認知單元

Cell membrane
Ion channel and diseases
細胞膜
離子通道與疾病

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大綱

- 細胞，細胞膜，細胞膜蛋白質
- 研究離子通道的方法
- 離子通道的種類和功能
- 離子通道相關疾病

Size of Cells
細胞的大小

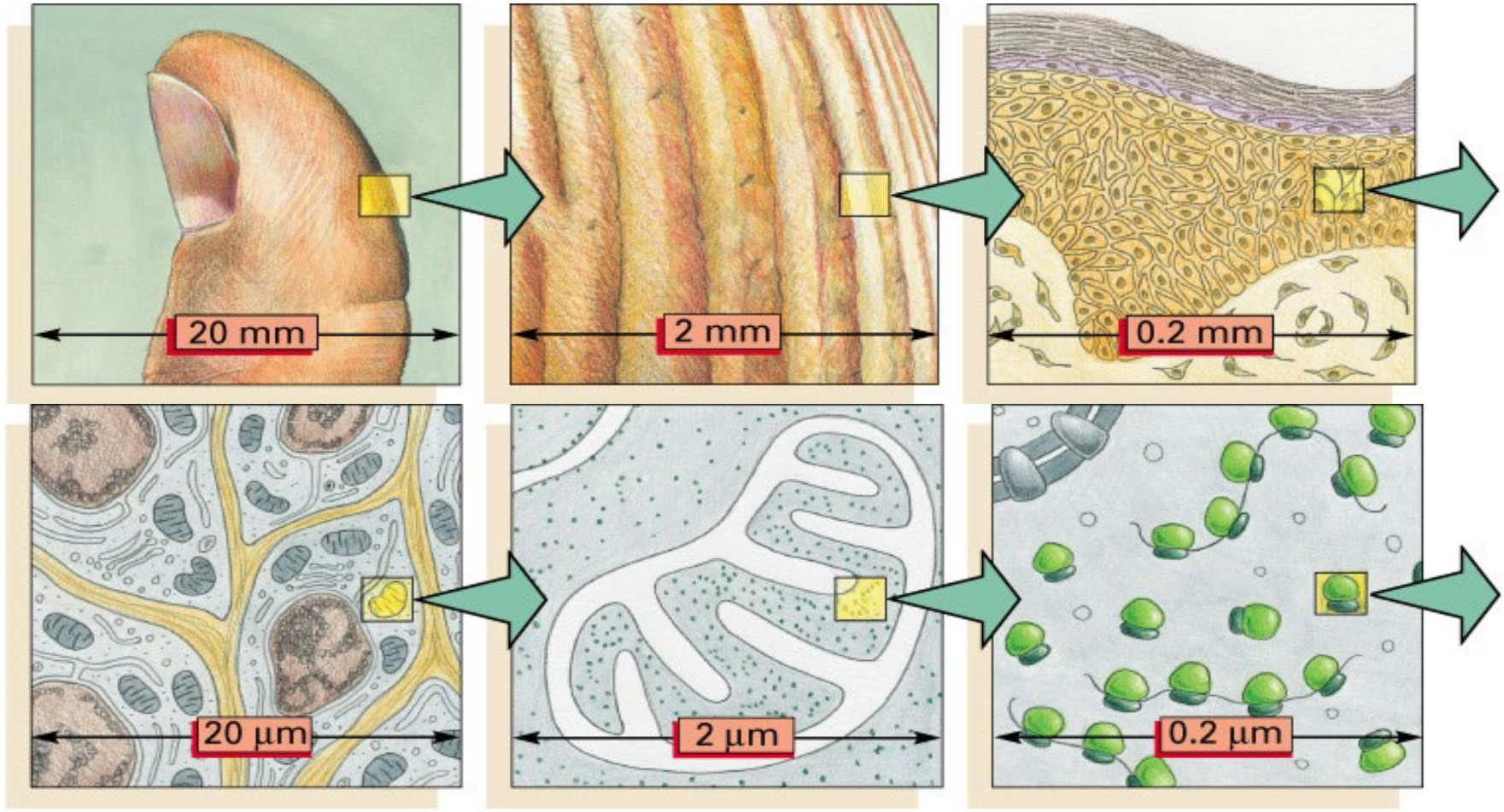
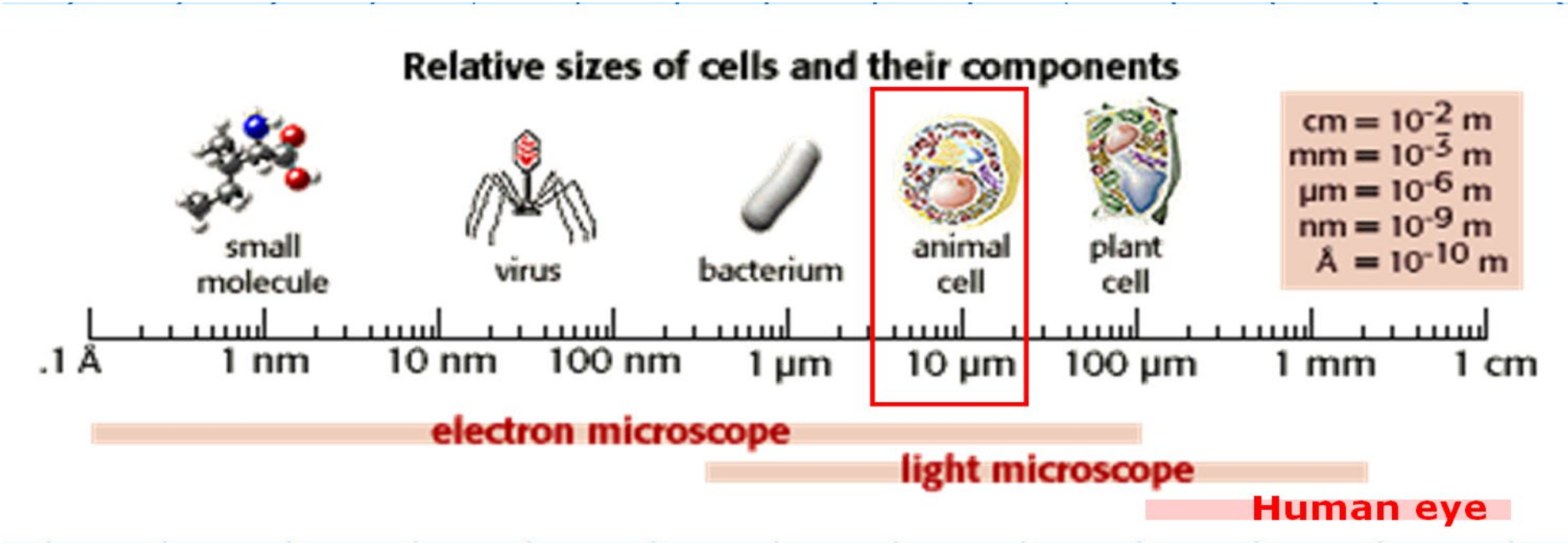


Figure 9–1 part 2 of 3. Molecular Biology of the Cell, 4th Edition.



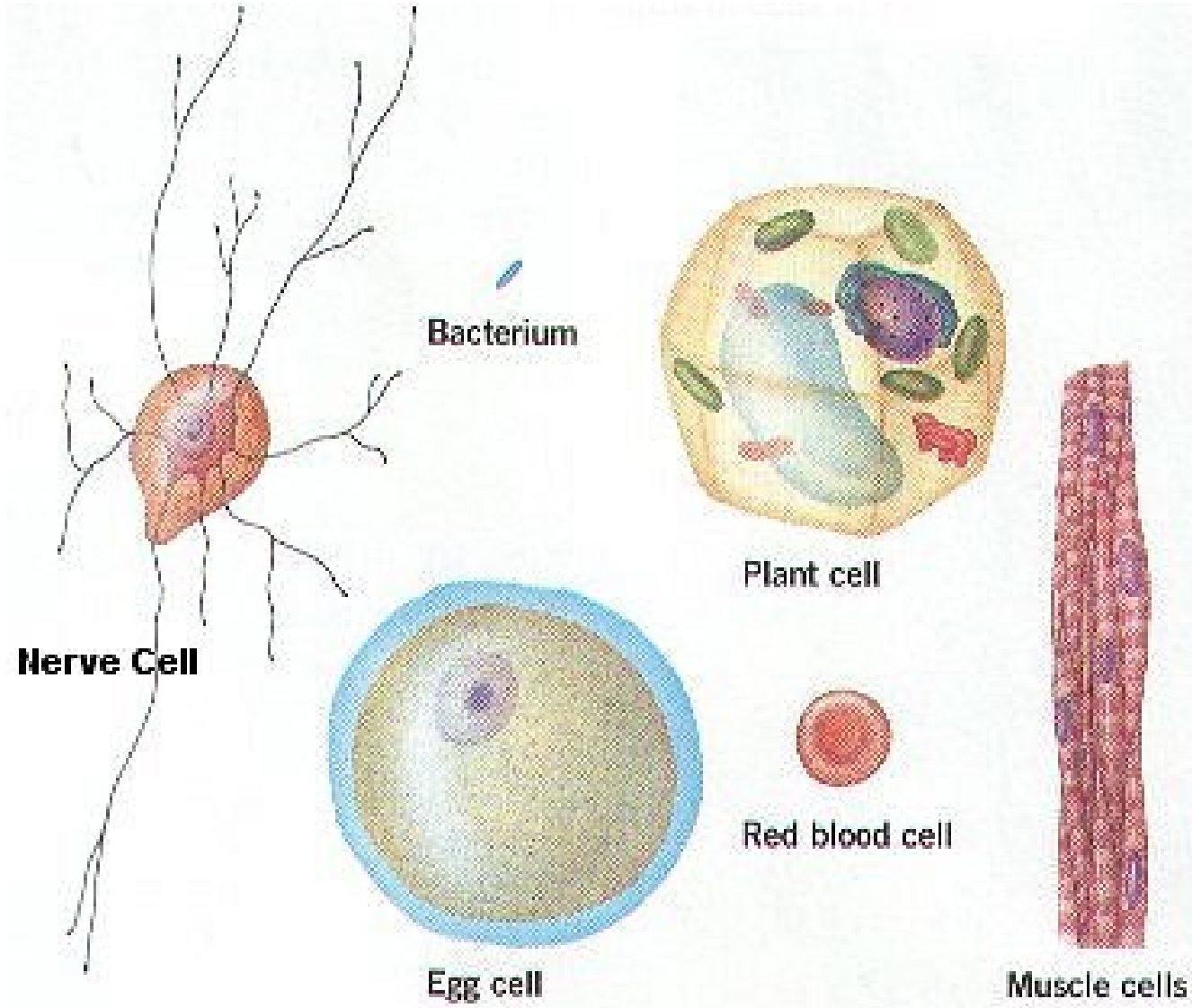
Diameter of a typical animal cell - 10 to 20 microns

micron = micrometer = um = 0.001 mm

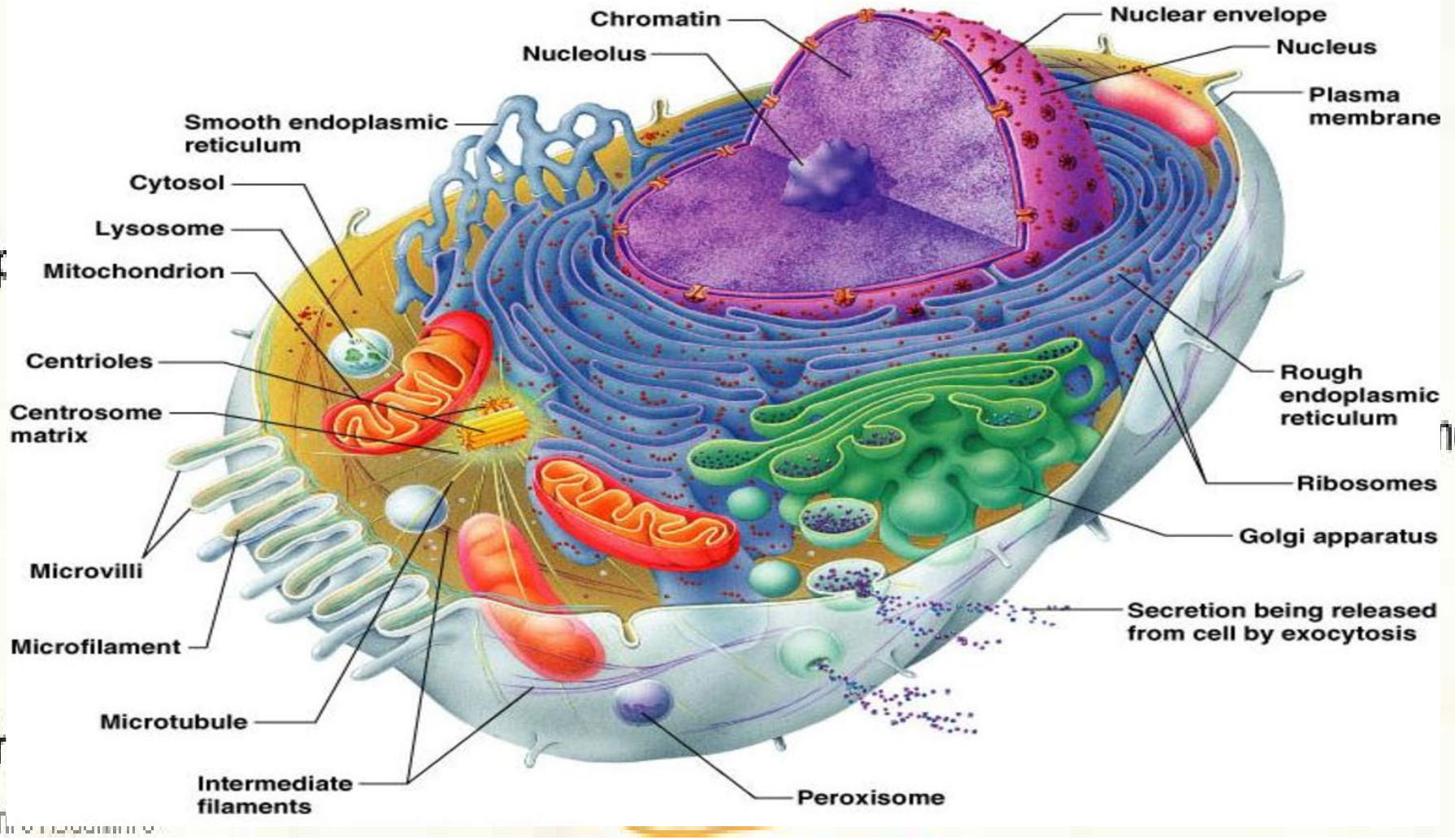
針頭的直徑大約是1 毫米, 因此細胞是大約1/100 針頭的直徑

http://sps.k12.ar.us/massengale/cell%20%20notes%20bi.htm

Cells come with different shape and size
不同形狀及大小的細胞

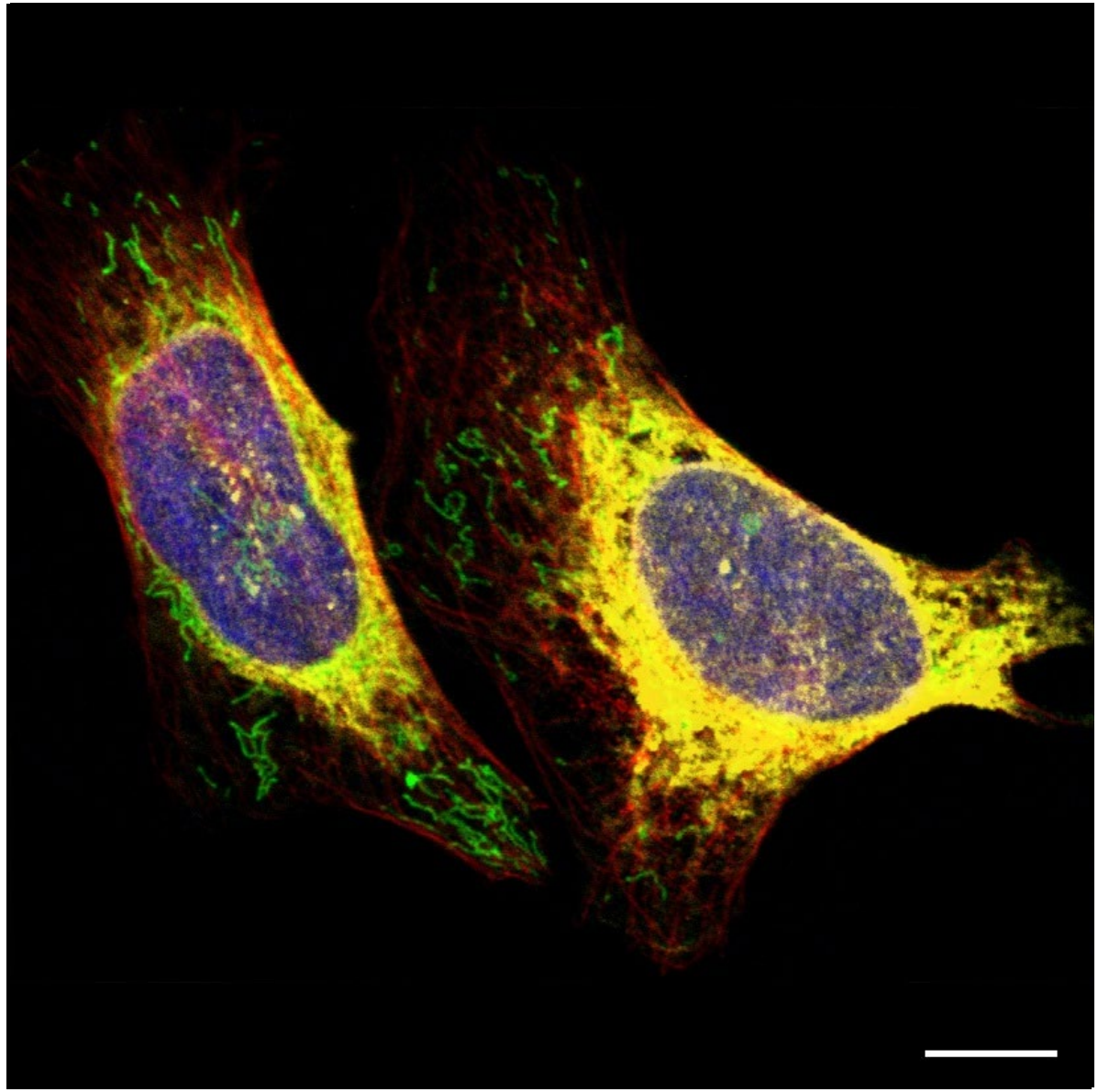


Structure of a Generalized Cell



http://www.infovisual.info/03/001_en.html

http://www.transcendancing.net/tag/cell-structure/



http://www.proteinatlas.org/learn/dictionary/cell/mitochondria

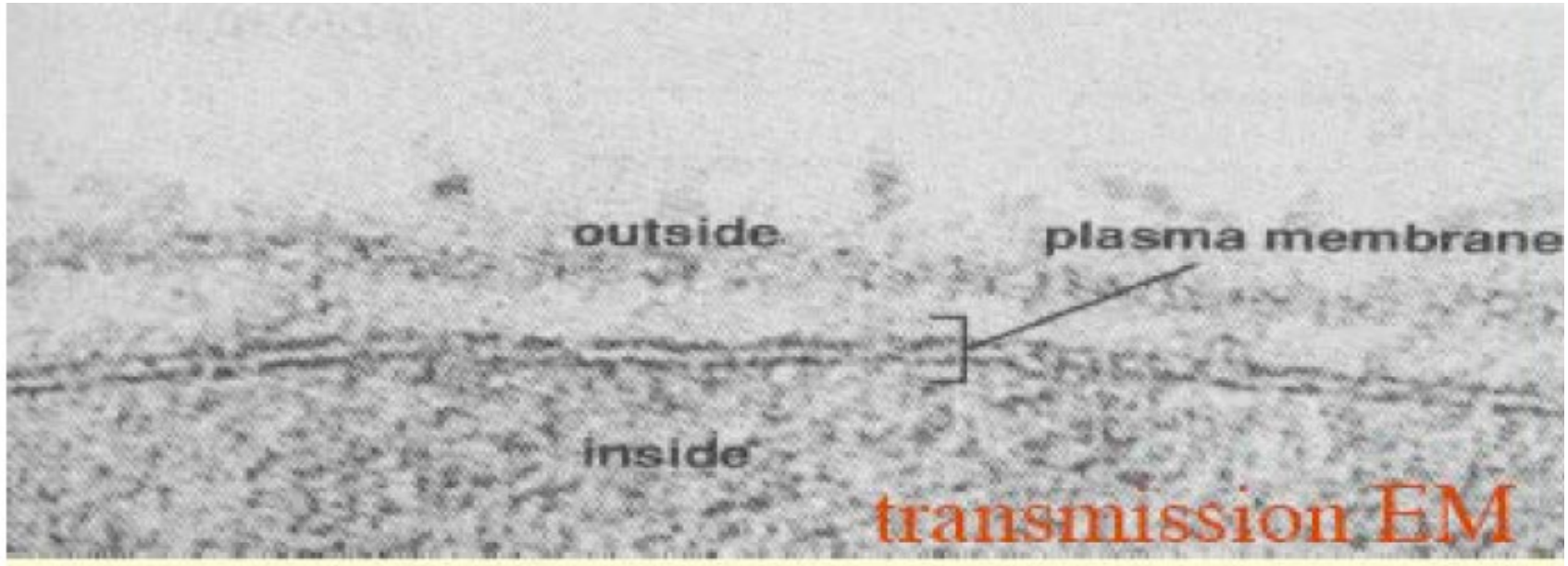
細胞就像一座城堡

http://www.kottke.org/plus/photos/200105europe/castle.jpg

Membrane Functions/細胞膜功能

Form compartments/ 隔間

7-8 nm



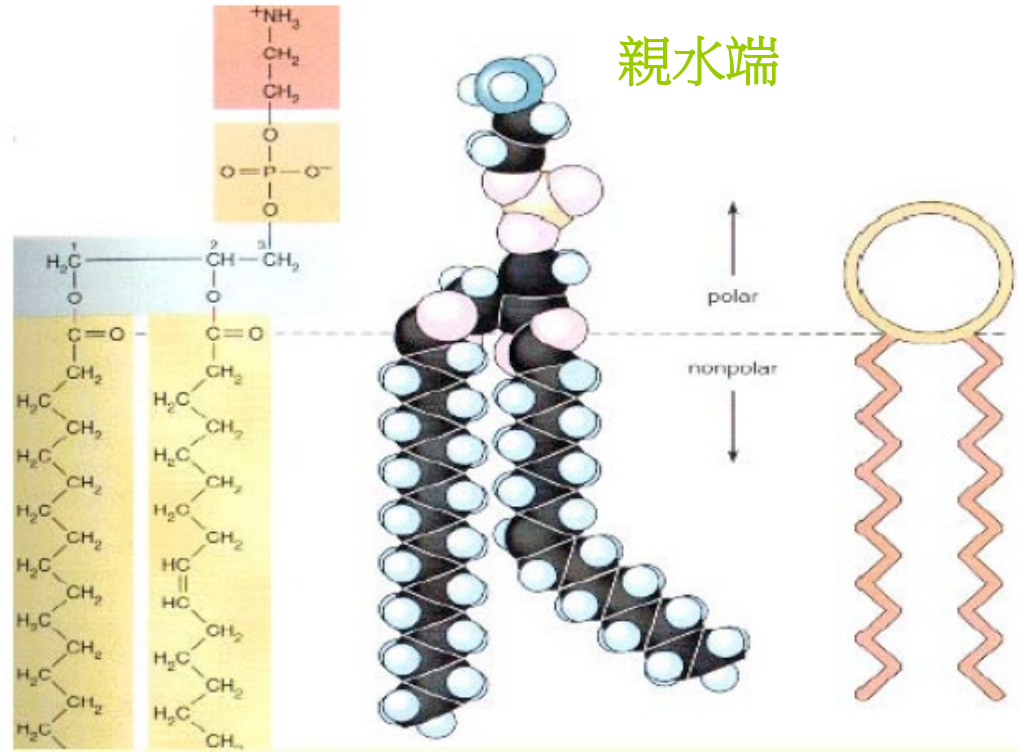
Cell Membrane

Phospholipids and proteins
First compartment formed

Prokaryotes (bacteria)/原核生物
Just one compartment

Eukaryotic cells)/真核生物
Many different compartments

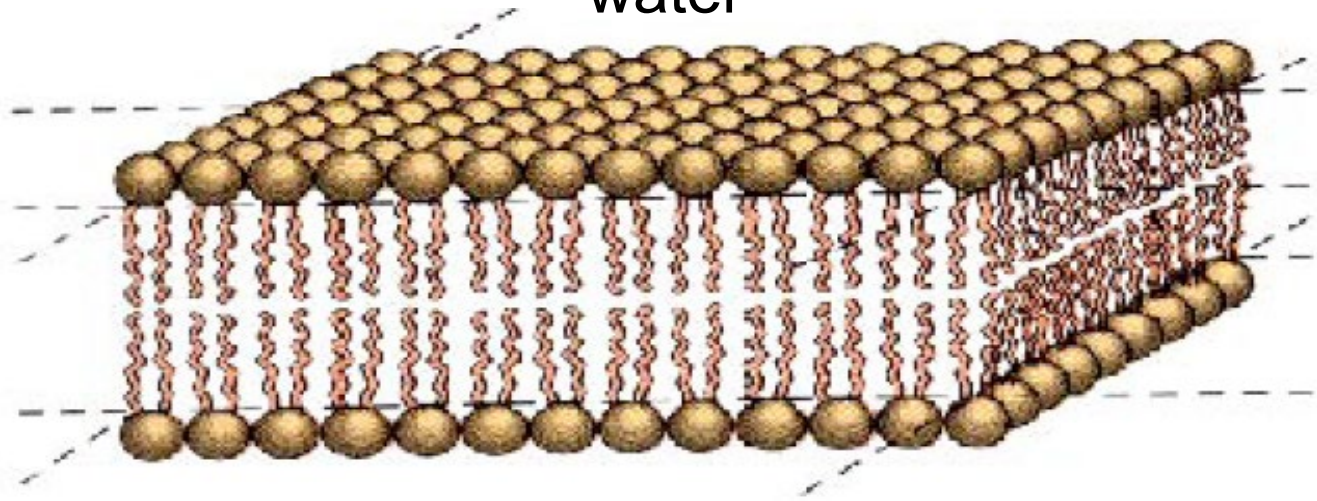
磷脂質



air

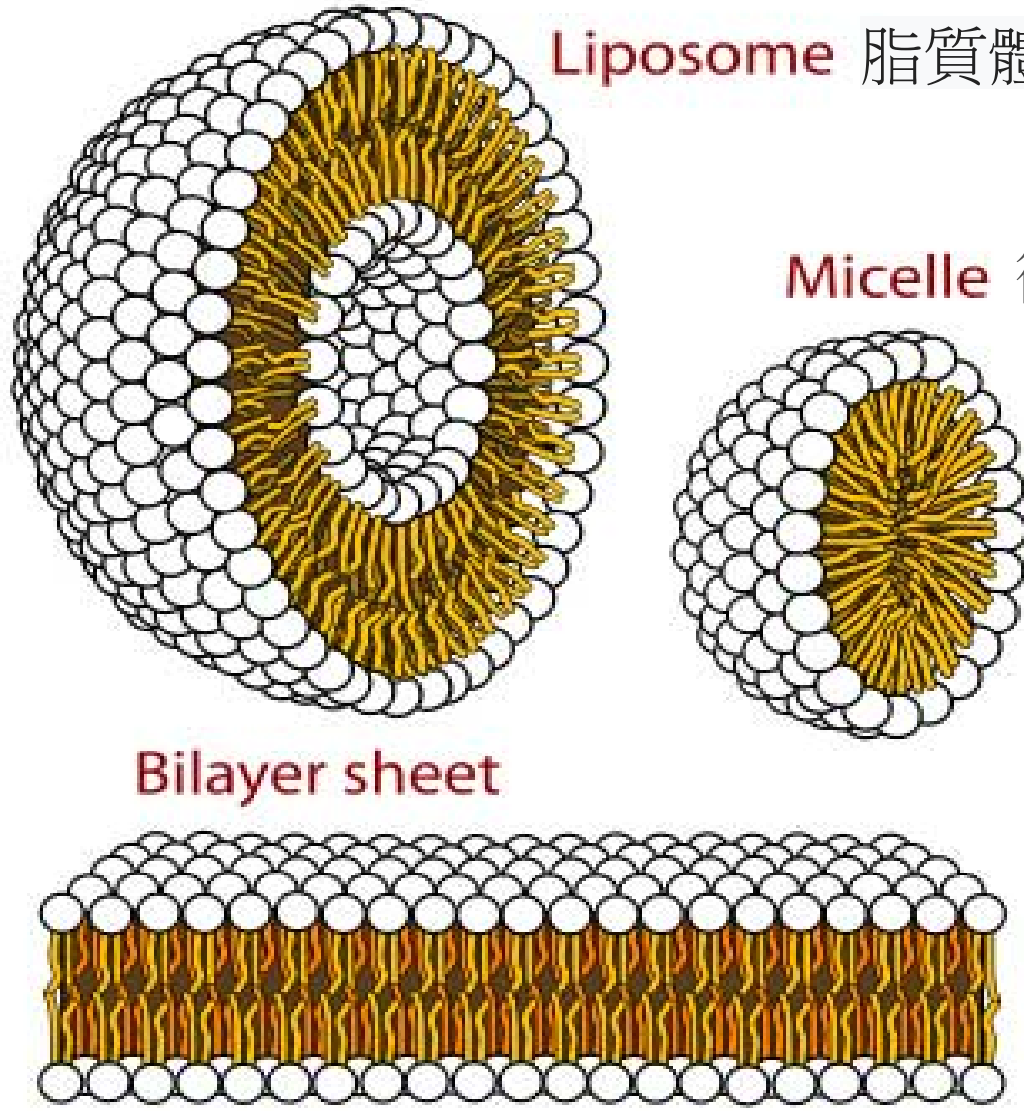
water

water



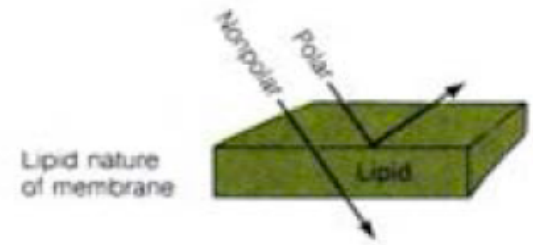
water

-

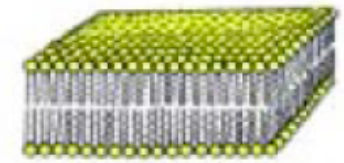

Liposome 脂質體
Micelle 微胞
Bilayer sheet

Membranes- History 1

- 1890 Charles Overton
  - selective permeation of membranes
    - non-polar pass through (lipid soluble)
    - polar refractory
  - lipids present as a coat

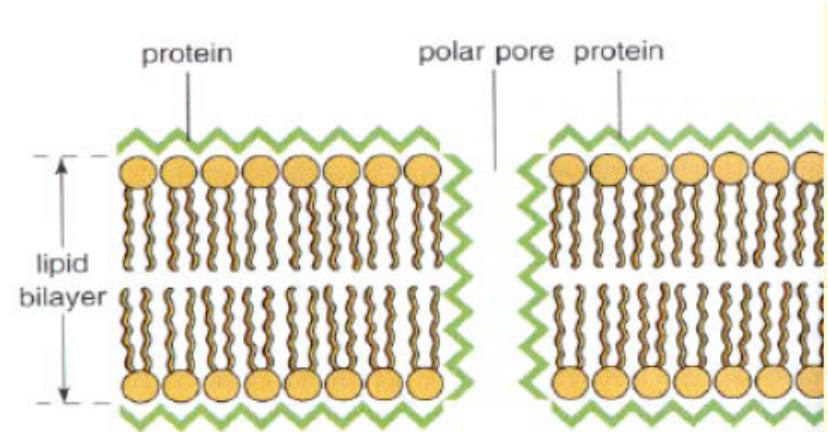


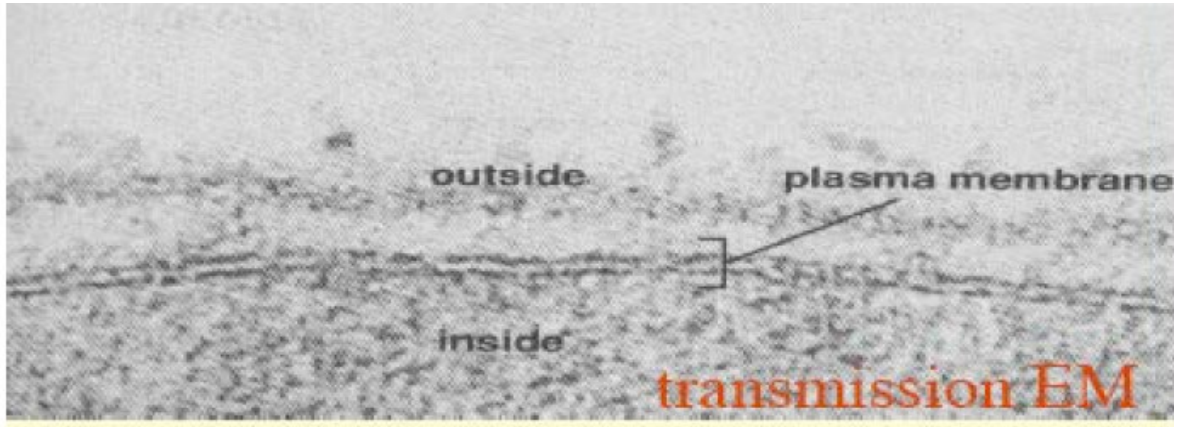
- 1905 Irving Langmuir
  - lipids faced with heads towards water away from organic solvents
- 1925 Gorter & Grendel
  - monolayer of lipid isolated from rbc's
  - 2x surface area of cell (bilayer)



Membranes- History 2

- 1930-40 Danielle-Davson Model
  - Proteins coat a bilayer with polar “pores”



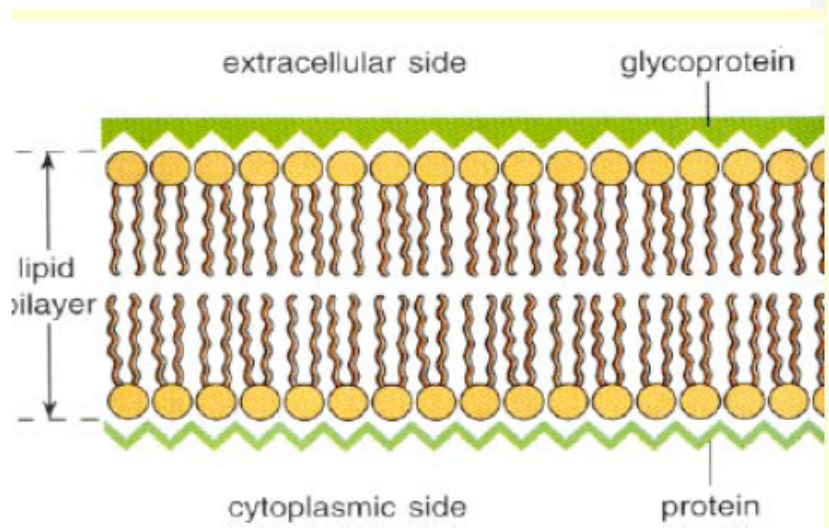


加了蛋白質

Sandwich model

- 1960s Robertson Modification
  - Glycoprotein on one side, therefore asymmetric

加了醣蛋白

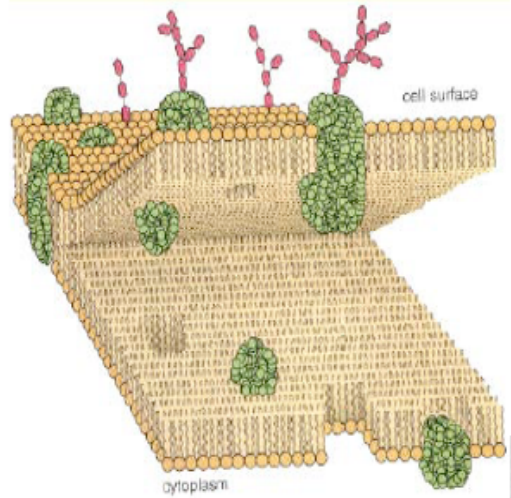


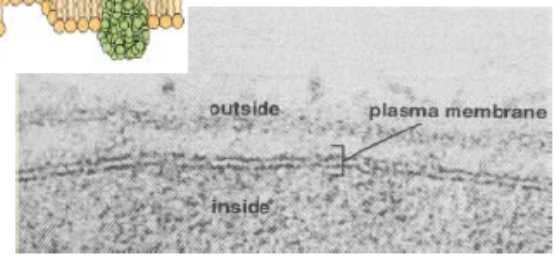
Q1: not all the membrane are the same, different lipid and protein compositions

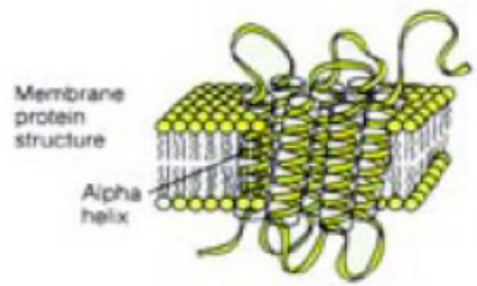
Q2: location of membrane proteins

Membranes- History 3

- 1972 Singer & Nicholson Model
  - proteins “floating” within lipid bilayer like a “liquid” surface
- 1975 Unwin & Henderson
  - integral membrane proteins
  - both hydrophobic and hydrophilic
    - alternating -phobic and -philic represent trans-membrane loops.
  - Glycoproteins
    - carbohydrate groups on outer surface







Fluid mosaic model 流動鑲嵌模型

Freeze-fracture method 冷凍碎裂法

Fluid Mosaic Model

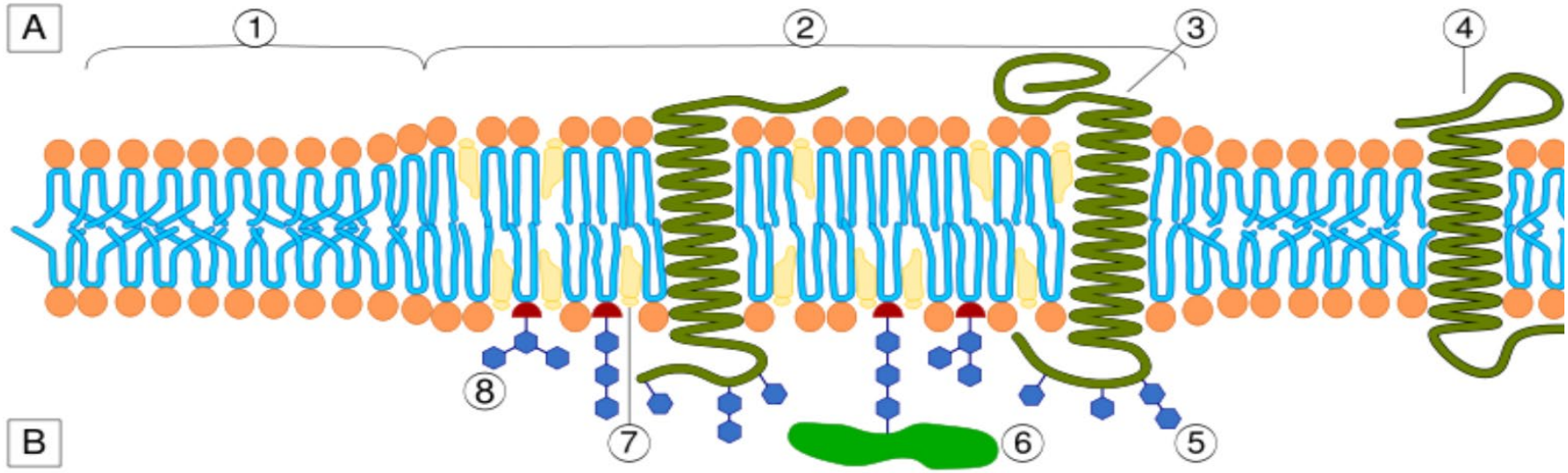
Membranes- History 4

Lipid raft/脂筏

- 1997 “Membrane Rafts”
  - “A new aspect of cell membrane structure is presented, based on the dynamic clustering of sphingolipids and cholesterol to form rafts that move within the fluid bilayer. It is proposed that these rafts function as platforms for the attachment of proteins when membranes are moved around inside the cell and during signal transduction.”
    - Simons K, Ikonen E. Nature 1997 Jun 5;387(6633):569-72

鞘脂

Lipid raft (脂筏)



A Intracellular space or cytosol
B Extracellular space or vesicle/Golgi apparatus lumen
1. Non-raft membrane
2. Lipid raft
3. Lipid raft associated transmembrane protein
4. Non-raft membrane protein
5. Glycosylation modifications (on glycoproteins and glycolipids)
6. GPI-anchored protein
7. Cholesterol 膽固醇
8. Glycolipid

Caveolae (胞膜窖)

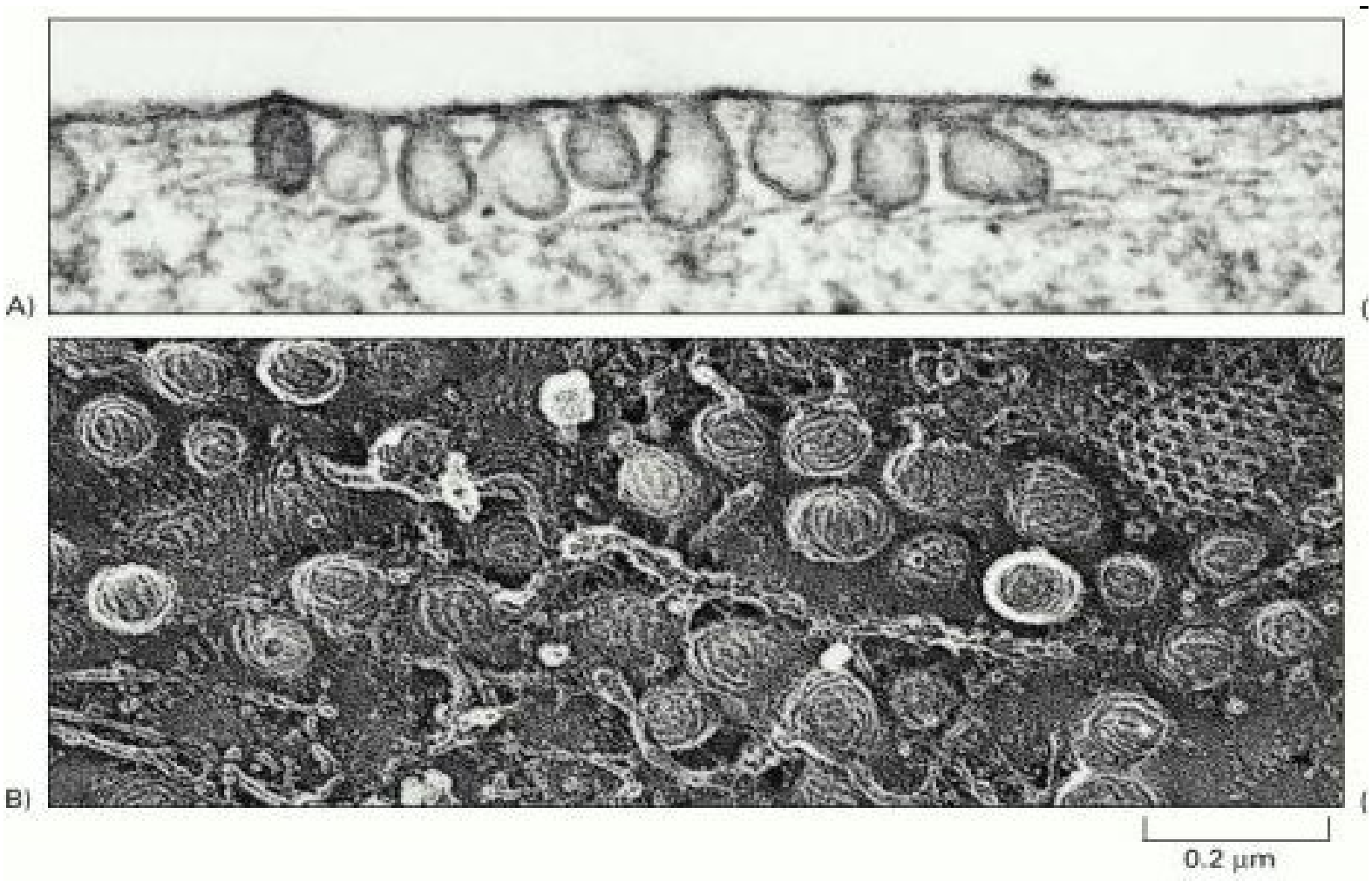


Figure 13-42. Caveolae in the plasma membrane of a fibroblast.

Discover in 1953

細胞膜的流體性質

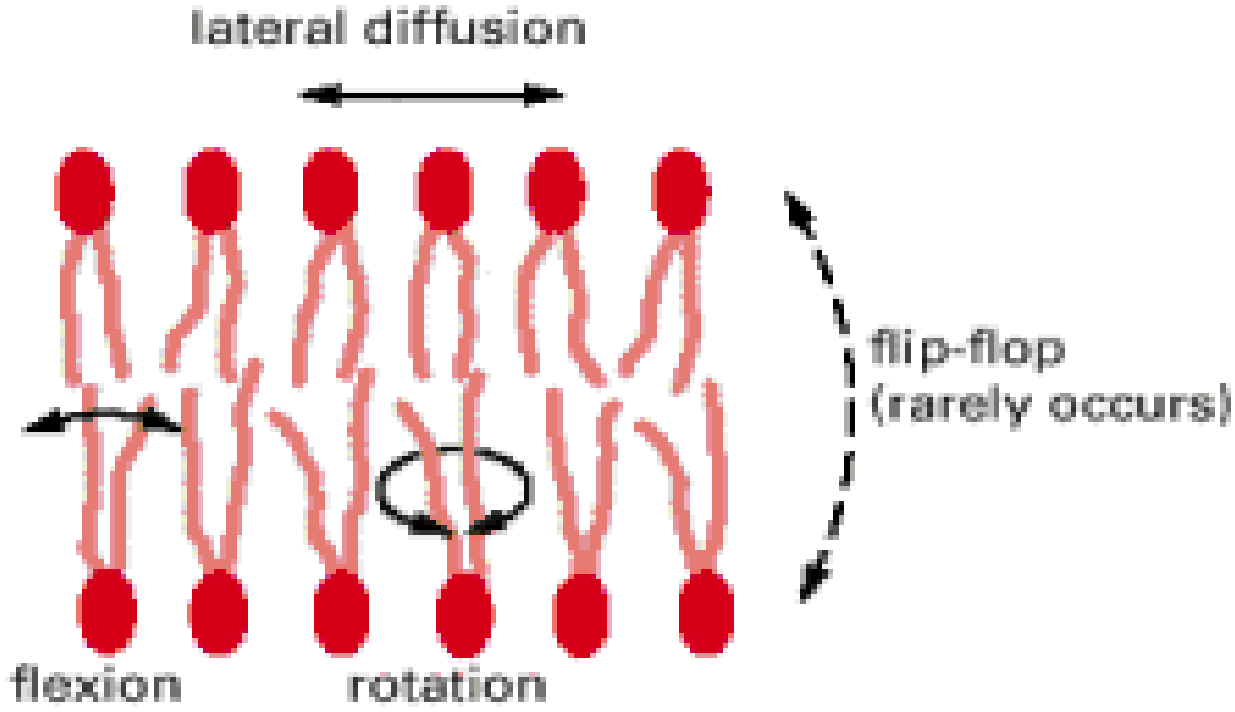
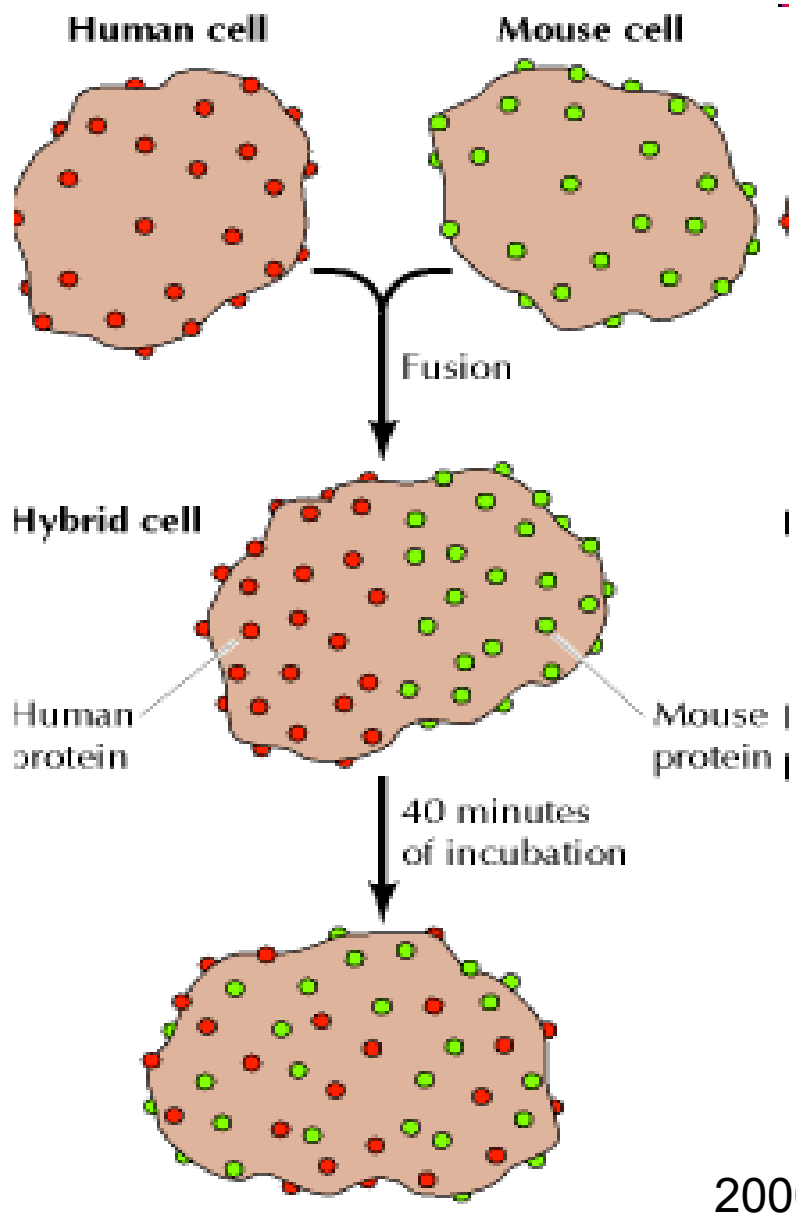


Figure 10-8. Phospholipid mobility.

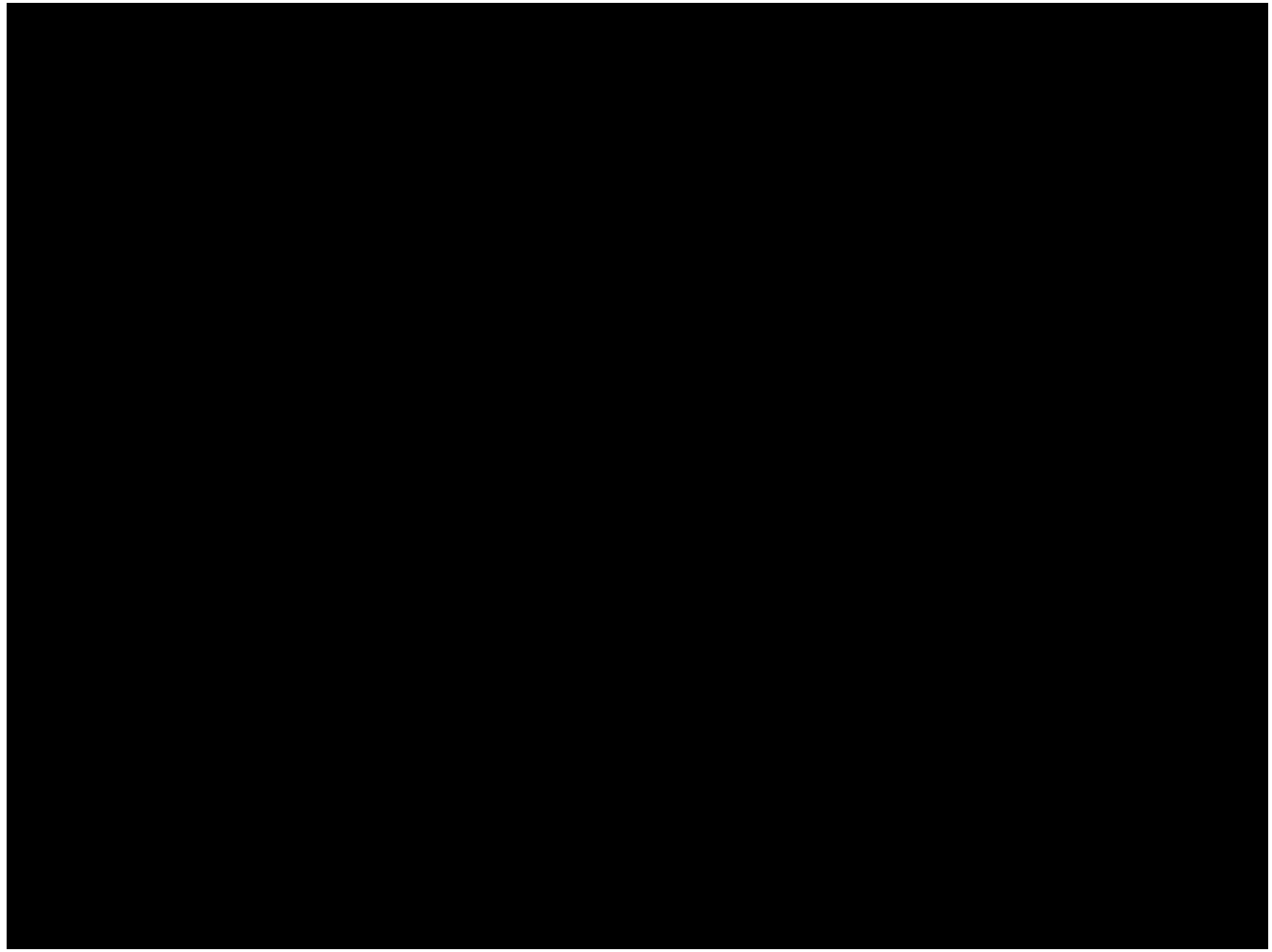
Membrane Fluidity



螢光標示的膜蛋白

細胞融合

殺手 T 細胞



https://www.youtube.com/watch?v=ntk8XsxVDi0

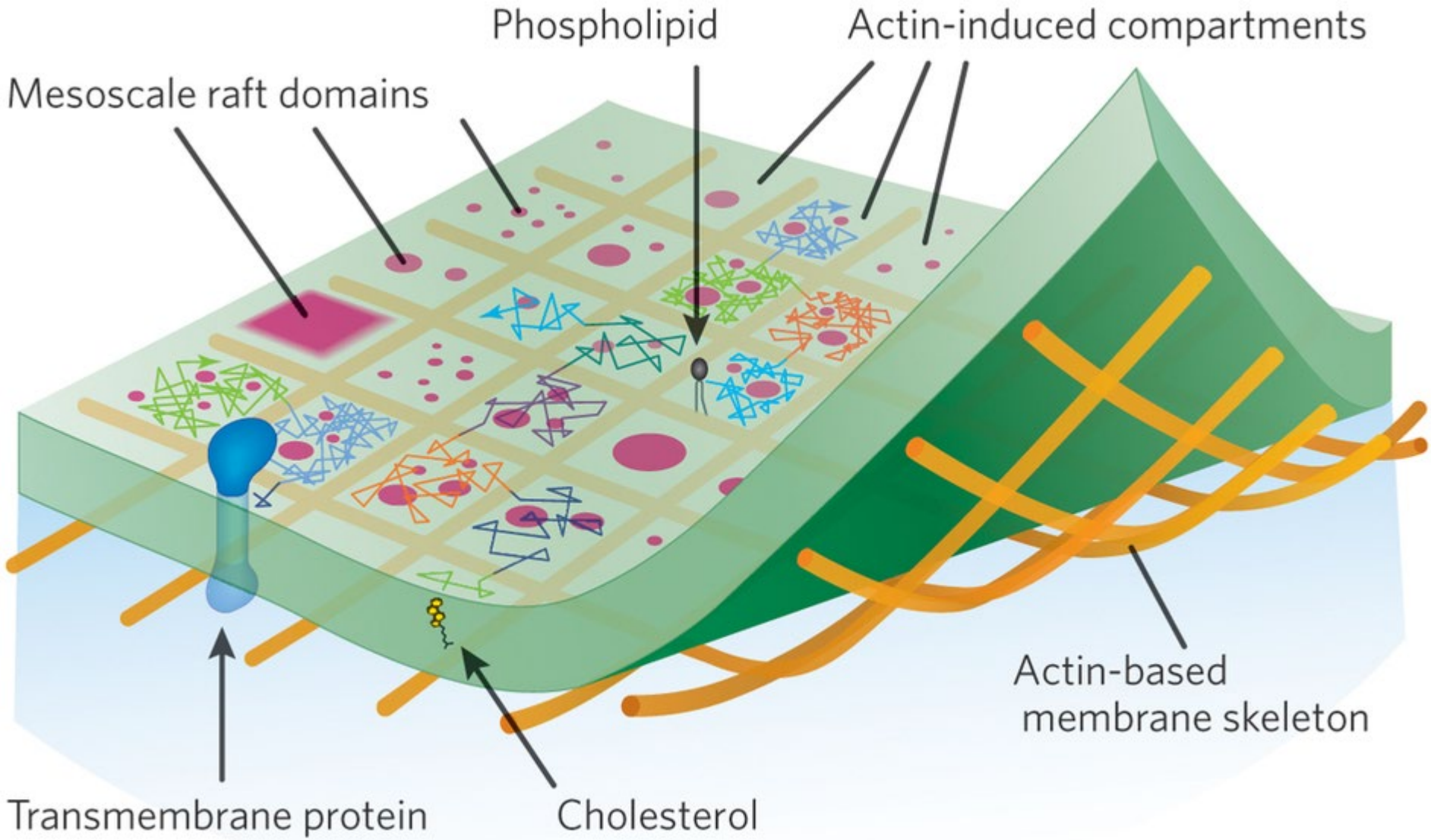
Professor Akihiro Kusumi

Institute for Integrated Cell-Material Sciences, Kyoto University
Okinawa Institute of Science and Technology

Membrane mechanisms: Concerted action of membrane domains for signal transduction in the plasma membrane revealed by single-molecule tracking

Watch video

0-1:50
4:40-6:00
17:14-1903



Nature Chemical Biology **10**, 524–532 (2014)

Animal cell membrane
細胞膜

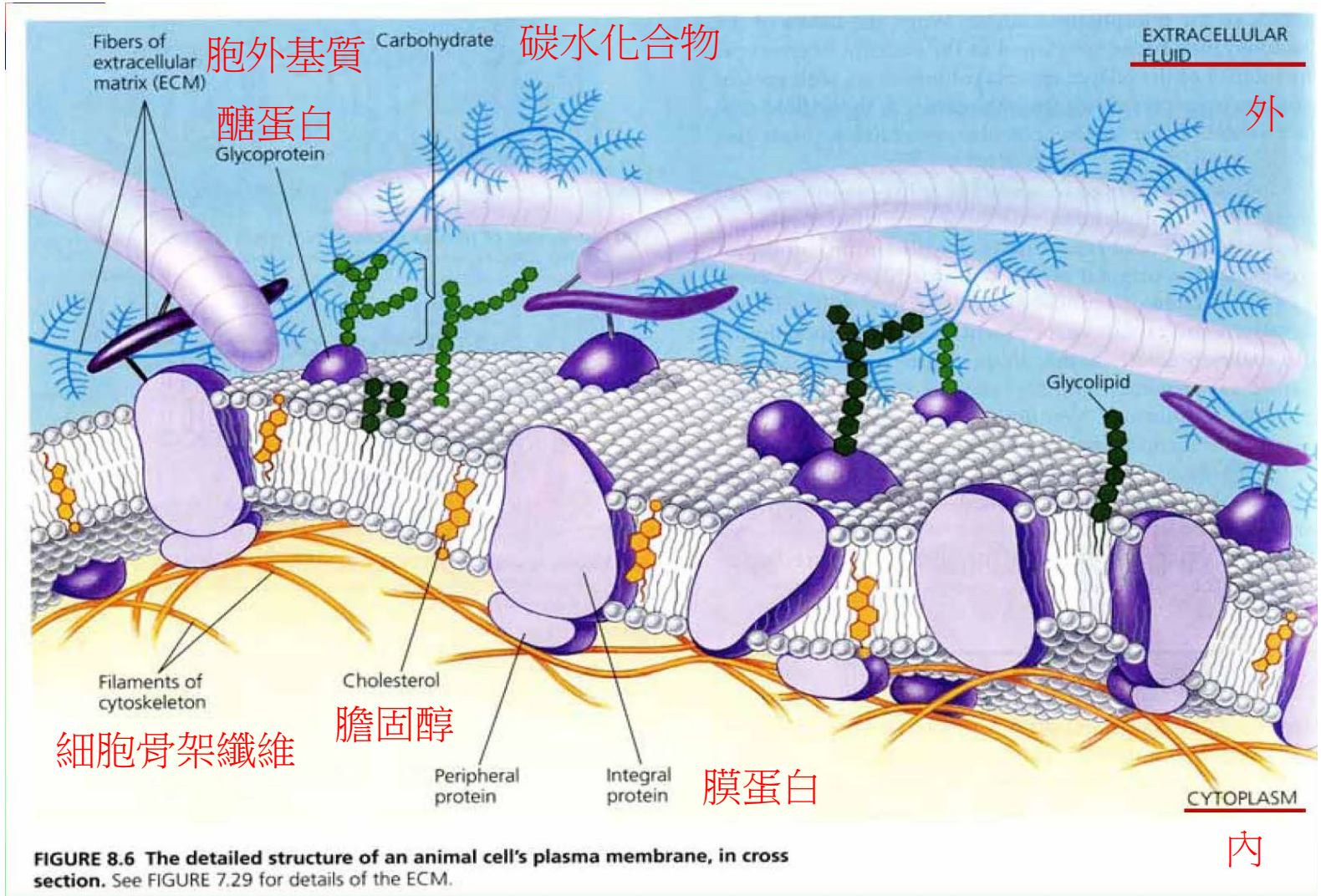


FIGURE 8.6 The detailed structure of an animal cell's plasma membrane, in cross section. See FIGURE 7.29 for details of the ECM.

Campbell/Biology

Functions of membrane proteins
細胞膜蛋白質的功能

1. 作為接收外界訊號的偵測器，準確地接收外界聲光的刺激，或是來自身體其他細胞的激素或神經傳導物等訊息。
2. 作為與外界交換物質的通道。
3. 作為細胞與細胞間的連接。
4. 作為細胞與細胞間的辨認。
5. 作為細胞內與細胞外的連接。

細胞膜的通透性

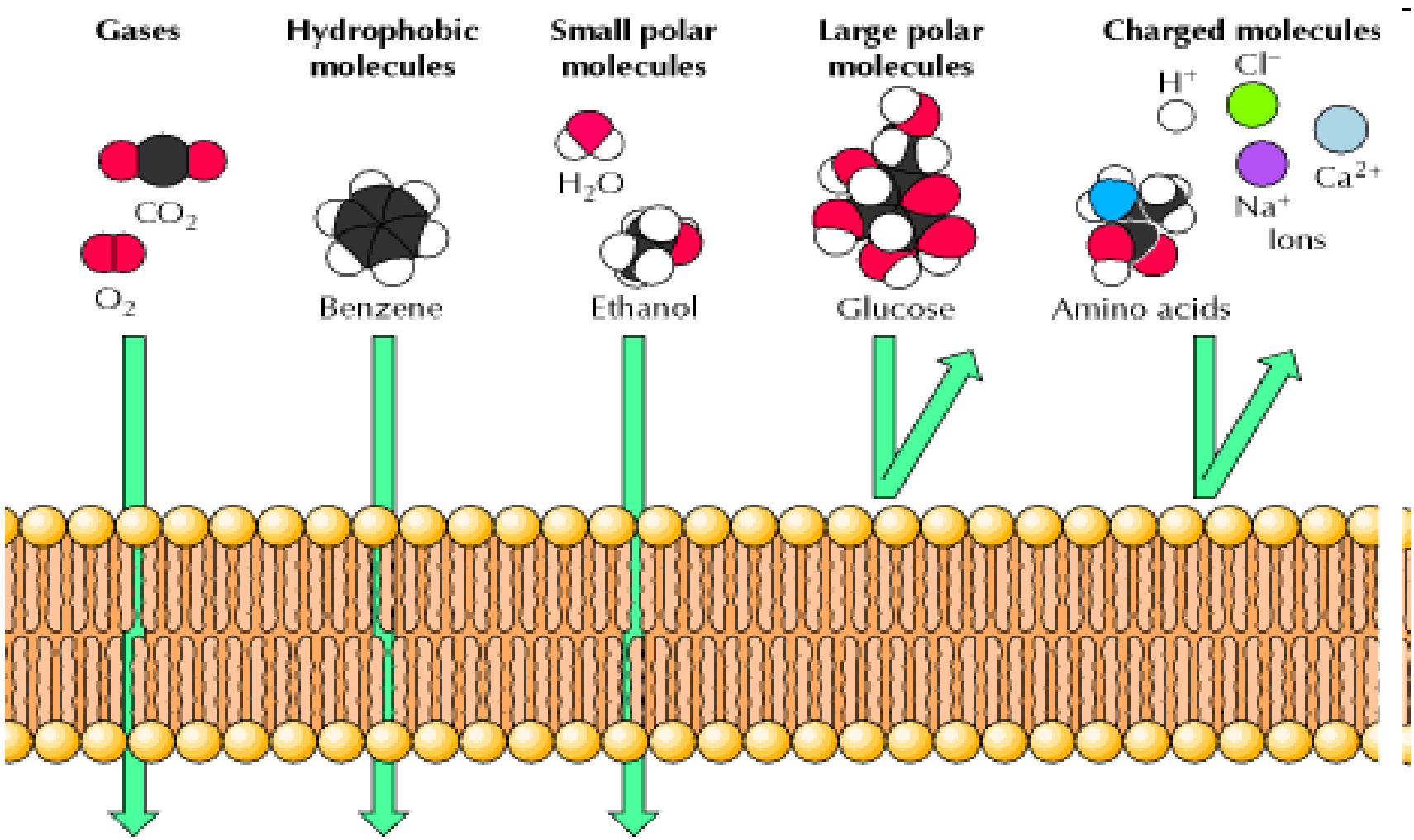


Figure 12.15. Permeability of phospholipid bilayers

Passive transport

Active transport

吞噬作用

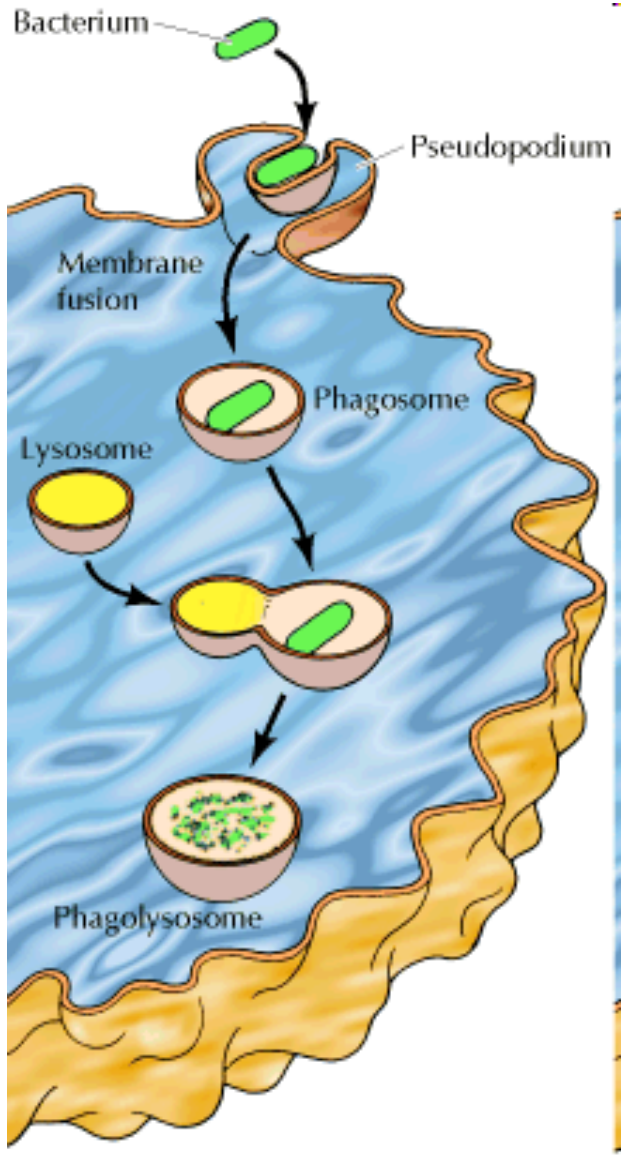
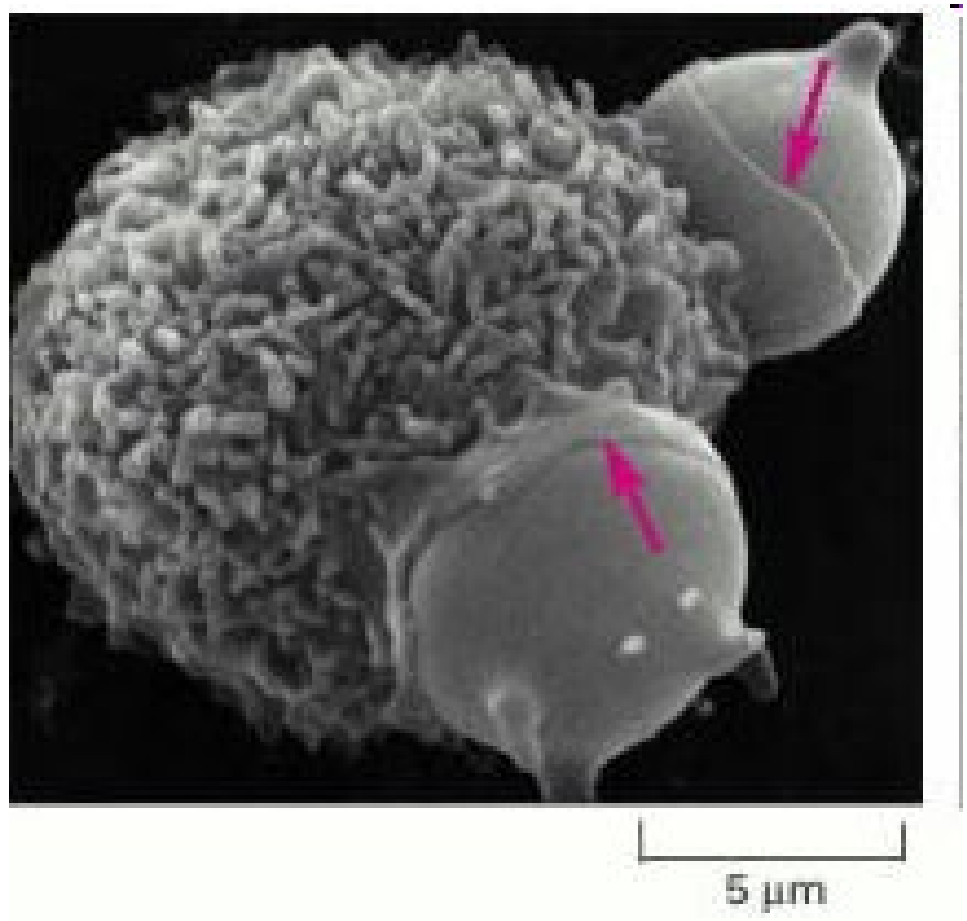
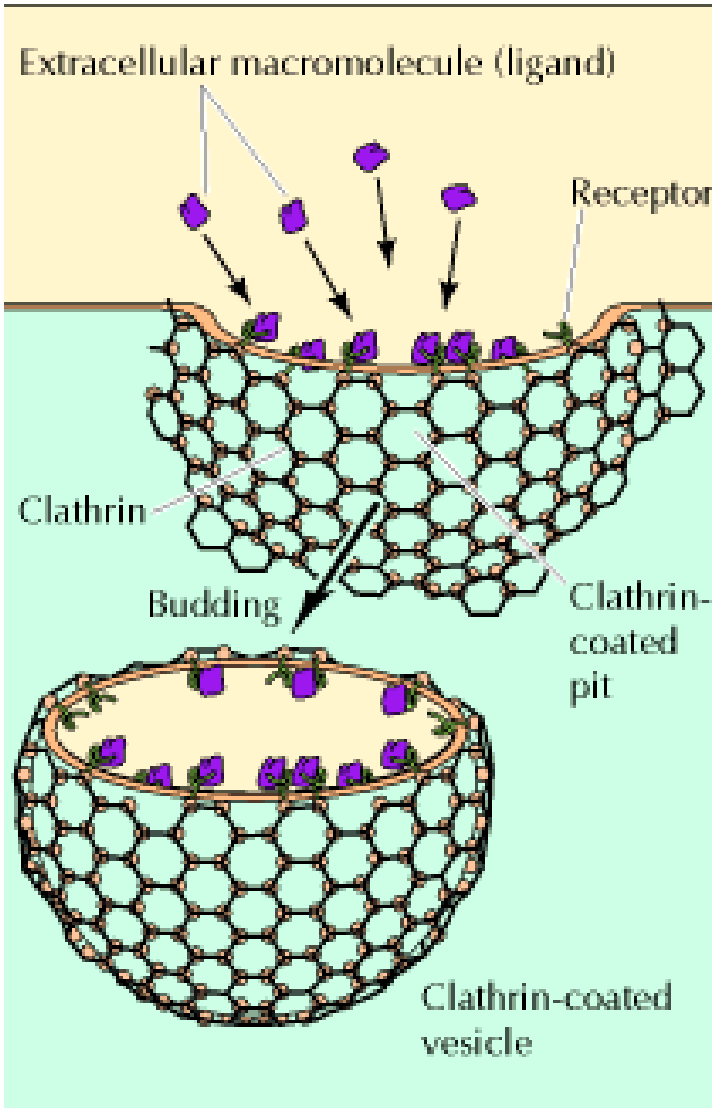


Figure 12.34. Phagocytosis



Phagocytosis by a macrophage.

胞吞作用



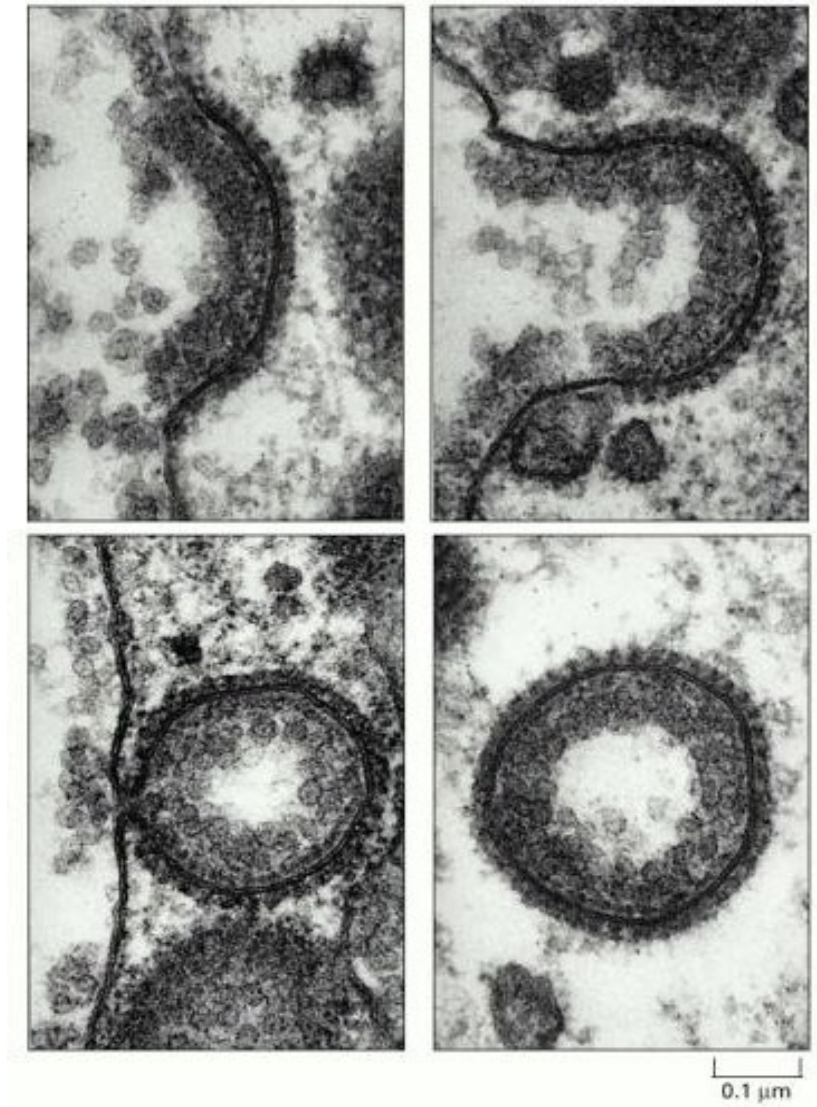


Figure 12.36. Clathrin-coated vesicle formation

Exocytosis & Endocytosis

https://www.youtube.com/watch?v=r2PiumV8KEY&index=13&list=PLXwnjgs_UWpLcVHARCbbglQJPwFl-kD_v

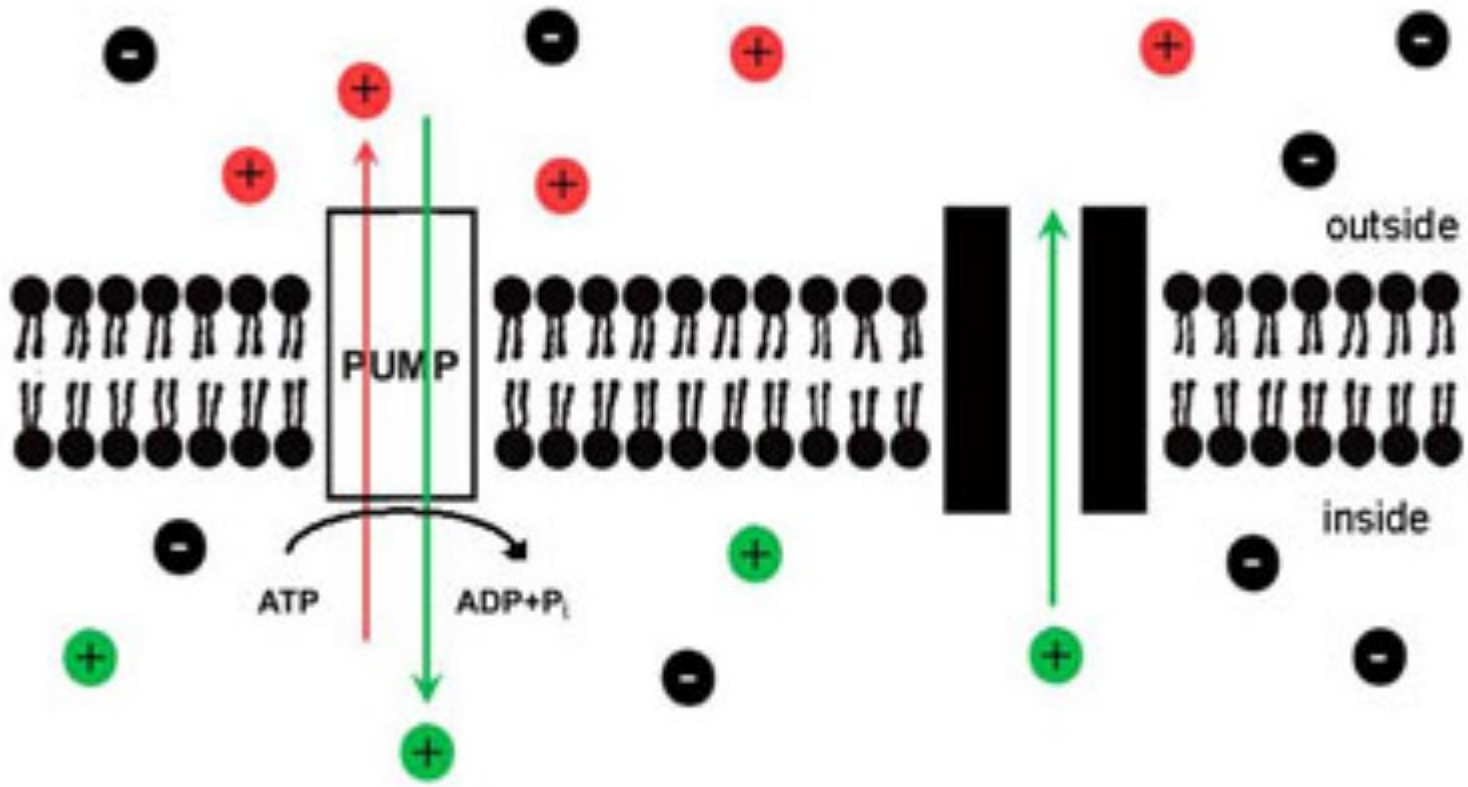
- 細胞，細胞膜，細胞膜蛋白質
- 研究離子通道的方法
- 離子通道的種類和功能
- 離子通道相關疾病

TABLE 11-1 A Comparison of Ion Concentrations Inside and Outside a Typical Mammalian Cell

COMPONENT	INTRACELLULAR CONCENTRATION (mM) 内	EXTRACELLULAR CONCENTRATION (mM) 外
Cations		
Na^+	5–15	145
K^+	140	5
Mg^{2+}	0.5	1–2
Ca^{2+}	10^{-4}	1–2
H^+	7×10^{-5} ($10^{-7.2}$ M or pH 7.2)	4×10^{-5} ($10^{-7.4}$ M or pH 7.4)
Anions*		
Cl^-	5–15	110

*The cell must contain equal quantities of positive and negative charges (that is, be electrically neutral). Thus, in addition to Cl^-, the cell contains many other anions not listed in this table; in fact, most cellular constituents are negatively charged (HCO_3^-, PO_4^{3-}, proteins, nucleic acids, metabolites carrying phosphate and carboxyl groups, etc.). The concentrations of Ca^{2+} and Mg^{2+} given are for the free ions. There is a total of about 20 mM Mg^{2+} and 1–2 mM Ca^{2+} in cells, but this is mostly bound to proteins and other substances and, for Ca^{2+}, stored within various organelles.

Pumps build ion gradients, ion channels dissipate gradients



Active transport

Passive transport

Na^+/K^+ Pump
鈉鉀幫浦

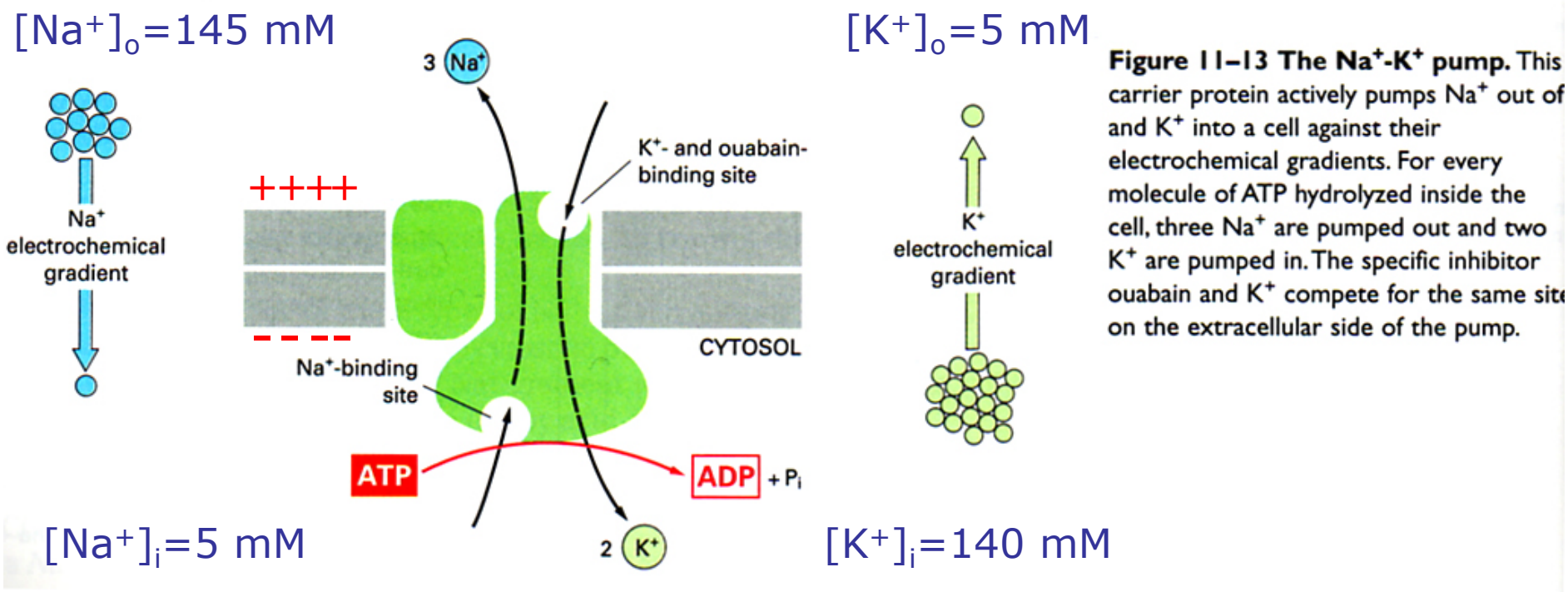


Figure 11–13 The Na^+-K^+ pump. This carrier protein actively pumps Na^+ out of and K^+ into a cell against their electrochemical gradients. For every molecule of ATP hydrolyzed inside the cell, three Na^+ are pumped out and two K^+ are pumped in. The specific inhibitor ouabain and K^+ compete for the same site on the extracellular side of the pump.

Molecular Biology of the Cell

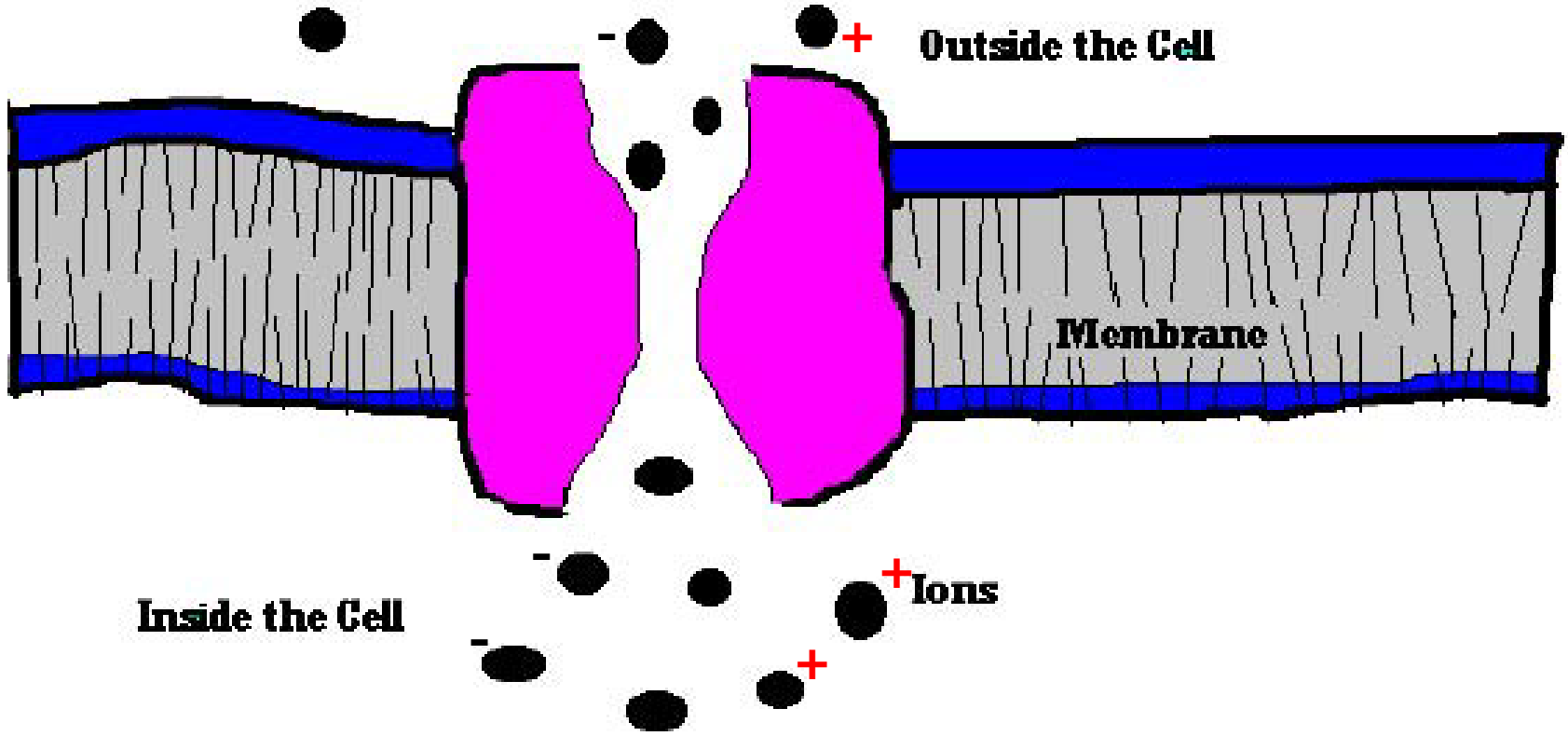
polarization
細胞膜極化

https://www.youtube.com/watch?v=QD0pOVbVUQQ&index=7&list=PLXwnjgs_UWpLcVHARCbbglQJPwFI-kD_v

Nerve transduction
神經傳導

可興奮性細胞
- 神經細胞
- 骨骼肌細胞
- 心肌細胞
- 平滑肌細胞

How to study ion channel?
如何研究離子通道?



Ohm's Law: V =IR 電壓＝電流 X 電阻

http://opal.msu.montana.edu/cftr/IonChannelPrimers/beginners.htm

Voltage-clamp technique 電壓箝制技術

二十世紀中葉（1950年代）：

霍去金 (**Hodgkin**) &赫胥黎 (**Huxley**)研究烏賊的巨大神經元軸突

→發現神經細胞內外具有電位差（神經細胞內的電位較低≒－65mV）

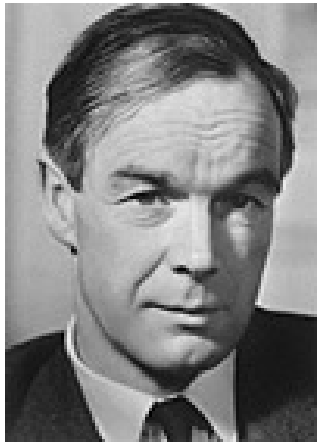
(1)無脊椎動物（烏賊、龍蝦、蚯蚓）具有巨大的神經元

(2)烏賊的神經元軸突直徑＞1mm

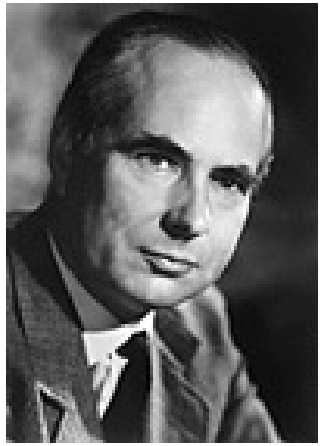
可用來測量靜止膜**電位**的伏特數（烏賊的靜止膜電位≒－65mV）

可用來記錄在神經衝動傳遞時，離子流動所造成的電位變化

(烏賊的動作電位≒＋40mV）

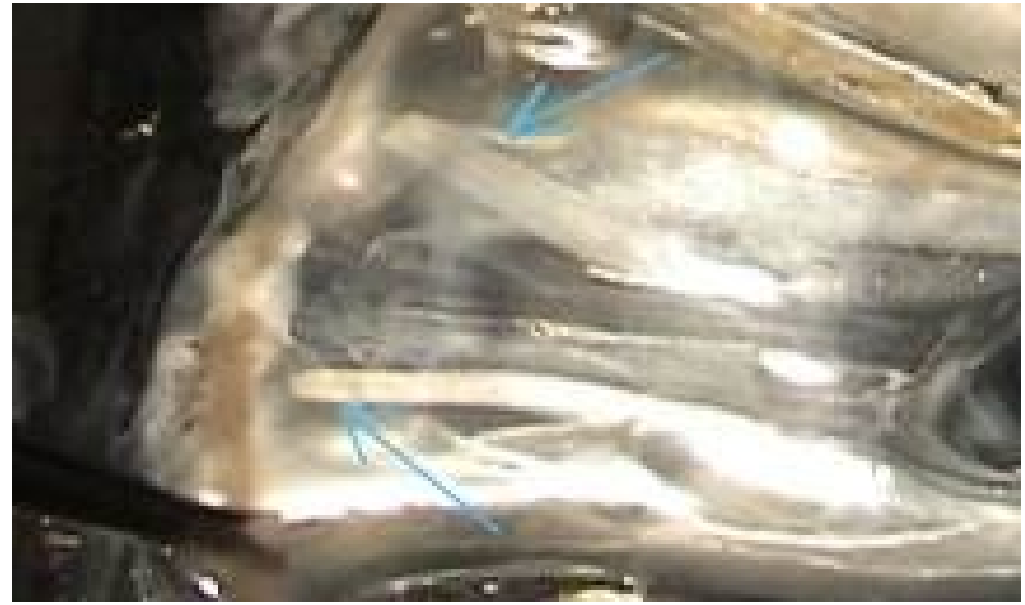


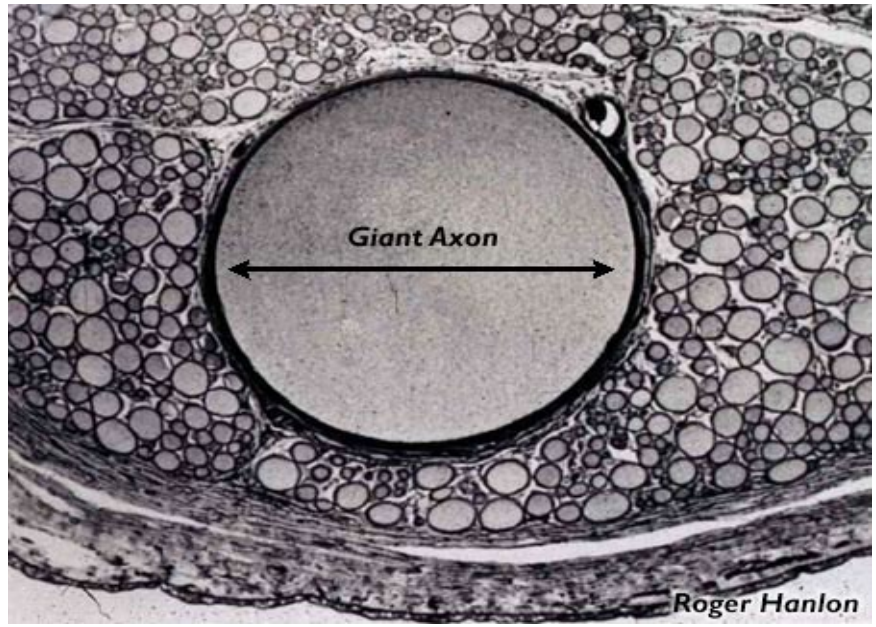
Hodgkin



Huxley

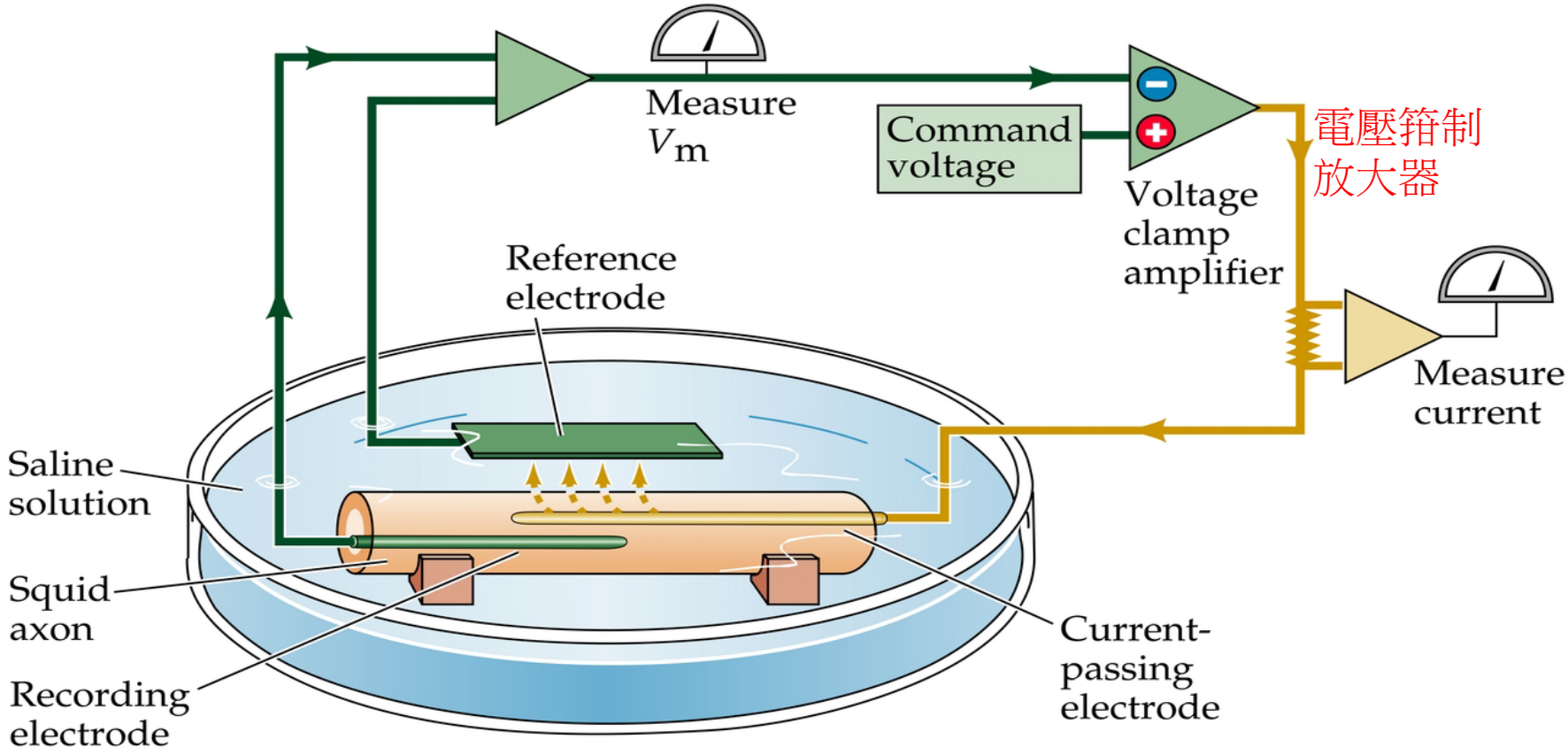
Nobel Prize in 1963





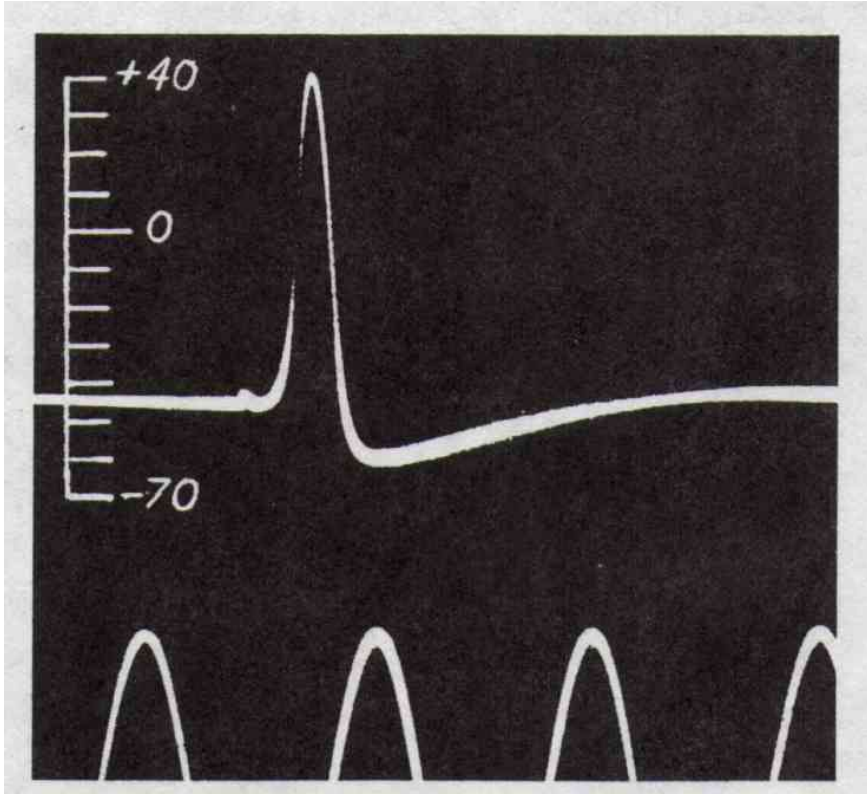
1 mm dia

Voltage-clamp methodology of Hodgkin and Huxley

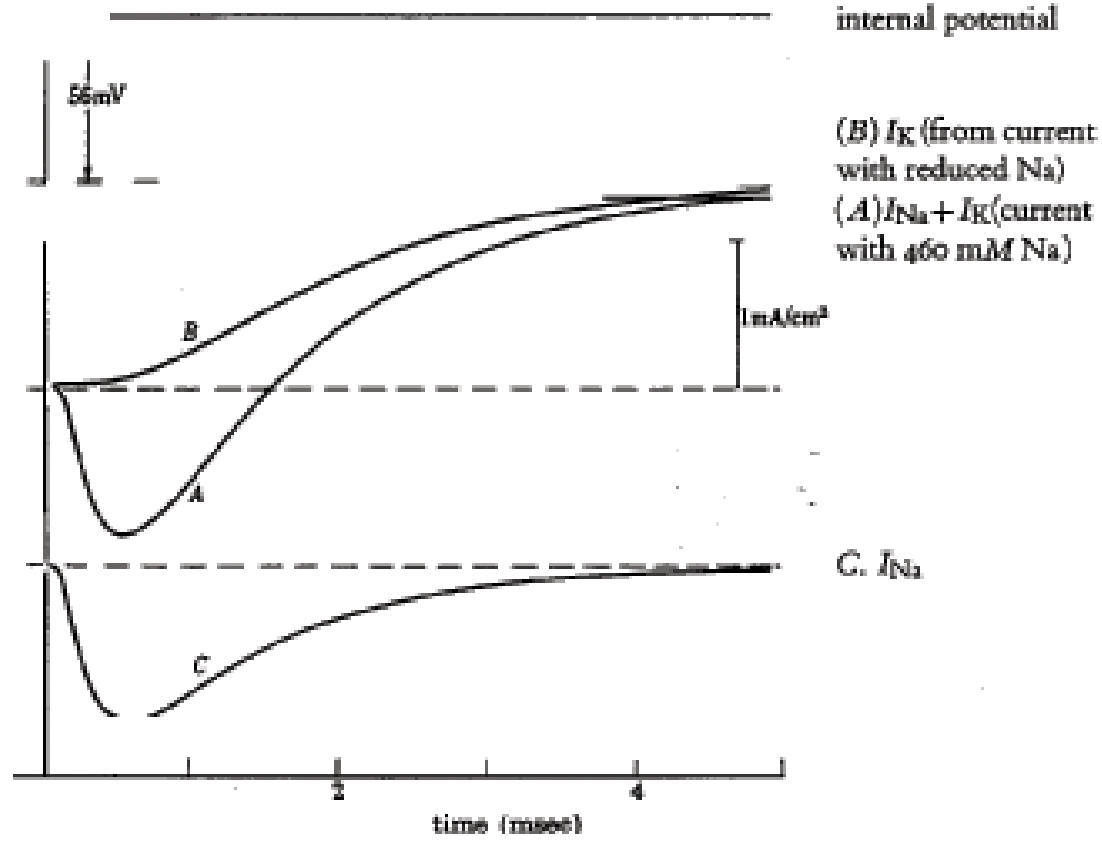


Neuroscience by Purves et al.

Action potential and Na^+ and K^+ currents recorded from squid axon



最早的細胞內紀錄-動作電位
1939

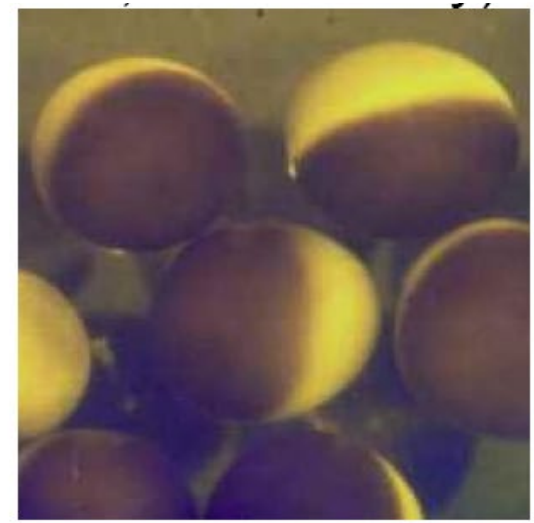


Hodgkin and Huxley

Gurdon J. B., Lane D. C., Woodland H. R., and Marbaix G. (1971) Use of frog eggs and oocytes for the study of messenger RNA and its translation in living cells. *Nature (Lond.)* **233**, 177–182.

Gundersen Miledi R., and Parker I. (1984) Messenger RNA from human brain induces drug-and voltage-operated channels in *Xenopus* oocytes. *Nature (Lond.)* **308**, 421–424.

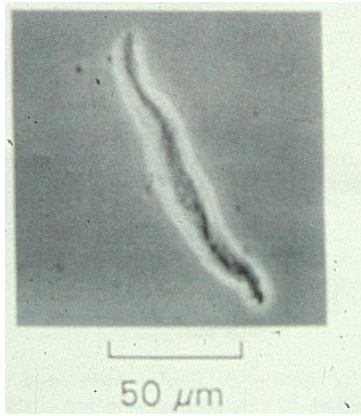
Inject mRNA in oocytes; wait 2-5 days; protein in membrane.

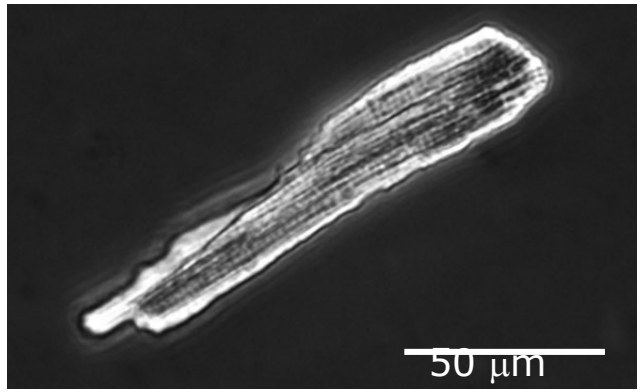


www.mpibp-frankfurt.mpg.de/schwarz/oocytes.html

How to record a single cell?
如何記錄單一細胞？

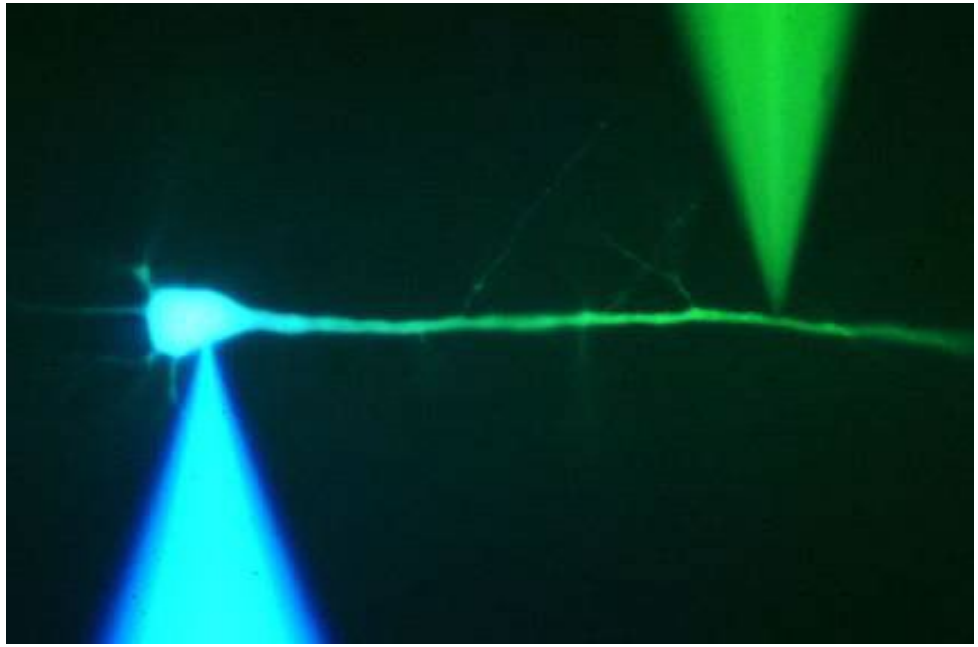
Smooth muscle cells
(diameter <10 μm)
平滑肌細胞





Mouse
ventricular myocytes
小鼠心室細胞

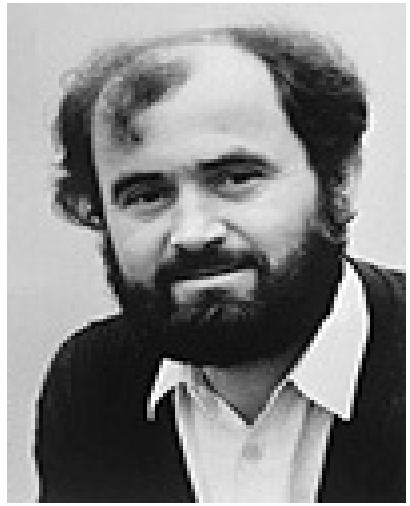
Cortical
pyramidal neuron



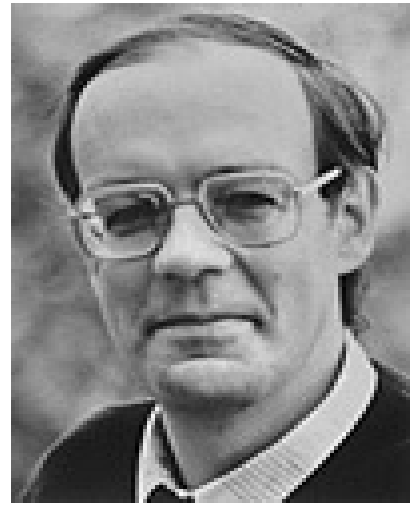
Stuart and Sakmann, 1994

Patch-Clamp Technique 「膜片箝制」

Erwin Neher



Bert Sakmann



Nobel Prize in 1991

Patch-Clamp Setup

Optical parts

Microscope
CCD camera

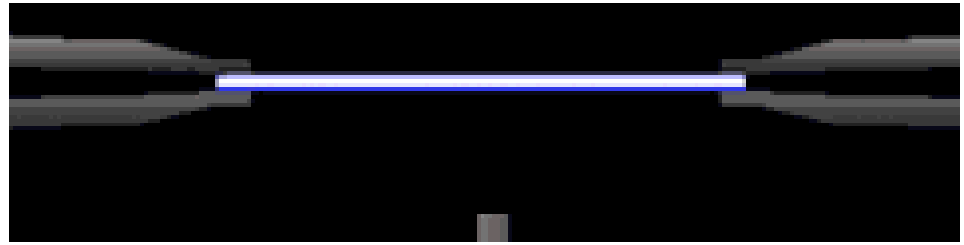
Mechanical parts

Vibration-free table
Micromanipulators

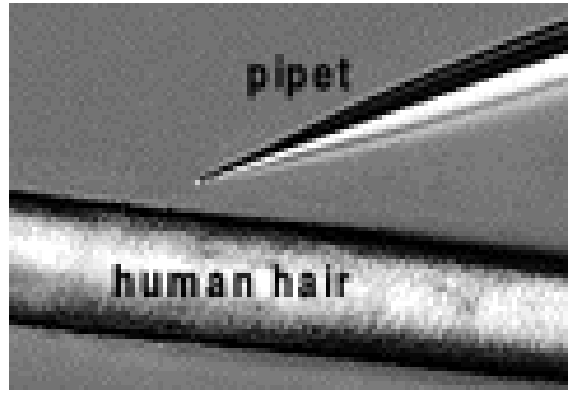
Electrical parts

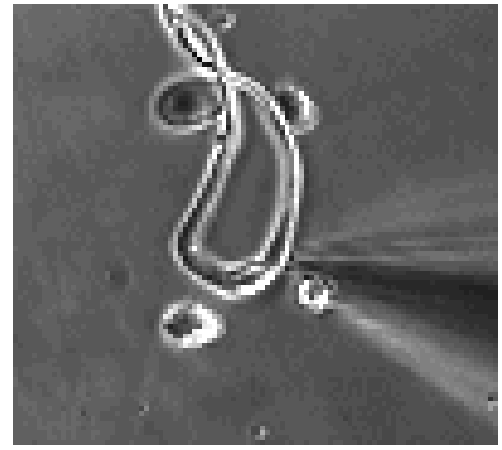
Amplifiers
Oscilloscope
AD/DA Converter
Computer

Patch-Clamp Technique「膜片箝制」的技術

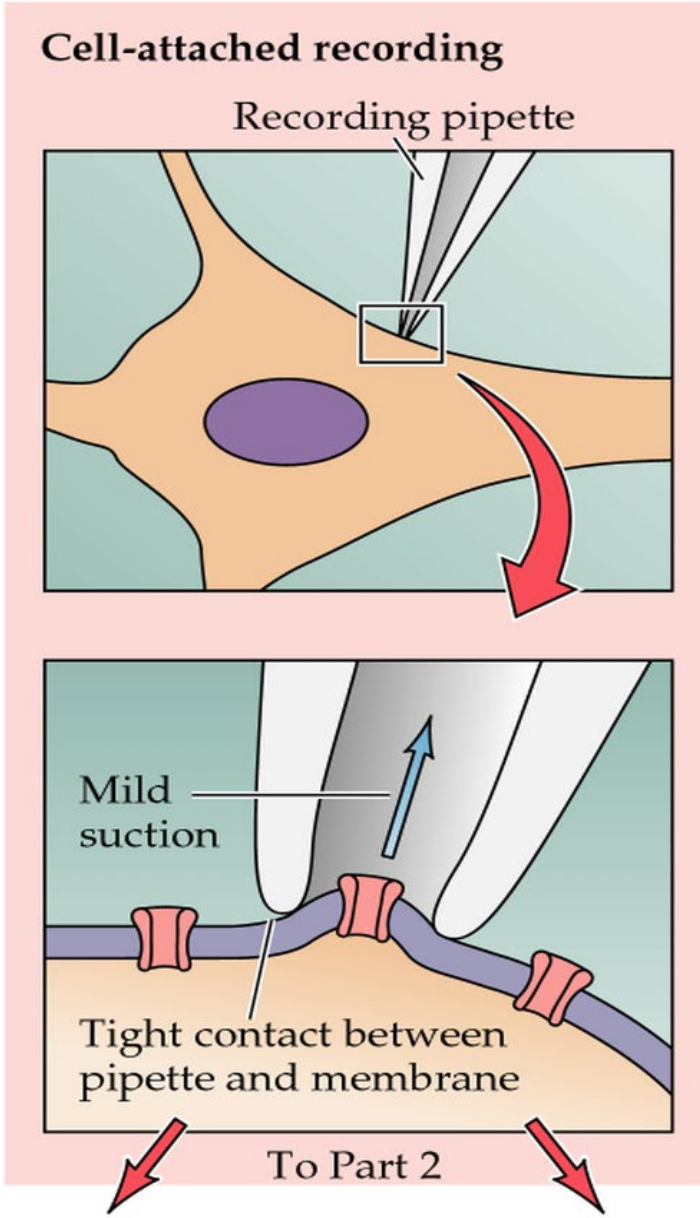


電極尖端
1-2 μM



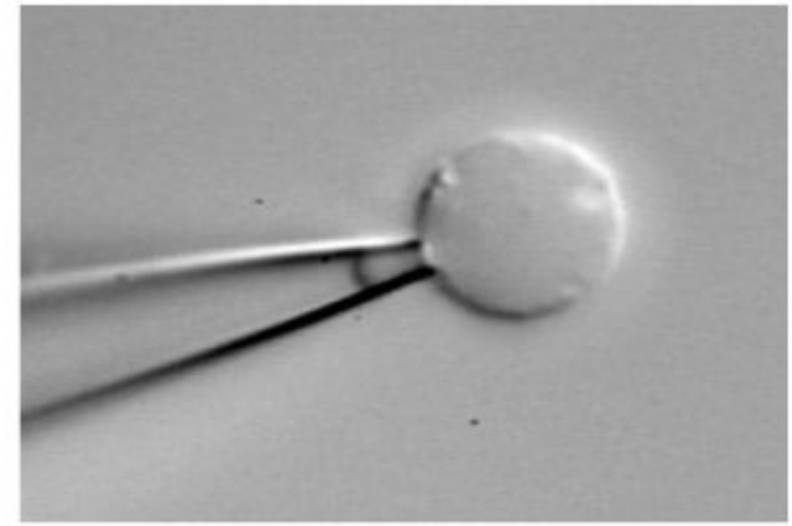


http://www.cellsalive.com/patch.htm



電壓＝電流 X 電阻

- Tight seal onto the membrane – GΩ seal
- Ion channel is trapped under the pipette.
-
-



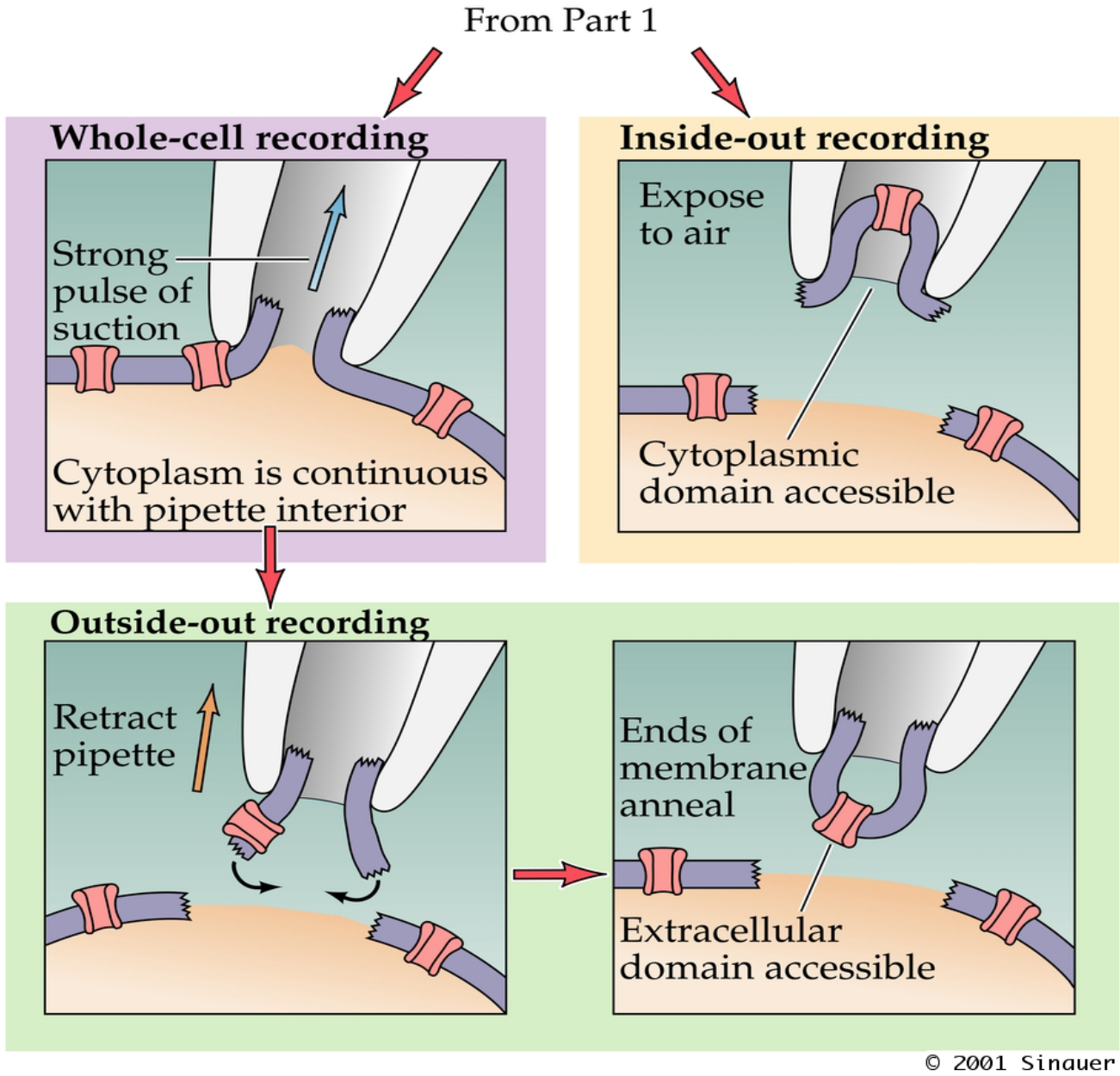
:y

Neuroscience by Purves et al.

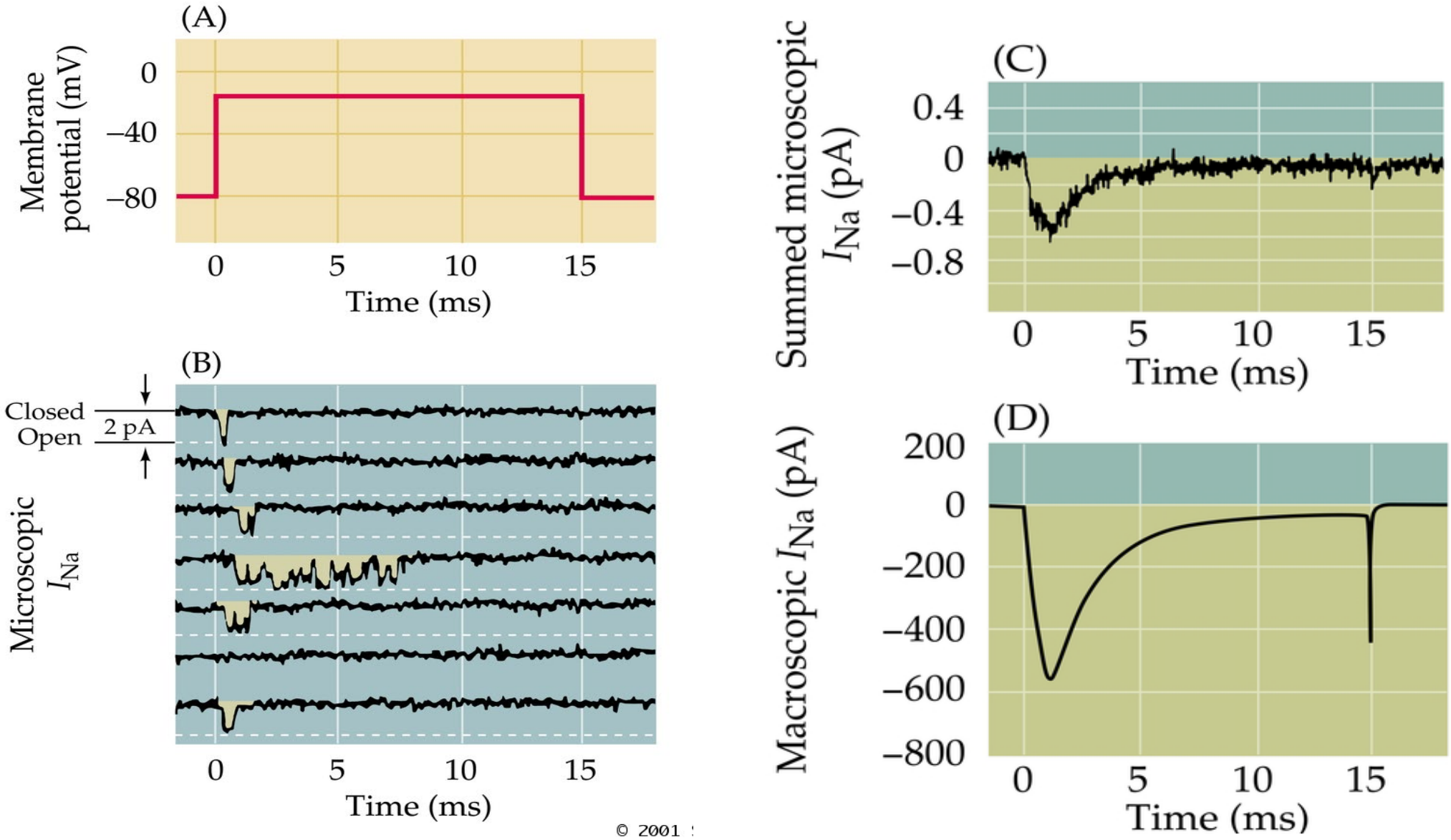
細胞接連記錄

內側向外記錄

外側向外記錄



Variations of the patch clamp technique.

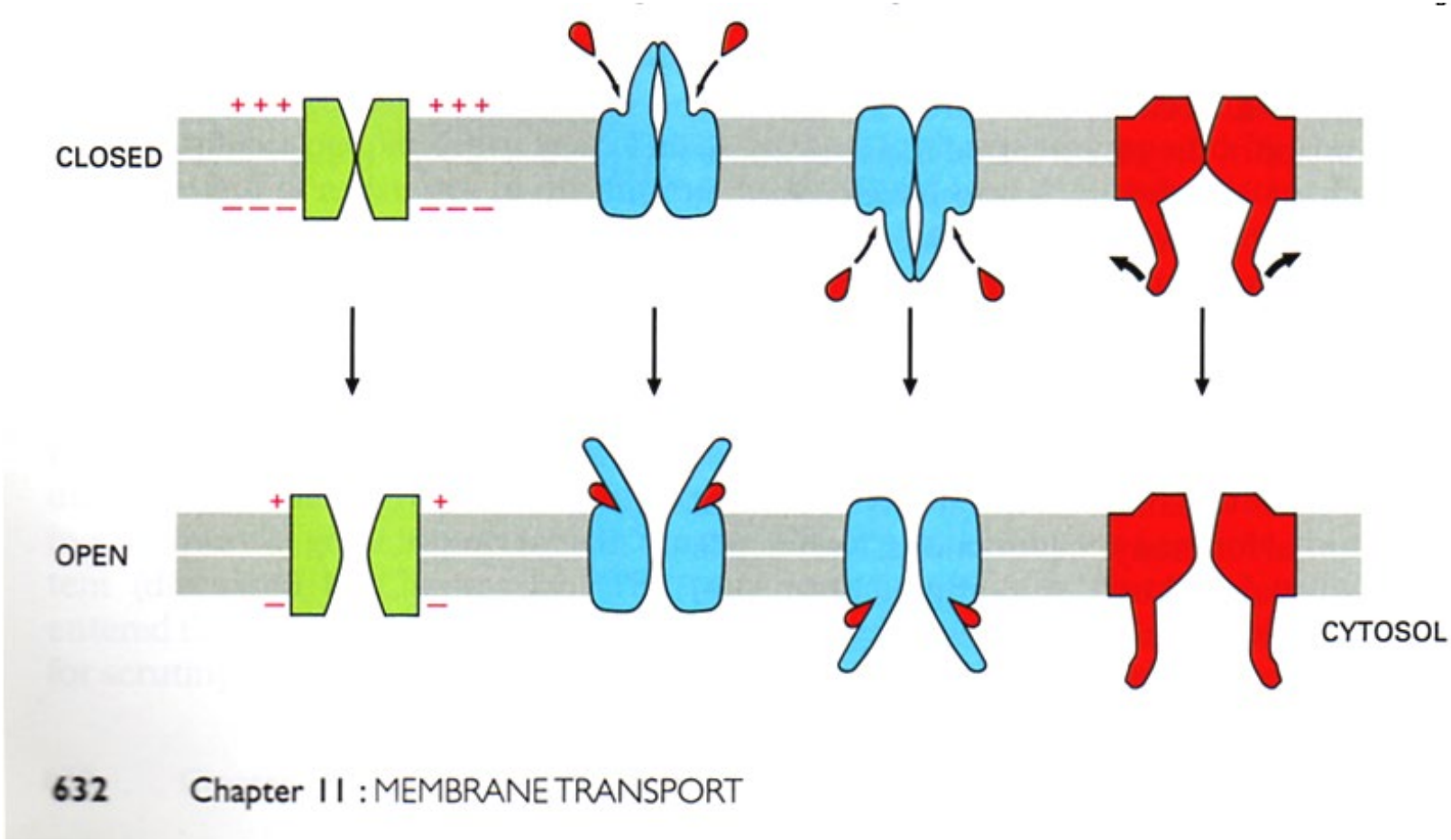


Na^+ channels : comparison of single channel with whole cell recordings

- 細胞，細胞膜，細胞膜蛋白質
- 研究離子通道的方法
- 離子通道的種類和功能
- 離子通道相關疾病

Types of ion channels
離子通道的種類

Voltage-gated 電壓驅動式　　Ligand-gated 配體驅動式　　Mechanical-gated 機械驅動式



Molecular Biology of the Cell

Types of ion channels
離子通道的種類

電壓驅動式離子通道

Na^+ 鈉離子　K^+ 鉀離子　Ca^{2+} 鈣離子

可興奮性細胞
- 神經細胞
- 骨骼肌細胞
- 心肌細胞
- 平滑肌細胞

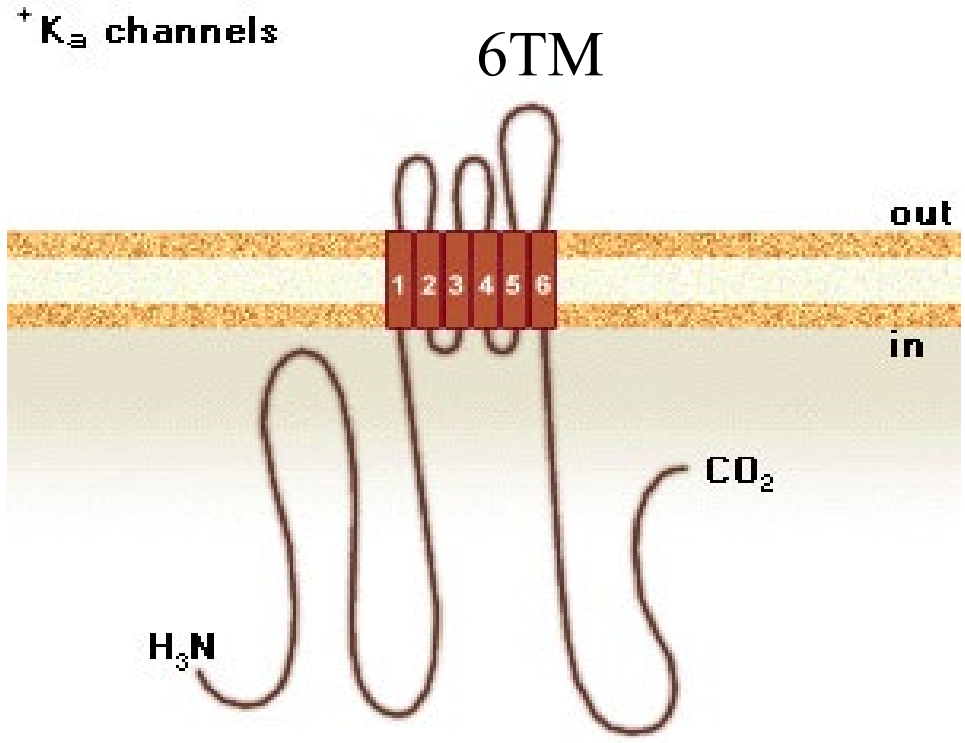
配體驅動式離子通道

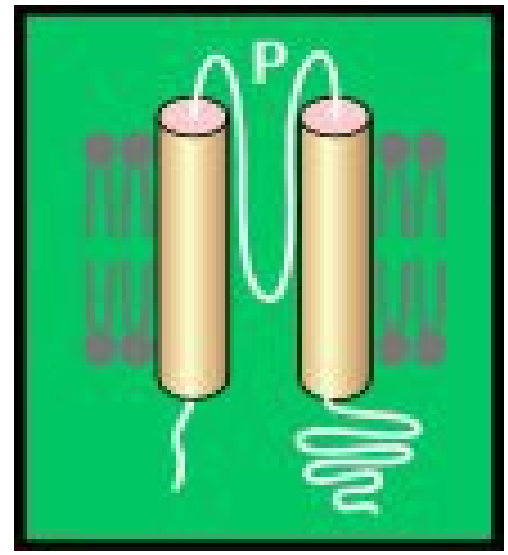
acetylcholine 乙烯膽鹼　glutamate 谷氨酸鹽　glycine 甘氨酸

Excitable neuron
興奮性神經細胞

Inhibitory neuron
抑制性神經細胞

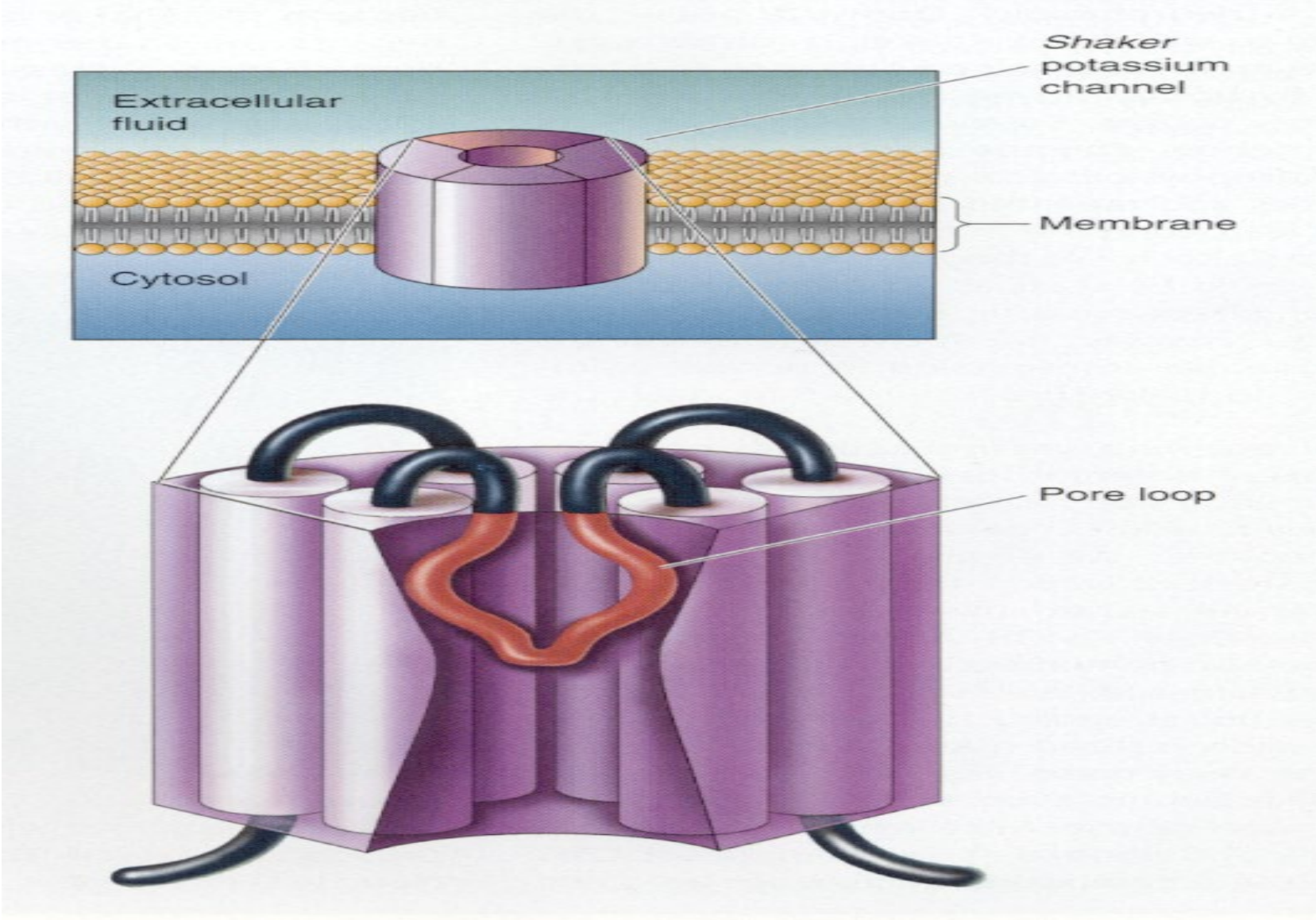
Structure features of K^+ channels
鉀離子通道的結構特徵

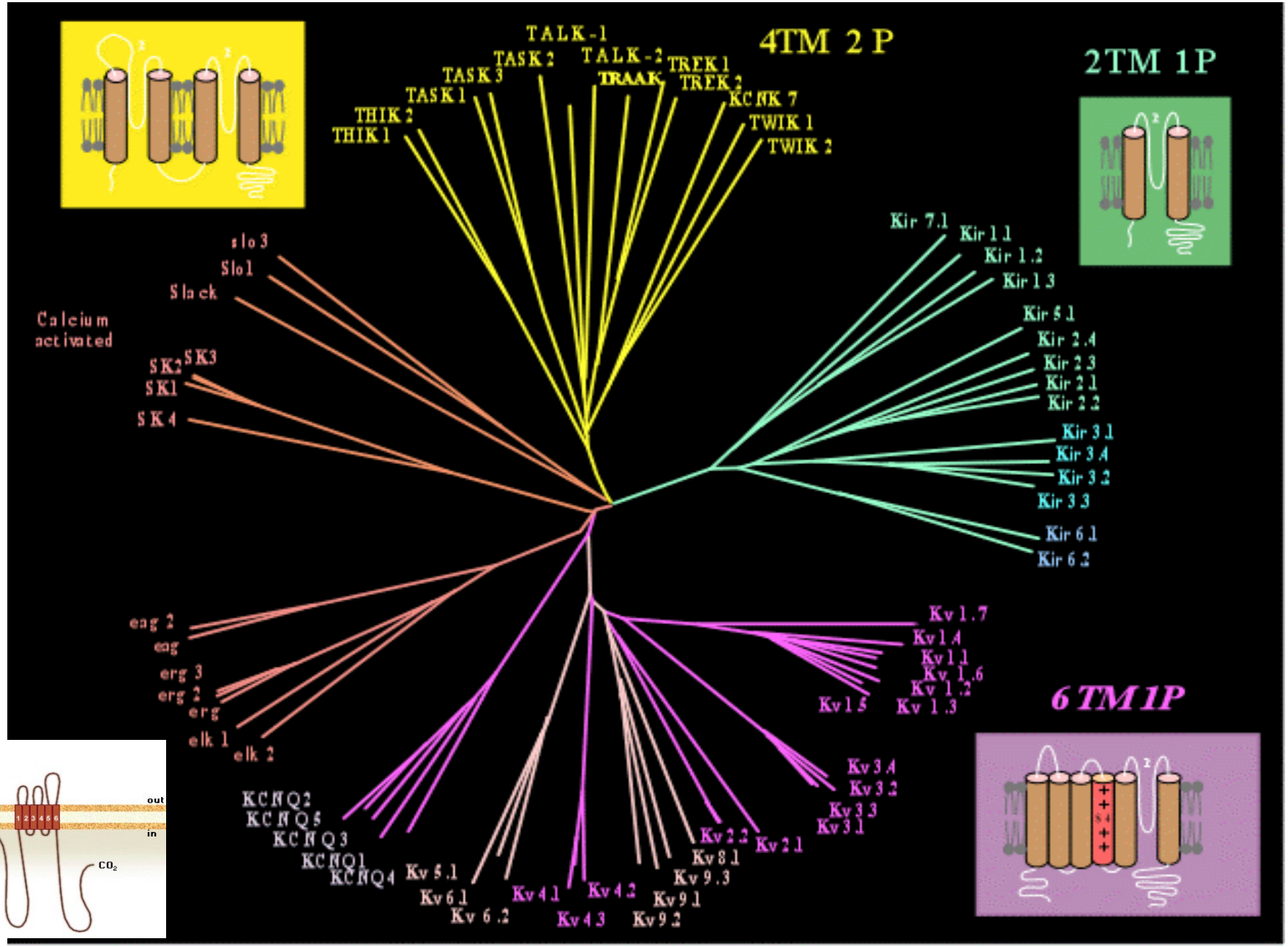




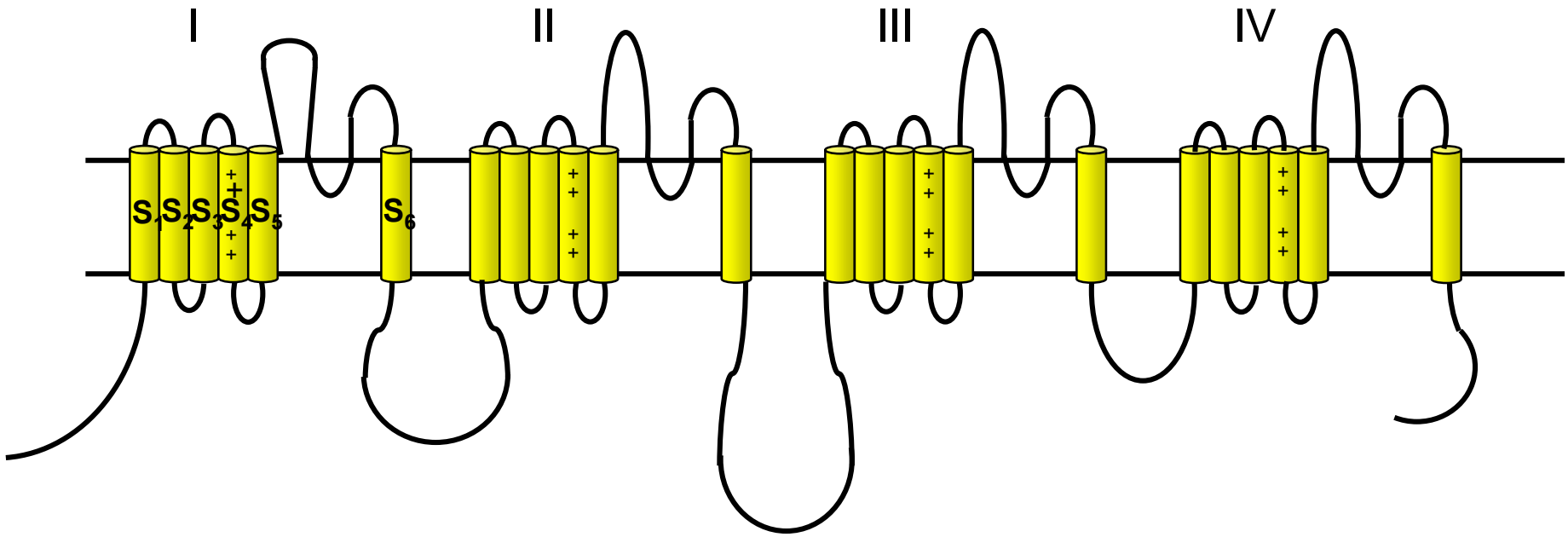
六個穿透膜的區段 **(6 TM)**
(transmembrane region)

K^+ channels form tetramers



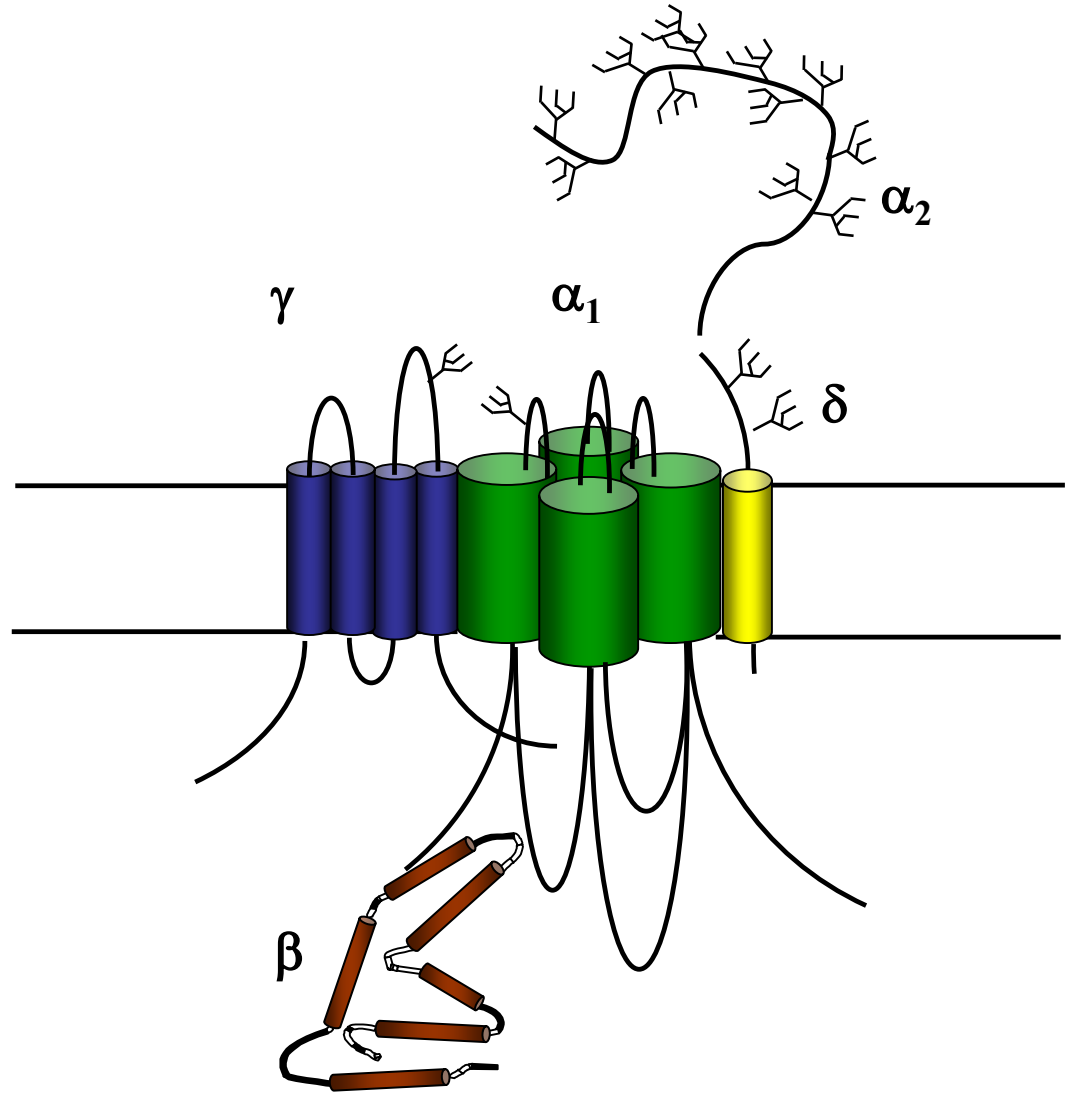

4TM 2 P
2TM 1P
6 TM 1P
TALK-1
TASK 2
TALK-2
TASK 3
TRAAK
TREK 1
TASK 1
TREK 2
KCNK 7
THIK 2
TWIK 1
THIK 1
TWIK 2
Kir 7.1
Kir 1.1
Kir 1.2
Kir 1.3
Kir 5.1
Kir 2.4
Kir 2.3
Kir 2.1
Kir 2.2
Kir 3.1
Kir 3.4
Kir 3.2
Kir 3.3
Kir 6.1
Kir 6.2
slo 3
Slo1
Slack
Calcium
activated
SK2
SK3
SK1
SK 4
eag 2
eag
erg 3
erg 2
erg
elk 1
elk 2
Kv 1.7
Kv 1.4
Kv 1.1
Kv 1.6
Kv 1.2
Kv 1.5
Kv 1.3
Kv 3.4
Kv 3.2
Kv 3.3
Kv 3.1
Kv 2.2
Kv 2.1
Kv 8.1
Kv 9.3
Kv 9.1
Kv 9.2
KCNQ2
KCNQ5
KCNQ3
KCNQ1
KCNQ4
Kv 5.1
Kv 6.1
Kv 6.2
Kv 4.1
Kv 4.2
Kv 4.3
+K channels
out
in
1 2 3 4 5 6
CO2
H3N

電壓驅動式鈣/鈉離子通道 α1 subunit

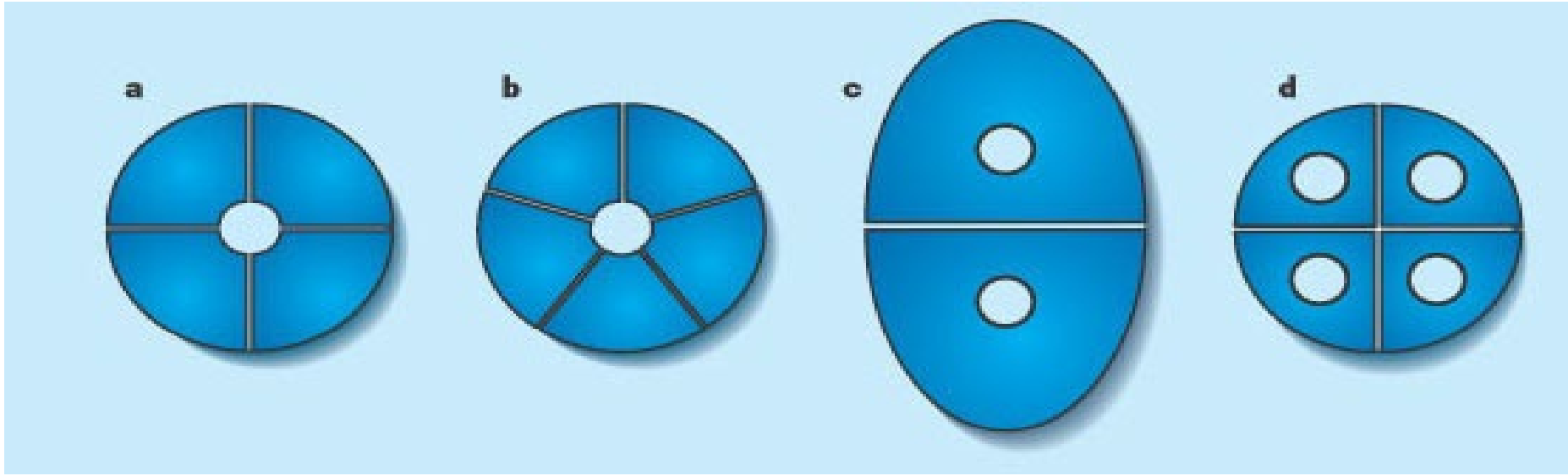


24個穿透膜的區段

Subunit Composition of High Voltage-Gated Ca^{2+} channel
高電壓驅動式鈣離子通道的組成



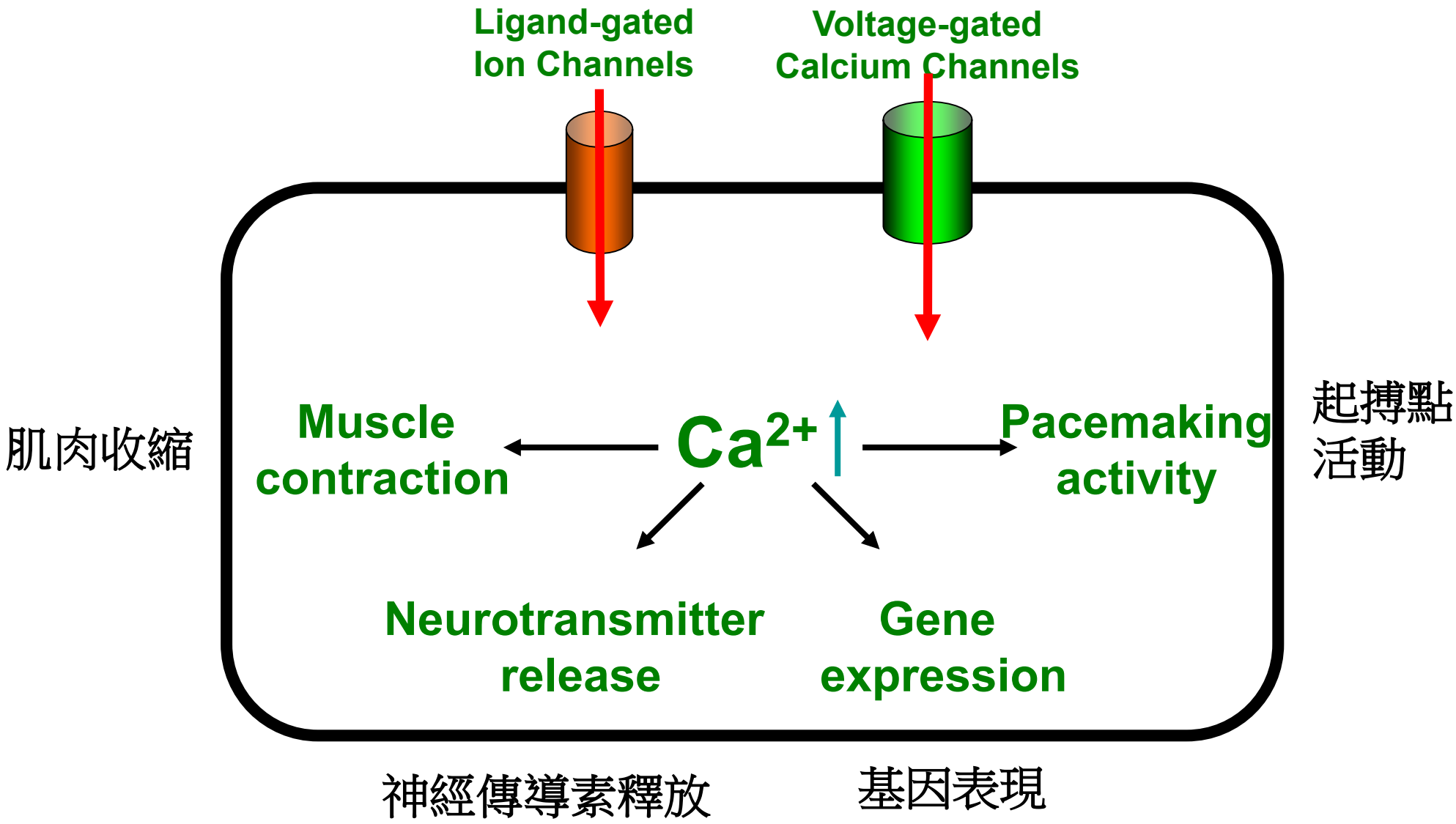
The different ways in which ion channels composed of more than one protein can form pores.



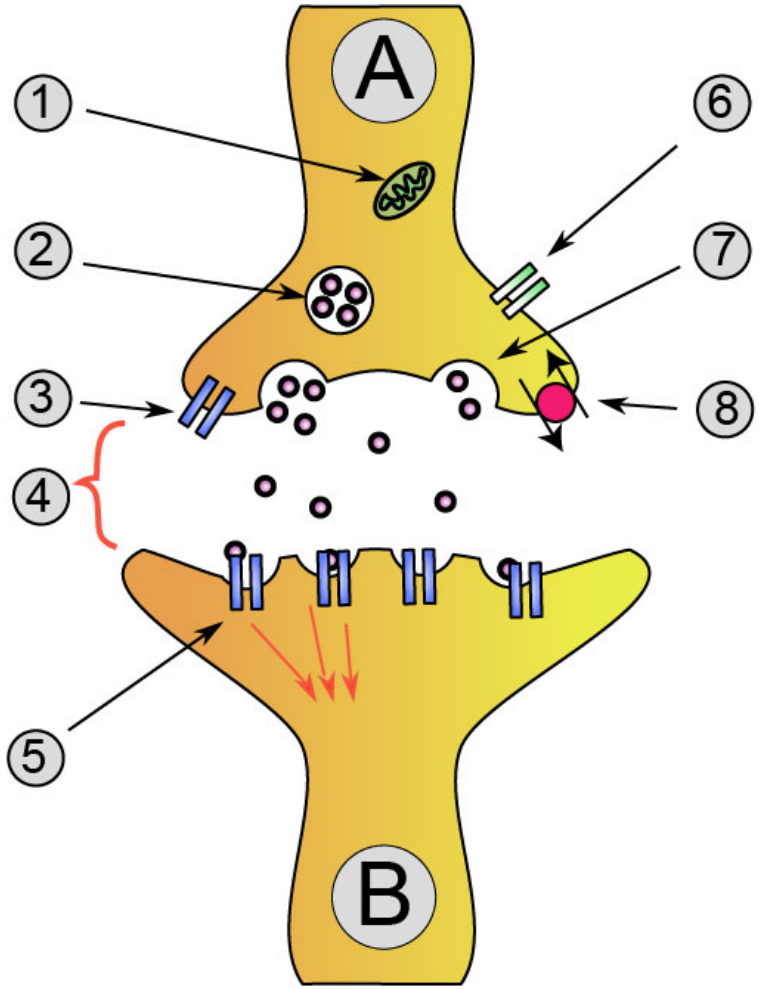
Voltage-gated ion channels	Ligand-gate ion channel	Chloride channel	Water channel
電壓驅動式	配體驅動式	氯離子	水通道

Thomas J. Jentsch
Nature **415**, 276-277(17 January 2002)

Functions of Ca^{2+} channels
鈣離子通道的功能



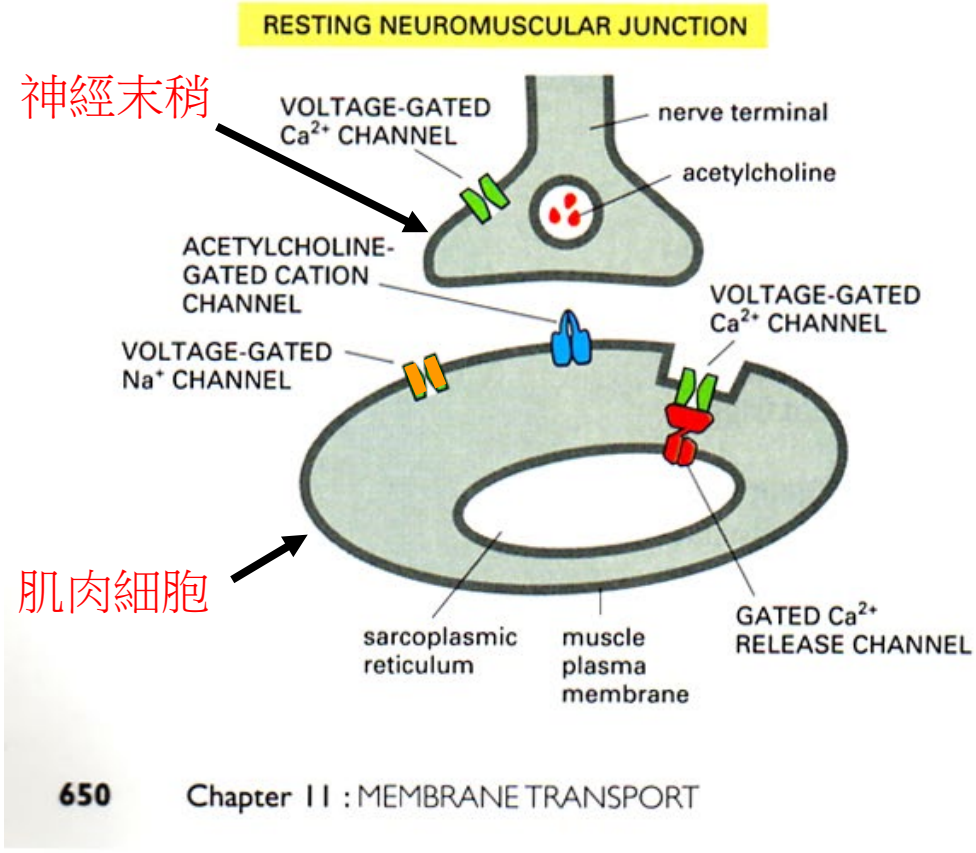
典型的突觸結構

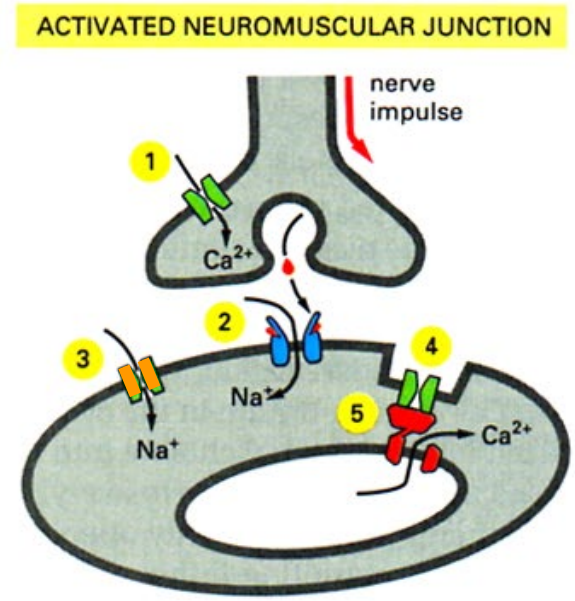


A. 突觸前膜。
B. 突觸後膜。
1. **線粒體**：突觸的能量供應者。
2. **突觸小泡**：內含待釋放的神經遞質。
3. 突觸前膜上的神經遞質**受體**。
4. 突觸間隙。
5. 突觸後膜上的神經遞質**受體**。
6. 突觸前膜上的**鈣通道**。
7. 突觸前膜。
8. 離子幫浦。

維基百科

Neuromuscular junction
神經肌肉接點

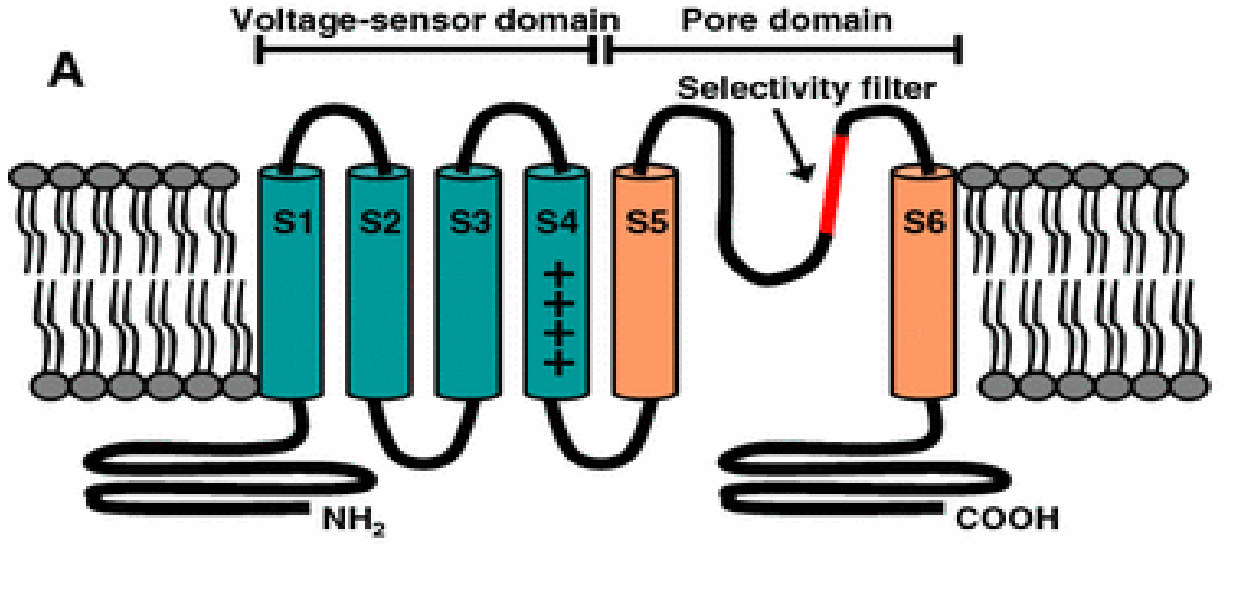


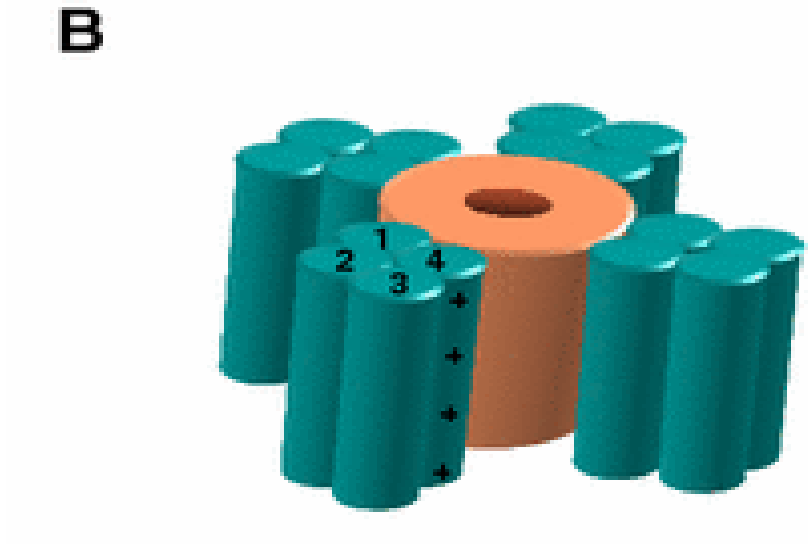



乙烯膽鹼接受器


電壓驅動式鈣離子通道


電壓驅動式鈉離子通道

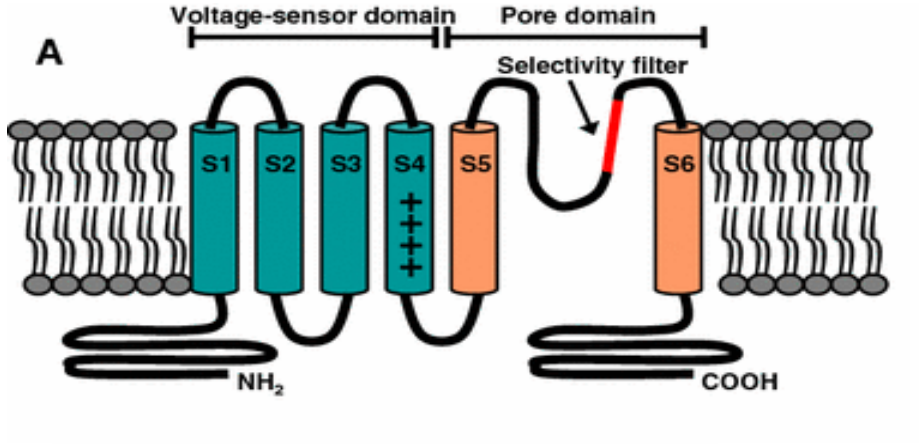


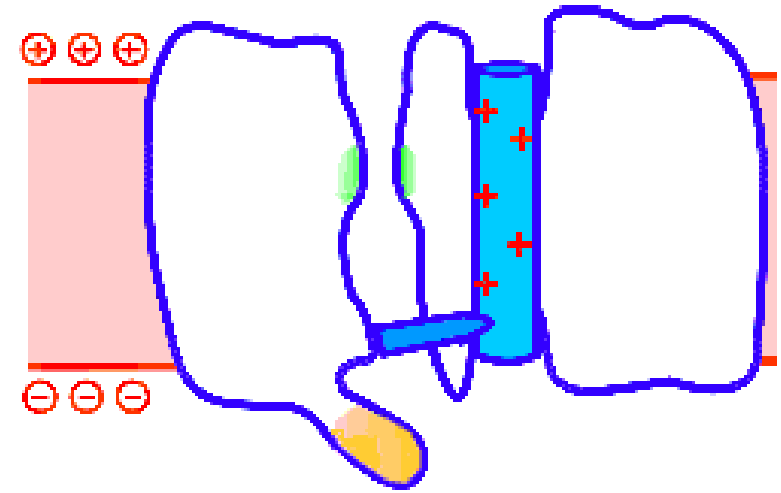


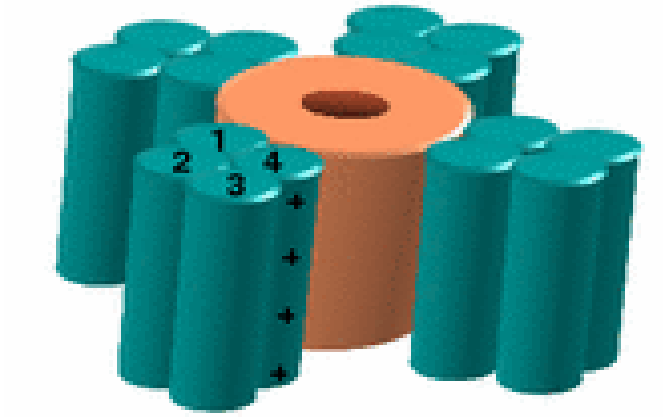
Cell Biochemistry and Biophysics 2008

How does the channel sense change in voltage?
離子通道如何感應膜電位的變化？

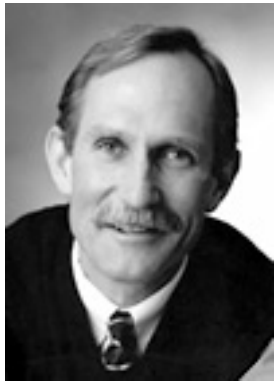
- Positively charged residues within the S4 TM segment.
- Evidence that the segment rotates out of the membrane in response to change in voltage: gating charges





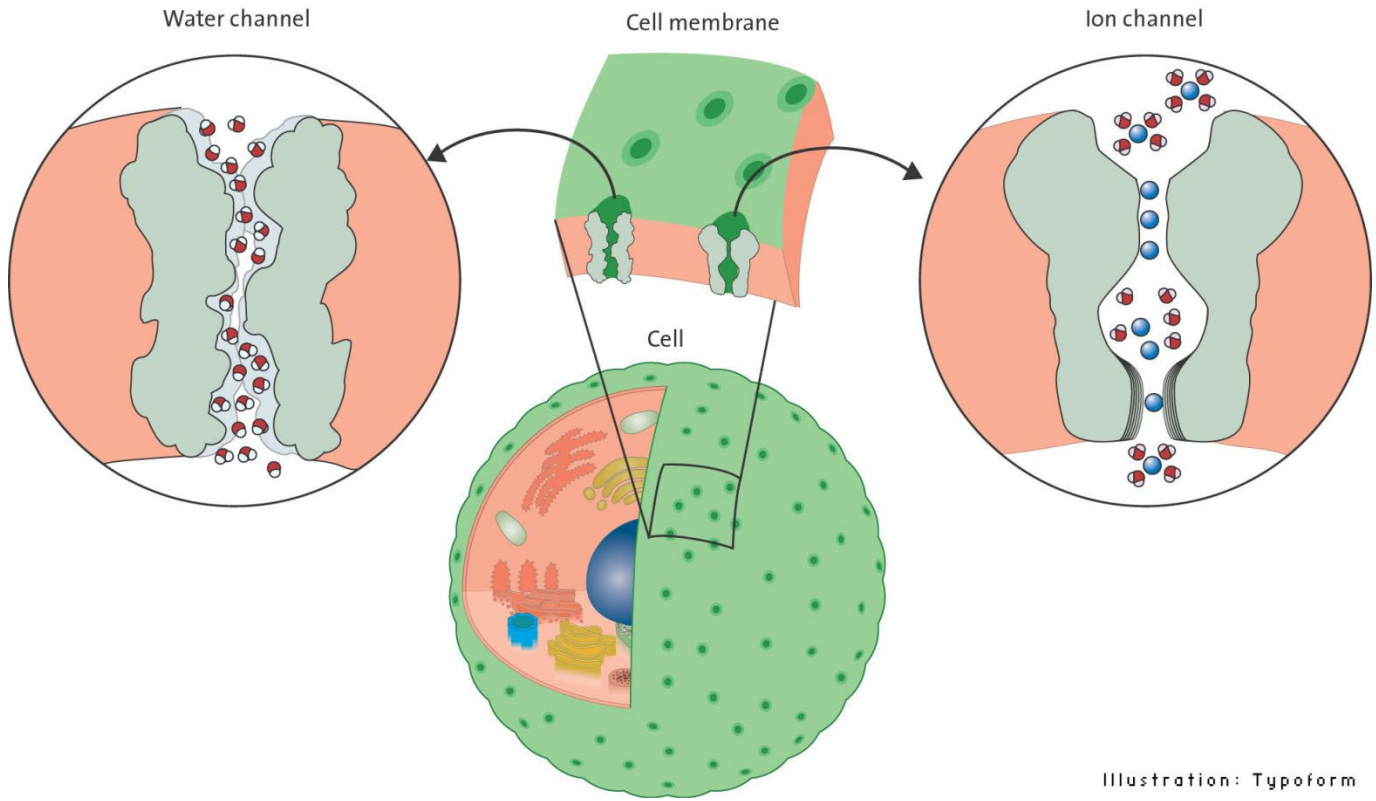


The third Nobel Prize for ion channel research



Agre

阿格雷



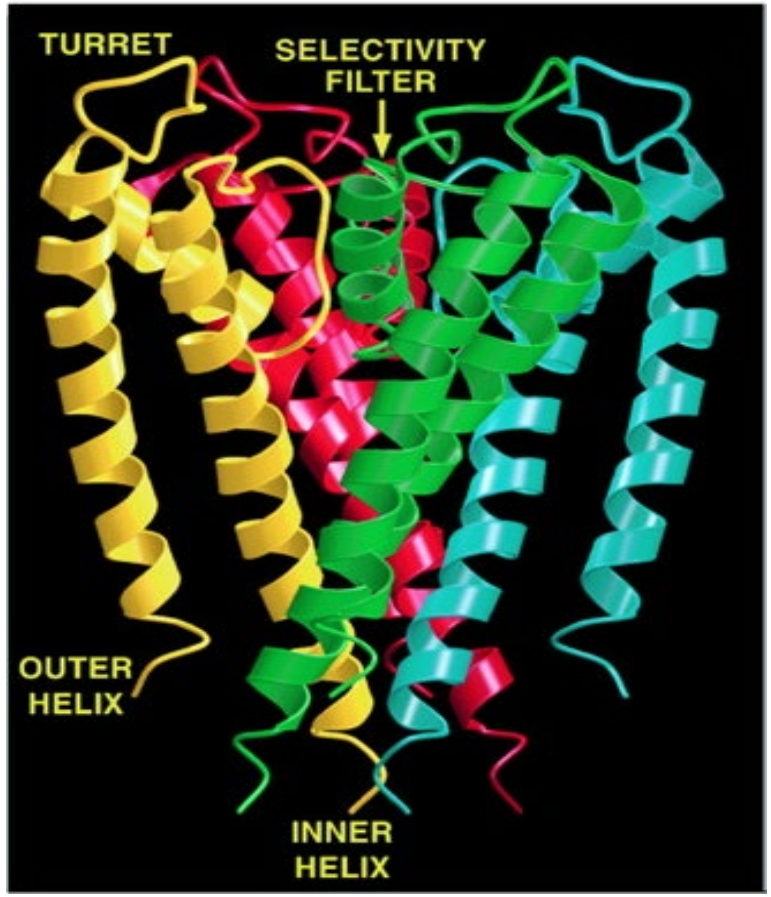
MacKinnon

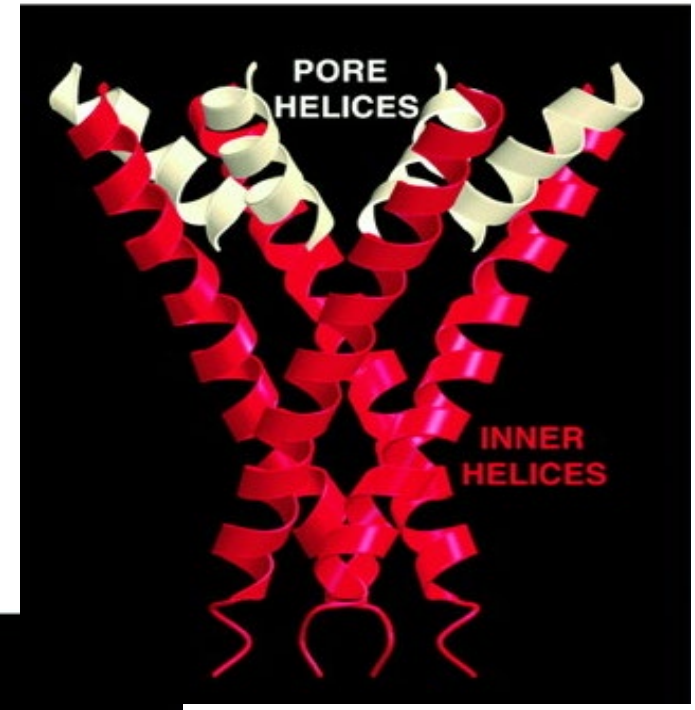
麥金農

Nobel Prize in 2003

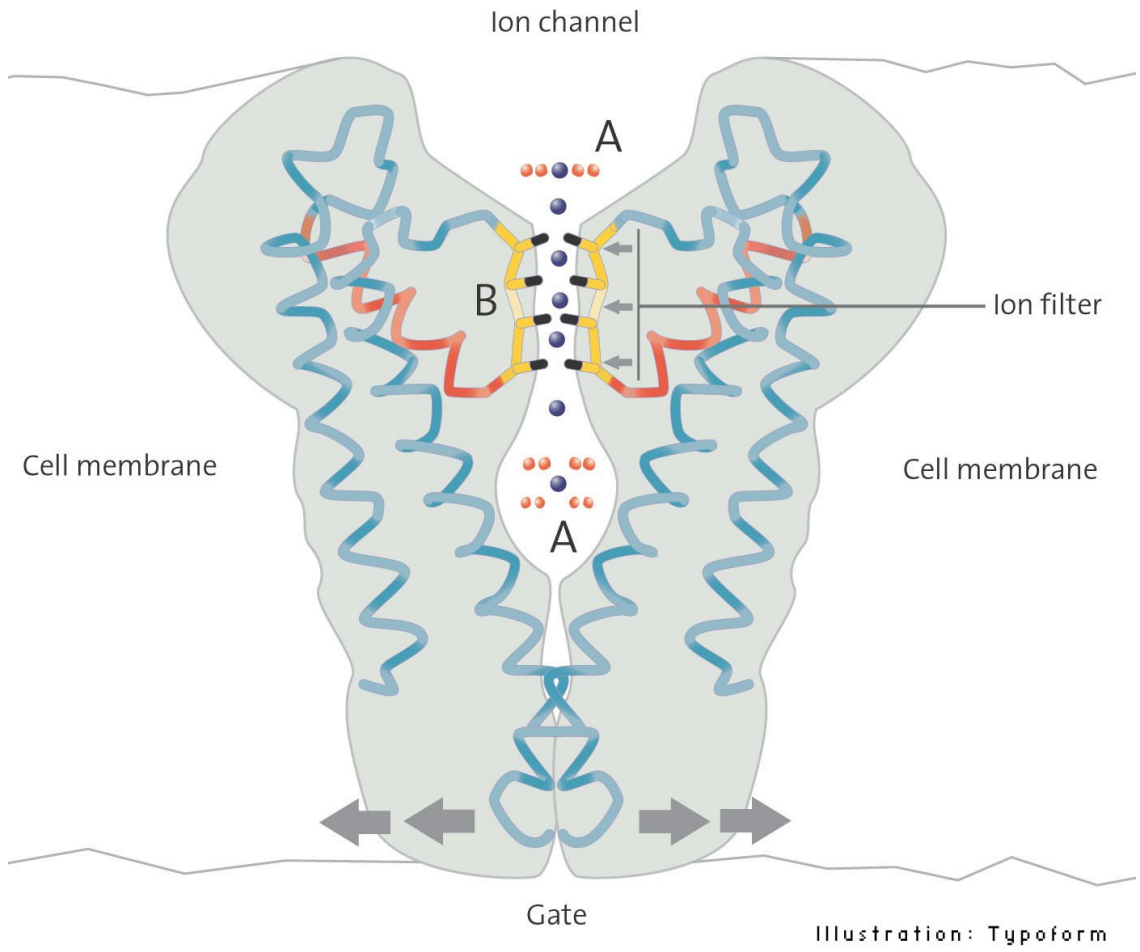
What they look like:

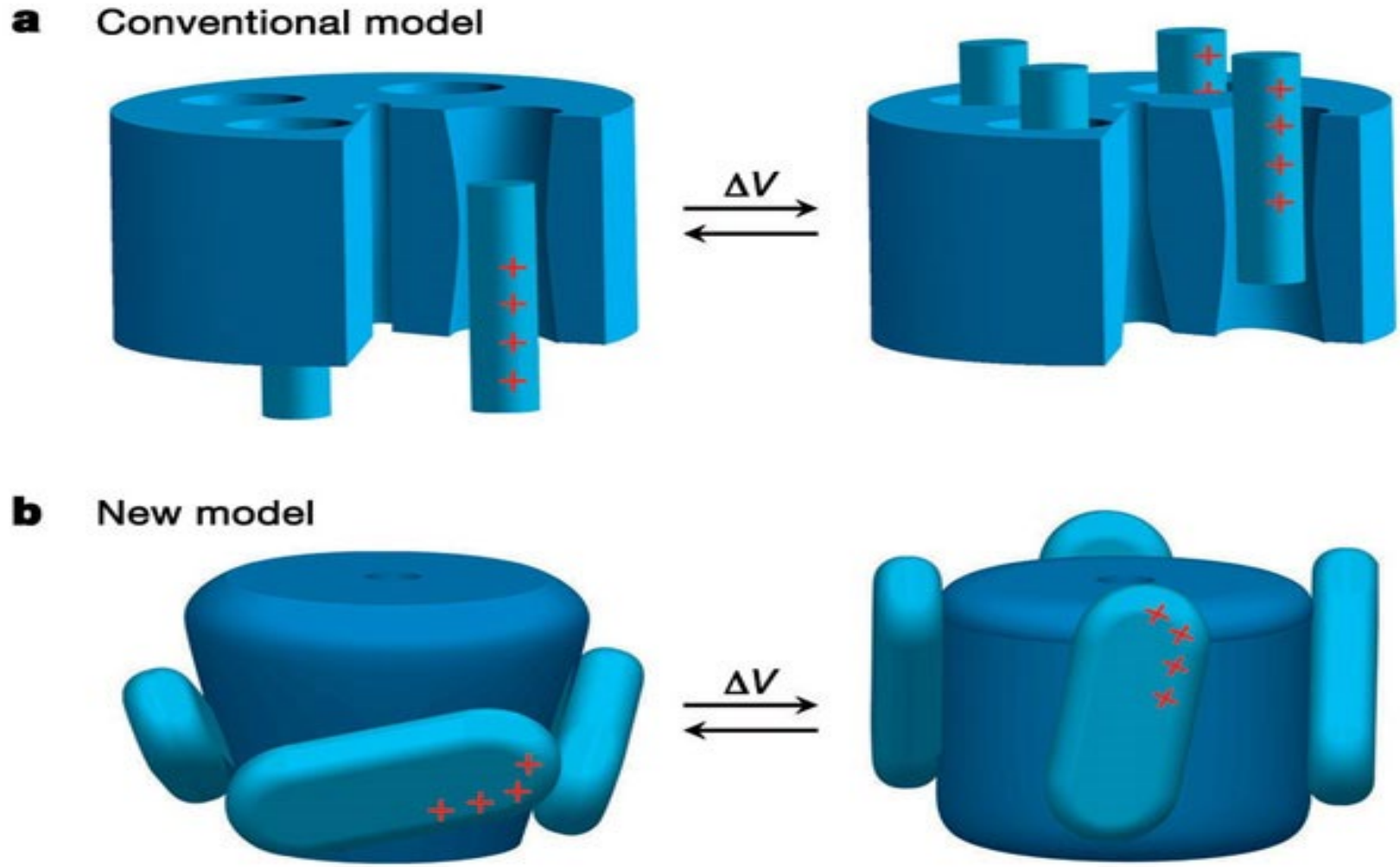
Bacterial KcsA channels





K^+ channel-鉀離子通道



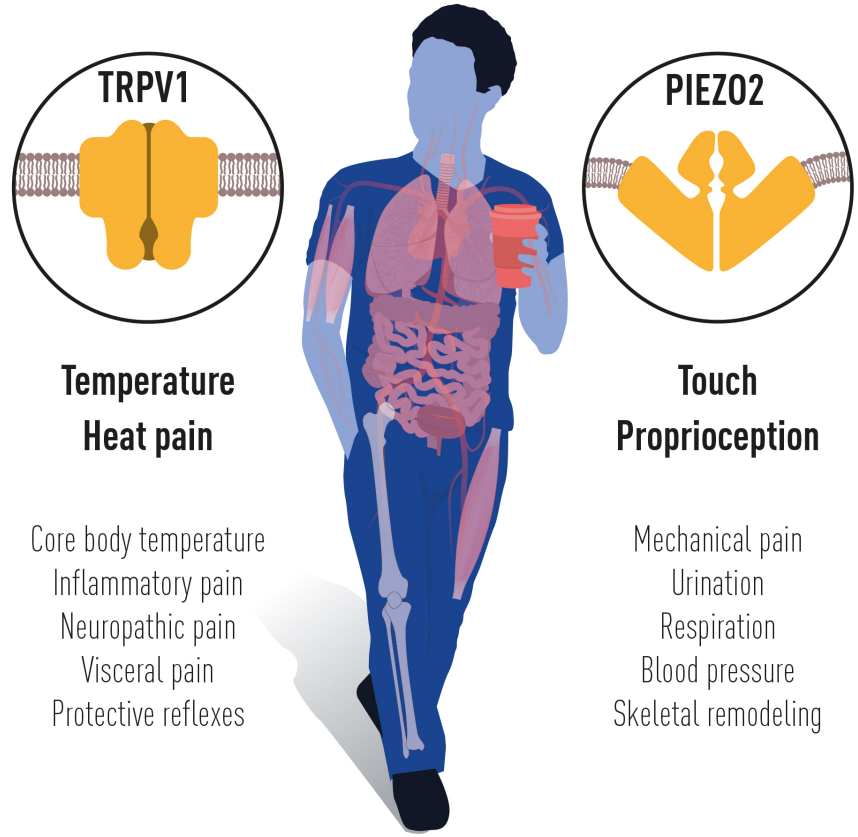


Jiang et al., Nature (2003)

The fourth Nobel Prize for ion channel research

David Julius

朱利叶斯

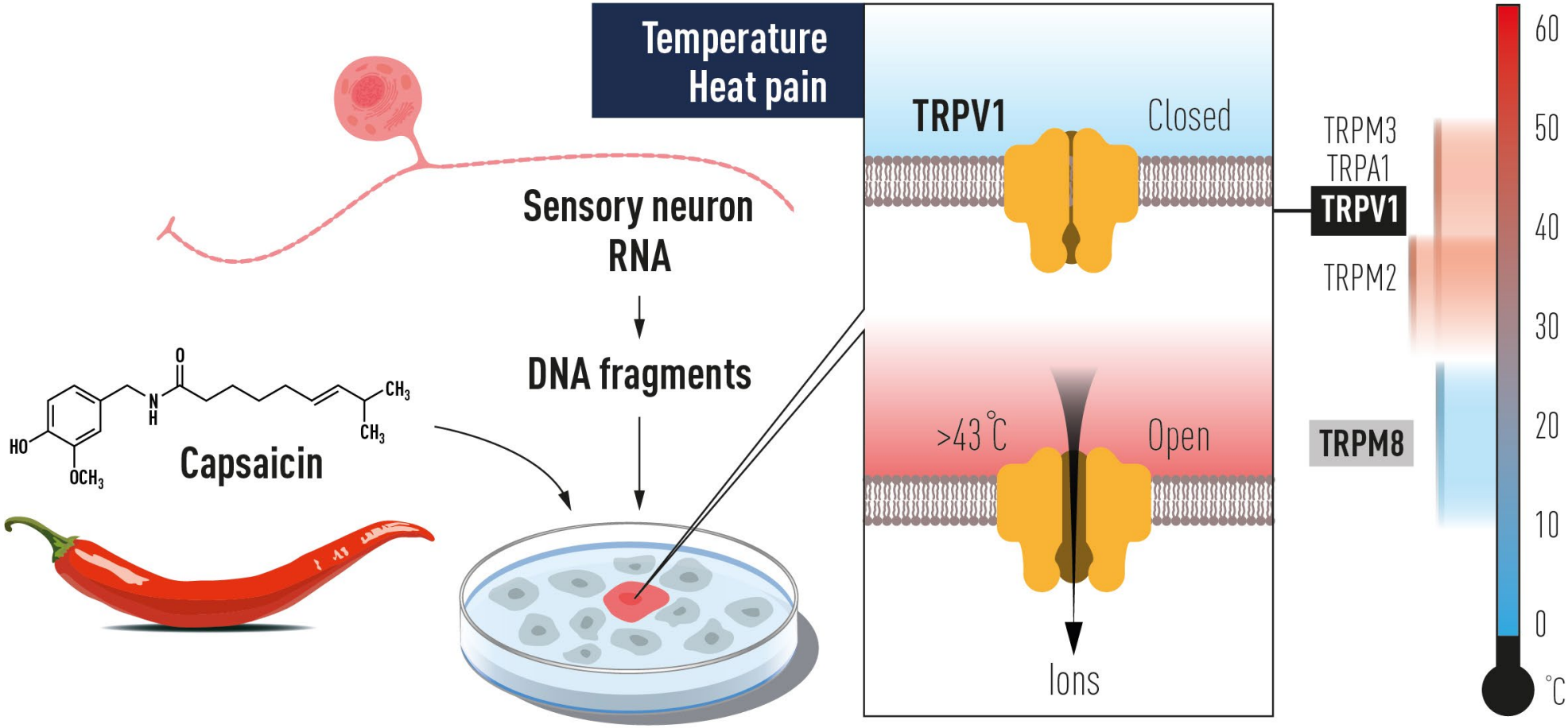


Ardem Patapoutian

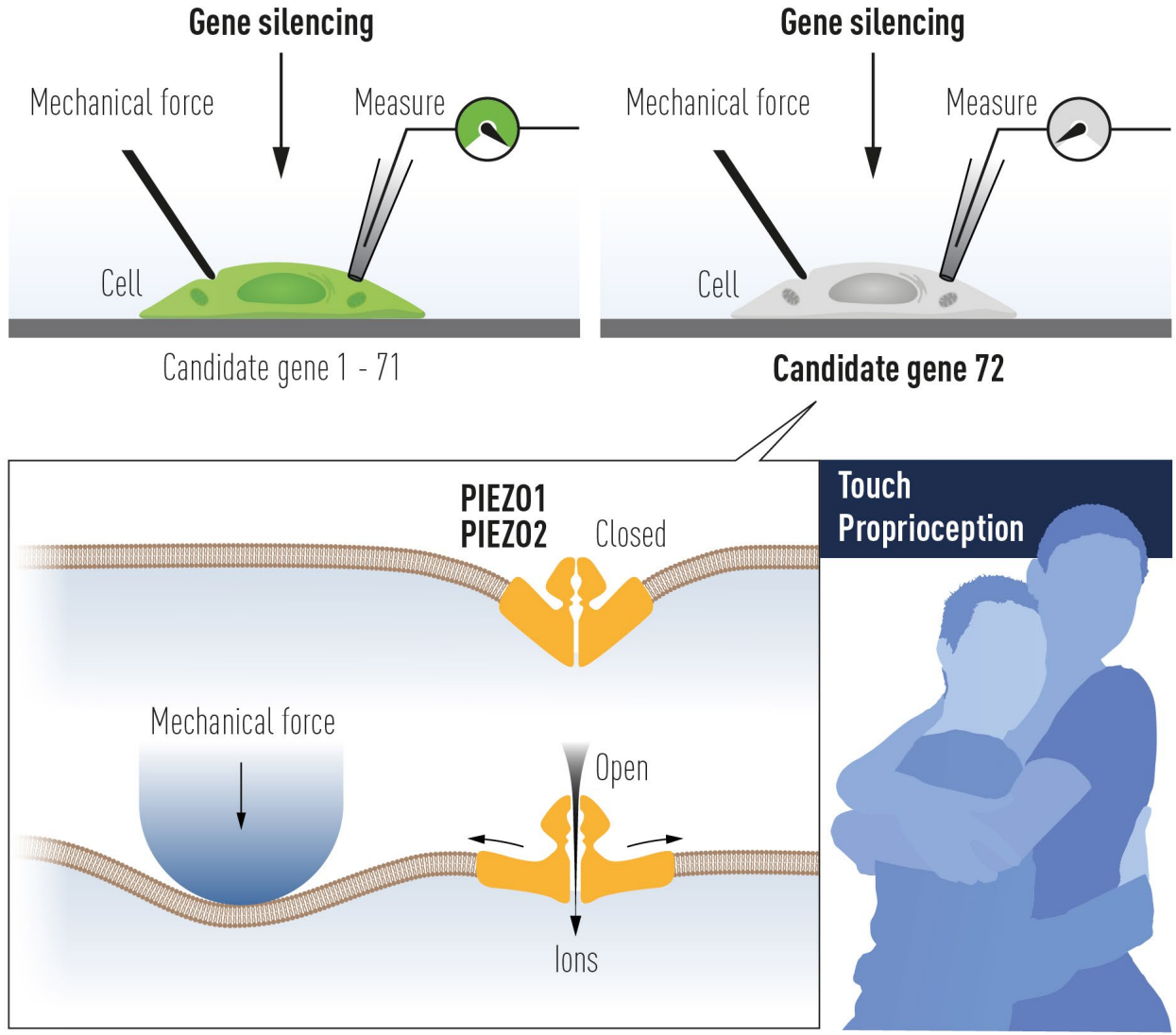
帕塔普蒂安

Nobel Prize in 2021

David Julius



Ardem Patapoutian



- 細胞，細胞膜，細胞膜蛋白質
- 研究離子通道的方法
- 離子通道的種類和功能
- 離子通道相關疾病

Ion Channelopathies
離子通道相關疾病

Cystic fibrosis (Cl^- channel; CFTR)
Thomsen Myotonia congenita(Cl^- channel; CLC-1)
Becker Myotonia congenita (Cl^- channel; CLC-1)
Hypercalciuric nephrolithiasis (Cl^- channel; CLC-5)
Bartter's syndrome type 1 (Cl^- channel; CLC-Kb)
Angleman / Prader-Willi (GABA channel; GABAAB3)
Low molecular weight proteinuria (CLCN5)
Bartter's syndrome type 3 (SLC12A3)
Startle disease (hyperexplexia) (glycine receptor)

Liddle's syndrome (ENaC; SCNN1A, SCNN1B)
Paramyotonia congenita (Na^+ channel; SCN4A)
Hyperkalemic periodic paralysis (Na^+ channel; SCN4A)
Myotonia Fluctuans (Na^+ channel; SCN4A)
Myotonia Permanens (Na^+ channel; SCN4A)
Acetzolamide-responsive myotonia (Na^+ channel; SCN4A)
Malignant hyperthermia (Na^+ channel; SCN4A)
Idiopathic ventricular fibrillation (Na^+ channel; SCN5A)
Long QT Syndrome (LQT3 Na^+ channel; SCN5A)
Epilepsy with febrile seizures (Na^+ channel; SCN1B immune)
Acute motor axonal neuropathy (Na^+ channel; immune)
Guillain-Barré & CIDP (Na^+ channel; immune)
Multifocal Motor Neuropathy (Na^+ channel; immune)

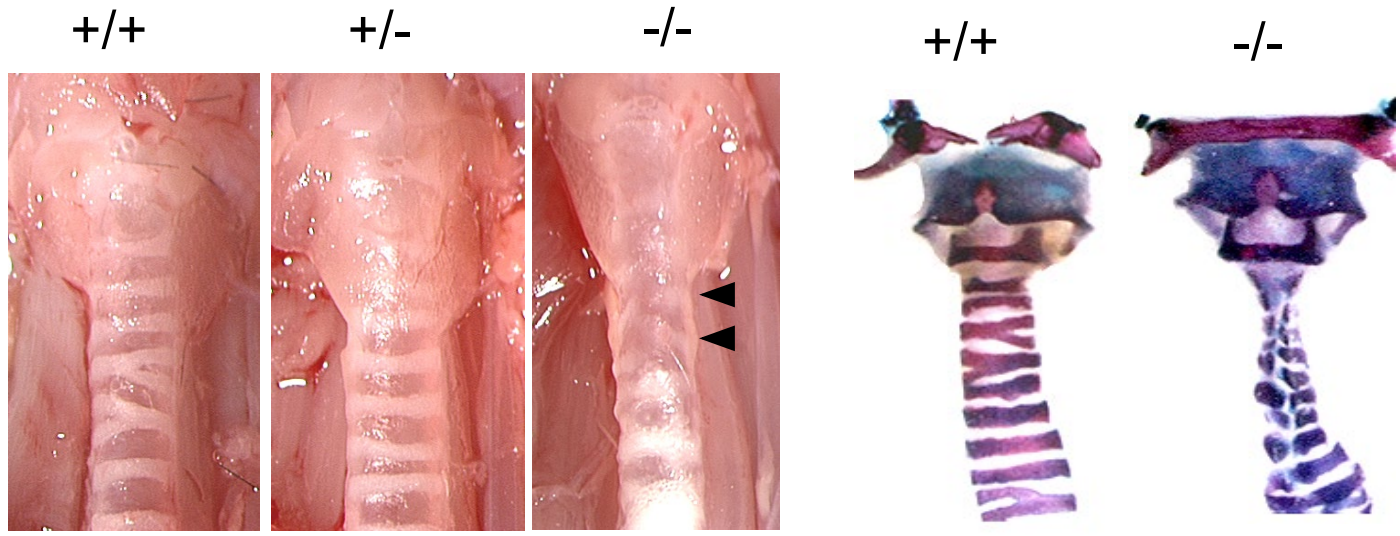
Nephrogenic diabetes incipidus (AQP-2)
Total color blindness (CNGA3)

Hypokalemic periodic paralysis (Ca^{2+} channel; CACNL1A3)
Malignant Hyperthermia (Ca^{2+} channel; CACNL1A3, RyR 1)
X-linked congenital night blindness (Ca^{2+} channel; CSNB2)
Muscular dysgenesis (rodent Ca^{2+} channel; CACNL1A3)
Episodic ataxia type-2 (Ca^{2+} channel; CACNL1A4)
Familial hemiplegic migraine (Ca^{2+} channel; CACNL1A4)
Spinocerebellar ataxia (Ca^{2+} channel; CACNL1A4)
Congenital myasthenic syndrome (nAChR)
Lambert-Eaton Myasthenic Syndrome (Ca^{2+} channel; immune)
Insulin-Dependent Diabetes (Ca^{2+} channel; immune)
Antenatal Bartter's Syndrome type 2 (K^+ channel; KCNJ1)
Long QT Syndrome (LQT1; K^+ channel; KCNA8)
Long QT Syndrome (LQT2 K^+ channel; HERG)
Jervell & Lange-Nielsen Syndrome (K^+ channel; KCNE1, KCNQ1)
Episodic Ataxia / Myokymia Syndrome (K^+ channel; KCNA1)
Benign neonatal epilepsy (K^+ channel; KCNQ2, KCNQ3)
Schizophrenia (K^+ channel; KCNN3)
Retinitis pigmentosa (K_{NS} channel; CNGA1)
Rod monochromacy (K_{NS} channel; CNGA3)
Hyperinsulinism of Infancy (K^+ channel; SUR1)
Hyperinsulinism of Infancy (K^+ channel; Kir6.2)

Visceroatrial Heterotaxia (gap junction; CXA1)
CMT-X (gap junction; CXB1)
Non-syndromic deafness (gap junction; CXB2)

Abnormal Vocalization of $\alpha_{1H}^{-/-}$ Mice

Abnormal Trachea Formation



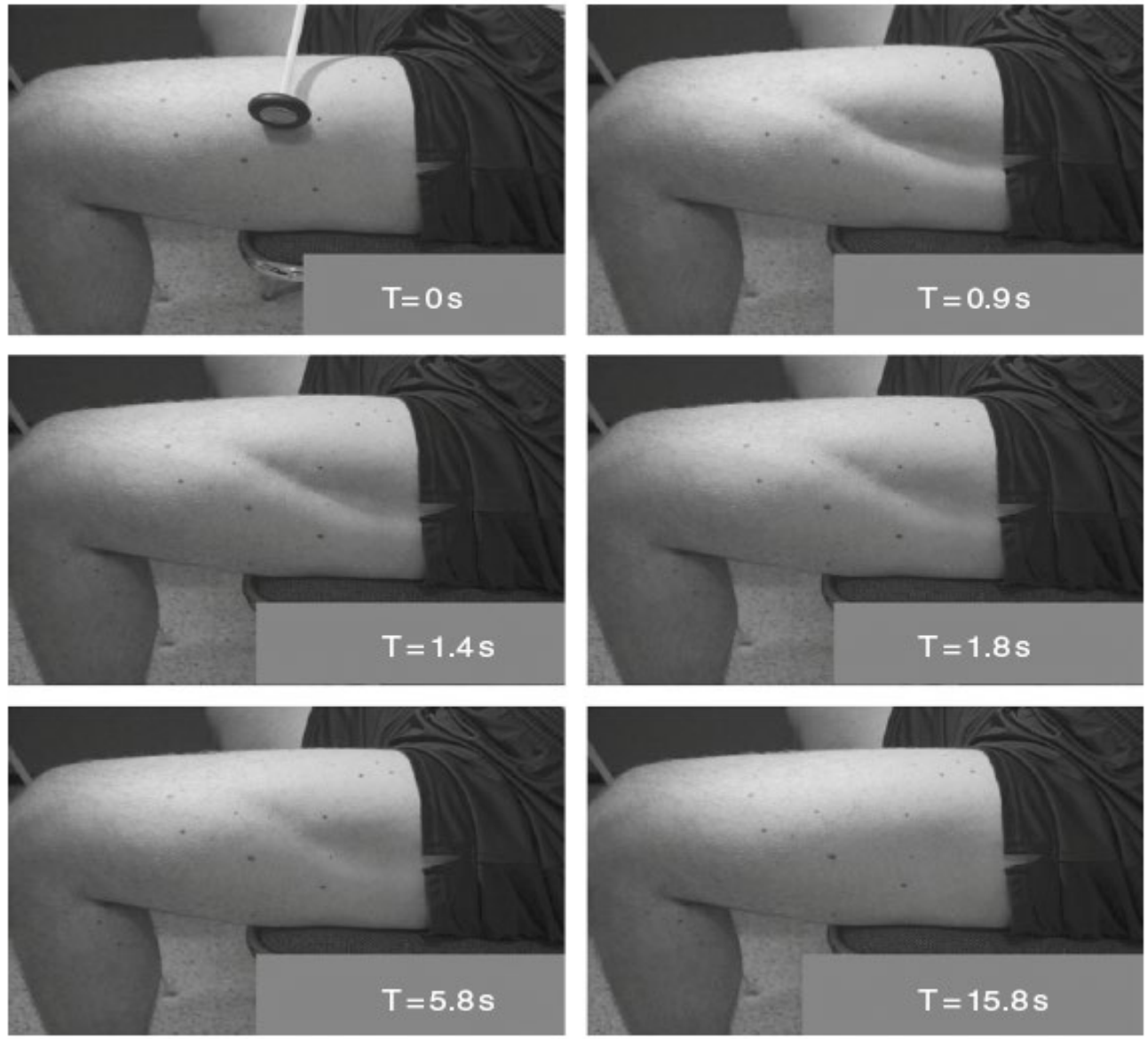
myotonia - 肌強直

There are two forms of the disorder: Becker-type (autosomal recessive), which is the most common form; and Thomsen's disease (autosomal dominant), which is a rare and milder form.

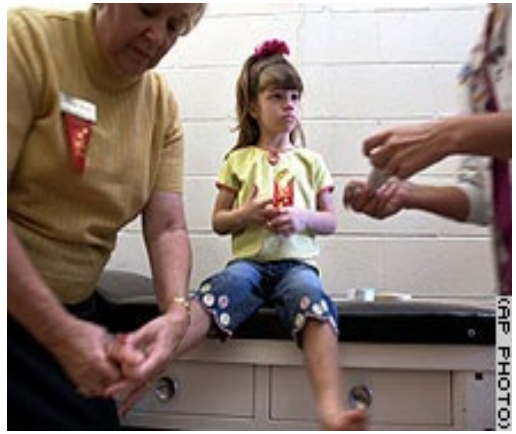
The disorder is cause by mutations in *CLCN1* gene responsible for shutting off electrical excitation in the muscles.

Fainting Goats

Becker myotonia



Congenital Insensitivity To Pain/先天性痛覺不敏感症



patients with a complete absence of pain

the absence of nocifensive behavior leads to an accumulation of painless injuries, bites, bruises, bone fractures, and a reduction of life expectancy.

14 CIP-inducing mutations (**Nav1.7, SCN9A**) identified so far introduce a stop codon which leads to premature protein truncation

鈣離子通道疾病

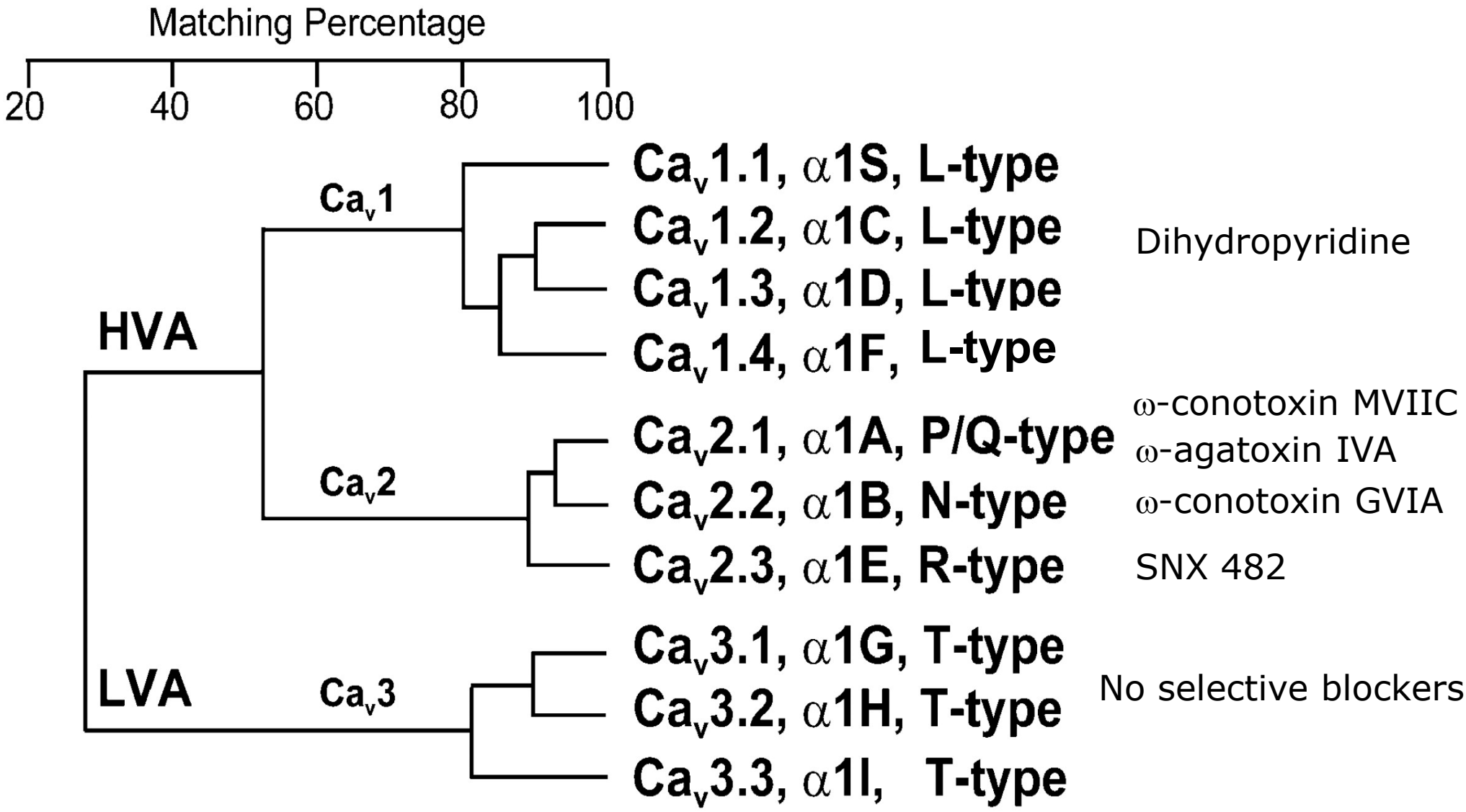
- 低血鉀週期性無力症 Hypokalemic periodic paralysis (α1S)
- 惡性高熱綜合症 Malignant Hyperthermia (α1S,RyR 1)
- 肌肉萎縮症 Muscular dysgenesis (α1S)

- 先天性夜盲症 X-linked congenital night blindness (α1F)

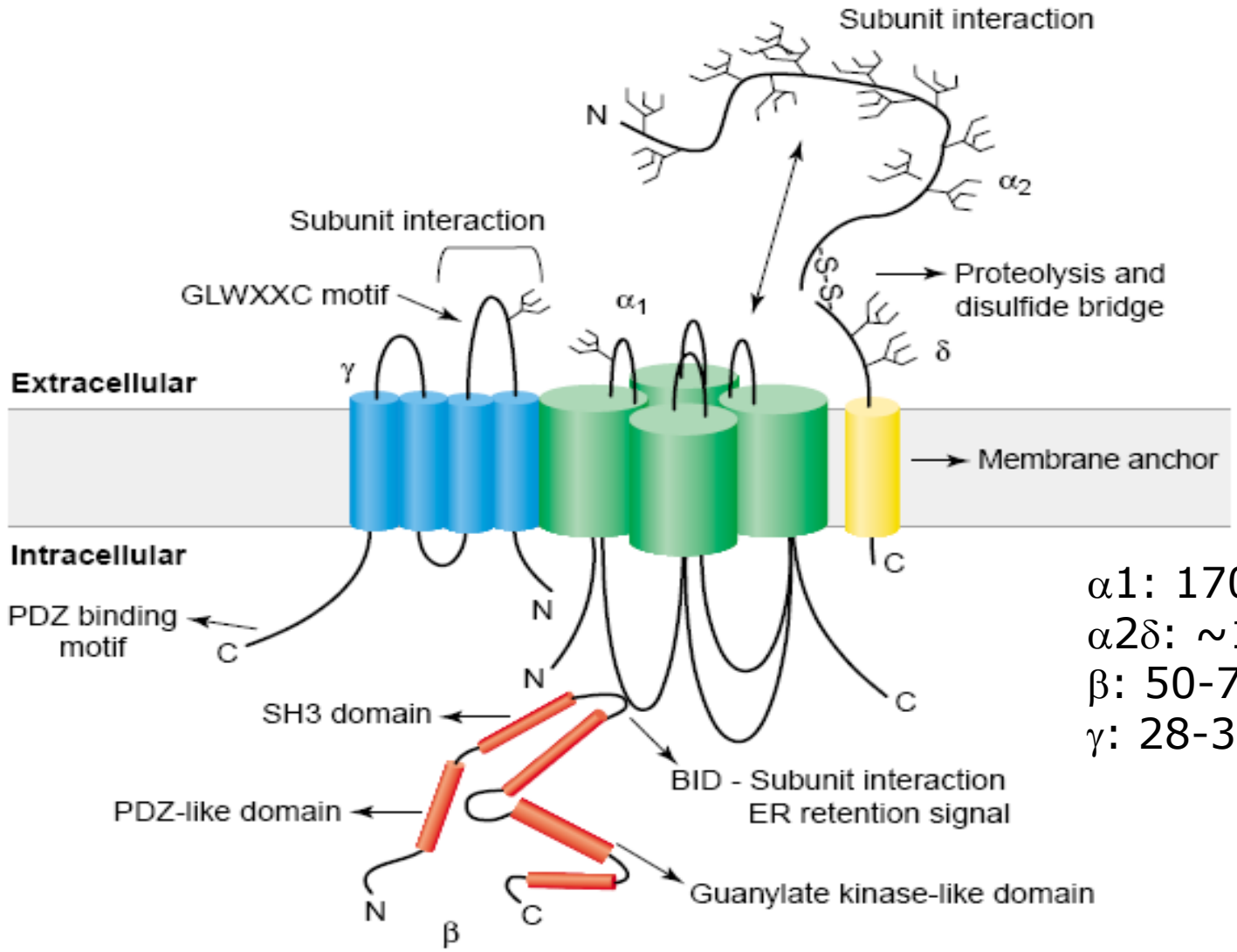
- 陣發性運動失調症 Episodic ataxia type-2 (α1A)
- 偏頭痛 Familial hemiplegic migraine (α1A)
- 脊髓小腦萎縮症 Spinocerebellar ataxia (α1A)
- 癌肌症 Lambert-Eaton Myasthenic Syndrome (auto-immune, α1A)

- 糖尿病 Diabetes (α1C, α1D Ca^{2+} channel; immune)
- Timothy syndrome (α1C)
- Autism (α1C, α1H)
- Childhood absence epilepsy (α1H)

Classification of voltage-gated Ca^{2+} channels



Subunit composition of voltage-gated Ca^{2+} channels



α1: 170-250 kDa
α2δ: ~170 kDa
β: 50-78 kDa
γ: 28-36 kDa

Diseases of retinal Ca^{2+} channels
視網膜鈣離子通道疾病

- Incomplete X linked congential stationary night blindness (CSNB2) (α1F) (先天性靜止性夜盲)
- autosomal recessive cone–rod dysfunction in a substrain of C57BL/10 mice ($\alpha 2\delta 4$)(隱性視錐-視桿細胞功能不良)
- *nob2* (no b wave) mice (α1F)
- CNS-β2 null mice

Incomplete X linked congential stationary night blindness (CSNB2) 先天性静止性夜盲

An L-type calcium-channel gene mutated in incomplete X-linked congenital stationary night blindness

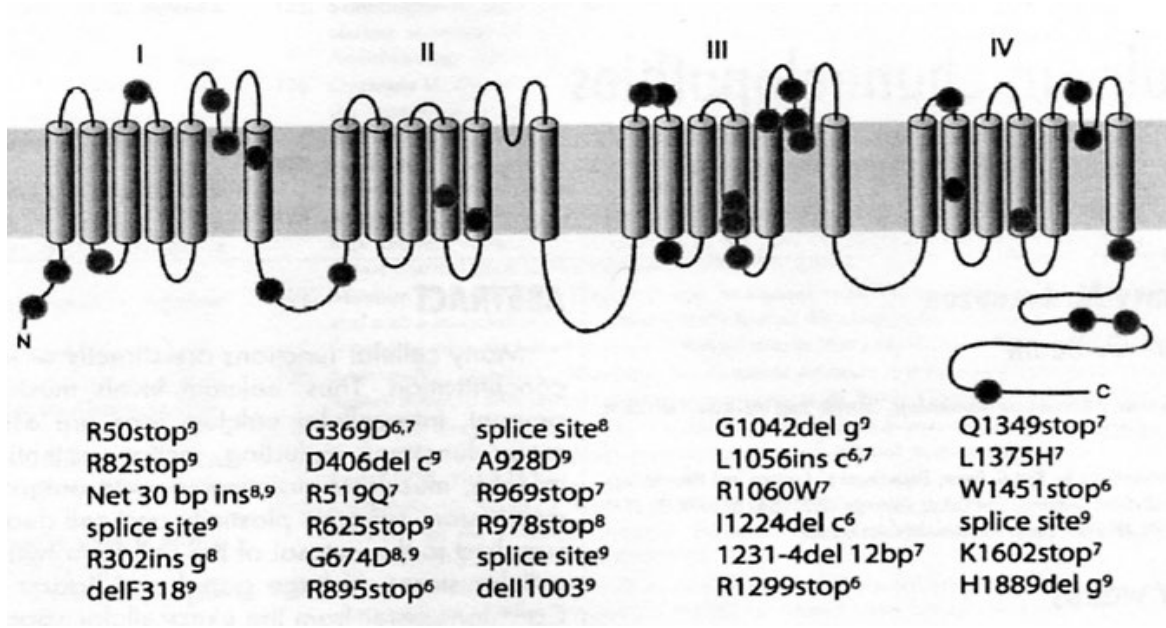
Nat Genet. 1998 Jul;19(3):260-3.

Loss-of-function mutations in a calcium-channel alpha1-subunit gene in Xp11.23 cause incomplete X-linked congenital stationary night blindness

Nat Genet. 1998 Jul;19(3):264-7.

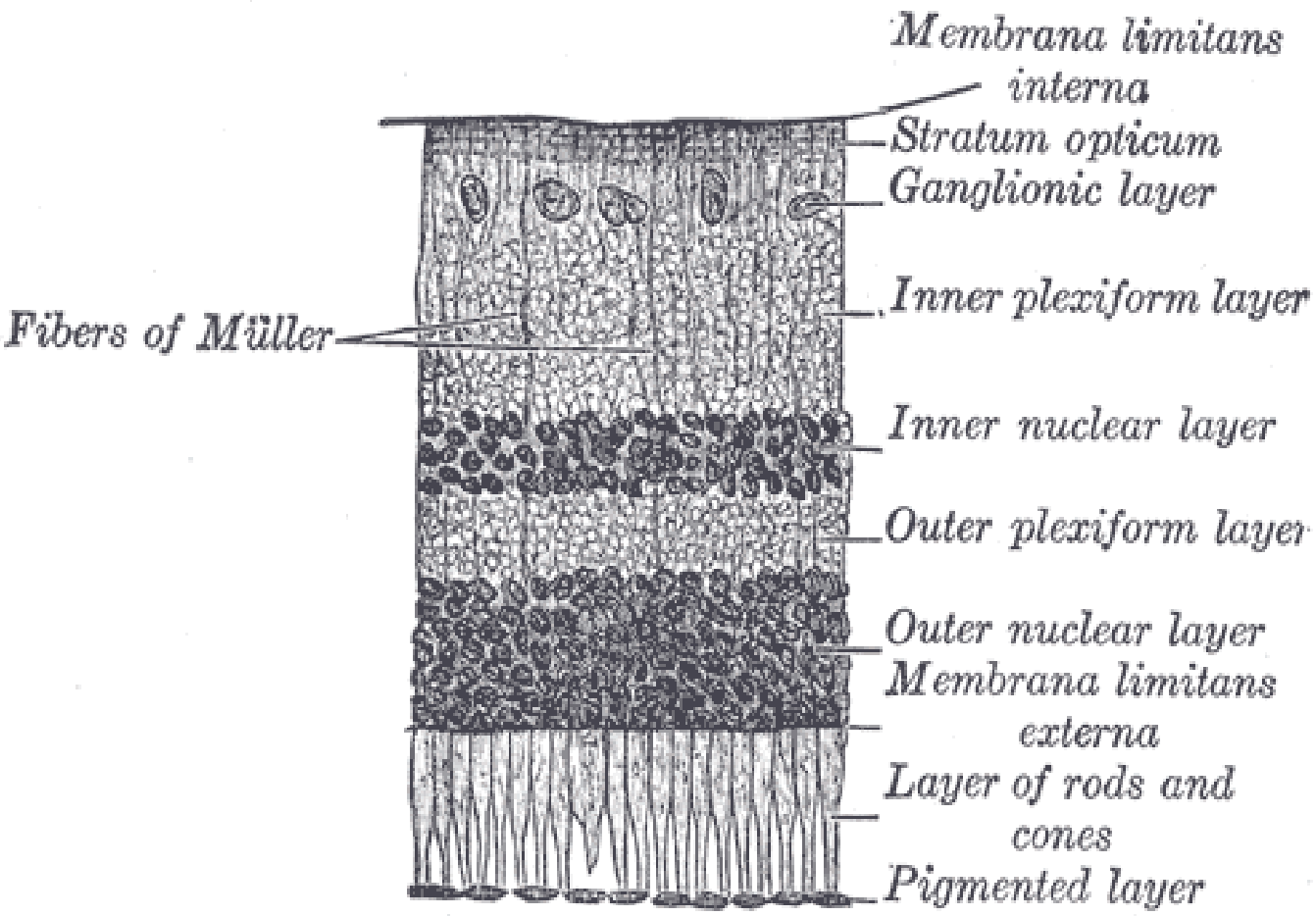
Incomplete X linked congential stationary night blindness (CSNB2) 先天性靜止性夜盲

CSNB2 is a non progressive, dominantly inherited disorder.
Symptoms include night blindness, decreased visual acuity, myopia (近視), nystagmus (眼振), strabismus (斜視) and abnormal ERG results.
Impairments resulted from alter synaptic transmission from photoreceptor cells to 2nd order neurons.
30 Mutations in the α1F L-type voltage gated calcium channel (VGCC) ($Ca_v1.4$)



(Eurekah Bioscience1:2, 125, 2005)

視網膜構造



內界膜

神經纖維層

神經節細胞層—這個層含有神經節細胞的細胞核

內網層

核心層

外網層（形成突觸的位置）

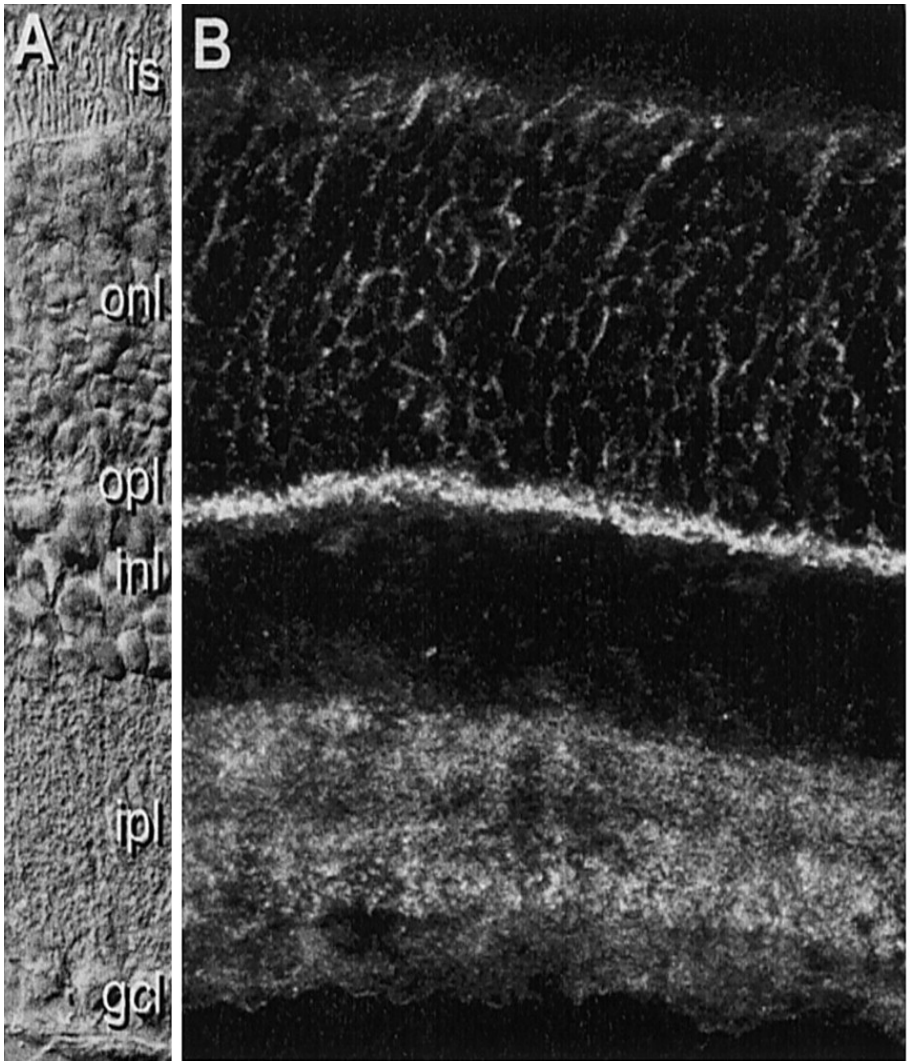
外核層

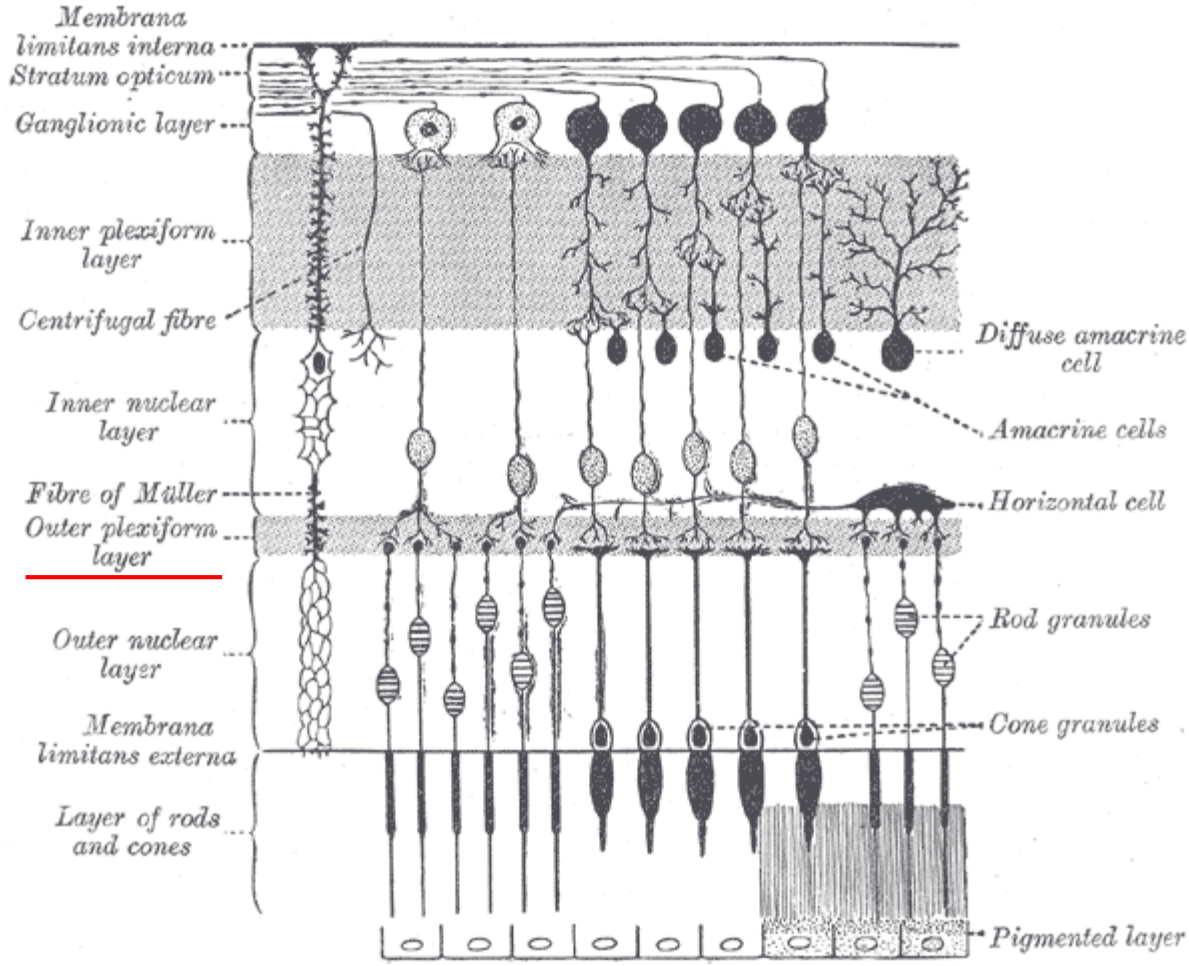
外界膜

感光層（錐-桿型視覺細胞）

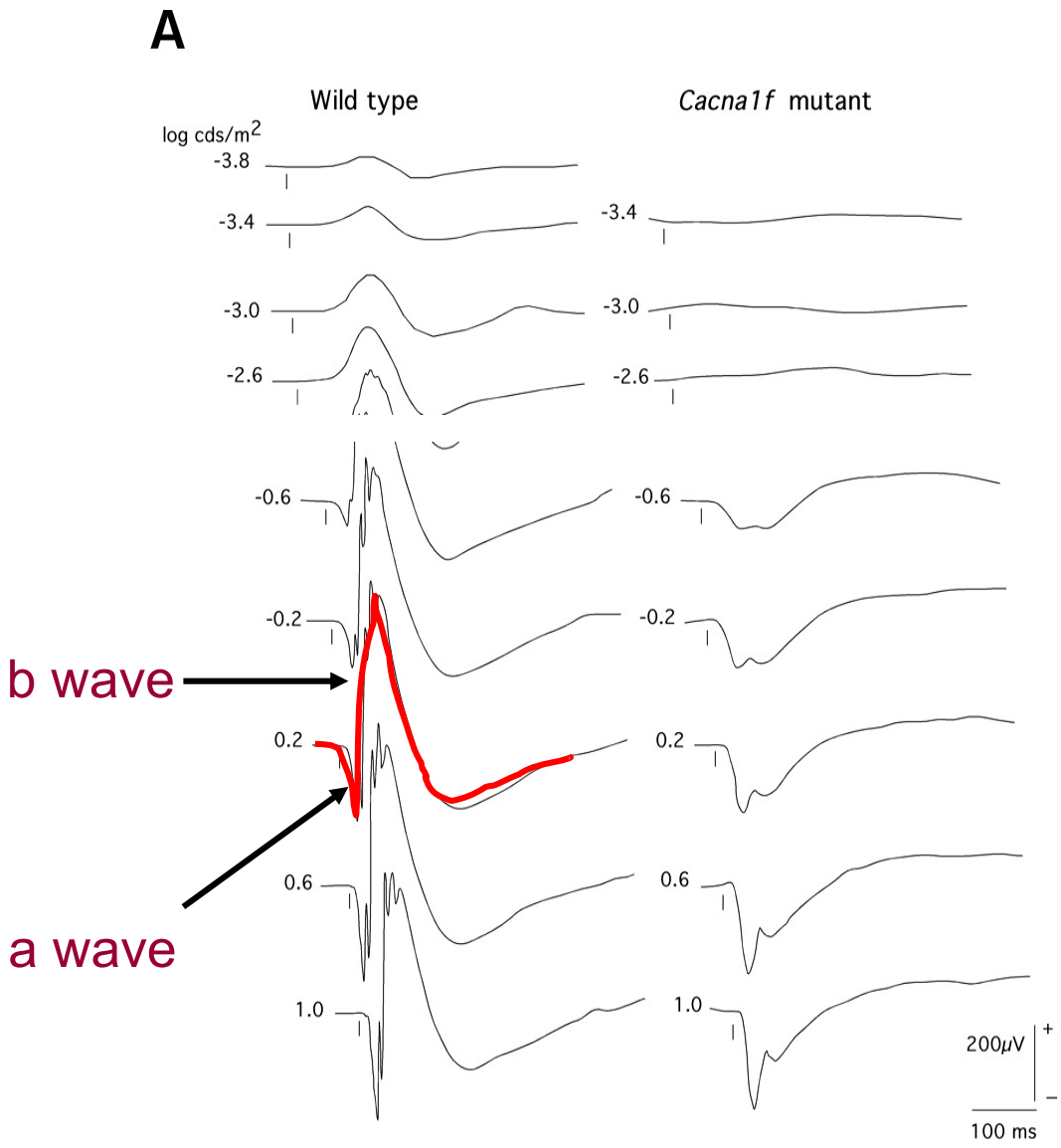
視網膜色素上皮

Localization of α1F in rat retina





Mutation of the calcium channel gene *Cacna1f* disrupts calcium signaling, synaptic transmission and cellular organization in mouse retina. Hum Mol Genet. 2005 Oct 15;14(20):3035-46



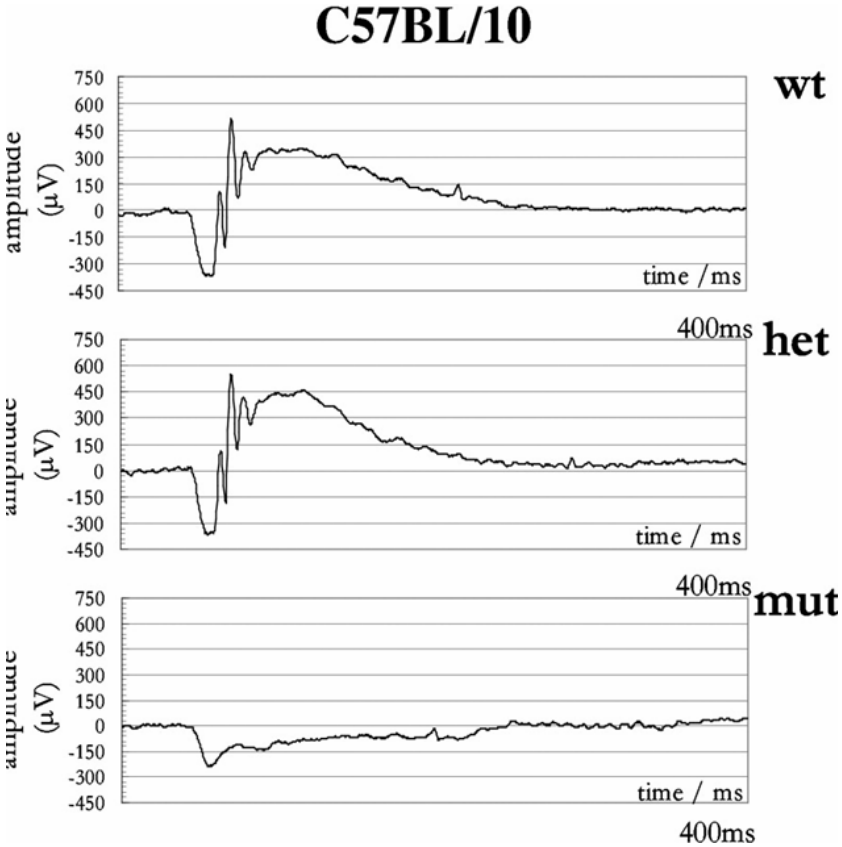
視網膜電圖記錄

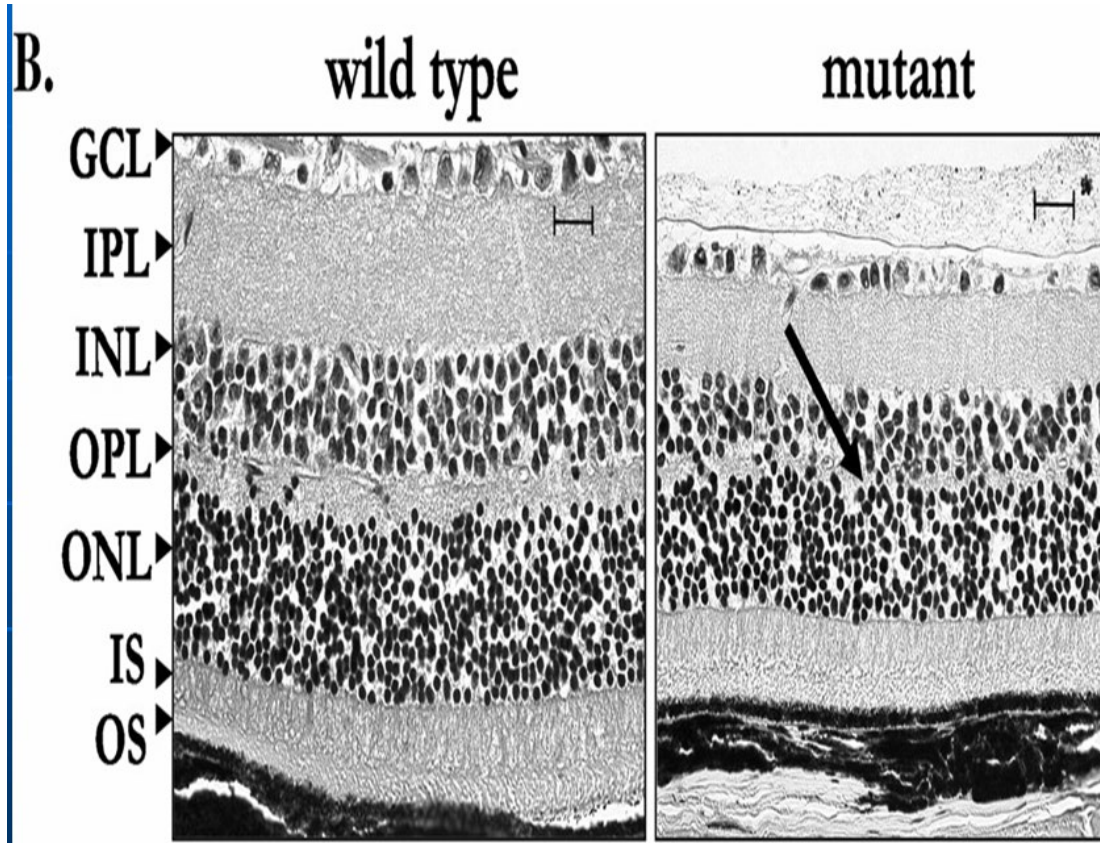
Electroretinography (ERG): a test to measure the electrical response of the eye's light-sensitive cells (rods and cones). Electrodes are placed on the cornea and the skin near the eye

The **a-wave**, which is the first negative peak, refers to the hyperpolarization of photoreceptors.

The **b-wave** is the first positive peak, which follows the a-wave, and is principally generated by Muller cells, which required synaptic transduction

Structural and Functional Abnormalities of Retinal Ribbon Synapses due to *Cacna2d4* Mutation. *Investigative Ophthalmology and Visual Science*. 2006;47:3523-3530.



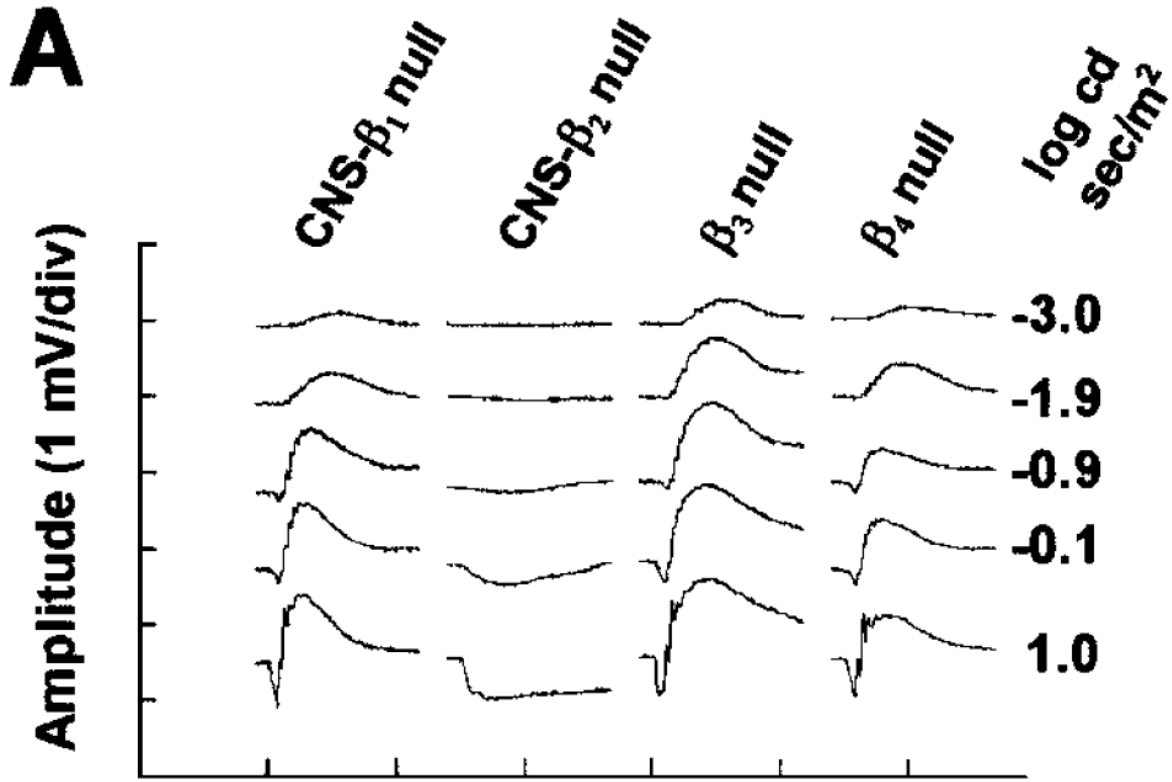


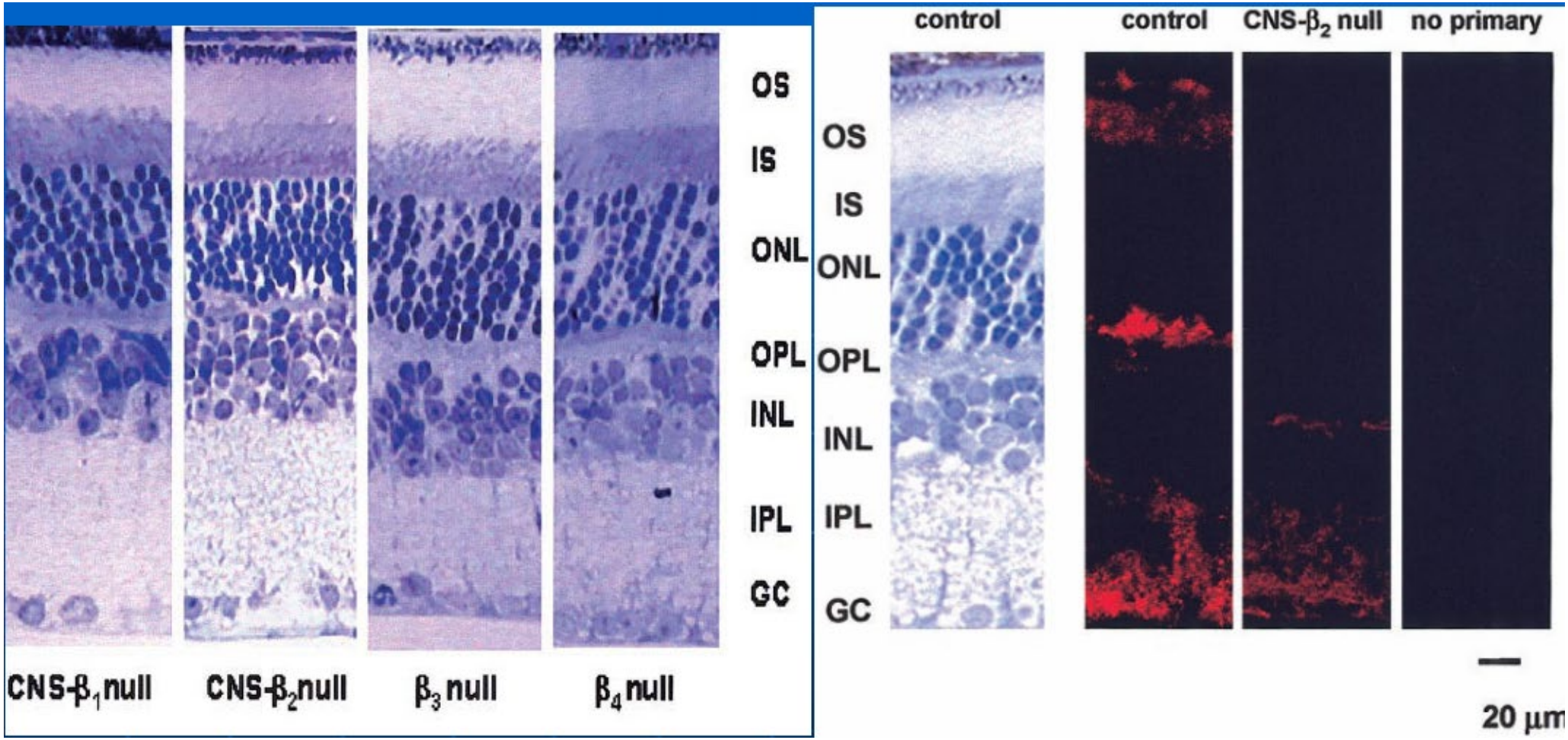
Abnormalities of the photoreceptor-bipolar cell synapse in a substrain of C57BL/10 mice. *Invest Ophthalmol Vis Sci.* 2000;41: 4039–4047.

Investigative Ophthalmology and Visual Science. 2006;47:3523-3530.)

Role of the ß2 Subunit of Voltage-Dependent Calcium Channels in the Retinal Outer Plexiform Layer. ***Investigative Ophthalmology and Visual Science.*** **2002;43:1595-1603**

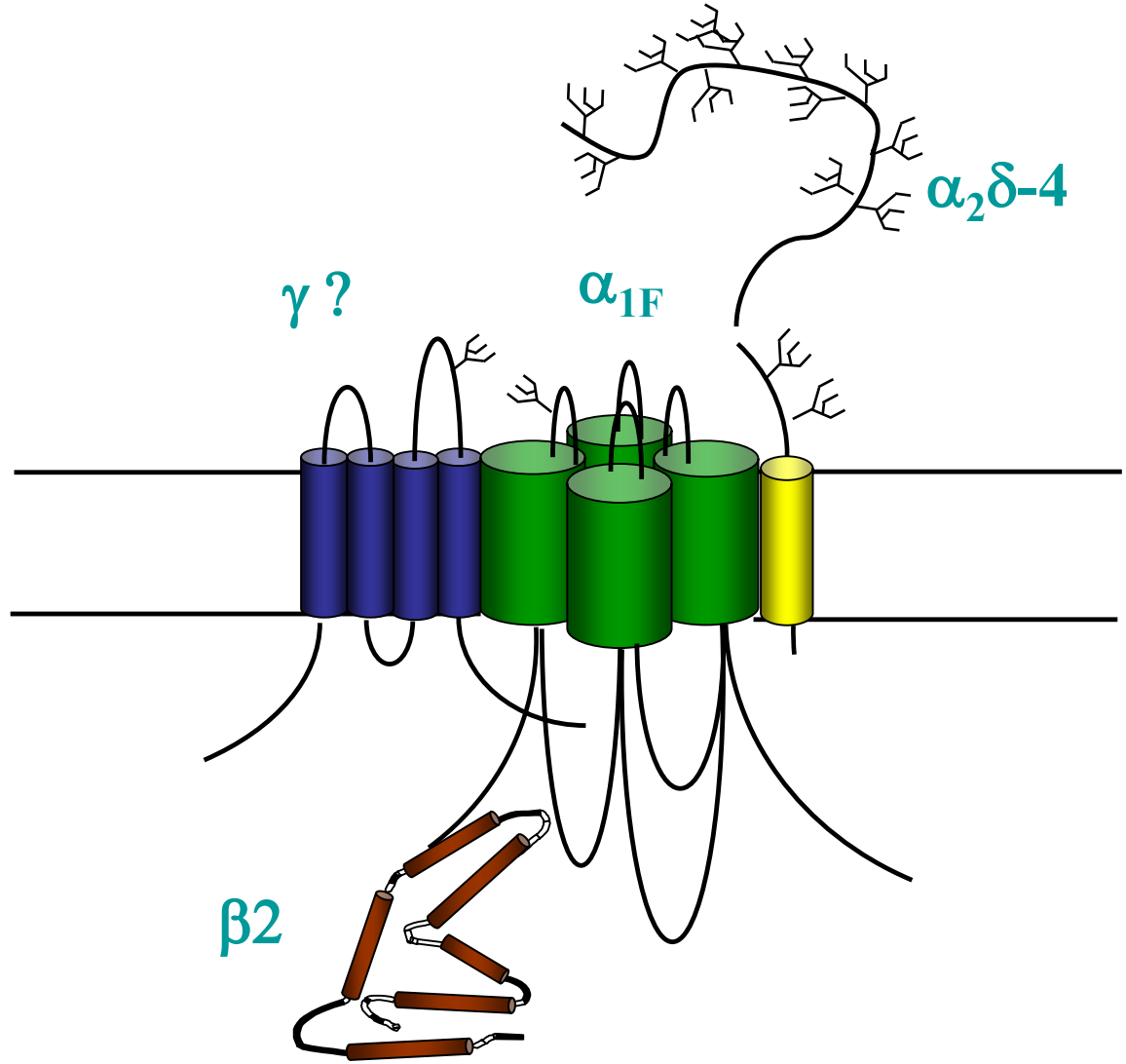
Histologic analyses indicated that the CNS-$ß_2$–null mice had altered retinal morphology. Eyes of these mice had a **thinner outer plexiform layer (OPL)** than eyes of control animals. In addition, the labeling pattern of the α1F subunit in the OPL was altered in CNS-$ß_2$–null mice. CONCLUSIONS. The normal distribution of the α1F subunit of the VDCCs in the OPL is dependent on the expression of the $ß_2$ subunit. The expression of both of these subunits is required for normal maintenance and/or formation of the OPL and synaptic transmission.




OS
IS
ONL
OPL
INL
IPL
GC
CNS-β1 null
CNS-β2 null
β3 null
β4 null
control
control
CNS-β2 null
no primary
OS
IS
ONL
OPL
INL
IPL
GC
20 µm

The nob2 mouse, a null mutation in Cacna1f: anatomical and functional abnormalities in the outer retina and their consequences on ganglion cell visual responses. Vis Neurosci. 2006 Jan-Feb;23(1):11-24

視網膜的高電壓驅動式鈣離子通道組成



Diseases of neuronal Ca^{2+} channels

- 癌肌症 Lambert-Eaton Myasthenic Syndrome (auto-immune, α1A)
- 偏頭痛 Familial hemiplegic migraine (α1A)
- 脊髓小腦萎縮症 Spinocerebellar ataxia (α1A)
- α1A 基因剔除小鼠
- Timothy syndrome (α1C)
- 自閉症 Autism (α1C, α1H)
- 兒童癲癇症候群 Childhood absence epilepsy (α1H)

The Lambert-Eaton myasthenic syndrome (LEMS) (癌肌症)

- Lambert-Eaton myasthenic syndrome (LEMS) is a rare condition in which weakness results from an abnormality of acetylcholine (ACh) release at the neuromuscular junction.
- ~40% of small cell lung cancer (SCLC)(小細胞肺癌) patients with LEMS
- LEMS results from an autoimmune attack against P/Q type voltage-gated calcium channels (VGCC) on the presynaptic motor nerve terminal.
- Prednisone, plasma exchange (PEX) are effective treatments.
- 肌肉因持續收縮而變得衰弱的疾病，主要發生於四十歲以上的男士

運動失調症 (Episodic Ataxia)

運動失調（Ataxia）意為缺乏協調。 體染色體顯性遺傳的陣發性運動失調症（Episodic Ataxia，EA），是一群在臨床上和遺傳上複雜的疾病，它的特色是會有一再發生陣發性的小腦運動失調，通常始於幼年期或青春期。目前已分出兩型，分別是第一型陣發性運動失調症和第二型陣發性運動失調症。

在第一型陣發性運動失調症，受驚嚇或運動可引起短暫的發作，不發作時合併有肌躍（myokymia）的現象。第一型陣發性運動失調症是由於第十二條染色體短臂上鉀離子通道的（KCNA1）基因變異所致。
在第二型陣發性運動失調症, 發作的時間較長（有時到數小時甚至數日），情緒或身體壓力（不是被驚嚇反射所激起）會促使發作，不發作時仍有眼振（Nystagmus）現象

第二型陣發性運動失調症是由於第十九條染色體短臂上**鈣離子通道基因（CACNA1A）**變異所致，它是**P/Q型鈣離子通道上**pore-forming 1A次單位的基因。 P/Q型鈣離子通道廣泛在神經元中表現，但主要表現在小腦，是Purkinje's cells（小腦神經細胞）主要的鈣通路， 它們和細胞膜激發性的控制及神經傳導素的釋放有關。

http://sca.ym.edu.tw/scaweb/scaitem/disease/what/ch01_5.htm

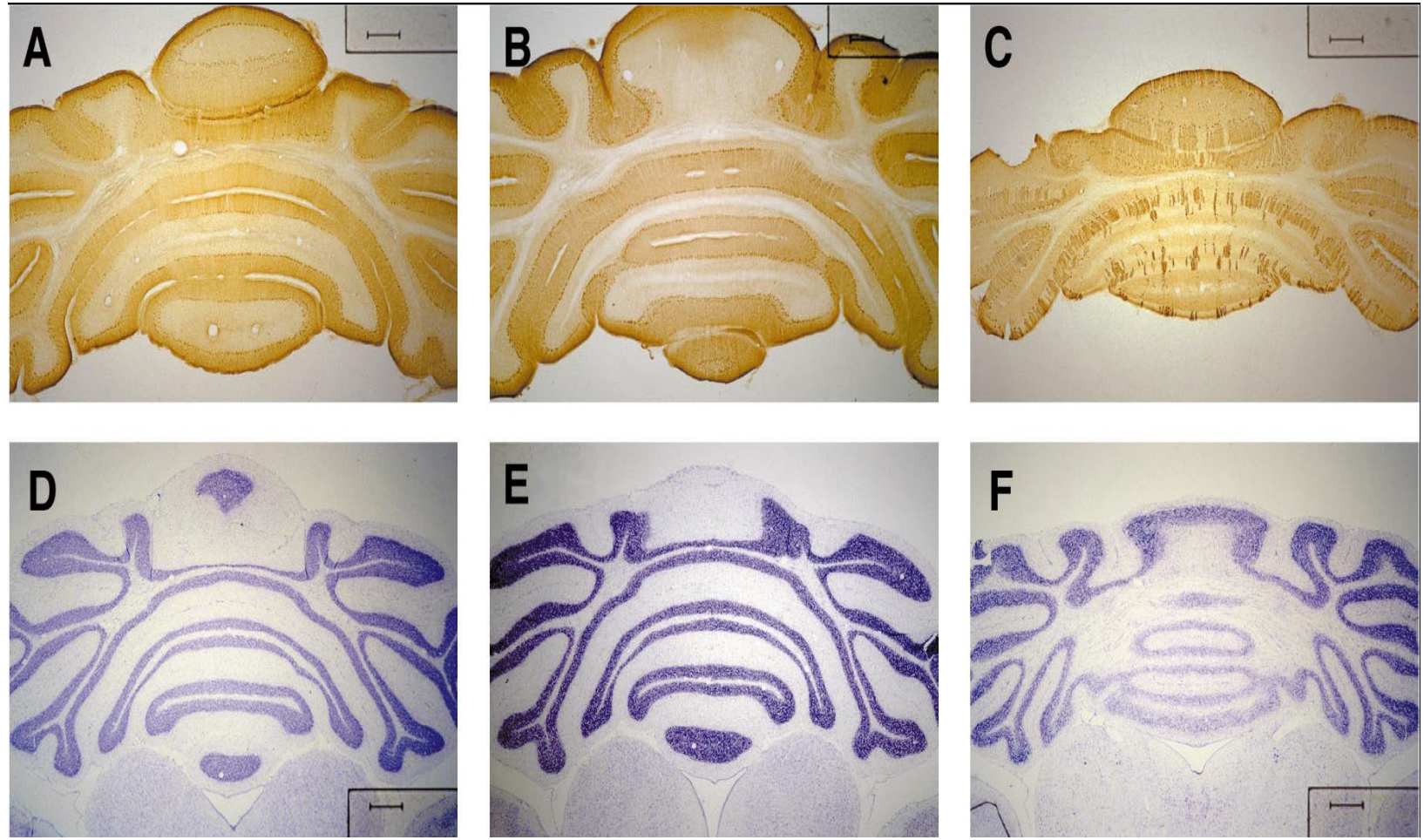
Spinocerebellar Ataxia 6 (SCA6)
(遺傳性小腦脊髓運動失調症)

- SCA 6 is a dominantly inherited human disorder with symptoms such as ataxia, nystagmus, dysarthria and neuronal loss in the cerebellum and the dentate and the inferior olivary nuclei.
- Late onset (40-50 years of age)
- Expanded CAG repeat in exon 47 of **α1A** gene.
- Healthy individuals normally have 4-18 glutamine repeat, SCA6 patients 19-33 glutamines. The age of onset is inversely correlated with the length of the repeat.
- SCA6 mutations can both increase or decrease the Ca currents depending on the model system used.--**Channelopathy**
- The big intra-familial variability in penetrance and symptoms suggests that environmental, hormonal and/or genetic factors other than the α1A mutation are important for the phenotype of EA2 and SCA6.

●步態失調，發音障礙，單純的小腦症狀、家族史不明確、較晚發病

Dystonia and cerebellar atrophy in Cacna1a null mice lacking P/Q calcium channel activity FASEB J, 2001, 15:1288

肌張力障礙:是由於身體的肌肉不隨意地持續收縮，造成肌肉產生變形，而無法依照自身的意思活動



PNAS,1999, 96,26:15245

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