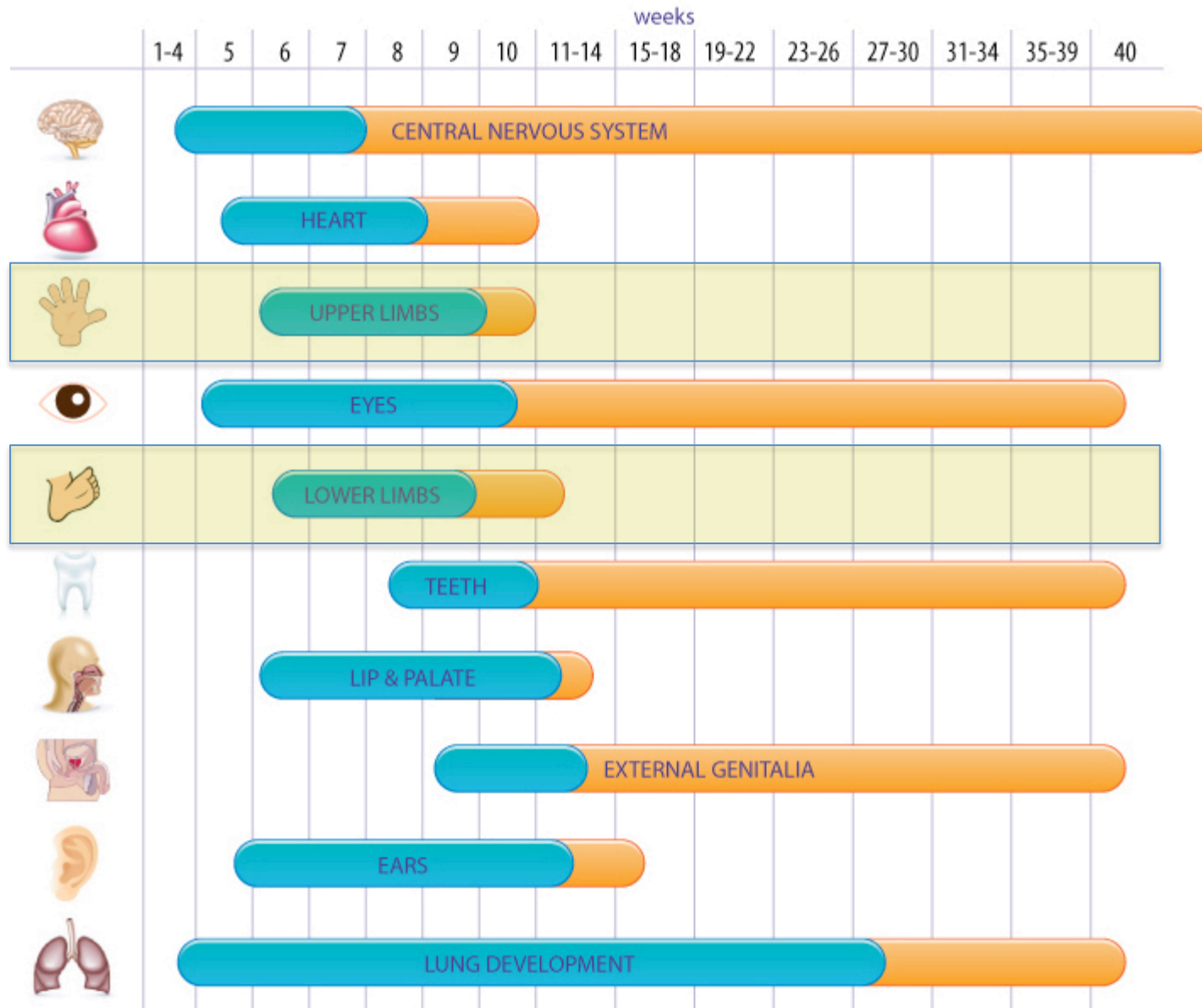


# ORGANOGENESE:

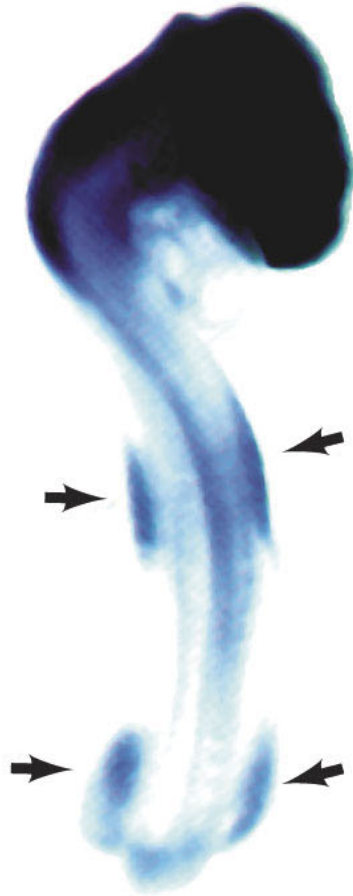


 Period of greatest sensitivity for induction of major birth defects

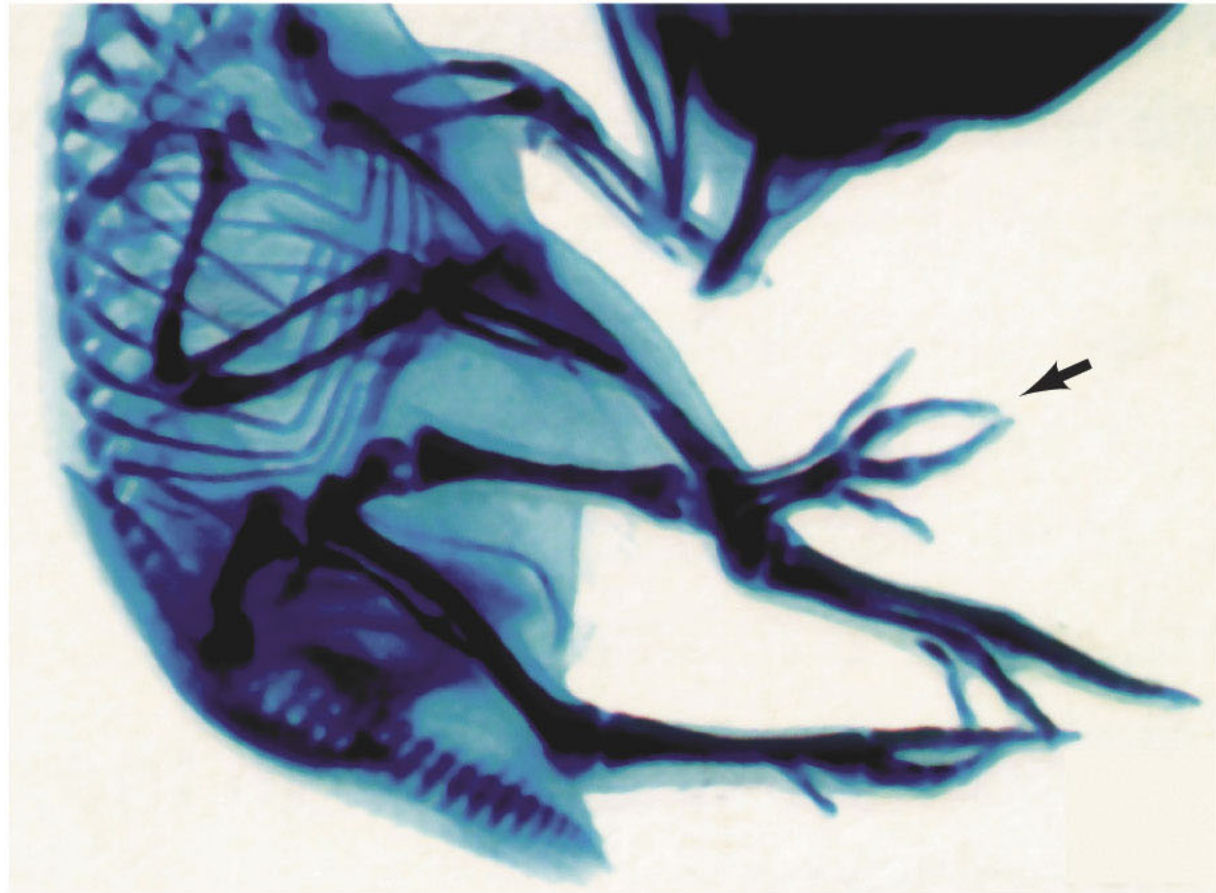
 Period of induction of minor birth defects and functional deficits

# Fgf10 expression and action in the developing chick limb

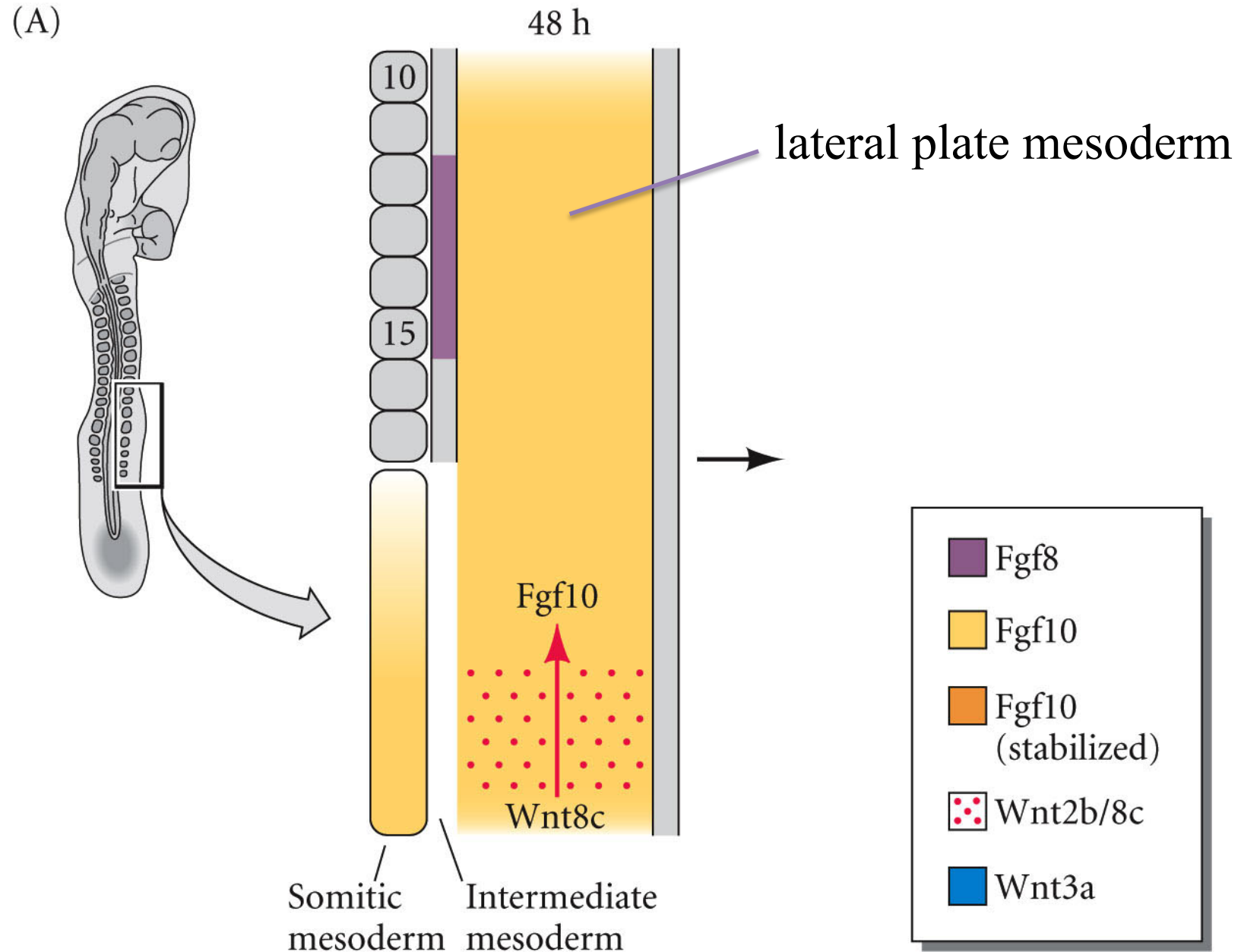
(A)



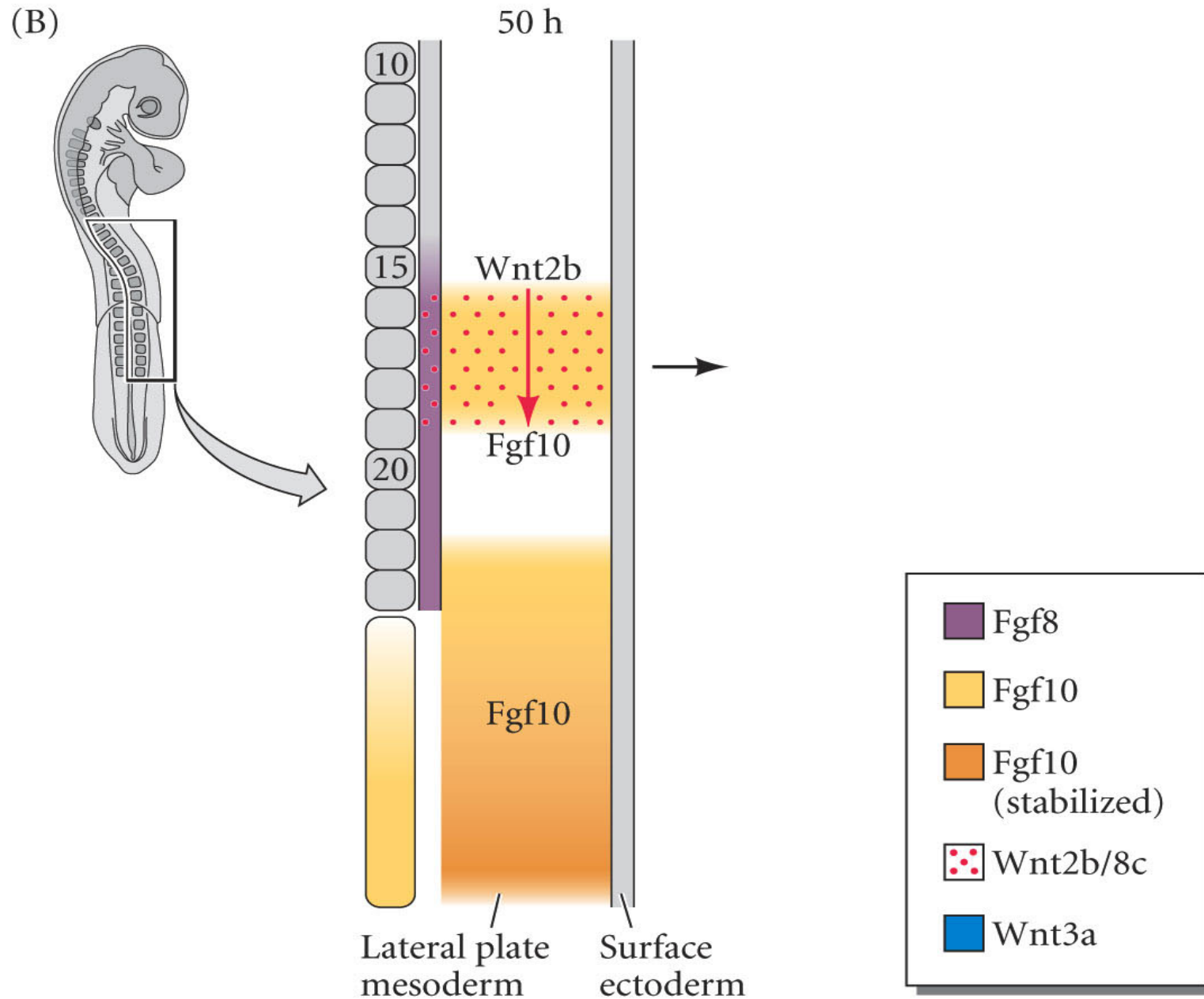
(B)



# Molecular model for the initiation of the limb bud in the chick at 48 hours of gestation (Part 1)



# Molecular model for the initiation of the limb bud in the chick at 50 hours of gestation (Part 2)

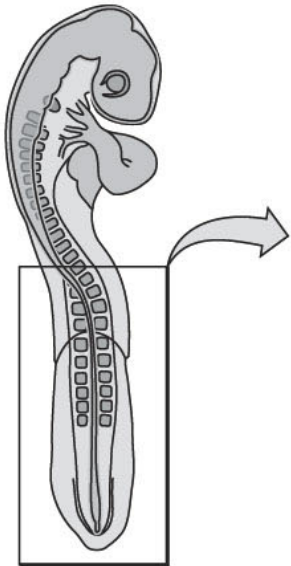




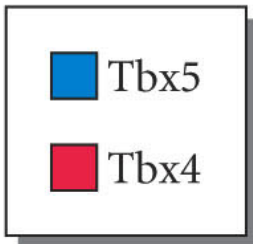
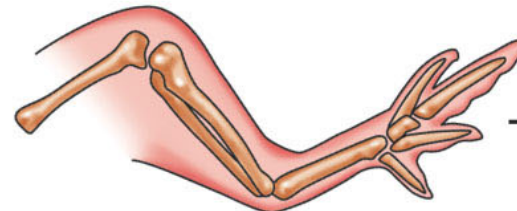
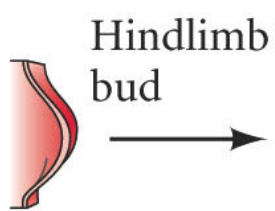
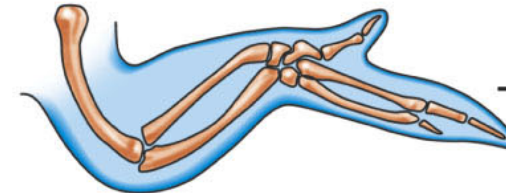
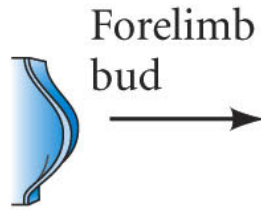
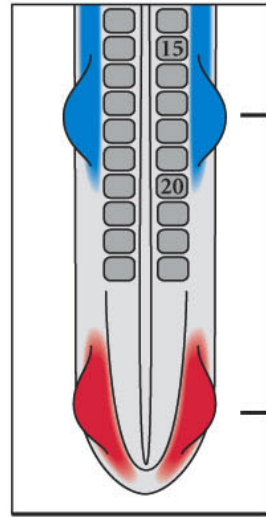


# Forelimb and hindlimb identity: Specification of limb type by Tbx4 and Tbx5 (Part 1)

Stage 14/15  
(early day 3)

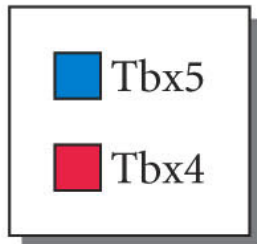
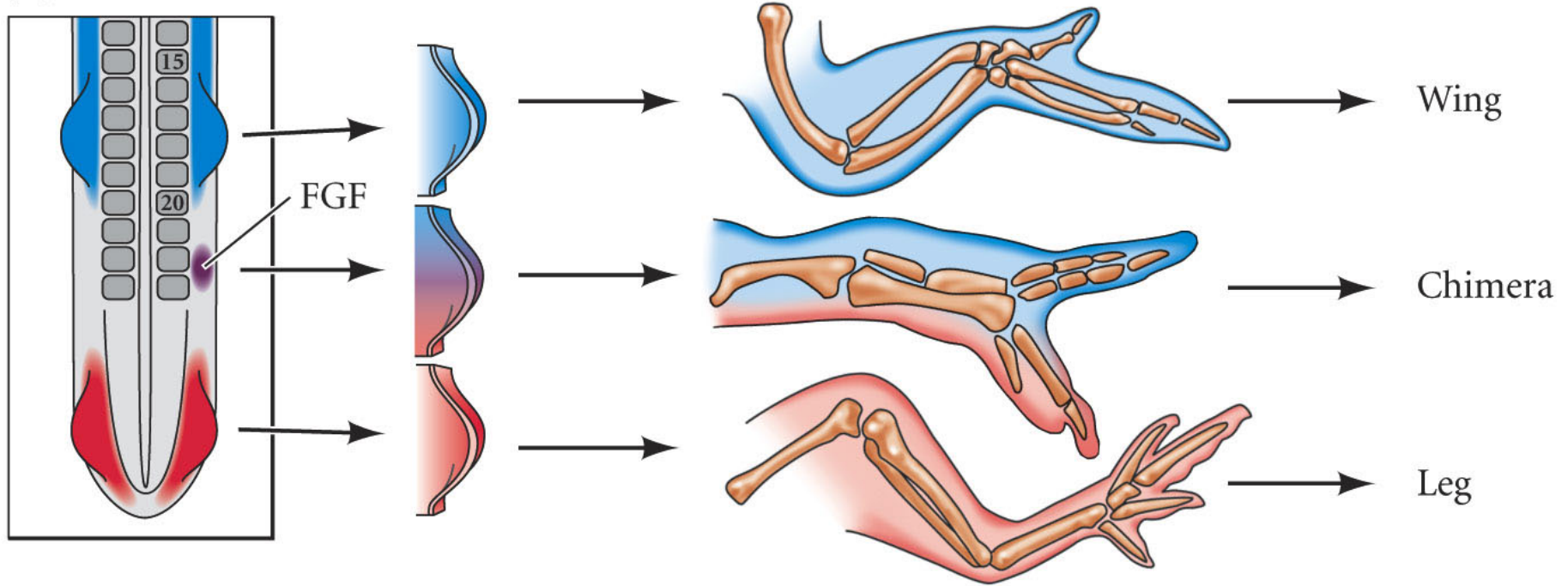


(A) Normal

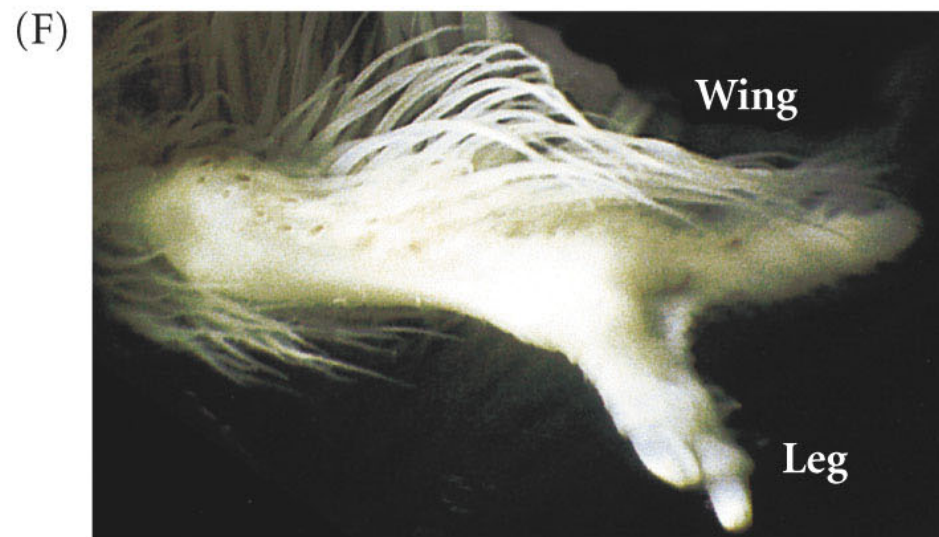
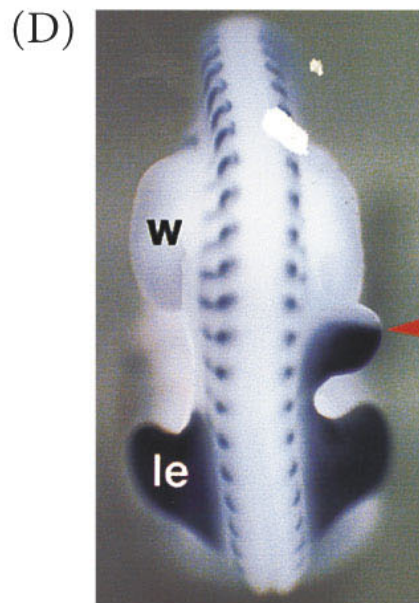
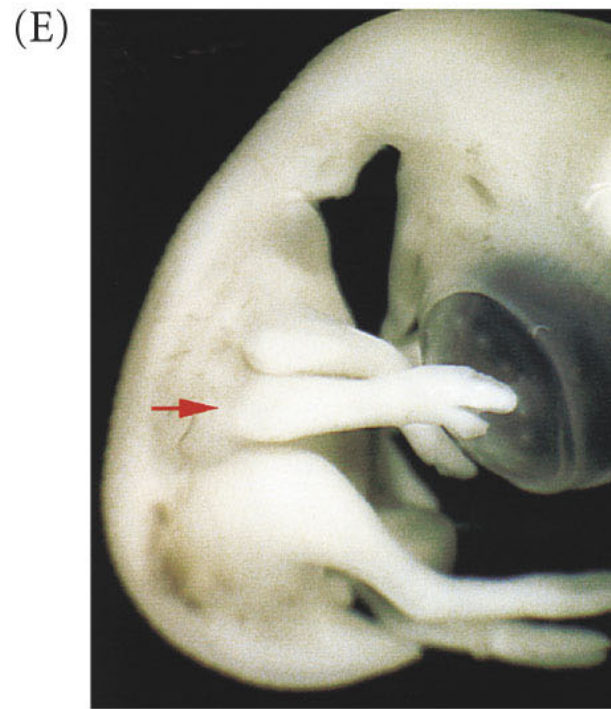
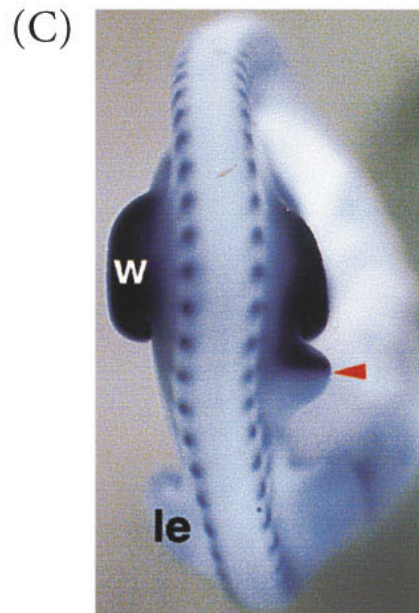


# Forelimb and hindlimb identity: Specification of limb type by Tbx4 and Tbx5 (Part 2)

(B) FGF induced

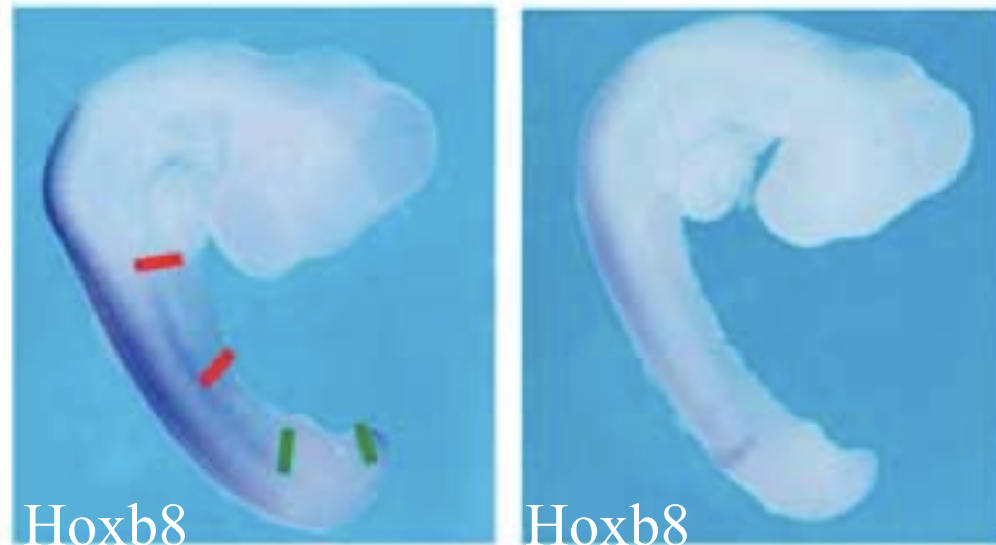


# Forelimb and hindlimb identity: Specification of limb type by Tbx4 and Tbx5 (Part 3)





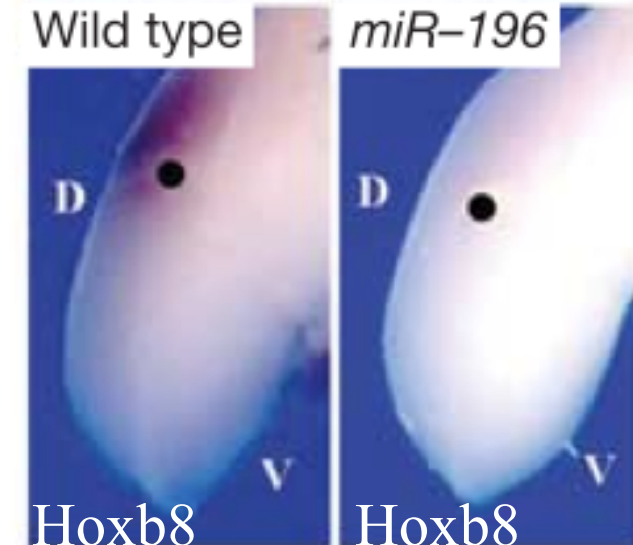
Forelimb and hindlimb identity: *miR-196* regula *Hoxb8* durante o desenvolvimento das extremidades



Hoxb8

Hoxb8

embrión de pollo (st. 16)



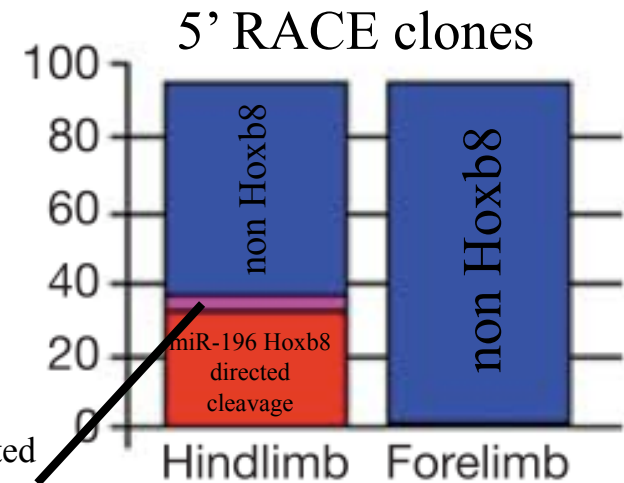
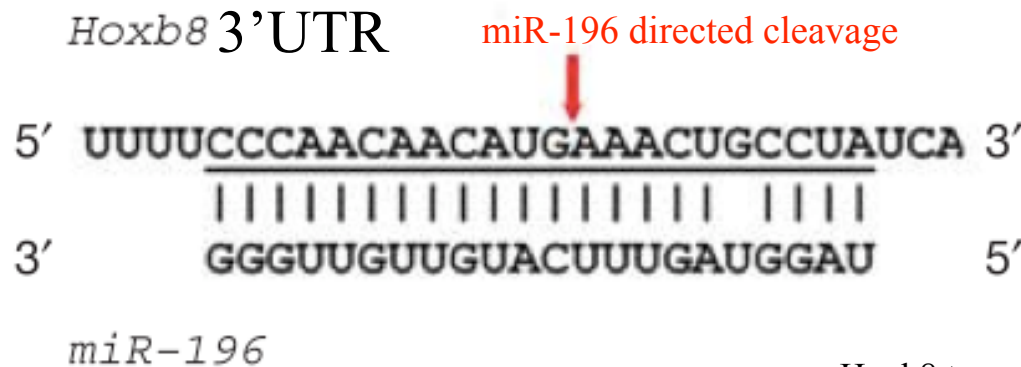
Wild type

*miR-196*

Hoxb8

Hoxb8

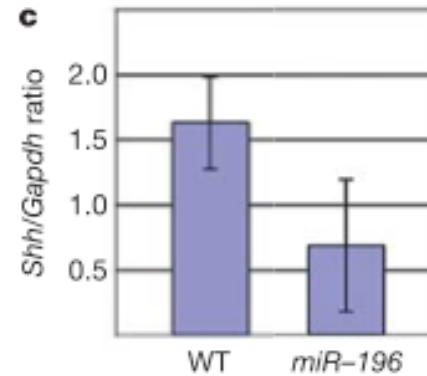
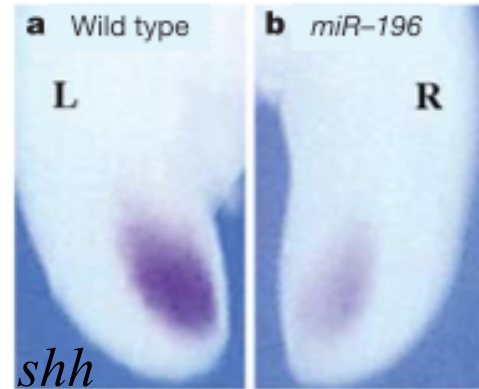
extremidad anterior de pollo (st. 22)



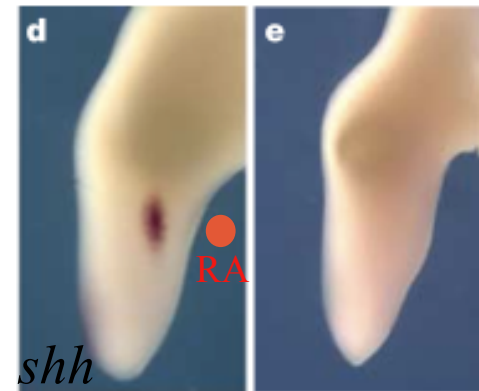
Hoxb8 truncated on other sites

Forelimb and hindlimb identity: *miR-196* regula *Hoxb8* durante o desenvolvimento das extremidades

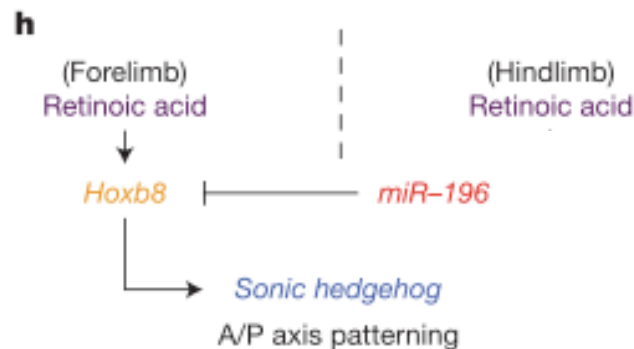
extremidad anterior



extremidad anterior



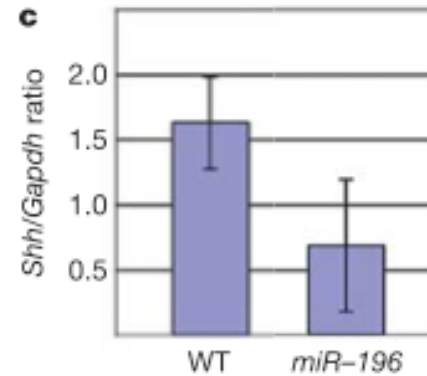
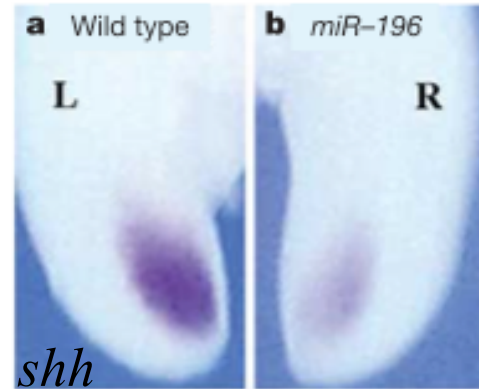
Modelo de regulación:



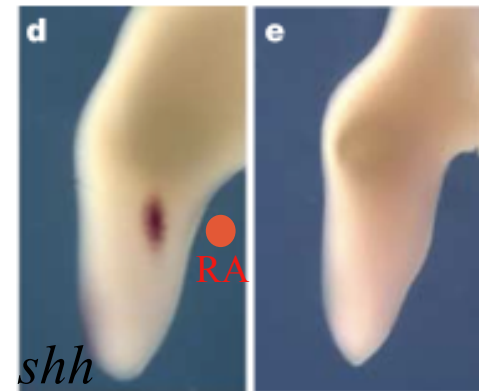


Forelimb and hindlimb identity: *miR-196* regula *Hoxb8* durante o desenvolvimento das extremidades

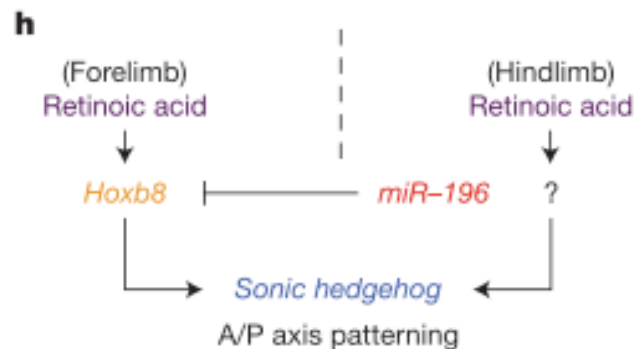
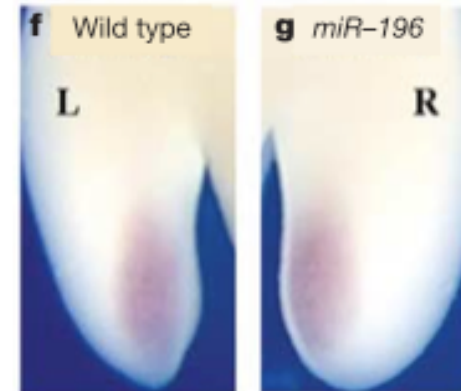
extremidad anterior



extremidad anterior

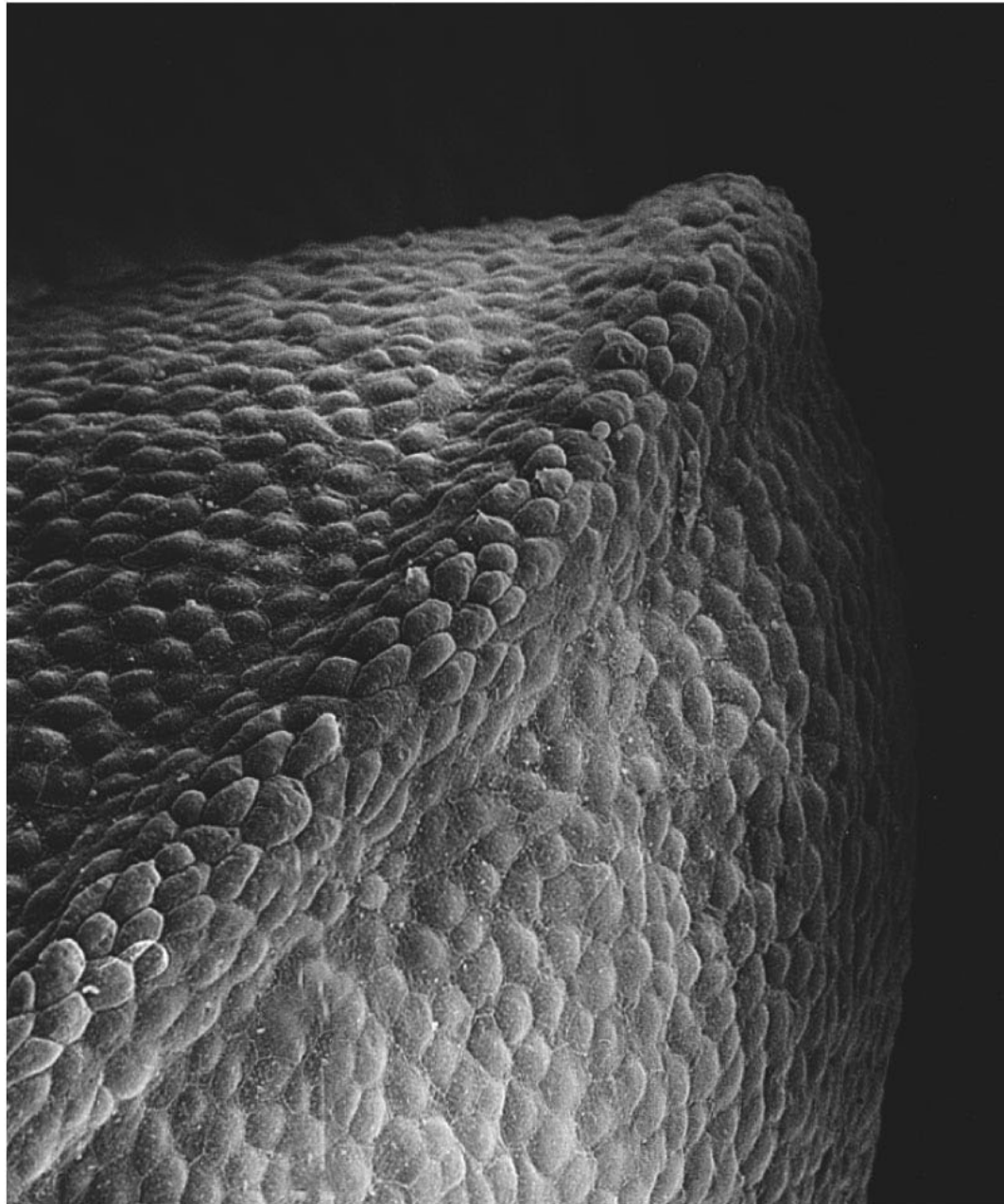


extremidad posterior

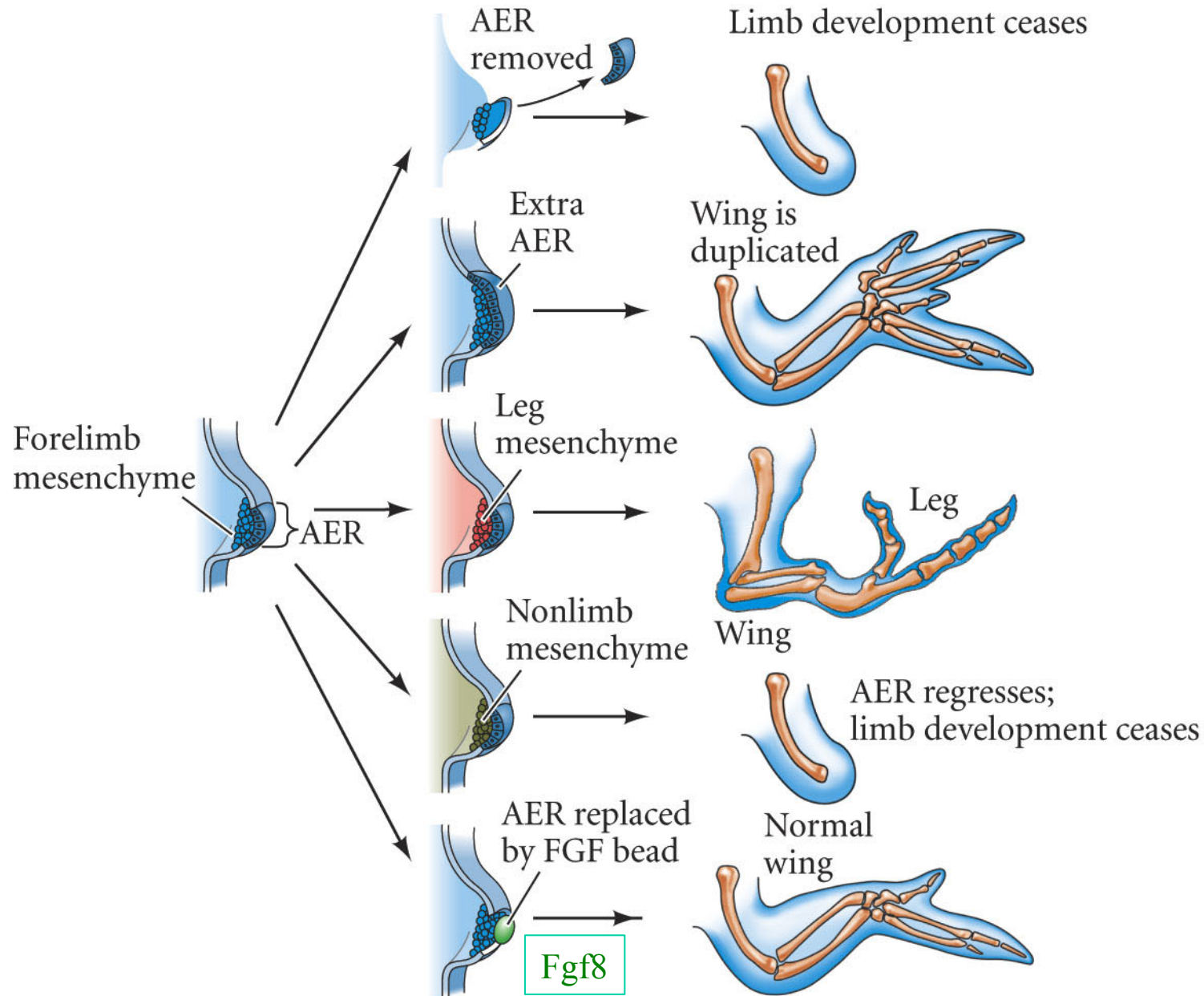


Modelo de regulación:

Early chick forelimb bud, with its apical ectodermal ridge in the foreground



# Summary of experiments demonstrating the effect of the apical ectodermal ridge on the underlying mesenchyme

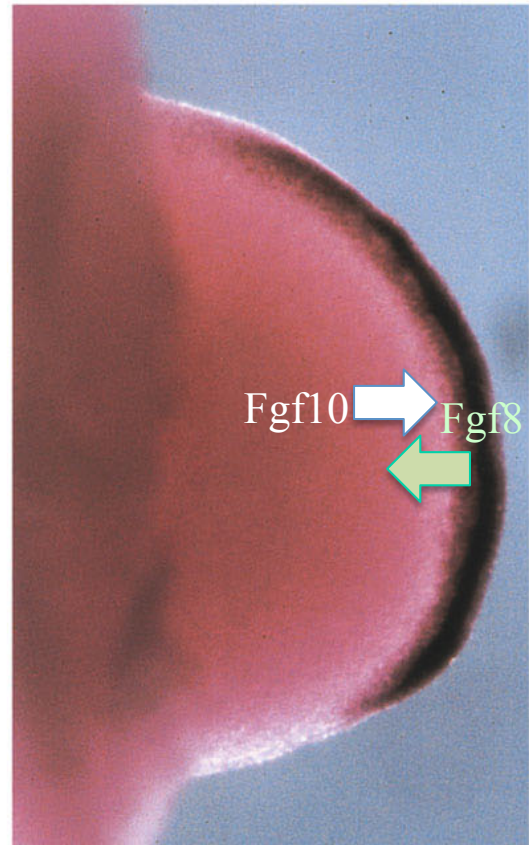


## Fgf8 in the apical ectodermal ridge

(A)



(B)



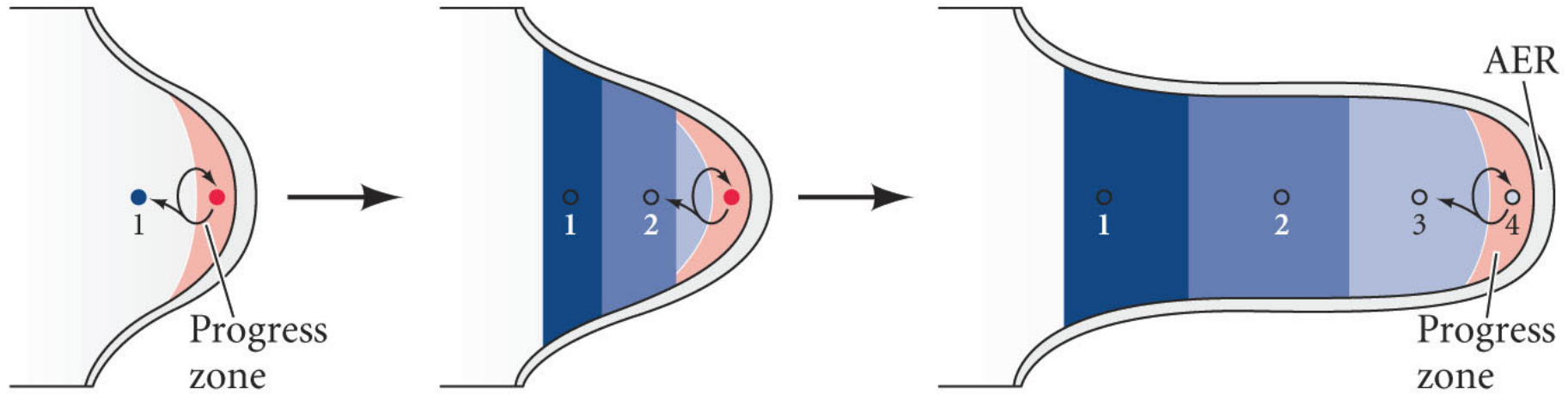
(C)



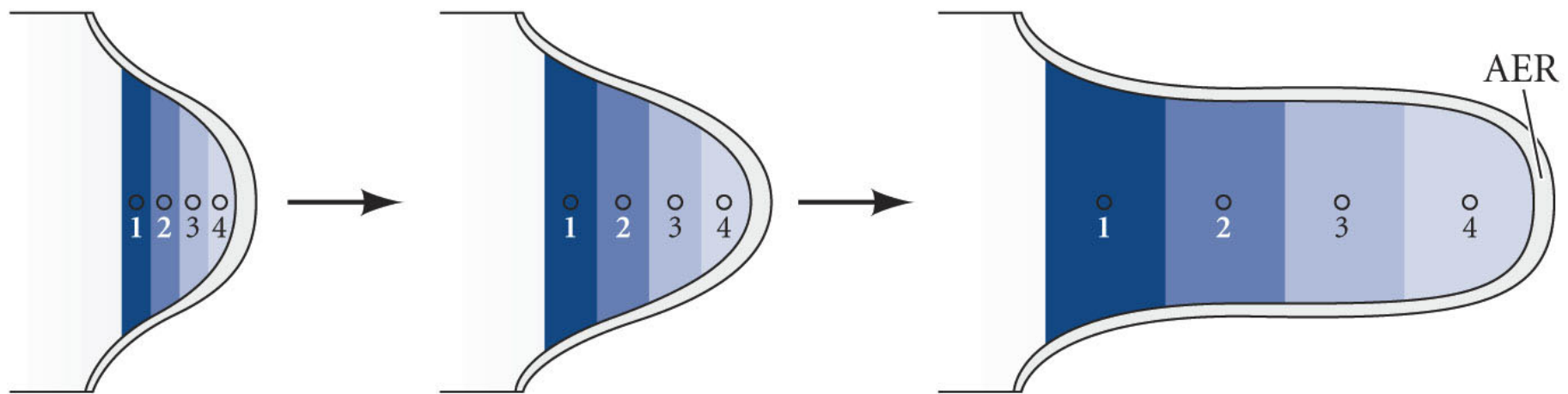


# Two models for the mesodermal specification of the proximal-distal axis of the limb

(A) Progress zone model



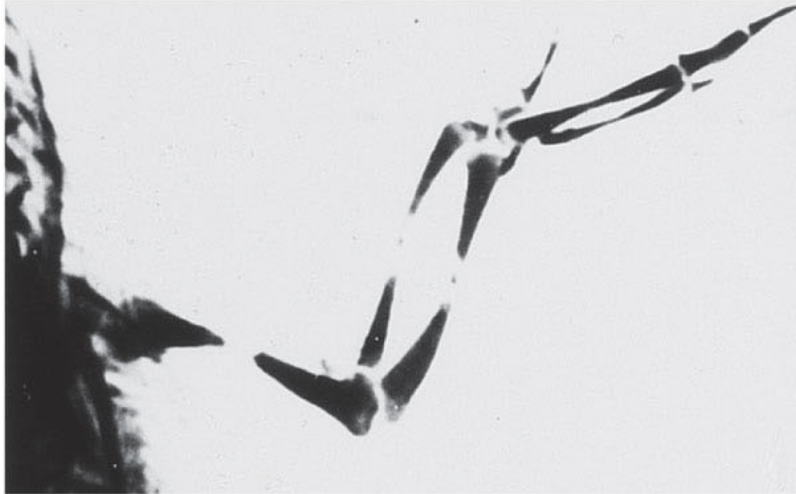
(B) Early allocation and progenitor expansion model



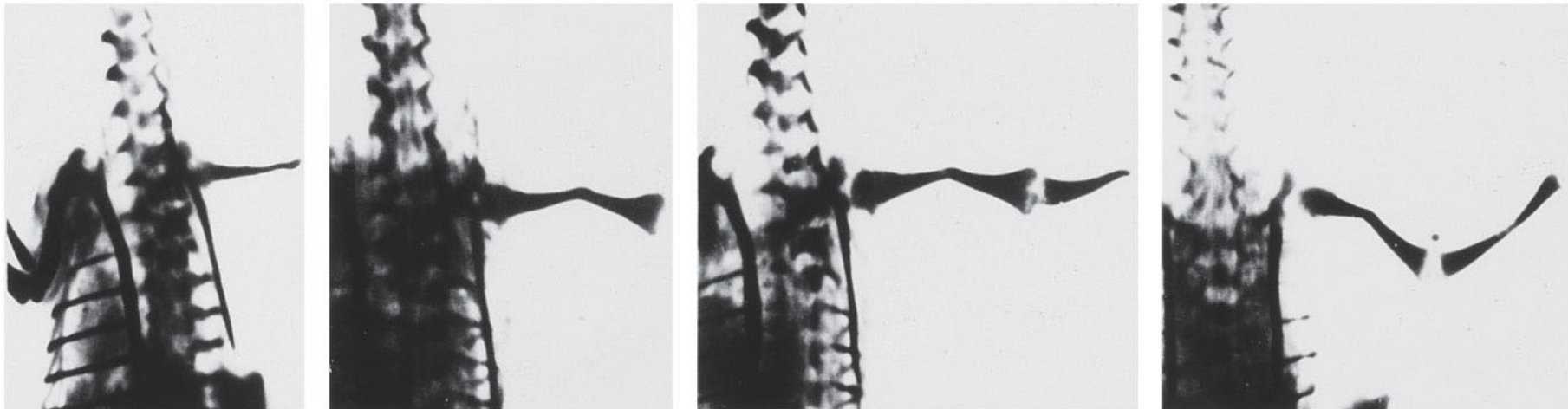
What experiments would you do to test these two models?

# The AER is necessary for wing development

(A)



(B)

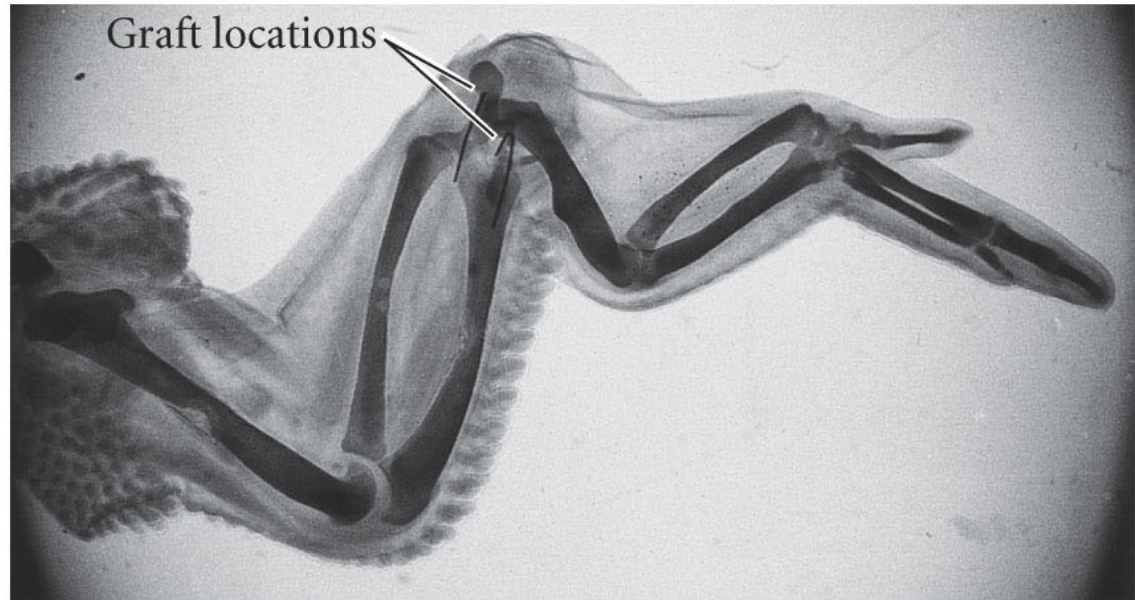


AER Vade mecum

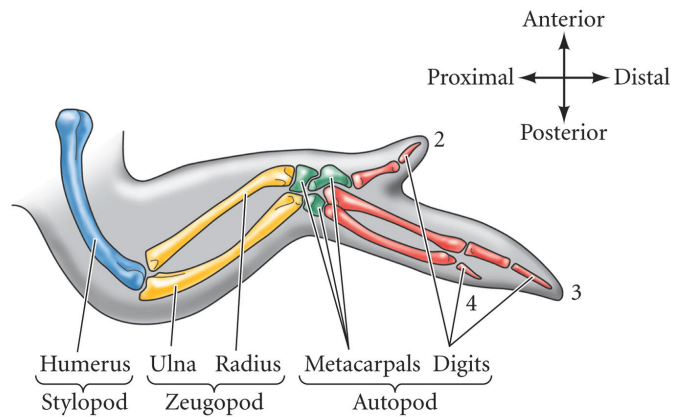
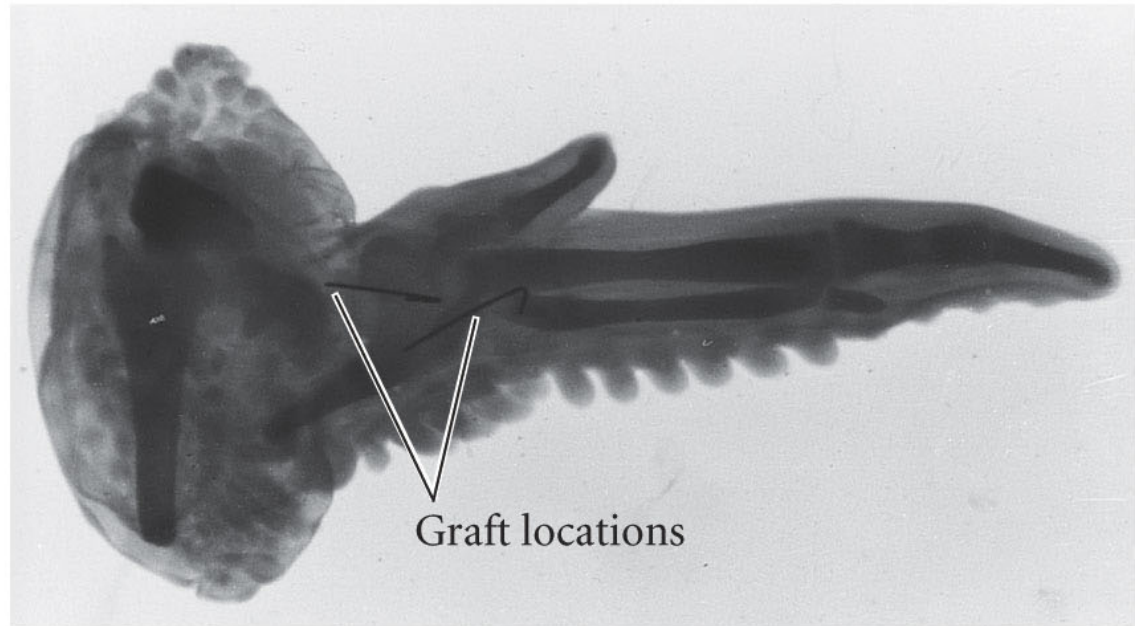


# Control of proximal-distal specification by the progress zone mesenchyme

(A)



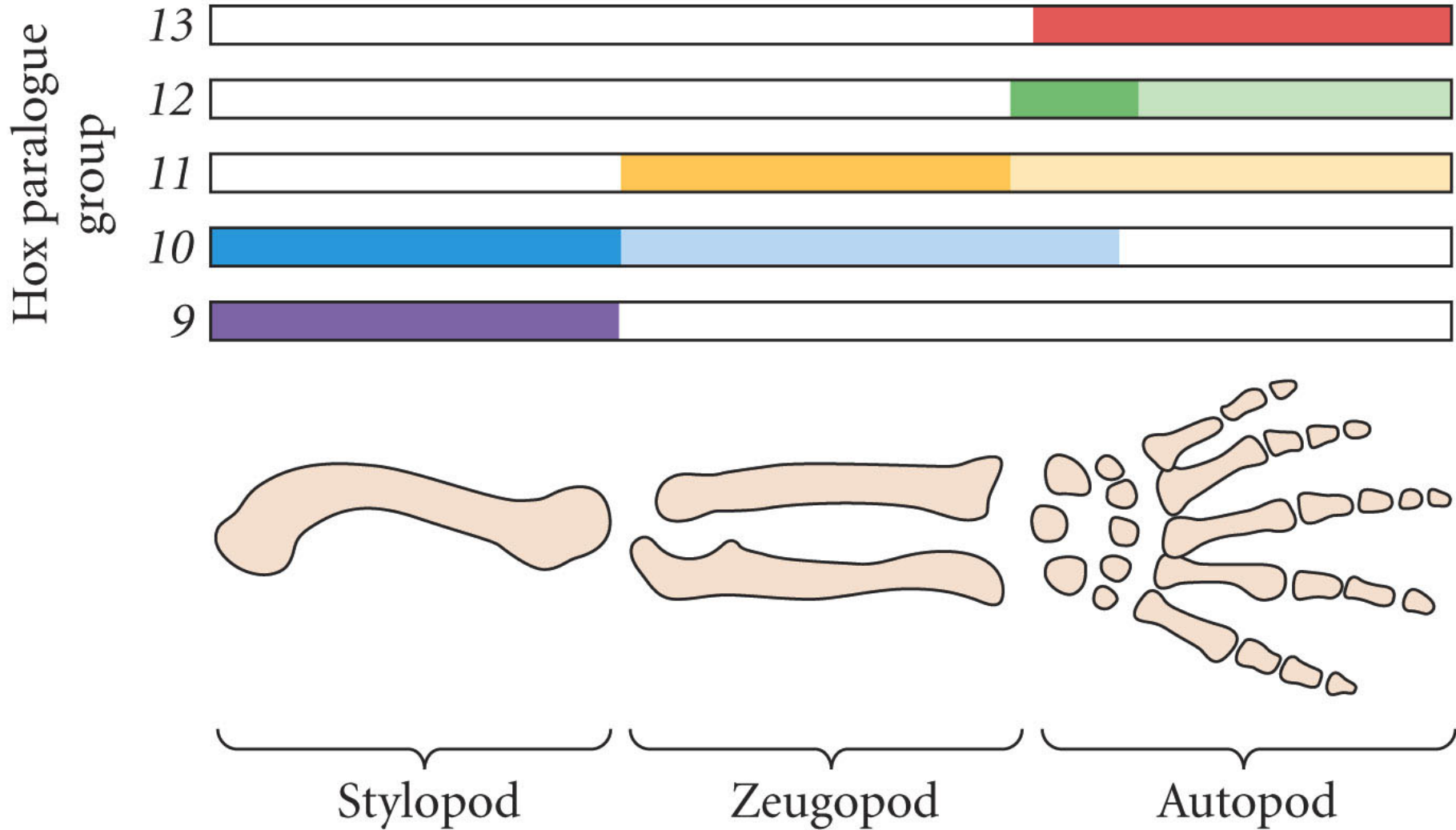
(B)



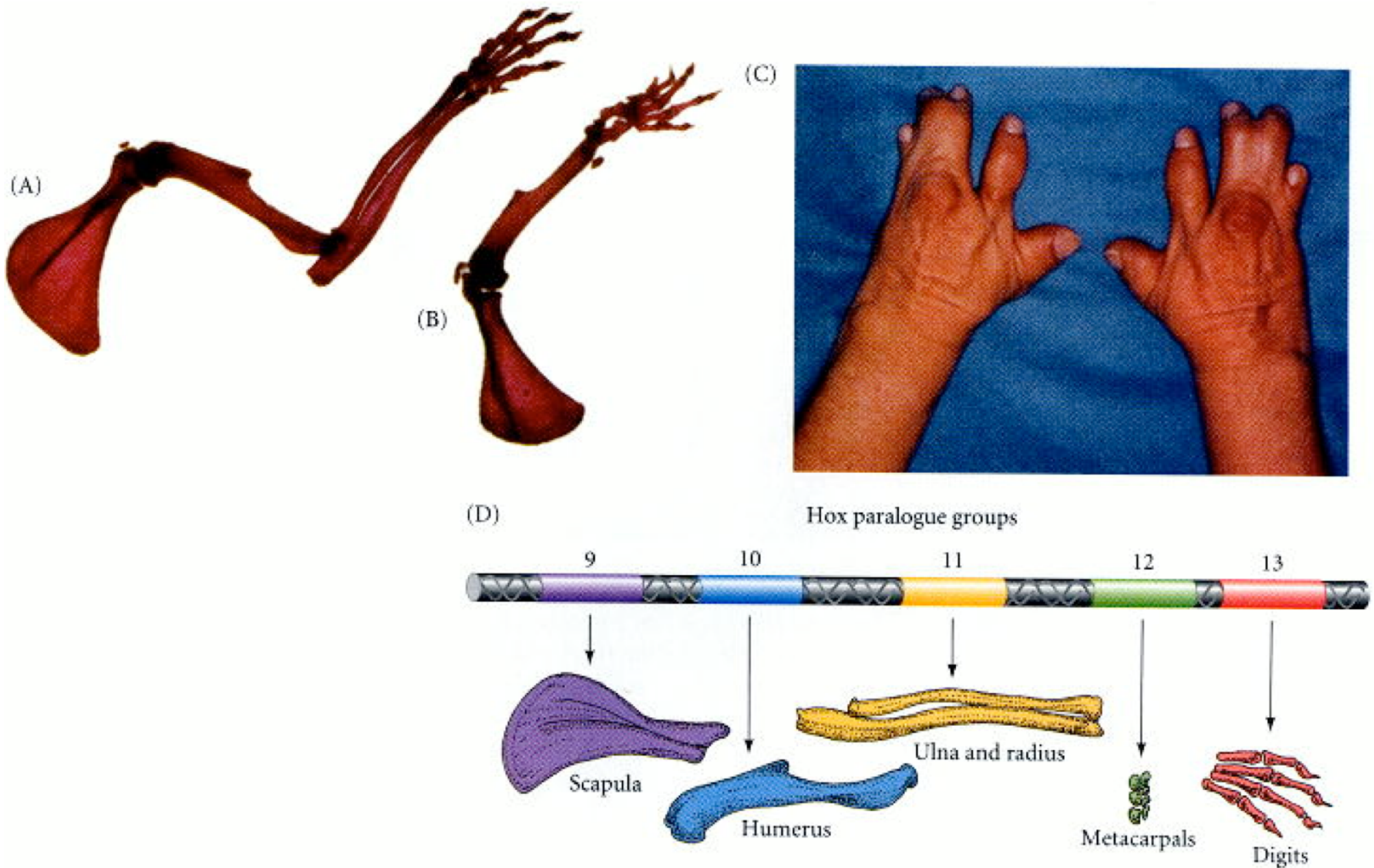
PD patterning: Deletion of limb bone elements by the deletion of paralogous Hox genes (Part 1)

(A)

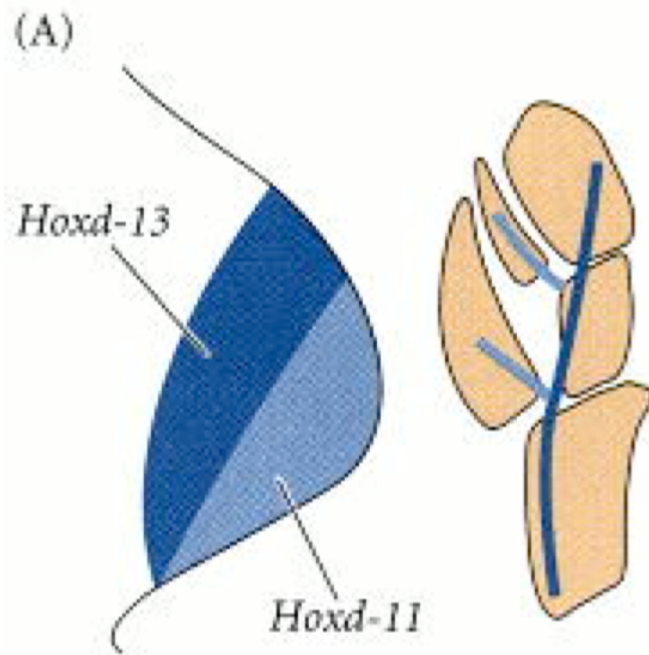
Forelimb



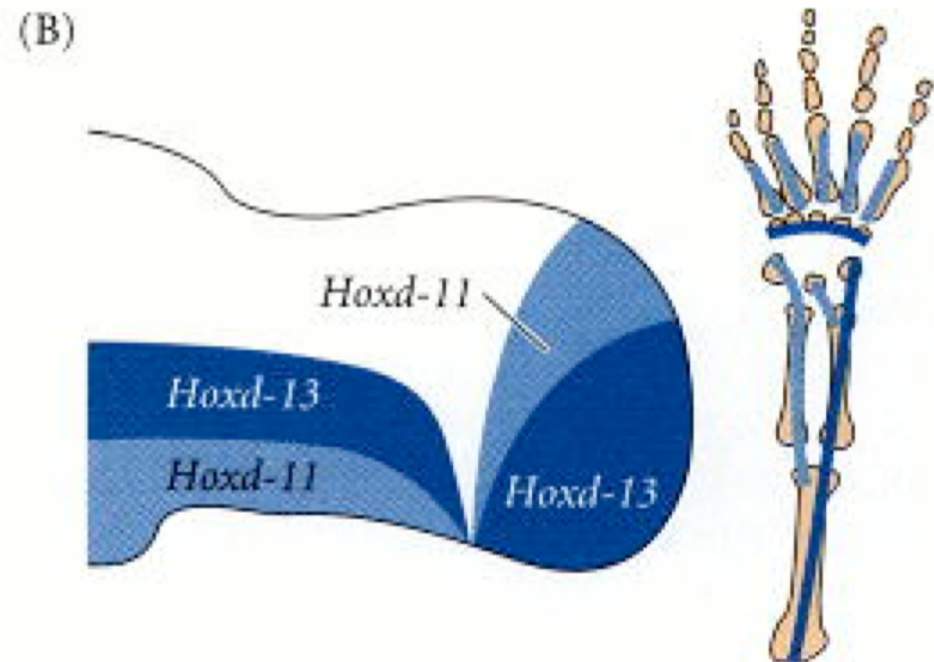
# PD patterning: Deletion of limb bone elements by the deletion of paralogous Hox genes (Part 1)



Peixe:

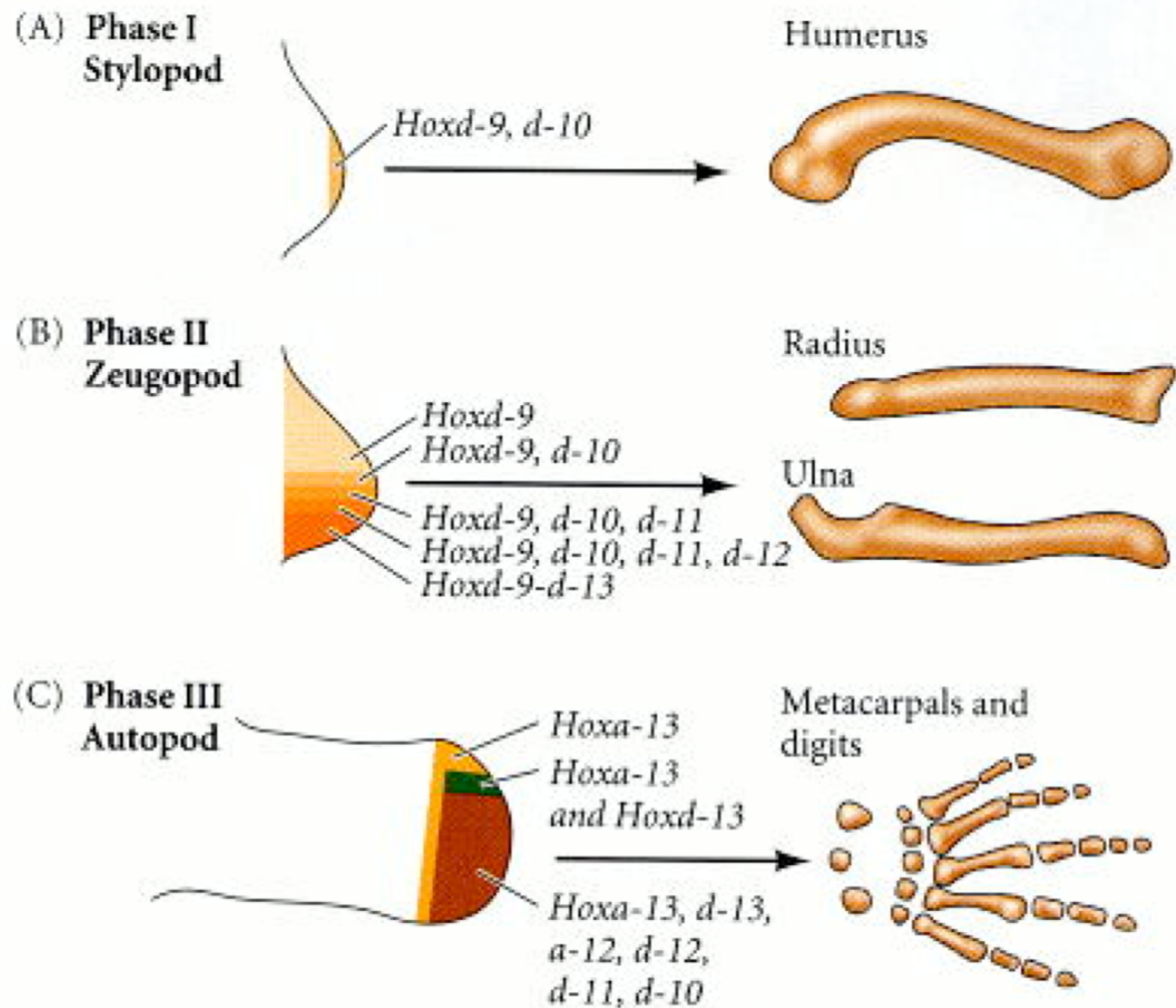


Tetrapodo:



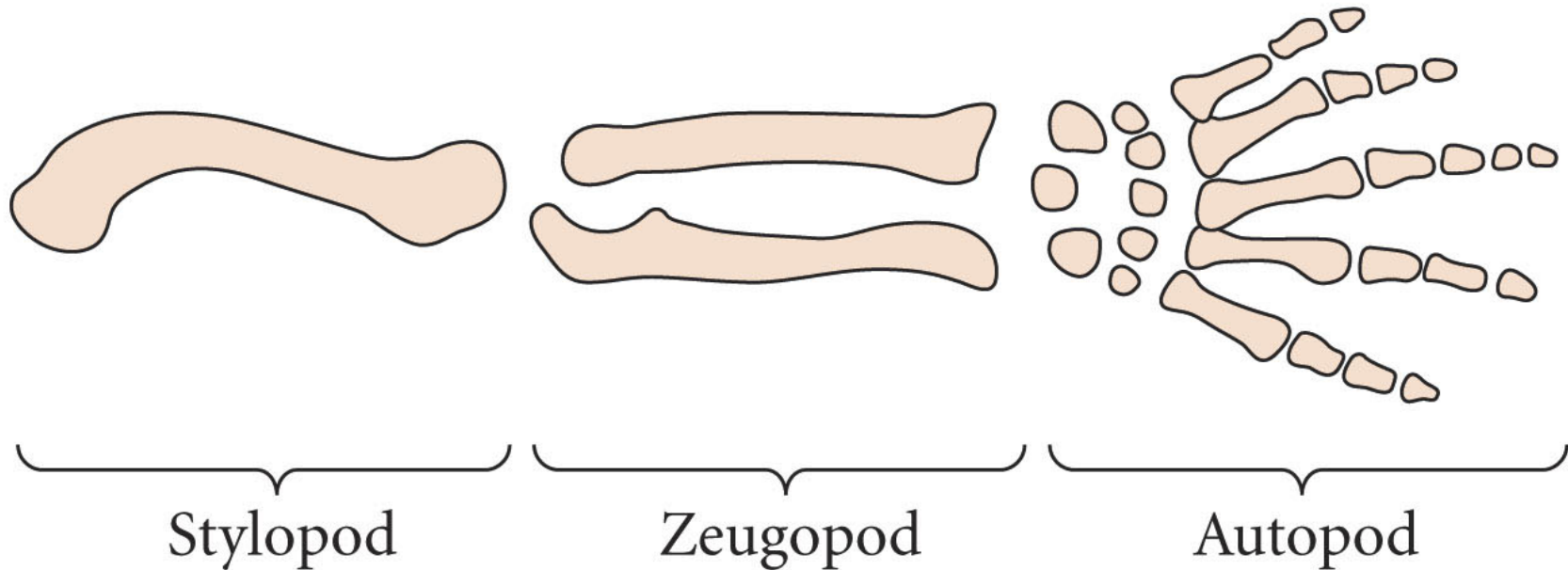
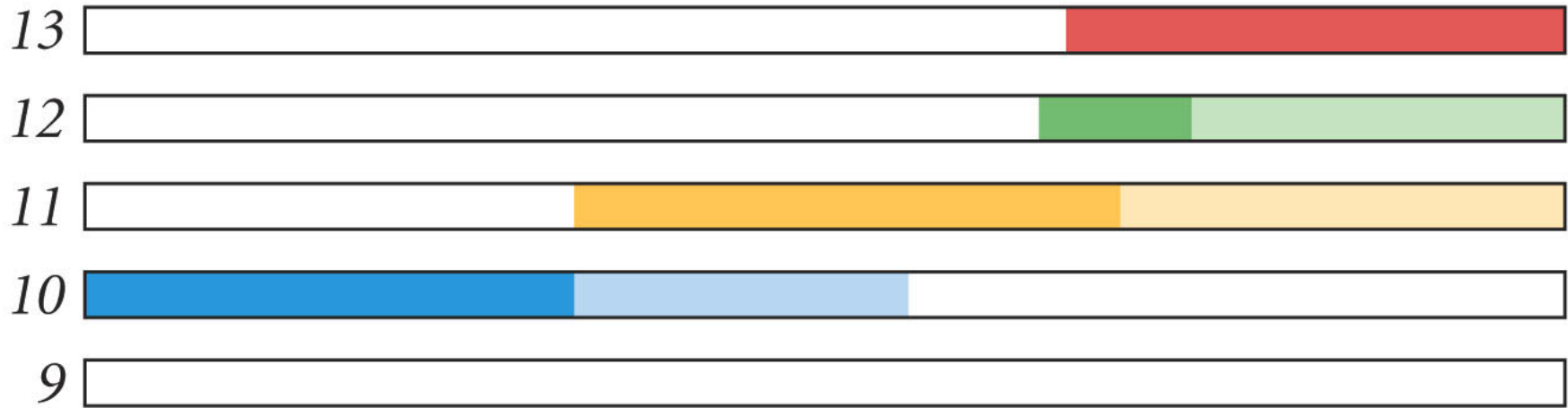


## AP patterning: Hox e desenvolvimento dos membros



(B)

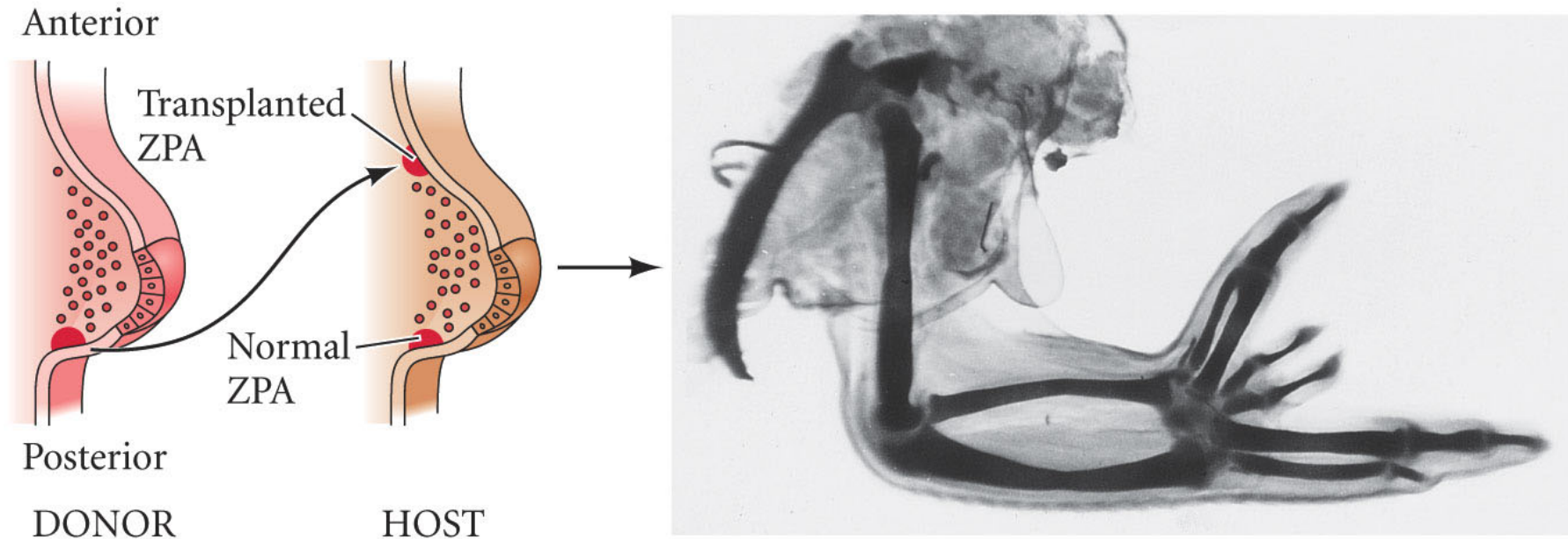
### Hindlimb





**AP patterning:** When a ZPA is grafted to anterior limb bud mesoderm, duplicated digits emerge as a mirror image of the normal digits

Discovering the ZPA: *Vade mecum*



ZPA= zone of polarizing activity

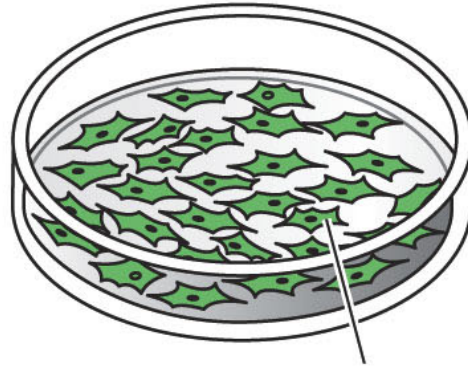
AP patterning: Sonic hedgehog protein is expressed in the ZPA (Part 1)

(A)



Is it sufficient?

(B) Transfect *shh*-expressing virus  
and allow viral spread



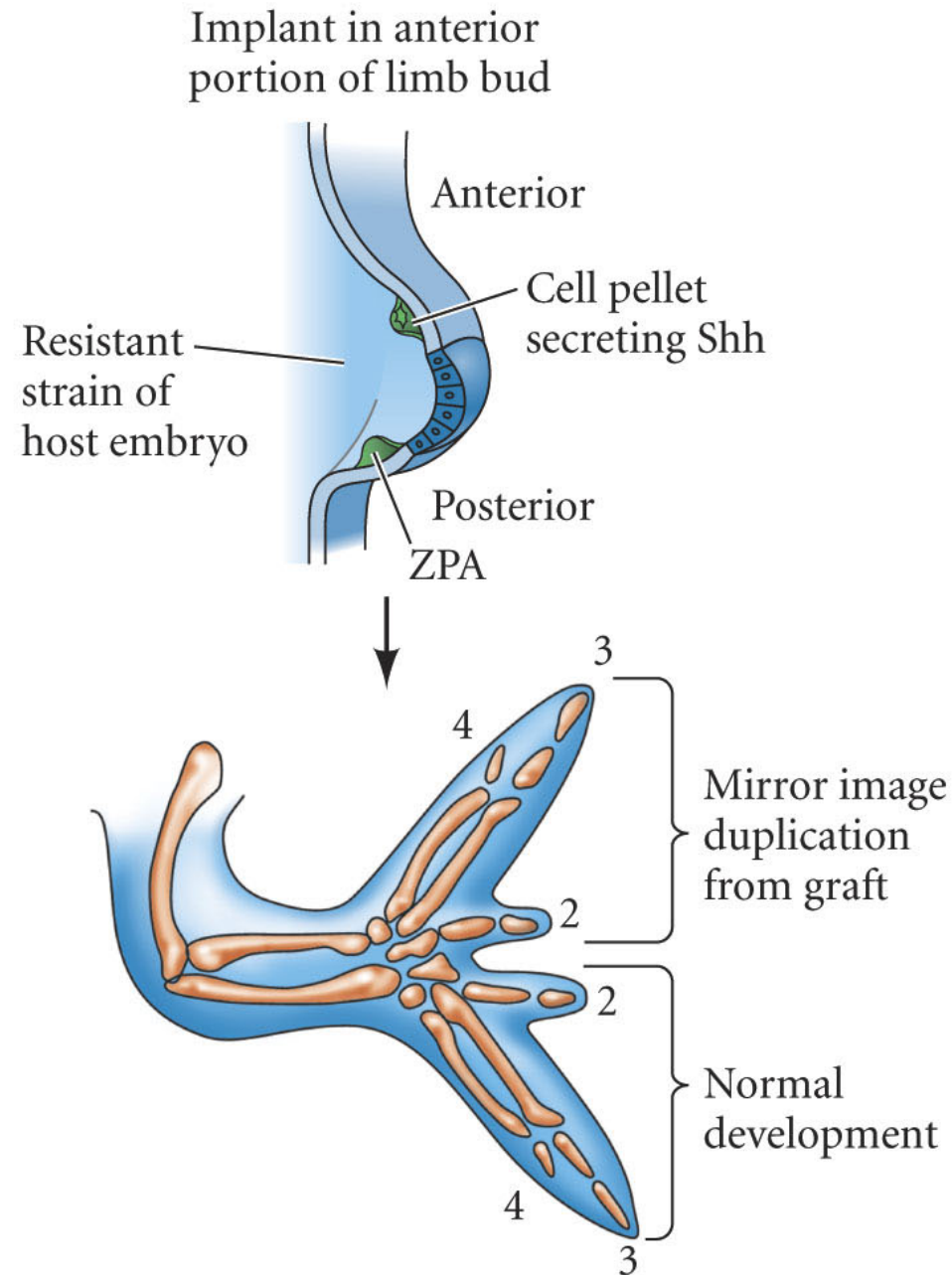
Infectable strain of chick  
embryo fibroblast cells

Centrifuge cells

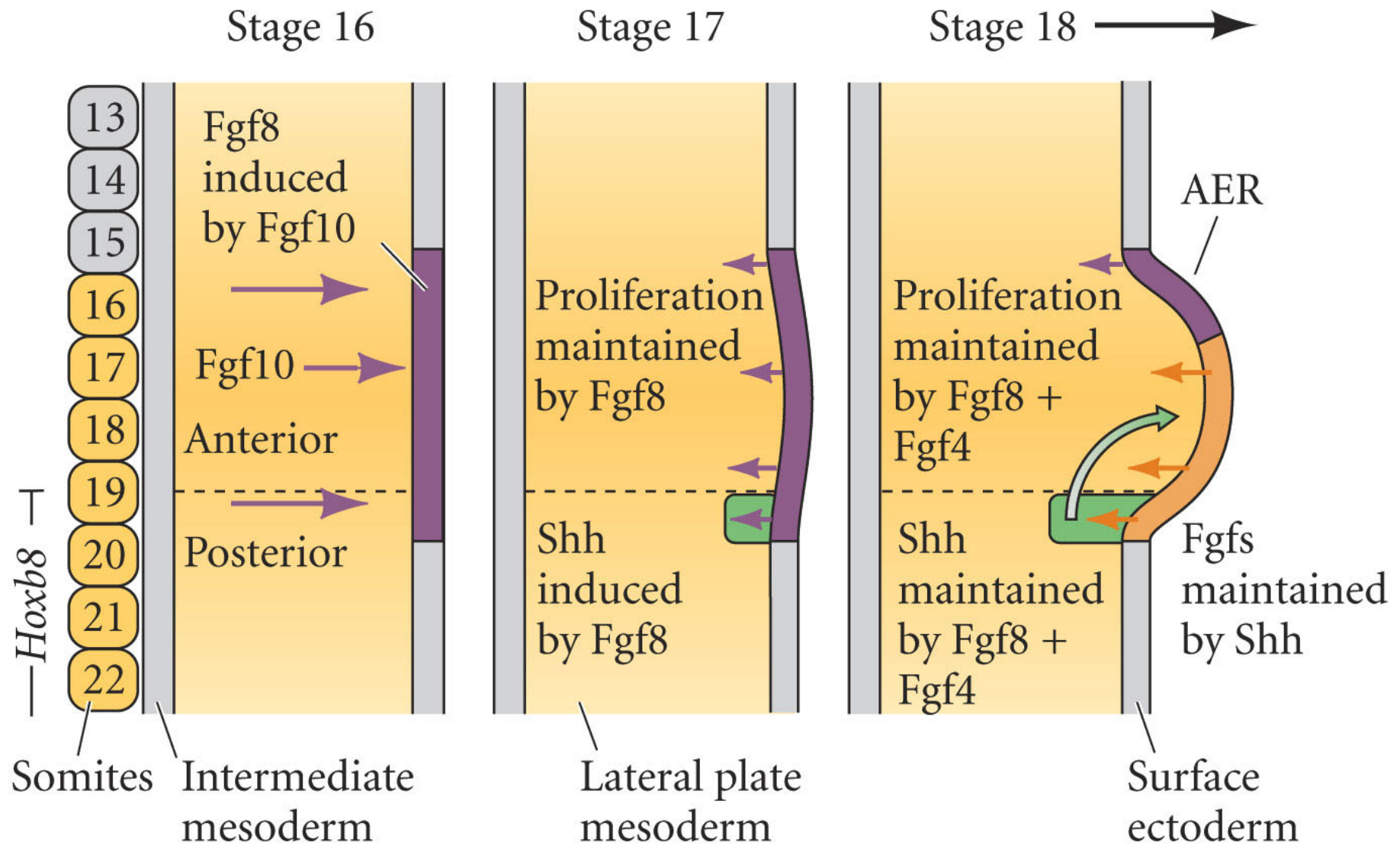


Cells containing  
the *shh* gene

# AP patterning: Sonic hedgehog protein is expressed in the ZPA (Part 3)

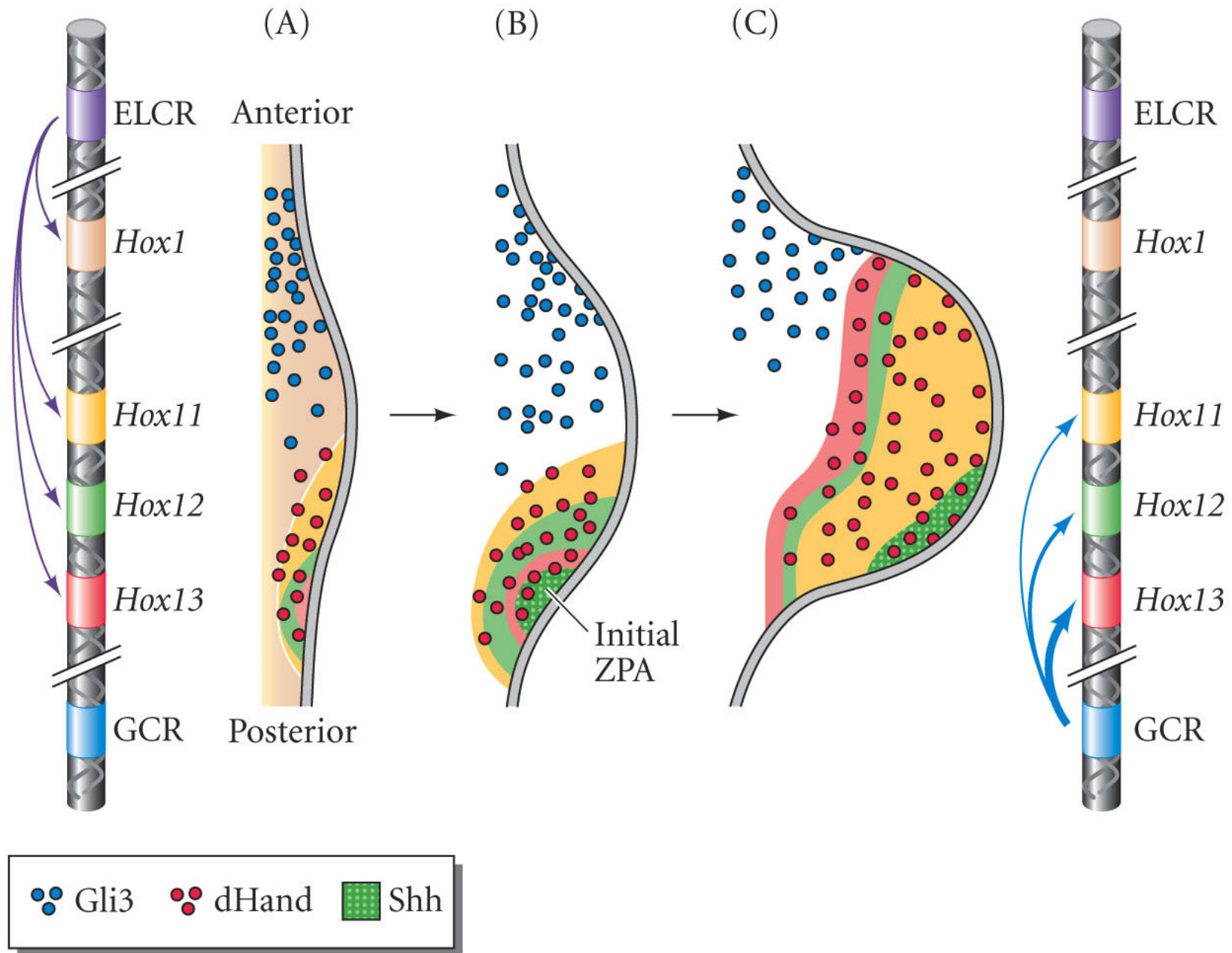


Patterning and growth of the bud: Feedback between the AER and the ZPA in the forelimb bud



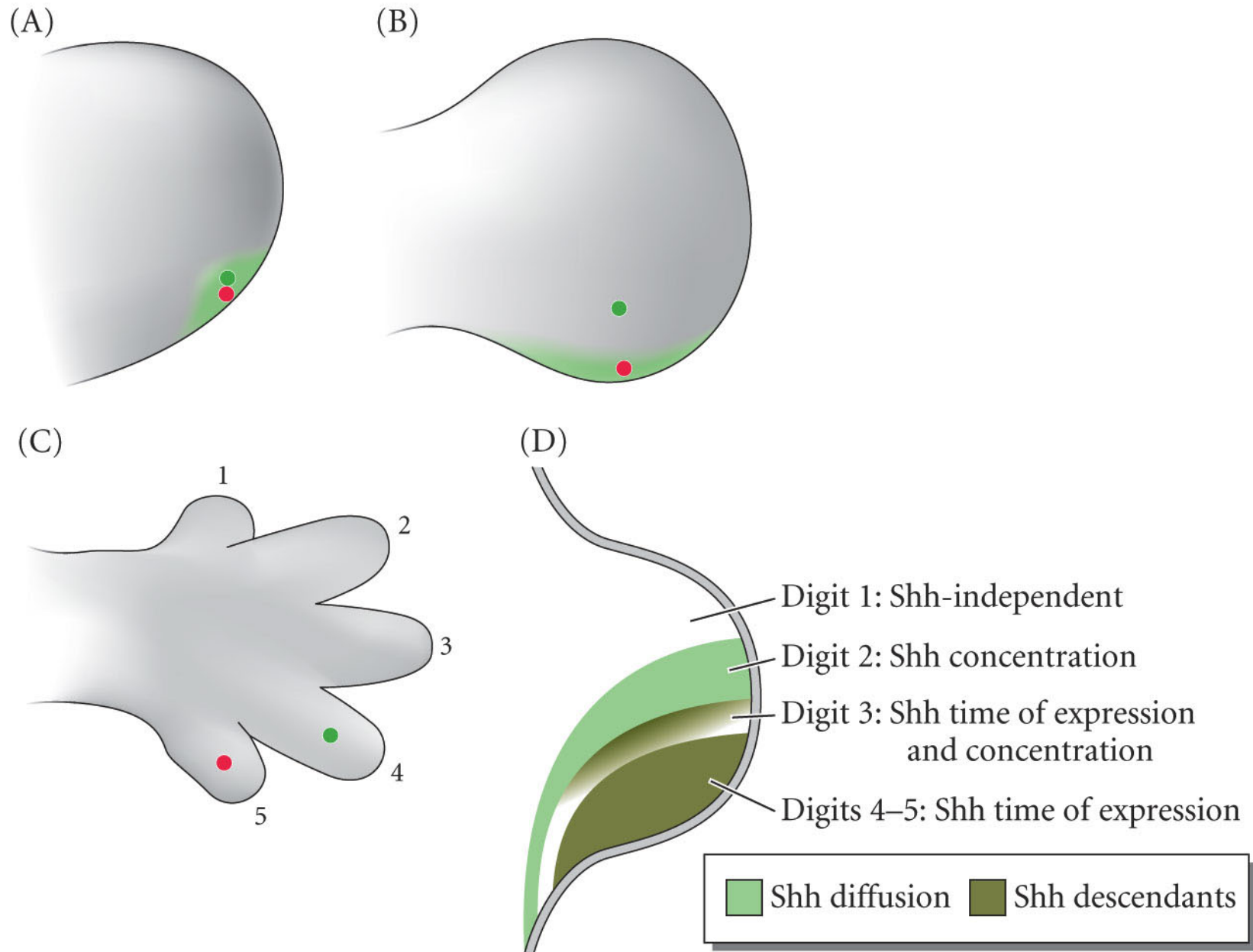


# AP patterning: Hox gene expression changes during the formation of the tetrapod limb

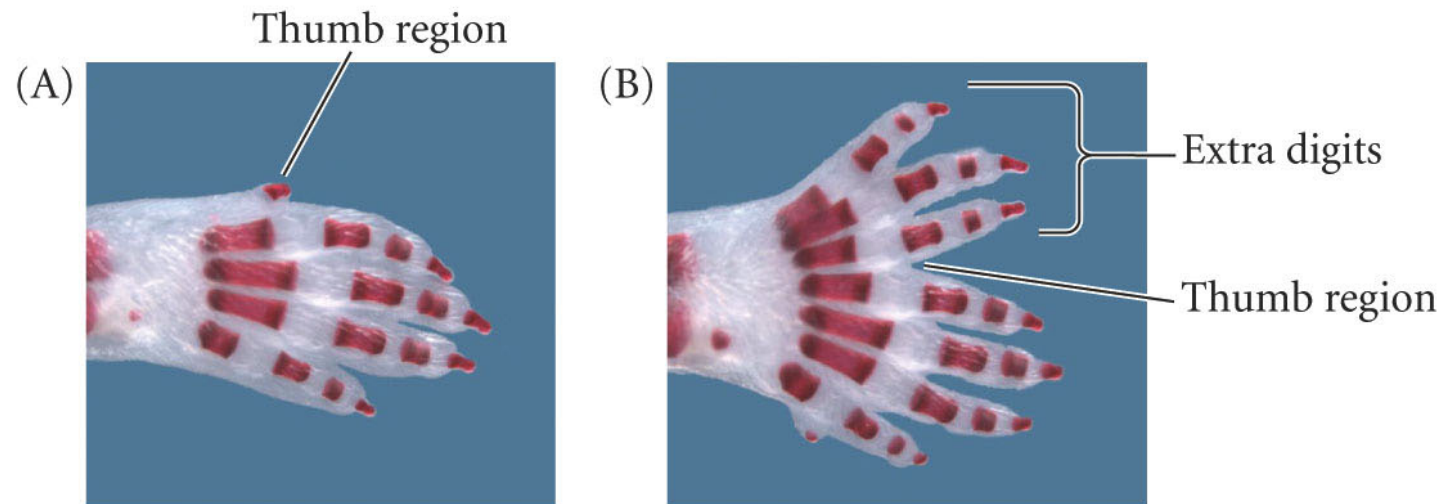




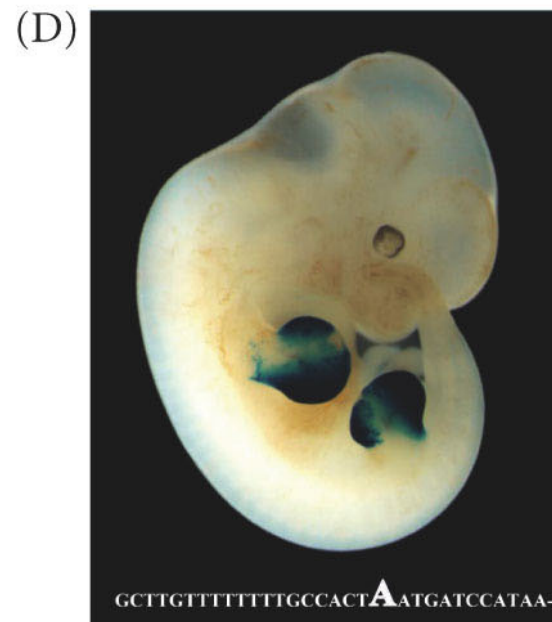
**AP patterning and digit identity:** The Shh-secreting cells form digits 4 and 5, and contribute to the specification of digits 2 and 3 in the mouse limb



**AP patterning:** Ectopic expression of mouse *sonic hedgehog* by a mutation in *Hx* in the anterior limb causes extra digit formation

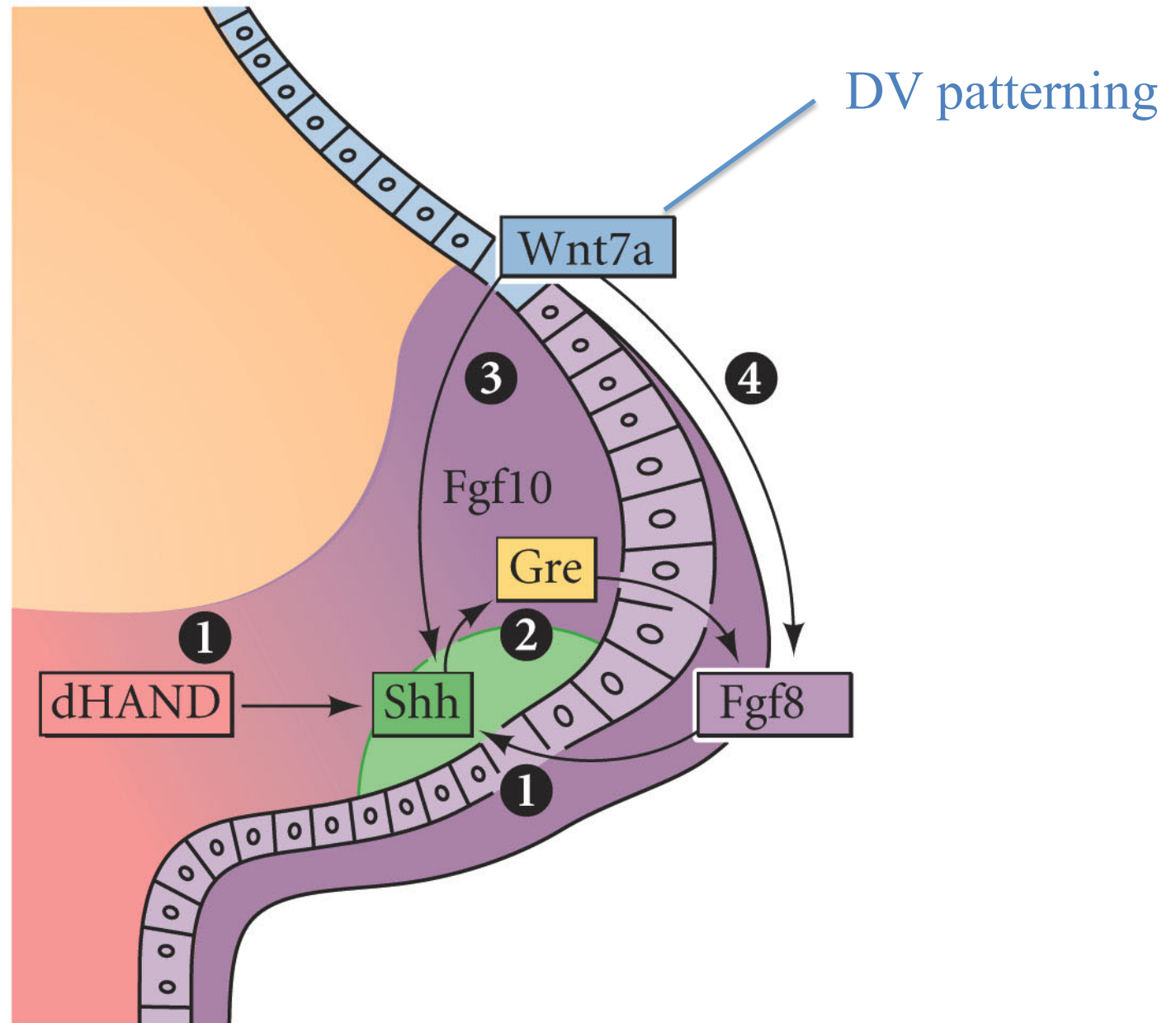


Wild-type



*Hx* mutant

**Patterning and growth of the bud:** Some of the molecular interactions by which limb bud formation and growth are initiated and maintained



DV Patterning: Vade mecum

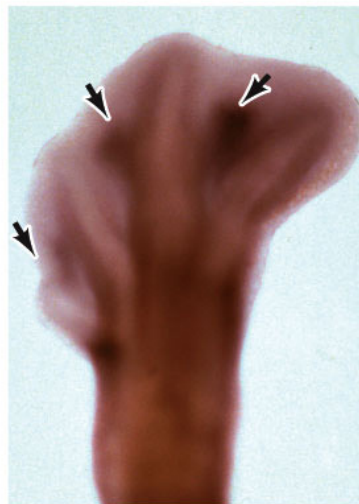
Apoptosis in late digit formation: Inhibition of cell death by inhibiting BMPs by Gremlin

Patterning through cell death: Vade mecum

Chick  
hindlimb



Duck  
hindlimb



BMP

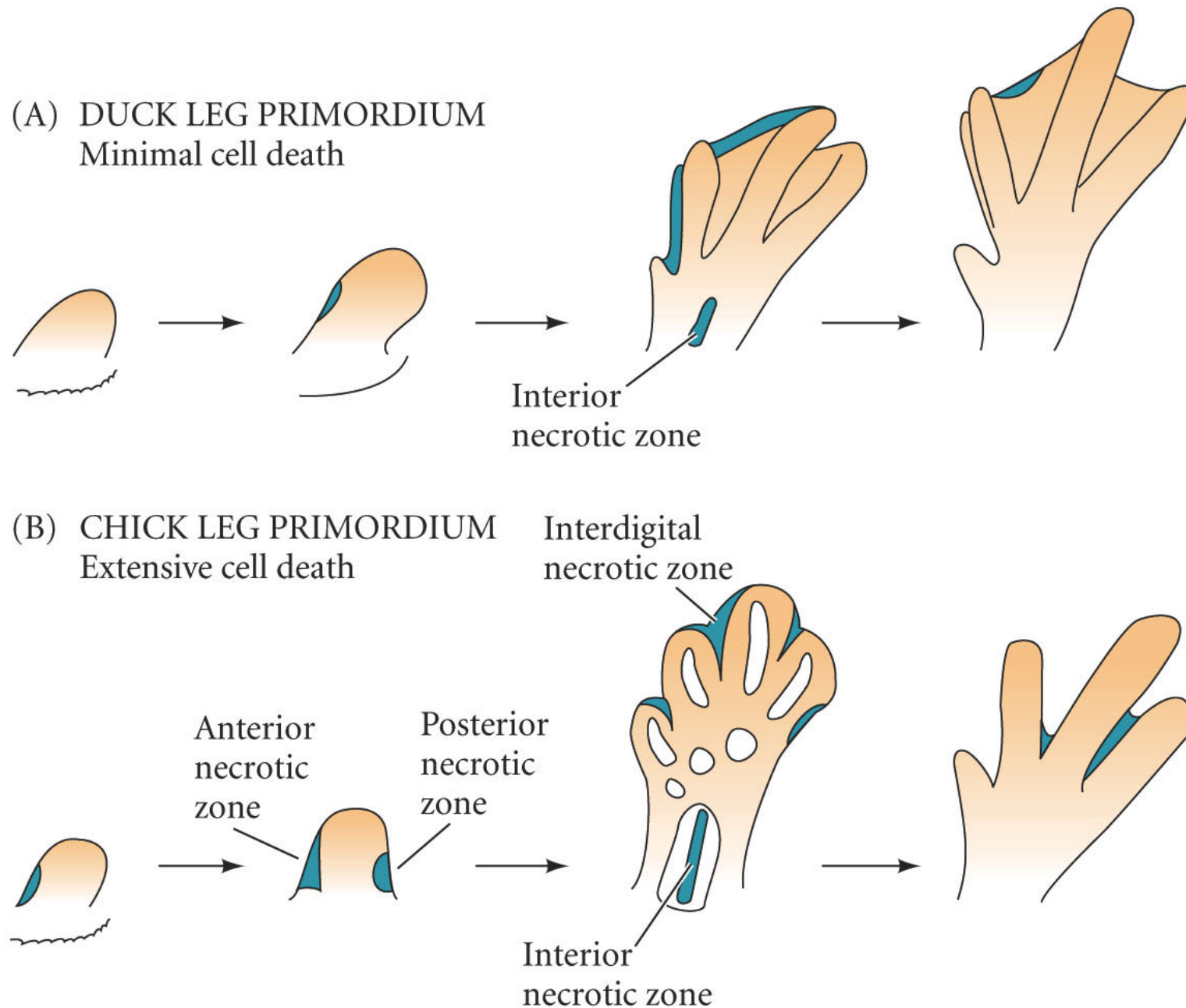
Gremlin

Apoptosis

Newborn



Late digit formation: Patterns of cell death in leg primordia of (A) duck and (B) chick embryos





Apoptosis in late digit formation: Inhibition of cell death by inhibiting BMPs in chick leg

(A)



(B)



Jõao Botelho (Brazilian researcher) et al. at the Vargas Lab (Universidad de Chile)

<https://www.sciencedaily.com/releases/2016/03/160307153051.htm>

