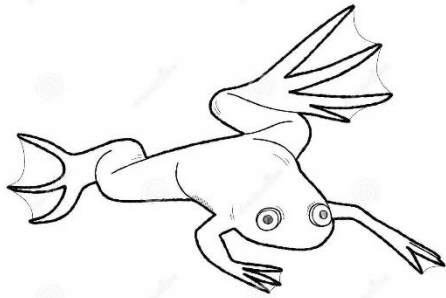


Neurulação



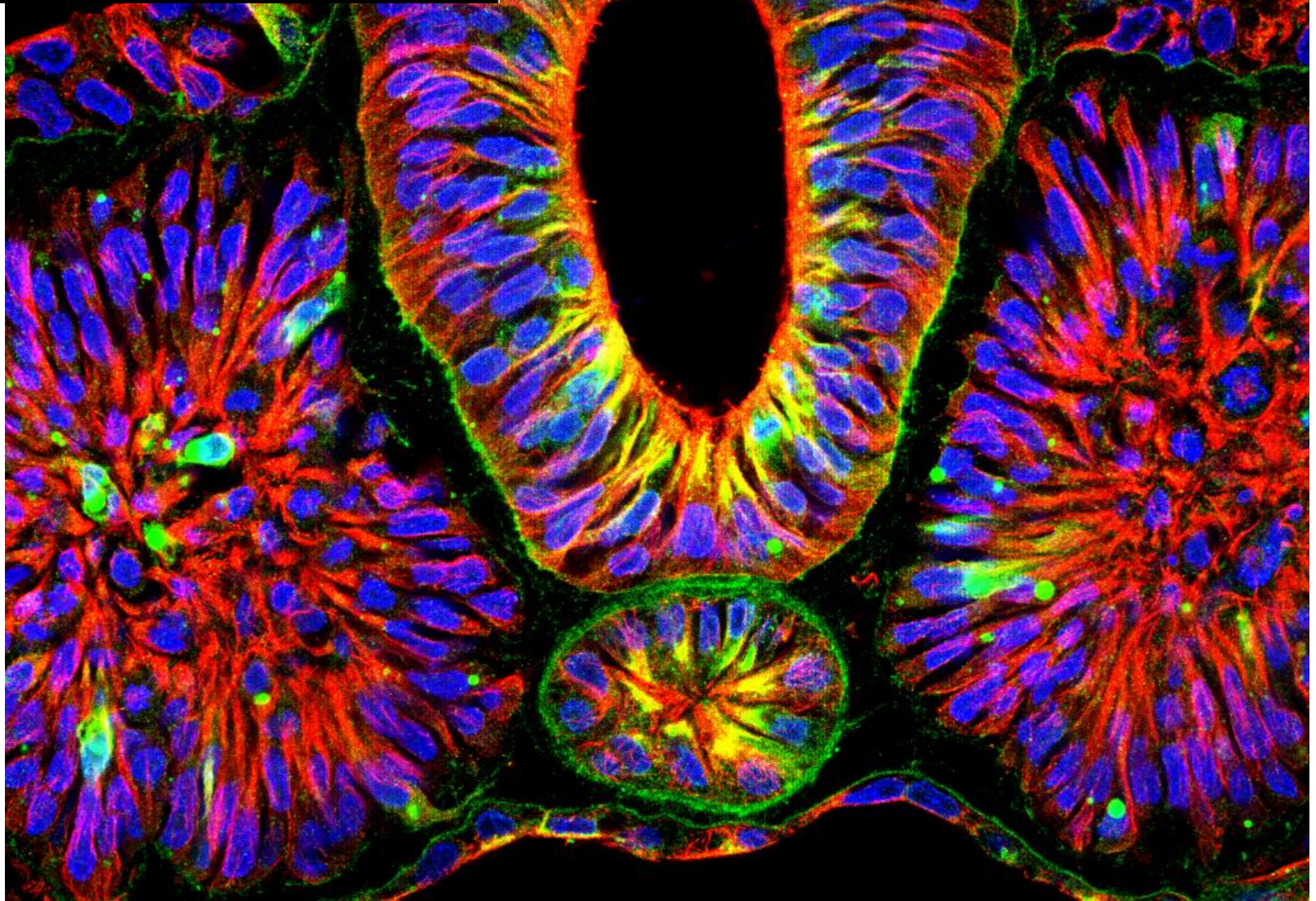
Aluna de mestrado Cecilia Magalhães

Laboratório de Embriologia Molecular de Vertebrados – ICB I, 4º andar , sala 407
Profa. Dra. Chao Yun Irene Yan

Developmental Biology

TENTH EDITION

SCOTT F. GILBERT



“What is perhaps the most intriguing question of all is whether the brain is powerful enough to solve the problem of its own creation.”

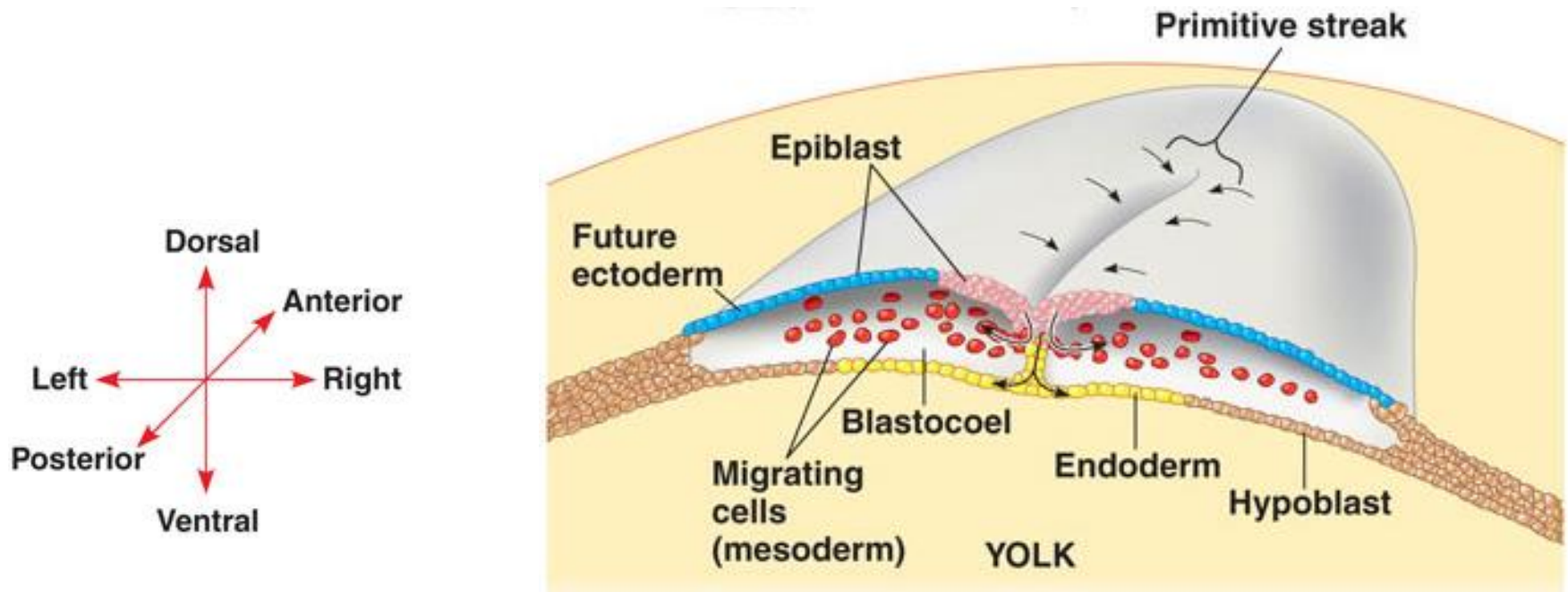
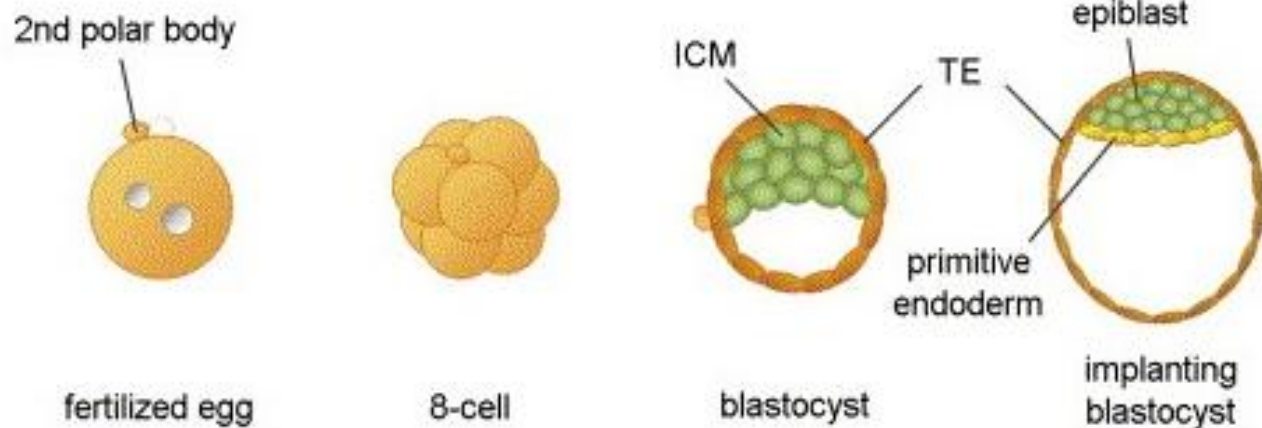
GREGOR EICHELE 1992

PRINCIPAIS EVENTOS DO DESENVOLVIMENTO

- Gametogênese e Fertilização
- Clivagem
- Gastrulação
- Neurulação
- Organogênese

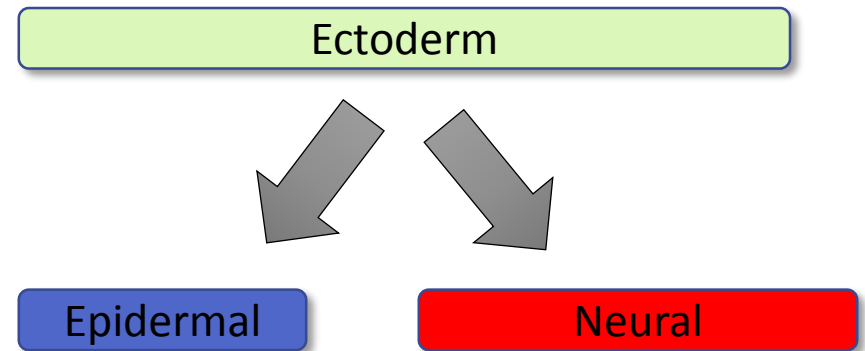


RELEMBRANDO A GASTRULAÇÃO DO EMBRIÃO DE GALINHA....



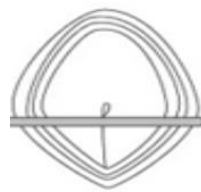
PRIMEIRA DECISÃO: Epidermal OU Neural?

Indução



Ectoderm

— Gives rise to the epidermis and nervous system



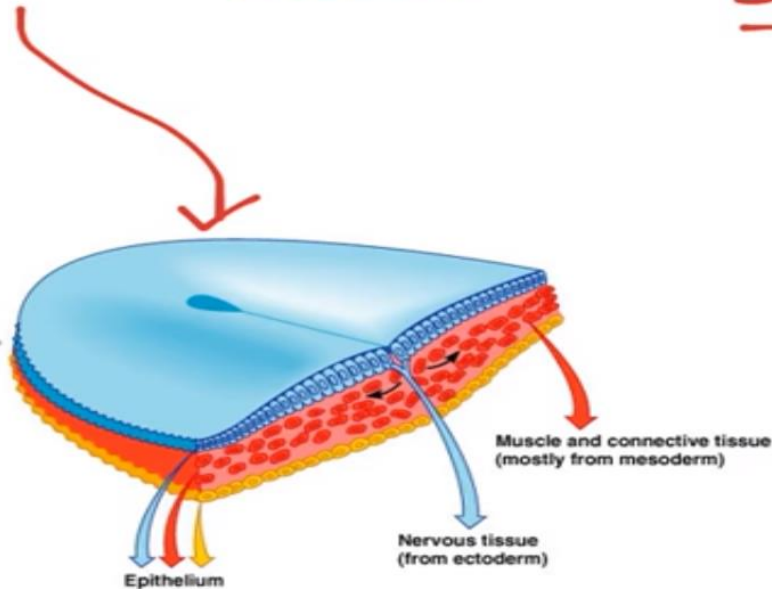
16-day-old embryo
(dorsal surface view)

Key:

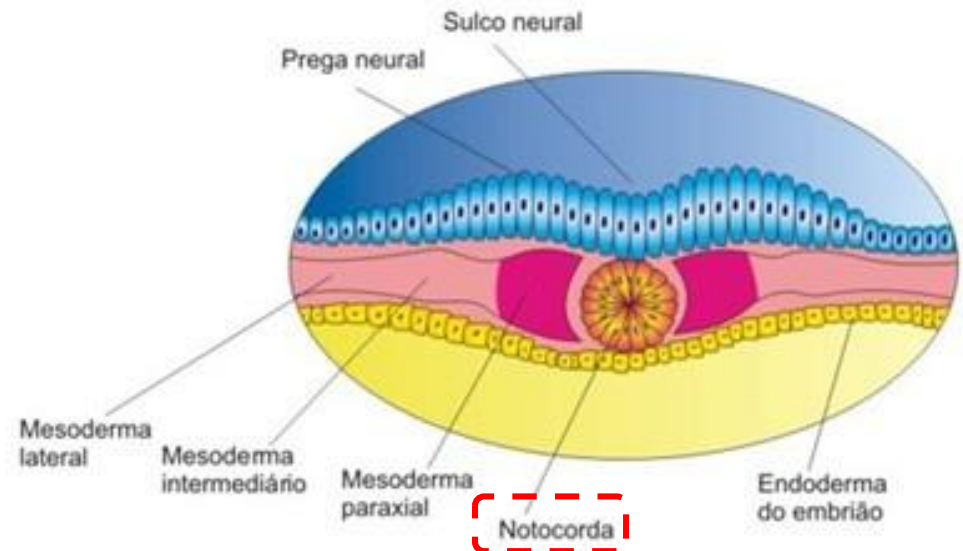
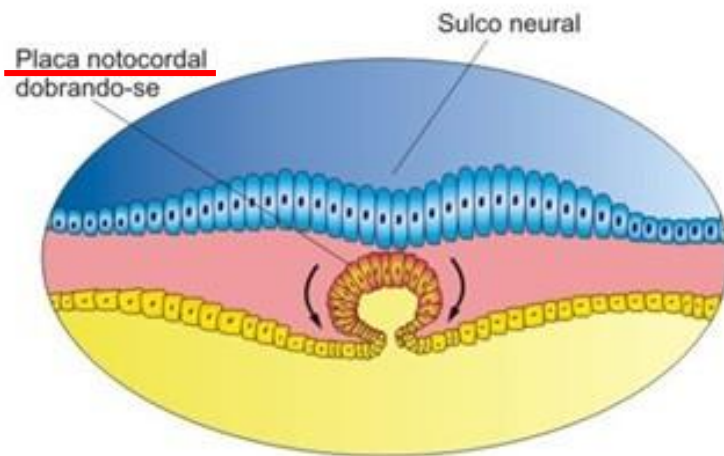
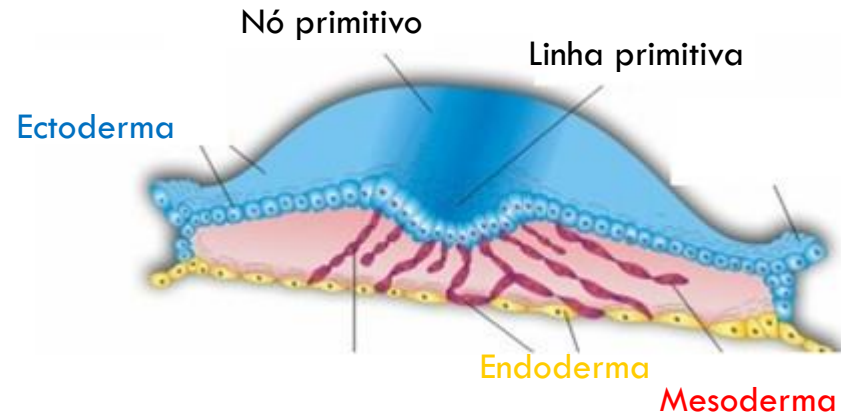
■ = Ectoderm

■ = Mesoderm

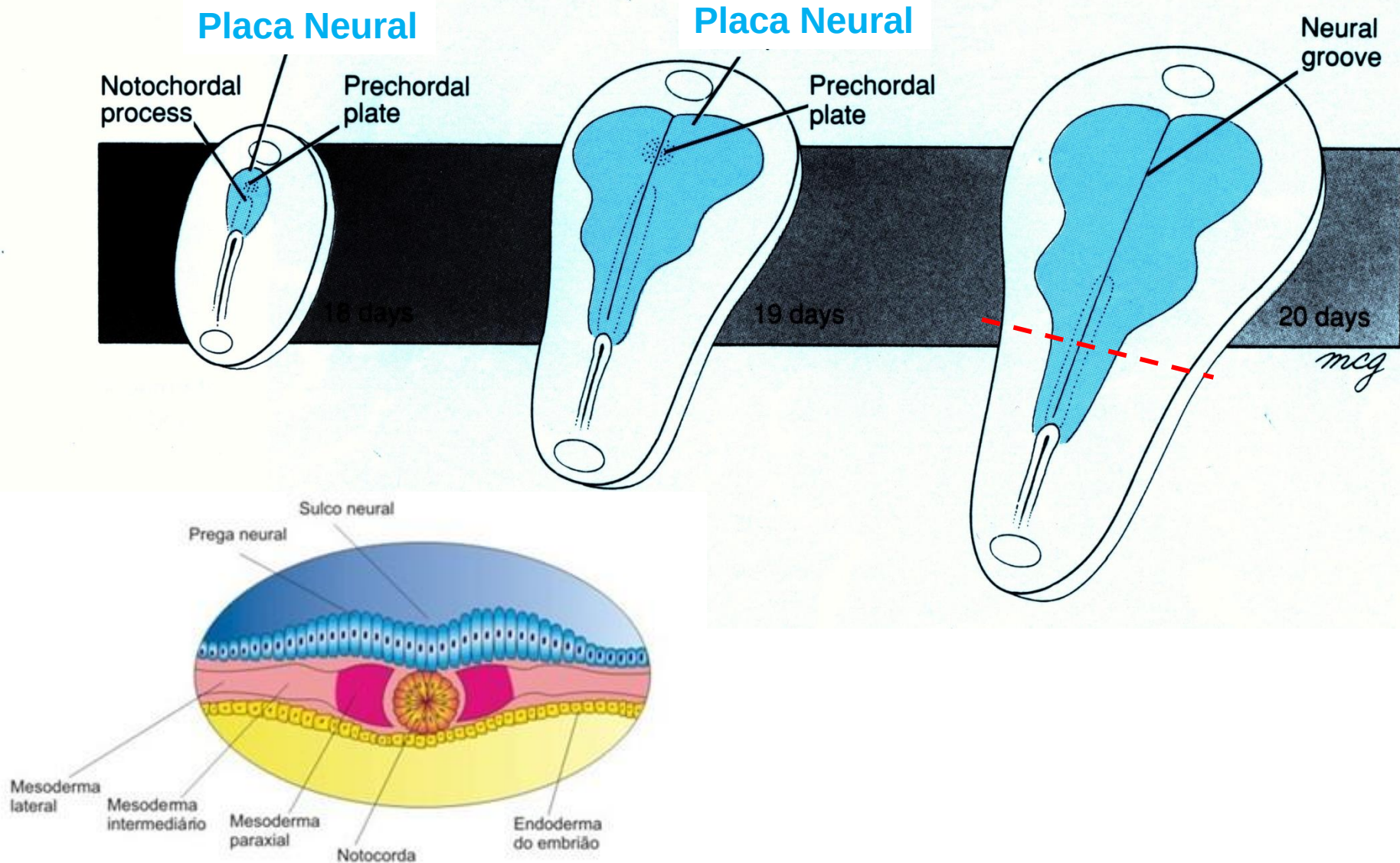
■ = Endoderm



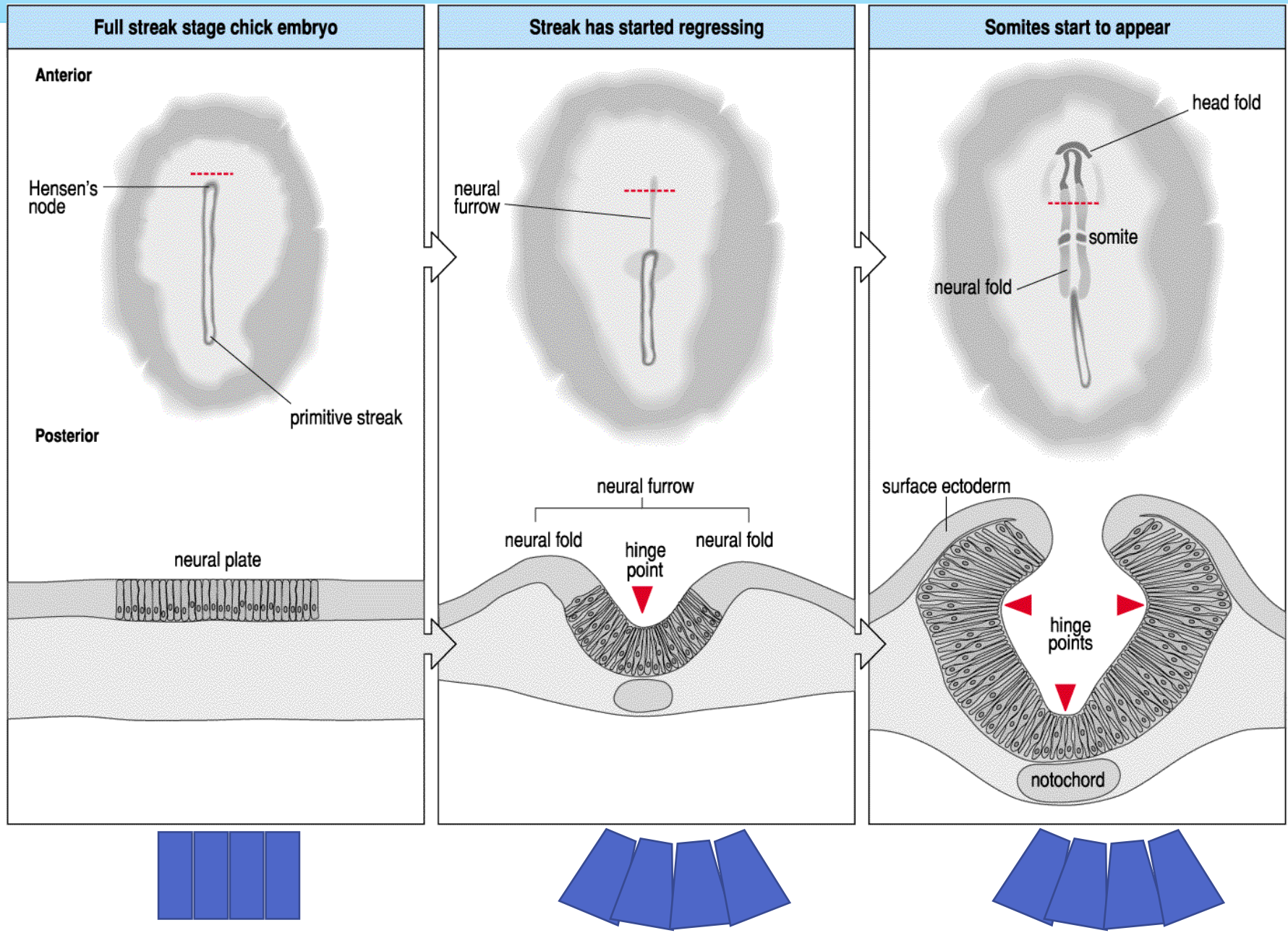
FORMAÇÃO DA LINHA PRIMITIVA E DA NOTOCORDA



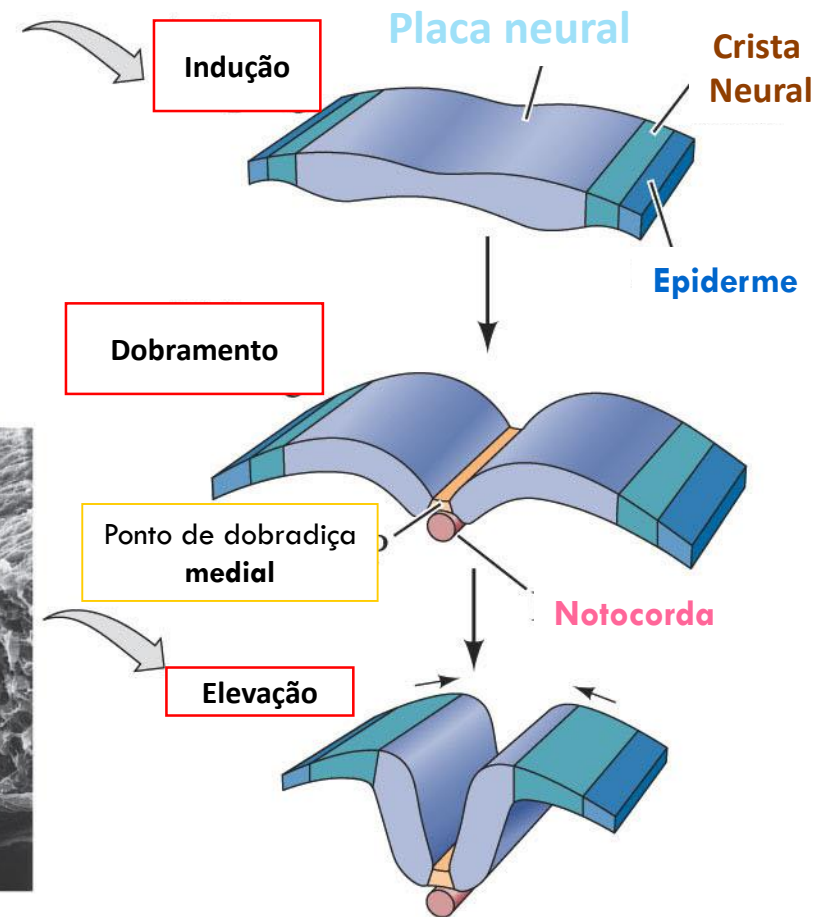
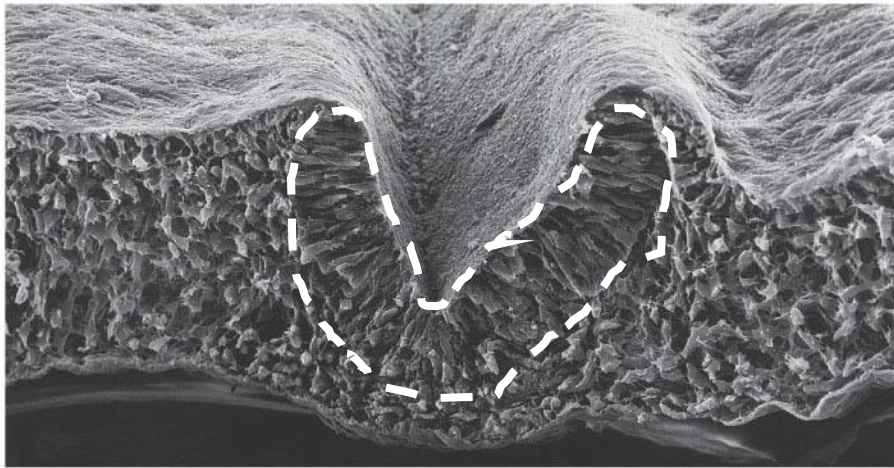
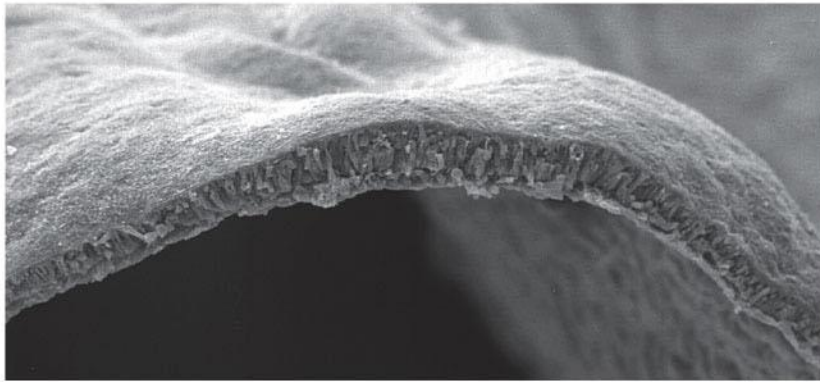
A NOTOCORDA INDUZ O ECTODERMA A FORMAR A PLACA NEURAL



FORMAÇÃO DO TUBO NEURAL

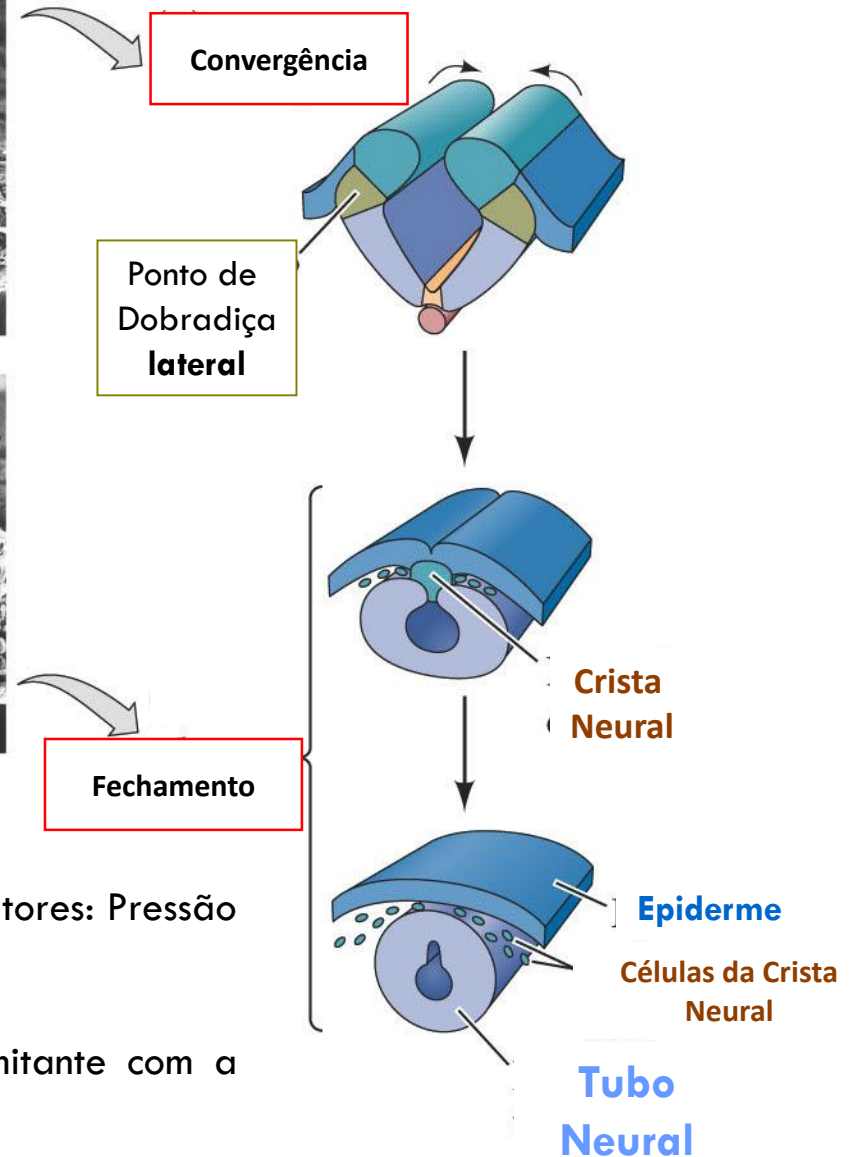
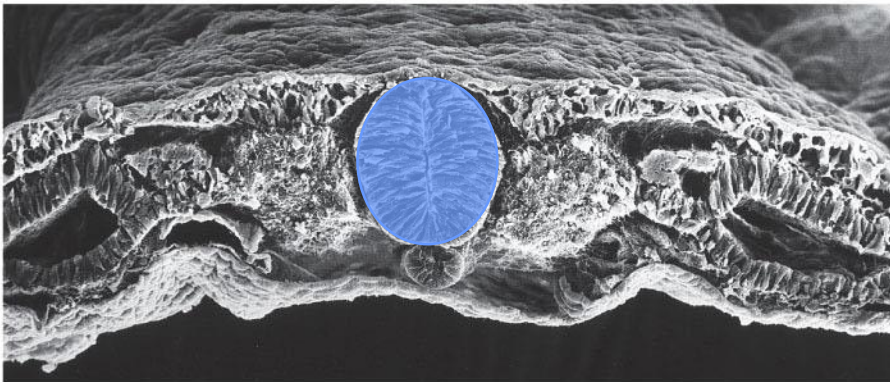
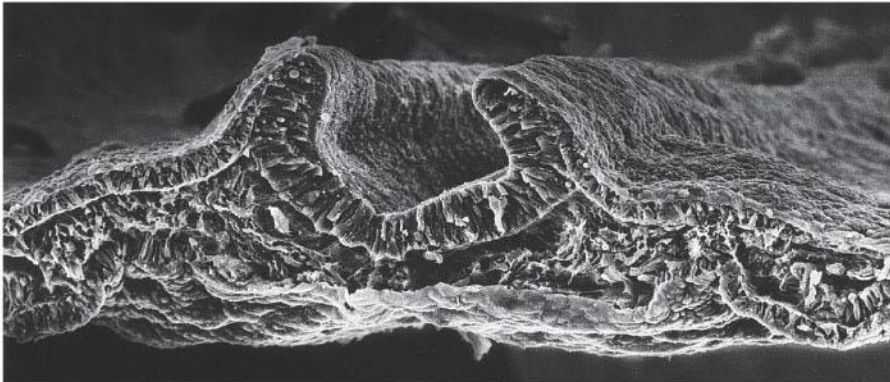


NEURULAÇÃO EM AVES – 6 EVENTOS



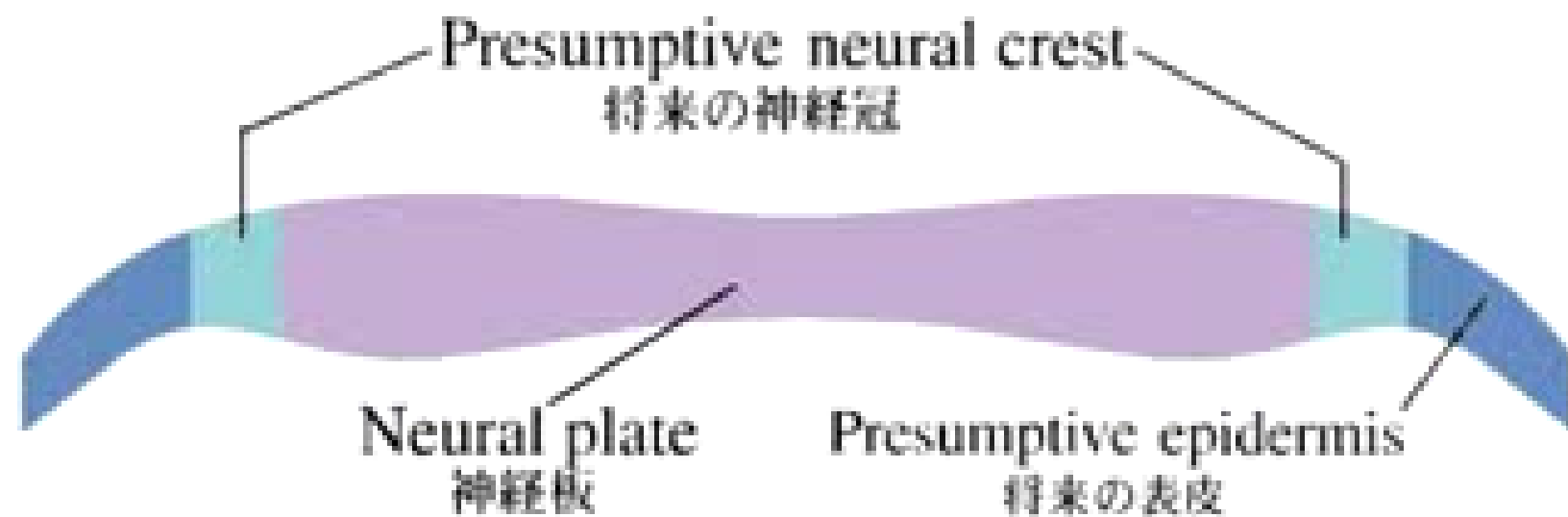
1. **Indução** da formação da PLACA NEURAL pela **Notocorda**, Constrrição apical nas células da borda da Placa Neural
2. **Dobramento** da Placa Neural
3. **Elevação** das dobras neurais

NEURULAÇÃO EM AVES – 6 EVENTOS



5. A **convergência** do Tubo Neural é uma combinação de fatores: Pressão lateral e constrição nos pontos de dobradiça

6. **Fechamento** do Tubo Neural na porção dorsal concomitante com a Migração da Crista Neural



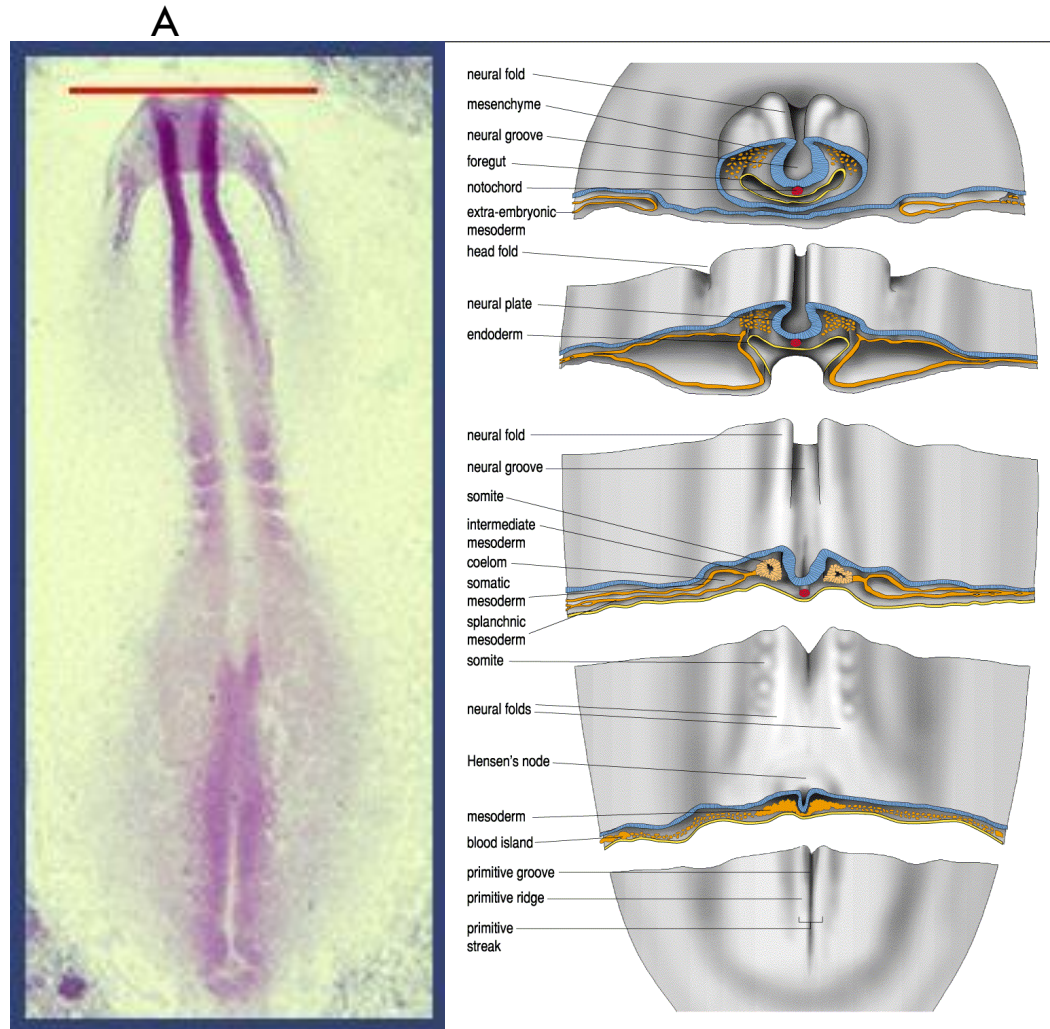
A



P



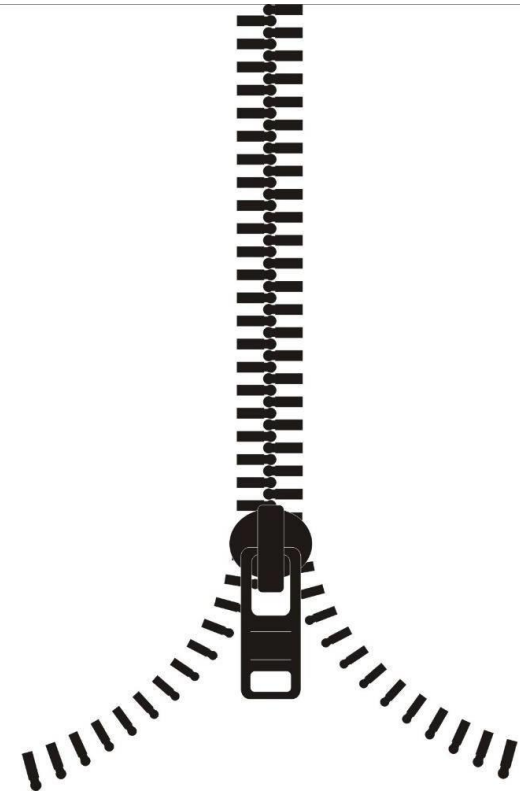
O FECHAMENTO DO TUBO NEURAL OCORRE DE FORMA DESIGUAL AO LONGO DO EIXO EMBRIONÁRIO



P

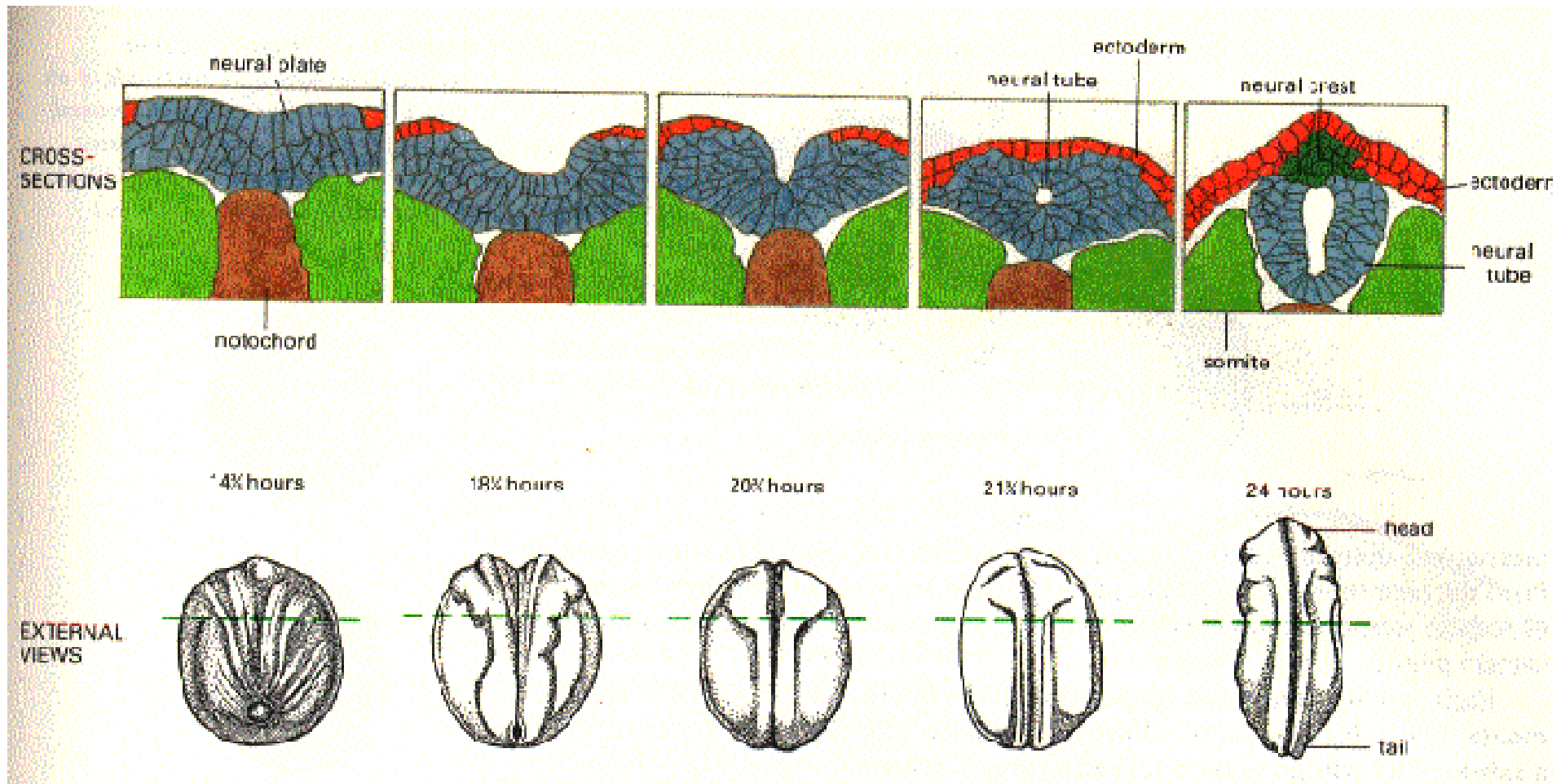
Embrião de galinha

Região céfálica/anterior

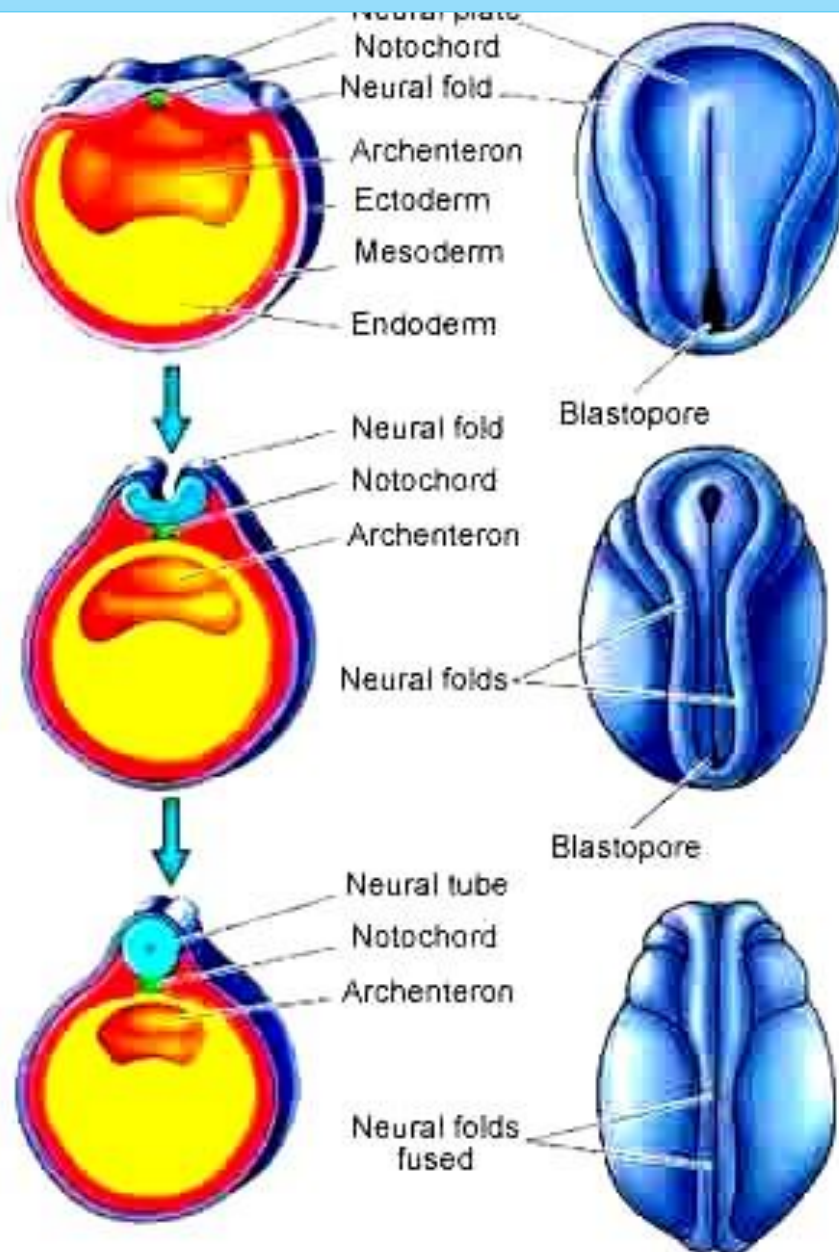


Região caudal/posterior

NEURULAÇÃO EM ANFÍBIOS



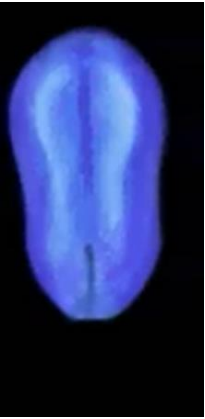
NEURULAÇÃO EM ANFÍBIOS



Dobras neurais

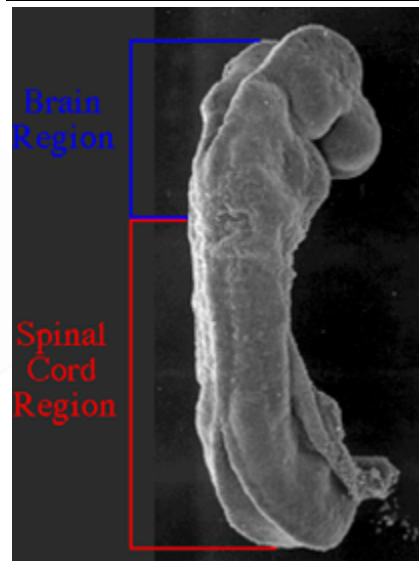


NEURULAÇÃO EM MAMÍFEROS X AVES



Diferença:

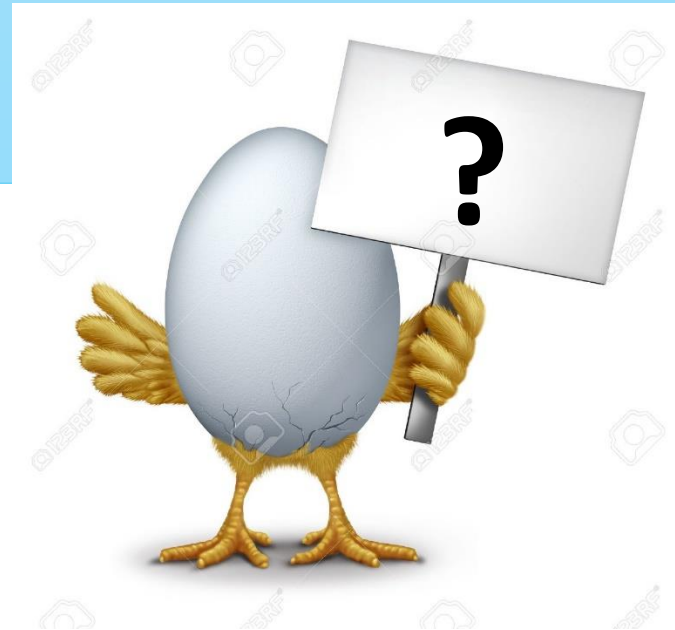
* Fechamento do tubo neural



OK...MAS E DEPOIS?

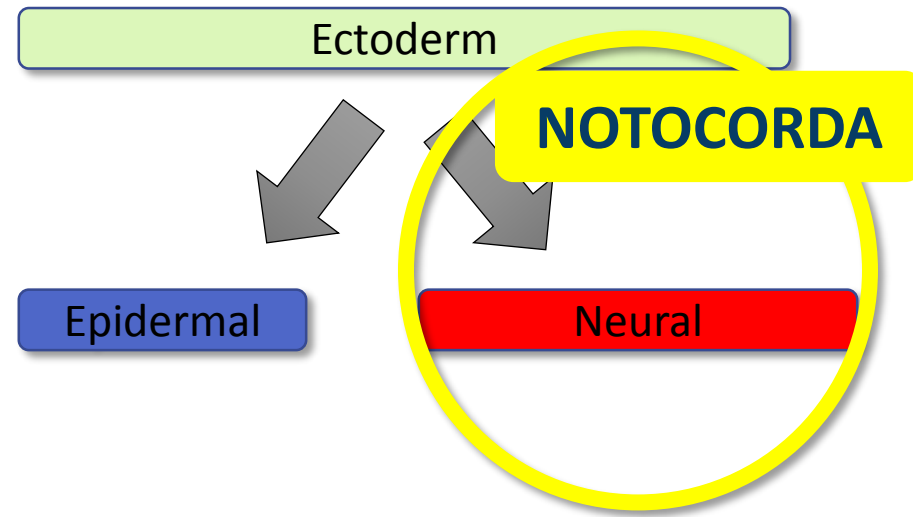
Como é decidido onde será formado o SNC e o SNP?

Como a célula sabe se será um neurônio motor ou sensorial?



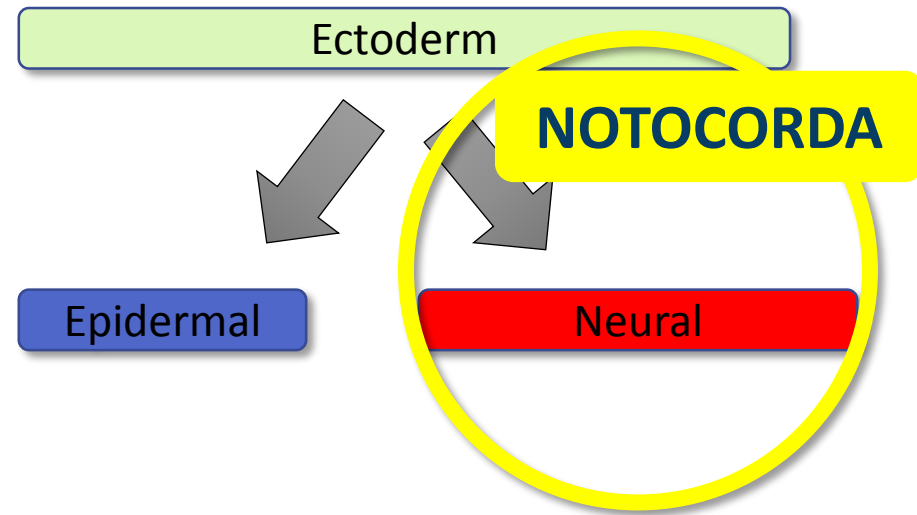
**PRIMEIRA
DECISÃO:
Epidermal OU
Neural?**

Indução

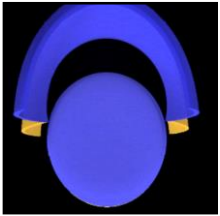


**SEGUNDA
DECISÃO:
PADRONIZAÇÃO**

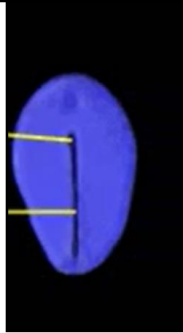
Indução



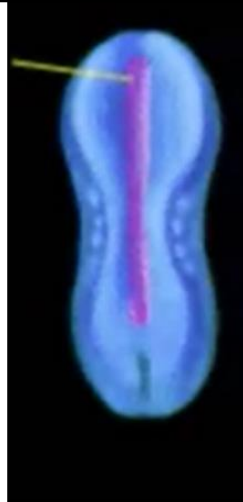
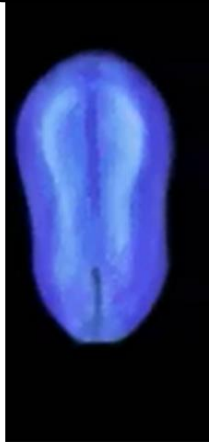
Epiblast



Ectoderma



Neurectoderma



Progenitores Neurais

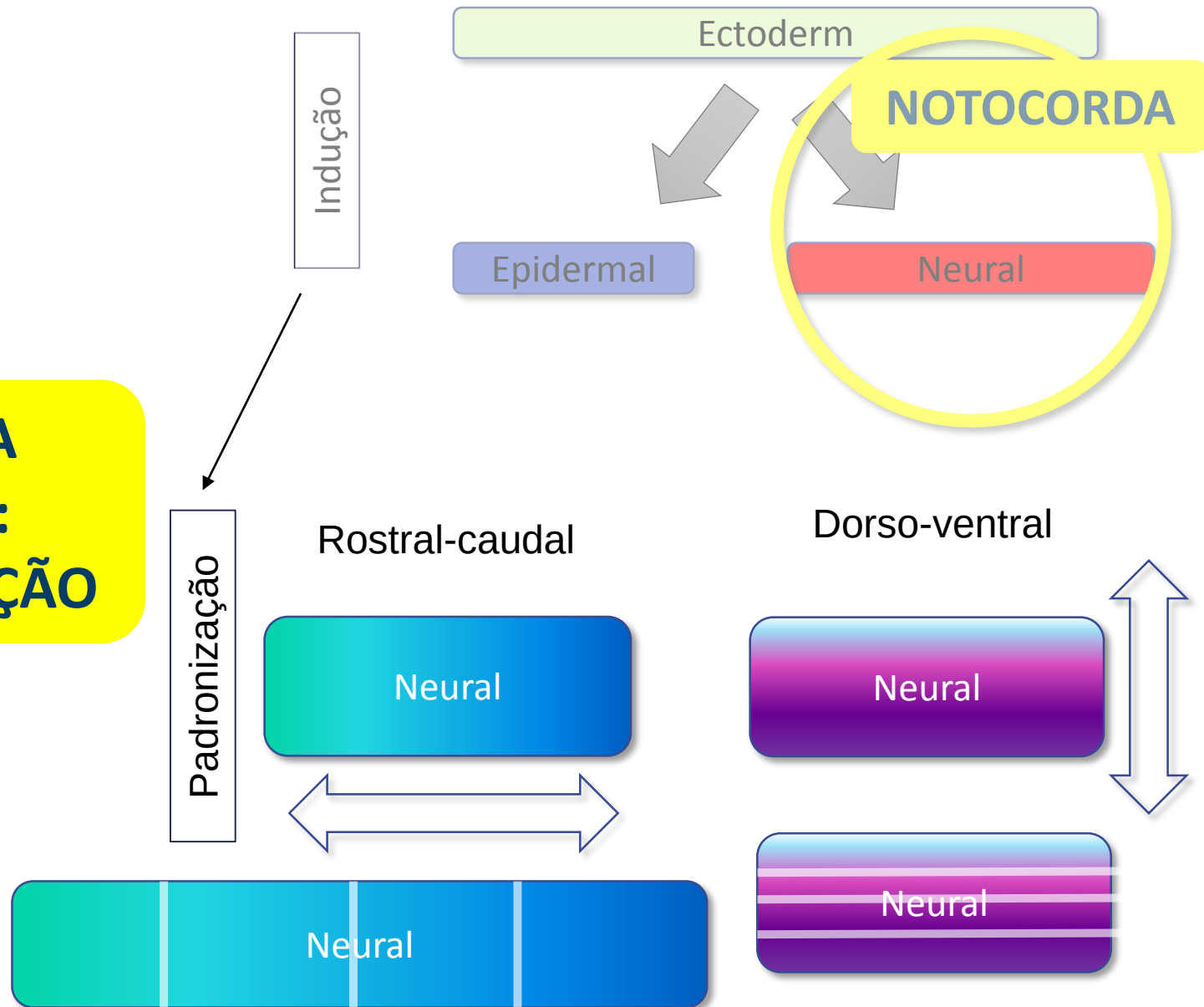


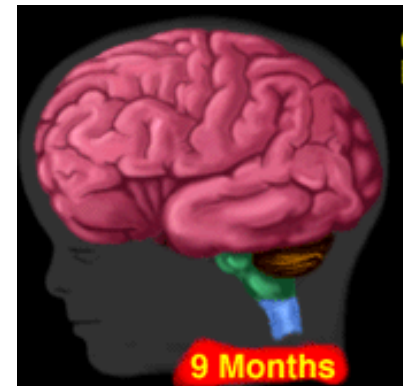
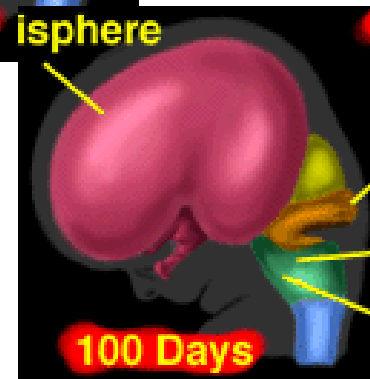
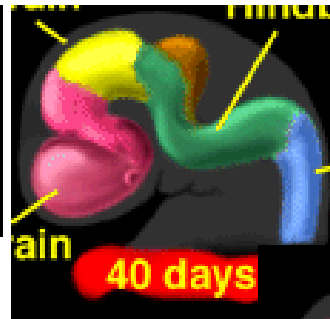
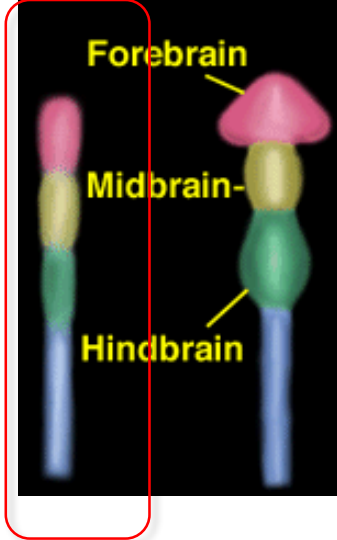
Indução

Padronização

Diferenciação

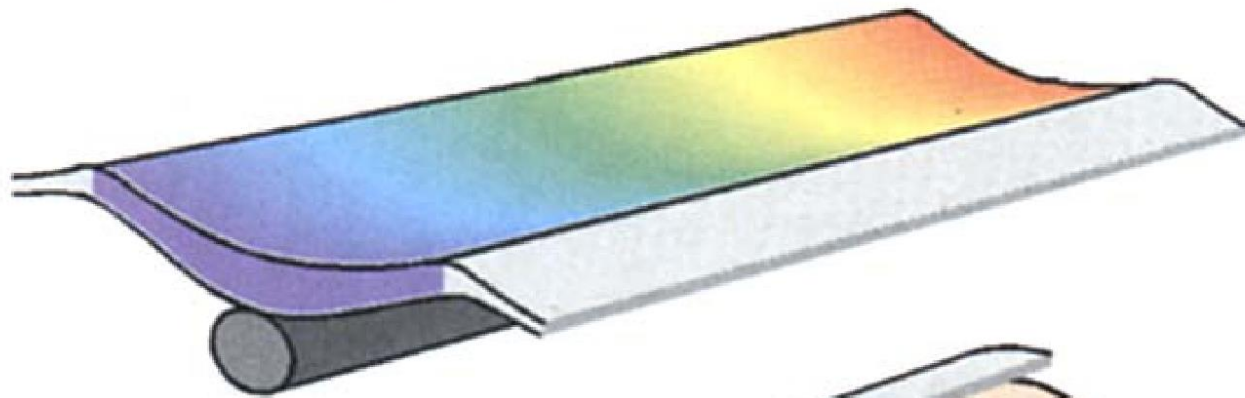
**SEGUNDA
DECISÃO:
PADRONIZAÇÃO**



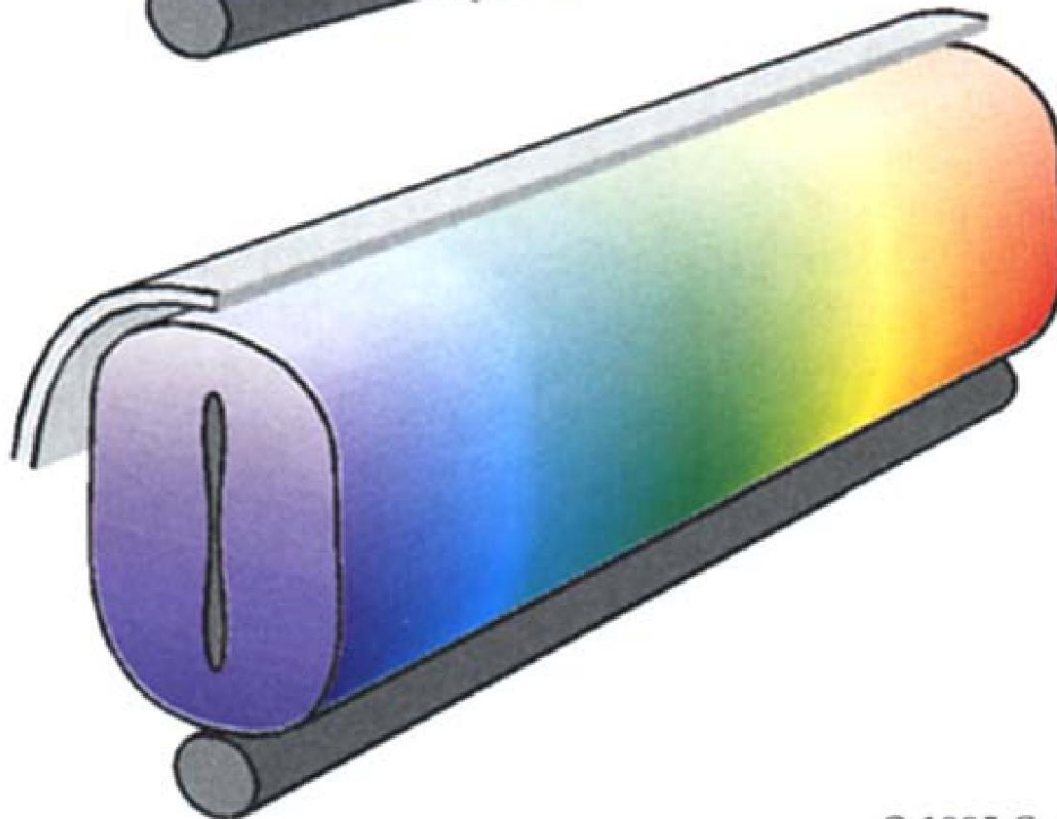


O que determina a padronização antero-posterior (rosto-caudal)?

(a)



(b)

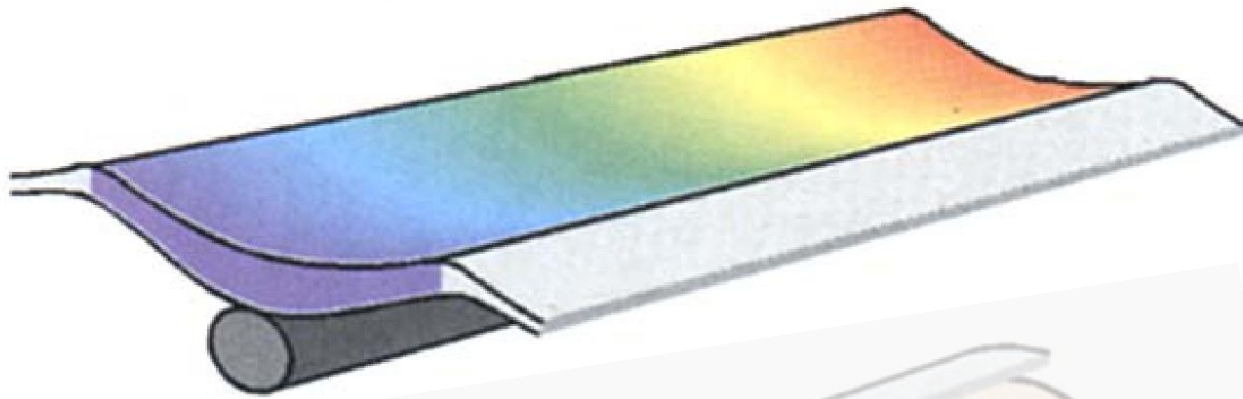


© 1995 Current Biology

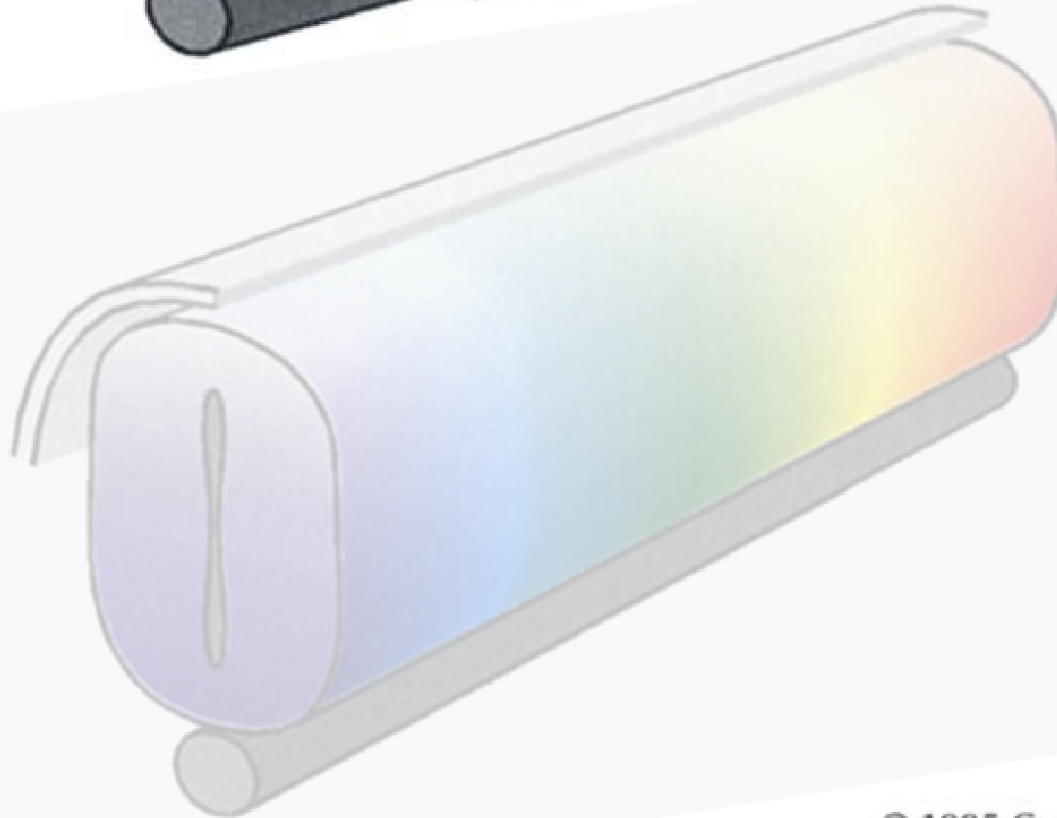
Lumsden, A. & Graham, A., 1995. *Current Biology*, 5(12), pp.1347–1350.

PADRONIZAÇÃO ROSTRO-CAUDAL DO TUBO NEURAL

(a)



(b)

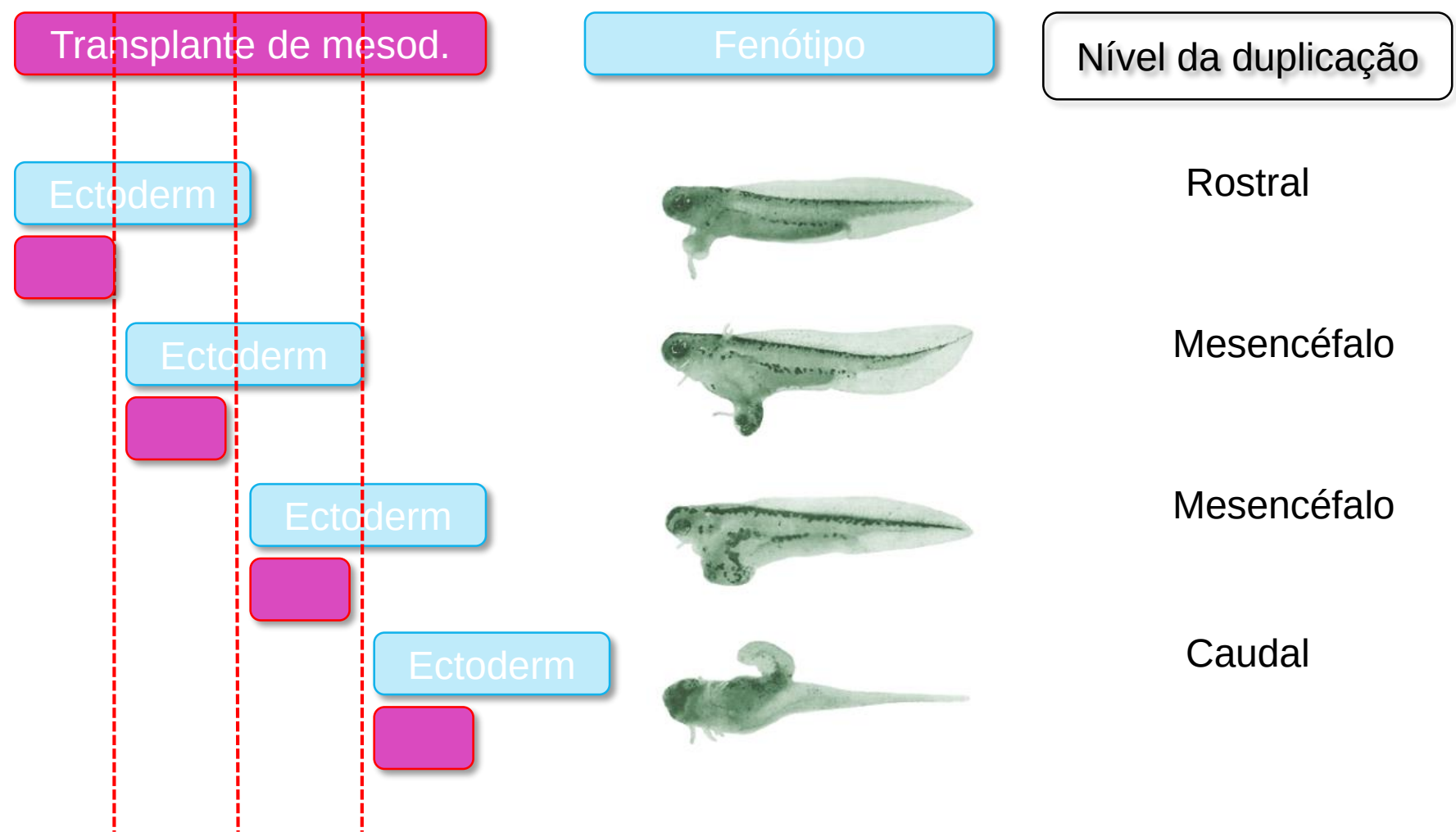


© 1995 Current Biology

Lumsden, A. & Graham, A., 1995. *Current Biology*, 5(12), pp.1347–1350.

Existe um segundo sinal que “modula” a indução neural?

Otto Mangold’s experiment

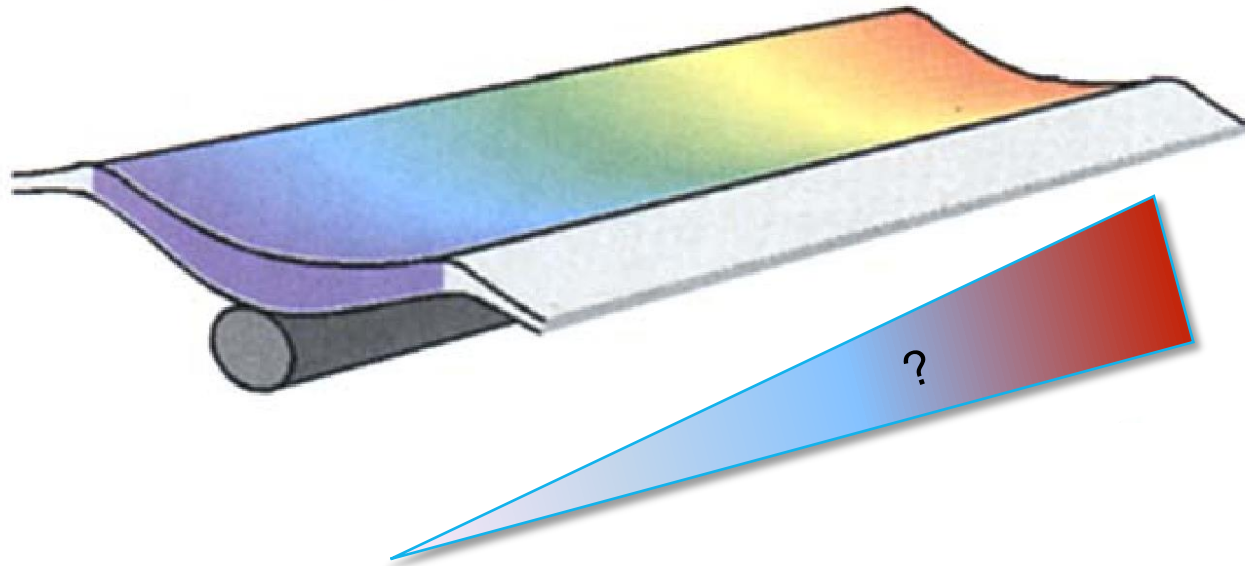


Existe um segundo sinal que “modula” a indução neural?

Otto Mangold's experiment

O mesoderma subjacente a placa neural transmite um gradiente de sinal rostro-caudal (antero-posterior)

(a)



Excesso de ÁCIDO RETINÓICO gera *mutantes caudais*

controle

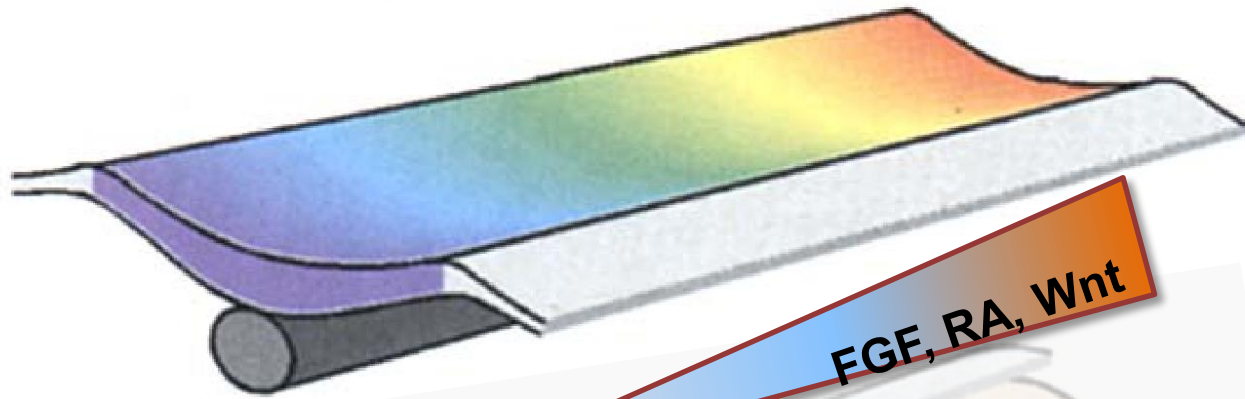


Ácido Retinóico

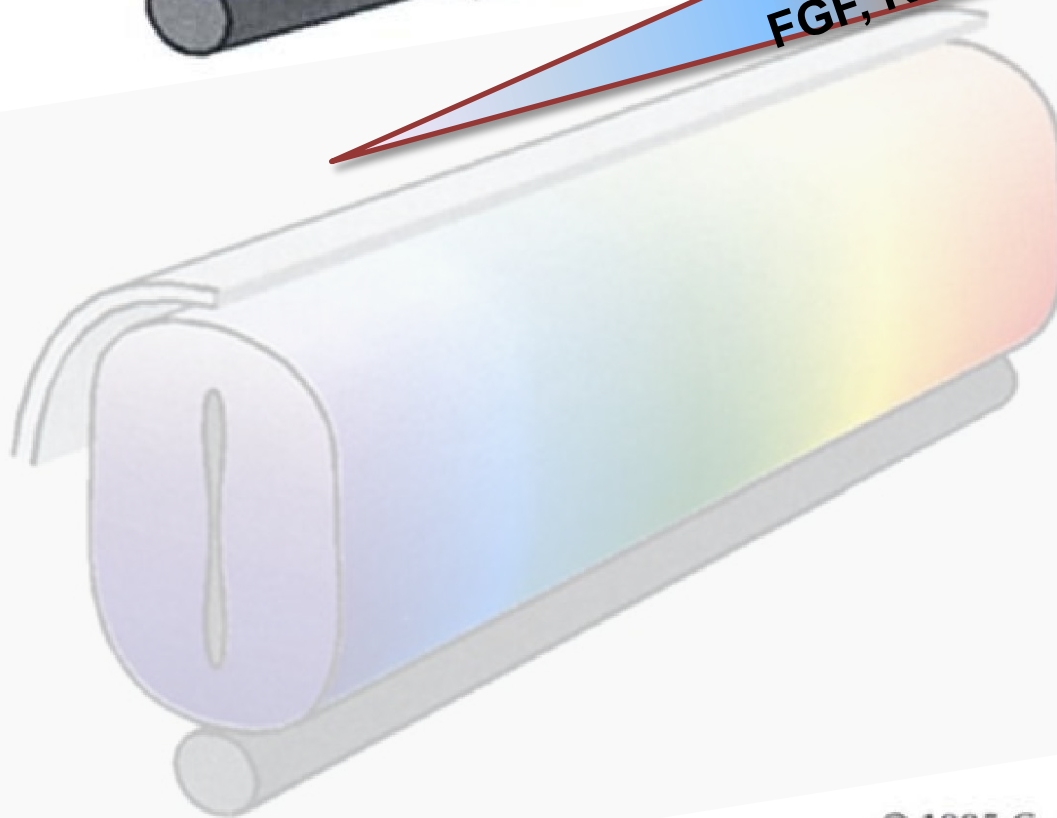


PADRONIZAÇÃO ROSTRO-CAUDAL DO TUBO NEURAL

(a)



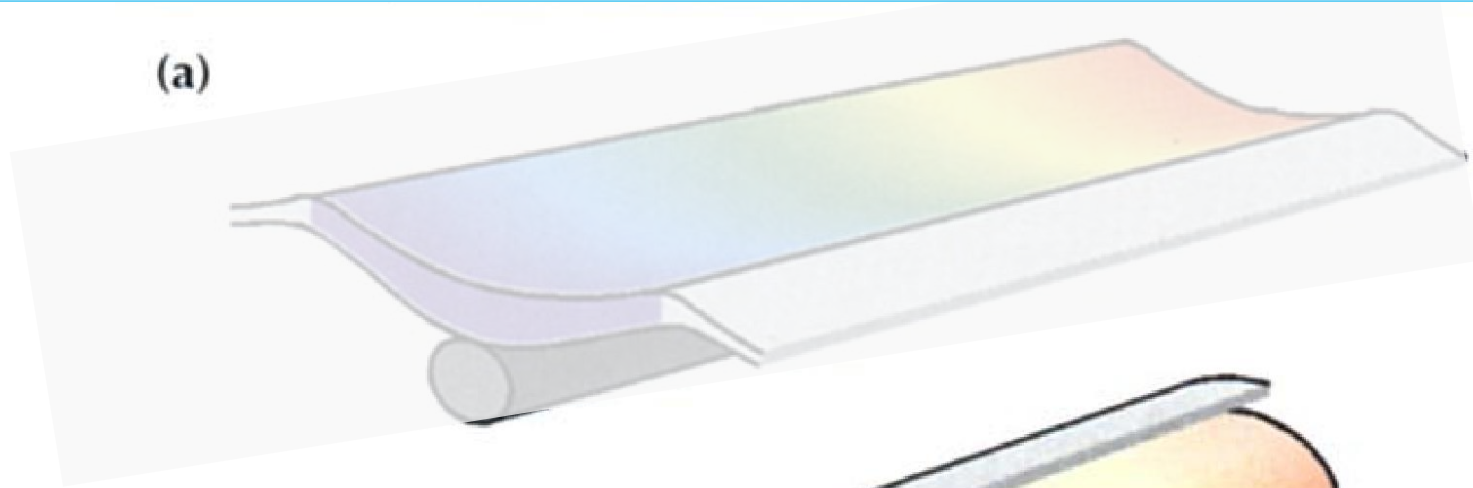
(b)



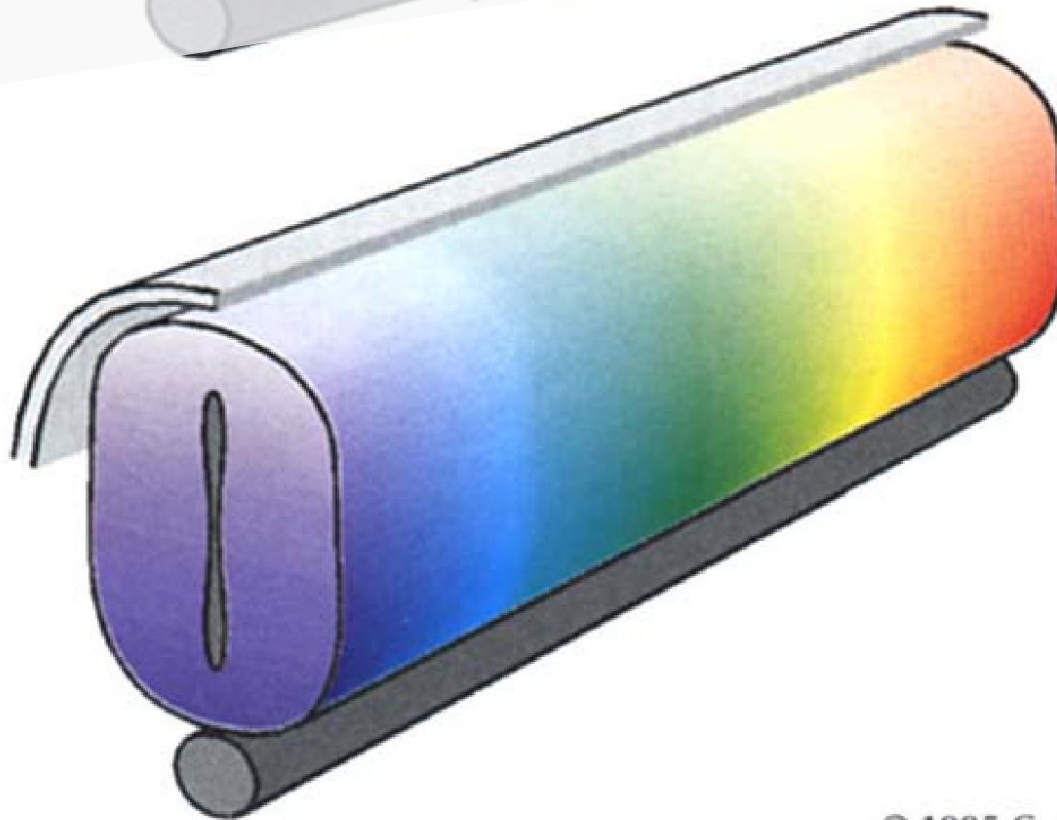
© 1995 Current Biology

Lumsden, A. & Graham, A., 1995. *Current Biology*, 5(12), pp.1347–1350.

PADRONIZAÇÃO DORSO-VENTRAL DO TUBO NEURAL



(b)

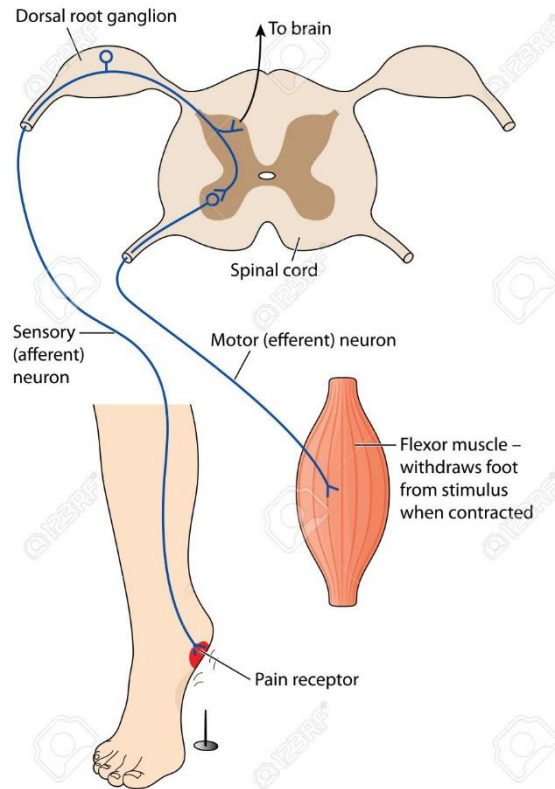


© 1995 Current Biology

Lumsden, A. & Graham, A., 1995. *Current Biology*, 5(12), pp.1347–1350.

SENSORIAL – DORSAL

MOTOR - VENTRAL



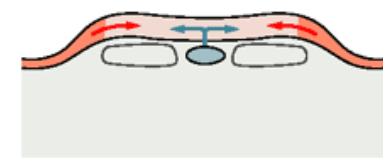
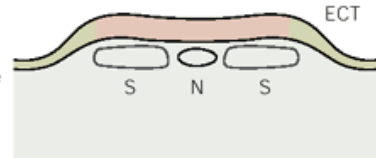
O TN ESTÁ EXPOSTO À DUAS FONTES DE SINALIZAÇÃO: EPIDERMIS E NOTOCORDA

A Developmental stages

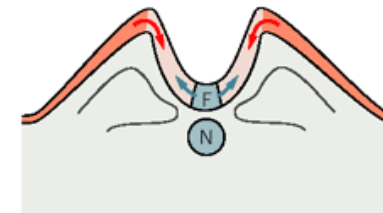
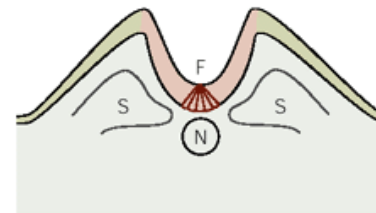
B Inductive signals



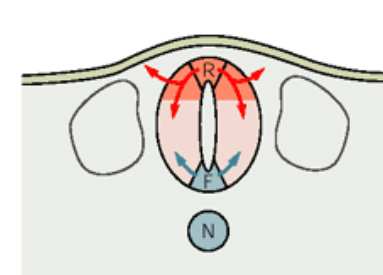
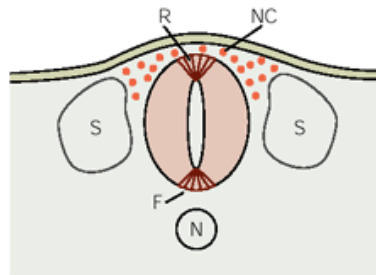
1 Neural plate



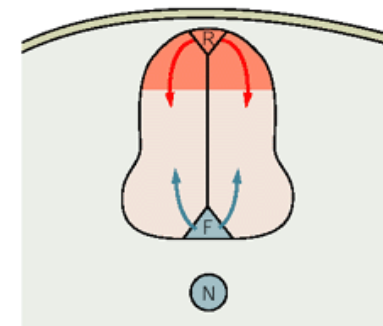
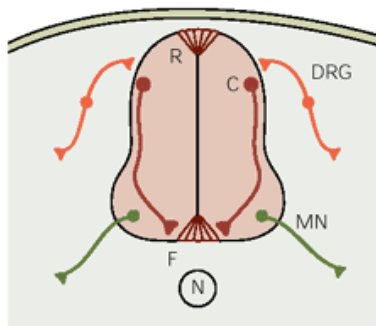
2 Neural fold



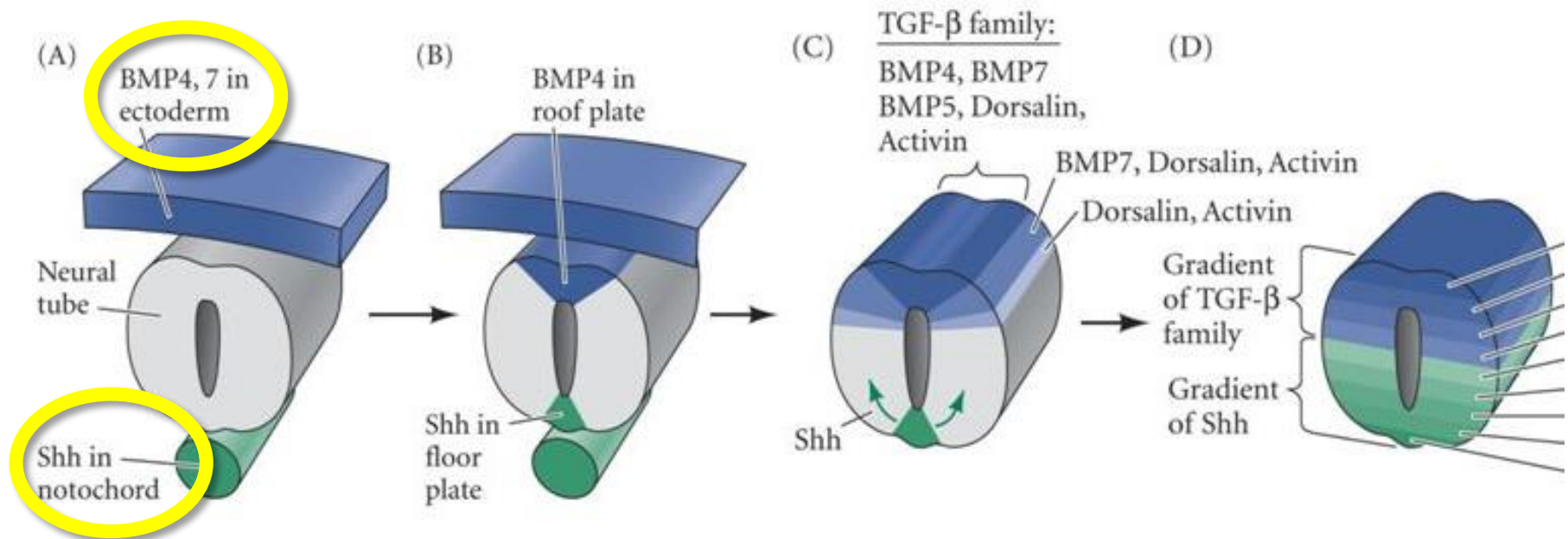
3 Neural tube



4 Spinal cord

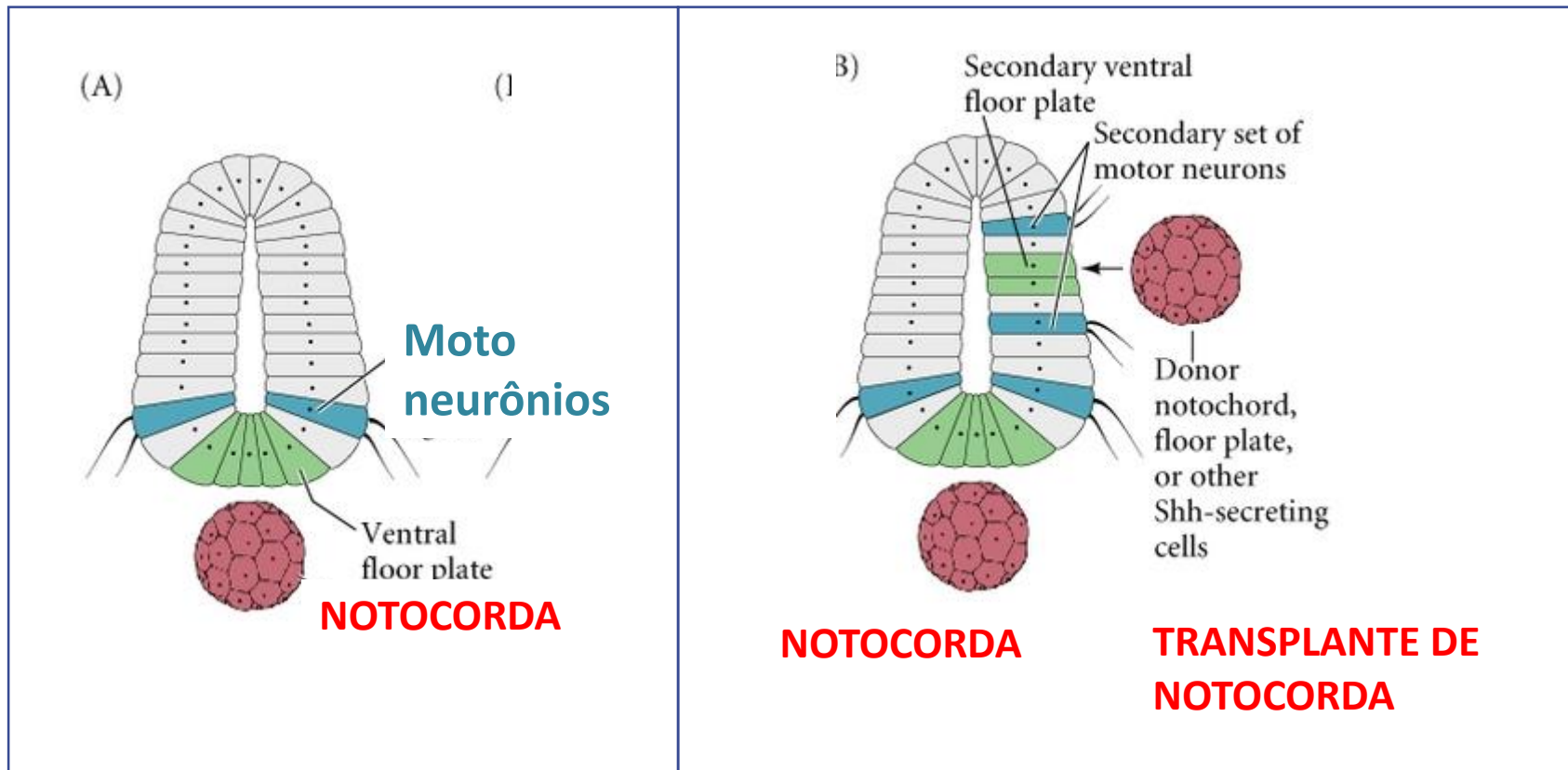


O TN ESTÁ EXPOSTO À DUAS FONTES DE SINALIZAÇÃO: EPIDERMIS E NOTOCORDA

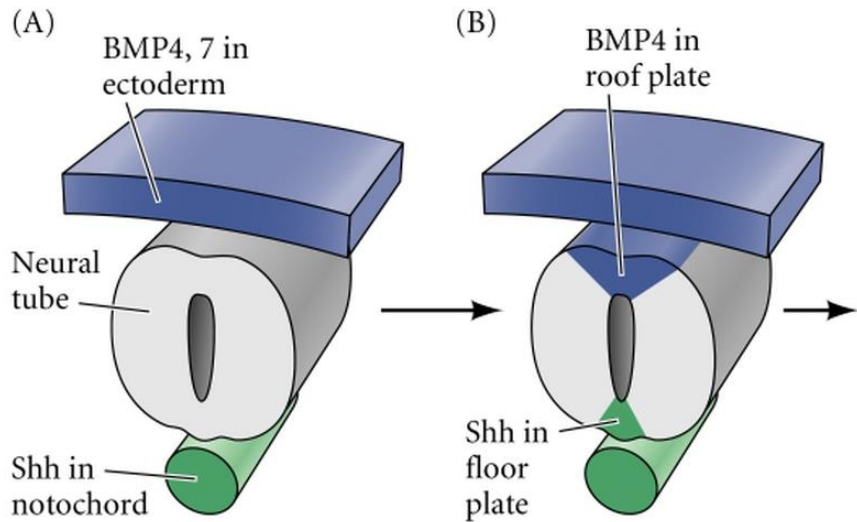


Hipótese: A Notocorda direciona o desenvolvimento dorso-ventral do tubo neural

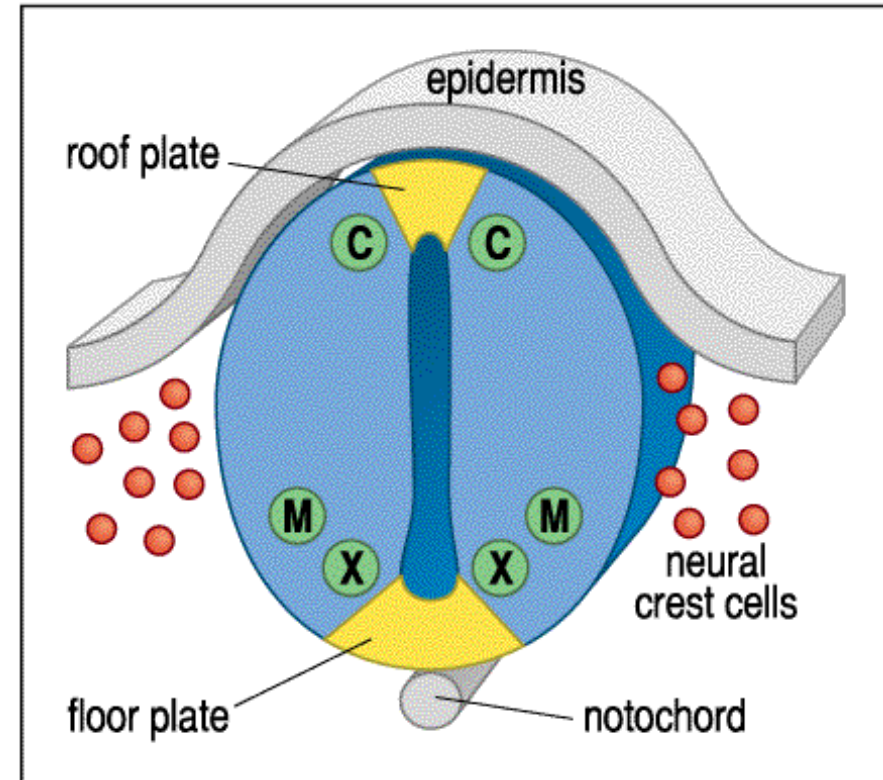
Comprovação: Transplante de notocorda na região lateral induz **motoneurônios**



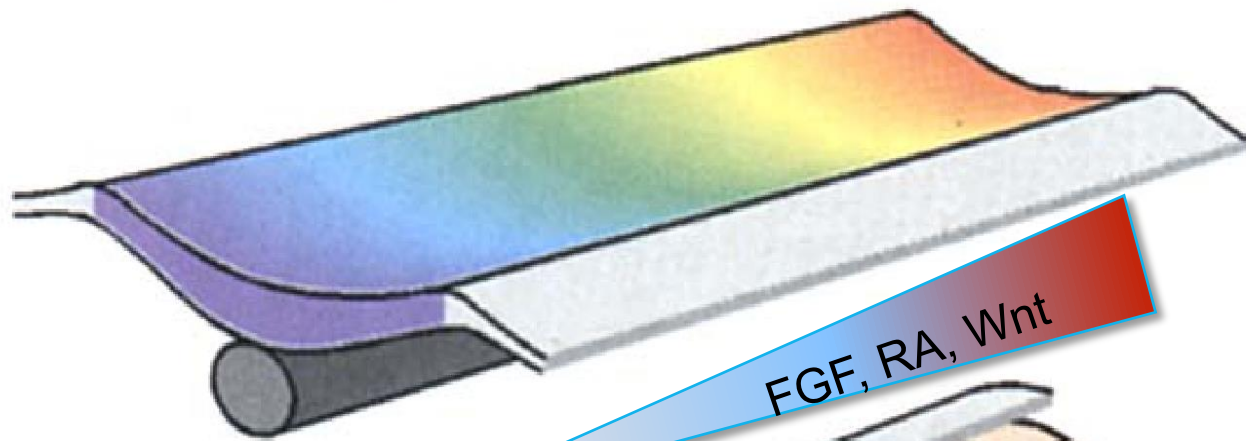
A notocorda direciona a diferenciação de motoneurônios **através do Shh**



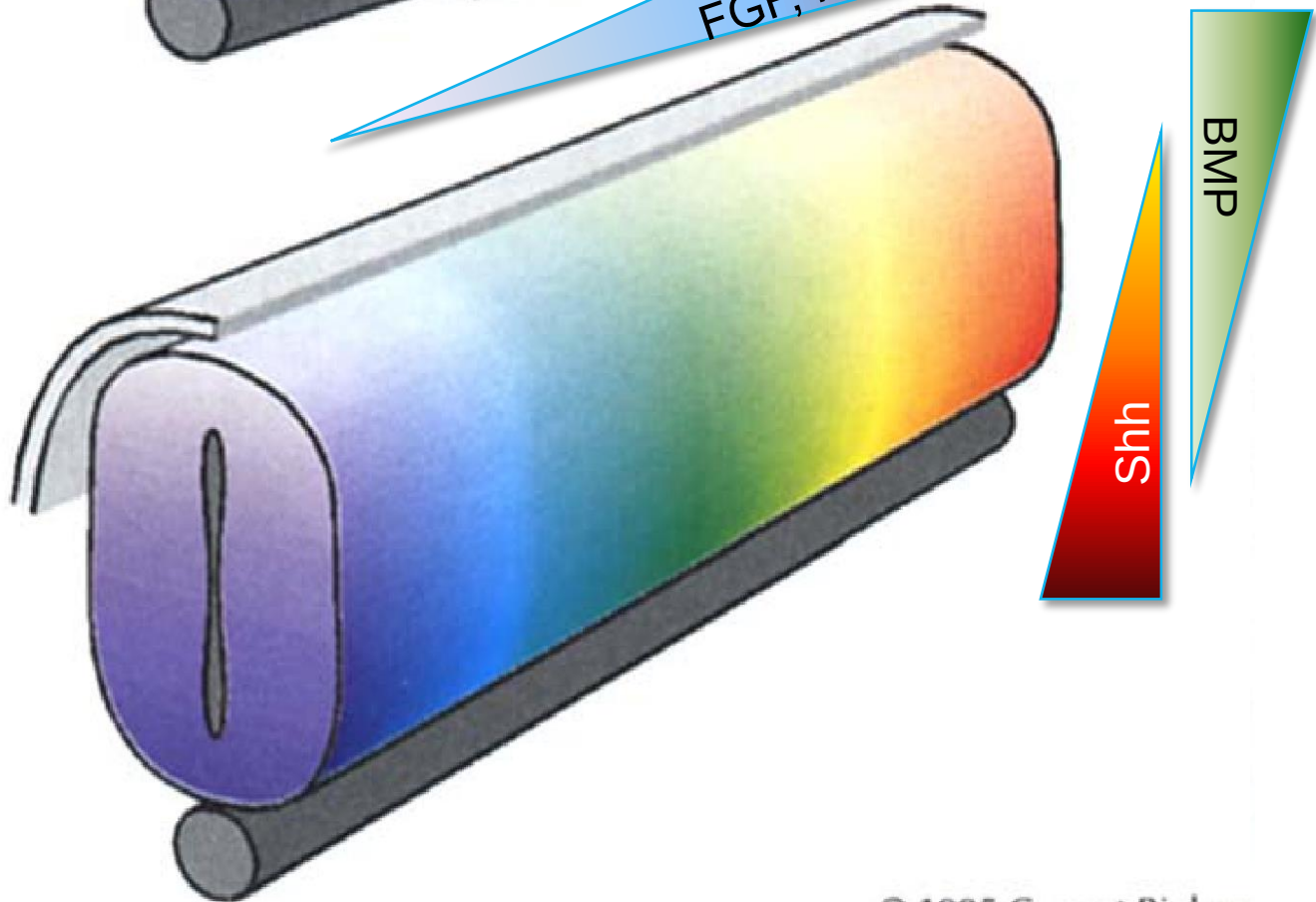
© 2000 Sinauer Associates, Inc.



(a)

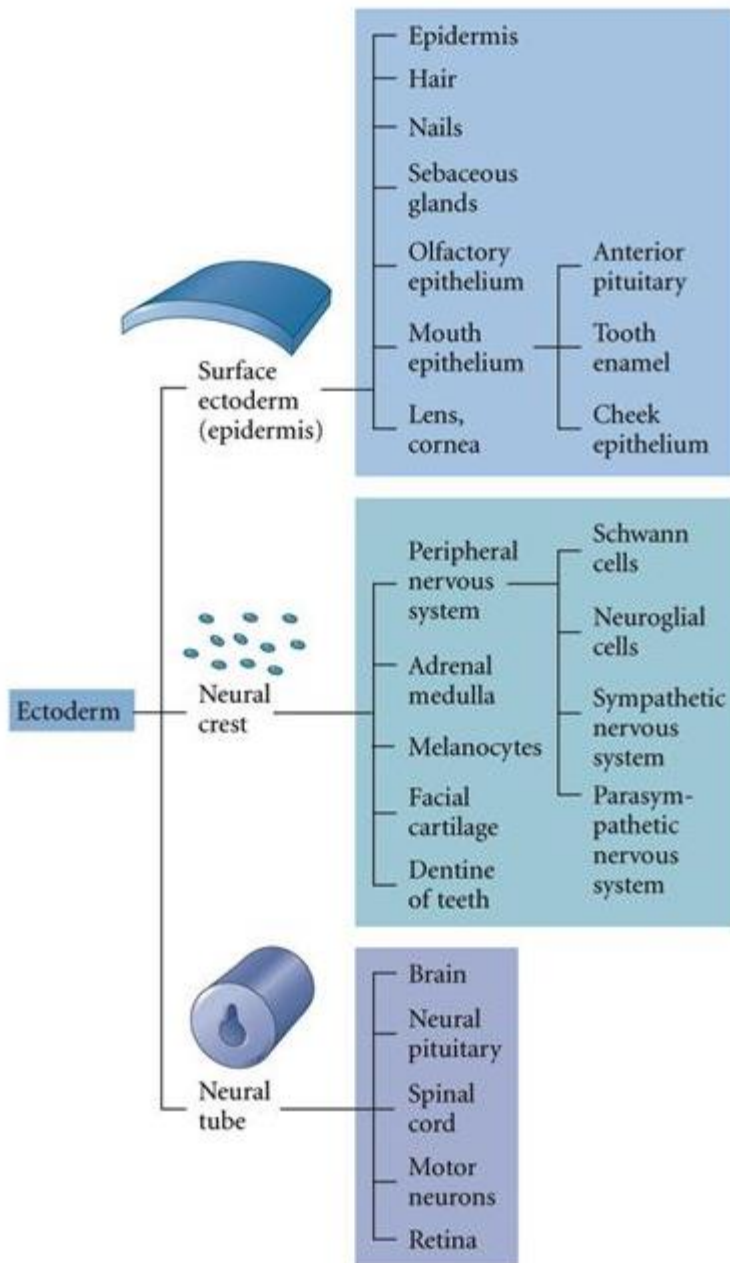


(b)

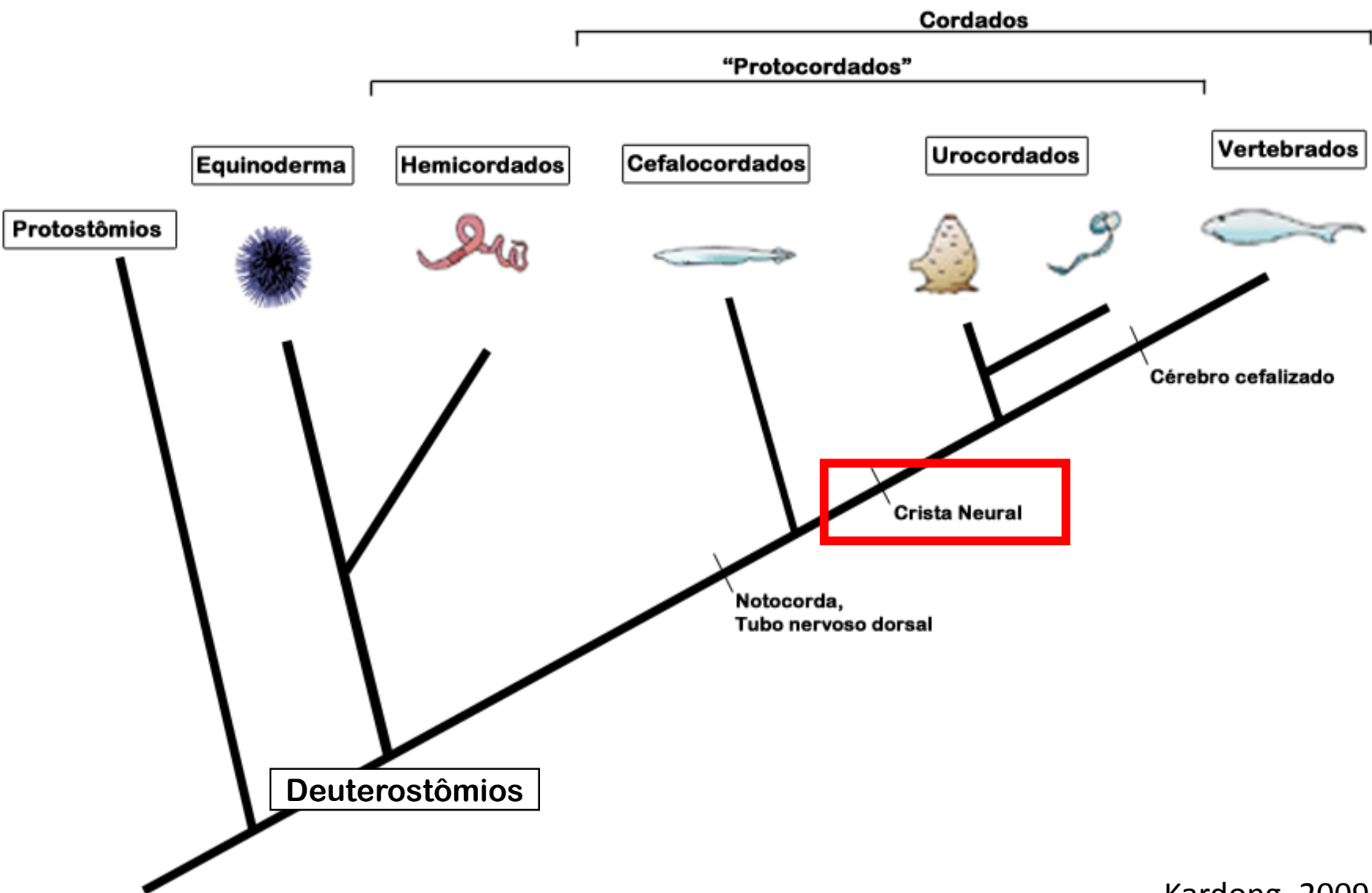


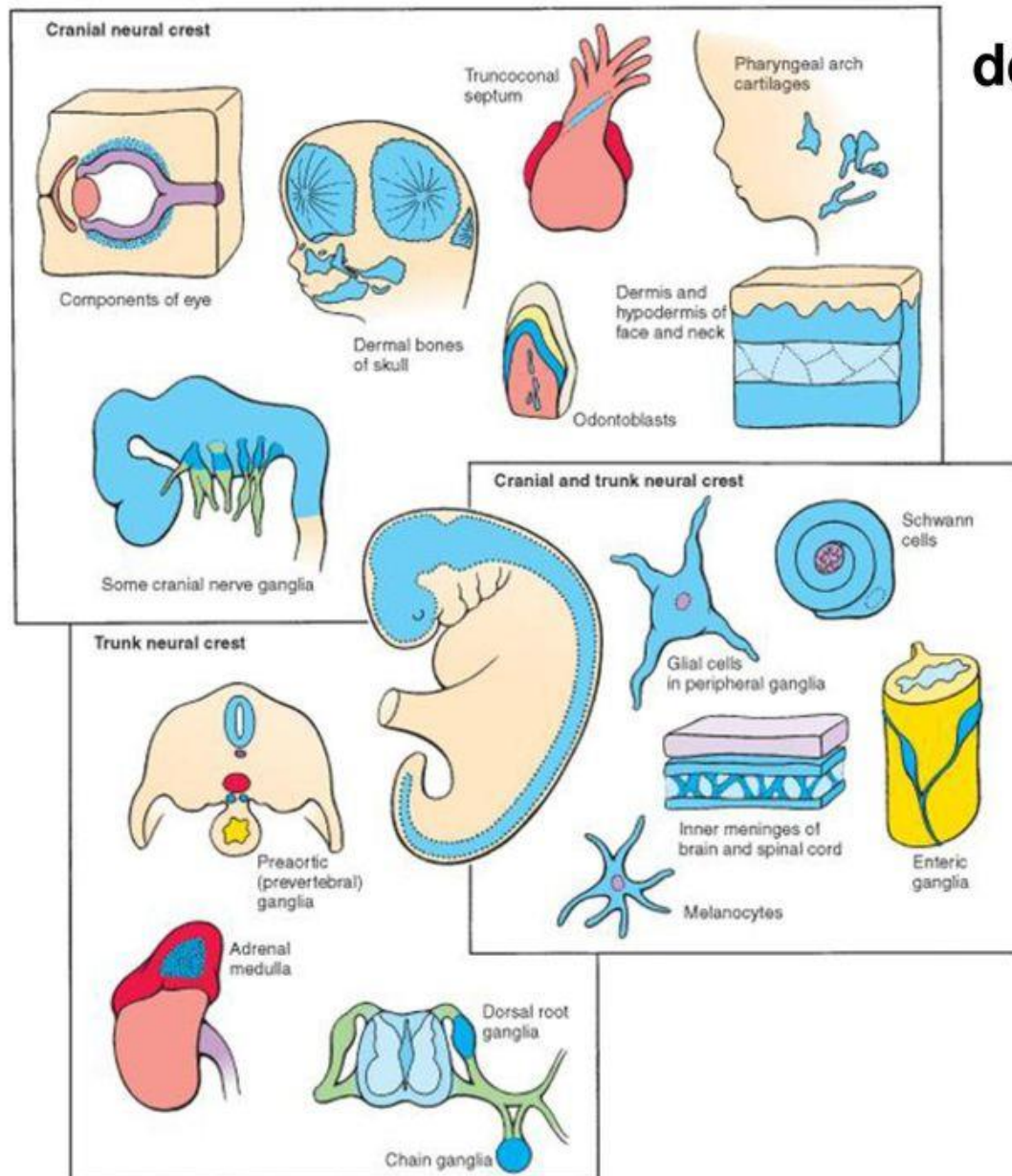
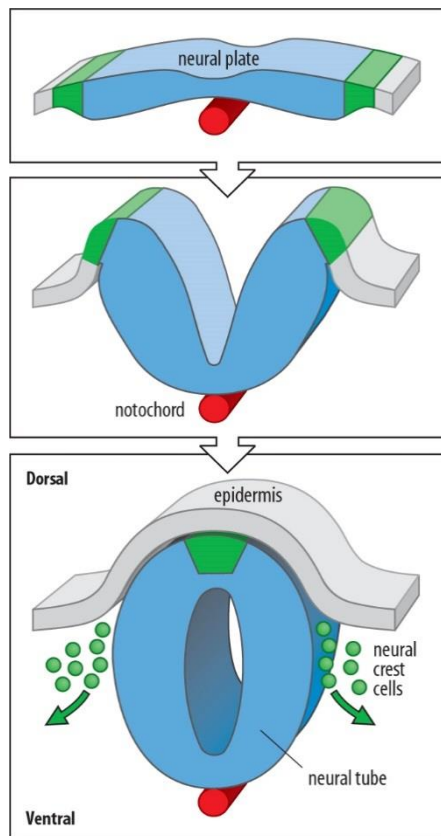
© 1995 Current Biology

Lumsden, A. & Graham, A., 1995. *Current Biology*, 5(12), pp.1347–1350.

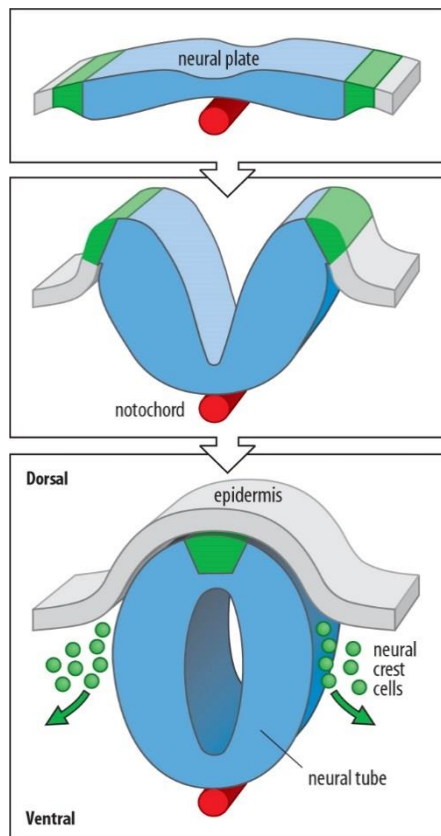


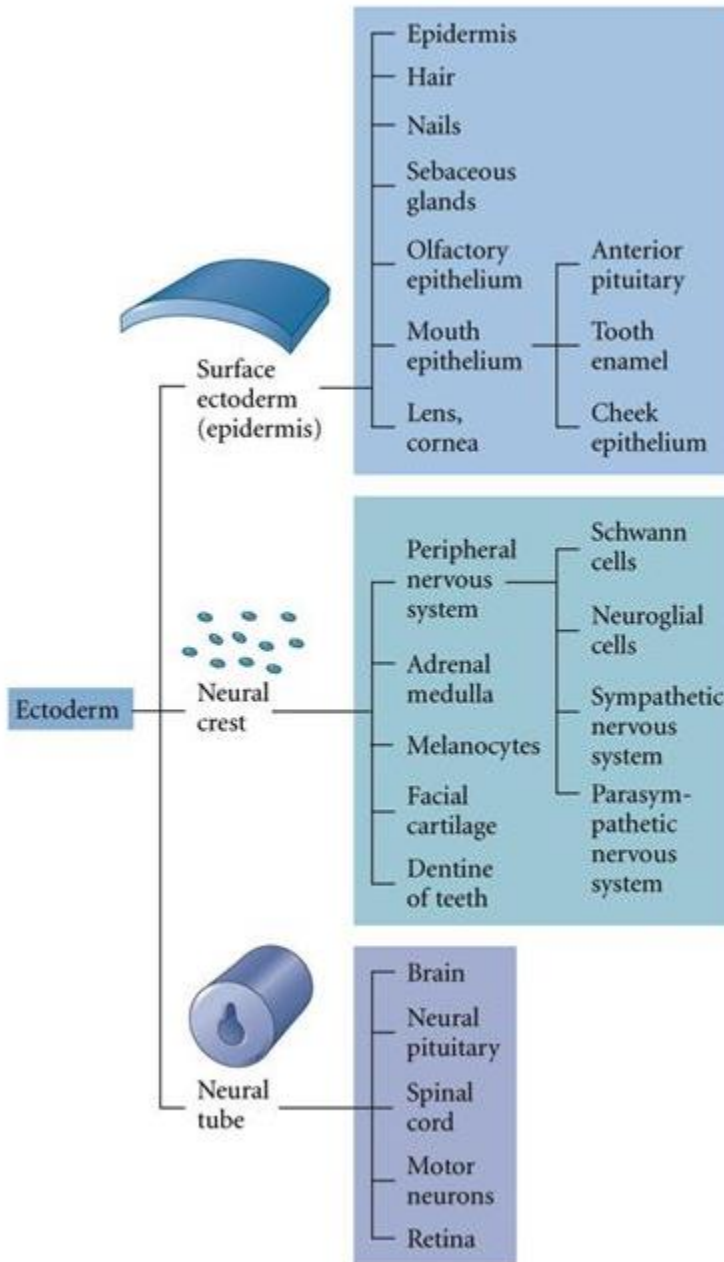
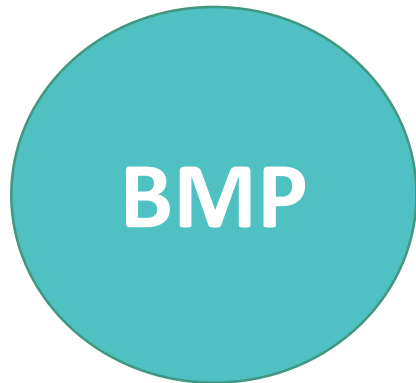
CÉLULAS DA **CRISTA NEURAL**
TAMBÉM SÃO DERIVADAS DA
ECTODERME!

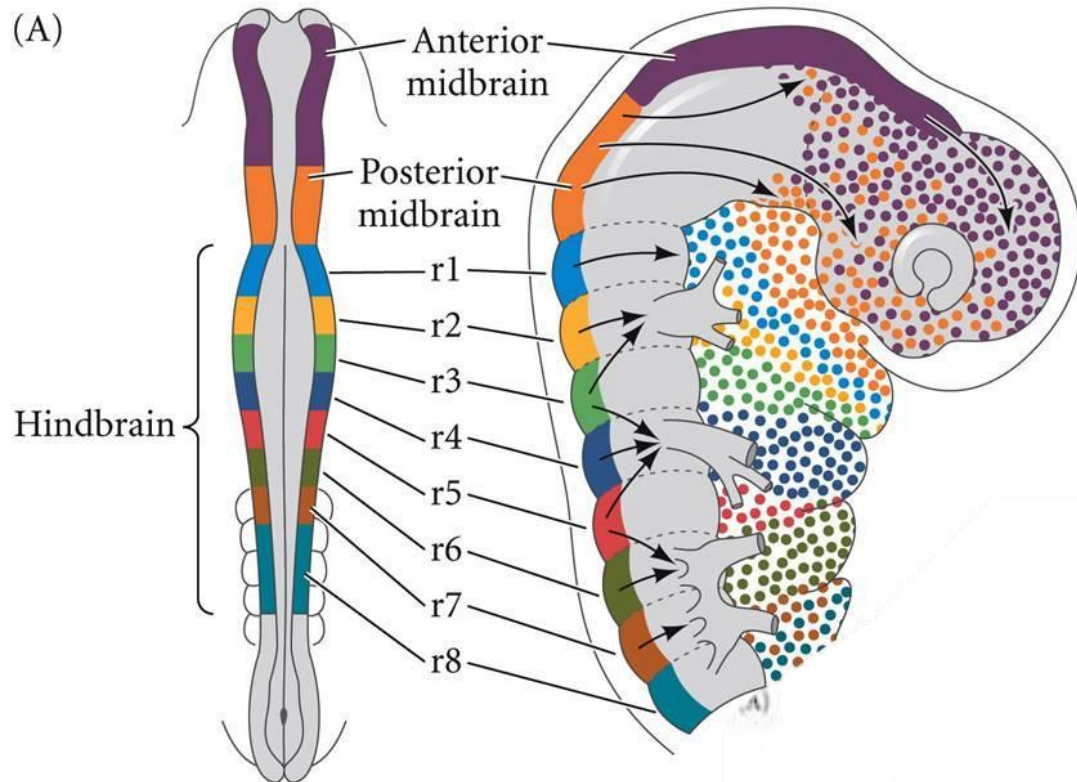




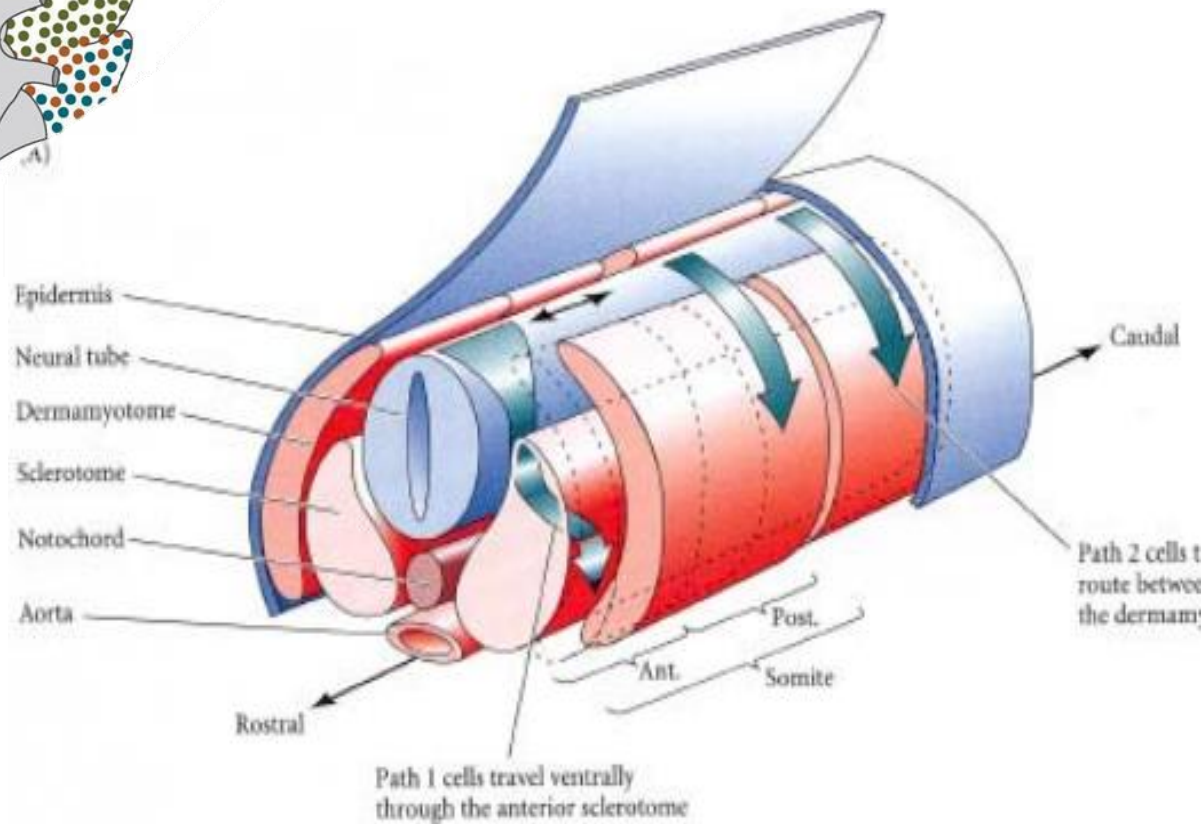
de



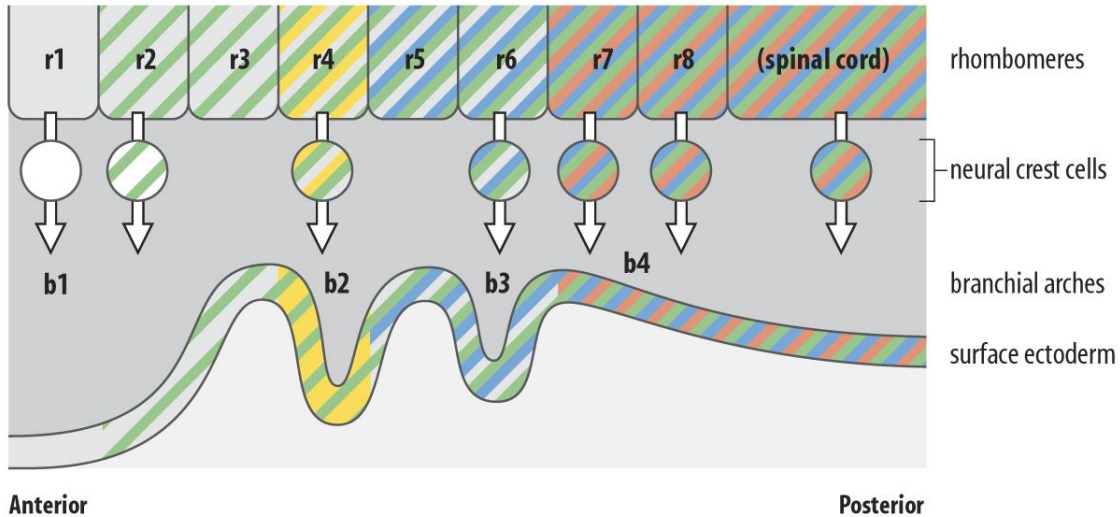




DEVELOPMENTAL BIOLOGY, 9e, Figure 10.10 (Part 1)



Expression of Hox genes of paralogous subgroups 1 to 4 in the hindbrain (r1 to r8), migrating neural crest cells, and the surface ectoderm of the branchial arches (b1 to b4)



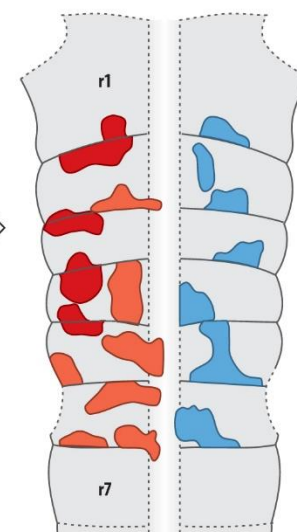
■ *Hox1*
 ■ *Hox2*
 ■ *Hox3*
 ■ *Hox4*

Single neuroepithelial cells labeled at early and late stages and the labeled clones mapped at 2 days

Early-stage labeling



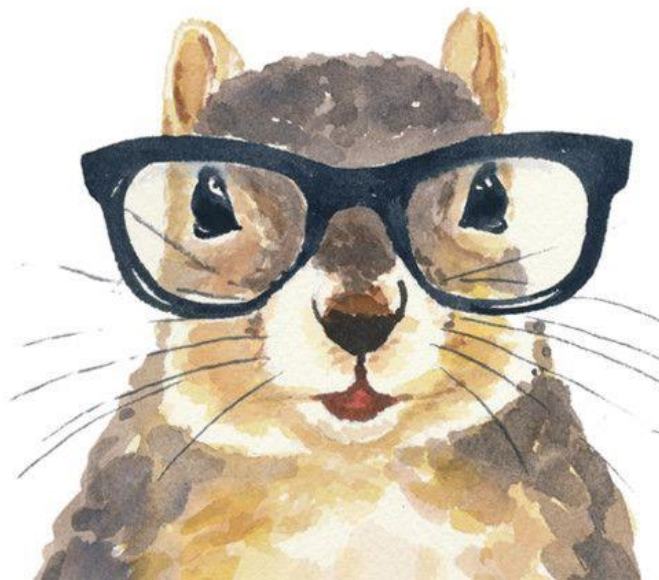
Pattern of clones



Late-stage labeling

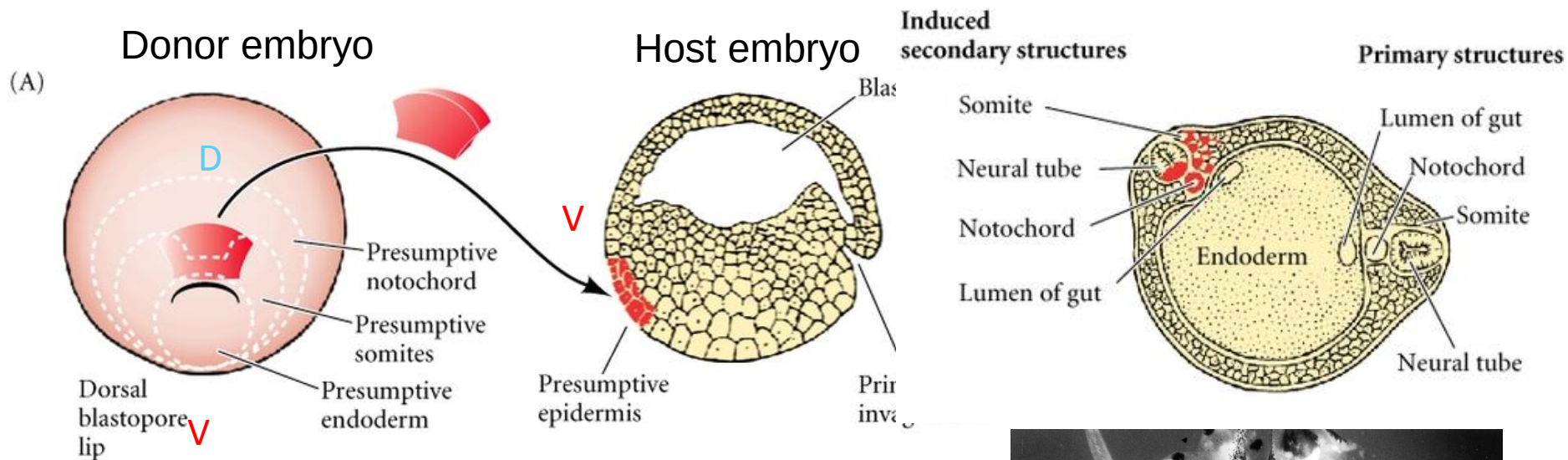


**Vamos falar de
sinalização
molecular!**



Duplicação do lábio do blastoporo dorsal gera um segundo sistema nervoso.

Spemman and Mangold, 1924

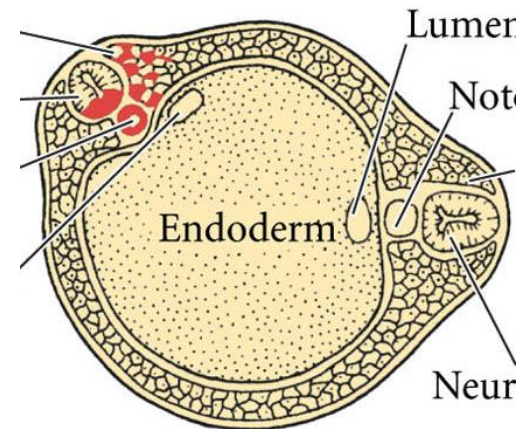




"Über Induktion von Embryonalanlagen durch Implantation artfremder Organisatoren", Hans Spemann and Hilde Mangold *Archiv für Mikroskopische Anatomie und Entwicklungsmechanik*, 100: 599-638, 1924.

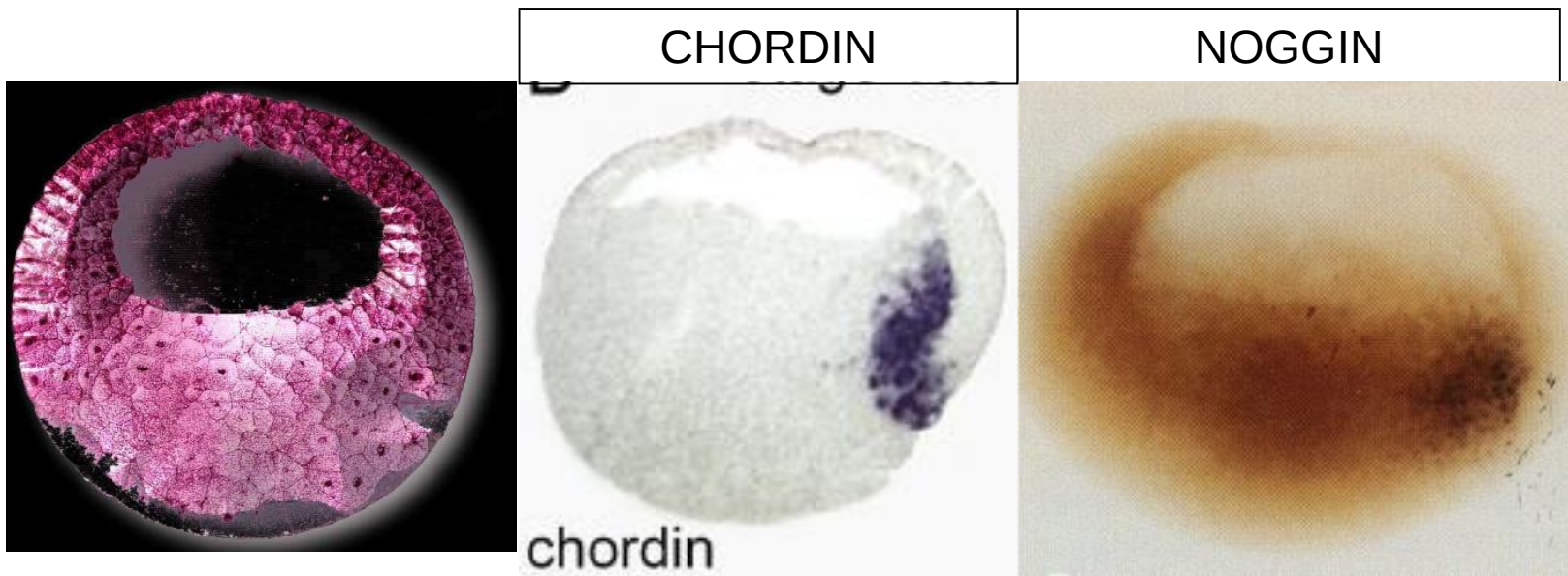
Propriedades do Organizador:

1. Inicia Gastrulação
2. Participa do Mesoderma Dorsal
3. Induz formação de tecido Nervoso a partir do Ectoderma

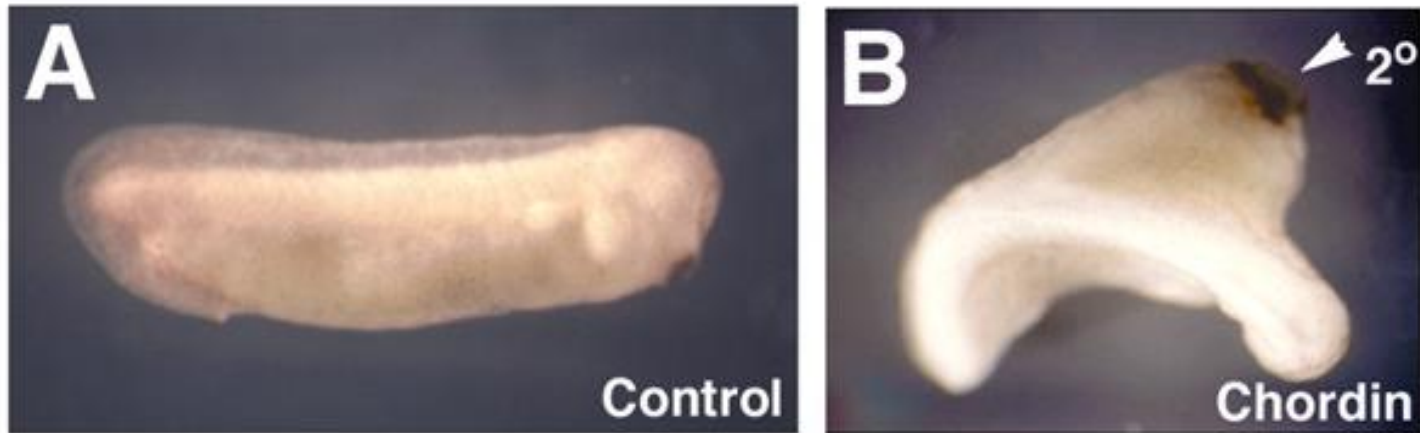


O que é que o lábio do blastóporo dorsal *secreta* que pode ***induzir*** diferenciação neural no ectoderma?

O lábio do blastóporo dorsal produz inibidores de BMP como Chordin, Noggin e Follistatin.



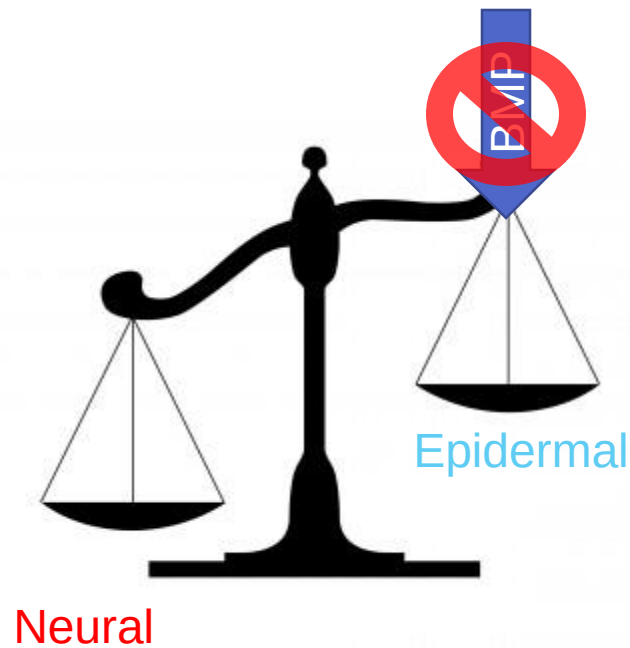
Superexpressão de inibidores de BMP induzem um segundo eixo neural.



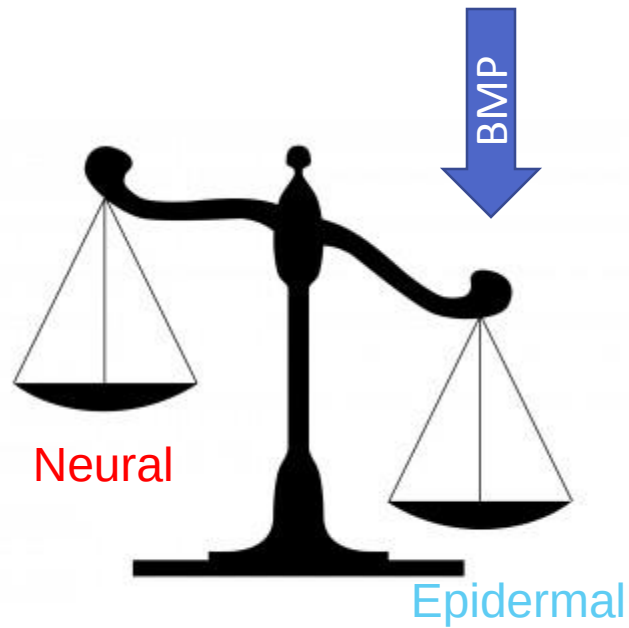
O que é que o lábio do blastóporo dorsal *secreta* que pode *induzir* diferenciação neural no ectoderma?

Inibidores de BMP

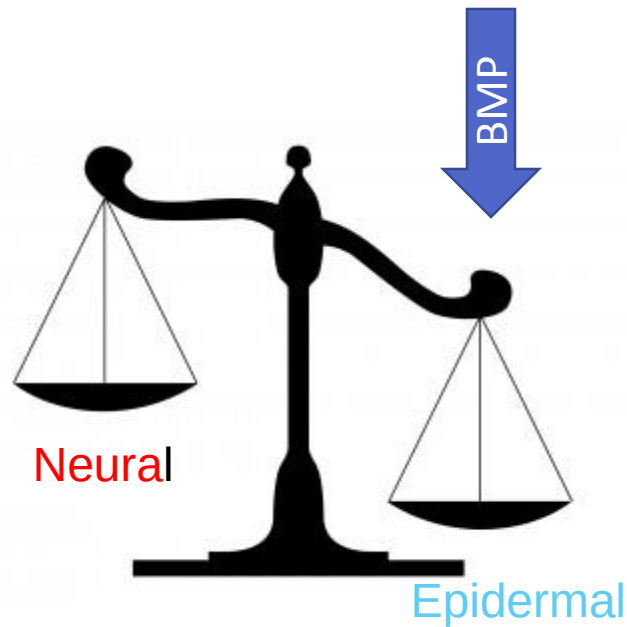
SE inibição do BMP induz destino neural



ENTÃO BMP induz destino epidermal



SE BMP induz epidermal



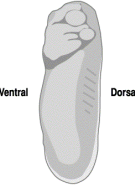
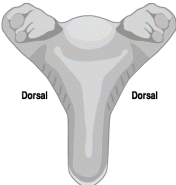
ENTÃO ausência de sinal deve favorecer a diferenciação neural



Neural

Epidermal

Remoção da via de sinalização de BMP>> neural

mRNA para <u>receptor dominante negativo de BMP</u> (pg)	 Normal	 Duplicação
0	88%	0
20	52%	27%
200	7%	76%

ENTÃO ausência de qualquer sinal favorece NEURAL



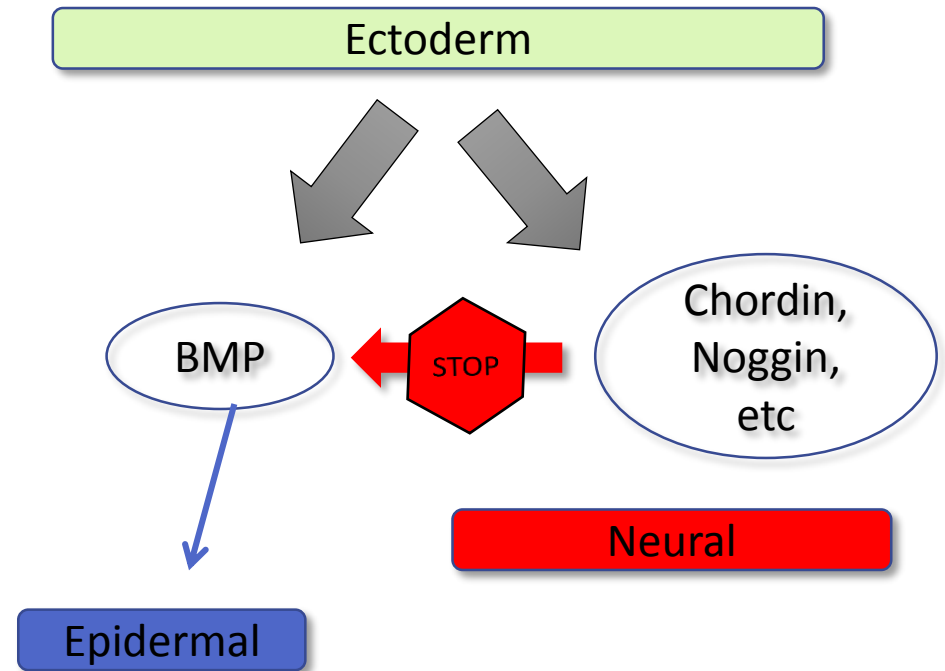
Modelo de diferenciação neural por *default*



Neural

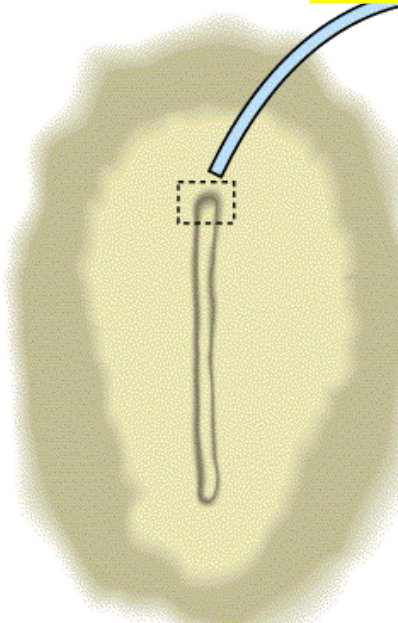
**PRIMEIRA
DECISÃO:
Epidermal OU
Neural?**

Indução

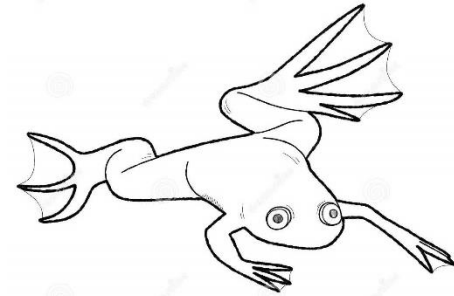
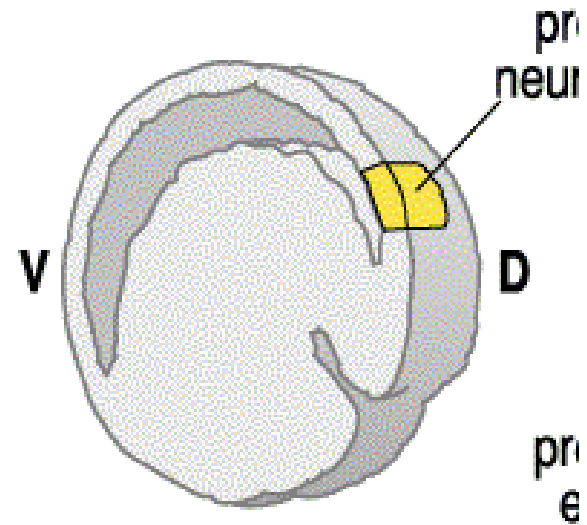


Estas conclusões de aplicam a qualquer vertebrado?

O **nó de Hensen** tem propriedades indutivas similares ao **lábio do blastóporo dorsal** de anfíbios.

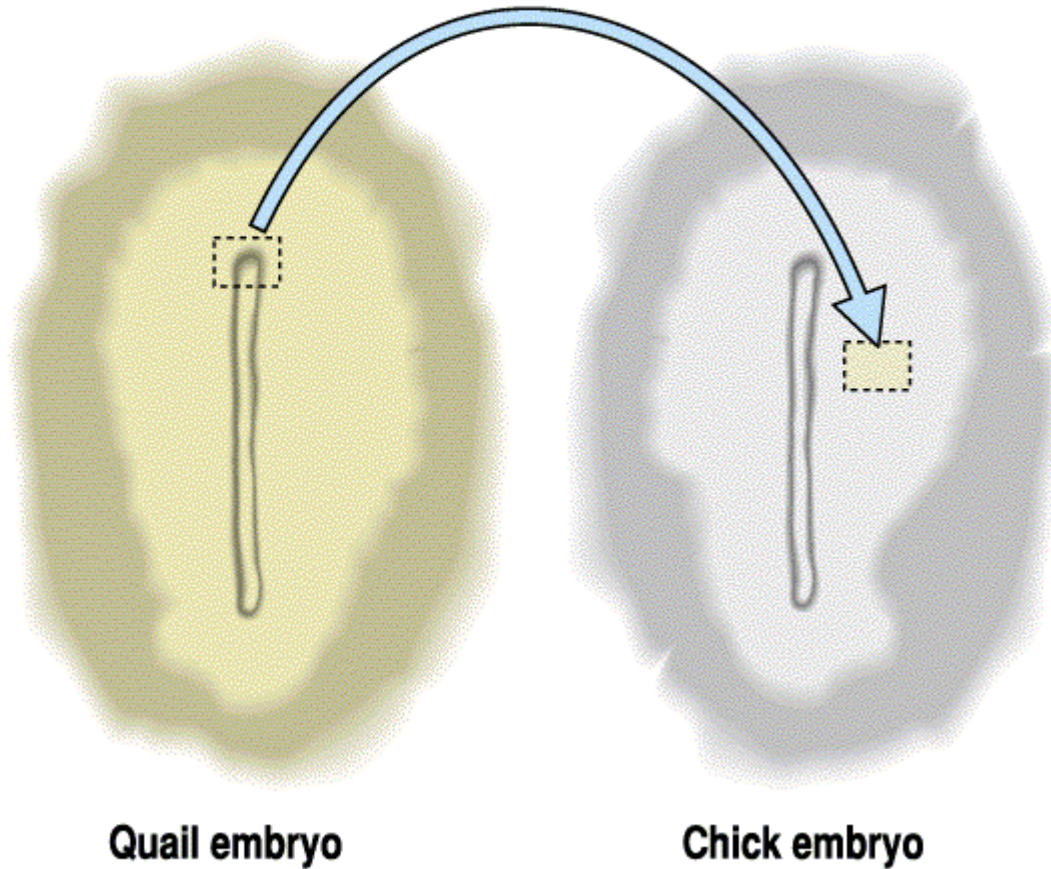


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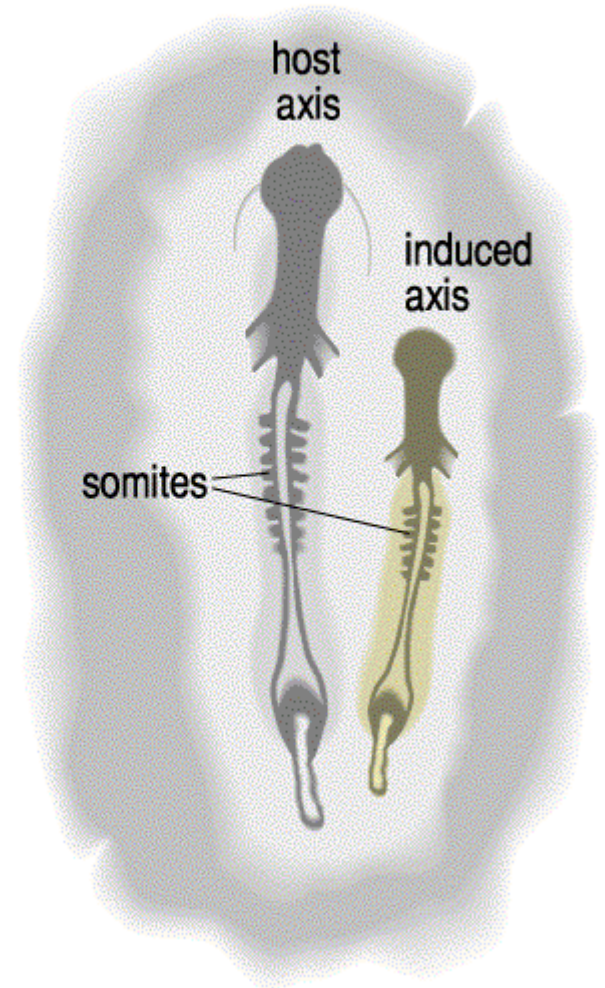


Explantos de nó de Hensen também produzem duplicação do eixo nervoso

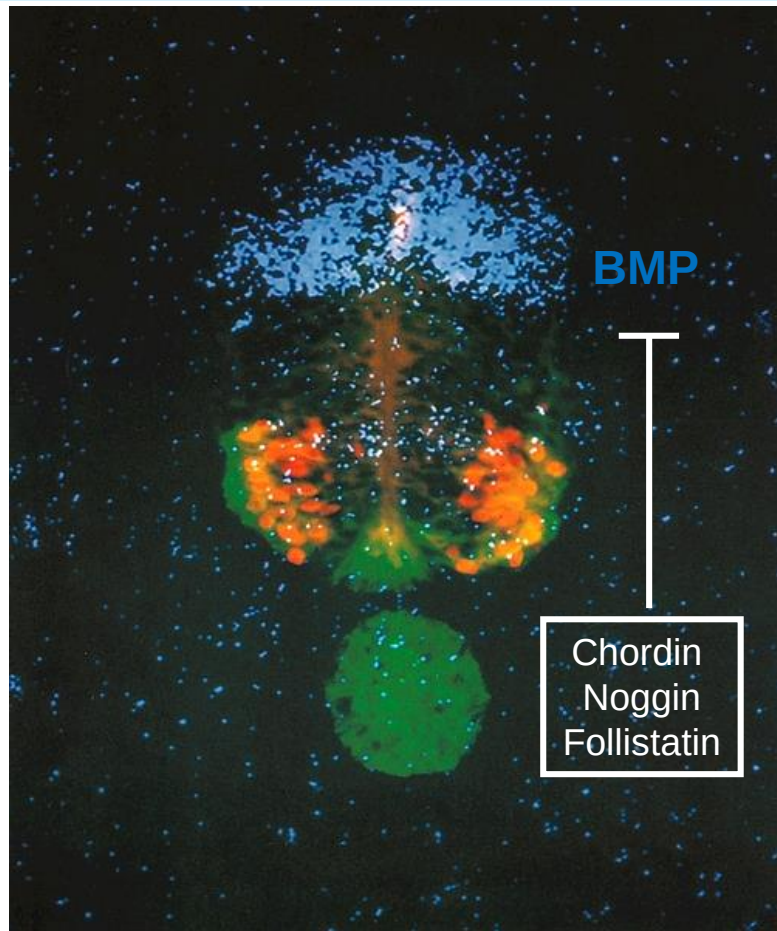
Hensen's node grafted from quail embryo to chick host



New axis induced in host

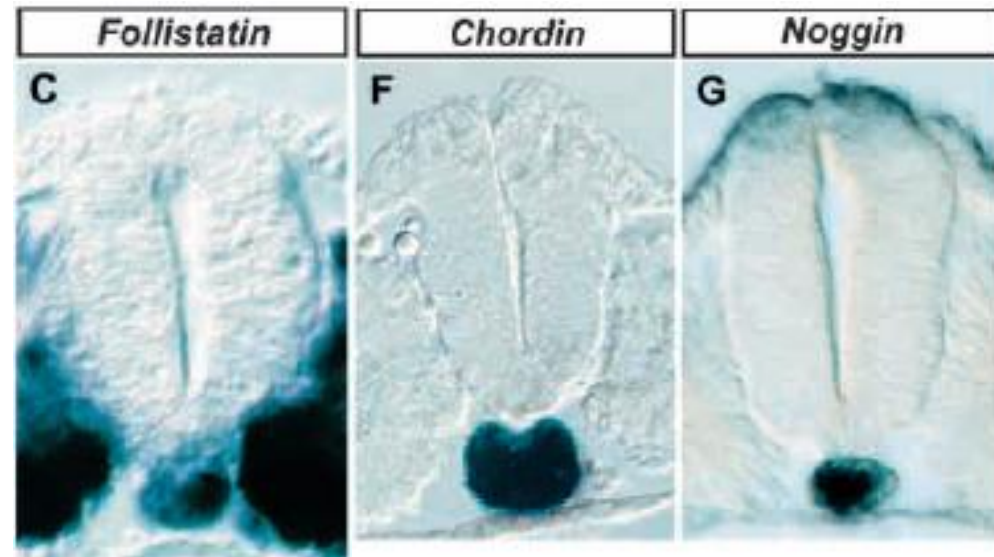


A NOTOCORDA EXPRESSA INIBIDORES DE BMP



BMP

Sonic Hedgehog e INIBIDORES de
BMP



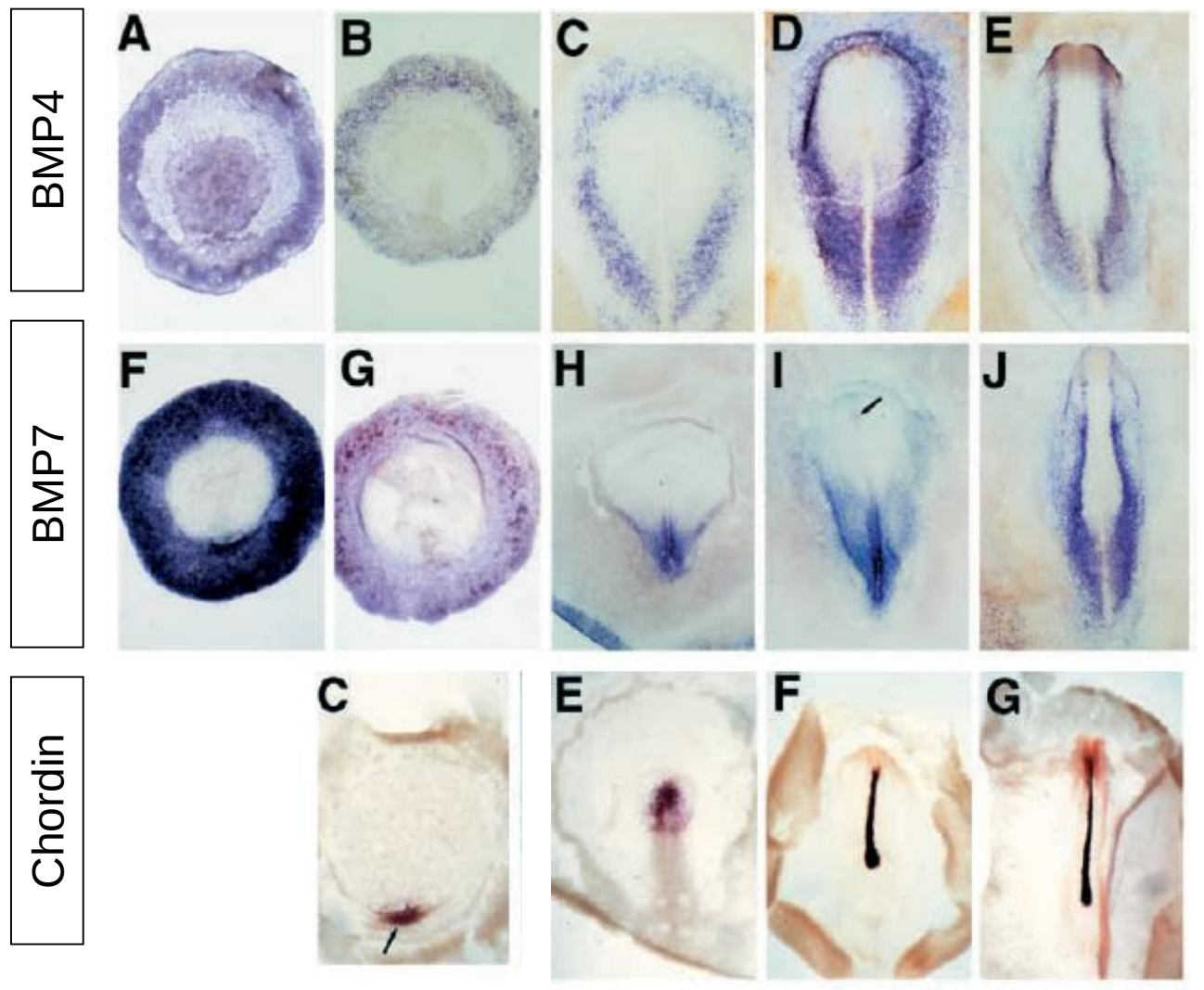
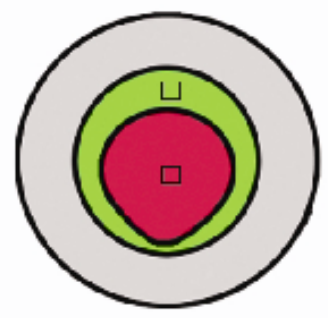
A indução neural em **aves**
também ocorre pela inibição
de sinalização de BMP?

O padrão de expressão de BMP e de seus inibidores são complementares

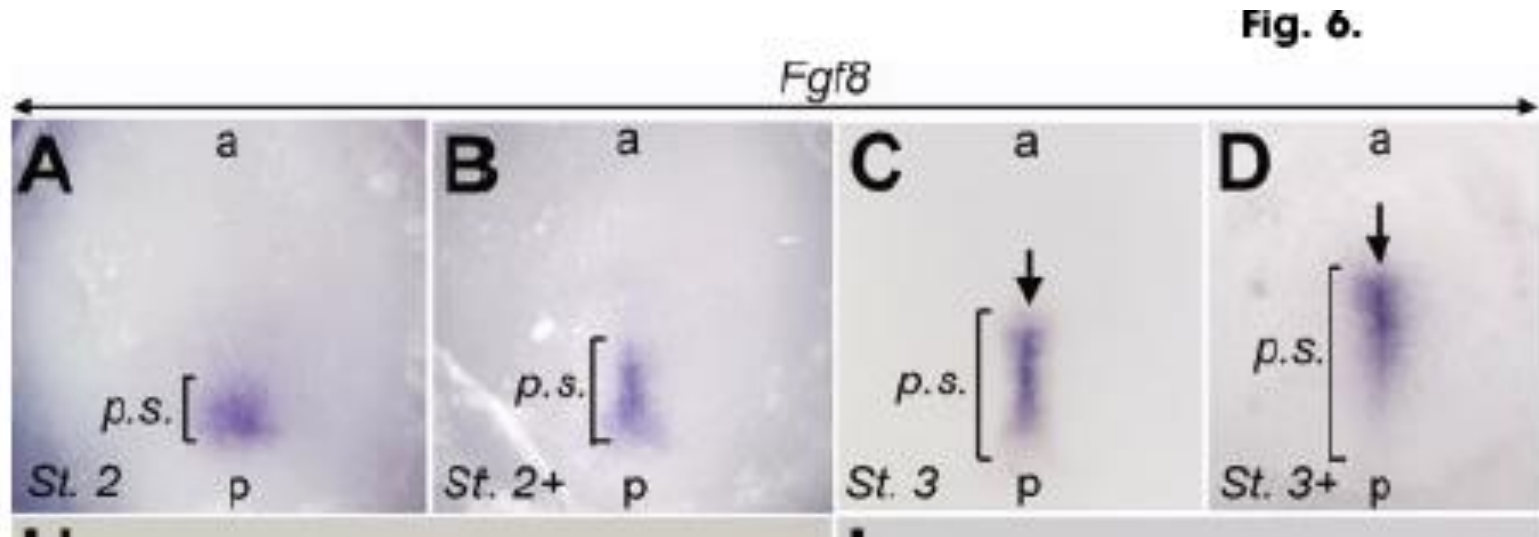
BMP está no domínio epidermal

Chordin está no domínio neural

Neural/epidermal



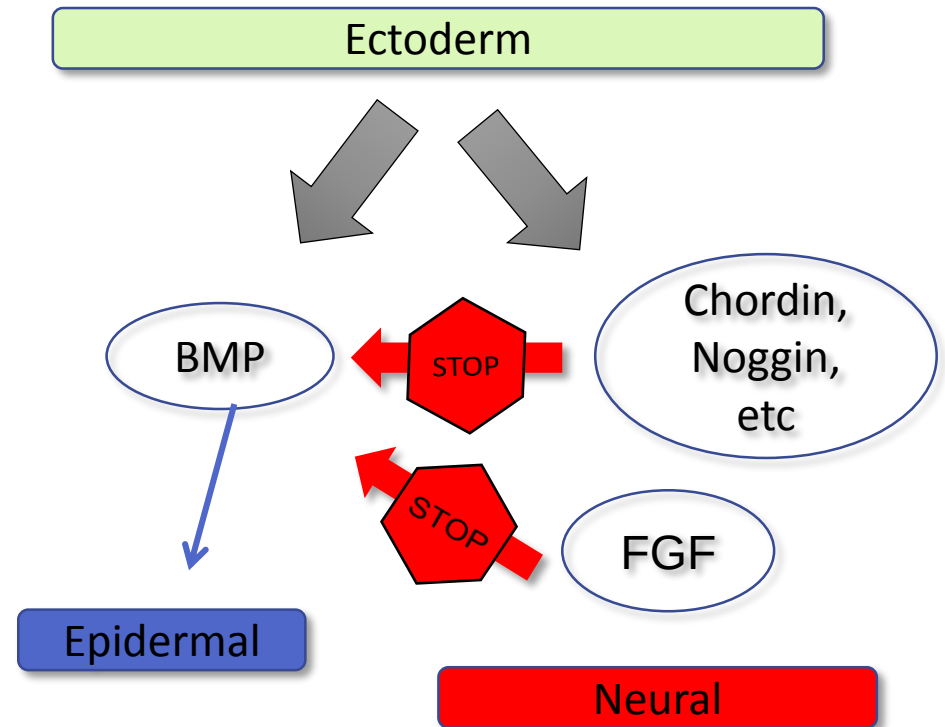
A linha primitiva (sítio da gastrulação) expressa FGF

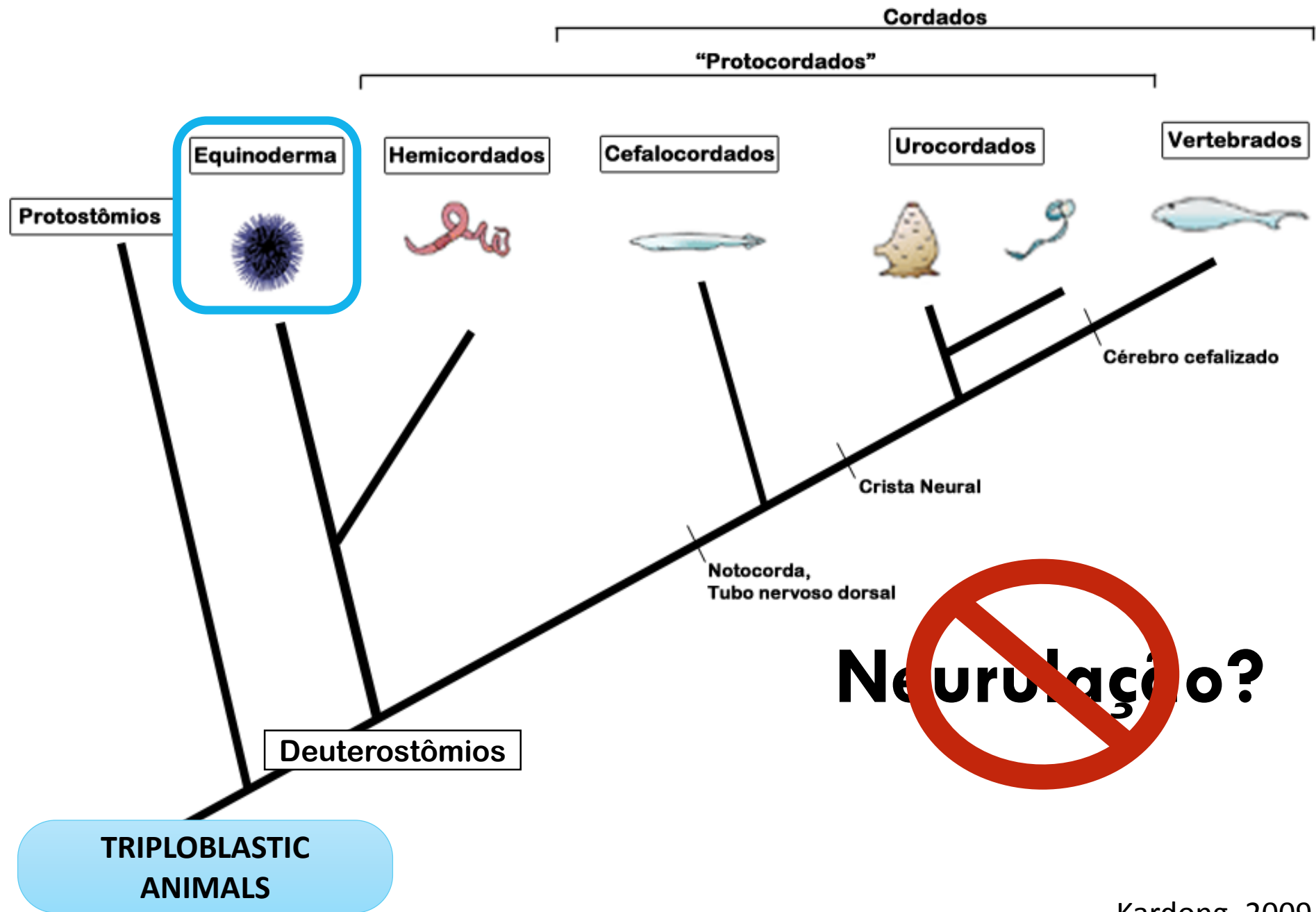


PRIMEIRA DECISÃO: Epidermal OU Neural?

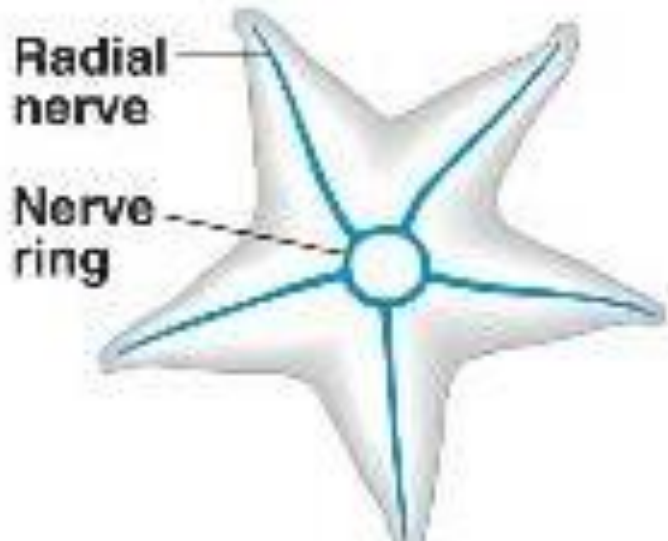


Indução

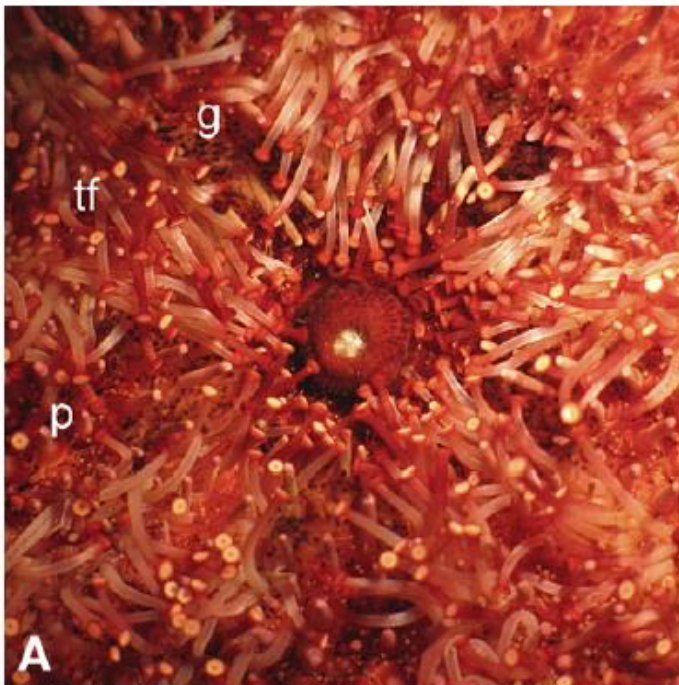




SISTEMA NERVOSO DOS ECHINODERMA



- Equinodermas possuem Sistema nervoso radial devido à sua simetria corporal.
- Sistema formado por um anel central na região oral e nervos radiais e na parede do corpo.
- Alguns possuem gânglios.
- Função: realizar movimentos sincronizados das **pedicelárias e pés ambulacrais**.
- ESTATOCISTOS

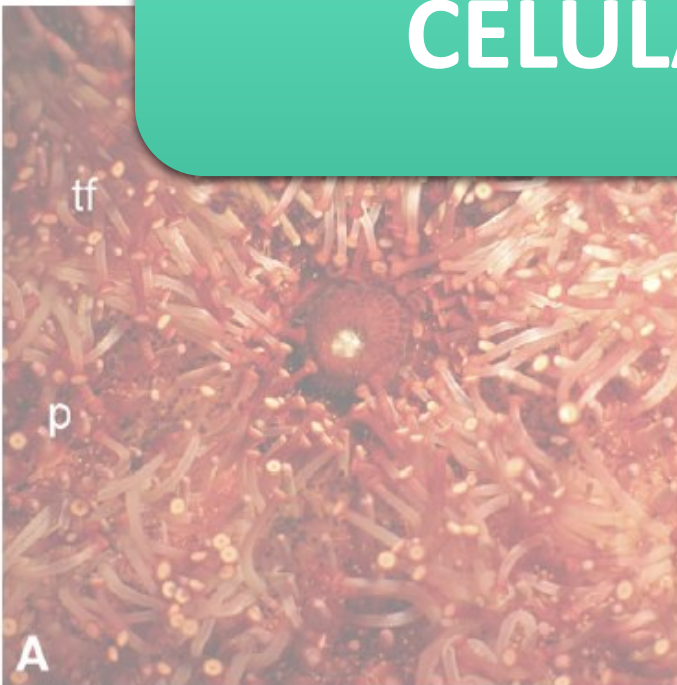


SISTEMA NERVOSO DOS ECHINODERMA



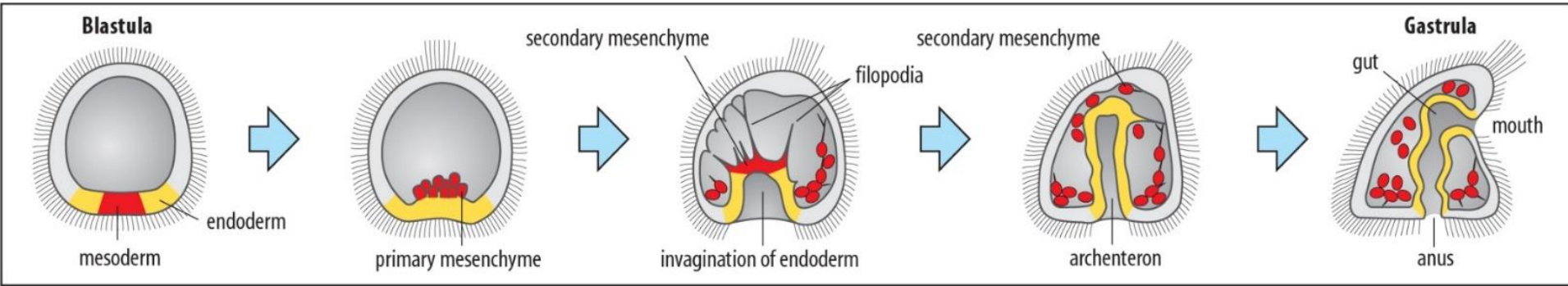
- Equinodermas possuem Sistema nervoso radial devido à sua simetria corporal.

QUAL A ORIGEM DESSAS CÉLULAS NERVOSAS?

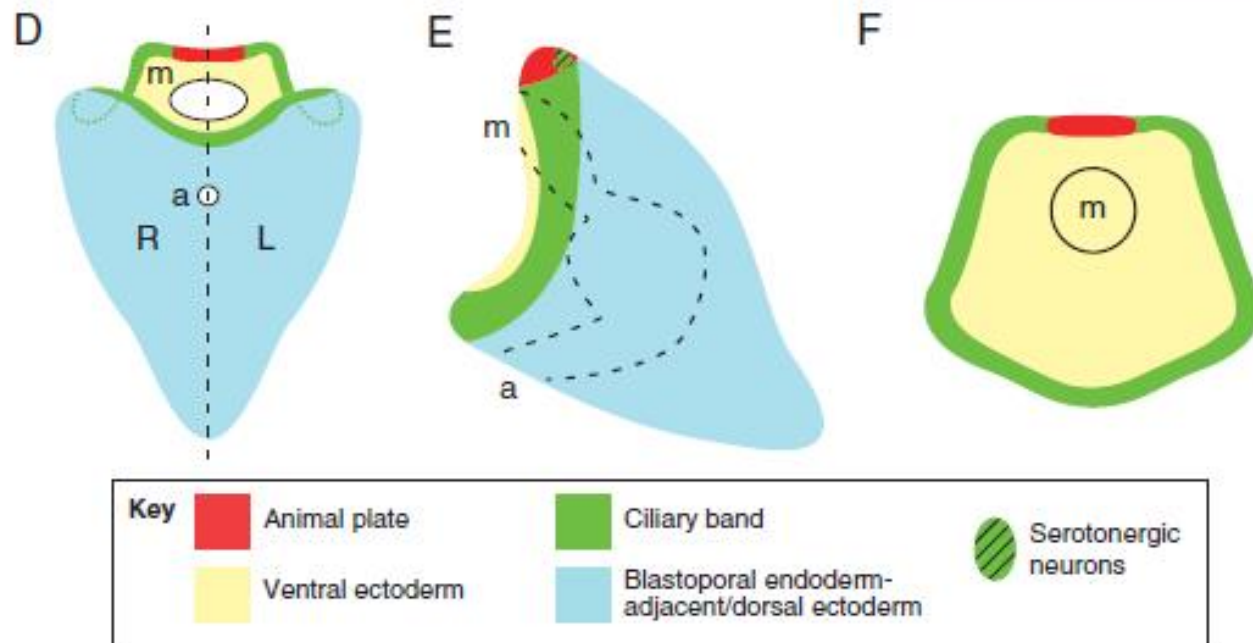
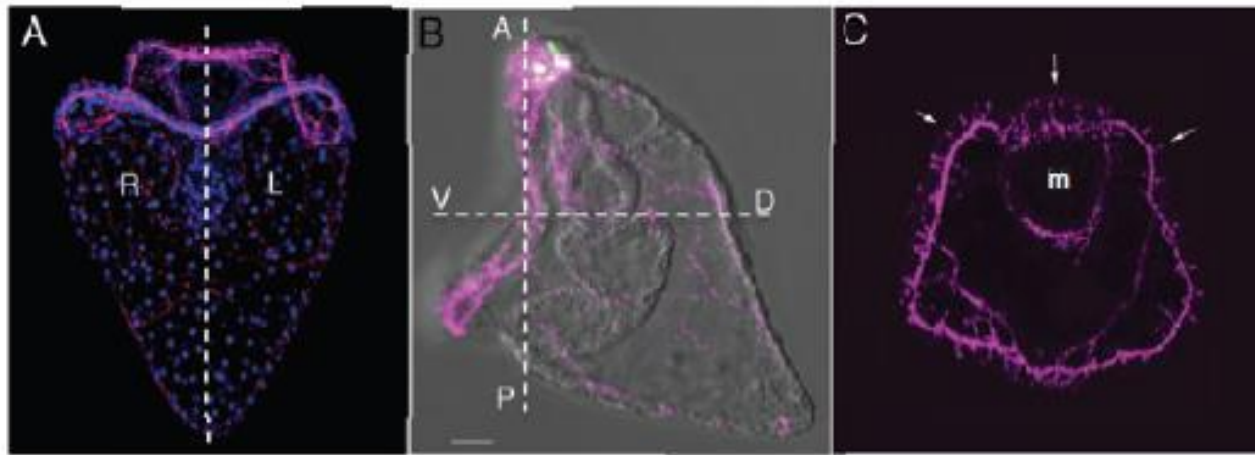


- Função: realizar movimentos sincronizados das **pedicelárias e pés ambulacrais**.
- ESTATOCISTOS

RECAPITULAÇÃO: GASTRULAÇÃO EM OURIÇOS

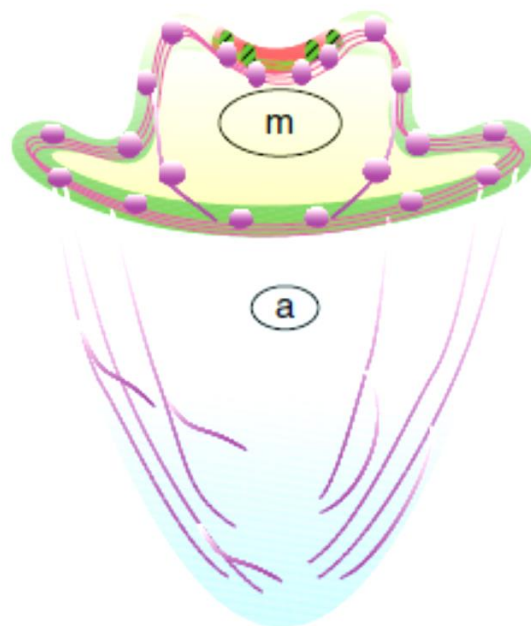


FORMAÇÃO DO SN – DESENVOLVIMENTO POSTERIOR

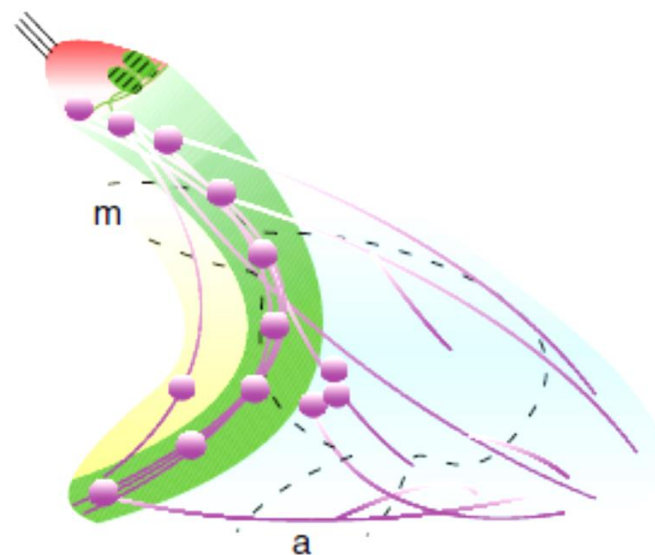


Neurônios serotoninérgicos na margem dorsal do polo animal.

A Ventral/posterior view



B Lateral view



Key



Animal plate



Ciliary band



Ventral ectoderm



Blastoporal endoderm-adjacent/dorsal ectoderm



Serotonergic neurons

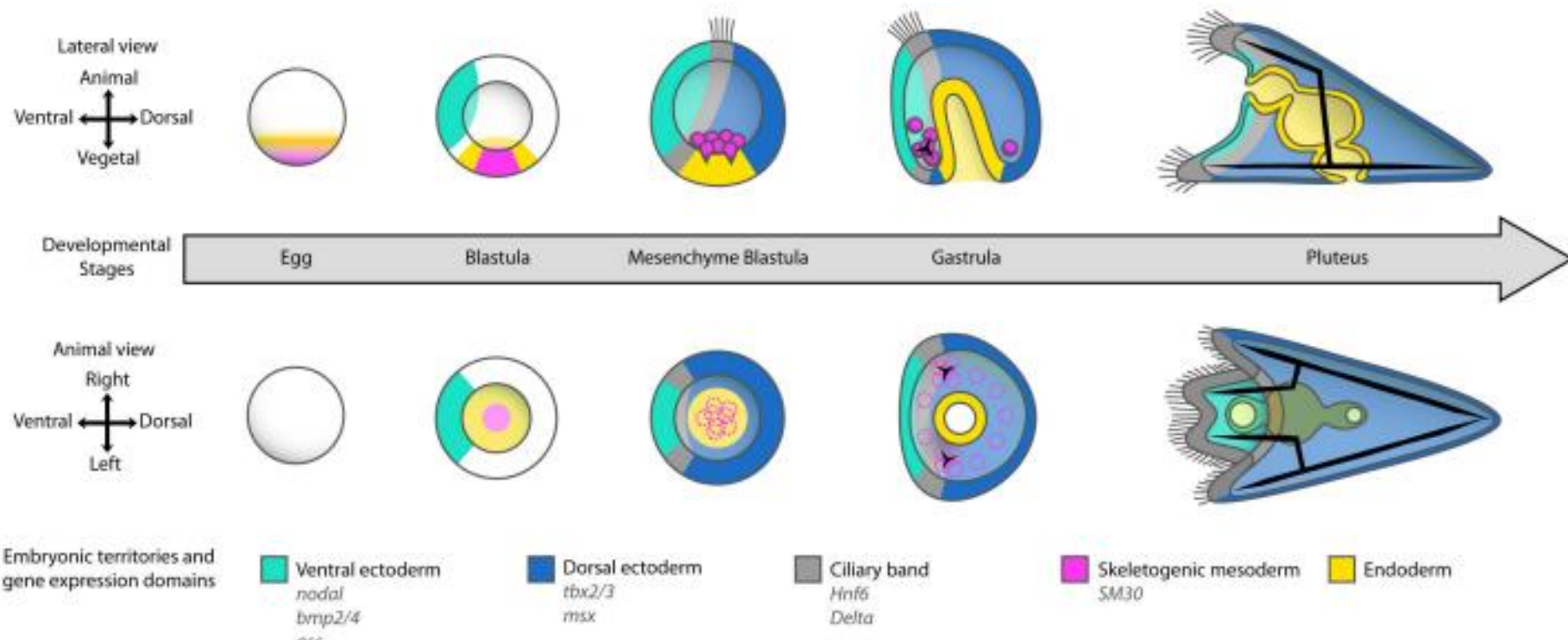


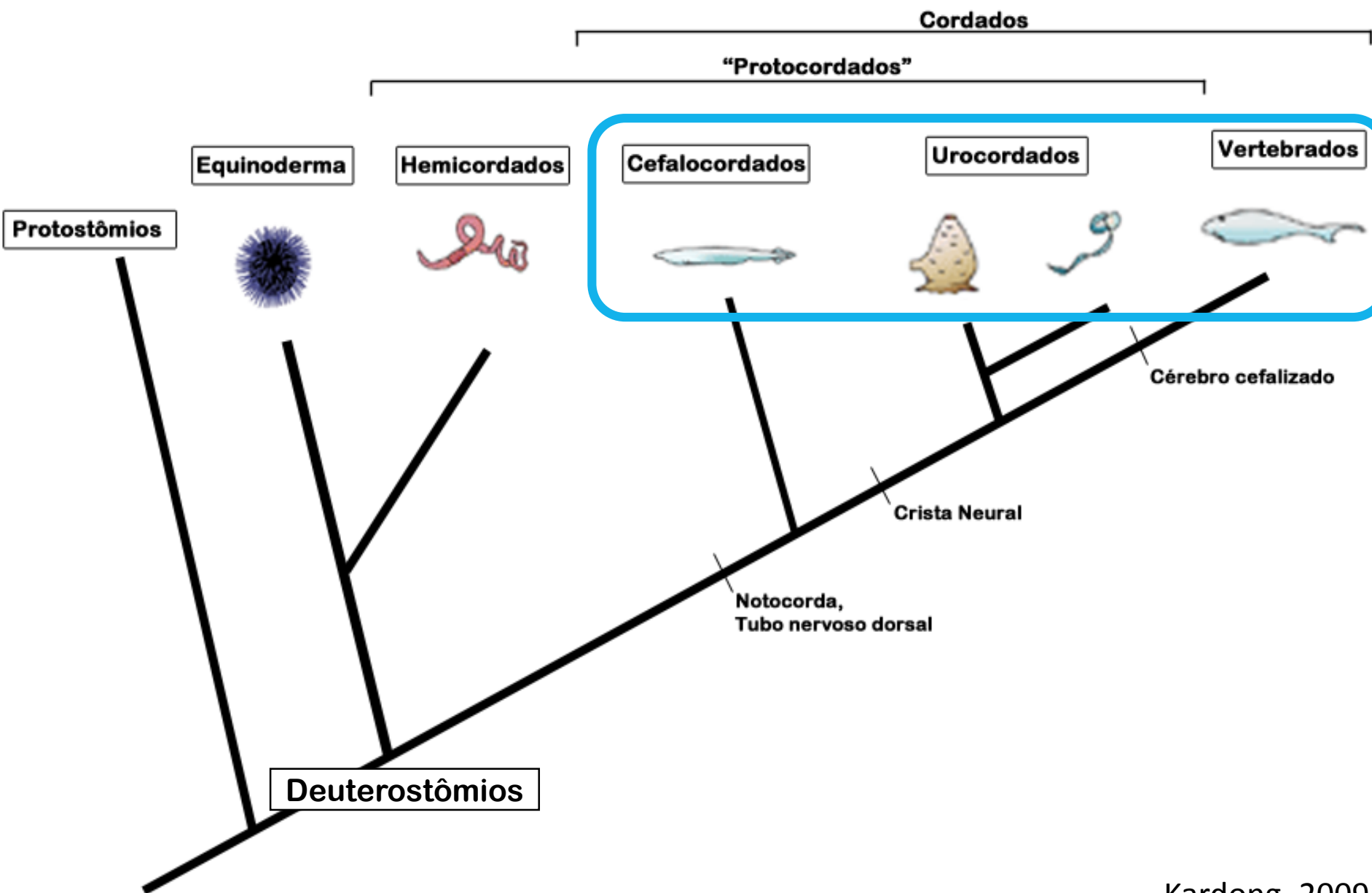
Ciliary band neurons

Patterning of the Dorsal-Ventral Axis in Echinoderms: Insights into the Evolution of the BMP-Chordin Signaling Network

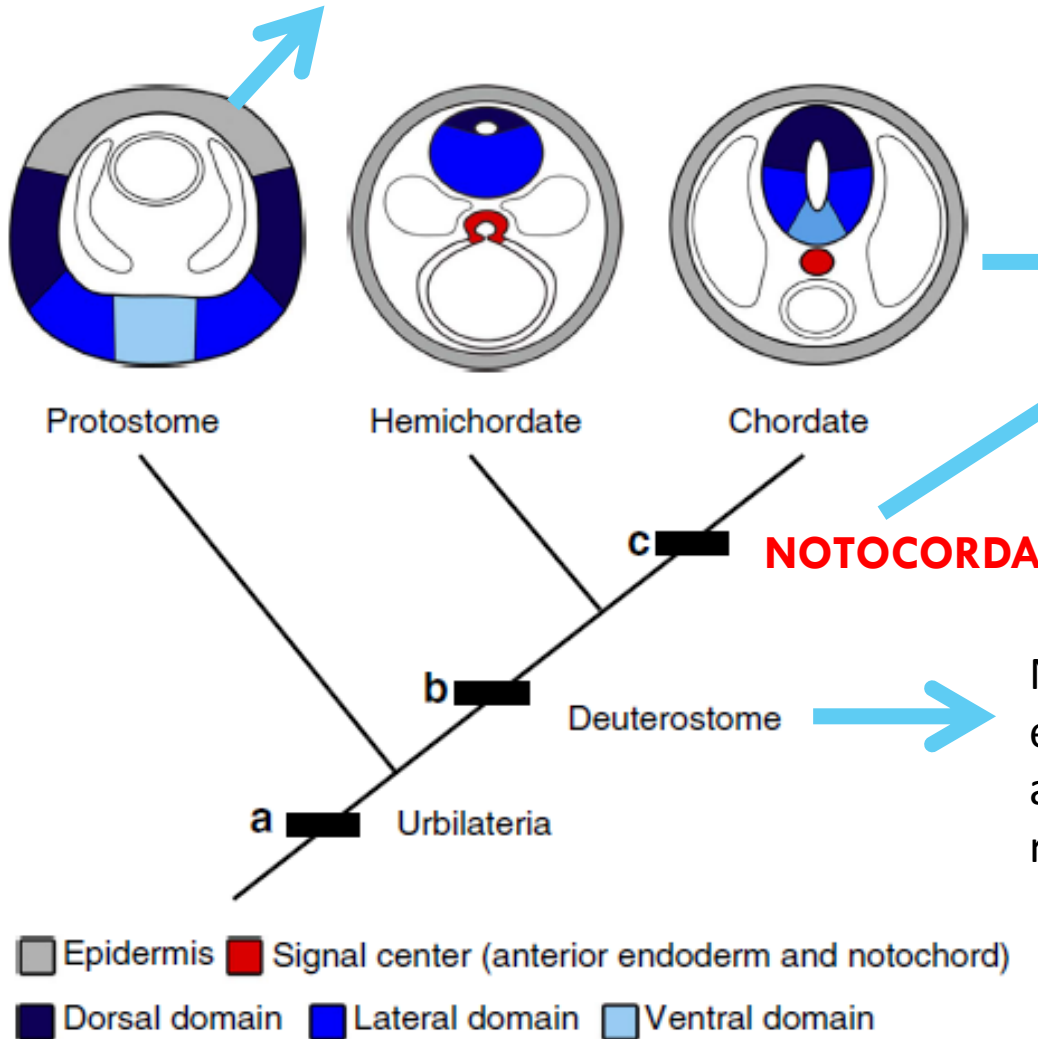
François Lapraz, Lydia Besnardeau, Thierry Lepage*

UPMC (University of Paris 06), CNRS, UMR7009, Biologie du Développement, Observatoire Océanologique, Villefranche-sur-Mer, France





Um complexo padrão dorsoventral no neuroectoderma estava presente no ancestral comum dos protostomos e deuterostomos



O sinal endodérmico foi ativado para o mesoderma da linha média dorsal, por meio da notocorda induzindo a formação do TN.

Na linhagem de deuterostomios, uma estrutura neural tubular foi adquirida e a padronização dorsoventral foi recrutada para o tubo.

FUNÇÕES DA NOTOCORDA

- Age como um eixo rígido de apoio para o embrião

- Precursor da Coluna Vertebral (discos intervertebrais)

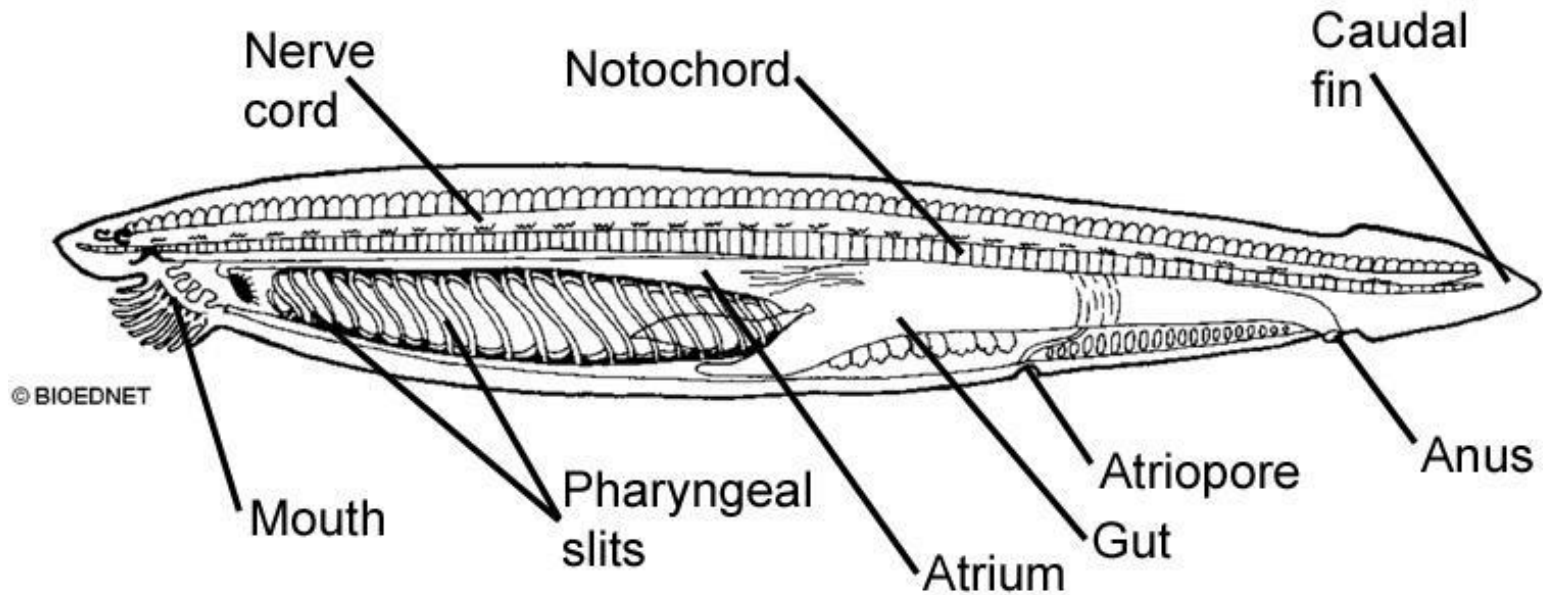


**Apenas nos
Vertebrados!**

- Induz a formação da PLACA NEURAL

CEFALOCORDADOS

- - Notocorda na Cabeça



CEFALOCORDADOS

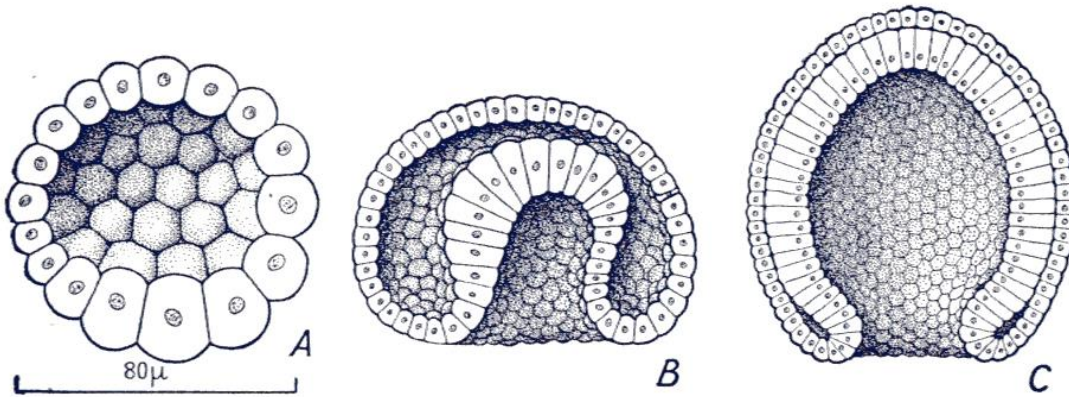
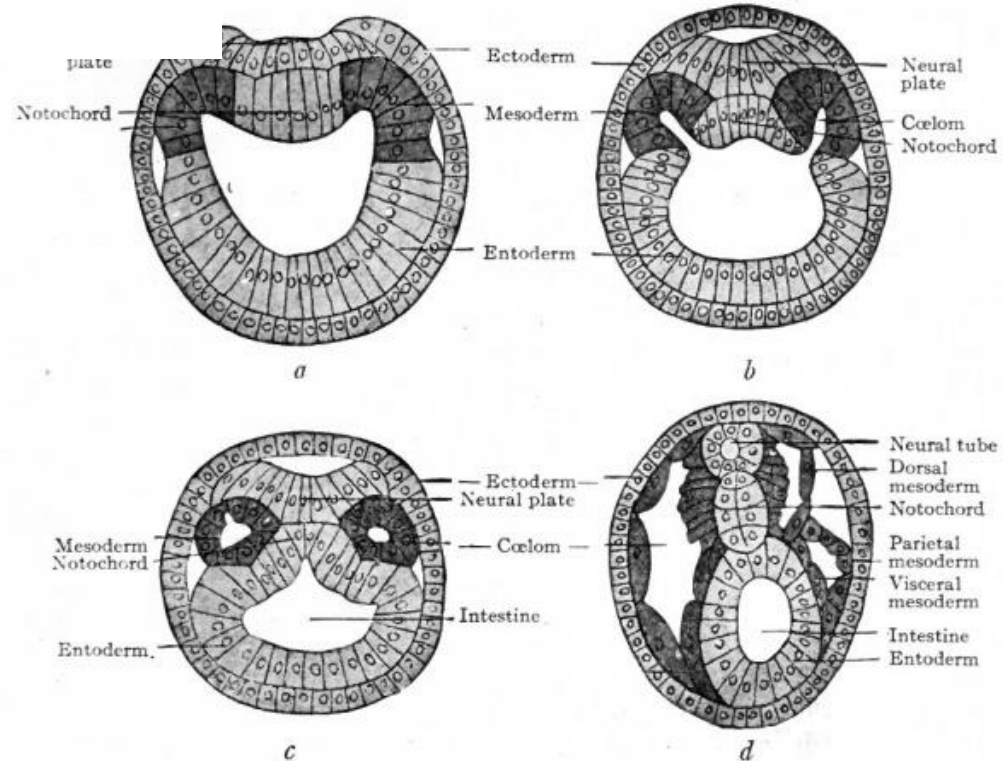
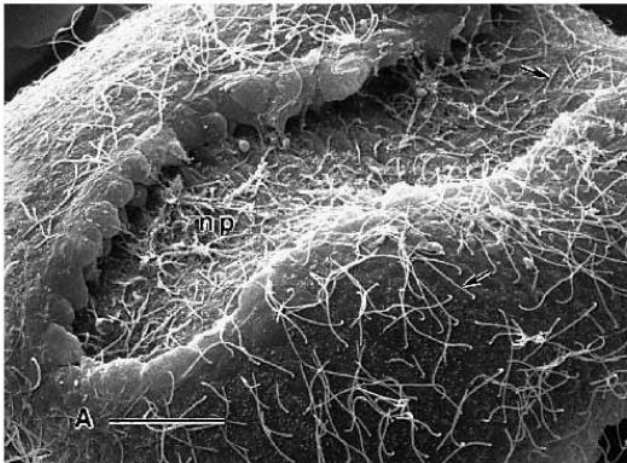
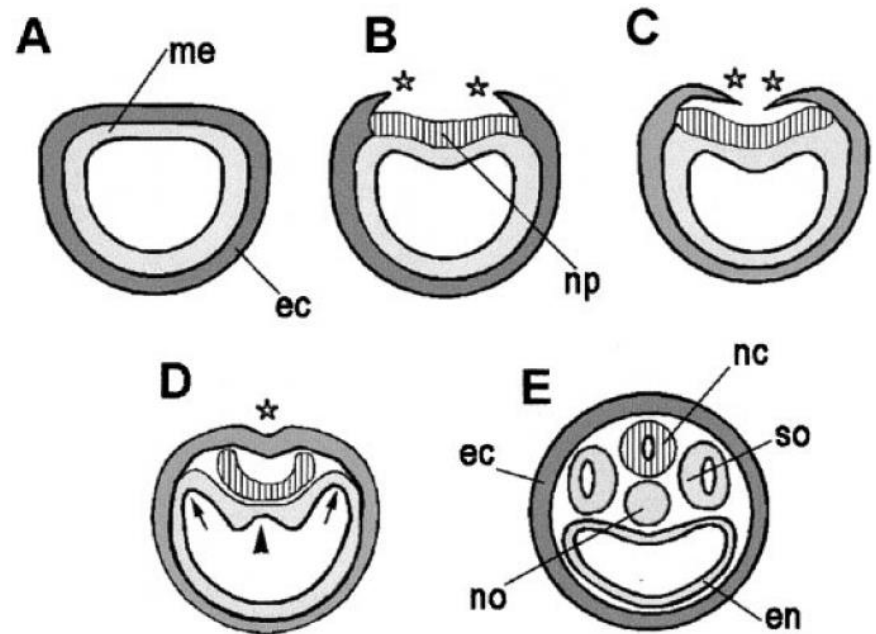
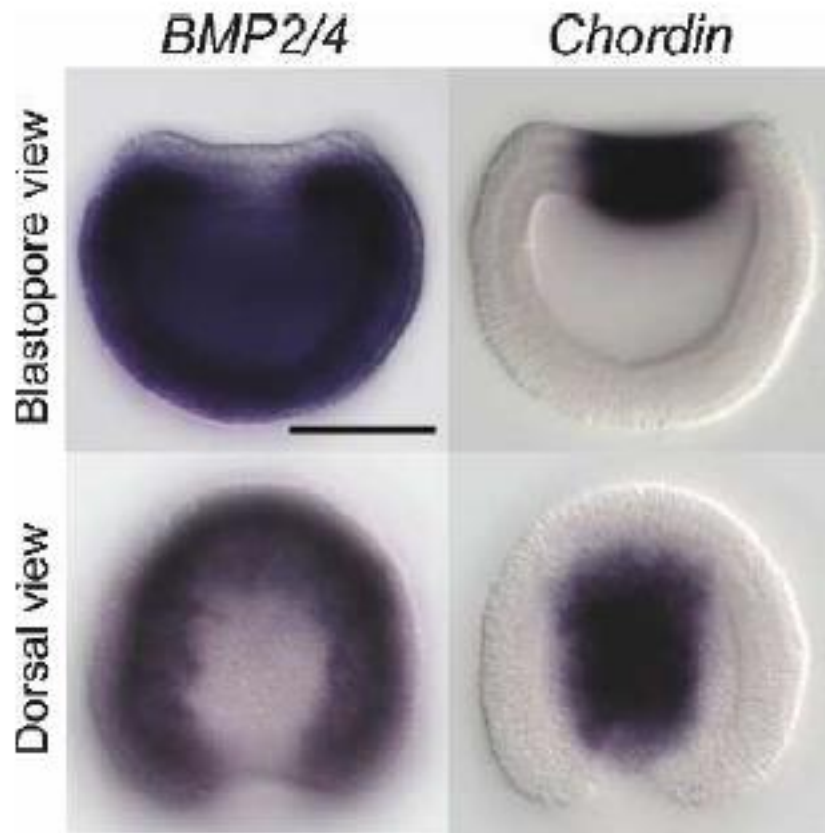


FIG. 17. Three stages in the development of amphioxus as seen in stained preparations.

A, the blastula; B, early, and C, later gastrula.

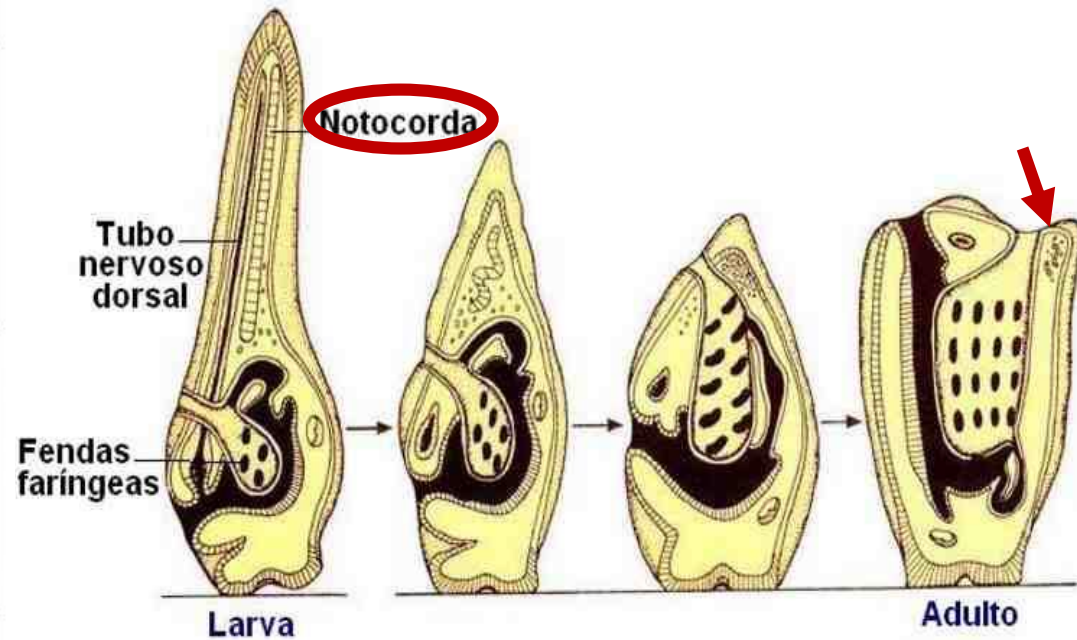
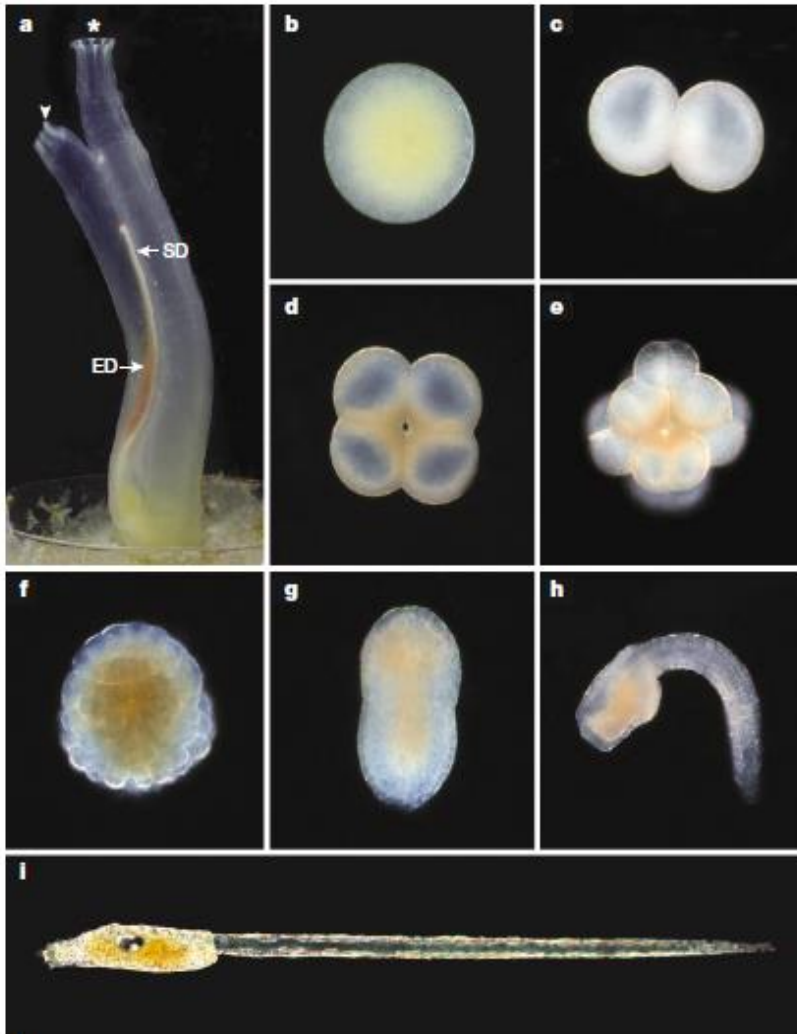


CEFALOCORDADOS

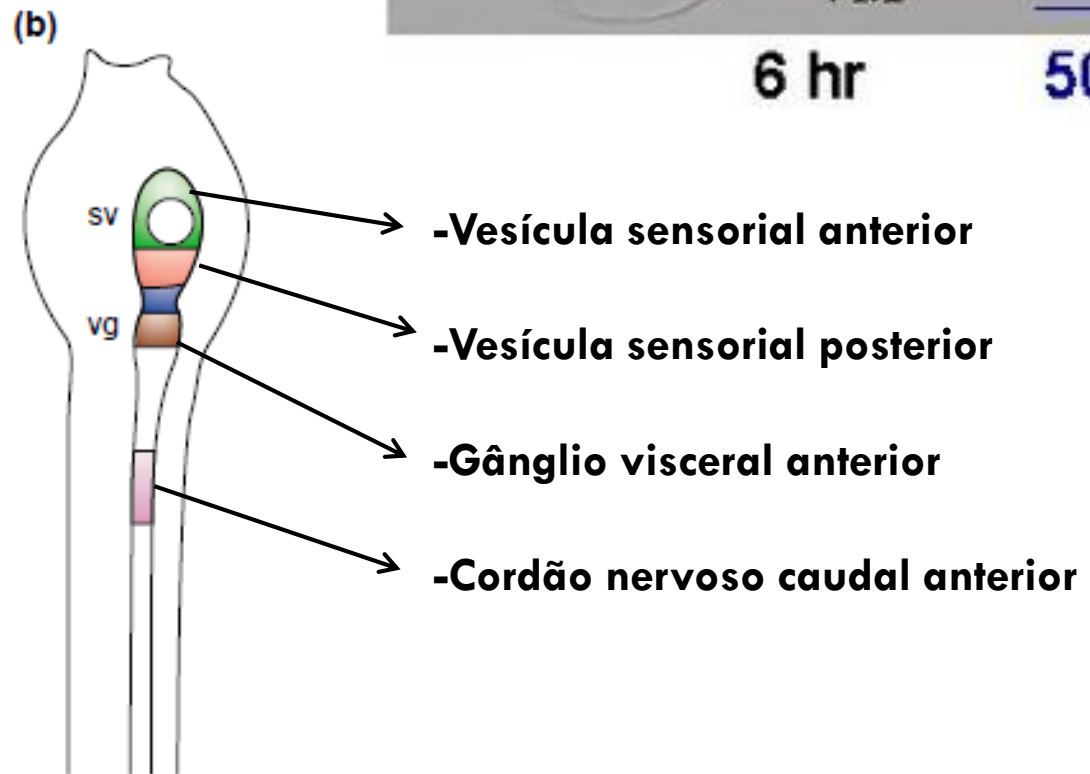
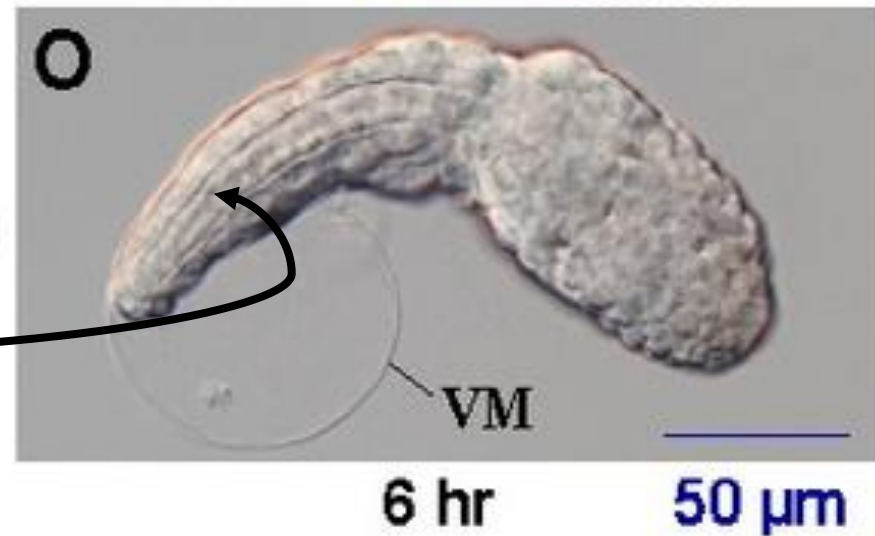
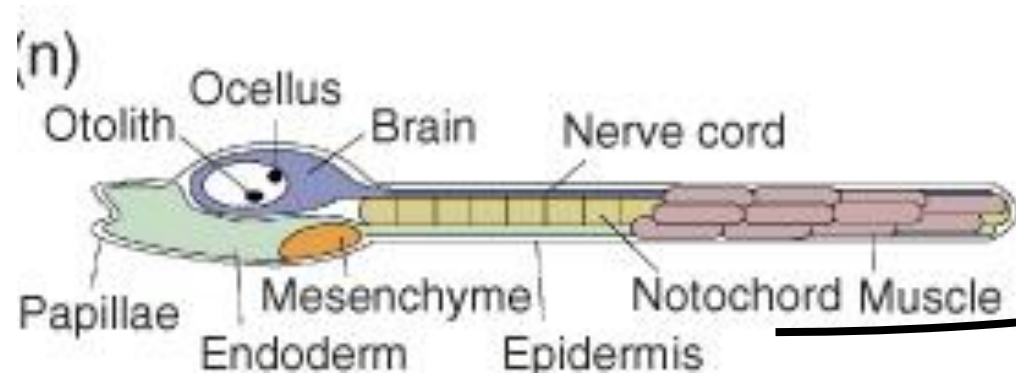


UROCORDADOS

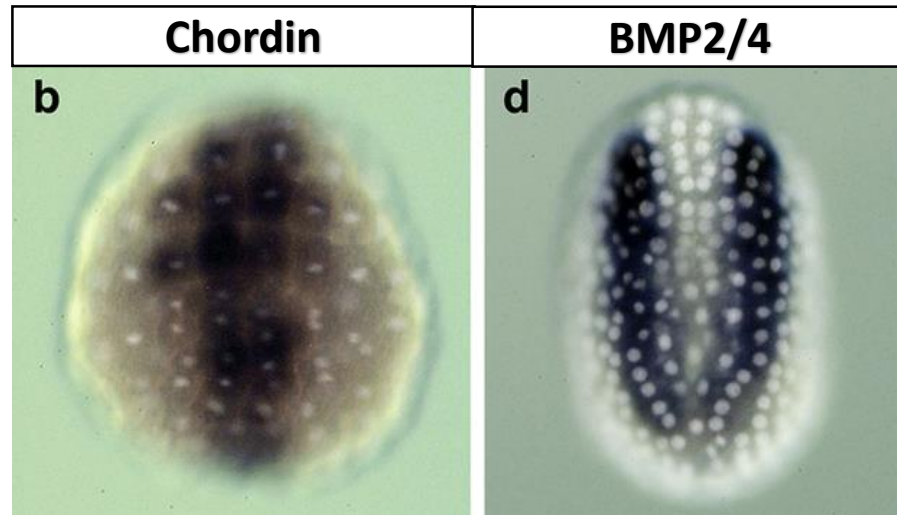
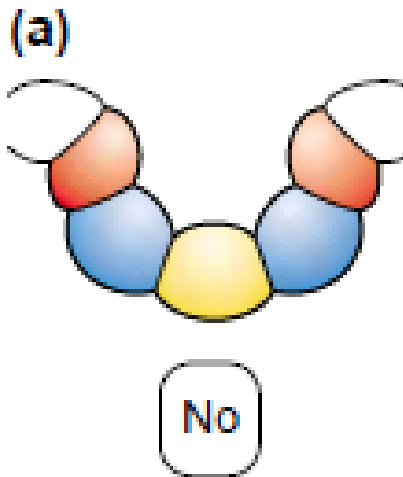
- - Notocorda na Cauda
- ~2,600 células



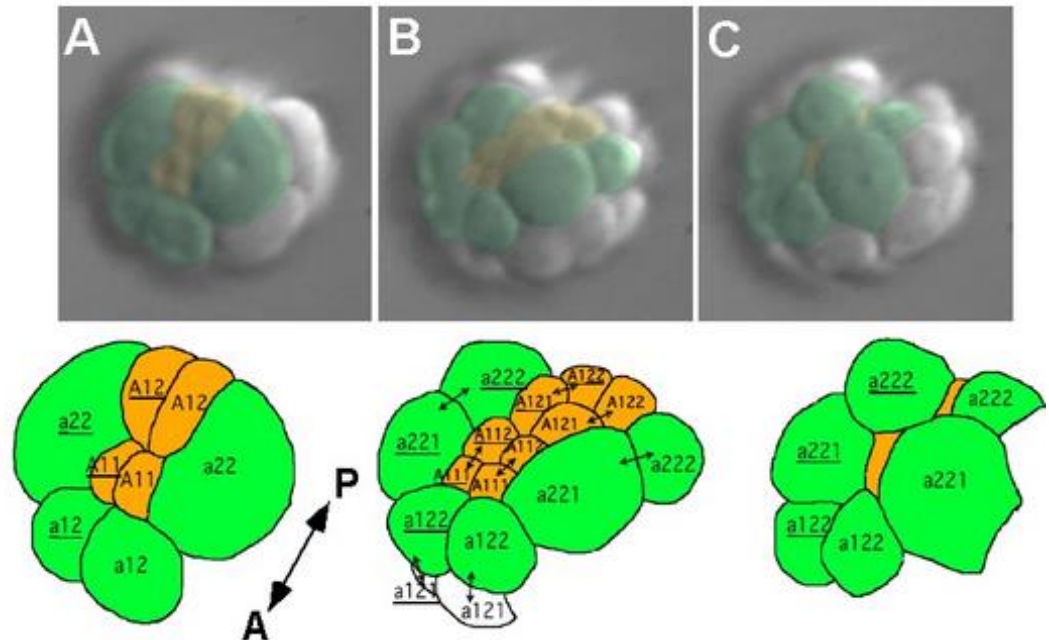
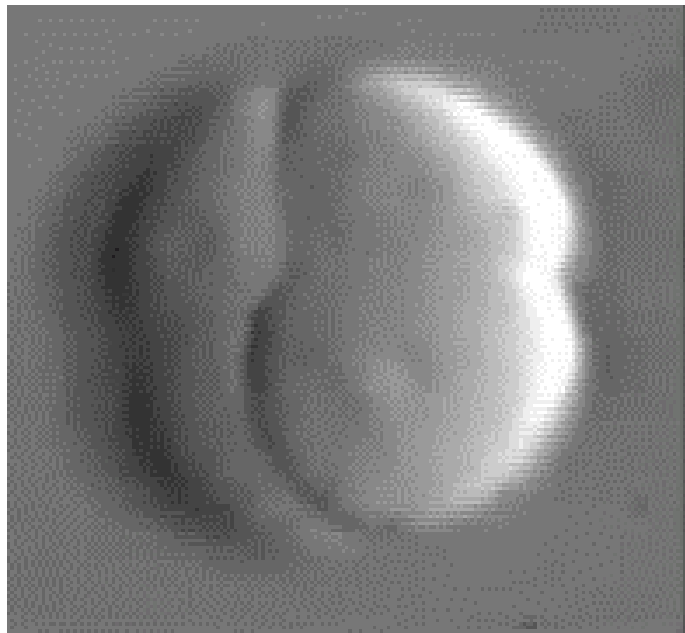
UROCORDADOS

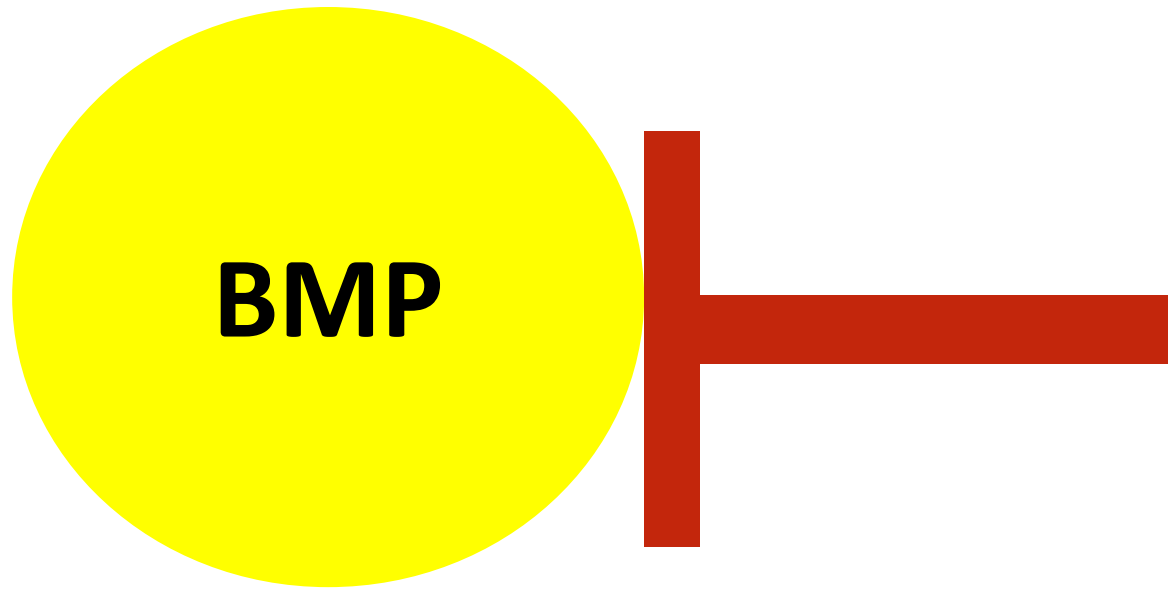


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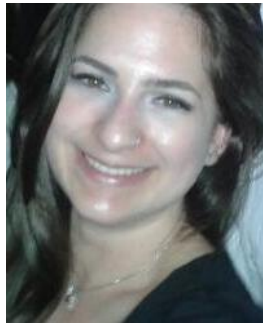


*Necessidade de inibição de BMP4 para formação da placa neural.





OBRIGADA!



LABORATÓRIO DE EMBRIOLOGIA MOLECULAR DE VERTEBRADOS
Departamento de Biologia Celular e do Desenvolvimento – ICB-USP

