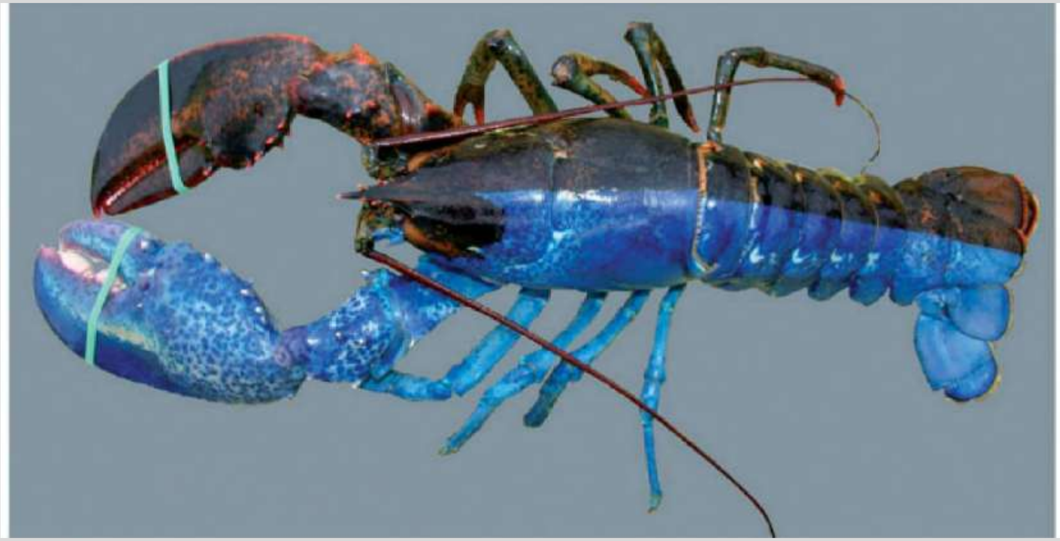
The genetics of body axis formation



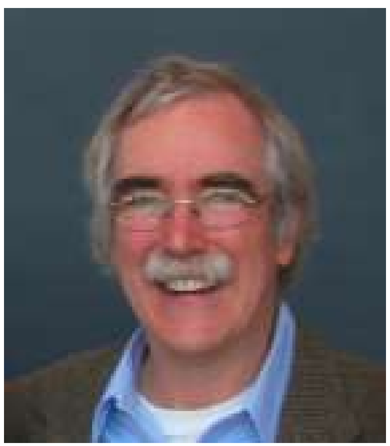
Máté Varga – ELTE Department of Genetics

mvarga@ttk.elte.hu

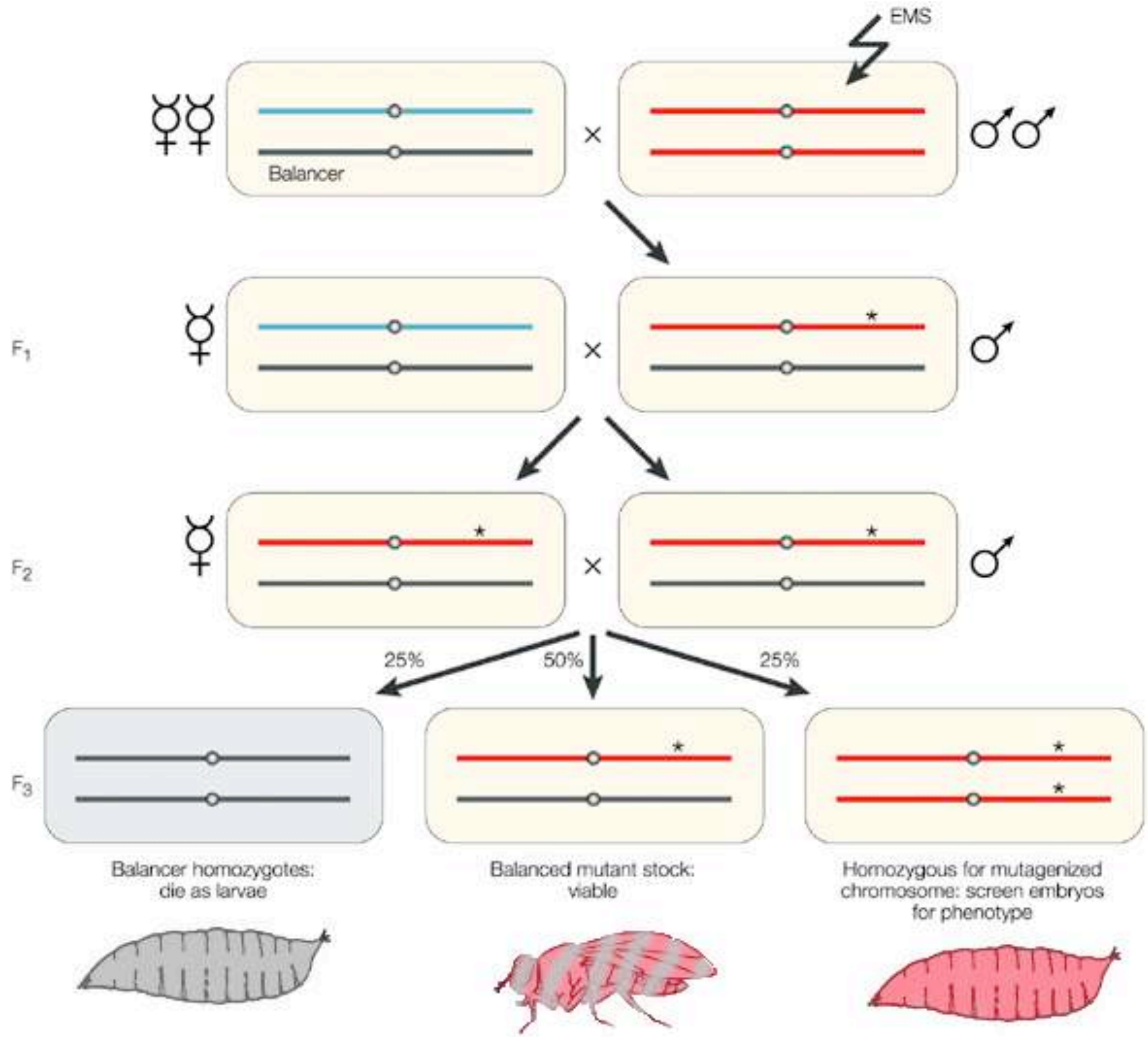
16.11.2022

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

Christiane Nüsslein-Volhard

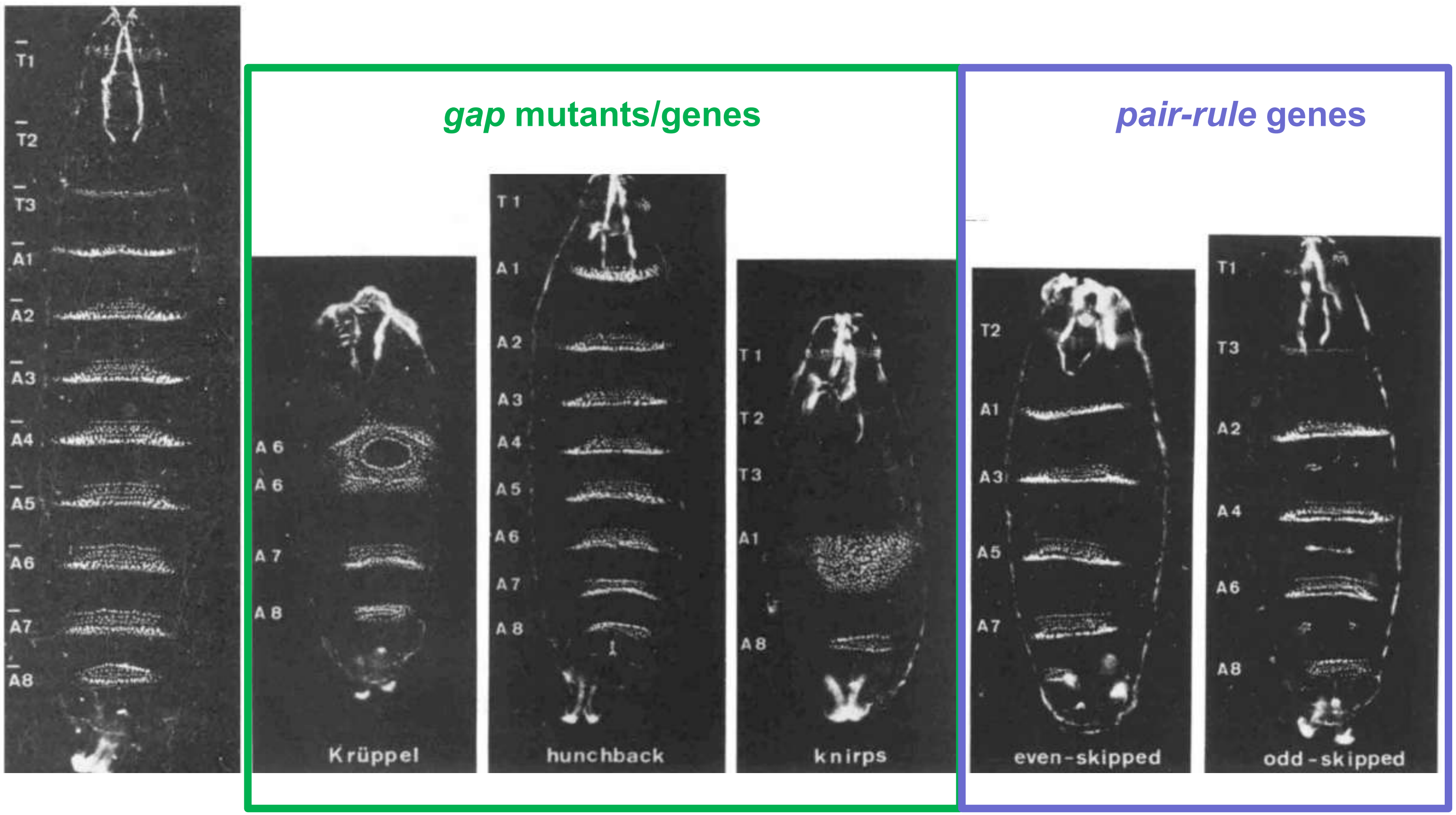


Eric Wieschaus



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

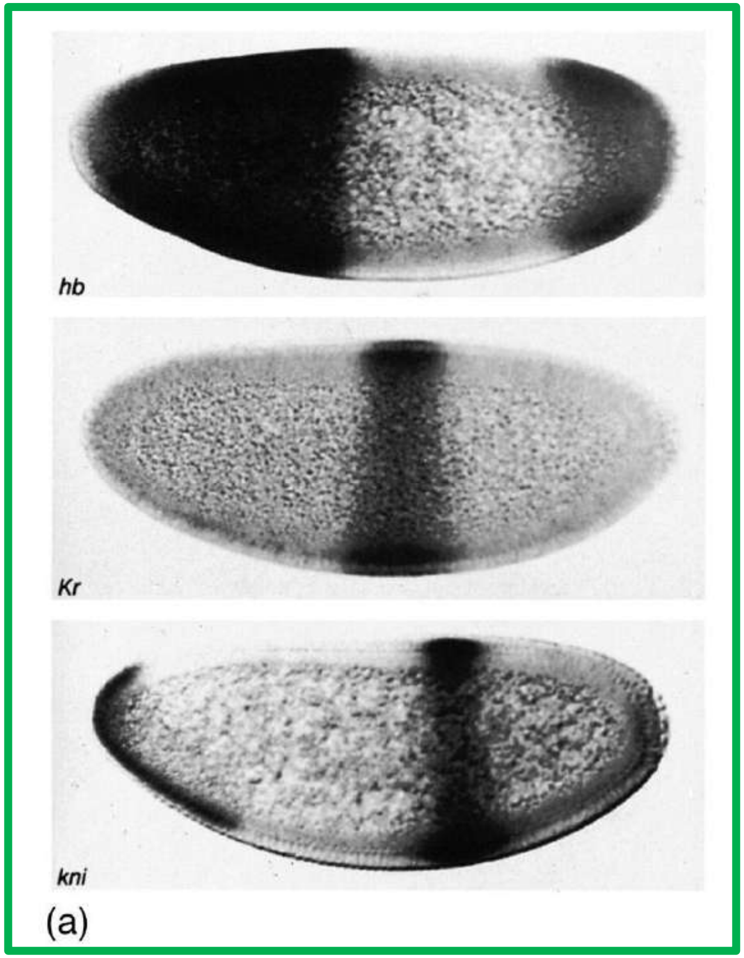
Zygotic genes involved in the formation of the antero-posterior (AP) axis



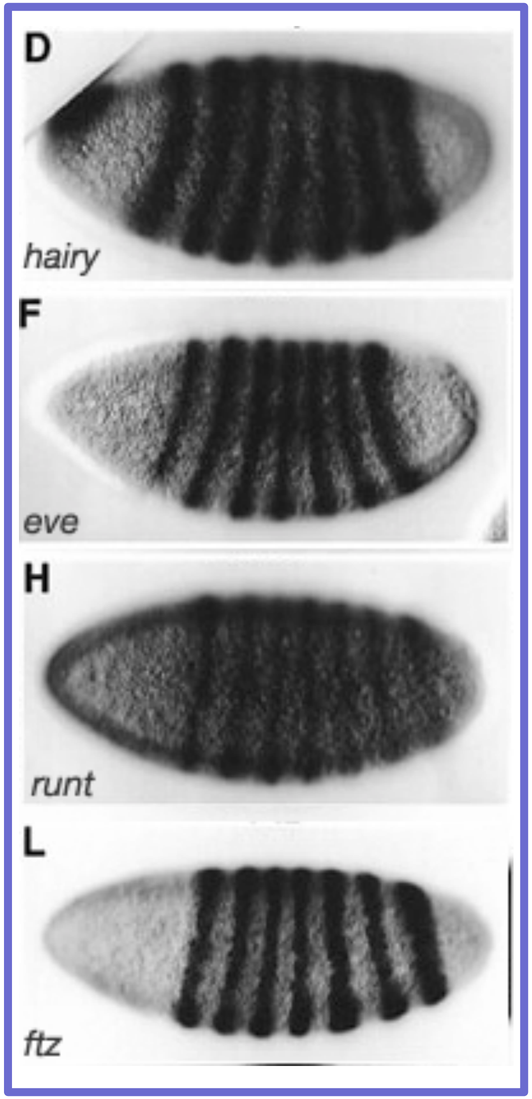
(Nüsslein-Volhard & Wieschaus (1980) *Nature*)

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

gap genes

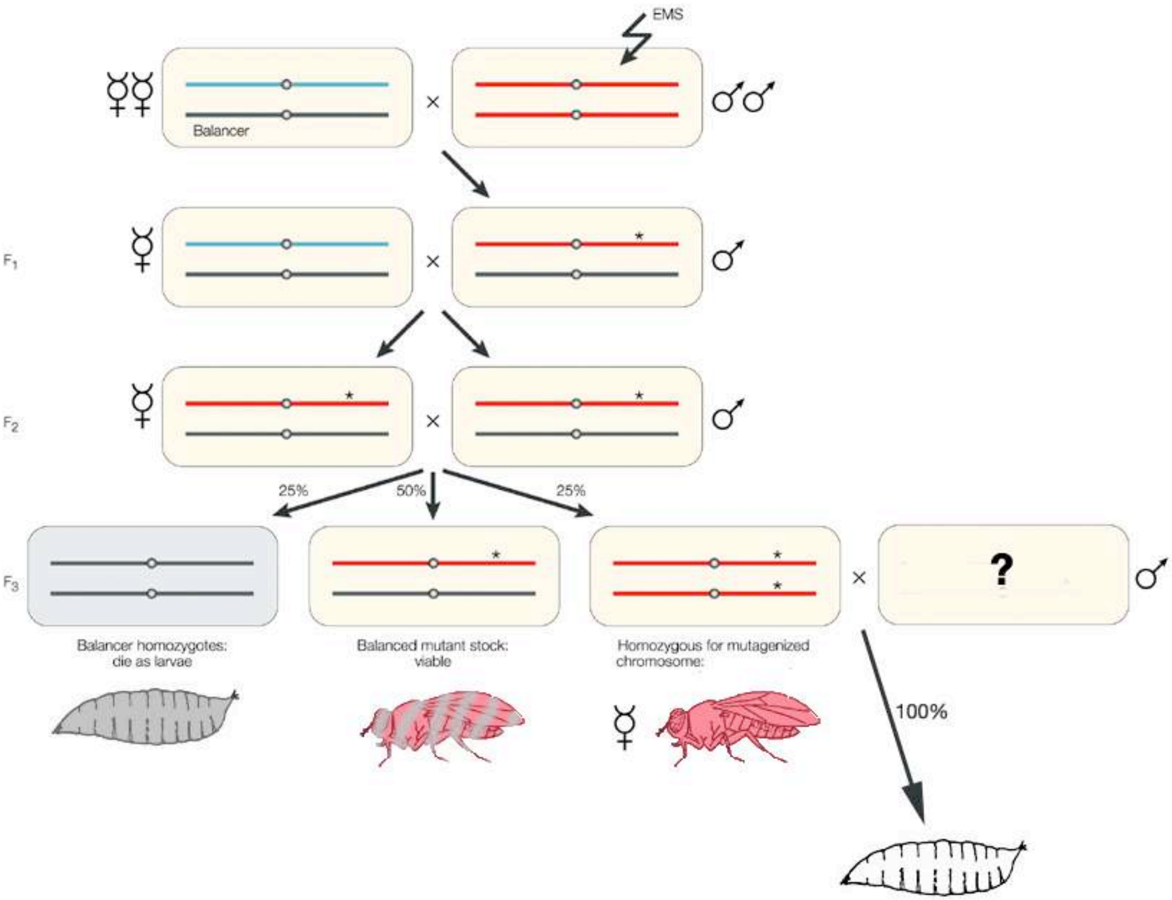


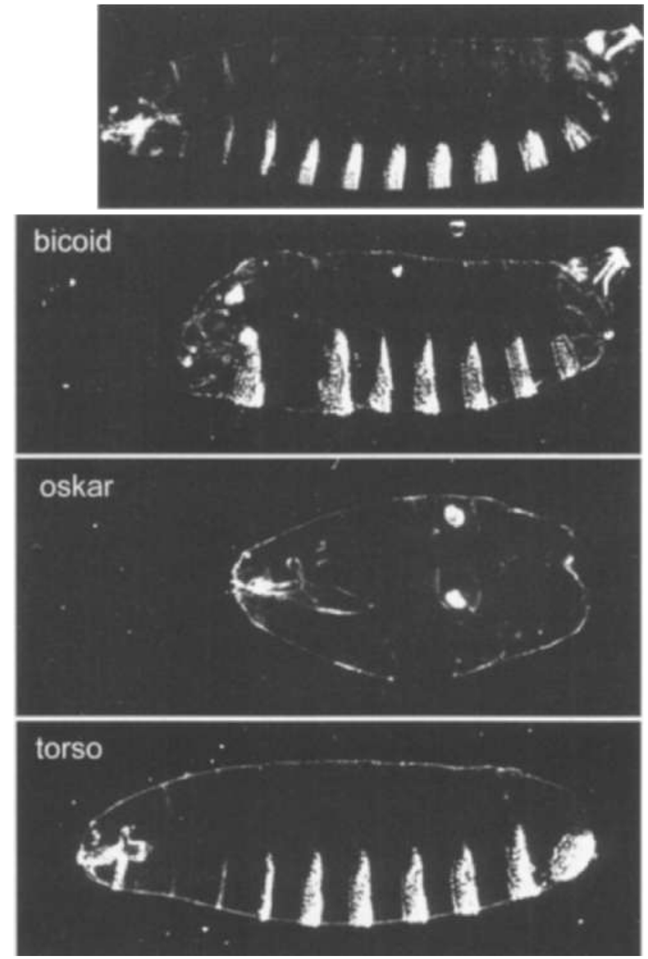
pair-rule genes



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

Looking for maternal mutants





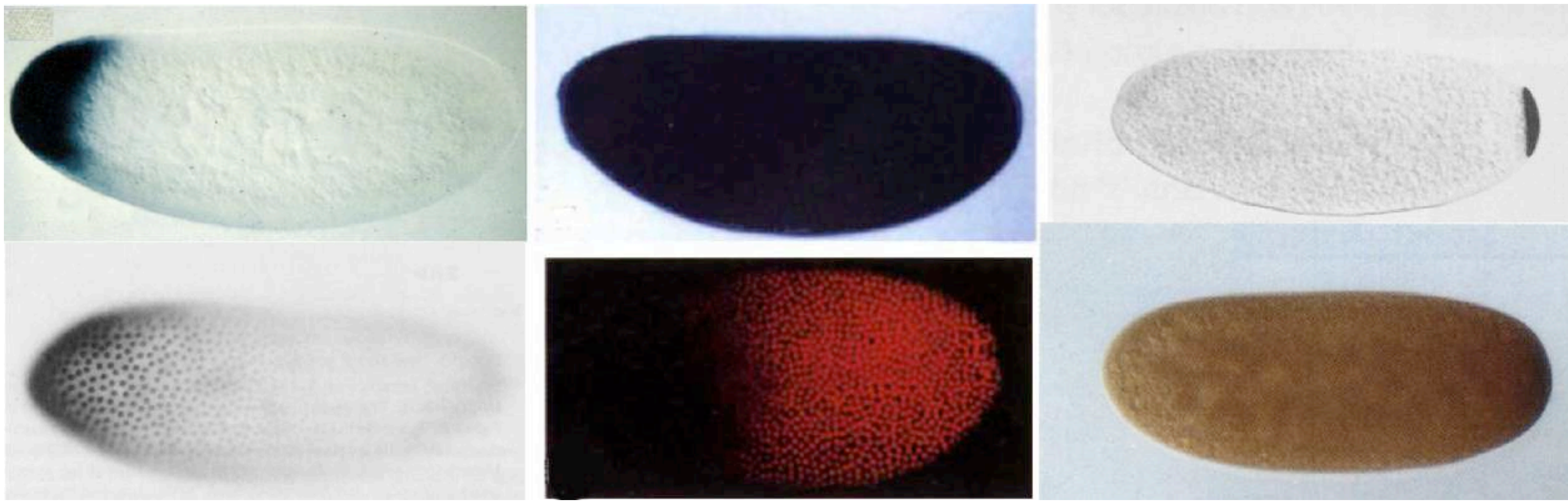
(Nüsslein-Volhard (2004) *Cell*)

Looking for maternal mutants

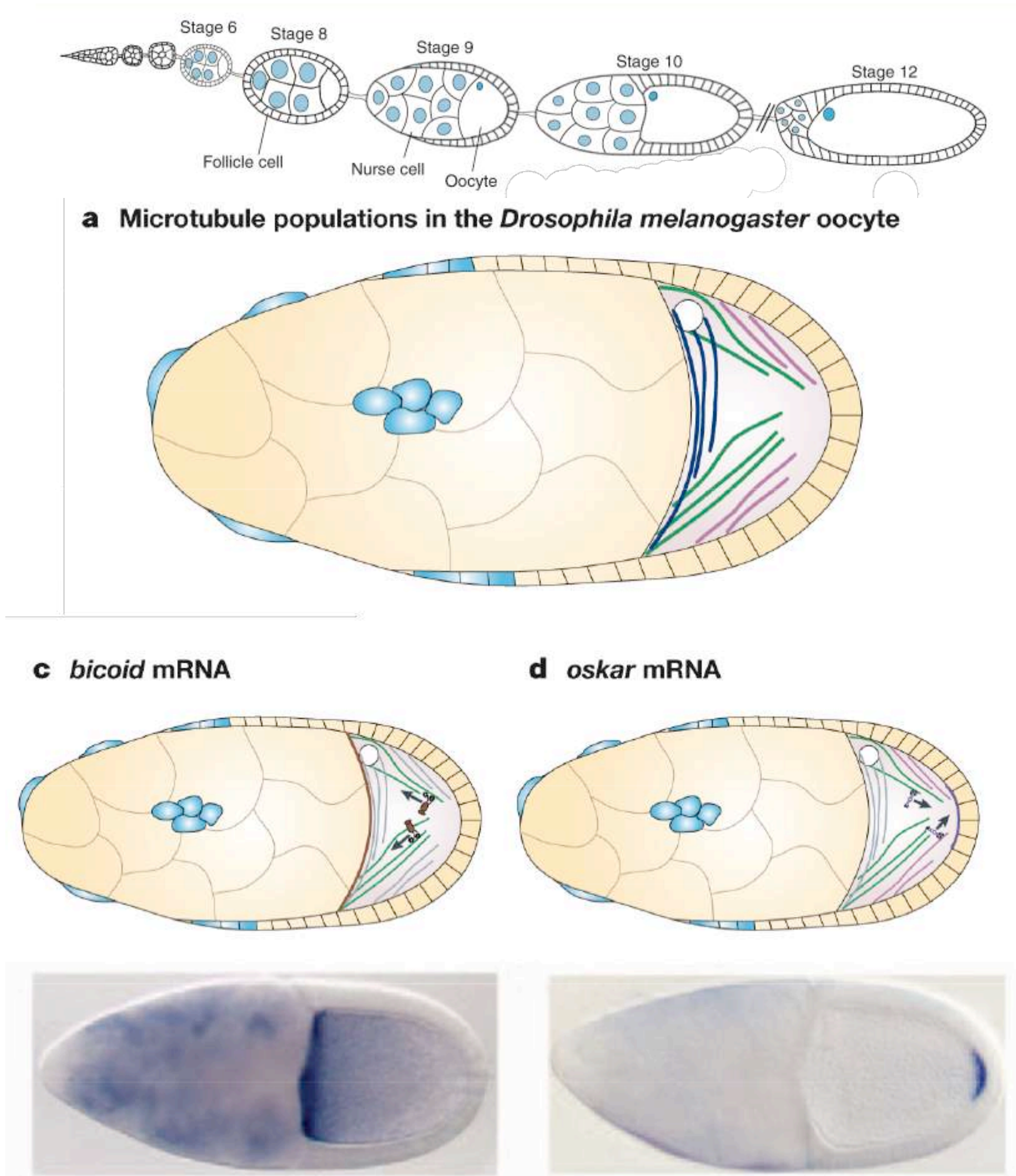
bicoid (bcd) | *caudal (cad)* | *nanos (nos)*

mRNA

protein



Localization of maternal mRNAs with the help of microtubules

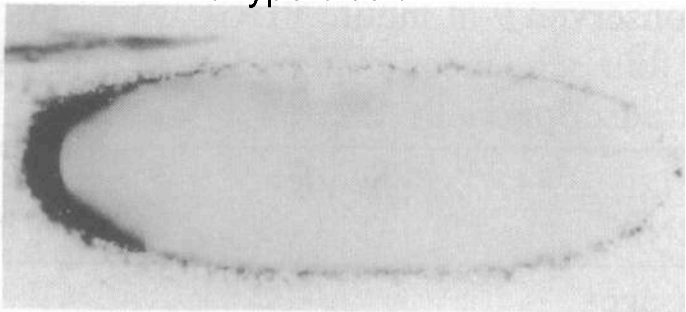


(*Drosophila* oogenesis)

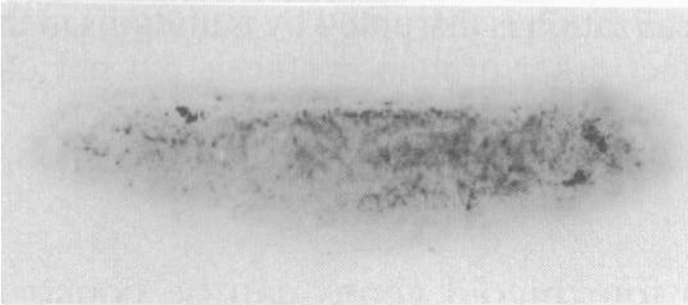
(St Johnston (2005) *Nat Rev Mol Cell Bio*)

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

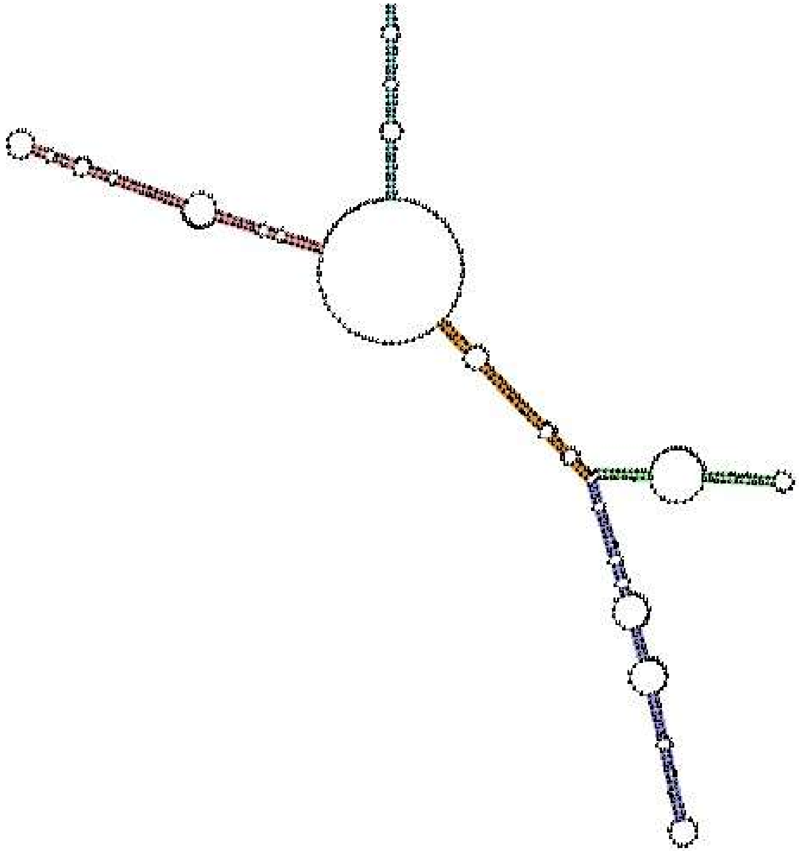
Wild type *bicoid* mRNA



No 3’ UTR *bicoid* mRNA



(Gottlieb et al. (1992) *PNAS*)



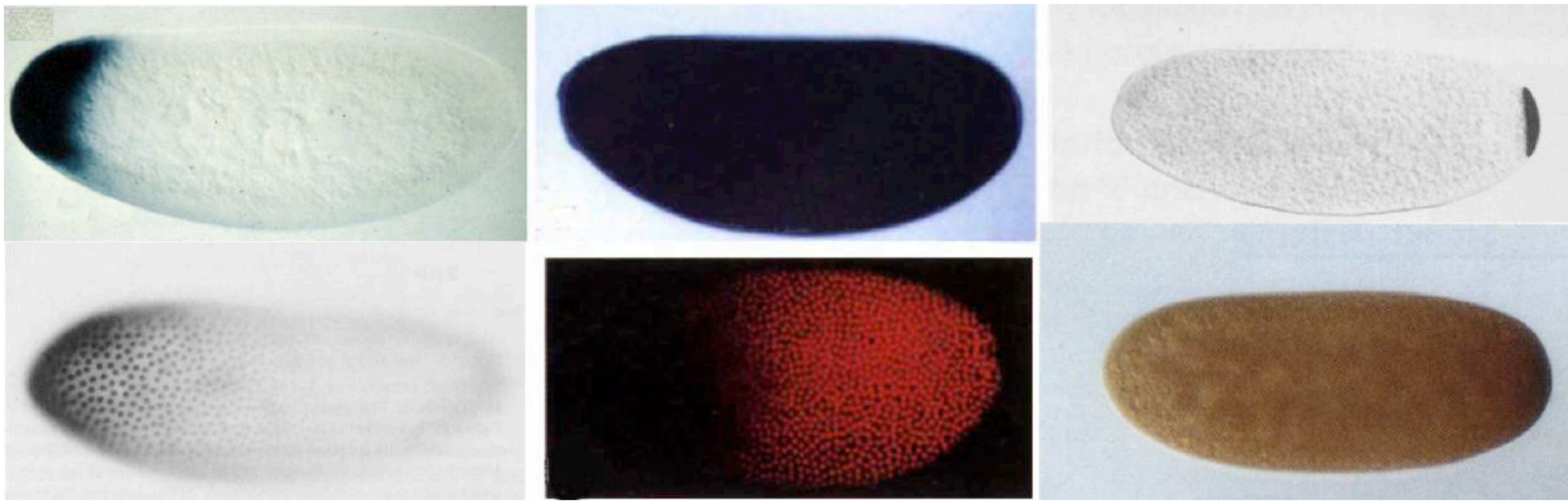
Secondary structure of the *bicoid* mRNA 3’ UTR

Looking for maternal mutants

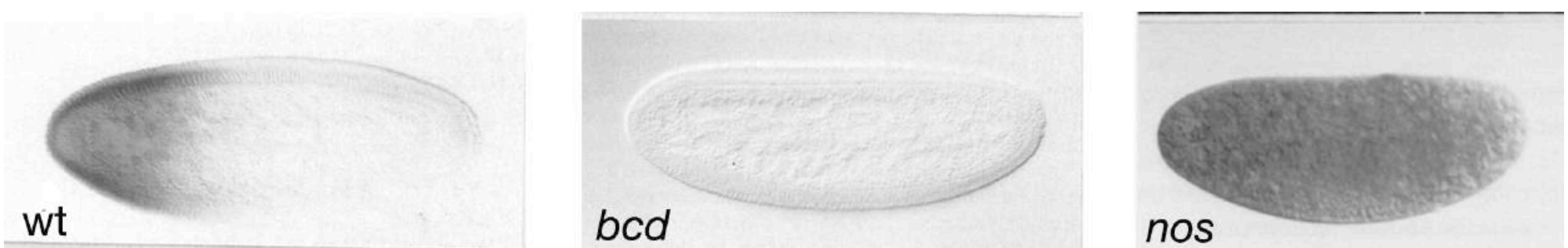
bicoid (bcd) *caudal (cad)* *nanos (nos)*

mRNA

protein

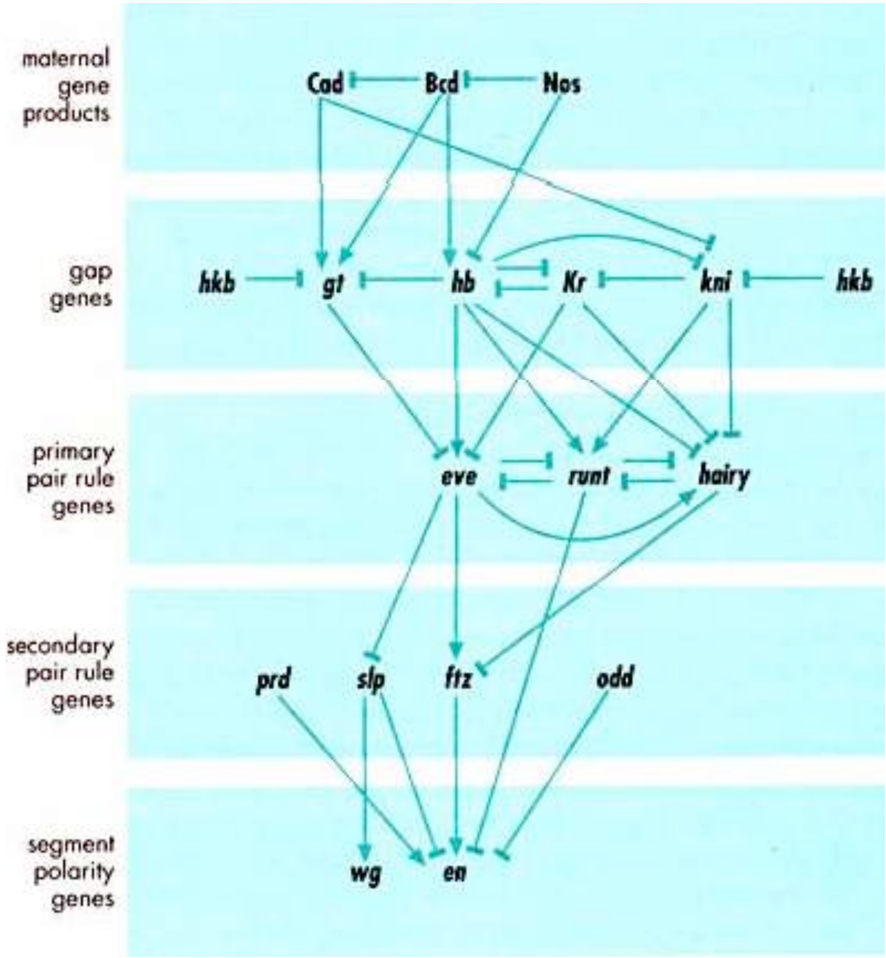


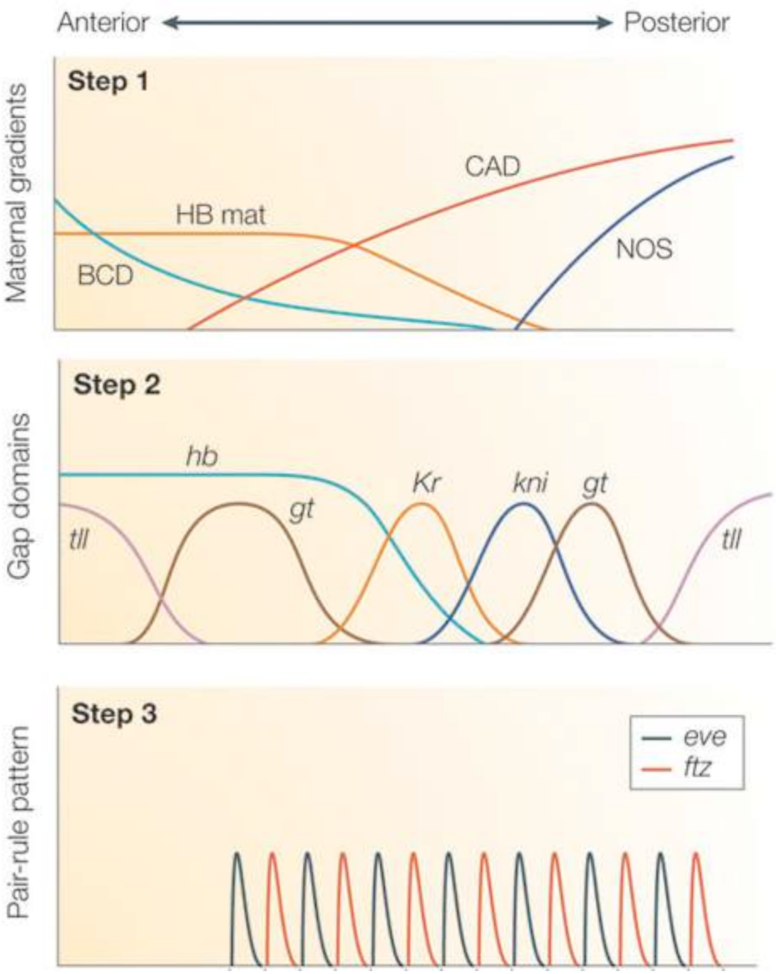
- Bicoid and Nanos are the regulators of *hunchback*



hb mRNA Hb protein

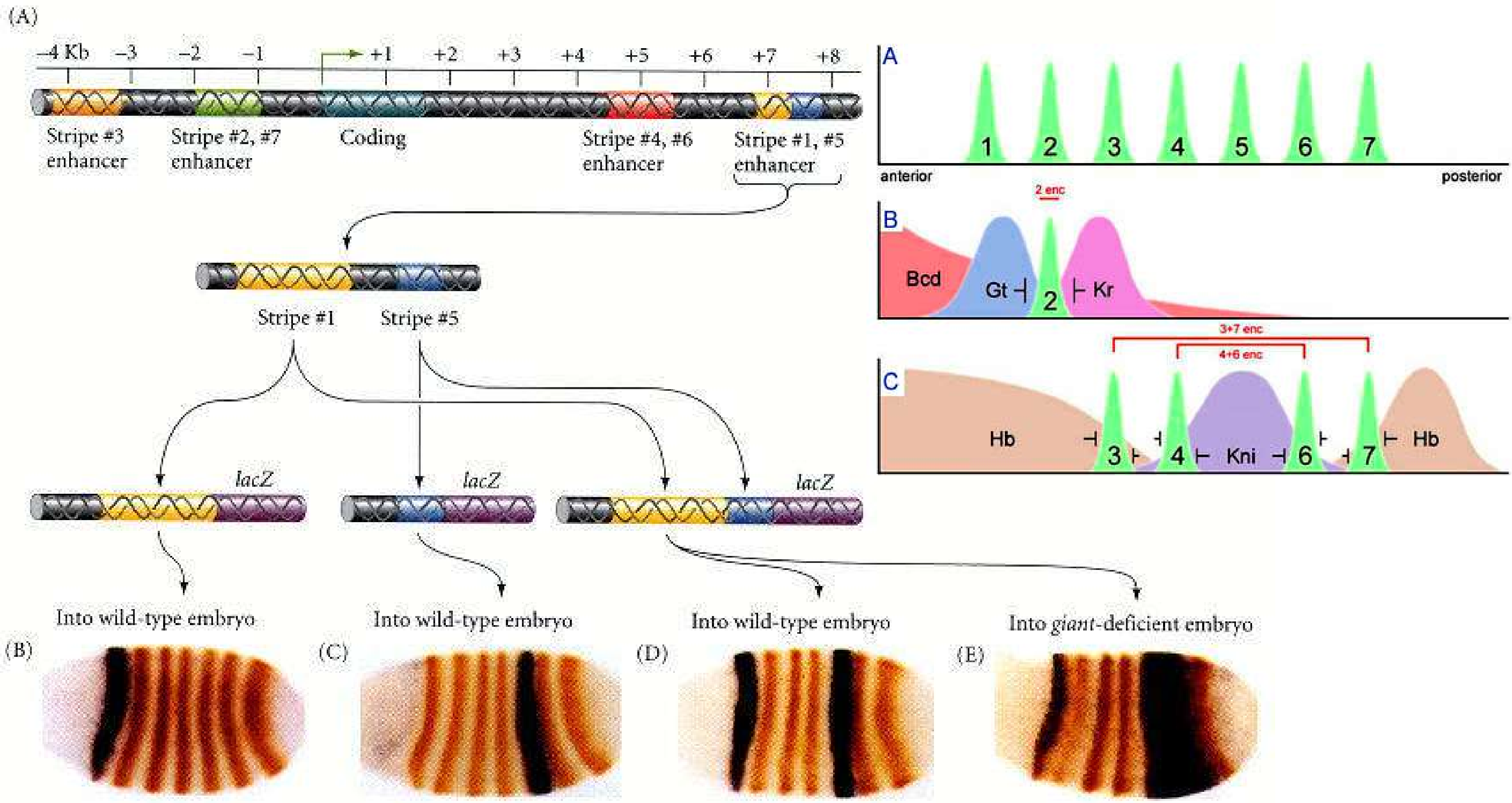
Segmentation in *Drosophila*





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

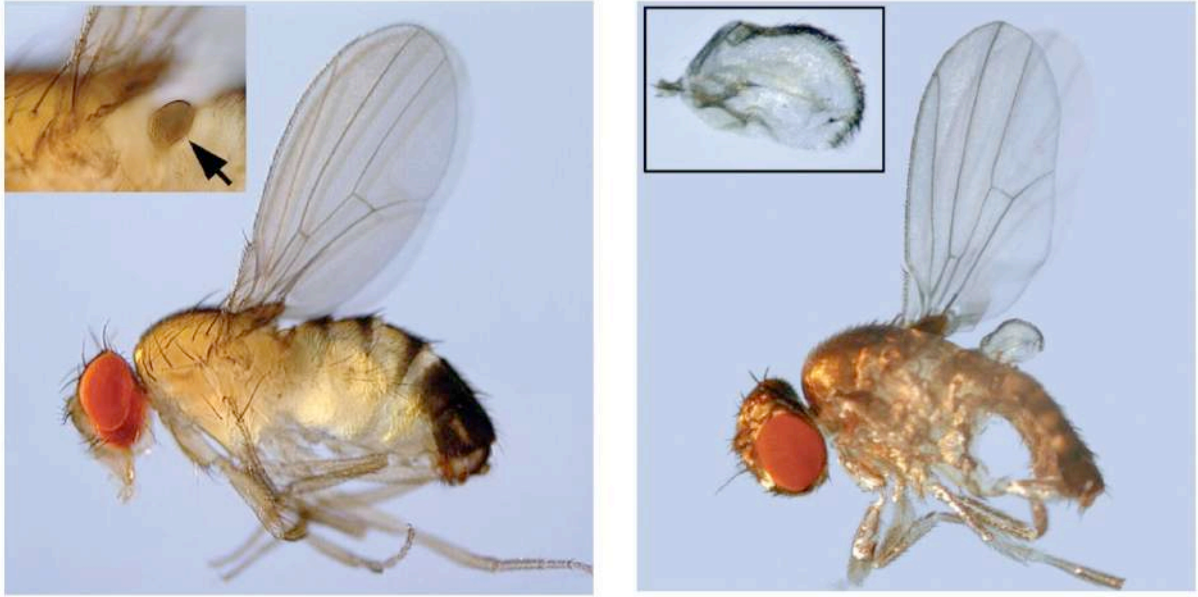
Segmentation in *Drosophila*: the regulation of the *even-skipped* (*eve*) gene



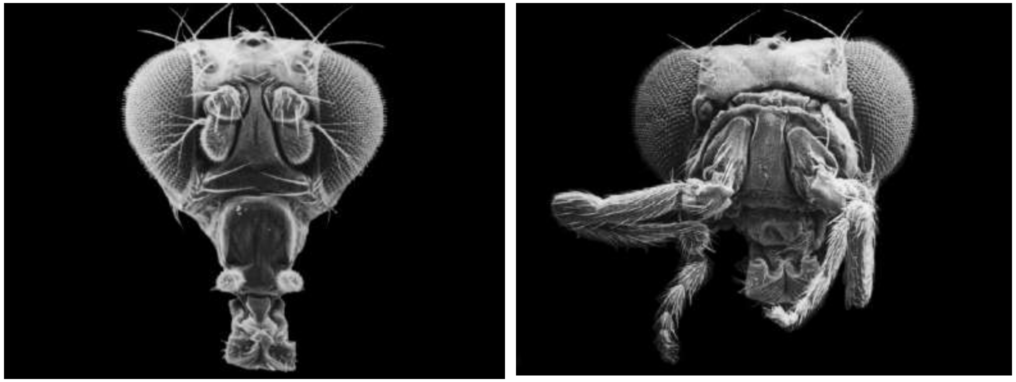
(Gilbert (2000) Developmental Biology, 6th ed.)

Segment identity: homeotic mutants

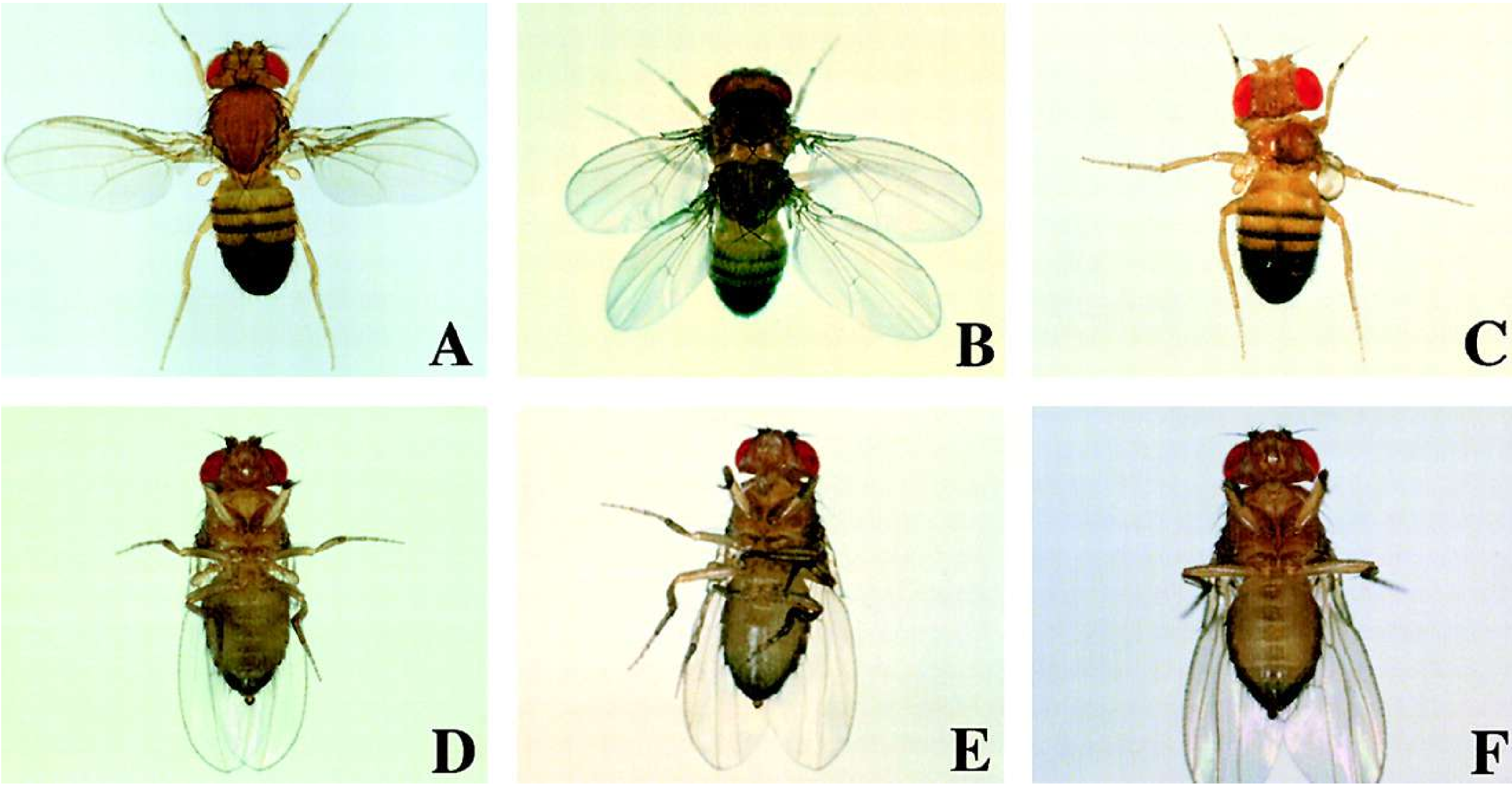
- the *bithorax* mutation



- the *antennapedia* mutation

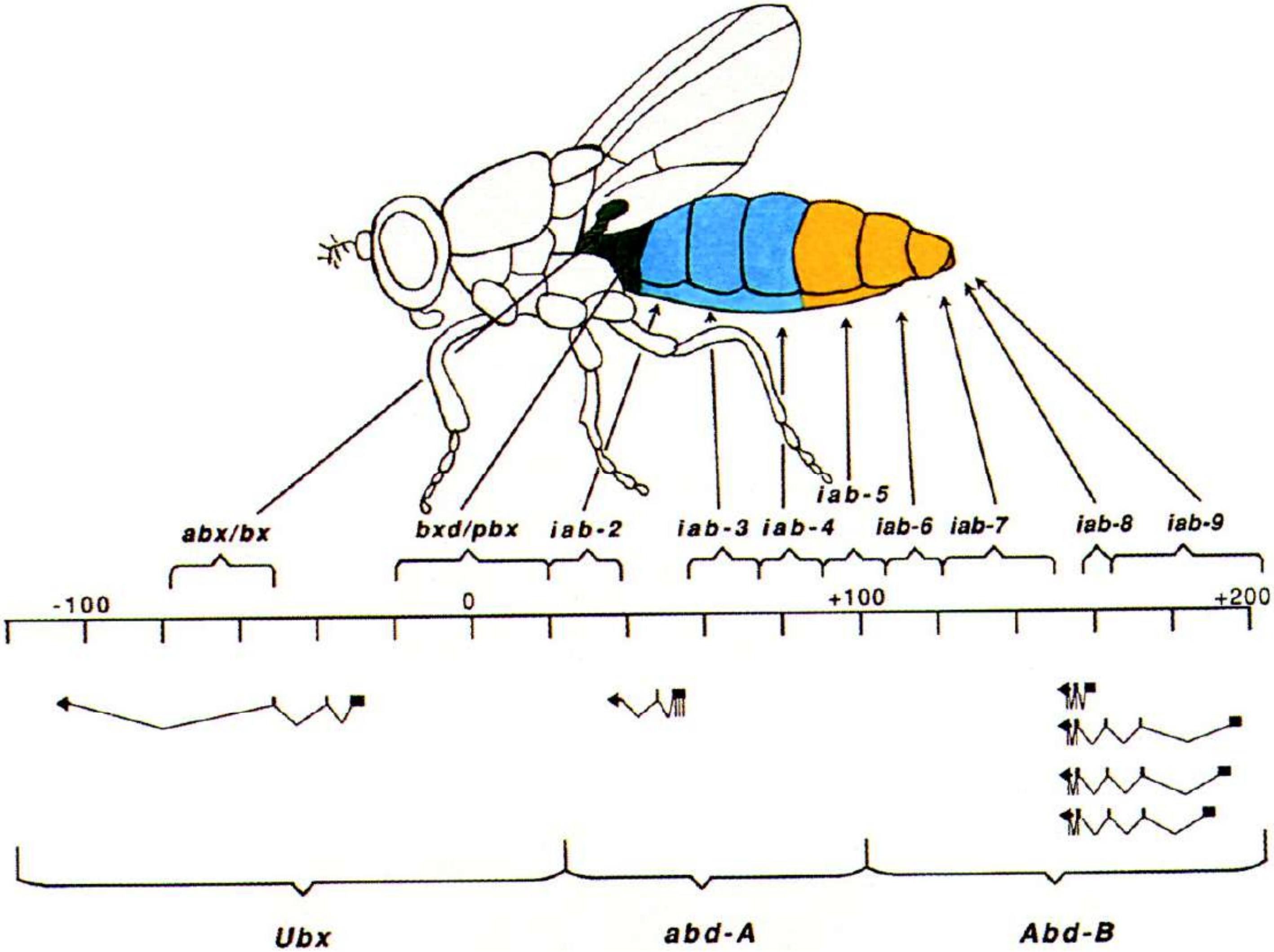


Segment identity: homeotic mutants



(Duncan and Montgomery (2002a) *Genetics*)

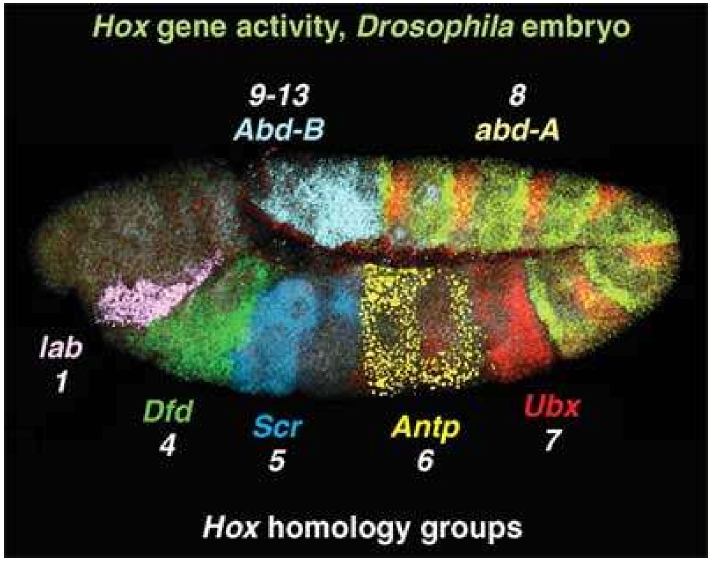
Segment identity: the *bithorax* complex

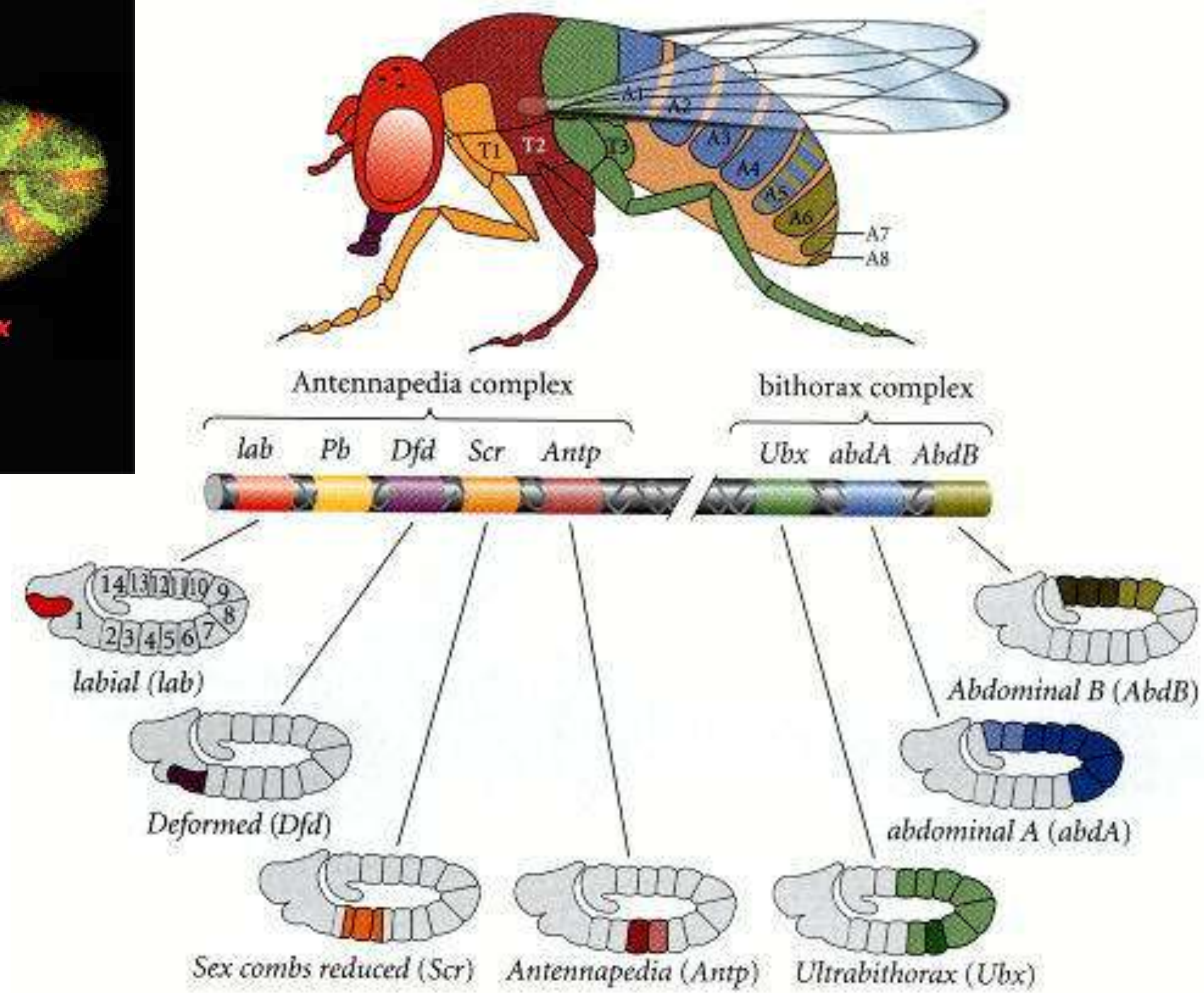


Edward B. Lewis

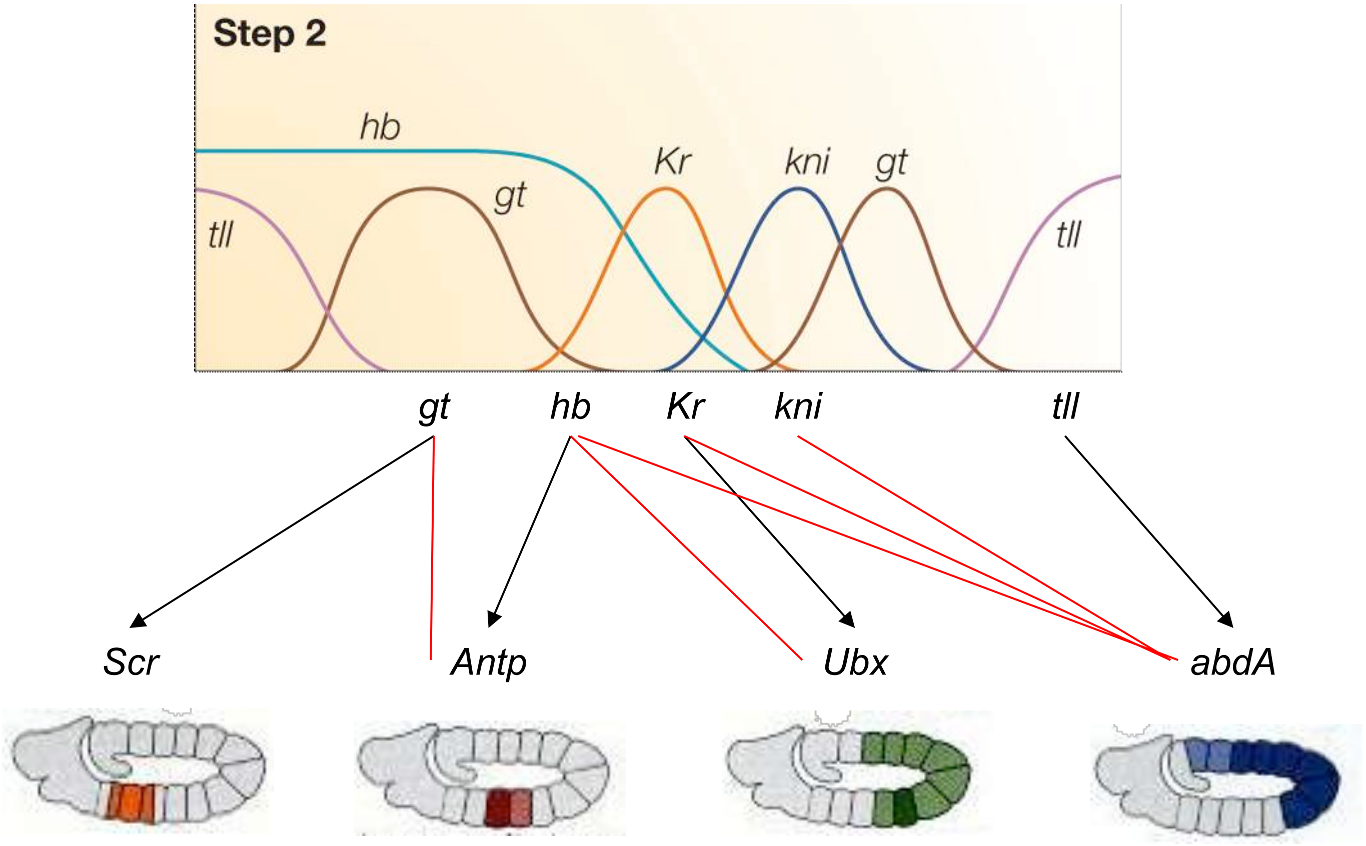
(Duncan and Montgomery (2002b) *Genetics*)

Segment identity: *Hox* genes



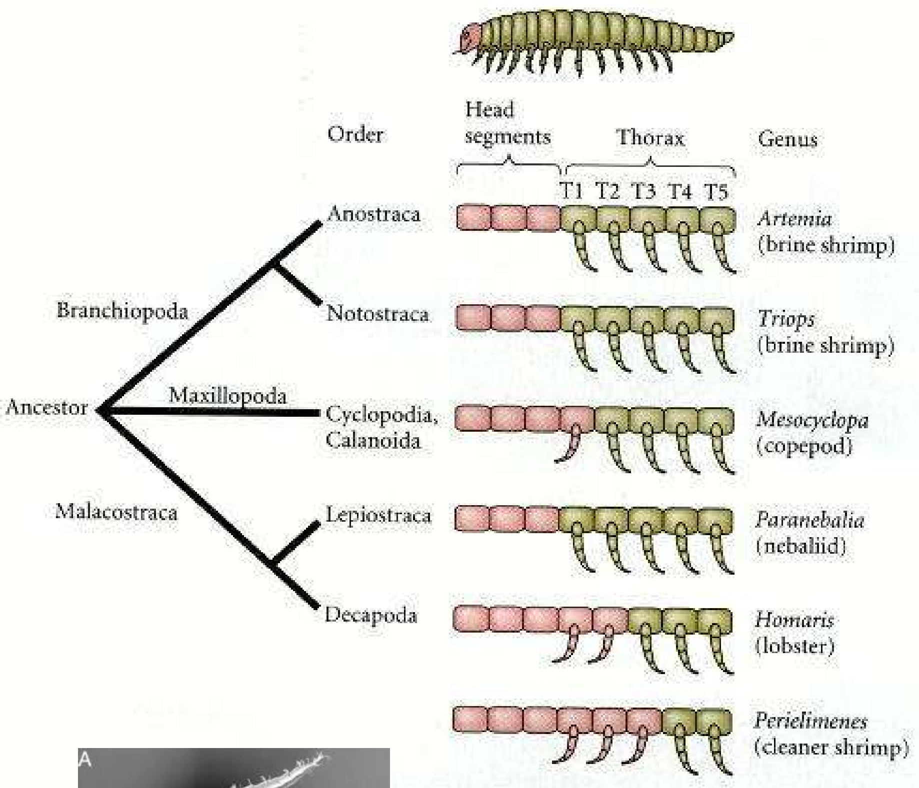


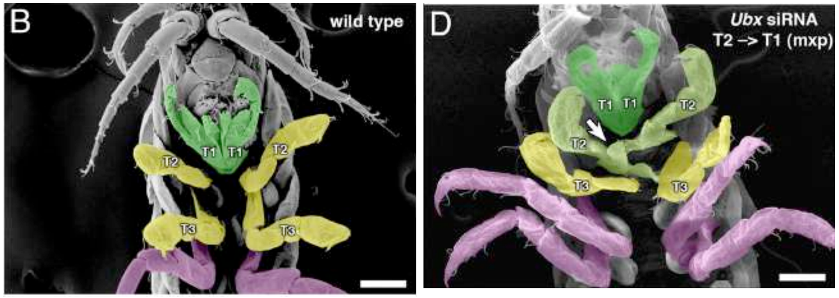
Hox genes are regulated by *gap* genes



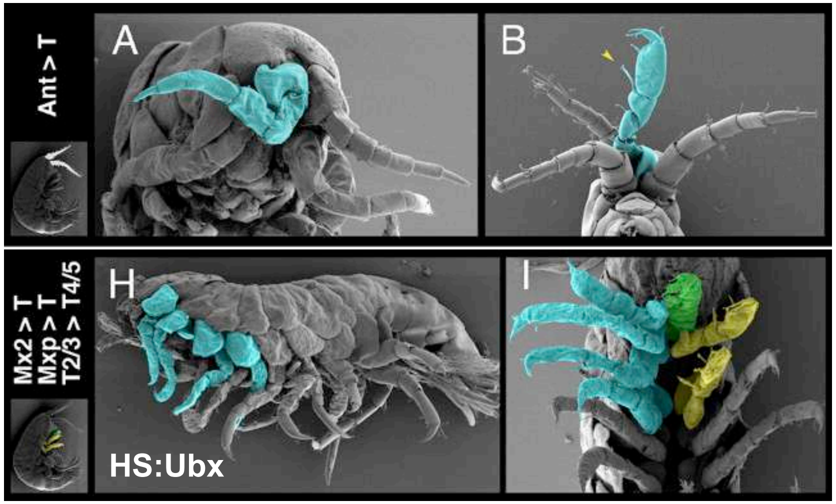
(Wu et al. (2001) és Casares et al. (1995) alapján)

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

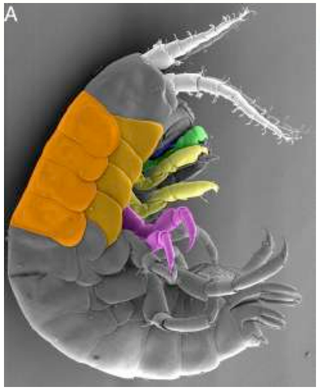


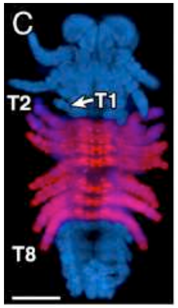


(Liubicich et al. (2009) *PNAS*)



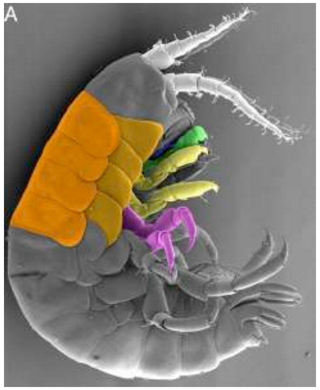
(Pavlopoulos et al. (2009) *PNAS*)

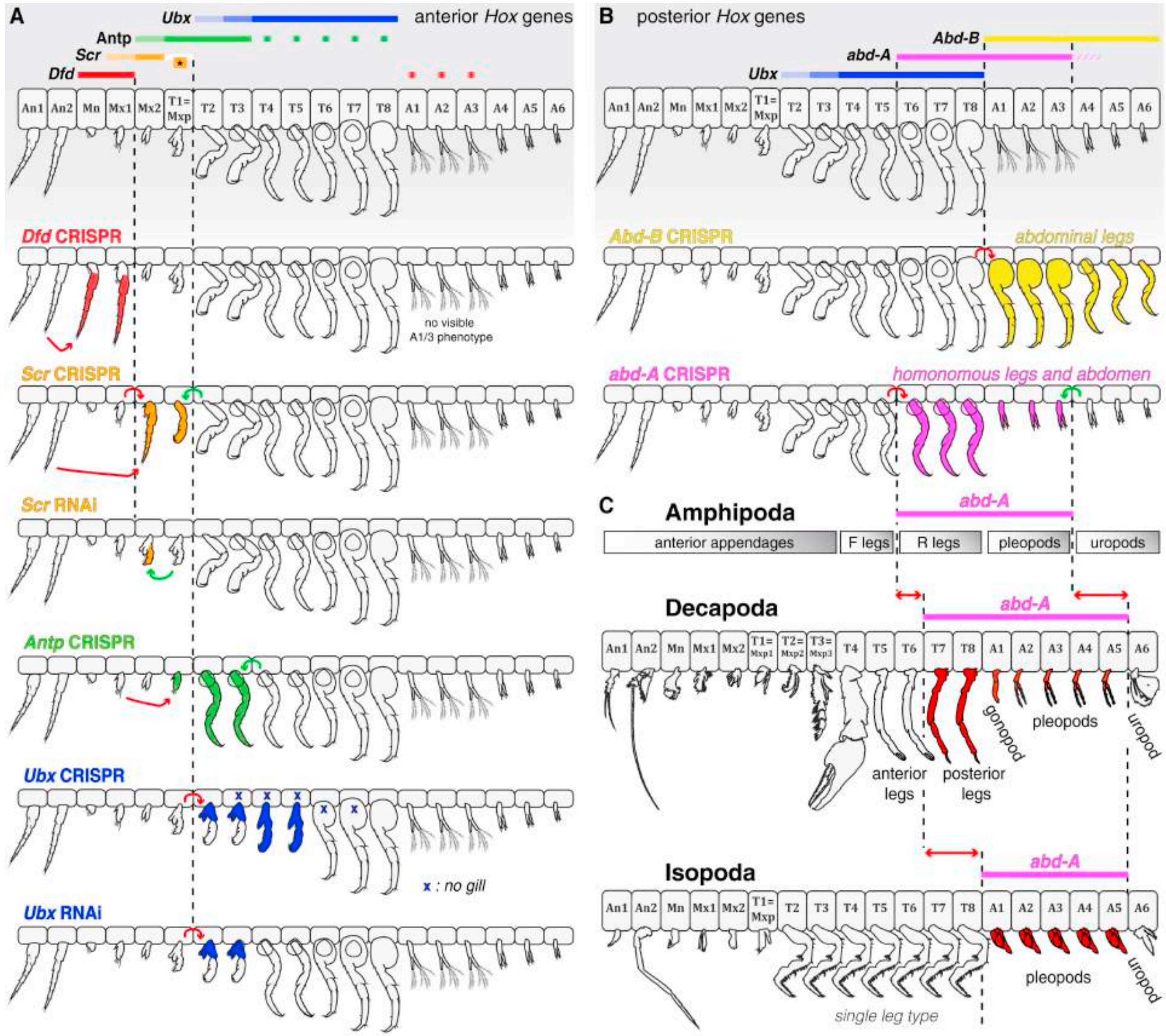




Parhyale hawaiensis

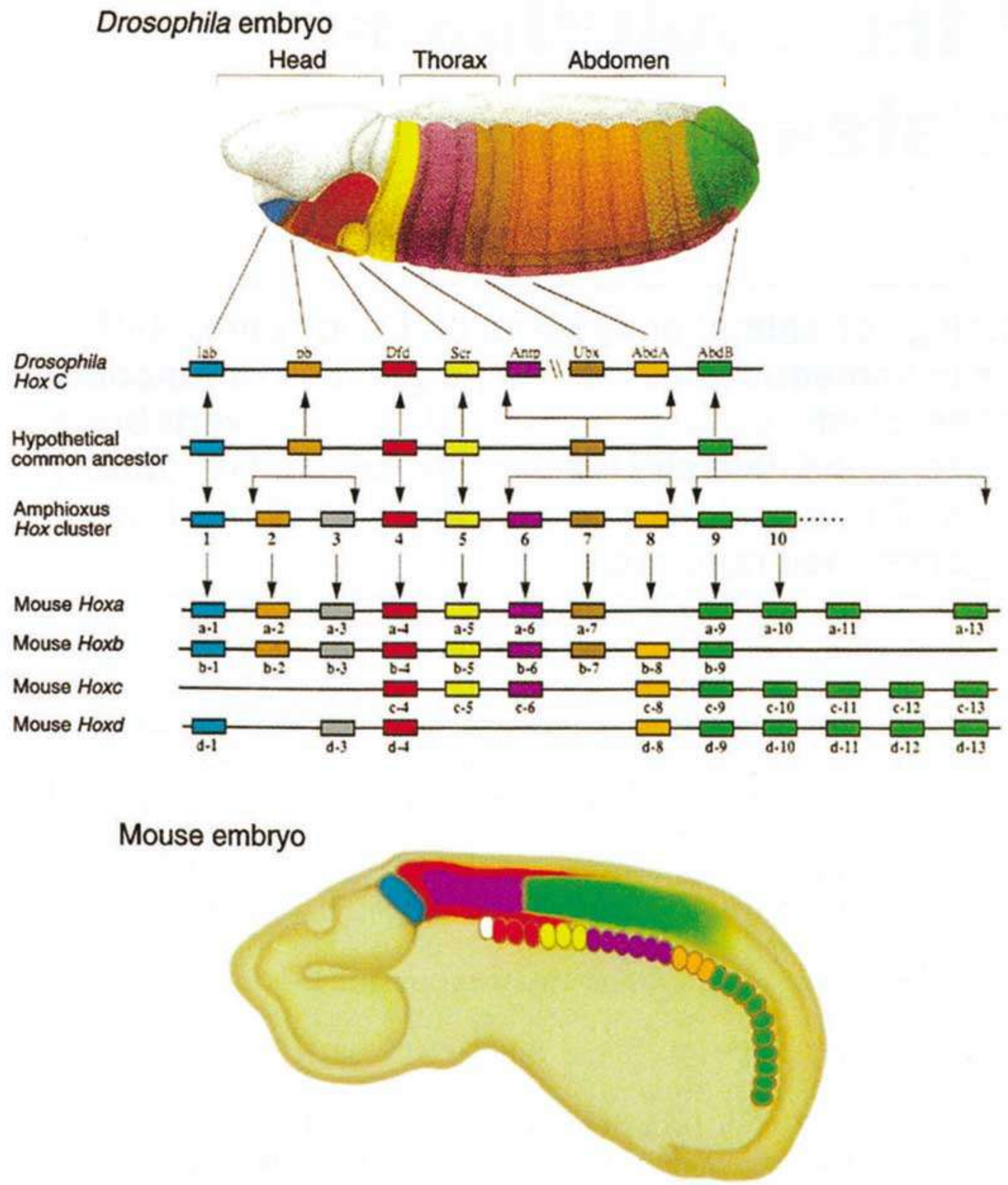
Hox genes and the evolution of the arthropod bodyplan: uropods



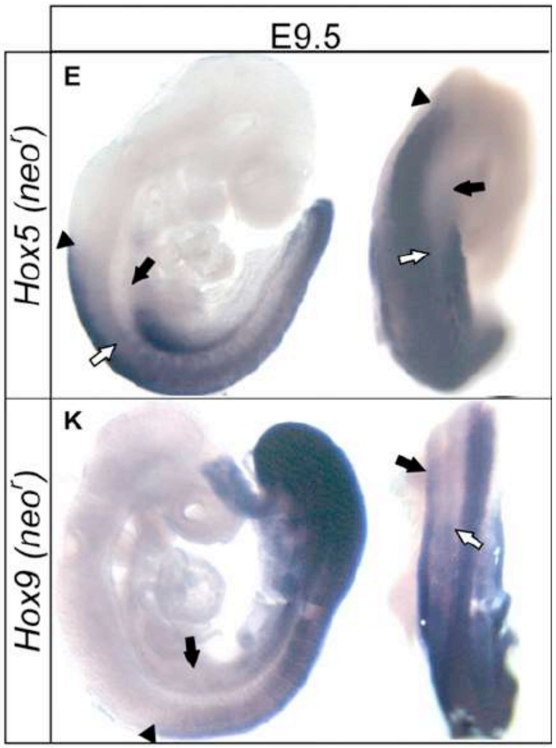


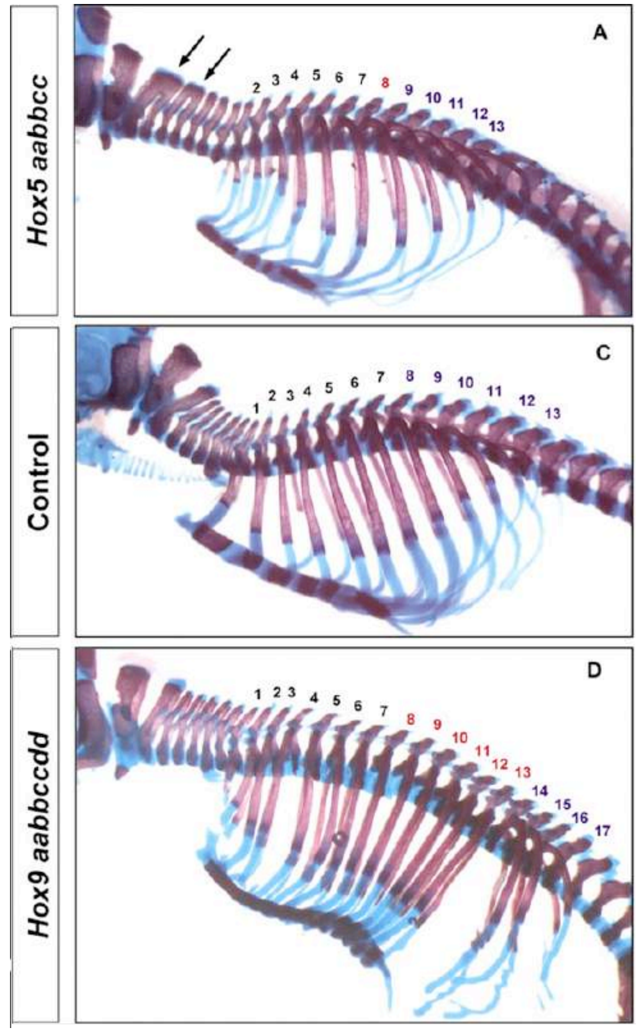
(Martin et al. (2016) *Curr Bio*)

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



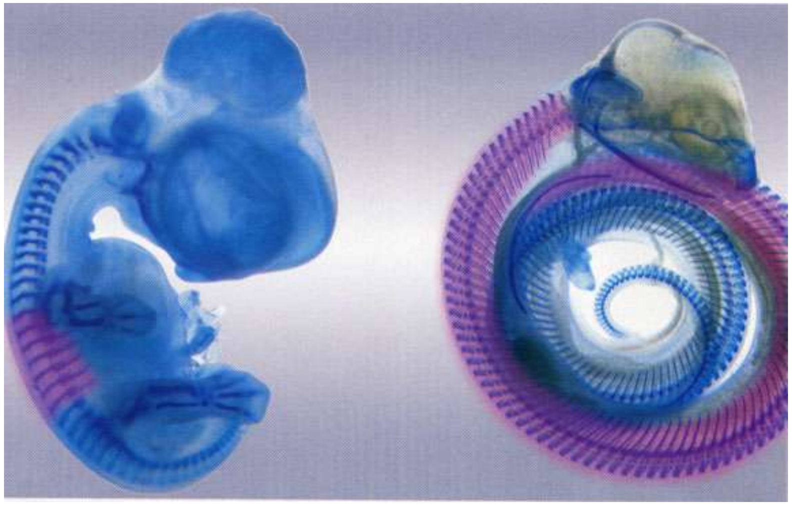
Homeotic mutants in vertebrates



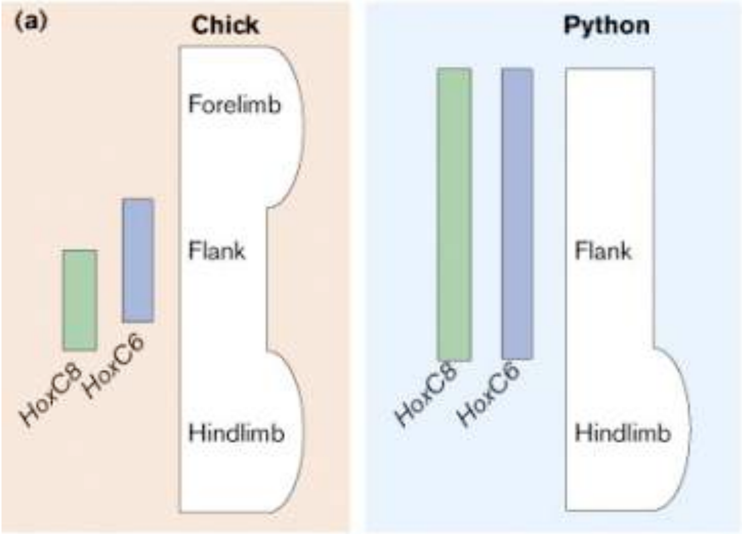


(McIntyre et al. (2007) *Development)*

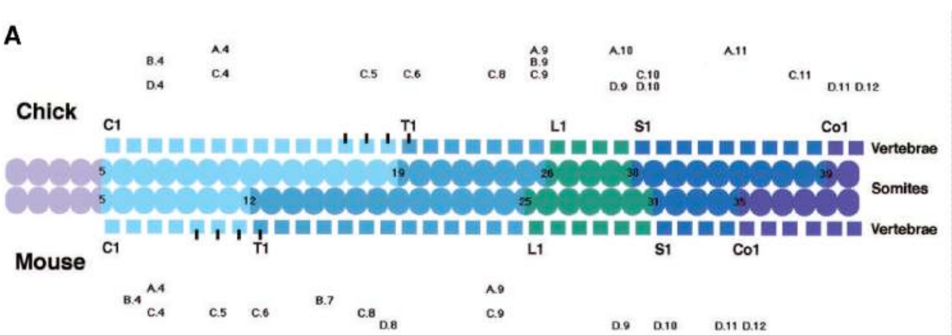
Hox genes and vertebrate evolution



hoxc6 expression pattern

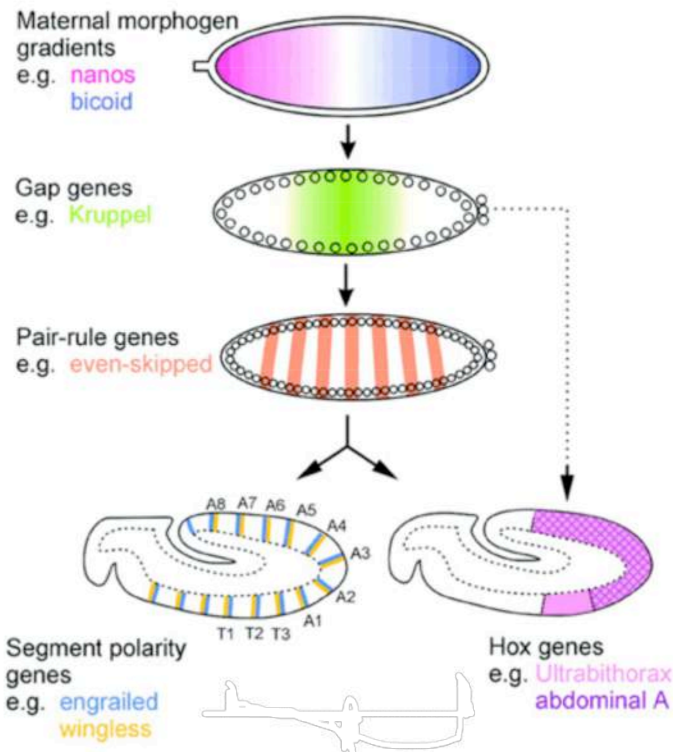


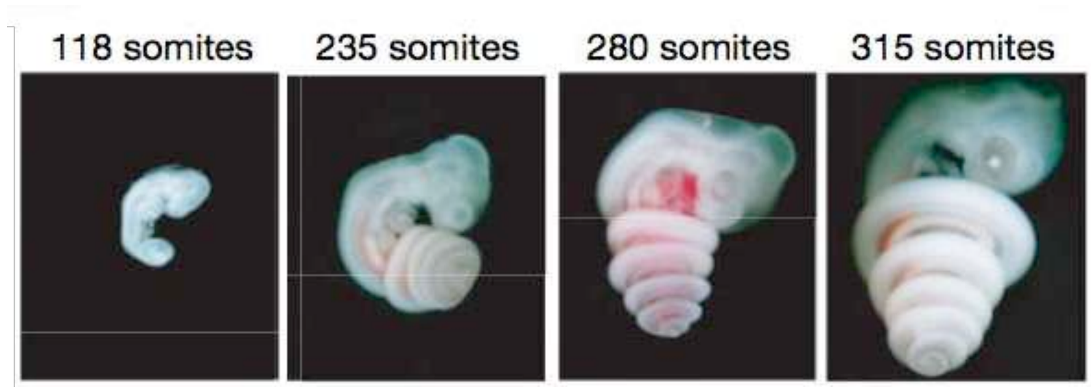
(Cohn and Tickle (1999) *Nature*)



(Burke et al. (1995) *Development*)

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



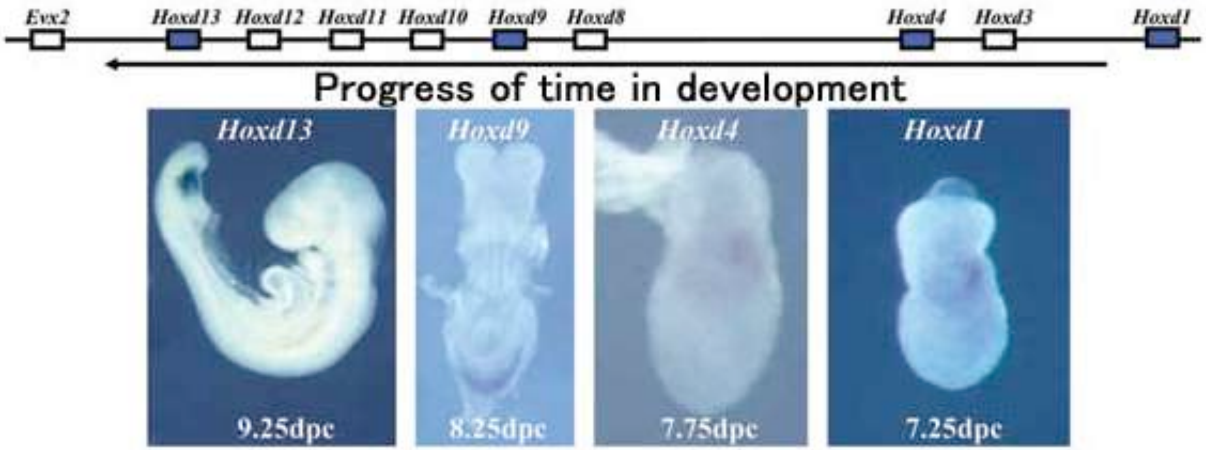


In a *Drosophila* embryo the primordia of all future segments are present from the very beginning (this is not general even for insects = “long germ insect”)

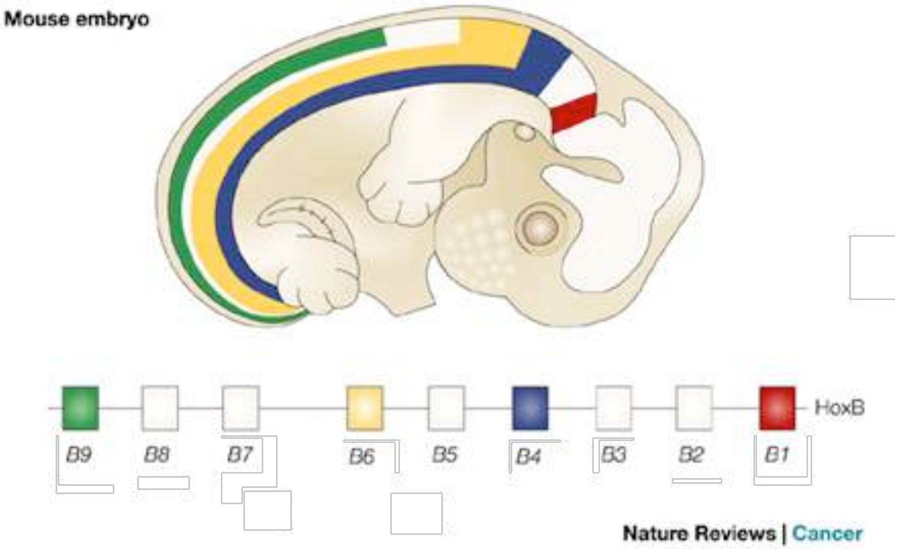
In vertebrates by the end of gastrulation only the anterior structures are specified and later segments arise from the growth zone of the embryonic tailbud.

Hox genes and colineartity

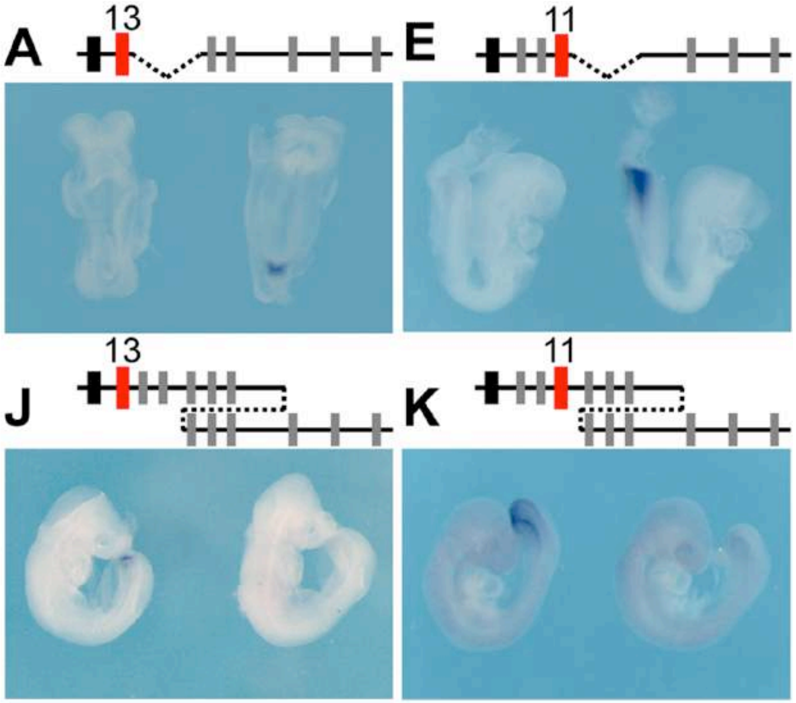
- **Temporal colinearity**: *Hox* genes that more 3' in the cluster are expressed earlier



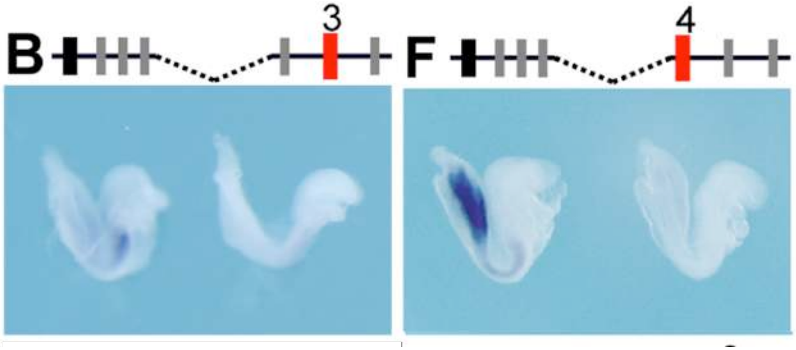
- **Spatial colinearity**: *Hox* genes that more 3' in the cluster are expressed more anteriorly



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



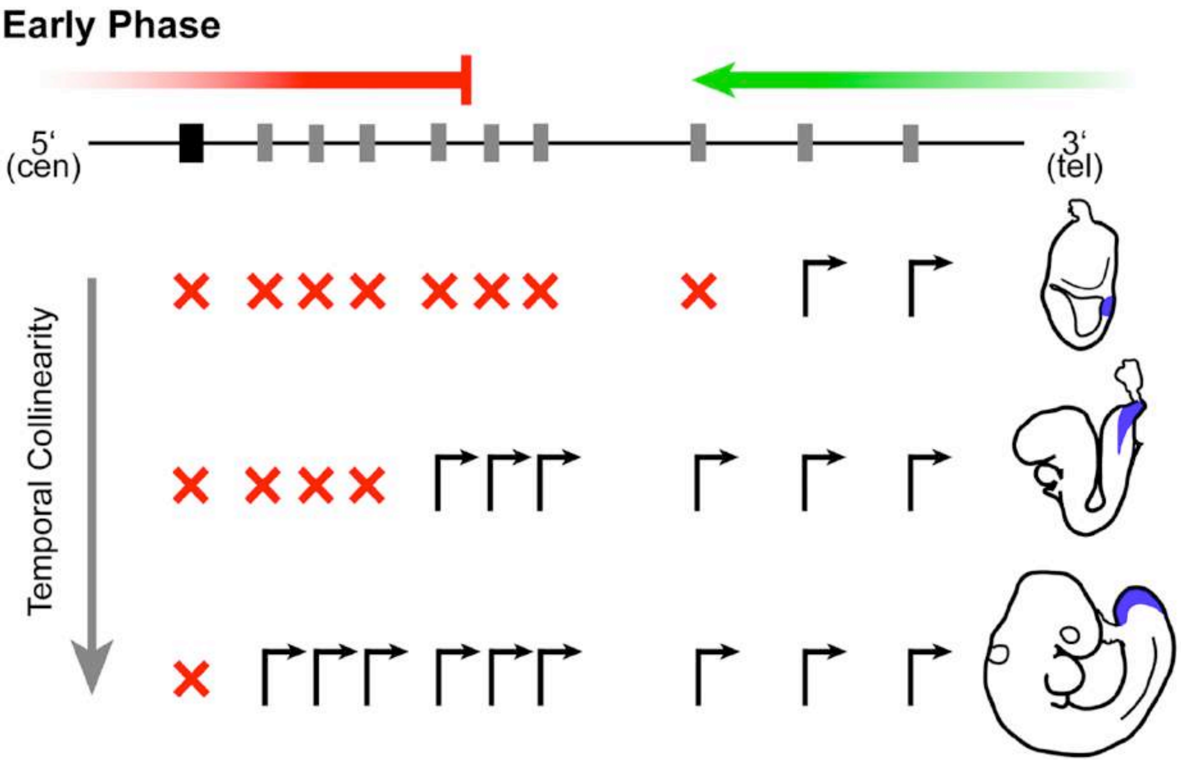
The closer the telomere, the faster the activation of a given *Hox* gene can be observed.



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

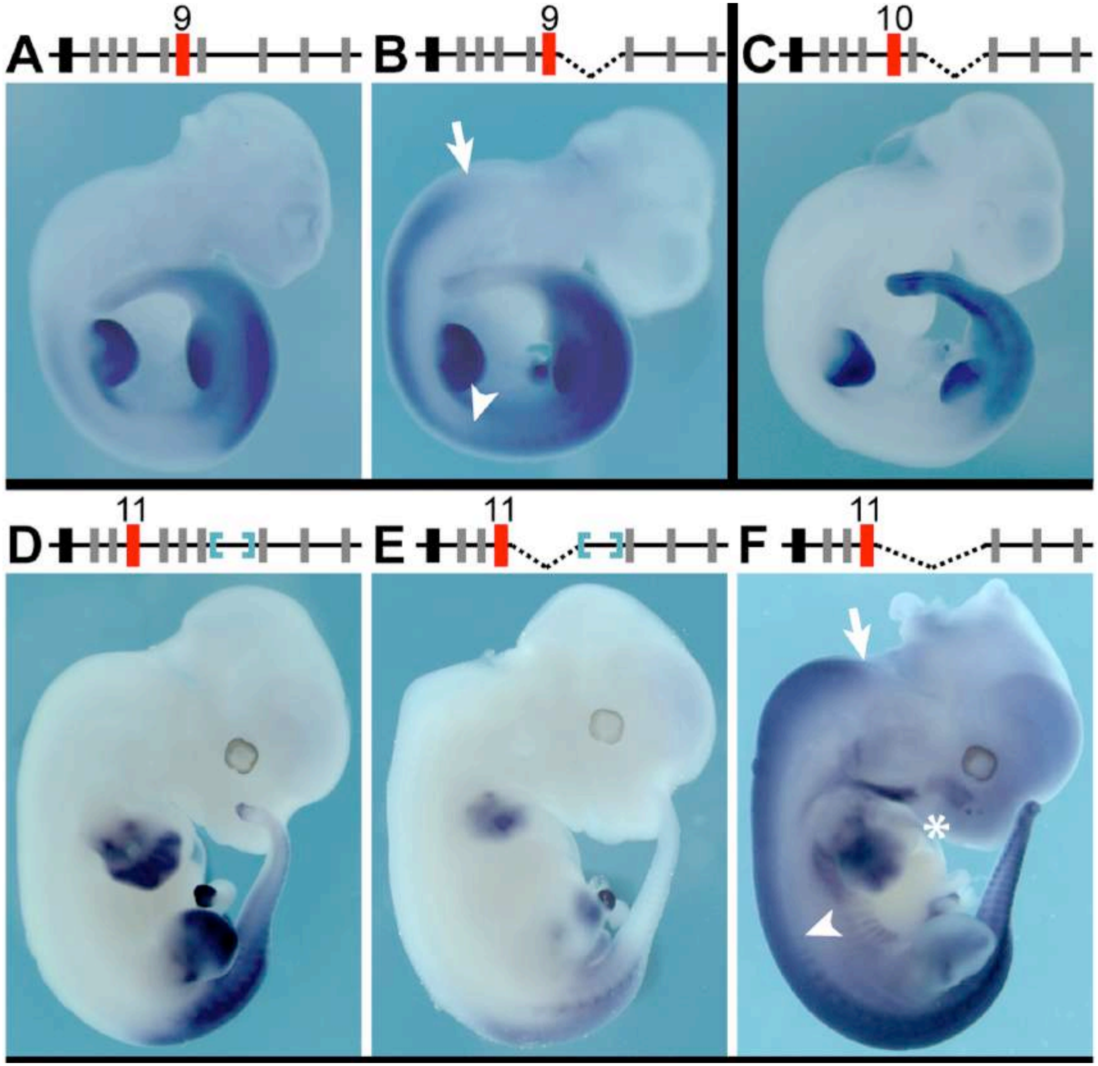
(Tschopp et al. (2009) *PLoS Gen)*

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



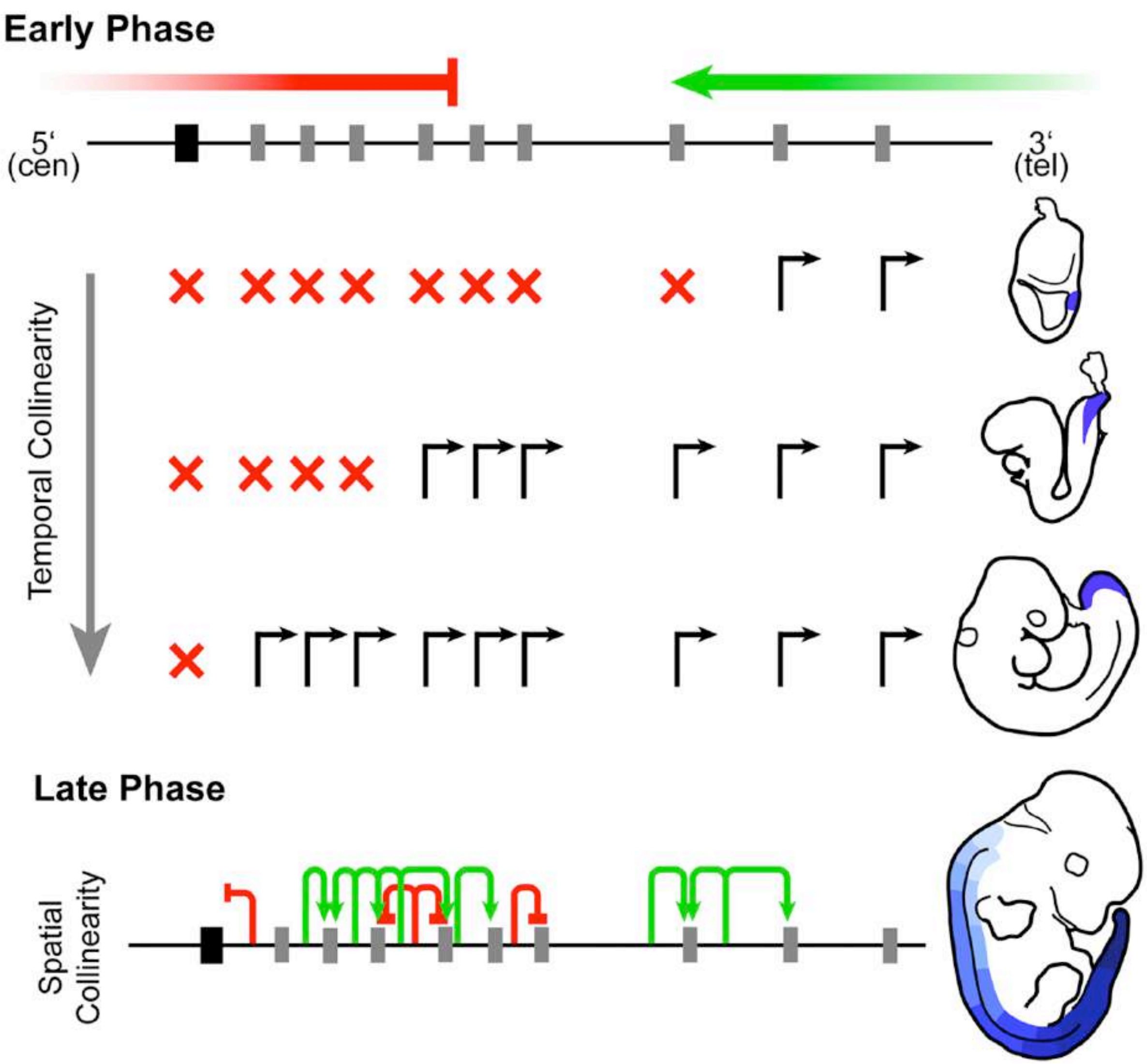
(Tschopp et al. (2009) *PLoS Gen)*

Spatial colinearity is dependent on local interactions



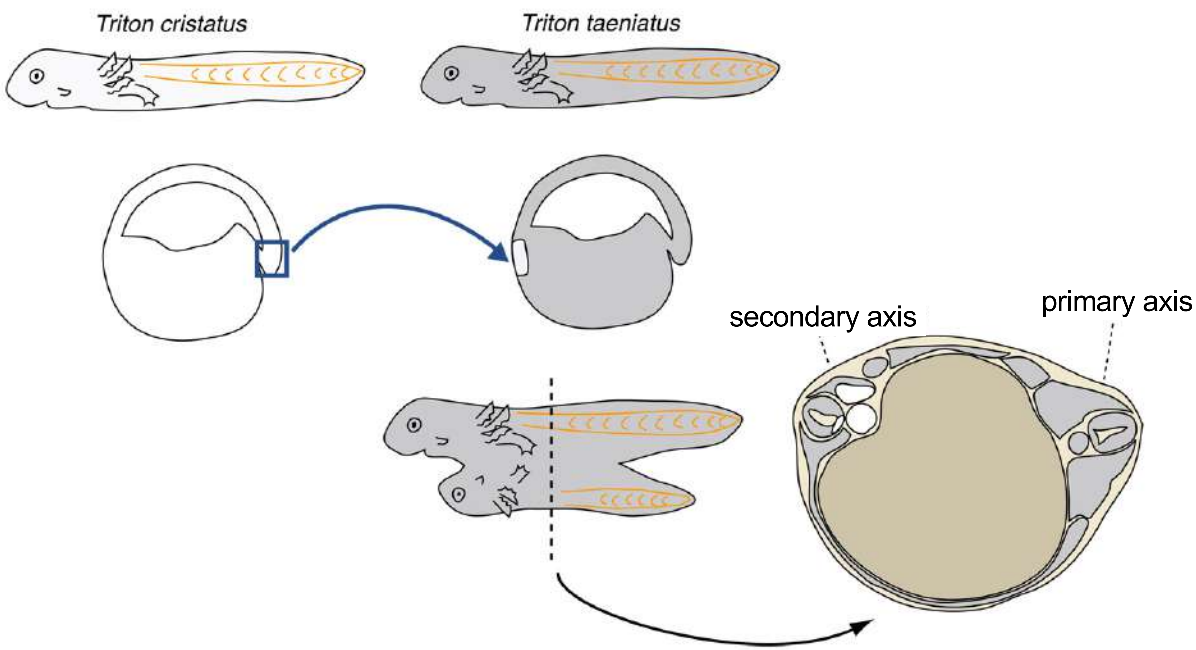
(Tschopp et al. (2009) *PLoS Gen)*

Spatial colinearity is dependent on local interactions



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

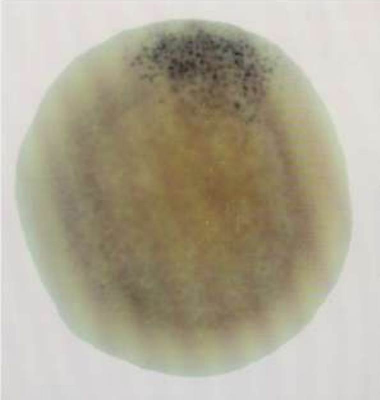
The Spemann-Mangold experiment and the discovery of the dorsal organizer (1924)



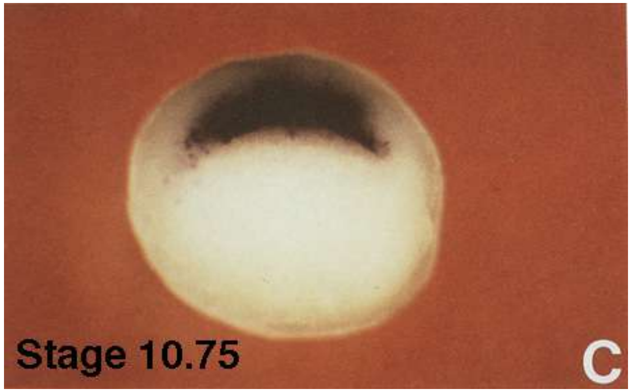
Hilde Mangold

Hans Spemann

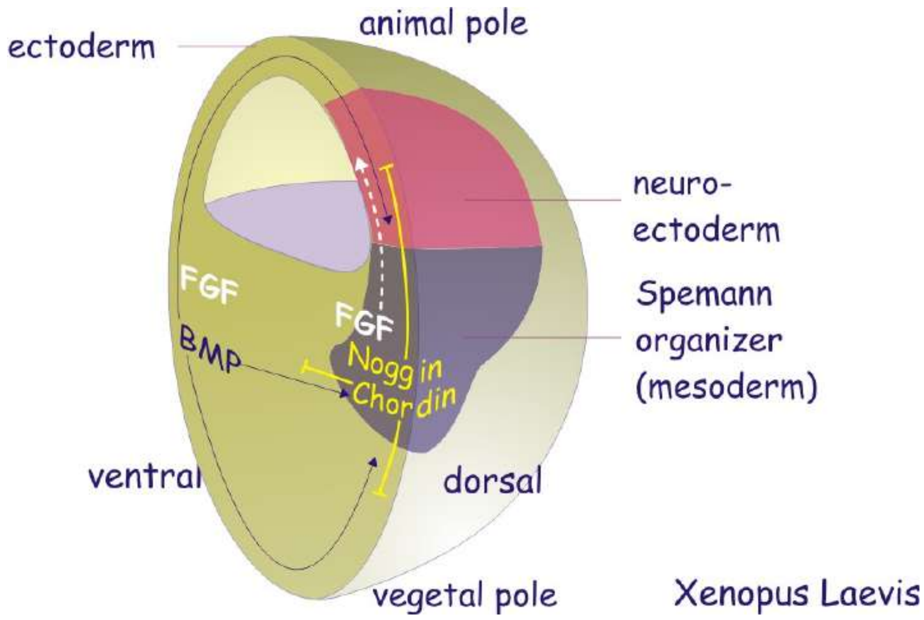
The Spemann-Mangold organizer expresses BMP antagonists



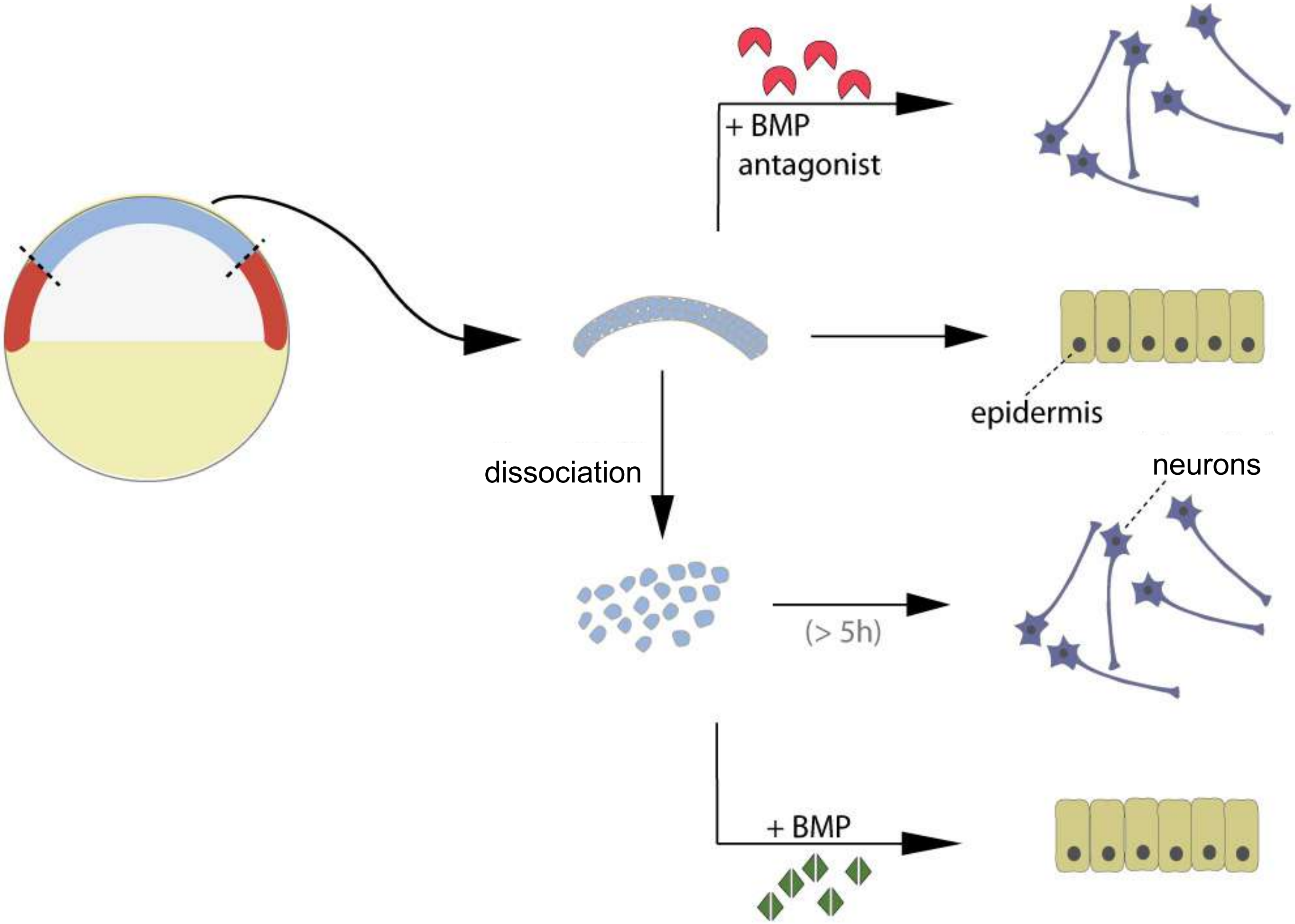
noggin
Smith and Harland (1992)



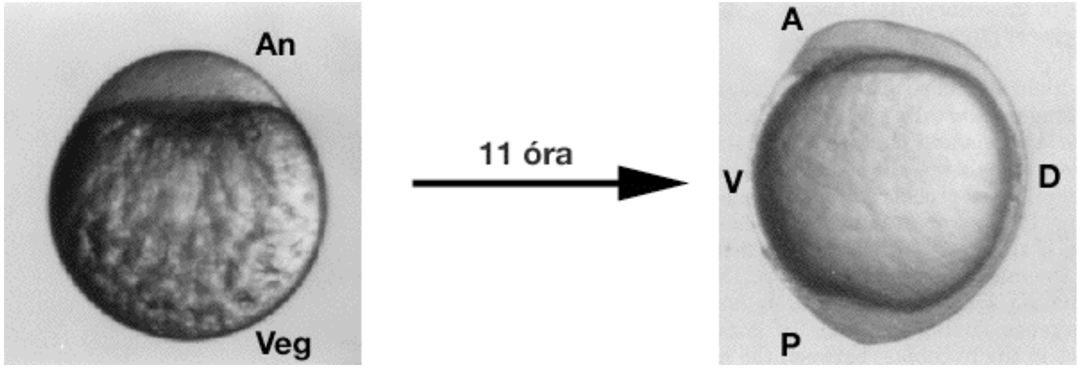
chordin - Sasai et al. (1994)



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

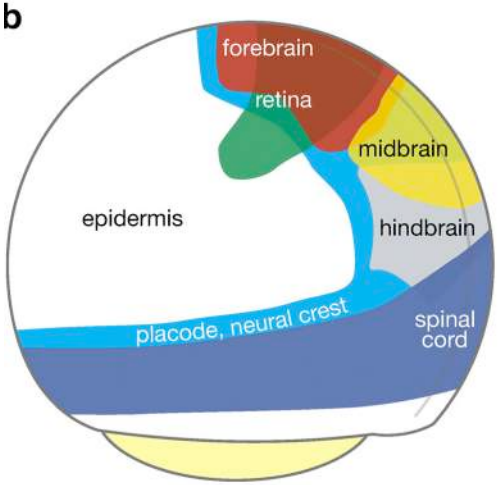


The development of the dorsoventral (DV) axis is interdependent with the specification of the nervous system

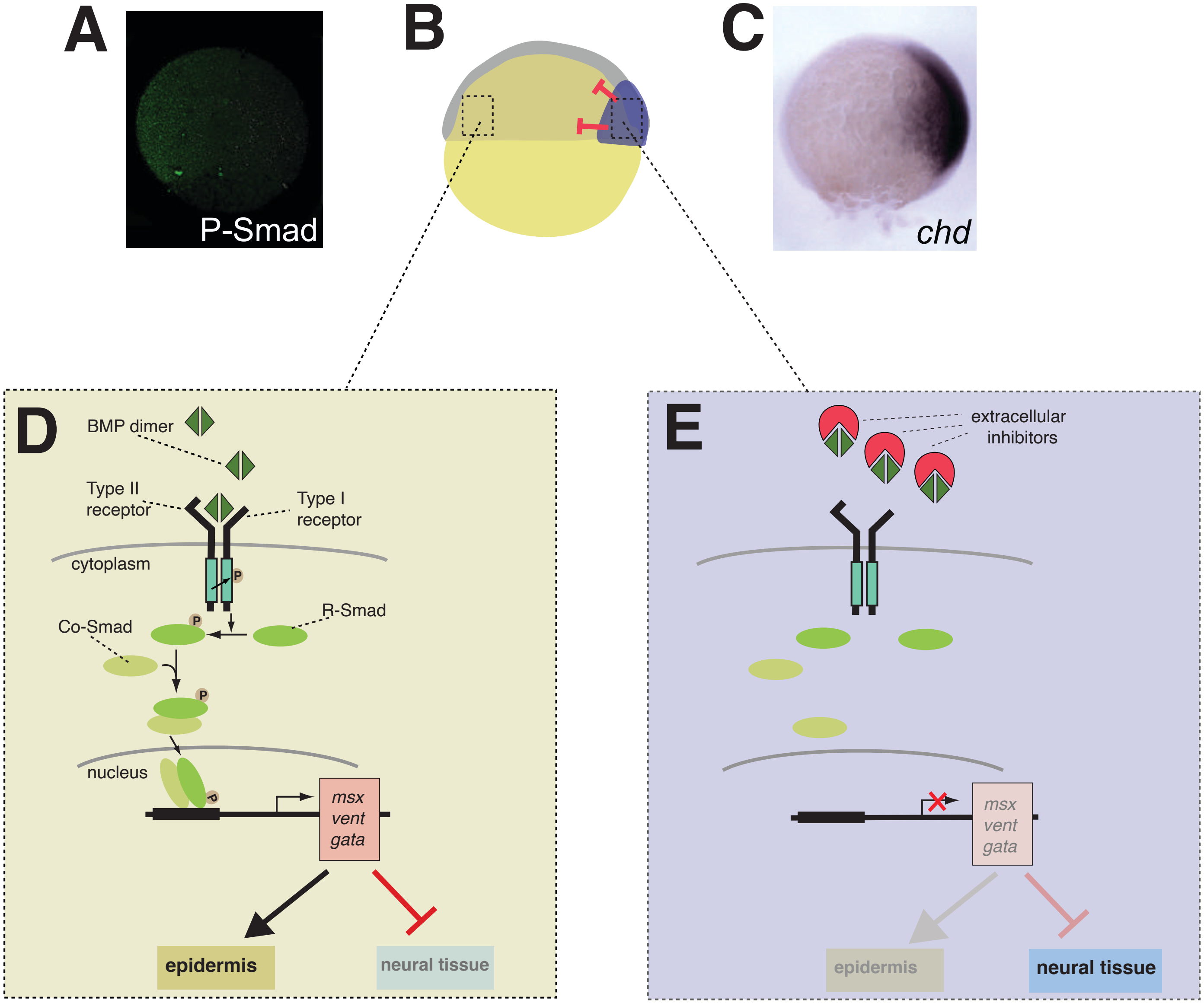


The zebrafish fate-map demonstrated that the “dorsal” ectoderm will develop into neural tissue, whereas ventral ectoderm will become epidermis.

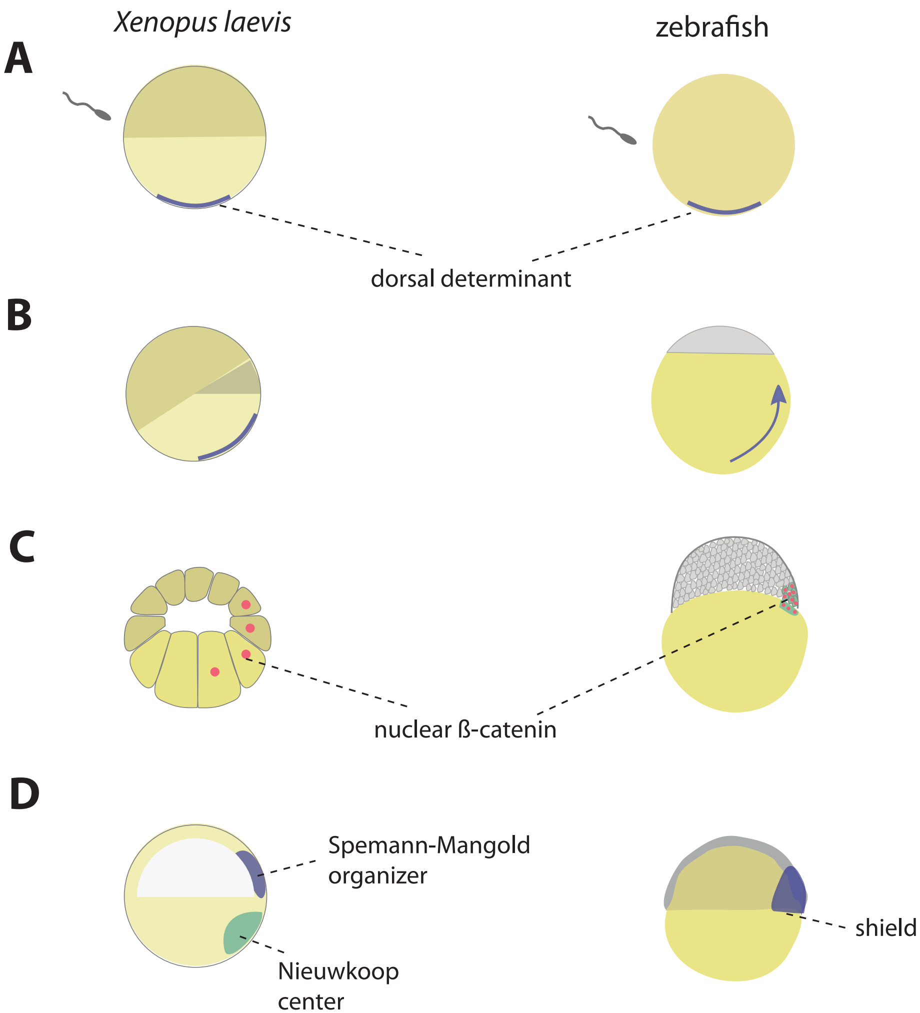
b

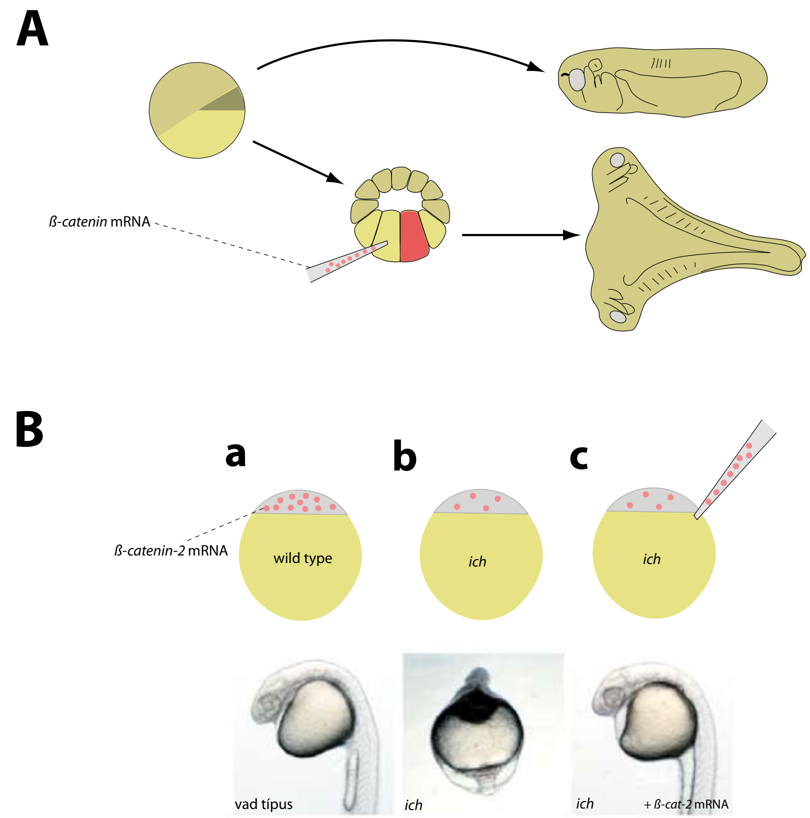


BMP-antagonists are expressed in the Speman-Mangold organizer

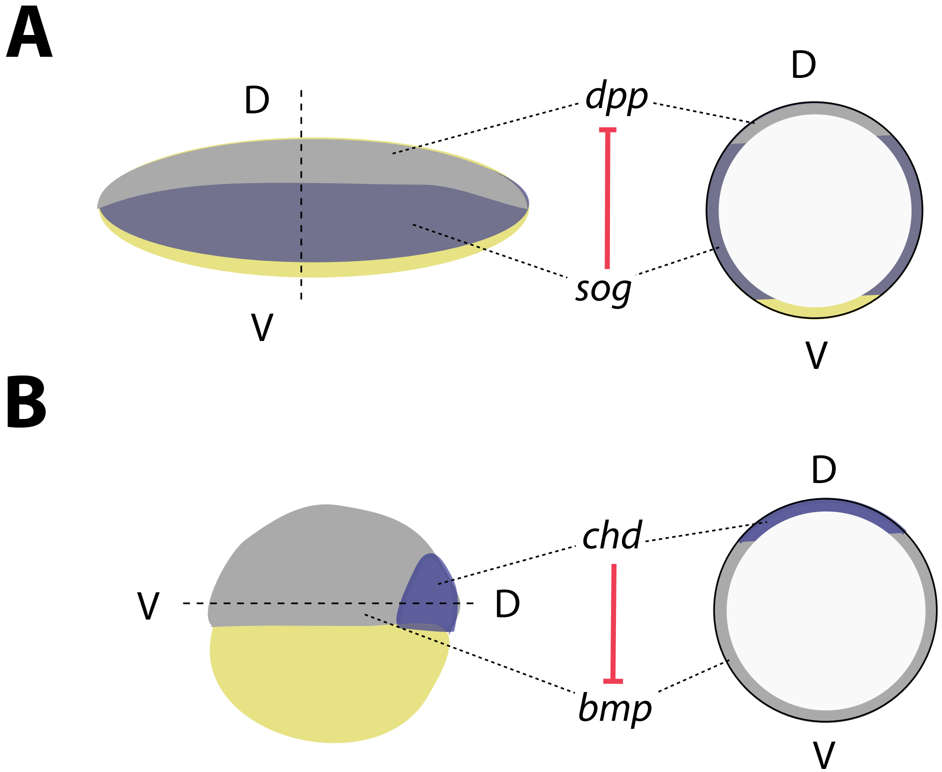


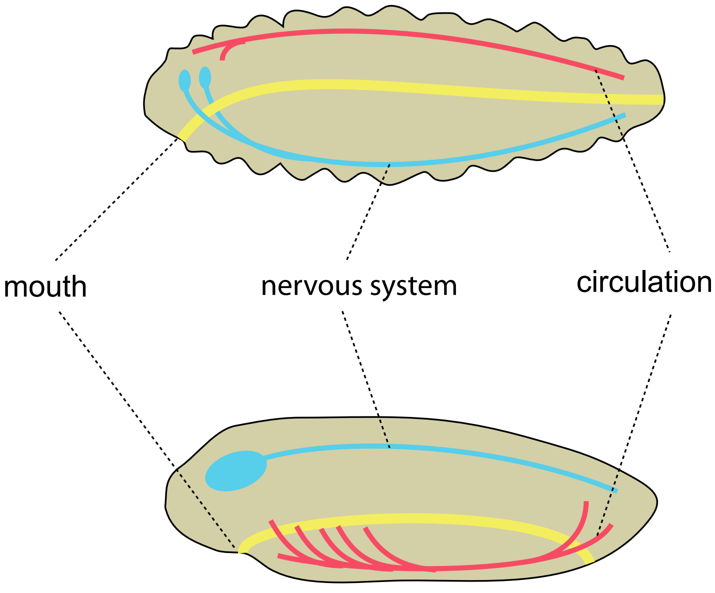
The induction of the dorsal organizer: cortical rotation and the induction of the Wnt-pathway



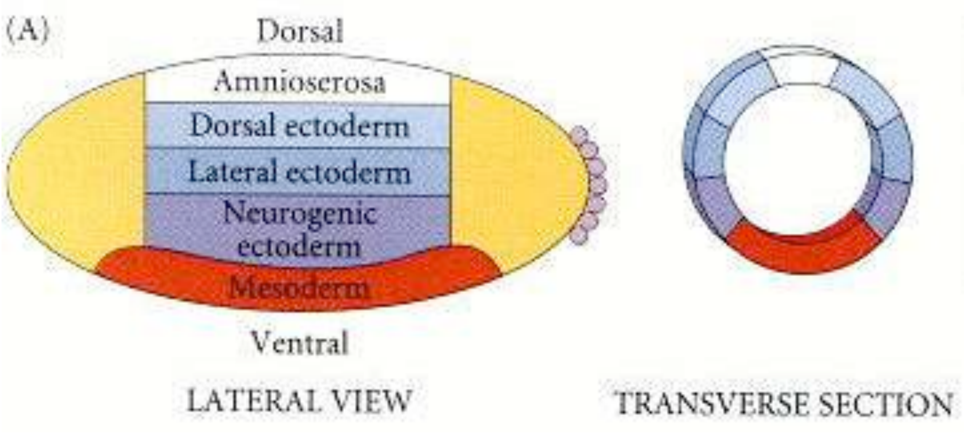


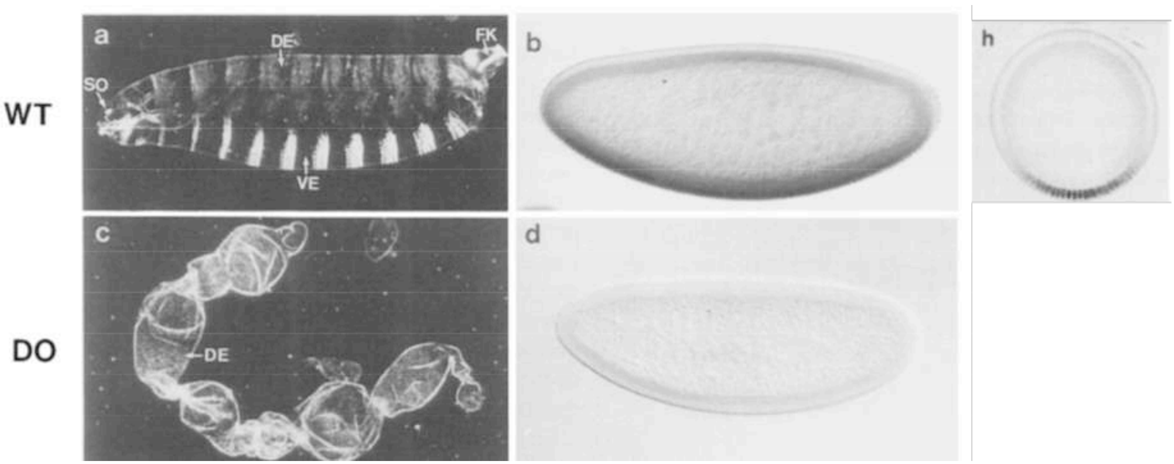
A BMP - anti-BMP DV tengely evolúciósan ősi

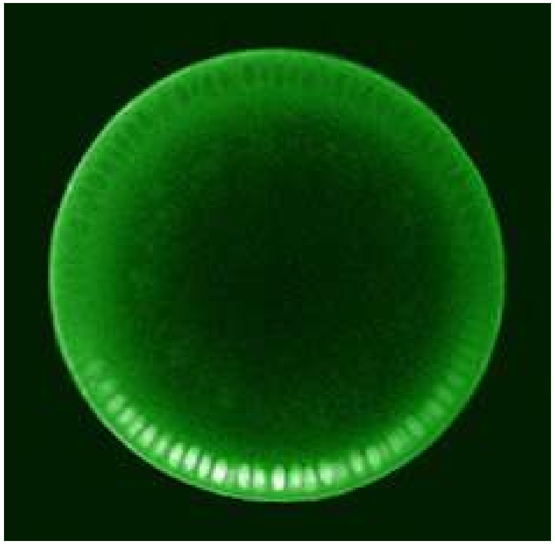




dorsal – the regulator of *Drosophila* DV axis





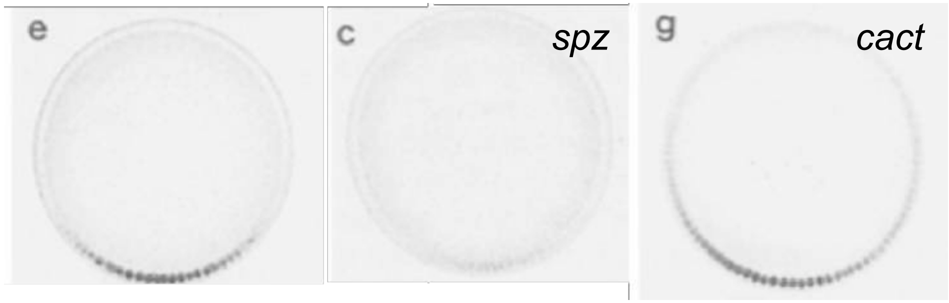


Dorsal is present in all cells, but it is nuclear only in the cells of the ventral side

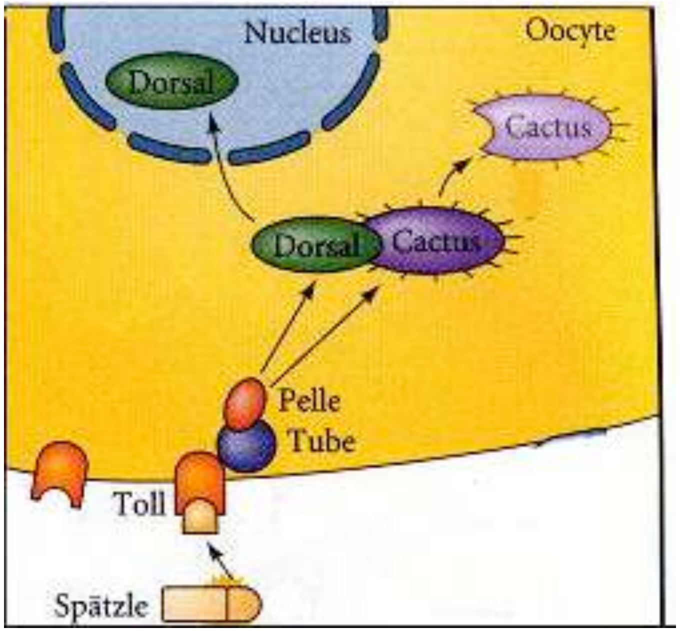
(Roth et al. (1989) *Cell)*

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

- Localisation of Dorsal in DV mutants



(Roth et al. (1989) *Cell)*



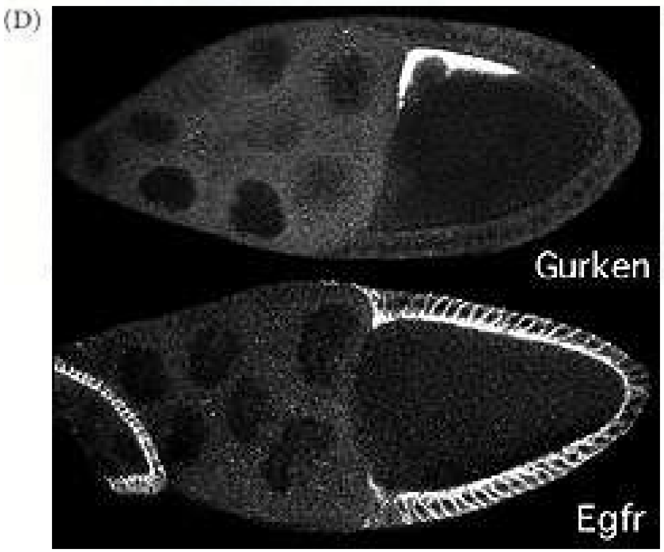
- Dorsal and Cactus are the *Drosophila* orthologs of NF-Κβ és IF-Κβ
- Extracellular cleavage of Spätzle is necessary for its function

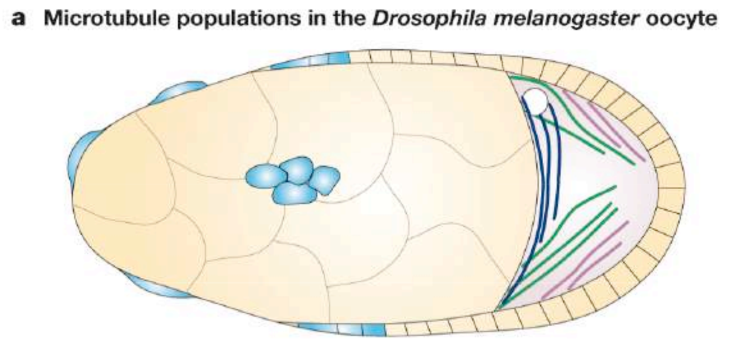
=> The follicular cells surrounding the oocytes also have an important role in DV axis formation!

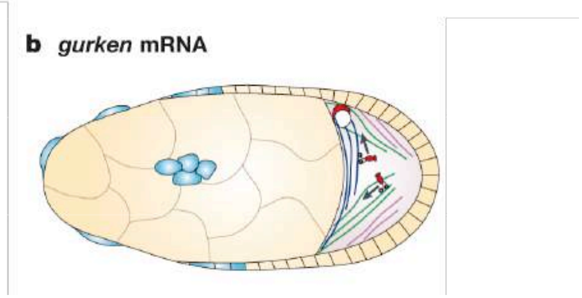
Maternal determination of the future dorsal side by *gurken*

gurken mRNA

Gurken protein







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

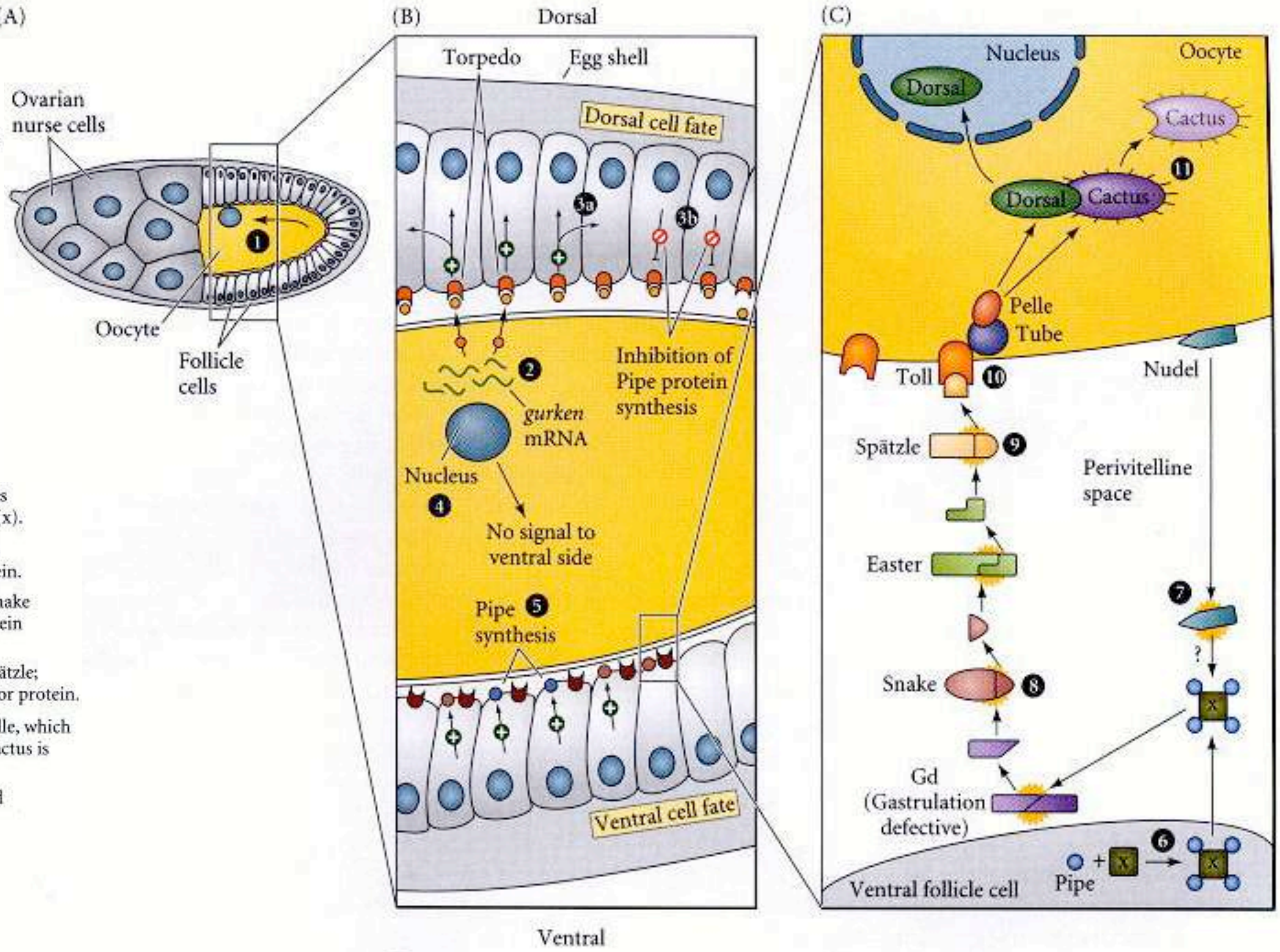
The genetics of *Drosophila* DV polarity

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.

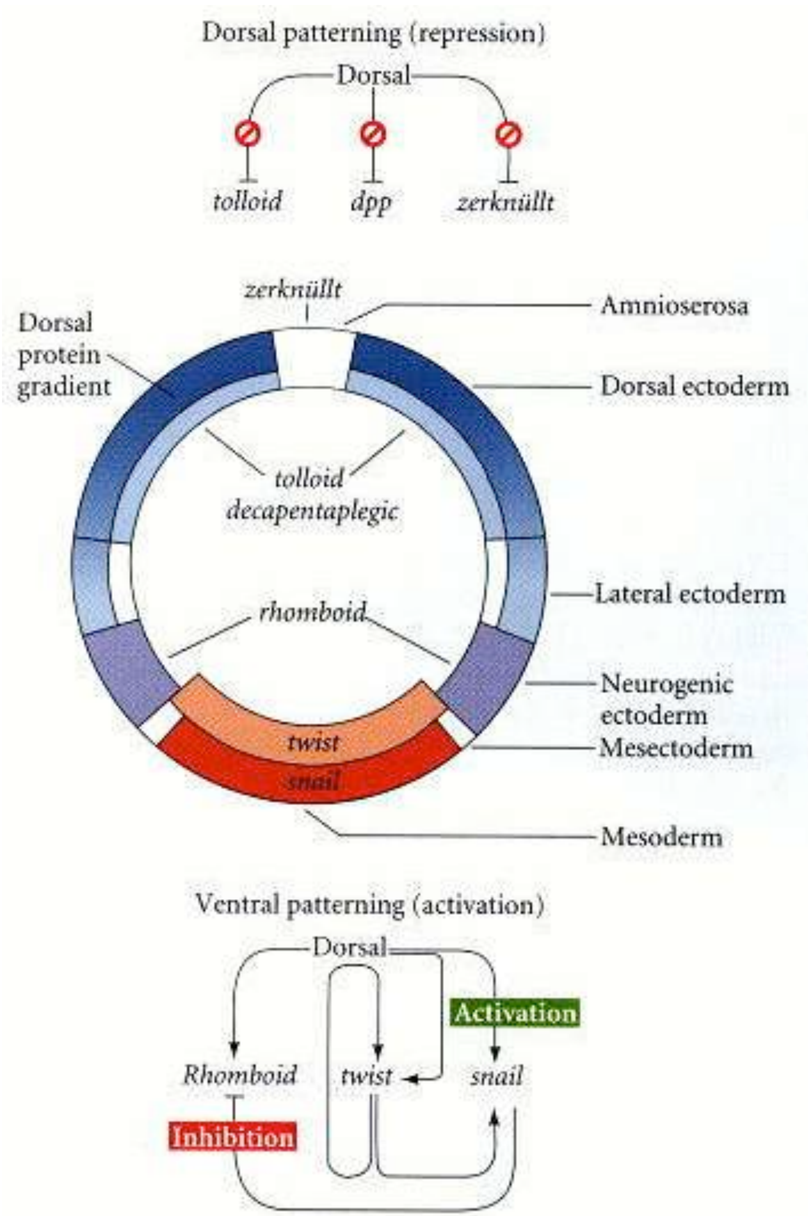
3b. Synthesis of Pipe protein is inhibited in dorsal follicle cells.

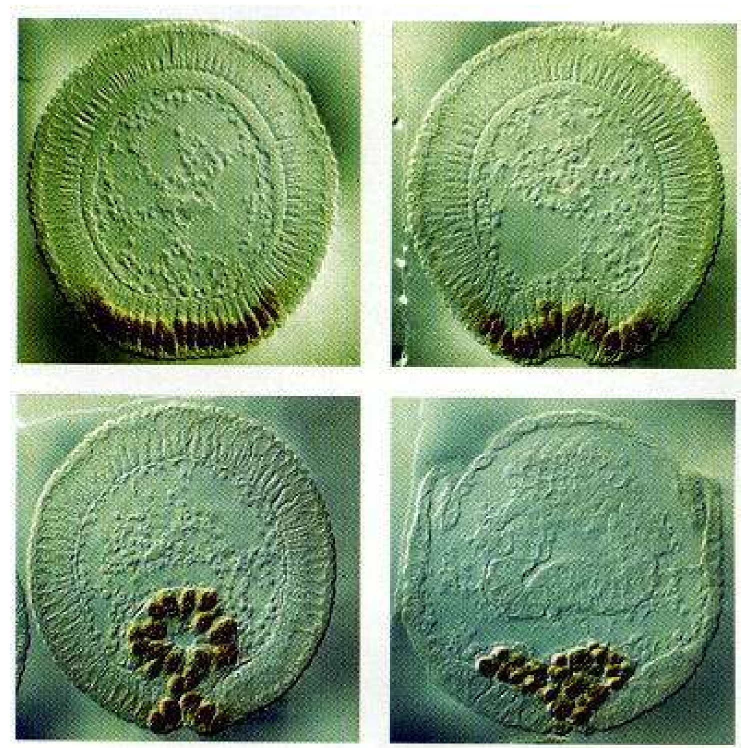
4. Gurken protein does not diffuse to ventral side.
5. Ventral follicle cells synthesize Pipe proteins.
6. In ventral follicle cells, Pipe completes the modification of unknown factor (x).
7. Nudel and factor (x) interact to split the Gastrulation-deficient (Gd) protein.
8. The activated Gd protein splits 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.)

Dorsal regulates mesoderm and neuroectoderm formation through *twist*, *snail* and *rhomboid*





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