

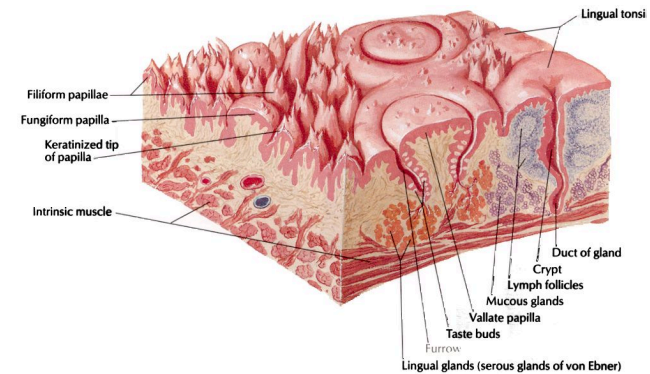
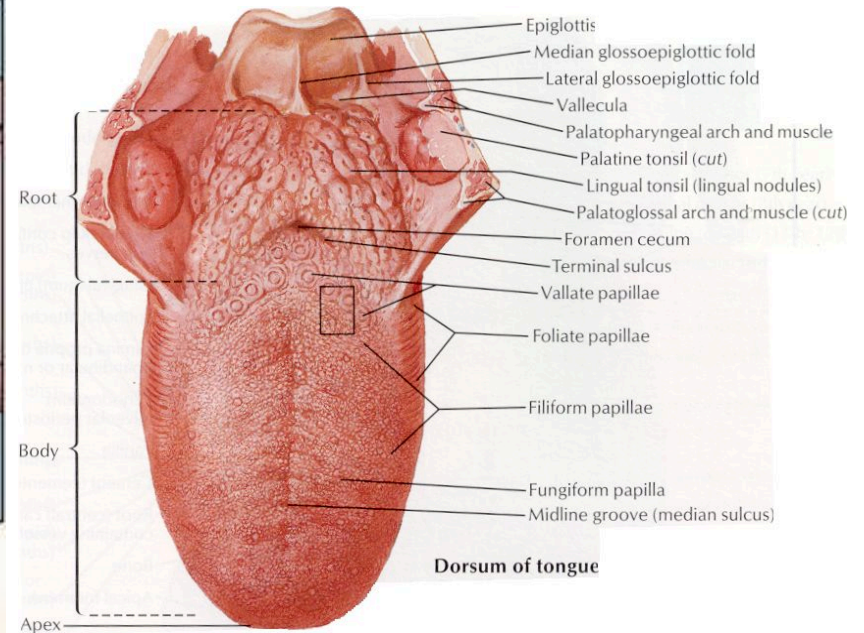
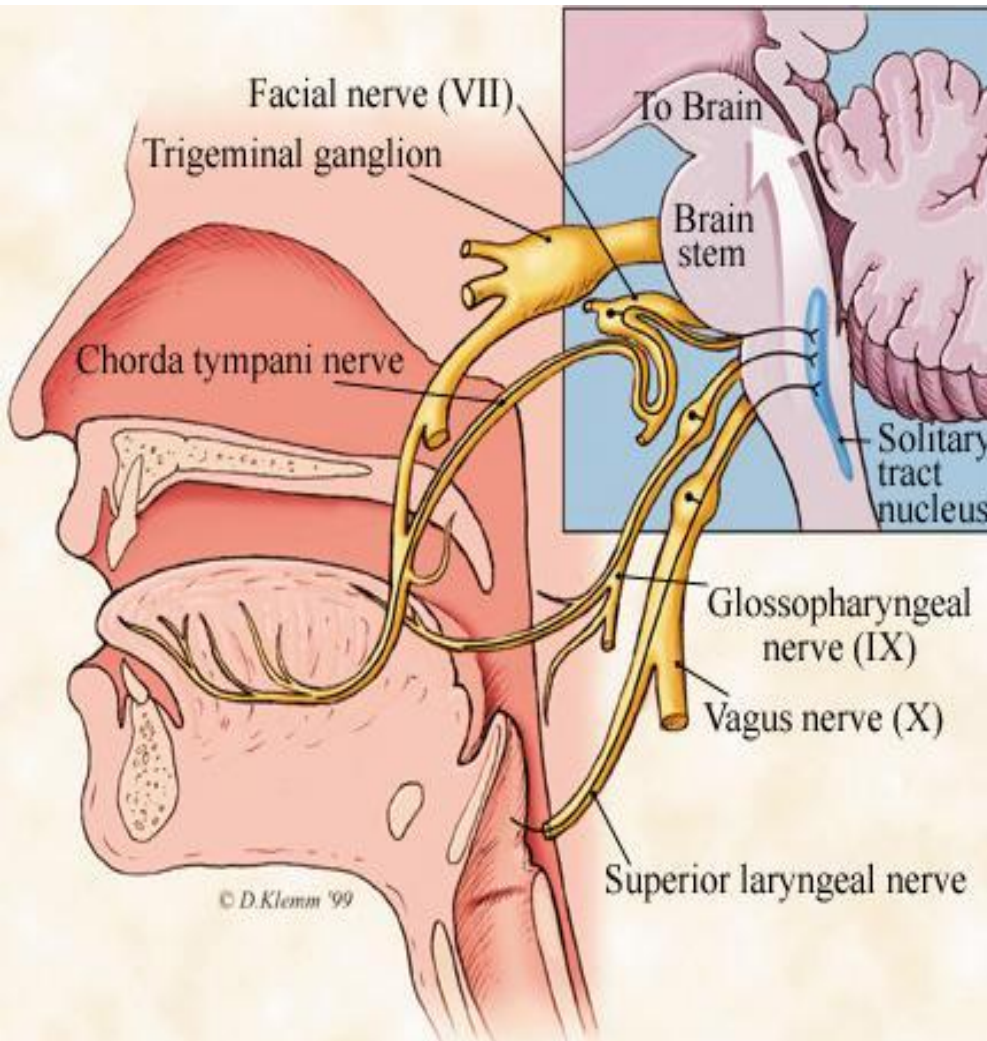
Making Sense of the sweet taste

- Peihua Jiang
- Mount Sinai School of Medicine

Human Taste perception

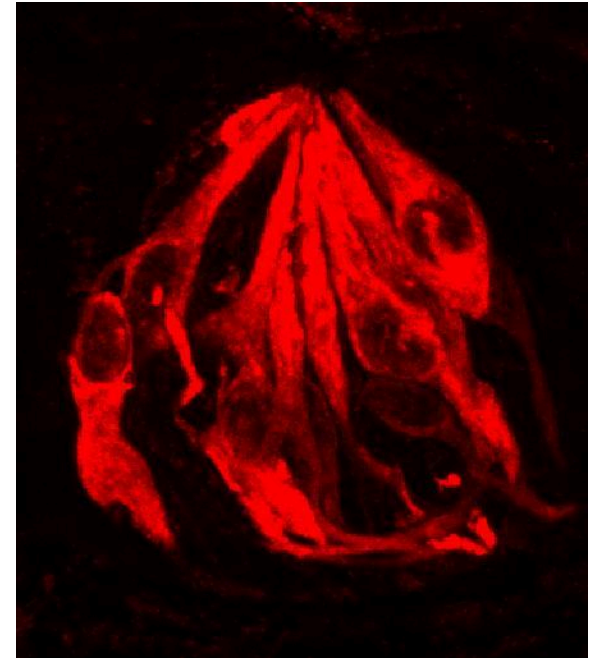
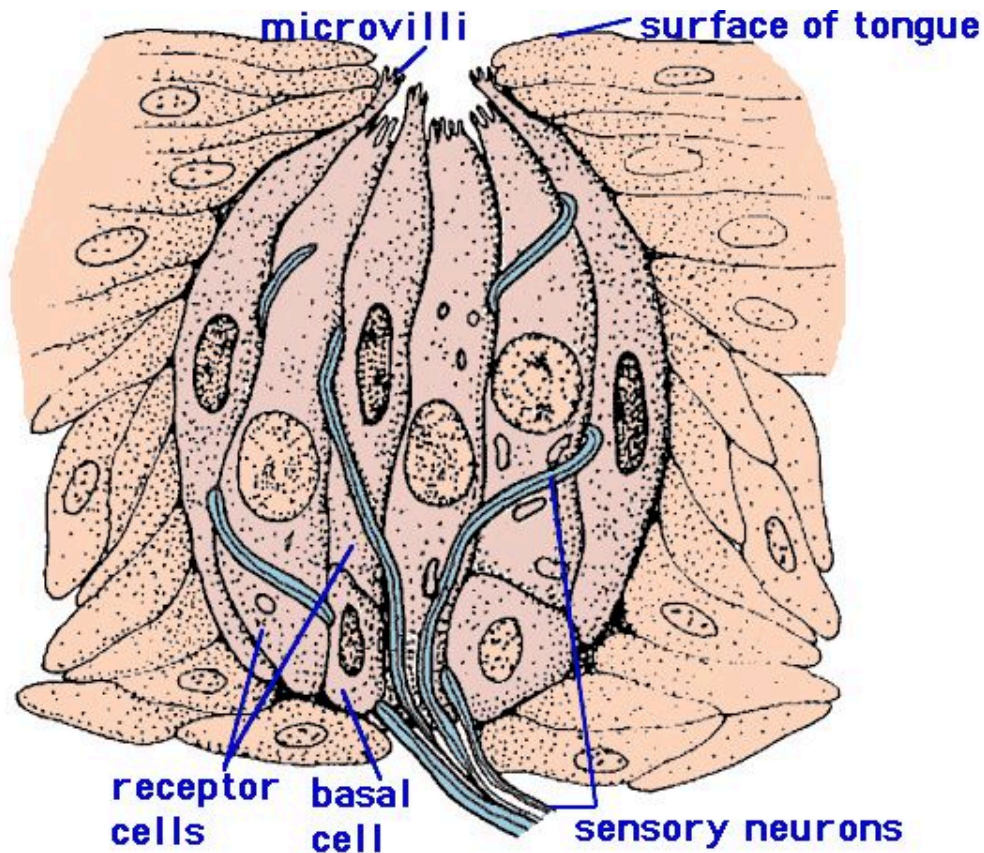
- Sweet
- Bitter
- Sour
- Salty
- Umami (the taste of monosodium glutamate)

Human Taste System



Schematic stereogram: area indicated above

Taste Buds & Receptor Cells

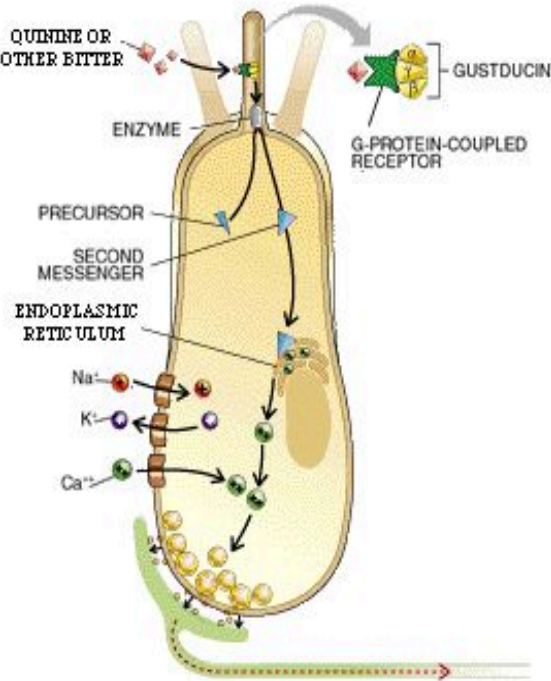


Gustducin immunostaining

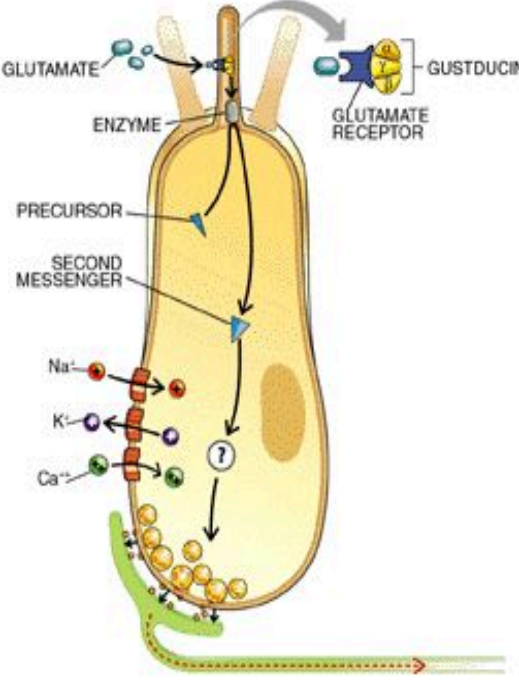
Gustducin, a taste-specific G protein

Mice with deficiency in gustducin show altered response to sugar (sweet) and quinine (bitter)

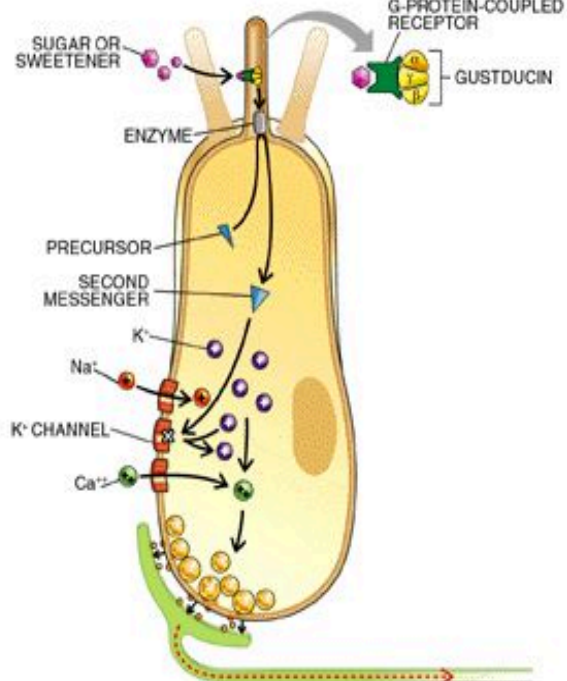
Taste Qualities: Bitter, *Umami* & Sweet



BITTER
Quinine
T2Rs



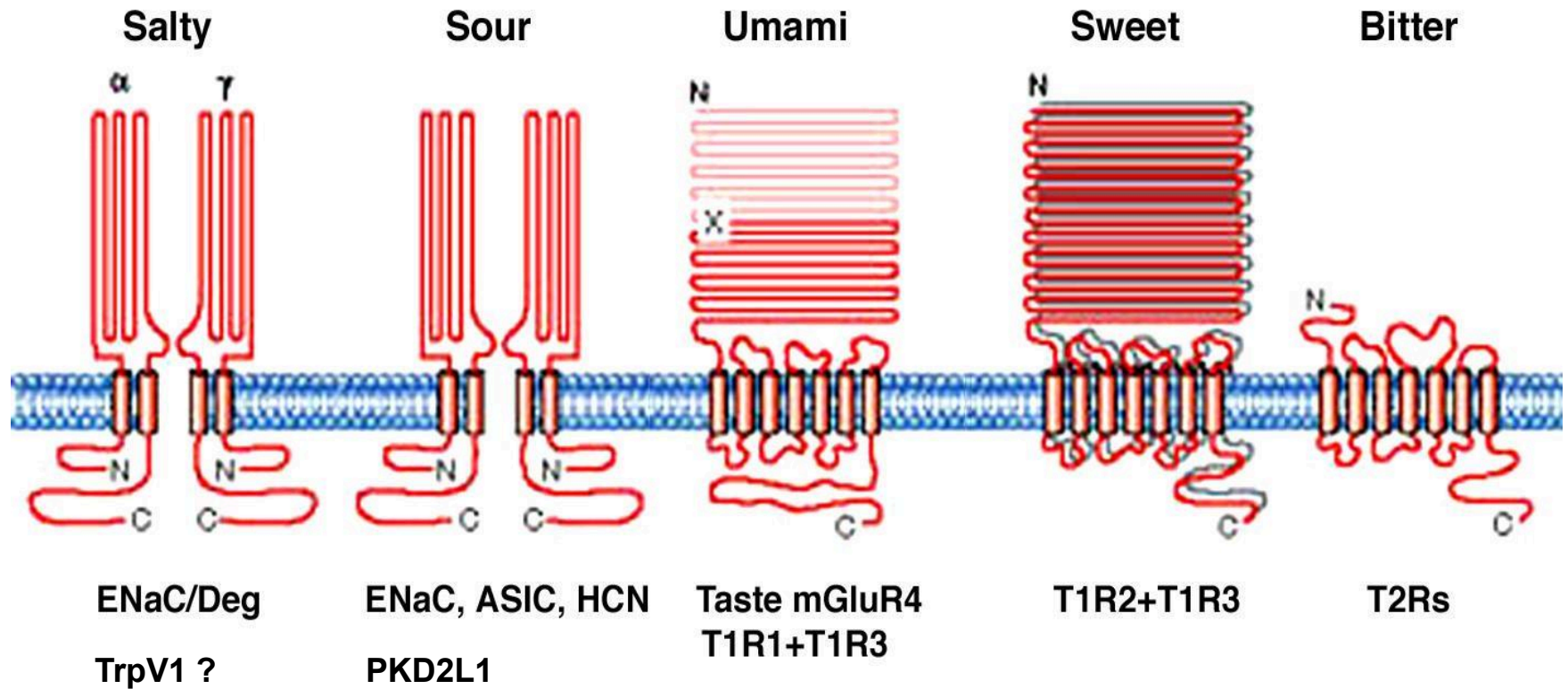
UMAMI
Glutamate
T1R1+T1R3



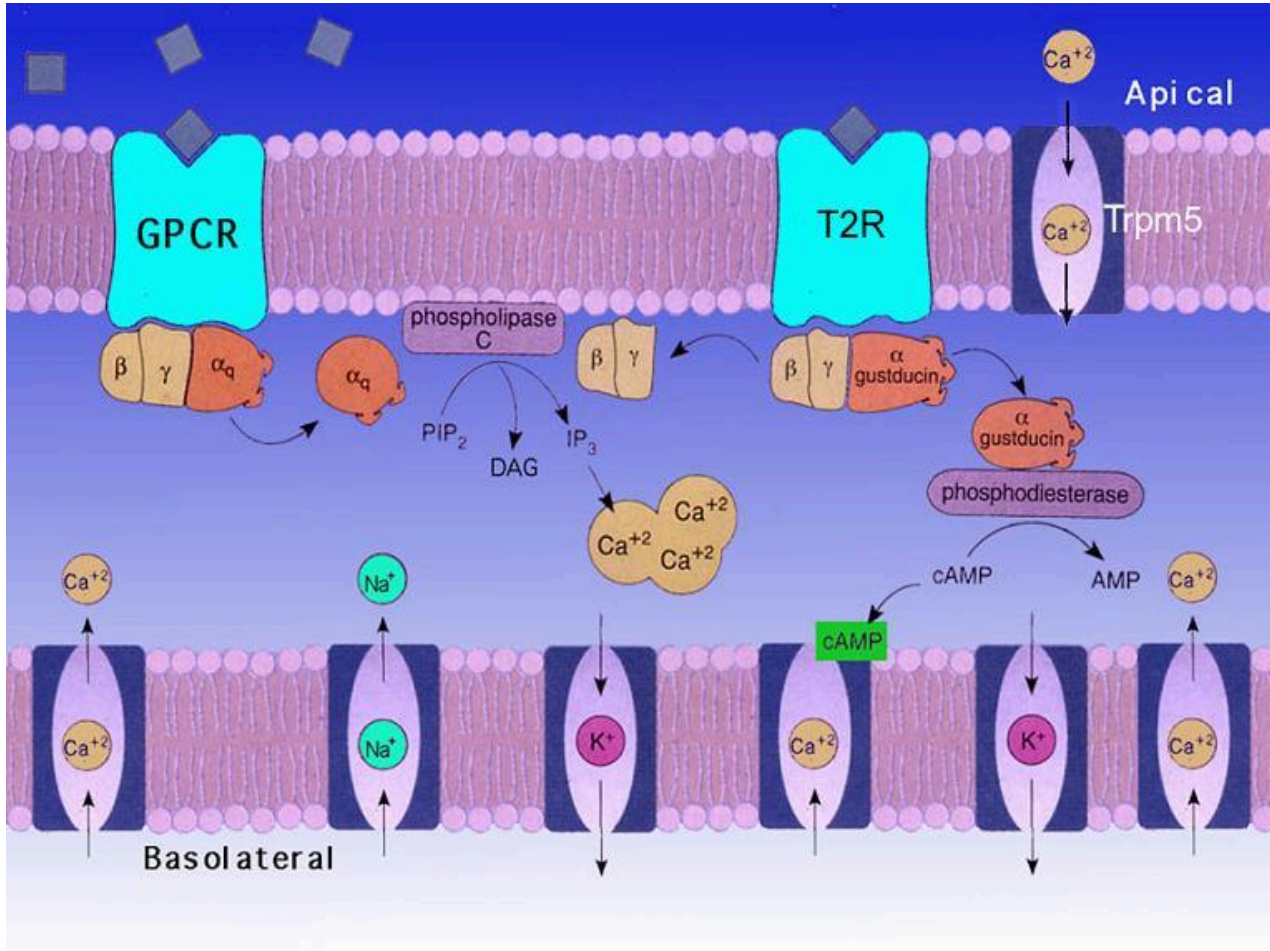
SWEET
Sucrose
T1R2+T1R3

Smith & Margolskee, *Scientific American* 284: 32-39 (2001)

Taste Receptors

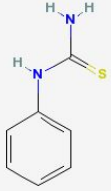


• Bitter Taste Transduction



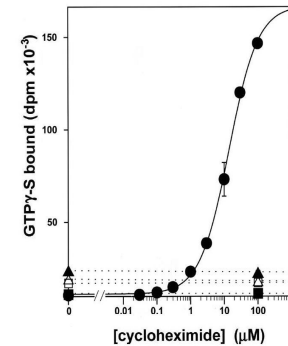
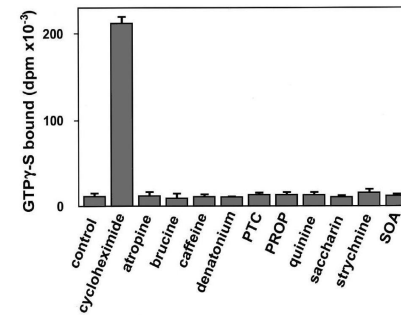
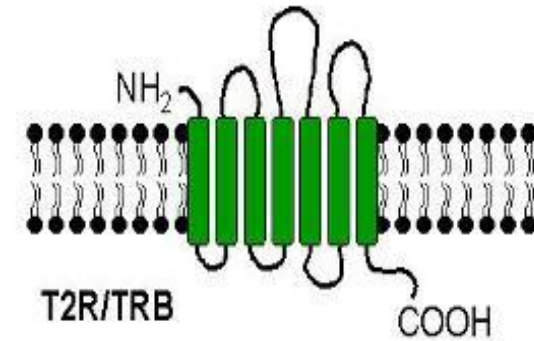
Implicated in Bitter
T2R Receptors
 α -gustducin
Gb3
Gg13
PDE1A
PLCb2
IP₃ Receptor III
Trpm5

T2R Taste Receptors Mediate Bitter Taste



Phenylthiocarbamide (PTC)

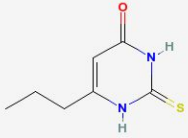
- 7 Transmembrane-helix GPCRs with small extracellular domain
- ~25 member gene family
- Map to 3 bitter-response loci
- 30-70% identity
- Individual taste cells express multiple T2r/Trb receptors
- Co-expressed with gustducin
- mT2r5 selectively couples with gustducin
- mT2r5 specifically responds to bitter cycloheximide



Adler et al., *Cell* 100: 693-702 (2000)

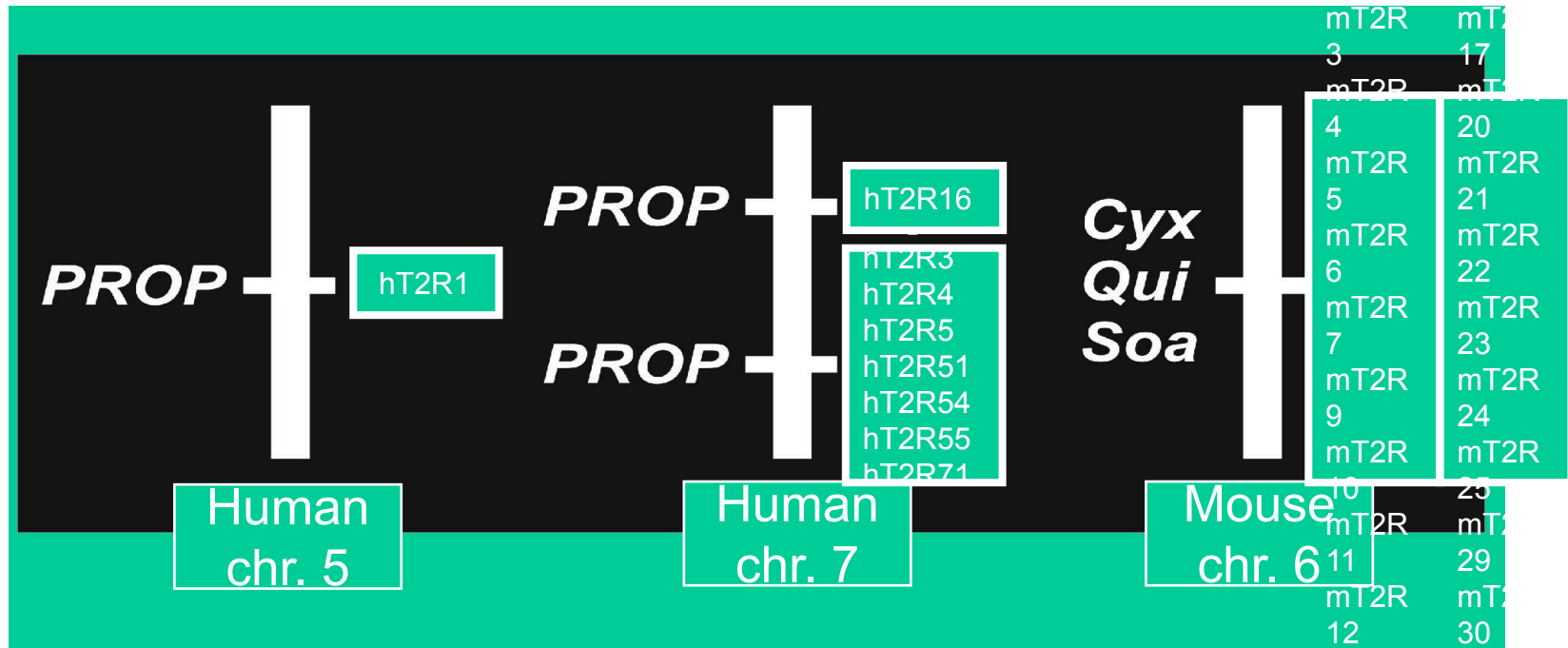
Chandrashekar et al., *Cell* 100: 703-711 (2000)

Montmayeur et al., *Nature* 404: 601-604 (2000)



T2R Genes Map to Bitter Response Loci

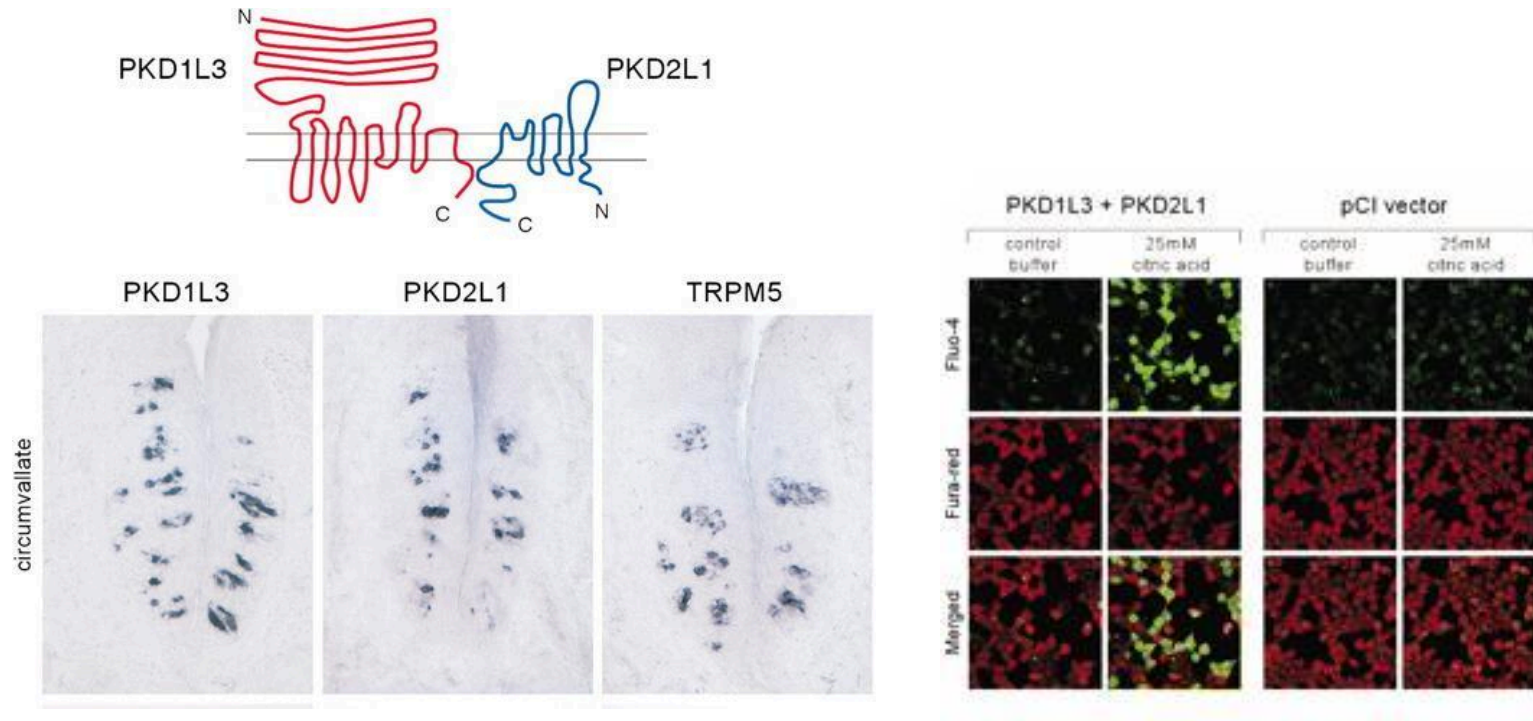
6-n-propyl-2-thiouracil
(PROP)



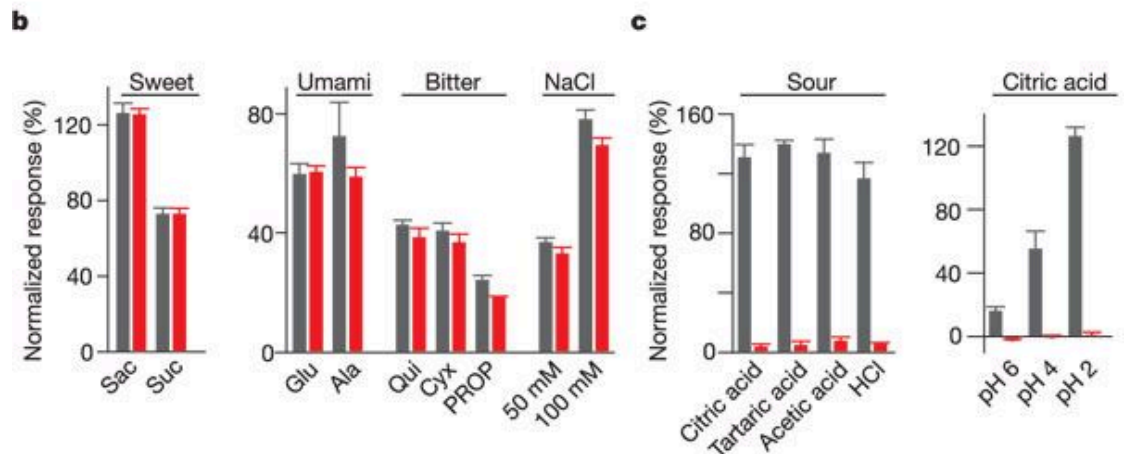
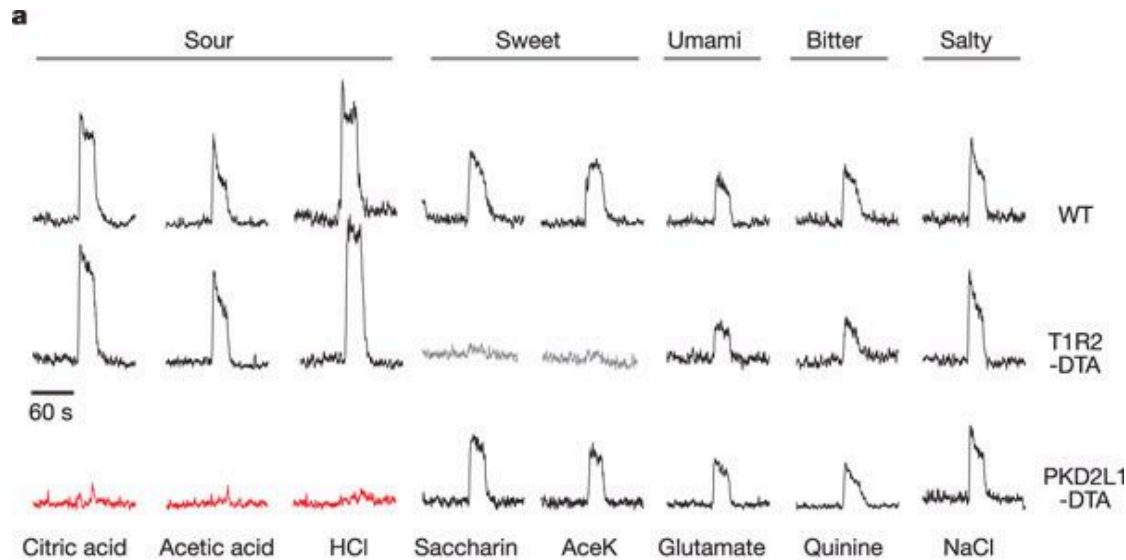
hT2Rs on Human Chr. 5, 7, 12
mT2Rs on Mouse Chr. 6, 15

Adler et al., *Cell* 100, 693-702 (2000)
Chandrashekar et al., *Cell* 100, 703-711 (2000)
Montmayeur et al., *Nature* 404, 601-604 (2000)

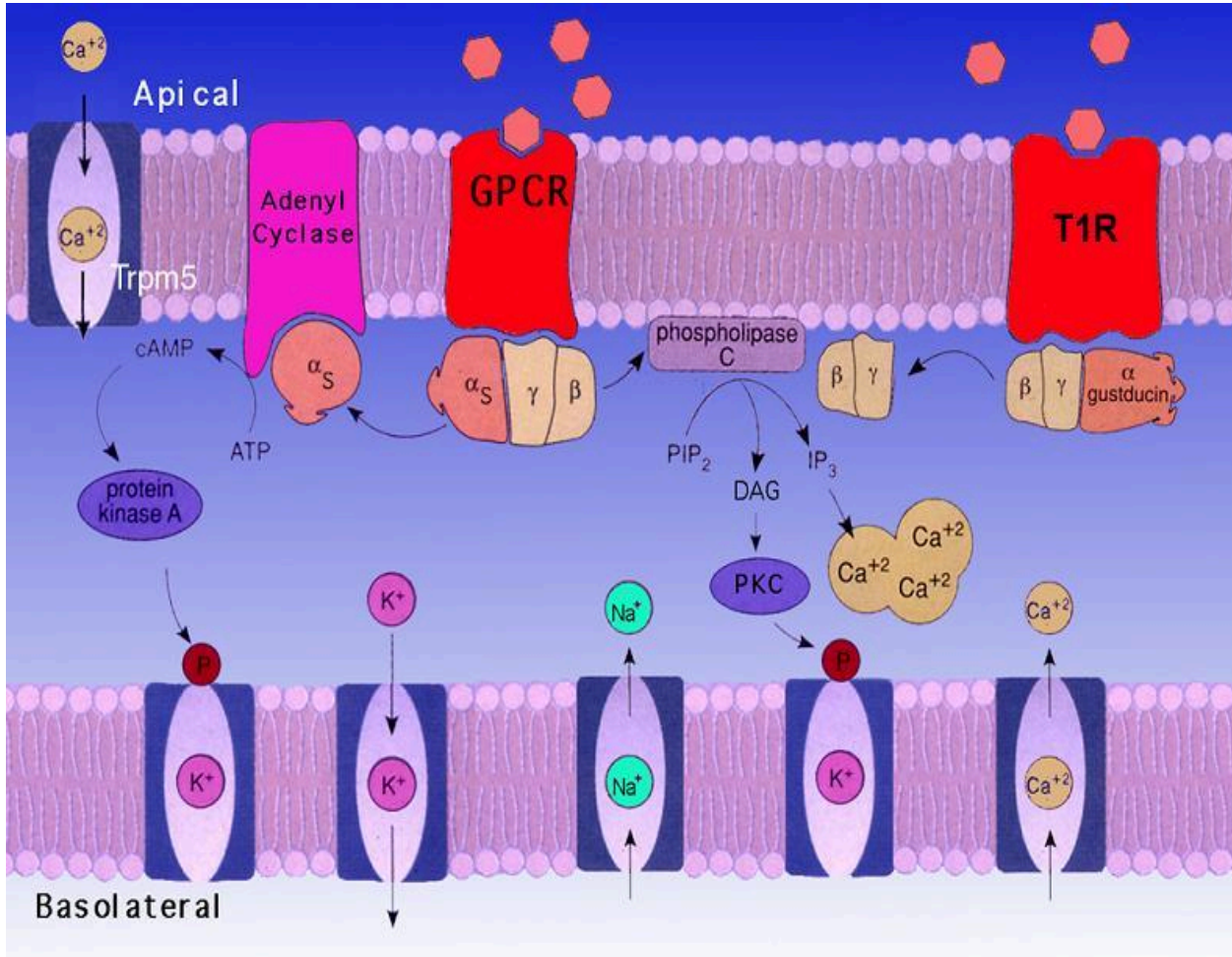
PKD2L1 encodes the sour taste receptor



Introducing toxin to PKD2L1 cells abolished sour taste



• Sweet Taste Transduction



Implicated in Sweet
T1r2 + T1r3
a-gustducin
a-s
adenyl cyclase
PLCb2
IP₃ Receptor III
Trpm5

Sweet Taste Genetics

• Mouse *Sac* Locus

- The major genetic determinant of behavioral preference and nerve responses to saccharin, sucrose and other sweeteners

- Taster strains: C57BL/6J, FVB/N, SWR, ST/bJ

- Non-tasters: 129, DBA/2, C3H/He, BALB/c

- Acts peripherally

- Maps to distal end of mouse chromosome 4

- Closest marker: *D18346*

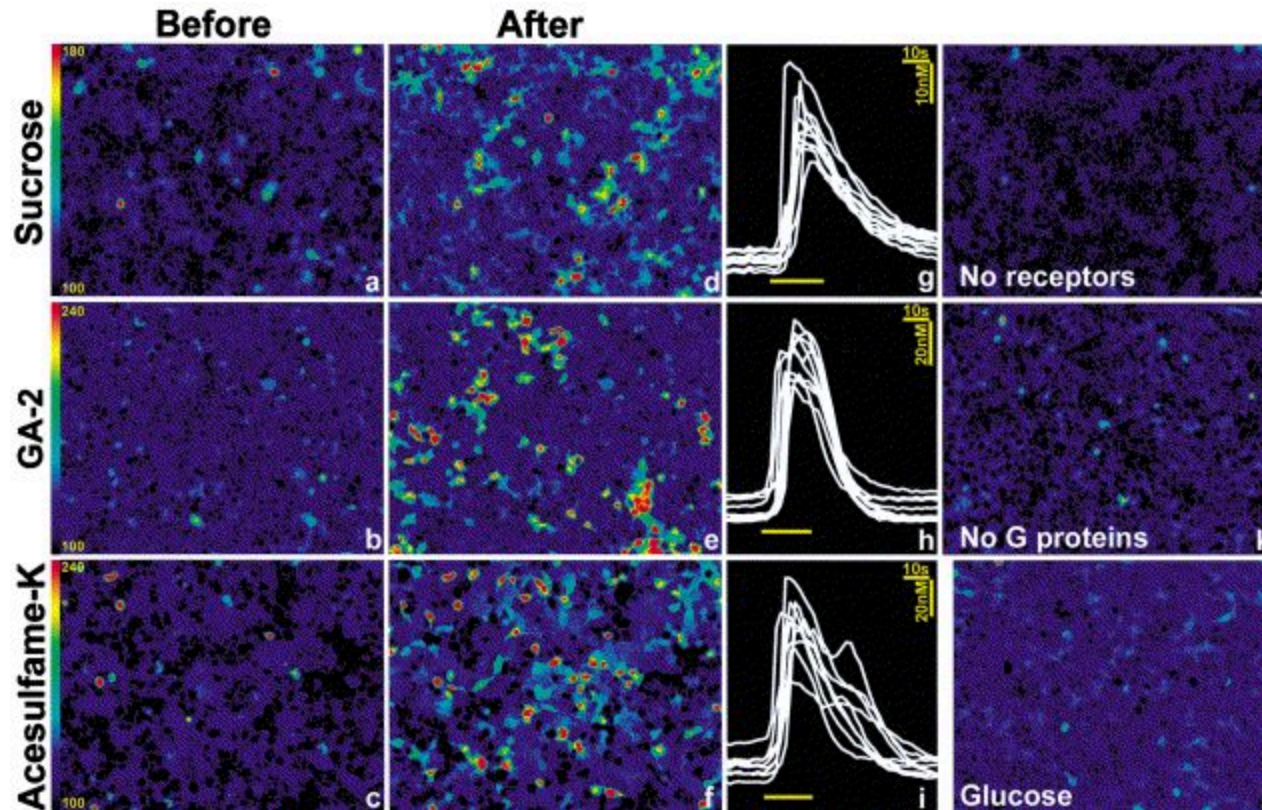
Fuller, *J Heredity* 65: 33-36 (1974)

Lush, *Genetic Research* 53: 95-99 (1989)

Bachmanov et al., *Mammalian Genome* 8: 545-548 (1997)

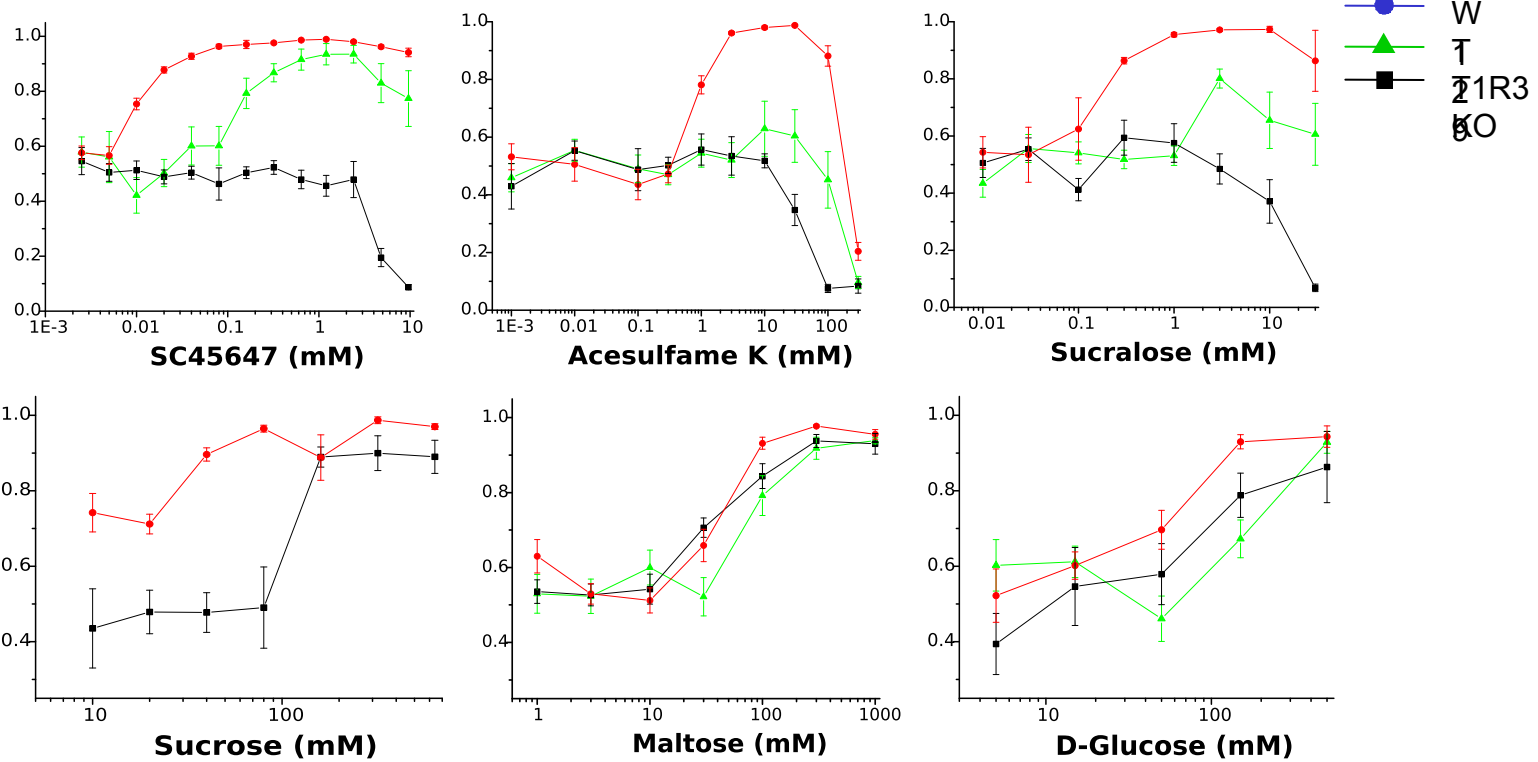
Li et al., *Mammal Genome* 12: 13-16 (2001)

T1R2+3 Responds to Sweet Tastants

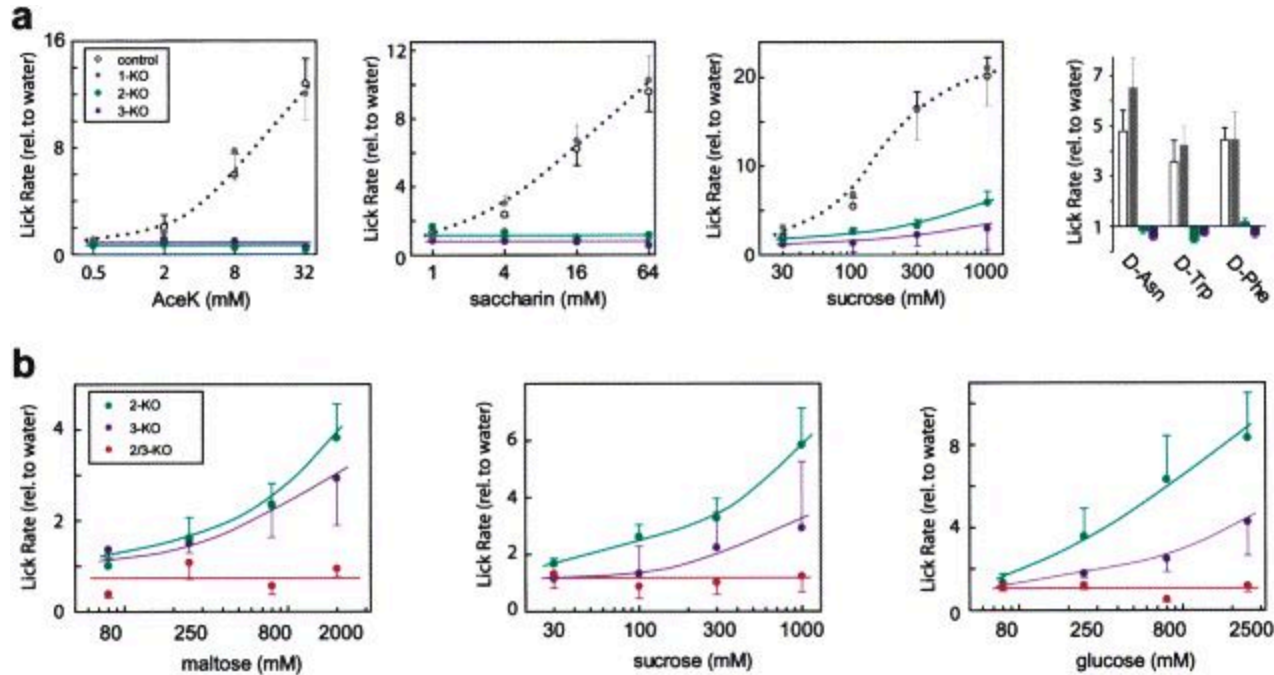


Nelson et al., Cell 106:381-90, 2001

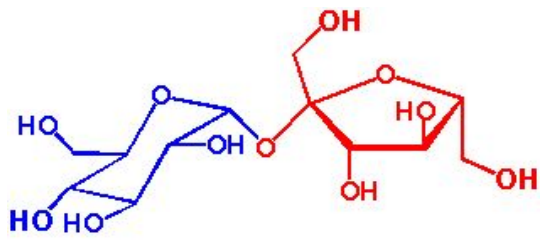
T1r3 KO Mice Show Diminished Preference and Nerve Responses for Sweeteners in T1R3 Deficient Mice



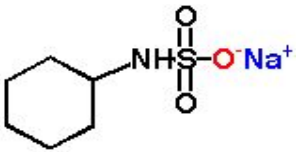
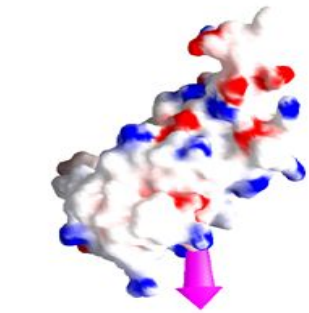
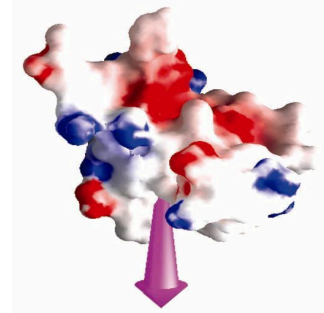
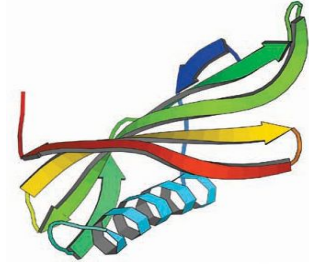
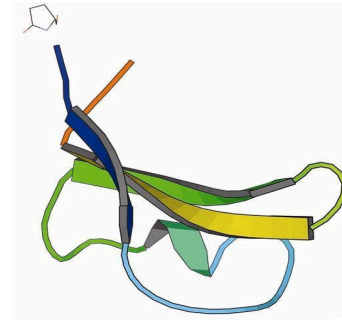
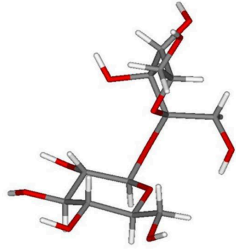
T1R2,3 Knockout Mice Show a Complete Loss in their Preference for Sweet Compounds



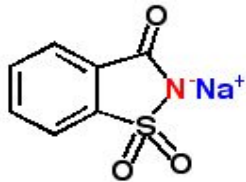
Diverse Compounds are Sweet



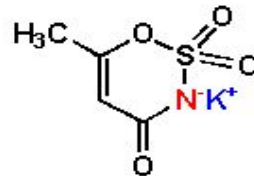
Sucrose



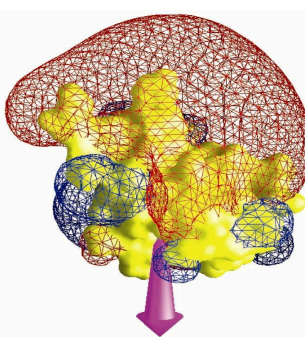
Cyclamate



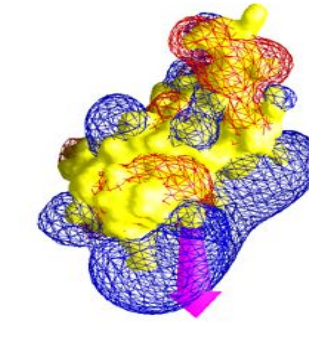
Saccharin



Acesulfame K

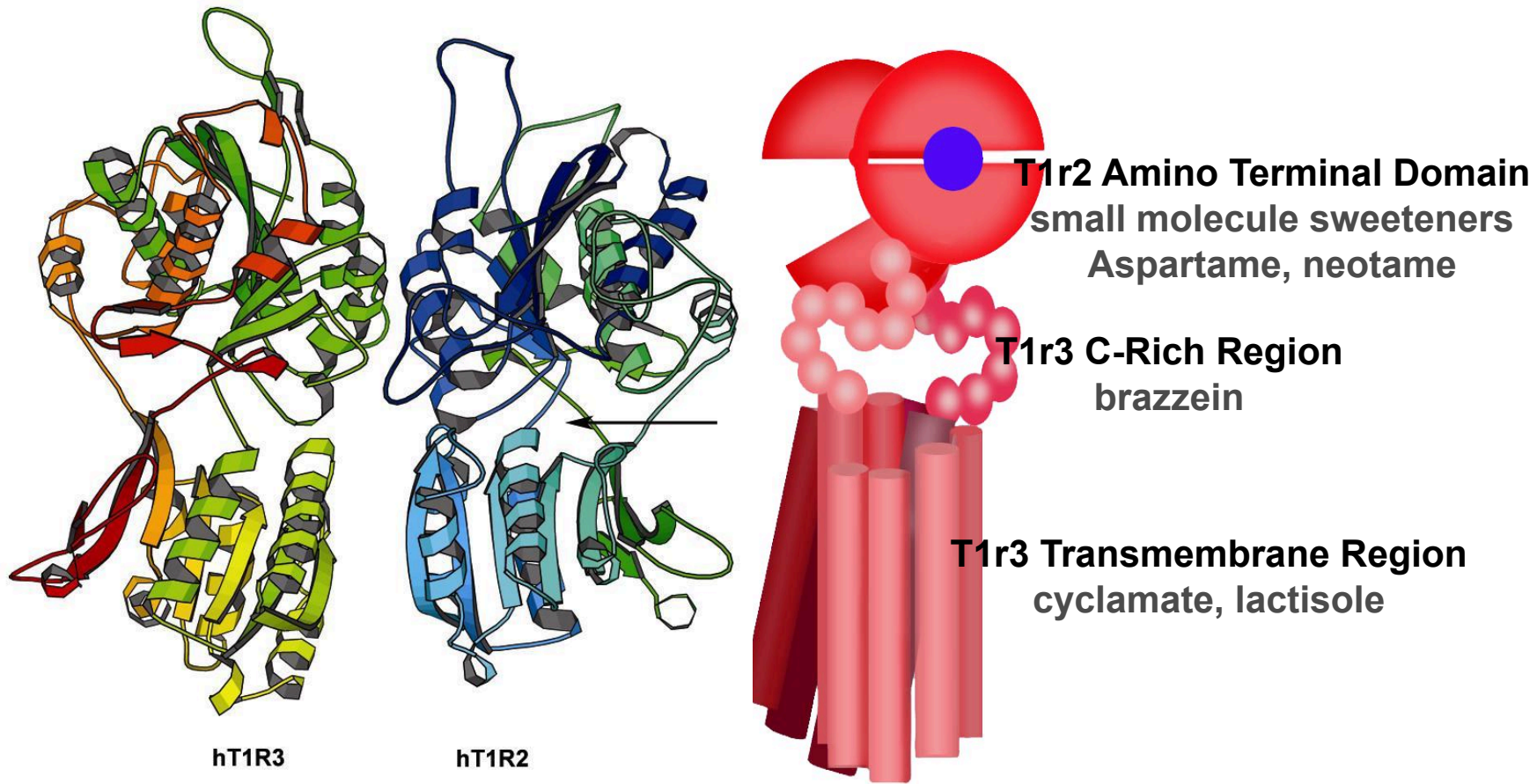


Brazzein

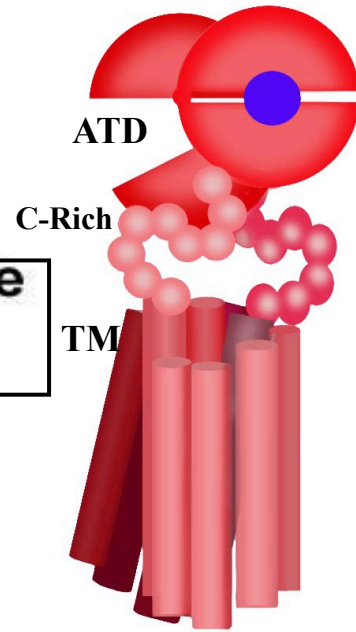
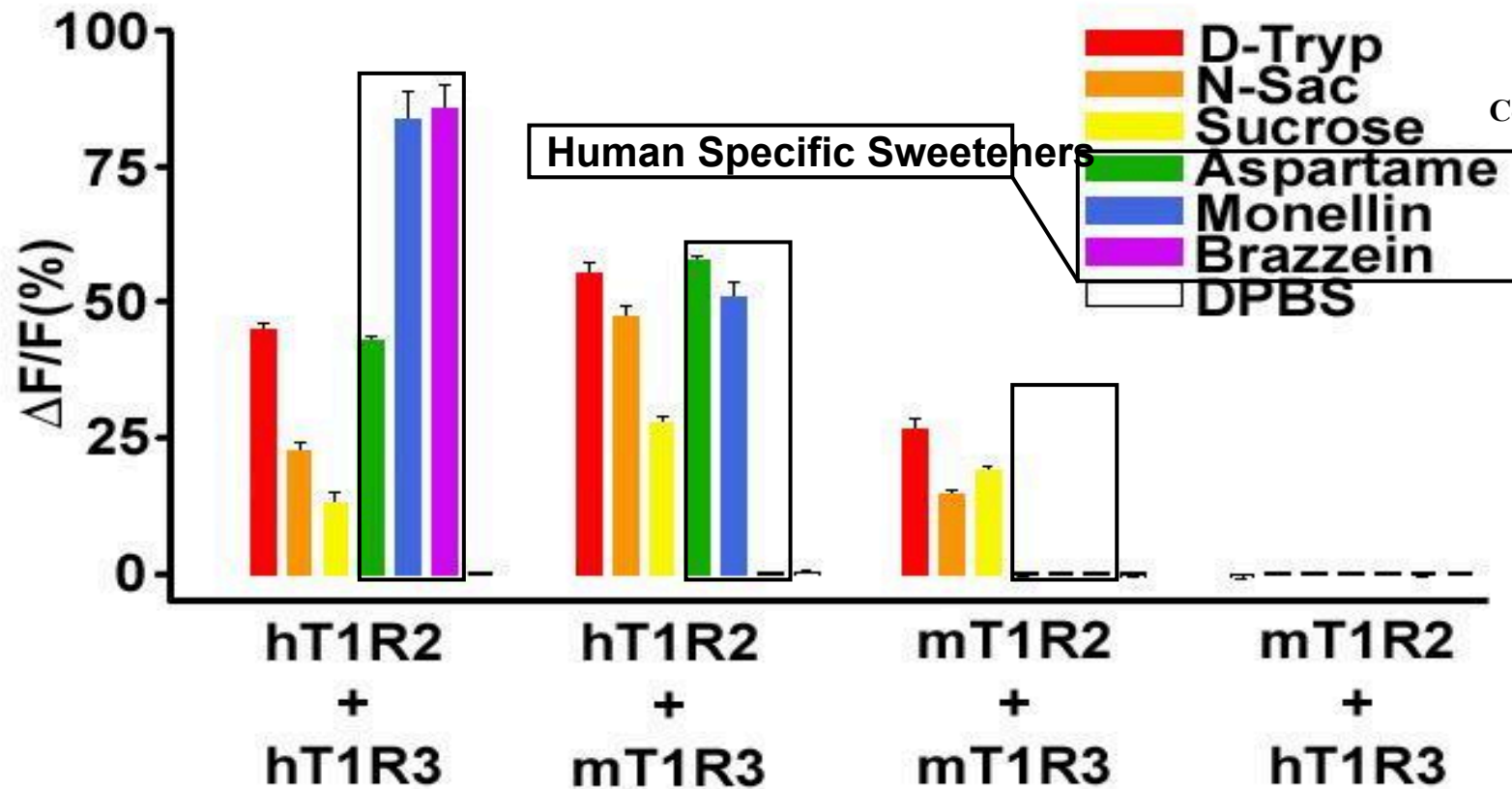


Monellin

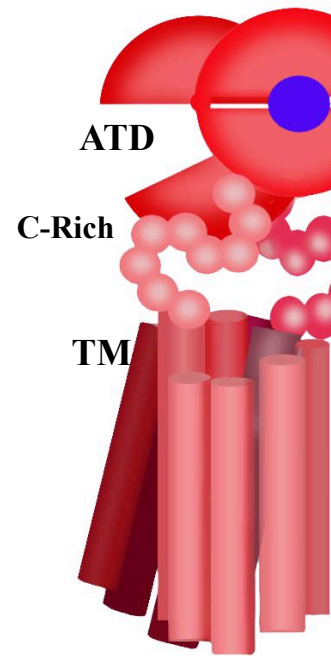
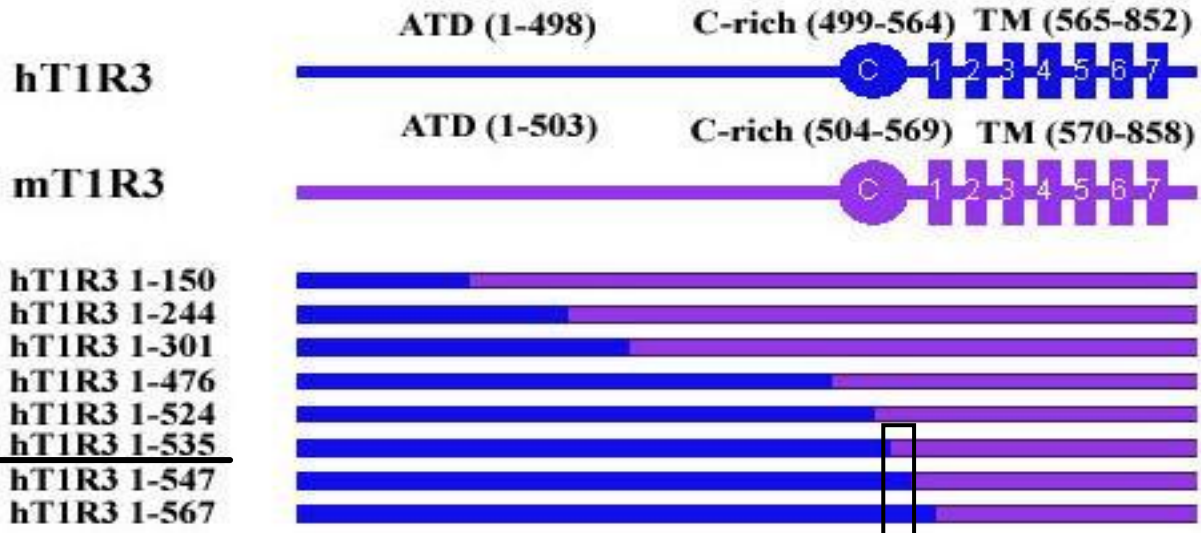
Multiple Regions of T1R2+T1R3 are Required for Effective Interaction with Different Sweet Compounds



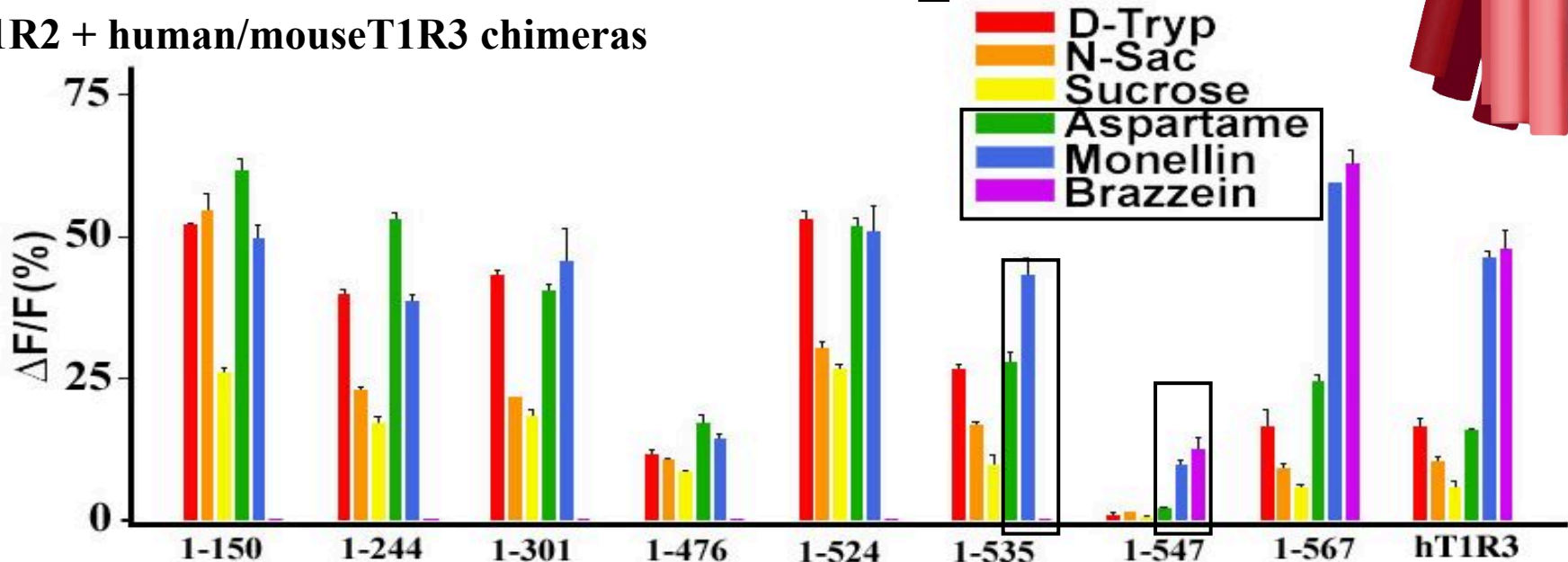
Heterodimerized T1R2 + T1R3 Form a Sweet Receptor



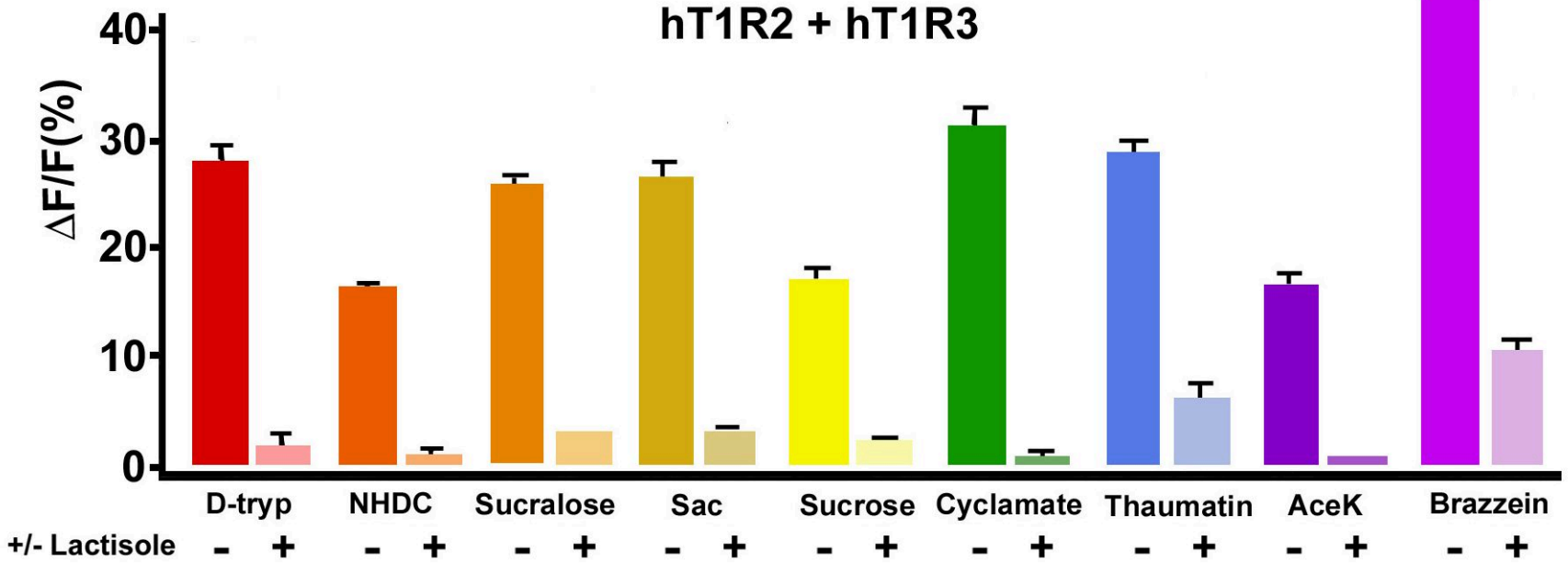
The C-Rich Region of T1R3 Determines Sensitivity to Brazzein



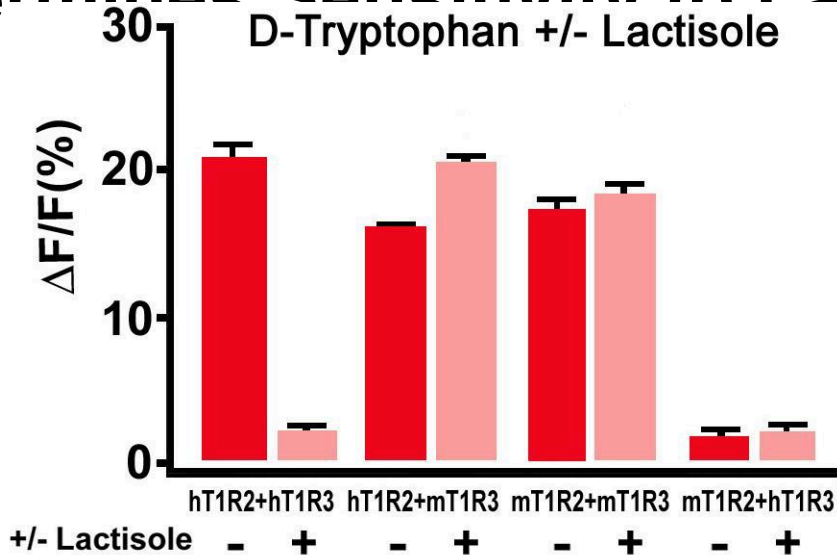
hT1R2 + human/mouse T1R3 chimeras



Human T1R2 + T1R3 is Inhibited by Lactisole



hT1R3 Determines Sensitivity to Lactisole

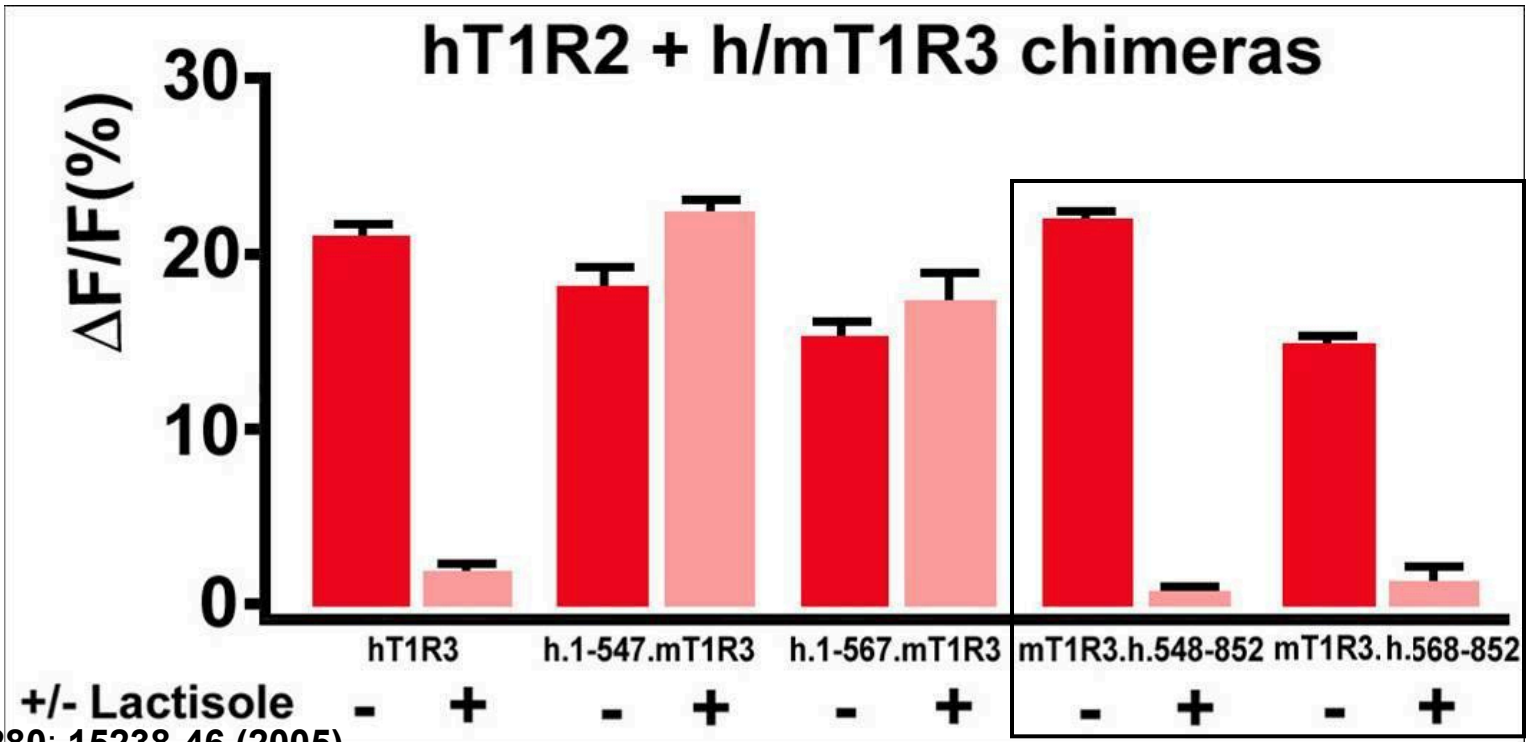


hT1R3's TM Domain Determines Sensitivity to Lactisole

ATD(1-498)

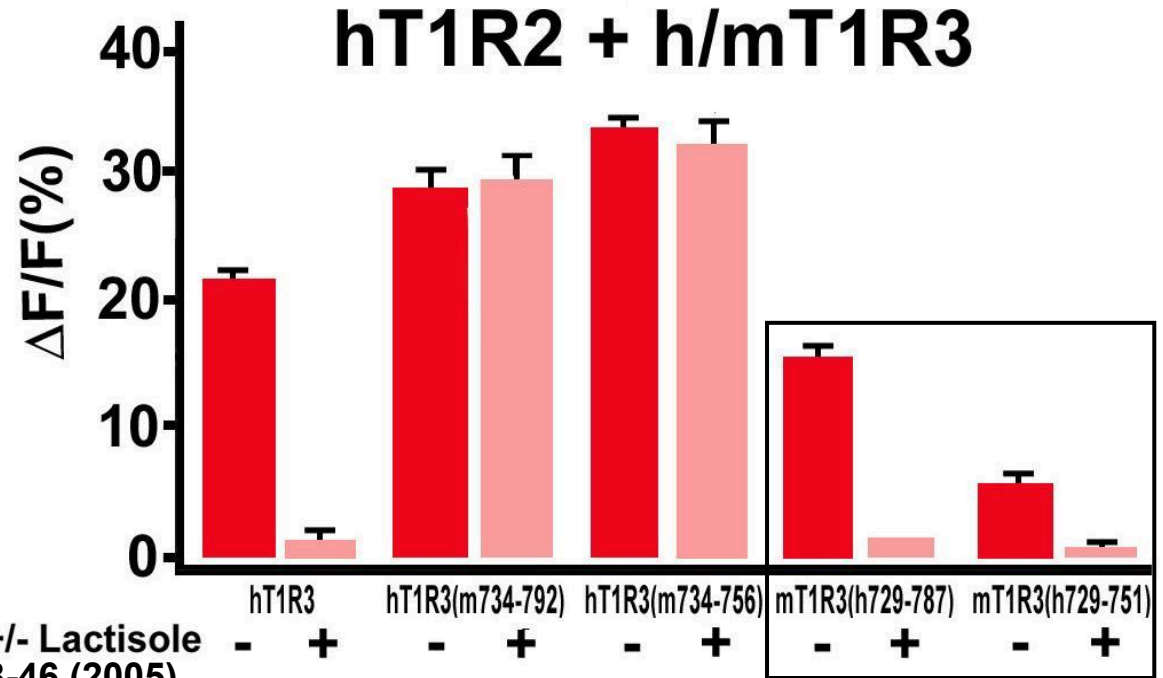
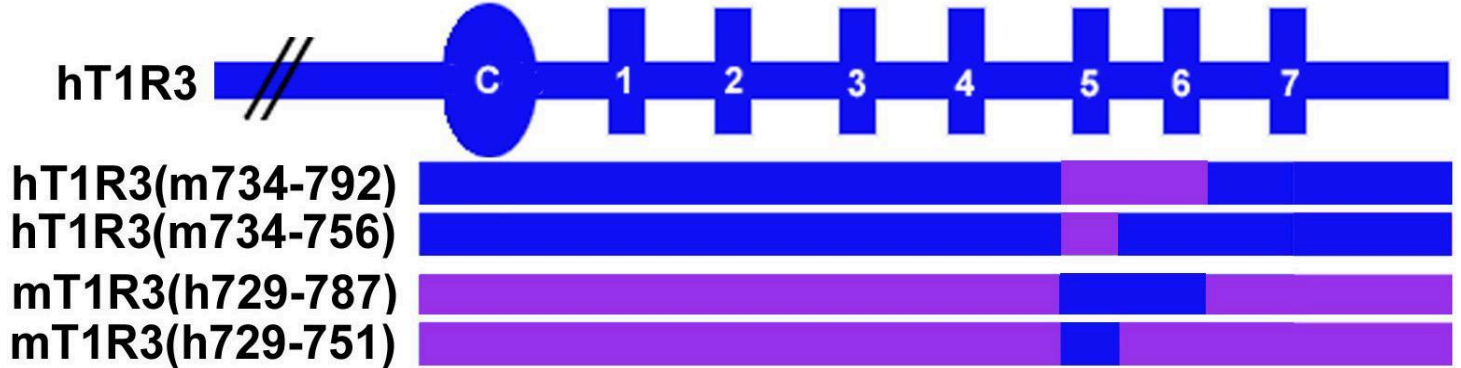
C-Rich(499-564)

TM(564-852)



T1R3 TM Helices 5 & 6 Determine Sensitivity to Lactis

ATD(1-498) C-Rich(499-564) TM(564-852)



Jiang et al., *JBC* 280: 15238-46 (2005)

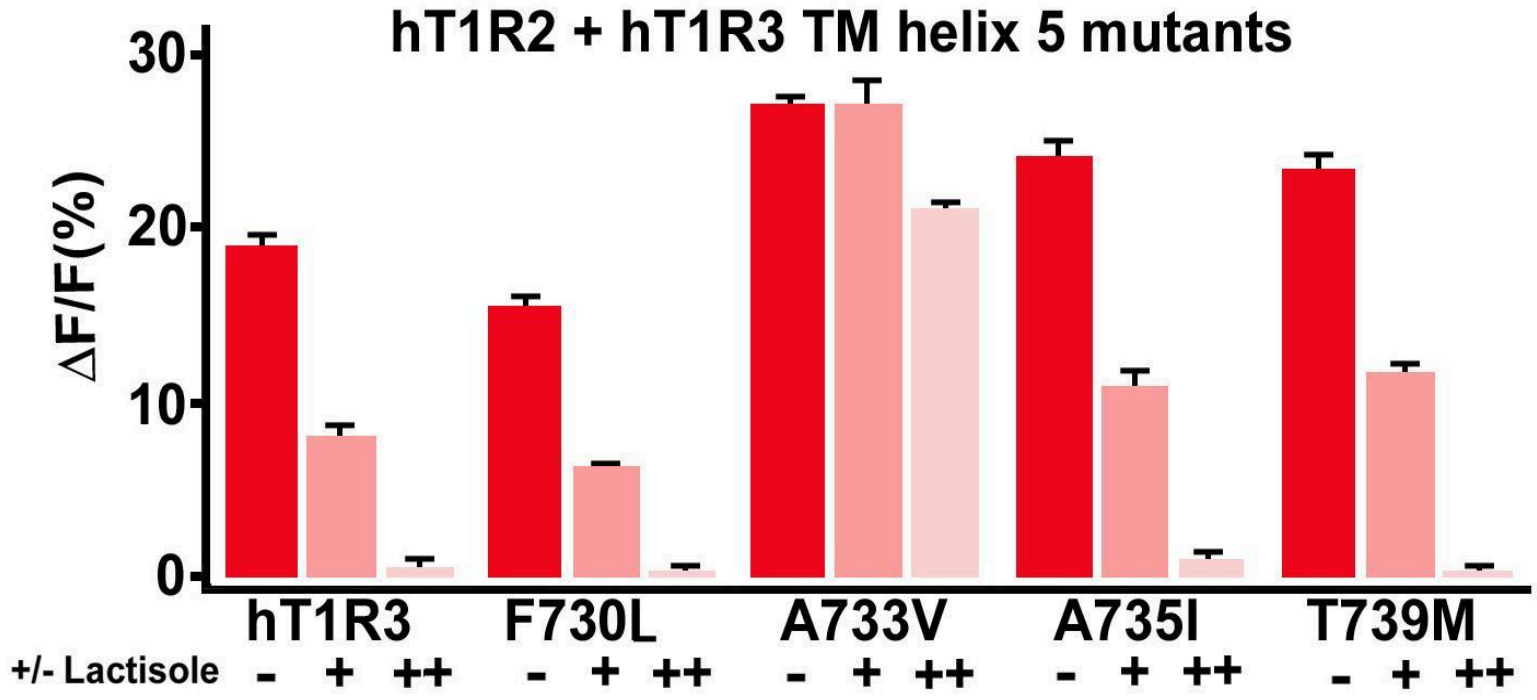
A733 in TM Helix 5 Determines Sensitivity to Lactisole

TM helix 5

Consensus ⁷²⁵ RSWVS-GL-H-TNA-LAFLCFLGTFL

Human T1R3F..A..A...T.....

Mouse T1R3L..V..I...M.....



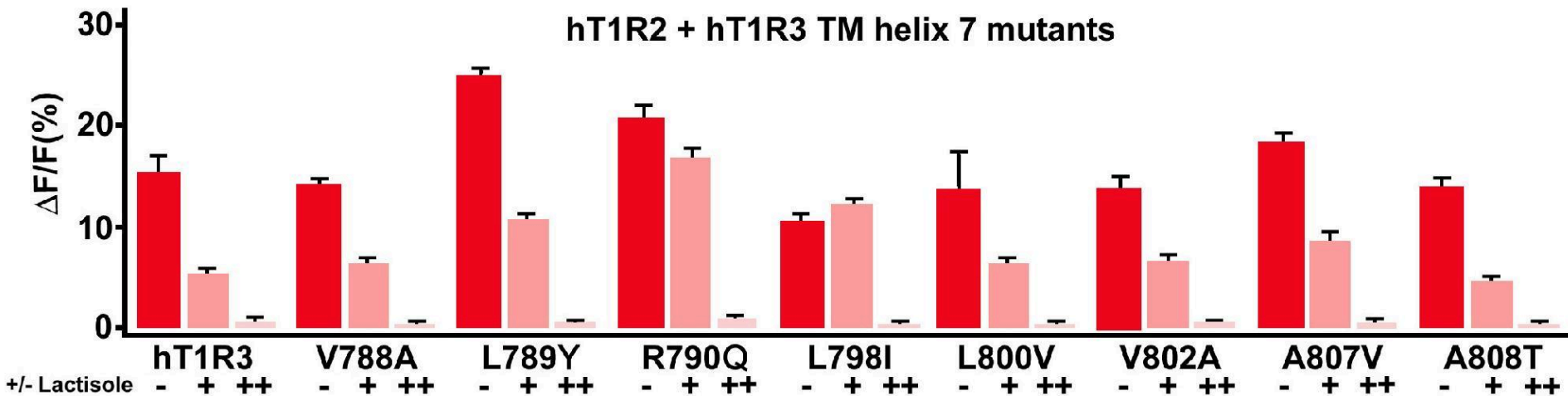
R790 in Extracellular Loop 3 & L798 in TM Helix 7 Determine Sensitivity to Lactisole

EX3 / TM helix 7

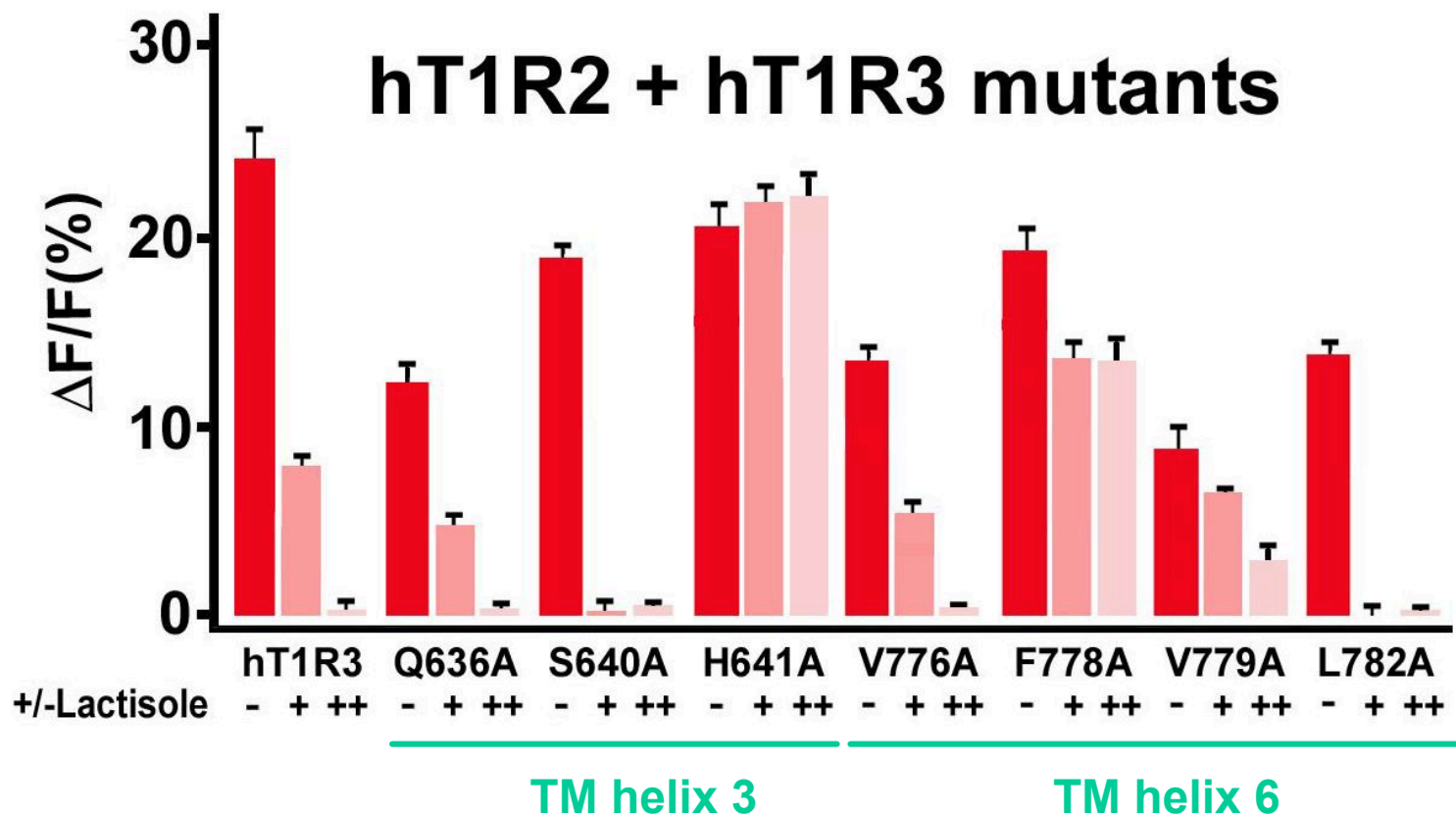
Consensus ⁷⁸⁷ V - - - PAVQMGA - L - C - LGIL - - F

Human T1R3 . VLR L . L . V AA .

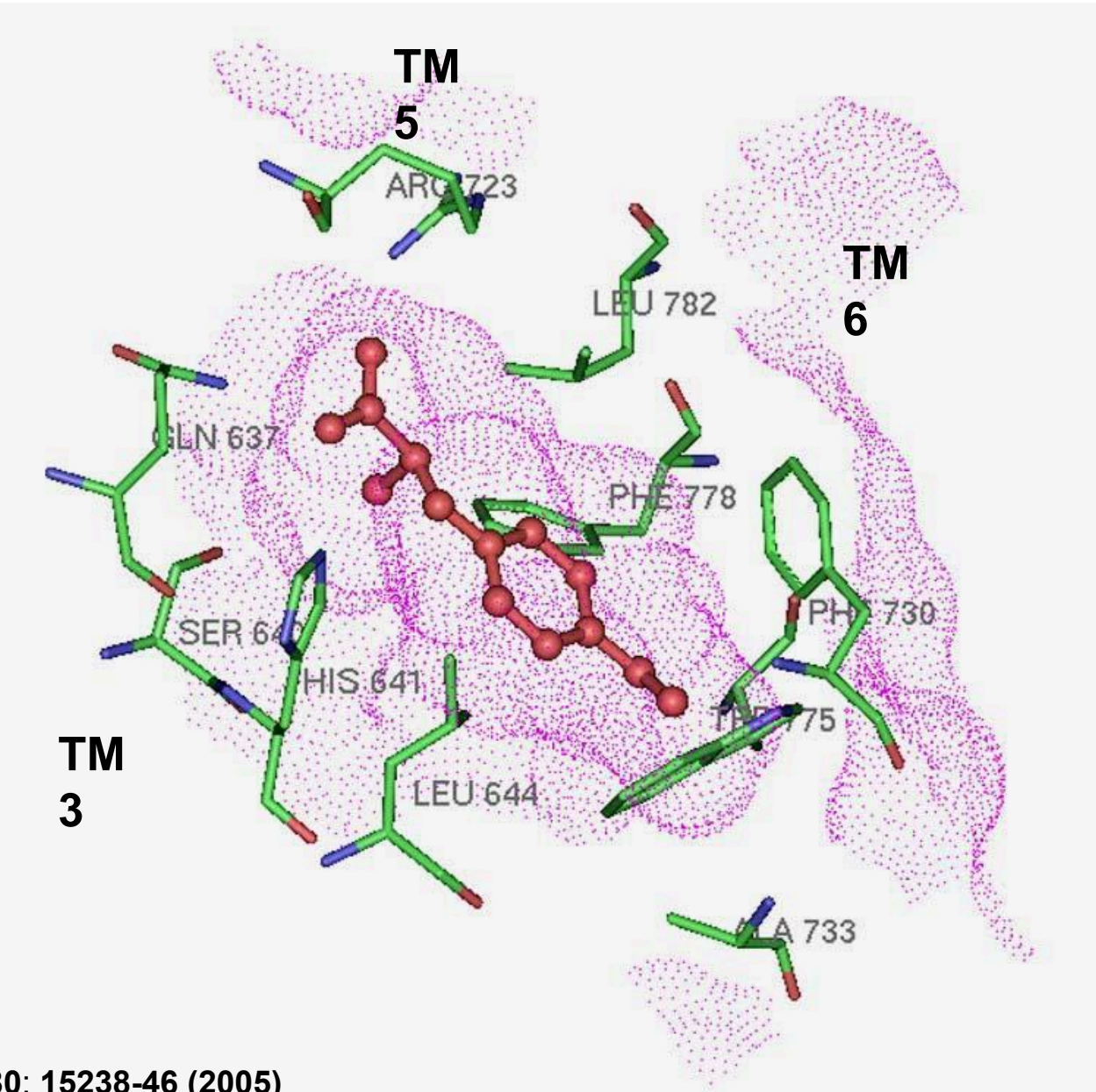
Mouse T1R3 . AYQ I . V . A VT .



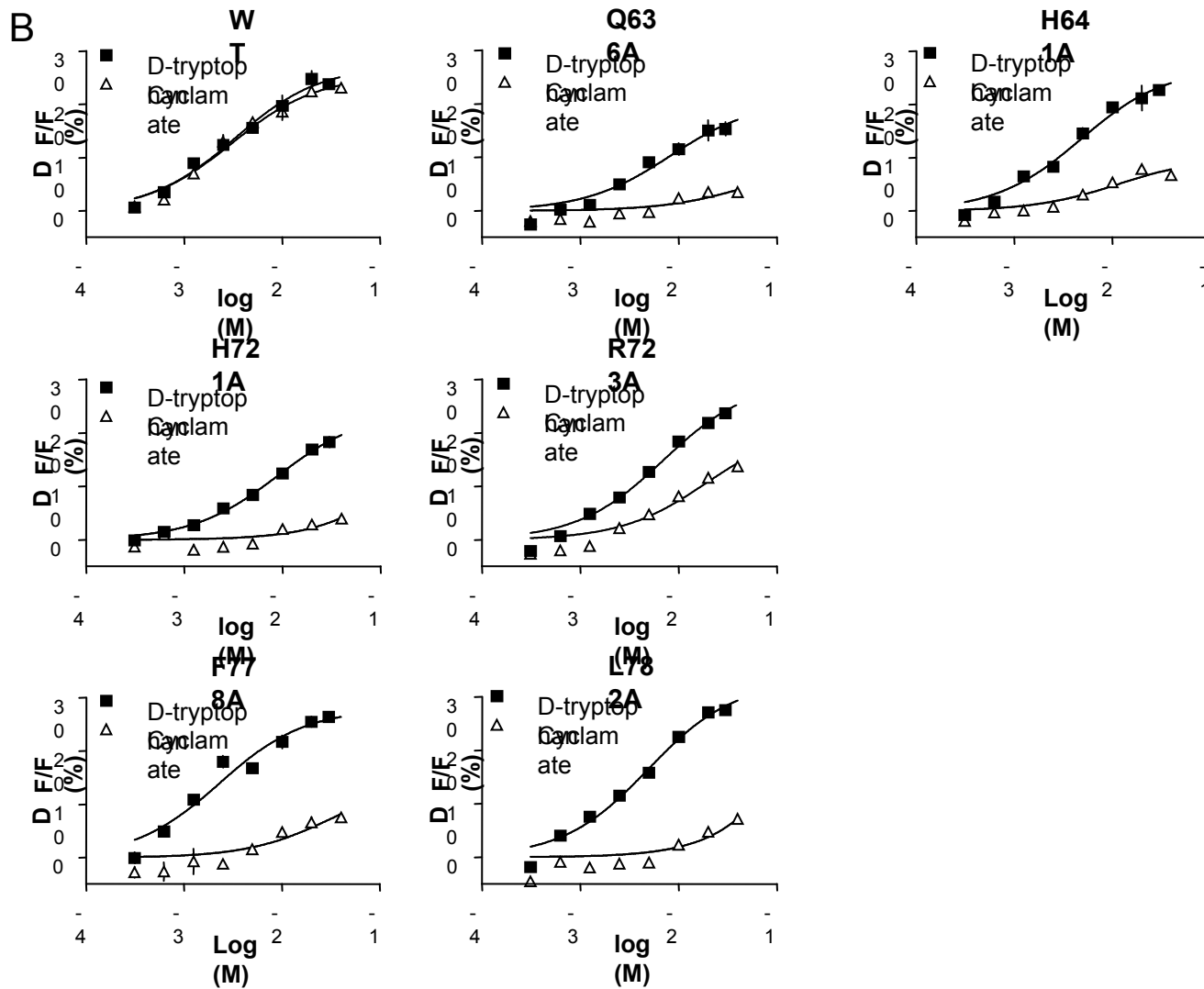
S640 & H641 in TM Helix 3 and F778 & L782 in TM Helix 6 Determine Sensitivity to Lactisole



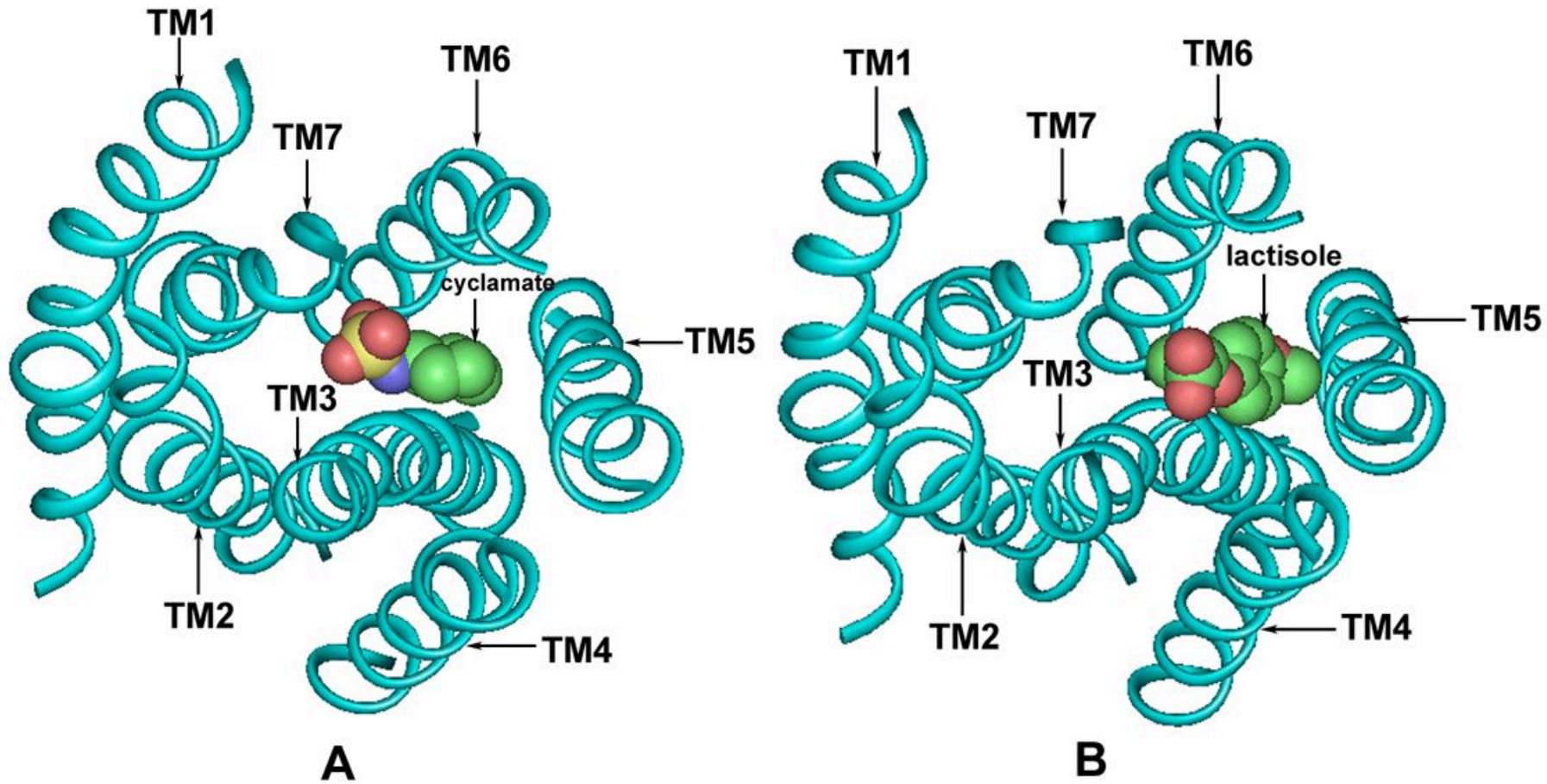
Model of the Lactisole Binding Pocket of hT1R3



Cyclamate binds to TMD of hT1R3



Transmembrane Domain Binding Pocket of hT1R3



Jiang et al., *JBC* 280: 15238-46
(2005)

Two sweeteners better than one -sweet synergy

- synergistic effect observed for some sweeteners
 - Aspartame + Acek
 - Saccharin + cyclamate

Acknowledges

- Dr. Robert F. Margolskee
- Dr. Marianna Max
- Dr. Meng Cui
- Dr. Roman Osman
- Supported by NIH and Revson Foundation