

서울대 약대 13:00-14:00

# Odorant GPCRs beyond Olfaction



*Koo*  
ODORANTRECEPTORLAB.

JaeHyung Koo, Ph.D.

New Biology, DGIST

Nov. 14. 2019

# The Nobel Prize (odorant GPCRs)

in Physiology/Medicine 2004

Richard Axel & Linda B. Buck

for their discoveries of "odorant receptors (OR)"  
and the organization of the olfactory system"



At the Nobel Prize Award Ceremony at the Stockholm Concert Hall. Richard Axel (left) who shared the 2004 Nobel Prize in Physiology or Medicine with Linda B. Buck (middle).

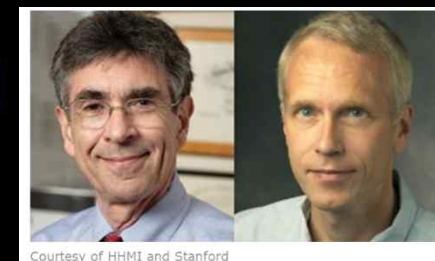
in Chemistry 2012

Robert J. Lefkowitz & Brian K. Kobilka

G-Protein- Coupled Receptors  
(GPCRs)

for developing insights into the role of chemicals at the  
molecular level in the body.

for describing the structure and function of the receptors  
through which cells sense and respond to chemical signals



Courtesy of HHMI and Stanford

## The total number of GPCRs in the repertoires of mouse and human

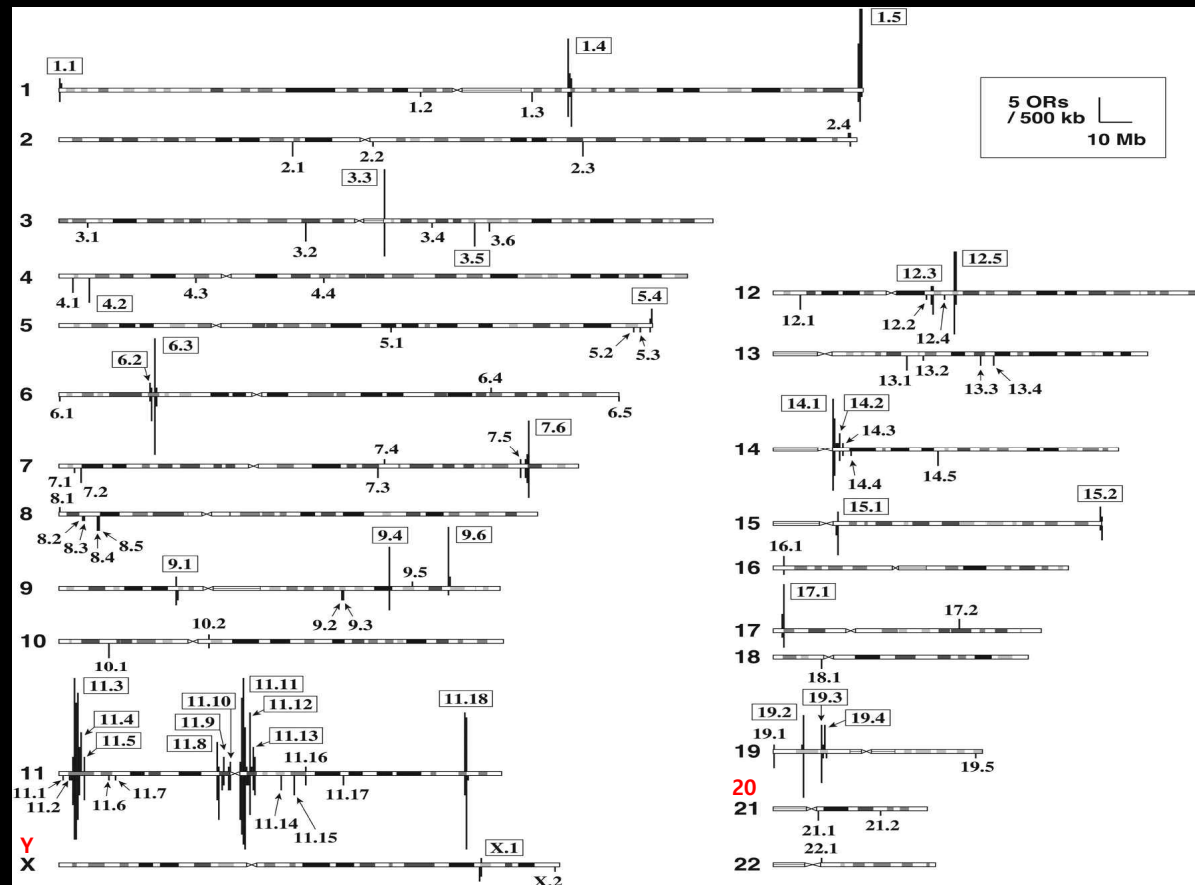
Group	Number in mouse	Number in human
<i>Glutamate</i>	79	22
<i>Rhodopsin</i> ( $\alpha$ )	105	101
<i>Rhodopsin</i> ( $\beta$ )	46	43
<i>Rhodopsin</i> ( $\gamma$ )	67	64
<i>Rhodopsin</i> ( $\delta$ )	82	63
Adhesion	31	33
<i>Frizzled</i>	11	11
<i>Taste type 2</i>	34	25
Secretin	15	15
<i>VIR</i>	165	3
<i>Olfactory</i>	1037	388
<i>Others</i>	25 <sup>a</sup>	23 <sup>a</sup>
Total	1697	791

Bjarnadottir et al., 2006

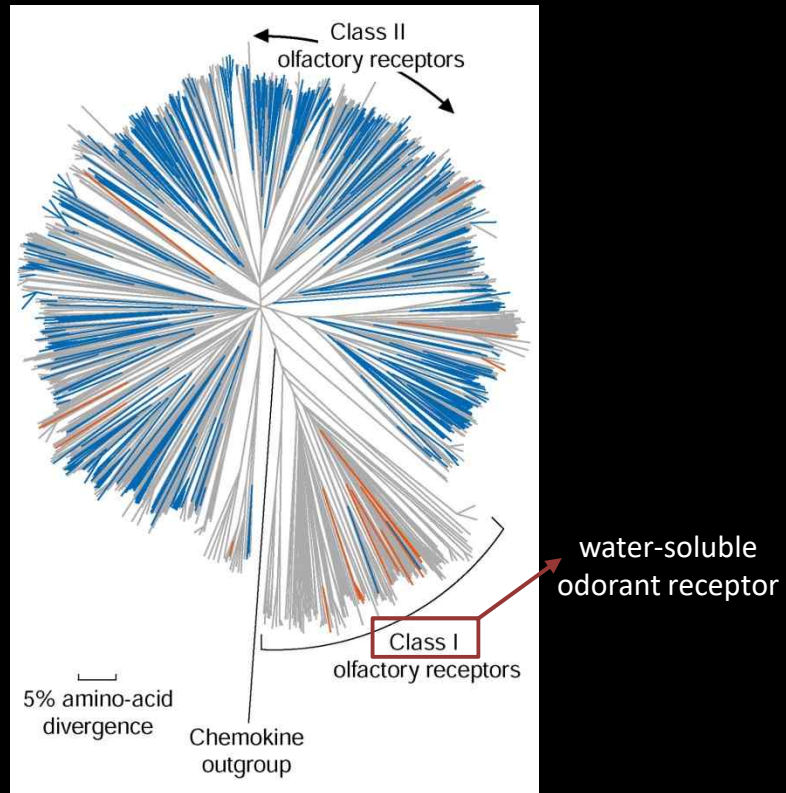
## OR features

- Less 300 Da ligands by physical and chemical characteristics of OR structure
- Intronless ORF in a exon
- ~310 amino acid
- 20~60% pseudogene (high fraction)
- Gene duplication & pseudogenization events
- Chordates, insects, nematodes – no sequence similarity (multiple origin)
- Gene clustering in centromere & telomere of chromosome

# Distribution of OR genes on human chromosomes



# Phylogenetic tree of odorant receptor



Young et al., 2003

## Ectopic odorant receptor is drug target? -> physiological Role

- 게놈의 2-3%를 차지하는 OR가 과연 코에서만 기능을 할까?
- 40-60% pseudogenization이 일어난 OR가 비후각조직에서 기능을 하지 않는다면, 어떻게 여전히 기능을 할 수 있는 형태로 남아 있지?
- 비후각조직에서 발현하는 OR 중에 종들 간에 아미노산 유사성이 높은 OR이 다수 존재
- Soluble odorant가 body fluid or blood를 solvent로 몸의 여러 곳으로 이동이 가능하지 않을까?
- OR도 비후각조직이나 세포에서 기능을 할 수 있지 않을까?
- If yes, GPCRs이 drug target의 50-60%를 차지 하는데 GPCR의 largest subfamily인 후각수용체는 drug target이 될 수 있을까?

# 1<sup>st</sup> review article for ectopic odorant receptors

BMB  
Reports

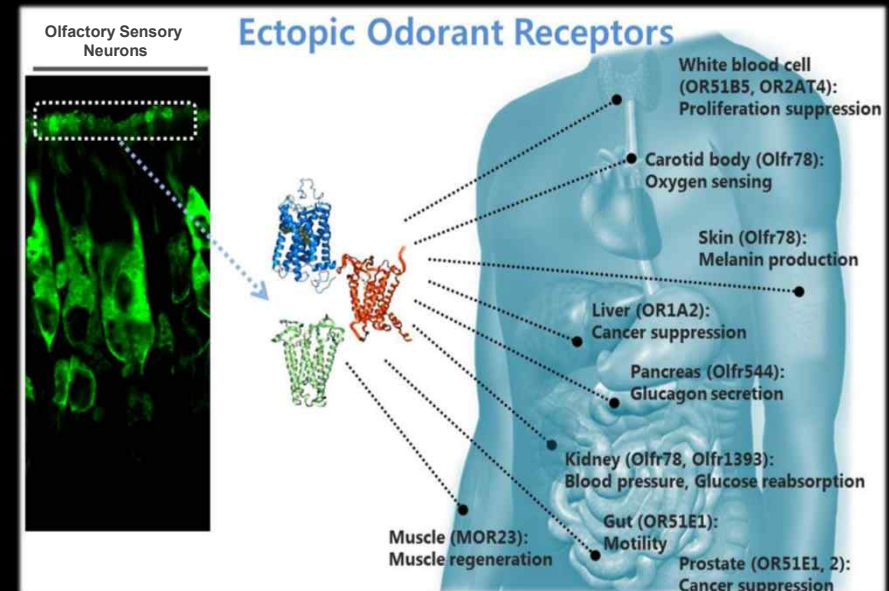
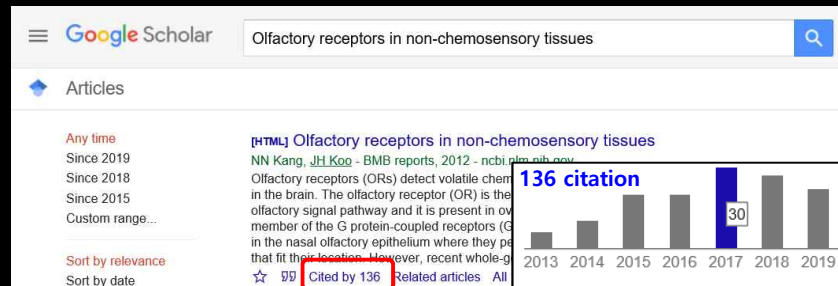
Invited Mini Review

## Olfactory receptors in non-chemosensory tissues

NaNa Kang & JaeHyung Koo\*

Department of Brain Science, Daegu Gyeongbuk Institute of Science and Technology (DGIST), Daegu 711-873, Korea

Kang & Koo, 2012



Kim & Koo, 2017



# Odorant receptors in non-olfactory tissues

1. Identification of a testicular odorant receptor mediating human sperm chemotaxis .

Spher, et al. (2003) Science

2. MOR23 promotes muscle regeneration and regulates cell adhesion and migration.

Griffin, et al. (2009) Dev. Cell.

3. Olfactory receptor responding gut microbiota-derived signals plays a role in renin secretion and blood pressure regulation.

Pluznick, et al. (2013) PNAS

4. Oxygen regulation of breathing through an olfactory receptor activated by lactate.

Chang, et al., (2015) Nature

5. Olfactory receptor 544 reduces adiposity by steering fuel preference toward fats.

Wu, et al., (2017) J Clin Invest.

6. Enterochromaffin cells are gut chemosensors that couple to sensory neural pathways.

Bellono, et al., (2017) Cell

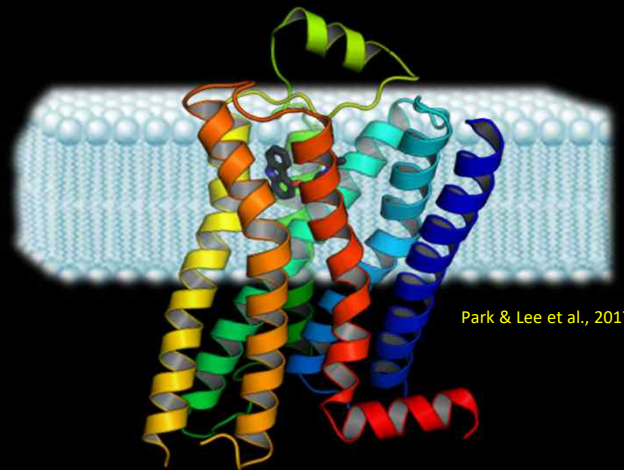
7. Olfactory receptor OR2AT4 regulates human hair growth.

Cheret, et al., (2018) Nature Commun.

## Possible problems for ectopic OR study

- Low expression level of ectopic OR
- Rare numbers of specific cells expressing OR
- Not enough high quality specific OR antibody (40~90% homology)
- Less than 100 OR-ligand pairs in above 1,000 OR genes

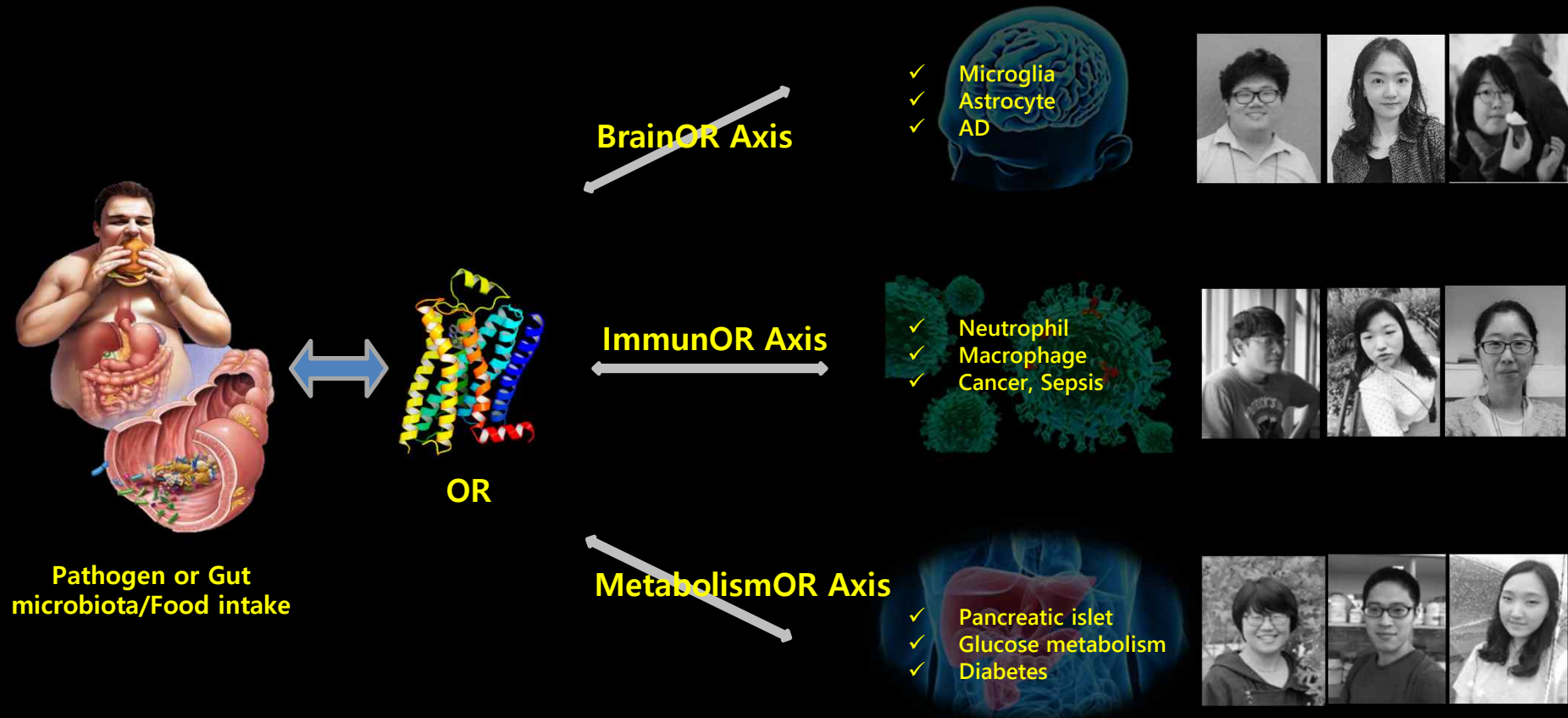
**Our research aims to understand how the body interacts with the chemical cues (metabolites, fatty acids, odorants) generated in and out of the body.**



Park & Lee et al., 2017

**Research topics: ectopic expression & functional studies of odorant receptors**

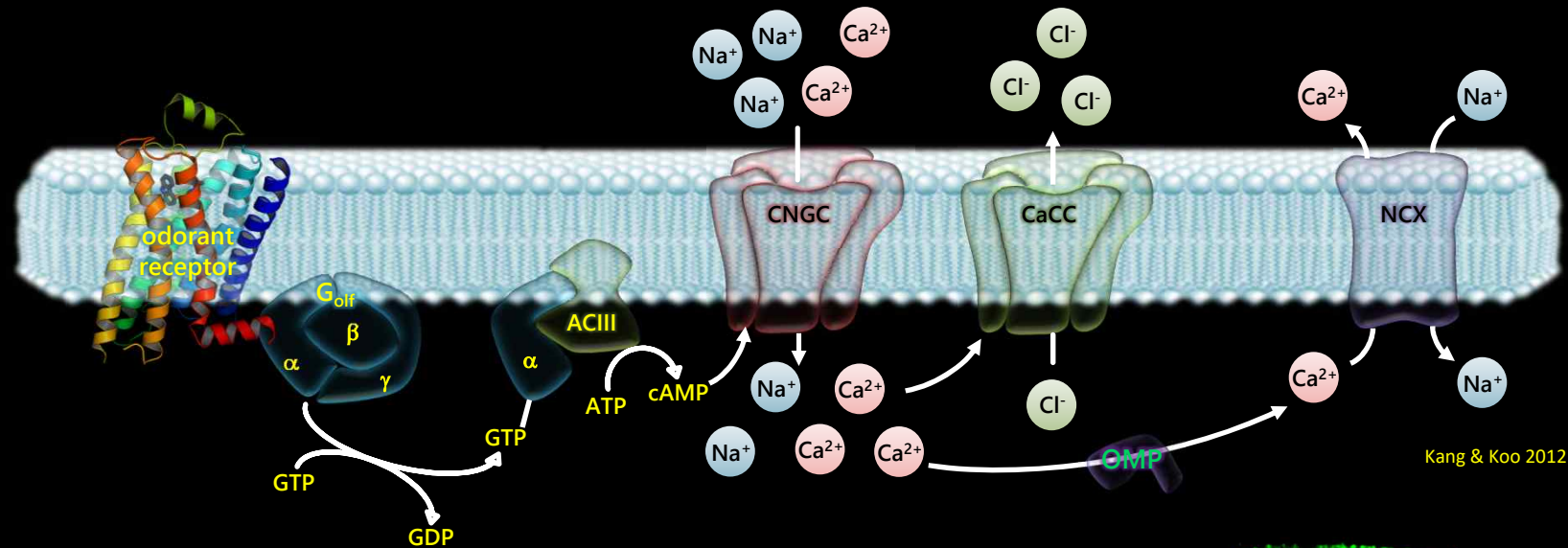
# Koo Lab by odorant receptor (ORLab)



# Screening

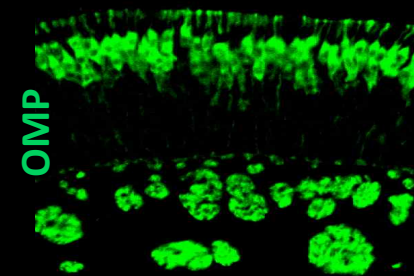
IHC with marker protein & RNA-seq

# Canonical olfactory signal transduction

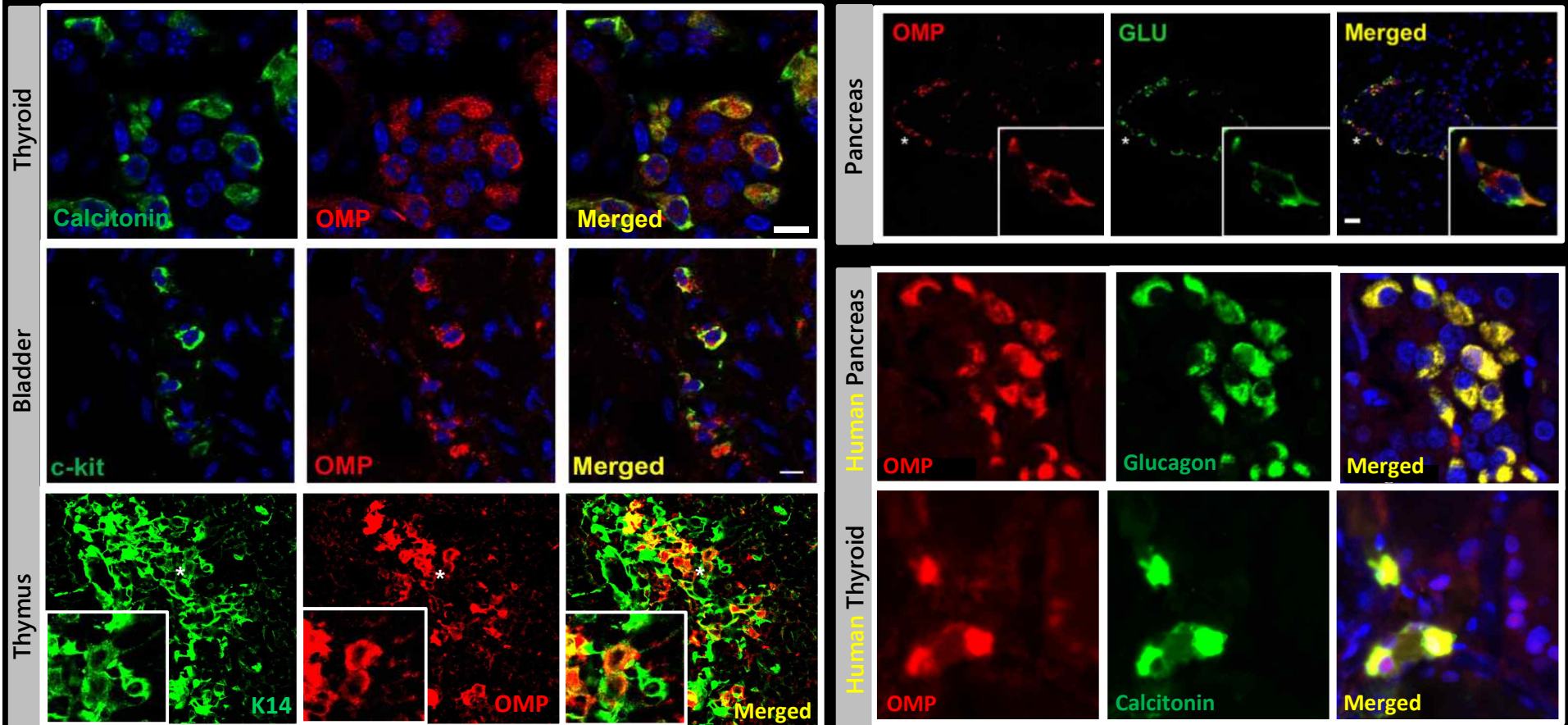


Olfactory specific molecules

→ Odorant receptor,  $G_{olf}$ , ACIII, **OMP**

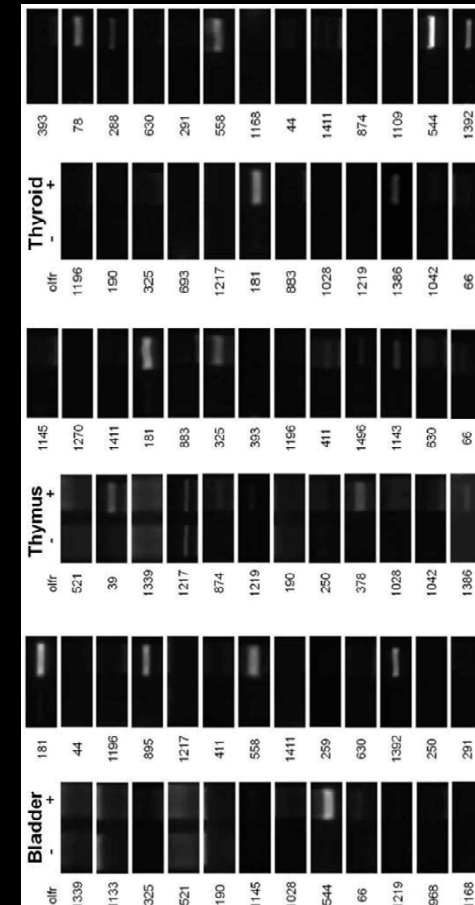
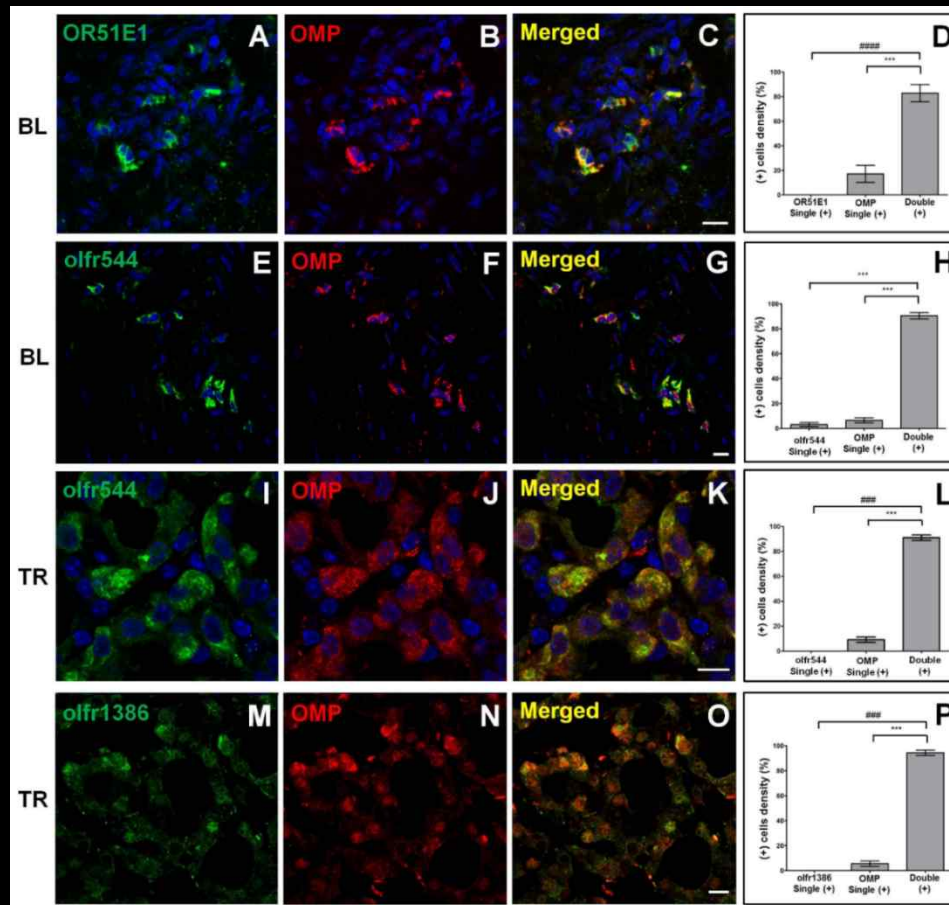


## Identification of OMP (+) cells in non-olfactory tissues





# Odorant receptors are expressed in OMP (+) cells





## ➤ Summary

**Odorant receptors are extensively expressed in non-olfactory tissue.**



- OMP expression may reflect odorant receptor expression  
in non-olfactory tissues.

*Kang, et al. 2015*

# DGIST



## The Koo Lab

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Lee, NaHye  
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- Ho Lee (KCC)
- In Kyu Lee (KNU)
- Jae-Yong Park (KU)
- Je Kyung Seong (SNU)
- Jennifer Plunznick (JHU)
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