 3); and a dose-dependent increase of OR11A1 receptor activity is observed for 1 polycyclic Musks (Vulcanolide), but not the macrocyclic Musks, the alicyclic Musks or the nitro Musk or the other polycyclic Musks (Figure 3).

Example 3

Identification of compounds that enhance the activation of musk receptors.

A musk receptor is exposed to a binary mixture of a known musk compound and a compound to be evaluated. Any enhancement of the “Musk” receptor activity provided by the

compound is measured. This is done by performing Musk dose response measurement in the presence and in the absence of specific compounds that enhance the activity of the receptor. The same cell-based assay is used as in example 2. If the compound enhances the receptor activity, then the concentration of Musk compound needed to attain the equivalent level of receptor activation in the absence of the compound is reduced. Typically this is done with a dose response experiment and is illustrated with a dose response curve that is for example displayed or indicated by a leftward shift in the curve and reduction in the calculated EC50 value.

THE CLAIMS

What is claimed is:

1. A host cell transformed to express a polypeptide having an amino acid sequence that is at least 75% identical to SEQ ID NO: 2 or SEQ ID NO: 4.
2. The host cell as recited in claim 1 wherein the polypeptide comprises a sequence that is identical to SEQ ID NO: 2.
3. The host cell as recited in claim 1 wherein the polypeptide comprises a sequence that is identical to SEQ ID NO: 4.
4. An expression vector comprising a nucleic acid that encodes for a polypeptide having an amino acid sequence that is at least 75% identical to SEQ ID NO: 2 or SEQ ID NO: 4.
5. The expression vector as recited in claim 4 wherein the nucleic acid encodes a polypeptide having an amino acid sequence that is identical to SEQ ID NO: 2.
6. The expression vector as recited in claim 4 wherein the nucleic acid encodes a polypeptide having an amino acid sequence that is identical to SEQ ID NO: 4.
7. The expression vector as recited in claim 4 wherein the nucleic acid comprises a nucleotide sequence that is at least 75% identical to SEQ ID NO: 1 or SEQ ID NO: 3.
8. The expression vector as recited in claim 4 wherein the nucleic acid comprises a nucleotide sequence identical to SEQ ID NO: 1.
9. The expression vector as recited in claim 4 wherein the nucleic acid comprises a nucleotide sequence identical to SEQ ID NO: 3.
10. A cell that is recombinantly modified to express a polypeptide of having an amino acid sequence that is at least 75% identical to SEQ ID NO: 2 or SEQ ID NO: 4.
11. The cell that is recited in claim 10 that is recombinantly modified to express a polypeptide having an amino acid sequence that is identical to SEQ ID NO: 2.
12. The cell that is recited in claim 10 that is recombinantly modified to express a polypeptide having an amino acid sequence that is identical to SEQ ID NO: 4.
13. The cell as recited in any one of claims 10-12 wherein the cell is a eukaryotic cell.
14. The cell as recited in one of claims 10-12 wherein the cell is a prokaryotic cell.
15. The cell as recited in claim 13 that is selected from the group consisting of HEK293, CHO, Xenopus oocytes, COS, yeast and cells derived from the olfactory placode.
16. A method for identifying a compound that activates, mimics, blocks, inhibits, modulates, and/or enhances the activity of an olfactory receptor that is activated by a polycyclic musk compound, wherein the receptor is a polypeptide having an amino acid sequence

that is at least 75% identical to SEQ ID NO: 2 or SEQ ID NO: 4 wherein the method comprises:

a) contacting the receptor, or a chimera or fragment thereof with a compound;

b) determining whether the compound has an effect on the activity of the receptor.

17. The method as recited in claim 16, wherein the polycyclic compound is selected from the group consisting of a tonalide, vulcanolide, and cashmeran.

18. A method for identifying a compound that activates, mimics, blocks, inhibits, modulates, and/or enhances the activity of an olfactory receptor that is activated by musk X, wherein the receptor is a polypeptide having an amino acid sequence that is at least 75% identical to SEQ ID NO: 2 or SEQ ID NO: 4 wherein the method comprises:

a) contacting the receptor, or a chimera or fragment thereof with a compound;

b) determining whether the compound has an effect on the activity of the receptor.

19. The method as recited in claim 16 to 18 wherein the polypeptide has an amino acid sequence that is identical to SEQ ID NO: 2.

20. The method as recited in claim 16 to 18 wherein the polypeptide has an amino acid sequence that is identical to SEQ ID NO: 4.

21. The method as recited in any one of claims 16 to 18 wherein the Musk compound is selected from the group consisting of, Tonalide, Vulcanolide, Cashmeran, and Musk X.

22. The method as recited in claim 21 wherein the c compound is Vulcanolide.

23. The method as recited in claim 21 wherein the compound is Tonalide.

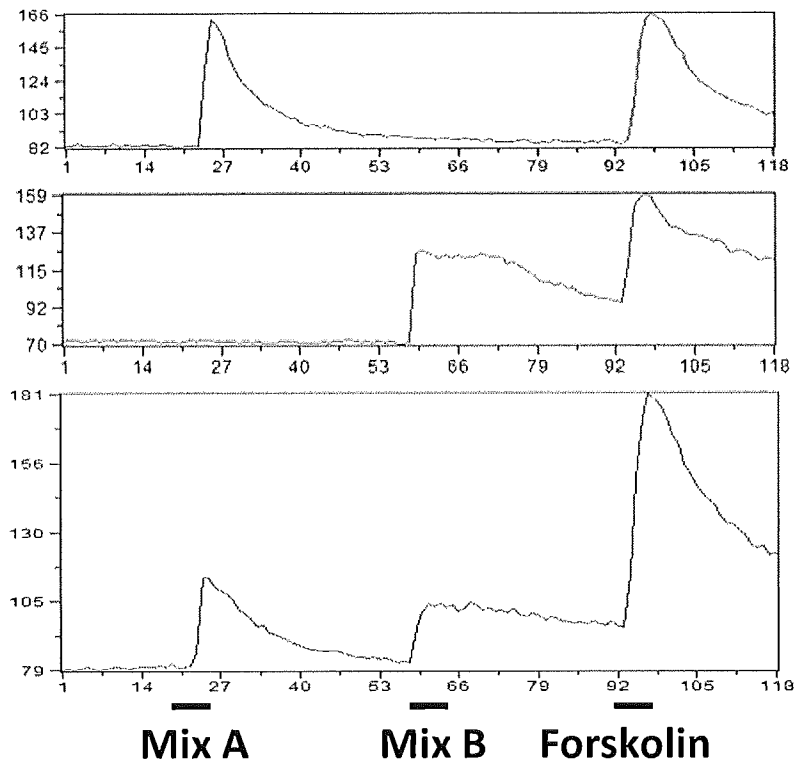
24. The method as recited in claim 21 wherein the compound is Cashmeran.

25. The method as recited in claim 21 wherein the compound is Musk X.

26. A musk compound that activates, mimics, blocks, inhibits, modulates, and/or enhances the activity of an olfactory receptor and that is identified by the method of claim 16 or claim 18.

27. Use of a polypeptide having an amino acid sequence that is at least 75% identical to SEQ ID NO: 2 or SEQ ID NO: 4 for identifying a musk compound

A)


166
145
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103
82
159
137
115
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70
181
156
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14
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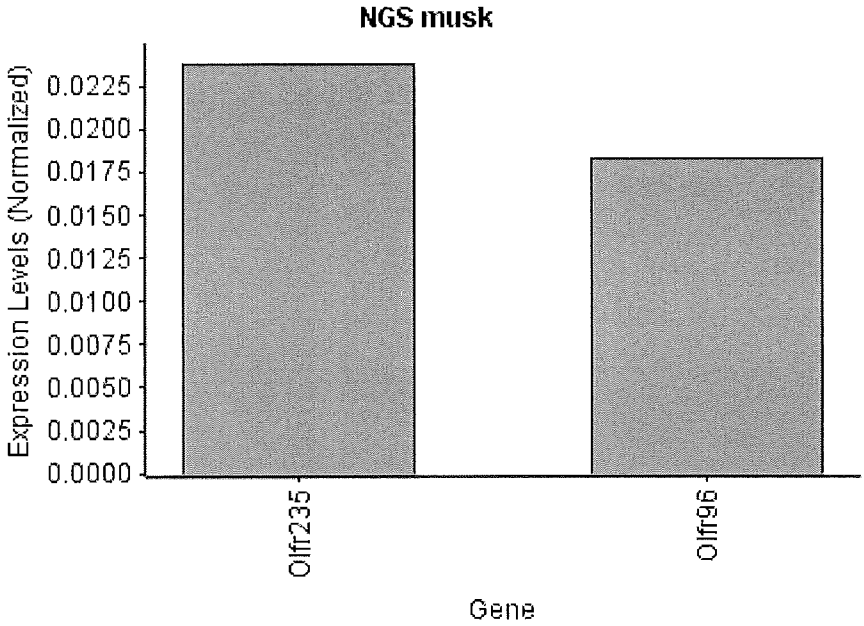
79
92
105
118
Mix A
Mix B
Forskolin

B)


NGS musk
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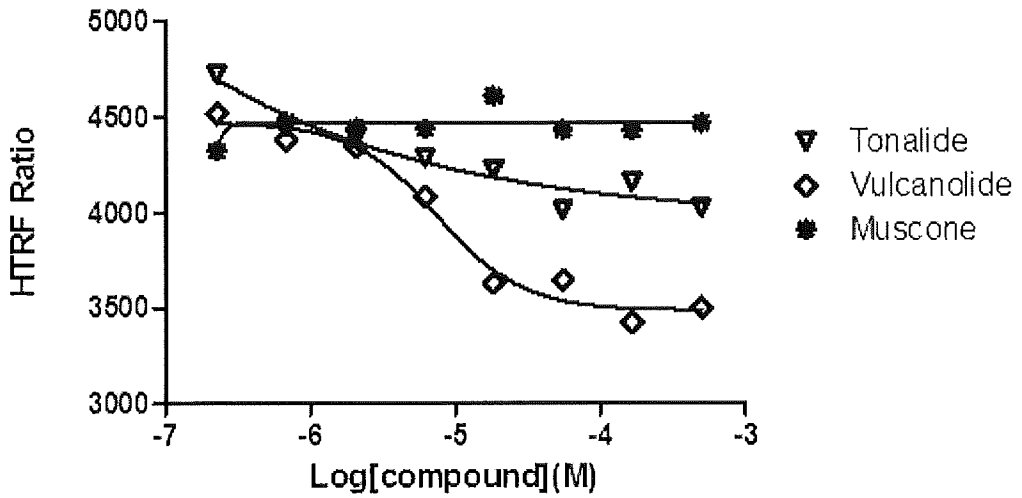
0.0025
0.0000
Olfr235
Olfr96
Gene

FIGURE 1


5000
4500
4000
3500
3000
HTRF Ratio
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-6
-5
-4
-3
Log[compound](M)
Tonalide
Vulcanolide
Muscone

FIGURE 2

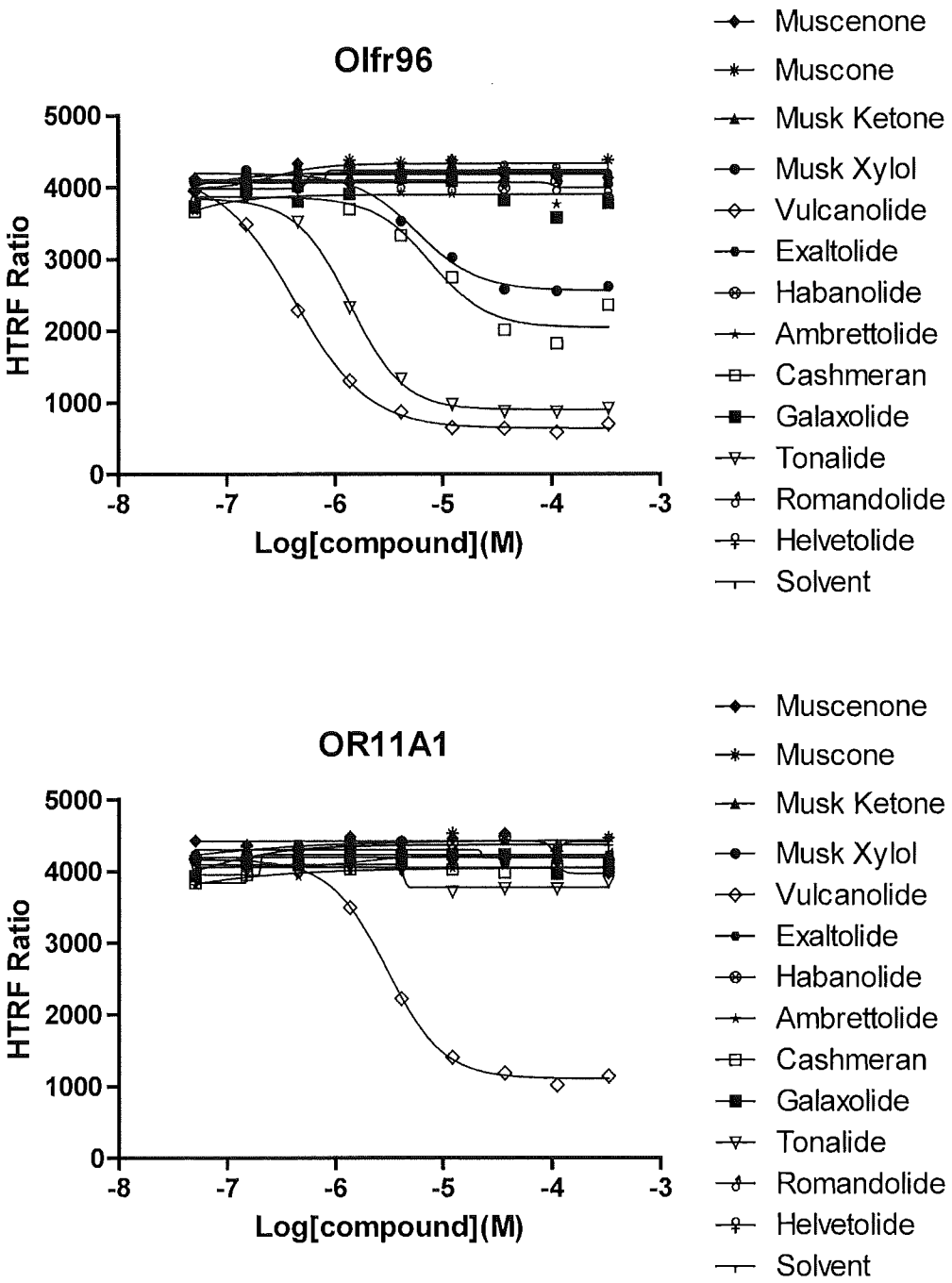
Olfr96
HTRF Ratio
5000
4000
3000
2000
1000
0
-8
-7
-6
-5
-4
-3
Log[compound](M)
Muscenone
Muscone
Musk Ketone
Musk Xylol
Vulcanolide
Exaltolide
Habanolide
Ambrettolide
Cashmeran
Galaxolide
Tonalide
Romandolide
Helvetolide
Solvent
OR11A1
HTRF Ratio
5000
4000
3000
2000
1000
0
-8
-7
-6
-5
-4
-3
Log[compound](M)
Muscenone
Muscone
Musk Ketone
Musk Xylol
Vulcanolide
Exaltolide
Habanolide
Ambrettolide
Cashmeran
Galaxolide
Tonalide
Romandolide
Helvetolide
Solvent

FIGURE 3

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/036776

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07K14/72
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07K G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, Sequence Search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/27158 A2 (DIGISCENTS [US]; YEDA RES & DEV [IL]; BELLENSON JOEL [US]; SMITH DEXST) 19 April 2001 (2001-04-19)	1-15
A	abstract claims 1-12 page 1, line 20 ff. page 5, line 24 ff. -& DATABASE EPO Proteins [Online] 26 September 2001 (2001-09-26), "Sequence 1344 from Patent WO0127158.", XP002760380, retrieved from EBI accession no. EPOP:AX242596 Database accession no. AX242596 sequence -/--	16-27

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 July 2016	17/08/2016

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Brero, Alessandro

3

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	US 2010/248390 A1 (MATSUNAMI HIROAKI [US] ET AL) 30 September 2010 (2010-09-30)	1-15
A	abstract paragraph [0048] -& DATABASE Geneseq Proteins [Online] 25 November 2010 (2010-11-25), "Odorant receptor identification related protein, SEQ ID 1119.", XP002760384, retrieved from EBI accession no. GSP:AYJ85275 Database accession no. AYJ85275 sequence -& DATABASE Geneseq Proteins [Online] 25 November 2010 (2010-11-25), "Odorant receptor identification related protein, SEQ ID 1118.", XP002760385, retrieved from EBI accession no. GSP:AYJ85274 Database accession no. AYJ85274 sequence ----- -/--	16-27

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 2 832 347 A1 (TAKASAGO PERFUMERY CO LTD [JP]) 4 February 2015 (2015-02-04) abstract paragraph [0026] paragraph [0028] -& DATABASE EPO Proteins [Online] 24 March 2015 (2015-03-24), "Sequence 2 from Patent EP2832347.", XP002760386, retrieved from EBI accession no. EPOP:JD592755 Database accession no. JD592755 sequence -& DATABASE Geneseq Proteins [Online] 26 March 2015 (2015-03-26), "Human olfactory receptor family 11 subfamily A member 1 protein, SEQ 2.", XP002760387, retrieved from EBI accession no. GSP:BBU46526 Database accession no. BBU46526 sequence -----	1-25
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A	abstract page 6, line 16 - line 20 page 24, line 16 - page 25, line 5 -& DATABASE Geneseq Proteins [Online] 15 June 2007 (2007-06-15), "Human OR11A1 protein sequence.", XP002760388, retrieved from EBI accession no. GSP:AAU79199 Database accession no. AAU79199 sequence -----	16-27
X	SHIRASU MIKA ET AL: "Olfactory Receptor and Neural Pathway Responsible for Highly Selective Sensing of Musk Odors", NEURON, CELL PRESS, US, vol. 81, no. 1, 19 December 2013 (2013-12-19), pages 165-178, XP028813092, ISSN: 0896-6273, DOI: 10.1016/J.NEURON.2013.10.021 cited in the application	26
A	page 168 -----	1-25,27

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2016/036776

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EP 2832347 A1	04-02-2015	NONE	
WO 0218657 A1	07-03-2002	AU 9060301 A	13-03-2002
		WO 0218657 A1	07-03-2002