The genetics of body axis formation

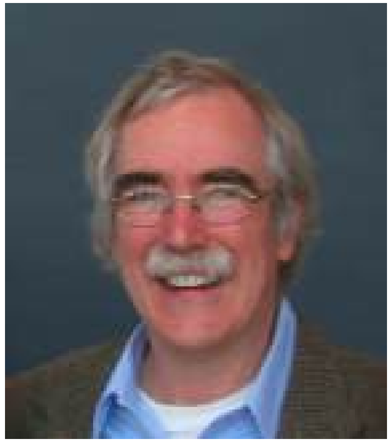
Genetics and Population Genetics

Máté Varga - Department of Genetics

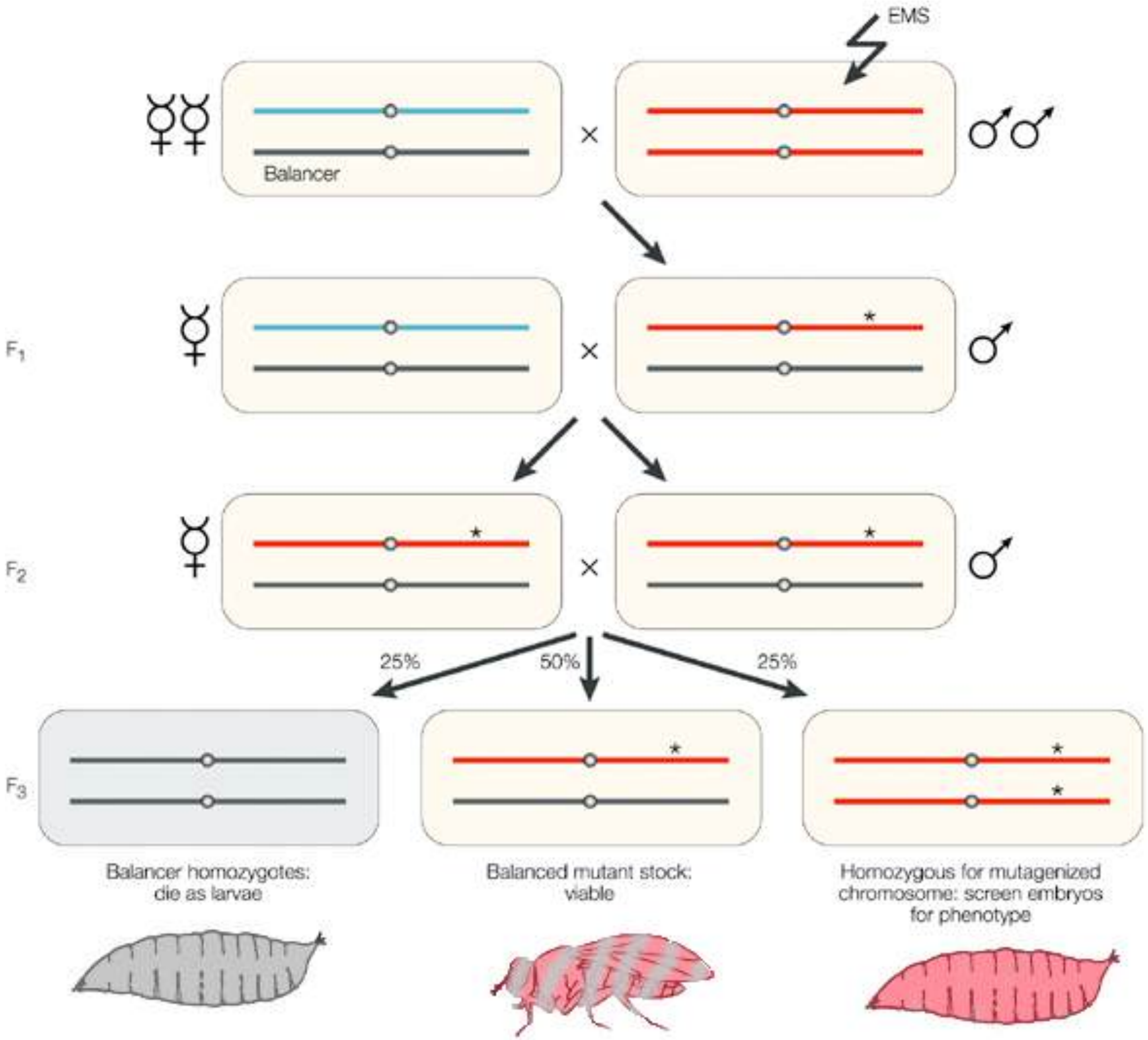
14.10.2024

First genetic screen to study embryonic development: 1978-1980 Heidelberg

Christiane Nüsslein-Volhard

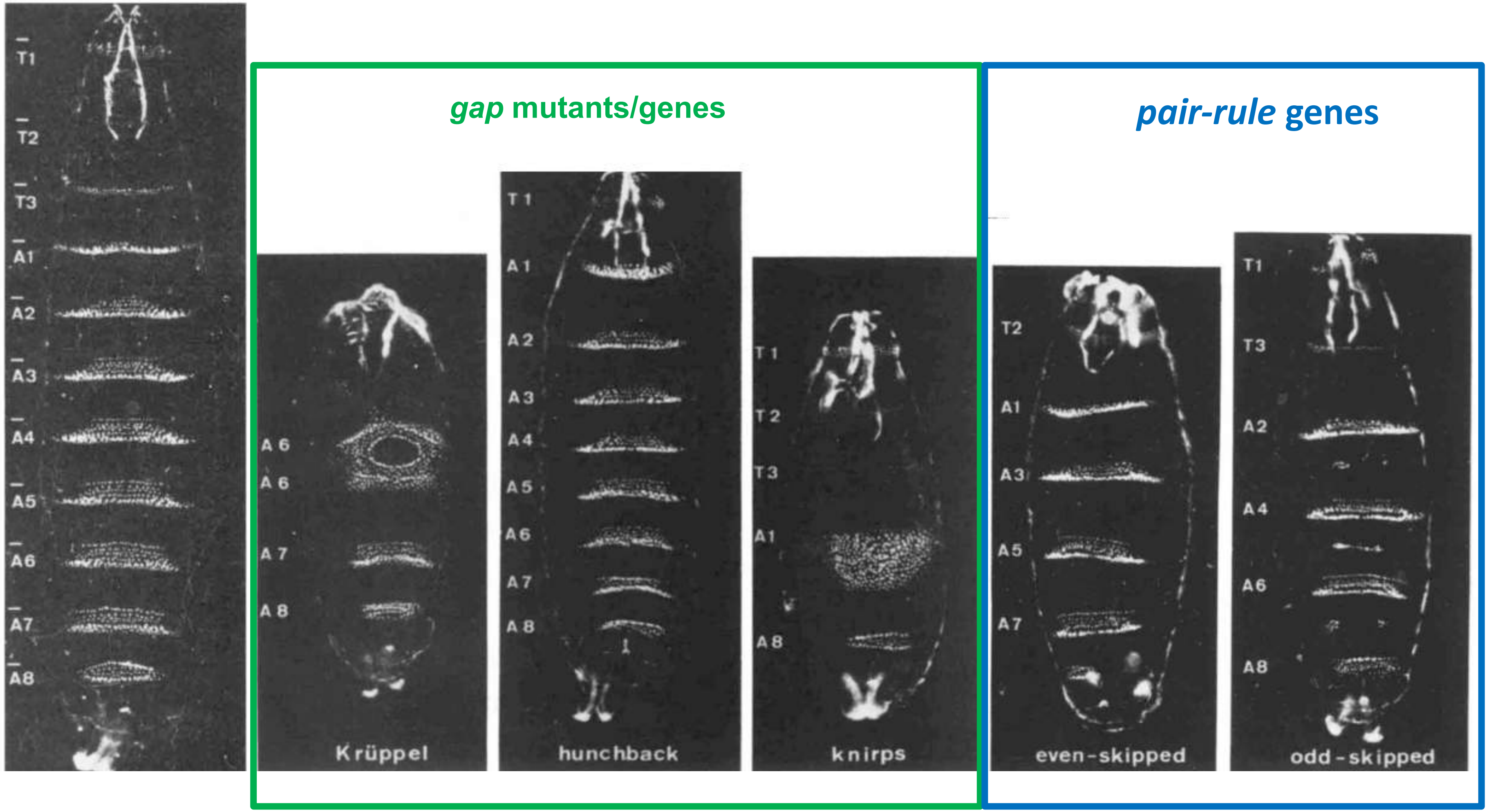


Eric Wieschaus



(St. Johnston, 2002 *Nat Rev Gen*)

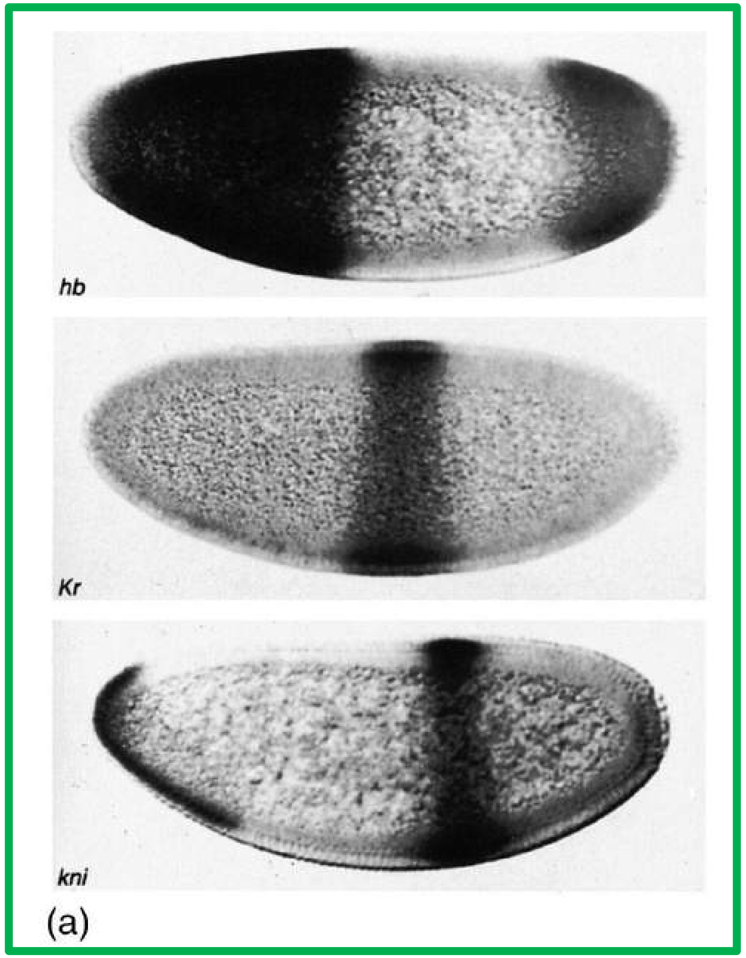
Zygotic genes involved in the formation of the antero-posterior (AP) axis



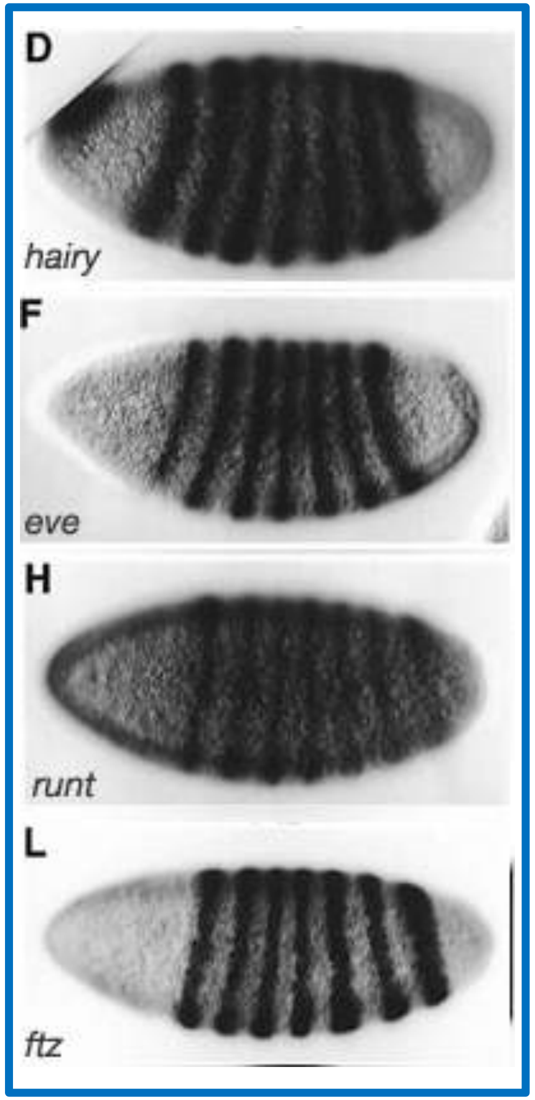
(Nüsslein-Volhard and Wieschaus, 1980 *Nature*)

Zygotic genes involved in the formation of the antero-posterior (AP) axis

gap genes



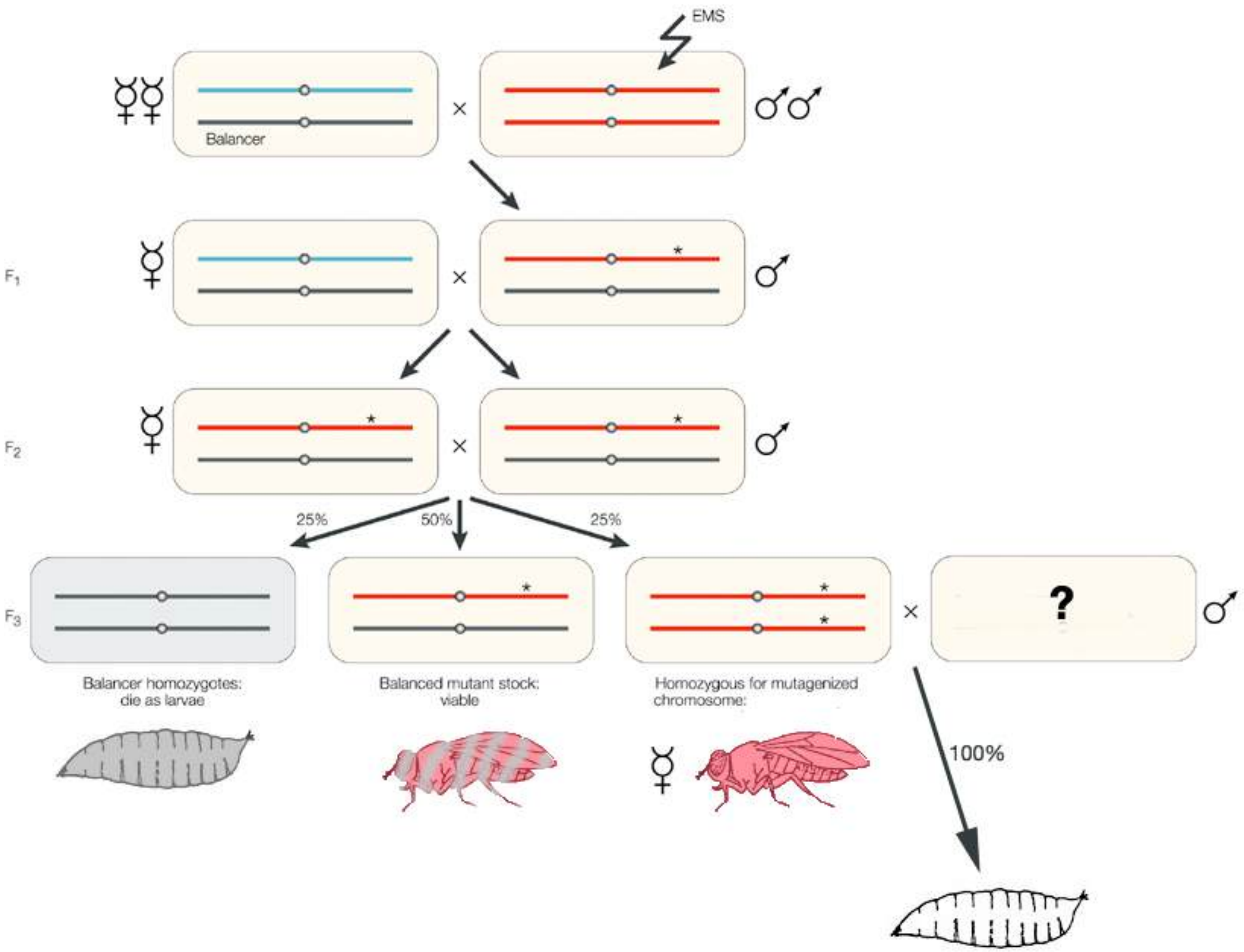
pair-rule genes

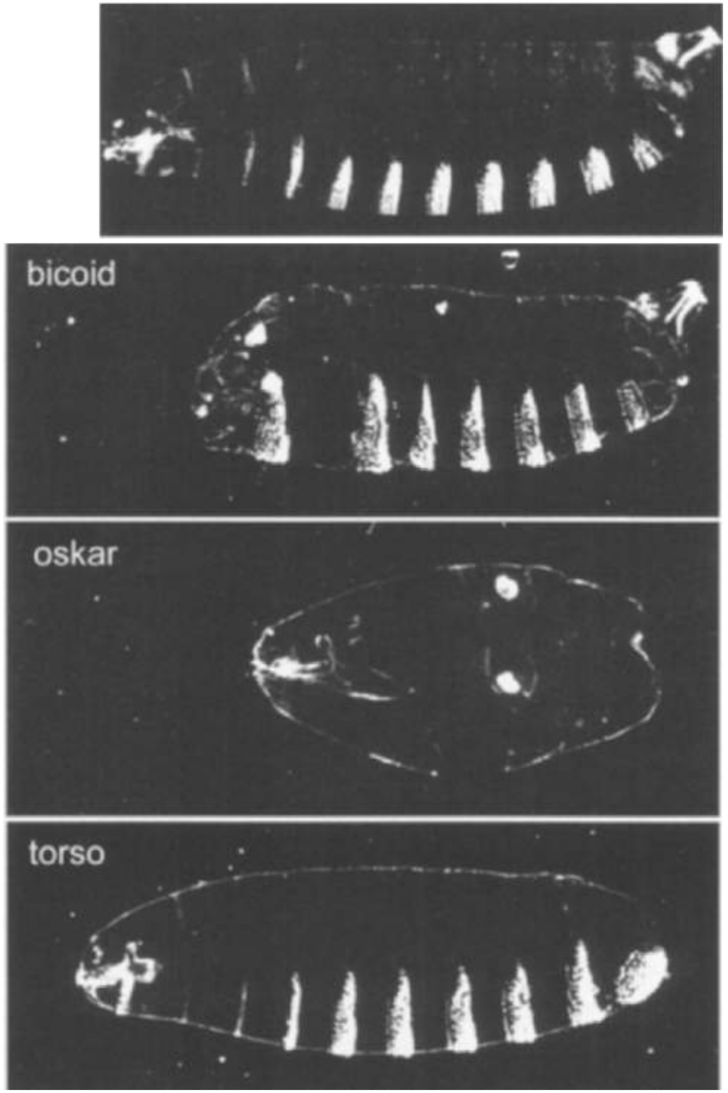


BUT: what regulates the expression of *gap* genes?

(Nüsslein-Volhard and Wieschaus, 1980 *Nature*)

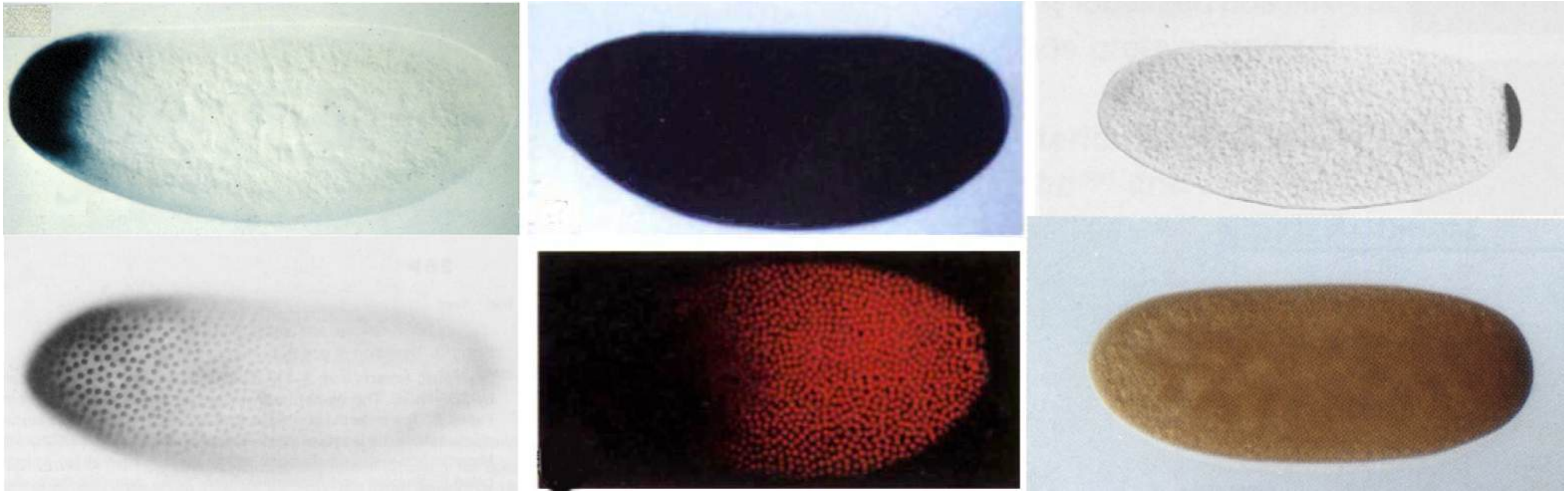
Looking for maternal mutants



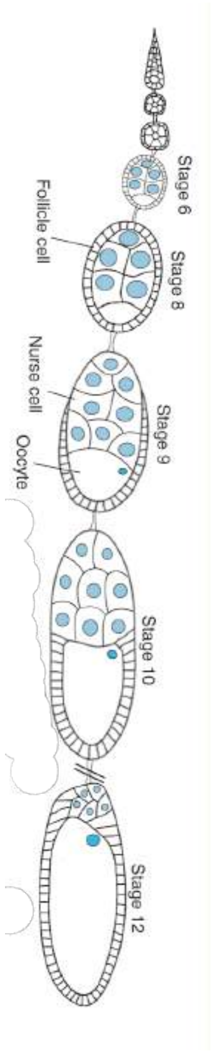


(Nüsslein-Volhard, 2004 *Cell*)

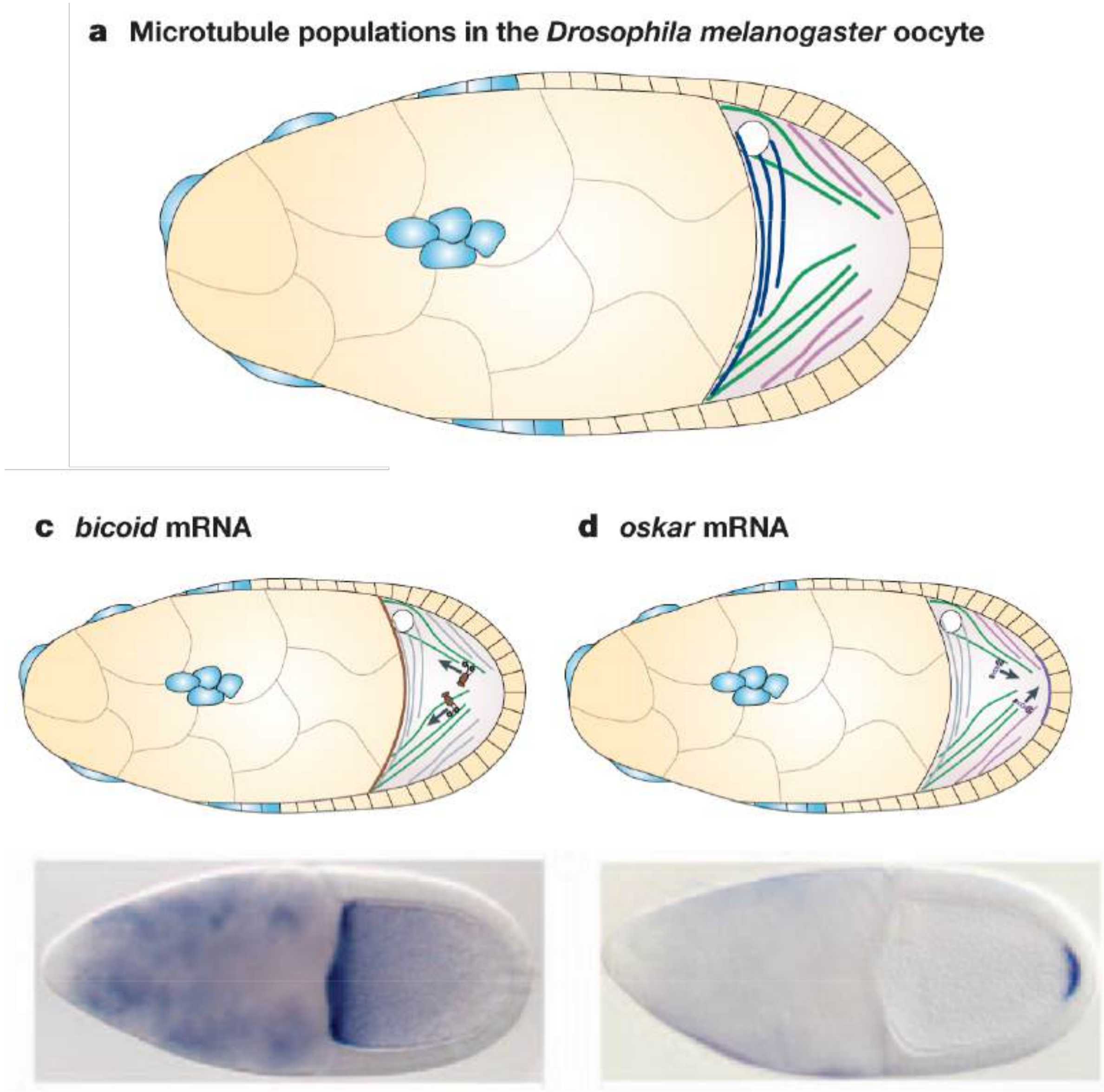
Looking for maternal mutants



Localization of maternal mRNAs with the help of microtubules



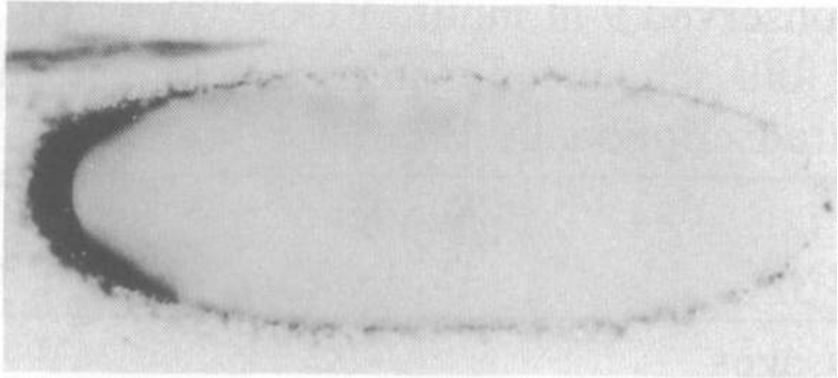
(*Drosophila* oogenesis)



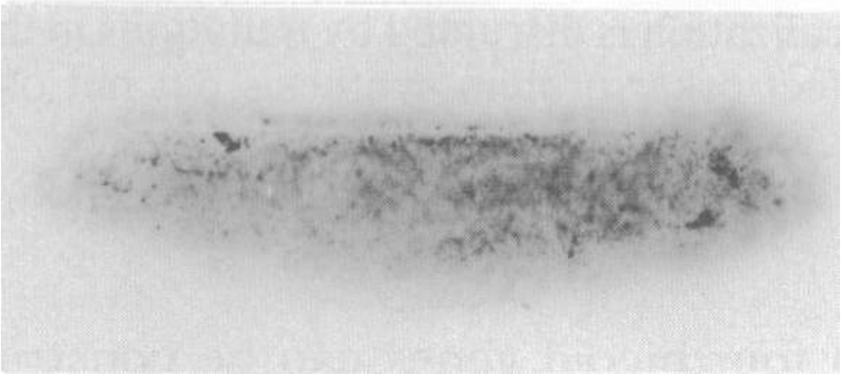
(St Johnston, 2005 *Nat Rev Mol Cell Bio*)

The 3'UTR of the *bcd* mRNA is involved in mRNA localisation

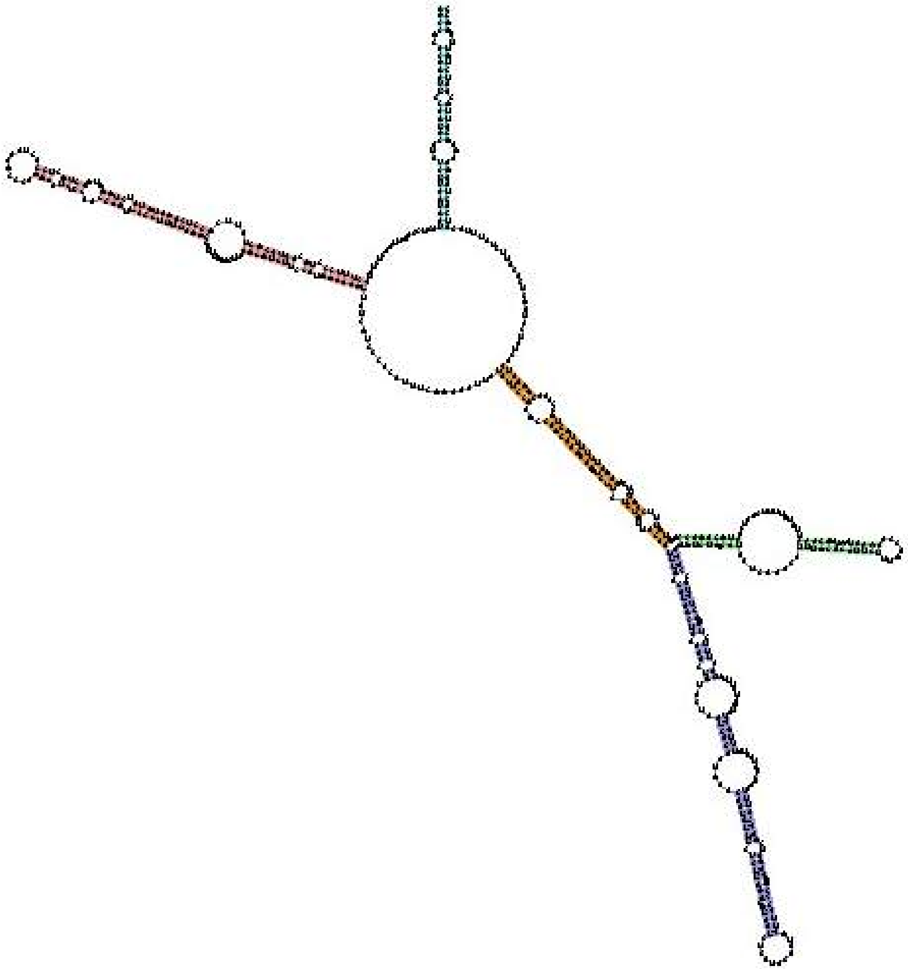
Wild type *bicoid* mRNA



No 3' UTR *bicoid* mRNA



(Gottlieb et al., 1992 *PNAS*)



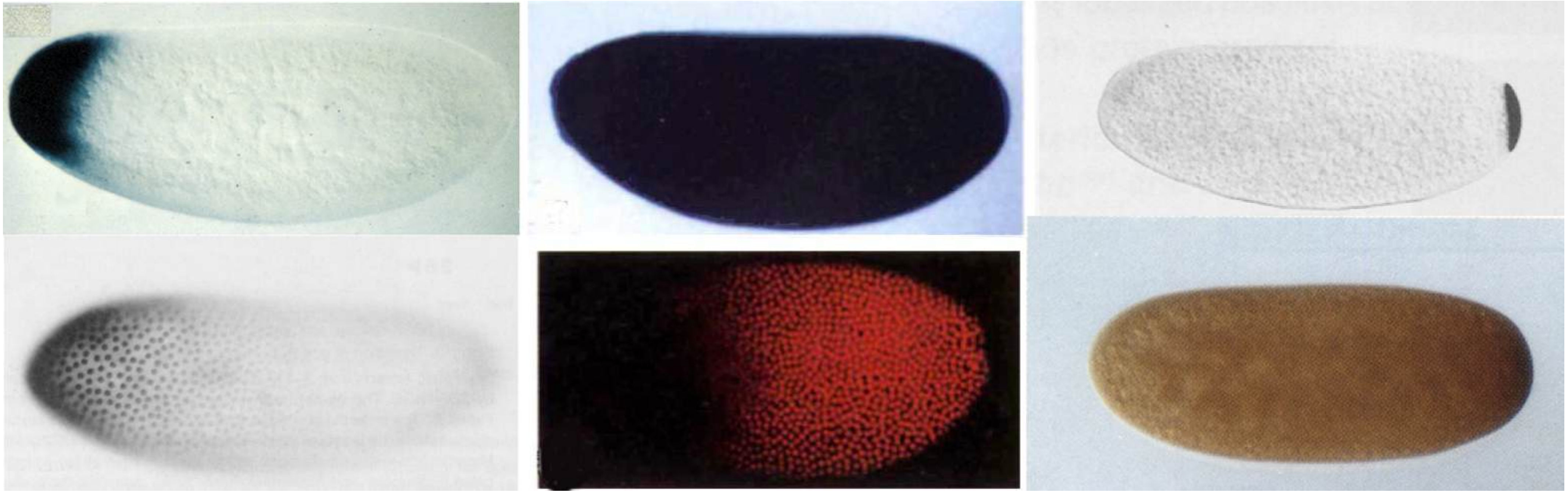
Secondary structure of the *bicoid* mRNA 3' UTR

Looking for maternal mutants

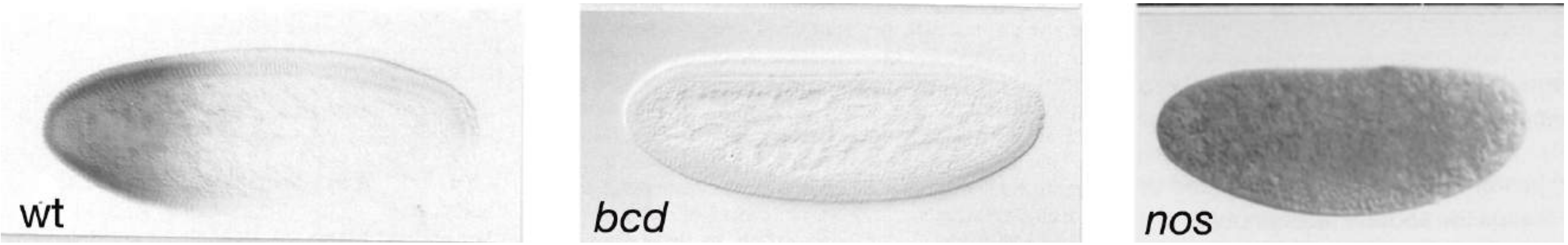
bicoid (bcd) | *caudal (cad)* | *nanos (nos)*

mRNA

protein

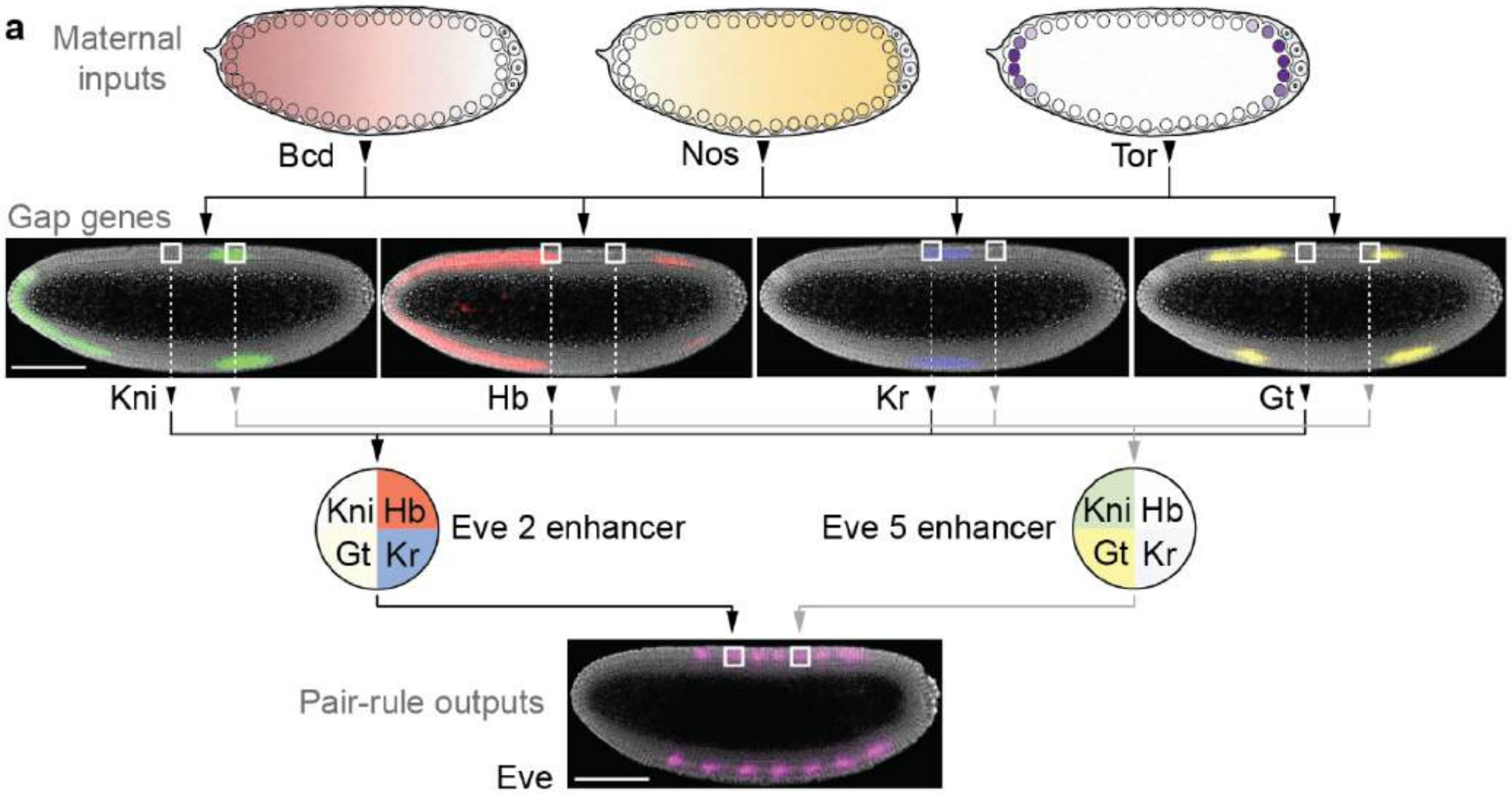


Bicoid and Nanos are the regulators of *hunchback*

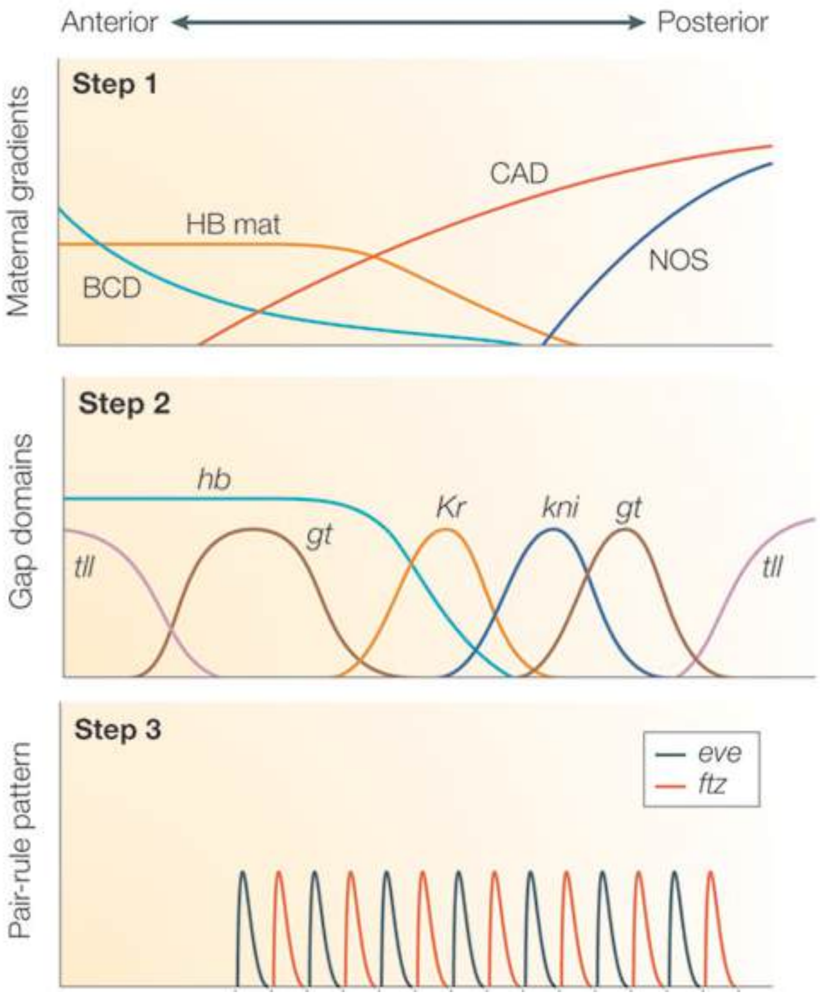


hb mRNA | Hb protein

Segmentation networks in *Drosophila*

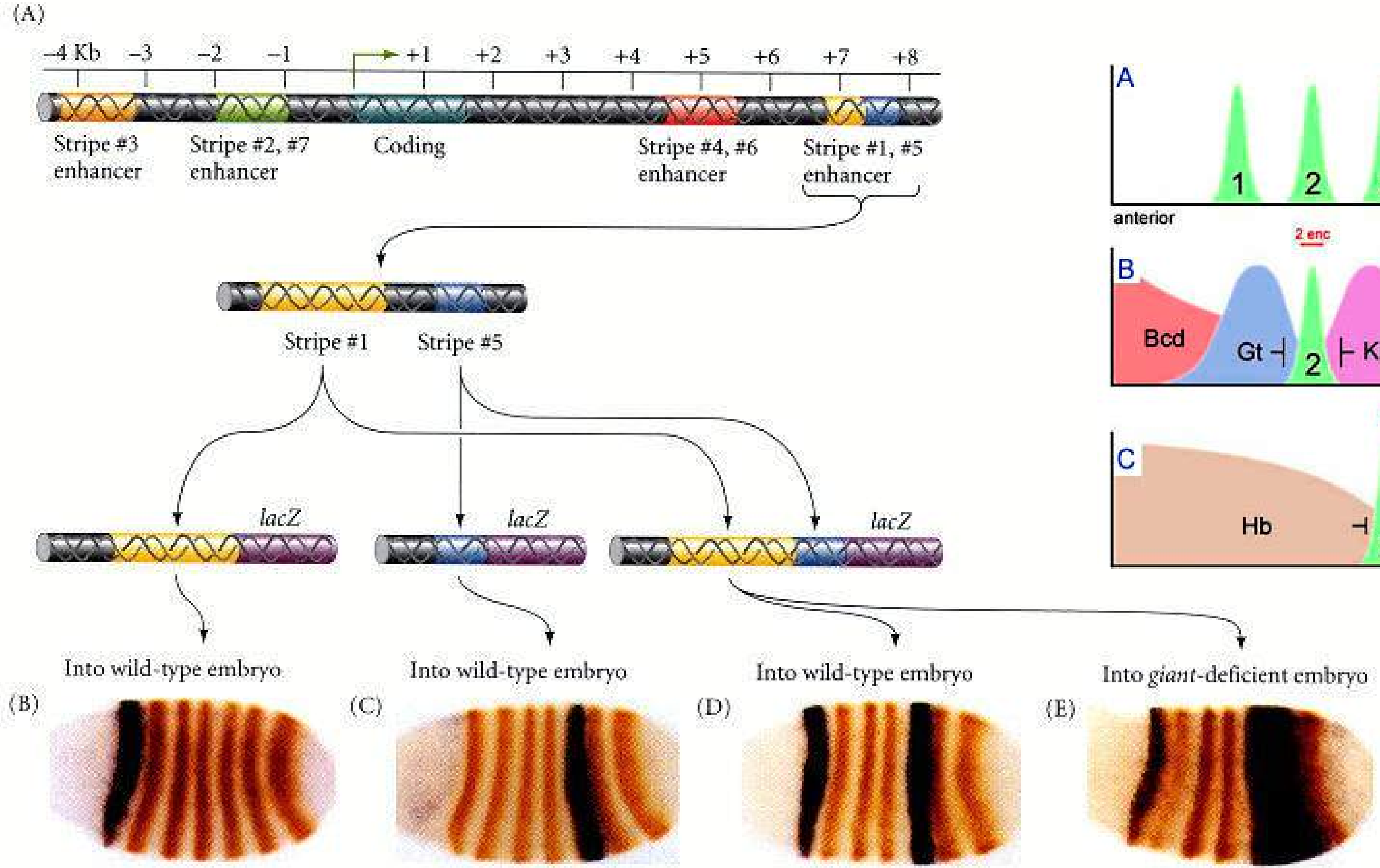


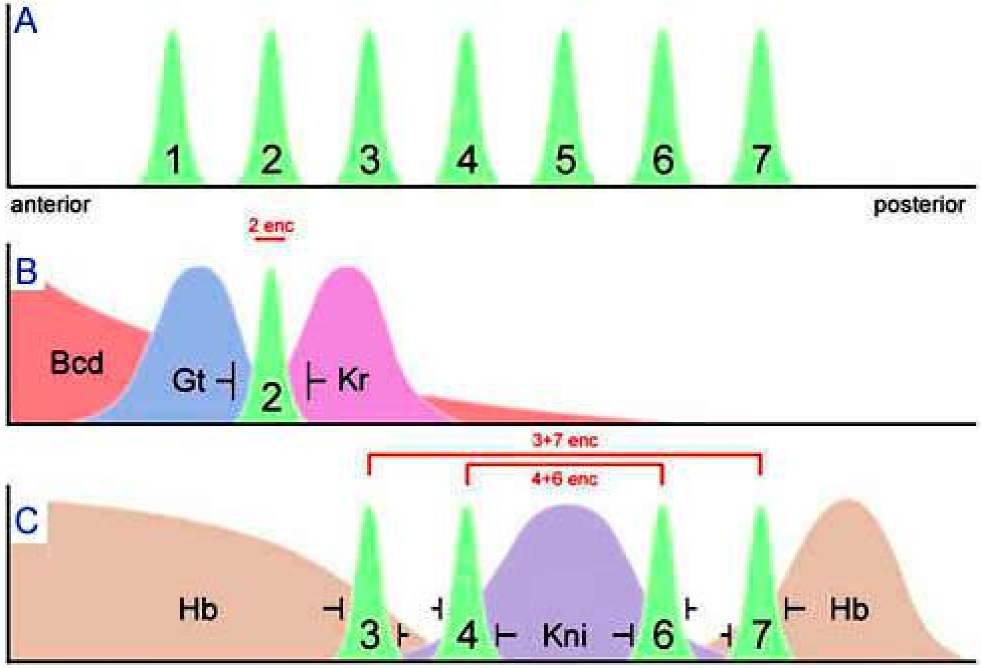
(Petkova et al., 2016 *arXiv*)



(Peel et al., 2005 *Nat Rev Gen*)

Segmentation in *Drosophila*: the regulation of the *even-skipped* (*eve*) gene



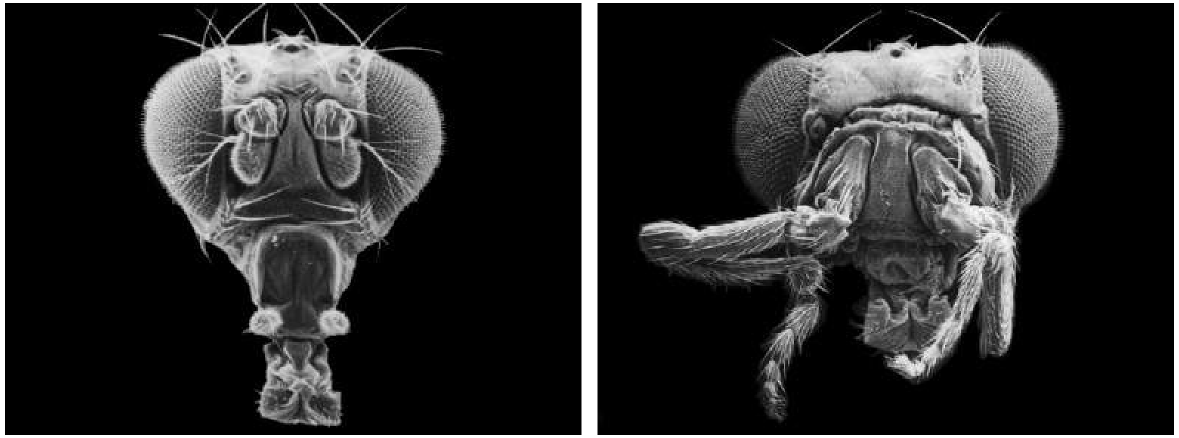


(Gilbert, 2000 *Developmental Biology, 6th ed.)*

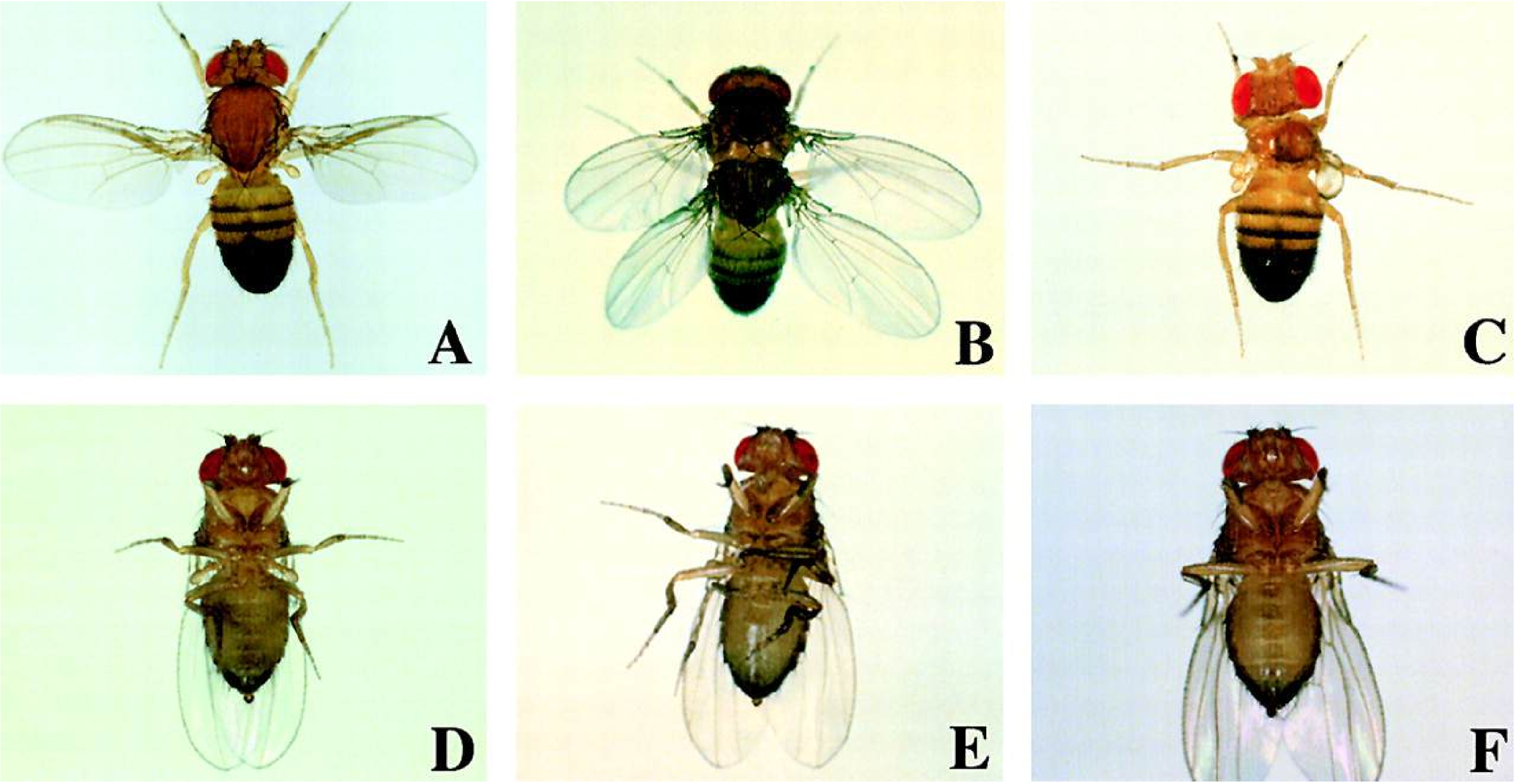
Segment identity: homeotic mutants

- the *bithorax* mutation

- the *antennapedia* mutation

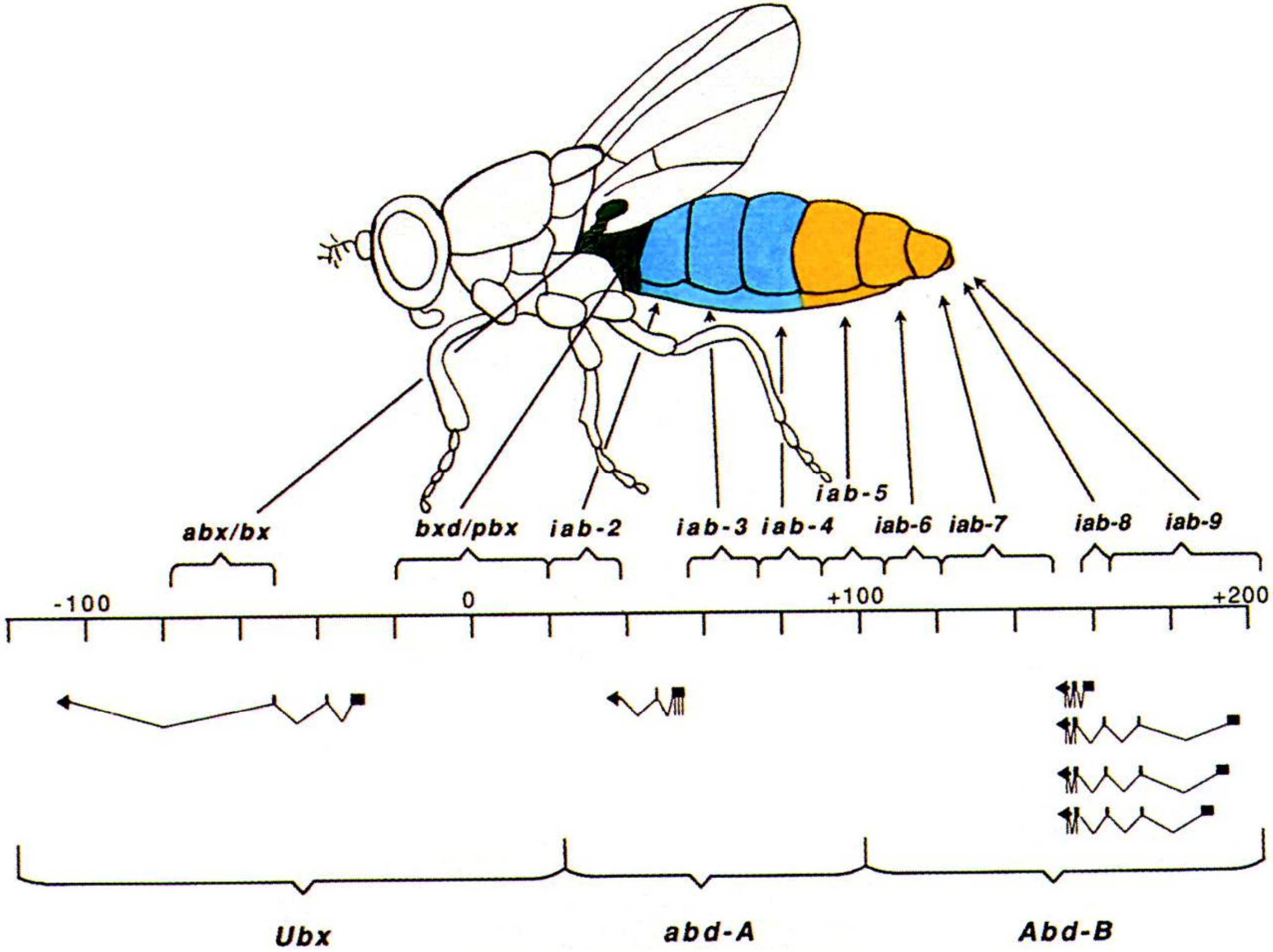


Segment identity: homeotic mutants



(Duncan and Montgomery, 2002a *Genetics*)

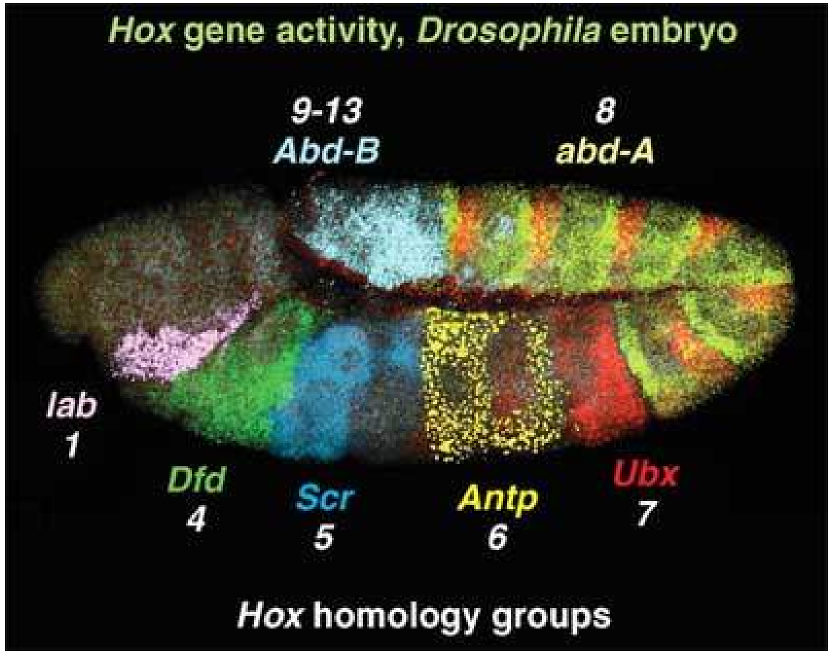
Segment identity: the *bithorax* complex

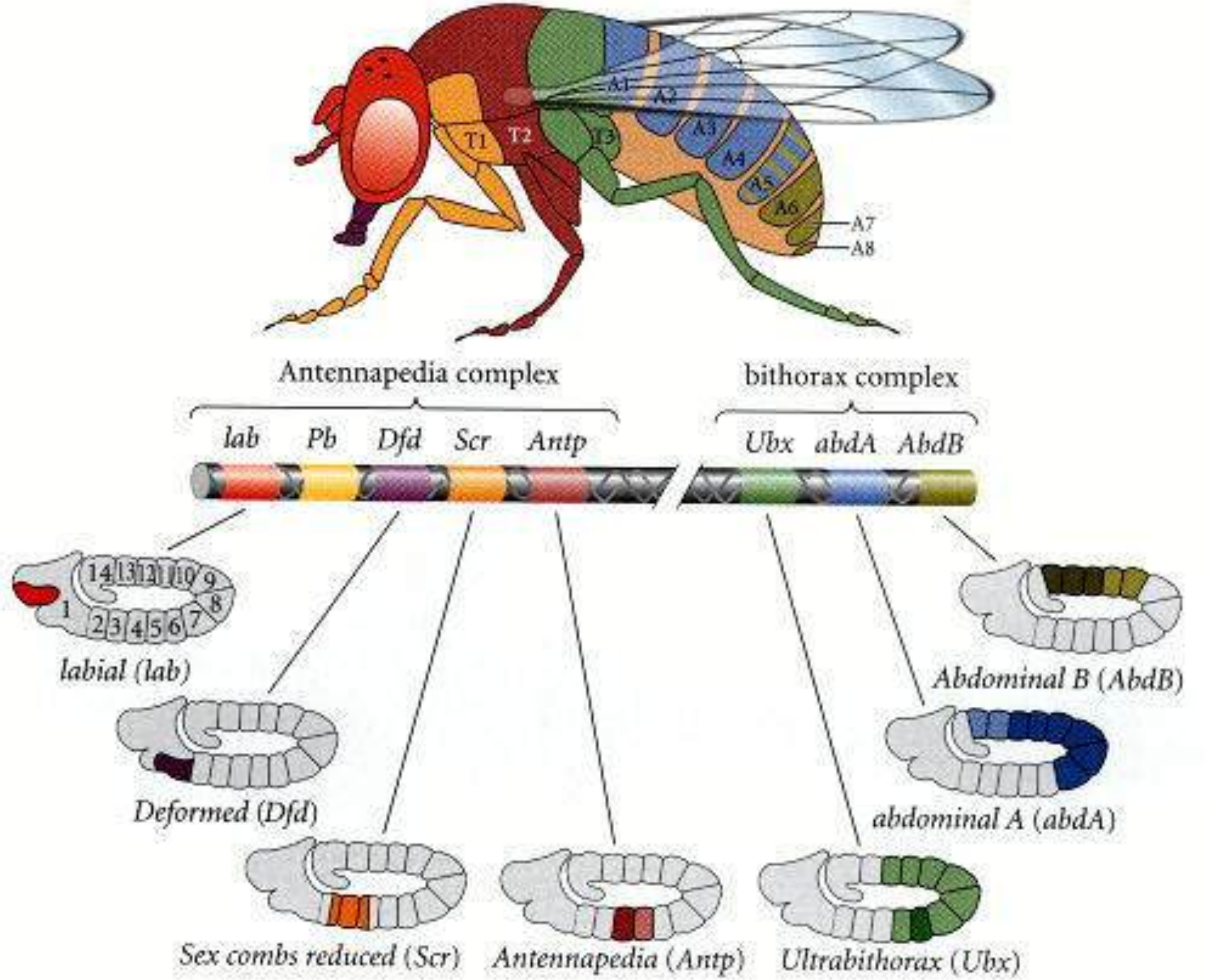


Edward B. Lewis

(Duncan and Montgomery, 2002b *Genetics*)

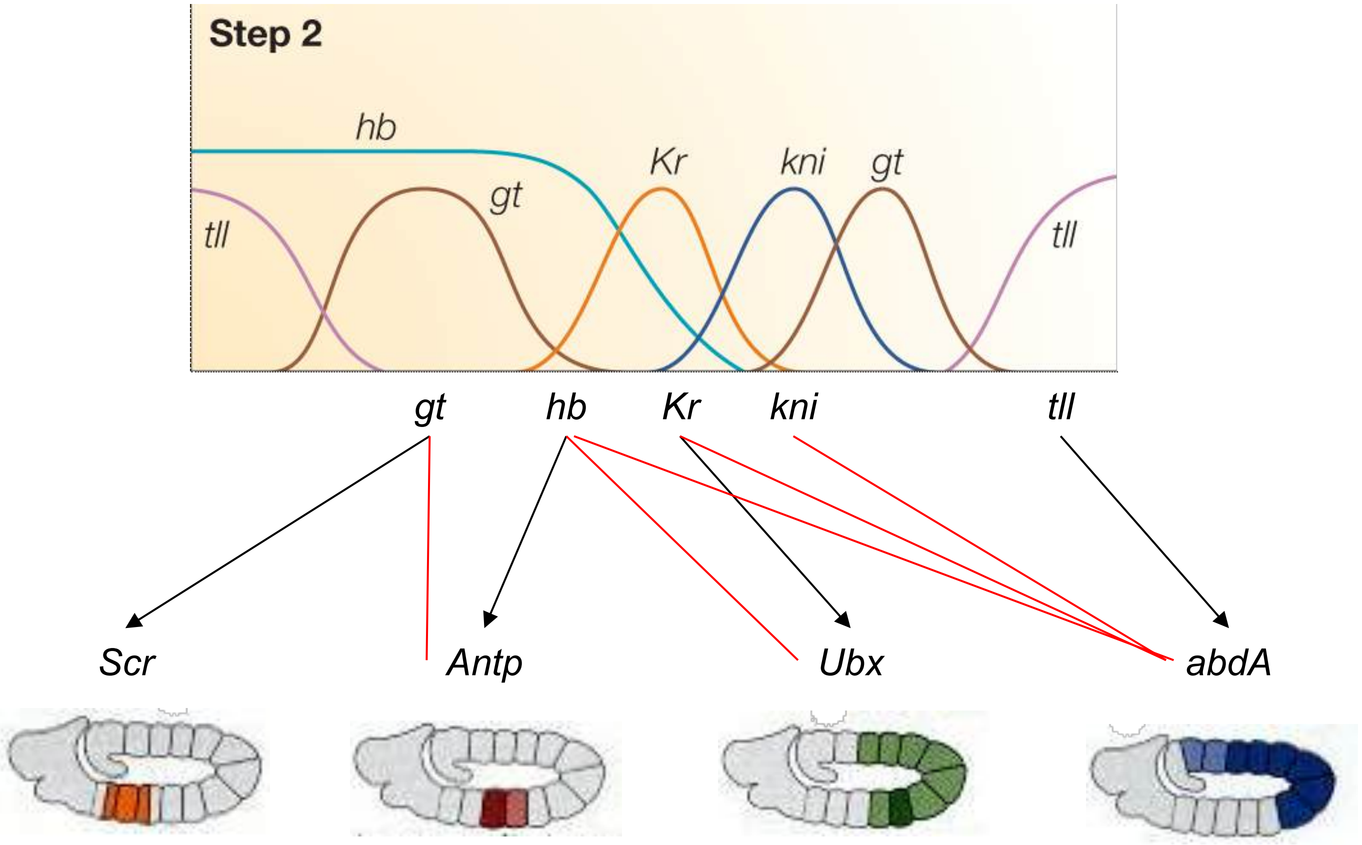
Segment identity: *Hox* genes





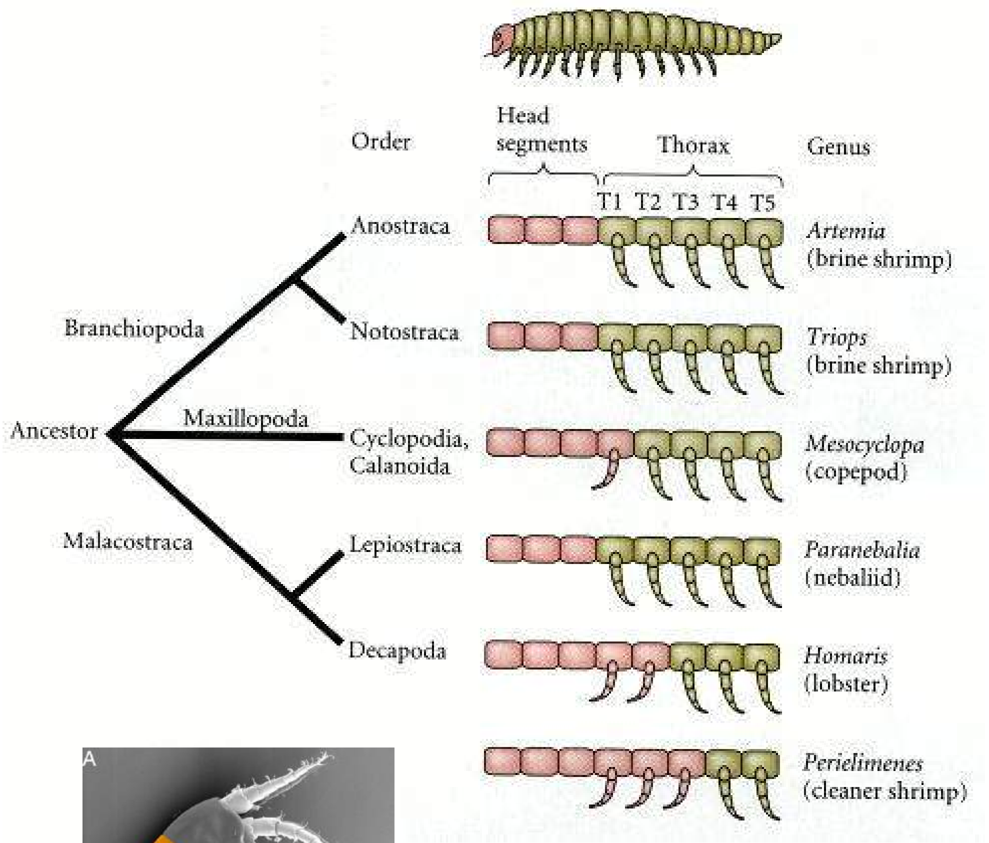
(Gilbert, 2000 *Developmental Biology, 6th ed.)*

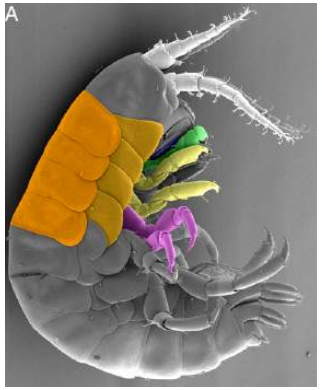
Hox genes are regulated by *gap* genes



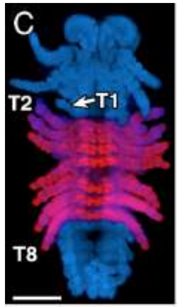
(Based on Wu et al., 2001 and Casares et al., 1995)

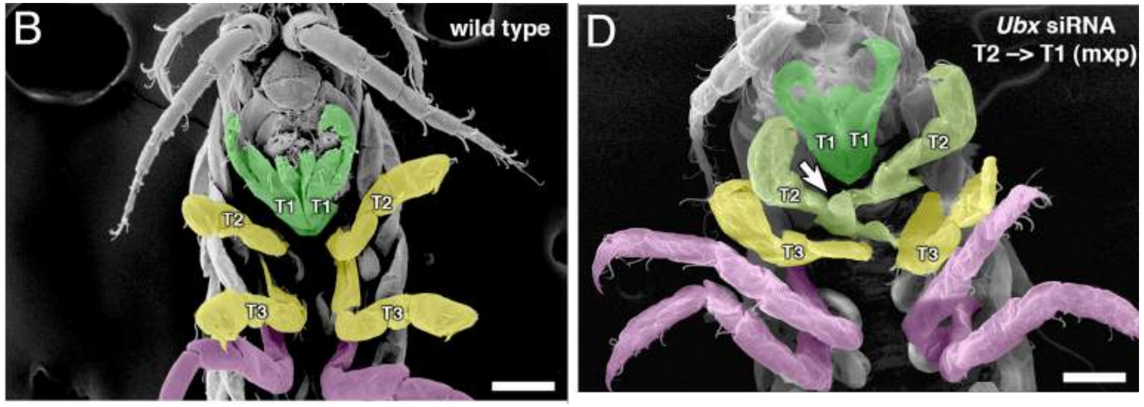
Hox genes (*Ubx*) and evolution of the arthropod bodyplan



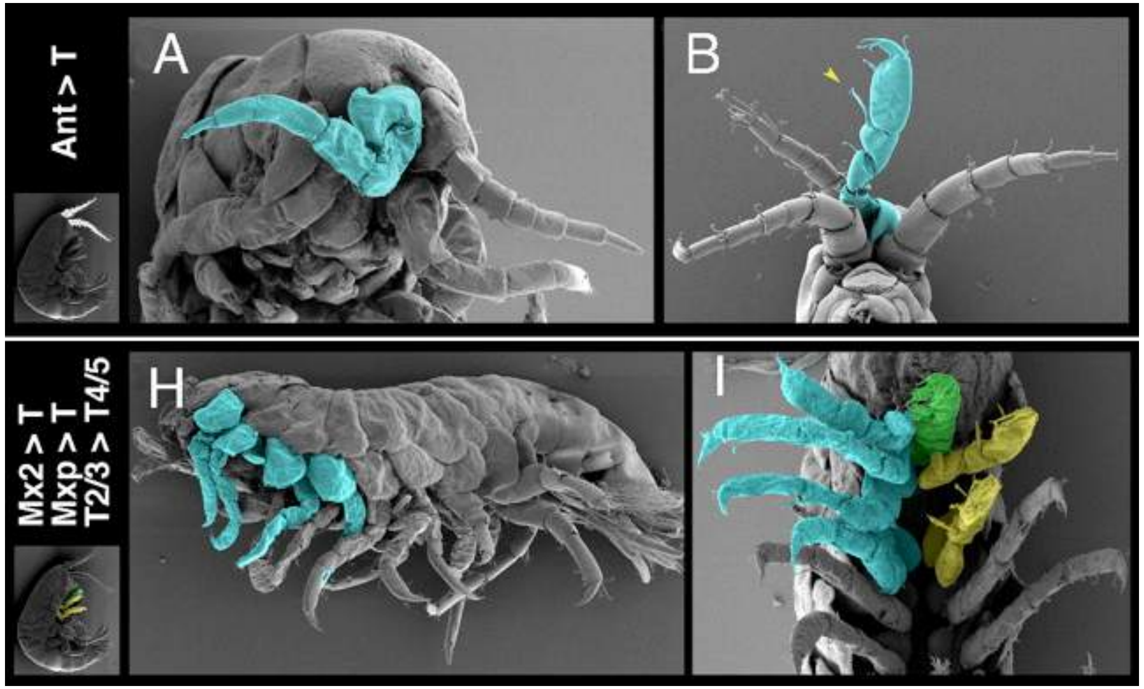


Parhyale hawaiensis



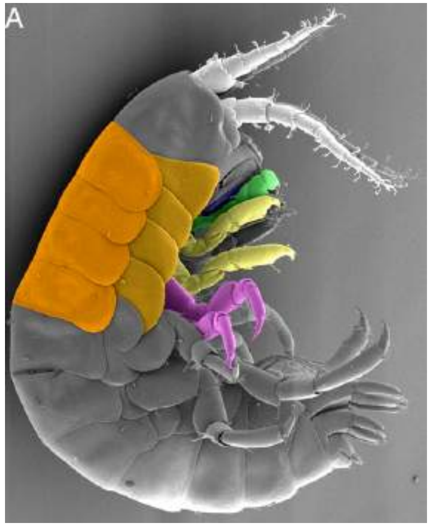


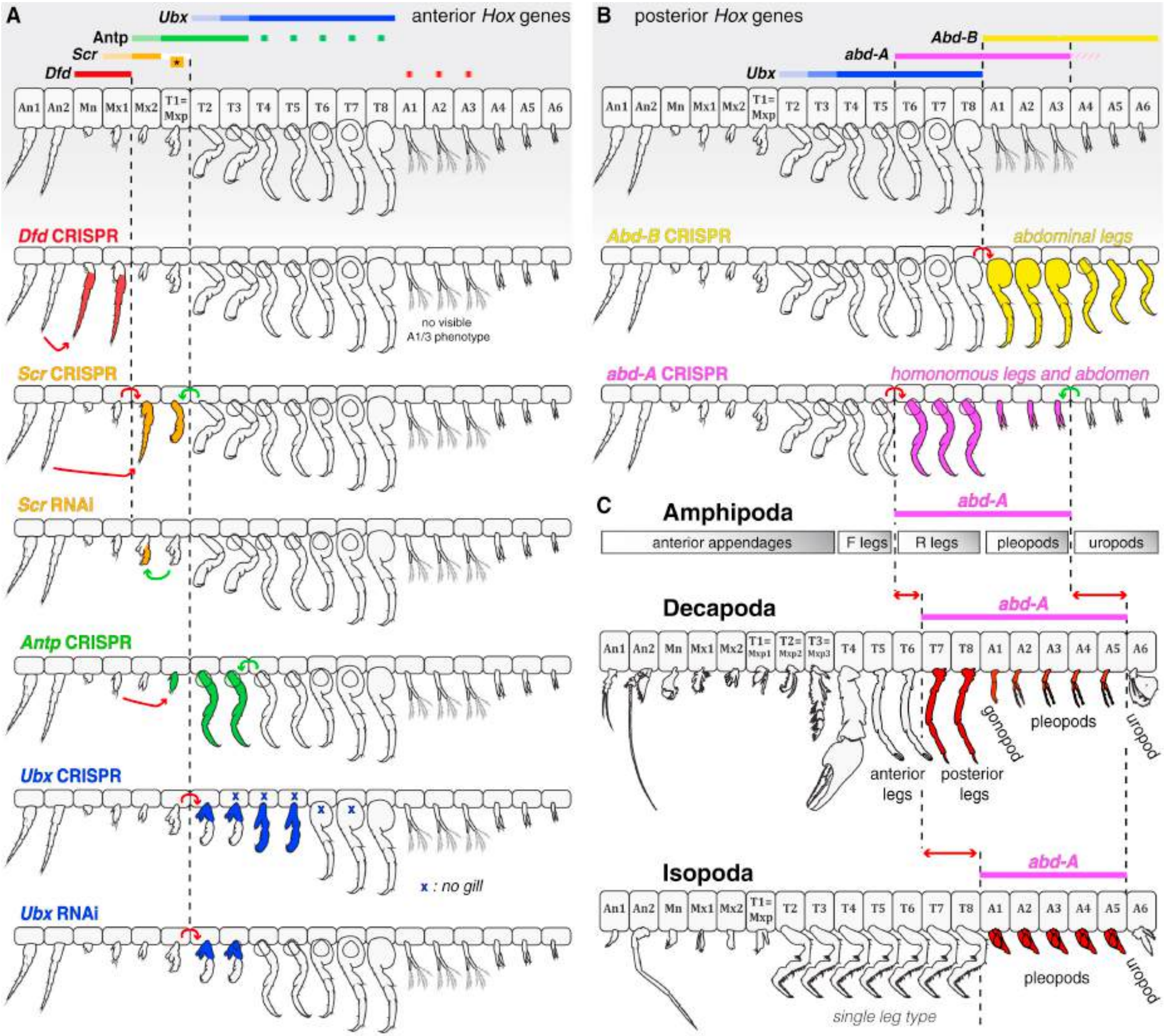
(Liubicich et al., 2009 *PNAS*)

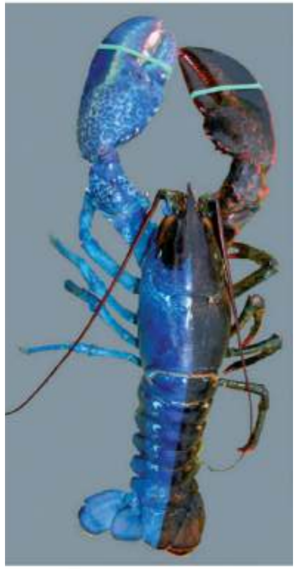


(Pavlopoulos et al., 2009 *PNAS*)

Hox genes and the evolution of the arthropod bodyplan: uropods

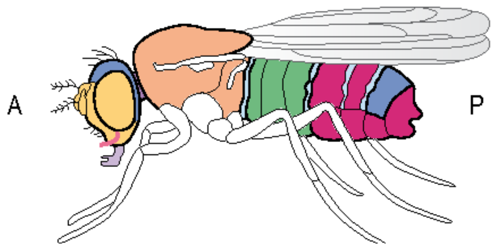


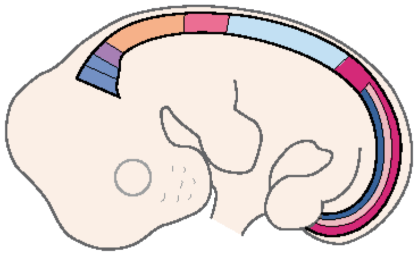


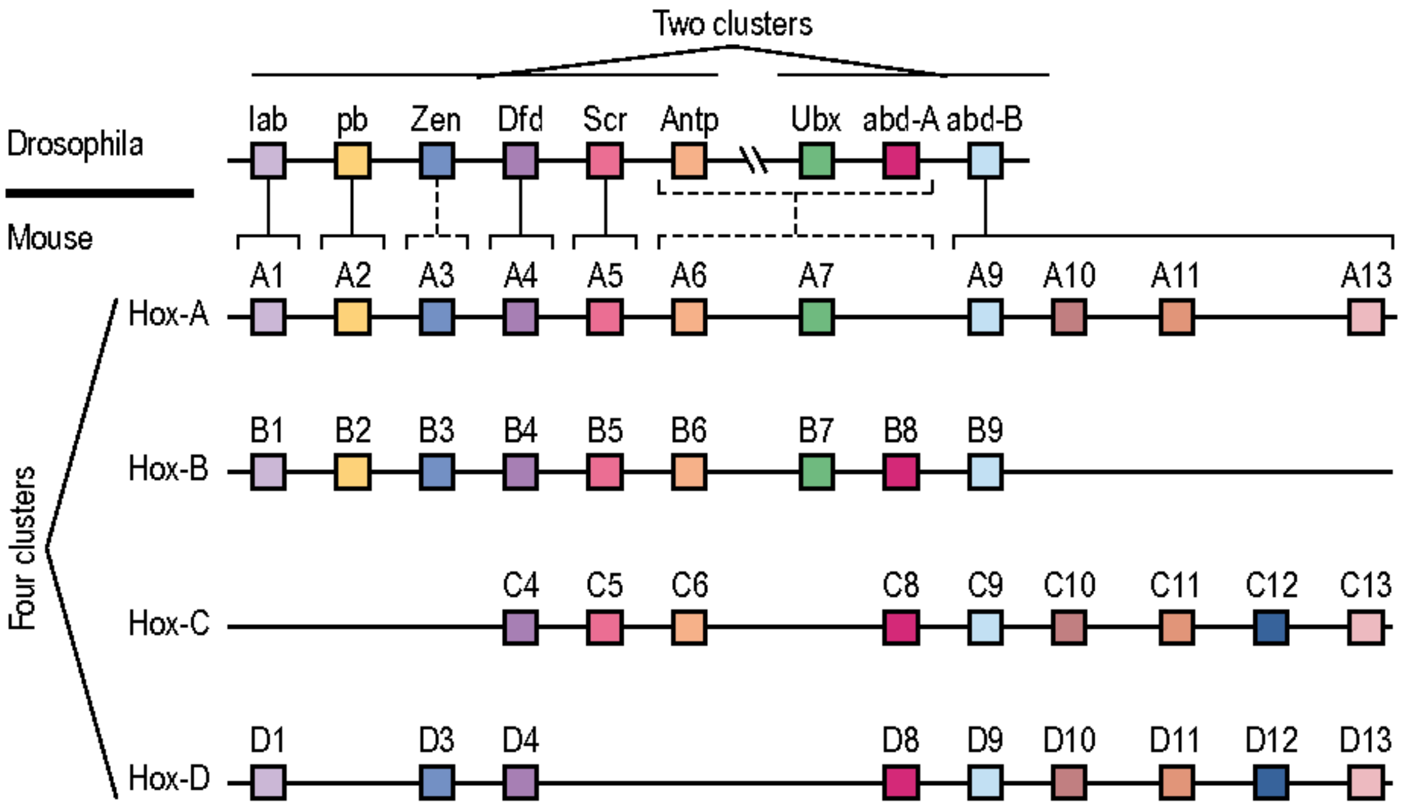


(Martin et al., 2016 *Curr Bio*)

The *Hox* cluster is (almost) universal amongst animals

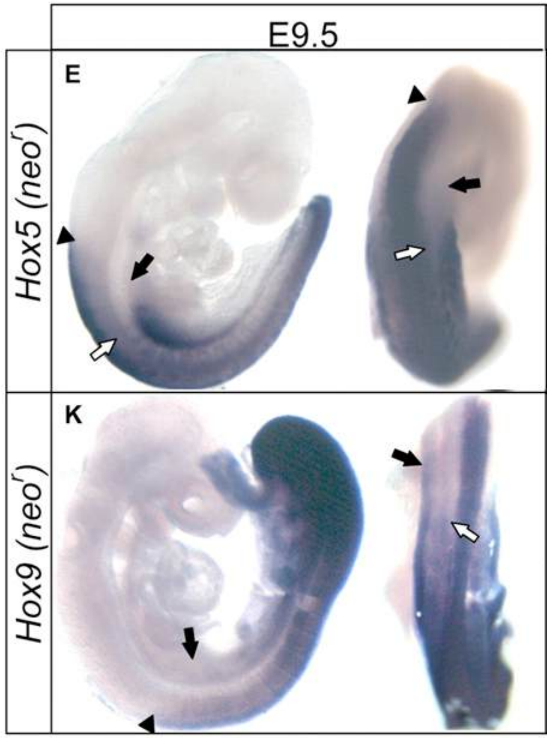




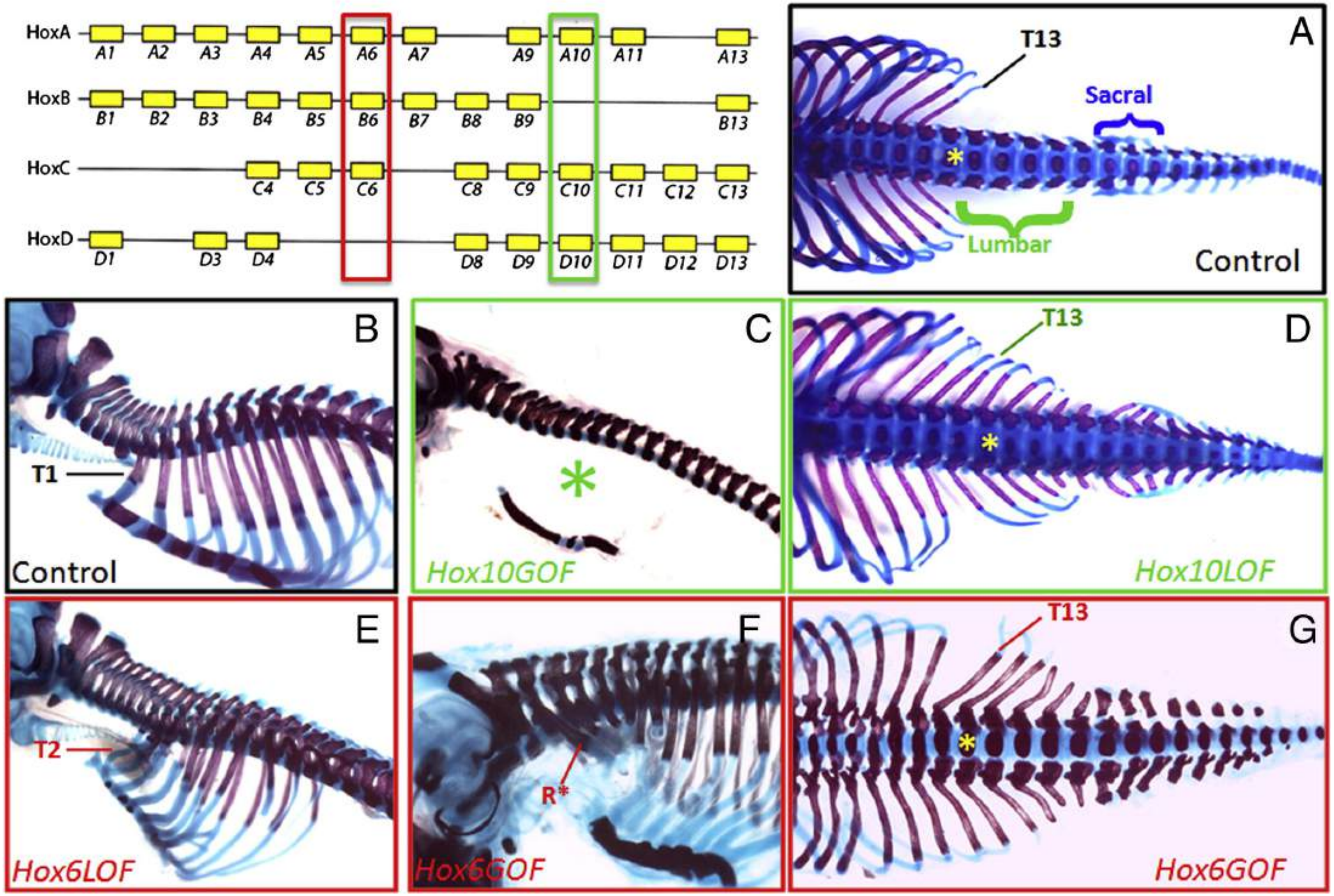


(Vejlsted 2017)

Homeotic mutants in vertebrates



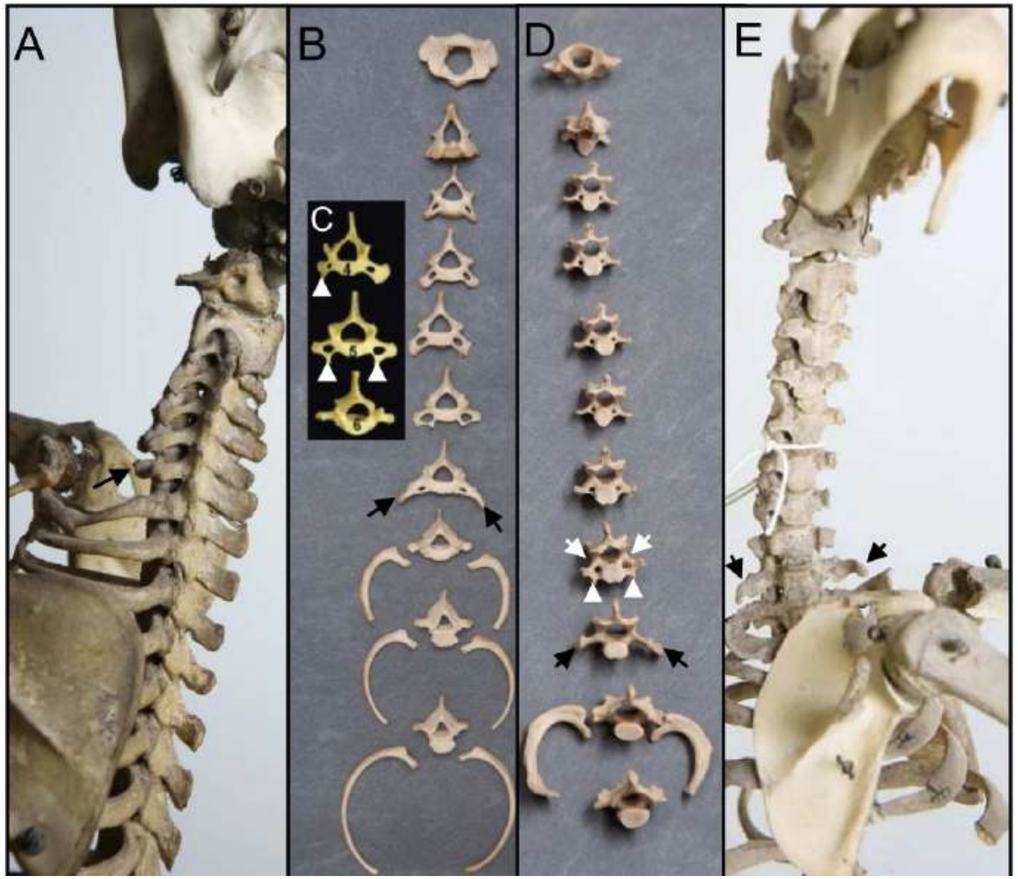
(McIntyre et al., 2007 *Development*)



(Mallo et al., 2010 *Dev Biol*)

Homeotic mutants in vertebrates

14.17: © Bone Clones, www.boneclones.com.

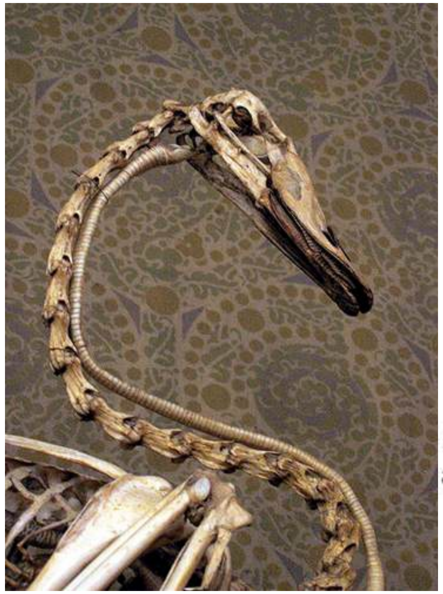


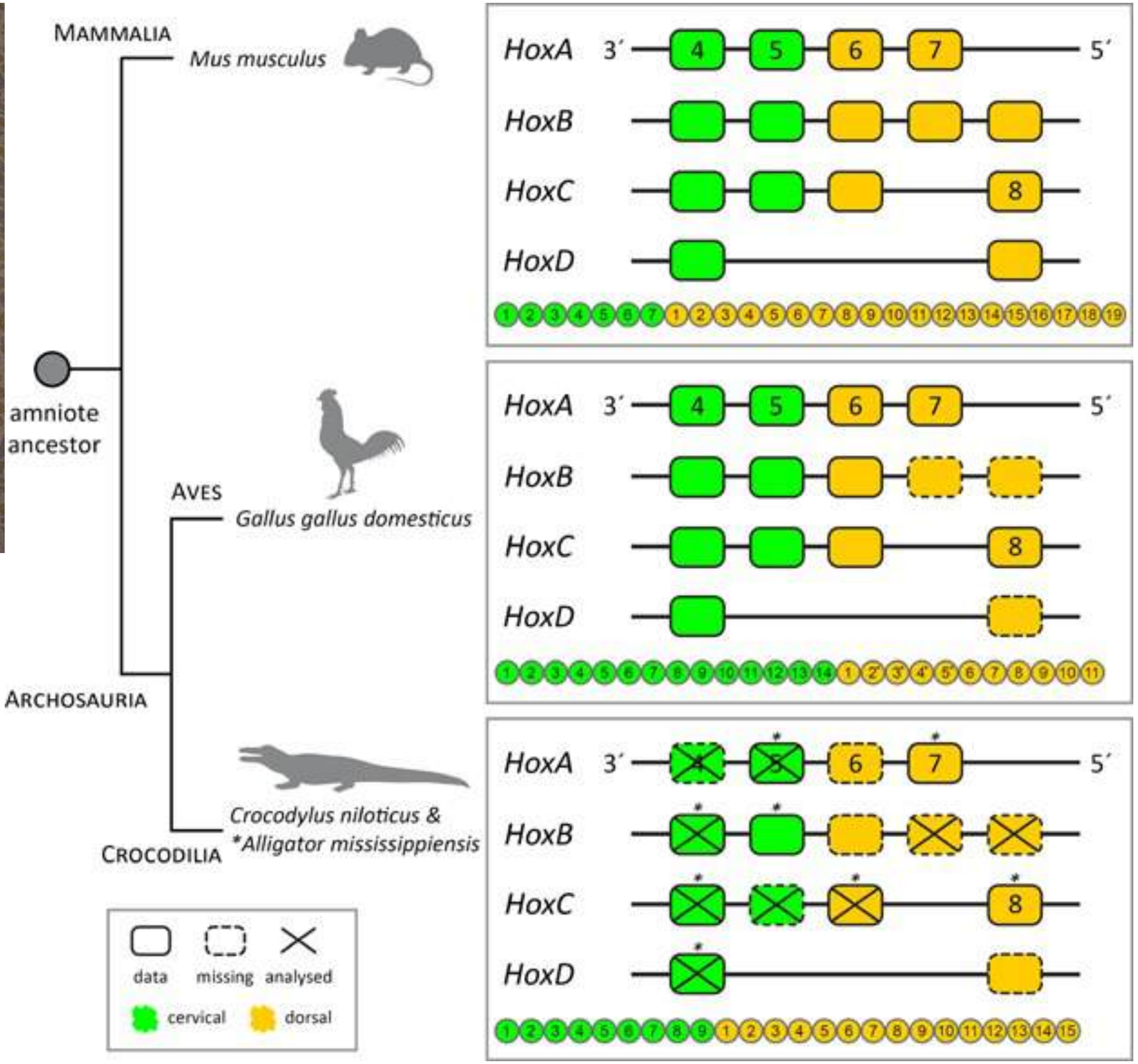
sloths

manatees

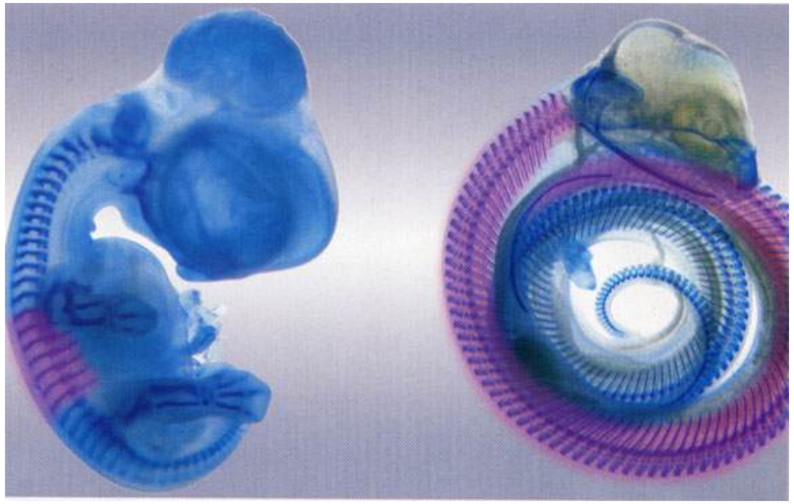
(Varela Lasheras et al., 2011 *EvoDevo*)

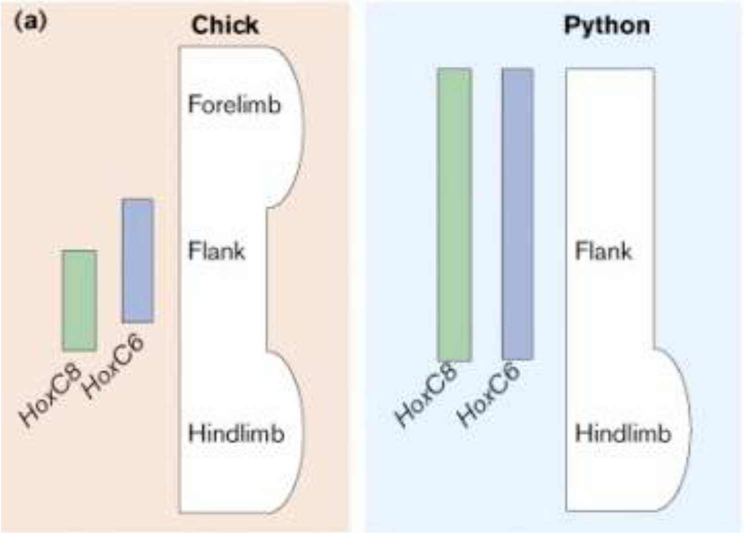
Hox genes and vertebrate evolution





hoxc6 expression pattern

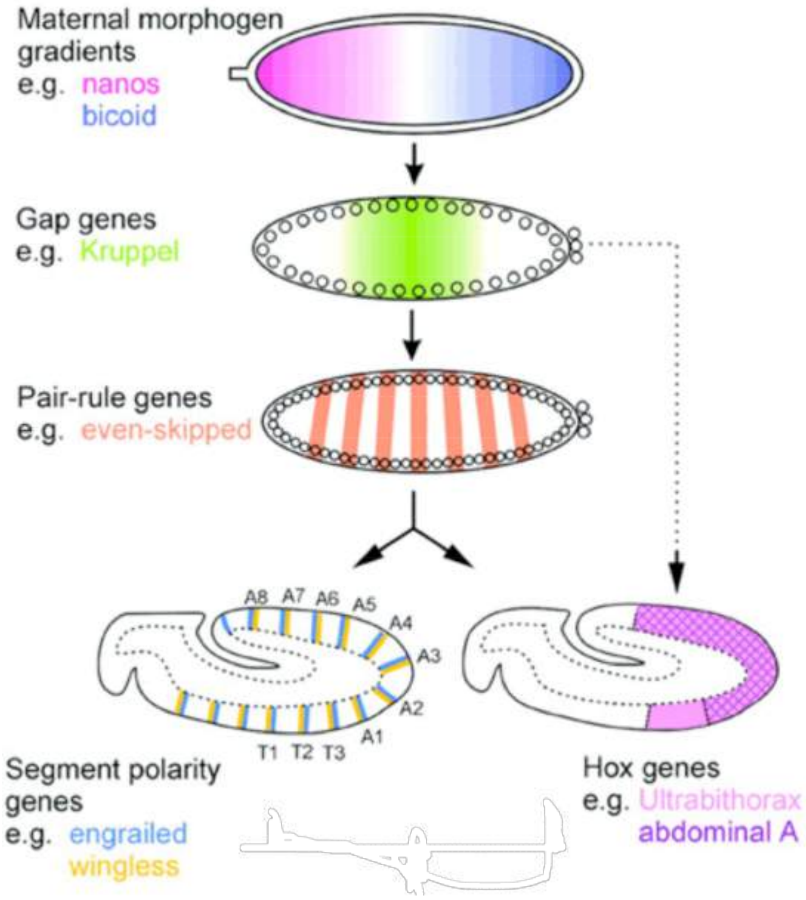


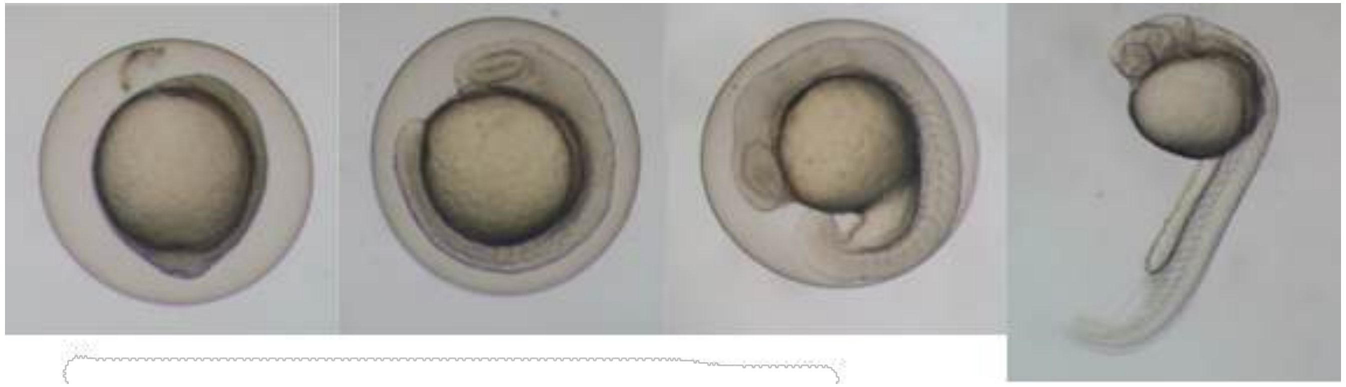


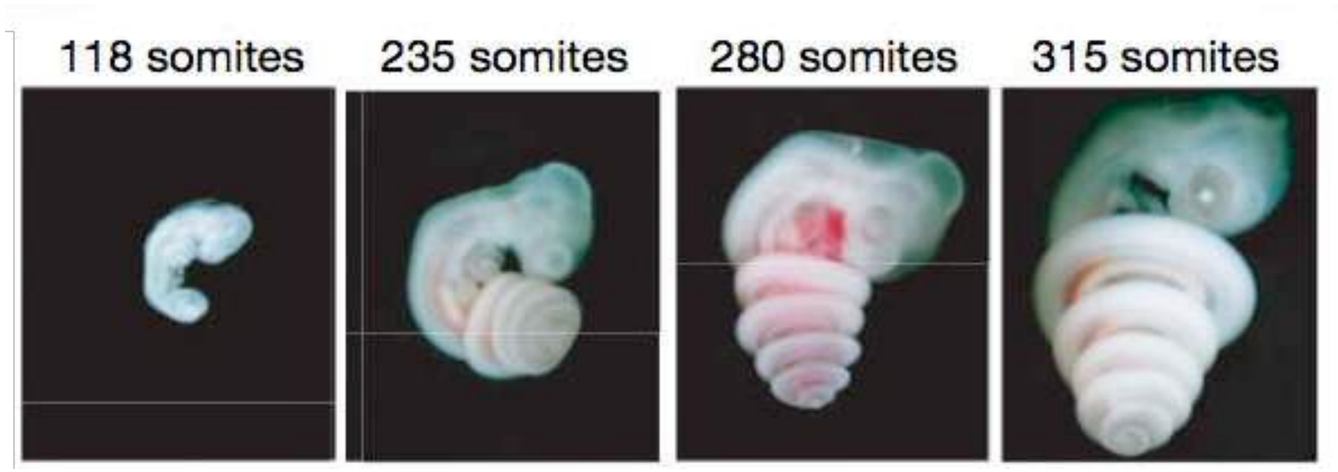
(Böhmer et al., 2015 *Evol Dev*)

(Cohn and Tickle, 1999 *Nature*)

The AP axis formation in *Drosophila* and vertebrates is fundamentally different



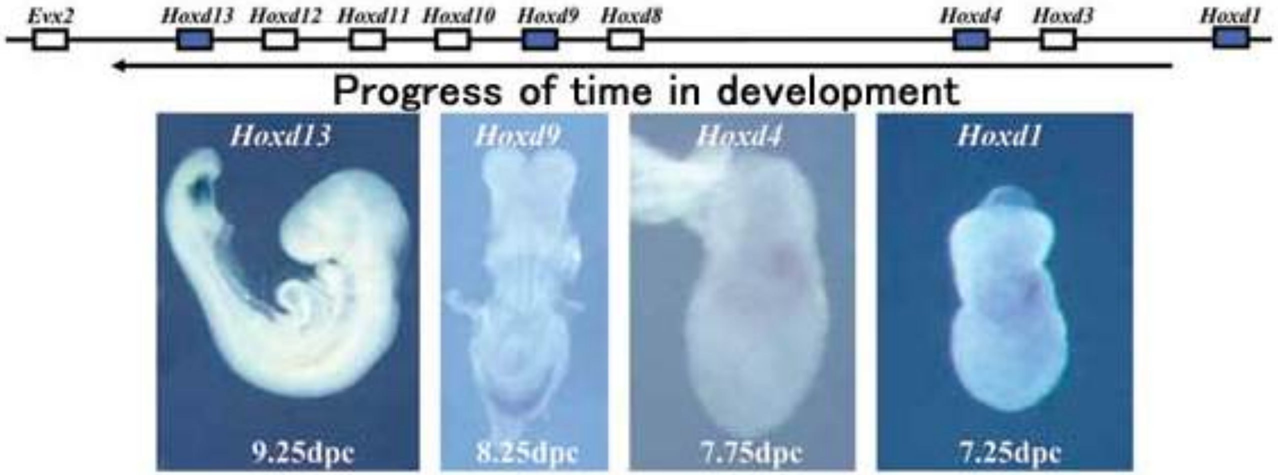


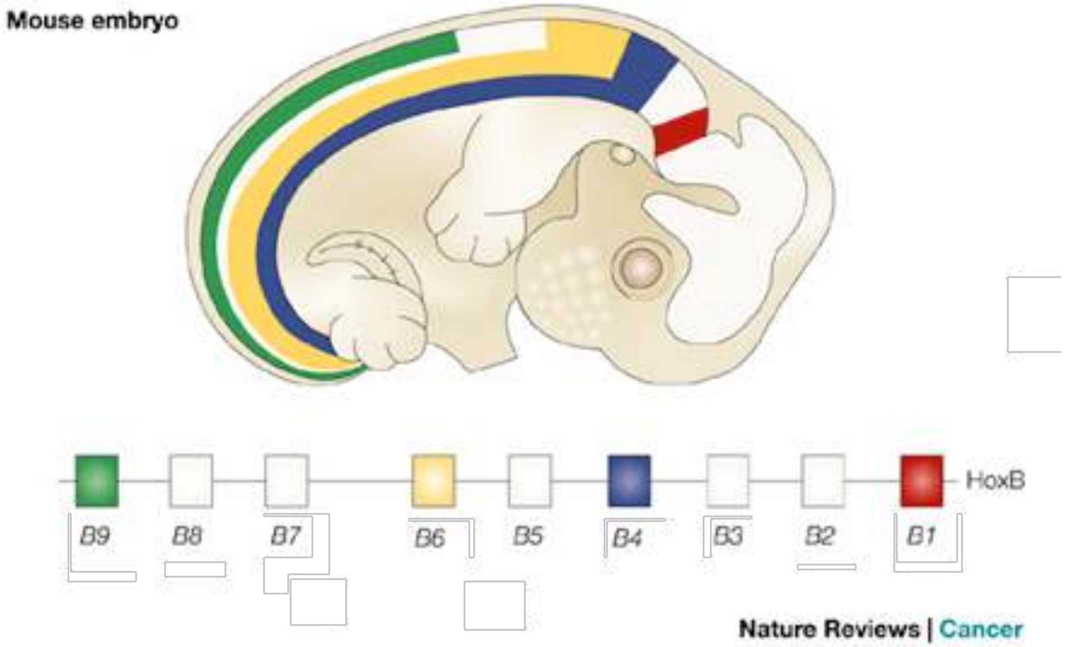


In a *Drosophila* embryo the primordia of all future segments are present from the very beginning (this is not general even for insects = "long germ insect")

In vertebrates by the end of gastrulation only the anterior structures are specified and later segments arise from the growth zone of the embryonic tailbud.

Hox genes and colineartity

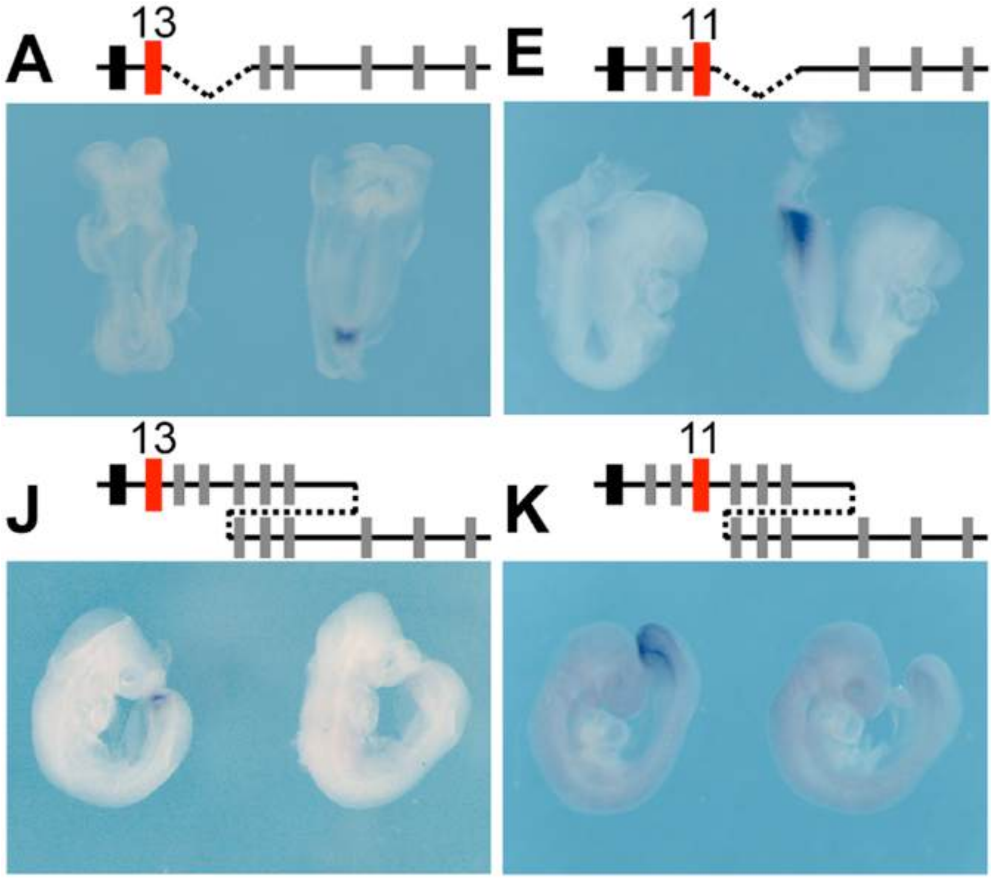




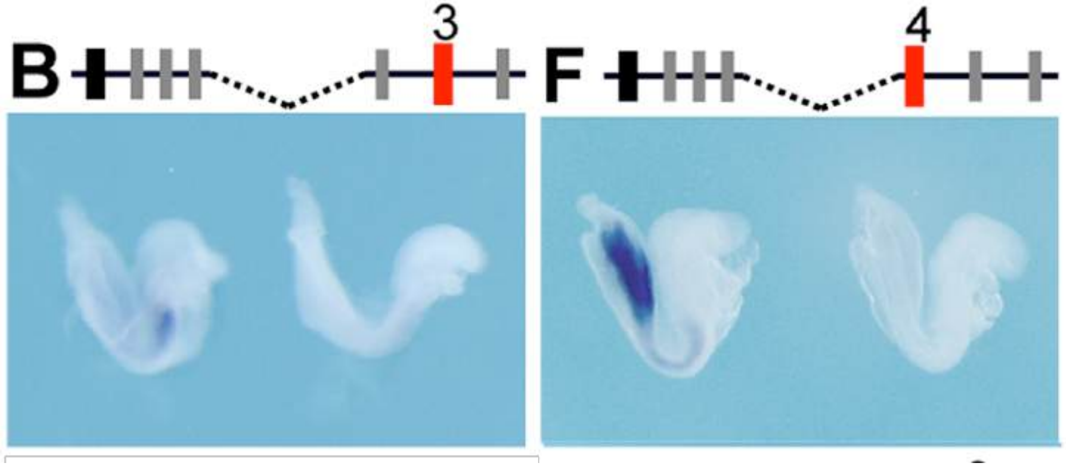
- **Temporal colinearity**: *Hox* genes that more 3' in the cluster are expressed earlier

- **Spatial colinearity**: *Hox* genes that more 3' in the cluster are expressed more anteriorly

Temporal colinearity is dependent on the relative position to the telomeres and centromeres



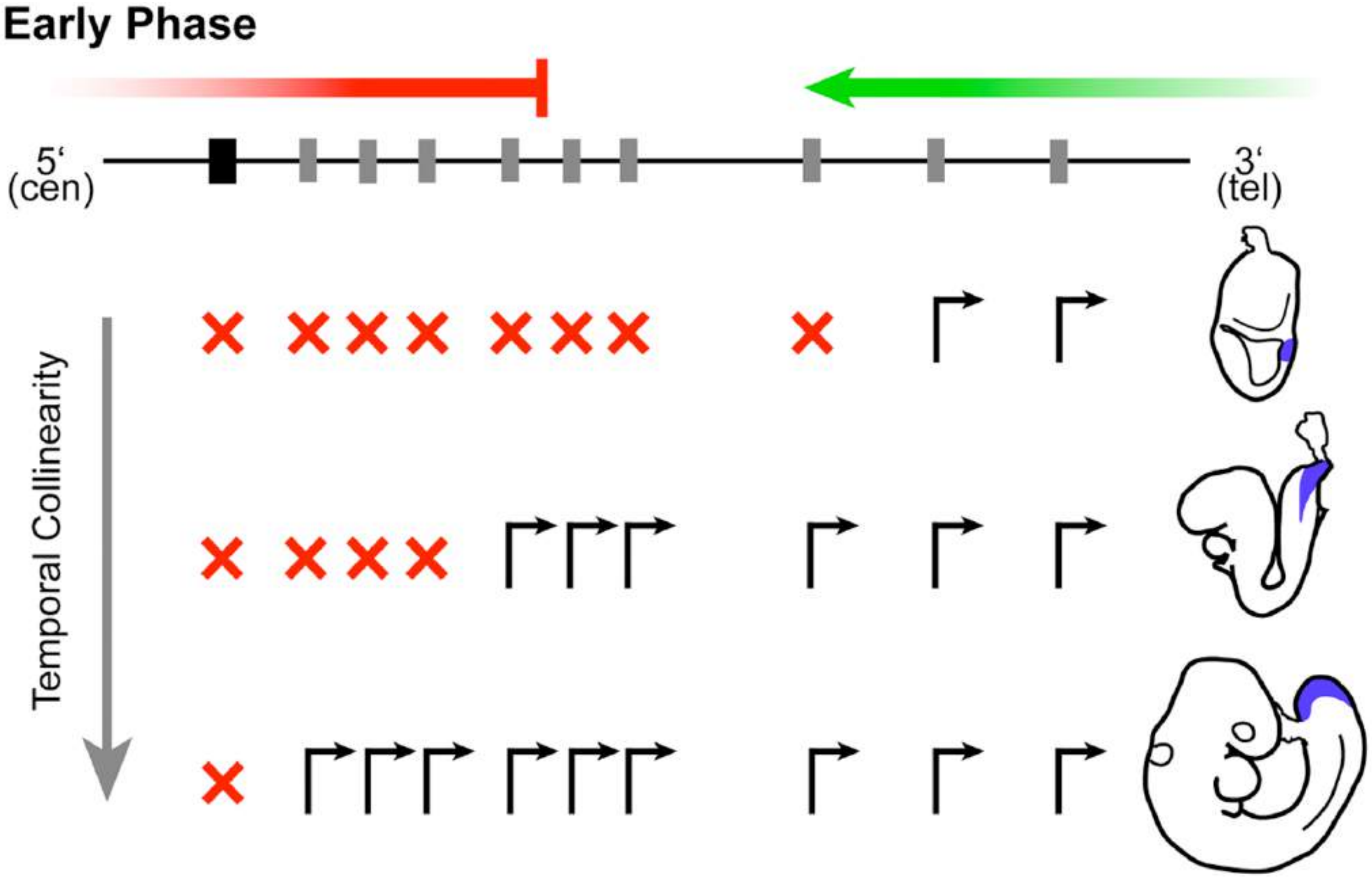
The closer the telomere, the faster the activation of a given *Hox* gene can be observed.



The proximity of the centromere inhibits *Hox gene expression.*

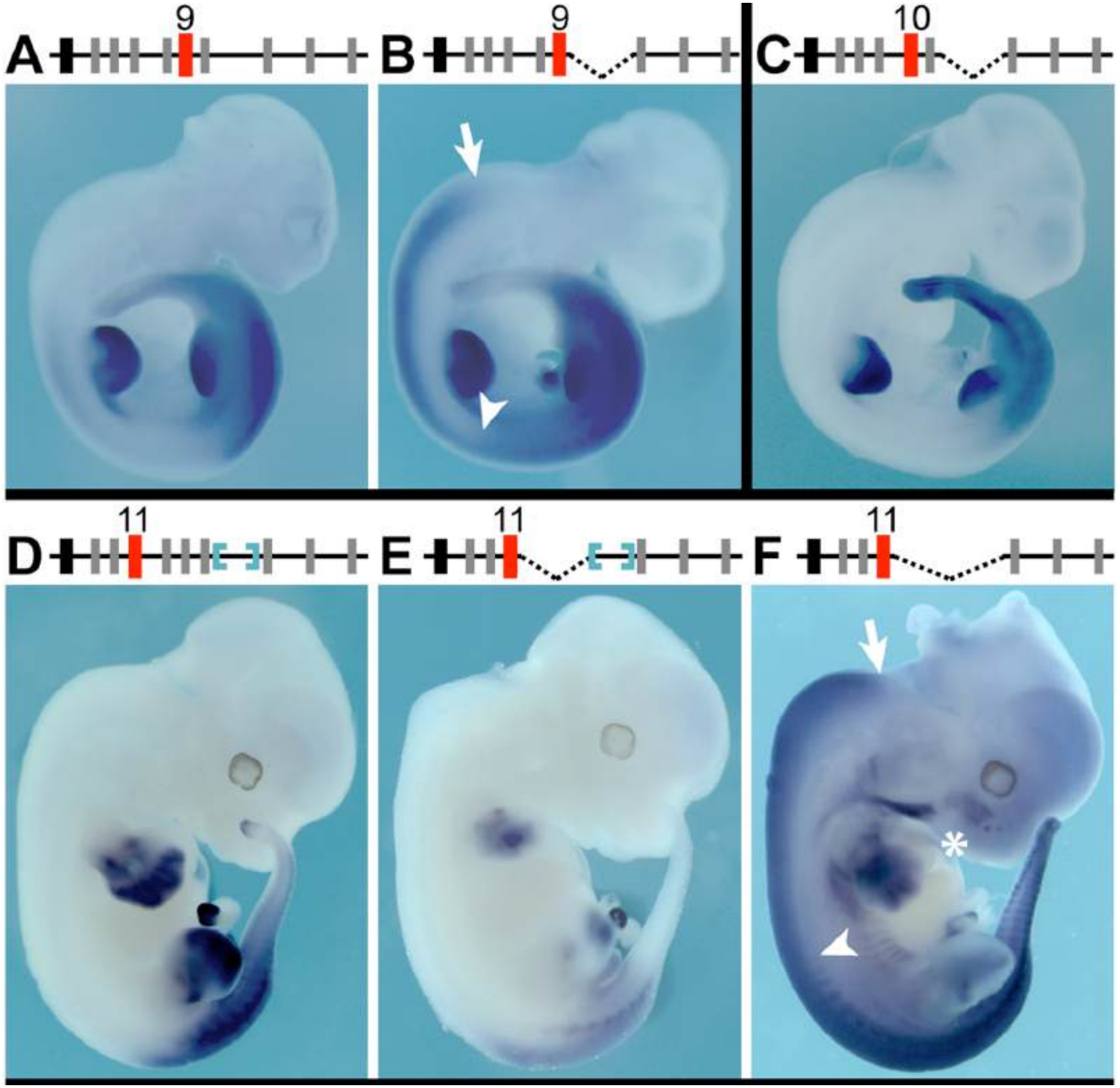
(Tschopp et al., 2009 *PLoS Gen)*

Temporal colinearity is dependent on the relative position to the telomeres and centromeres



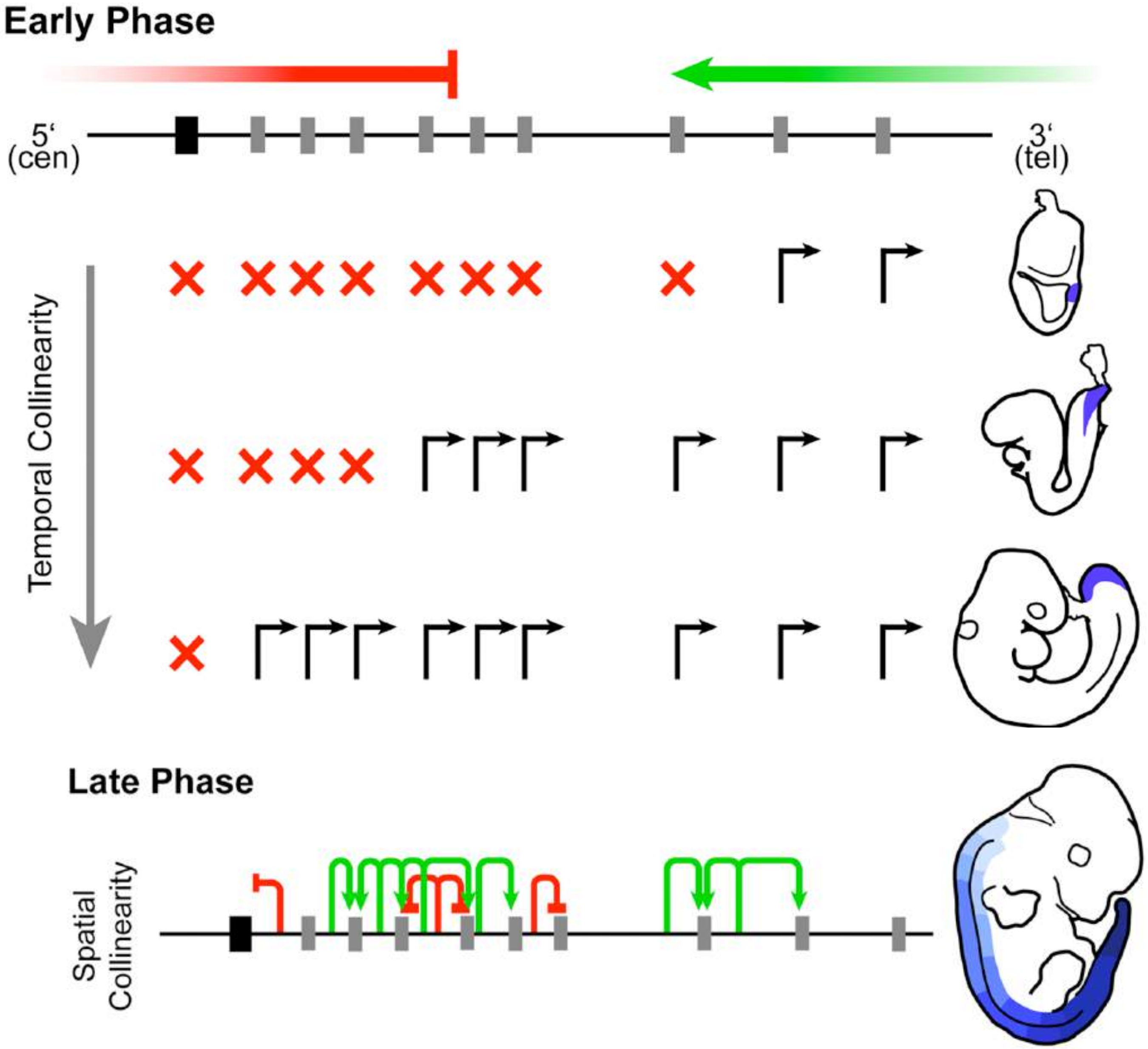
(Tschopp et al., 2009 *PLoS Gen)*

Spatial colinearity is dependent on local interactions



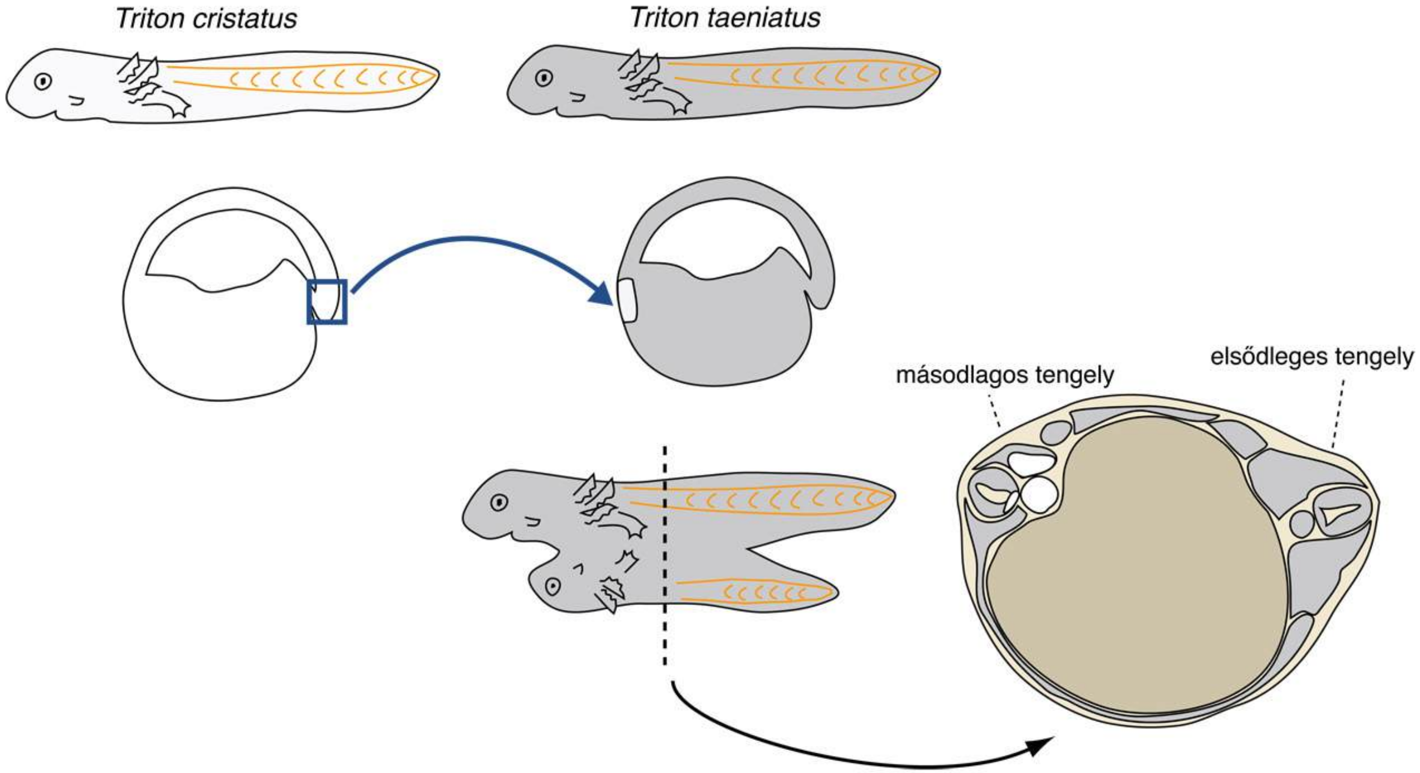
(Tschopp et al., 2009 *PLoS Gen)*

Spatial colinearity is dependent on local interactions



(Tschopp et al., 2009 *PLoS Gen)*

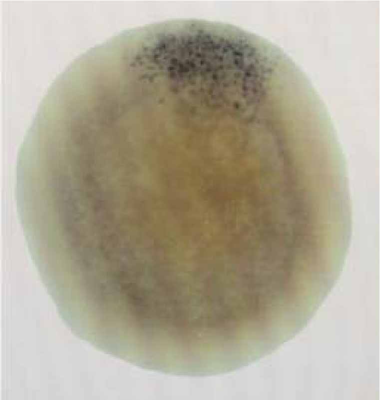
The Spemann-Mangold experiment and the discovery of the dorsal organizer (1924)



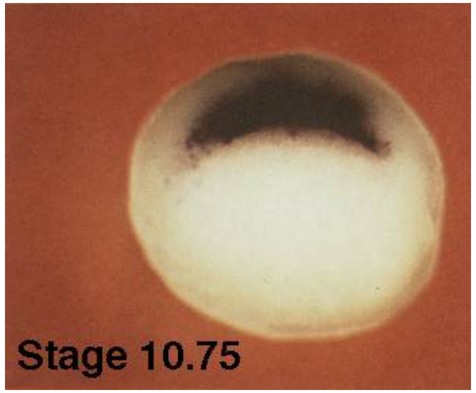
Hilde
Mangold
(née Pröschold)

Hans
Spemann

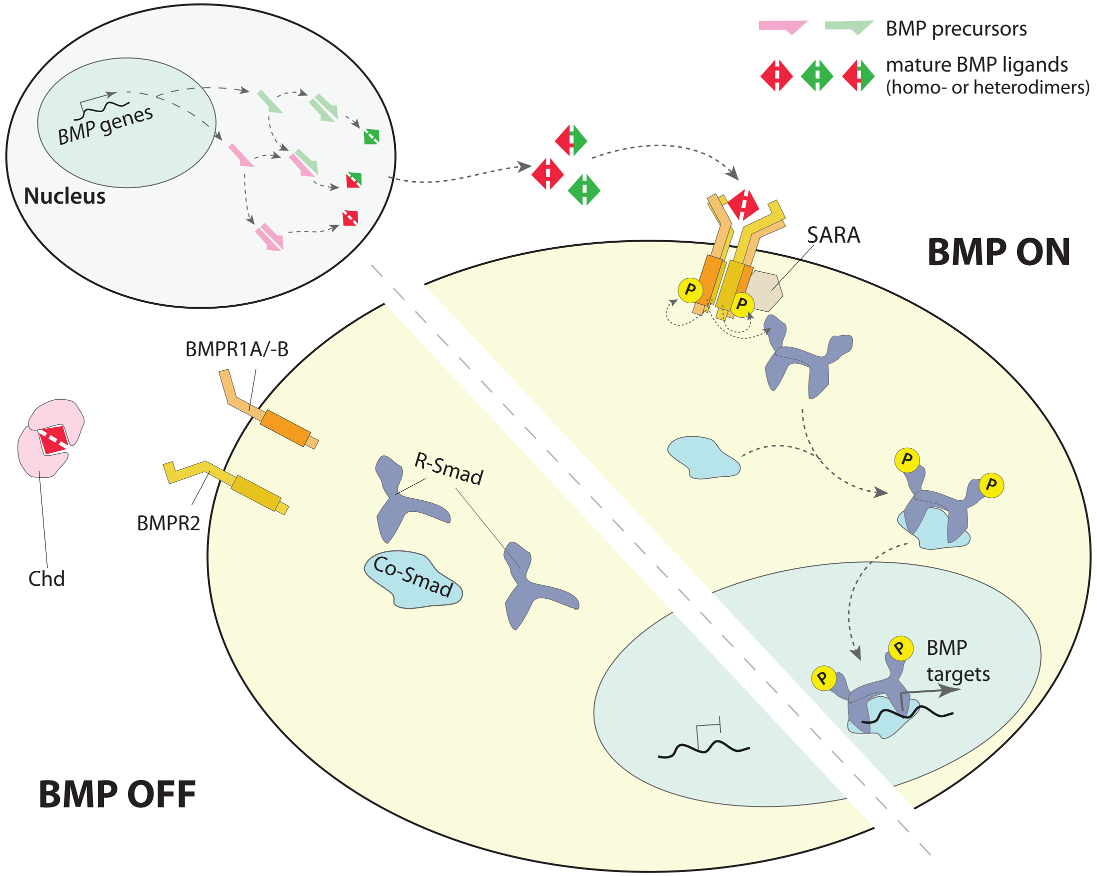
The Spemann-Mangold organizer expresses BMP antagonists



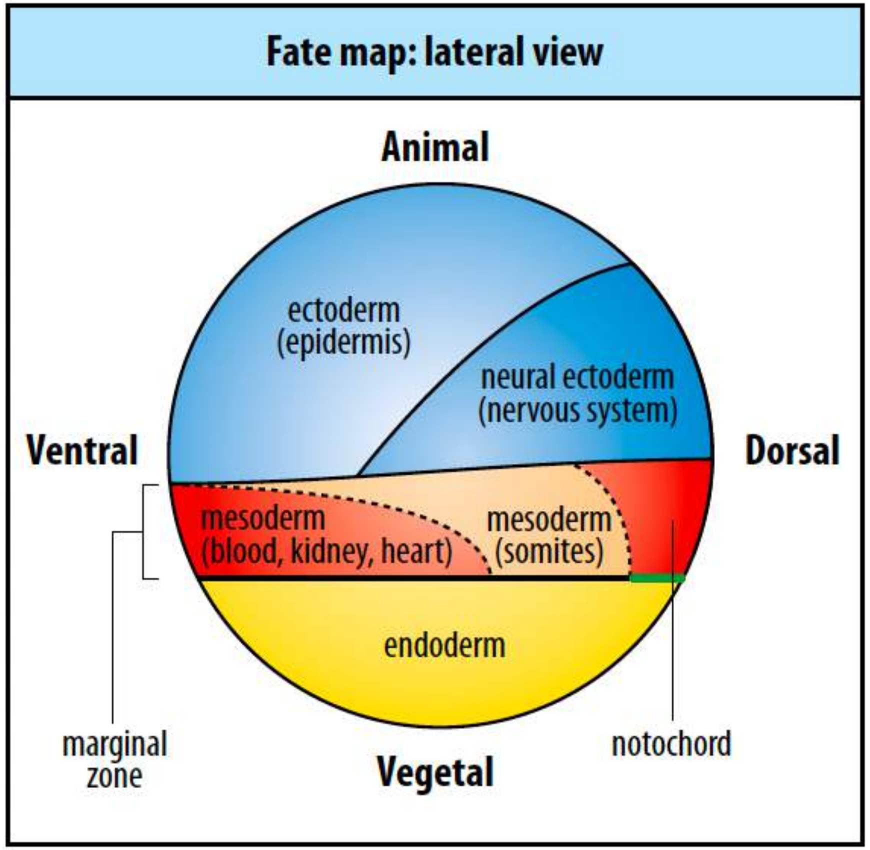
noggin
Smith and Harland (1992)

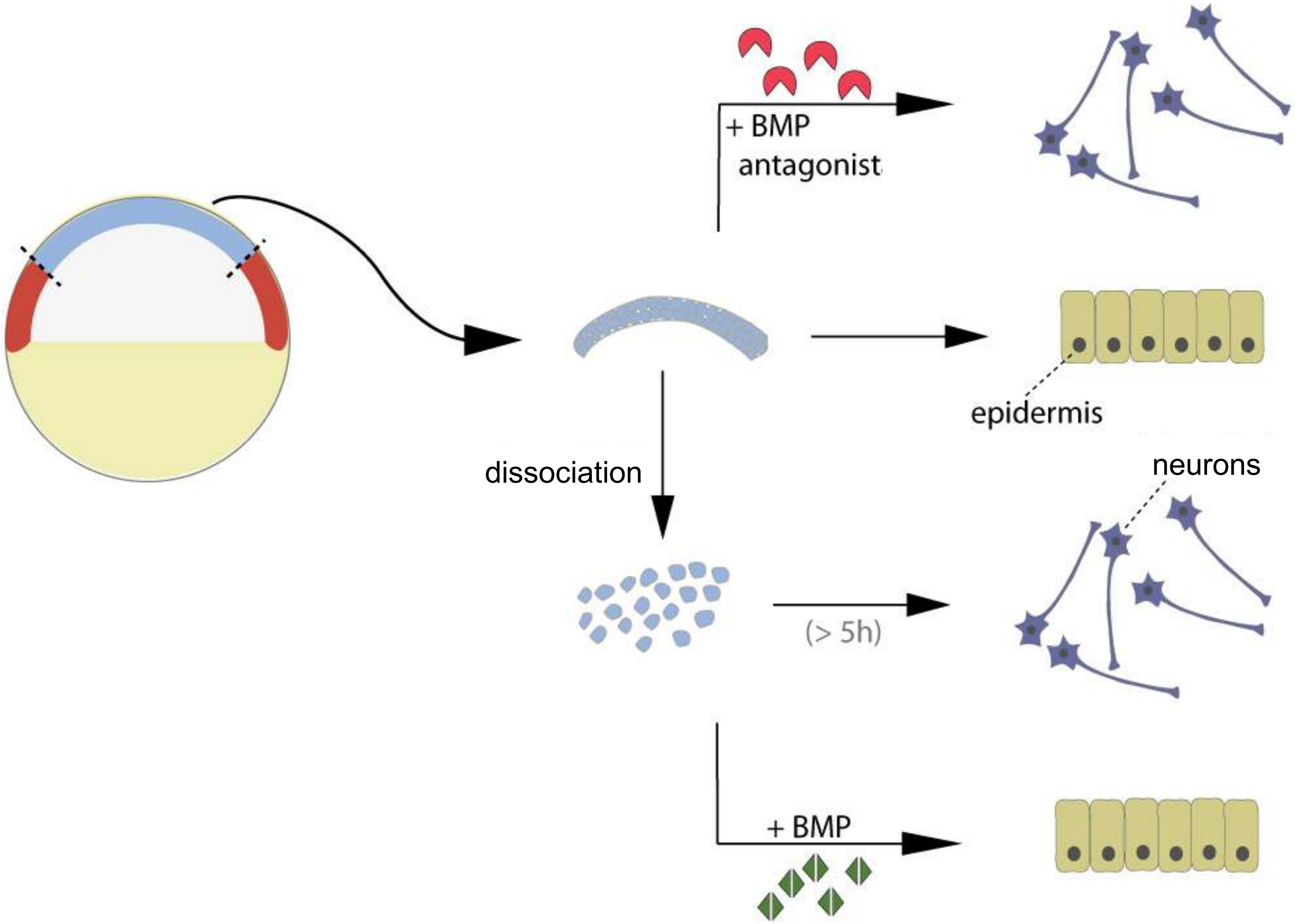


chordin - Sasai et al. (1994)



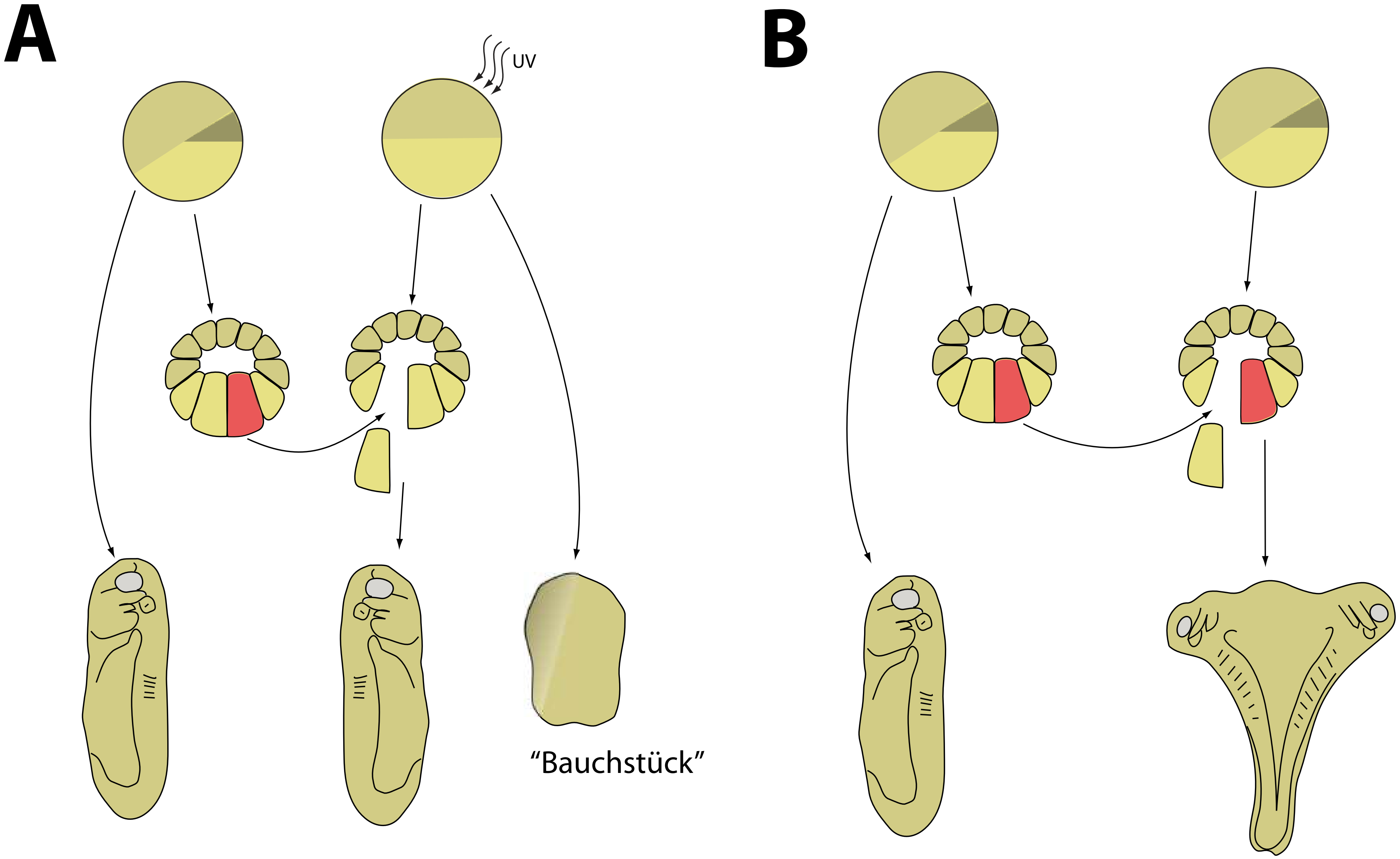
The role of BMPs in the specification of the future nervous system





(*Principles of Development*)

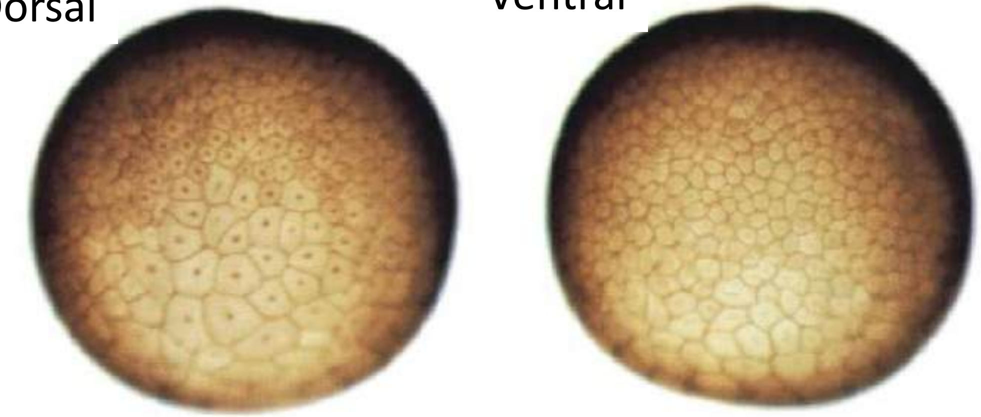
The Nieuwkoop centre and the origins of dorso-ventral (DV) polarity



Ectopic induction of canonical Wnt-pathway mimics the organizer

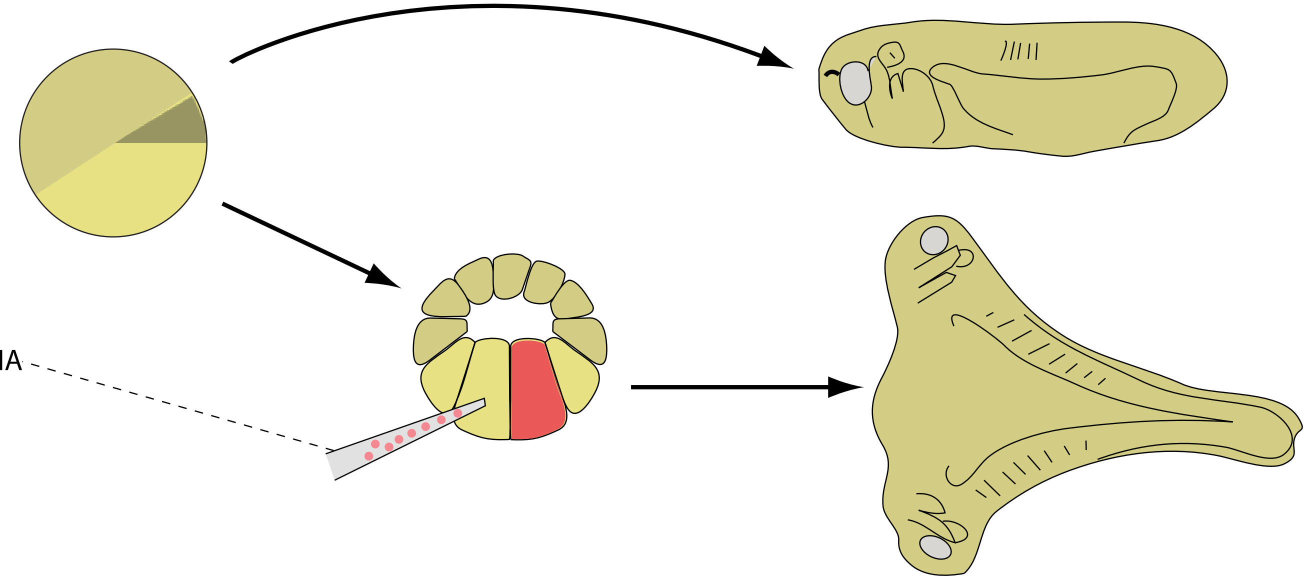
Dorsal

Ventral

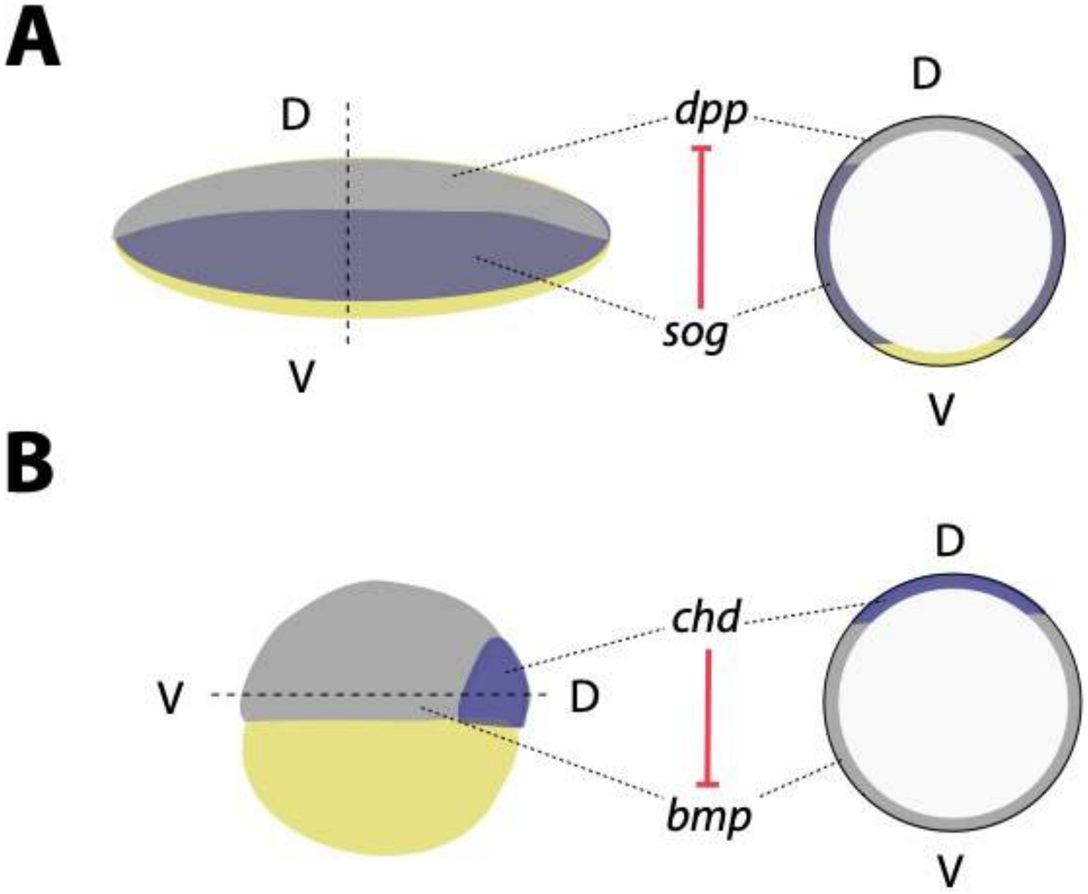


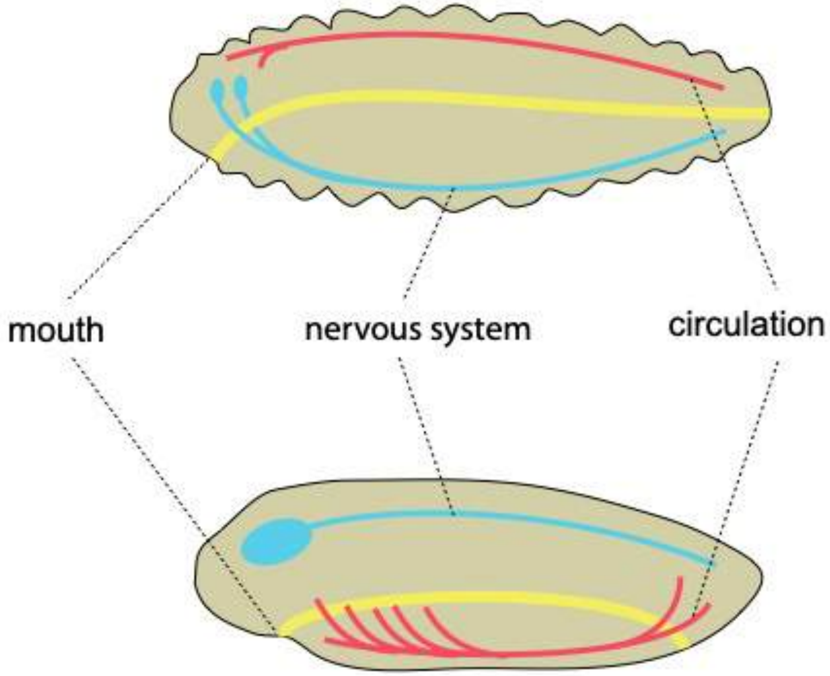
Nuclear β-catenin

Membrane β-catenin

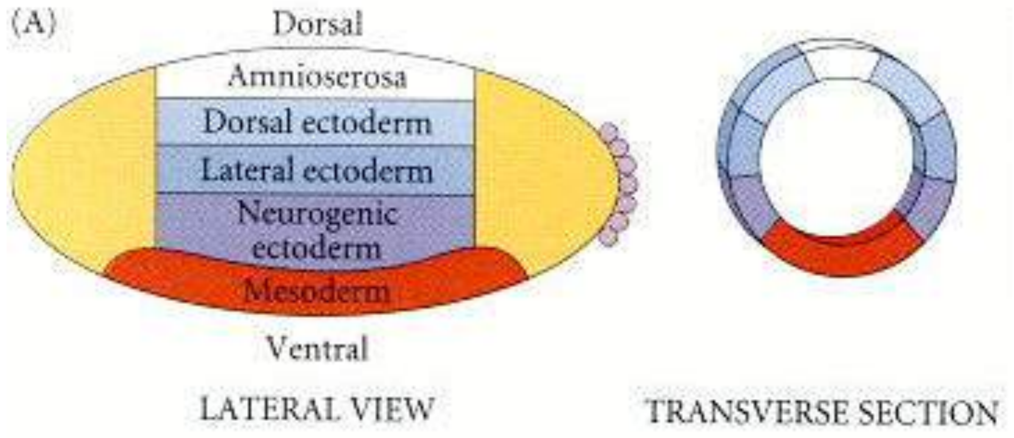


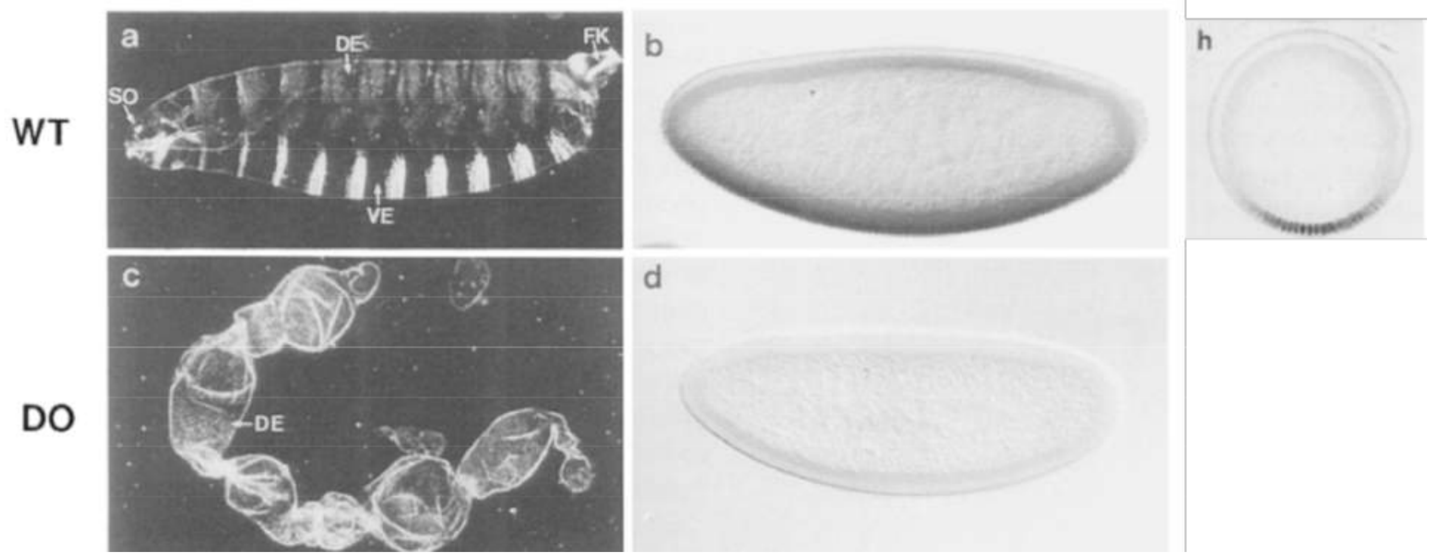
The urbilaterian origin of DV patterning mechanisms

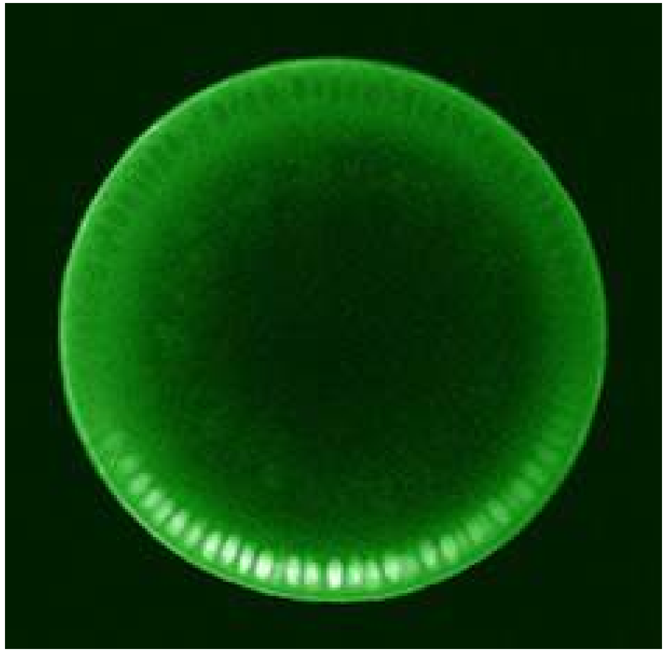




The urbilaterian origin of DV patterning mechanisms





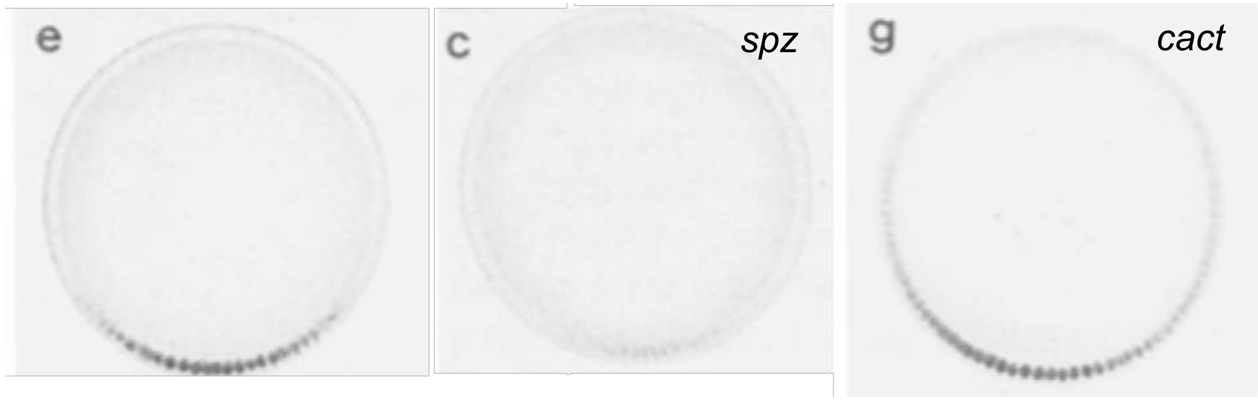


Dorsal is present in all cells, but it is nuclear only in the cells of the ventral side

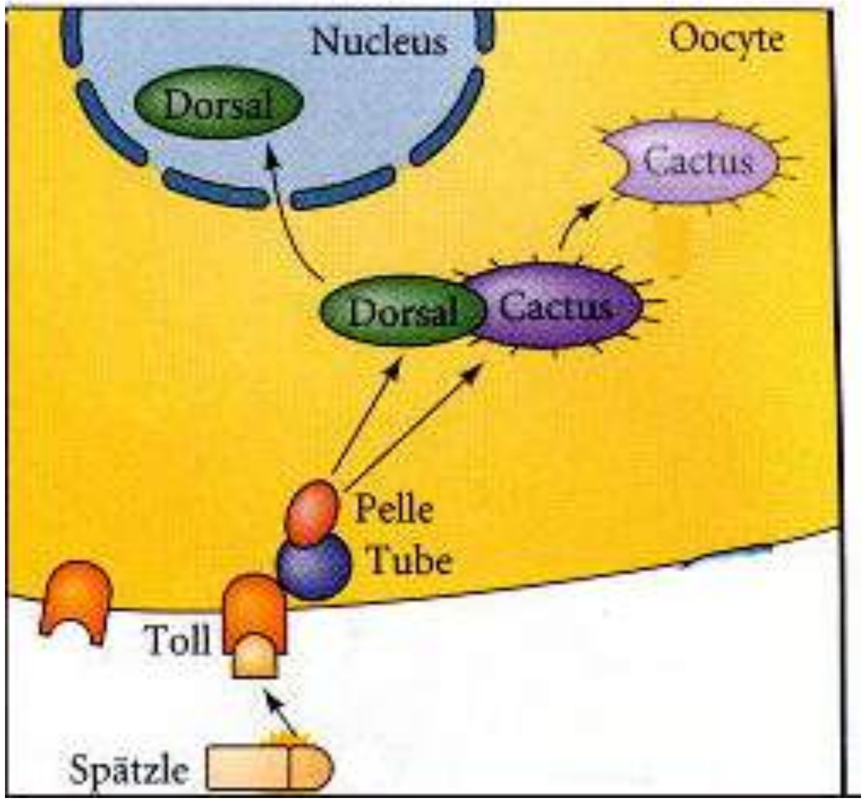
(Roth et al., 1989 *Cell)*

spätzle (spz) and cactus (*cact*) – regulators of *dorsal*

Localisation of Dorsal in DV mutants



(Roth et al., 1989 *Cell)*



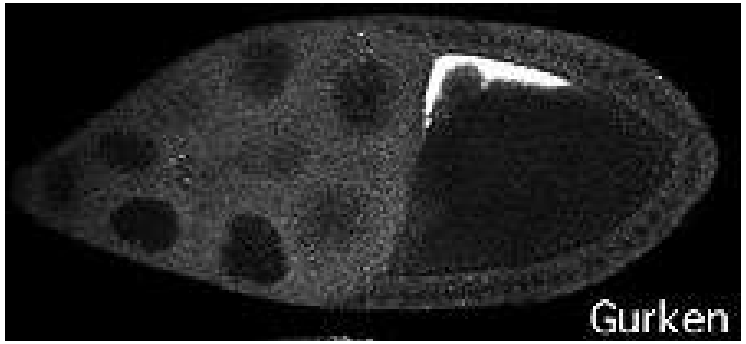
- Dorsal and Cactus are the *Drosophila* orthologs of NF-Kβ and IF-Kβ
- Extracellular cleavage of Spätzle is necessary for its function

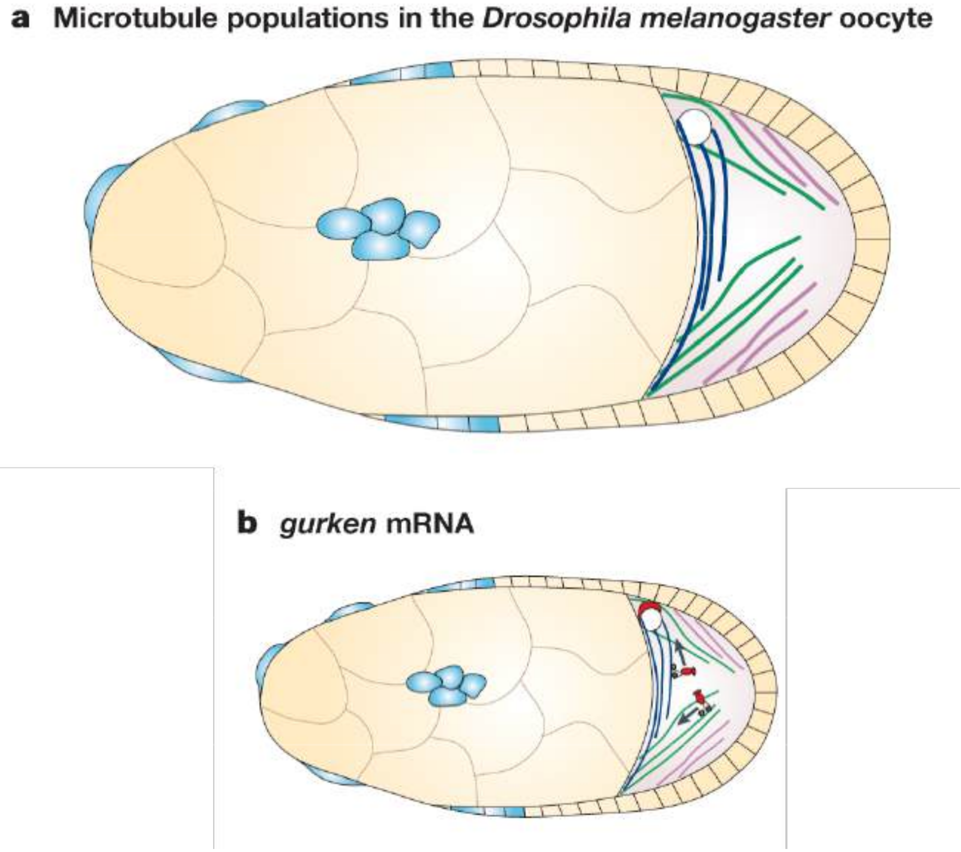
  => The follicular cells surrounding the oocytes also have an important role in DV axis formation!

Maternal determination of the future dorsal side by *gurken*

gurken mRNA

Gurken protein





(StJohnston, 2005 *Nat Rev Mol Cell Bio*)

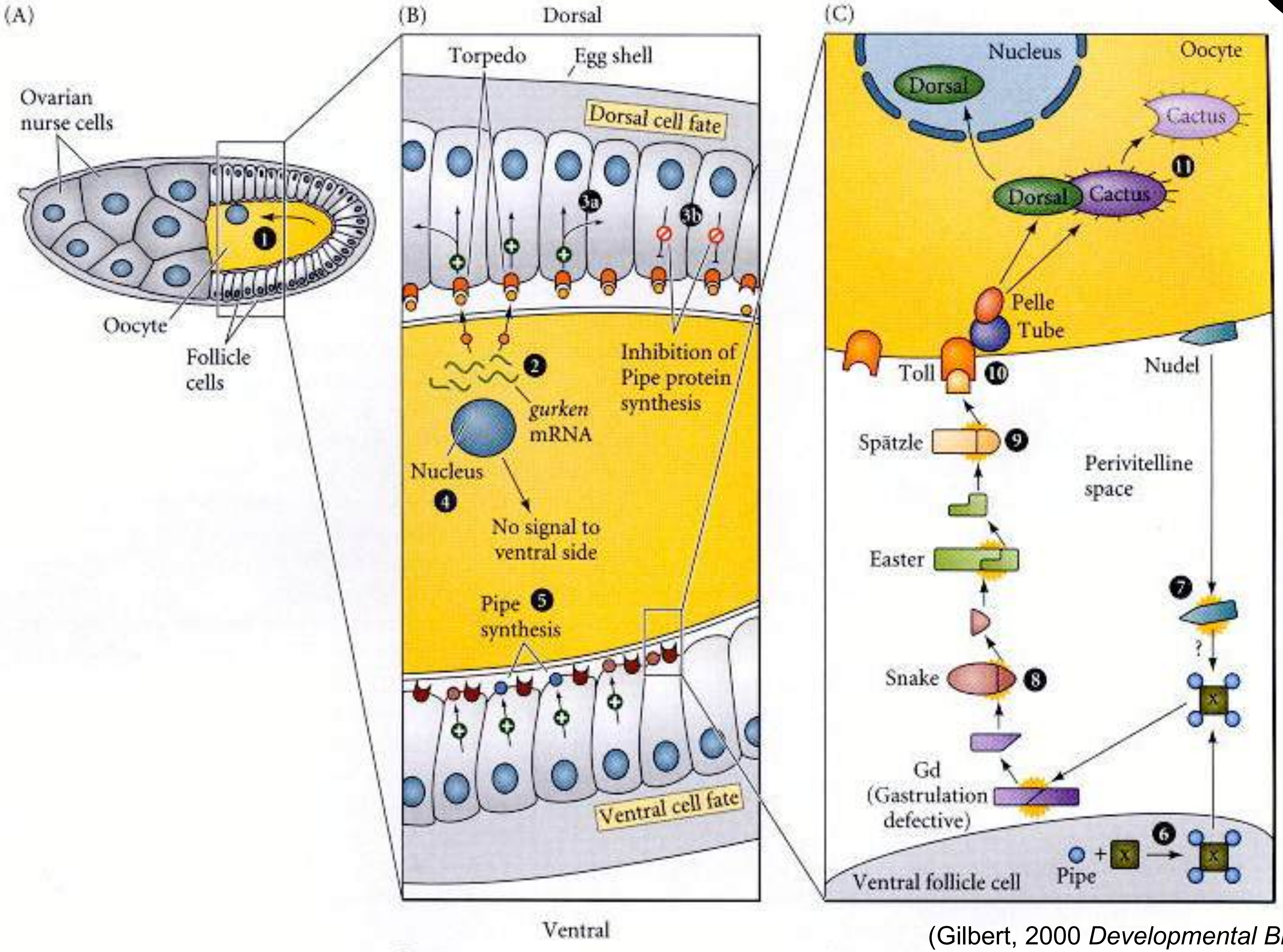
The genetics of *Drosophila* DV polarity

1. Oocyte nucleus travels to anterior dorsal side of oocyte. It synthesizes *gurken* mRNA which remains between the nucleus and the follicle cells.
2. *gurken* messages are translated. The Gurken protein is received by Torpedo proteins during mid-oogenesis.

3a. Torpedo signal causes follicle cells to differentiate to a dorsal morphology.

3b. Synthesis of Pipe protein is inhibited in dorsal follicle cells.

4. Gurken protein does not diffuse to ventral side.
5. Ventral follicle cells synthesize Pipe proteins.
6. In ventral follicle cells, Pipe completes the modification of unknown factor (x).
7. Nudel and factor (x) interact to split the Gastrulation-deficient (Gd) protein.
8. The activated Gd protein splits the Snake protein, and the activated Snake protein cleaves the Easter protein.
9. The activated Easter protein splits Spätzle; activated Spätzle binds to Toll receptor protein.
10. Toll activation activates Tube and Pelle, which phosphorylate the Cactus protein. Cactus is degraded, releasing it from Dorsal.
11. Dorsal protein enters the nucleus and ventralizes the cell.



(Gilbert, 2000 *Developmental Biology, 6th ed.*)