

# Proteochemometrics of olfaction



Draw me an odor!

# Survey on 7000 young adults

- ~50% would rather lose their sense of smell than give up access to technology, like laptops or cell phones

*McCann Worldgroup, The truth about youth, April 2011*
















ARTICLE



<https://doi.org/10.1038/s41467-020-18963-y>

OPEN

# Smell and taste changes are early indicators of the COVID-19 pandemic and political decision effectiveness

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Emmanuelle Bignon<sup>3</sup>, Omar Alva<sup>1</sup>, Julie Kabous<sup>1</sup>, Margit Heiske<sup>1</sup>, Jody Pacalon<sup>3</sup>, Renaud David<sup>4</sup>,  
Caterina Dinnella<sup>5</sup>, Sara Spinelli<sup>5</sup>, Erminio Monteleone<sup>5</sup>, Michael C. Farruggia <sup>6</sup>, Keiland W. Cooper <sup>7</sup>,  
Elizabeth A. Sell <sup>8</sup>, Thierry Thomas-Danguin <sup>9</sup>, Alyssa J. Bakke <sup>10</sup>, Valentina Parma <sup>11</sup>, John E. Hayes<sup>10</sup>,  
Thierry Letellier<sup>1</sup>, Camille Ferdenzi <sup>2,13,14</sup>, Jérôme Golebiowski <sup>3,12,13,14</sup>✉ & Moustafa Bensafi <sup>2,13,14</sup>✉

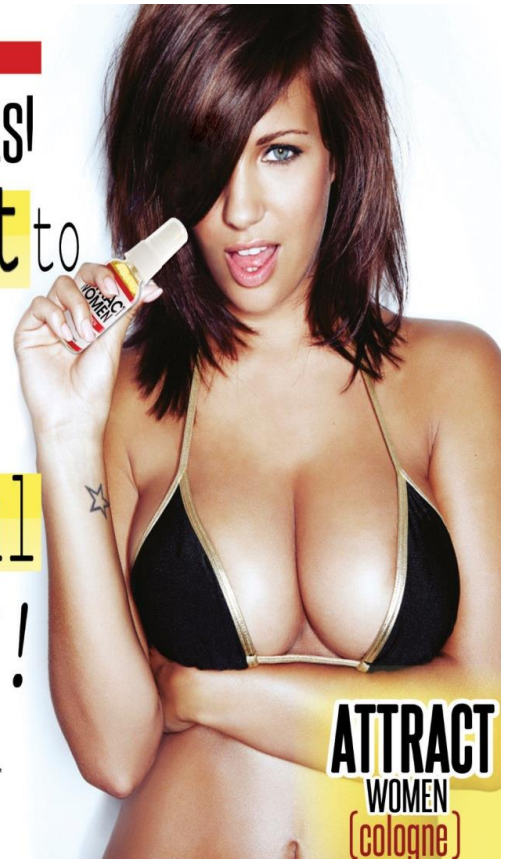


pheromoneXS

Androstenone

→ SEX ←  
 PHEROMONES!  
 The secret to  
 ATTRACT  
 Beautiful  
 WOMEN!

Pherma Labs™



Androstenonum®

increases desire in women  
 (subliminal perception)

1.5ml concentrate essence contains  
 reconstituted male pheromones

100% REAL SYNTHETIC PHEROMONE

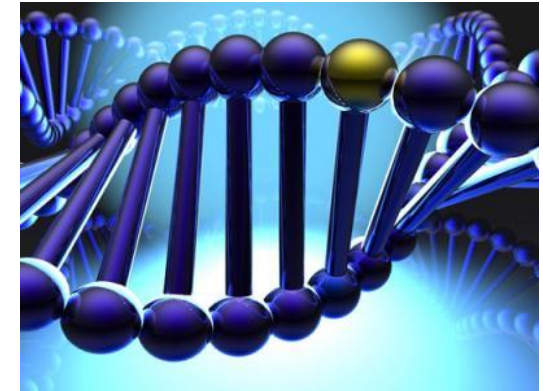
CRUELTY FREE

100% SATISFACTION GUARANTEED

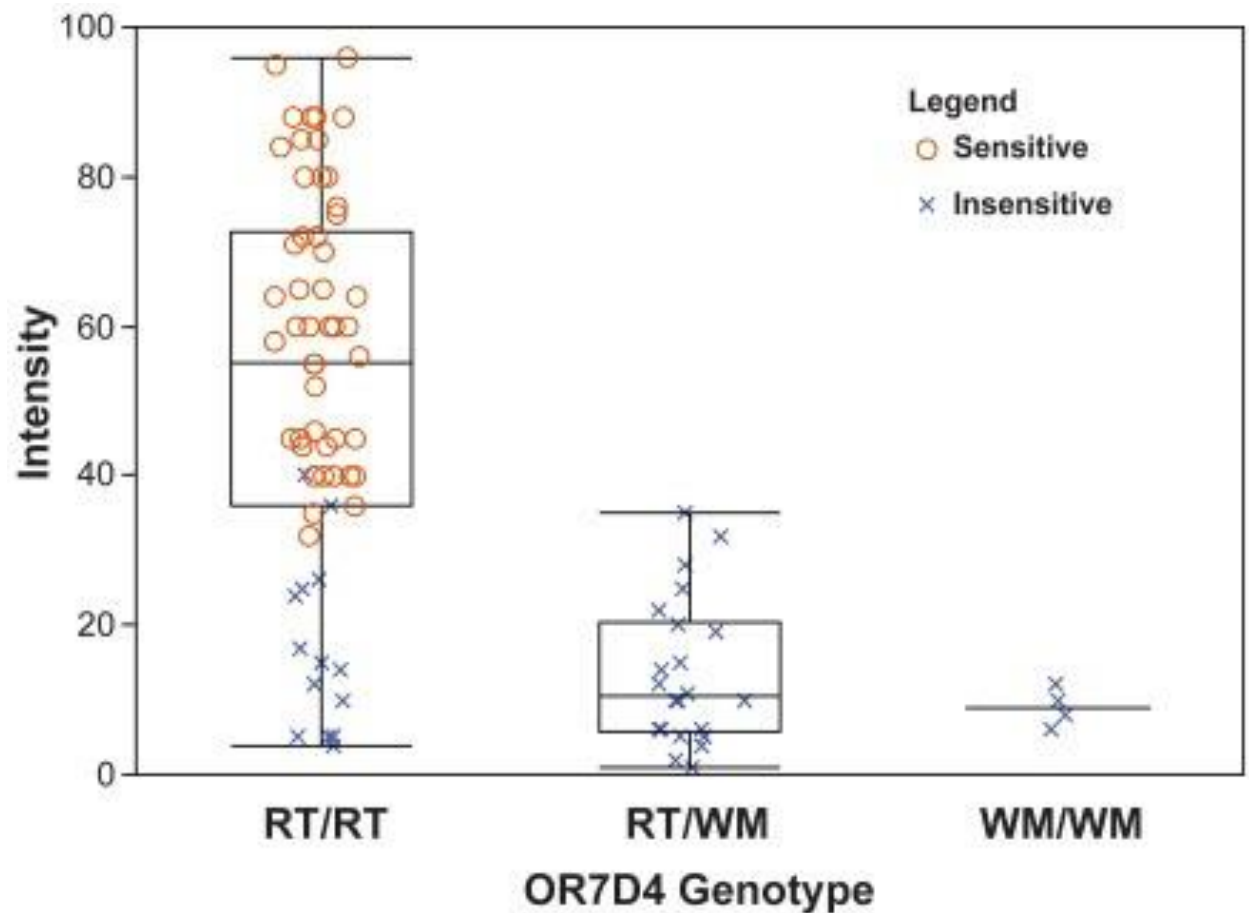
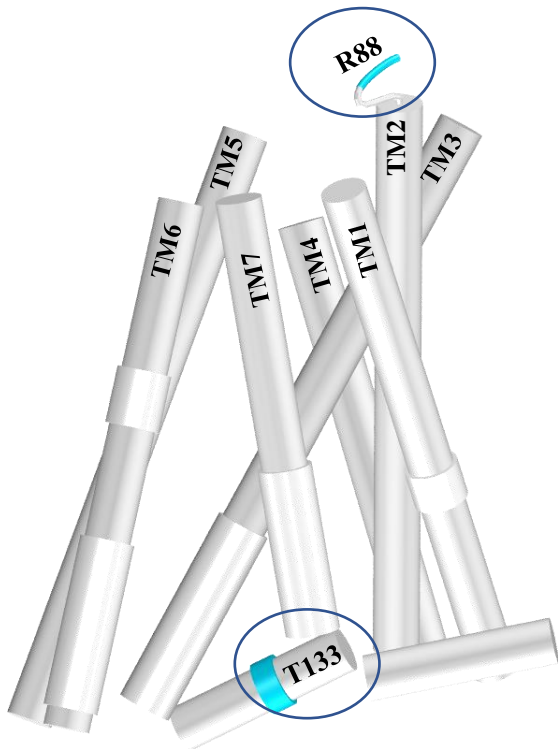
AMAZING RESULTS HOT DATES



# Androstene intensity is dependent on your genome!



Odorant Receptor 7D4  
(OR7D4)





Castration is very uncommon.



A minority of the animals are castrated by the farmer in non-conventional systems due to quality reasons.



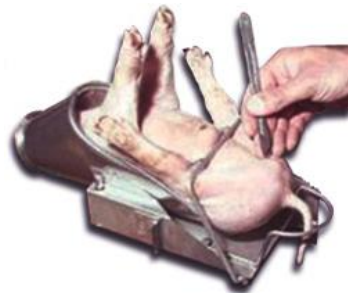
The majority of the pigs are castrated at an advanced age, frequently by a veterinarian or specialized staff.



The majority of the pigs are castrated at a young age, frequently by a veterinarian or by specialized staff.

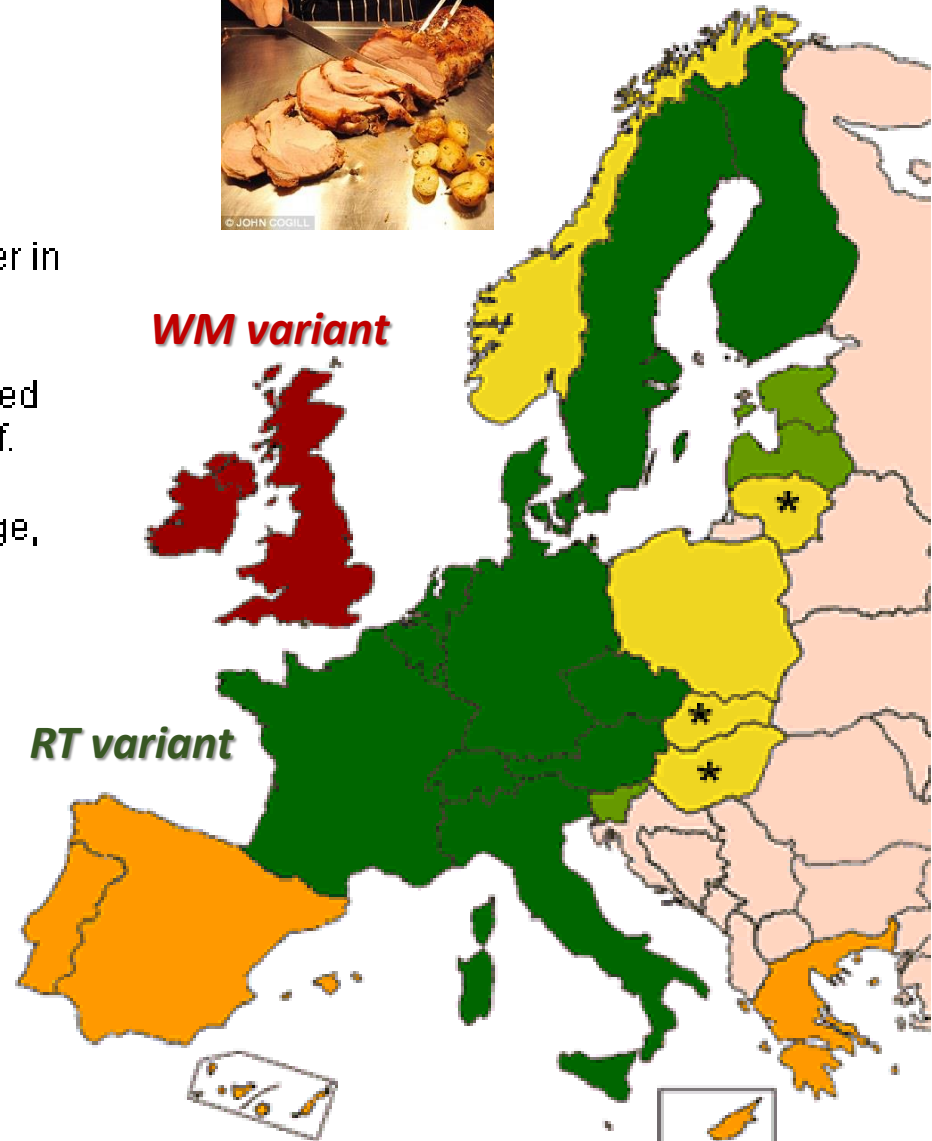


The majority of the pigs are castrated at a young age by the farmer.



*WM variant*

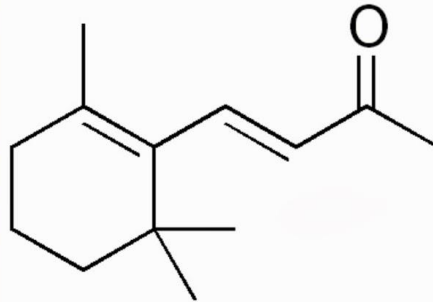
*RT variant*



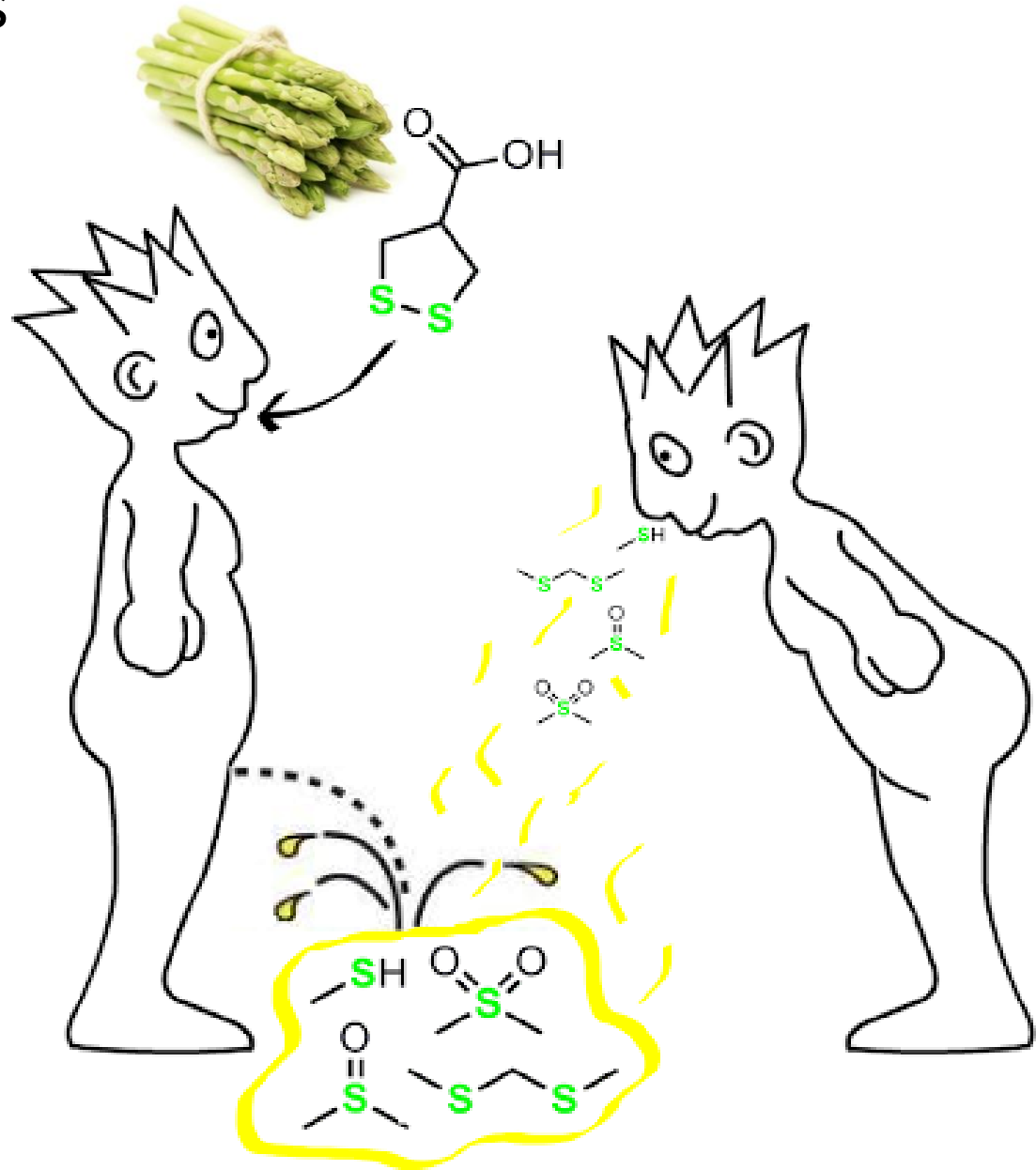
\* In many cases local anesthesia is used



# *OR5A1 receptor affects perception of $\beta$ -ionone*



OR7M2 and OR14C36 : affect perception of pee after eating asparagus



# Smells are symphonies of receptors activation

- ~5 million odorants
- 400 receptor genes
- A percept is a combinatorial activation of these 400 receptors



Angewandte  
International Edition  
Chemie

GDCh

A Journal of the  
Gesellschaft  
Deutscher Chemiker

[Explore this journal >](#)

Highlight

**The Molecular Basis of Olfactory Chemoreception<sup>†</sup>**

Uwe J. Meierhenrich Priv.-Doz. Dr., Jérôme Golebiowski Dr., Xavier Fernandez Dr.,  
Daniel Cabrol-Bass Prof. Dr.



Molecular dynamics  
decodes OR activation

Align 387 hOR sequences using constraints from *in vitro* data on 13 ORs

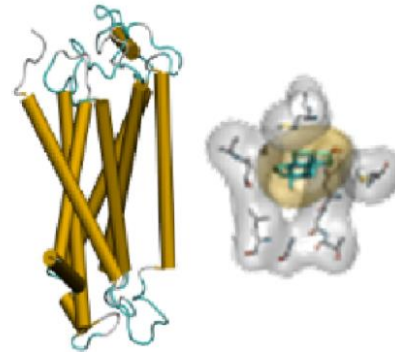
		120		130																					
OR7D4/1-289	Q	V	F	L	M	M	F	A	G	M	D	T	F	L	L	A	V	M	A	Y	D	R	F	V	
1U19A/1-348	E	G	F	E	A	T	L	G	G	E	I	A	L	W	S	V	V	L	A	I	E	R	Y	V	
3ODUA/27-369	V	H	V	I	Y	T	V	N	L	Y	S	S	V	W	I	L	A	F	I	S	L	D	R	Y	L
2YDM/3-325	I	A	C	F	V	L	V	L	T	A	S	S	I	F	S	L	L	A	I	A	I	D	R	Y	I
2LNL/29-324	V	S	L	L	K	E	V	N	F	Y	S	G	I	L	L	L	A	C	I	S	V	D	R	Y	L

fit to X-Ray templates

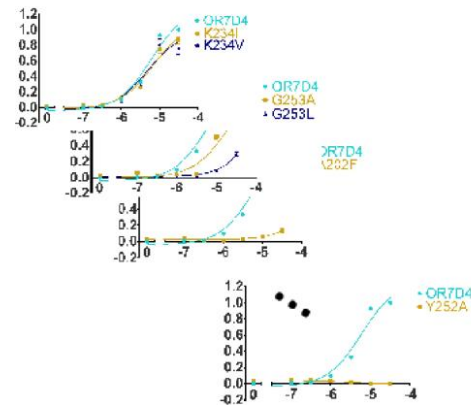
Build  
homology  
models



Dock  
ligands

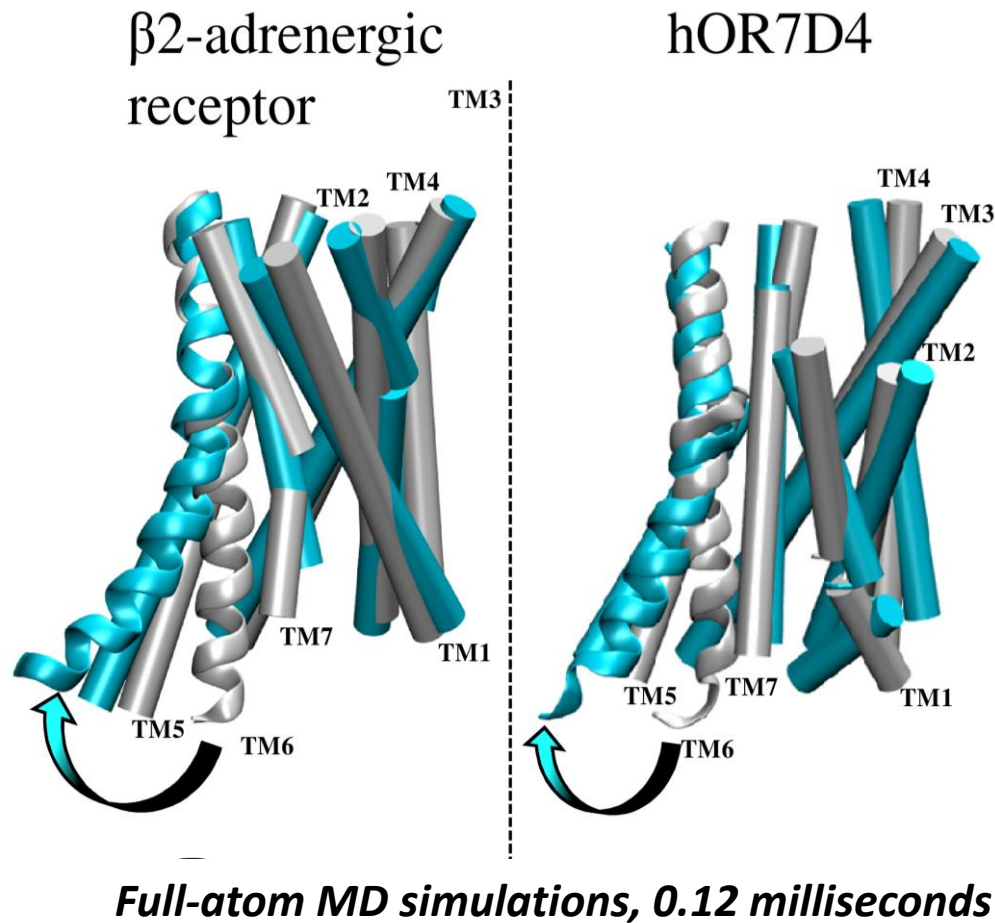


Select model  
using 28  
functional data



Monitor  
opening

# Activation mechanism as a benchmark for assessing agonists



GDCh

Communications

Angewandte  
International Edition  
Chemie

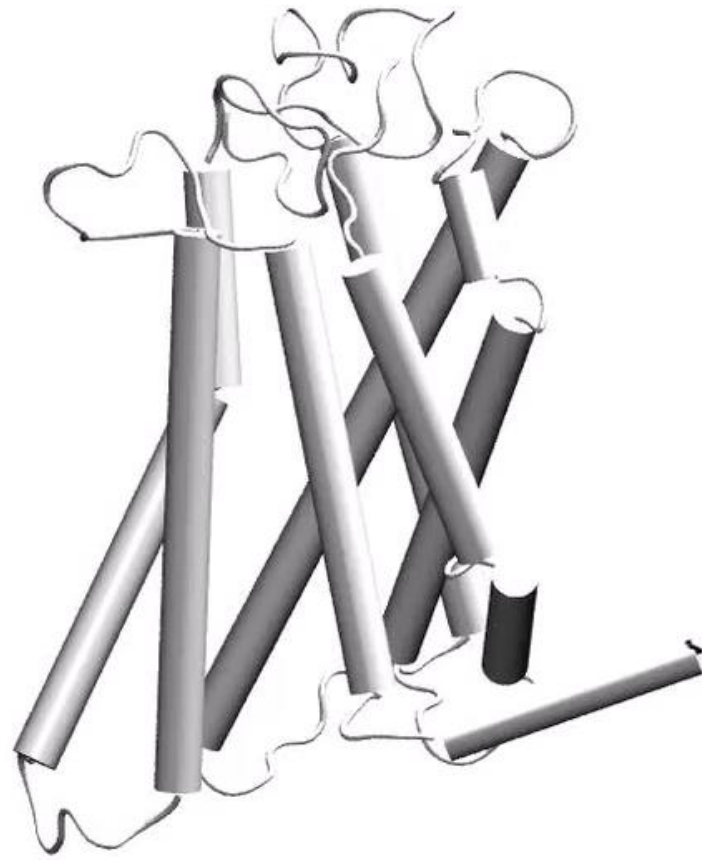
Molecular Dynamics

International Edition: DOI: 10.1002/anie.201713065  
German Edition: DOI: 10.1002/ange.201713065

## Odorant Receptor 7D4 Activation Dynamics

Claire A. de Marchi,<sup>†</sup> Jérémie Topin,<sup>†</sup> Elise Bruguera, Gleb Novikov, Kentaro Ikegami,  
Hiroaki Matsunami,\* and Jérôme Golebiowski\*

[<sup>†</sup>] Joint first authors



# Large scale G protein- coupled olfactory receptor - ligand pairing

ProteoChemoMetrics of olfaction

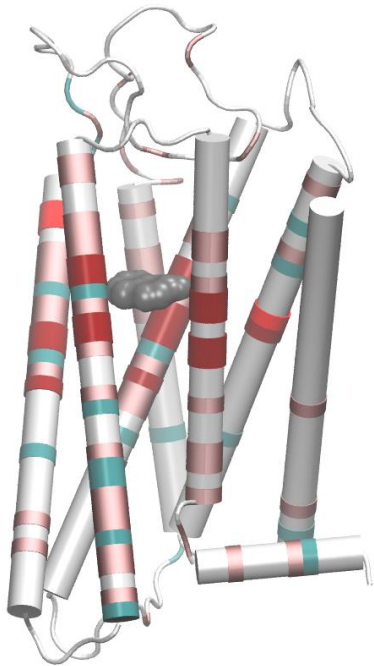


Xiaojing Cong

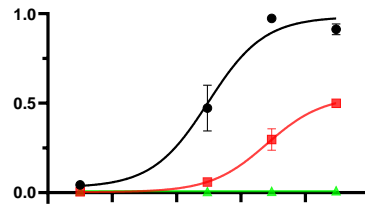


# Combination of various approaches

## Molecular modeling



## Site-directed mutagenesis

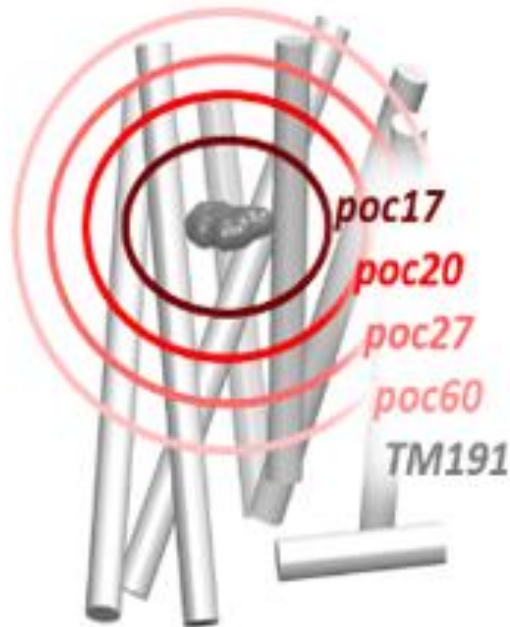


## Receptors sequence

```
hOR11H12 Q I F L F S L F T T T Y A L T I T G N G A I A F V L W C - -  
Olf924 Q L P L F L L F L A I Y V I T V V G N L G M I L L I T I - -  
Olf285 Q A L L F V A F L V I Y V L T L T G N S M I L L V I R V - -  
Olf1016 Q L V L F V M F L I M Y T L S V L G N I T L I V L I C N - -  
hOR5R1 Q A P C F G V F L V I Y L V T V L G N L G L I T L I K I - -  
hOR10G3 R T L F F V F F F L I Y I L T Q L G N L L I L I T V W A - -  
hOR12D3 Q P F F F G I F L I I Y L I N L I G N G S I L V M V V L - -  
hOR1N1 Q Q S L F G I F L C M Y L V T L T G N L L I I L A I G S - -  
hOR2G3 E A V L F V F V L F F Y L L T L V G N F T I I I S Y L - -
```

**Machine learning**

# Proteochemometric workflow



## Sequence alignment

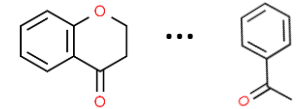
```

hOR11H12 Q I F L F S L F T T T Y A L T I T G N G A I A F V L W C - -
Olfr924  Q L P L F L L F L A I Y V I T V V G N L G M I L L I T I - -
Olfr285  Q A L L F V A F L V I Y V L T L T G N S M I L L V I R V - -
Olfr1016 Q L V L F V M F L I M Y T L S V L G N I T L I V L I C N - -
hOR5R1   Q A P C F G V F L V I Y L V T V L G N L G L I T L I K I - -
hOR10G3  R T L F F V F F F L I Y I L T Q L G N L L I L I T V W A - -
hOR12D3  Q P F F F G I F L I I Y L I N L I G N G S I L V M V V L - -
hOR1N1   Q Q S L F G I F L C M Y L V T L T G N L L I I L A I G S - -
hOR2G3   E A V L F V F V L F F Y L L T L V G N F T I I I S Y L - -
    
```

## Response to ligands

### Residue subset selection

Q I F L F S L F T T T Y A L T I T G N G A I A F V L W C	0	0	?
Q L P L F L L F L A I Y V I T V V G N L G M I L L I T I	1	?	0
Q A L L F V A F L V I Y V L T L T G N S M I L L V I R V	?	0	1
Q L V L F V M F L I M Y T L S V L G N I T L I V L I C N	1	?	0
R T L F F V F F F L I Y I L T Q L G N L L I L I T V W A	1	1	?
Q P F F F G I F L I I Y L I N L I G N G S I L V M V V L	?	1	1
E A V L F V F V L F F Y L L T L V G N F T I I I S Y L	0	?	?



## Machine learning

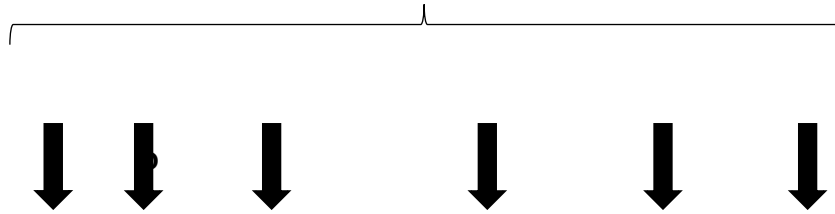
Model 1

Model 2

*In vitro* assays

Optimal model

## Subset of residues

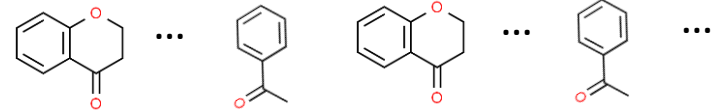


OR5P3 **AL**TLHYDRY**TT**S**RR**LD**PI**Q**LK**CVGGTAGCDSY**TP**K**VI**QCQ**NG**WDGYDV**Q**WE**CK**TDL**DI**  
 OR5R1 **AL**TLHYDRY**TT**S**RR**LD**PI**Q**LK**CVGGTAGCDSY**TP**K**VI**QCQ**NG**WDGYDV**Q**WE**CK**TDL**DI**  
 OR6X1 **AL**TLHYDRY**TT**S**RR**LD**PI**Q**LK**CVGGTAGCDSY**TP**K**VI**QCQ**NG**WDGYDV**Q**WE**CK**TDL**DI**  
 OR8K3 **AL**TLHYDRY**TT**S**RR**LD**PI**Q**LK**CVGGTAGCDSY**TP**K**VI**QCQ**NG**WDGYDV**Q**WE**CK**TDL**DI**  
 OR5M9 **AL**TLHYDRY**TT**S**RR**LD**PI**Q**LK**CVGGTAGCDSY**TP**K**VI**QCQ**NG**WDGYDV**Q**WE**CK**TDL**DI**  
 OR5T2 **AL**TLHYDRY**TT**S**RR**LD**PI**Q**LK**CVGGTAGCDSY**TP**K**VI**QCQ**NG**WDGYDV**Q**WE**CK**TDL**DI**  
 OR5T3 **AL**TLHYDRY**TT**S**RR**LD**PI**Q**LK**CVGGTAGCDSY**TP**K**VI**QCQ**NG**WDGYDV**Q**WE**CK**TDL**DI**  
 OR5V1 **AL**TL**Y**DRY**TT**S**RR**LE**PI**Q**LK**CVGGTAGCDSY**TP**K**VI**QCQ**NR**GDGYDV**Q**WE**CK**TDL**DI**  
 OR6A2 **AL**TL**H**DRY**TT**S**RR**LD**PI**Q**LK**CVGGTAGCDSY**TP**K**VI**QCQ**NG**WDGYDV**Q**WE**CK**TDL**DI**  
 OR6C65 **AL**TL**Y**SDRY**TT**S**RR**LD**PI**Q**LK**CVGGTAG**CE**AY**TP**R**VI**QCQ**NG**WDGYDV**Q**WE**CK**TDL**DI**  
 OR6C75 **AL**TL**Y**SDRY**TT**S**RR**LD**PI**Q**LK**CVGGTAG**CD**AY**TP**K**VV**QCQ**NG**WDGYDV**Q**WE**CK**TDL**DI**  
 OR6F1 **AL**TLHYDRY**TT**S**RR**LE**PI**Q**LK**CVGGTAG**CD**AY**TP**K**VI**QCQ**NG**WDGYDV**Q**WE**CK**TDL**DI**  
 OR6K6 **AL**TL**H**NR**Y**TT**S**RR**LD**P**V**Q**LK**CI**GG**TAGCNSY**TP**K**VI**QCQ**NG**WDGYDV**Q**WE**CK**TDL**DI**  
 OR6M1 **AL**TL**H**RD**R**FT**T**ARR**T**AP**I**Q**L**Q**CL**GG**S**AGCP**A**H**I**PE**I**V**Q**CR**NG**WDG**F**D**V**Q**WE**CK**A**E**L**D**T**  
 OR6P1 **V**LT**L**HR**G**R**Y**TT**A**RR**T**A**A**VP**Q**L**Q**CI**GG**SAGCS-D**I**PE**VV**Q**C**YN**R**GD**Y**D**V**Q**W**Q**CK**AD**L**EN  
 OR6V1 **T**IT**L**Y**A**DR**Y**T**N**ARR**S**AP**V**Q**L**K**CI**GG**N**AG**CH**AM**V**P**Q**V**V**Q**CH**NR**G**WD**GL**D**V**Q**WE**CR**V**D**M**DN  
 OR7A17 **A**IT**L**Y**A**DR**Y**T**N**ARR**S**AP**V**Q**L**K**CI**GG**S**AG**CH**T**M**V**P**Q**V**V**Q**CH**N**R**G**WD**G**F**D**V**Q**WE**CK**V**D**M**D**N  
 OR7A5 **V**LT**L**Y**R**GR**Y**TT**A**RR**S**SP**V**Q**L**Q**CI**GG**S**AG**CG**S**F**TP**EV**V**Q**C**YN**R**G**SD**G**I**D**A**Q**WE**CK**A**D**M**D**N  
 OR7C1 **V**LT**L**Y**K**GR**Y**TT**A**RR**S**SP**V**Q**L**Q**CV**GG**S**AG**CG**S**F**IP**EV**V**Q**C**K**NG**WD**G**V**D**A**Q**WE**CK**T**D**M**DN  
 OR7C2 **V**LT**L**Y**R**GL**Y**TT**A**RR**S**SP**V**Q**L**Q**CV**GG**S**AG**CH**AF**V**PE**VV**Q**C**Q**NG**WD**G**M**I**D**Q**WE**CR**T**D**M**D**N  
 OR7D4 **T**LT**L**Y**R**GR**Y**TT**A**RR**S**SP**V**Q**L**R**CV**GG**S**AG**CQ**AF**V**PE**VV**Q**C**Q**NR**GD**Y**D**V**Q**WE**CK**T**D**M**DN  
 OR7G1 **A**LT**L**Y**K**NR**Y**TT**A**RR**S**SP**V**Q**L**Q**CV**GG**S**AG**CQ**AF**V**PE**VV**Q**C**Q**NG**WD**G**V**D**V**Q**WE**CR**T**D**M**D**N  
 OR7G2 **V**LT**L**Y**K**GR**Y**TT**A**RR**S**SP**V**Q**L**Q**CA**GG**T**AG**CG**S**F**VP**EV**V**Q**C**YN**R**G**SD**G**I**D**T**Q**WE**CK**A**D**M**D**N  
 OR7G3 **A**IT**L**H**K**GM**TT**G**RR**V**S**PT**F**L**K**CVGG-S**A**K**G**AF**TP**K**VV**Q**C**AN**Q**GF**D**GS**D**V**Q**WR**CD**AD**L**PH  
 OR8A1 **A**IT**L**N**K**GM**TT**G**RR**V**AP**T**L**Q**CV**GG-S**A**K**G**AF**TP**K**VV**Q**C**SN**Q**GF**D**GS**D**V**Q**WR**CD**AD**L**PH  
 OR8B12 **A**IT**L**H**K**GM**TT**G**RR**V**AP**AL**Q**L**K**CVGG-S**A**K**G**Q**F**SP**K**V**V**Q**C**AN**Q**GF**D**GS**D**V**Q**WR**CD**AD**L**PH

.....

1518  
receptors

## Agonist?



## Molecular Descriptors

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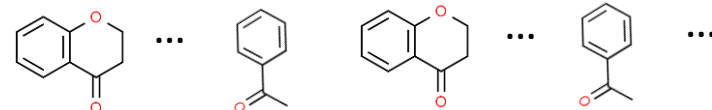
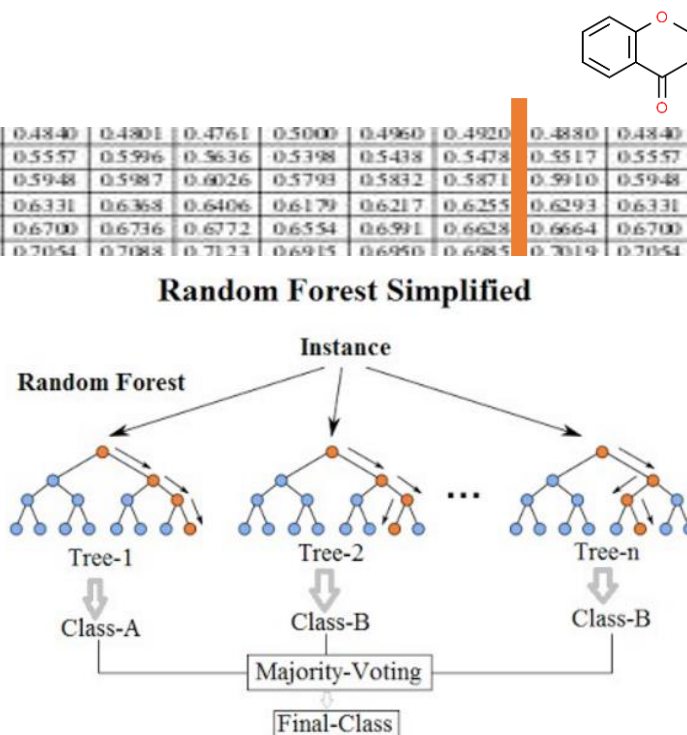
.

0	0	?
1	?	0
?	0	1
1	?	0
1	1	?
?	1	1
0	?	?
0	1	0
1	0	1
0	1	1
1	?	?
?	?	1
0	?	0
?	1	1
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1	1	?
0	1	1
?	1	1
?	?	1
?	0	0
?	1	?

# Agonist?

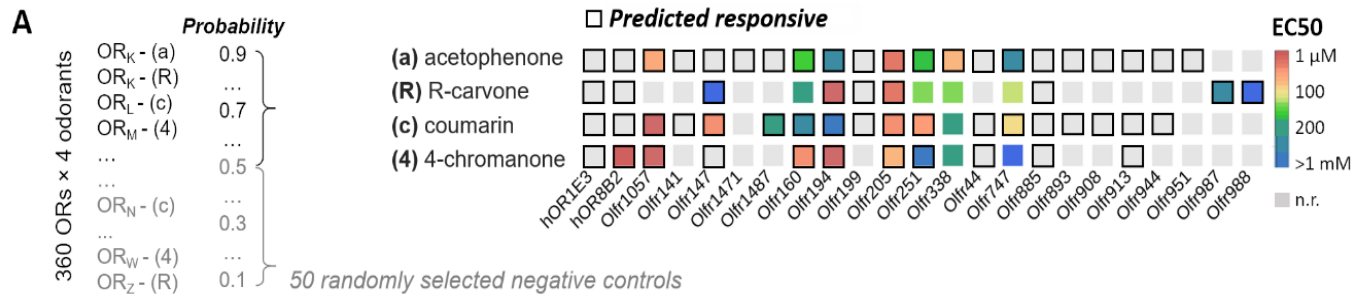
- OR5P3
- OR5R1
- OR6X1
- OR8K3
- OR5M9
- OR5T2
- OR5T3
- OR5V1
- OR6A2
- OR6C65
- OR6C75
- OR6F1
- OR6K6
- OR6M1
- OR6P1
- OR6V1
- OR7A17
- OR7A5
- OR7C1
- OR7C2
- OR7D4
- OR7G1
- OR7G2
- OR7G3
- OR8A1
- OR8B12

0.5000	0.4960	0.4920	0.4880	0.4840	0.4801	0.4761	0.5000	0.4960	0.4920	0.4880	0.4840	0.4801	0.4761
0.5398	0.5438	0.5478	0.5517	0.5557	0.5596	0.5636	0.5398	0.5438	0.5478	0.5517	0.5557	0.5596	0.5636
0.5793	0.5832	0.5871	0.5910	0.5948	0.5987	0.6026	0.5793	0.5832	0.5871	0.5910	0.5948	0.5987	0.6026
0.6179	0.6217	0.6255	0.6293	0.6331	0.6368	0.6406	0.6179	0.6217	0.6255	0.6293	0.6331	0.6368	0.6406
0.6554	0.6591	0.6628	0.6664	0.6700	0.6736	0.6772	0.6554	0.6591	0.6628	0.6664	0.6700	0.6736	0.6772
0.6915	0.6950	0.6985	0.7019	0.7054	0.7088	0.7123	0.6915	0.6950	0.6985	0.7019	0.7054	0.7088	0.7123
0.7257	0.7291	0.7324	0.7357	0.7390	0.7422	0.7454	0.7257	0.7291	0.7324	0.7357	0.7390	0.7422	0.7454
0.7580	0.7611	0.7642	0.7673	0.7704	0.7734	0.7764	0.7580	0.7611	0.7642	0.7673	0.7704	0.7734	0.7764
0.7881	0.7910	0.7939	0.7967	0.7995	0.8023	0.8051	0.7881	0.7910	0.7939	0.7967	0.7995	0.8023	0.8051
0.8159	0.8186	0.8212	0.8238	0.8264	0.8289	0.8315	0.8159	0.8186	0.8212	0.8238	0.8264	0.8289	0.8315
0.8413	0.8438	0.8461	0.8484	0.8507	0.8531	0.8554	0.8413	0.8438	0.8461	0.8484	0.8507	0.8531	0.8554
0.8643	0.8665	0.8686	0.8708	0.8729	0.8749	0.8770	0.8643	0.8665	0.8686	0.8708	0.8729	0.8749	0.8770
0.8849	0.8869	0.8888	0.8907	0.8925	0.8944	0.8962	0.8849	0.8869	0.8888	0.8907	0.8925	0.8944	0.8962
0.9032	0.9049	0.9066	0.9082	0.9098	0.9115	0.9131	0.9032	0.9049	0.9066	0.9082	0.9098	0.9115	0.9131
0.9192	0.9207	0.9222	0.9236	0.9250	0.9265	0.9279	0.9192	0.9207	0.9222	0.9236	0.9250	0.9265	0.9279
0.9332	0.9345	0.9357	0.9370	0.9382	0.9394	0.9406	0.9332	0.9345	0.9357	0.9370	0.9382	0.9394	0.9406
0.9452	0.9463	0.9474	0.9484	0.9494	0.9505	0.9515	0.9452	0.9463	0.9474	0.9484	0.9494	0.9505	0.9515
0.9554	0.9564	0.9573	0.9582	0.9591	0.9599	0.9608	0.9554	0.9564	0.9573	0.9582	0.9591	0.9599	0.9608
0.9641	0.9649	0.9656	0.9664	0.9671	0.9678	0.9686	0.9641	0.9649	0.9656	0.9664	0.9671	0.9678	0.9686
0.9713	0.9719	0.9726	0.9732	0.9738	0.9744	0.9750	0.9713	0.9719	0.9726	0.9732	0.9738	0.9744	0.9750
0.9772	0.9778	0.9783	0.9788	0.9793	0.9798	0.9803	0.9772	0.9778	0.9783	0.9788	0.9793	0.9798	0.9803
0.9821	0.9826	0.9830	0.9834	0.9838	0.9842	0.9846	0.9821	0.9826	0.9830	0.9834	0.9838	0.9842	0.9846
0.9861	0.9864	0.9868	0.9871	0.9874	0.9878	0.9881	0.9861	0.9864	0.9868	0.9871	0.9874	0.9878	0.9881
0.9893	0.9896	0.9898	0.9901	0.9903	0.9906	0.9909	0.9893	0.9896	0.9898	0.9901	0.9903	0.9906	0.9909
0.9918	0.9920	0.9922	0.9924	0.9926	0.9929	0.9931	0.9918	0.9920	0.9922	0.9924	0.9926	0.9929	0.9931
0.9938	0.9940	0.9941	0.9943	0.9944	0.9946	0.9948	0.9938	0.9940	0.9941	0.9943	0.9944	0.9946	0.9948
0.9953	0.9955	0.9956	0.9957	0.9958	0.9960	0.9961	0.9953	0.9955	0.9956	0.9957	0.9958	0.9960	0.9961
0.9965	0.9966	0.9967	0.9968	0.9969	0.9970	0.9971	0.9965	0.9966	0.9967	0.9968	0.9969	0.9970	0.9971
0.9974	0.9975	0.9976	0.9977	0.9978	0.9979	0.9980	0.9974	0.9975	0.9976	0.9977	0.9978	0.9979	0.9980
0.9981	0.9982	0.9982	0.9983	0.9984	0.9984	0.9985	0.9981	0.9982	0.9982	0.9983	0.9984	0.9984	0.9985
0.9987	0.9987	0.9987	0.9988	0.9988	0.9989	0.9989	0.9987	0.9987	0.9987	0.9988	0.9988	0.9989	0.9989

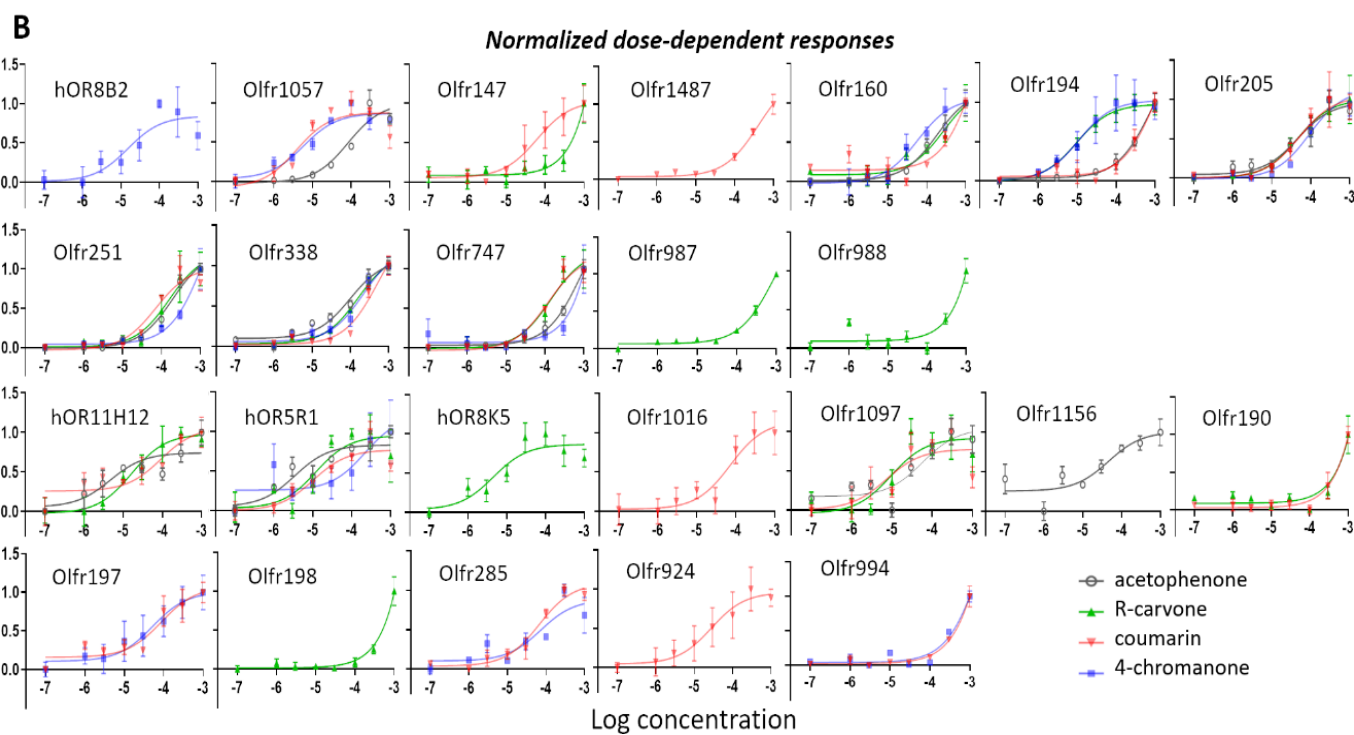
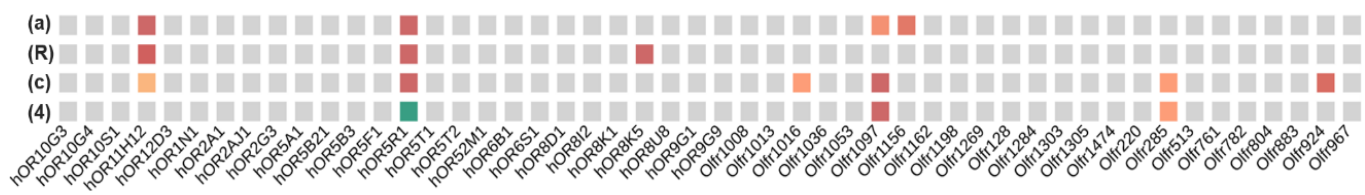


0	0	?
1	?	0
?	0	1
1	?	0
1	1	?
?	1	1
1	?	?
0	?	?
0	1	0
1	0	1
0	1	1
1	?	?
?	?	1
0	?	0
?	1	1
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1	1	?
0	1	1
?	1	1
?	?	1
?	0	0
?	1	?

1518 ORs



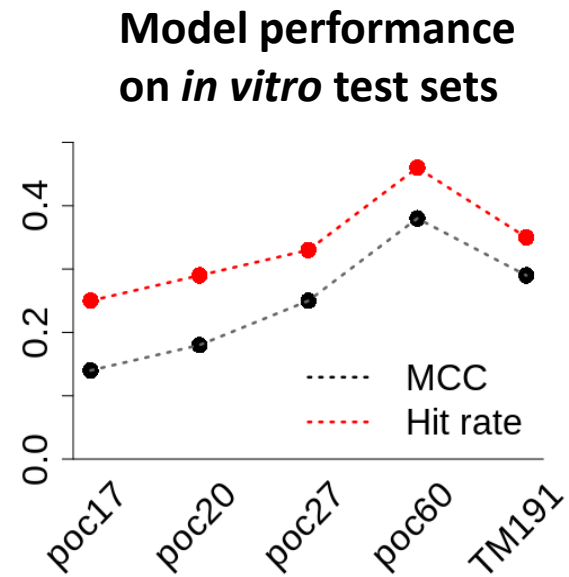
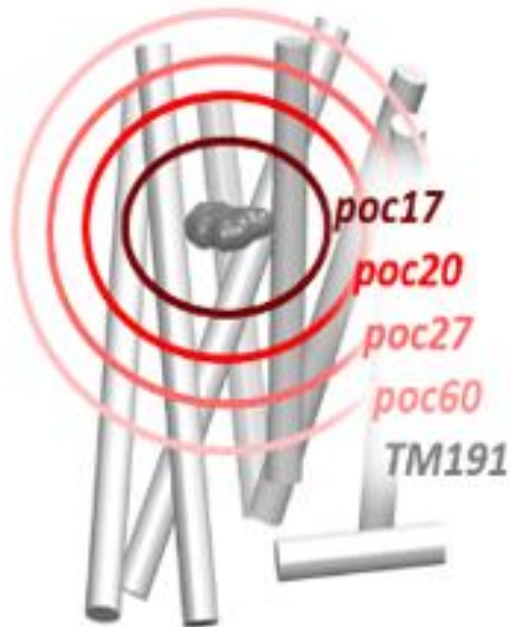
Xiaojing Cong



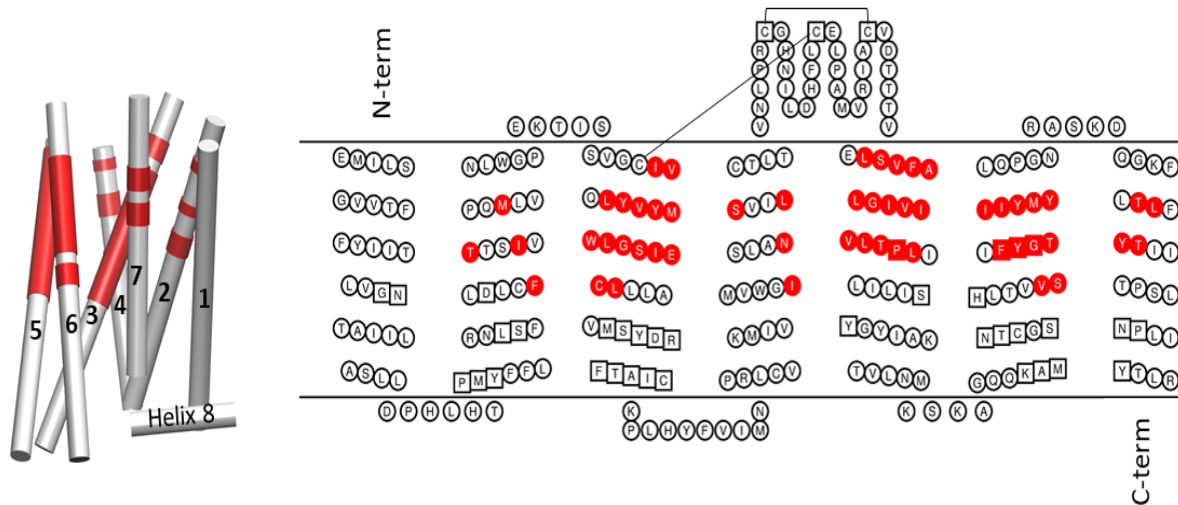
Yiqun Yu

Fudan Univ. Shanghai

# The subset of 60 residues performs better than the whole receptor



# The information is mostly encoded into the extended receptor pocket



- Hit rate 56% (assessed by *in vitro* functional assays on 96 receptors).
- 54 new receptor-ligand pairs were discovered
- 20 unknown receptors were deorphanized

# Thank you



**Dr. Xiaojing Cong**



**M. Jody Pacalon**



**Dr. Jérémie Topin**



**Pr. Yiqun Yu**

*Fudan Univ. Shanghai*



**Collaborative Research  
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