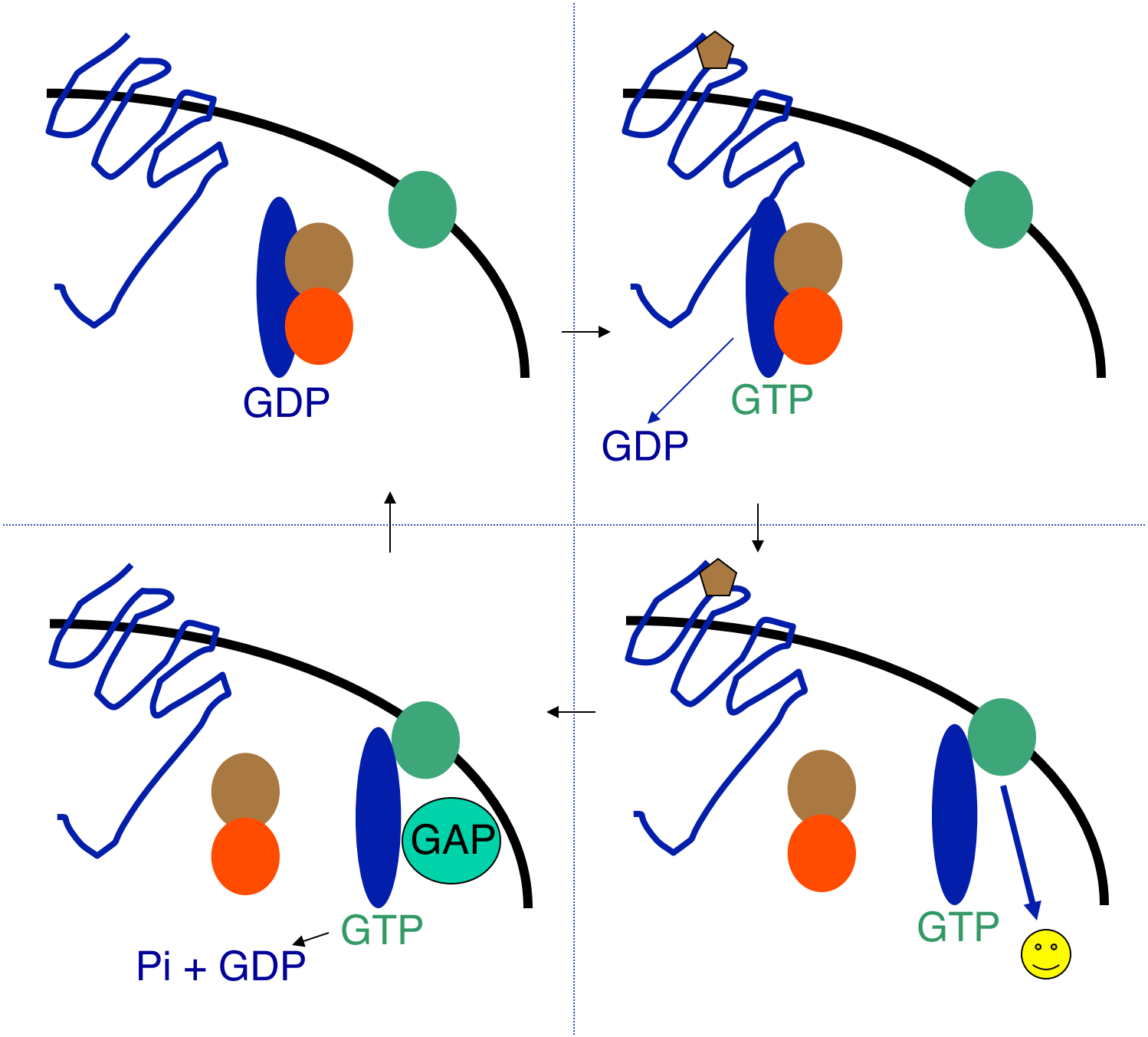
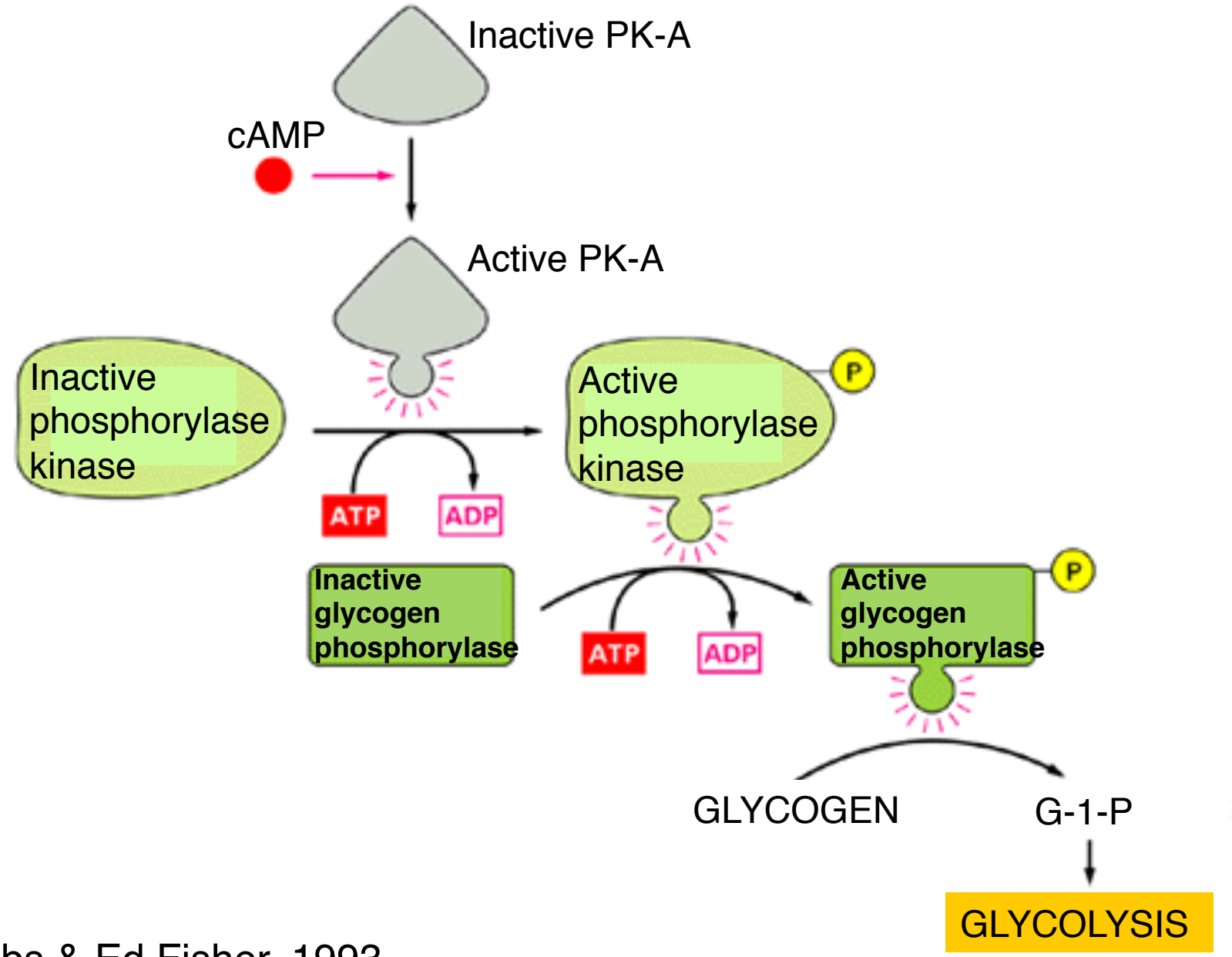
Cell signaling IV.

Serpentine receptors activate a wide variety of signal transduction pathways

Activation of serpentine receptors and GTPase cycle of G-proteins

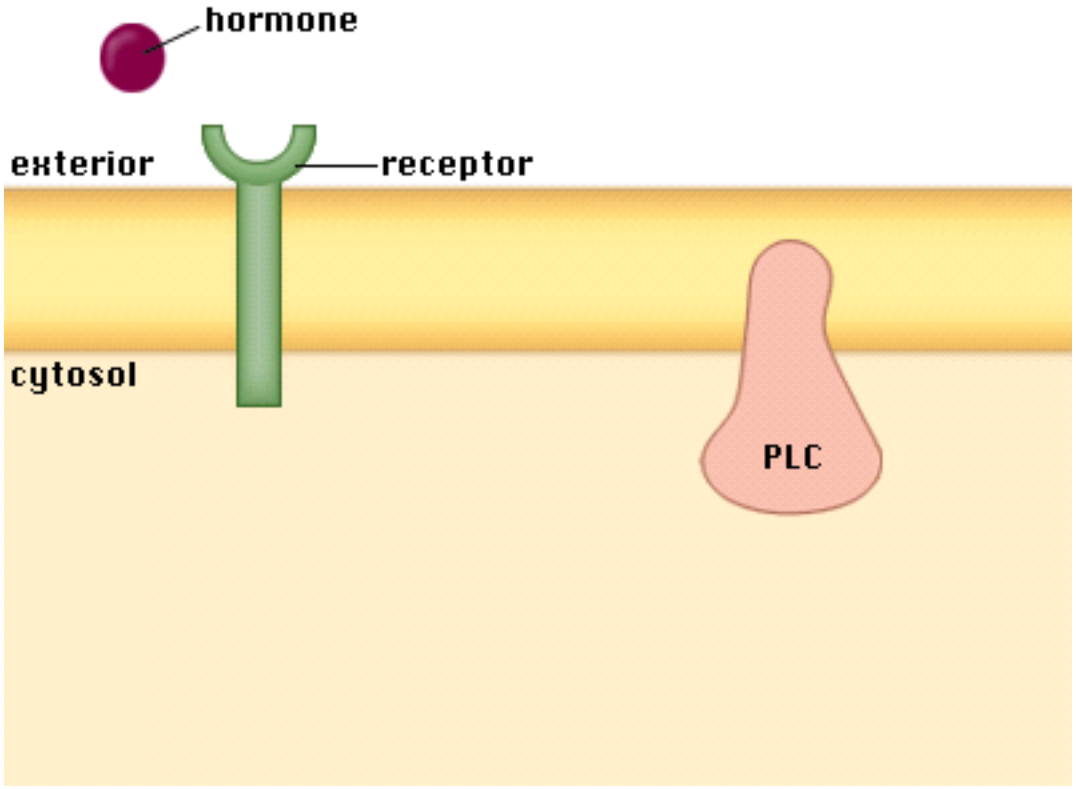


Nobel prize winning signaling cascade

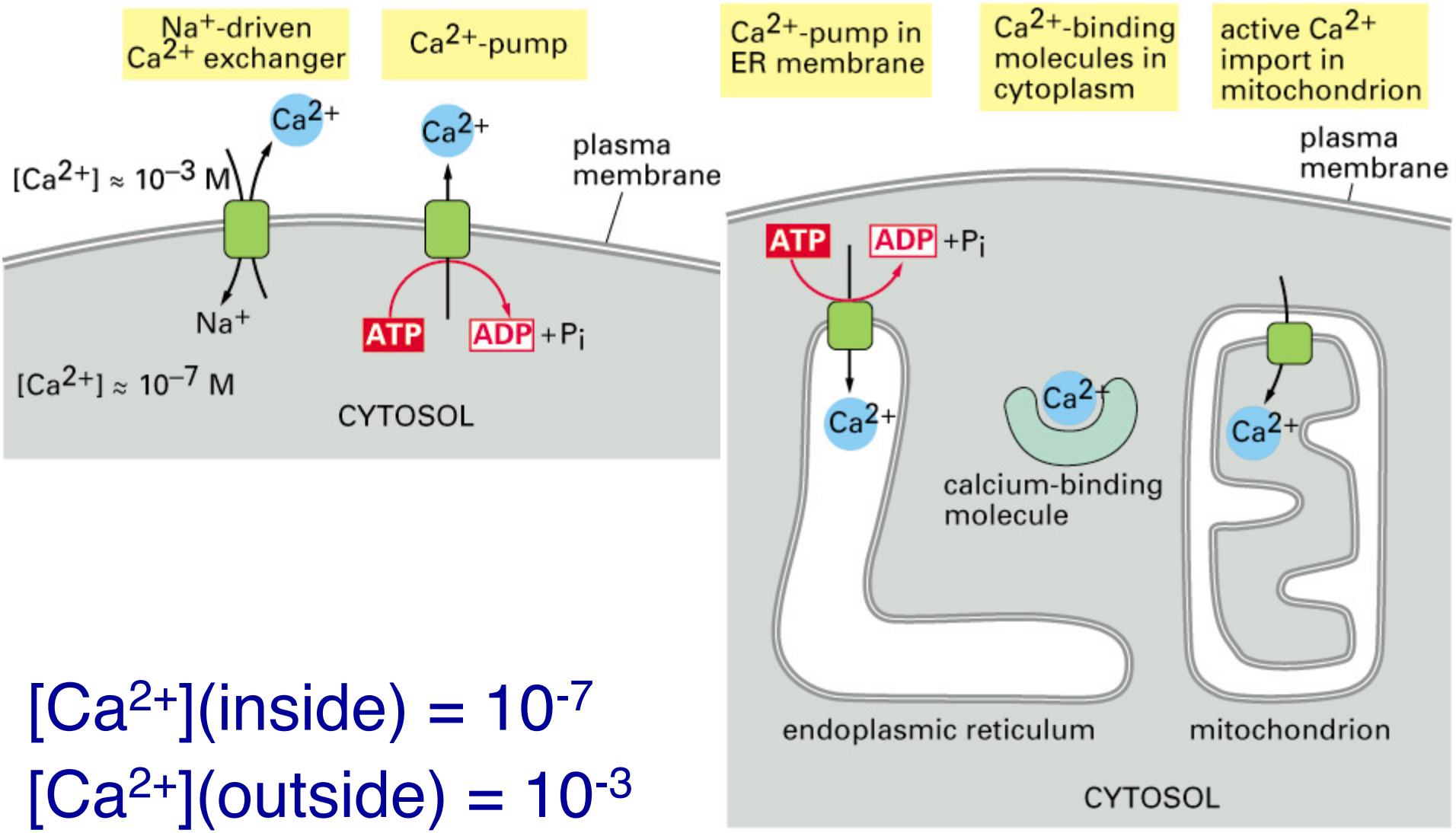


Ed Krebs & Ed Fisher, 1993

Signal transduction pathway leading to activation of phospholipase C (PLC) results in activation of Ca^{2+}-dependent protein kinase (PKC)



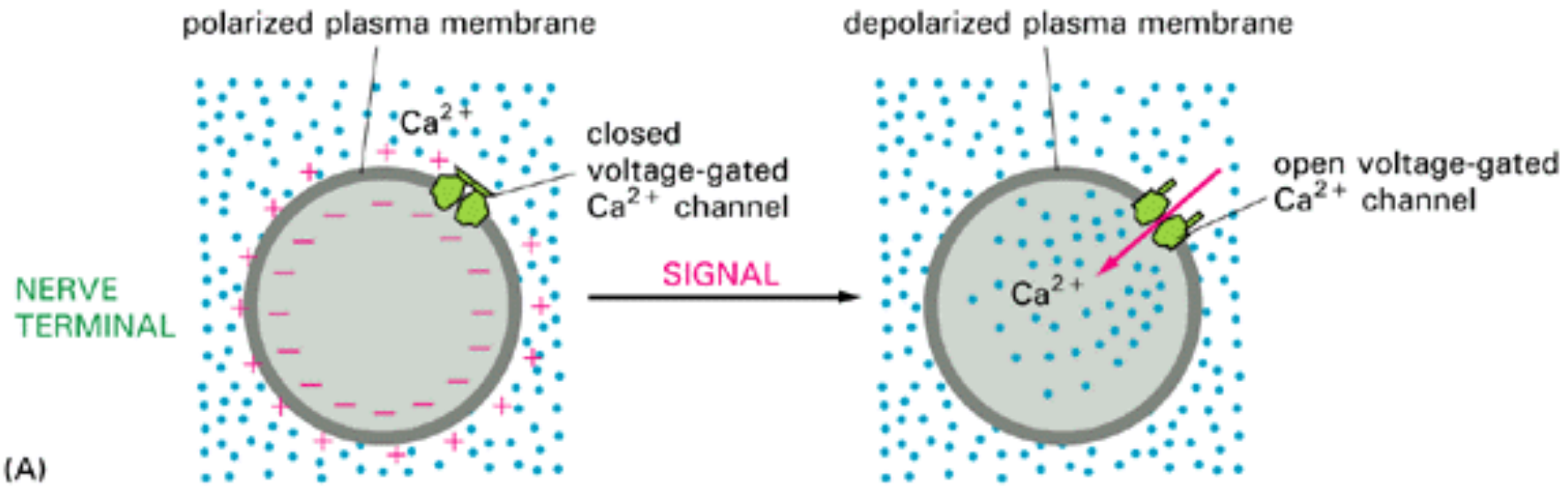
Maintenance of a low intracellular [Ca^{2+}]



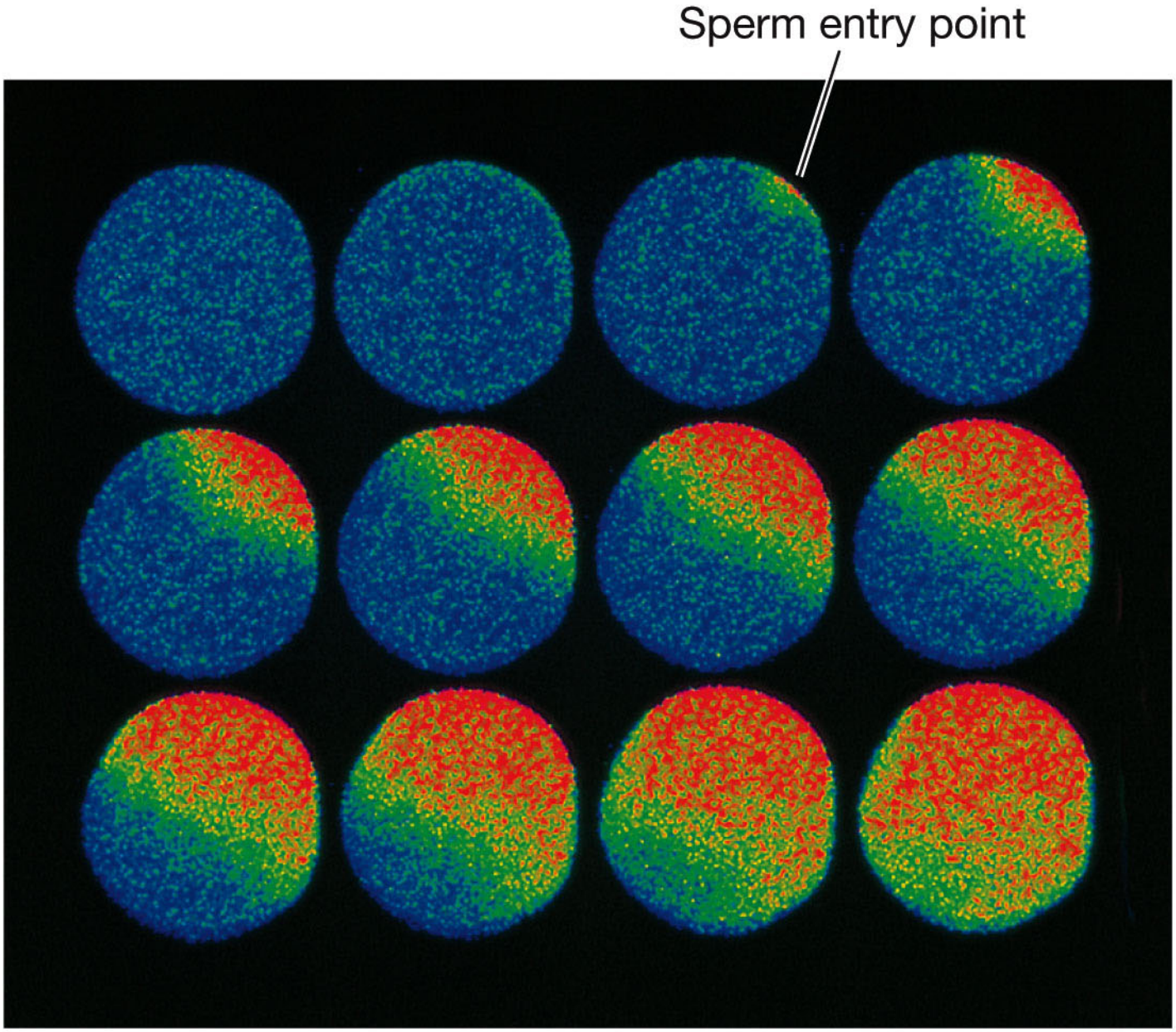
$[Ca^{2+}]$(inside) = 10^{-7}

$[Ca^{2+}]$(outside) = 10^{-3}

Entrance of calcium into cytosol must be tightly regulated

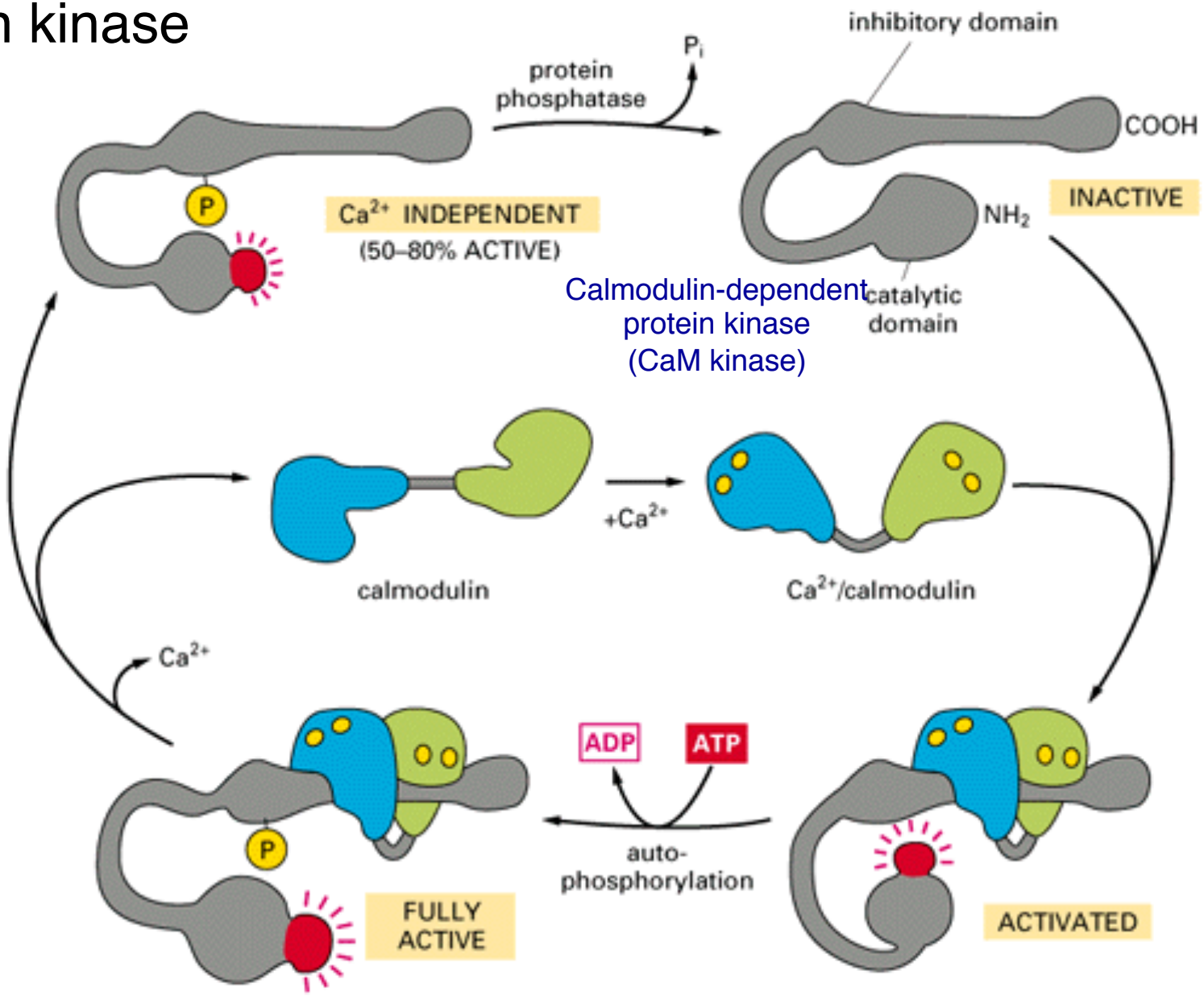


Calcium ions as second messengers

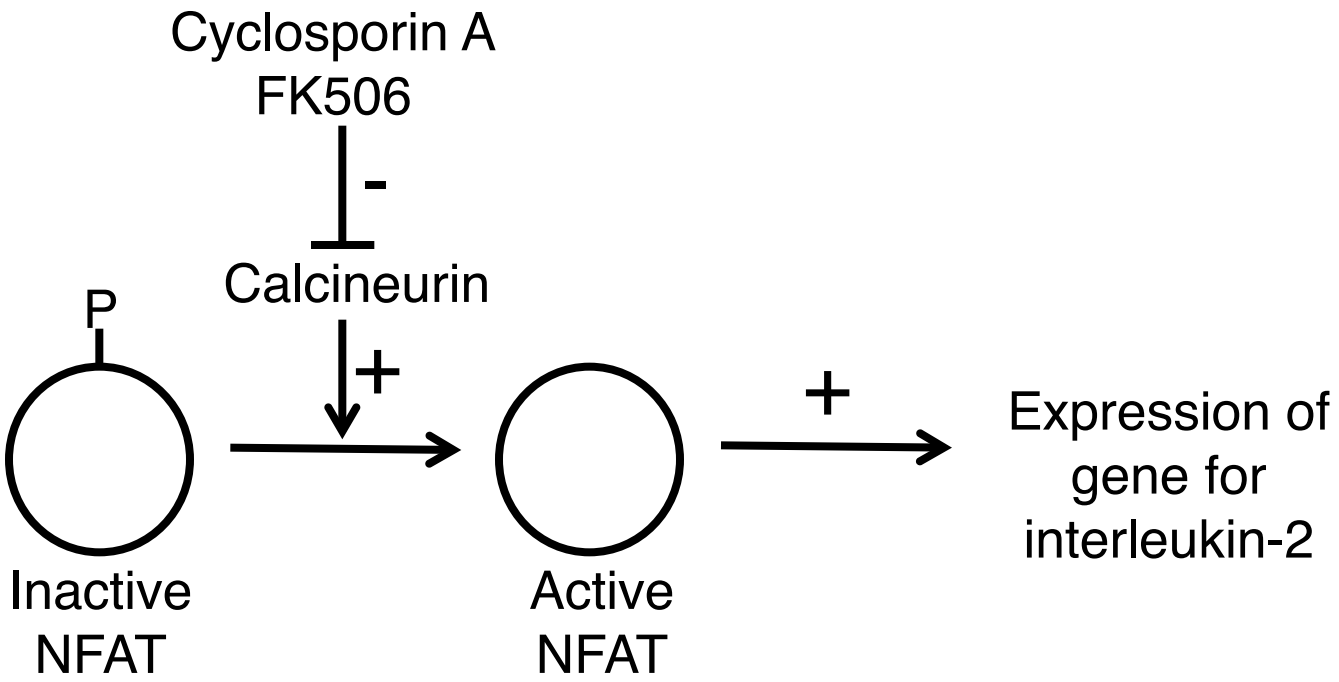


http://www.youtube.com/watch?v=07foN-1IUb4&feature=related

Increased levels of Ca^{2+} activate calmodulin-dependent protein kinase



Calcineurin is a Ca^{2+}-dependent protein serine/threonine protein phosphatase involved in activation of T lymphocytes



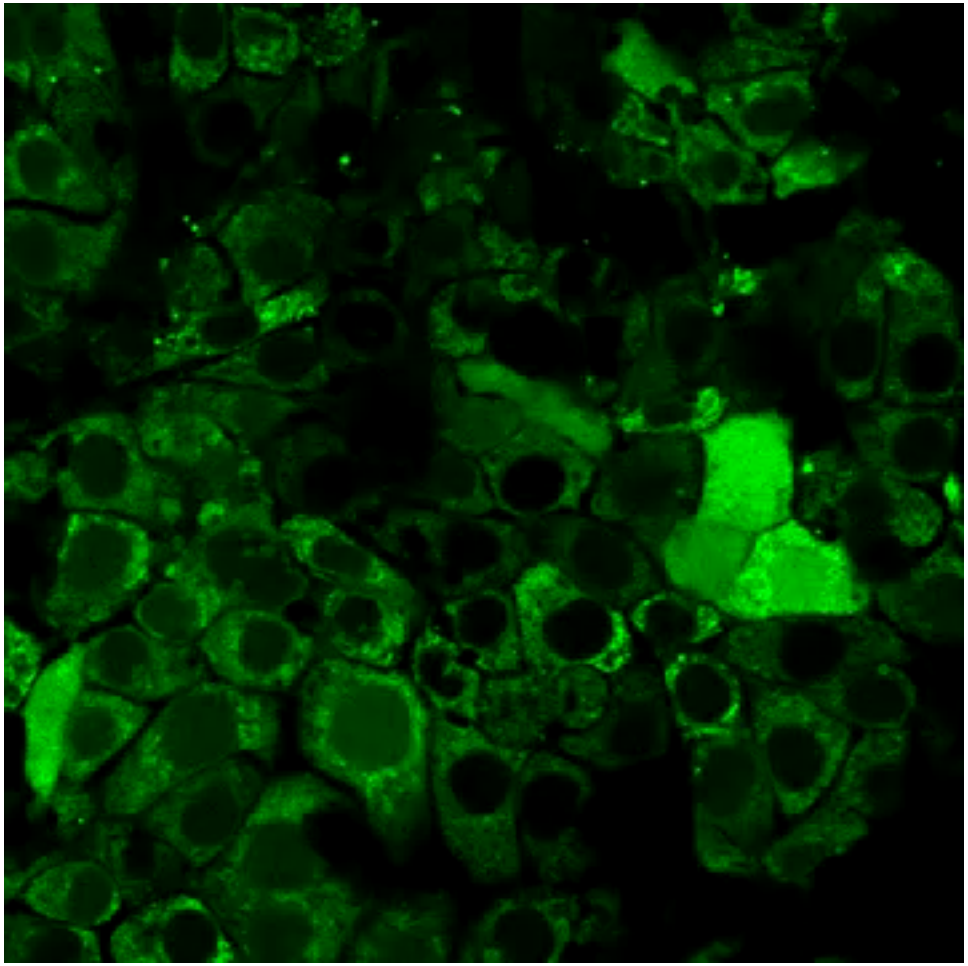
NFAT, nuclear factor of activated T cells (transcription factor)

Sperm calcineurin inhibition prevents mouse fertility with implications for male contraceptive

Haruhiko Miyata,[1] Yuhkoh Satouh,[1] Daisuke Mashiko,[1,2] Masanaga Muto,[1,3] Kaori Nozawa,[1,2] Kogiku Shiba,[4] Yoshitaka Fujihara,[1] Ayako Isotani,[5] Kazuo Inaba,[4] Masahito Ikawa[1,2,3,5]*

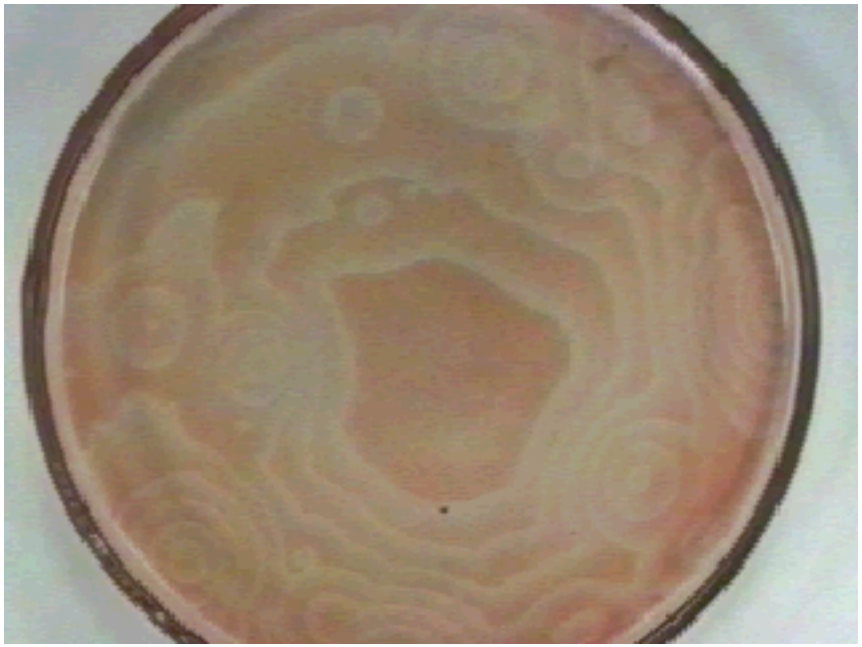
Science **350**: 442-445 (2015)

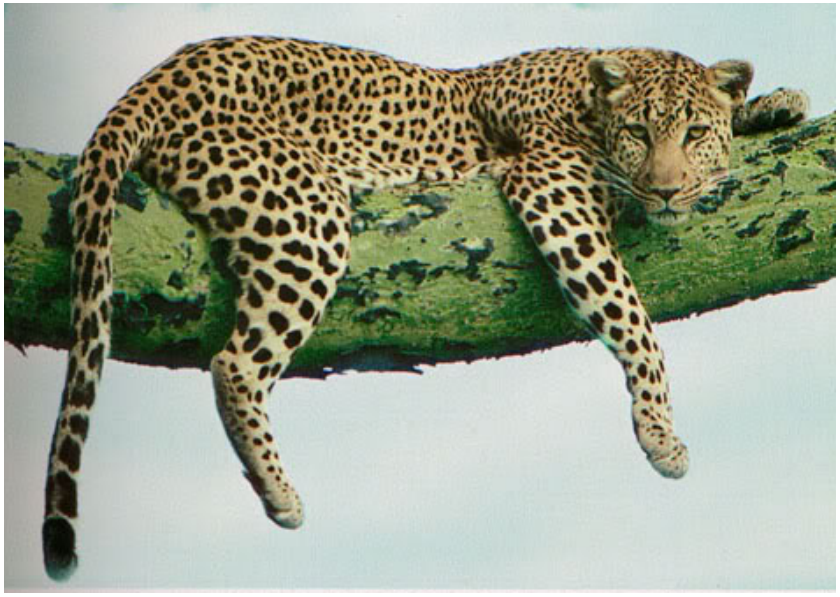
Cell signaling is mediated by oscillations of calcium ions

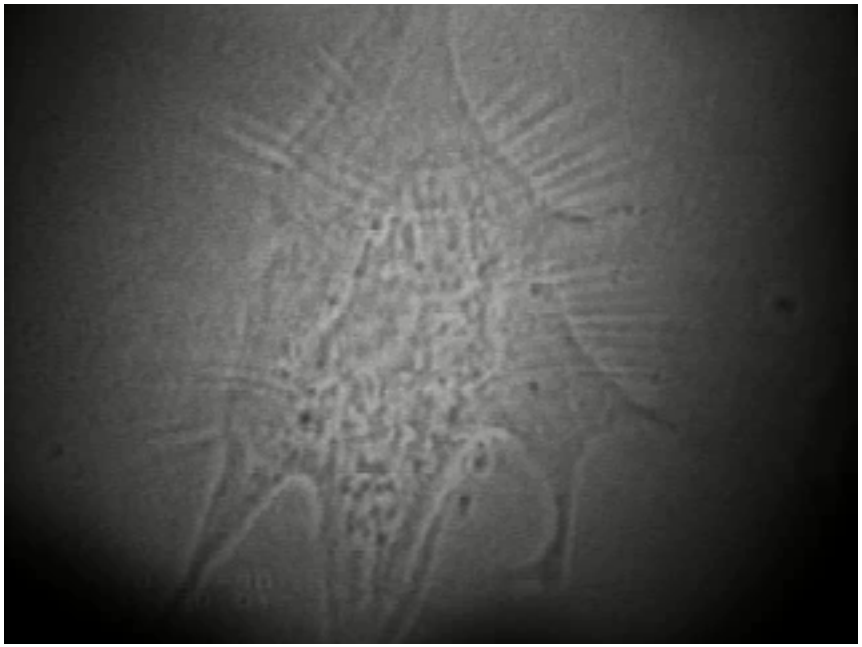


Cells pre-loaded with a fluorescent calcium sensor Fluo-4 and imaged every 3 seconds using a confocal microscope. [Rajesh Kumar]

Oscillations in anorganic and biological systems



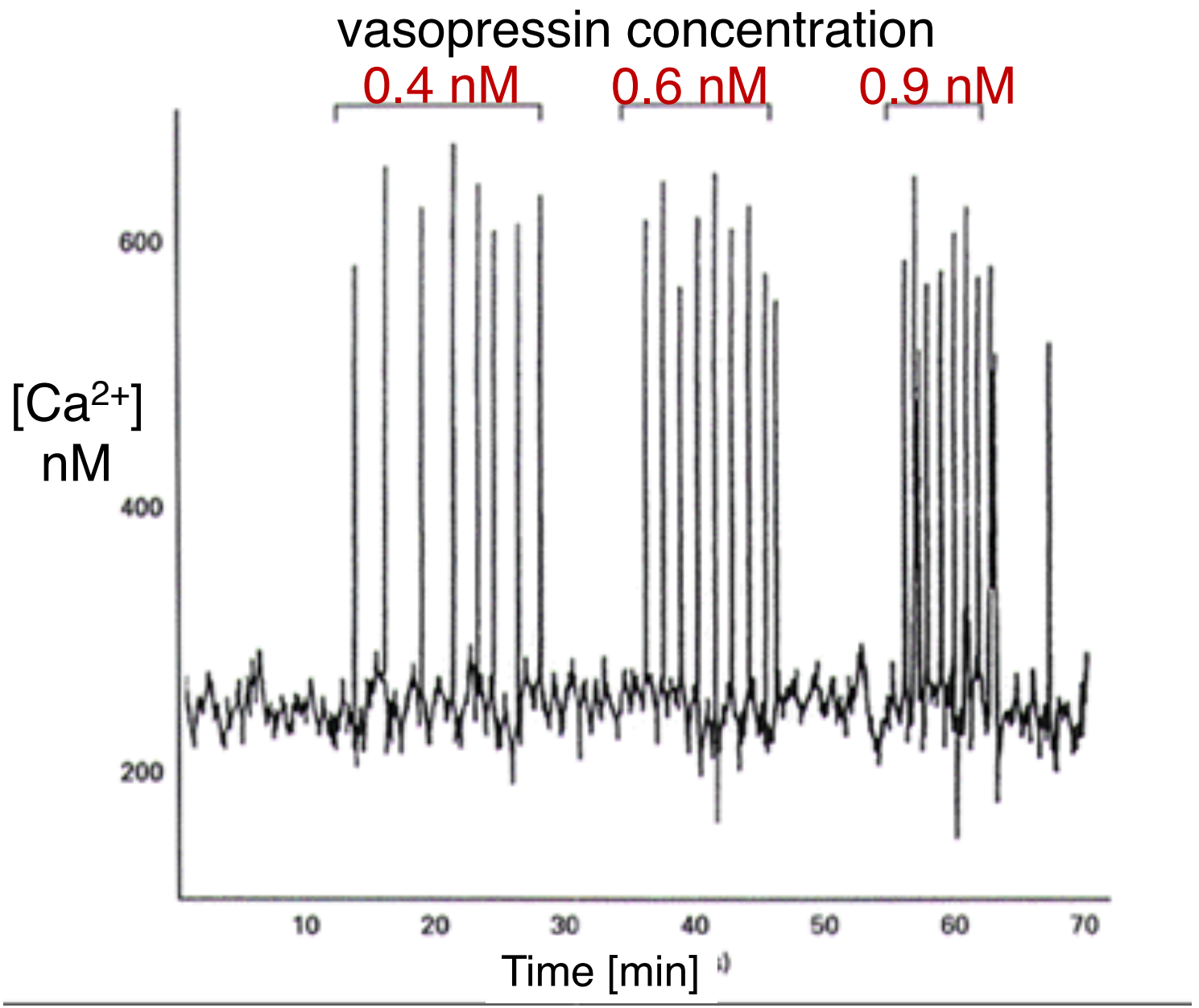




Alan Turing

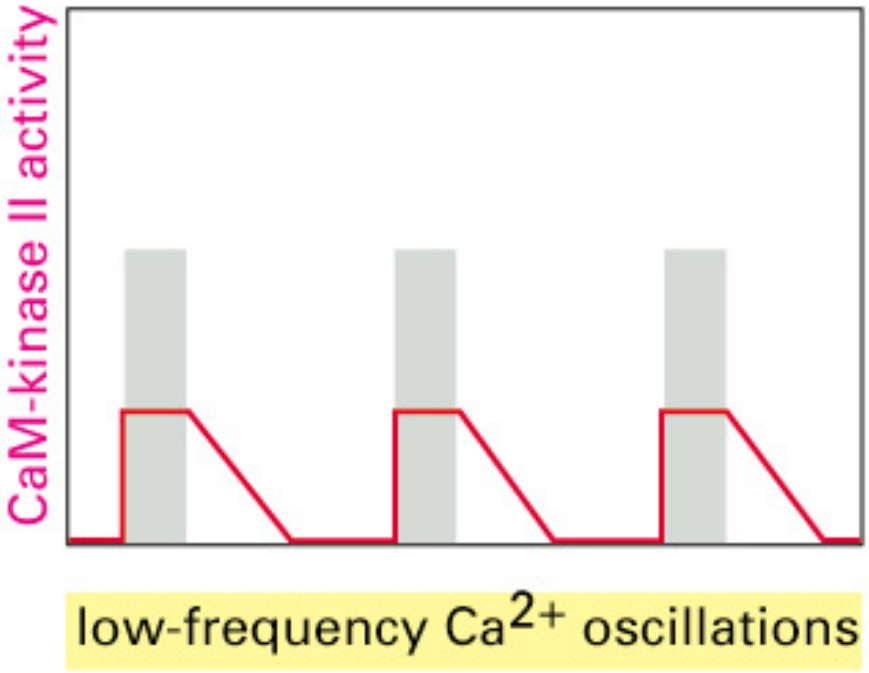
(1912-1954)

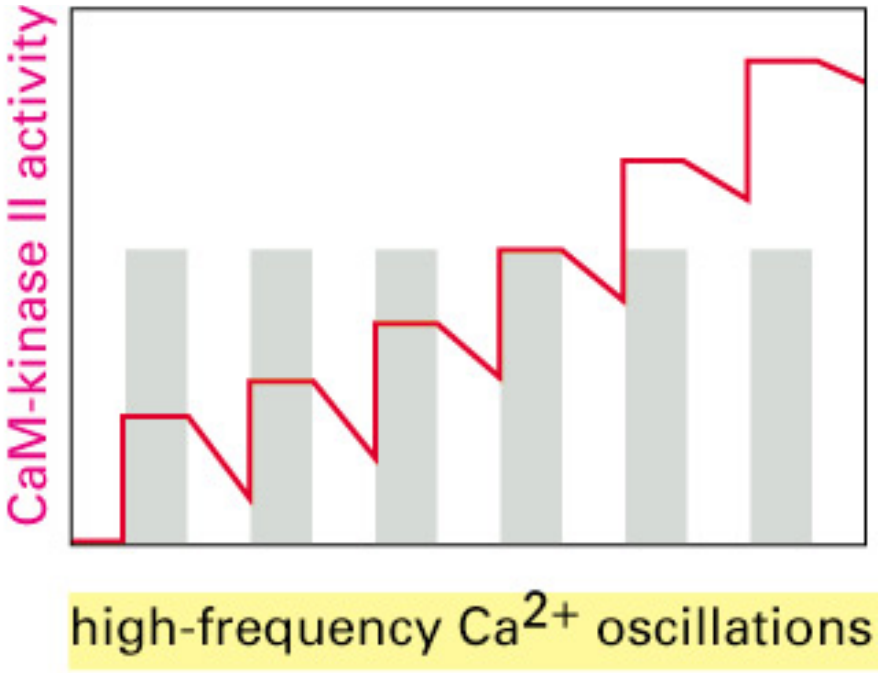
Oscillatory behavior of calcium appearance in cytosol



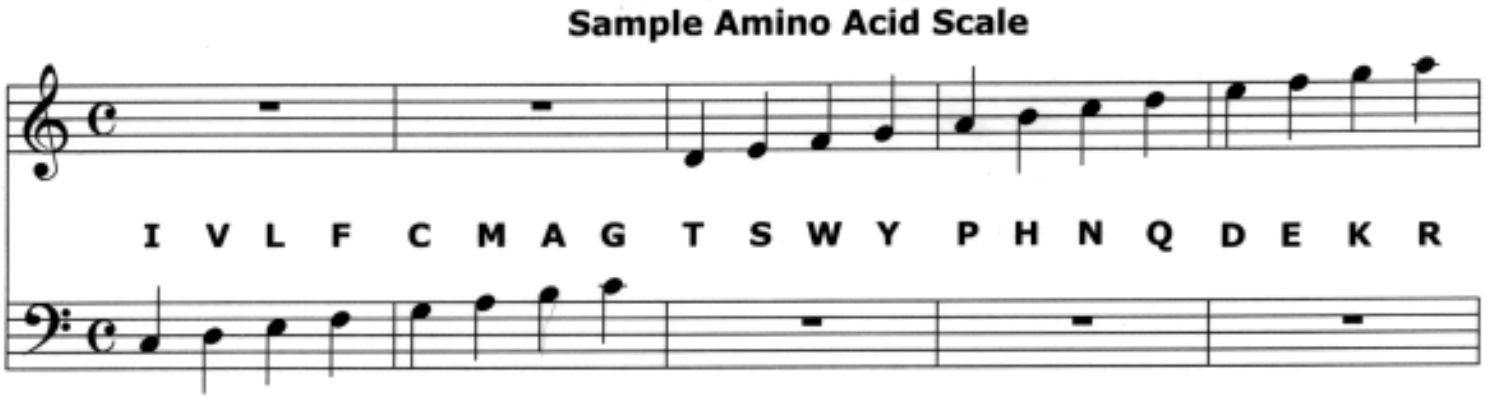
http://www.youtube.com/watch?v=FMonGtg_VW0
http://www.youtube.com/watch?v=WtzPwL88meM

CaM-kinase as frequency decoder of Ca^{2+} oscillations – a form of cellular memory





The sound of genes and proteins



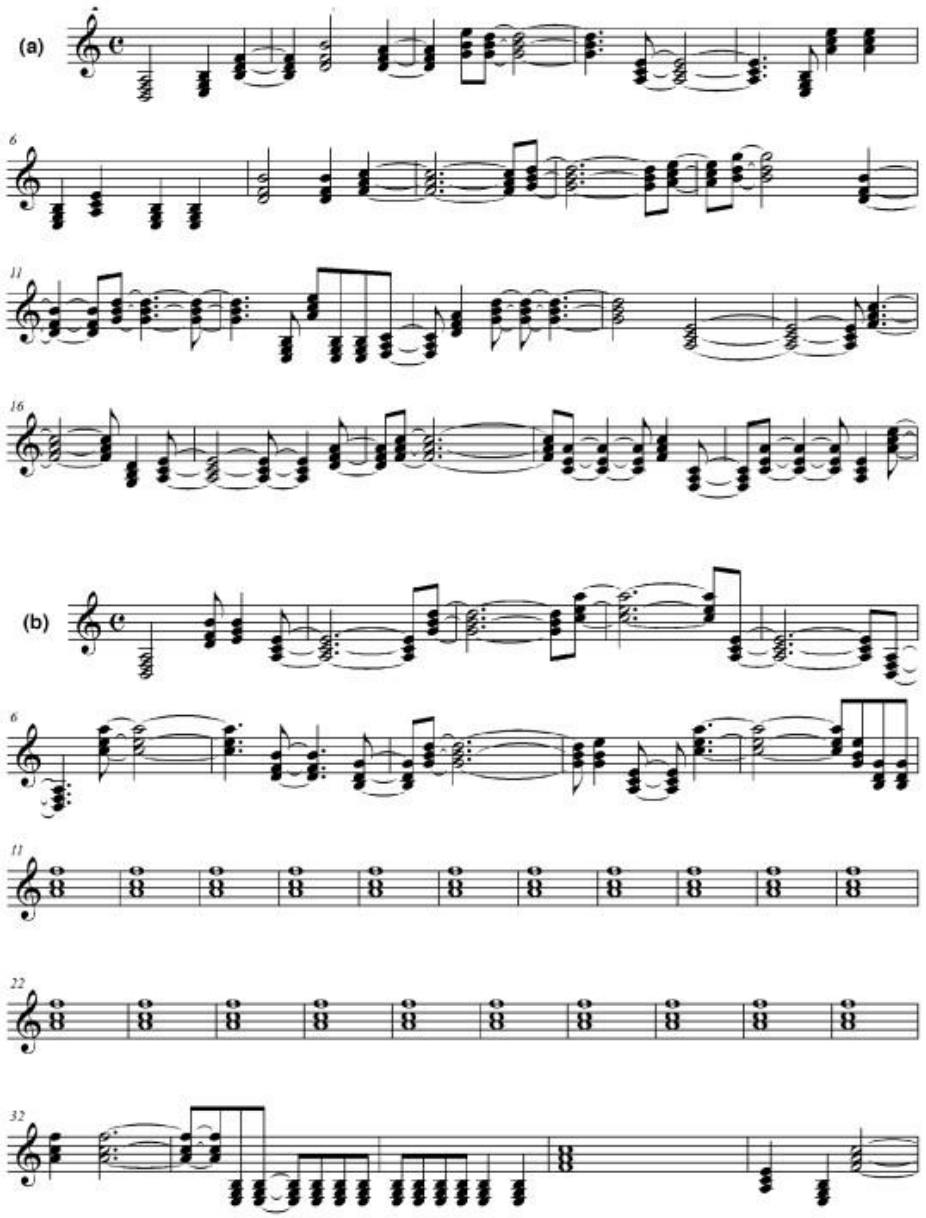
Ohno, S., Ohno, M. (1986). The all pervasive principle of repetitious recurrence governs not only coding sequence construction but also human endeavor in musical composition. *Immunogenetics* 24:71-78.

Takahashi, R., Miller, J.H. (2007). Conversion of amino-acid sequence in proteins to classical music:search for auditory patterns. Genome Biol. 8: 405.

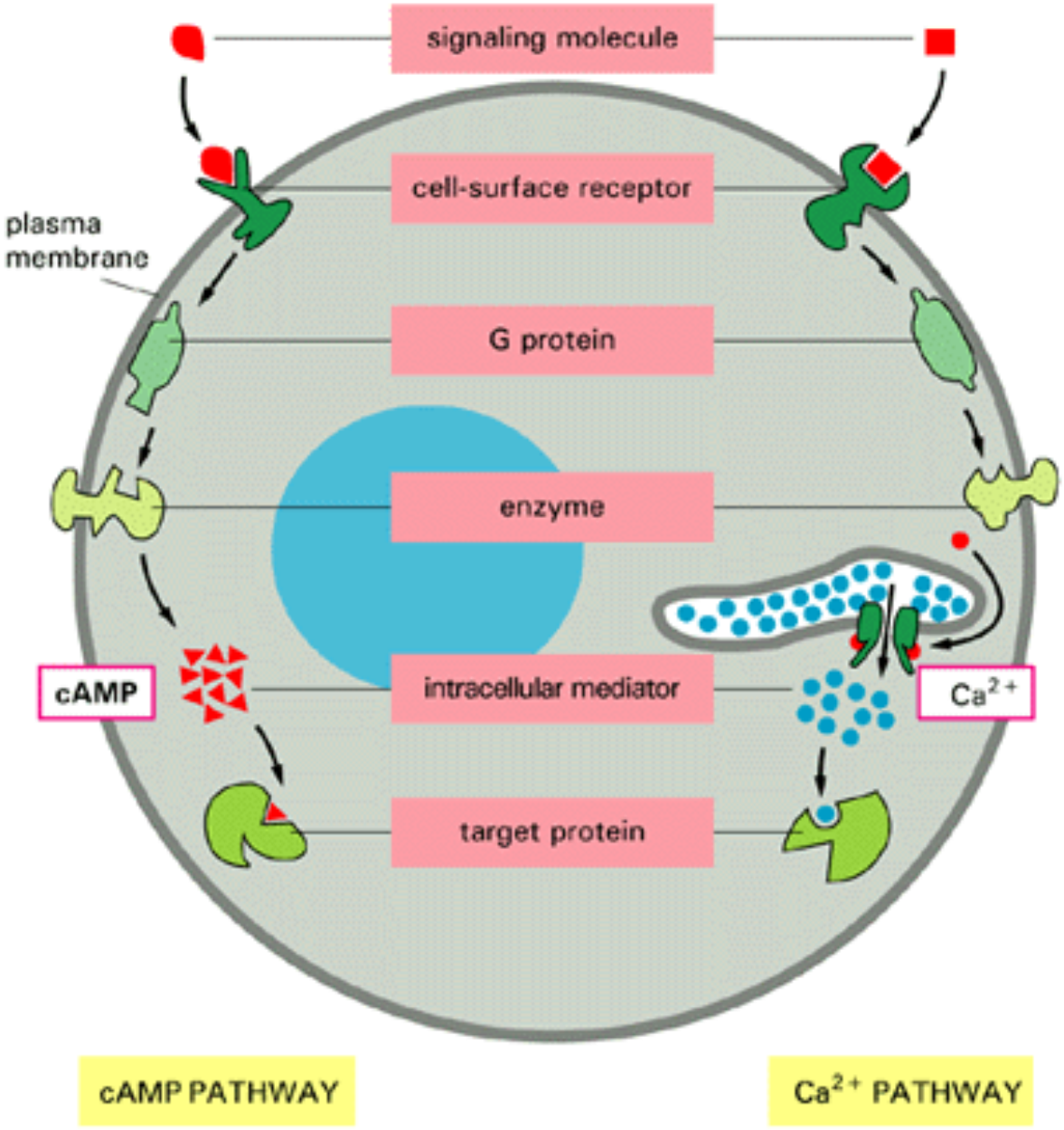
DNA and Protein Music: www.nslij-genetics.org/dnamusic/
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1929127/

http://www.youtube.com/watch?v=CM920dPFIHM

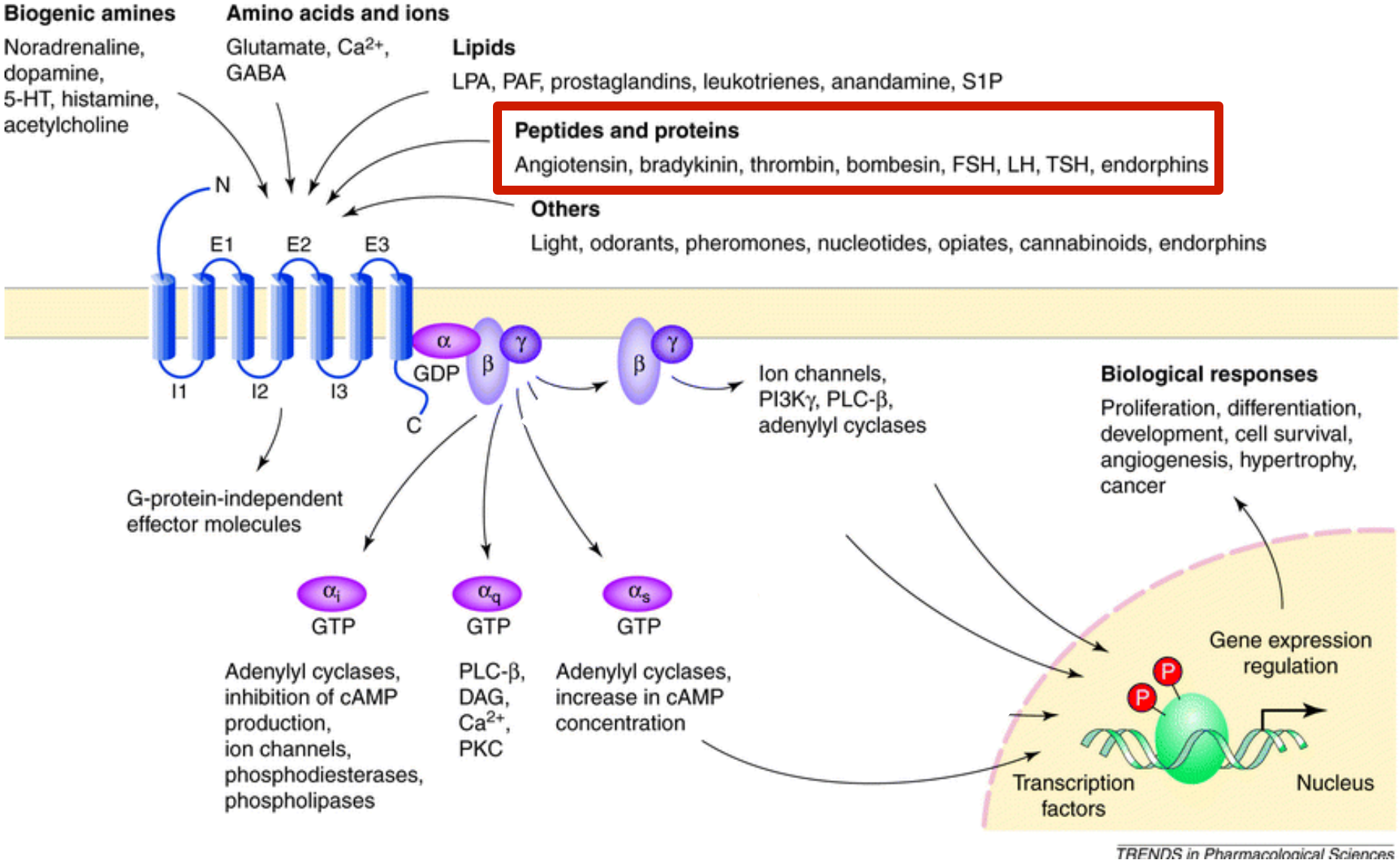
The sound of genes and proteins



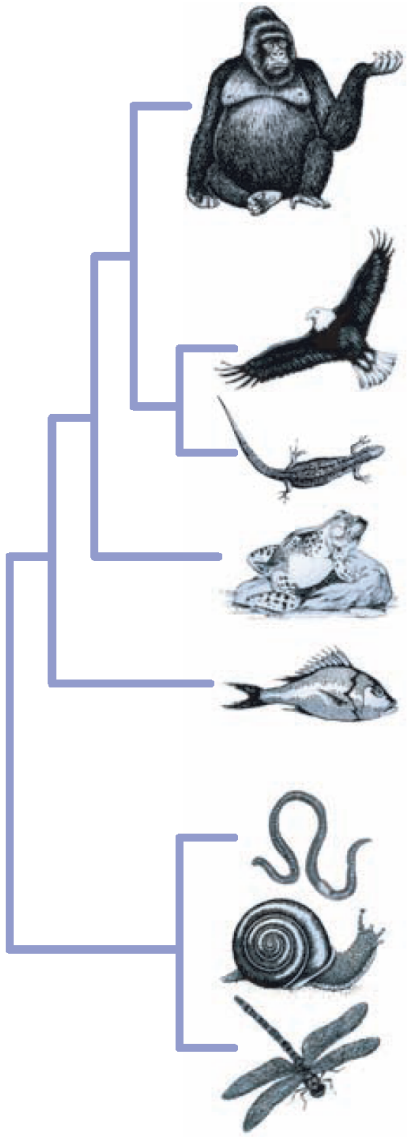
G proteins – transient summary



Ligands, efectors and biological responses for GPCRs



Vasopressin & oxytocin: simple peptides with roles in complex phenomena



Vasopressin (mammals)
Cys·Tyr·Phe·Gln·**Asn·Cys·Pro**·Arg·**Gly**·NH_2

Lysipressin (pigs, marsupials)
Cys·Tyr·Phe·Gln·**Asn·Cys·Pro**·Lys·**Gly**·NH_2

Phenypressin (marsupials)
Cys·Phe·Phe·Gln·**Asn·Cys·Pro**·Arg·**Gly**·NH_2

Oxytocin
Cys·Tyr·Ile·Gln·**Asn·Cys·Pro**·Leu·**Gly**·NH_2

Vasotocin
Cys·Tyr·Ile·Gln·**Asn·Cys·Pro**·Arg·**Gly**·NH_2

Mesotocin
Cys·Tyr·Ile·Gln·**Asn·Cys·Pro**·Ile·**Gly**·NH_2

Isotocin
Cys·Tyr·Ile·Ser·**Asn·Cys·Pro**·Leu·**Gly**·NH_2

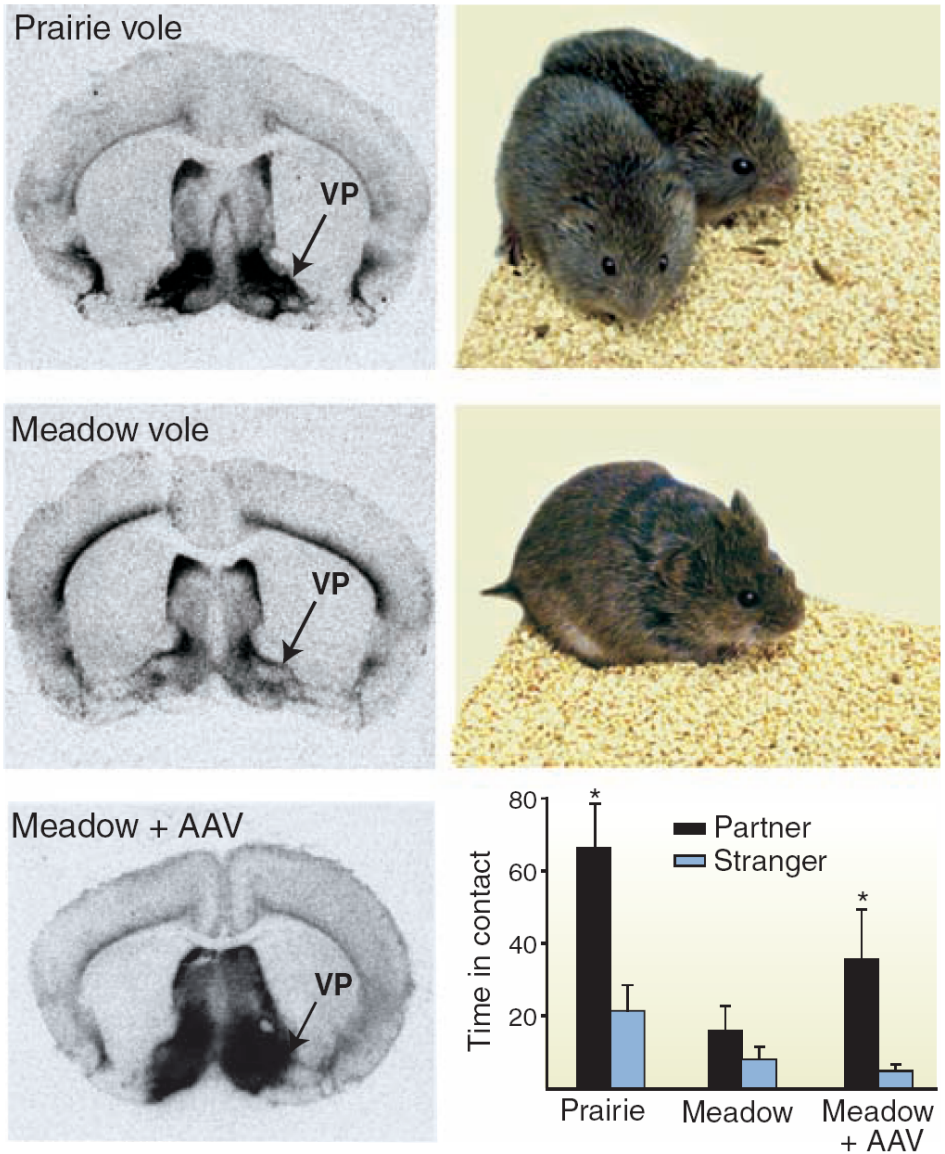
Annepressin (annelid worms)
Cys·Phe·Val·Arg·**Asn·Cys·Pro**·Thr·**Gly**·NH_2

Conopressin (snails, cones, sea hare, leeches)
Cys·Phe/Ile·Ile·Arg·**Asn·Cys·Pro**·Lys/Arg·**Gly**·NH_2

Inotocin (some insects)
Cys·Leu·Ile·Thr·**Asn·Cys·Pro**·Arg·**Gly**·NH_2

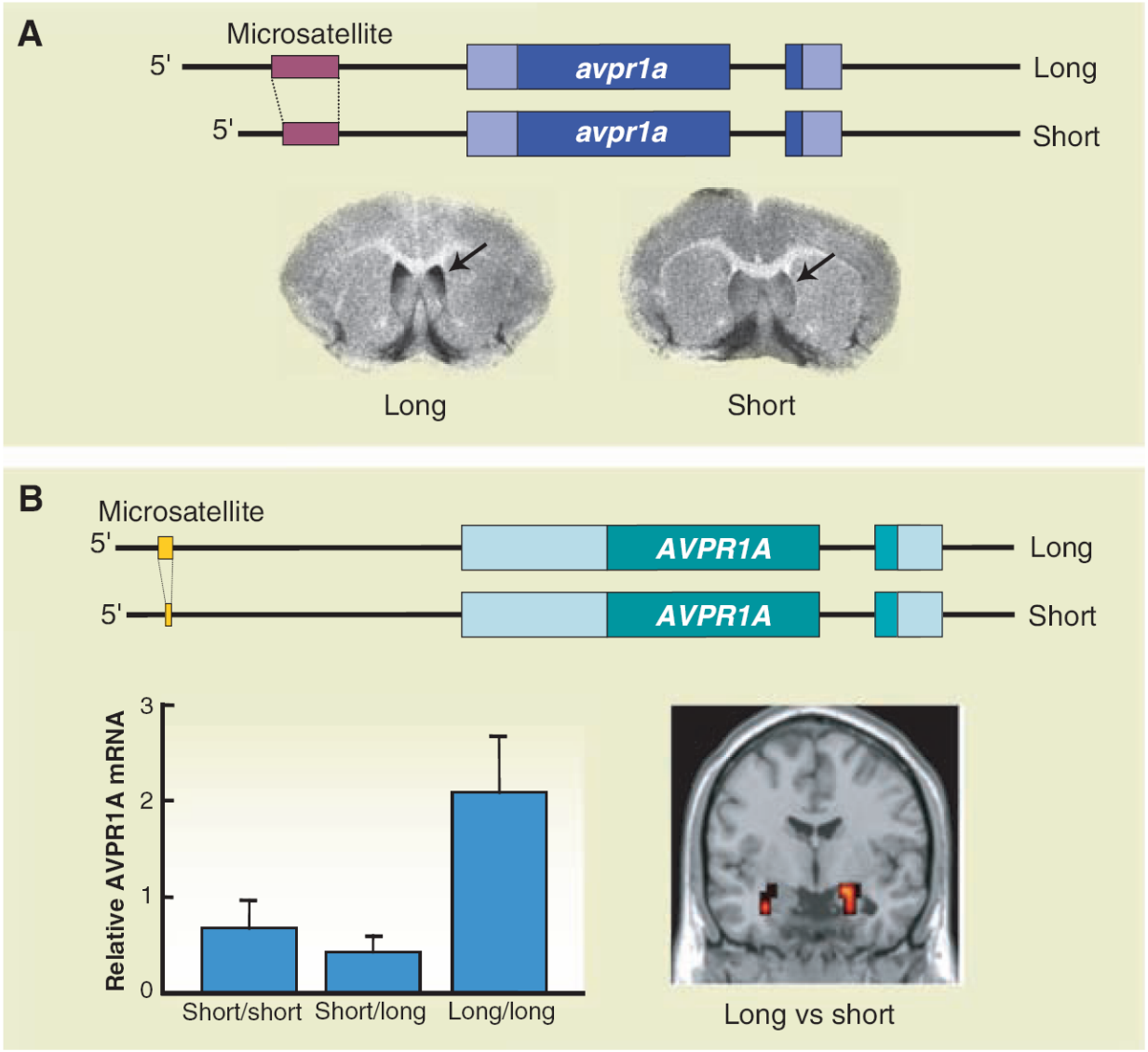
Donaldson, Z.J. & Young, R.J. (2008). Science 322: 900-904

Vasopressin R1a receptor: mono- *versus* polygamy



Donaldson, Z.J. & Young, R.J. (2008). *Science* 322: 900-904

Vasopressin R1a receptor: mono- *versus* polygamy



Donaldson, Z.J. & Young, R.J. (2008). *Science* 322: 900-904

NATURE|Vol 435|2 June 2005

Oxytocin increases trust in humans

Michael Kosfeld[1]*, Markus Heinrichs[2]*, Paul J. Zak[3], Urs Fischbacher[1] & Ernst Fehr[1,4]

BIOL PSYCHIATRY 2007;61:731–733

Oxytocin Improves "Mind-Reading" in Humans

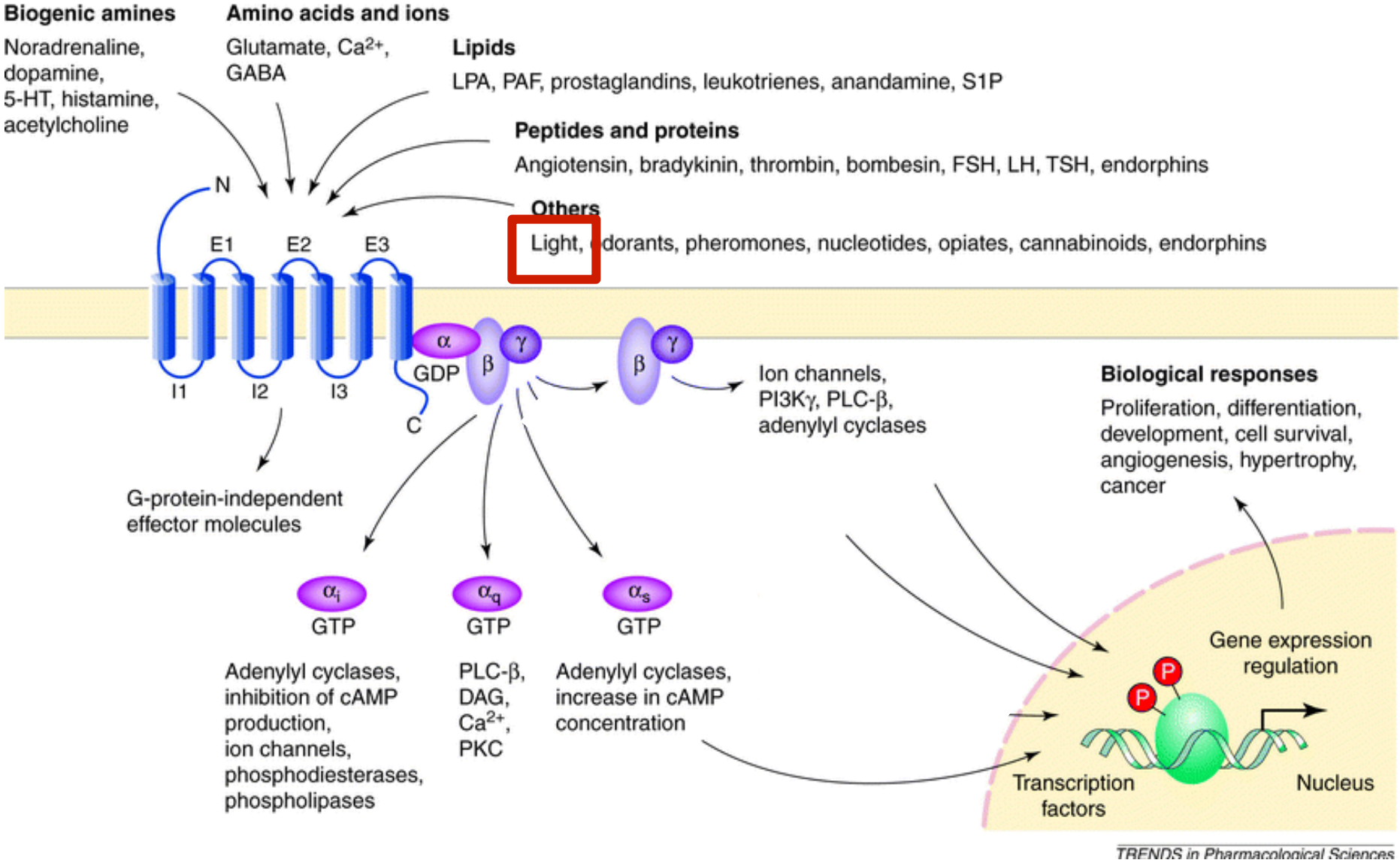
Gregor Domes, Markus Heinrichs, Andre Michel, Christoph Berger, and Sabine C. Herpertz

PLoS ONE 2007 | Issue 11 | e1128

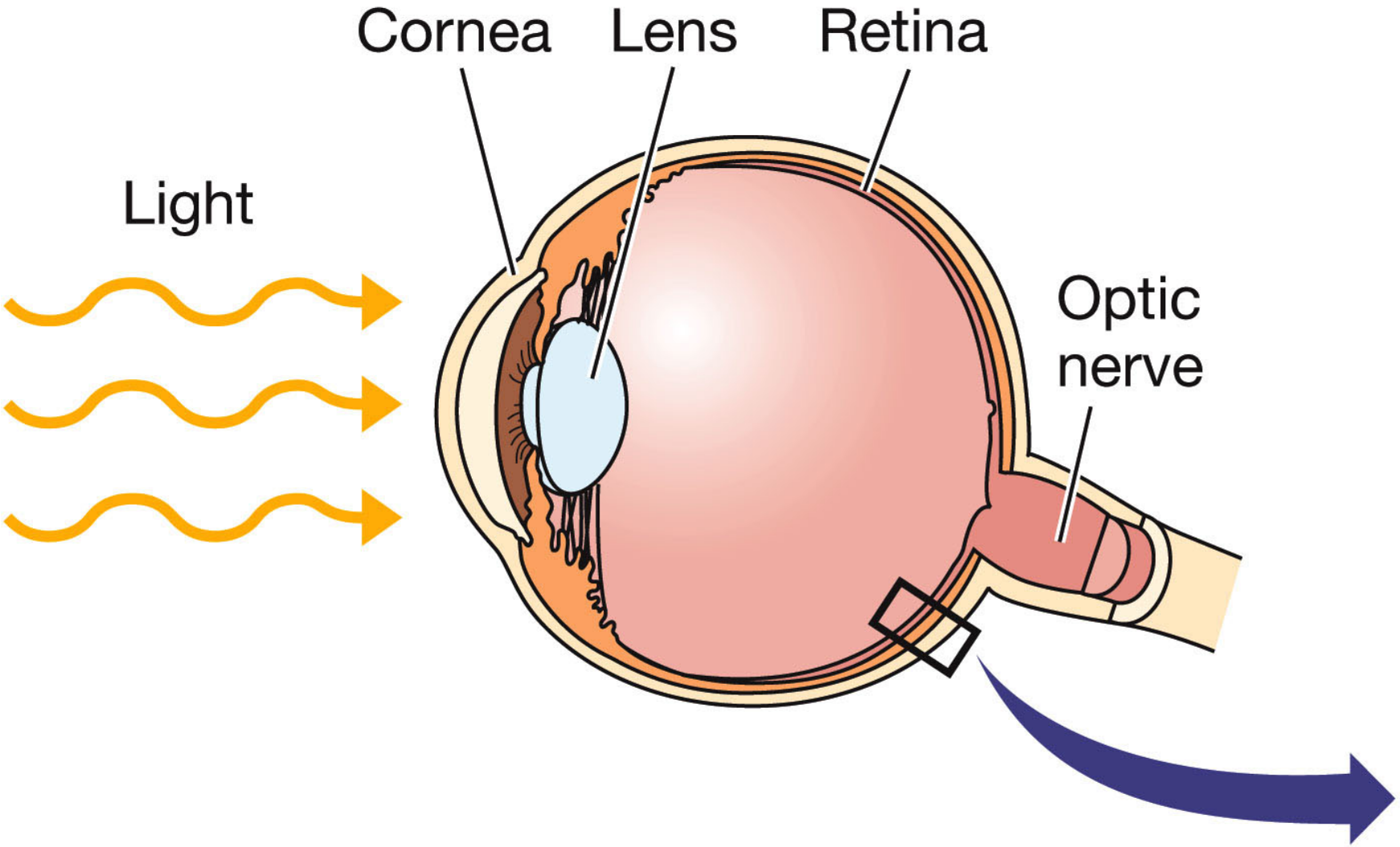
Oxytocin Increases Generosity in Humans

Paul J. Zak[1,2]*, Angela A. Stanton[3], Sheila Ahmadi[4]

Ligands, efectors and biological responses for GPCRs

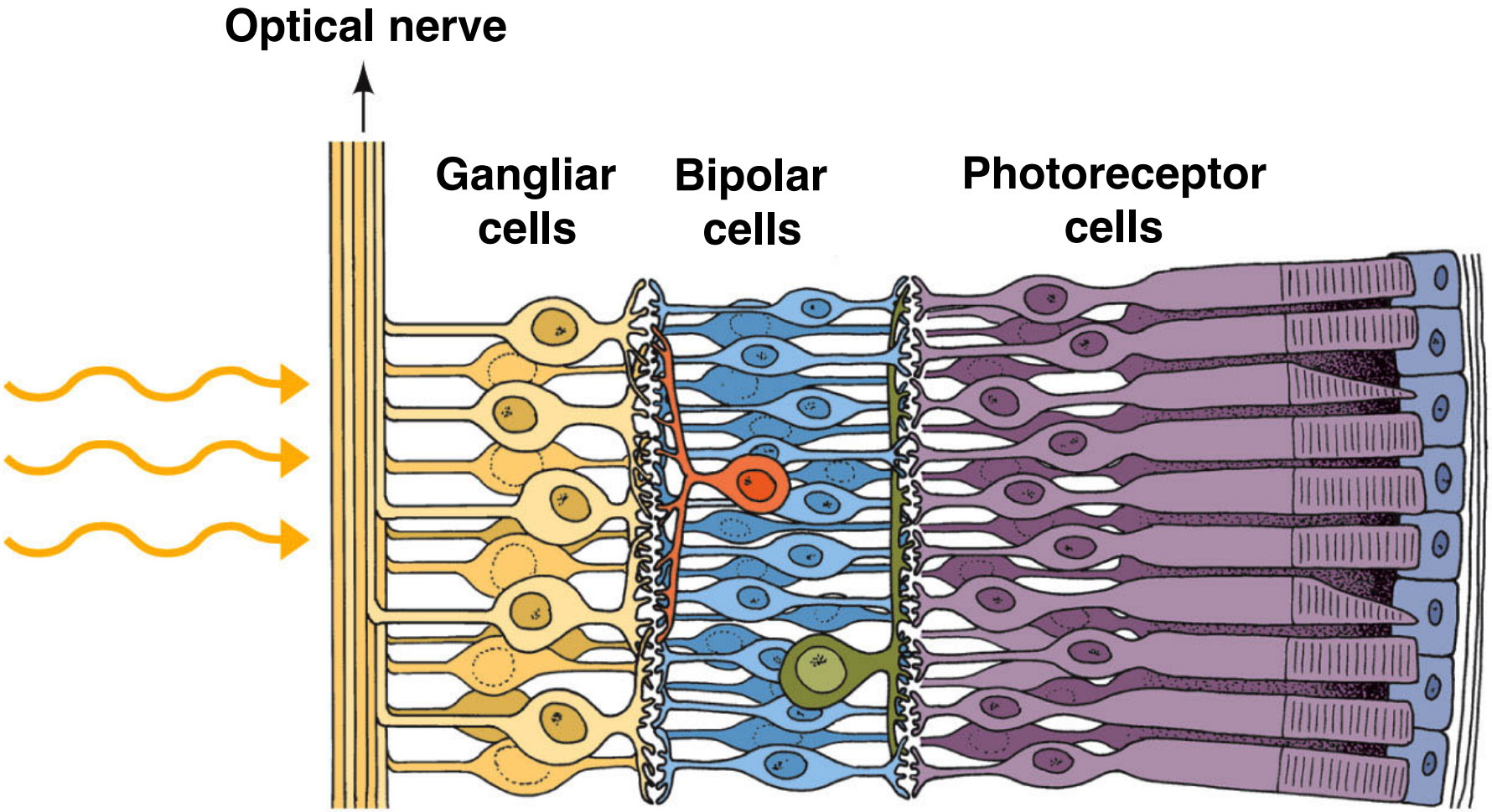


Architecture of a vertebrate eye



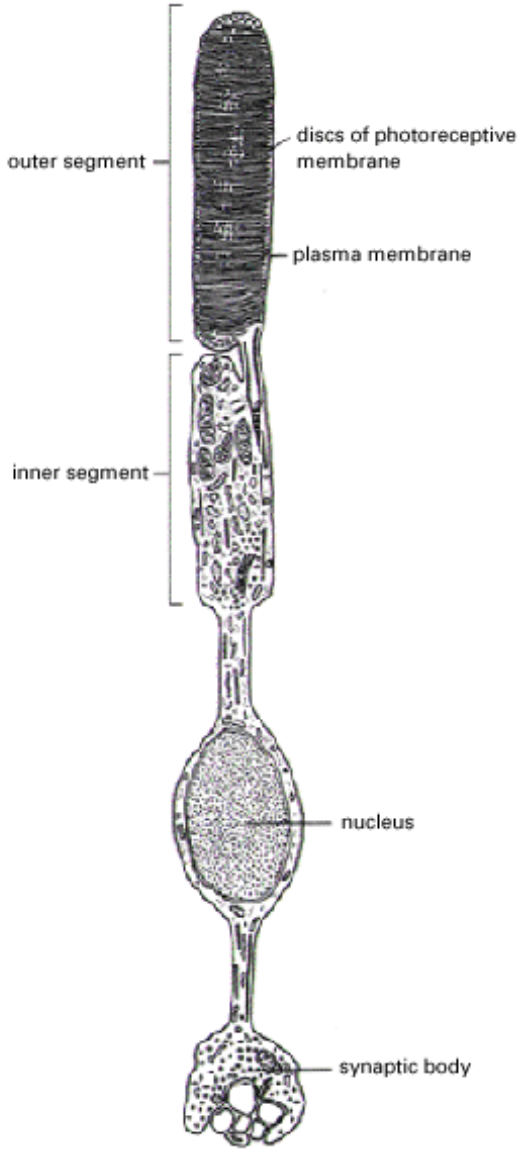
Sadava *a kol.* (2007). Life: The Science of Biology. Sinnauer Ass.

Architecture of a vertebrate eye

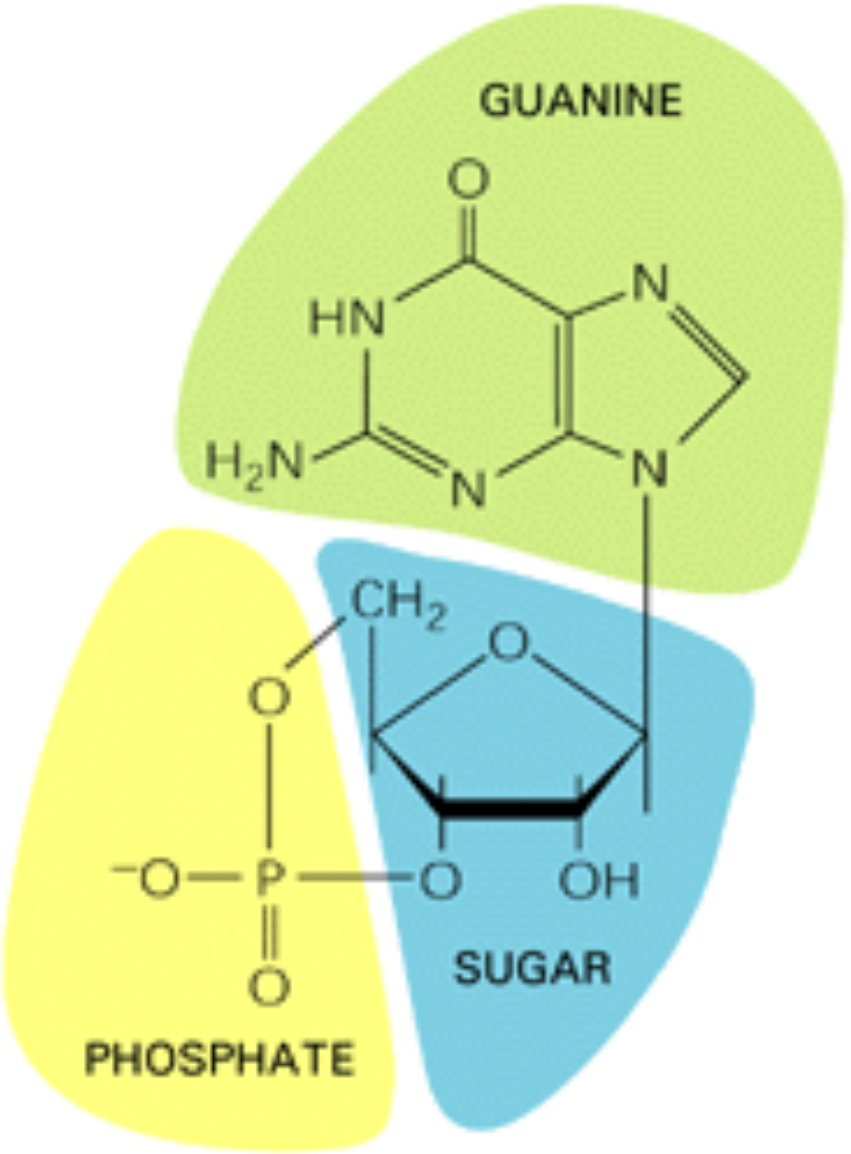


Sadava *a kol.* (2007). Life: The Science of Biology. Sinnauer Ass.

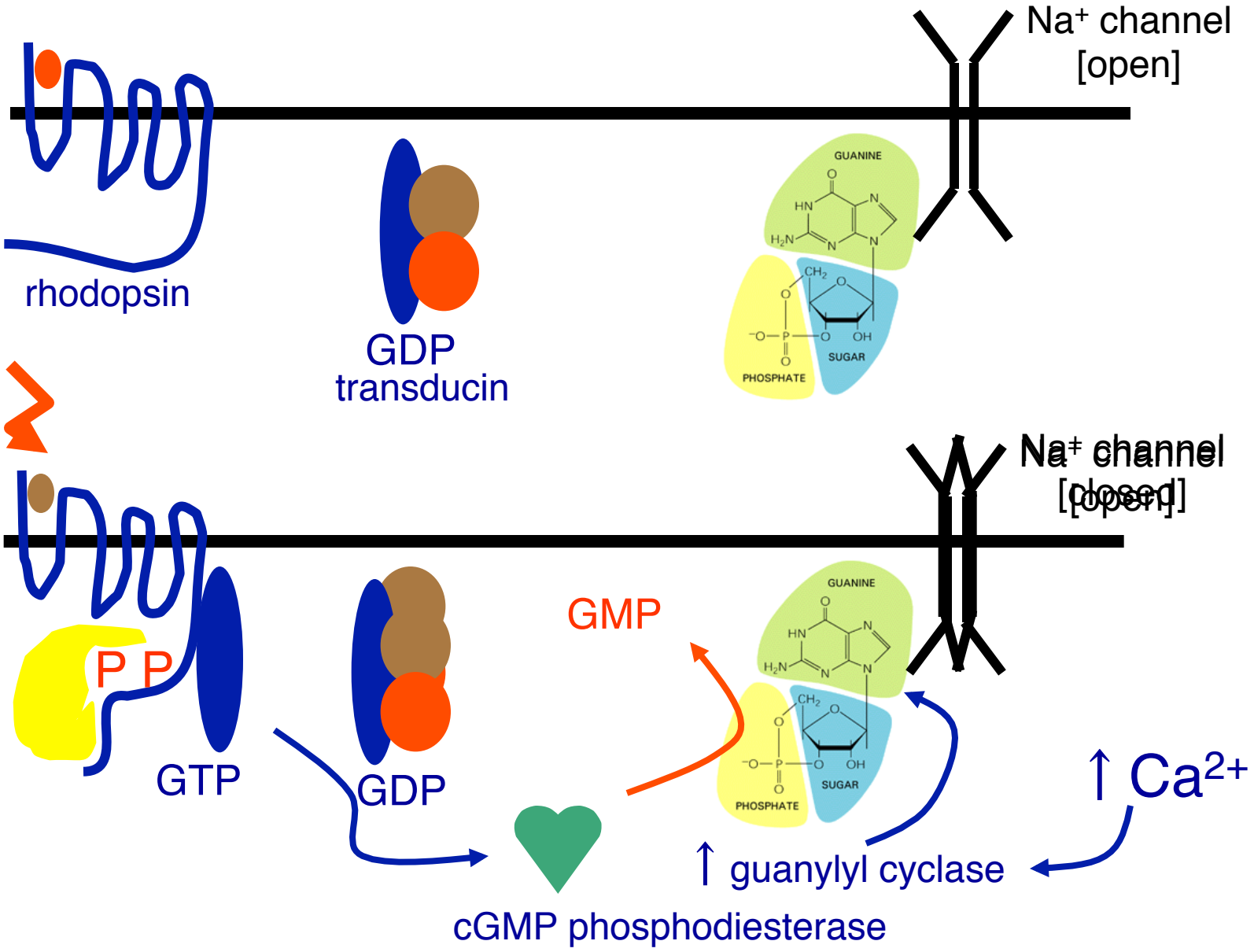
G proteins and visual signaling



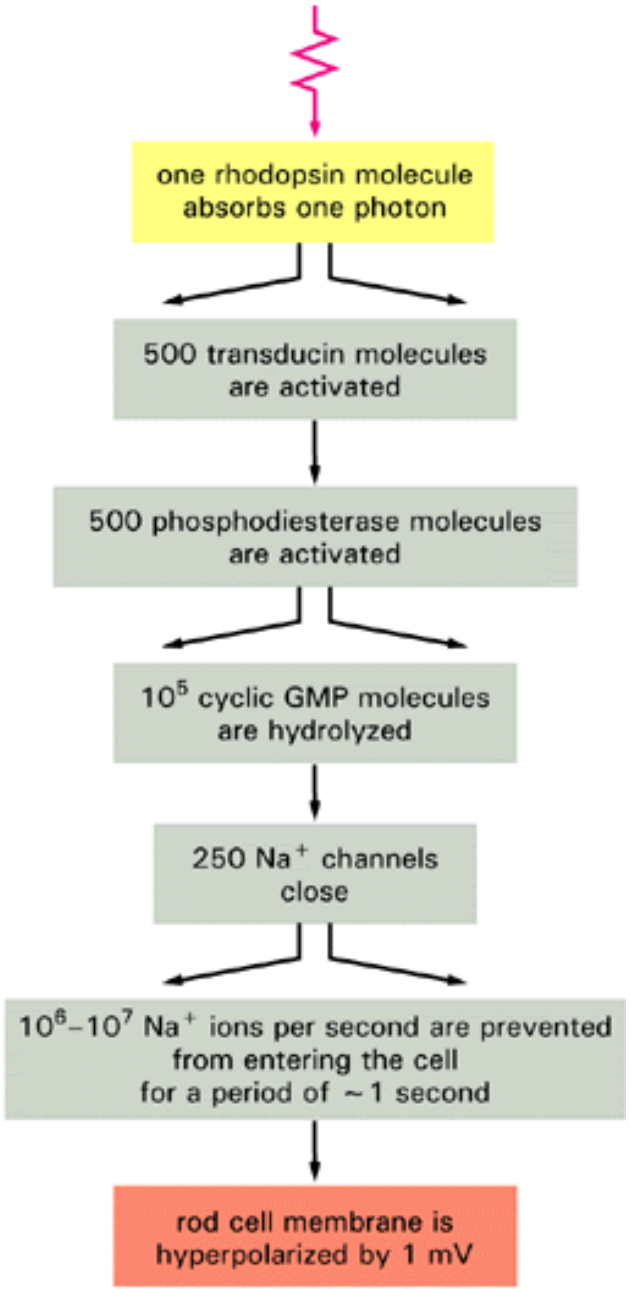
cGMP is the major second messenger in visual signalling



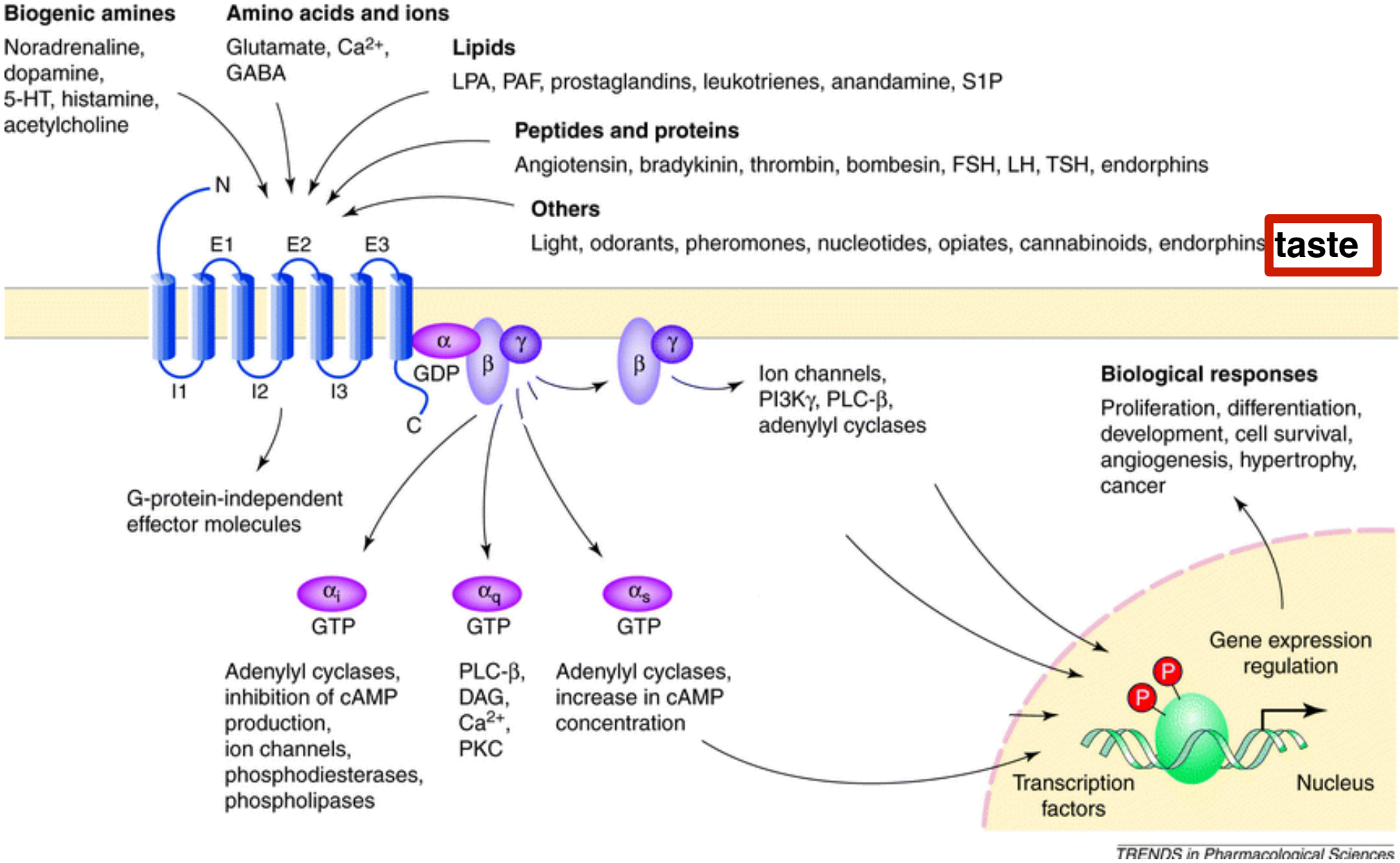
G proteins and visual signaling



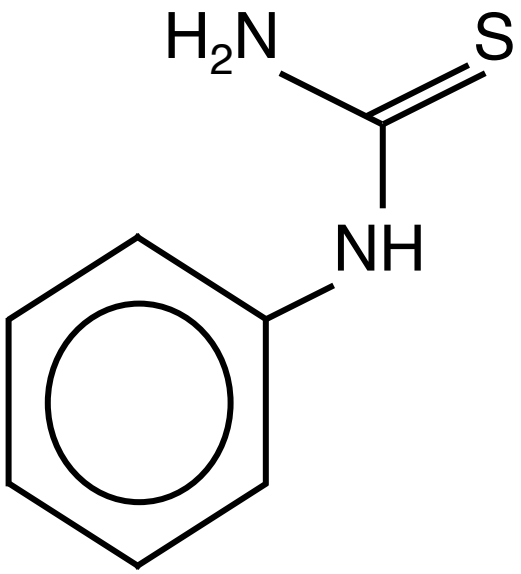
Signal amplification during visual signalling



Ligands, efectors and biological responses for GPCRs



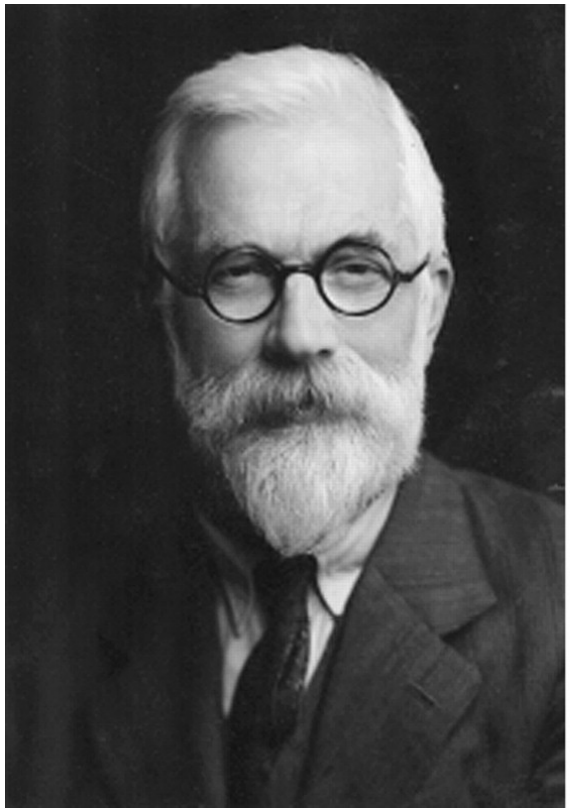
First clues to a genetic basis of gustatory signalling



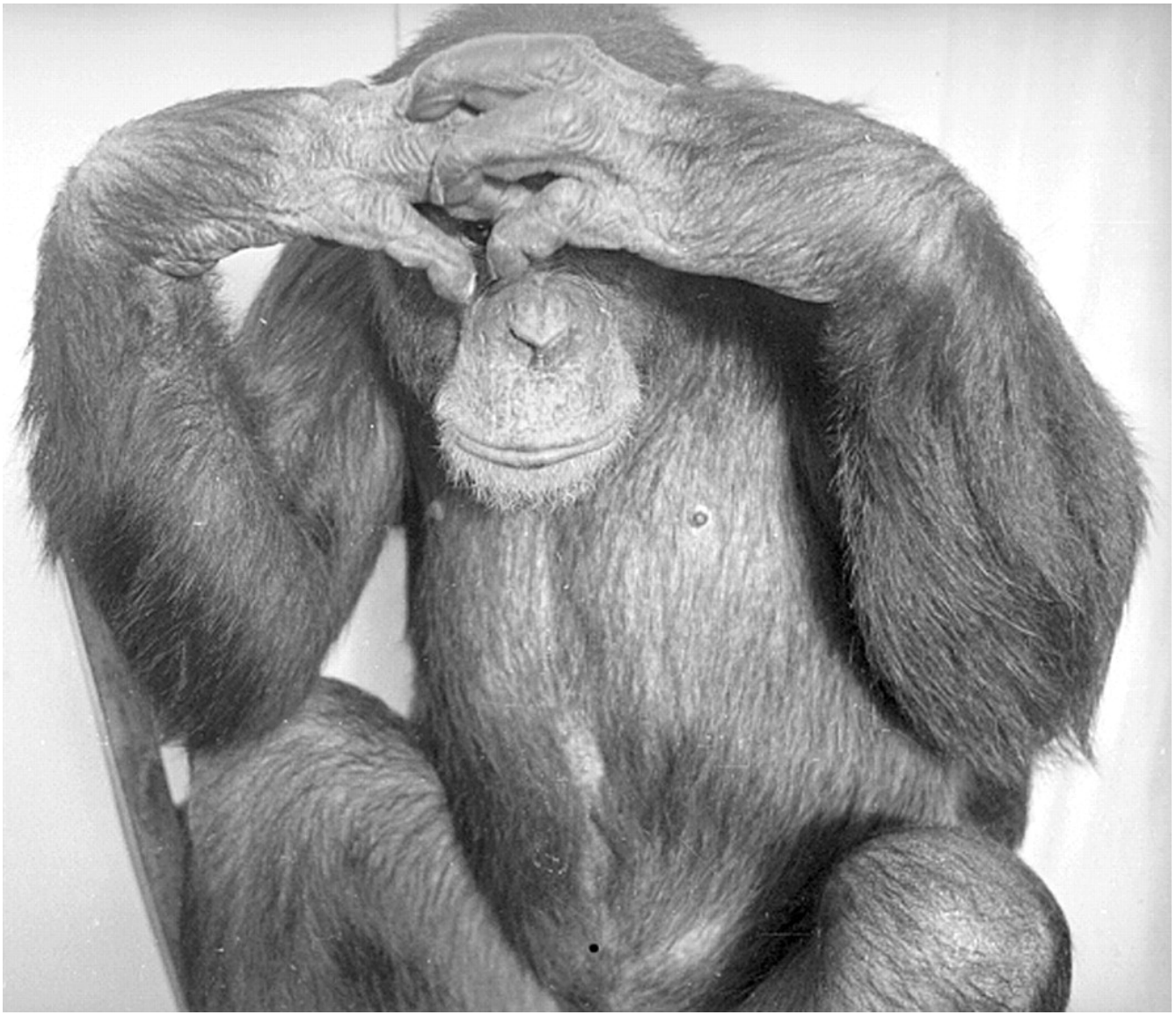
PTC

Fox, A.L. (1932). The relationship between chemical constitution and taste. *Proc. Natl. Acad. Sci USA* 18: 115-120.

Fisher, R. A., Ford, E. B., Huxley, J. (1939).
Taste-testing the anthropoid apes. *Nature* 144, 750



Jackie (Jacqueline)

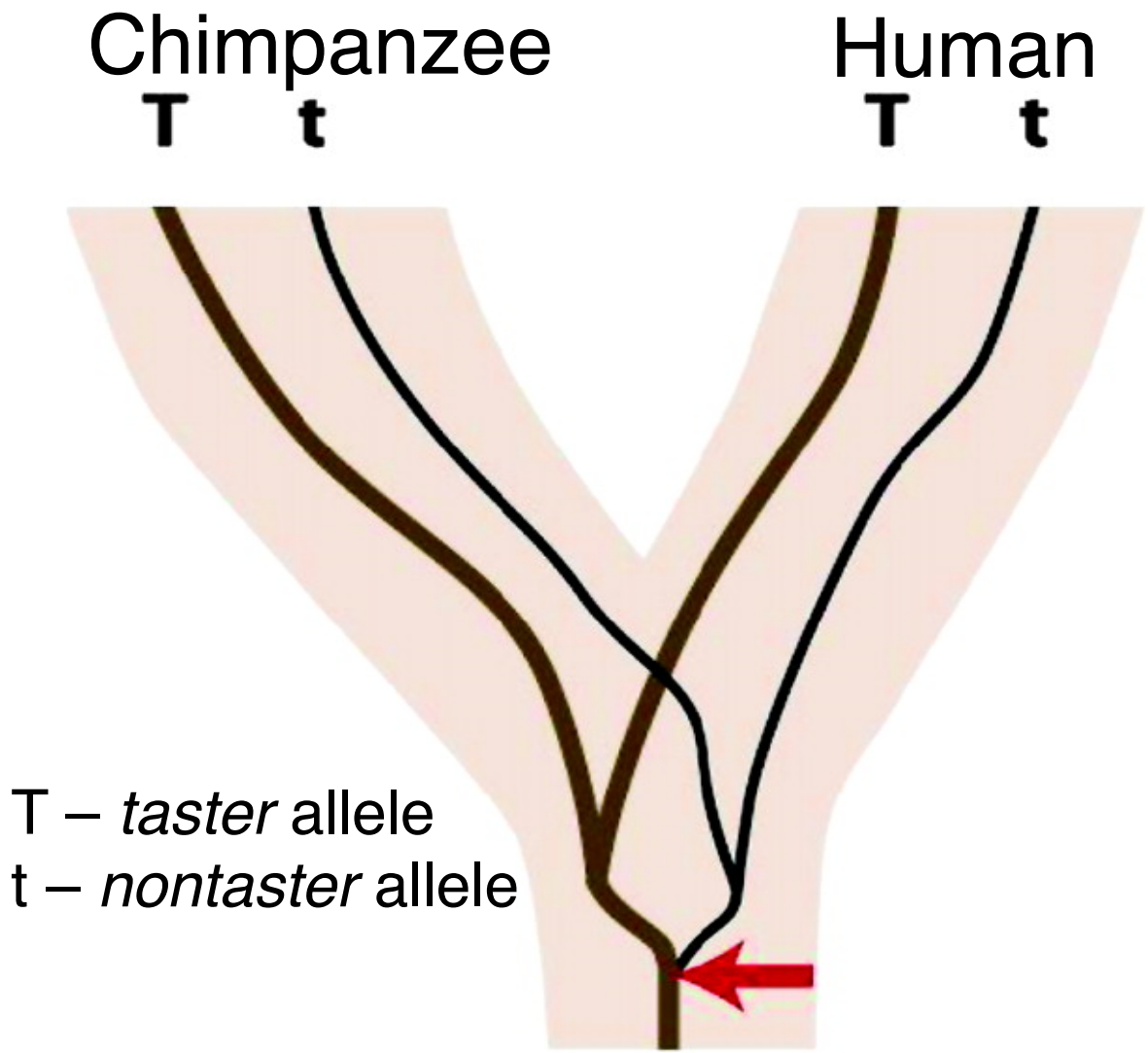


Sensitivity if tested chimps to PTC

$\sum$	tasters	nontasters
27	20	7
	(0.75)	(0.25)
	TT+Tt	*tt*

Fisher, R. A., Ford, E. B., Huxley, J. (1939) Taste-testing the anthropoid apes. *Nature* 144, 750.

Evolutionary origin of *T* and *t* alleles



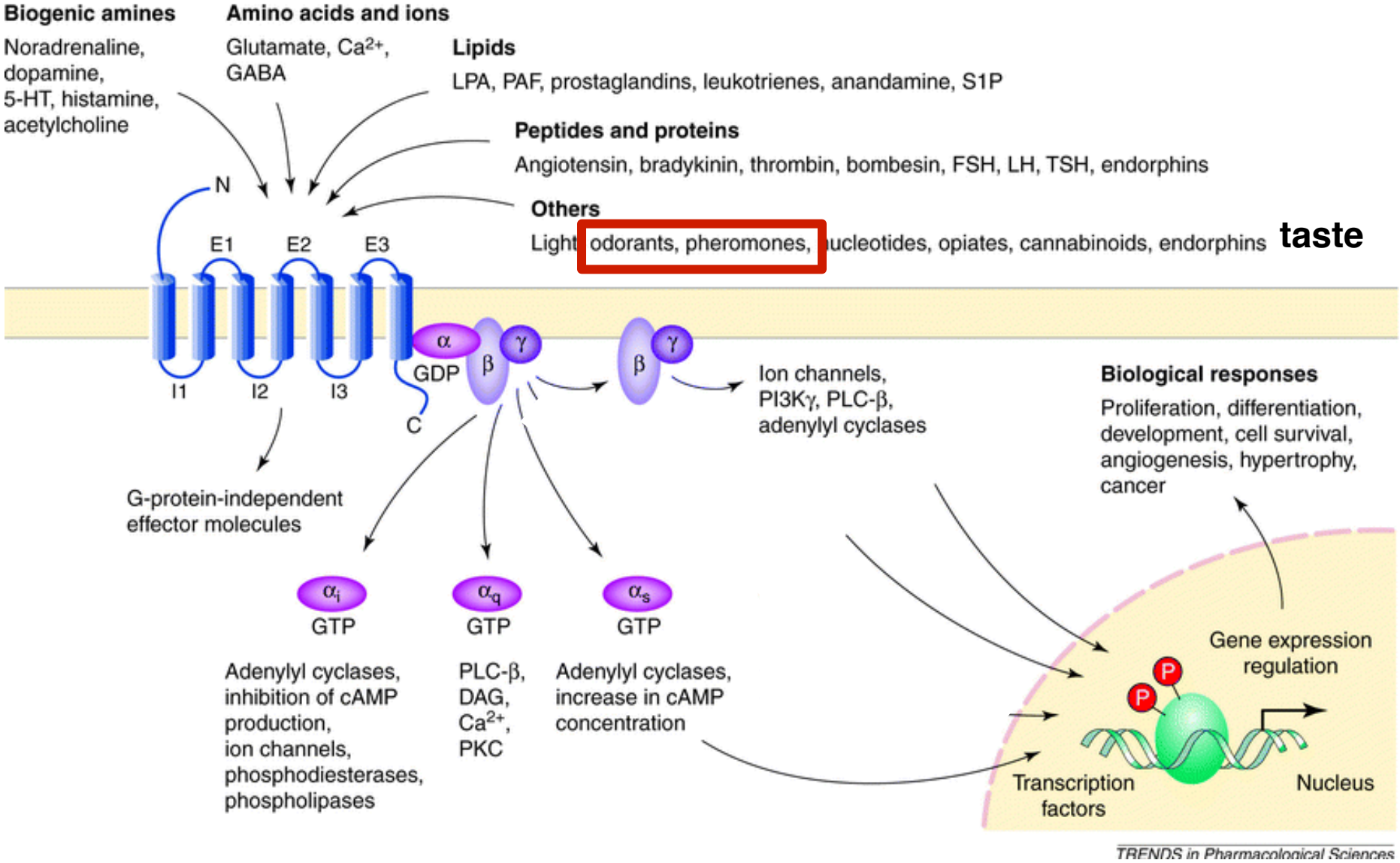
Fisher, R. A., Ford, E. B., Huxley, J. (1939) Taste-testing the anthropoid apes. *Nature* 144, 750.

What is the molecular nature of PTC sensitivity?

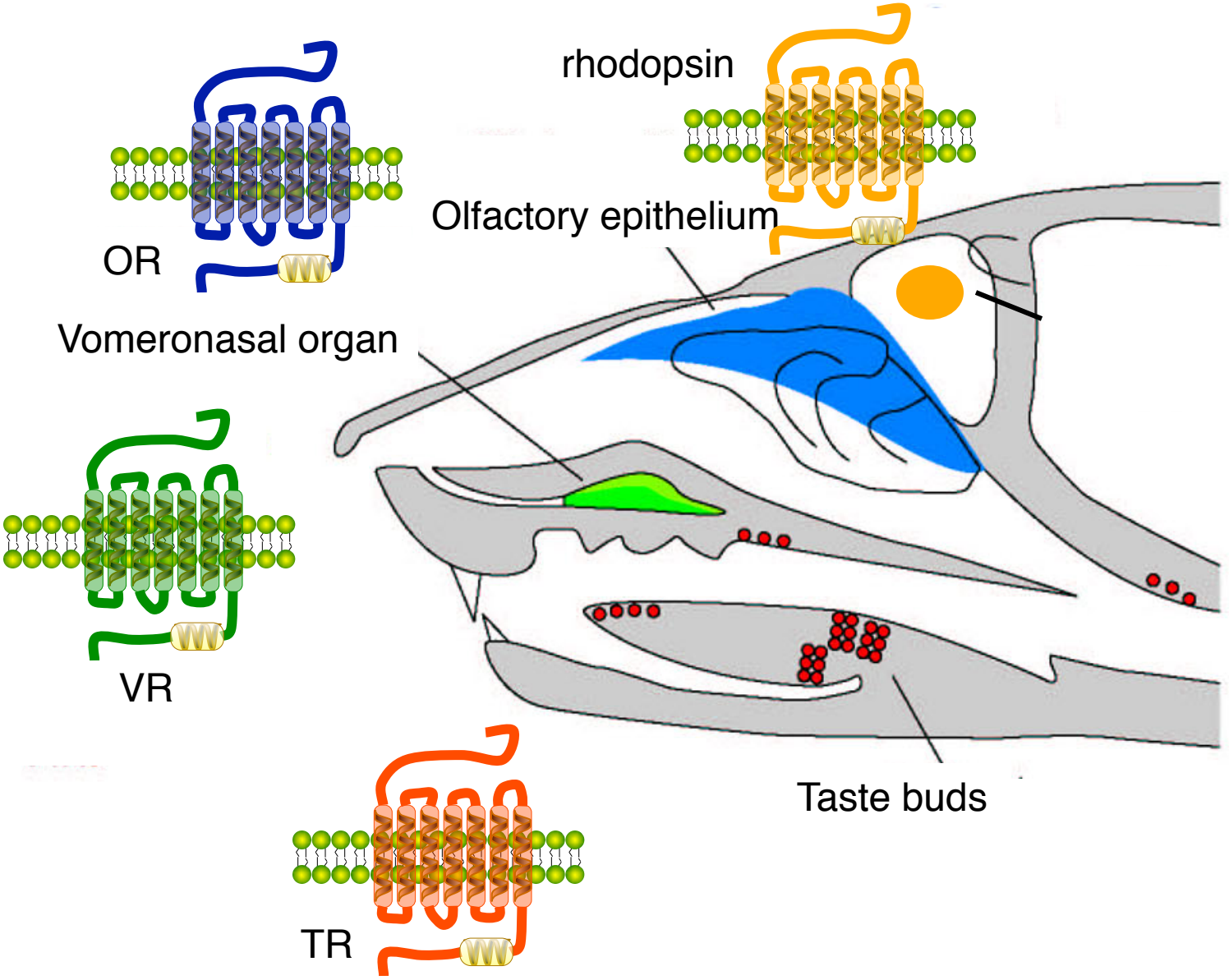
Adler, E., Hoon, M.A., Mueller, K.L., Chandrashekar, J., Ryba, N.J., Zuker, C.S. (2000). A novel family of mammalian taste receptors. *Cell* 100: 693-702.

Chandrashekar, J., Mueller, K.L., Hoon, M.A., Adler, E., Feng, L., Guo, W., Zuker, C.S., Ryba, N.J. (2000). T2Rs function as bitter taste receptors. *Cell* 100: 703-711.

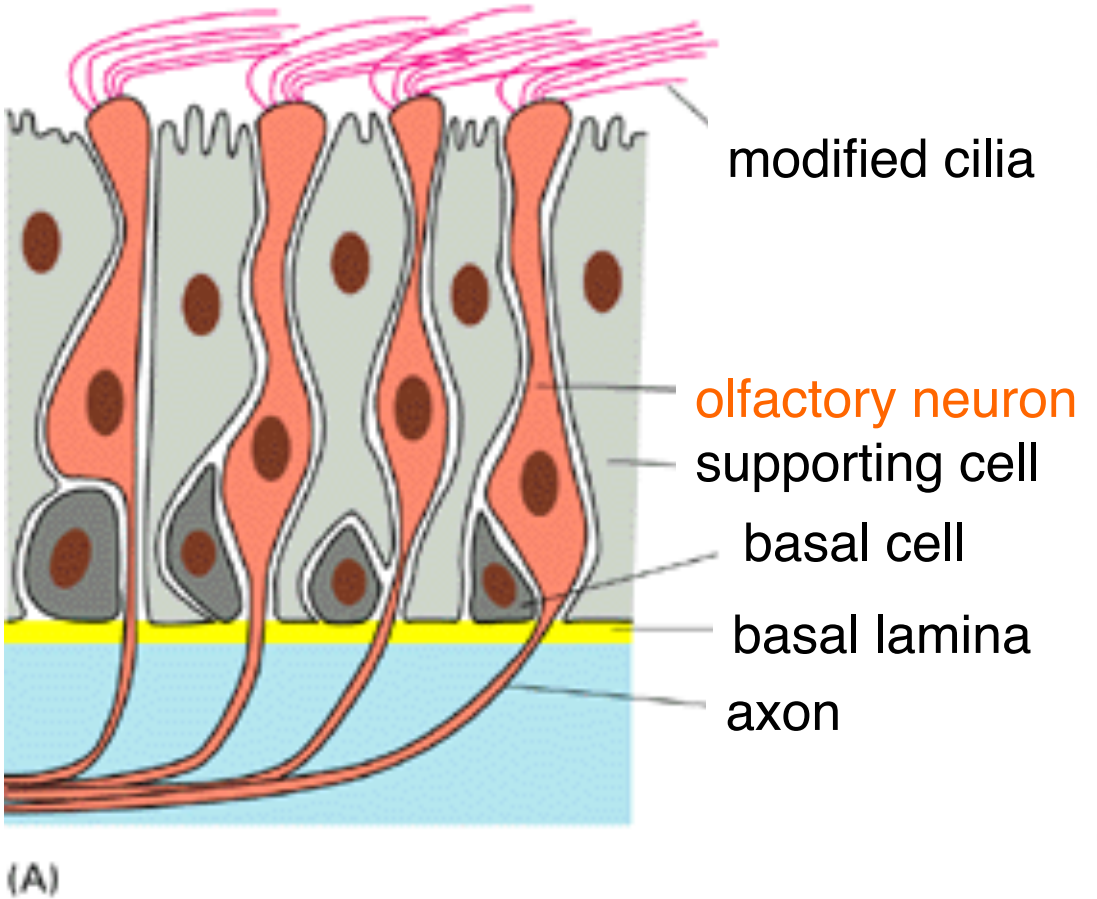
Ligands, efectors and biological responses for GPCRs



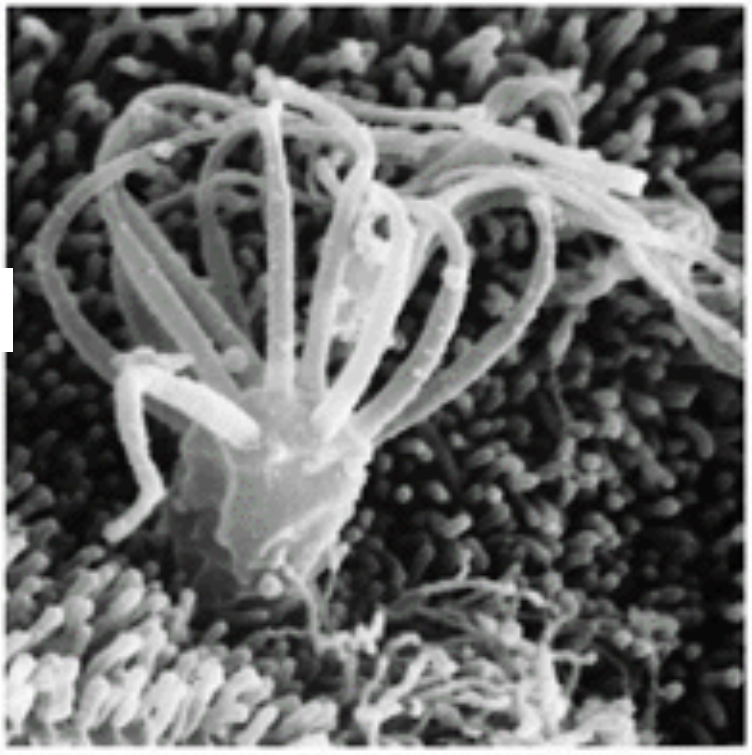
One type of receptor is employed for interpretation of many sensory stimuli



G proteins and olfaction

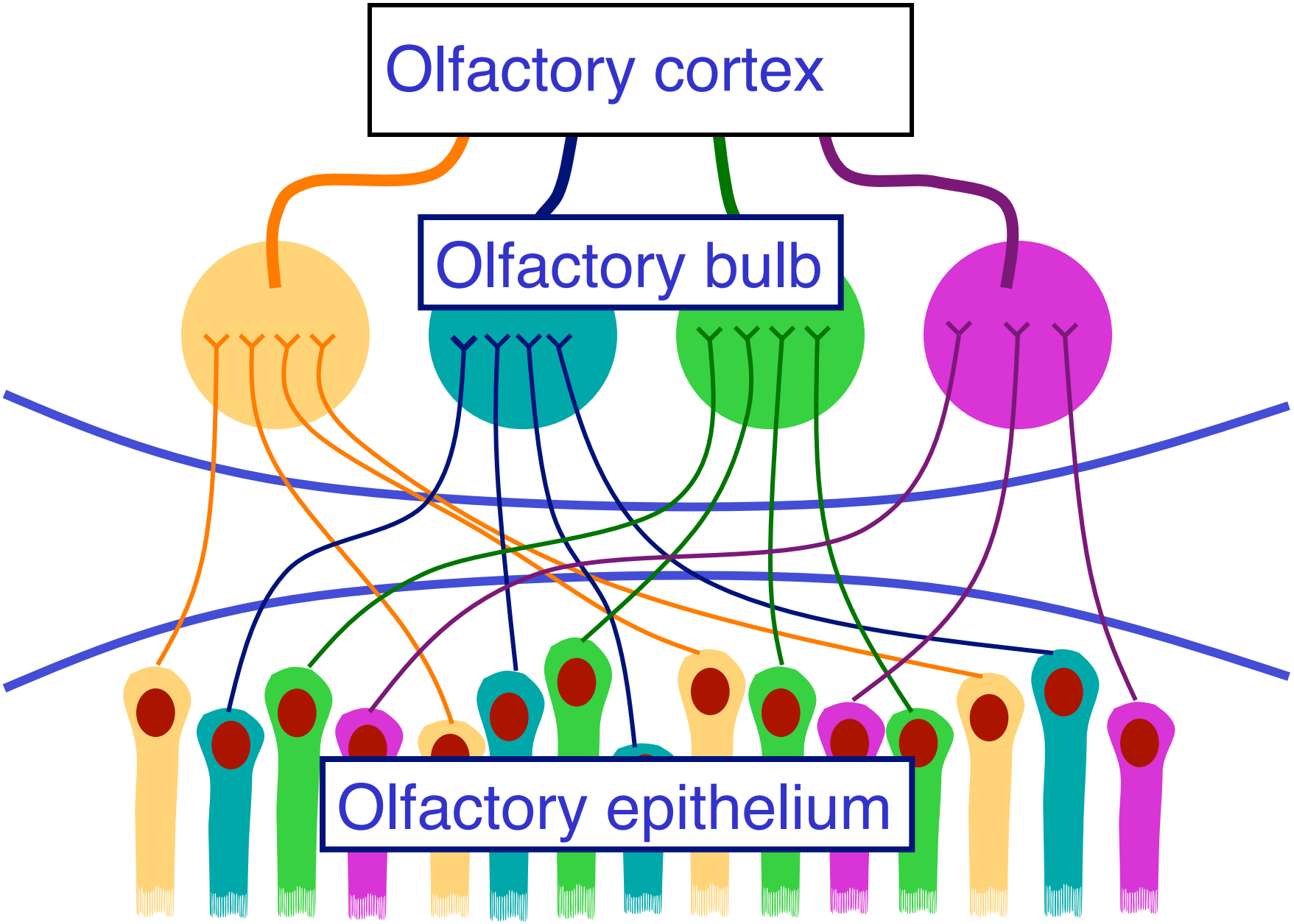


(A)

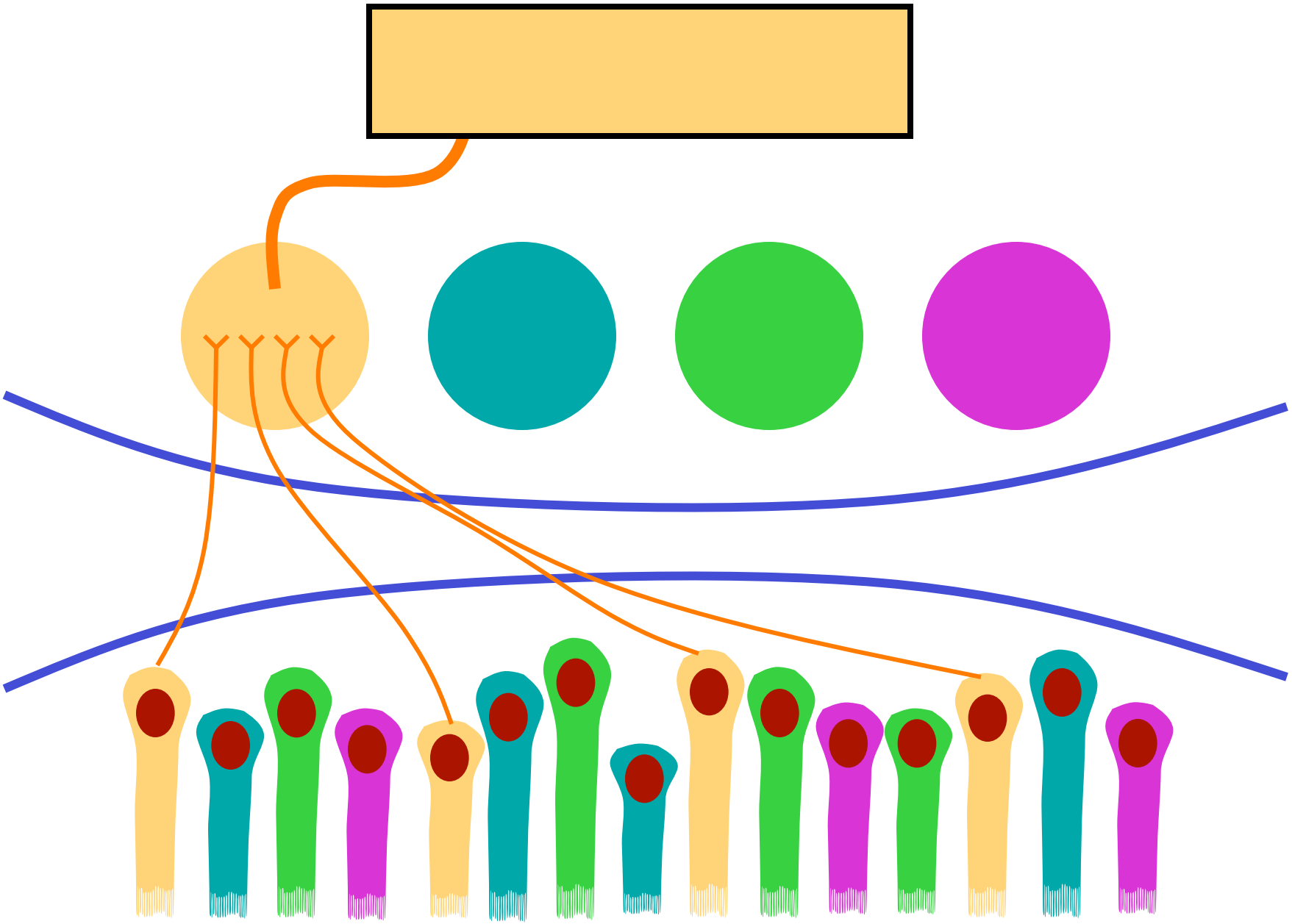


(B)

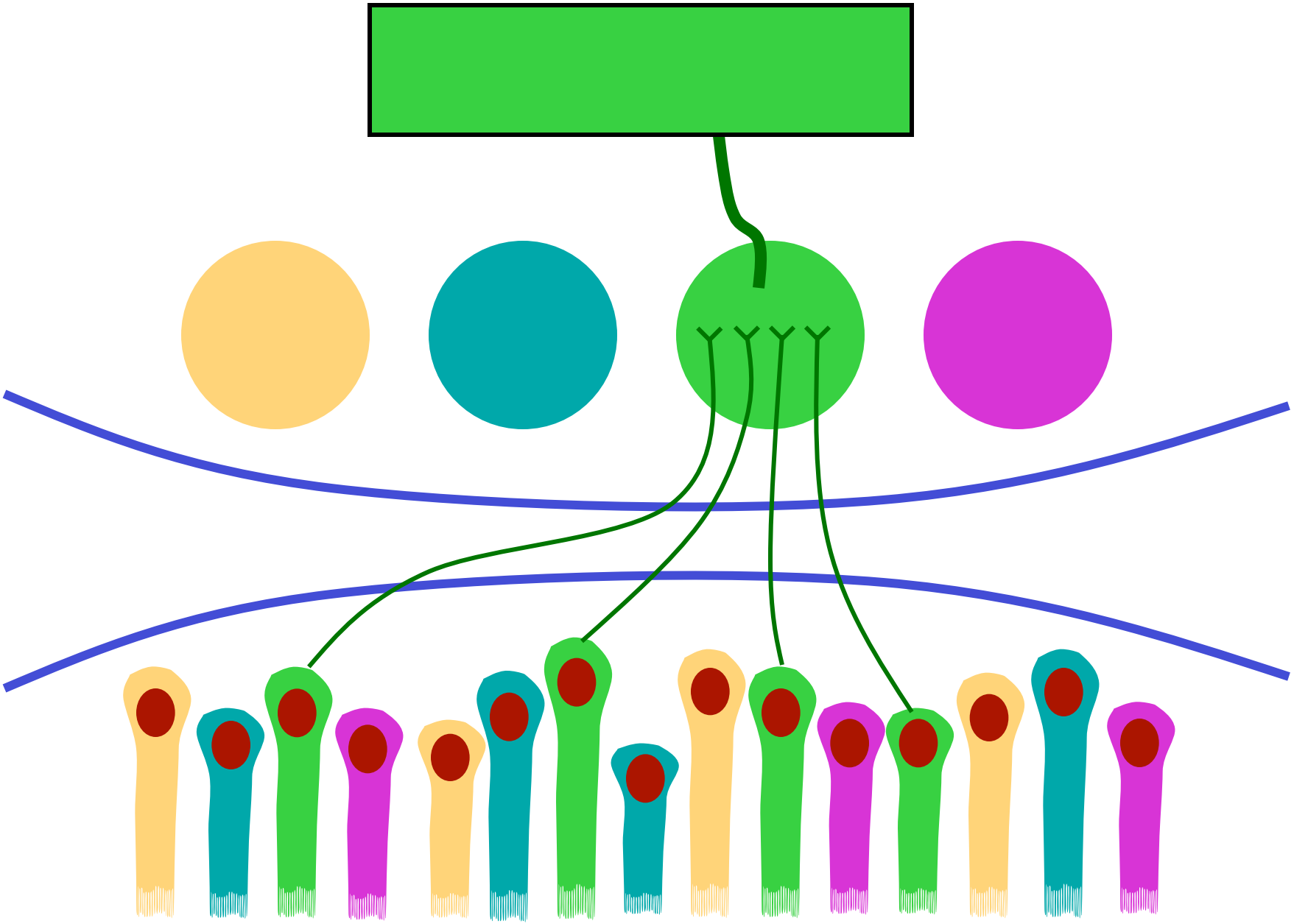
Molecular logic of smell



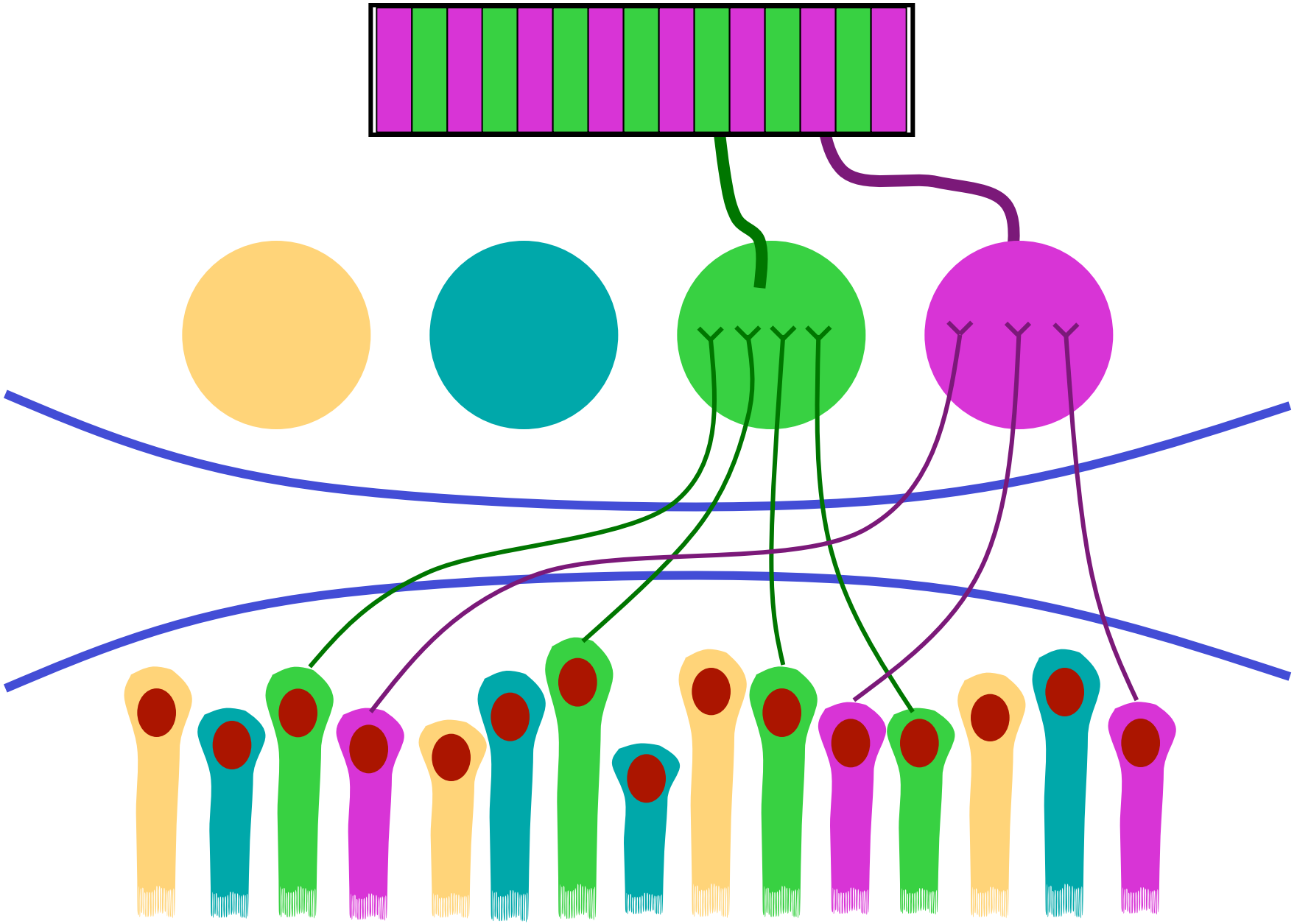
Molecular logic of smell



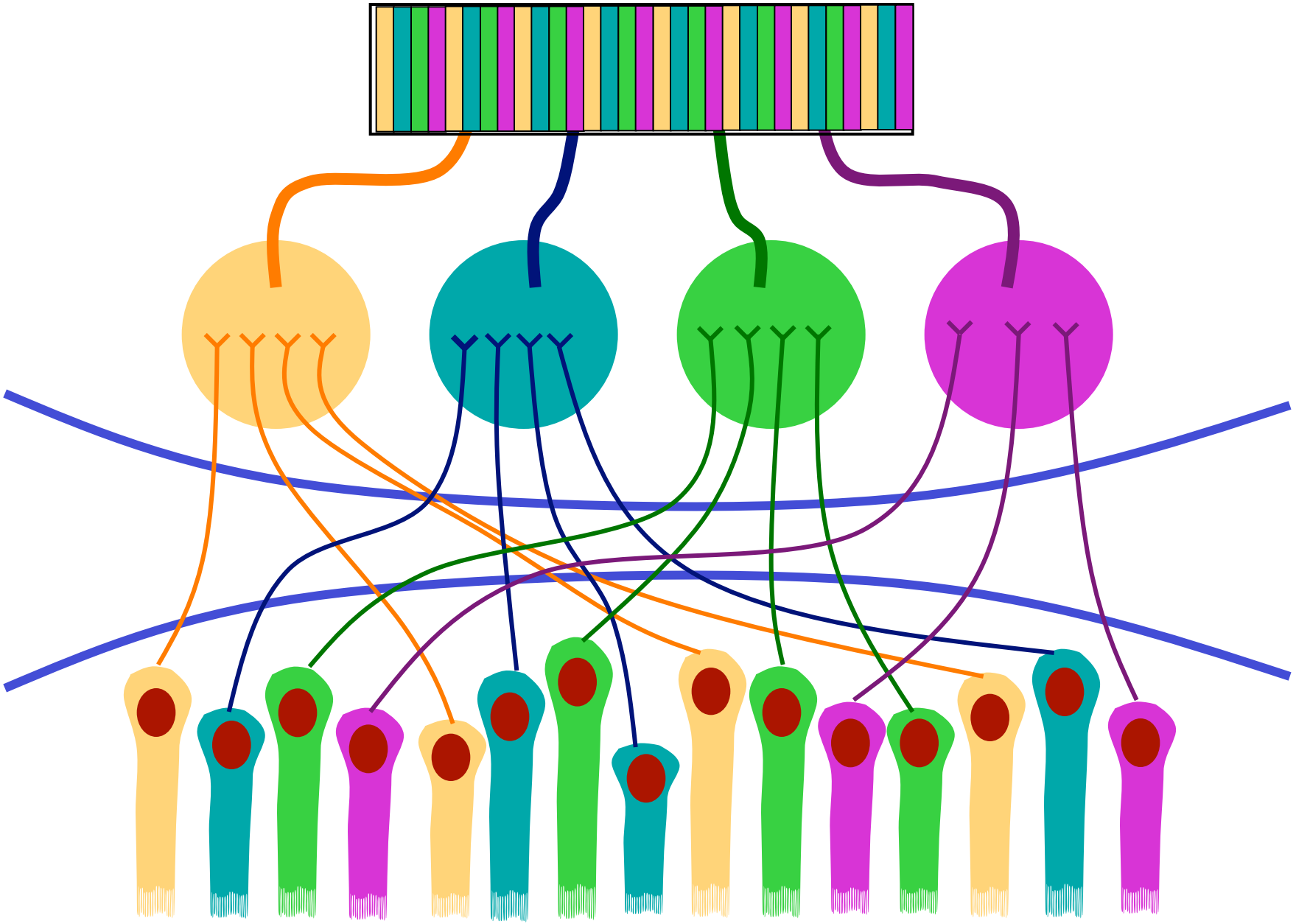
Molecular logic of smell



Molecular logic of smell



Molecular logic of smell



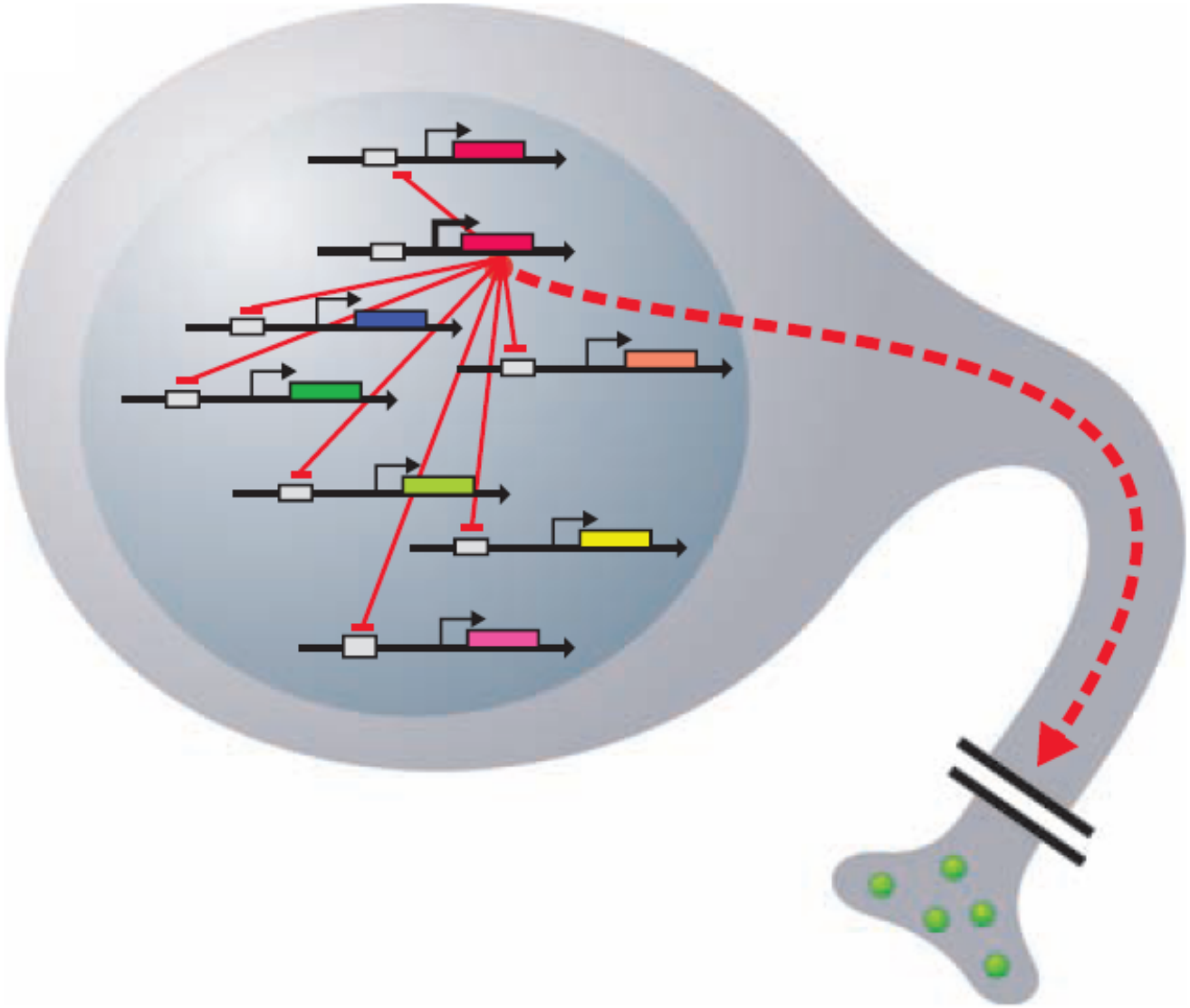
Decoding molecular logic of smell resulted in Nobel prize for Physiology or Medicine in 2004

Richard Axel

Linda Buck

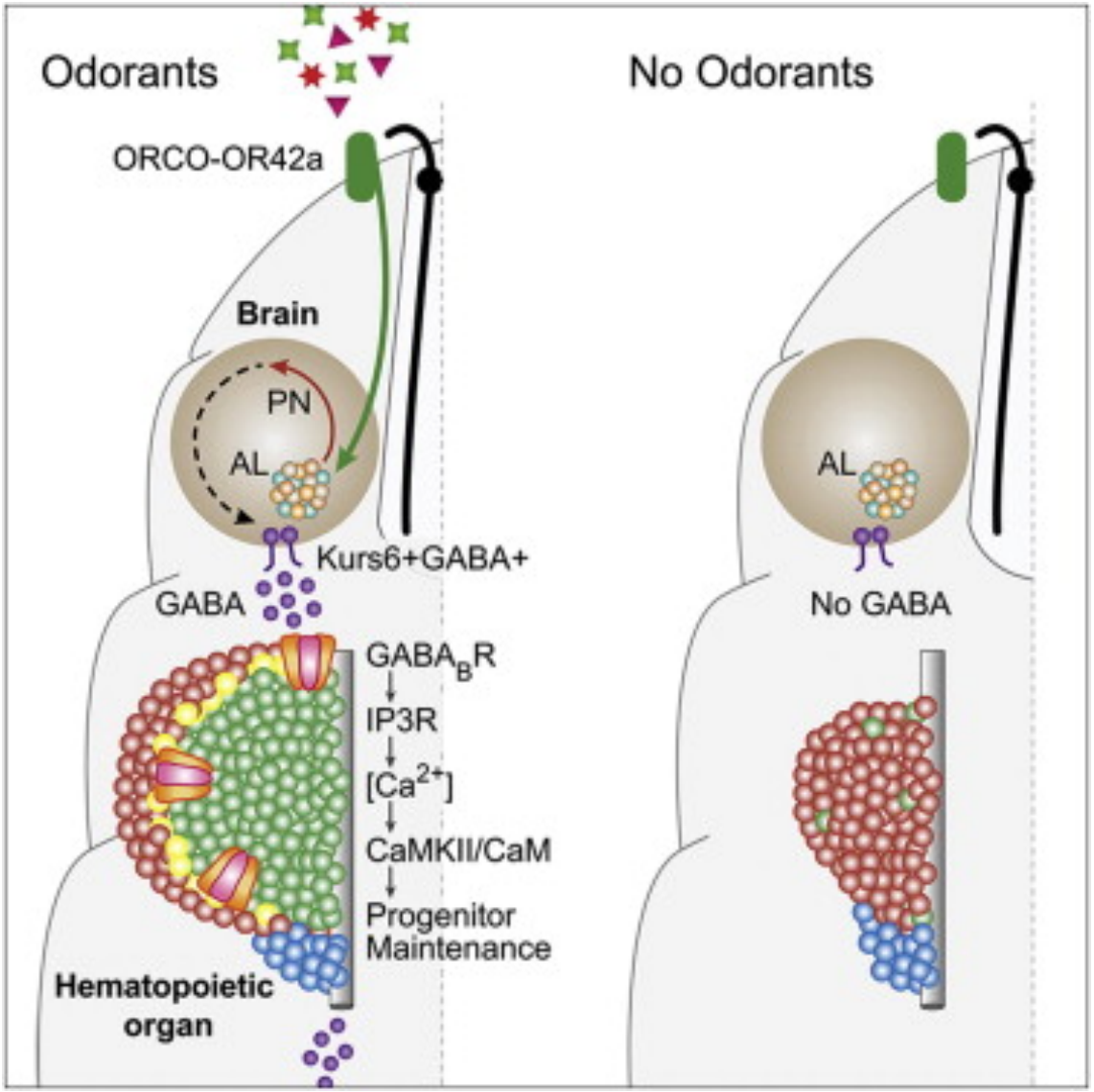
www.nobelprize.org

How to achieve monoallelic expression of a OR in a given neuron?



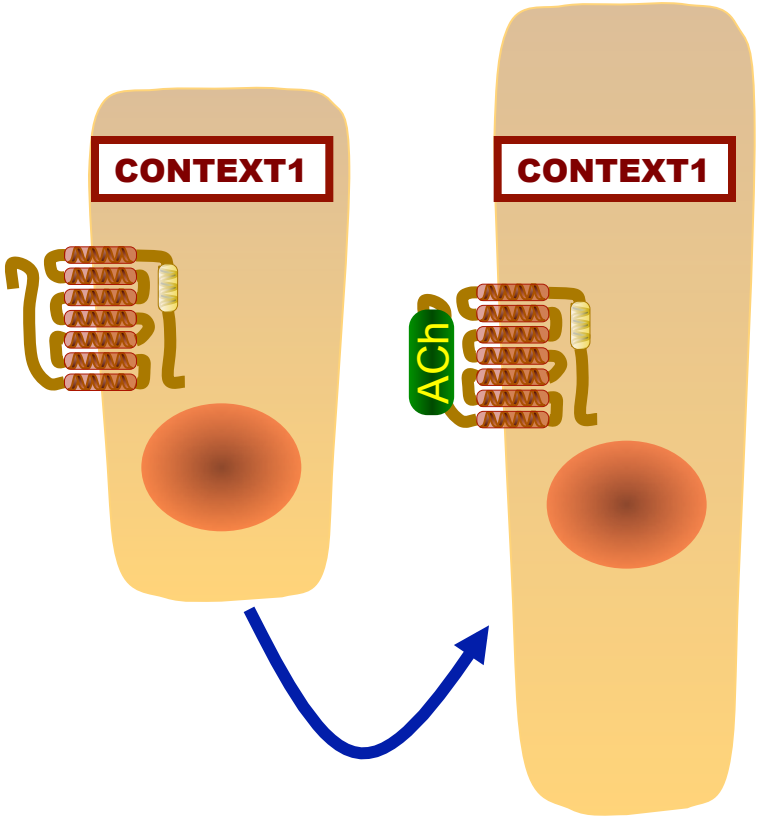
Lomvardas *et al*. (2006). *Cell* 126: 403-413.

Unexpected connection: Olfactory signals control hematopoietic progenitor maintenance

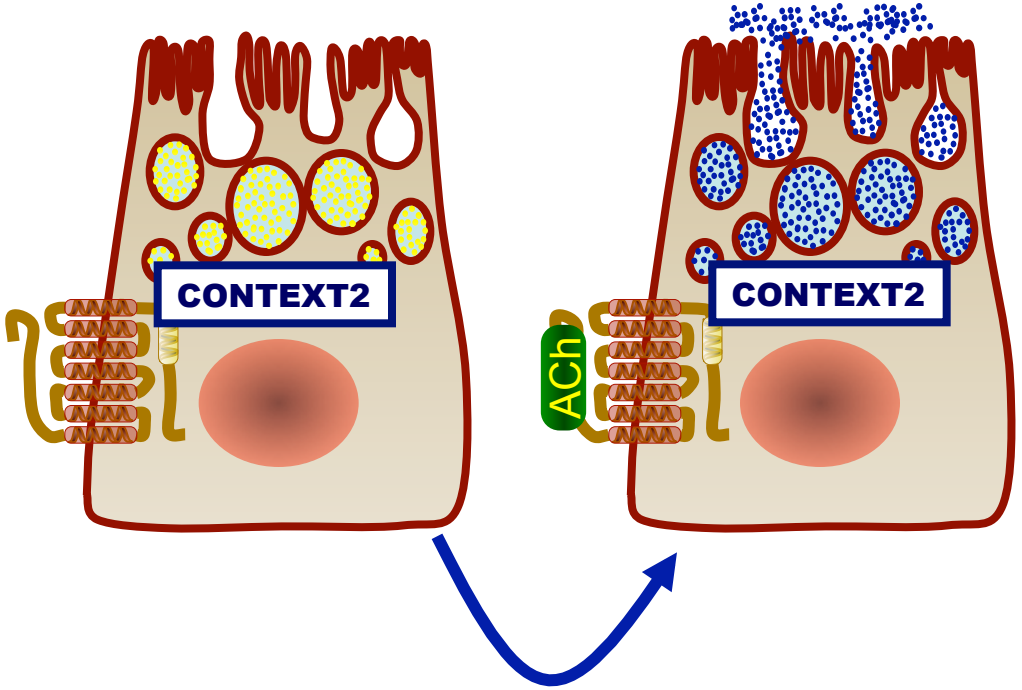


Shim et al. (2013). *Cell* **155**: 1141-1153
Silberstein & Scadden (2013). *Cell* **155**: 981-982

Interpretation of the instruction is dependent on a cellular context

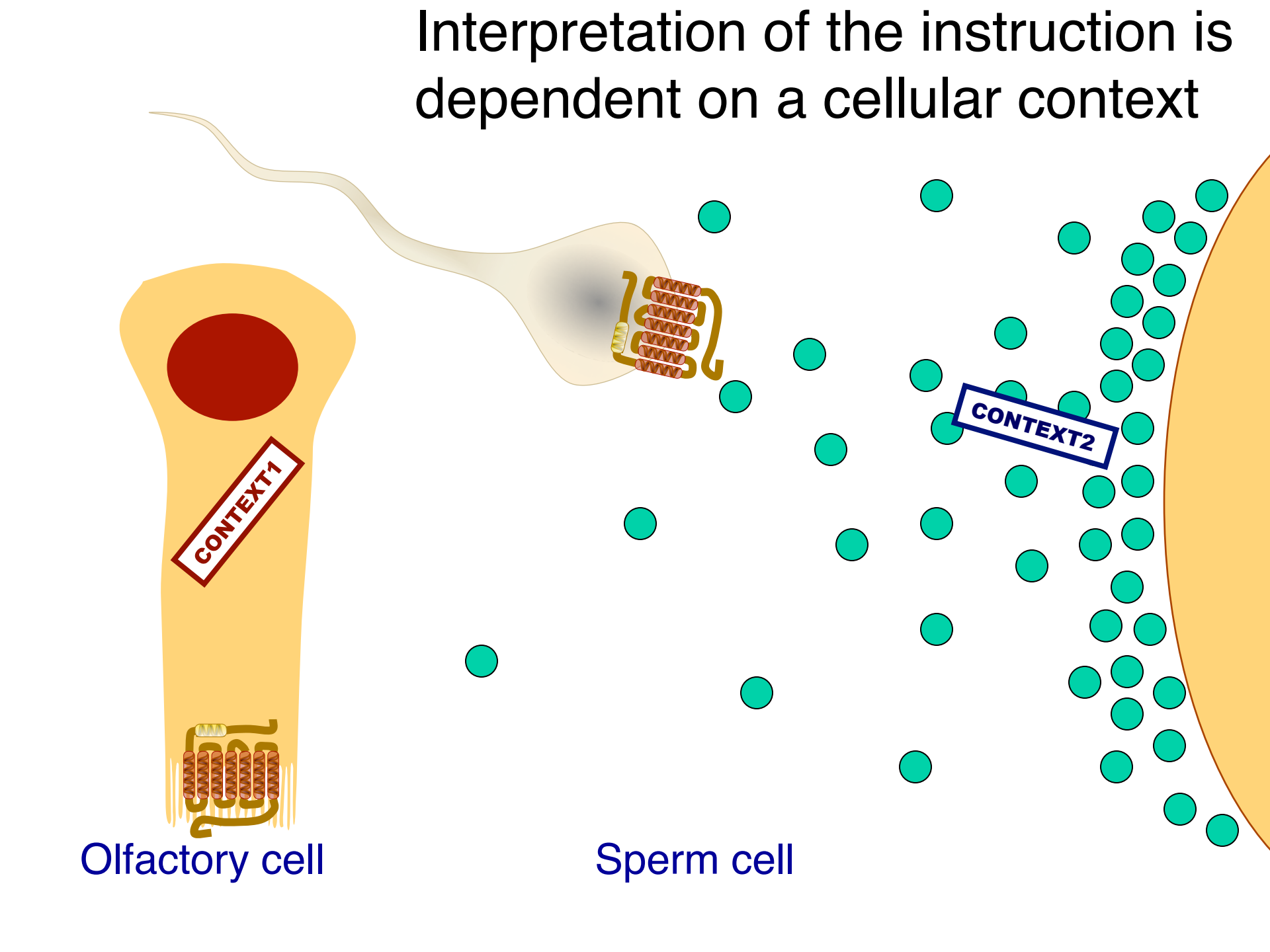


nonmuscle cell

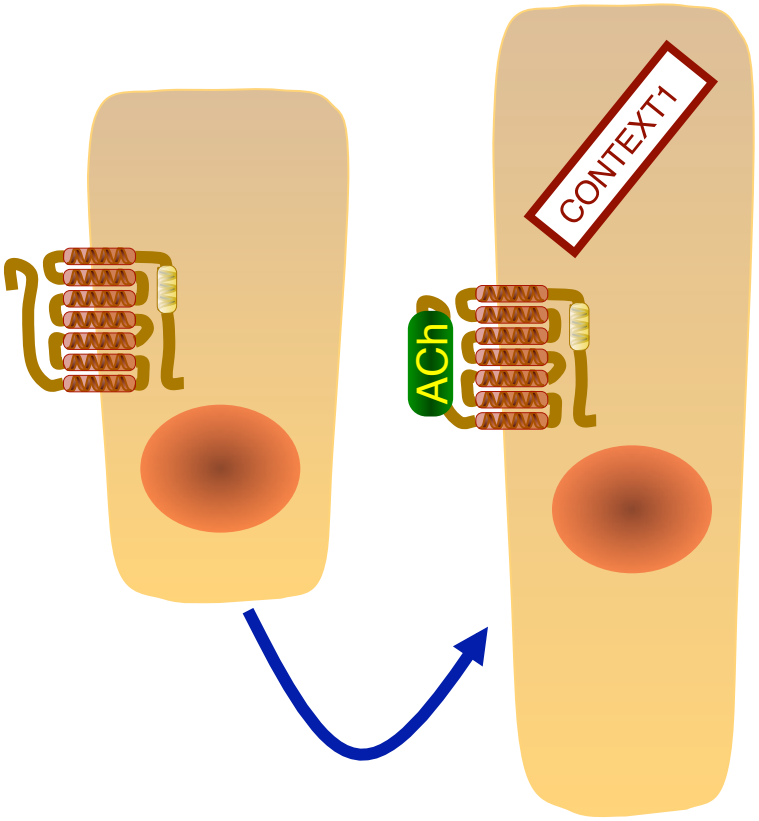


Secretory cell in salivary gland

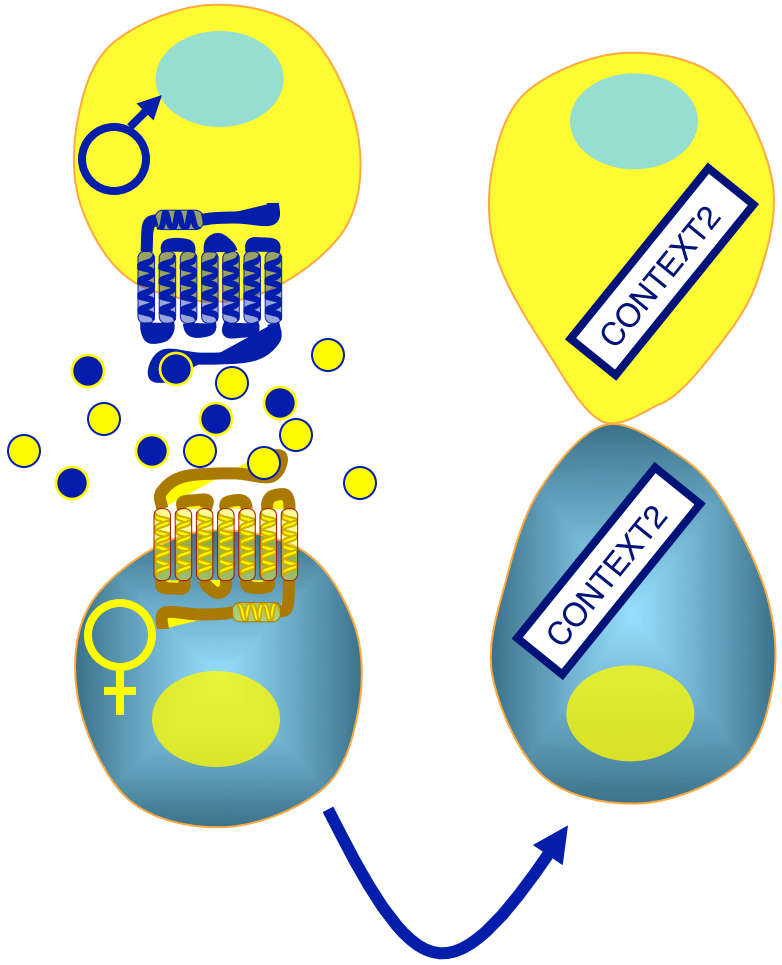
Interpretation of the instruction is dependent on a cellular context



Interpretation of the instruction is dependent on a cellular context

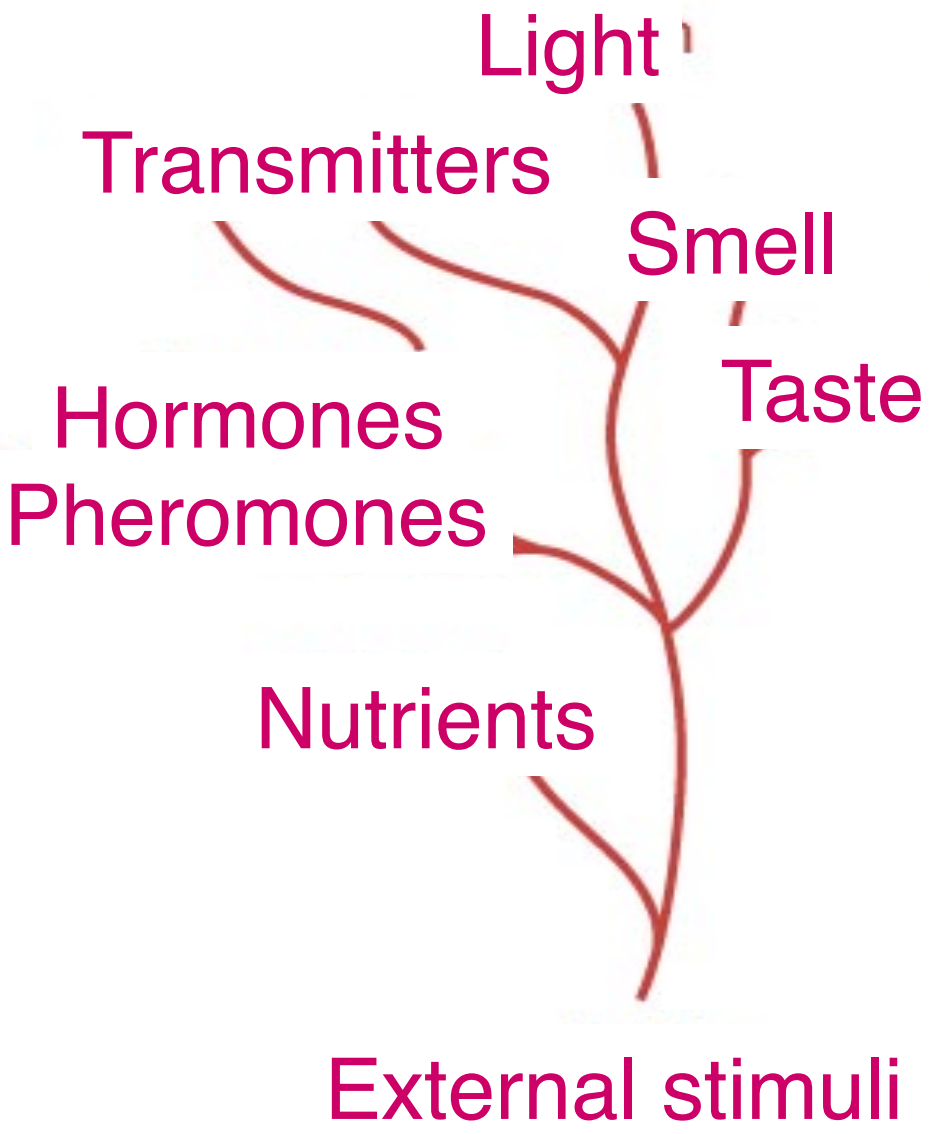


Muscle cell



Sexually active yeast cells

Repetoire of molecular tools is far more limited than the number of problems faced by living organisms…



GPRC and G proteins involved in human cancer pathogenesis

G protein or receptor	Type of tumor
Activating mutations affecting G proteins	
$G\alpha_s$	thyroid adenomas and carcinomas, pituitary adenomas
$G\alpha_{i2}$	ovarian tumors, adrenal cortical tumors
Activating mutations affecting G-protein–coupled receptors	
Thyroid-stimulating hormone receptor	thyroid adenomas and carcinomas
Follicle-stimulating hormone receptor	ovarian tumors
Luteinizing hormone receptor	Leydig cell hyperplasias
Cholecystokinin-2 receptor	colorectal carcinomas
Ca^{2+}-sensing receptor	various neoplasms
Virus-encoded G-protein–coupled receptors	
Kaposi's sarcoma herpesvirus (HHV-8)	Kaposi's sarcoma
Herpesvirus saimiri	primate leukemias and lymphomas
Jaagsiekte sheep retrovirus	sheep pulmonary carcinomas

Adapted from M.J. Marinissen and J.S. Gutkind, G-protein-coupled receptors and signaling networks: emerging paradigms, *Trends Pharmacol. Sci.* 22:368–376, 2001.