
学術俯瞰講義
奥深さと美しさによる全体像
可能性が生まれる
発生生物学からみた
生命科学
浅島　誠
東京大学大学院総合文化研究科 教授
分子モーターから観た
生命科学
廣川　信隆
東京大学大学院医学系研究科長
ウイルスからみた
生命科学
野本　明男
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ゲノムから見た
生命科学
黒岩　常祥
東京大学名誉教授
主題科目／テーマ講義
生命の科学
構造と機能の調和
10月16日→1月29日
月曜日 5時限
駒場キャンパス
16時20分▶17時50分
18号館ホール

Global Focus on Knowledge Lecture Series

2006 Winter Semester: “Science of Life”

Life Science: from the Perspective of Developmental Biology

The 1st Lecture Oct.16（Mon）

From an egg to an adult body-The Morphogenetic Mechanism

Professor Makoto Asashima
Graduate School of Arts and Sciences, University of Tokyo

Developmental Biology

gamete（sperm・ovum）

Conjugation
（fertilization）

zygote（egg cell）

Embryogenesis

Cell division
Cell differentiation
Morphogenesis
Apotosis
Cellular interaction, etc.

individual

How are diverse cell groups formed from a single cell?

What helps the system of multicellular organisms to be formed stably?

Diverse life forms live on the Earth.

It is important to know the morphology or natural history of those organisms.

The "evolutionary tree" inserted here was omitted according to copyright issue.

The Method of Developmental Biology

There are as many types of development as the number of organism species.

（more than 10 million species）

↓

Selection of model organisms

Example

Typical species:

- Round worms：Nematode
- Insects：Drosophila
- Fish：Zebrafish，Killifish
- Amphibians：Xenopus，Newt
- Mammals：Mouse
- Plants：Thaliana, etc.

- Research on development mechanisms of each organism
- Comparison of each organism’s development（comparative embryology）

“All the animals are born from an egg.”

(Ex ovo omnia)

The illustration in Harvey’s “De Generatione Ammalium”

William Harvey
A.D.1578-1657

Harvey indicated the importance of the egg in animal development.

1983 Idemitsu Shoten

An ovum is a single heterogeneous cell.
Substances are precisely positioned due to the polarity and gradient.

“The picture of mating xenopuses”
is omitted according to copyright issue.

Pairing of
Xenopus laevis

Substances in ovum are unevenly distributed.

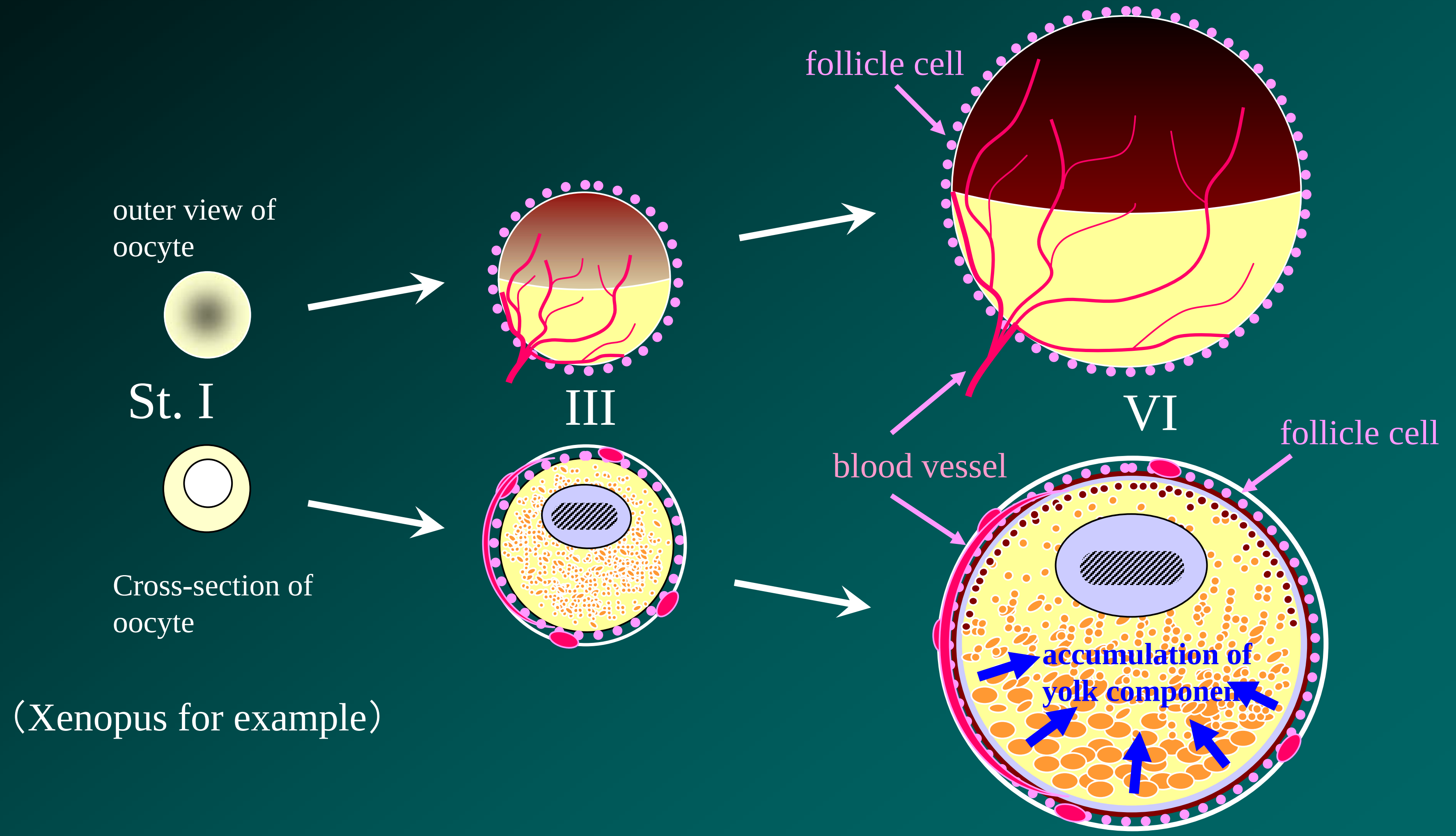
“The picture of unequal distribution in ovum” is omitted according to copyright issue.

wikipedia

Ovary of xenopus

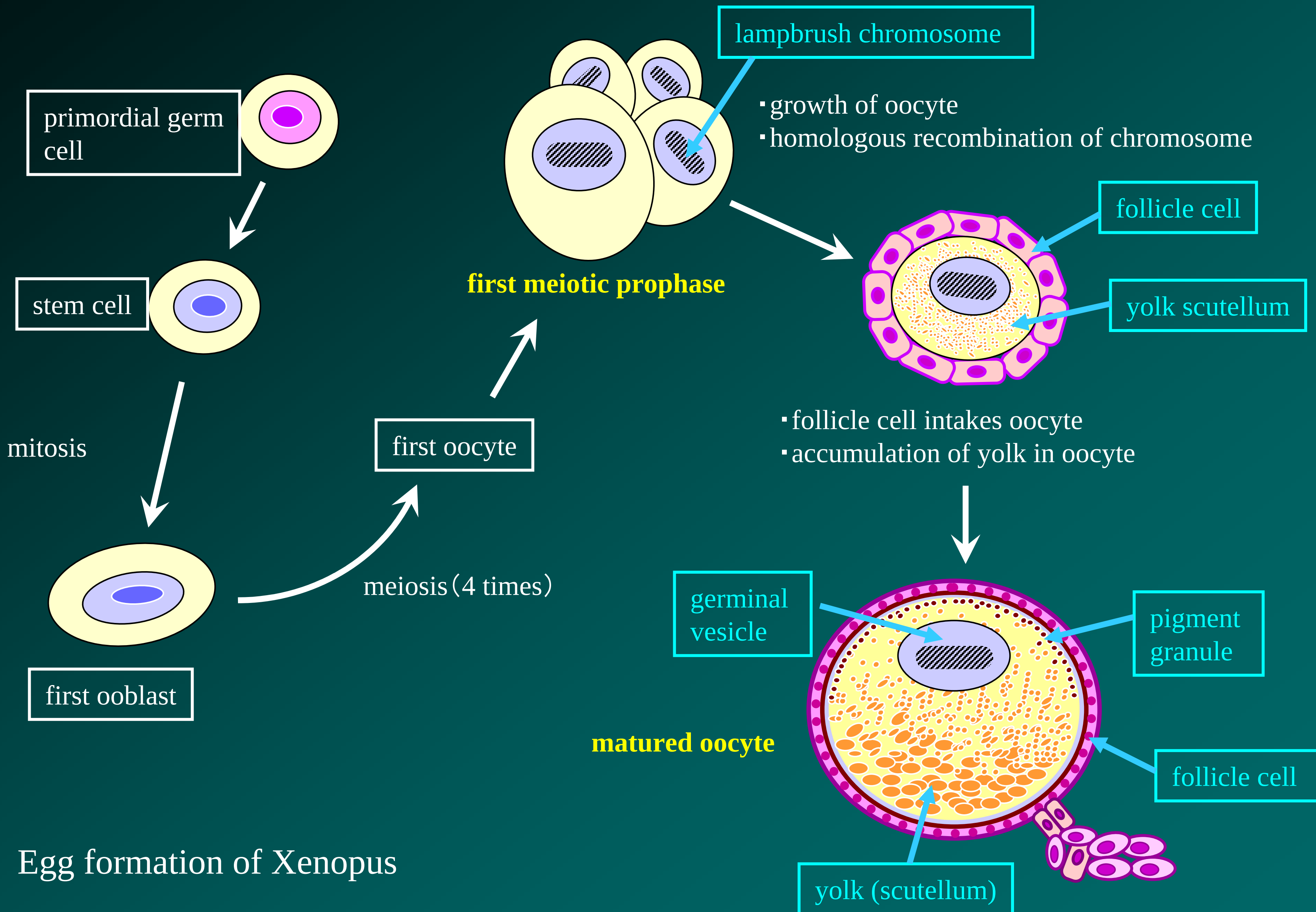
Polarity and gradient are made during oogenesis while ovums endocytose or produce substances.

Polarity and gradient are important notions in morphology.



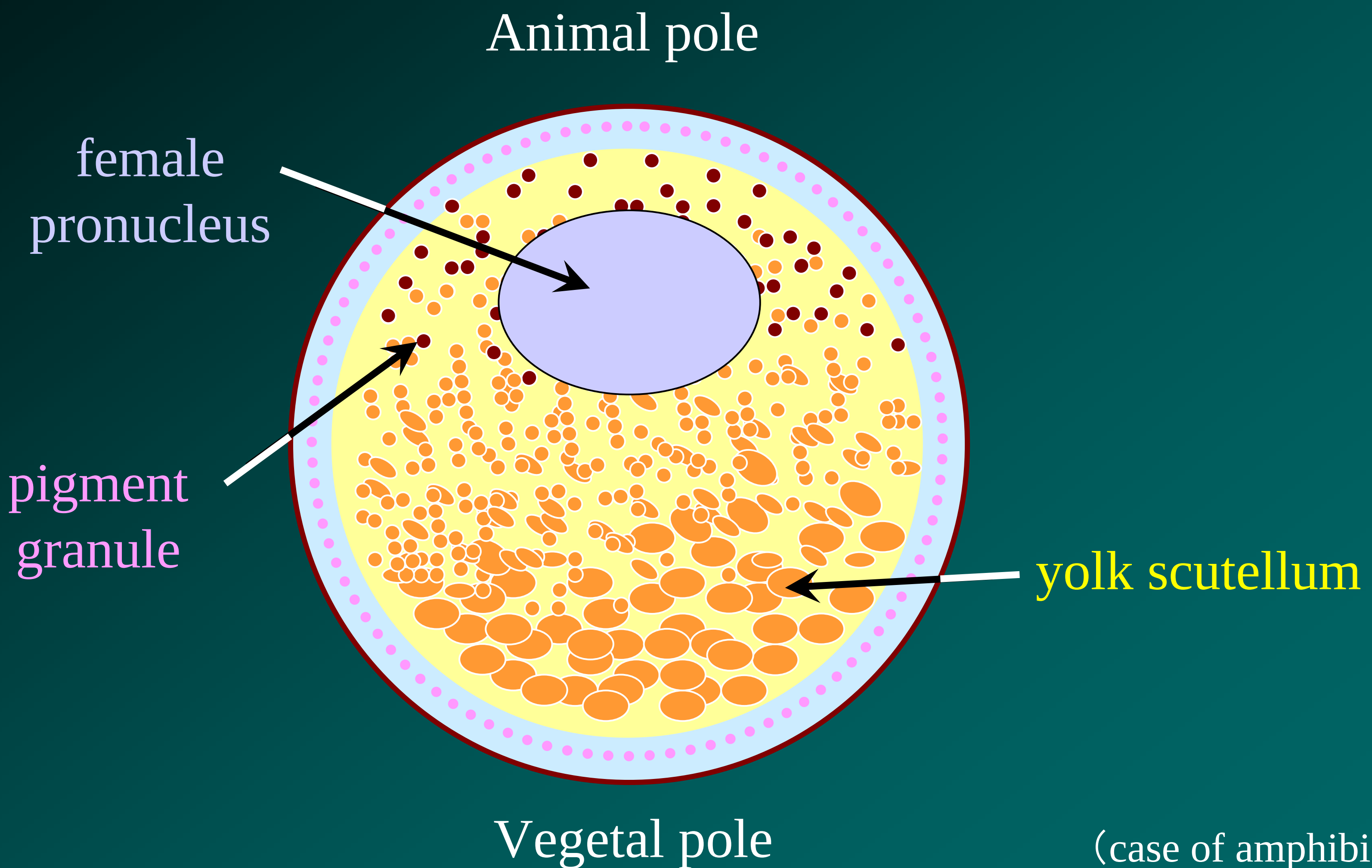
Along with maturation of oocyte, yolk proteins (vitellogenin etc.) supplied from blood vessel and various maternal factors newly produced are accumulated with polarity.

Oogenesis of Vertebrates



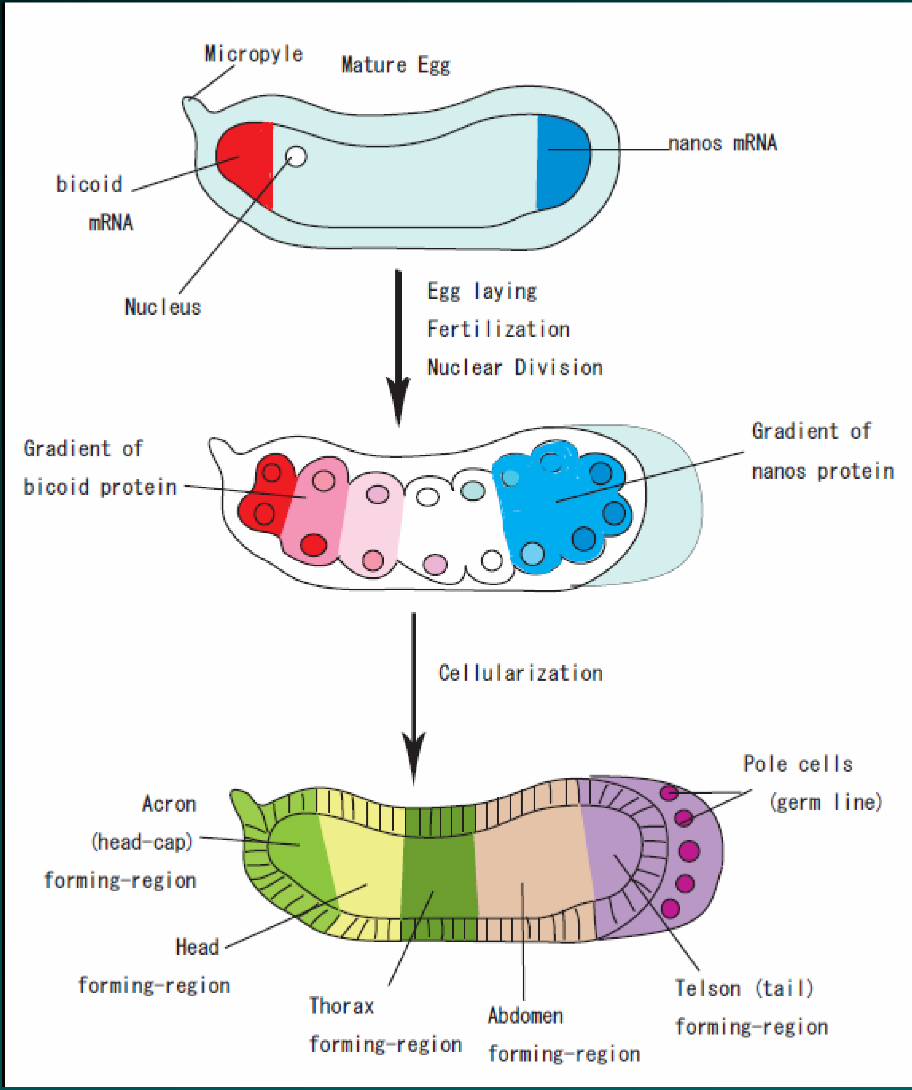
Egg formation of Xenopus

Each ovum has polarity and gradient before fertilization.



（case of amphibians）

Gradient Changes in Development of Drosophila Ovum



As an embryo develops, polarity causes a change in gradient. This causes gene expression and cell differentiation.

Elucidation of development mechanism ①

Directionality

① What makes parts of the body anterior, posterior, right, left, ventral, or dorsal ?

② Observe how various organs and tissues develop.

↓

Observe how typical parts of the body differentiate in a living creature.

From whole to parts（formation of each organ and tissue）
From parts to whole（head region・tail region・individual）

→ Integrity of individual body

Elucidation of development mechanism ②

Experiment Method

① Observation of normal development（morphology change・gene expression）

② Isolation & identification of various factors（protein etc.）and genes.

③ Artificially treat the embryo, and discover the mechanism via changes in the embryo

- embryo manipulation by microscopic operation
- mechanism analysis by gene transfer or inhibition, etc.

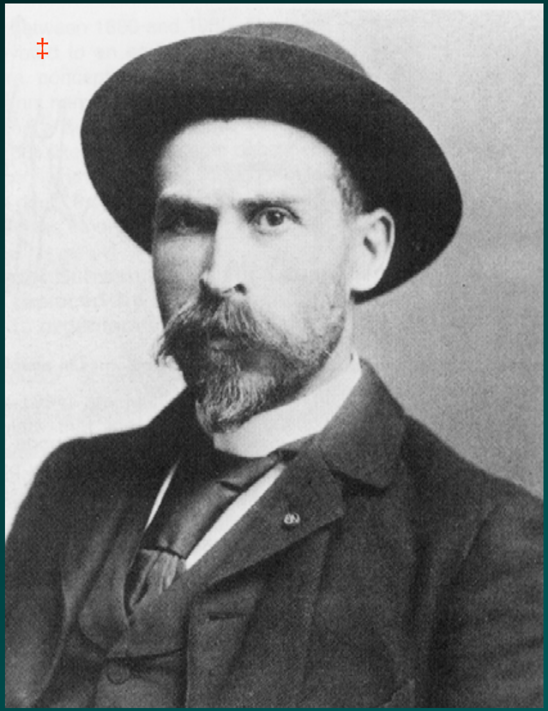
Frogs and newts were used in classical embryology experiments since they were easy to handle.

The Father of Experimental Embryology: Roux

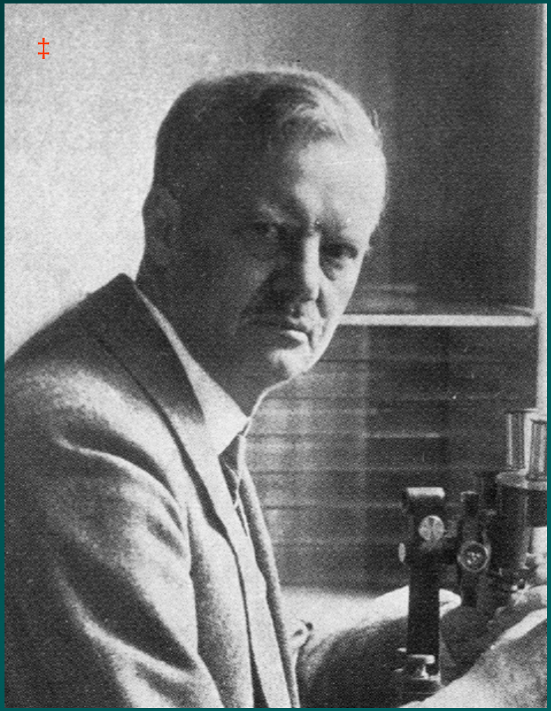
manipulated animal embryo(egg) and started positivistic experimental embryology.

Discoverers of Embryo Induction: Spemann and Mangold

discovered the organizer which is the center of morphology formation and found “induction”in embryo development for the first time→ **Established the modern developmental biology**



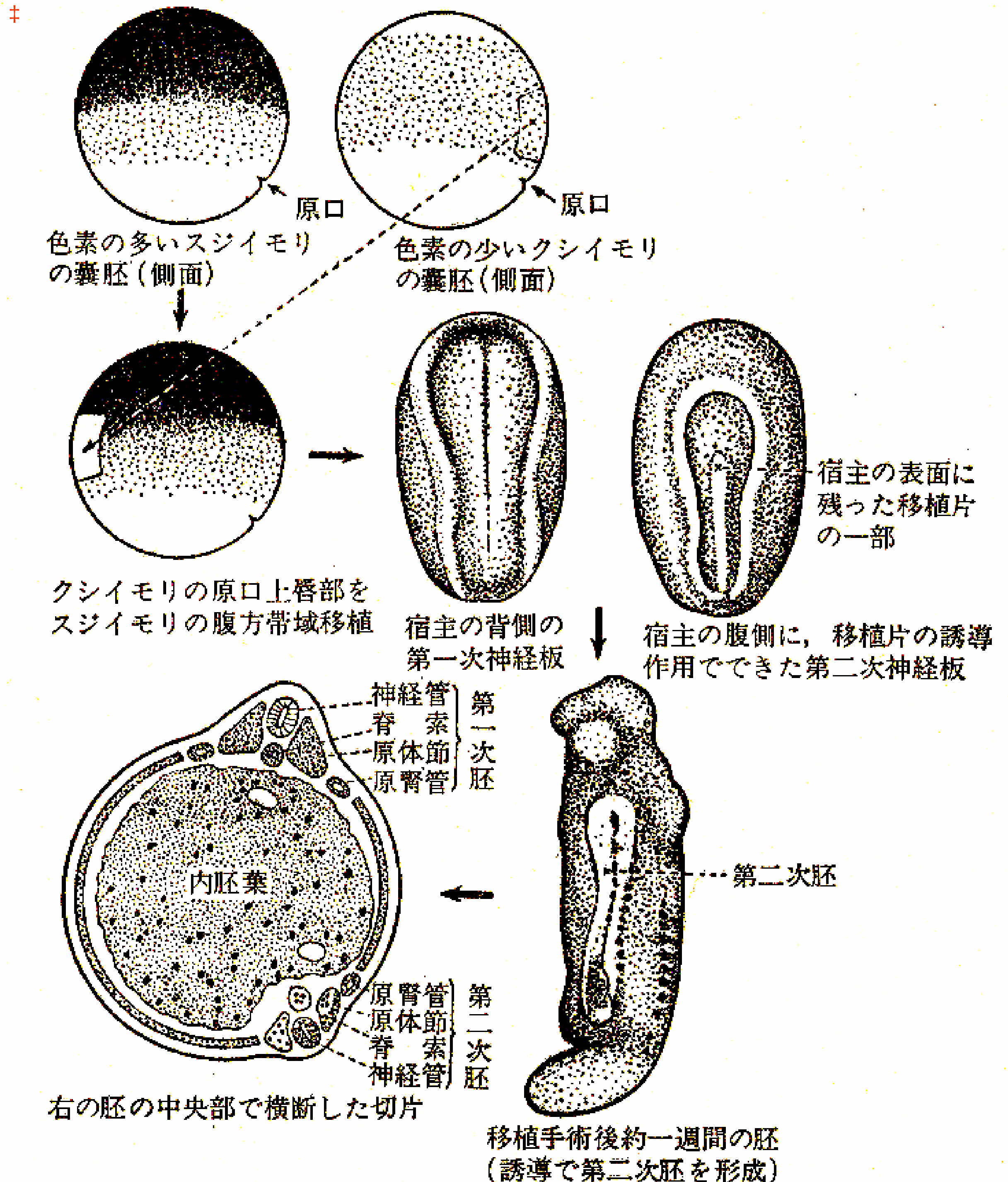
Wilhelm Roux (1850-1924)



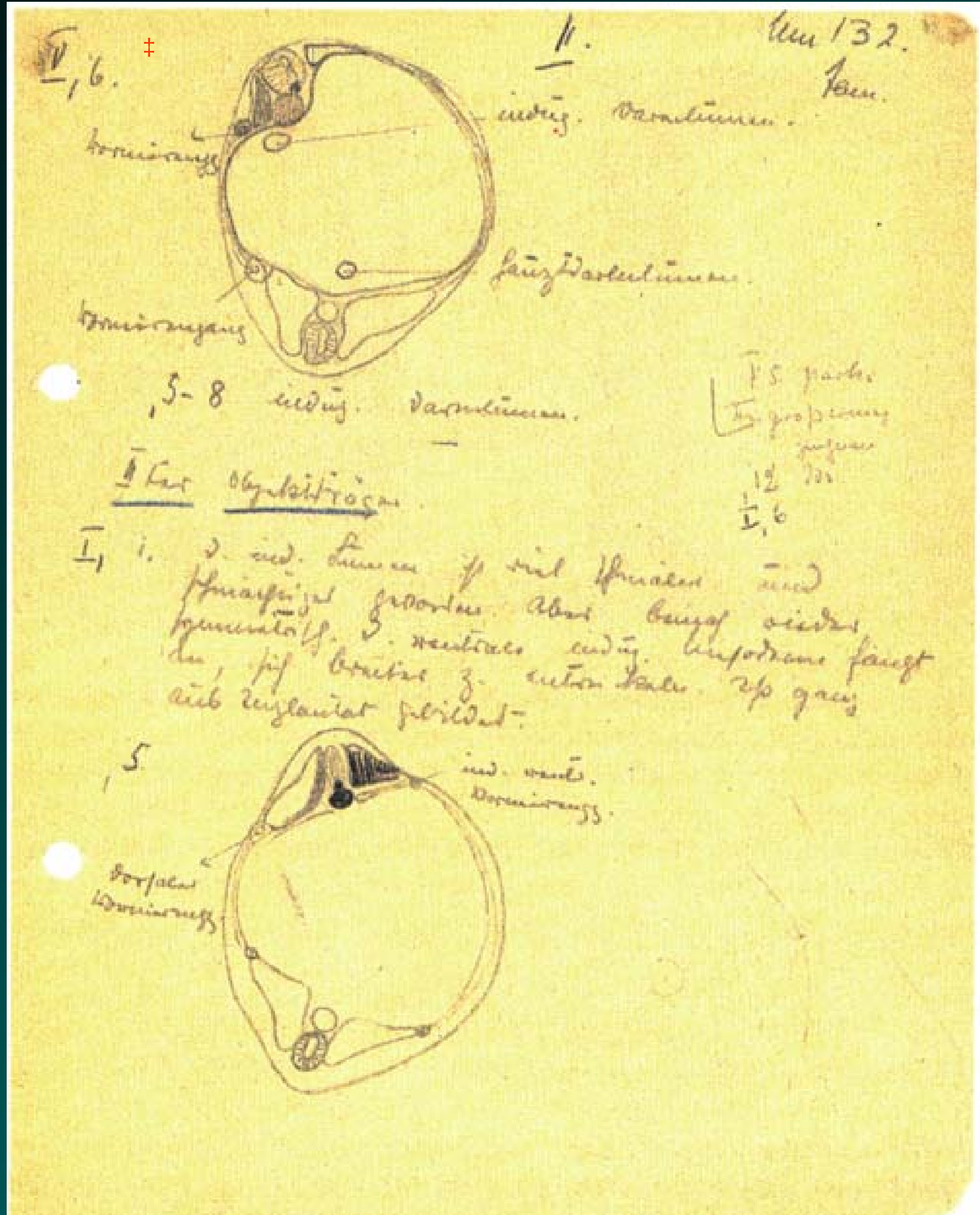
Hans Spemann (1869-1941)

Hilde Mangold (1898-1924)

"Int J Dev Biol, vol 40, No.1, 1996" p10-Fig.2(Klaus Sander), p60-Fig.1 (Viktor Hamburger), p54-Fig.8 (Peter E. Faessler)



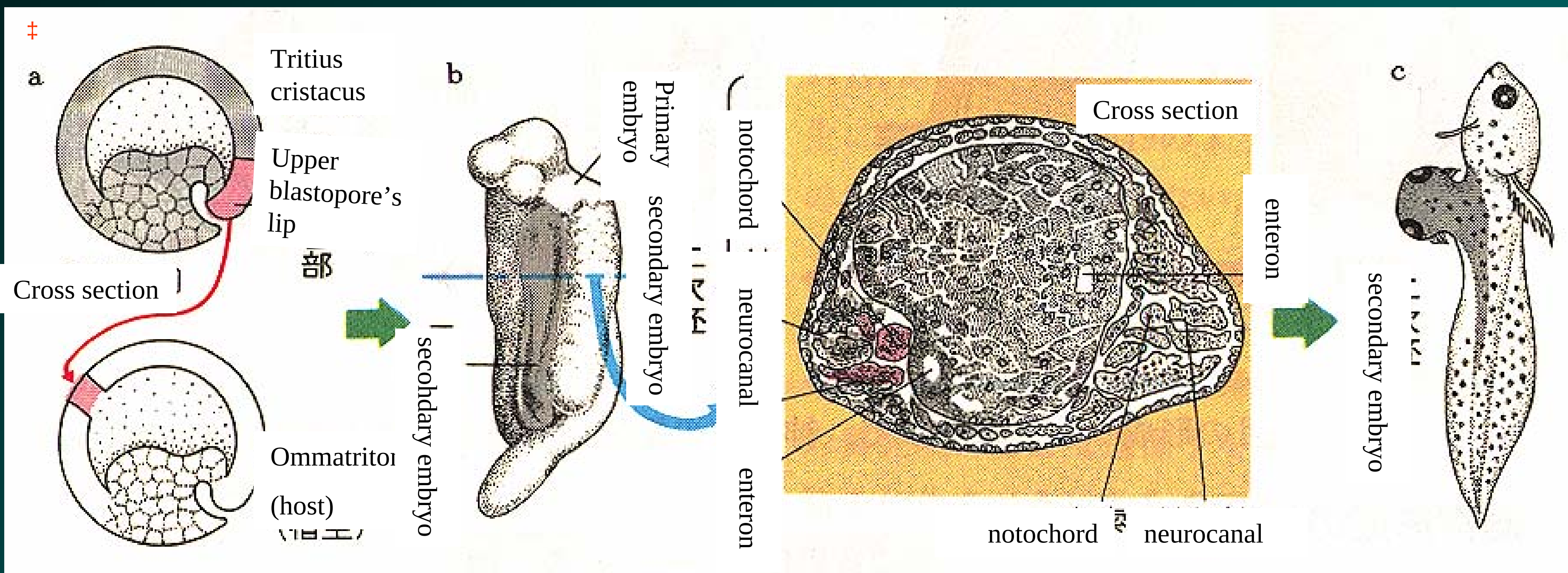
1983
Idemitsu Shoten



Sander K. et al. Int J Dev Biol, vol 45, p8- Fig.10, 2001

The Experiment of Spemann and Mangold

— transplant of an upper blastopore's lip（1924）



2001 Buneido

1924-impact of Spemann & Mangold's discovery of organizer

- Proved "embryo development by cellular interaction"
- Indicated efficiency of positivistic method (embryo manipulation)
- **Demonstrated the central part of the embryo that controls body formation**

↓

The inevitable question here

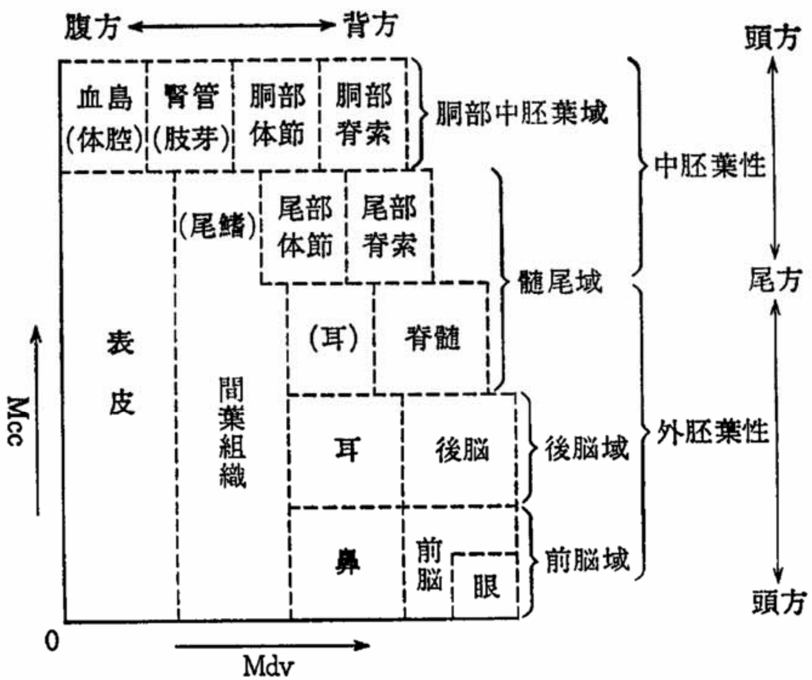
"On what does this interaction depend?"

↓

Focuses on proteins and nucleic acids along with development of physical chemistry and biochemistry
Main stream is to research life process by search of substance.

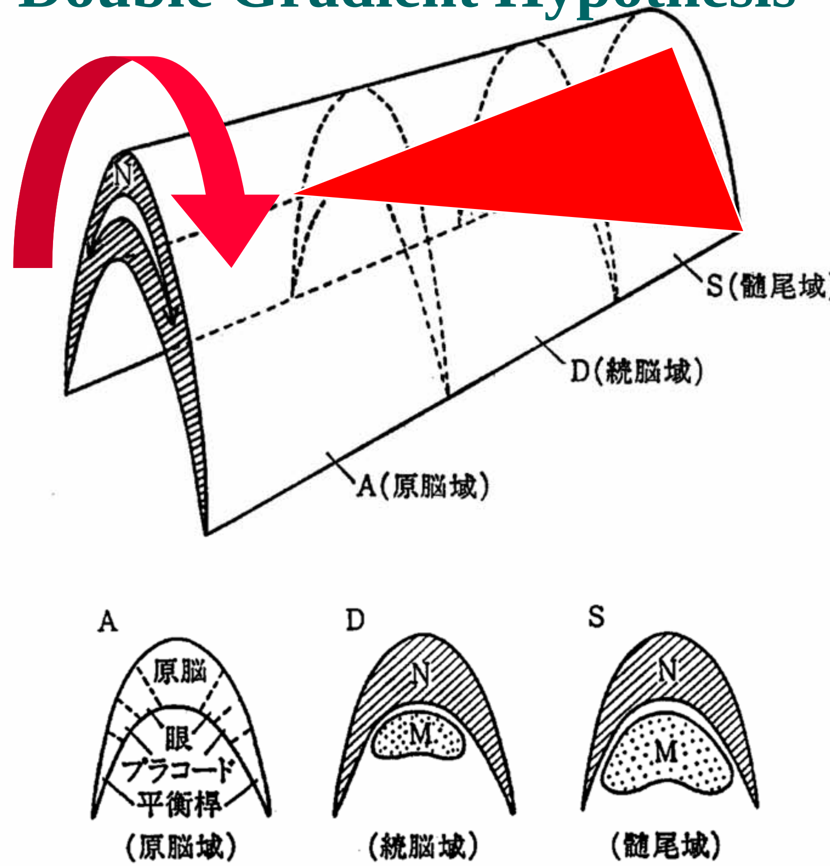
Hypotheses on concentration gradient of inducing factors

‡ Double Potential Hypothesis



重複ポテンシャル論による Mdv, Mcc が予定外胚葉に働いた際に生ずる各種分化過程の模式図.
(Yamada 1956, a. b.)
Mdv＝背腹規定能
Mcc＝頭尾規定能

Double Gradient Hypothesis



二勾配説の模式図. M, 中胚葉化活性；N, 神経化活性；A, 頭端部誘導；D, 続脳部誘導；S, 髄尾部誘導.
(Toivonen & Saxén, 1955 より)

‡

Fish	Amphibian	Aves	Mammalian

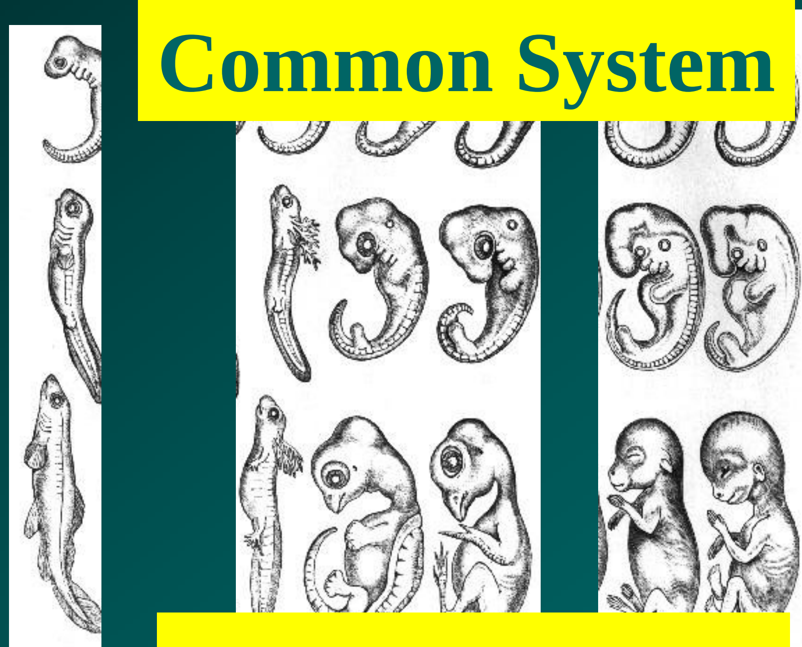
"Illustrations of embryogenesis" inserted here was omitted according to copyright issue.

Fertilized egg

Time

Blastula stage

Gastrula stage



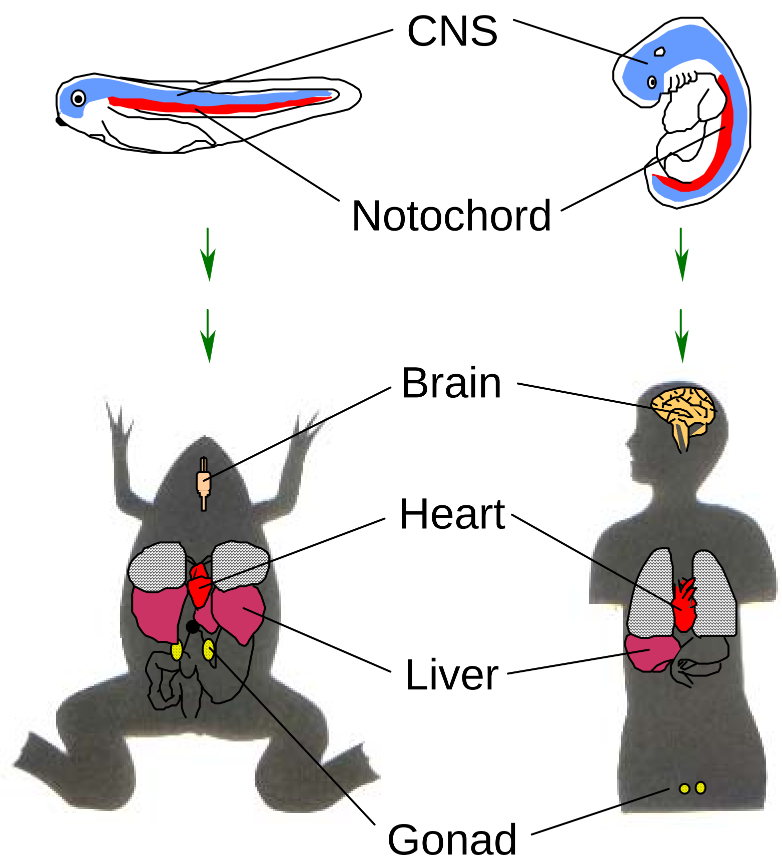
Common System

Embryonic Stage (Vivipary stage)

Common Organ

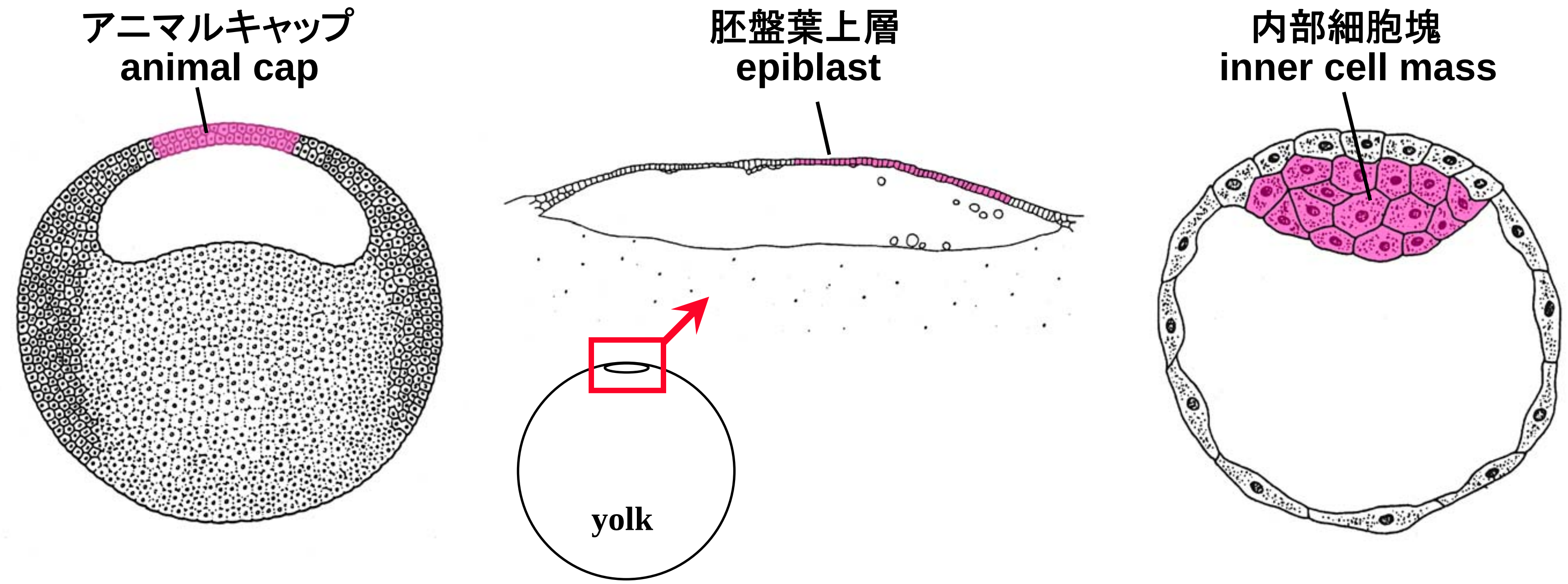
Early Vertebrate Development

Common System



Common Organ

Omnipotent stem cell of vertebrate embryo

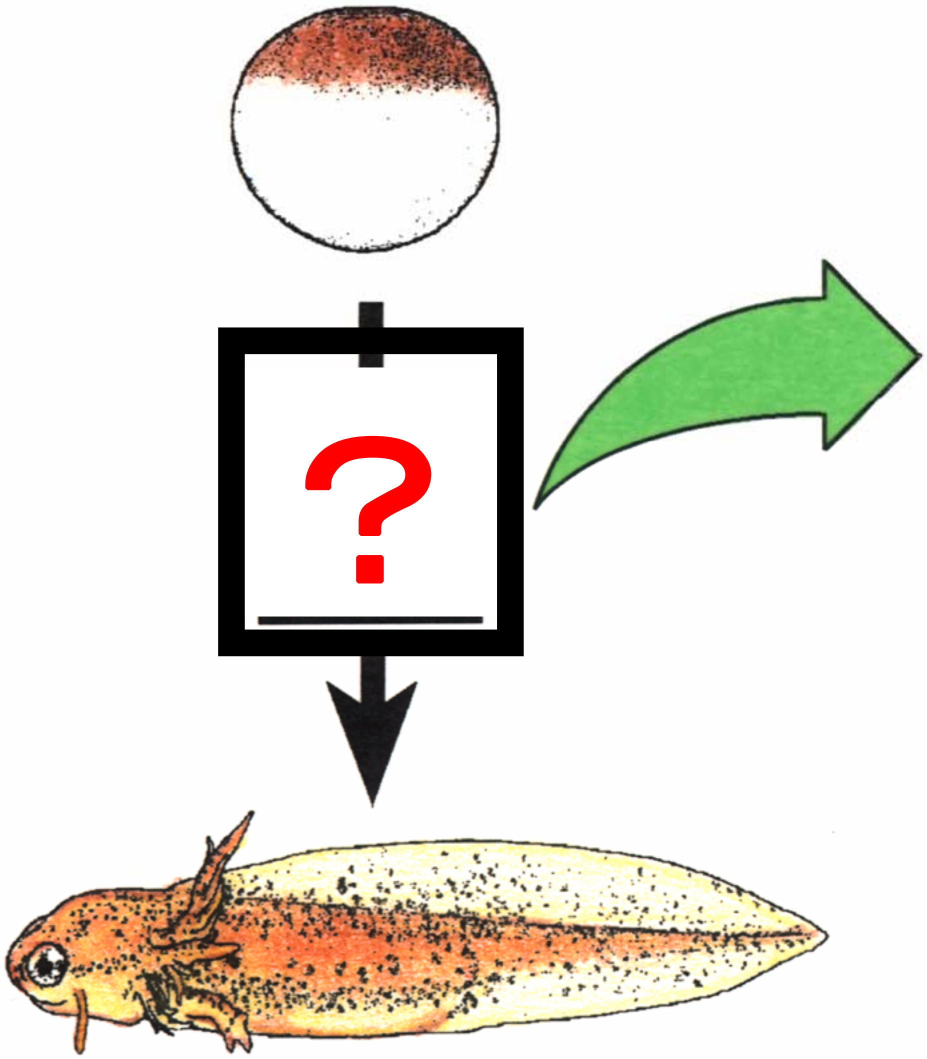


Xenopus laevis
newt
(amphibian)

chicken
(avian)

mouse
human
(mammal)

Morphology change from egg to tadpole



Embryo induction

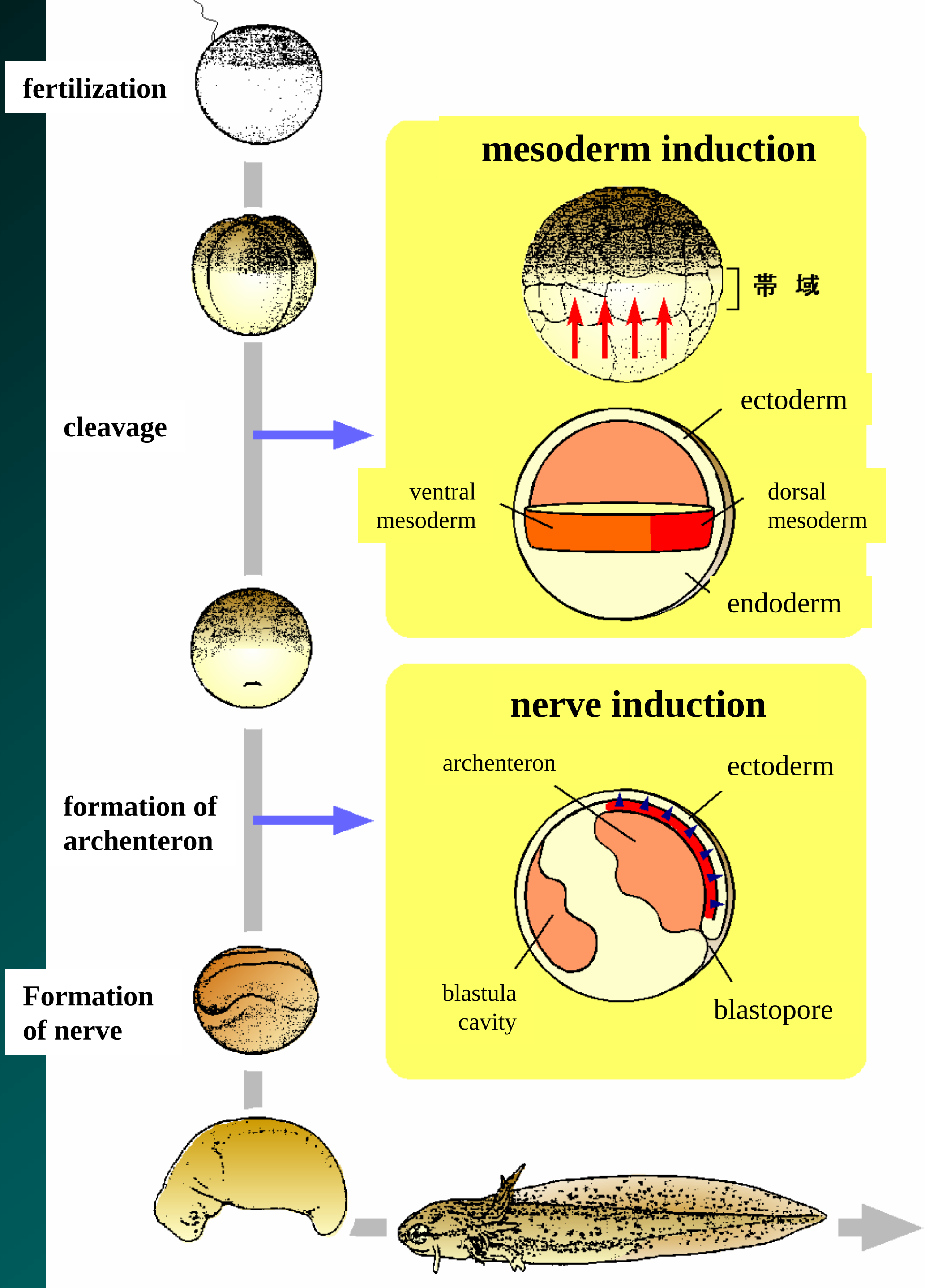
Cell differentiation

Morphogenesis

·
·
·

etc.

Primary development and embryo induction of amphibian

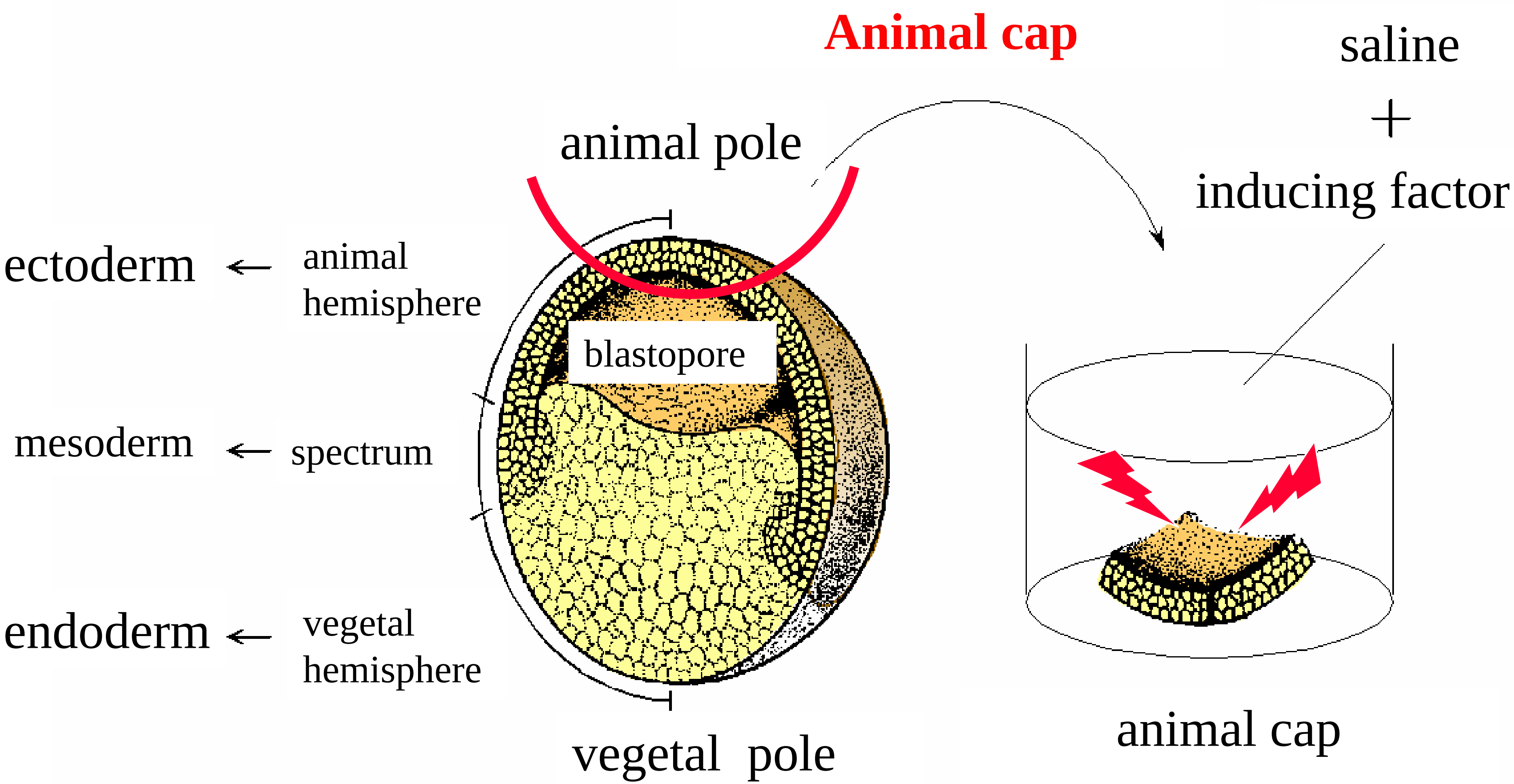


Development of Xenopus embryo

cleavage（view from vegetal pole）to neurula period

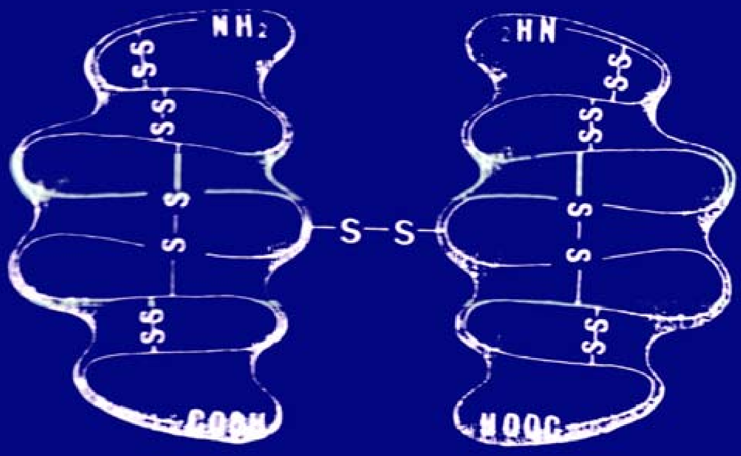
left： *Xenopus tropicalis*,　right：*Xenopus laevis*

Animal Cap Assay



blastopore (vertical section)

Structure of Activin A



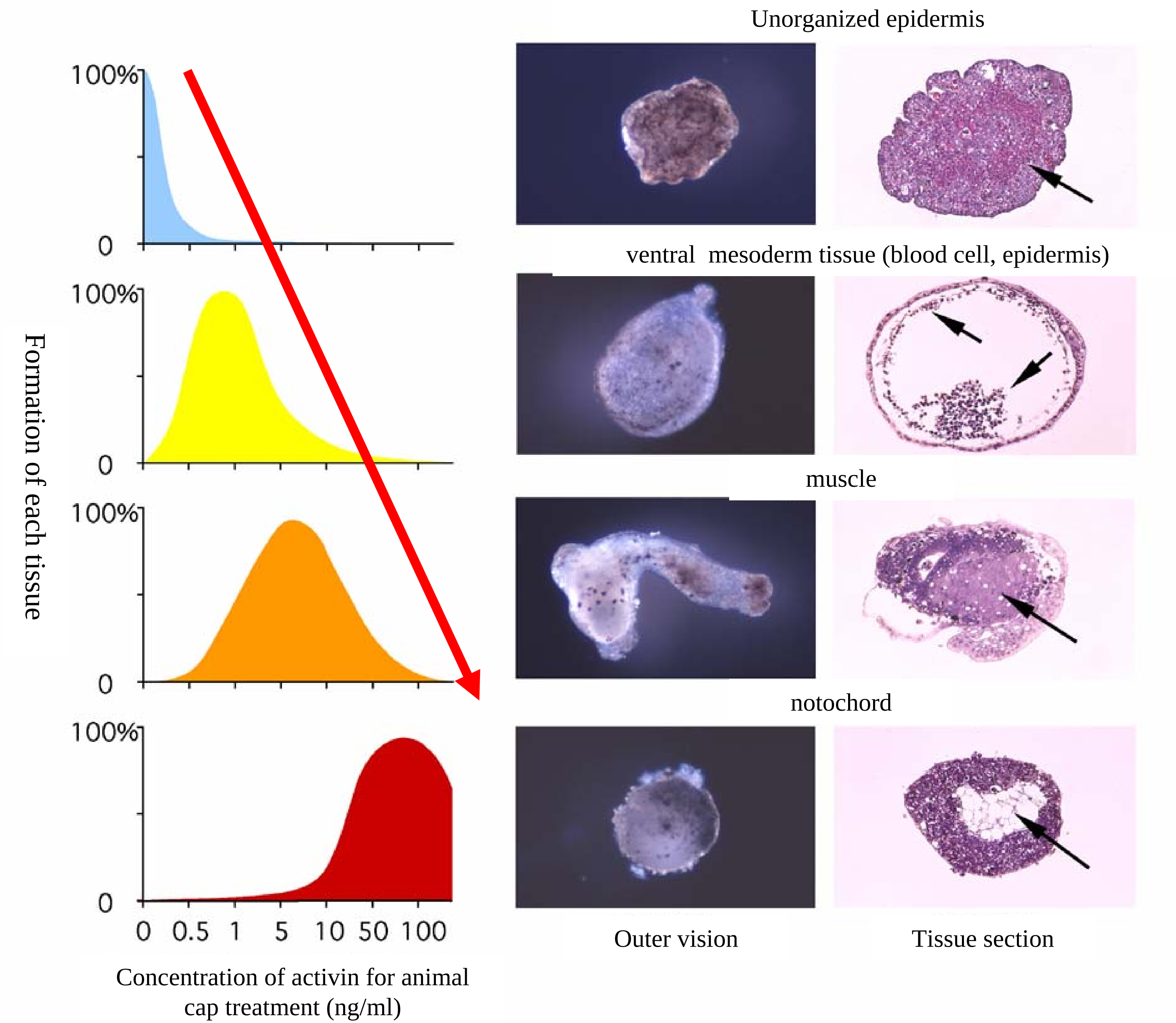
Molecular weight : 25,000 (12,500 X 2)

homodimer

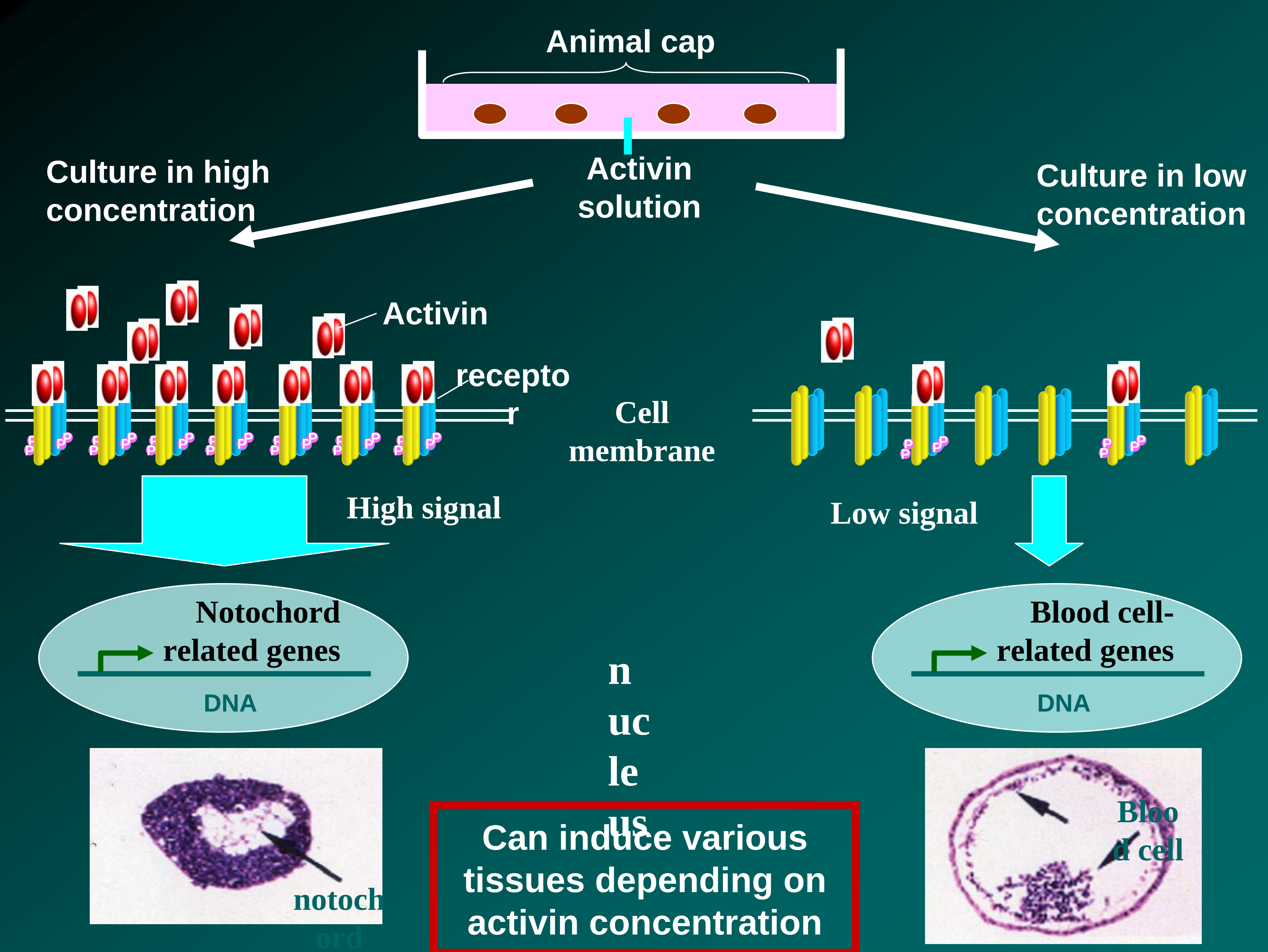
Amino acids : 232 (116 X 2)

SH = 18

Concentration dependent mesoderm differentiation of activin-treated animal cap

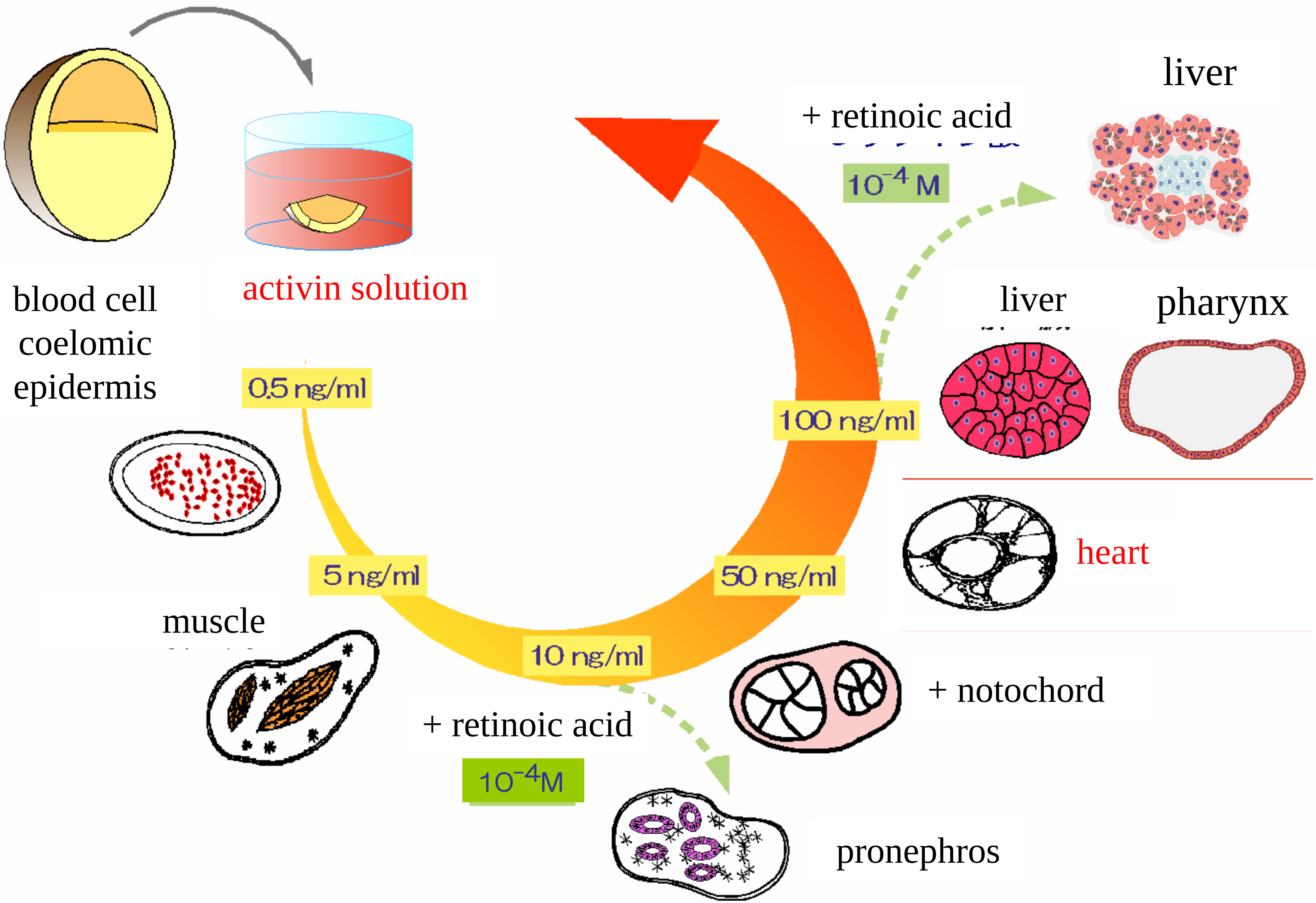


Extending movement and muscle differentiation of activin-treated animal cap



Animal cap
Activin solution
Culture in high concentration
Culture in low concentration
Activin
recepto
r
Cell membrane
High signal
Low signal
Notochord related genes
DNA
Blood cell-related genes
DNA
n
uc
le
us
notoch
ord
Bloo
d cell
Can induce various tissues depending on activin concentration

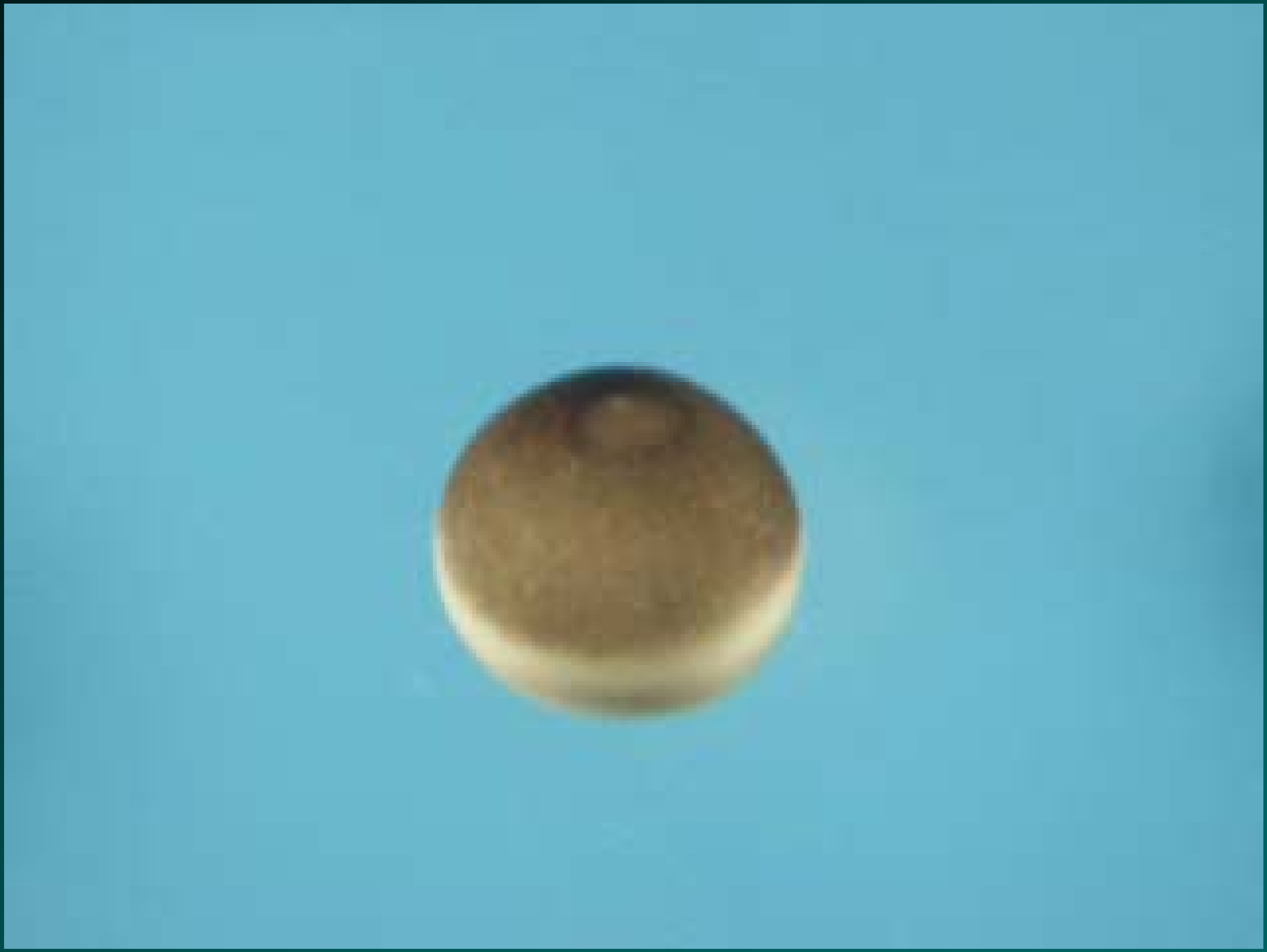
Organs and tissues formed from activin-treated animal cap



① What makes parts of the body anterior, posterior, right, left, ventral, or dorsal ?

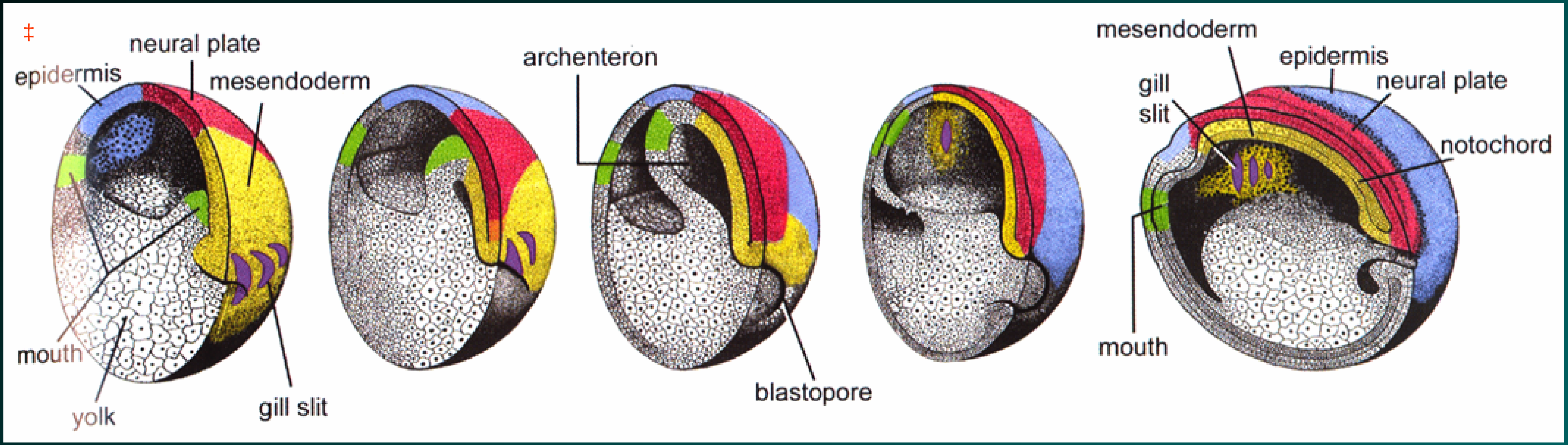
ex１：Position of sperm penetration determines ventral-dorsal axis
ex２：Formations of head-tail axis, ventral-dorsal axis, left-right axis

Cleavage of *Xenopus laevis* fertilized egg

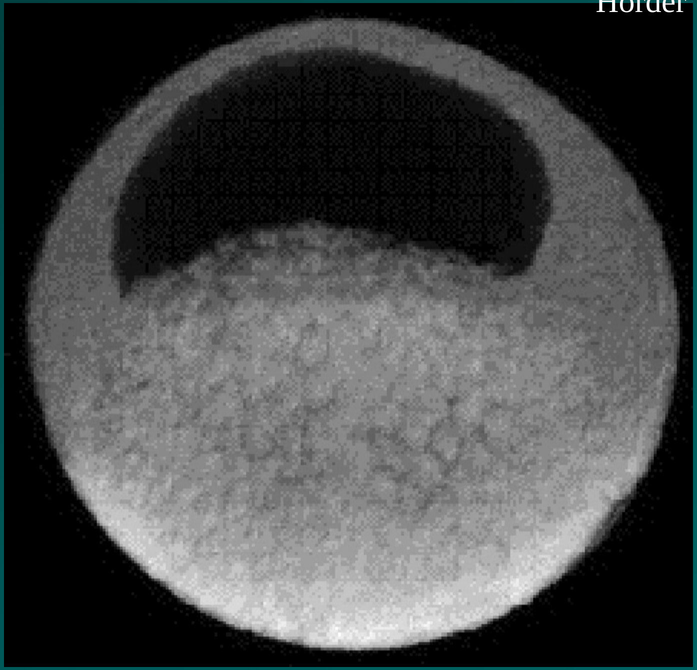


View from animal pole（1 cell period～128 cell period）

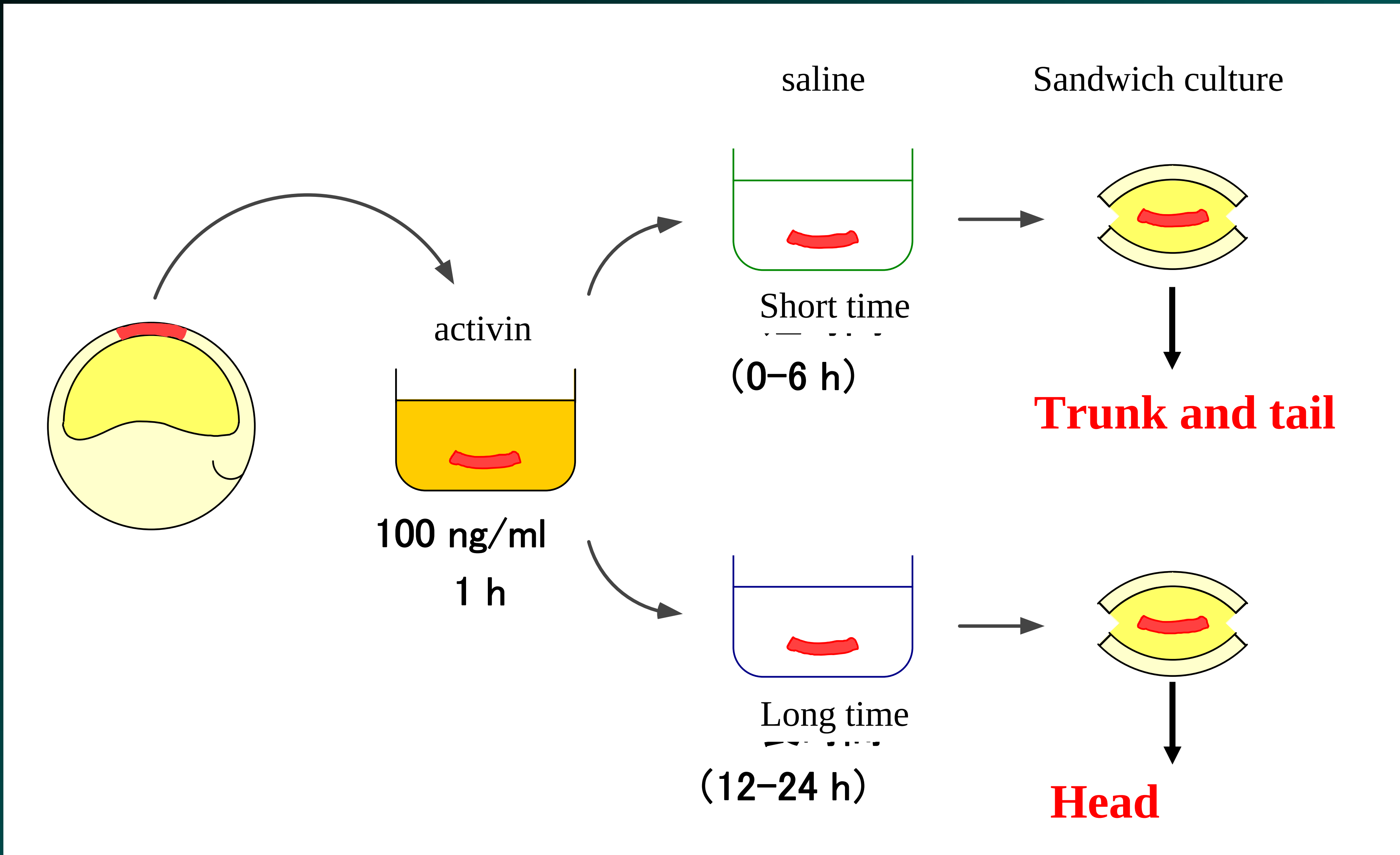
Gastrulation of Xenopus Embryo



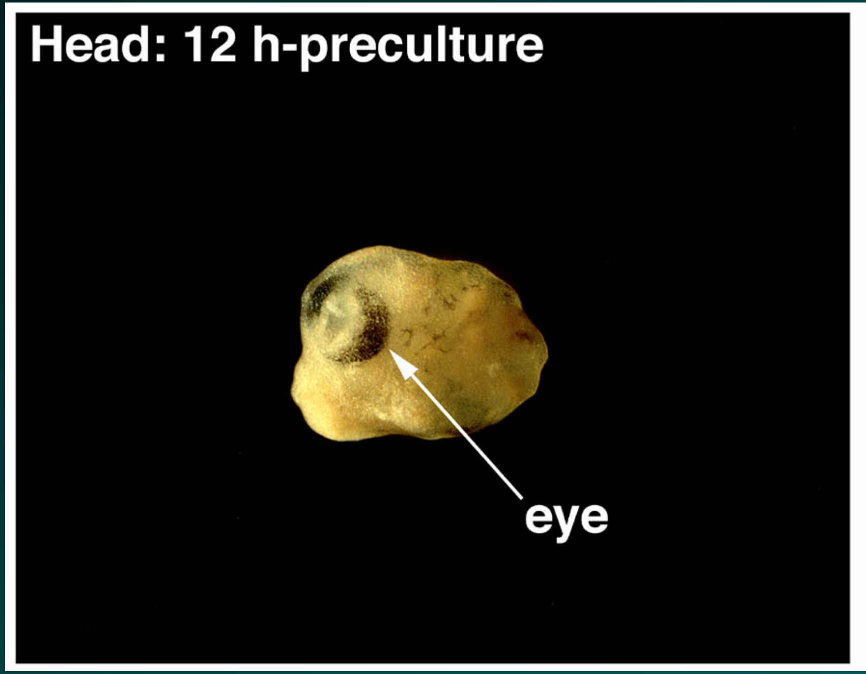
Horder TJ.   Int J Dev Biol, vol 45, p105-Fig.3, 2001



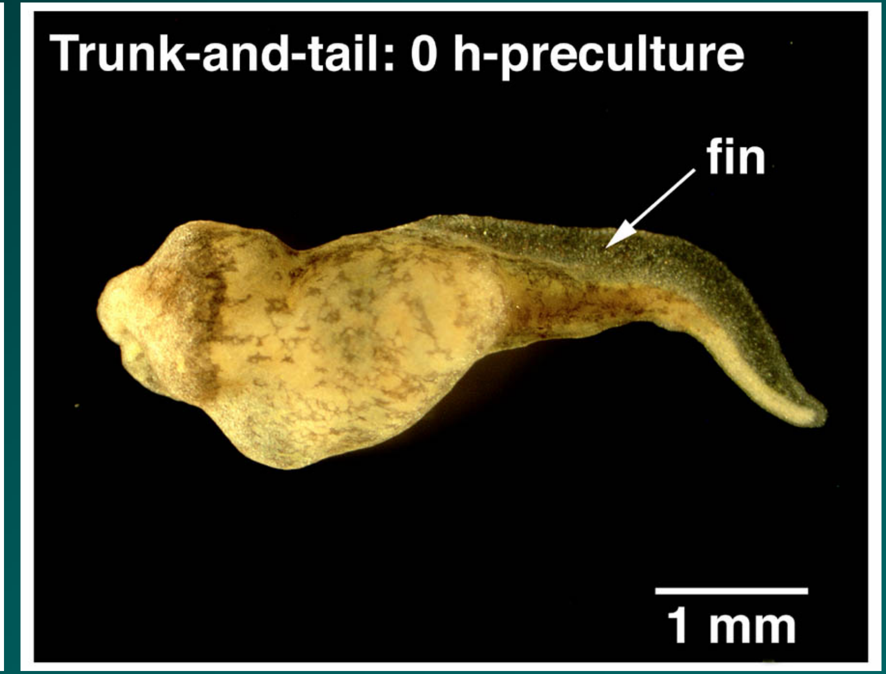
Experiment to make head part and tail part of larva in vitro



Head structure and trunk-and-tail structure induced artificially from undifferentiated cell of xenopus

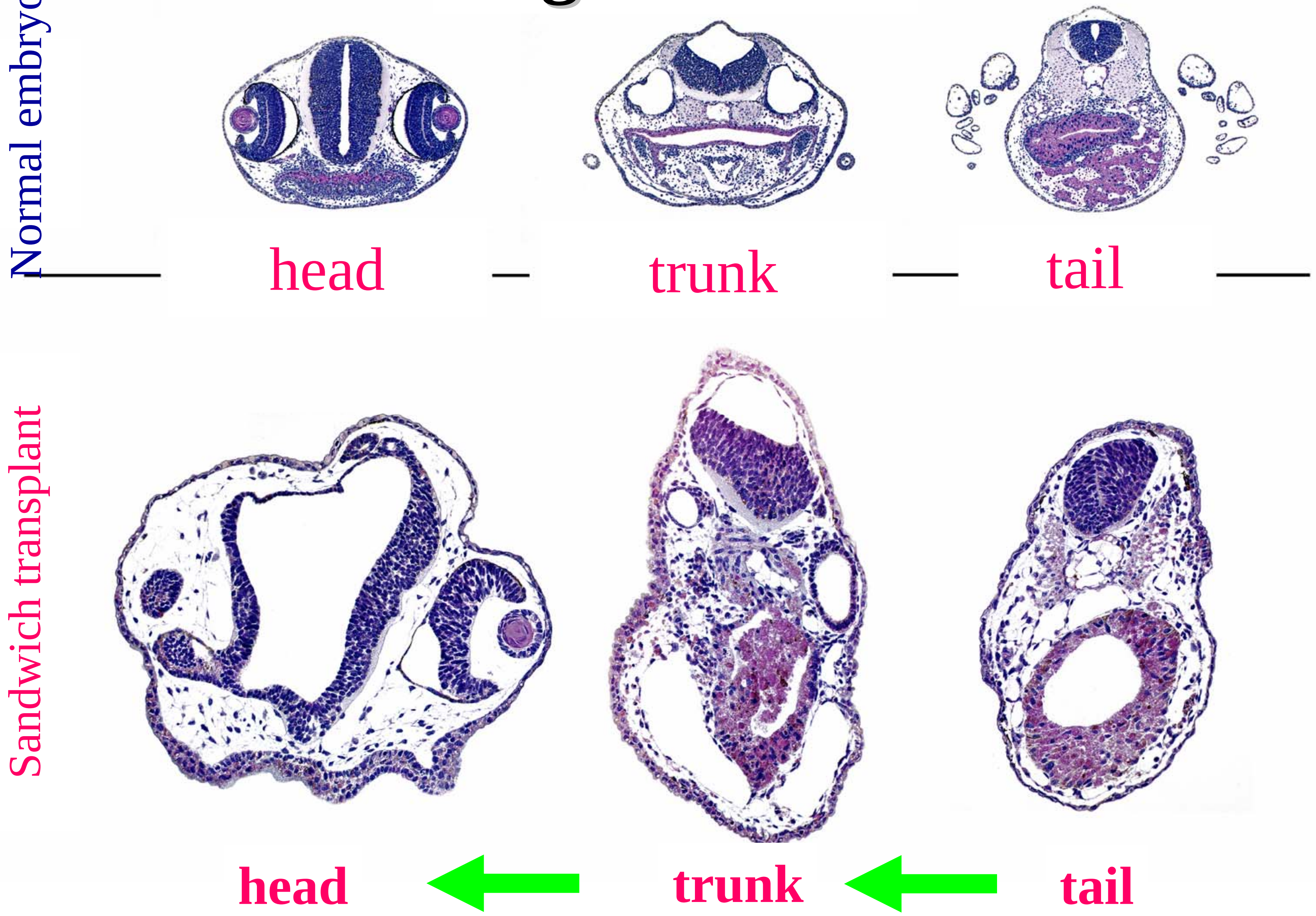


Head part

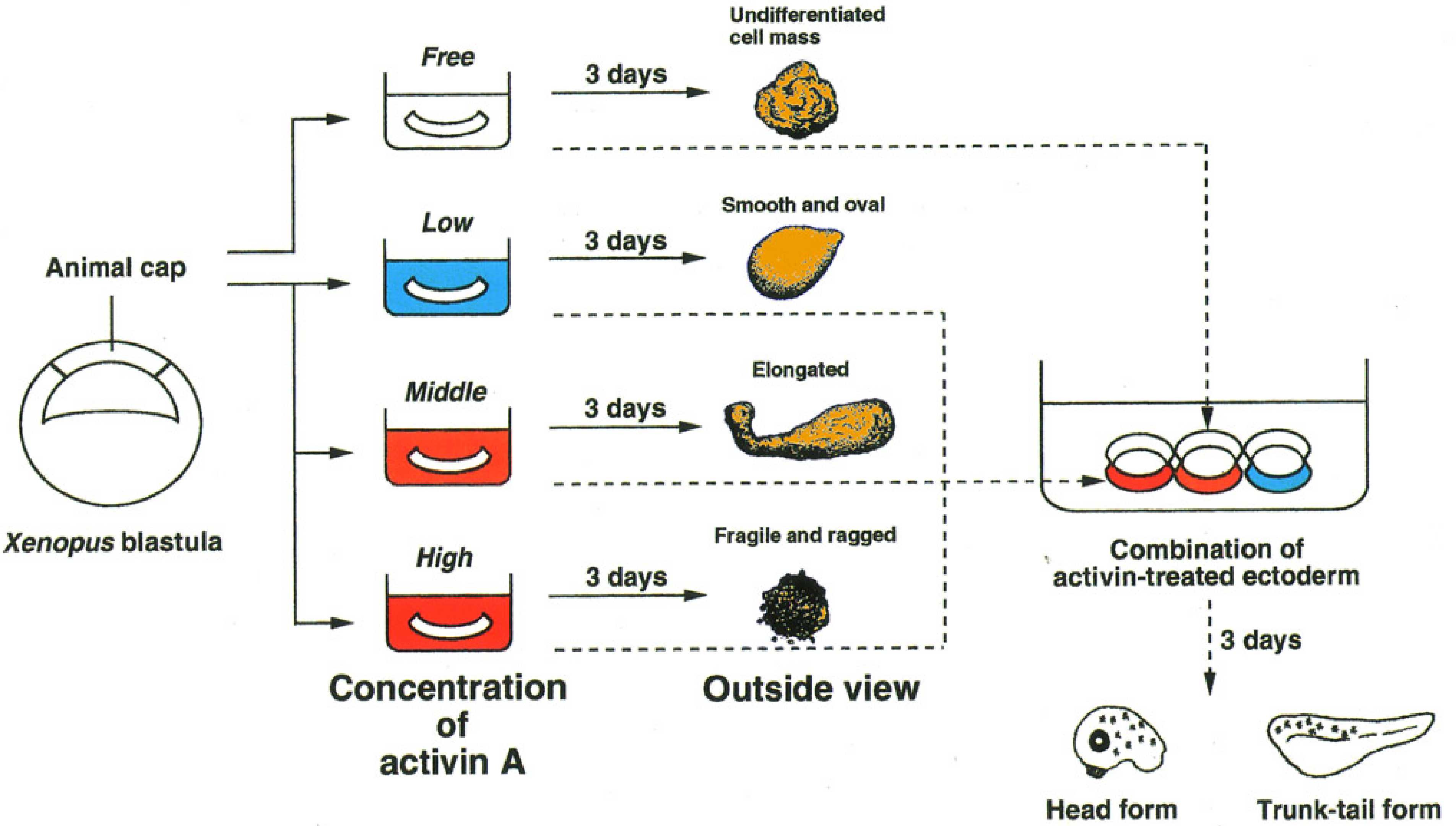


Trunk and Tail part

Organ section



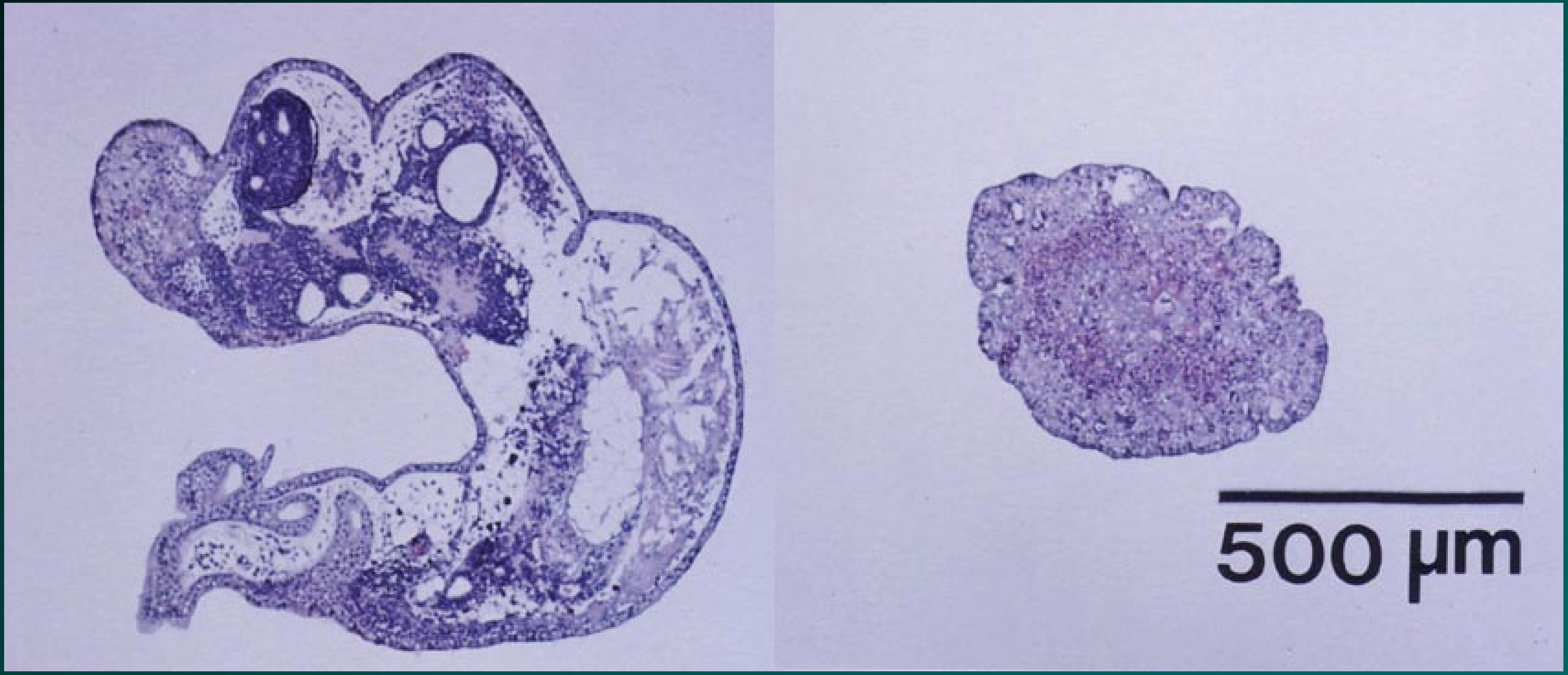
Reproduction of morphogenesis by activin gradient



Reproduction of morphogenesis by activin gradient

- outer image of tadpole-like structure induced artificially

Reproduction of morphogenesis by activin gradient



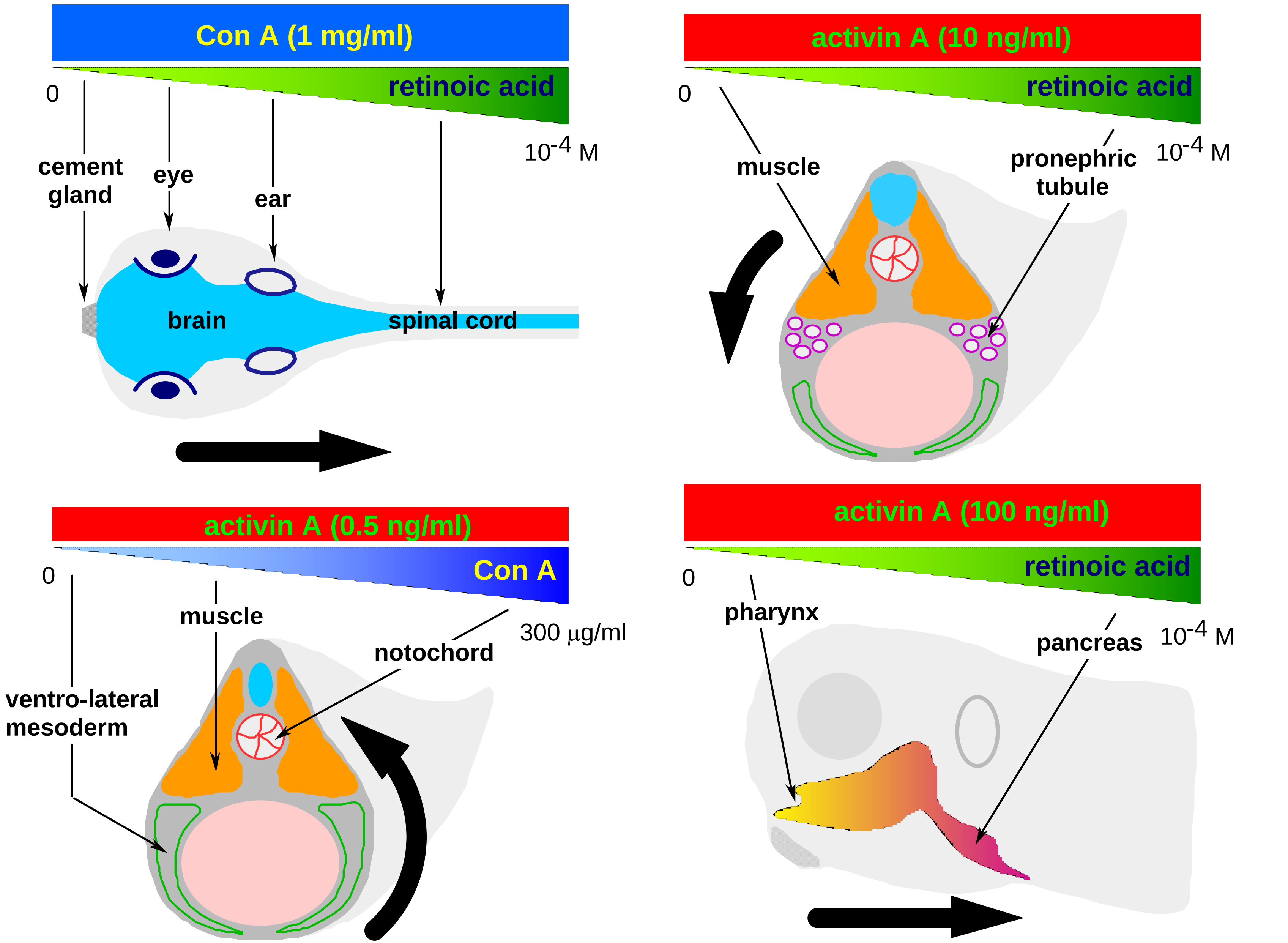
Tissue section of tadpole-like structure artificially induced

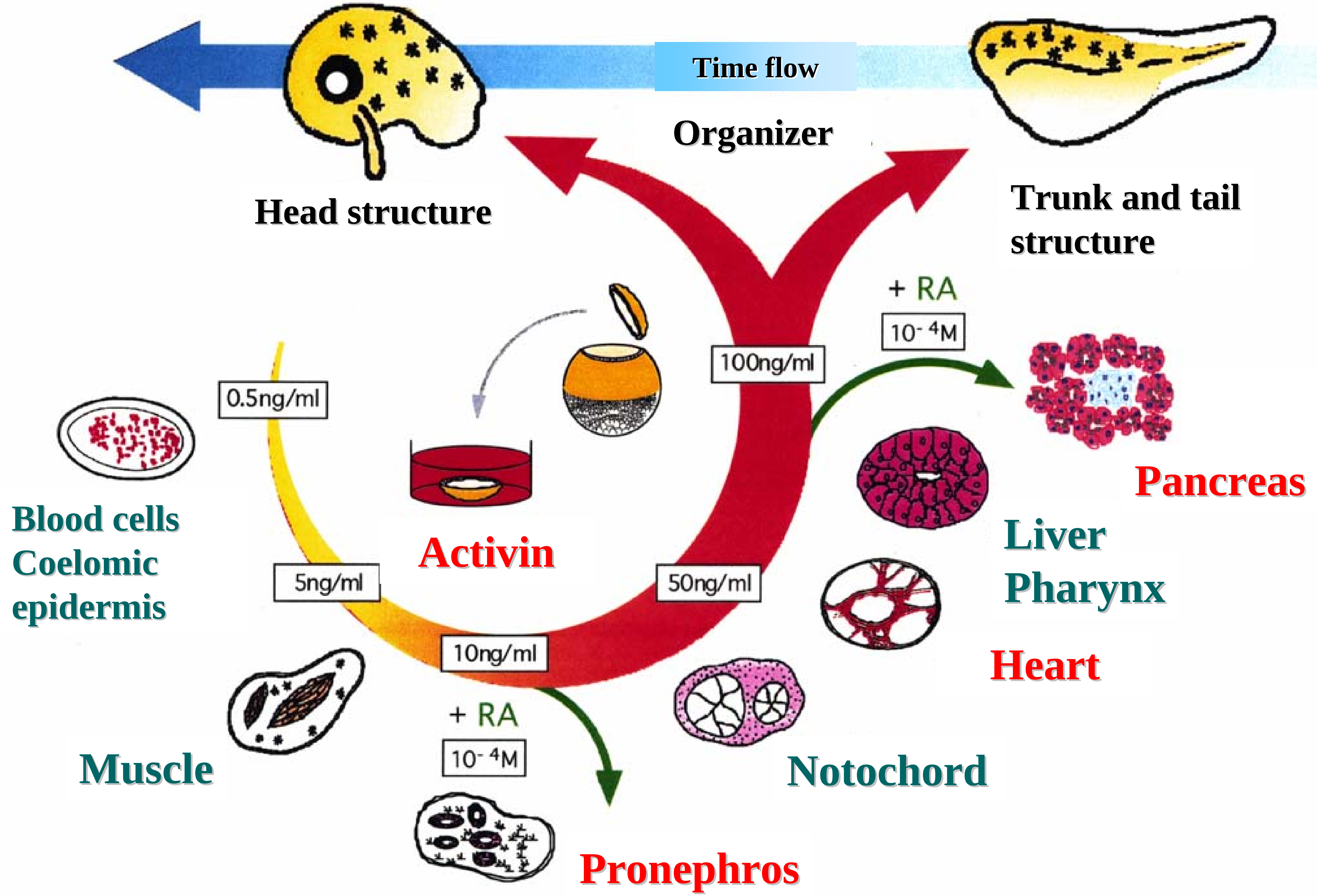
Cell mass untreated by activin（comparison）

↓

Most organs and tissues are formed (notochord, muscle, eye, brain, enteron, etc.)

Control of fundamental body plan by activin A, Con A and retinoic acid

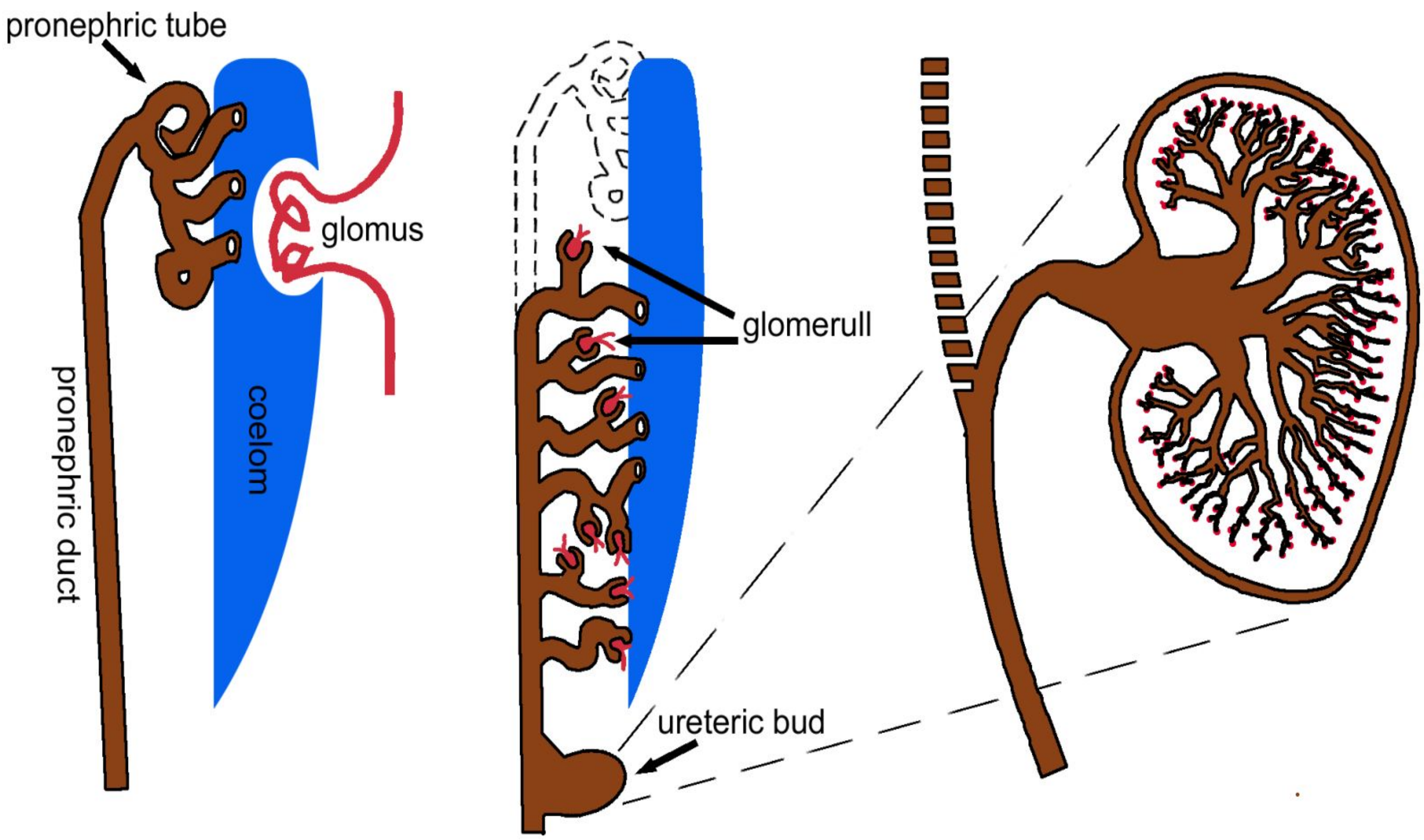



Time flow
Organizer
Head structure
Trunk and tail structure
+ RA
10^{-4}M
100ng/ml
0.5ng/ml
Pancreas
Liver
Pharynx
Blood cells
Coelomic
epidermis
Activin
5ng/ml
50ng/ml
10ng/ml
Heart
+ RA
10^{-4}M
Muscle
Notochord
Pronephros

② Focus on development of various tissues and organs

-an example of organ formation research using kidneys

Kidney development

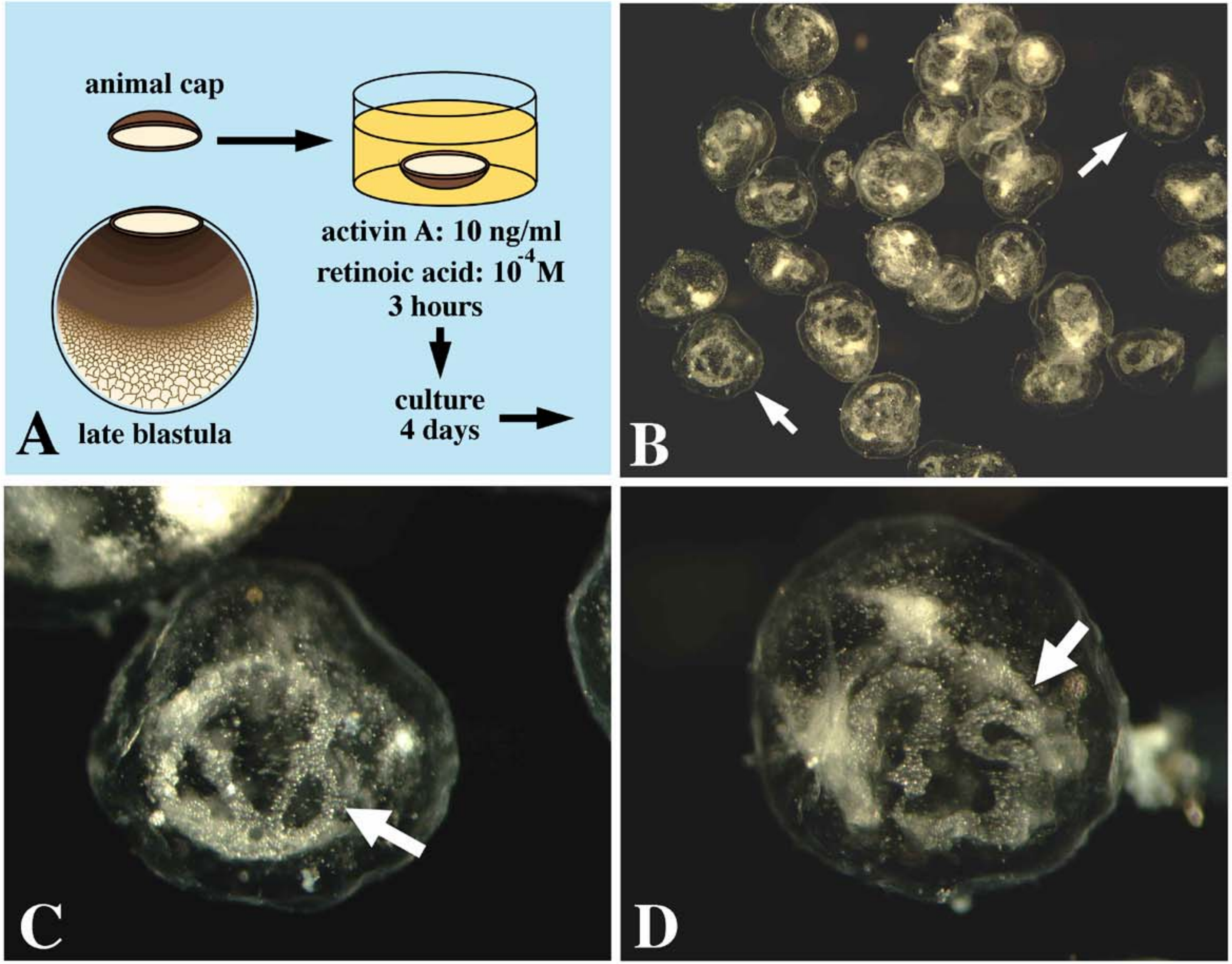


pronephros
（1 nephron）
tadpole

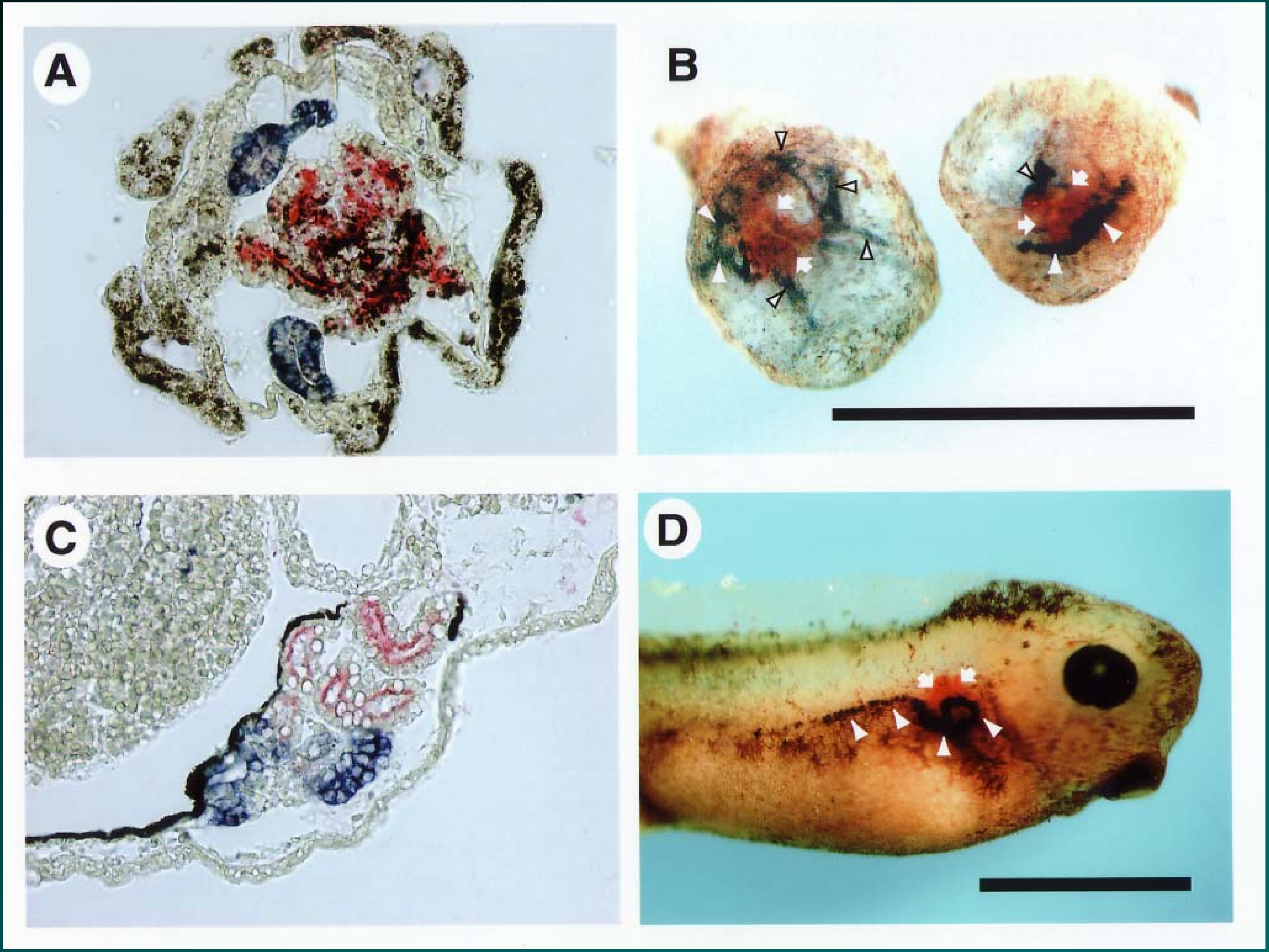
mesonephros
（30 nephron）
adult frog

metanephros
（about 1million nephron）
Human, etc.

Formation of pronephros from an animal cap in vitro

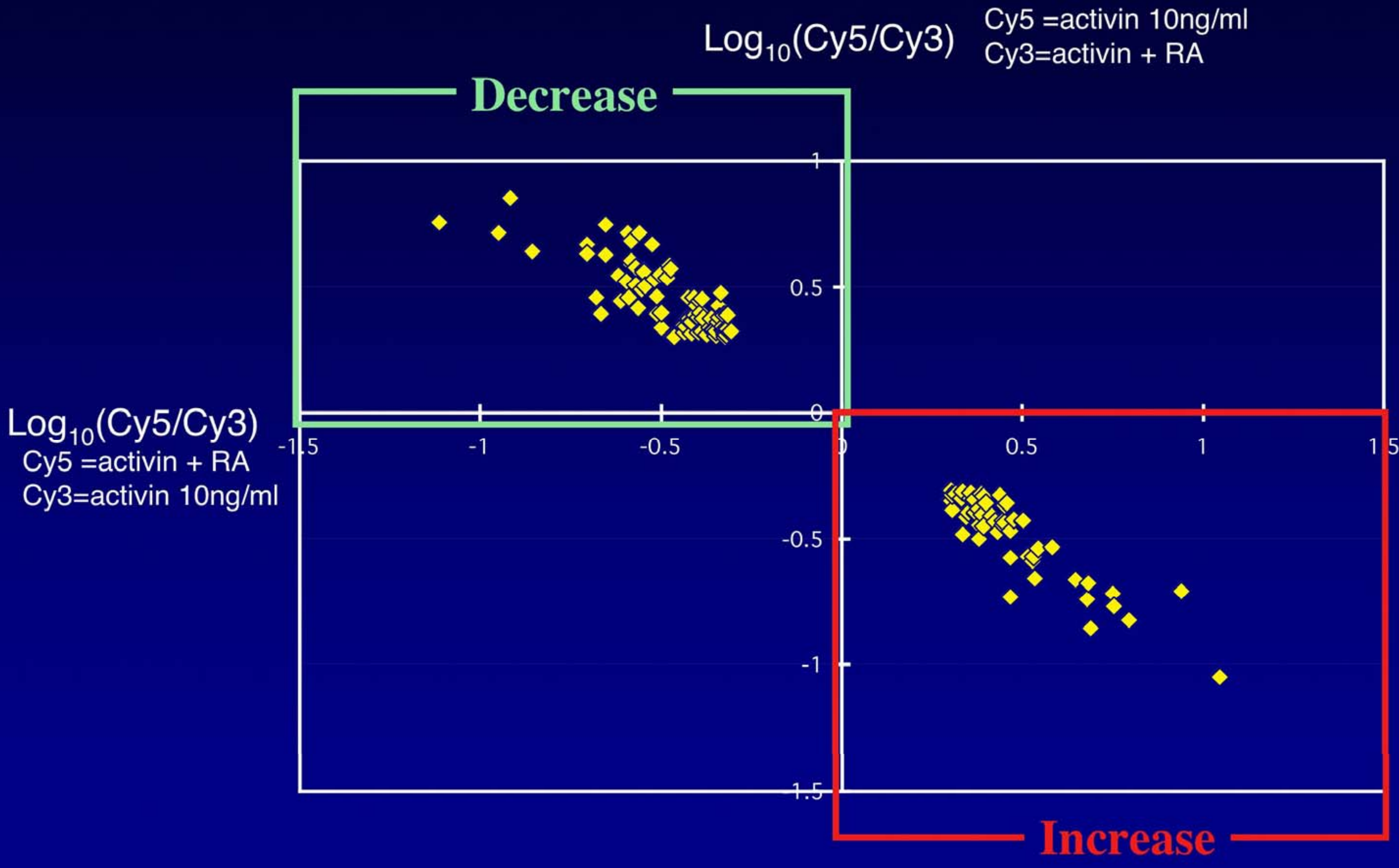


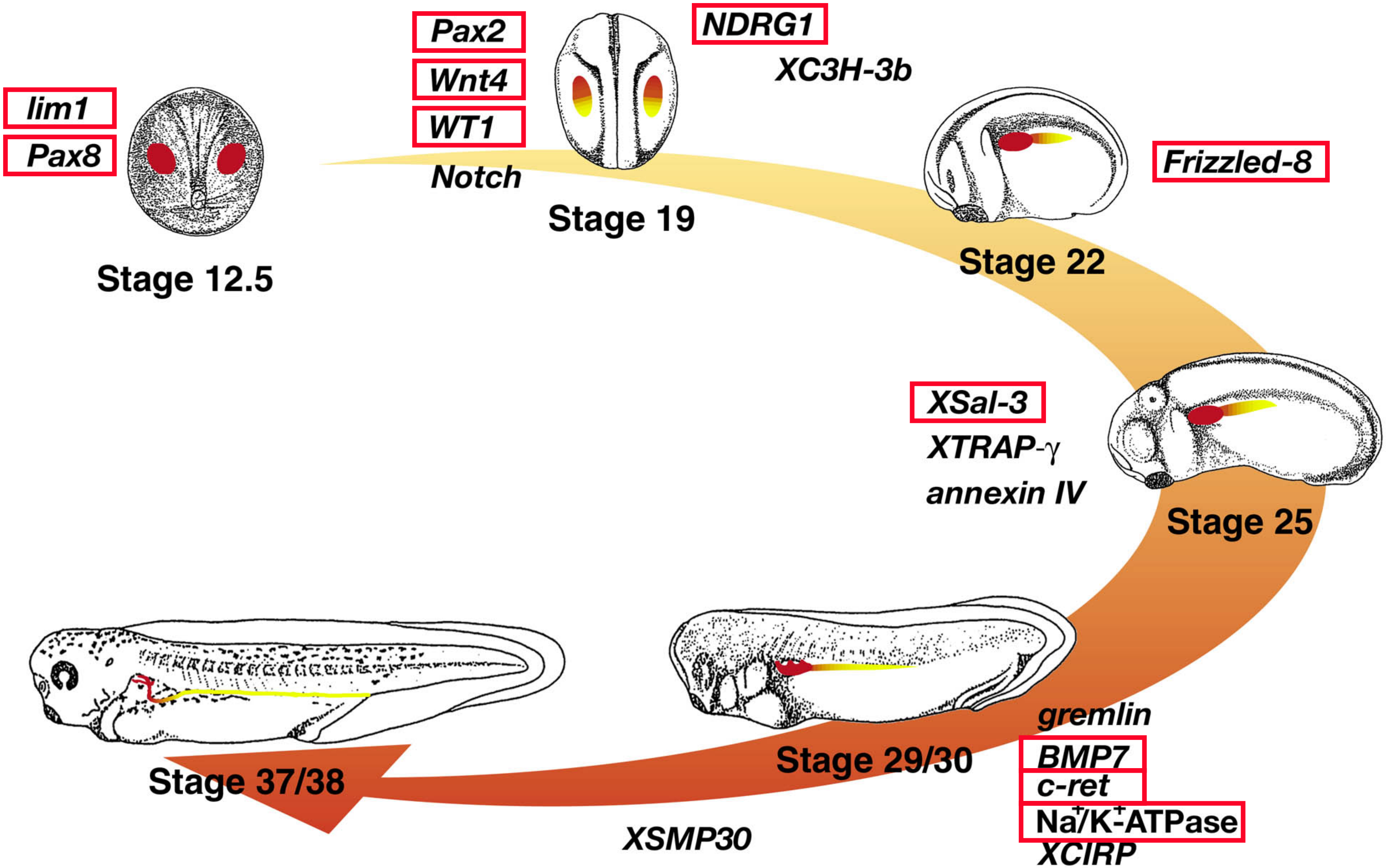
Formation of pronephric structure in vitro (A+B) and in vivo (C+D)



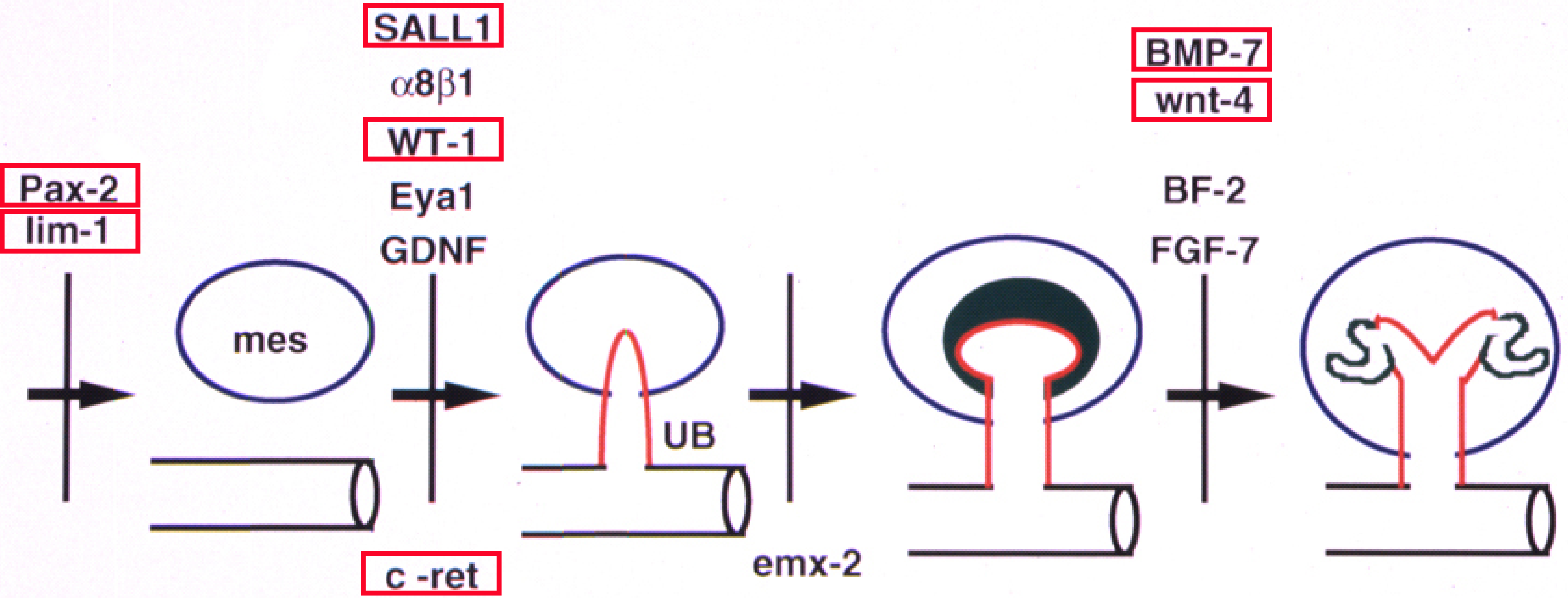
The Result of DNA Microarray Analysis of Pronephros

(*In Vitro*-Induced Pronephros of *Xenopus laevis*)



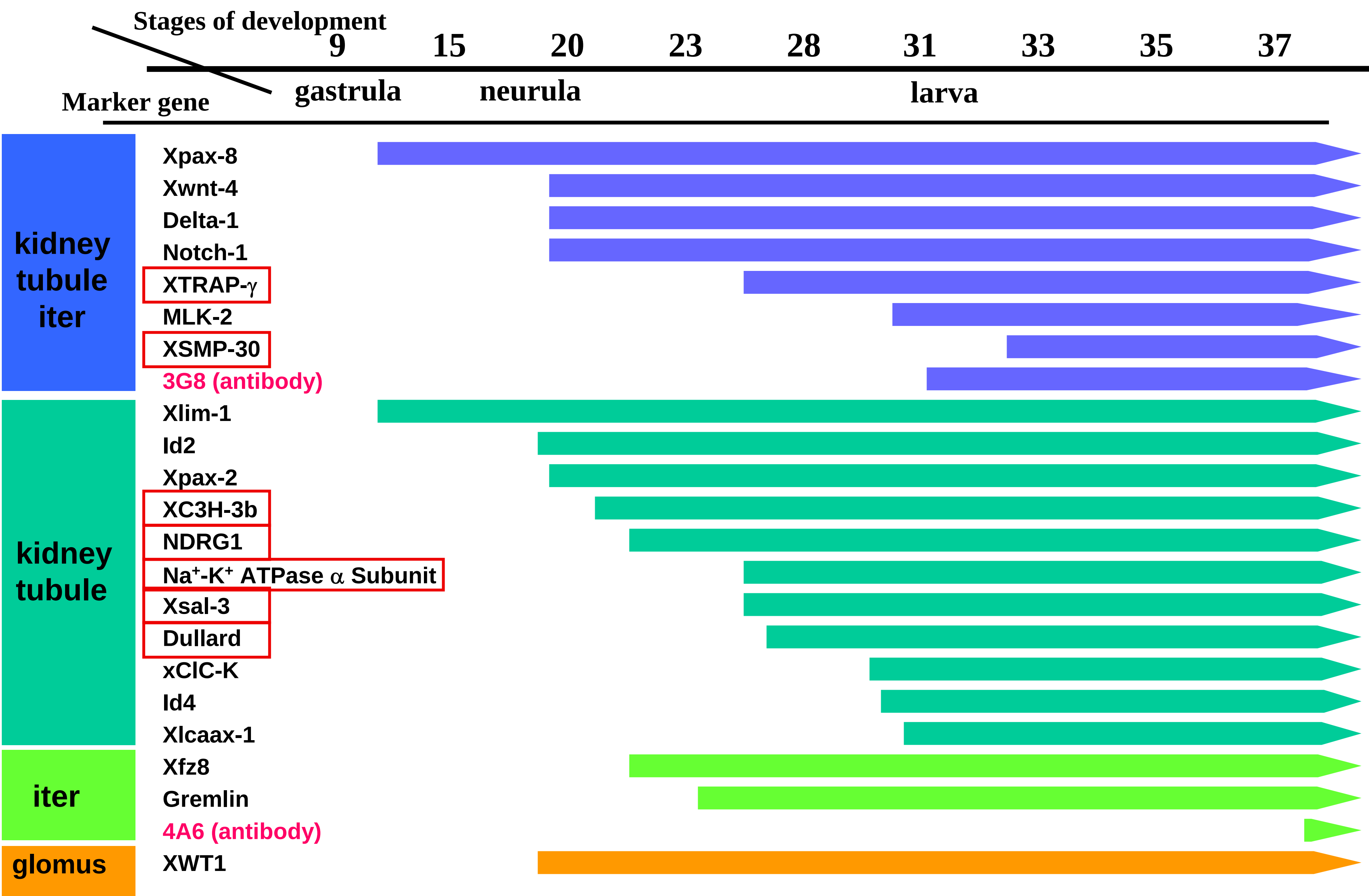


Kidney development and gene expression in amphibians (frog)

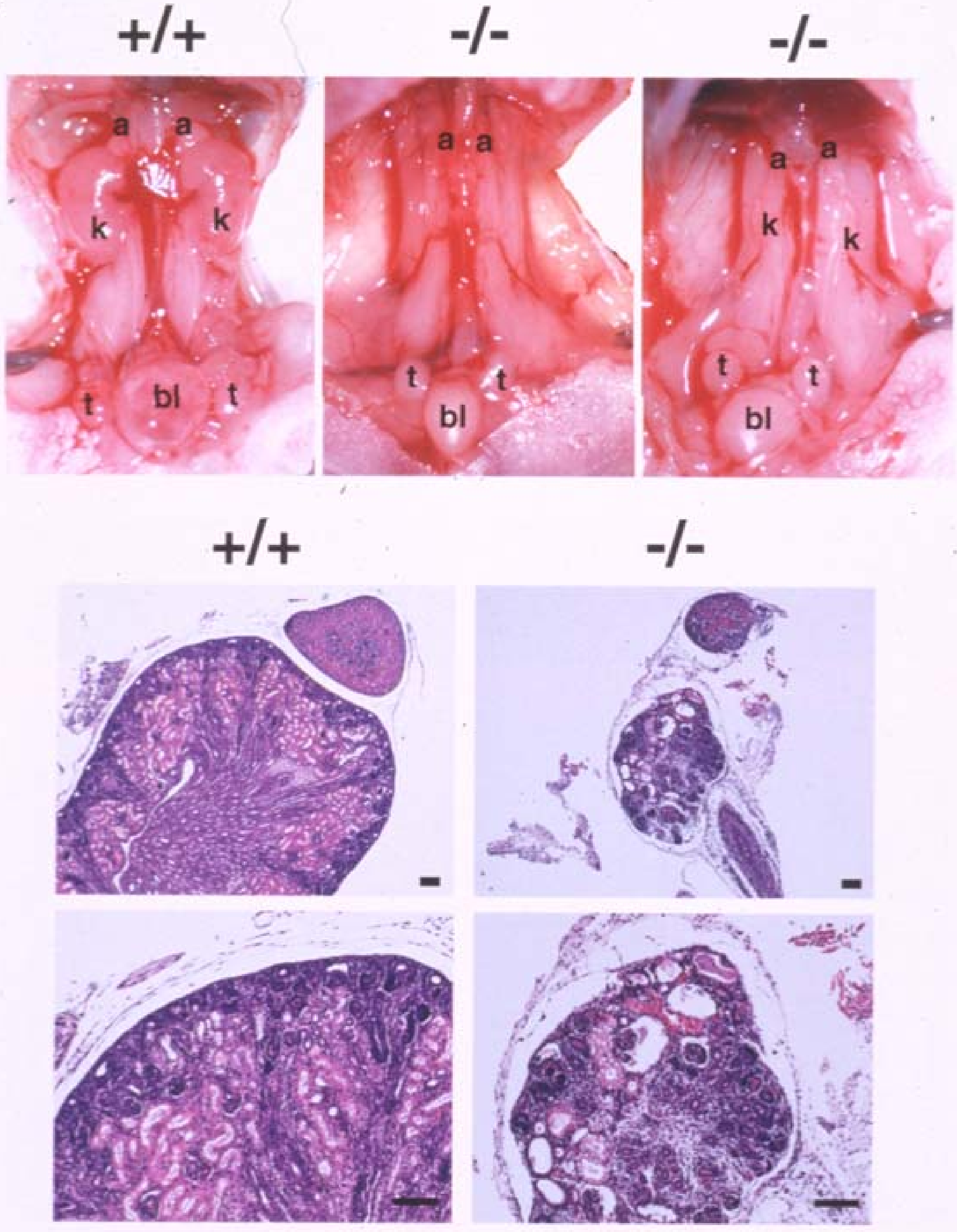


Kidney development and gene expression in mammals (human, mouse)

Gene groups expressed during kidney development



Kidney of a mouse embryo



Nishinakamura R. et al., Development, vol 128, p3110-Fig.4, 2001

Relationship between kidney development and genes

Knockout of the SALL gene (gene responsible for kidney development in a frog) would cause a kidney defect in a mouse.

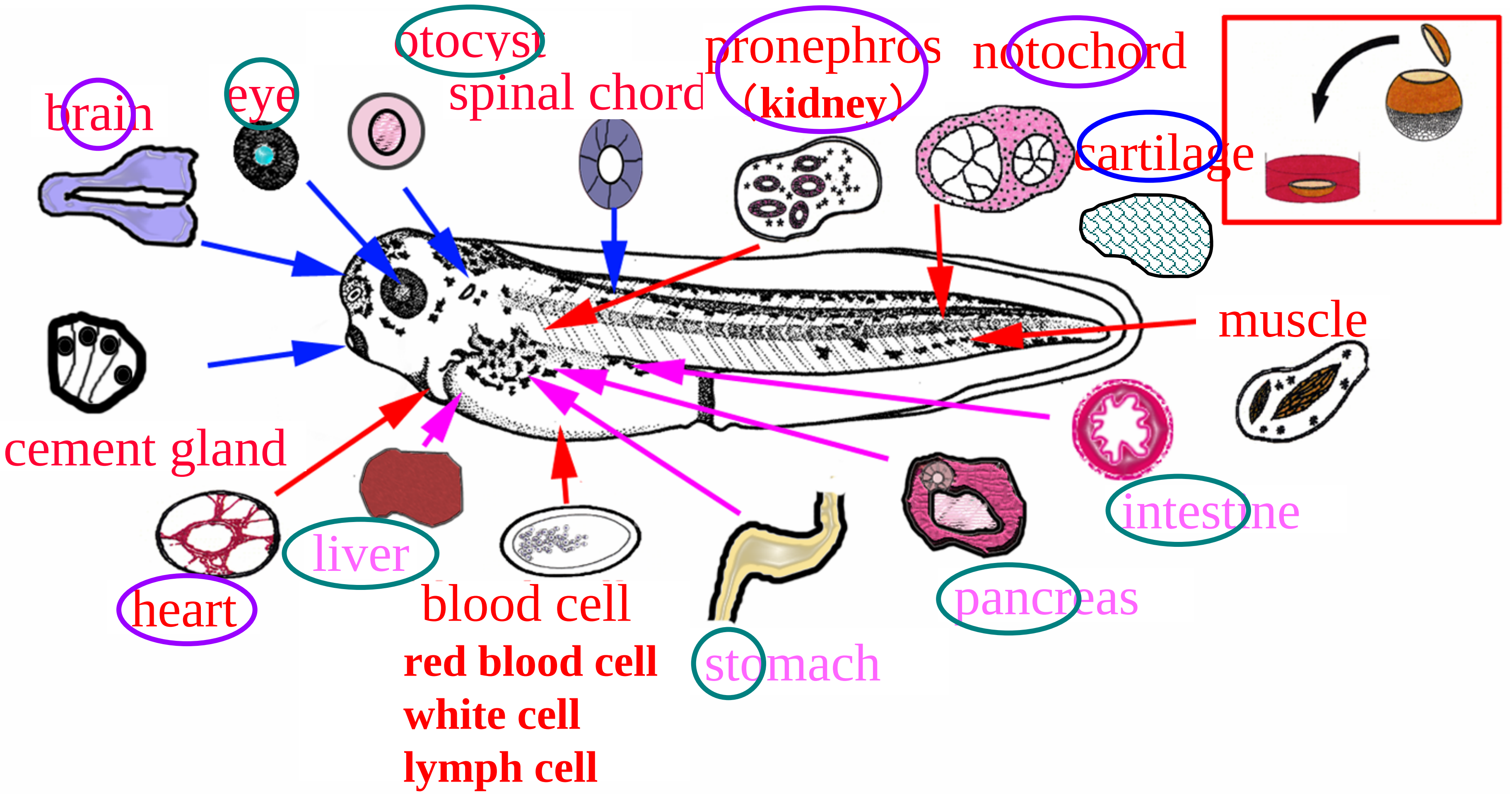
↓

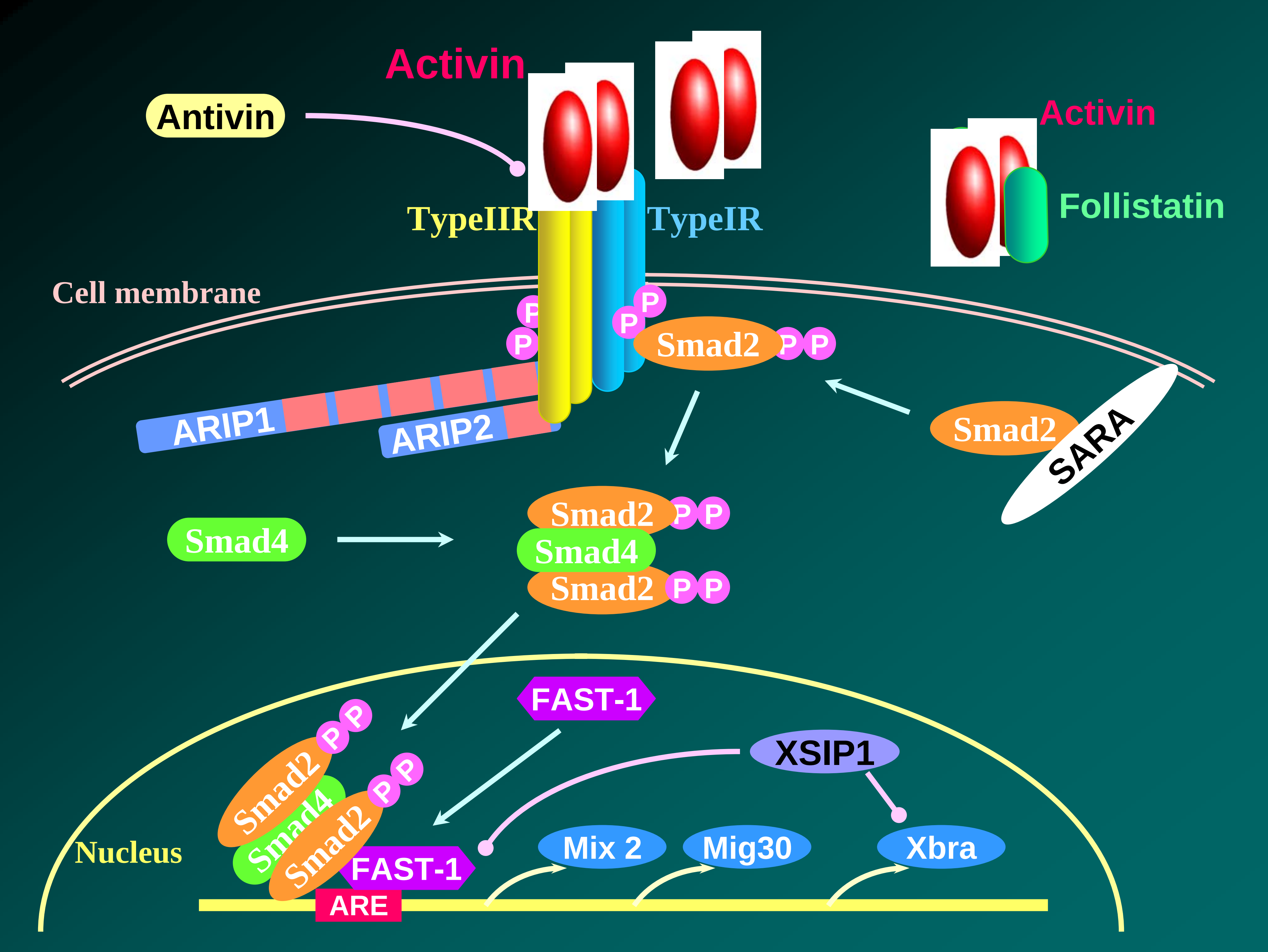
Cases of human babies without kidneys were reported.
(a.k.a.Townes-Brocks syndrome over a long time)
Cause of the syndrome was discovered to be a defect in the SALL gene.

↓

Function of the SALL gene in kidney development was discovered in frogs. SALL was found to be responsible for kidney development of all vertebrates.

Organs and tissues developed from undifferentiated xenopus cell (animal cap) in vitro (at Asashima Lab.)

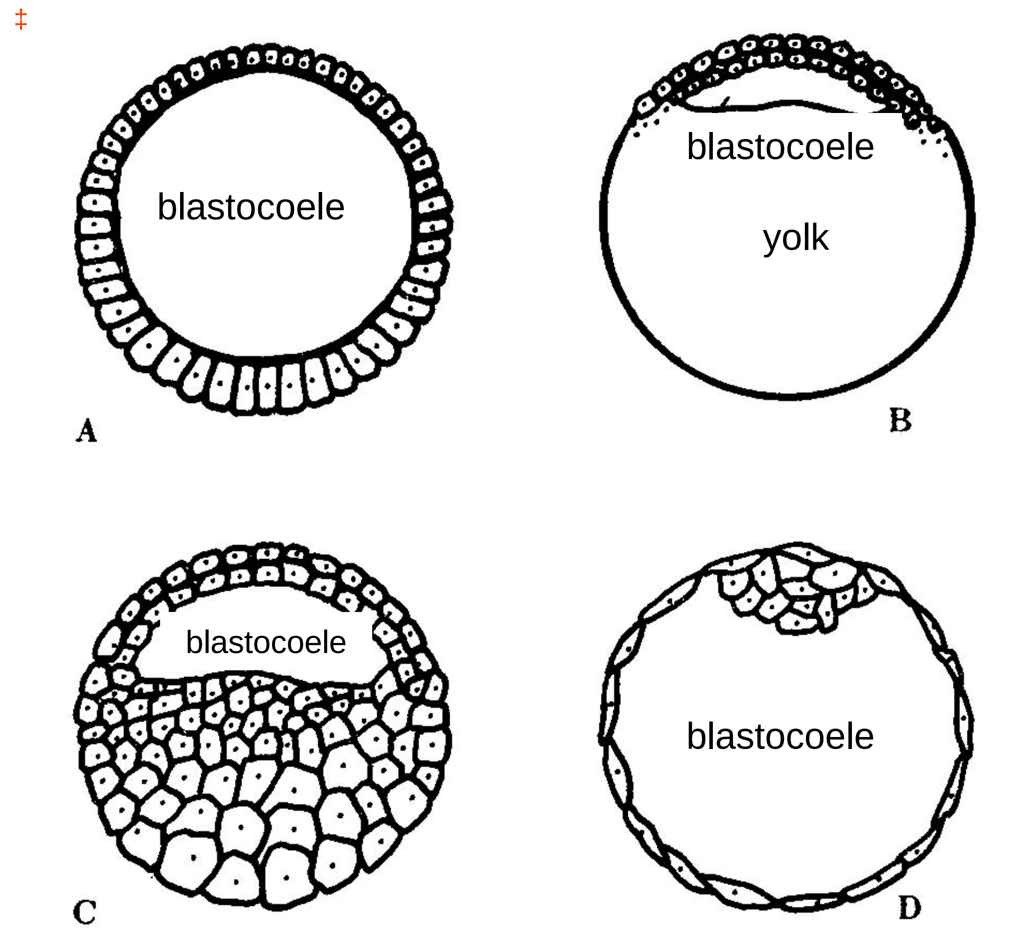



Activin
Antivin
TypeIIR
TypeIR
Activin
Follistatin
Cell membrane
P
P
P
P
Smad2
P
P
ARIP1
ARIP2
Smad2
SARA
Smad4
Smad2
P
P
Smad4
Smad2
P
P
FAST-1
XSIP1
Smad2
P
P
Smad4
Smad2
P
P
FAST-1
ARE
Nucleus
Mix 2
Mig30
Xbra

Morphogenesis and cavity

- the issue of post-genomes

Cavity formation is important in animal development



第30図 blastocoeles **A** amphioxus **B** Teleost fish
C amphibian **D** mammal

1983 Idemitsu Shoten

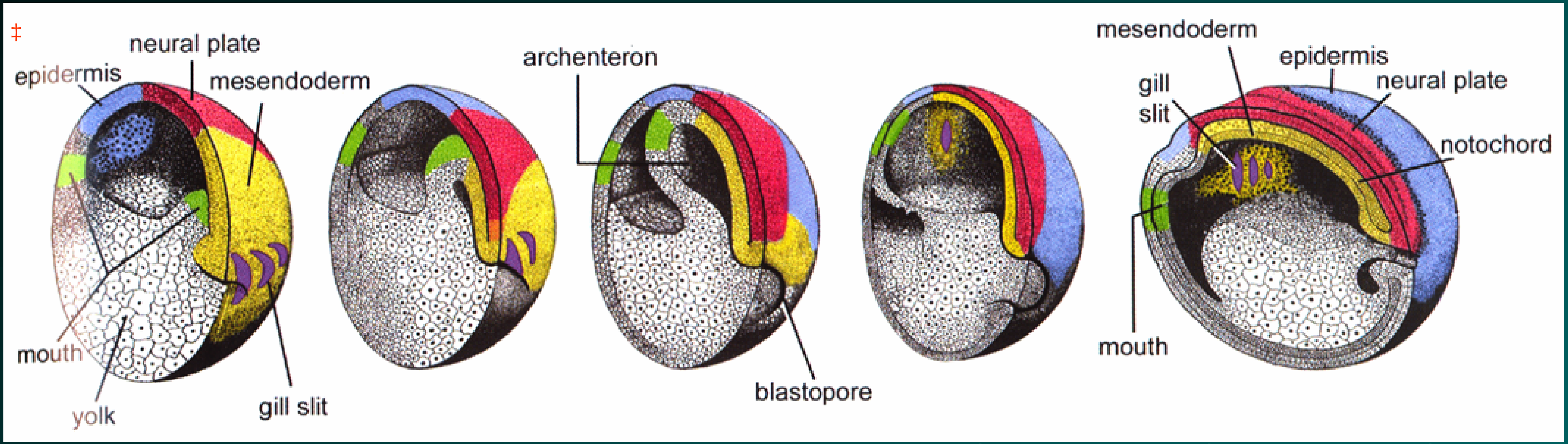
Cells move toward the cavity to produce a new cavity.
Simple form develops into a complex form.

Blastula of a sea urchin

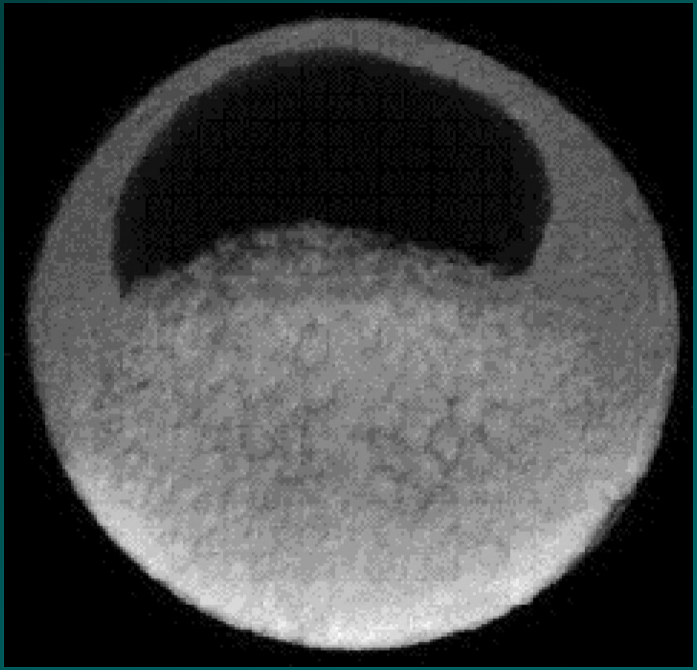
Claudio D. Stern ed. "Gastrulation" p21, 2004 Cold Spring Harbor Laboratory Press

Vegetal pole cells emboly toward the blastocoele.

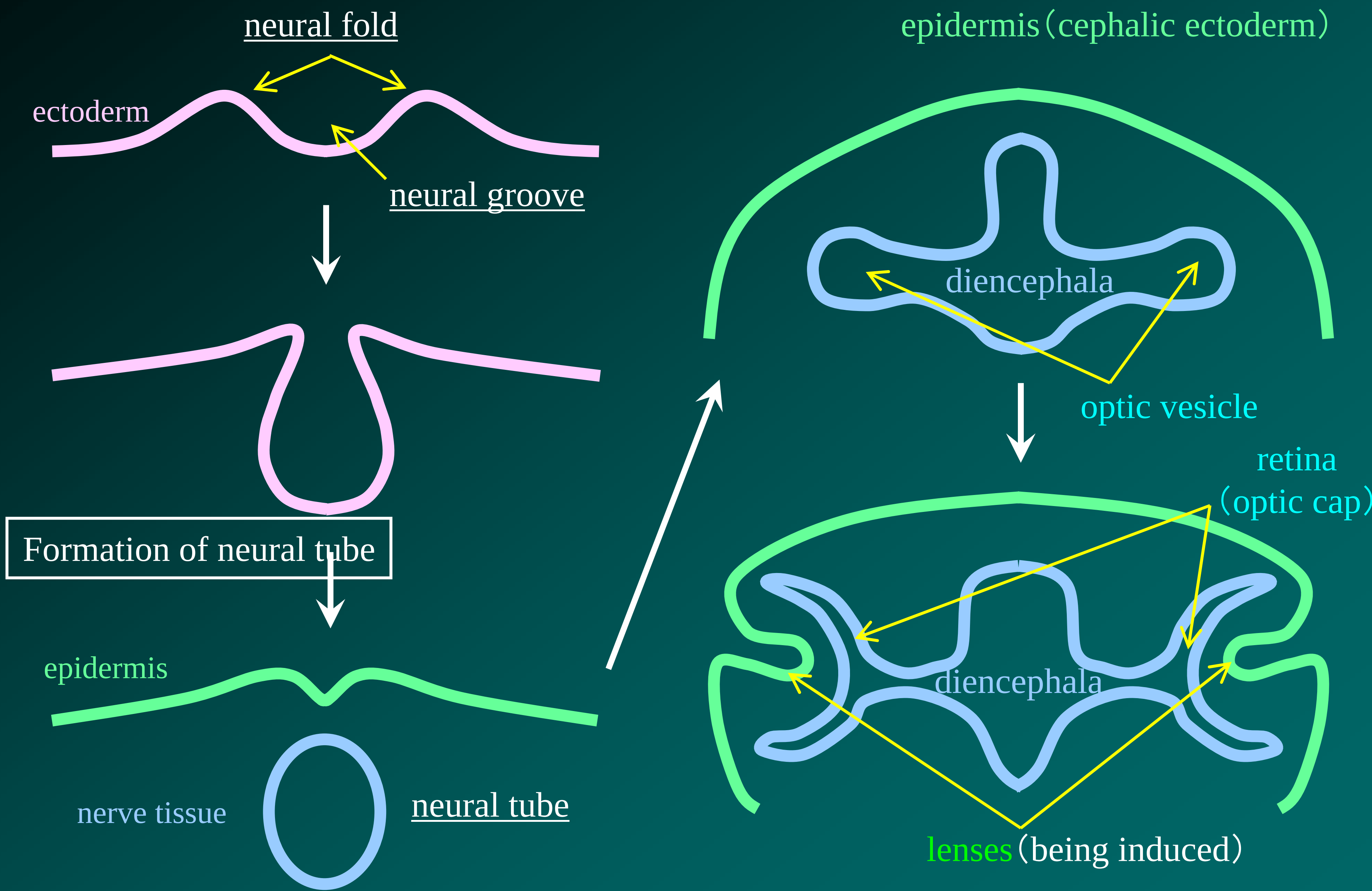
Gastrulation in Xenopus Embryo



Horder TJ. Int J Dev Biol, vol 45, p105-Fig.3, 2001



More complex cavity formation and neural formation①



More complex cavity formation and neural formation②

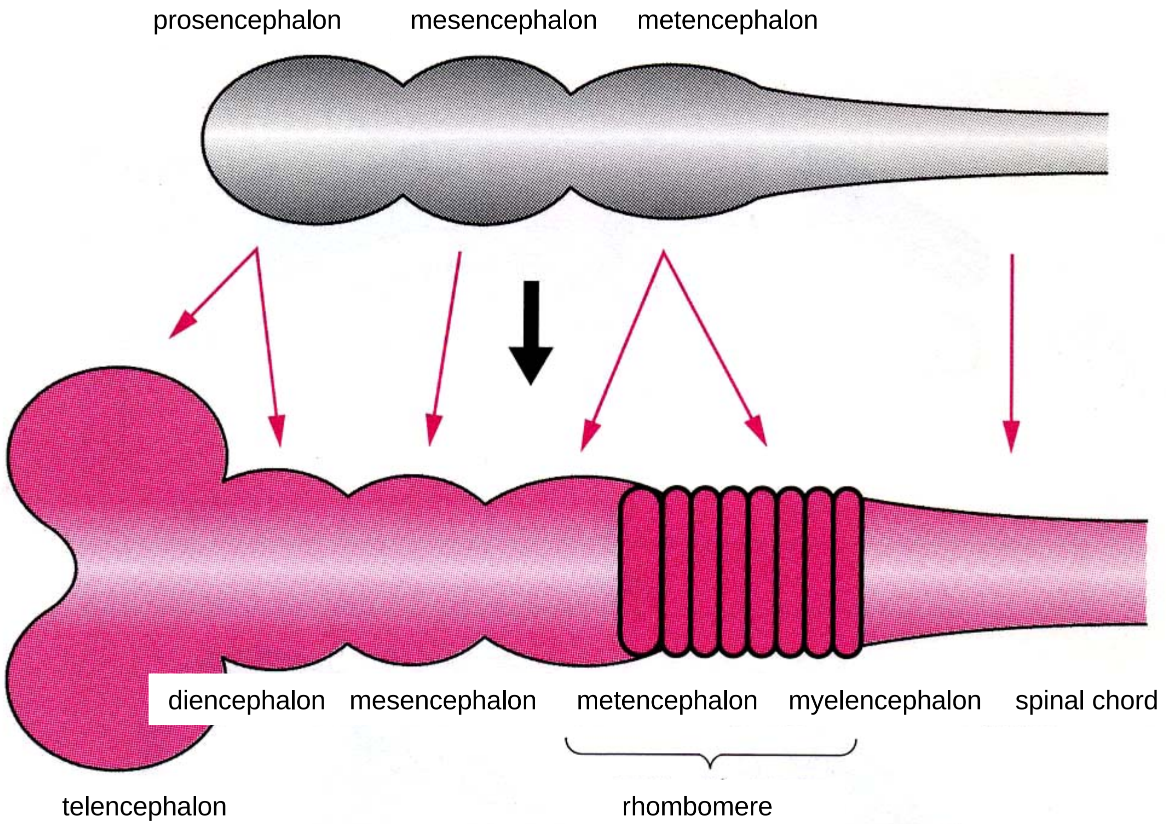


図 5・6 Development of the central nervous system in a mammal

Front part of the neural tube differentiates into several regions to form different parts of the brain structure.

More complex cavity formation and neural formation③

"The illustration of cavity and neural formation"

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More complex cavity and eye formation

"The illustration of cavity and eye formation"

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Broadening Developmental Biology