



胚胎及發育生物學

Embryogenesis, Developmental Biology and Stem Cell



(a)



(b)



中山大學
生物科學系
吳長益

生物學中最有趣的是甚麼問題??



生物多樣性
與
生命現象



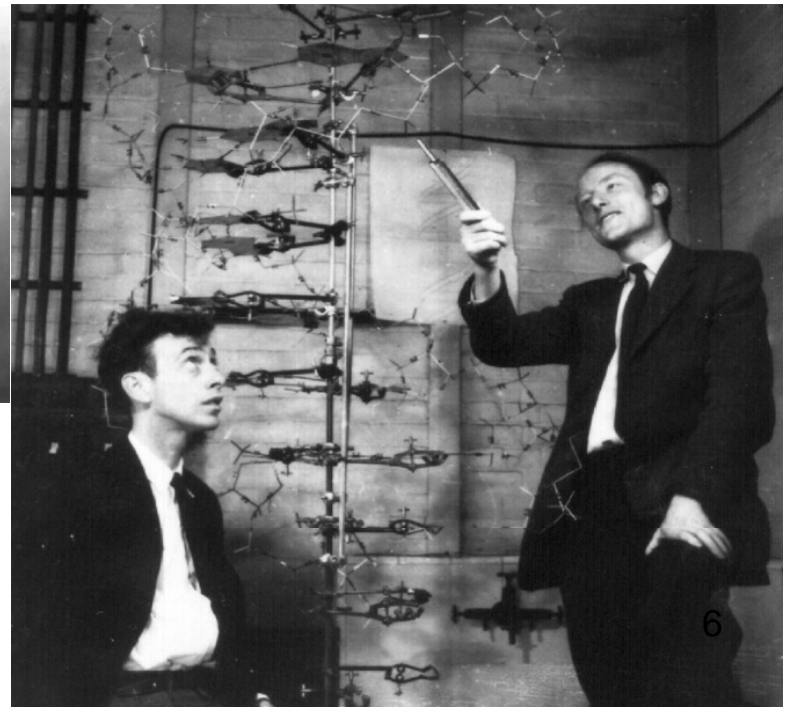
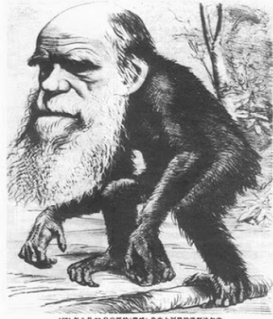
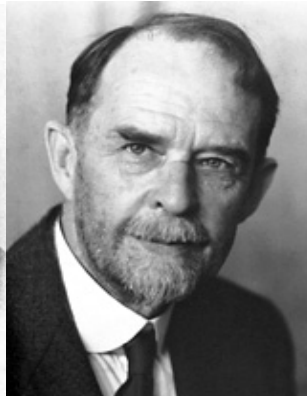
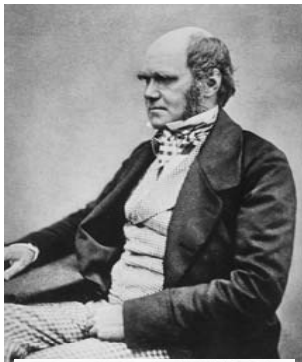
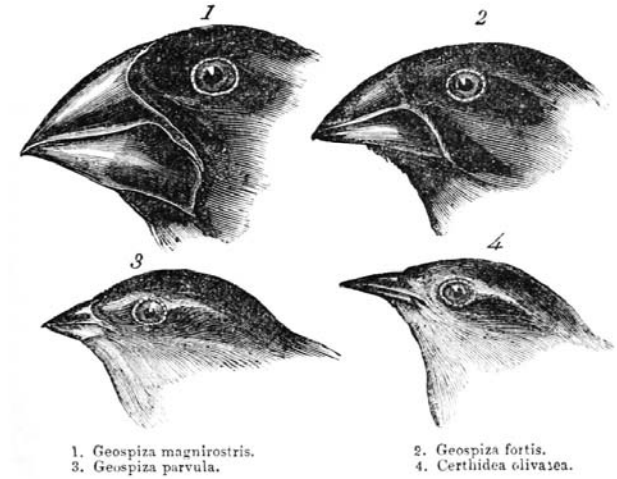
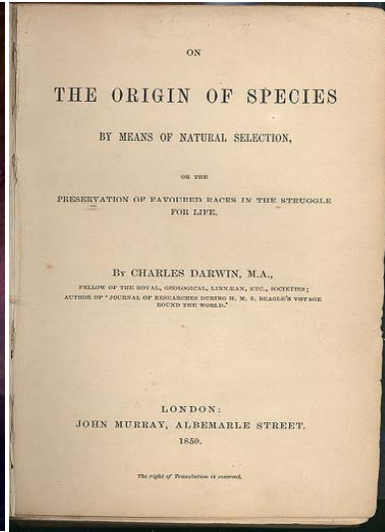
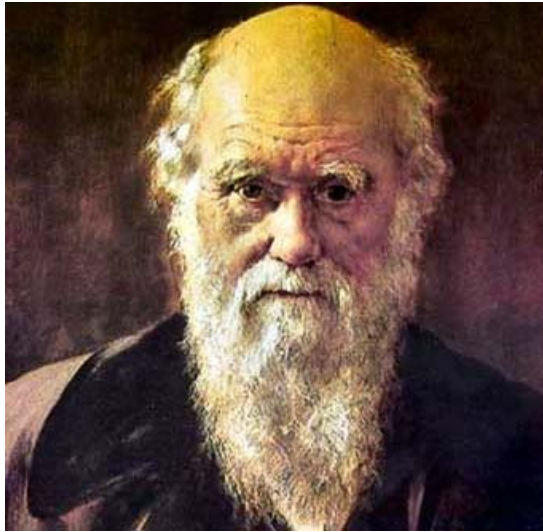
Genetics and Evolution

- **Variation** in the DNA sequence makes it possible for species to evolve over time.
- Organisms with similar DNA sequences are descended from a **common ancestor**.



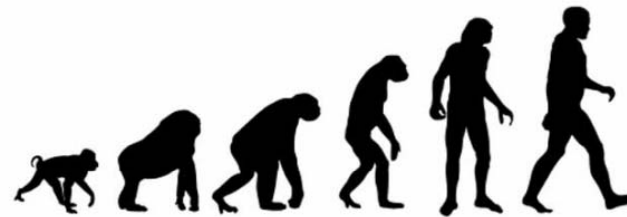
生物為何那樣多樣性?

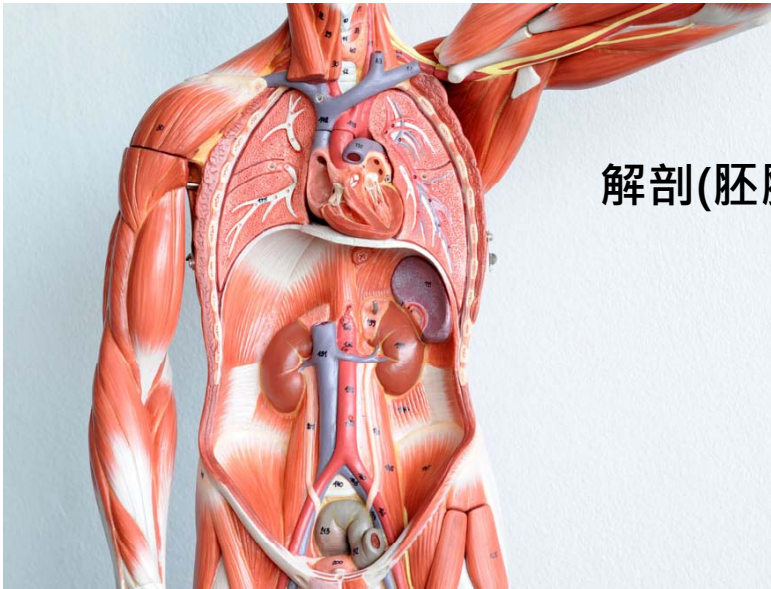
化繁為簡(小處著手)



生物學中最有趣的是甚麼問題??

生物多樣性 與 生命現象





生命現象的研究

解剖(胚胎)學/ 個體生物(生理)學 - 細胞生物學- 染色體/DNA
遺傳學

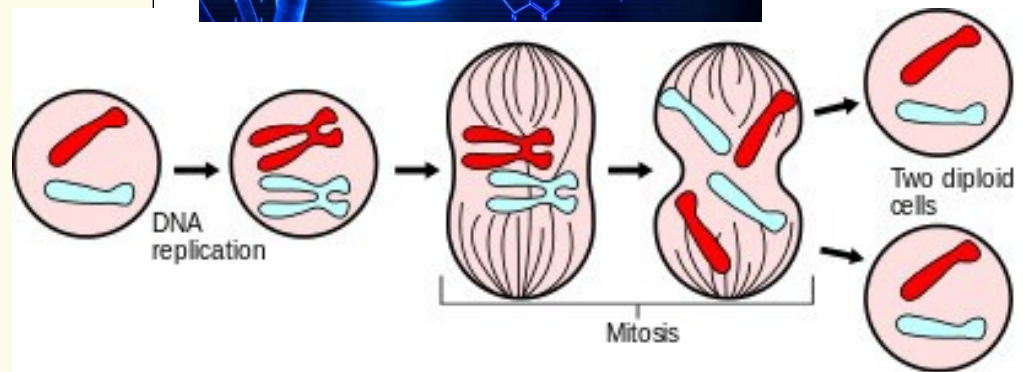
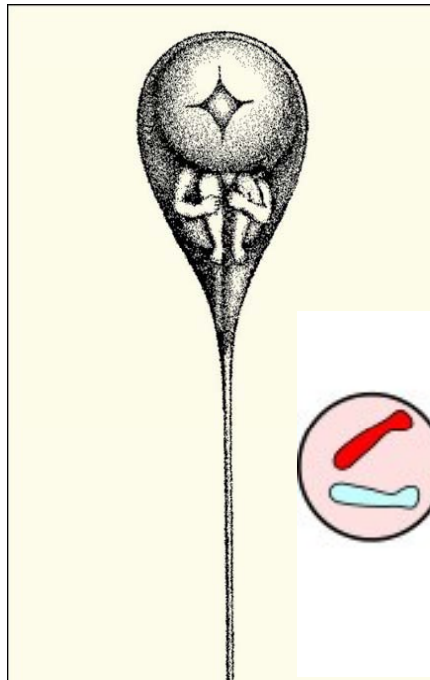
胚胎學上古老的爭論

Preformation theory (先成說)

胚胎的各部份是一開始就存在?

Epigenesis theory (漸成說)

還是在發育過程中逐漸形成的?



An homunculus in the head of each sperm (1694)

生物學中最有趣的是甚麼問題??

生物多樣性 與 生命現象



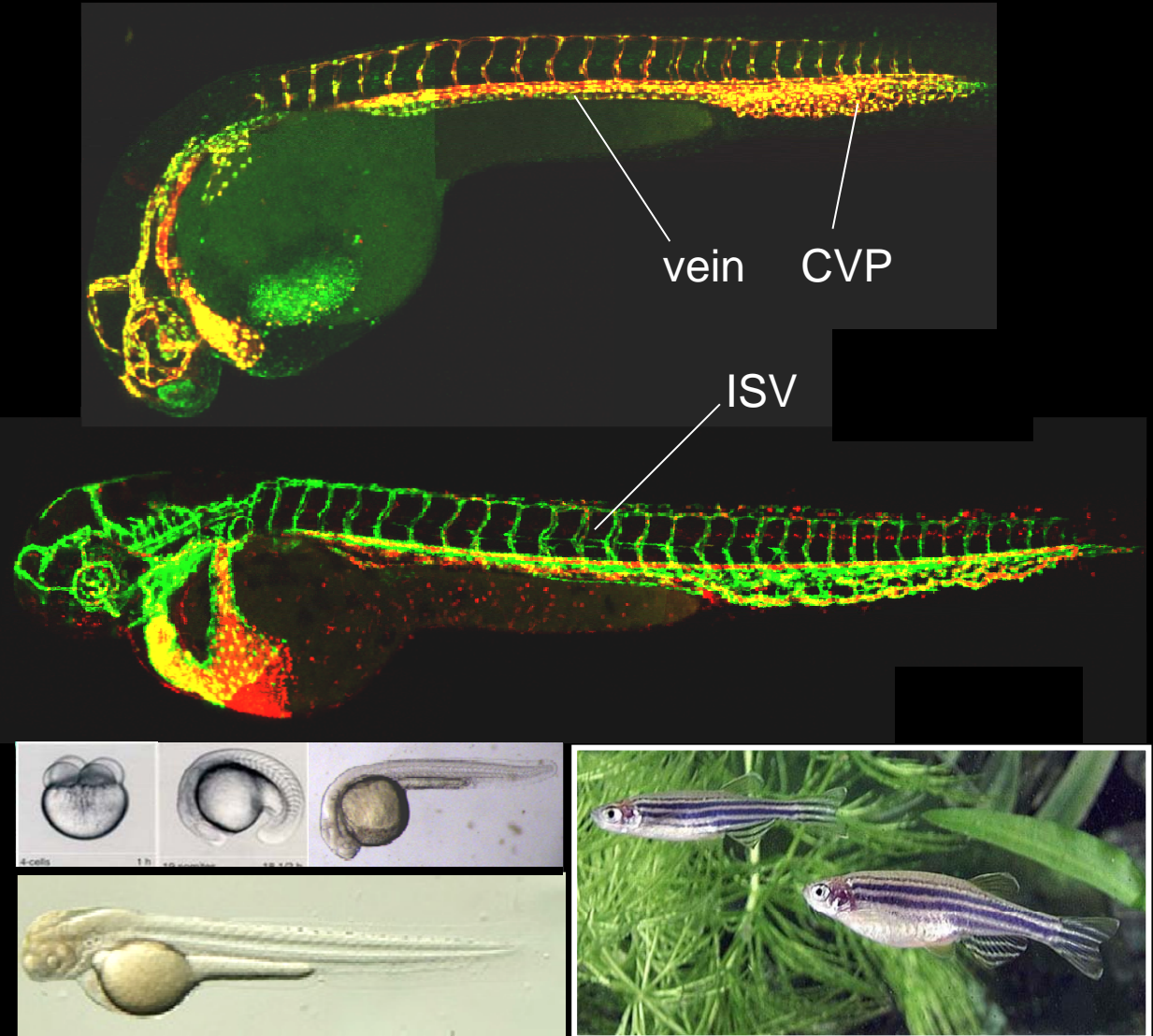
動 (低-高)
植 (低-高)
微生物
病毒

生物-環境

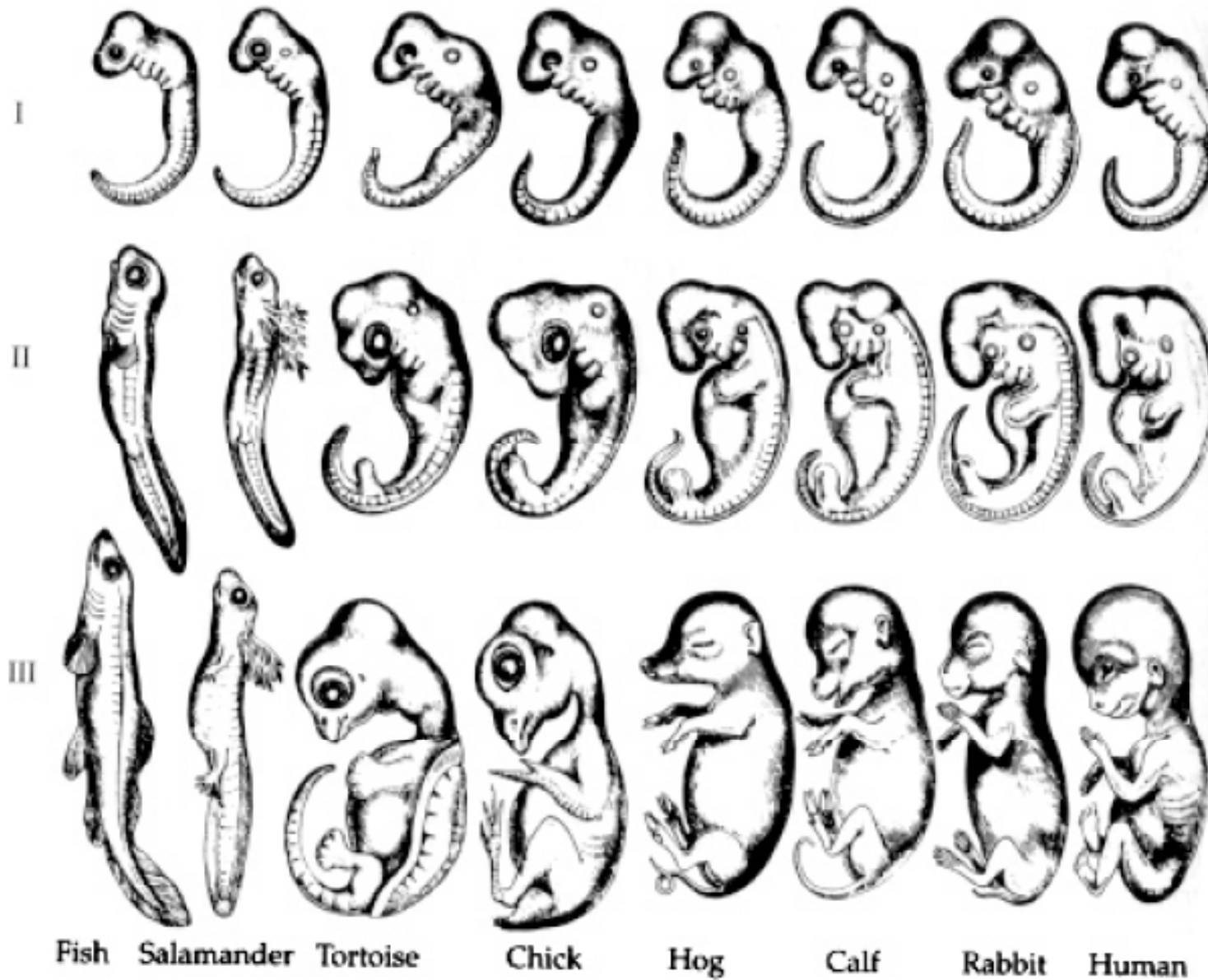
生物化學
解剖(胚胎)型態
生理
細胞生物
分子生物
發育生物



胚胎發育及幹細胞

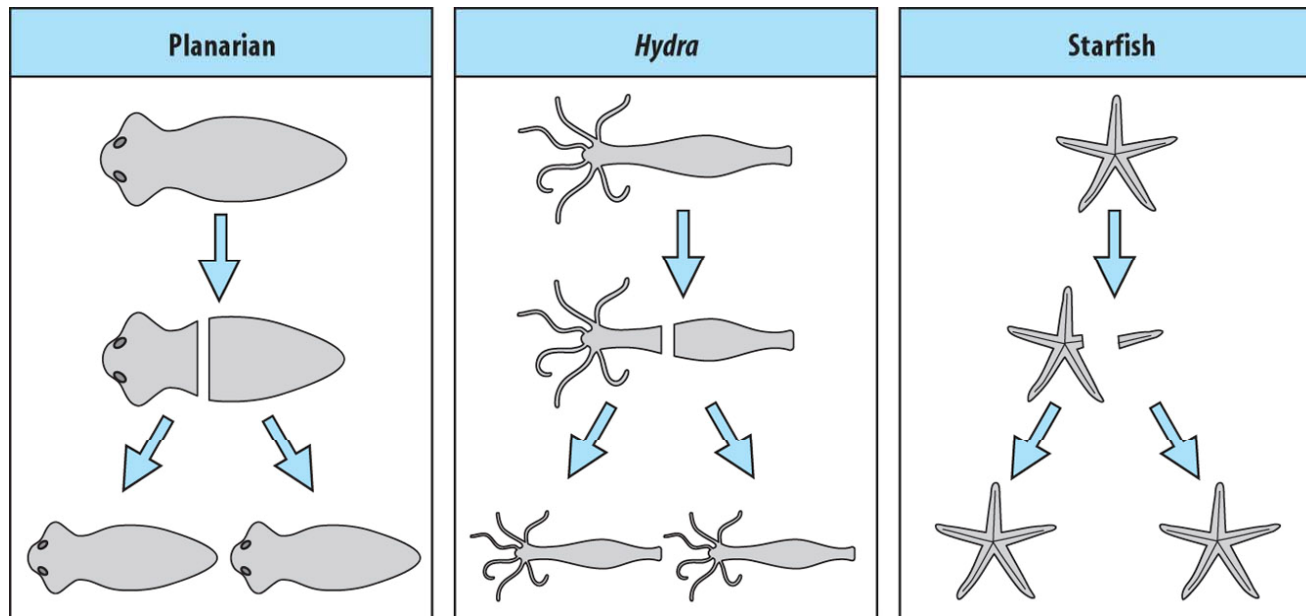


Embryos



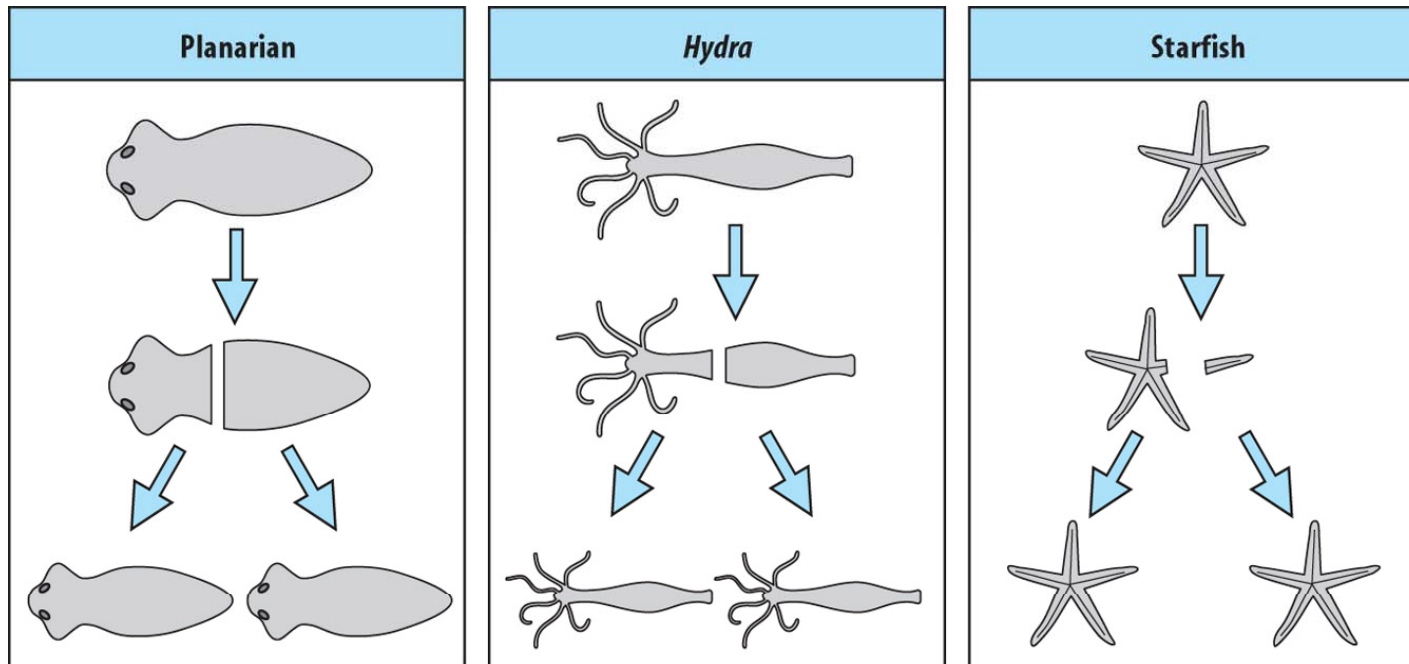
胚胎

複製/再生 ——— 幹細胞



Outline

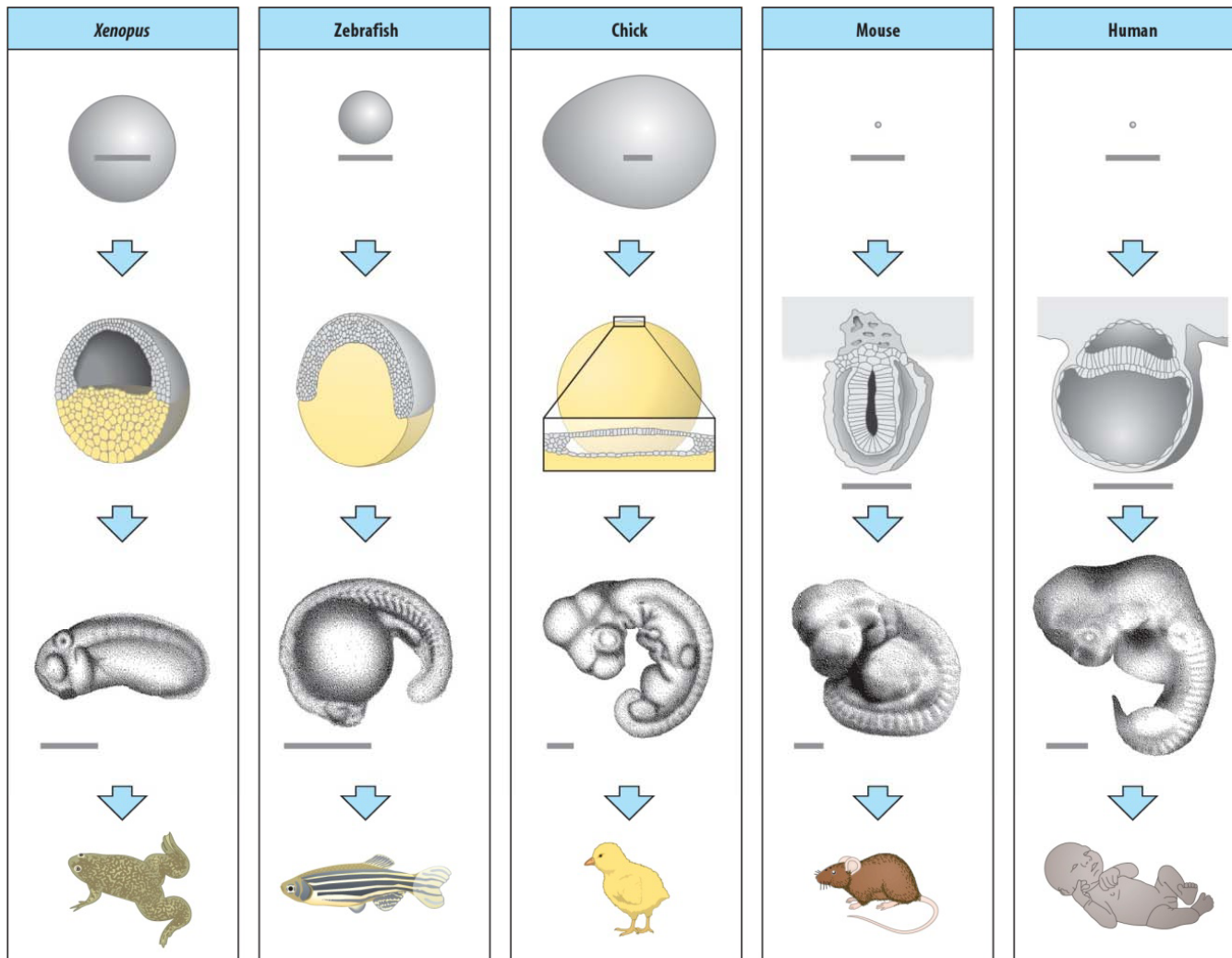
1. 胚胎學 (embryology) vs. 發育生物學 (developmental biology)
2. 模式生物 (model organisms)
3. 動物發育的主要階段
4. 發育過程之機制
5. 組織再生與幹細胞



胚胎學 (Embryology) : The development of an embryo from the fertilized egg

偏重述敘的科學, 探討如何形成個體正確及完整形態的各個步驟。

發育生物學 (Developmental Biology) is to understand how multicellular organism develop
着重於分子和細胞生物學層次上的胚胎學。



何謂發育生物學？

·發育生物學(developmental biology) 源自於胚胎學(embryology)

·胚胎學：探討受精卵到出生的過程
(A Body-Building Plan)

·發育生物學包含：

胚胎學

+

個體生長、器官及組織受損的修復與再生、老化、疾病的發生與治療等



胚胎學上古老的爭論

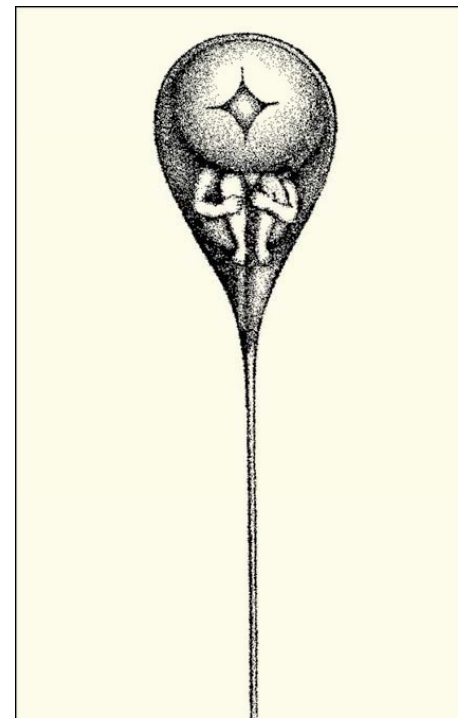
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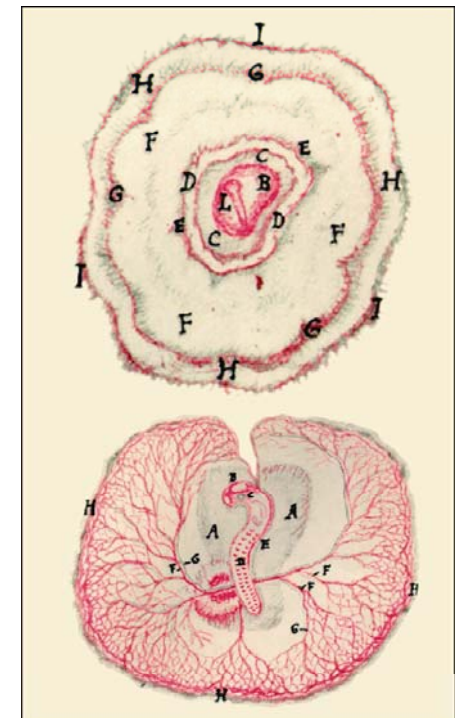


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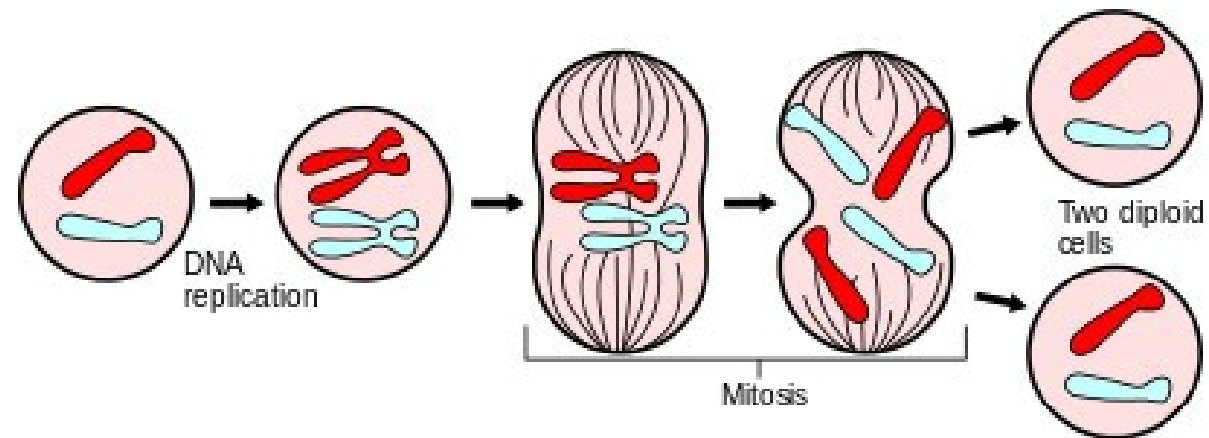
Malpighi's description of the chick embryo. (1673)

顯微鏡的發明

細胞學說的確立 (1820-1880)

基因概念的形成 (1900)

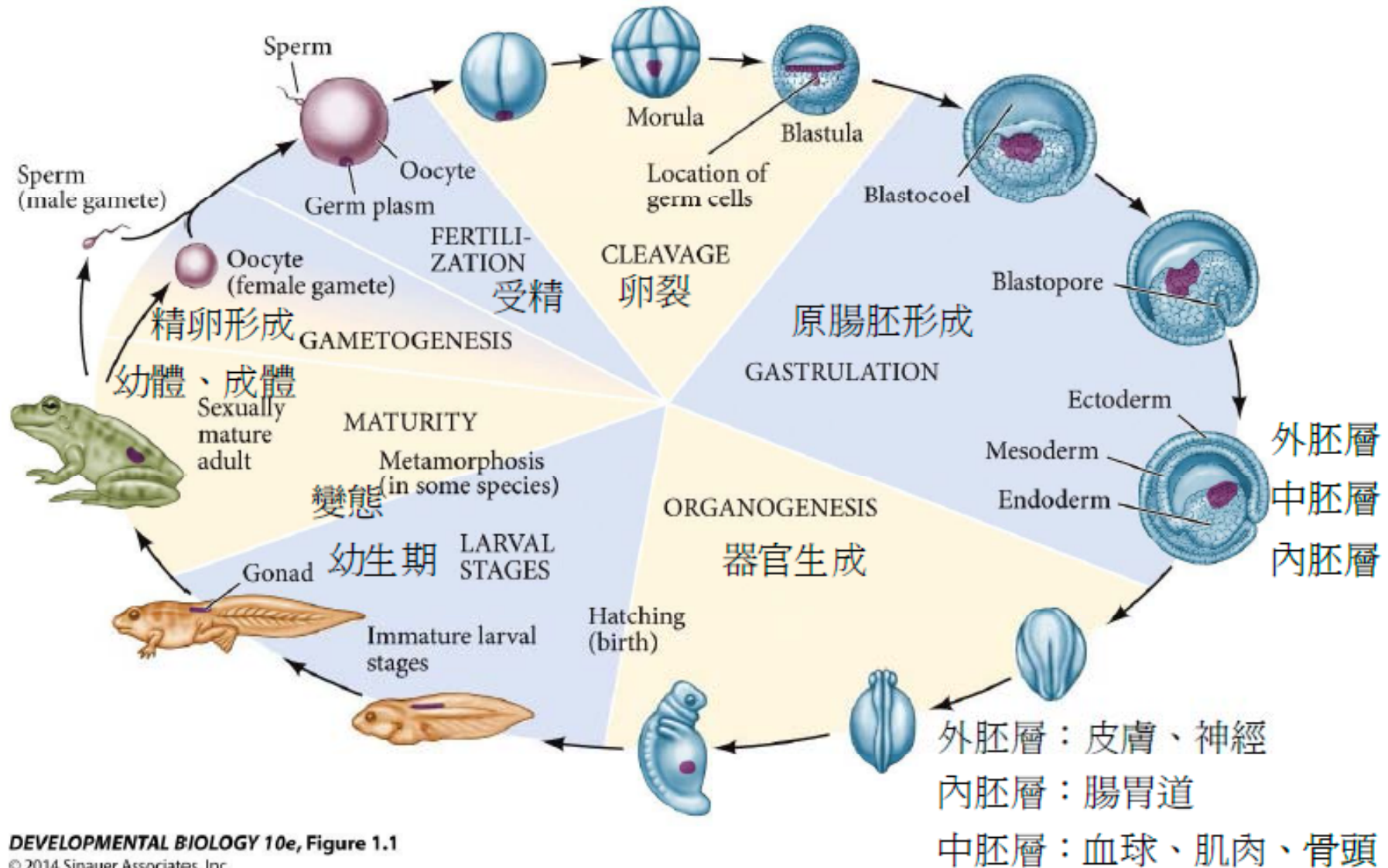
胚胎發育符合漸成說的理論



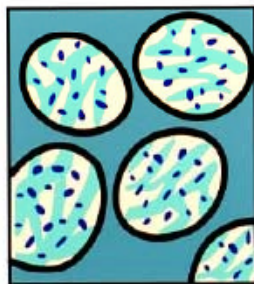
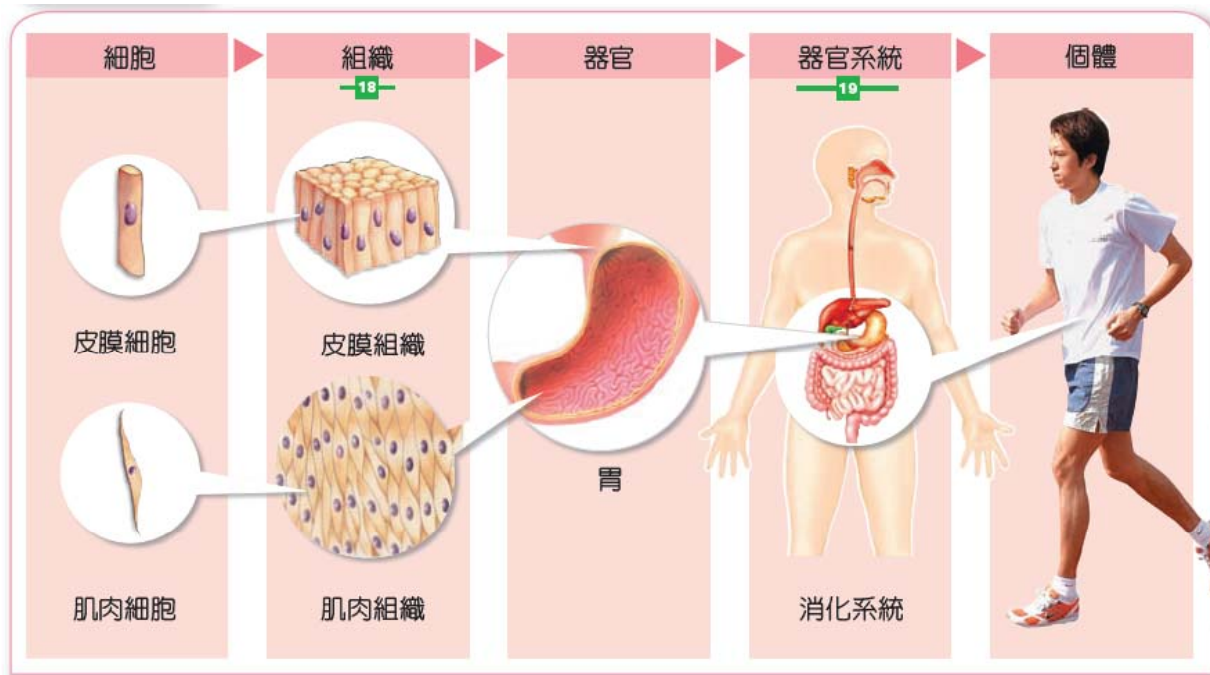
發育的觀念: A Life cycle of Frog

動物的發育 (發育生物學研究的範疇)

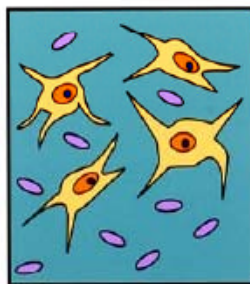
- 生命的週期，由單細胞至多細胞個體的過程



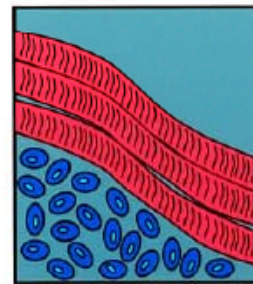
發育的三要素？



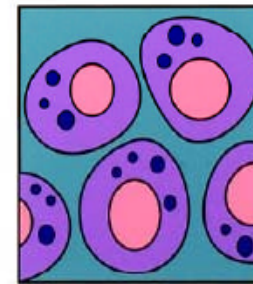
**Bone marrow
for leukemia
& chemotherapy**



**Nerve cells
for Parkinsons
& Alzhiemer's
disease**



**Heart muscle
cells for
heart disease**



**Pancreatic
islet cells
for diabetes**

發育的三要素:

1. 生長/分裂 growth/cleavage

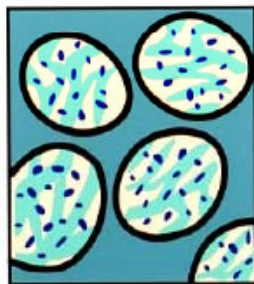
Increase in cell number
Increase in cell size

2. 分化 Differentiation

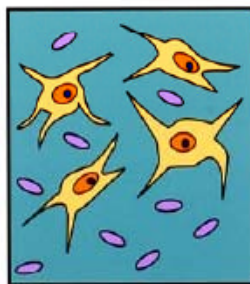
The fate of daughter cells

3. 形態發生 Morphogenesis

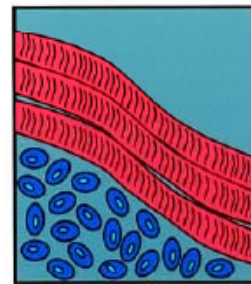
The formation of shapes and patterns



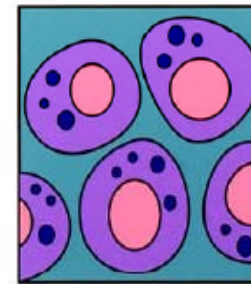
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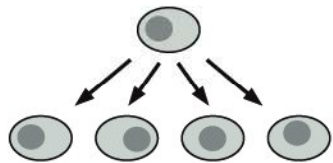
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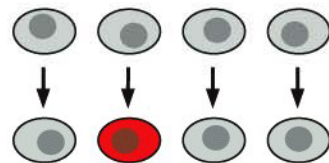
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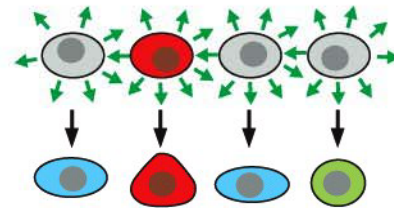
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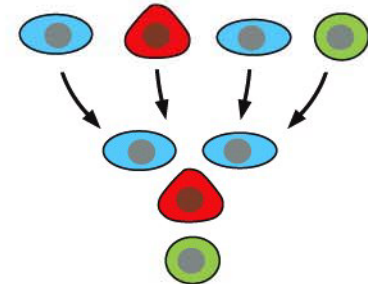
CELL PROLIFERATION



CELL SPECIALIZATION



CELL INTERACTION



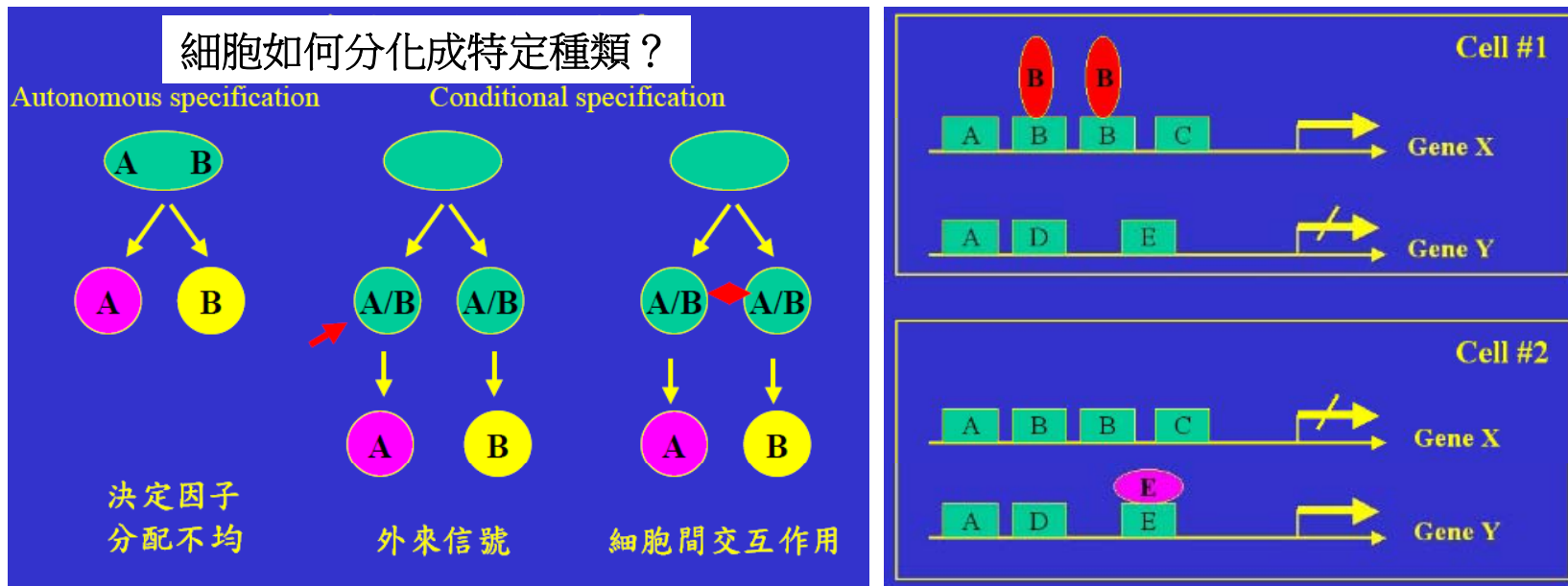
CELL MOVEMENT

發育生物學的 (研究)中心主題:

細胞如何分化成特定種類？

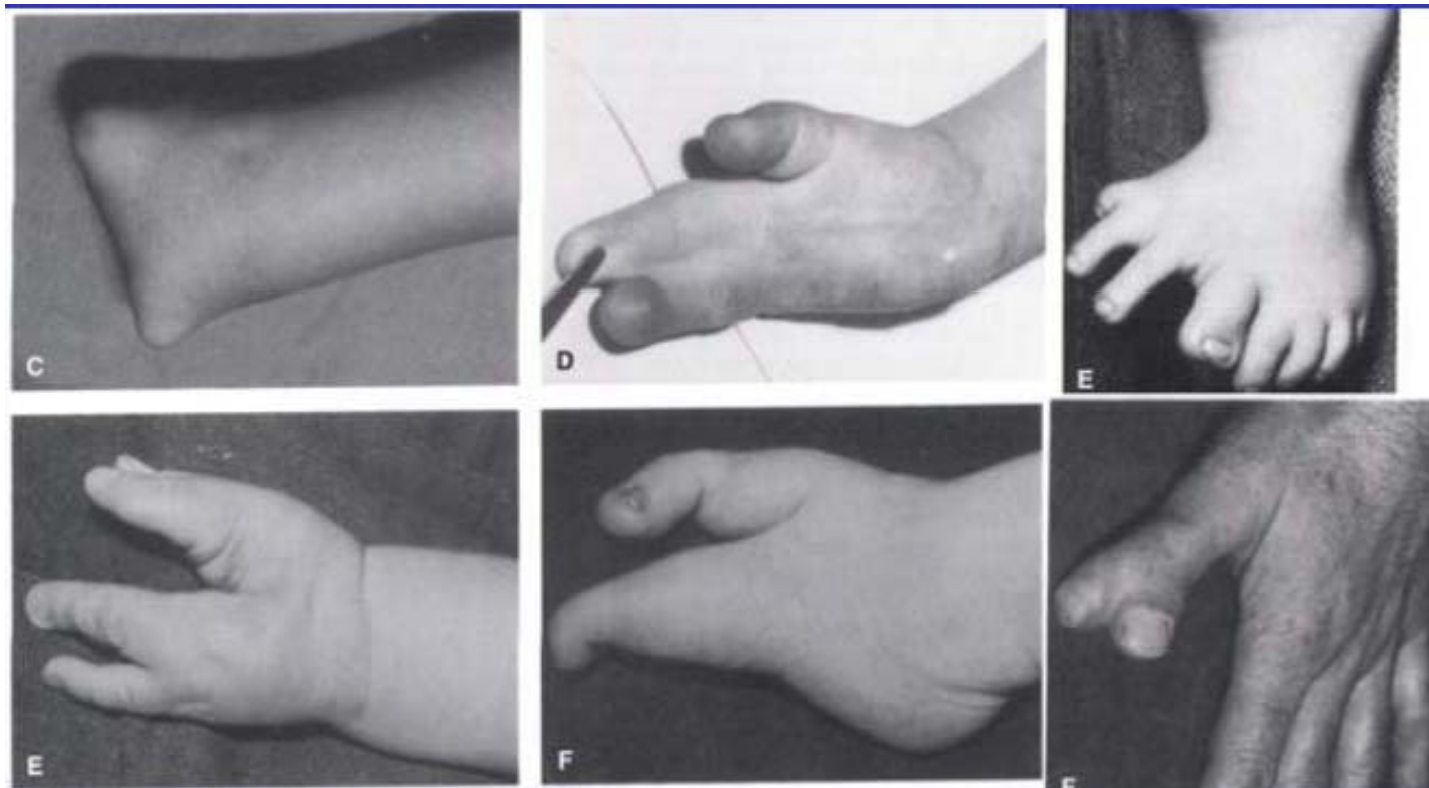
細胞如何移動到特定位置？

如何控制這些細胞發育成為不同類型的細胞組織？



What happen if genetic control goes wrong in limb development?

發育出問題, 有些會遺傳, 因為基因控制發育



1. 了解動物胚胎的發育(分子機制)

germ layers: ectoderm, mesoderm, endoderm
organogenesis

2. 了解發育生物學的研究發展及重要性

母體-胎兒保健, 預防新生兒缺陷

3. 發育生物學的相關應用

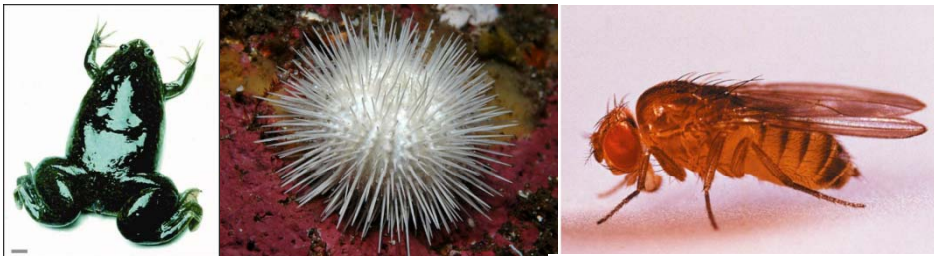
a. 幹細胞 b. 複製及器官再生 c. 細胞凋零 d. 老化 e. 癌症與疾病

Model organisms to study developmental biology

模式生物



- nematode (*C. elegans*) 線蟲
- fruit fly (*D. melanogaster*) 果蠅
- sea urchins 海膽
- South African Frog (*X. laevis*)
- Zebrafish (*D. Renio*)
- chick
- mouse
- plant (*A. thaliana*)



用以研究發育生物學, 人類疾病

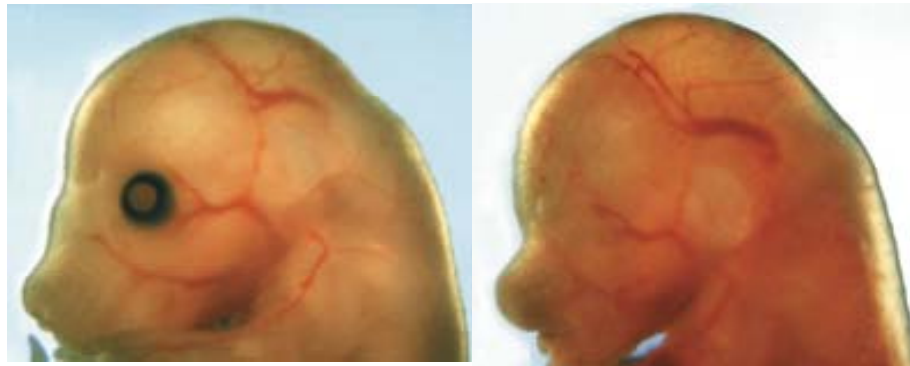
Universal mechanisms of animal development

通用機制

小腦



Drosophila with mutant alleles of the *eyeless* gene



Mouse embryos with wild-type (L) and mutant (R) alleles of the *Pax-6* gene

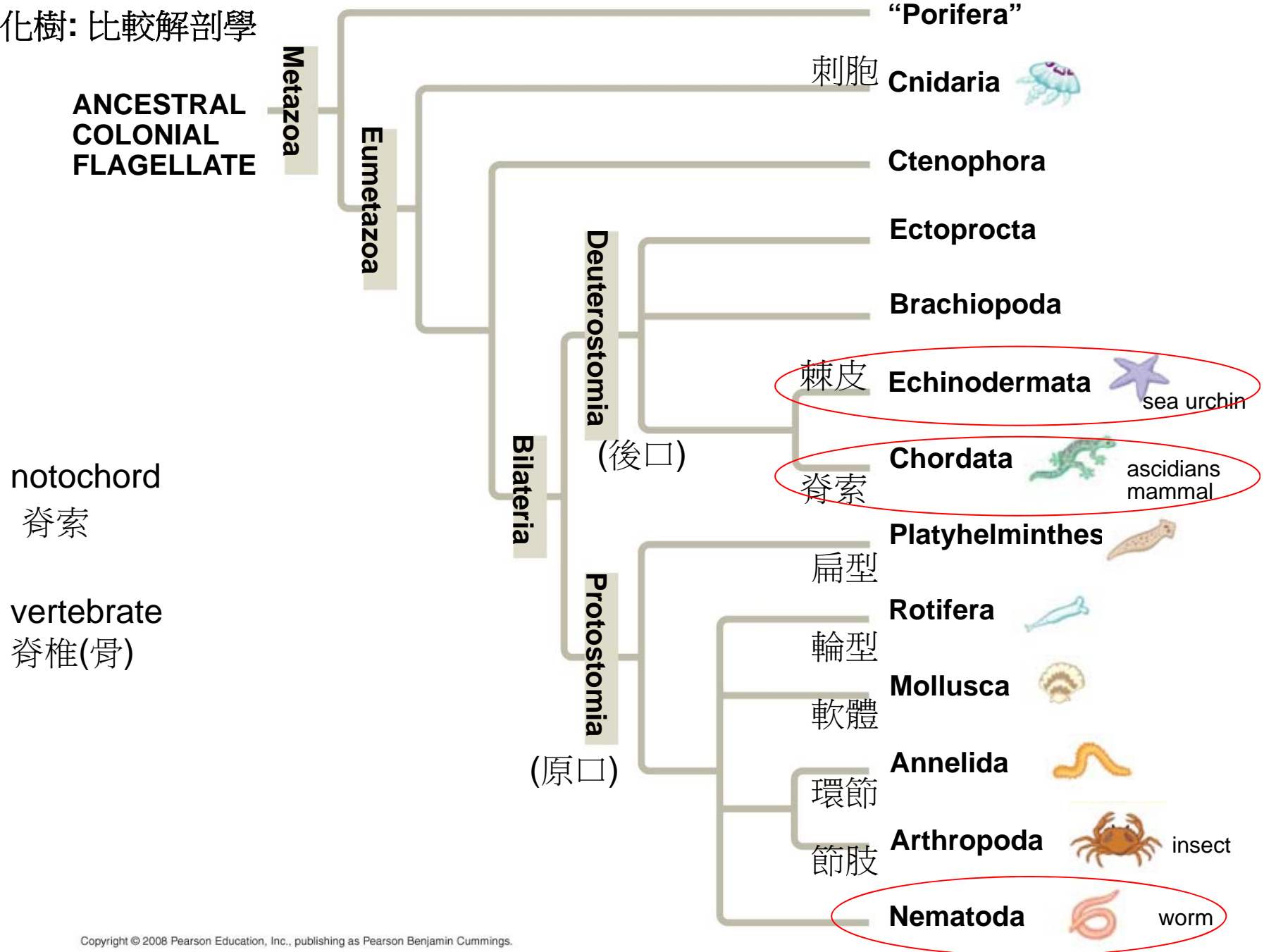
Fig. Homologous proteins functioning interchangeably in the development of mice and flies.

人類不利於作發育, 疾病模式之原因：

- 1. 壽命長。
- 2. 再生時間緩慢。
- 3. 子代少。
- 4. 極度異質性。
- 5. 無法長期控制飼養方式及社經生活。
- 6. 定量資料如飲食、飼養方面缺乏。
- 7. 道德上的問題。

Comparative anatomy and Embryology provide clues to animal phylogeny

演化樹: 比較解剖學

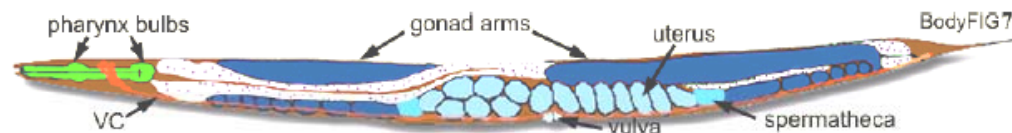
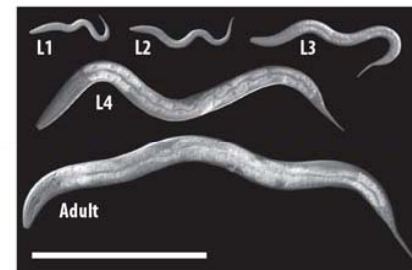
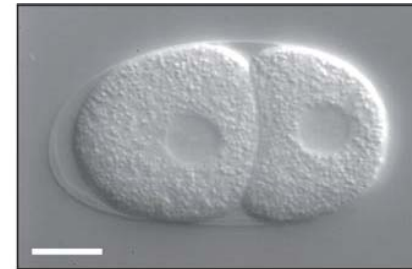
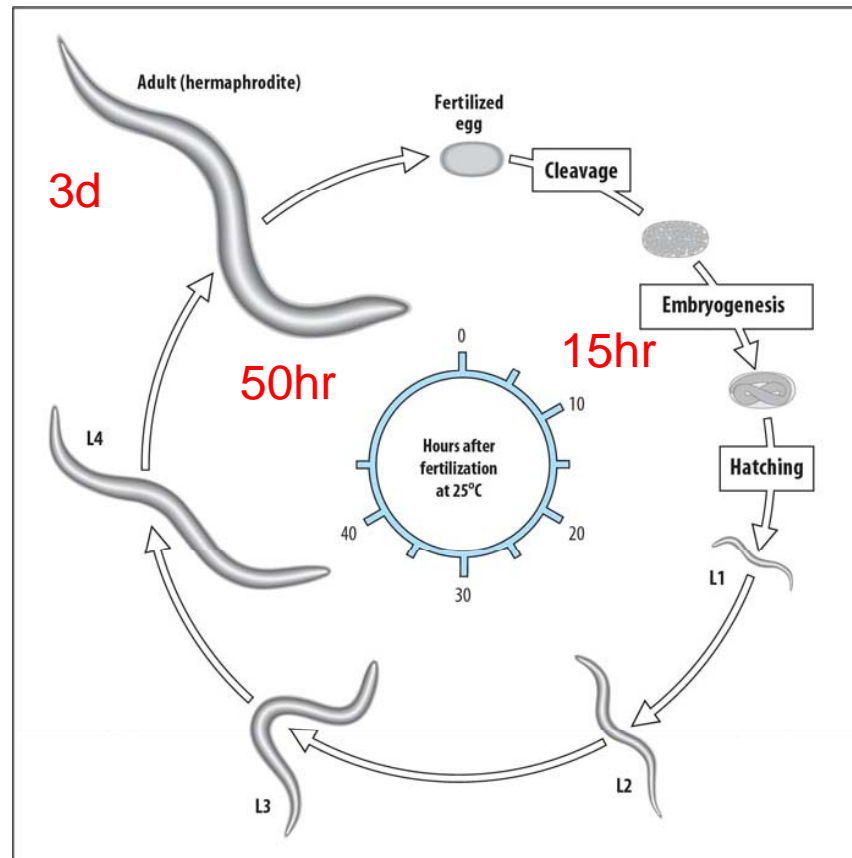


notochord
脊索

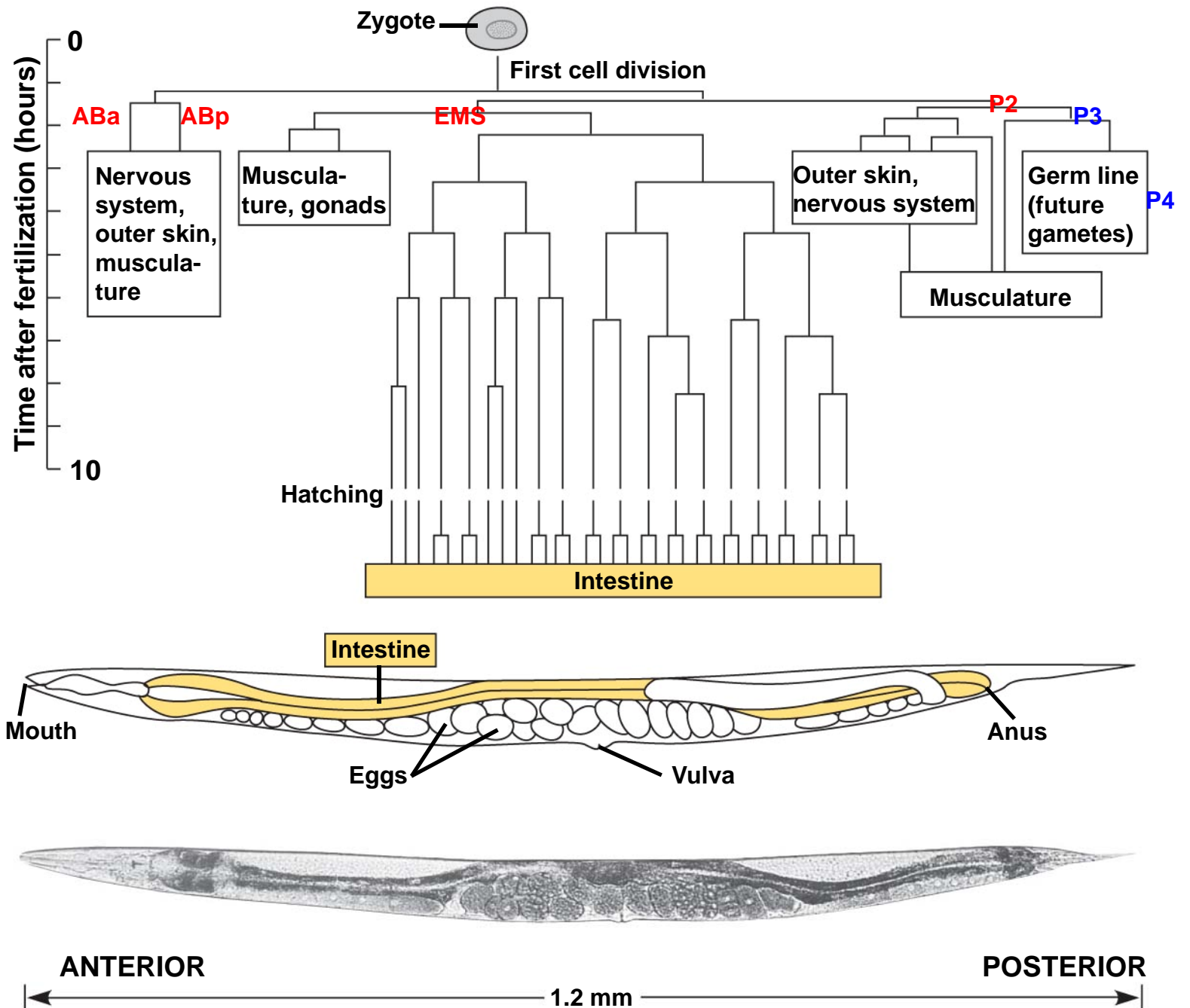
vertebrate
脊椎(骨)

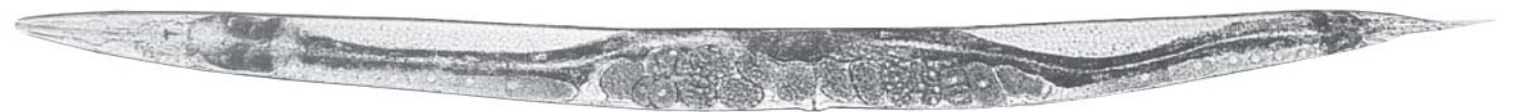
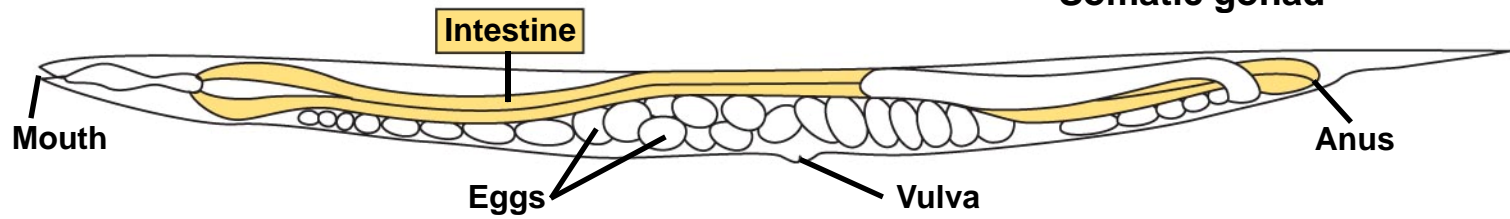
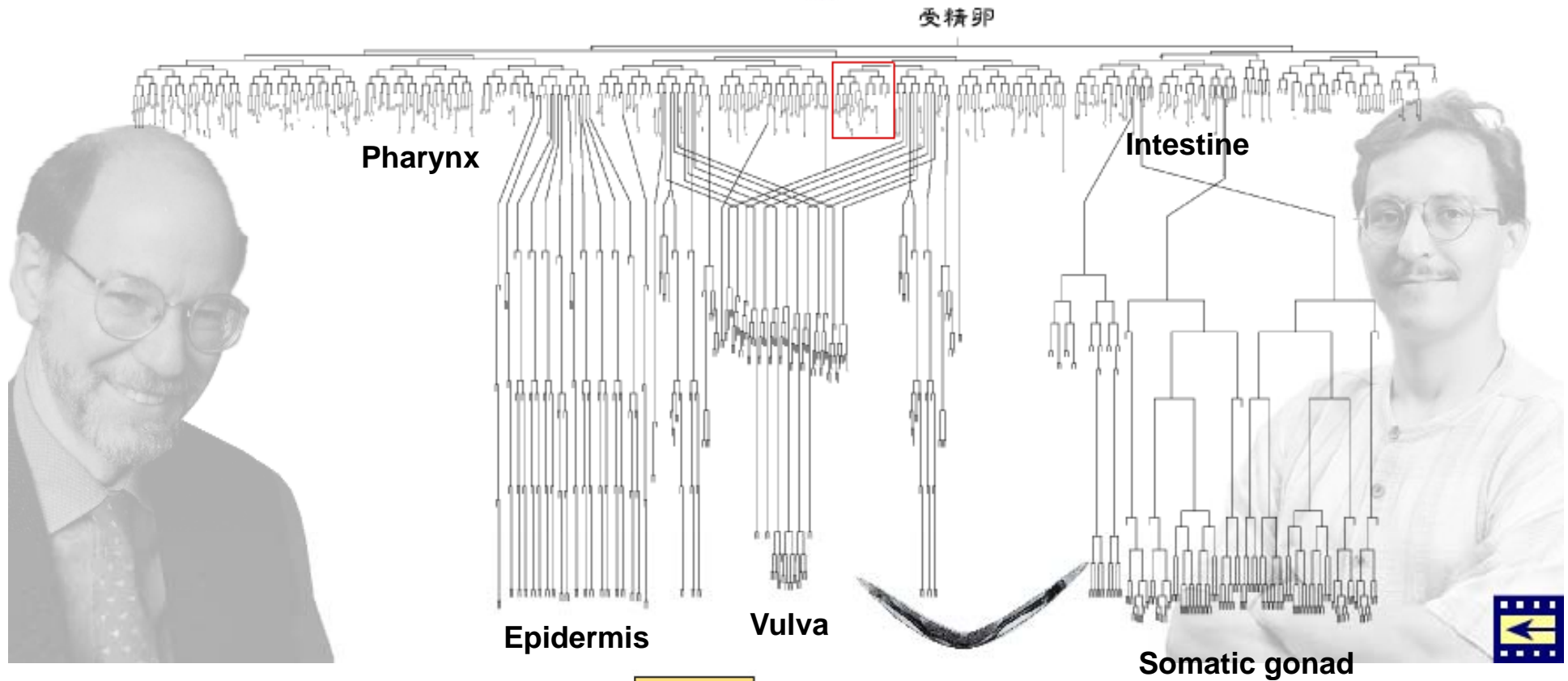
nematode (*Caenorhabditis elegans*)

線蟲



Nobel prizes: 2002 (lineage) Apoptosis, 2006 RNAi





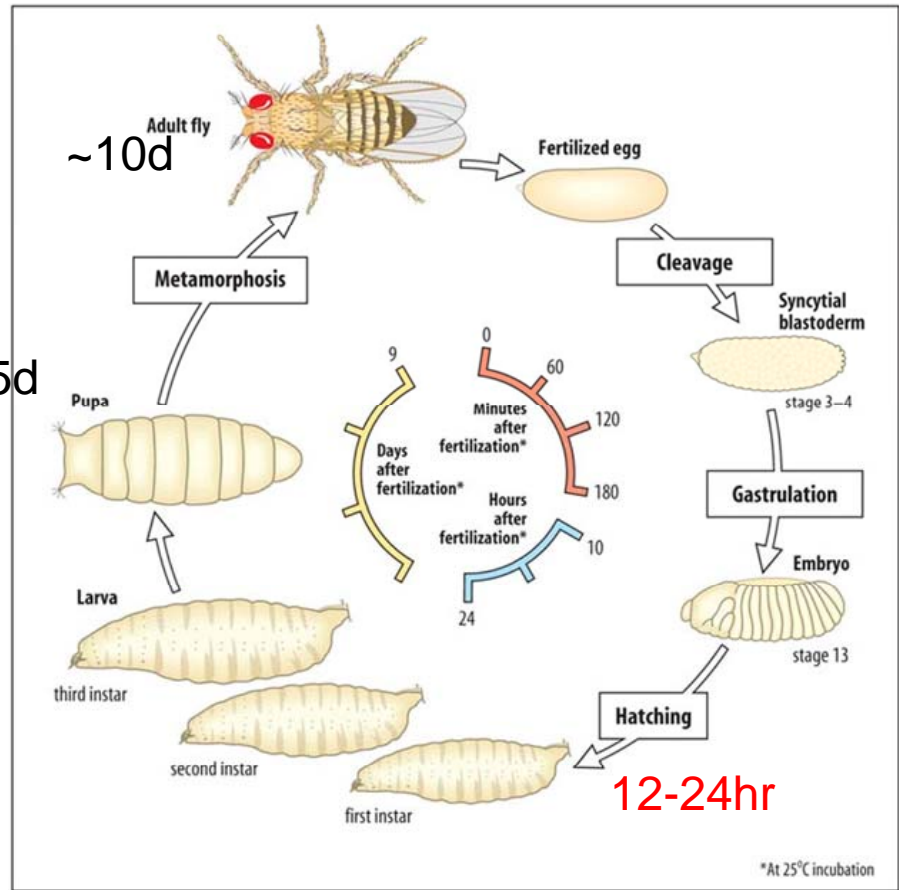
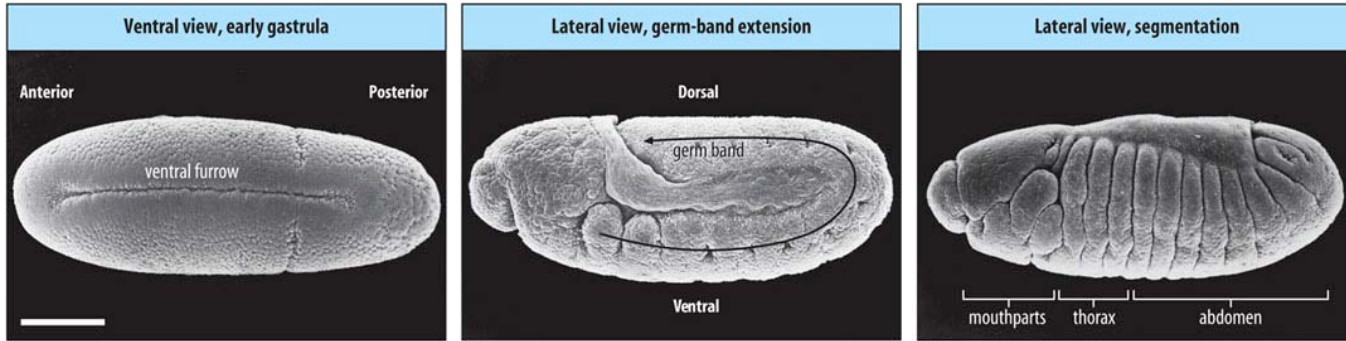
ANTERIOR

POSTERIOR

1.2 mm

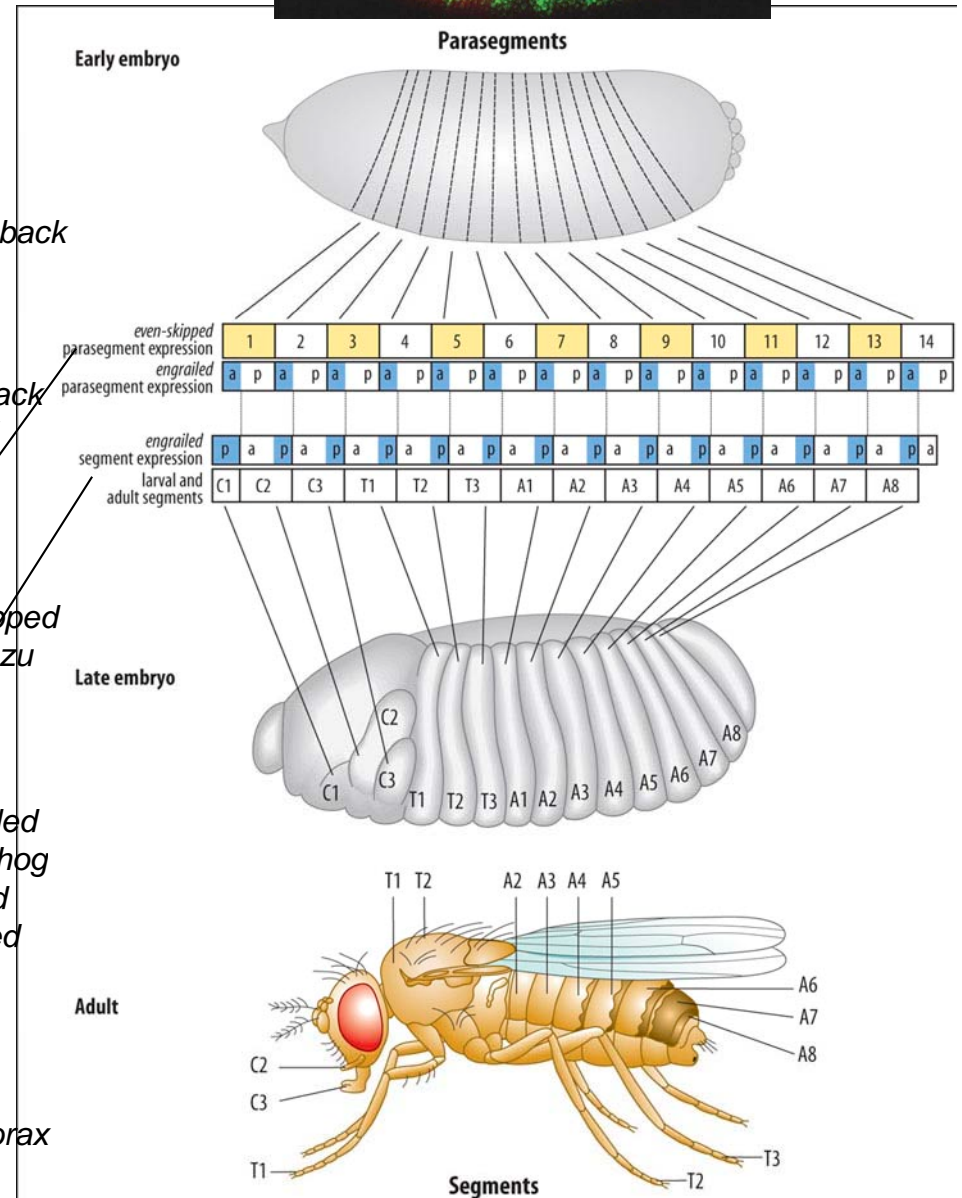
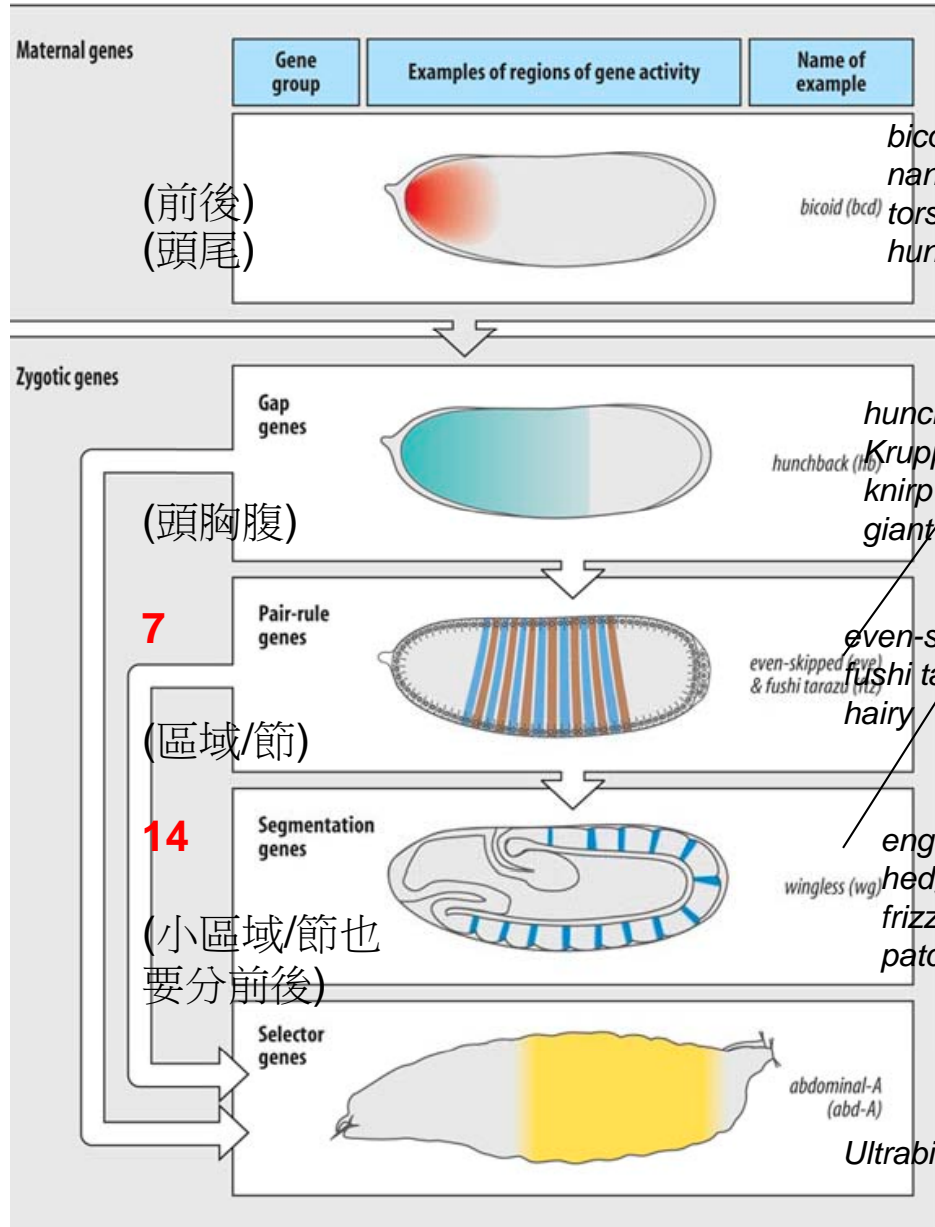
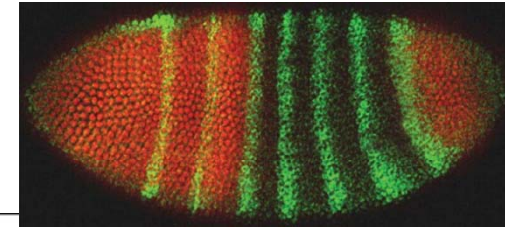
果蝇

fruit fly (*Drosophila melanogaster*)

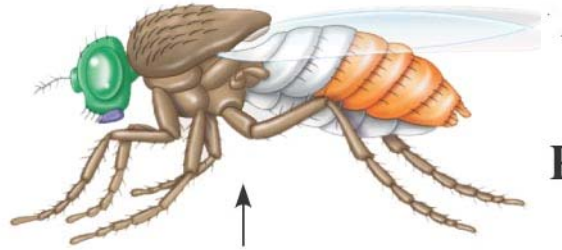


*At 25°C incubation

Body plan: To build a body



Adult fruit fly



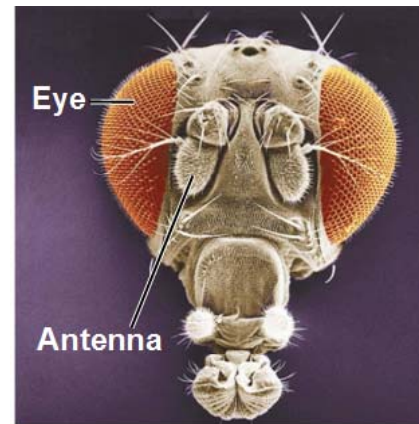
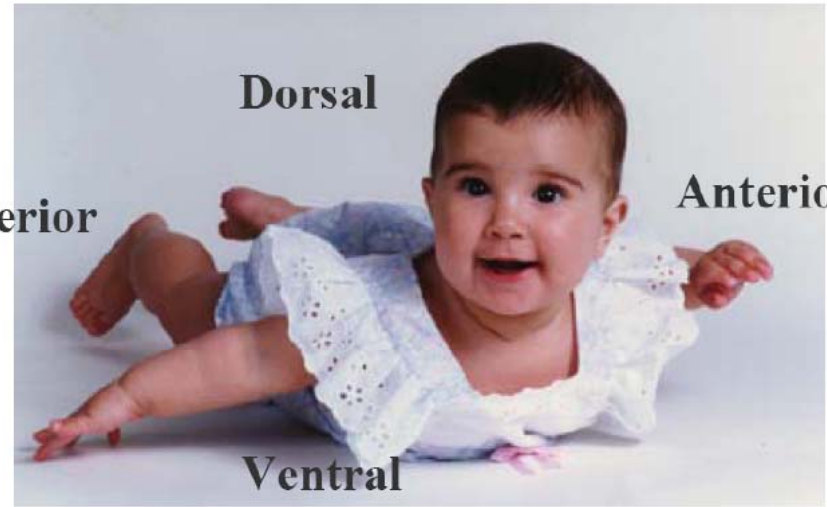
Fruit fly embryo (10 hours)



Fly chromosome



Homeobox genes

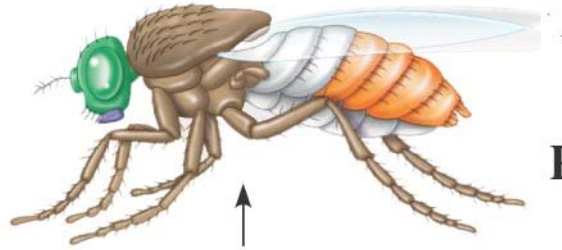


Wild type



Mutant

Adult fruit fly



Fruit fly embryo (10 hours)

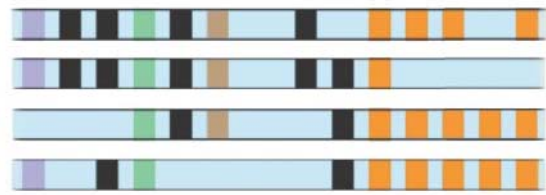


Fly chromosome

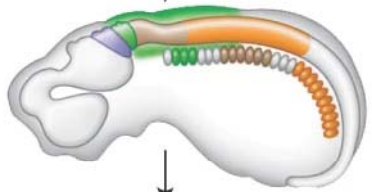


Homeobox genes

Mouse chromosomes



Mouse embryo (12 days)



Adult mouse

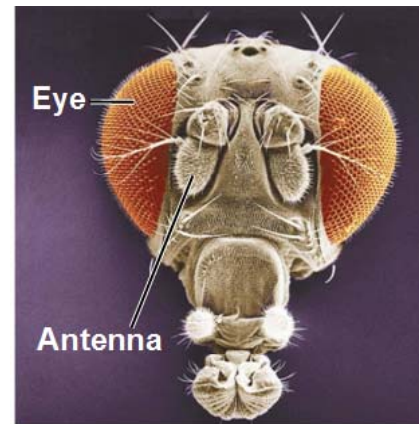
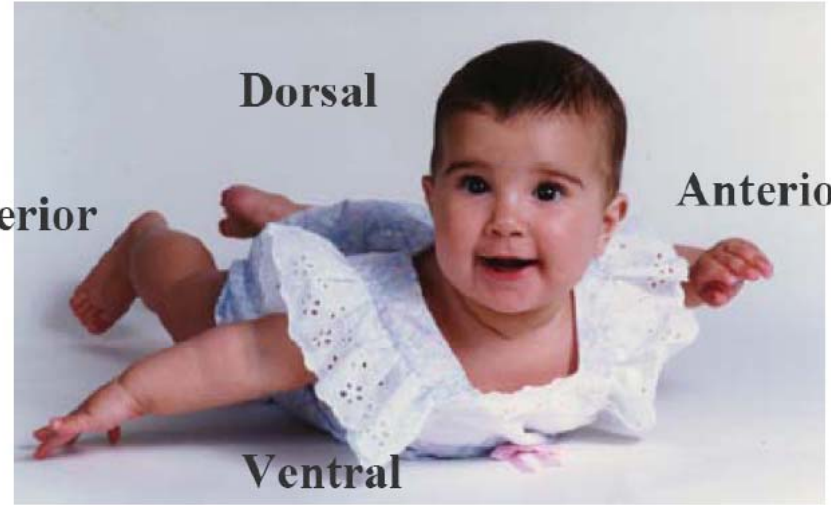


Posterior

Dorsal

Anterior

Ventral



Wild type




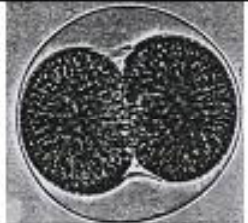
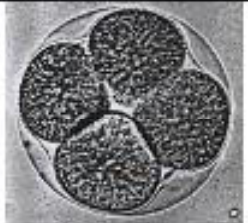
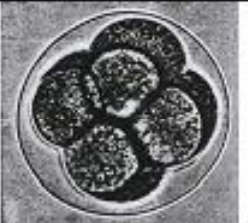
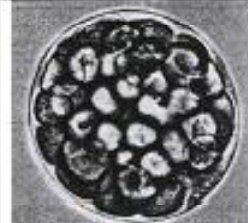



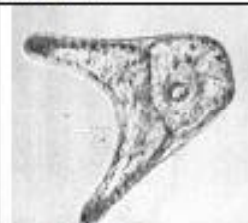






Mutant

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用以研究發育生物學, 人類疾病

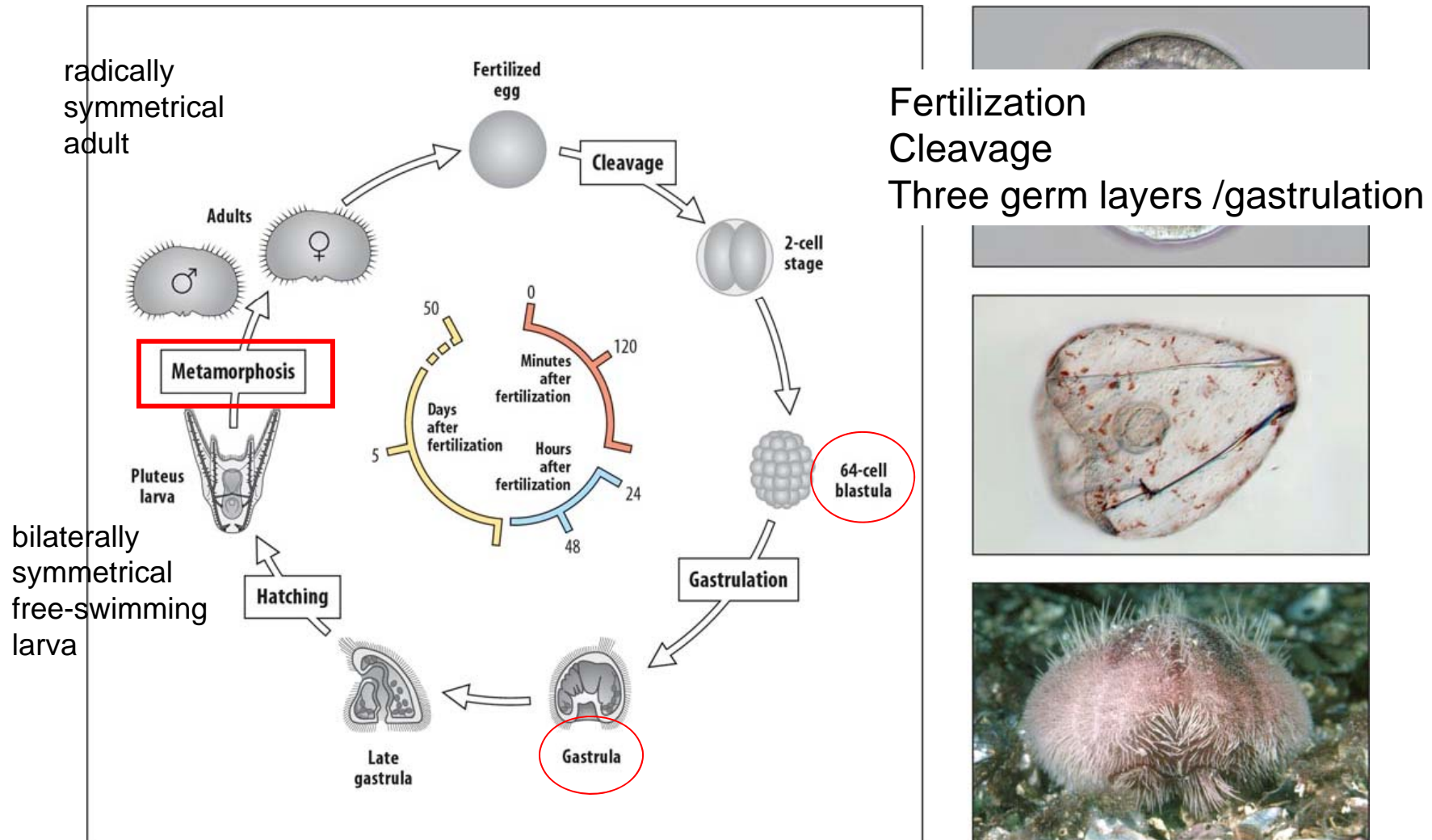
Development of sea urchins

			
受精卵	二分裂	四分裂	八分裂
			
桑葚期	囊胚期	原腸期	三角錐體期
			
二腕幼苗	四腕幼苗	六腕幼苗	八腕幼苗
			
變態完成的稚海膽			



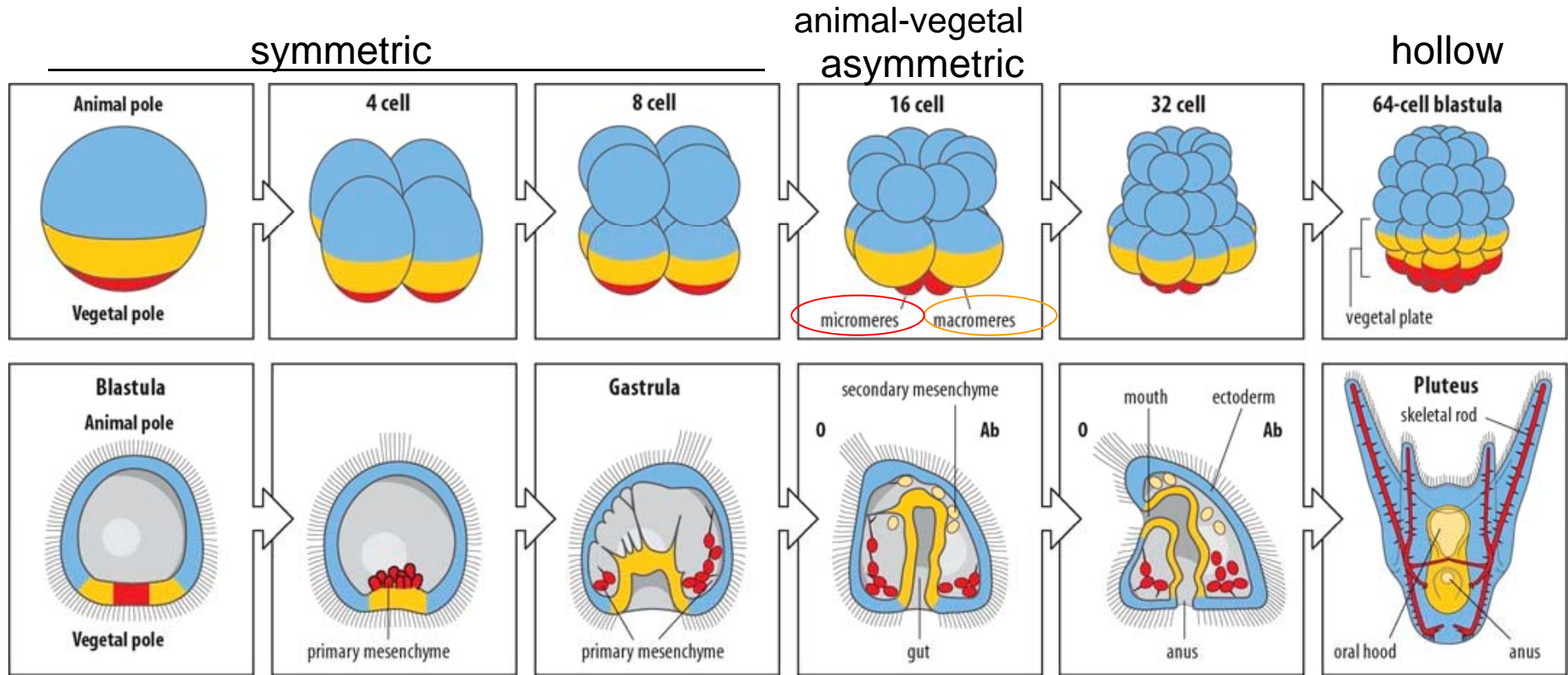
Sea urchin

經典的動物發育研究材料之一



The sea-urchin embryo develops into a free-swimming larva

Development of the sea urchin embryo.



初級間質

gut invaginate

骨棒(中胚層)

Blue: prospective ectoderm

Yellow: endoderm

Red: mesoderm

二級間質

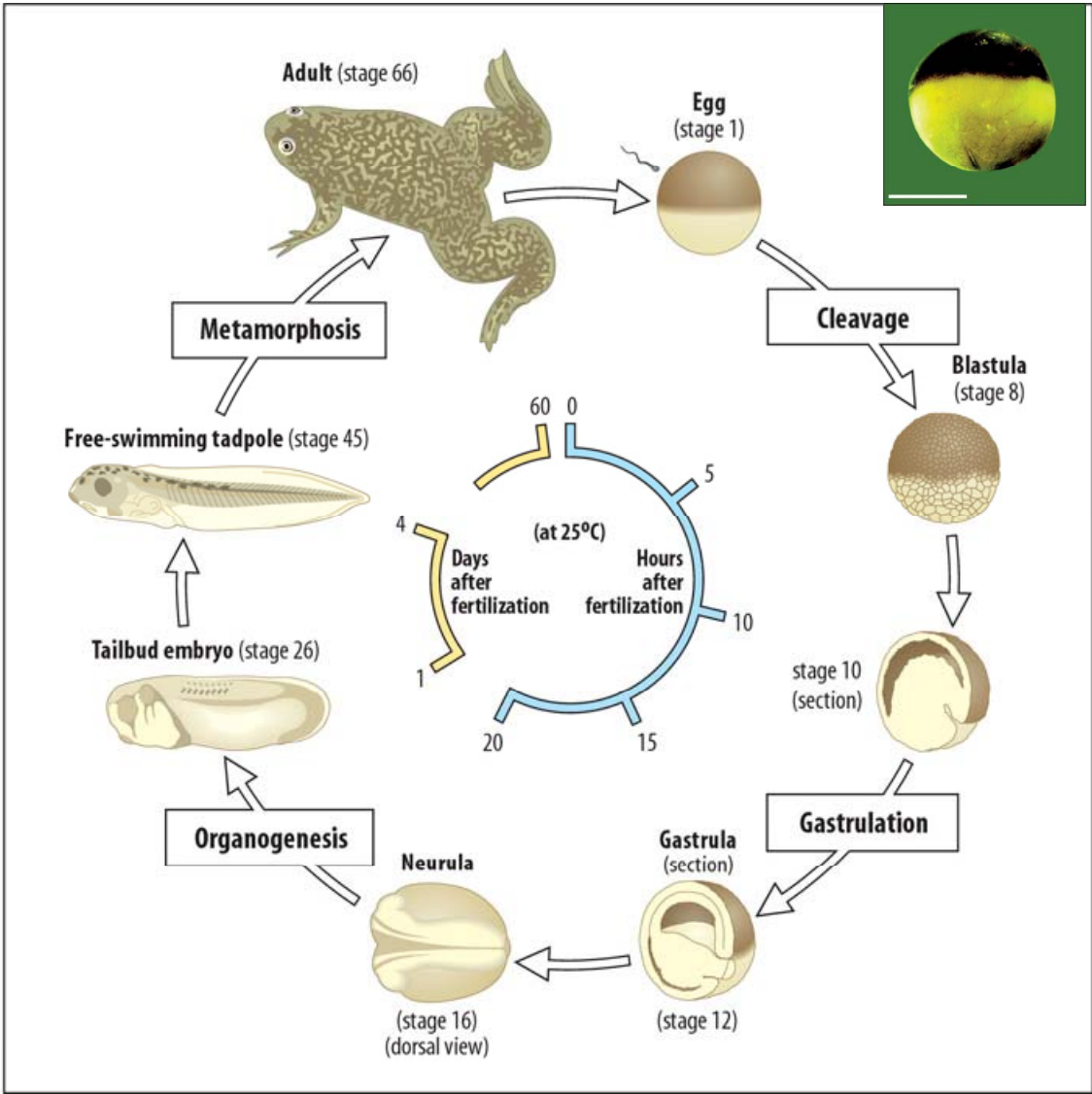
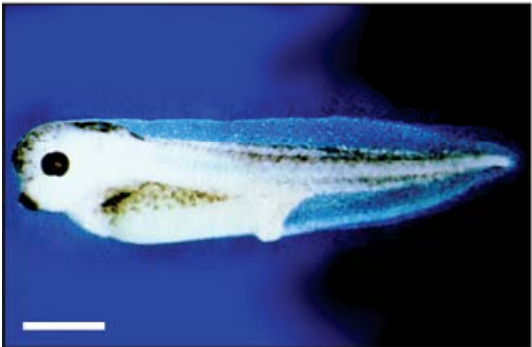
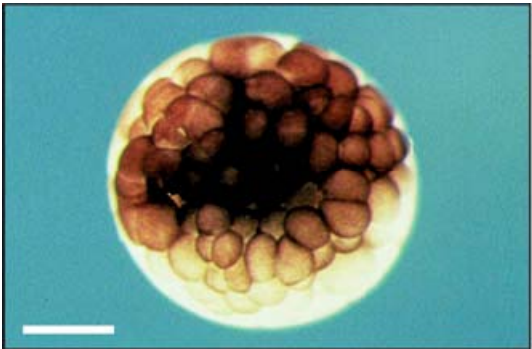
模式生物

無脊椎

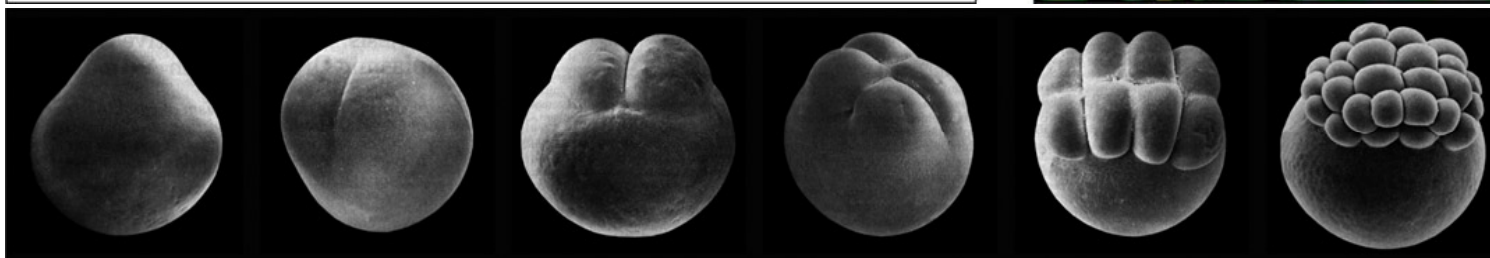
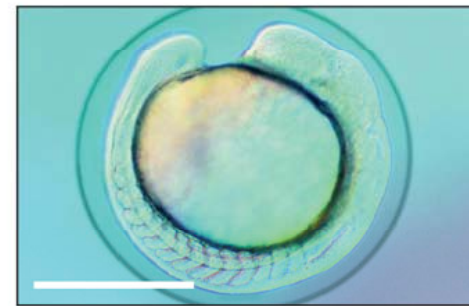
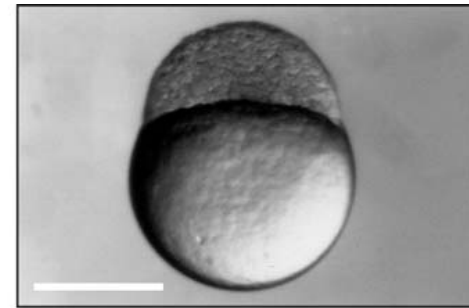
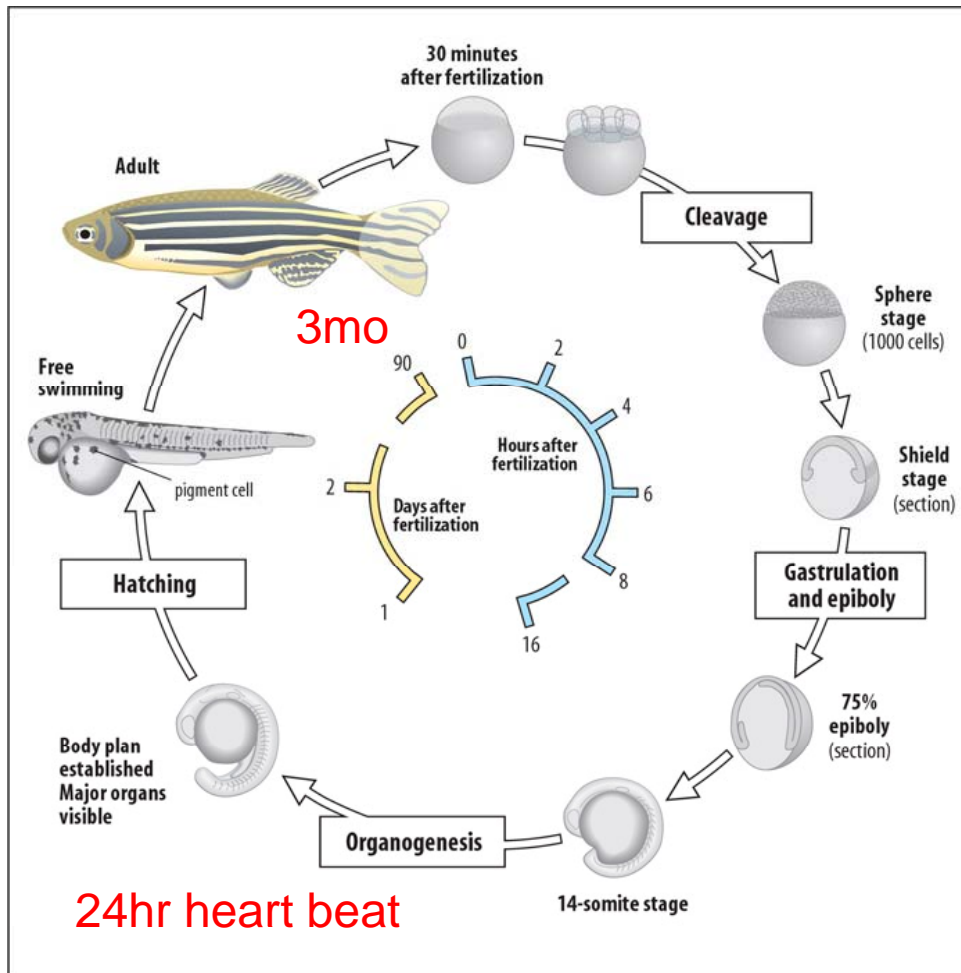
- nematode (*Caenorhabditis elegans*)
- fruit fly (*Drosophila melanogaster*)
- sea urchins
- South African Frog (*Xenopus laevis*)
- Zebrafish (*Danio Renio*)
- chick
- mouse
- plant (*Arabidopsis thaliana*)

用以研究發育生物學, 人類疾病

South African Frog (*Xenopus laevis*)



Zebrafish (*Danio Renio*)

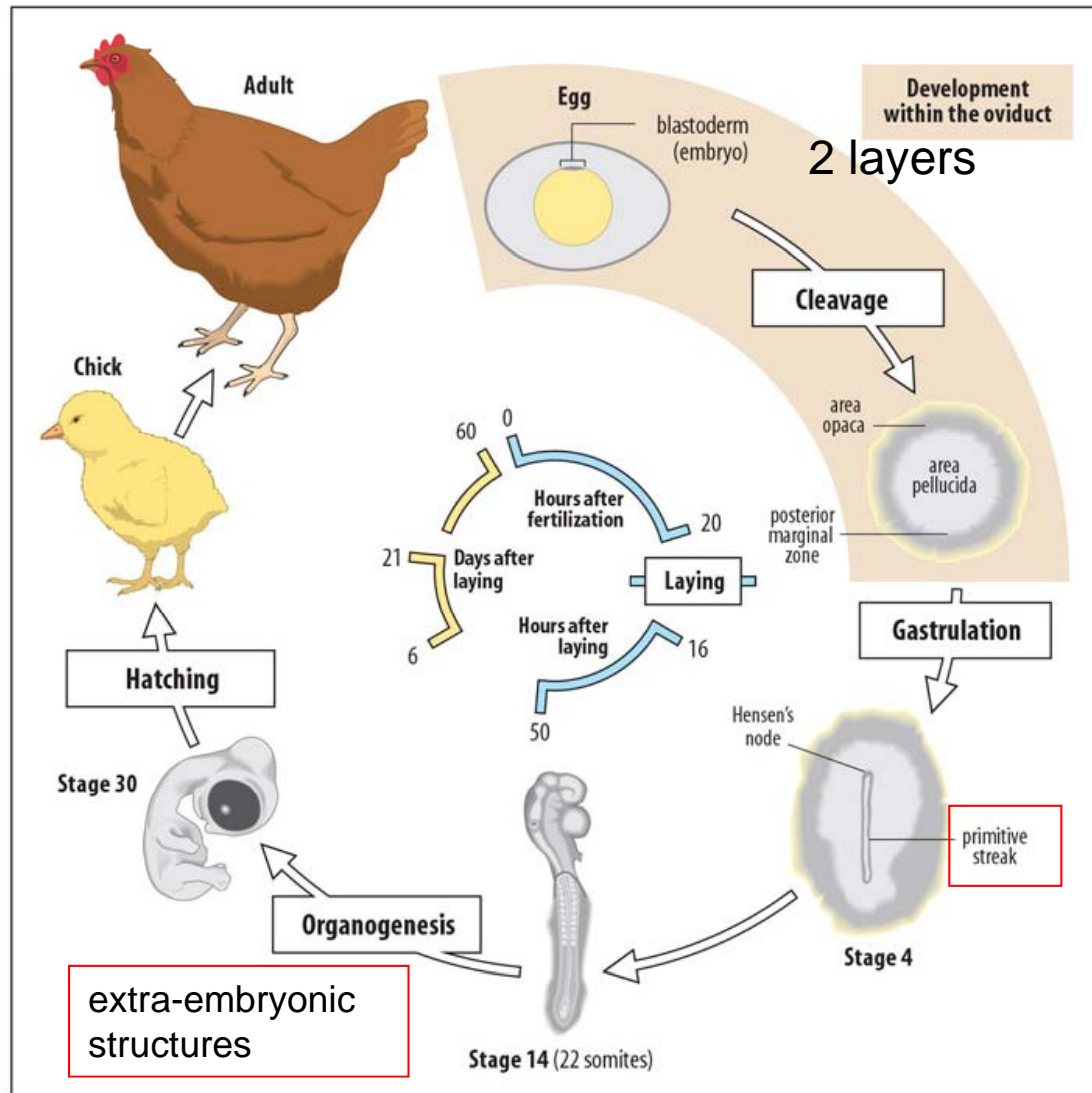
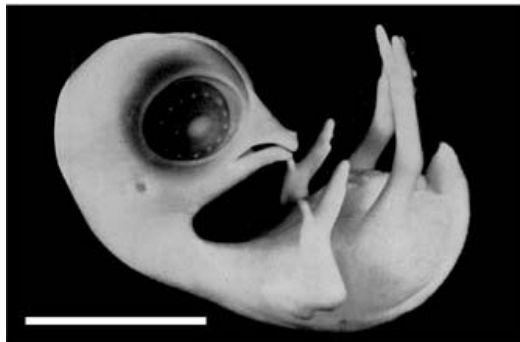
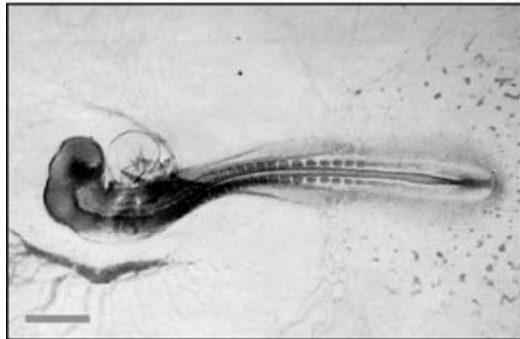
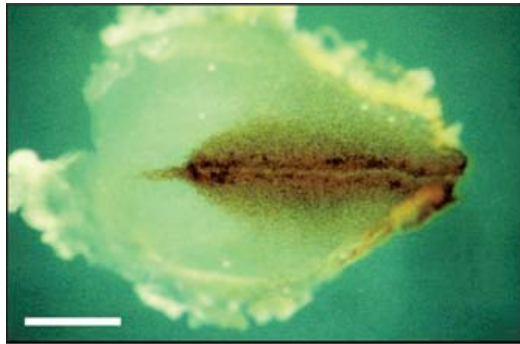


模式生物

- nematode (*Caenorhabditis elegans*)
- fruit fly (*Drosophila melanogaster*)
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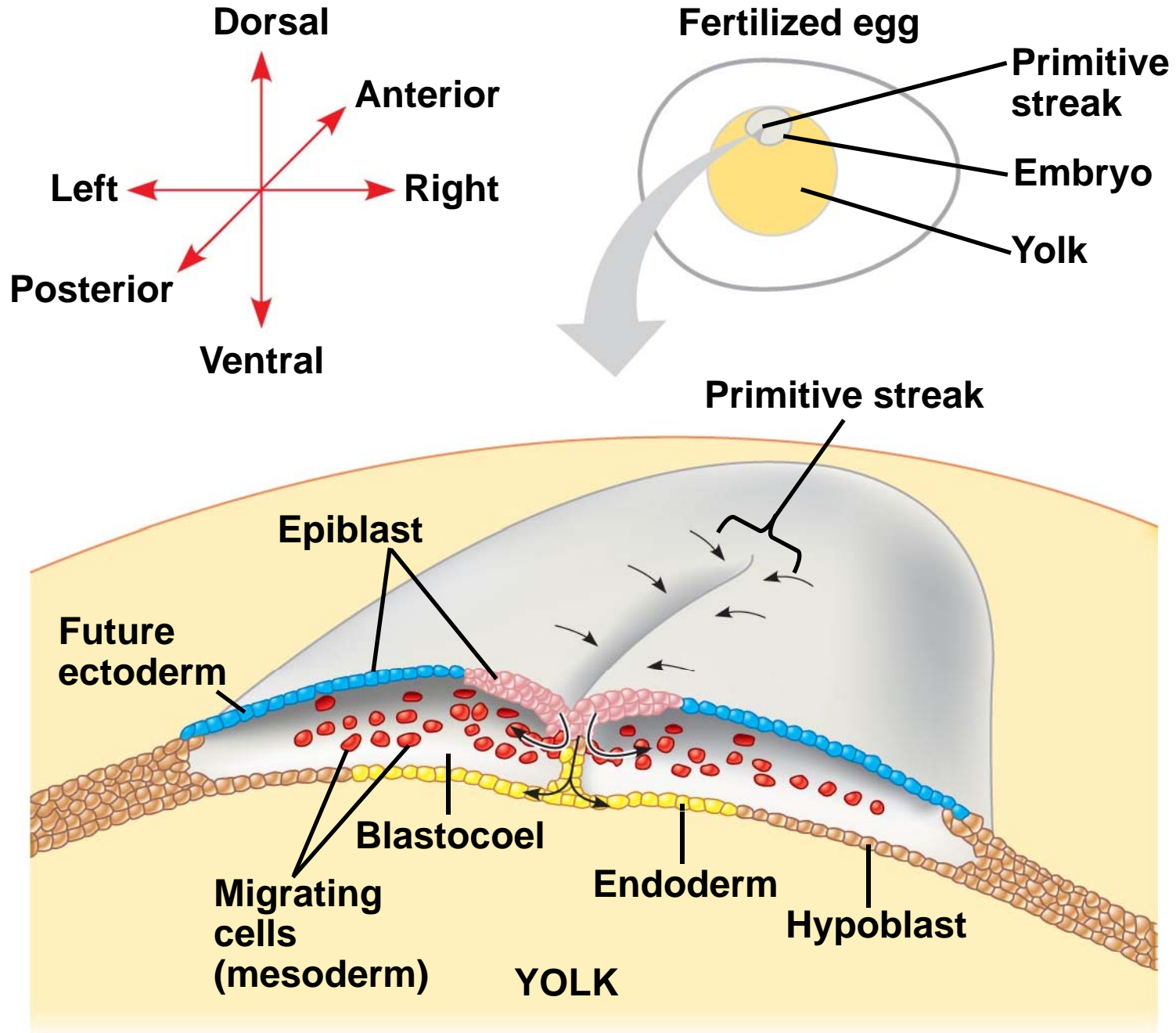
用以研究發育生物學, 人類疾病

Part 3 Life cycle of the chicken

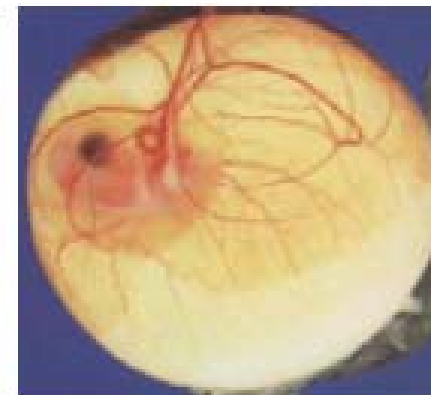
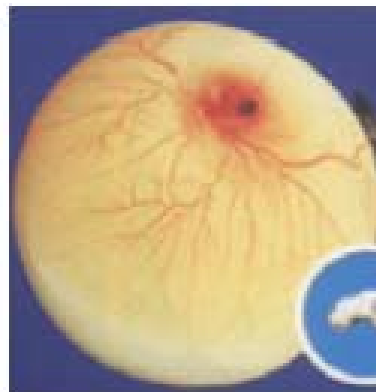
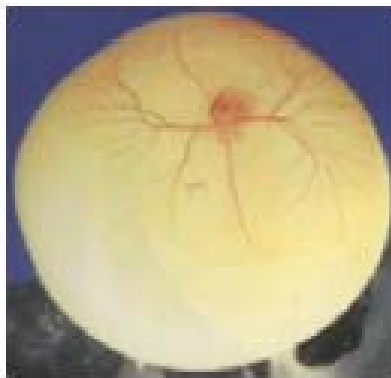


Birds and mammals resemble each other and different from frog in some important features of early development

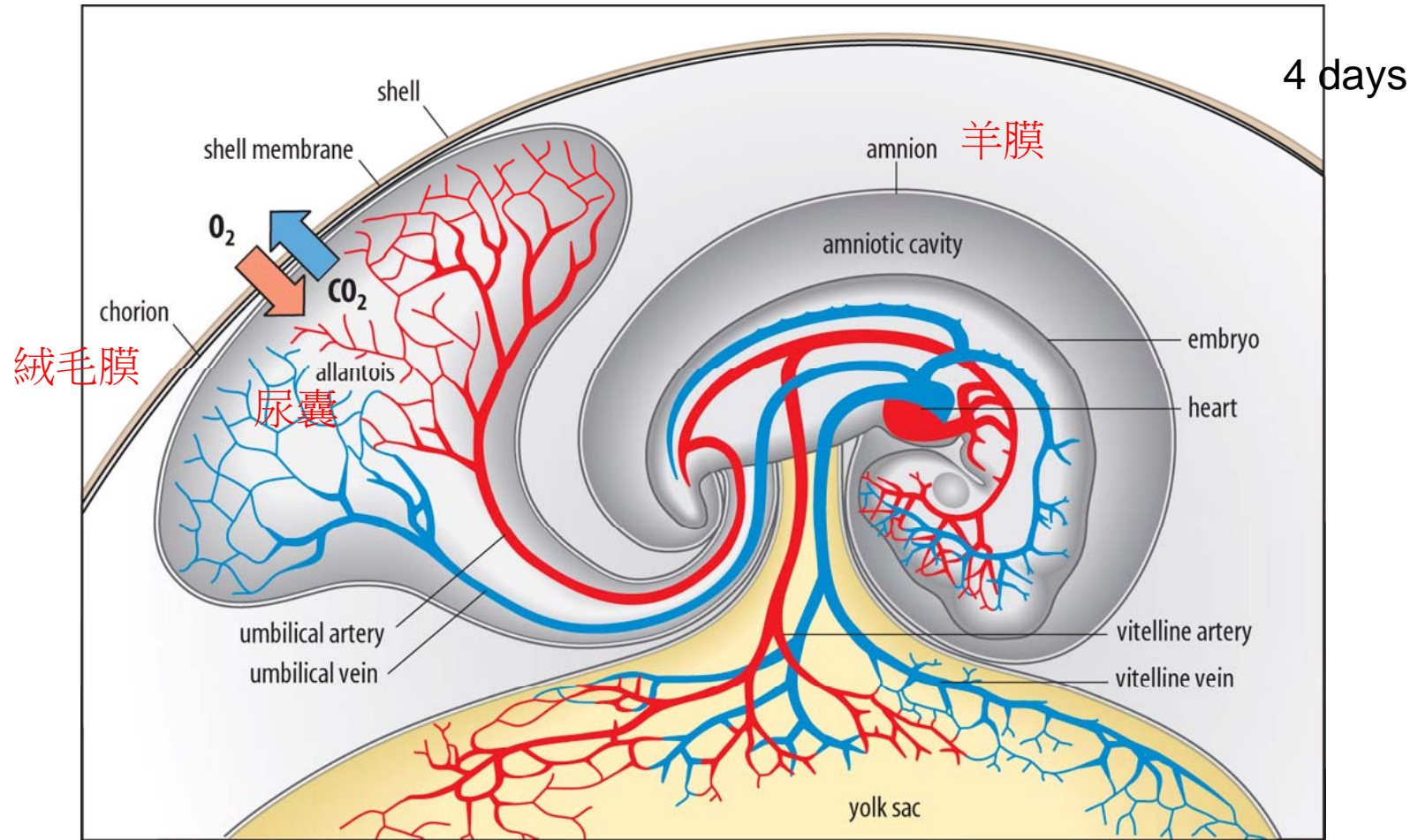
Fig. 47-11



Chick **embryogenesis**



The extra-embryonic structure and circulation of the chick embryo



具羊膜 (與哺乳類像)

Amnion and amniotic cavity provide mechanical protection

Chorion maintain shell

Allantois bridge for oxygen and waste

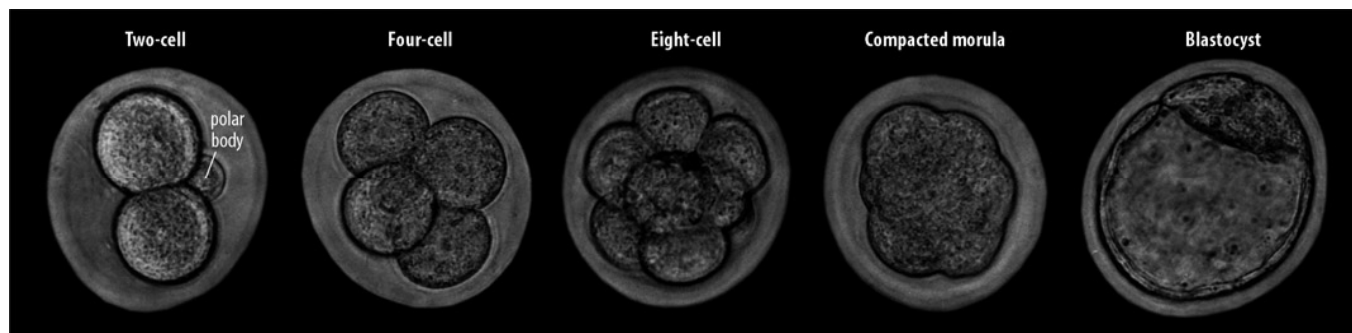
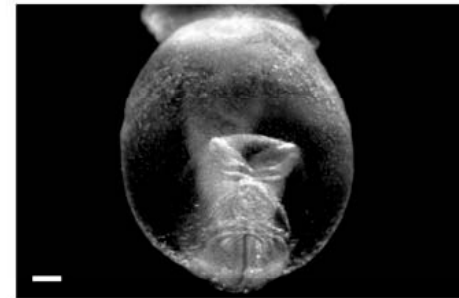
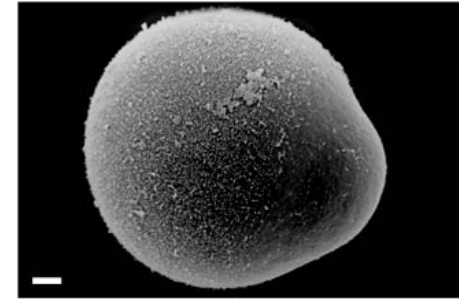
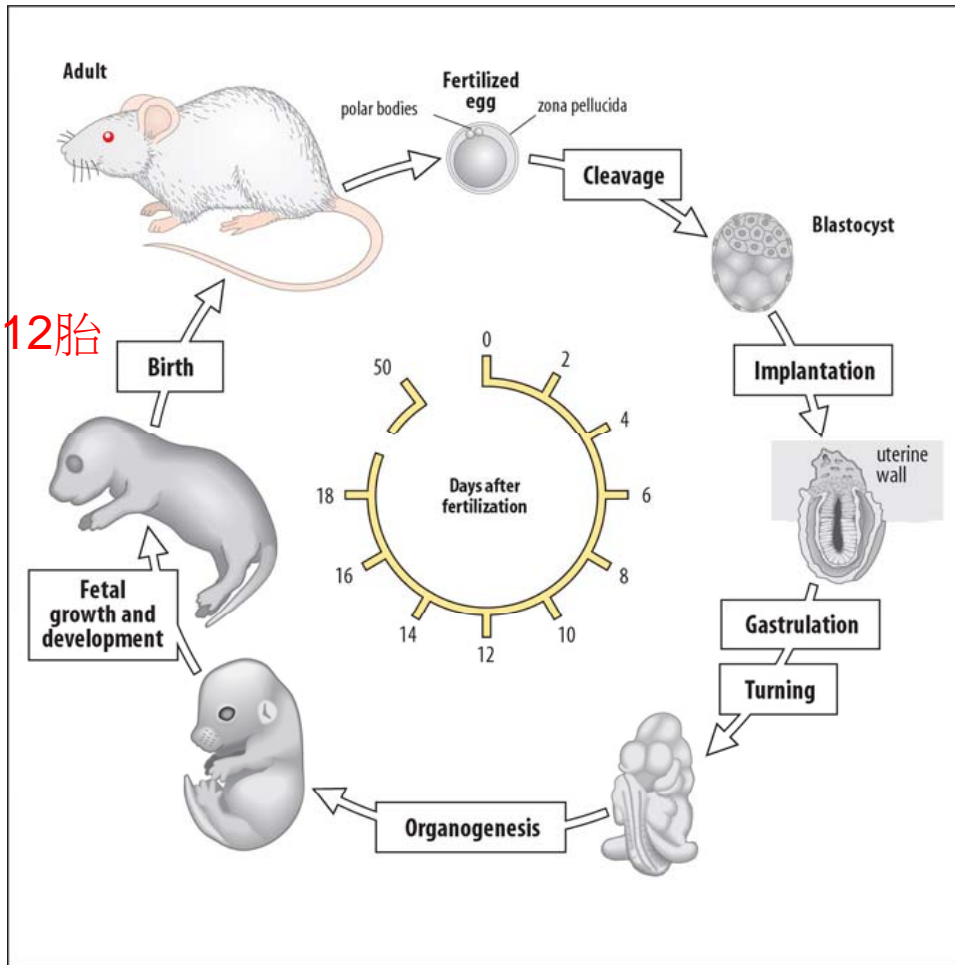
Vitelline vein take nutrient form yolk to embryo

Umbilical vein take oxygen to embryo

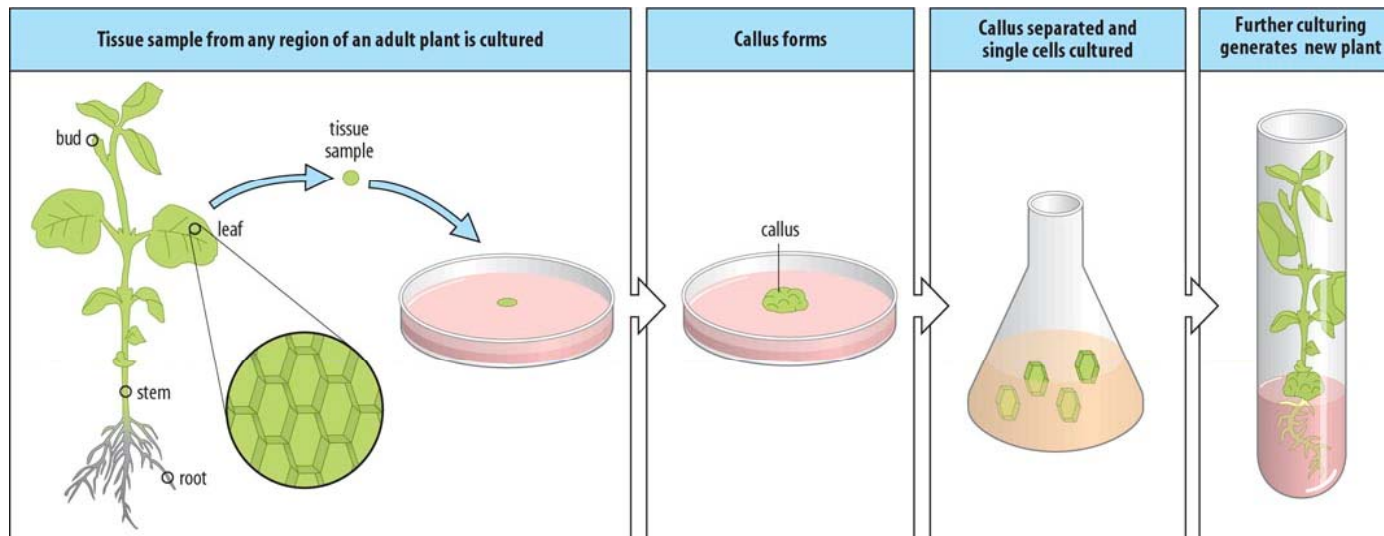
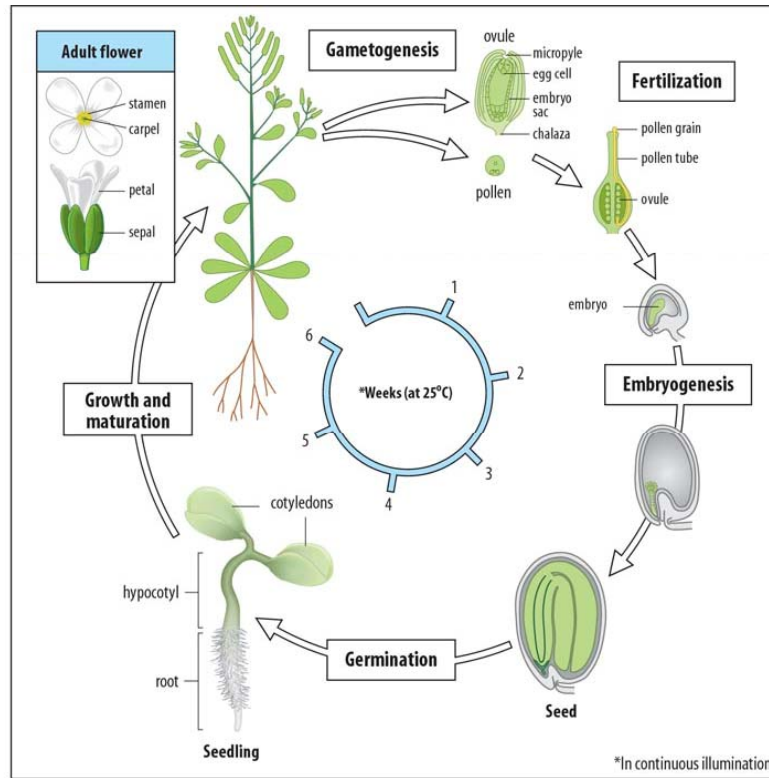
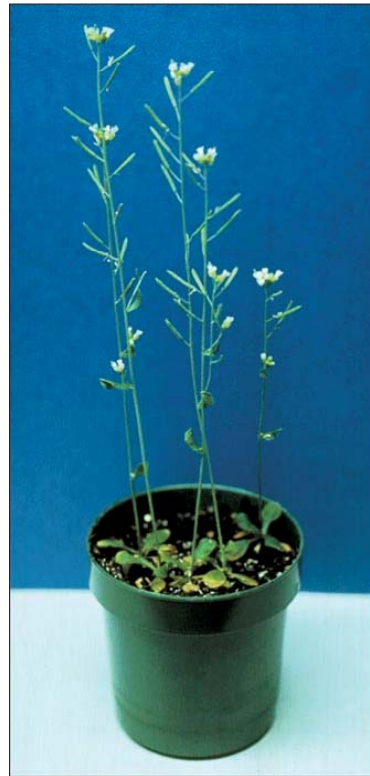
mouse

缺點?

19d, 8-12胎



plant (*Arabidopsis thaliana*)



模式生物(動物)的特性

1. 與人類有相似處 (功能相似, 有基因保留性)
2. 易培養 (經費少, 空間小, 生長周期短, 繁殖快, 子代多)
3. 易於實驗操作 (體外受精, 胚體透明, 容易進行基因操控)
4. 資料多 (基因已解碼)

Primate 黑猩猩: HIV, HBV, Behavior, Learning

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Wisconsin National Primate Research Center

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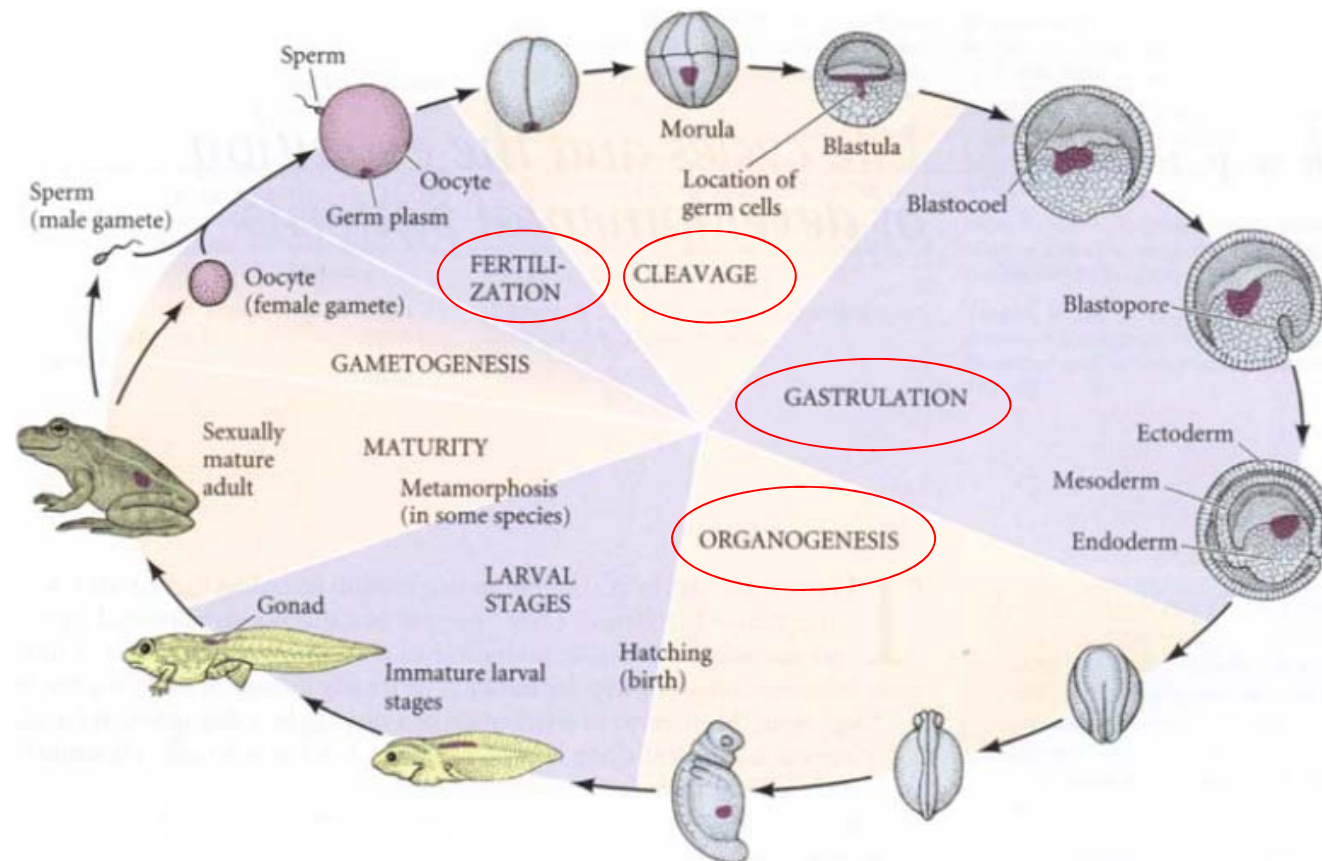
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PRIMATE CENTER NEWS
Calorie Restriction Does Not Affect Survival: Study Of

EVENTS
Wisconsin Science Festival
September 27-30, 2012

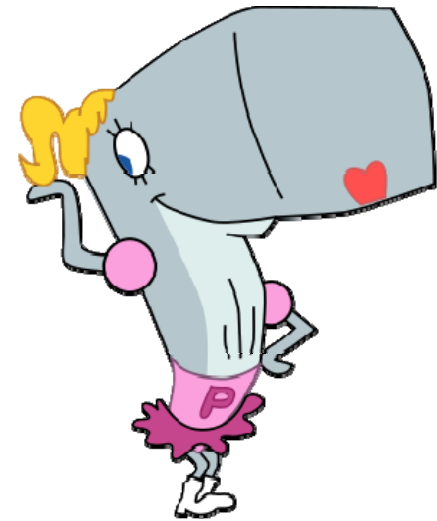
Outline

1. 胚胎學 (embryology) vs. 發育生物學 (developmental biology)
2. 模式生物 (model organisms)
3. 動物發育的主要階段
4. 發育過程之機制
5. 組織再生與幹細胞



動物發育的主要階段

所有動物皆一樣？



動物發育的主要過程

1. 受精 (Fertilization)

2. 卵裂 (Cleavage)

cell division creates a hollow ball of cells called a blastula

3. 原腸化 (Gastrulation)

cells are rearranged into a three-layered gastrula

4. 神經 (Neurulation)

5. 器官生成 (Organogenesis)

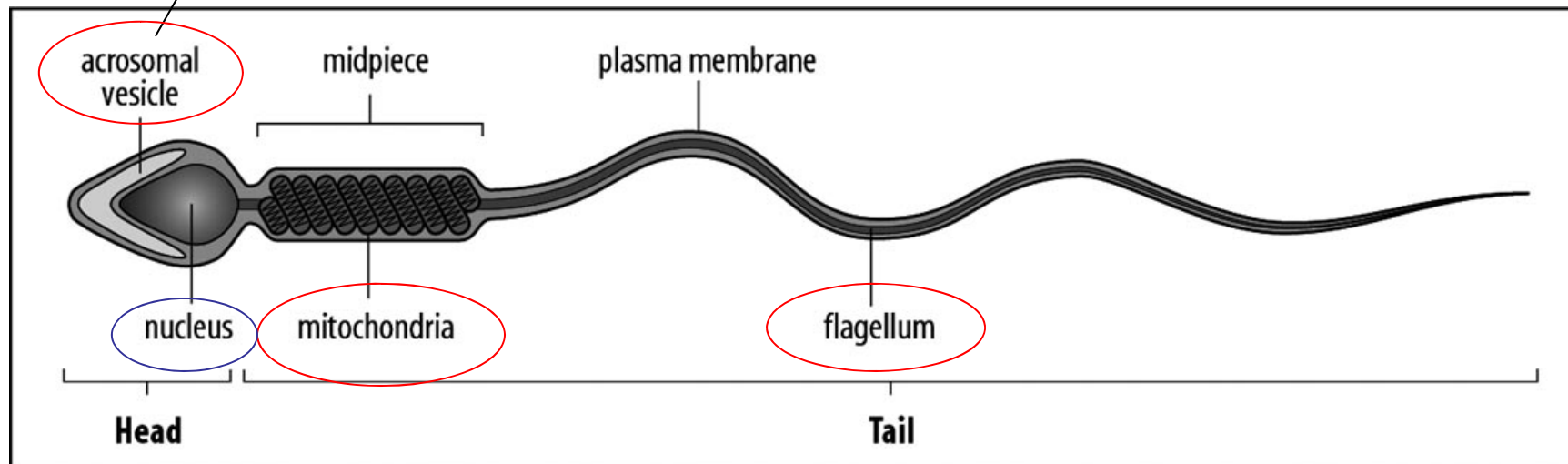
the three layers interact and move to give rise to organs

6. 個體生成 (Growth)

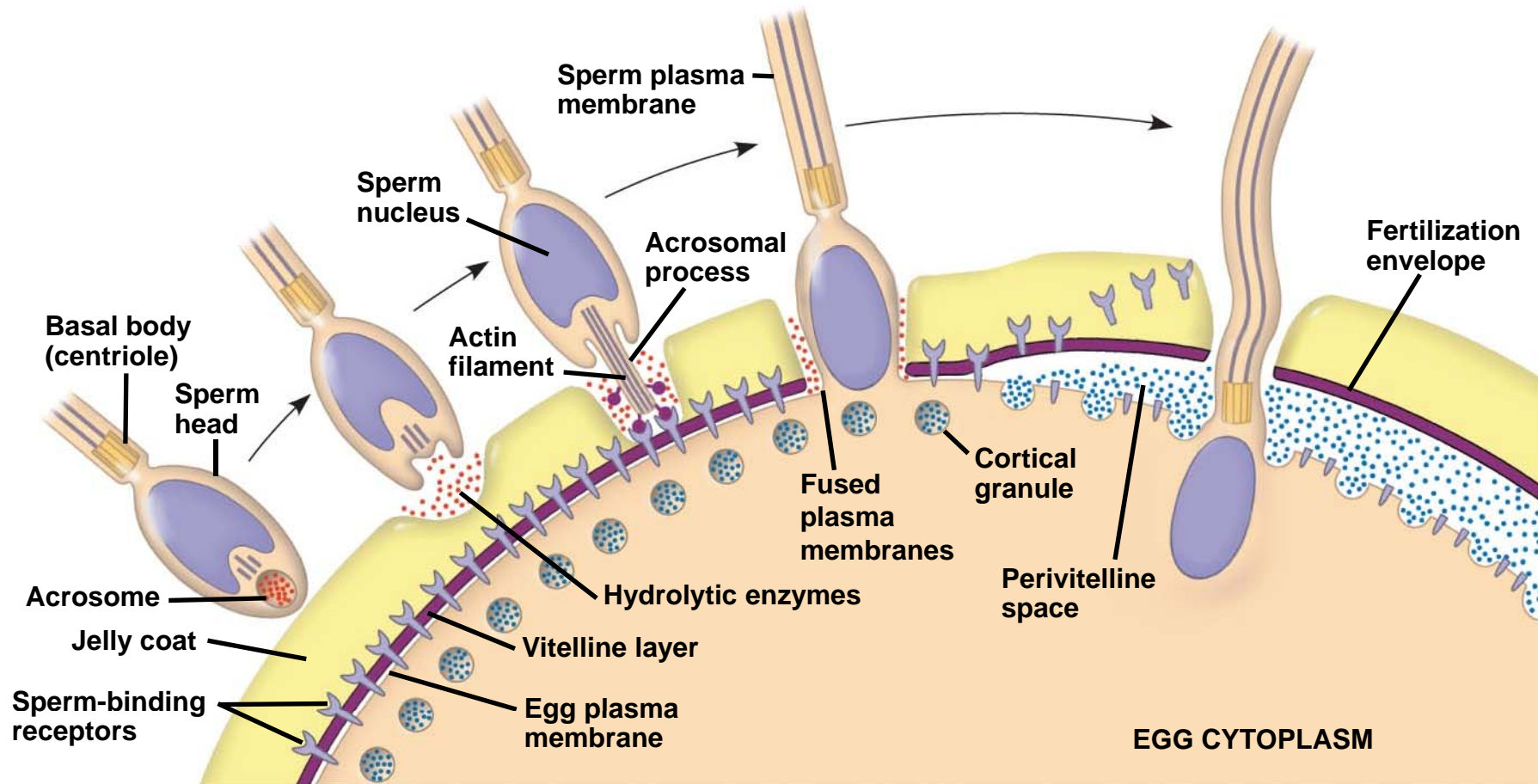
Fertilization

- Fertilization brings the haploid nuclei of sperm and egg together, forming a diploid zygote
- The sperm's contact with the egg's surface initiates metabolic reactions in the egg that trigger the onset of embryonic development

含酵素以分解卵表面膠質層



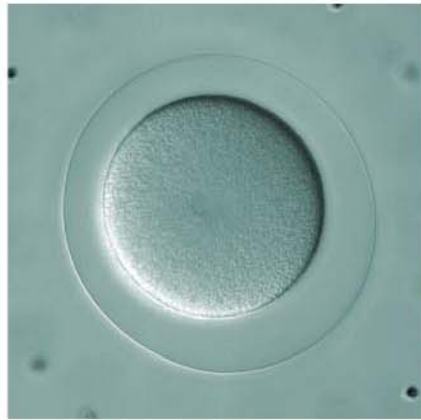
The acrosomal and cortical reactions during sea urchin fertilization



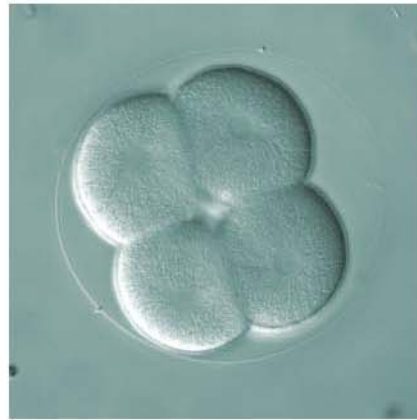
動物發育的主要過程

1. 受精 (Fertilization)
- 2. 卵裂 (Cleavage)**
3. 原腸化 (Gastrulation)
4. 神經 (Neurulation)
5. 器官生成 (Organogenesis)
6. 個體生成 (Growth)

Cleavage



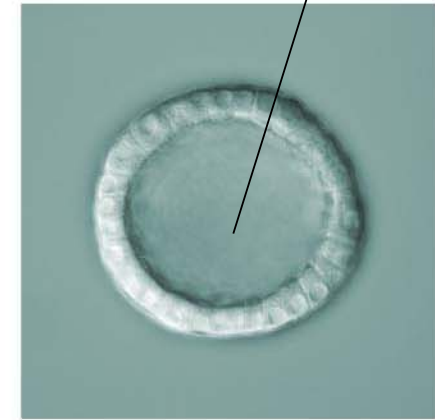
(a) Fertilized egg



(b) Four-cell stage

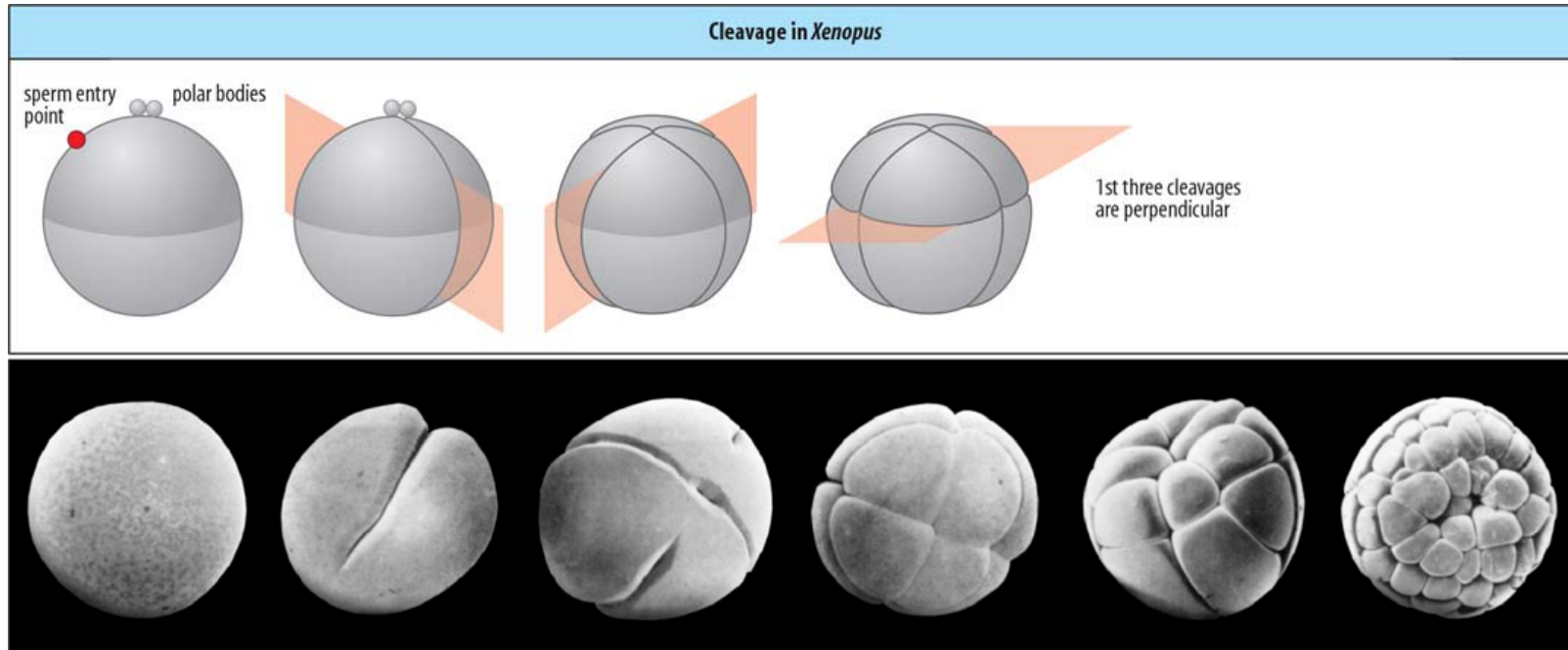


(c) Early blastula

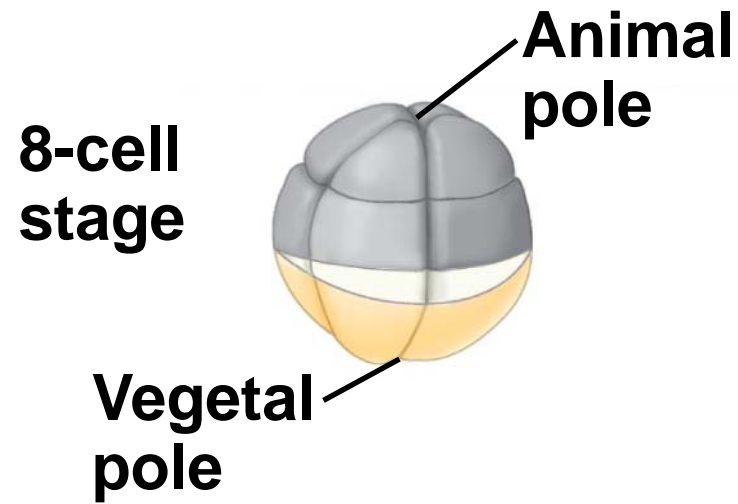


(d) Later blastula

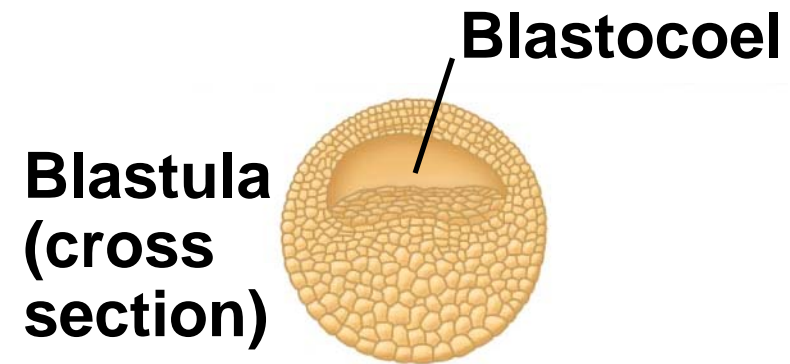
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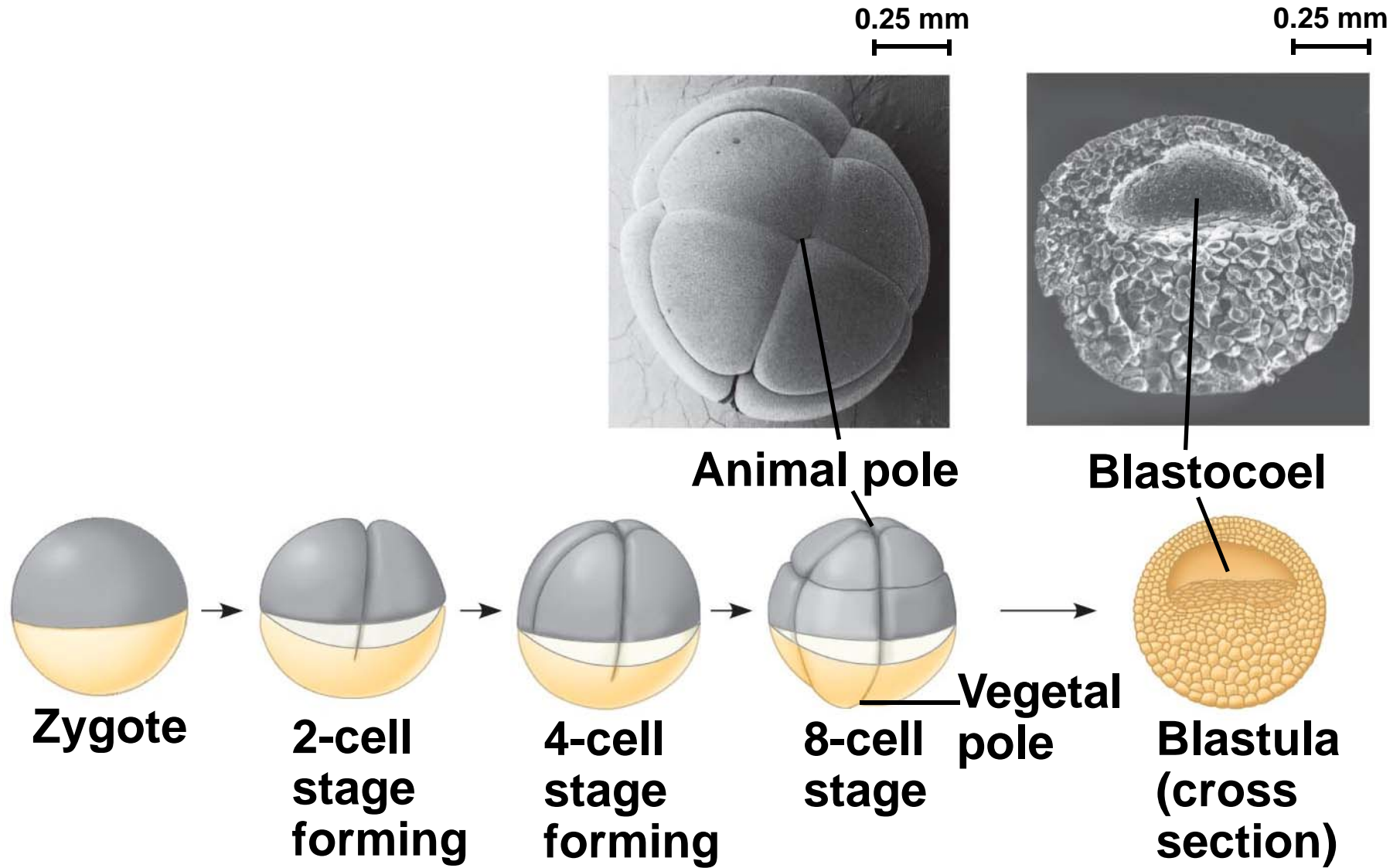
Cleavage in a frog embryo



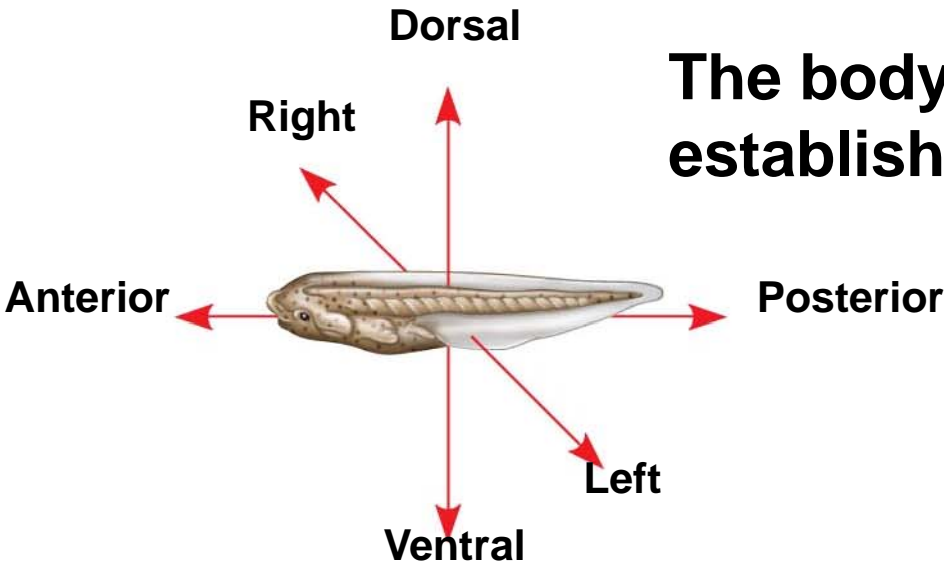
Cleavage in a frog embryo



Cleavage in a frog embryo

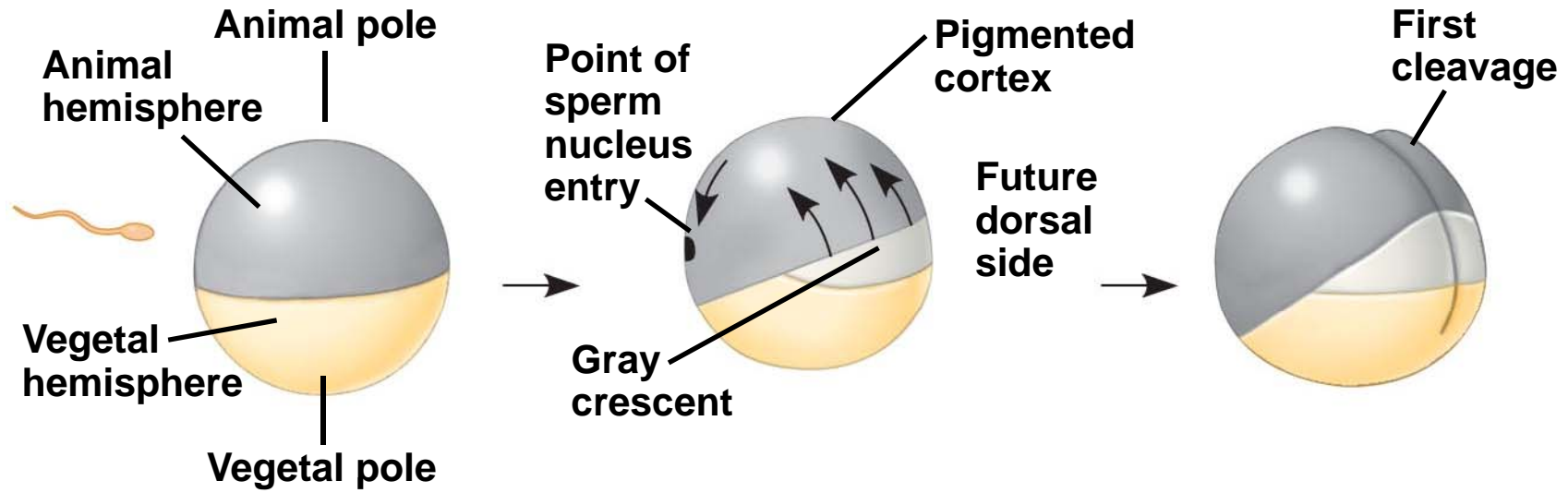


The body axes and their establishment in an amphibian



體軸
 前/後軸(A/P axis)
 背/腹軸(D/V axis)
 左/右軸(L/R axis)

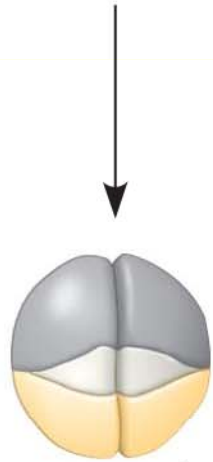
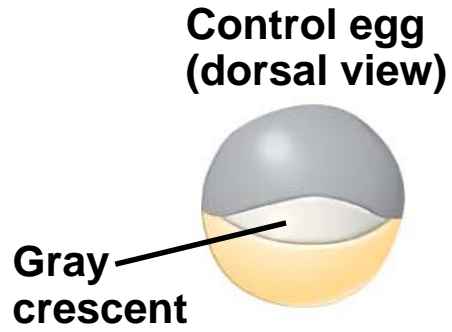
(a) The three axes of the fully developed embryo



(b) Establishing the axes

Fig. 47-23b

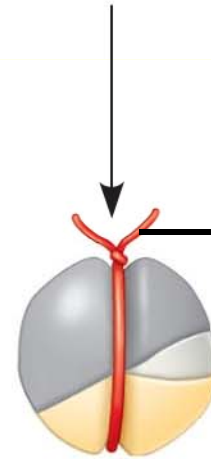
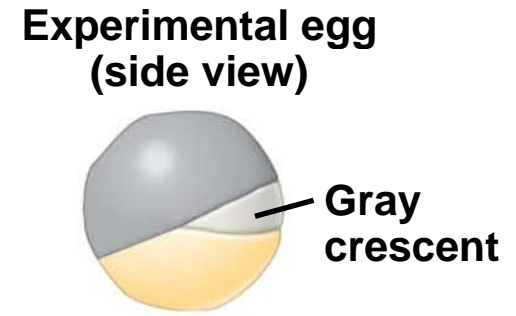
EXPERIMENT



RESULTS



Normal



Belly piece



Normal

動物發育的主要過程

1. 受精 (Fertilization)
2. 卵裂 (Cleavage)
- 3. 原腸化 (Gastrulation)**
4. 神經 (Neurulation)
5. 器官生成 (Organogenesis)
6. 個體生成 (Growth)

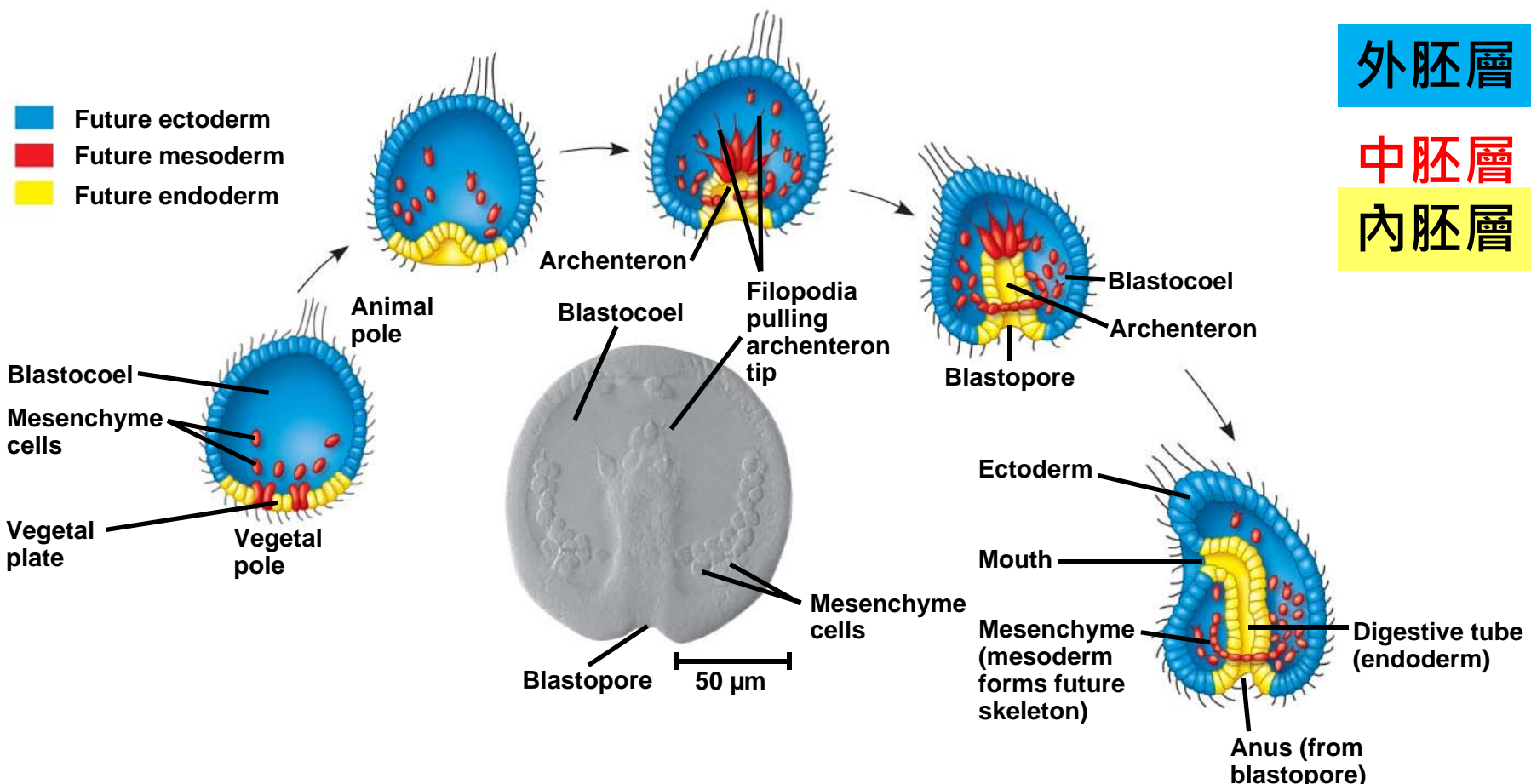
大量細胞轉移

胚層生成

體軸建立

Gastrulation in a sea urchin embryo

原腸化



外胚層

中胚層

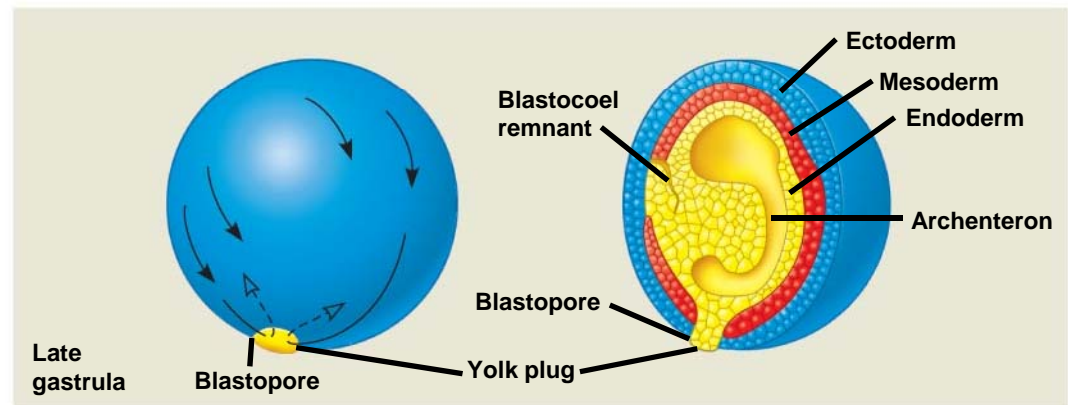
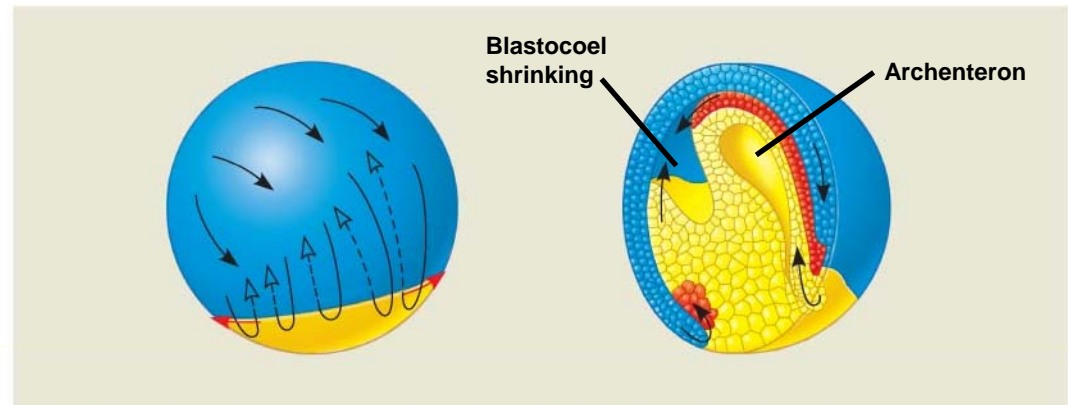
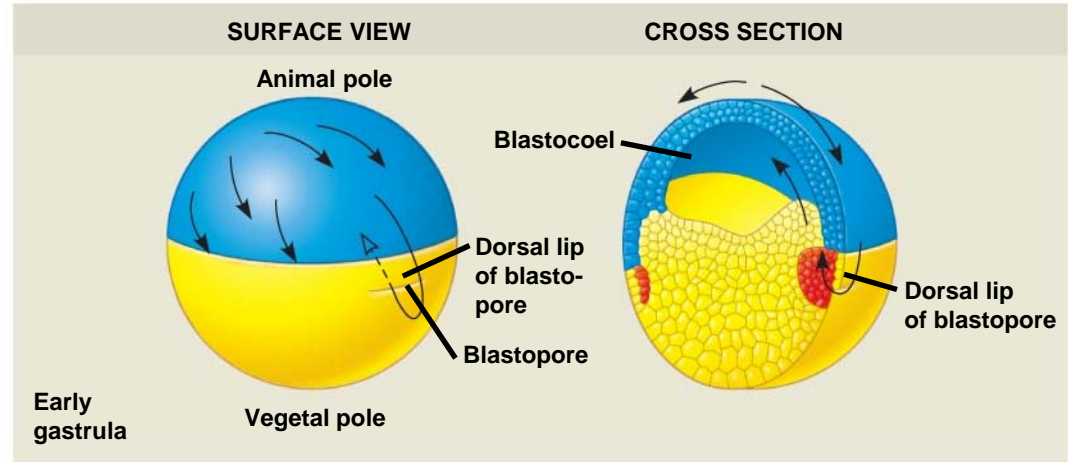
內胚層

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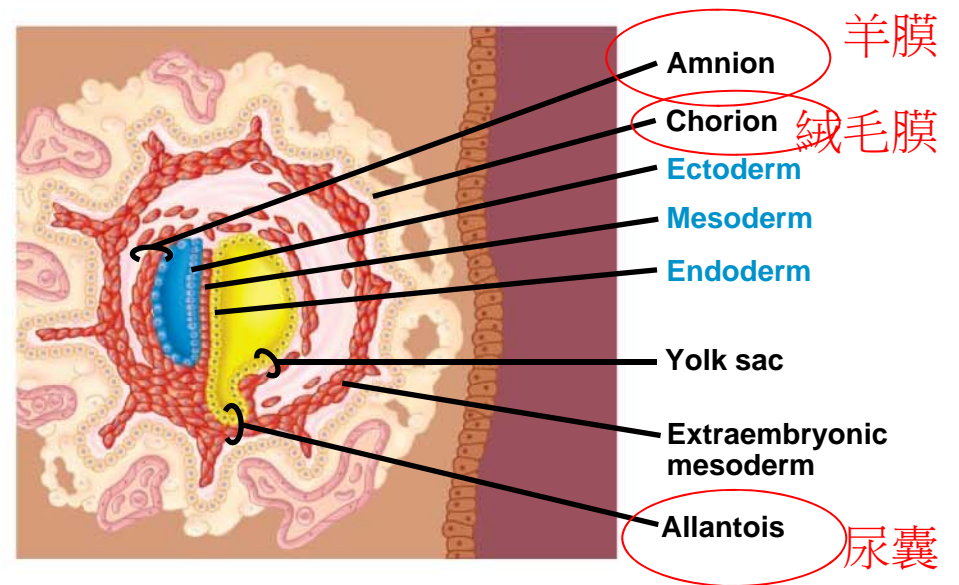
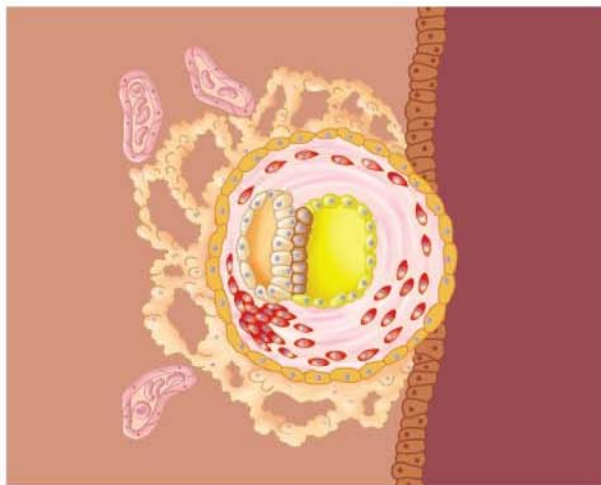
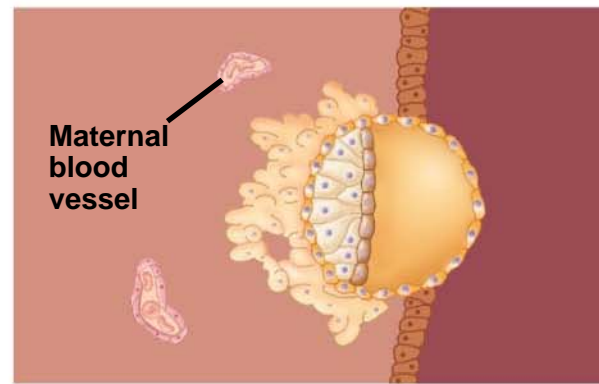
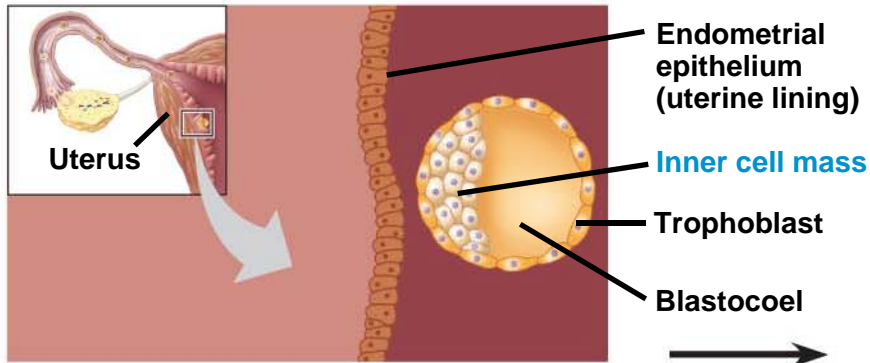
Gastrulation in the frog

- Cells of the **dorsal lip** originate in the **gray crescent** and **invaginate** to create the **archenteron**
- Cells continue to move by **involution**
- These cells become the **endoderm and mesoderm**
- The blastopore encircles a **yolk plug** when gastrulation is completed
- **ectoderm, endoderm, and mesoderm**



Key	
Blue	Future ectoderm
Red	Future mesoderm
Yellow	Future endoderm

Mammal (human)



胎盤素



「瑕疵 暗沉 斑點 通通掰掰」 輕鬆遮瑕 完美出擊! MICCOSMO

輕輕一抹 **斑點 OUT!** 純物理性防曬 溫和不刺激

立即擁有無瑕透明感嬰兒般白肌。

忙碌的早晨只需這一瓶就 OK! 上妝的同時也以胎盤素保養!

給想要修飾惱人的斑斑點點... 卻又不想要厚重妝感的您。

空氣感薄透觸感, 智慧遮蓋斑點! **新感覺BB霜!**

SPF25 PA++ 自然潤色

Point 1 忙碌的早晨也能瞬間擁有嬰兒般白肌

集合美容液、妝前乳、防曬霜、遮瑕膏、粉底, 全方位智慧機能, 添加「超細滑 & 遮瑕粉末」, 如同慕斯狀的保濕觸感, 極佳的延展性在肌膚上滑順的推開, 簡單上妝不NG!

什麼是「超細滑 & 遮瑕粉末」?

比尼龍柔軟的神奇微粒子粉末, 具高度遮瑕力, 輕輕塗一層就能呈現透明妝感, 實現了兼具遮瑕力與自然妝感。

超細滑粉 & 遮瑕粉

Before After

Point 2 添加日本國產 100% 胎盤素, 滋潤感維持一整天

奢華添加高保溼效果的胎盤素精華, 另外添加了膠原蛋白及玻尿酸, 賦予肌膚彈力光澤, 上妝同時維持肌膚滋潤。

BB霜成分

Point 3 抵禦紫外線! 敏感性肌膚也可安心使用!

不添加化學性防曬劑, 是一款專為敏感肌打造無添加配方, 添加防汗防水配方, 保護肌膚遠離紫外線, 預防因日曬引起的傷害, 貼膚力佳。

(無香料、合成色素、礦物油、防腐劑、酒精) 的 BB 霜。

胎盤素白肌 BB 霜 28g

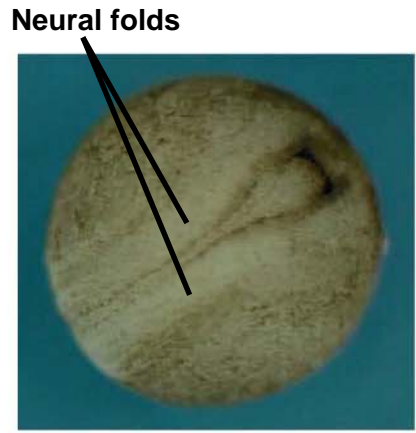
使用方法 使用化妝水後, 取適量 (紅豆大小) 均勻塗在全臉。薄薄地塗上推開是不脫妝的關鍵, 再以手指輕輕按摩。可與平時使用的蜜粉搭配。卸妝時以一般卸妝產品即可輕鬆卸除乾淨。



動物發育的主要過程

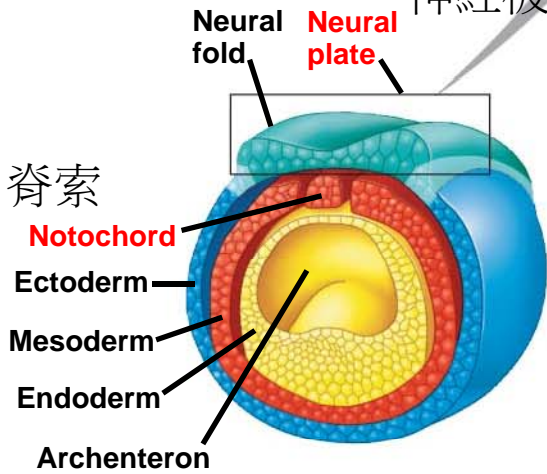
1. 受精 (Fertilization)
2. 卵裂 (Cleavage)
3. 原腸化 (Gastrulation)
- 4. 神經 (Neurulation)**
5. 器官生成 (Organogenesis)
6. 個體生成 (Growth)

neurulation (神經管的生成)

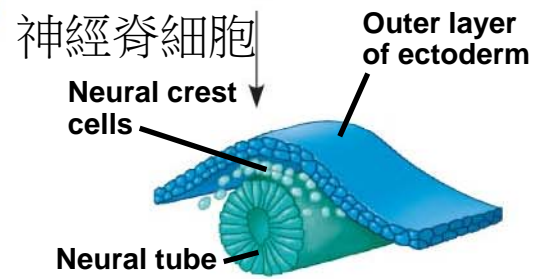
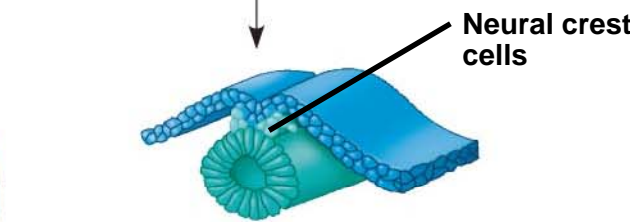
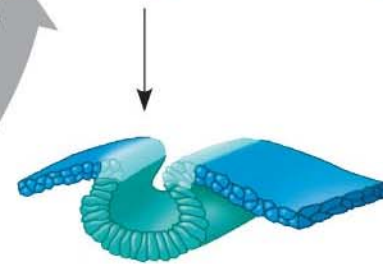
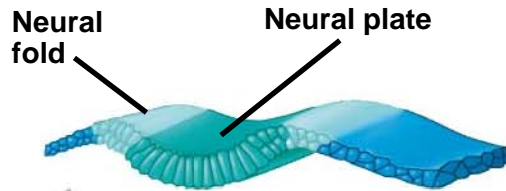


1 mm

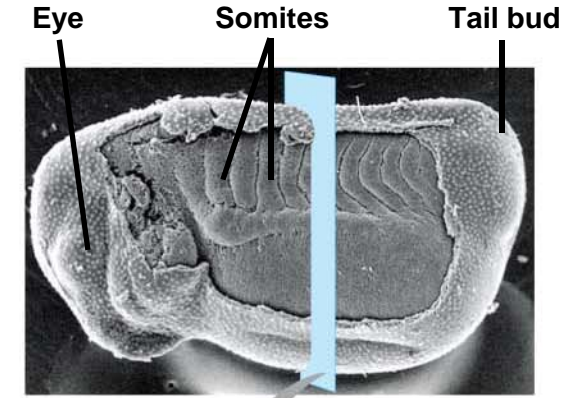
神經板



(a) Neural plate formation

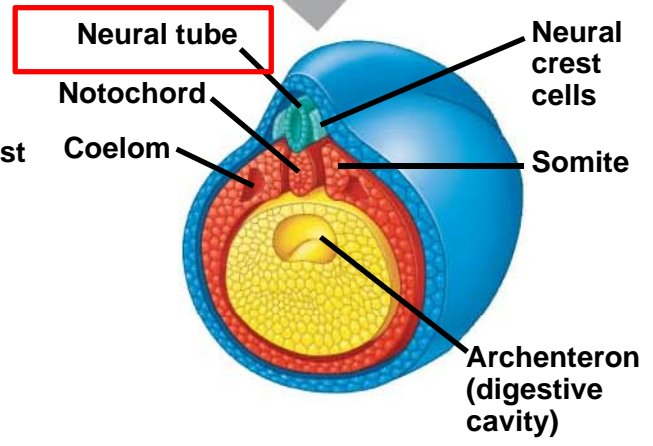


(b) Neural tube formation



SEM

1 mm



(c) Somites

動物發育的主要過程

1. 受精 (Fertilization)
2. 卵裂 (Cleavage)
3. 原腸化 (Gastrulation)
4. 神經 (Neurulation)
- 5. 器官生成 (Organogenesis)**
6. 個體生成 (Growth)

外胚層

ECTODERM

- Epidermis of skin and its derivatives (including sweat glands, hair follicles)
- Epithelial lining of mouth and anus
- Cornea and lens of eye
- Nervous system
- Sensory receptors in epidermis
- Adrenal medulla
- Tooth enamel
- Epithelium of pineal and pituitary glands

中胚層

MESODERM

- Notochord
- Skeletal system
- Muscular system
- Muscular layer of stomach and intestine
- Excretory system
- Circulatory and lymphatic systems
- Reproductive system (except germ cells)
- Dermis of skin
- Lining of body cavity
- Adrenal cortex

內胚層

ENDODERM

- Epithelial lining of digestive tract
- Epithelial lining of respiratory system
- Lining of urethra, urinary bladder, and reproductive system
- Liver
- Pancreas
- Thymus
- Thyroid and parathyroid glands

Germ Layers:

**Ectoderm,
Mesoderm,
Endoderm**

外胚層

中胚層

內胚層

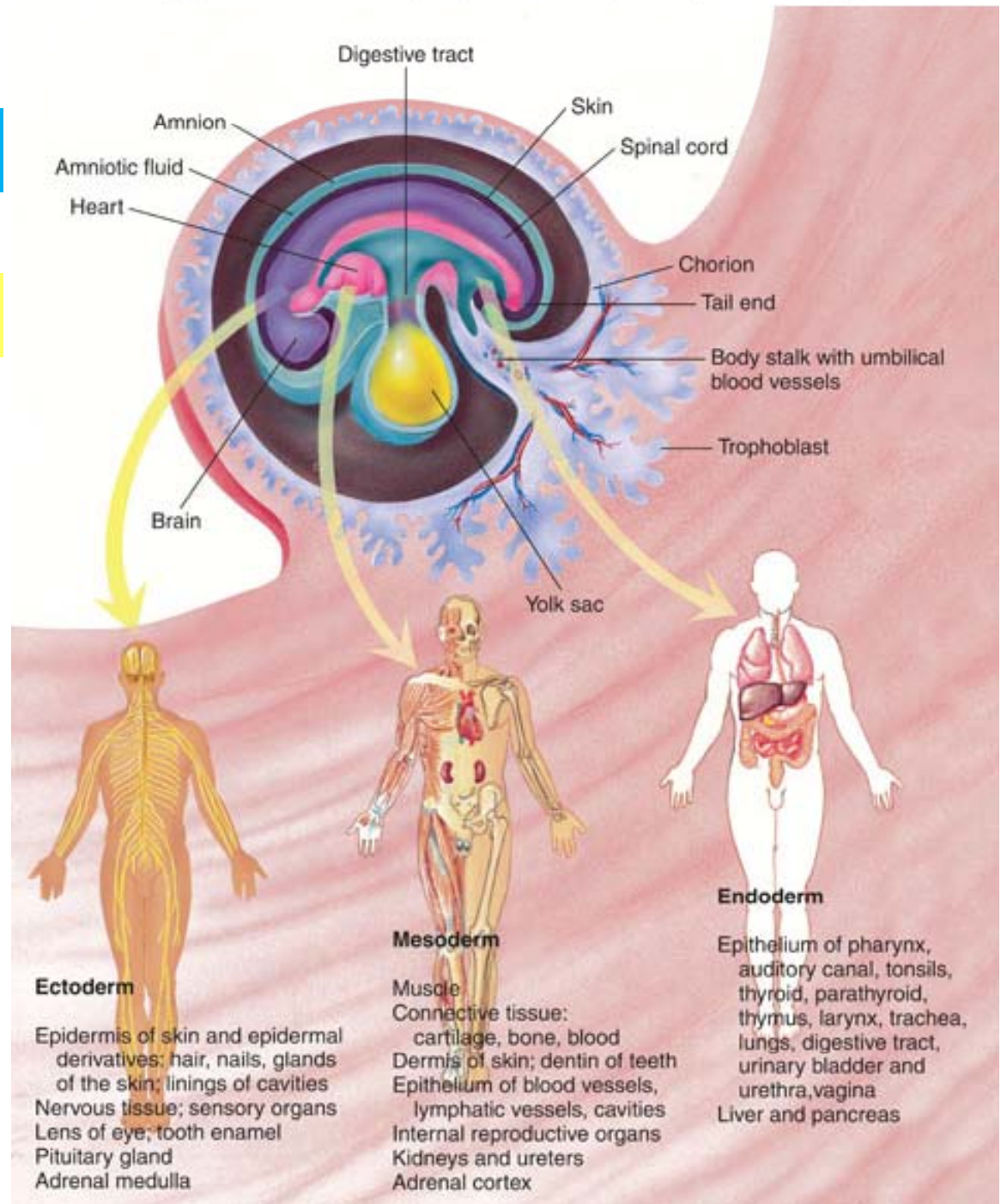


Figure 3.15 The primordial embryo. When the three basic layers of the embryo form at gastrulation, many cells become "fated" to follow a specific developmental pathway. However, each layer probably retains stem cells as the organism develops. Under certain conditions, these cells may produce daughter cells that can specialize as many cell types.

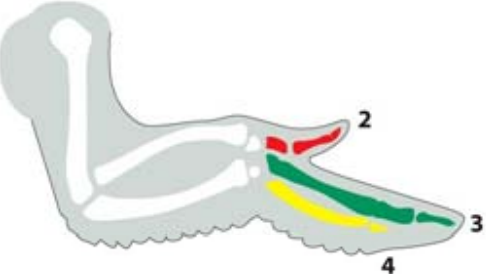
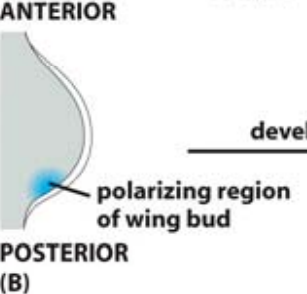
Organogenesis

Expression of Sonic hedgehog gene

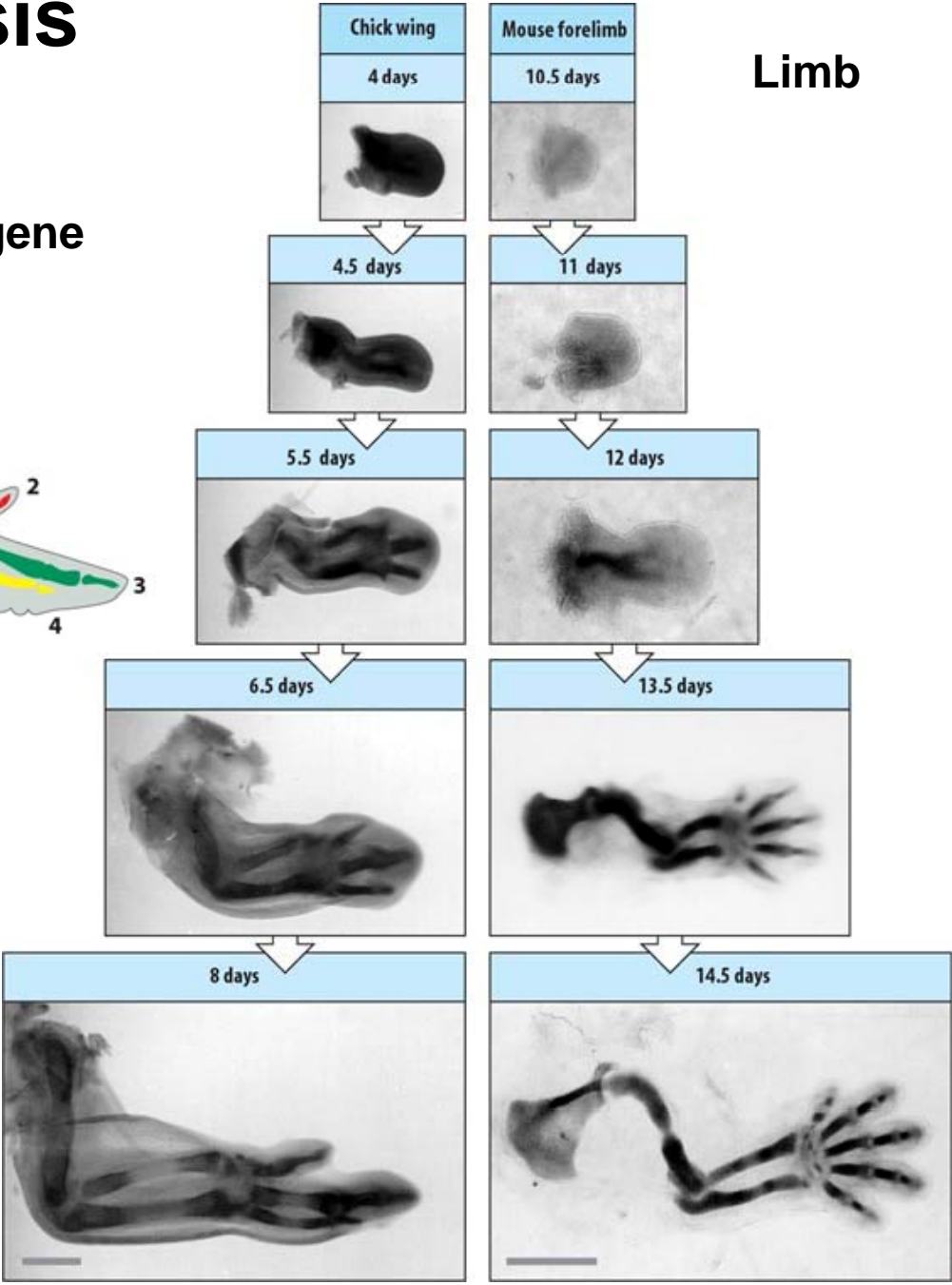
Limb



(A) 500 μm



develops into



thalidomide

「沙利竇邁」



在1997年，統計發現人類的新生兒中有2%的是畸形，這些缺陷的產生，有些是來自基因，另外的大宗，可能來自環境因子抑制了發育的過程。以1961年Lenz和Mcbride發現為例，他們證明一種用來鎮定孕婦憂鬱的藥(thalidomide)，會使新生兒四肢發育不全。Nowack(1965)研究發現，這藥物會在懷孕初期的20~36天左右，對四肢的發育產生抑制的作用，當時藥物包括台灣的遠東地區都有販售，因此可看見現年約40~50歲世代，有許多這樣的例子出現，造成許多悲劇與社會的成本，

Effect of reduced or no FGF10

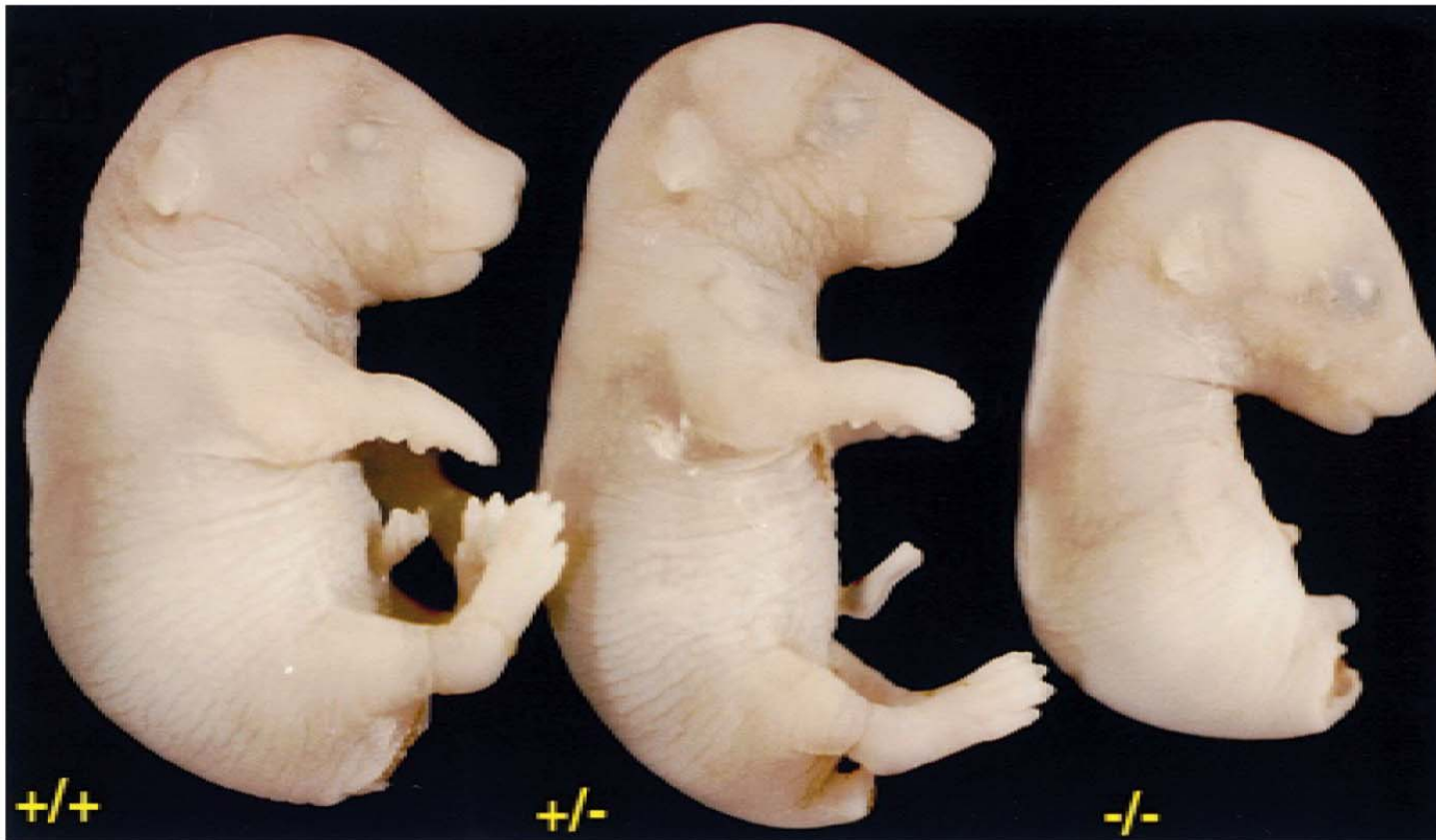
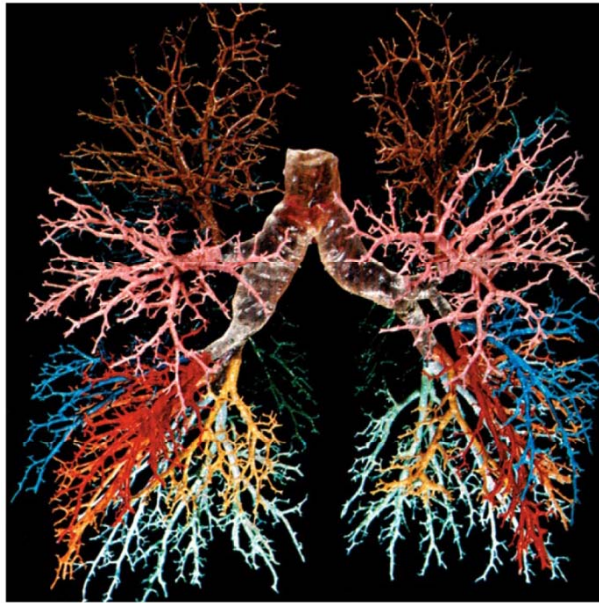
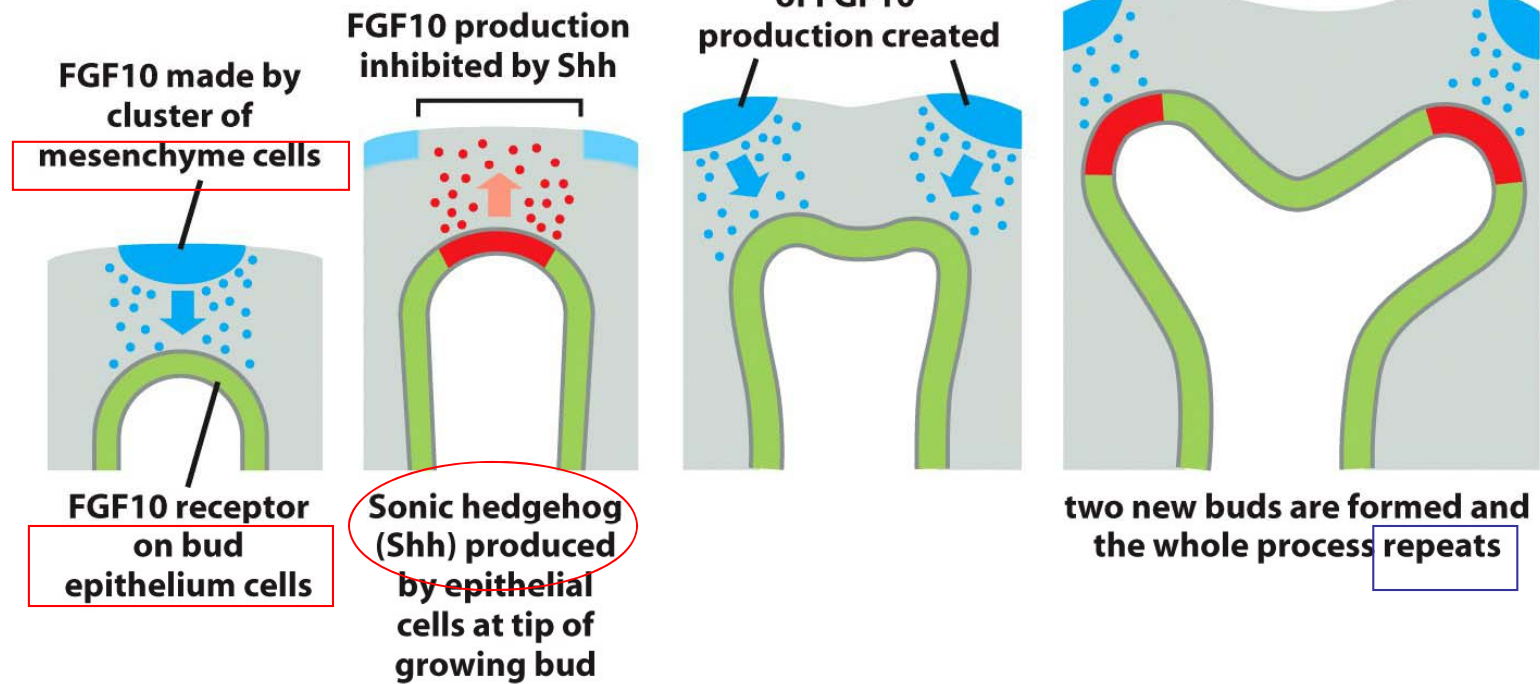


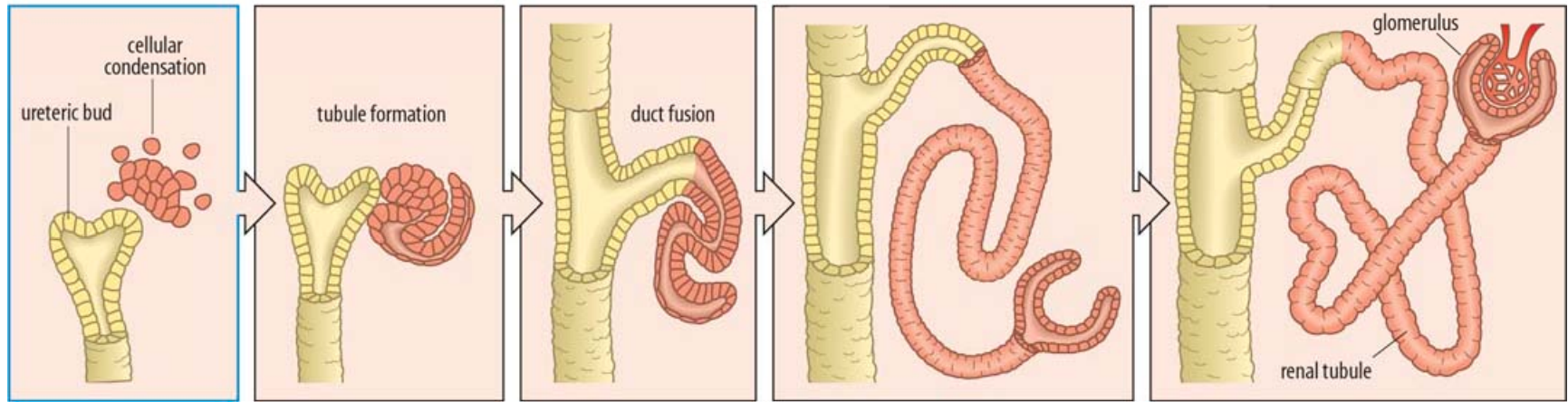
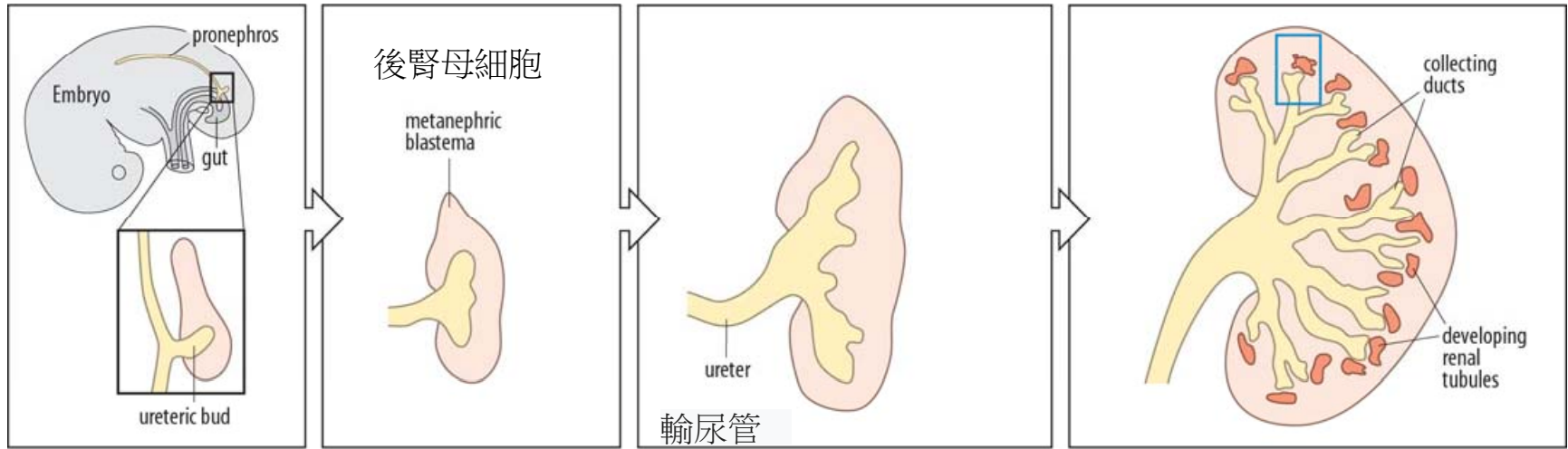
Figure 22-44a
Molecular Cell Biology, Sixth Edition
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Branching morphogenesis of lung mediated by FGF10 and Shh signaling

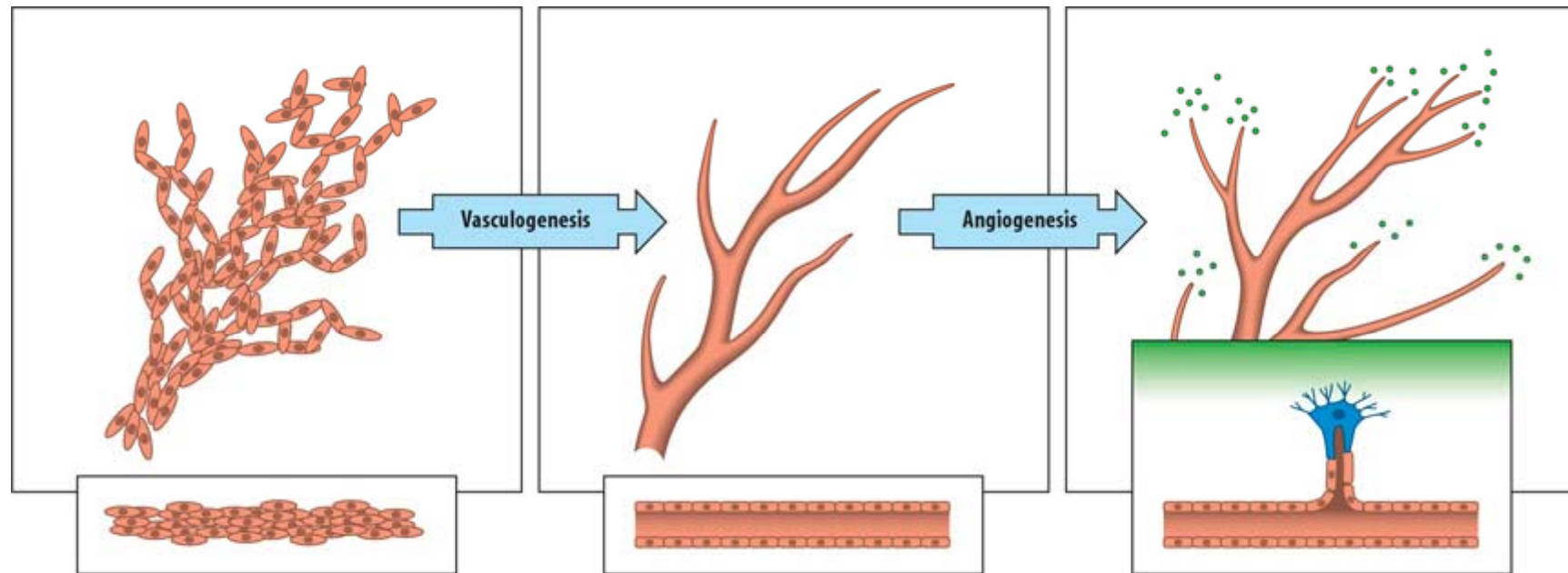


kidney



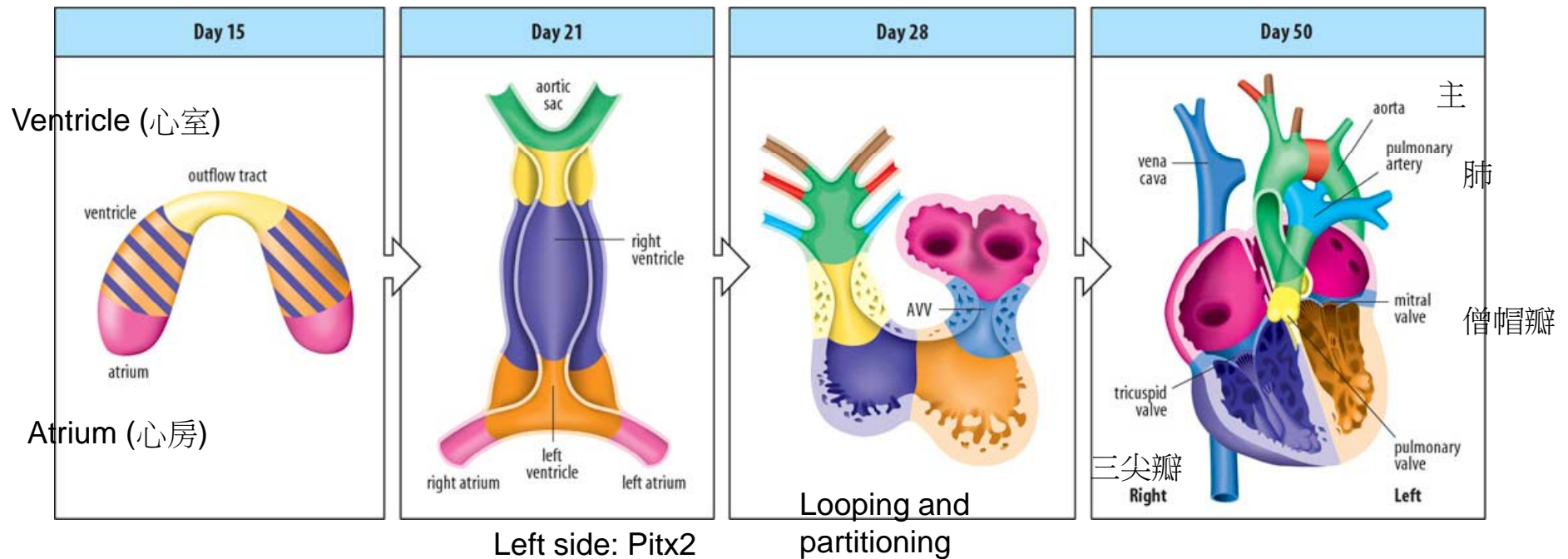
腎小管

Blood vessels



Angiogenesis and cancer

Schematic of human heart development



BMP → Nkx2.5 Transcription factor (7 activating regions and 3 repressor regions)
 Retinoic acid
 GATA

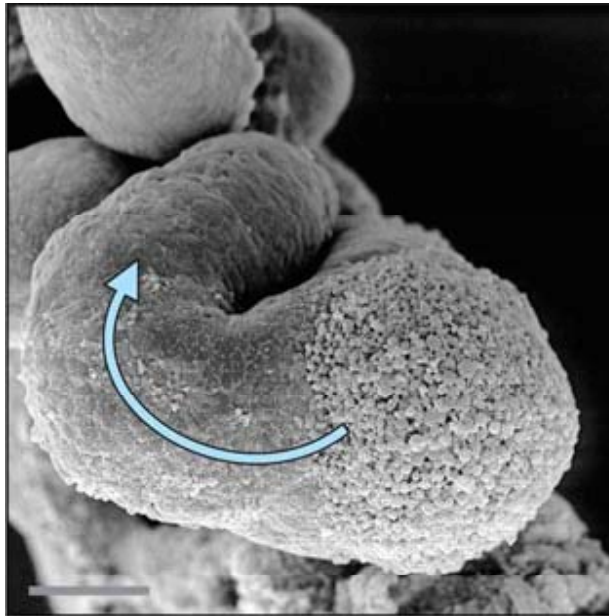
Turn cardiac cell differentiation gene expression

Organ handedness in vertebrates

In the mouse, the **iv gene** controls the handedness of internal organs. In **iv mutants**, organ handedness is random and some individuals show heterotaxis where normal and inverted organs are found in one animal.

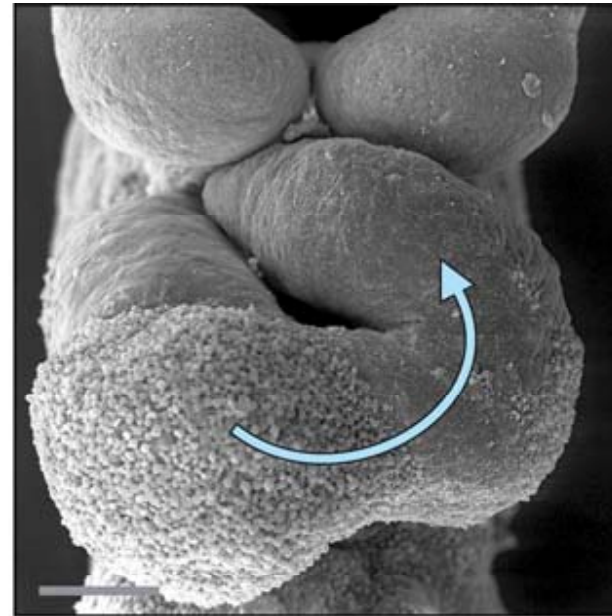
Heterotaxis (内臓易位): The organs of inverted normal and asymmetry are present in the same animal

Normal



It loops to the right

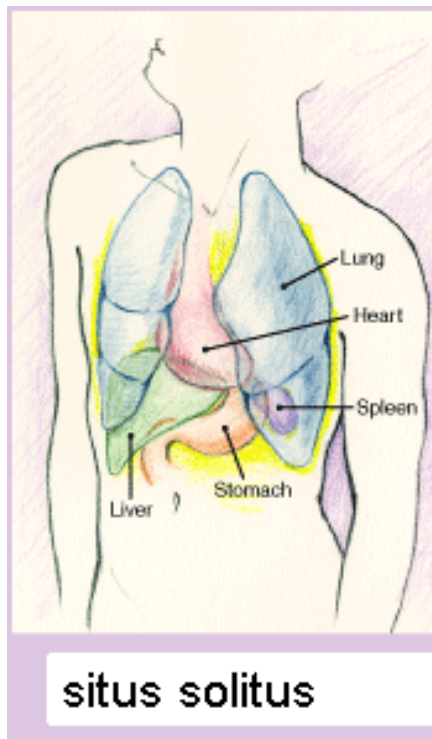
iv mutant



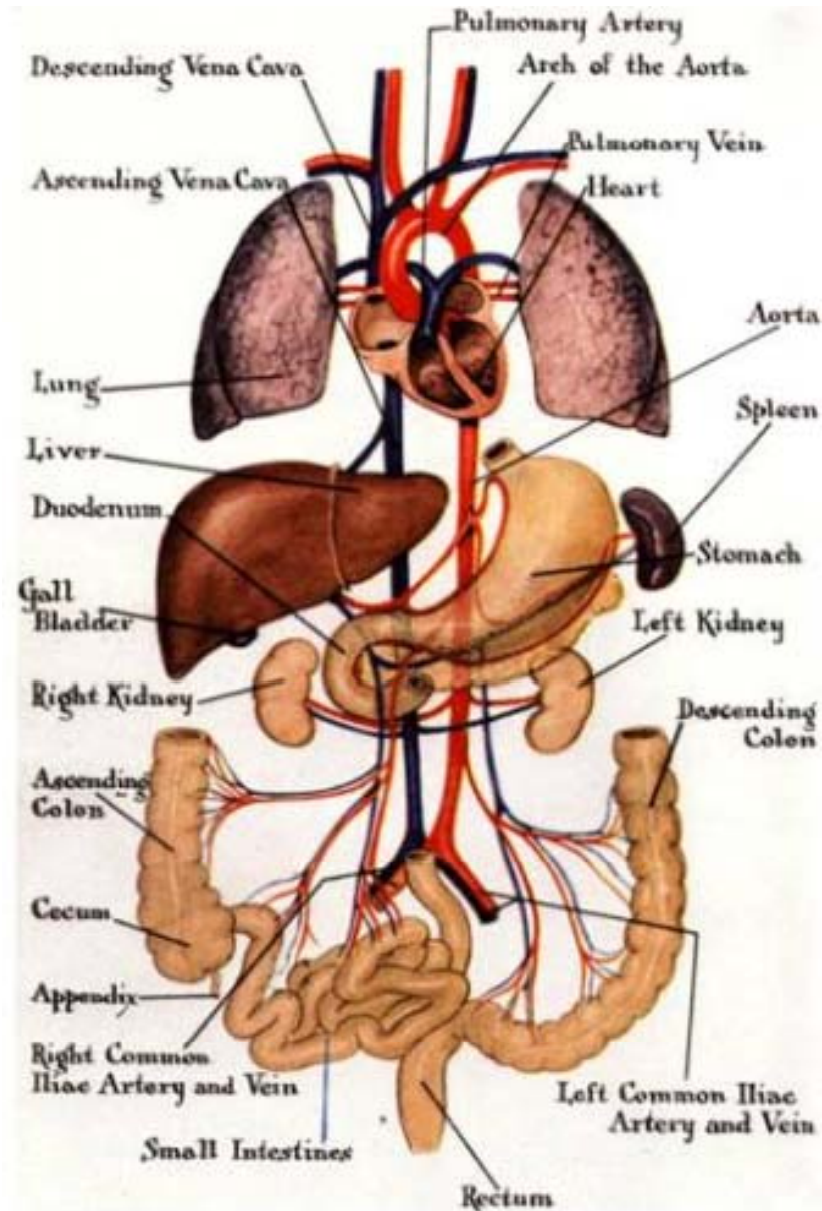
It loops to the left

The condition, *situs inversus*, found in 1 in 10,000 people, is a mirror reversal of the 'handedness' of the internal organs.

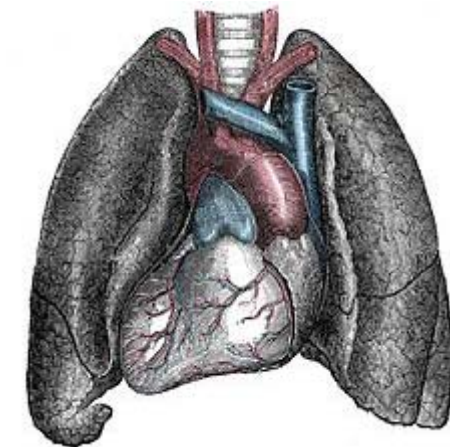
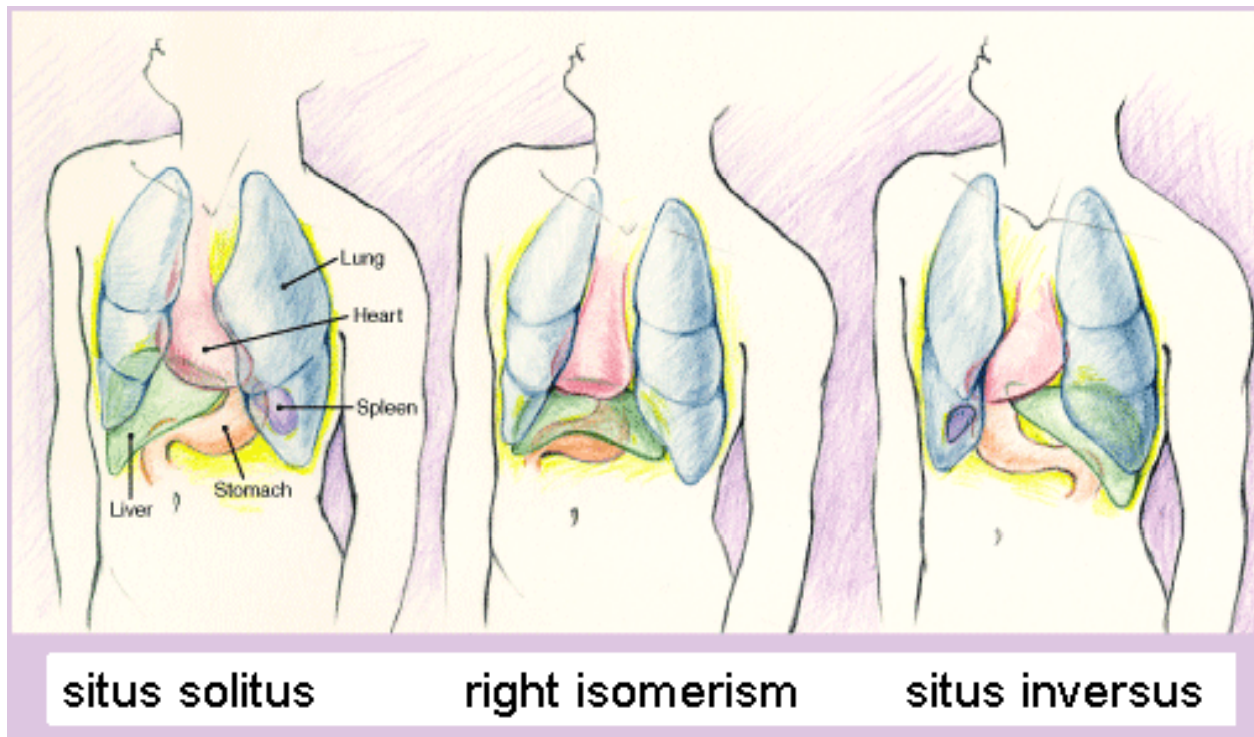
器官轉位



心臟偏左，
肺葉左二，右三葉，
腹腔右邊的器官是肝臟，膽囊，
腹腔左側的器官是脾臟，胃



The condition, *situs inversus*, found in 1 in 10,000 people, is a mirror reversal of the 'handedness' of the internal organs.



Situs inversus causes the positions of the heart and lungs to be mirrored.

心臟偏左，
肺葉左二，右三葉，
腹腔右邊的器官是肝臟，膽囊，
腹腔左側的器官是脾臟，胃

兩邊都是右邊的臟器

器官整個左右相反

動物發育的主要過程

1. 受精 (Fertilization)
2. 卵裂 (Cleavage)
3. 原腸化 (Gastrulation)
4. 神經 (Neurulation)
5. 器官生成 (Organogenesis)
6. 個體生成 (Growth)

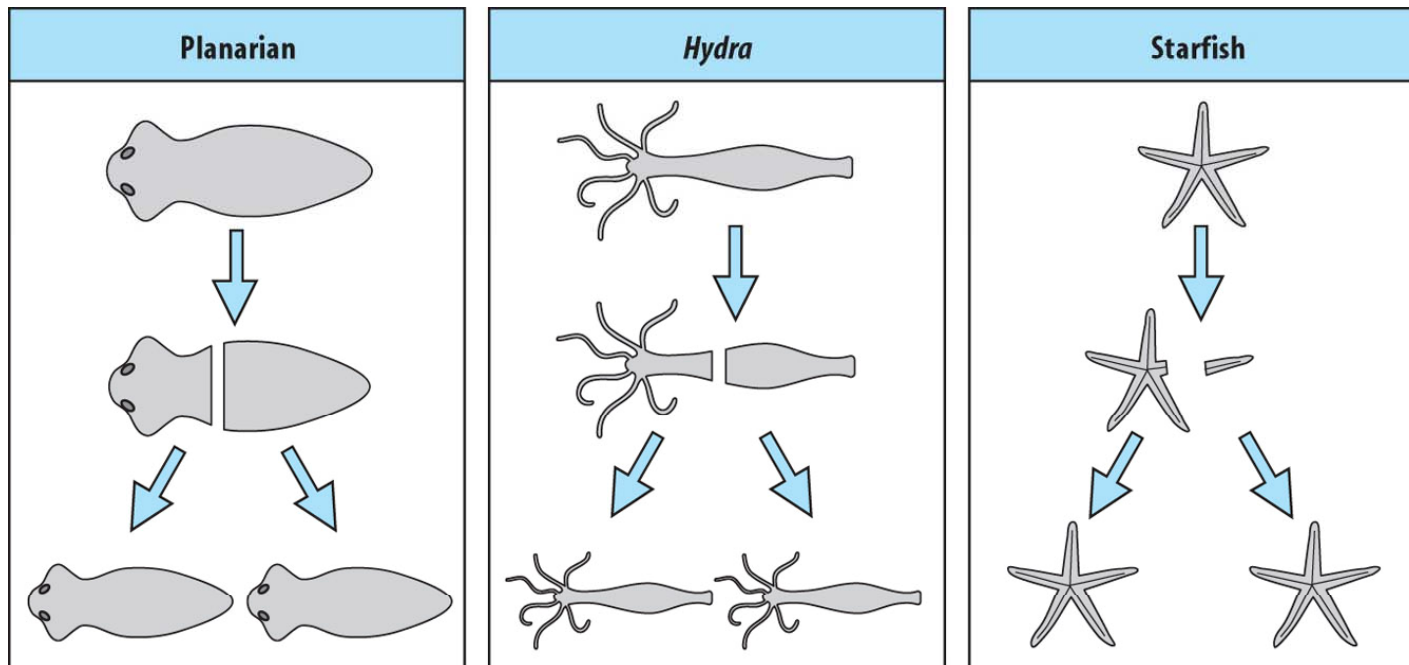
Pattern/ hair, spots, stripe

?



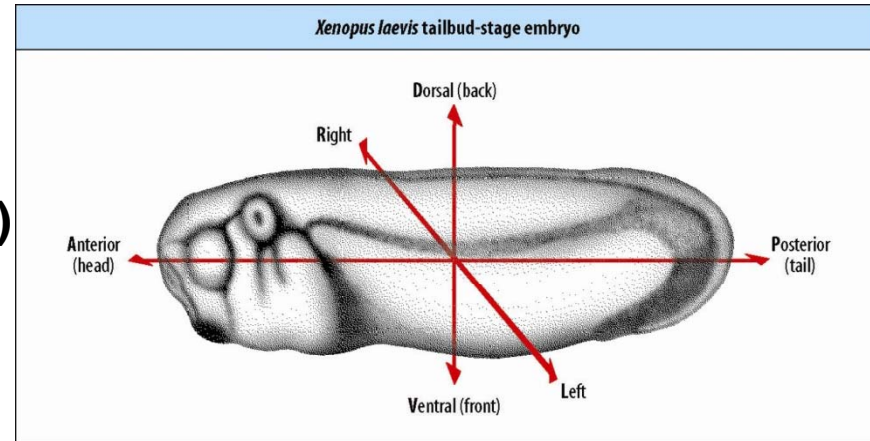
Outline

1. 胚胎學 (embryology) vs. 發育生物學 (developmental biology)
2. 模式生物 (model organisms)
3. 動物發育的主要階段
4. 發育過程之機制
5. 組織再生與幹細胞



發育過程包括

- Pattern formation (body plan)
- Morphogenesis (型態)
- Cell differentiation (分化)
- Growth (生長)



體軸

前/後軸(A/P axis)

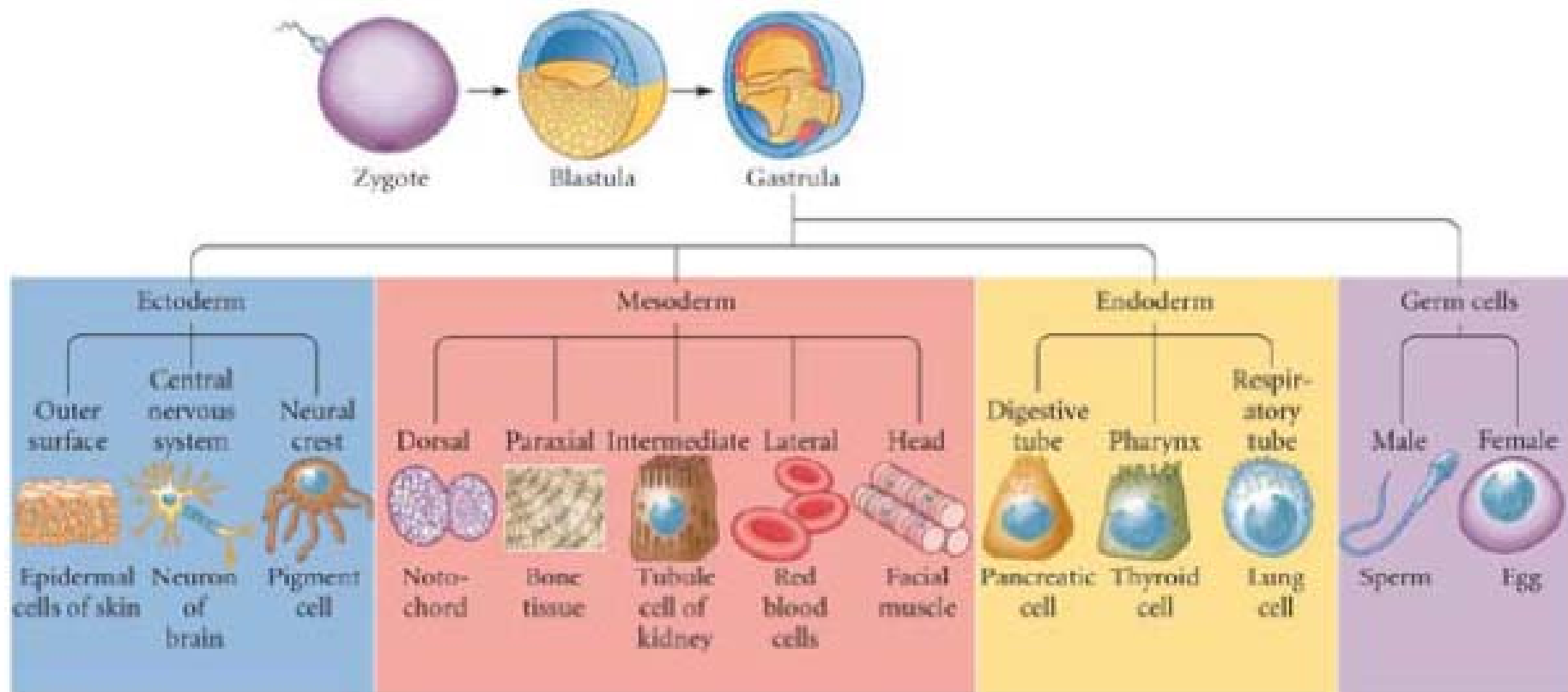
背/腹軸(D/V axis)

左/右軸(L/R axis)

4. 發育過程之機制

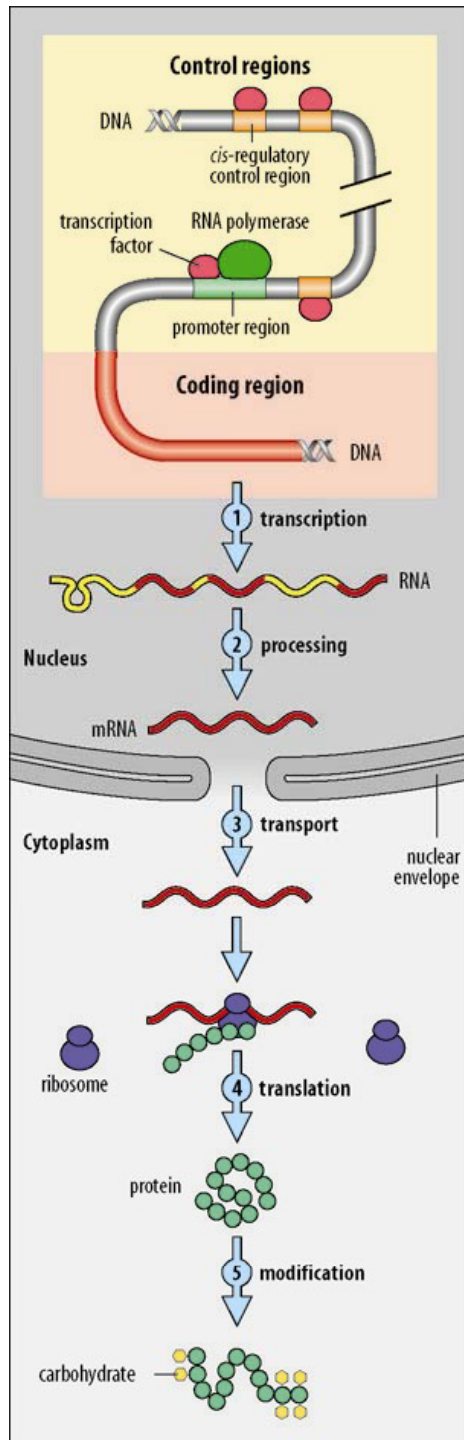
1. Differential gene expression/signaling (基因表現)
2. Cell fate determination 細胞命運決定
3. Induction 誘導
4. Pattern formation
 - a. Positional information
 - b. Lateral inhibition
5. Asymmetric division (不對稱分化)

4.1. Differential gene expression causes cell differentiation



Representative cell types of a vertebrate

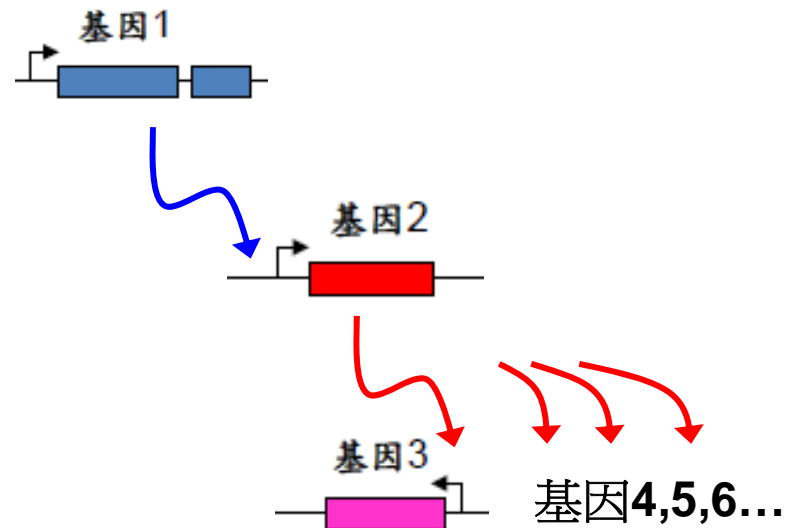
人類有**100億**cells, **250種**不同類型的細胞
線蟲**952 cells**.



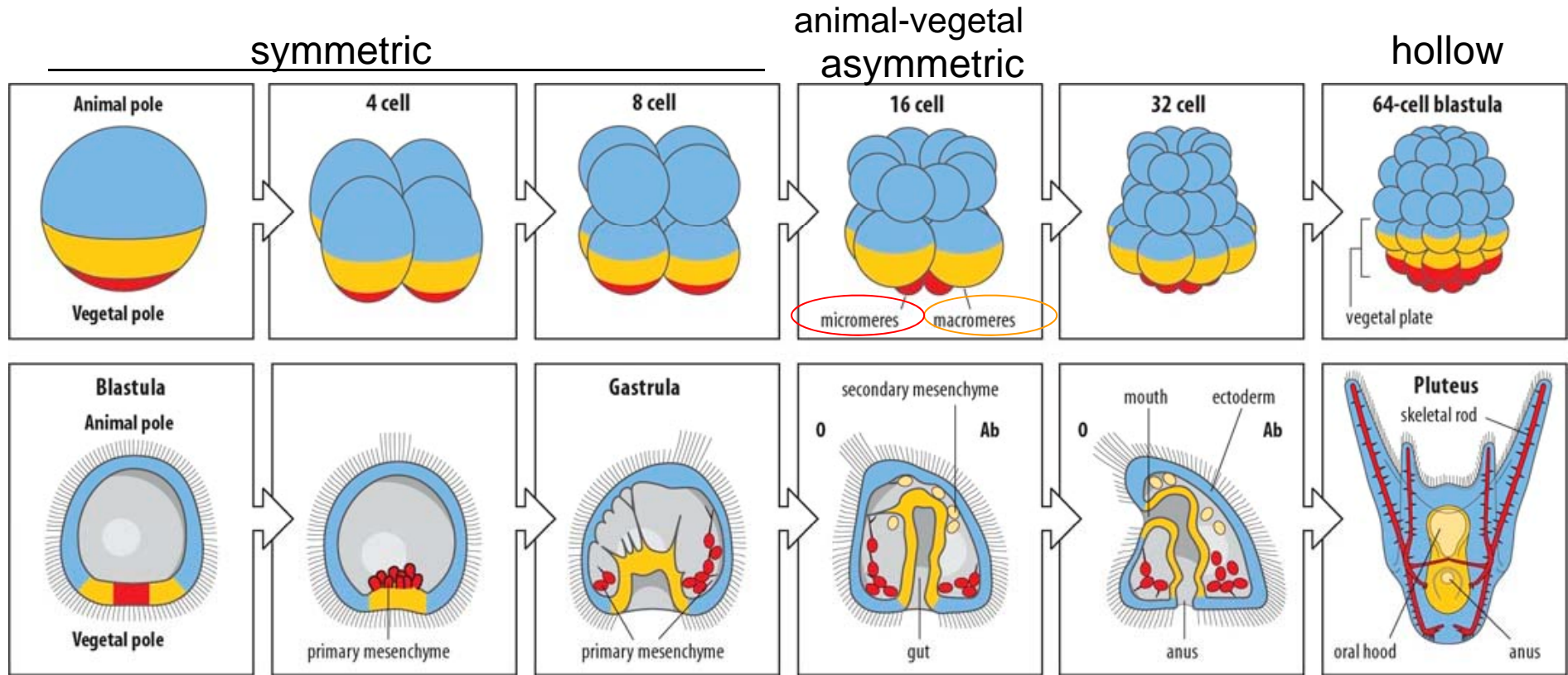
Gene expression and protein synthesis

In the early development of *Drosophila*, at least 60 genes are directly involved in pattern formation to form segments.

In *C. elegans*, at least 50 genes are needed to specify vulva (reproductive structure). About 9% of the genes (1722/ 20,000) are involved in development.



Development of the sea urchin embryo.



初級間質

gut invaginate

骨棒(中胚層)

Blue: prospective ectoderm

Yellow: endoderm

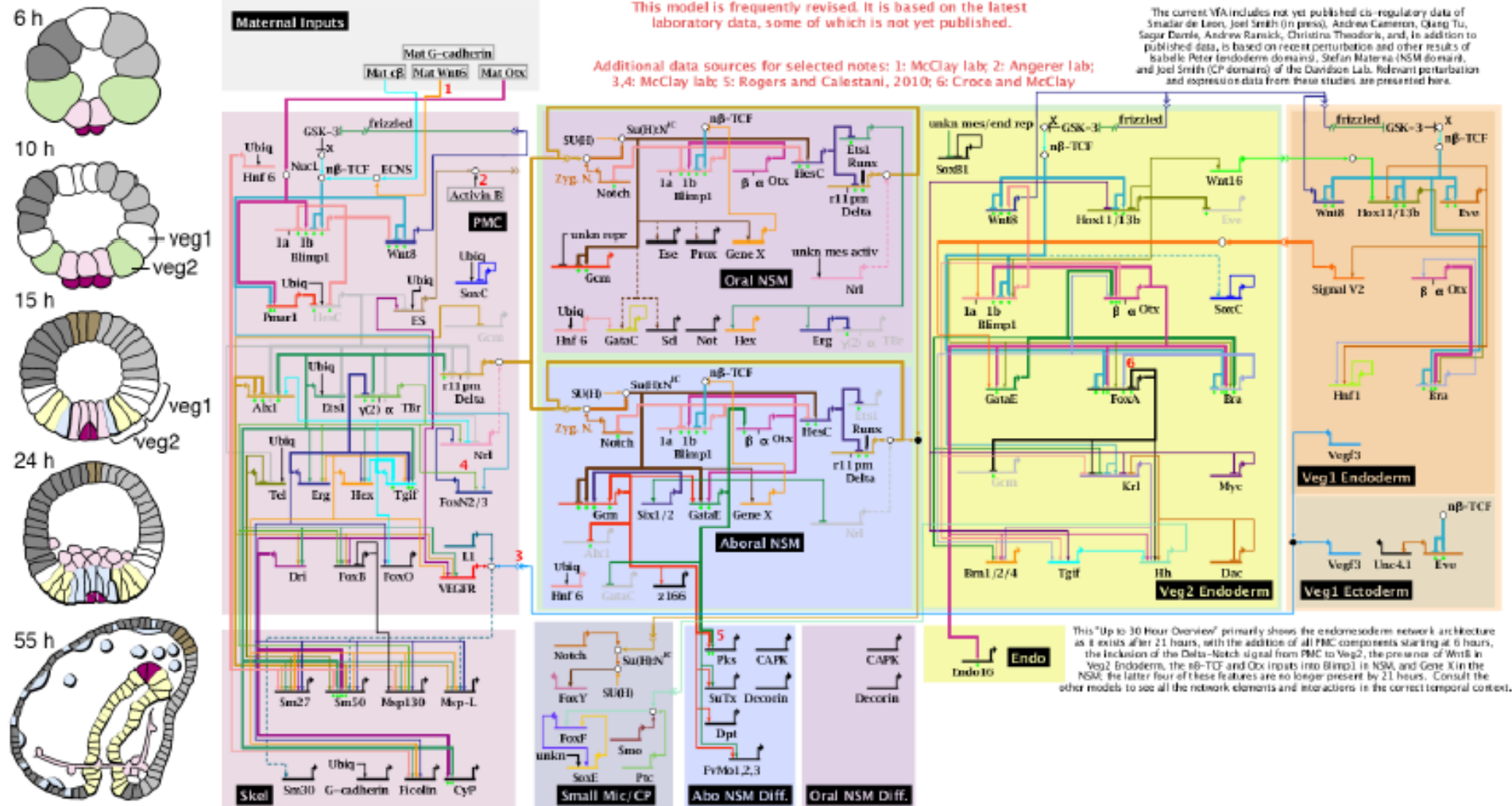
Red: mesoderm

二級間質

海膽胚胎的中內胚層發育基因調控網路

Endomesoderm Specification up to 30 Hours

November 21, 2011



This model is frequently revised. It is based on the latest laboratory data, some of which is not yet published.

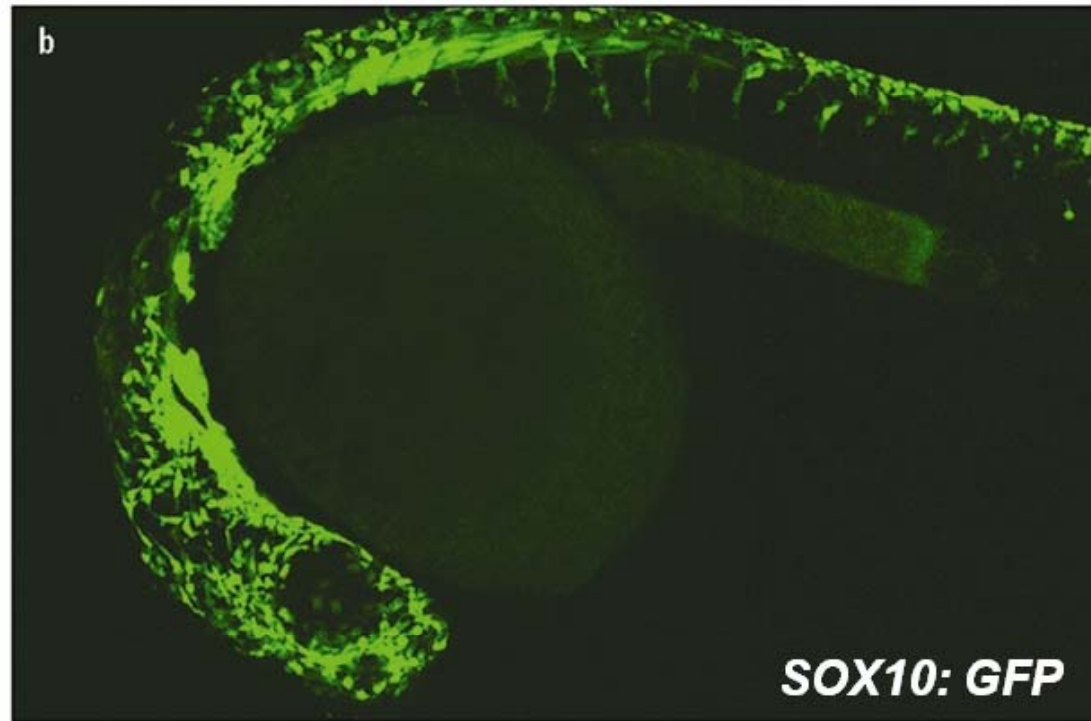
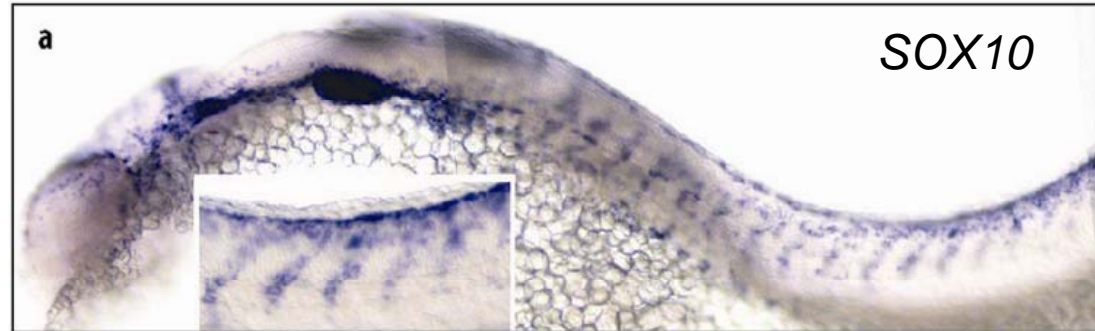
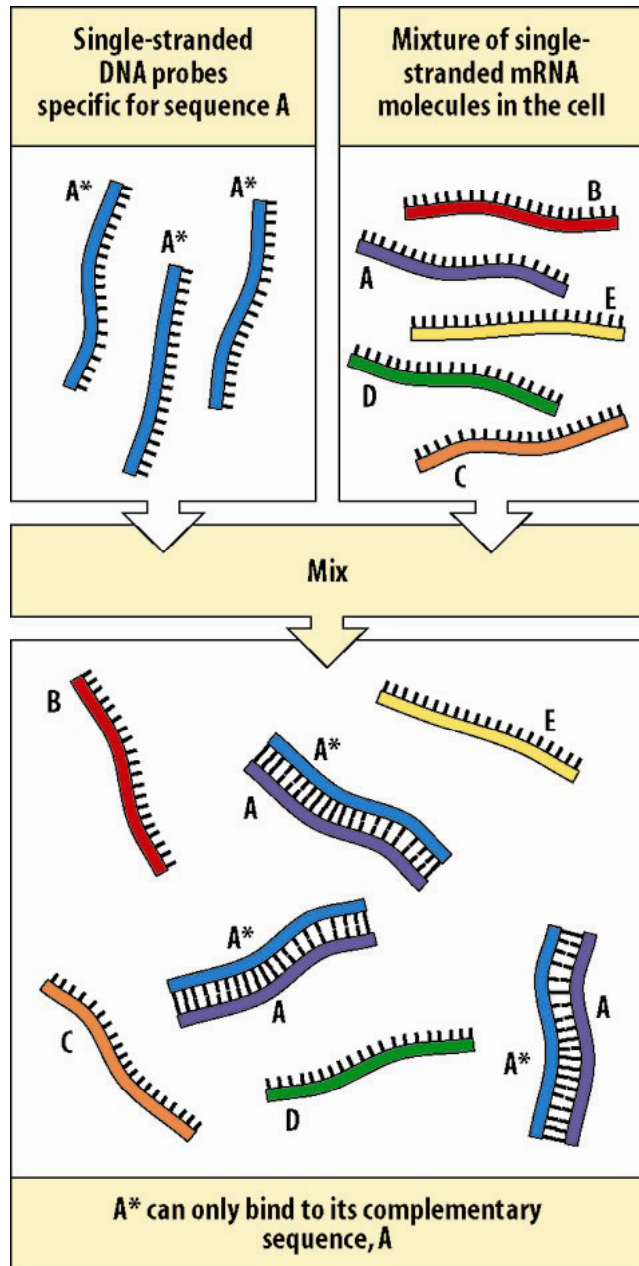
Additional data sources for selected notes: 1: McClay lab; 2: Angerer lab; 3,4: McClay lab; 5: Rogers and Calestani, 2010; 6: Croce and McClay

The current VFA includes not yet published cis-regulatory data of Smadar de Leon, Joel Smith (in press), Andrew Cameron, Qiang Tu, Sagor Dornik, Andrew Ramick, Christina Theodoris, and, in addition to published data, is based on recent perturbation and other results of Isabelle Peter (endomesoderm domains), Stefan Materna (NSM domain), and Joel Smith (CP domains) of the Davidson Lab. Relevant perturbation and expression data from these studies are presented here.

Ubq=ubiquitous; Mat = maternal; actv = activator; rep = repressor; unkn = unknown; NucL = nuclearization; x = β-catenin source; nβ-TCF = nuclearized β-catenin-Tcf; ES = early signal; ECNS = early cytoplasmic nuclearization system; Zyg. N. = zygotic Notch

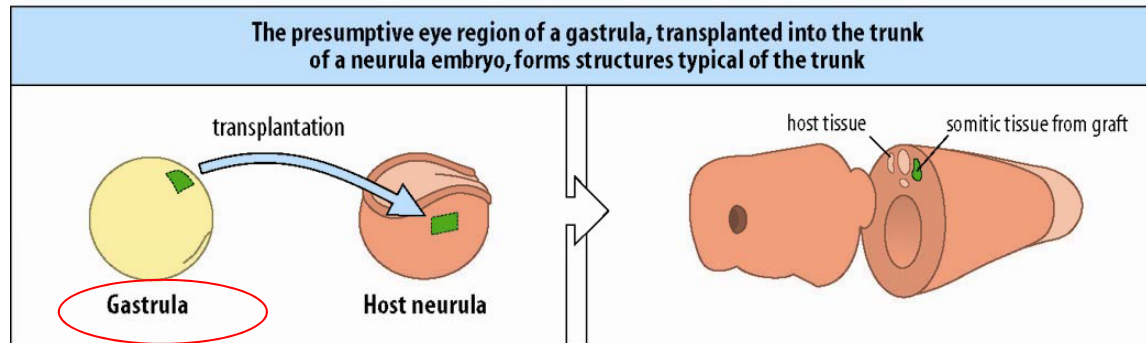
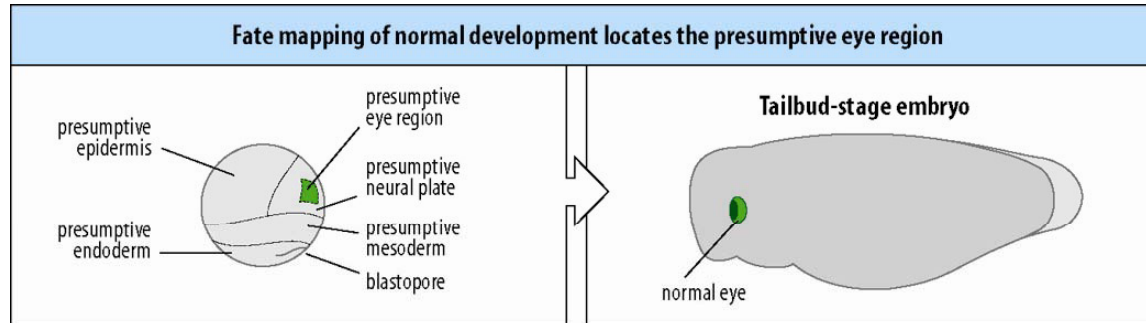
Copyright © 2001-2011 Hamid Belouiri and Eric Davidson

Study (tracking) gene expression in embryos

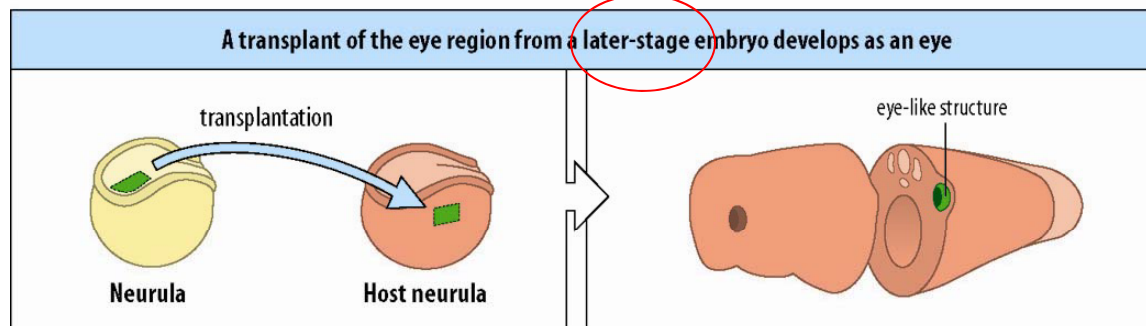


4.2. Cell fate determination

Cell transplantation



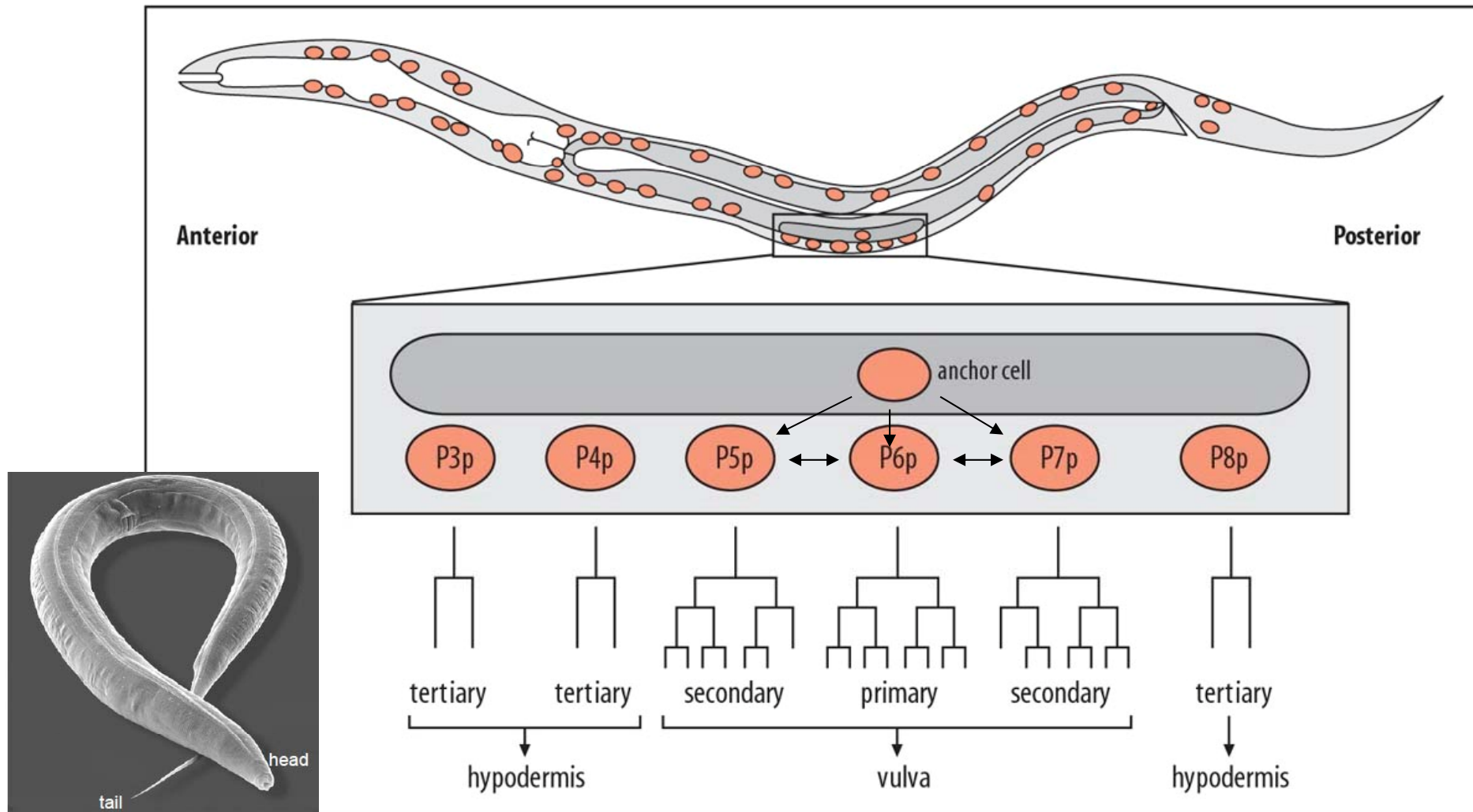
earlier stage: not determined



later stage: determined

2. Cell fate determination

Cell-lineage analysis

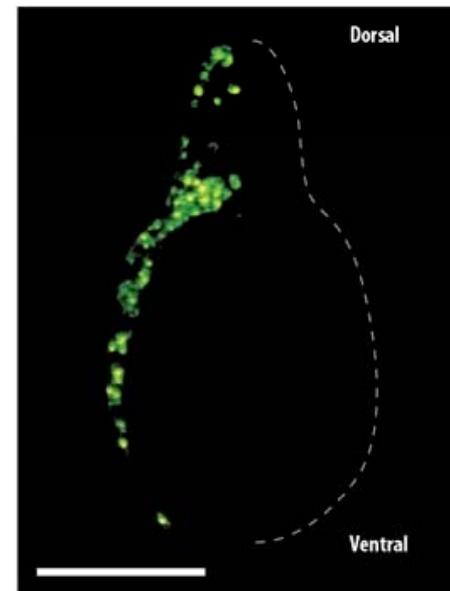
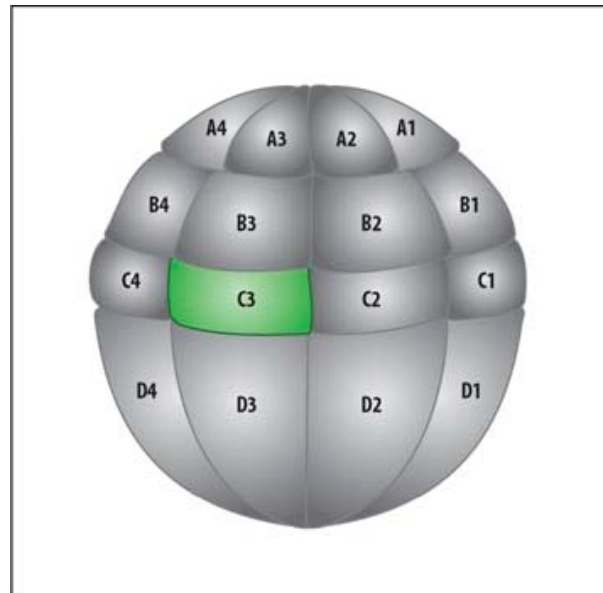
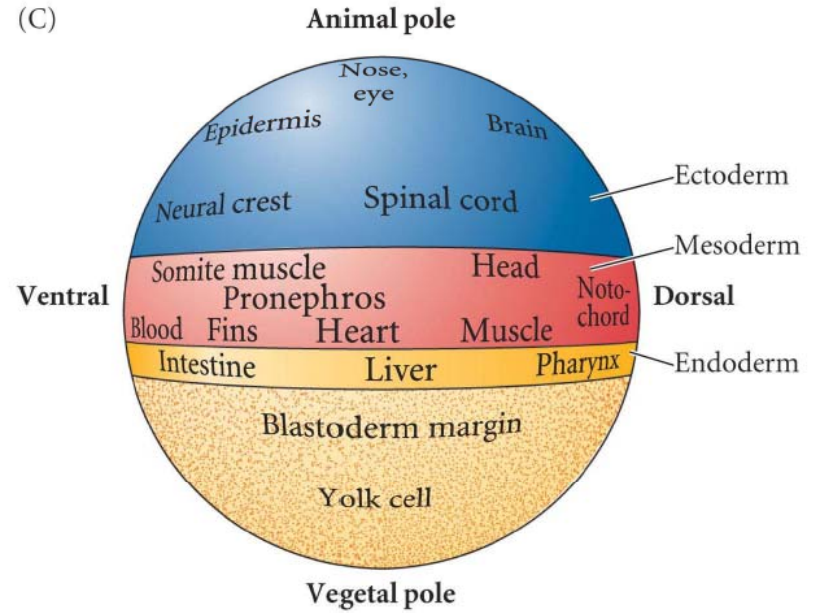


Development 4e

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University Press

4. 2. Cell fate determination

GFP labeled or Laser caged

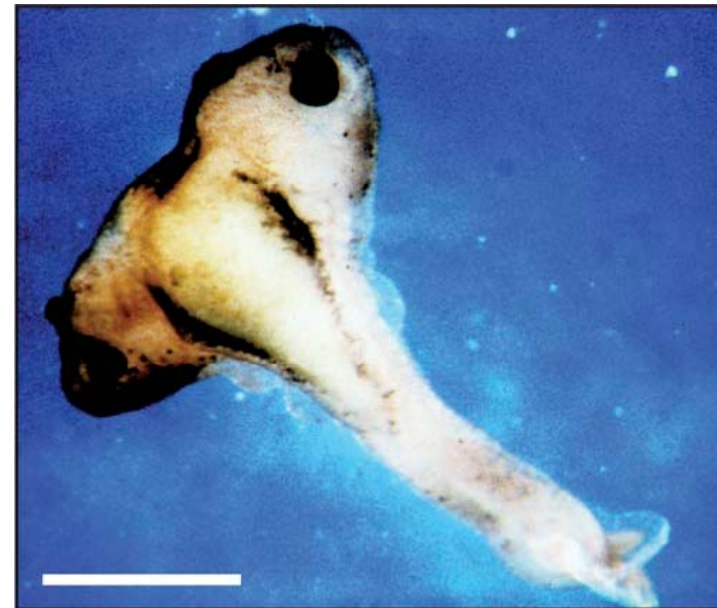
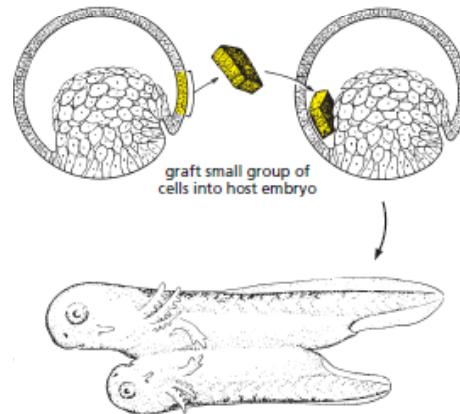
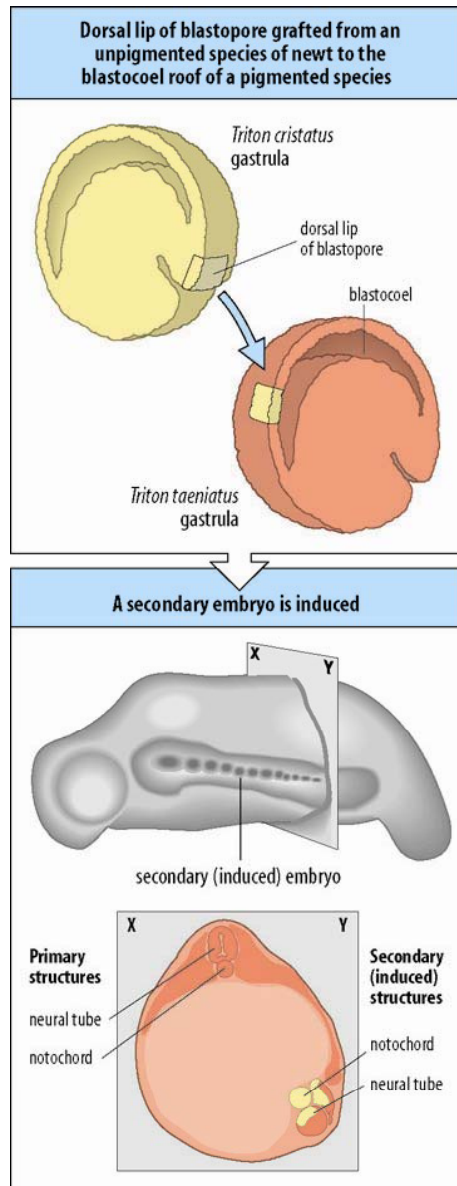


3. Induction

One group of cells could determine the development of neighboring cells

Spemann and Mangold experiment

(Spemann organizer, 1935 Nobel Prize)



The vertebrate eye develops from the neural tube and the ectoderm of the head

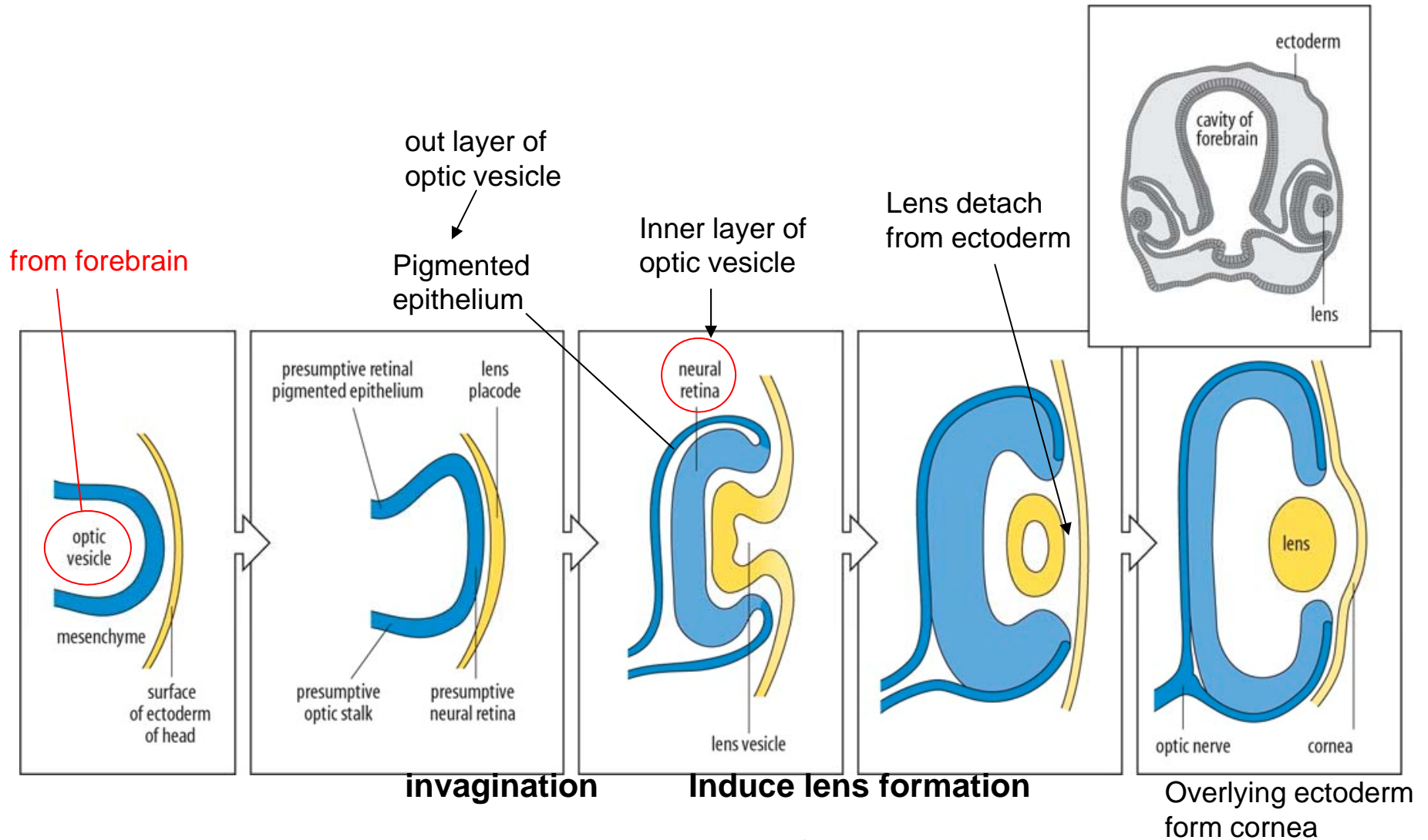


Fig. The main stages in the development of the vertebrate eyes

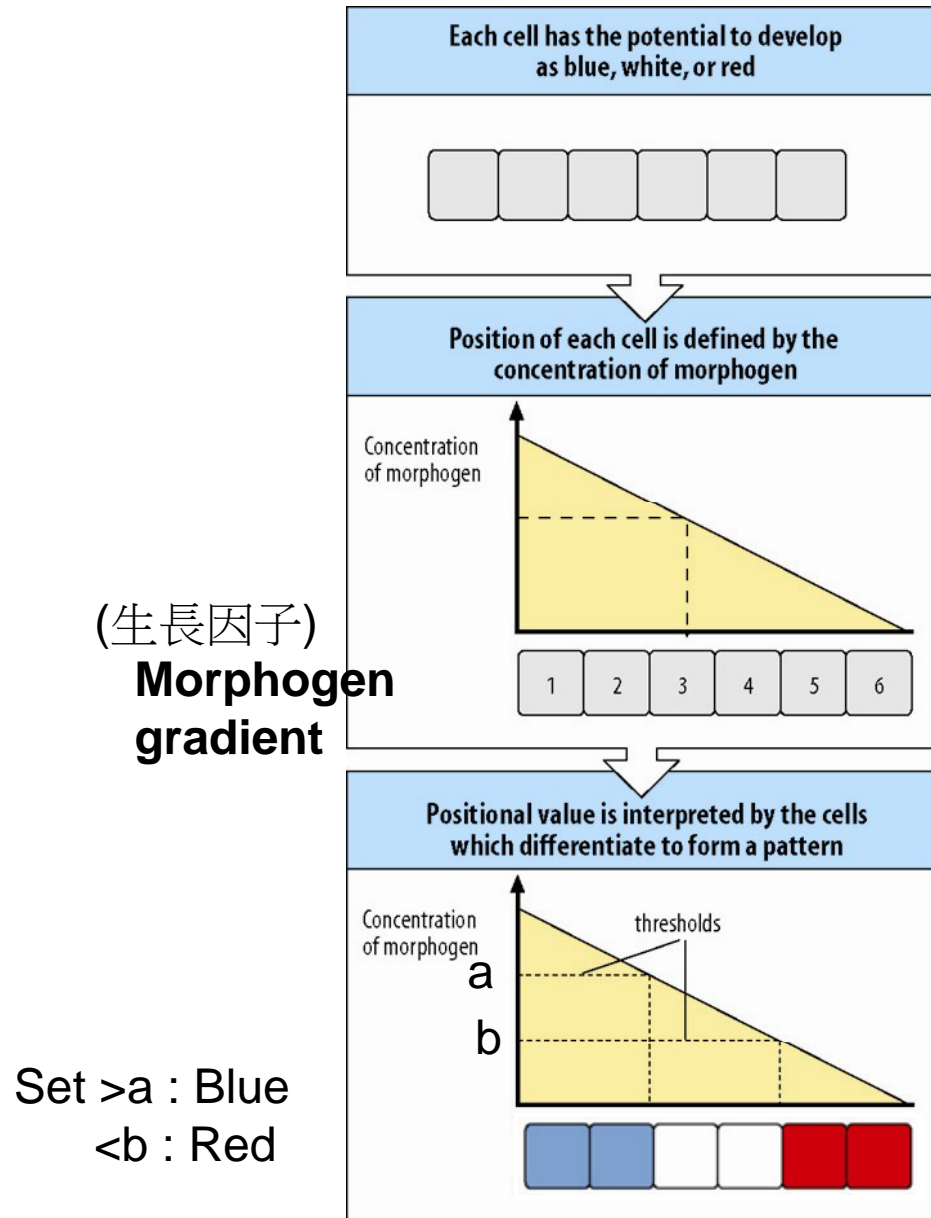
4. Pattern formation

a. Positional information

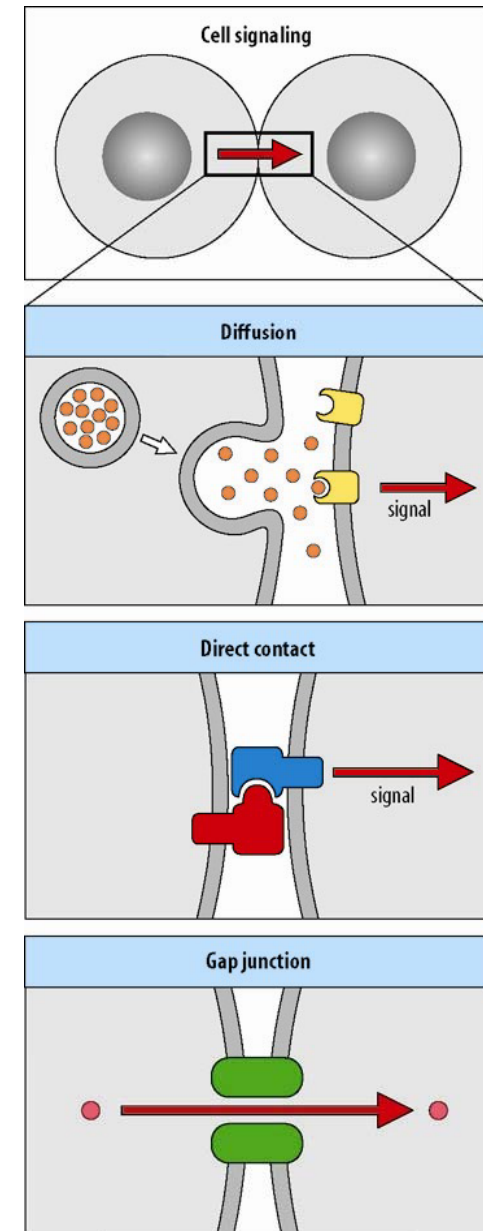


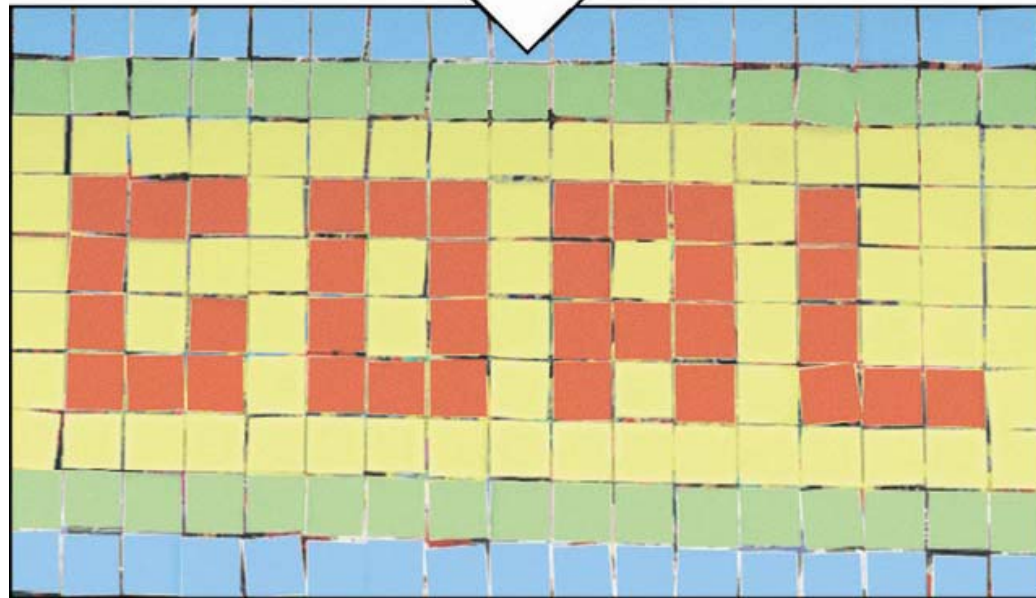
4. Pattern formation

a. Positional information

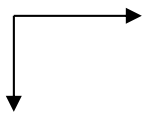


cell-cell communication

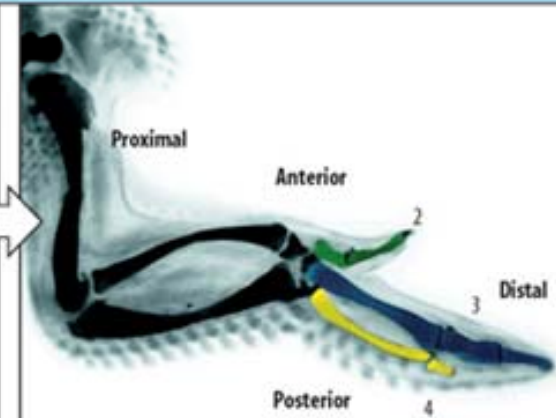
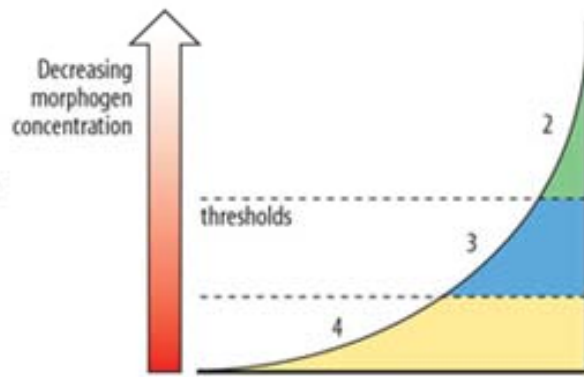
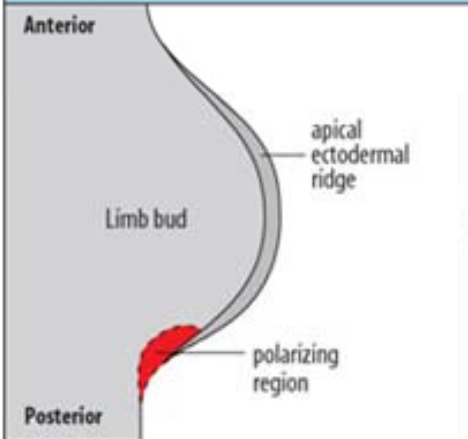




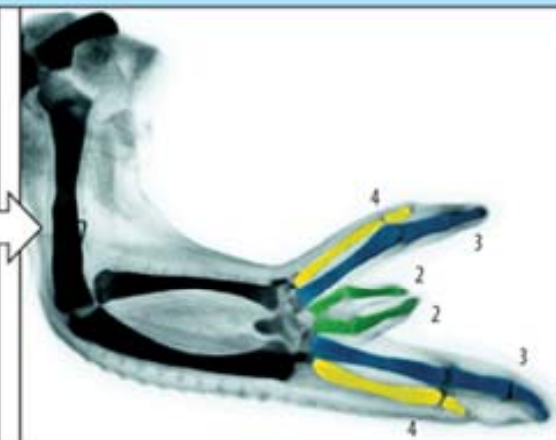
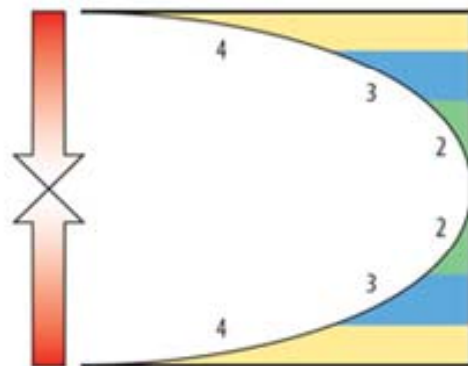
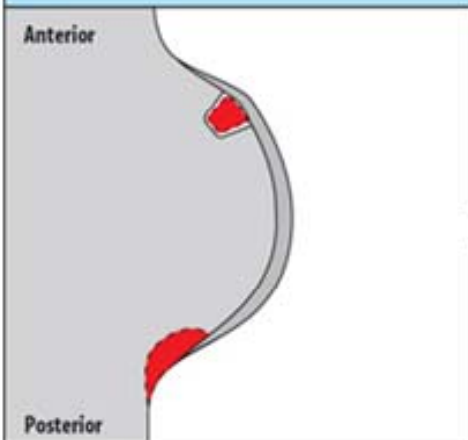
2D



Normal limb



Additional polarizing region grafted to anterior margin



Synpolydactyly (SPD), caused by mutations in *HOXD 13*, is characterized by extra fingers and toes and bone abnormalities in the hands and feet



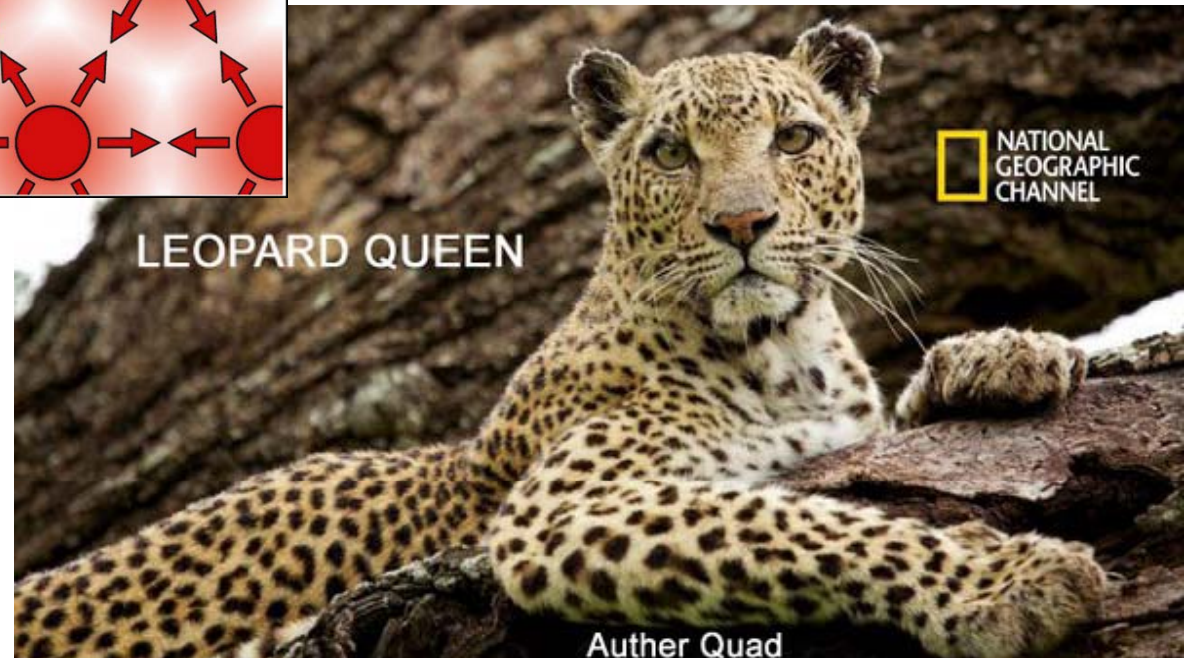
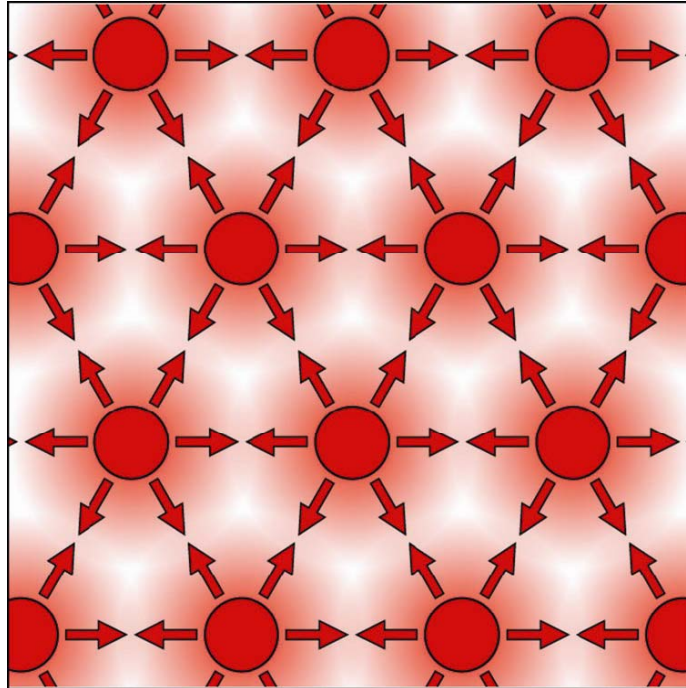
Mutations that affect antero-posterior patterning can cause polydactyly. With **preaxial polydactyly** has mutations in the *SHH* gene



4. Pattern formation (spacing patterns)

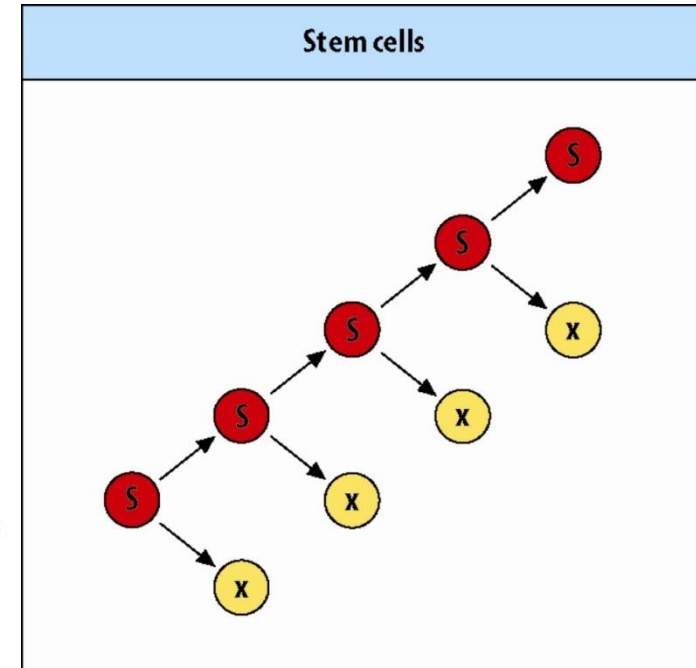
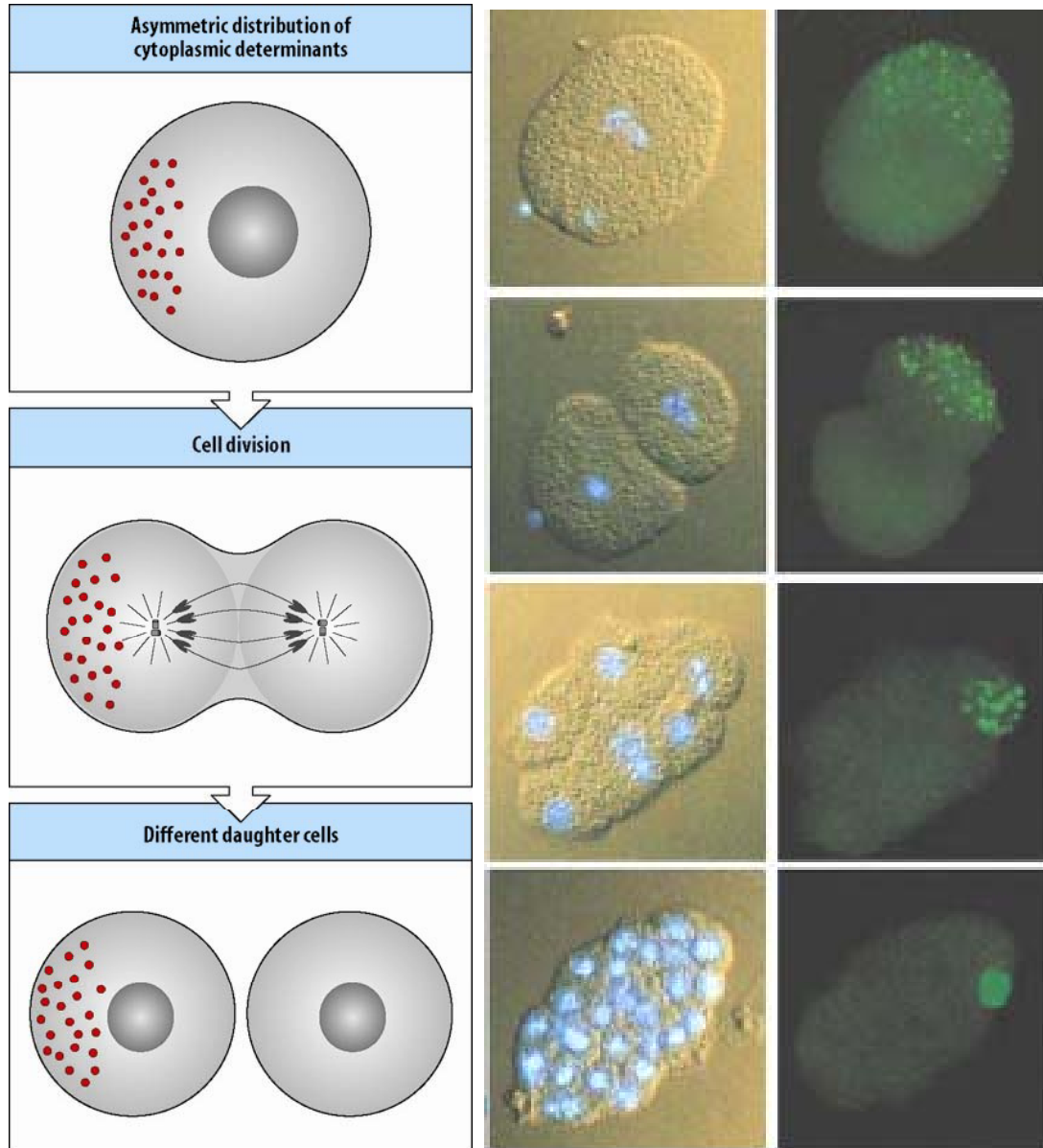
b. Lateral inhibition

Bird's skin, animal's spots



5. Asymmetric division

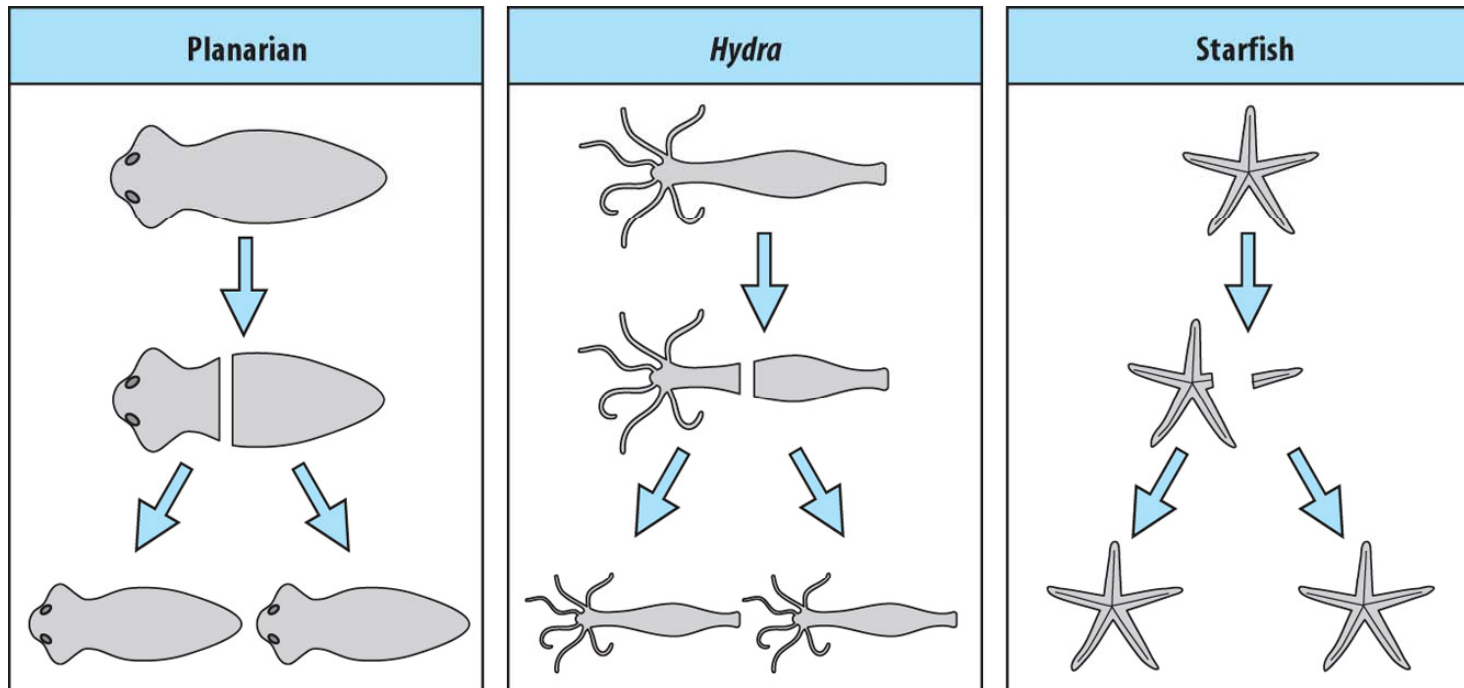
Cytoplasmic determinant



germline cell marker (green)
Cell nuclear (blue)

Outline

1. 胚胎學 (embryology) vs. 發育生物學 (developmental biology)
2. 模式生物 (model organisms)
3. 動物發育的主要階段
4. 發育過程之機制
5. 組織再生與幹細胞

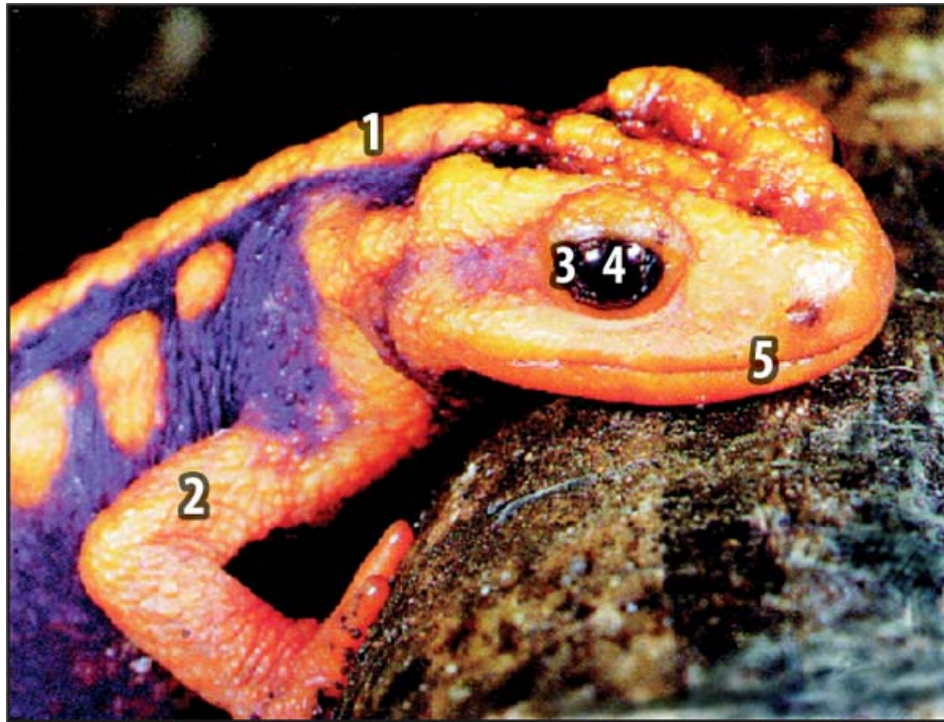
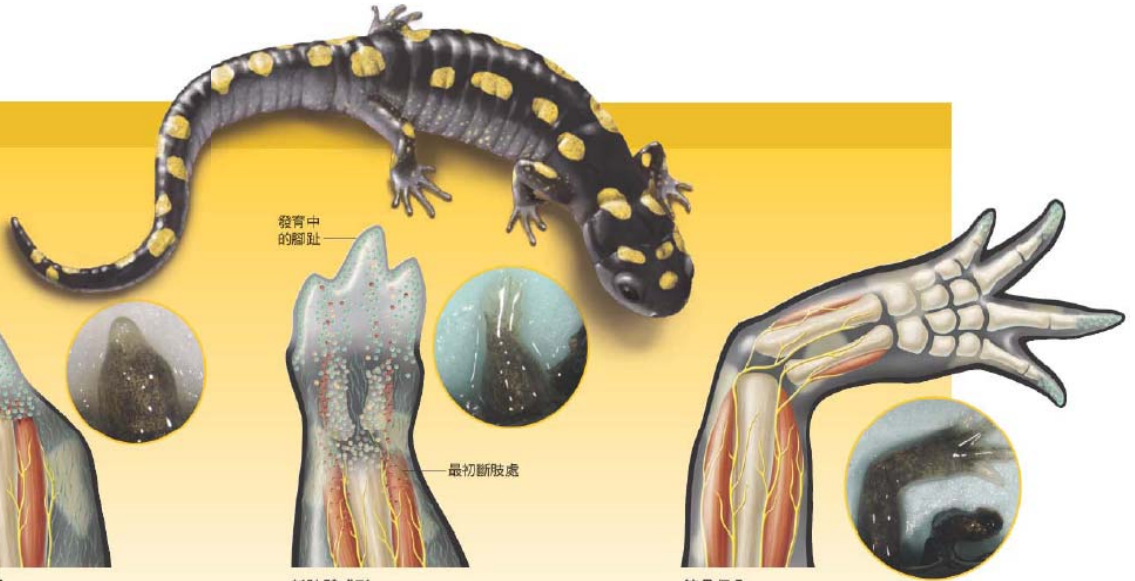
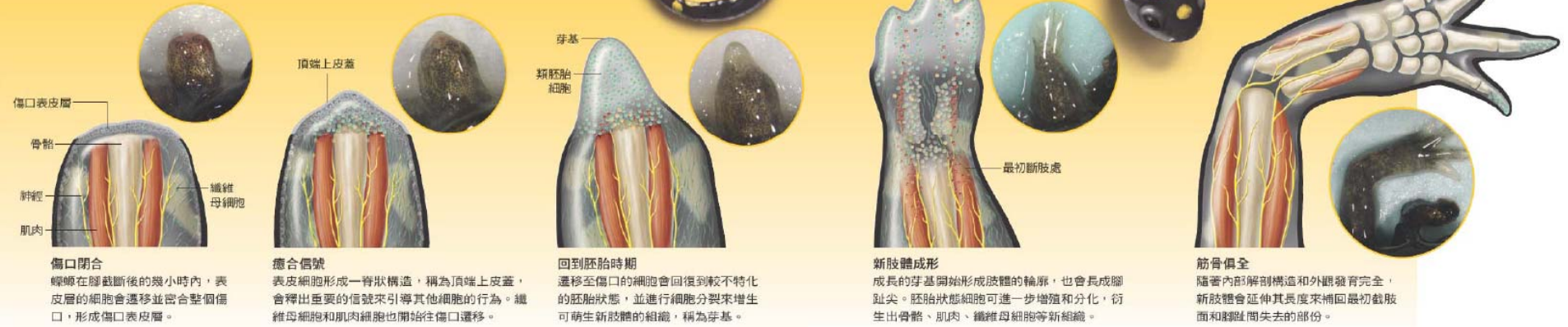


再生典範

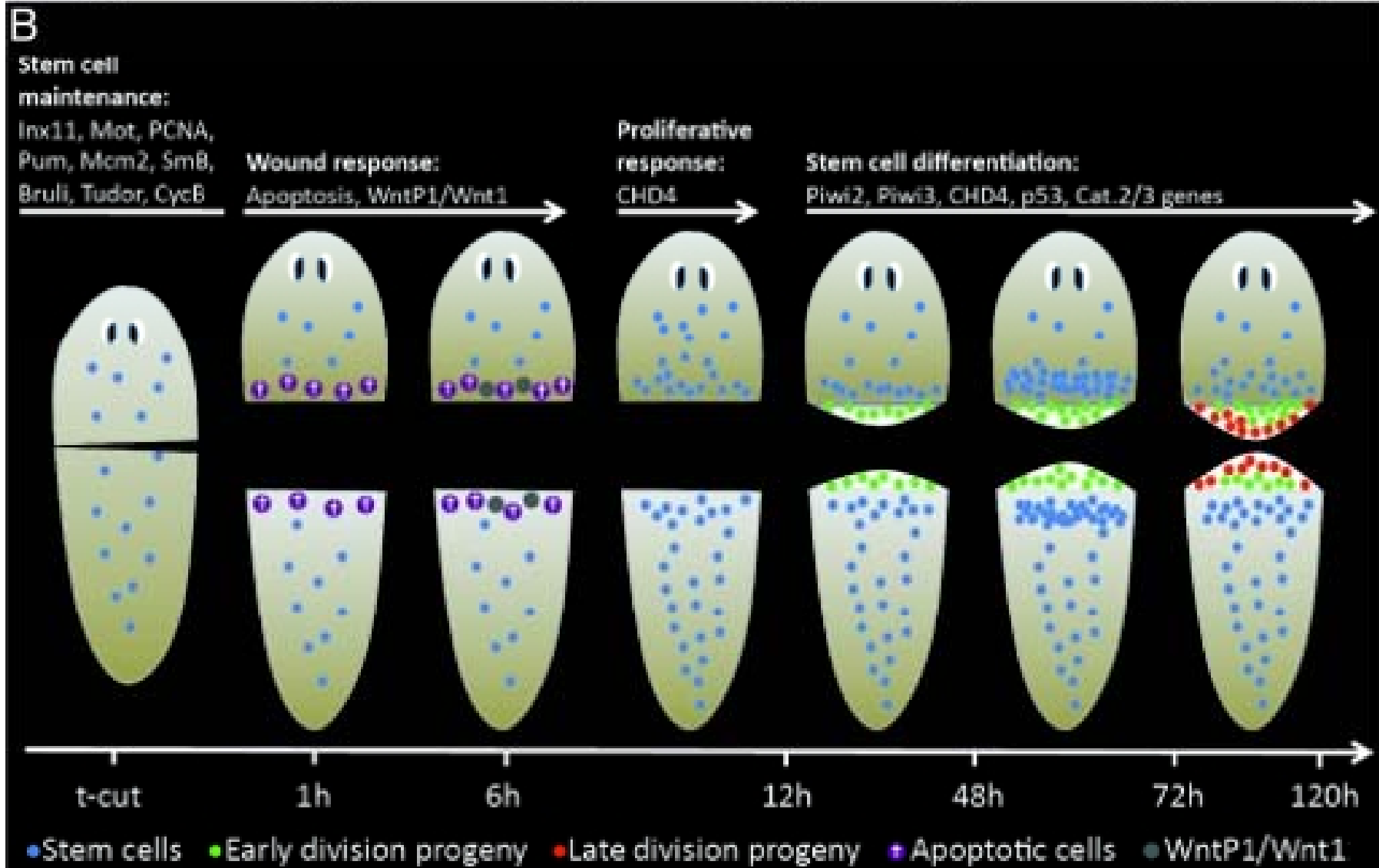
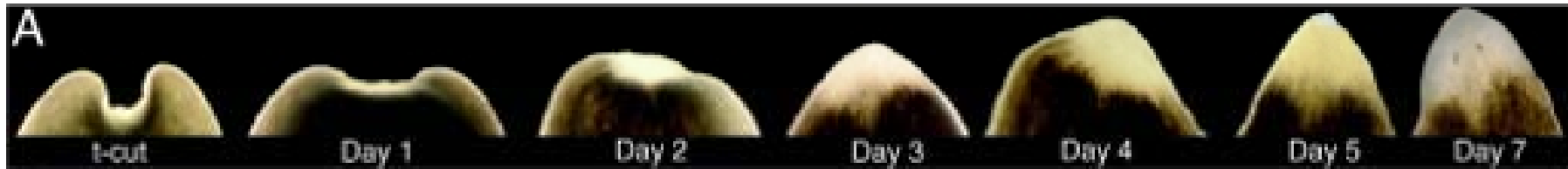
完美再生

蝾螈是唯一一生都能夠一次又一次長回失去肢體的脊椎動物。針對蝾螈如何長出肢體所做的研究，顯示再生過程始於快速的傷口閉合，

來自斷肢組織的細胞會聚集到截肢傷口，那些細胞會回復到胚胎狀態，然後依循胚胎發育的相同步驟來建造新肢體。



The capacity for regeneration in urodele amphibians (newt)
 (1) Dorsal crest, (2) limbs, (3,4) retina and lens, (5) jaw, and tail



幹細胞

1. 甚麼是幹細胞

2. 幹細胞來源

- a. 成體幹細胞 (adult stem cell):
骨髓，成體週邊血 (取得極為困難)
- b. 胚胎幹細胞 (embryonic stem cell):
胚胎，臍帶血 (取得容易)

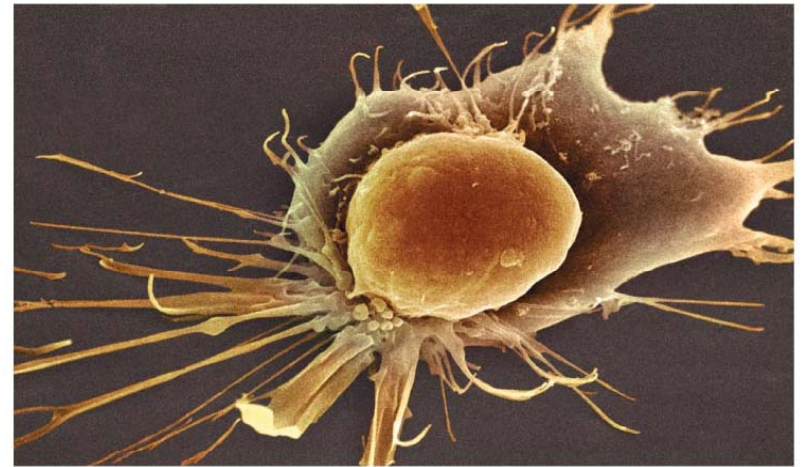
3. 幹細胞之運用 (複製, 組織再生)

4. 幹細胞研究之道德探討

(a)

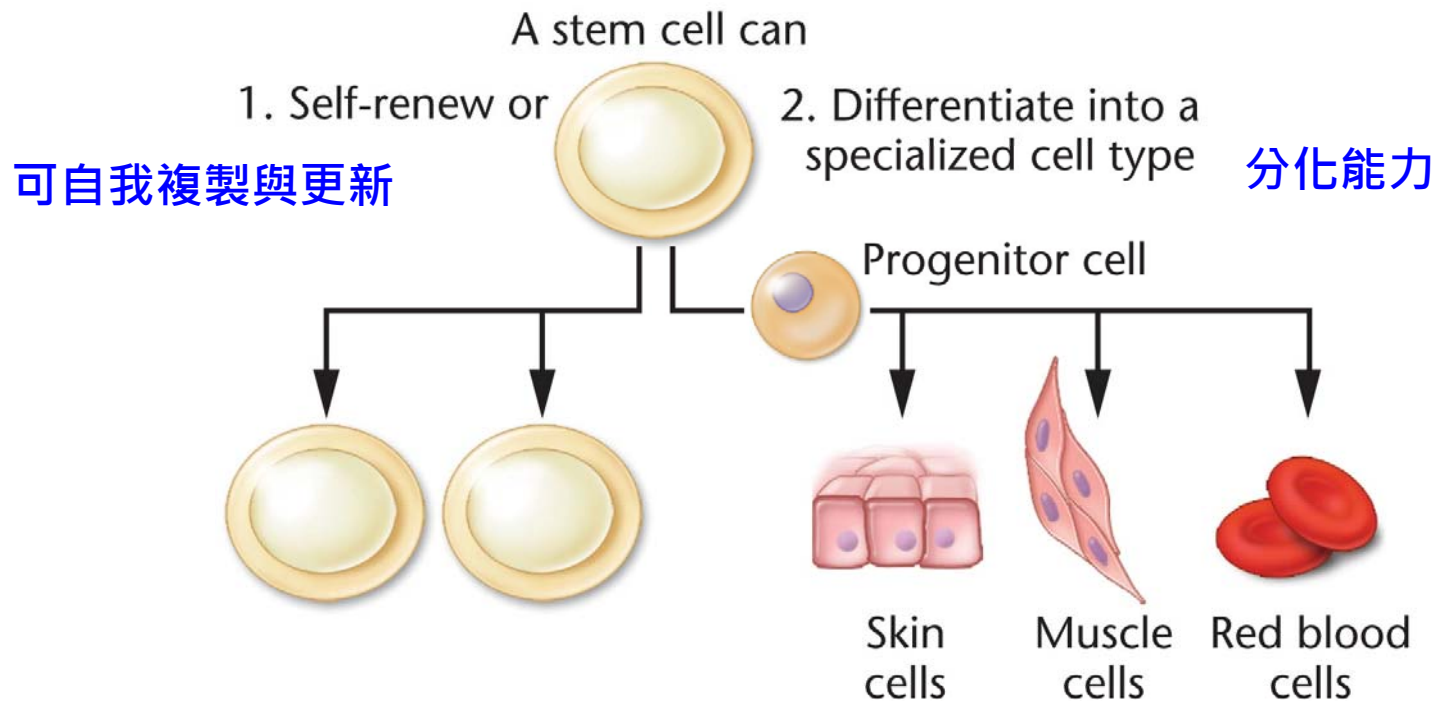


(b)



What Are Stem Cells?

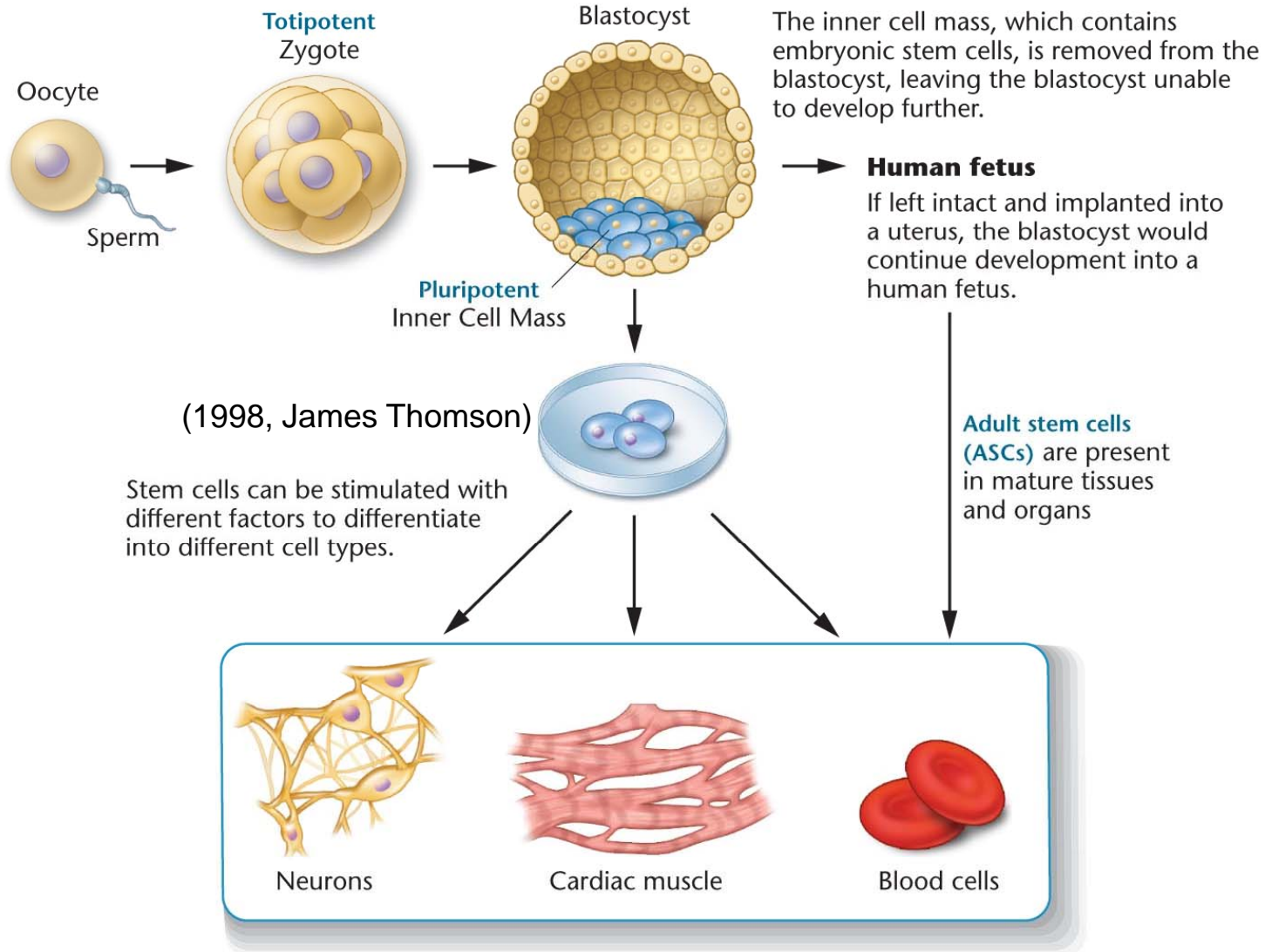
- Stem cells share two basic characteristics that make them distinctive from other cell types : **self-renewal** and **differentiation** into specialized cell types



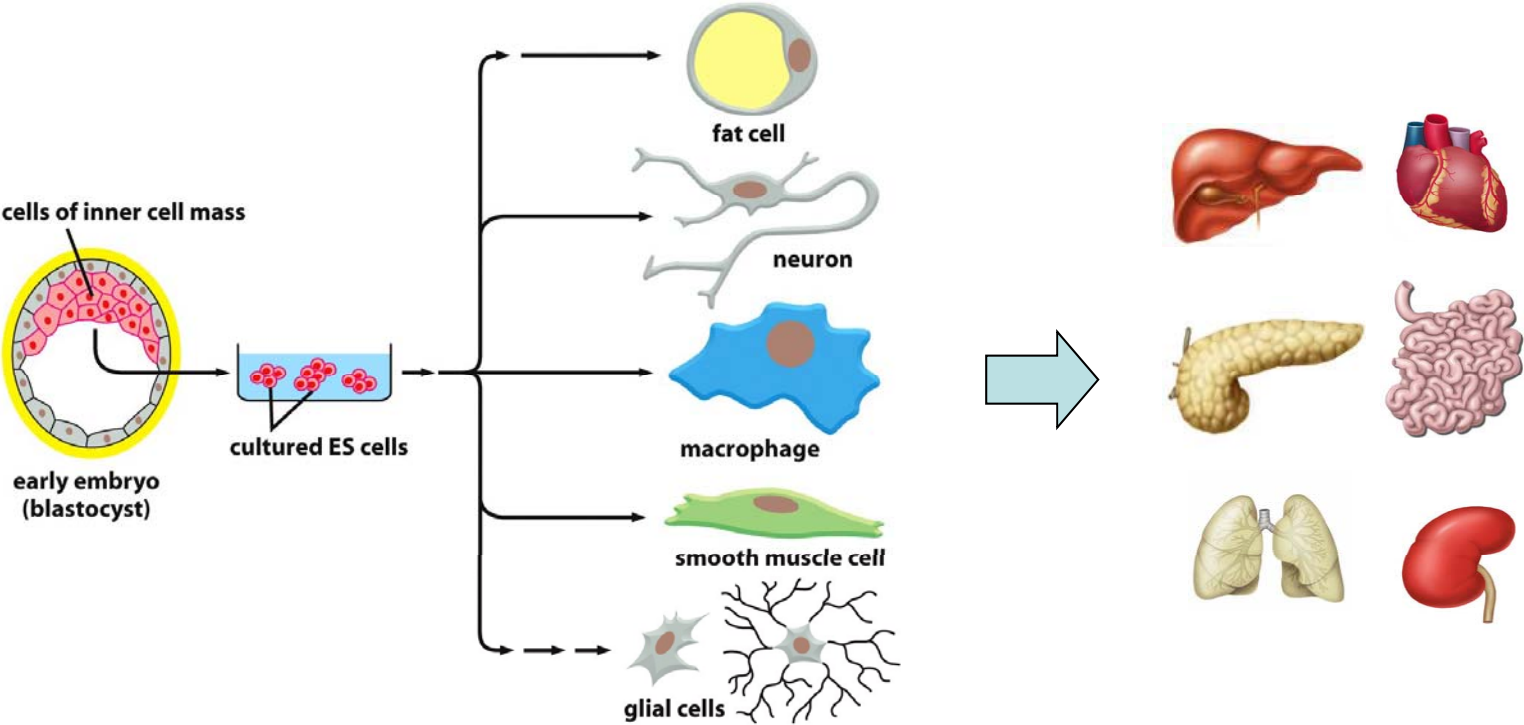
幹細胞來源之一

胚胎幹細胞

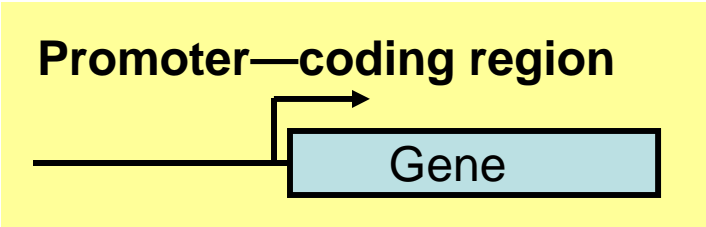
human embryonic stem cells (hESCs)



Cell differentiation (細胞分化)

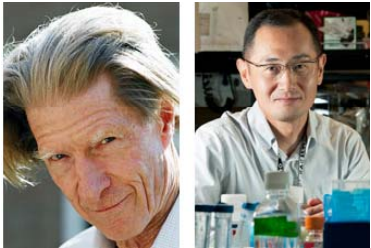


How to control the cell differentiation?
differential expression of gene?



Can differentiated cells reverse to ES cells? 返老還童?

The Nobel Prize in Physiology or Medicine 2012
Sir John B. Gurdon, Shinya Yamanaka



SCNT vs iPS

Somatic Cell Nuclear Transfer (體細胞核移殖)

SCNT

複製動物

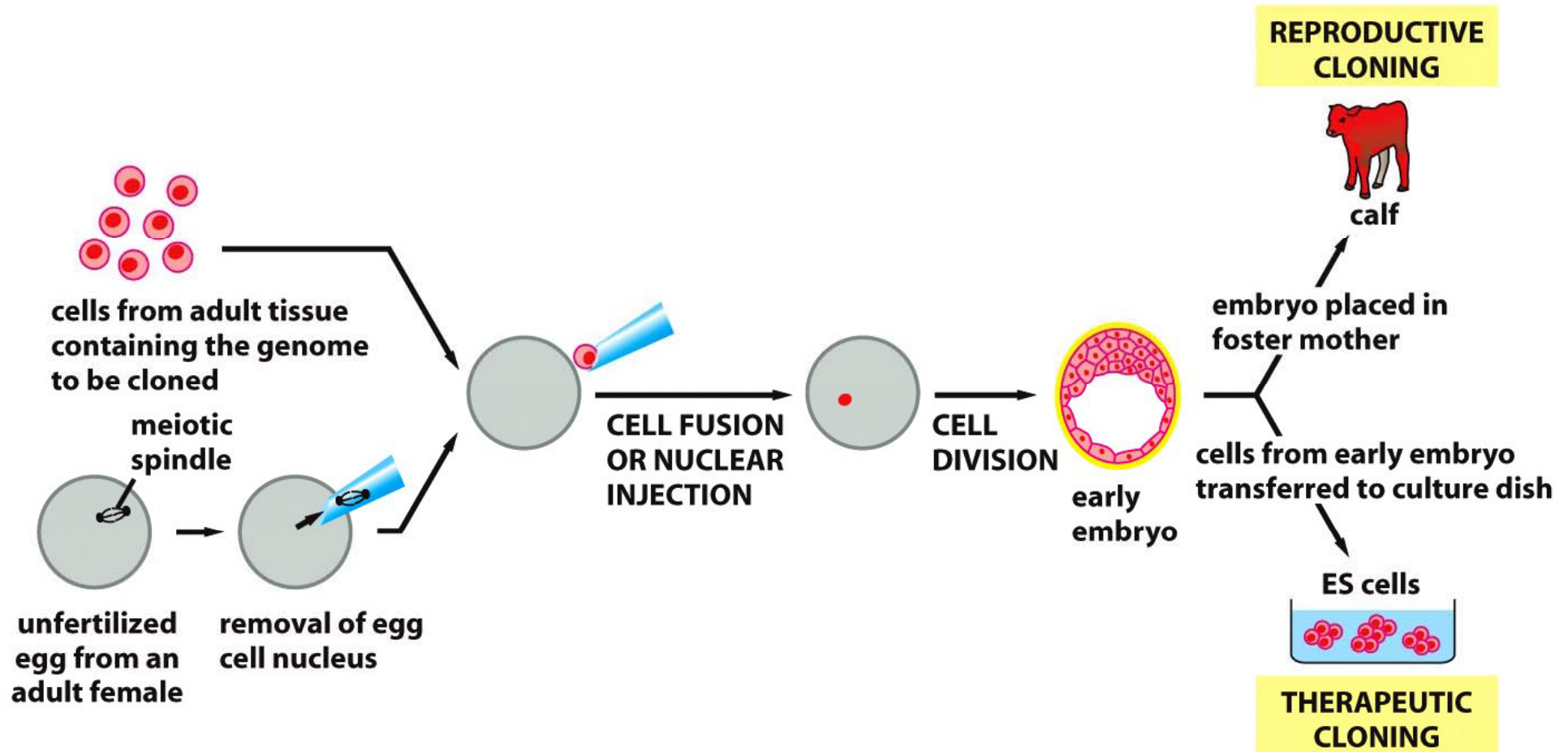
- 1997年2月27日英國Roslin研究所科學家於Nature雜誌上首先發表複製羊桃莉(Dolly)複製成功



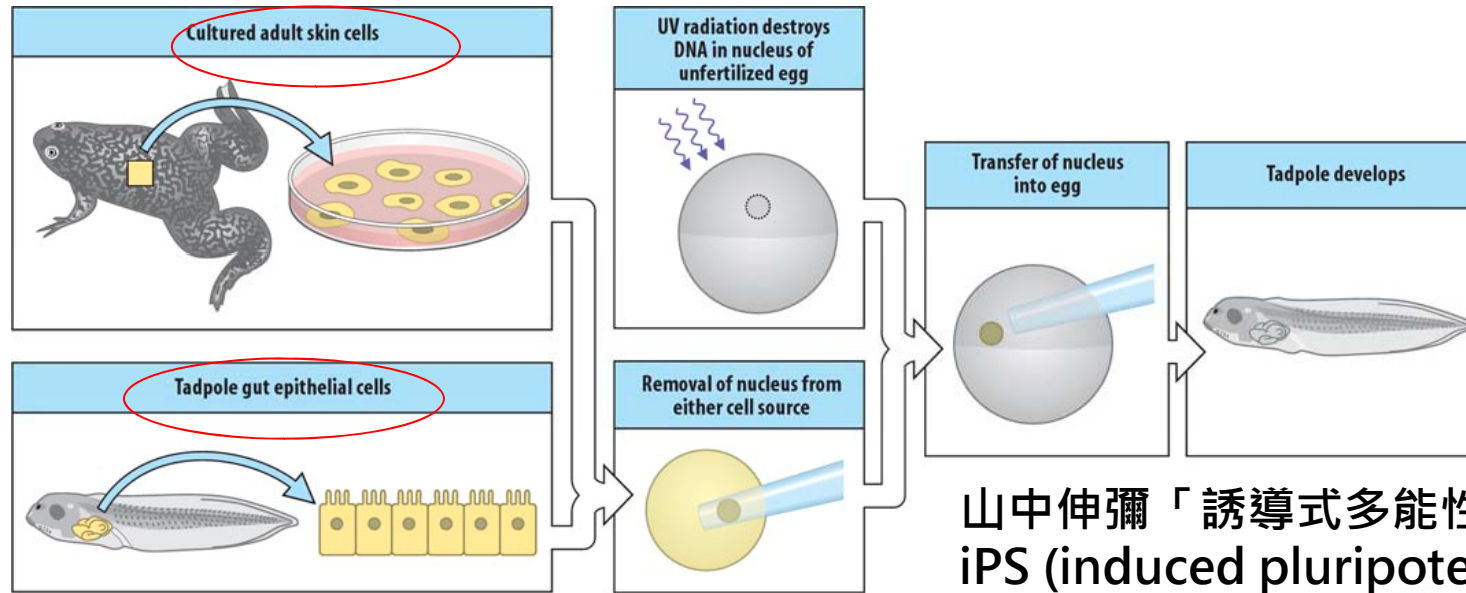
Nature 385: 810



Somatic Cell Nuclear Transfer (體細胞核移植)




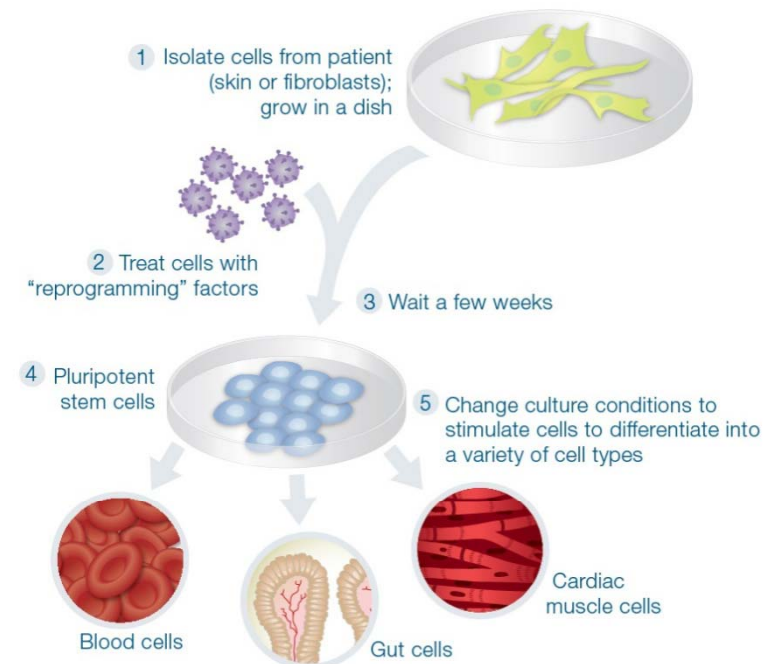
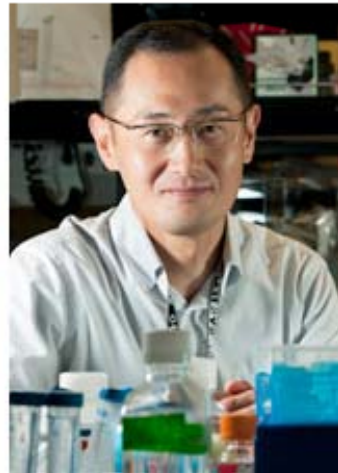
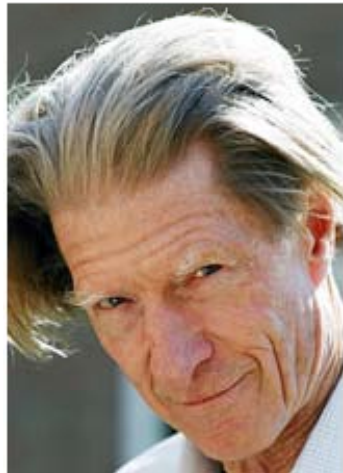
Somatic cell nuclear transplantation (SCNT) by John Gurdon



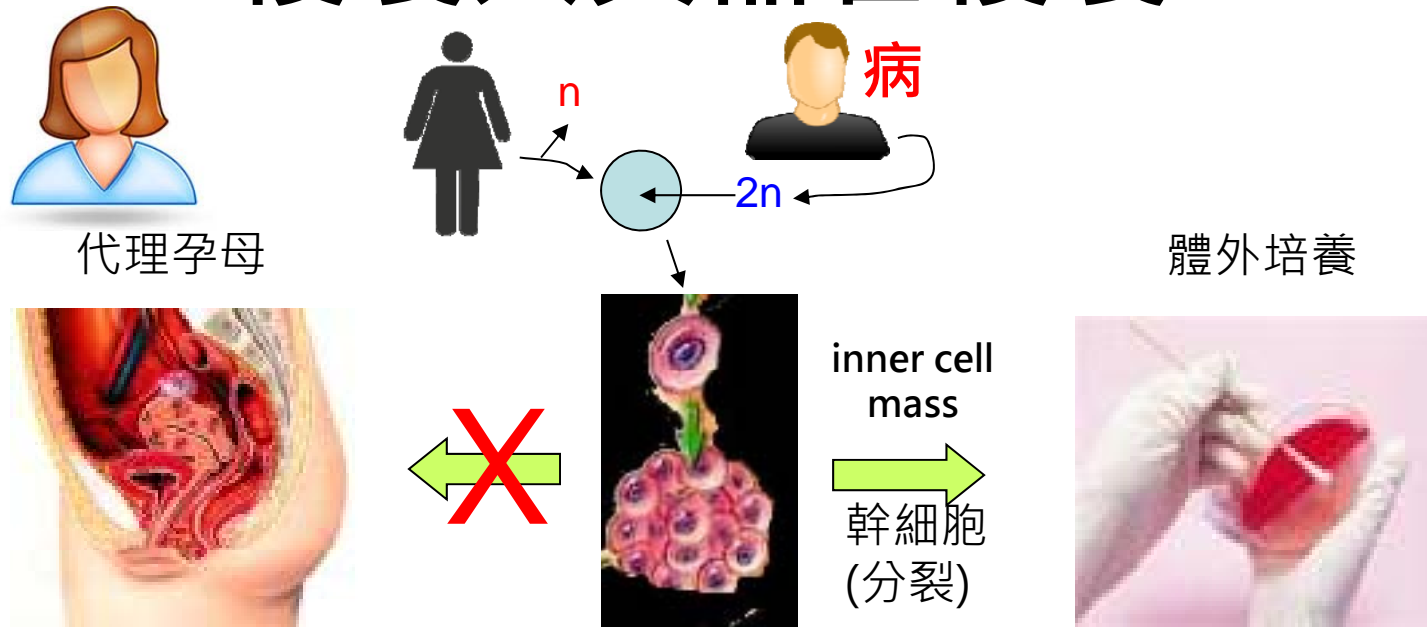
山中伸彌「誘導式多能性幹細胞」
iPS (induced pluripotent stem cells)

Creating **iPS cells**

 The Nobel Prize in Physiology or Medicine 2012
Sir John B. Gurdon, Shinya Yamanaka



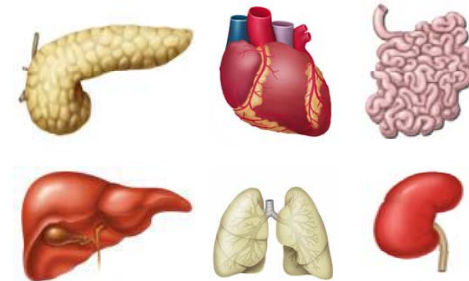
複製人與器官複製

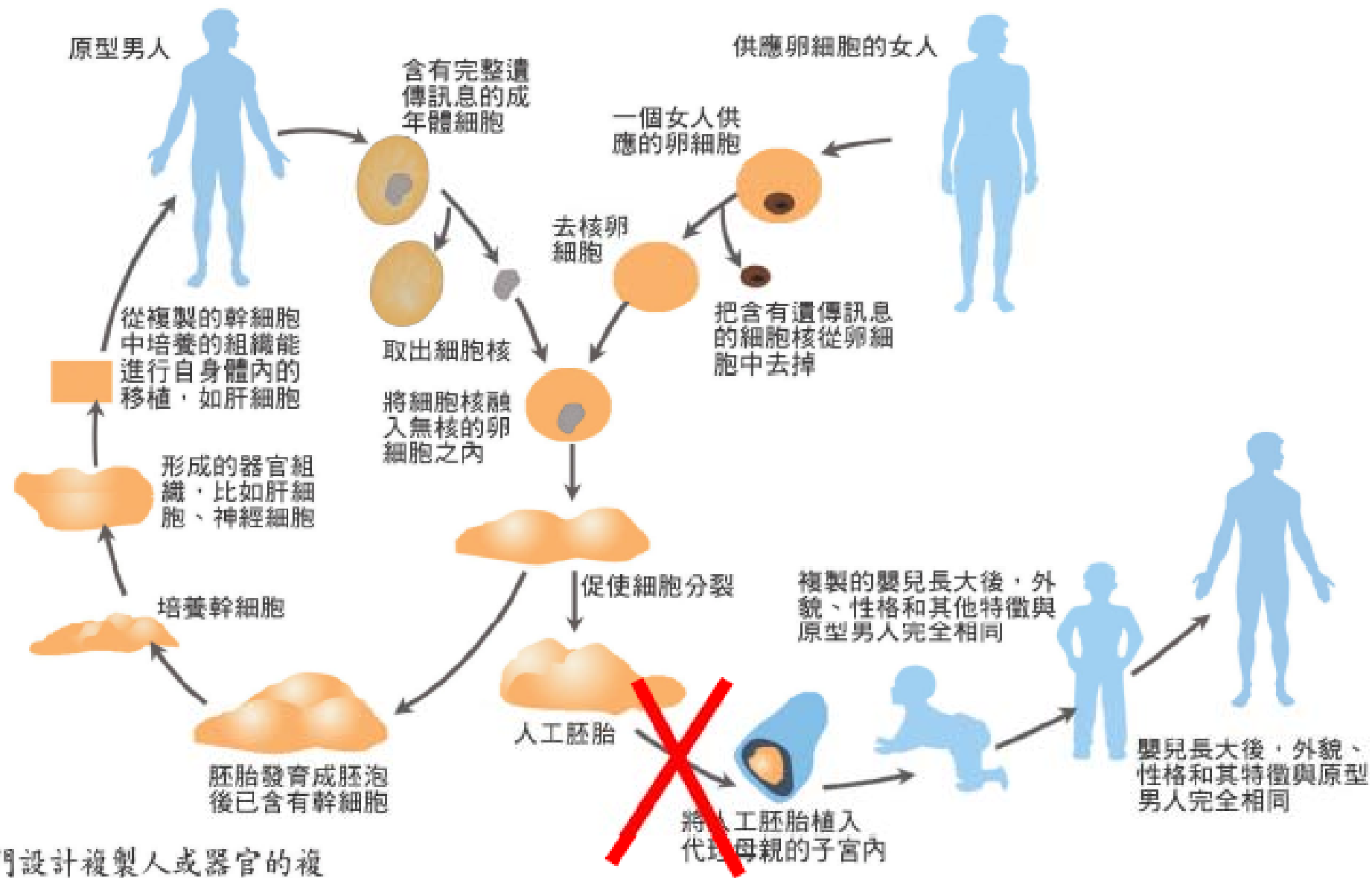


生命之開始
(法律定義) ↓ 幹細胞 (分化)



合法？合理？

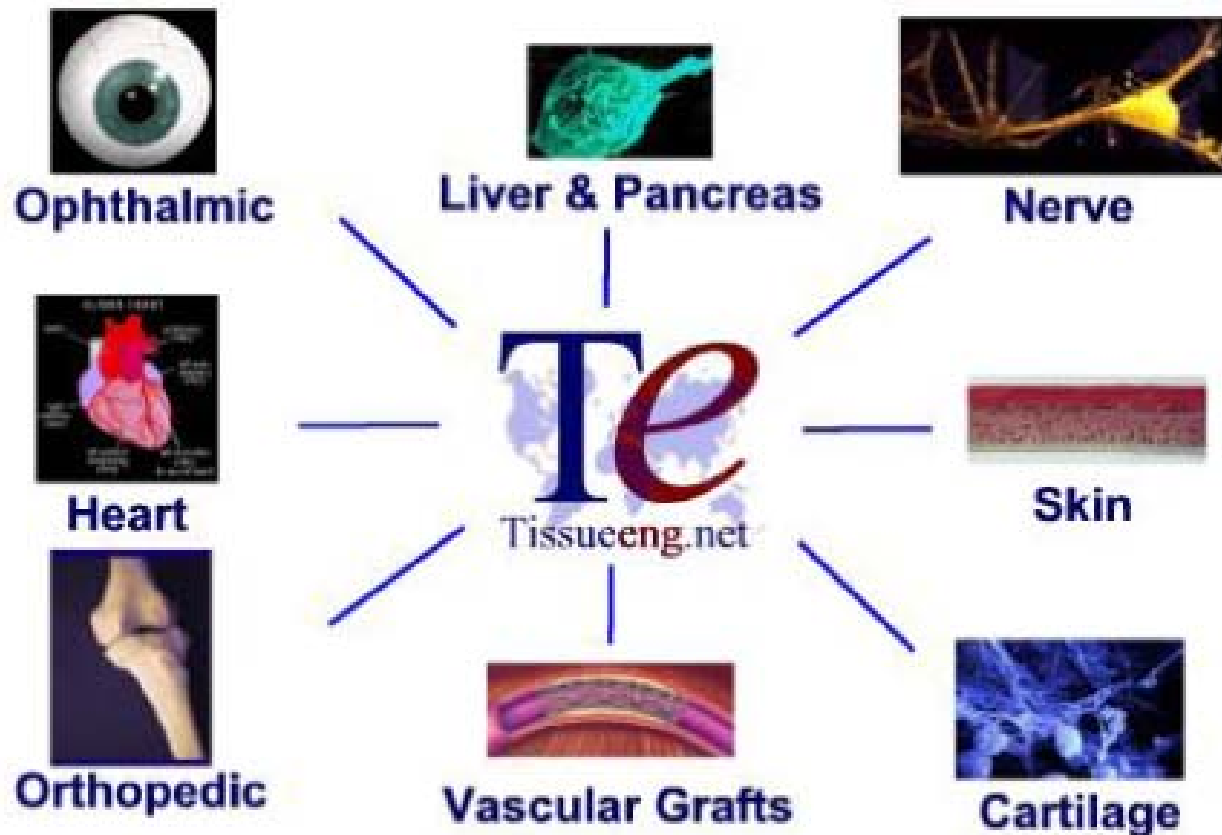




專門設計複製人或器官的複製技術與步驟

組織工程(Tissue Engineering)

- 皮膚移植 (燒燙傷、美容)
- 器官再造
- 1997 Dr. Charles Vacanti (University of Massachusetts)
利用小鼠製造人工義耳: 以可吸收性聚合物製造耳朵形狀，以牛
膠原細胞包覆, 埋放到裸鼠皮下，生長成人形耳朵
- 其他可能應用：膀胱、軟骨、血管...等



2008 自體幹細胞培育氣管移植

自體移植支氣管

一名哥倫比亞女子卡絲蒂約接受世界首例量身訂做的氣管移植手術，其方法是把她自己的幹細胞「種」在別人捐贈的器官上，以免身體發生排斥現象。

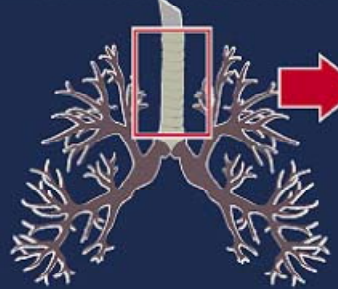
氣管萎縮

卡絲蒂約左肺的支氣管因肺結核受損萎縮



移植程序示意圖

1 西班牙巴塞隆納醫師找到一名過世的氣管捐贈者



酵素

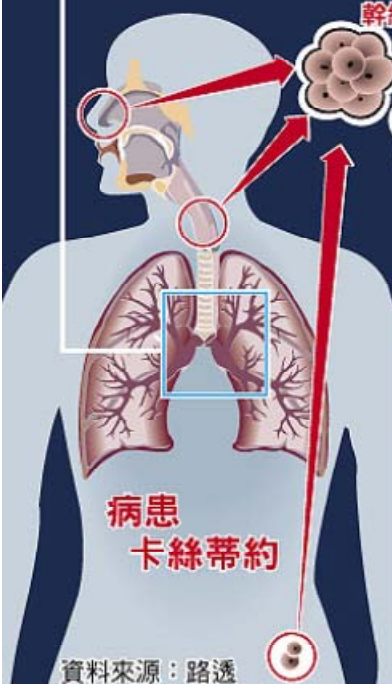
2 以酵素把氣管「洗淨」，去除原本屬於捐贈者、可能引發排斥反應的抗原和細胞，只保留膠原「支架」



膠原「支架」

3 從卡絲蒂約體內取出幹細胞，送往英國培育出新的軟骨和上皮細胞

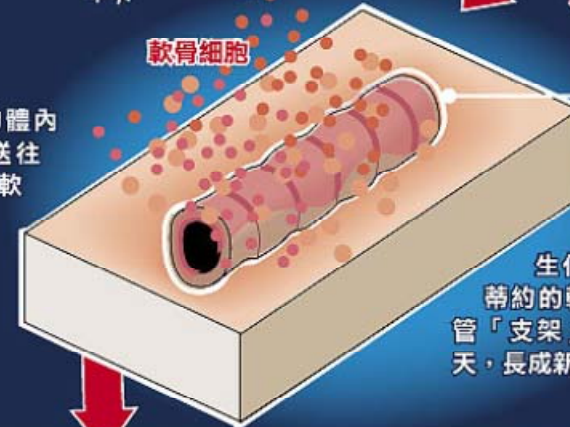
幹細胞



病患
卡絲蒂約

資料來源：路透

軟骨細胞



4

新培育出的細胞被送回巴塞隆納，利用義大利發明的生化反應器，將卡絲蒂約的幹細胞「種」在氣管「支架」上，浸泡旋轉3天，長成新的氣管

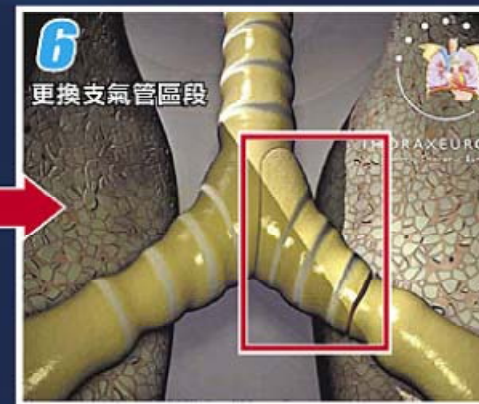
5

將新氣管裁切成合適的大小，用來取代卡絲蒂約的支氣管



6

更換支氣管區段



regenerative medicine (再生醫學)

- Scientists working in regenerative medicine are also optimistic about their ability to produce viable organs from stem cells
- **Sheets of skin** and other organs such as the **urinary bladder** have been created *in vitro*



QUESTIONS?

Summary

1. 胚胎學 (embryology) vs. 發育生物學 (developmental biology)
2. 模式生物 (model organisms)
3. 動物發育的主要階段
4. 發育過程之機制
5. 組織再生與幹細胞

