Neural Induction & Neural Organizer

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Embryonic origins of nervous system

- Following gastrulation, cells in each germ layer form anlagen
- Ectoderm thickens to form neural plate in dorsal side of embryo

  (structure of shape of keyhole)
- Cells in neural plate give rise to neural tube (neurulation)

Neural induction & neural organizer

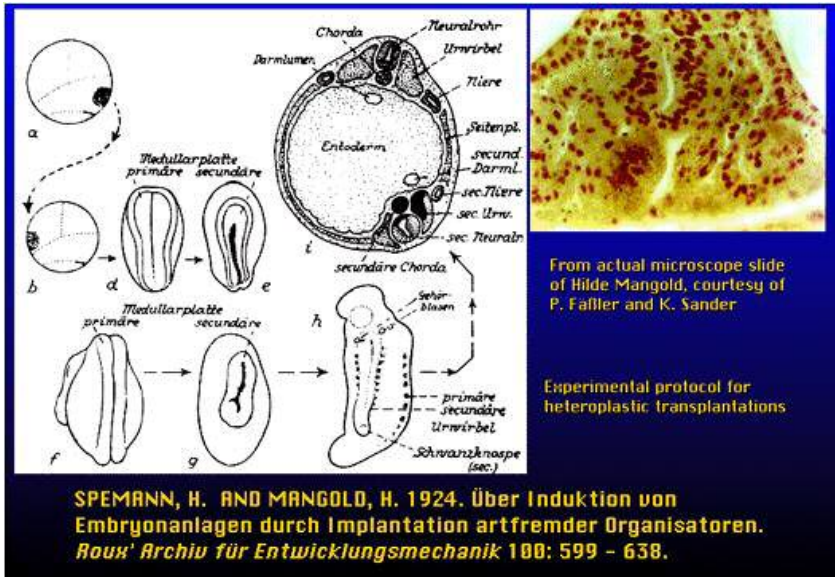
- Conversion of 2D neural plate into 3D neural tube – a complex problem of morphogenesis
- The concept of neural induction – **heteroplastic tissue grafting experiment** (*Mangold and Spemann 1924*)
- Spemann's organizer in avian or mammalian embryos – **Hensen's node**
- Temporal pattern of expression of factors from organizer

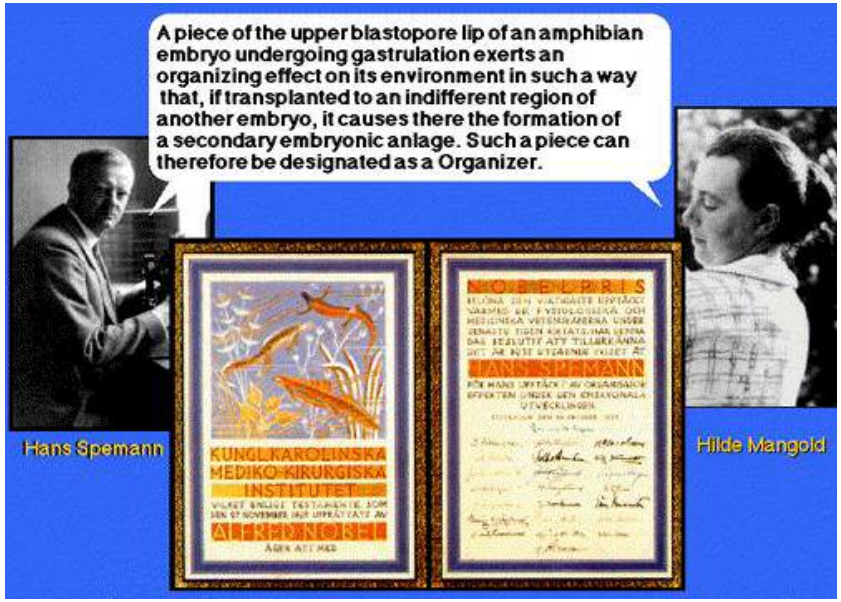
Searching for the elusive neural inducer – cytokines in neurobiology

- Identification of neural inducer – *Holy Grail* in developmental neurobiology

- Neural inducers are not instructive, but permissive in action

Transplantation of dorsal blastopore lip (DBL) from one-blastula stage embryo to ventral side of another embryo





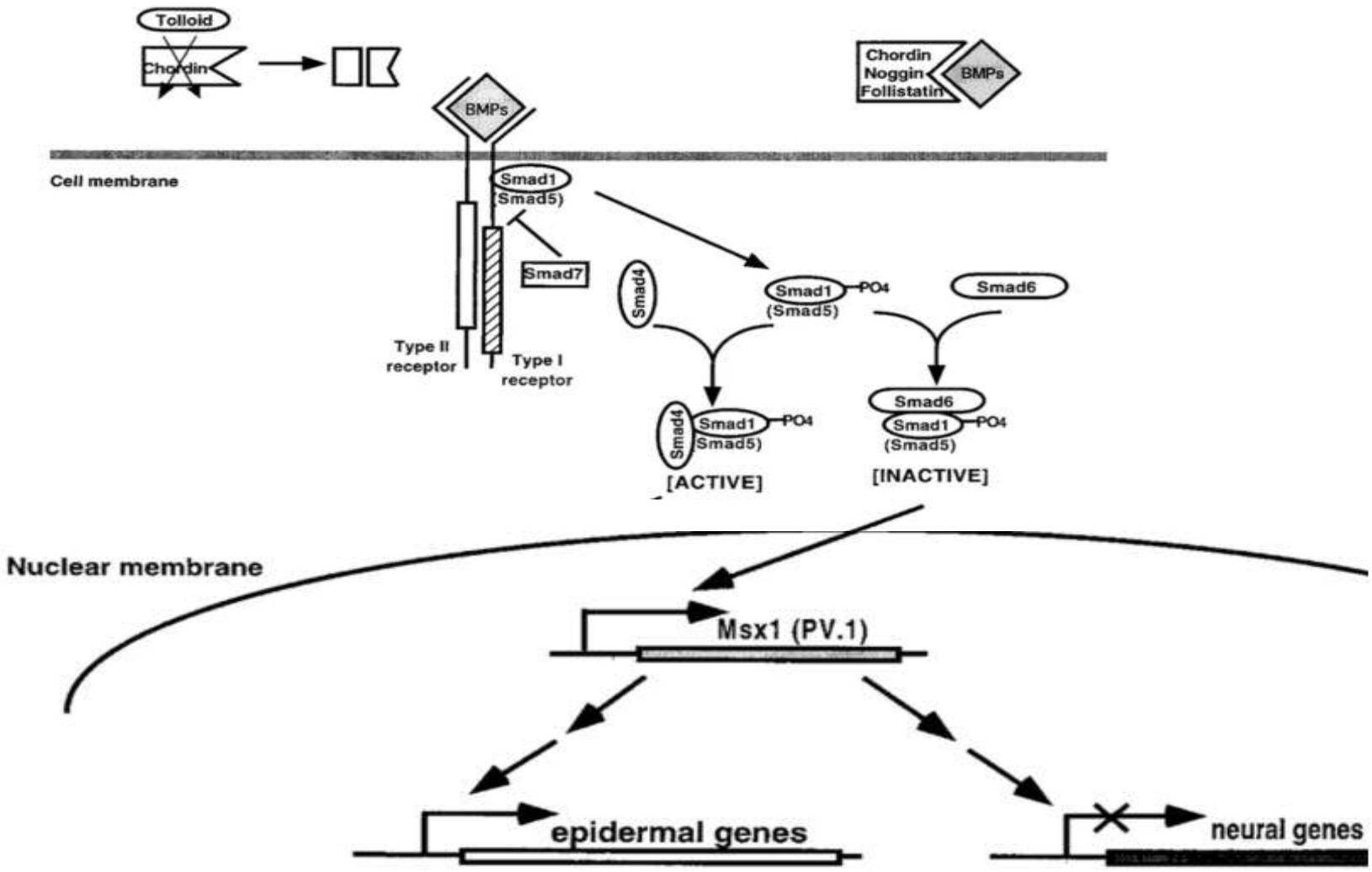
Molecular basis for ventral patterning

TGFβ family (PGF)

Serine / Threonine kinase activity of receptors lead to phosphorylation of *Smad* transcription factors

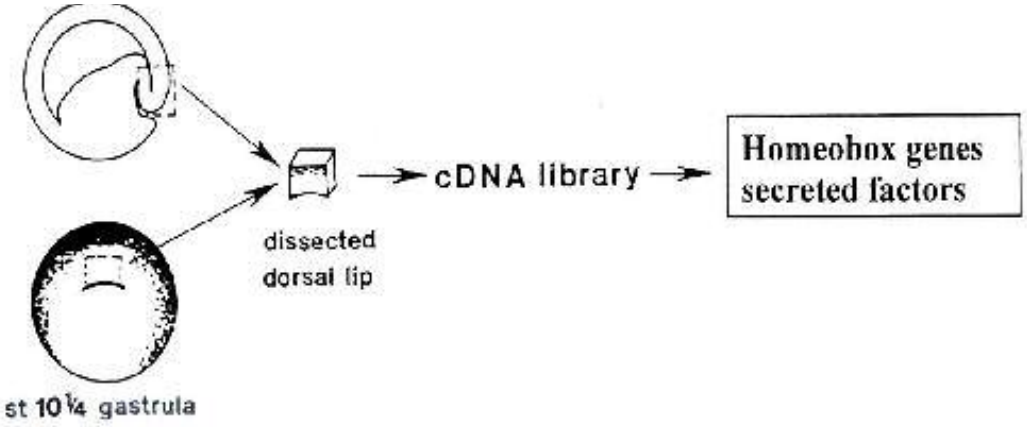
- BMPs (BMP-2&4)
- Activin
- GDF

BMP signaling pathway



Patterning by organizer effected through secreted antagonists of growth factors

Gene	Product
chordin	novel secreted protein
cerberus	novel secreted protein
goosecoid	homeobox/transcription factor
pintallavis/XFKH-1	transcription factor
PAPC	protocadherin/structural gene
Xnot-2	homeobox/transcription factor
Xlim-1	homeobox/transcription factor
Frzb-1	novel secreted protein



Neural induction by natural inhibitors of BMPs

- Follistatin
- Noggin
- Chordin
- Cerberus
- nr3

Mechanisms of action of noggin & follistatin

- XlPOU2 (POU transcription factor) – induced by noggin –

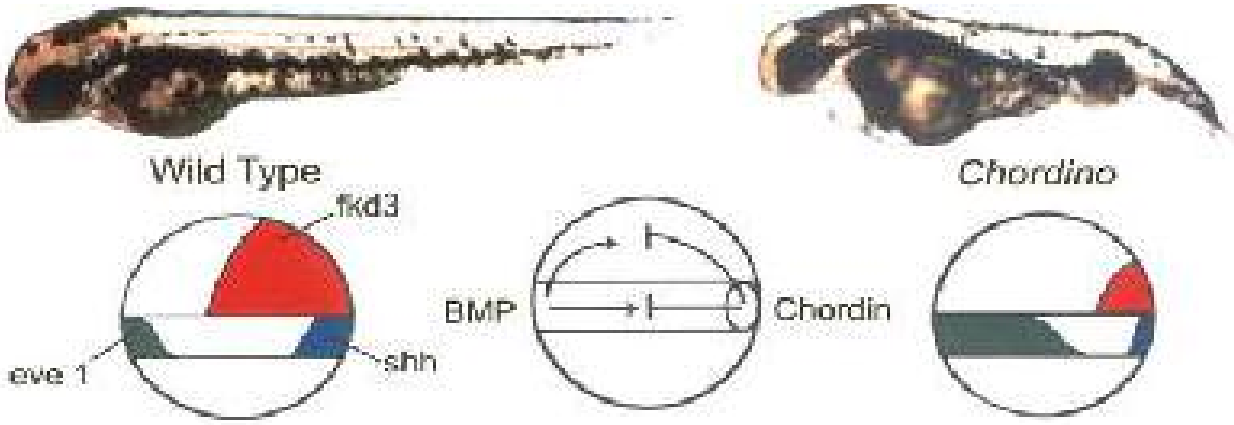
  converts ectodermal cells into neural tissue

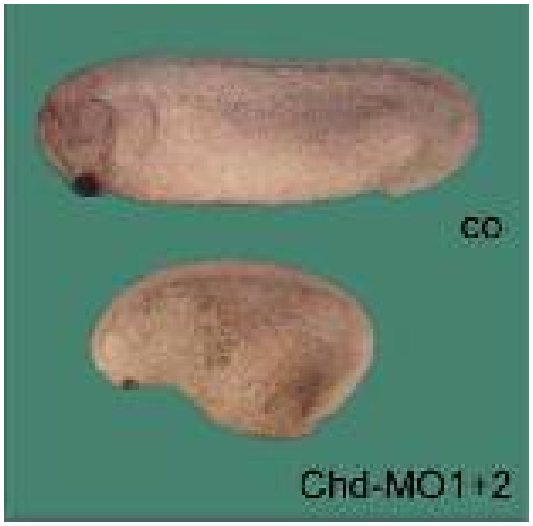
- Follistatin – activin antagonist

Dino (*chordino*) mutant

Chordino mutant zebrafish – reduced size of neural plate

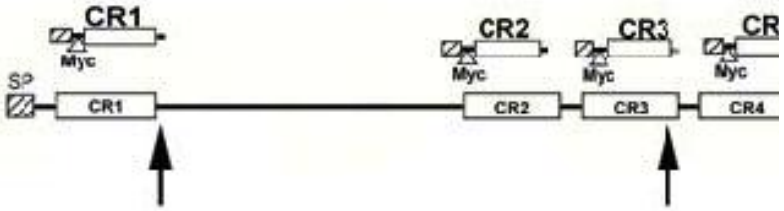
Loss of function mutation in BMP (***swirl***) – expanded neural plate



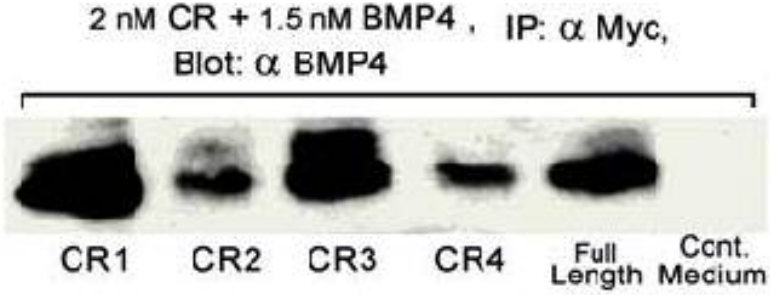


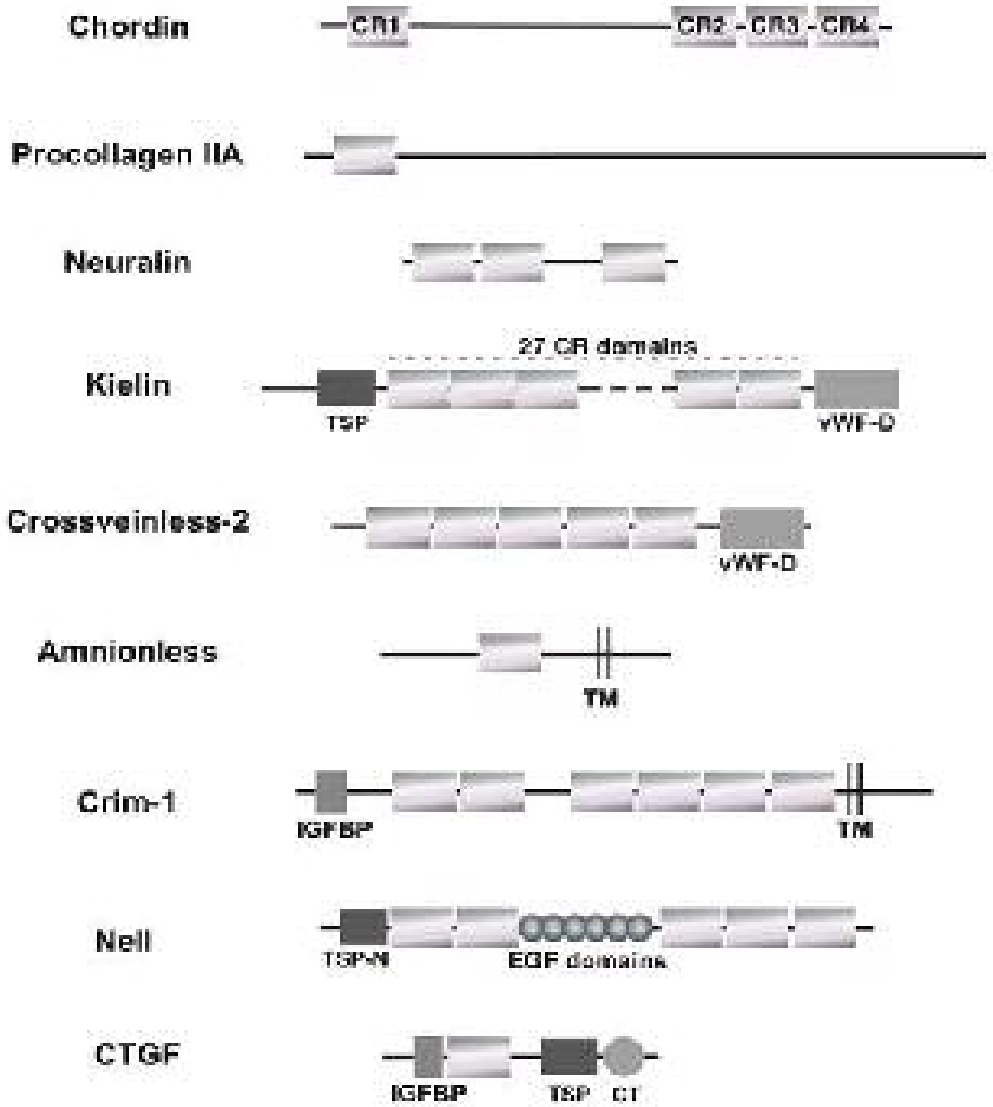
Antisense morpholino of chordin in *Xenopus*

Chordin has cysteine-rich (CR) domains – BMP-binding modules

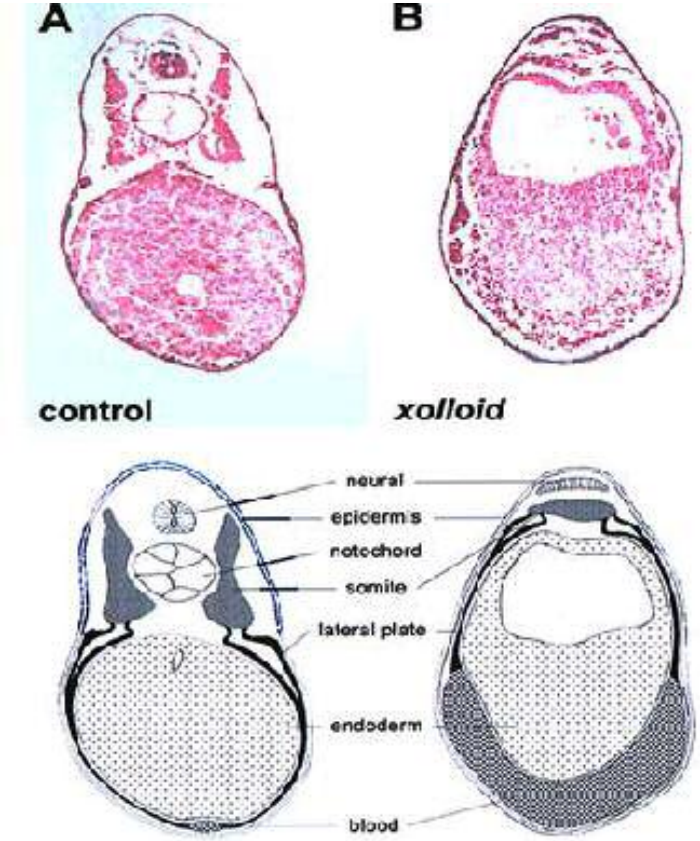


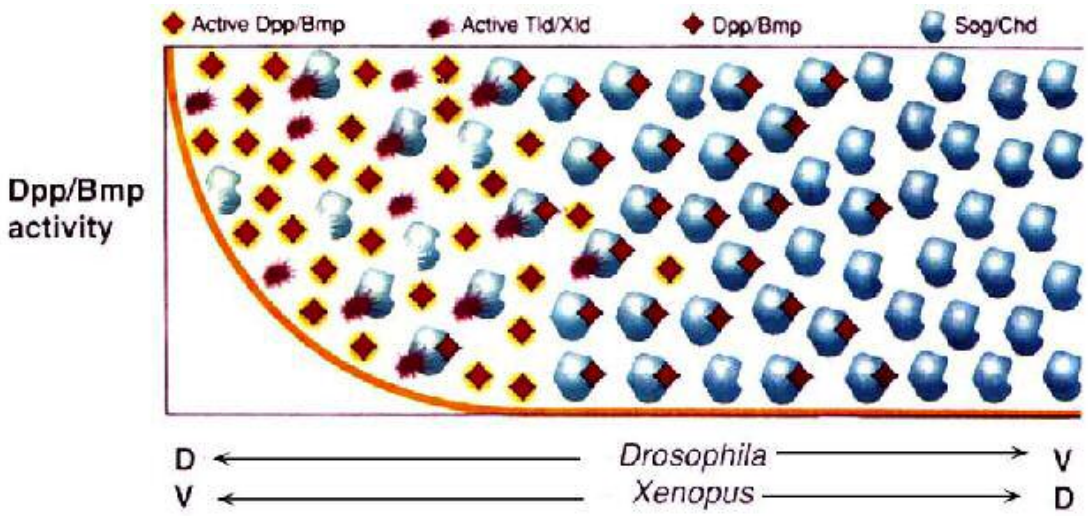
Immunoprecipitation of BMP4 with CRs





Proteolytic control plays crucial role in formation of gradients of growth factor

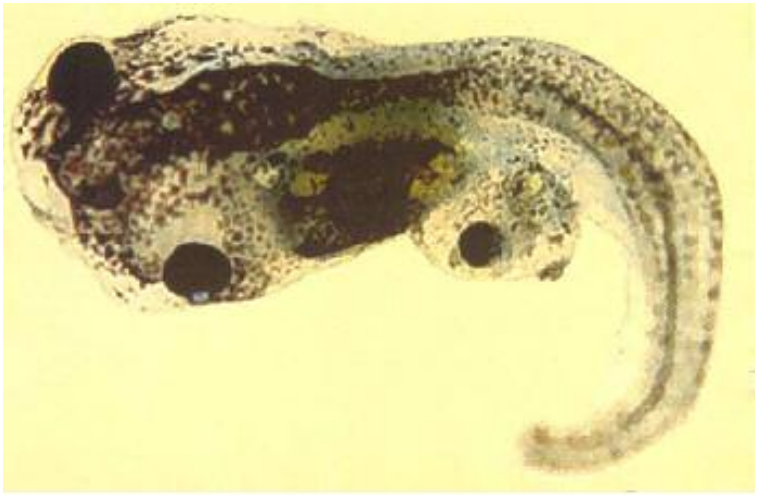




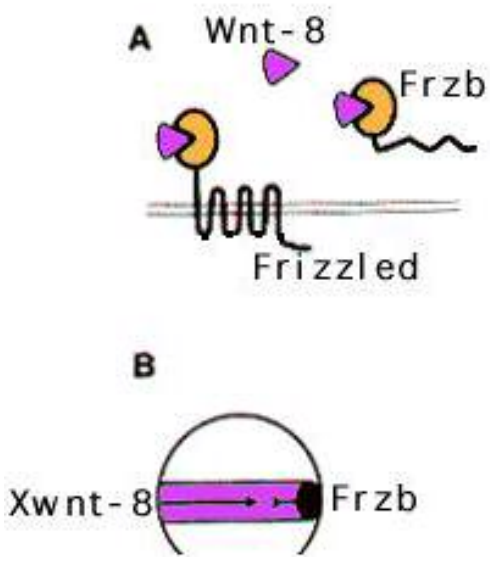
Chordin is cleaved by tolloid/xolloid

Inhibition of canonical *wnt* signaling

1. Cerberus
2. Frisbee
3. Dickkopf-1



Cerberus mRNA injected into 32-celled *Xenopus* blastomere



Noggin can induce anterior neural tissue, but cannot induce posterior neural tissue

- Noggin can induce anterior & general neural markers (NCAM & XIF3 mRNA, XAG-1 & otx2 [formerly otxA] in animal pole explants in absence of detectable mesoderm
- Noggin protein - no ability to induce posterior neural markers (*e.g.*, ß-tubulin mRNA, En-2, Krox20 & XlHbox6)
- Possible factors involved in posteriorization - FGF, retinoic acid & Wnt-3a

Strategy of neuralization by inhibition of inhibitor is evolutionarily conserved

Drosophila

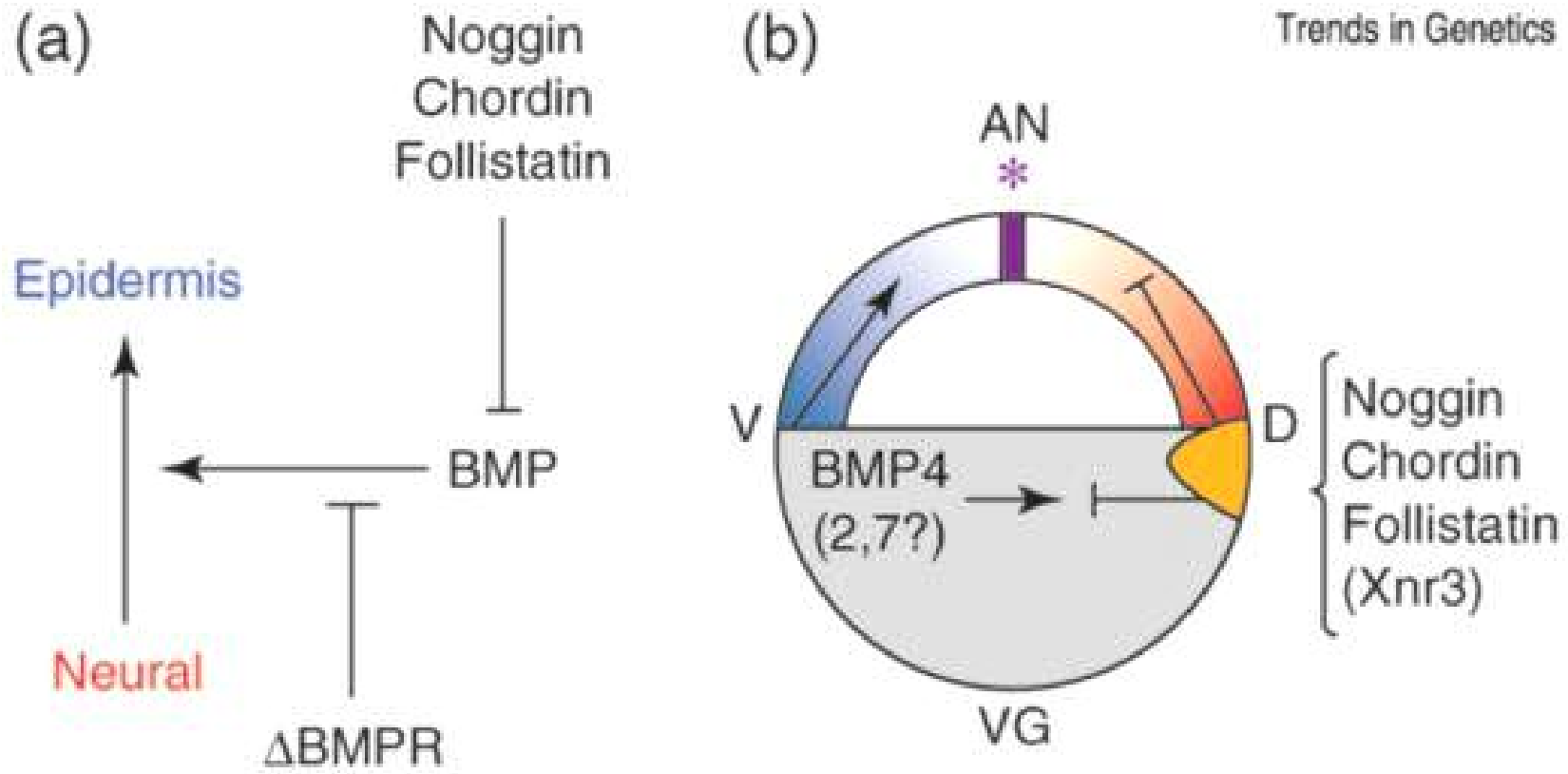
Short gastrulation (sog) – direct neural-inducer

Homolog of chordin

Decapentaplegic (dpp) – neural inhibitor

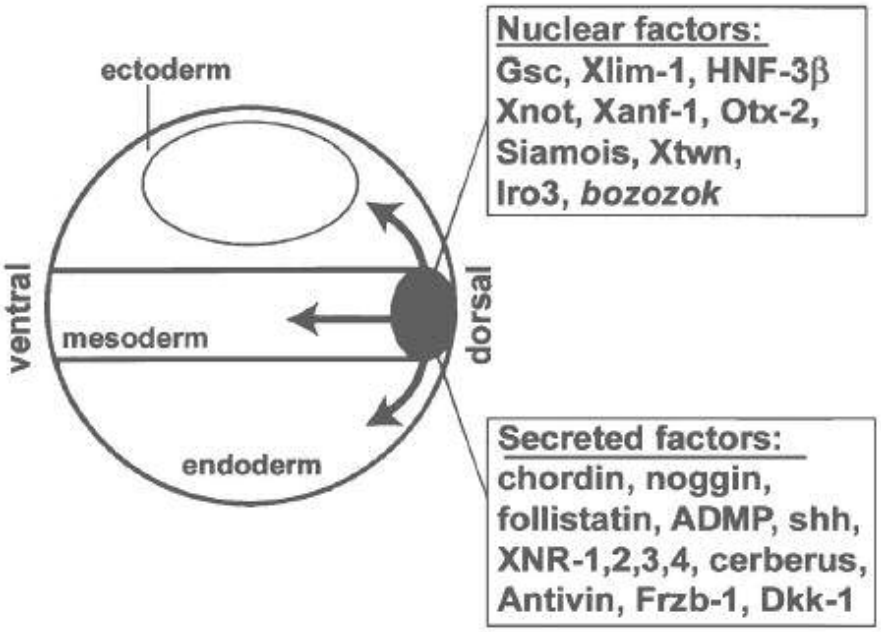
Homolog of BMP4

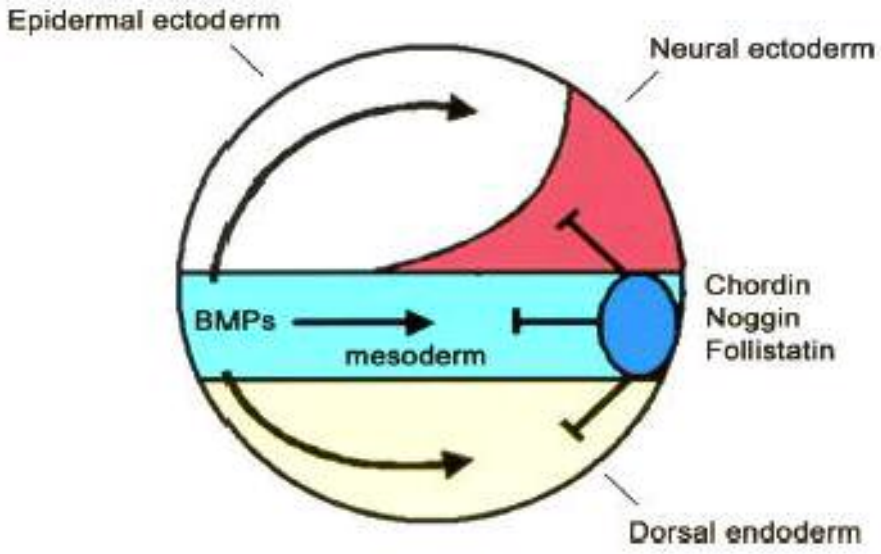
Default model of neural induction



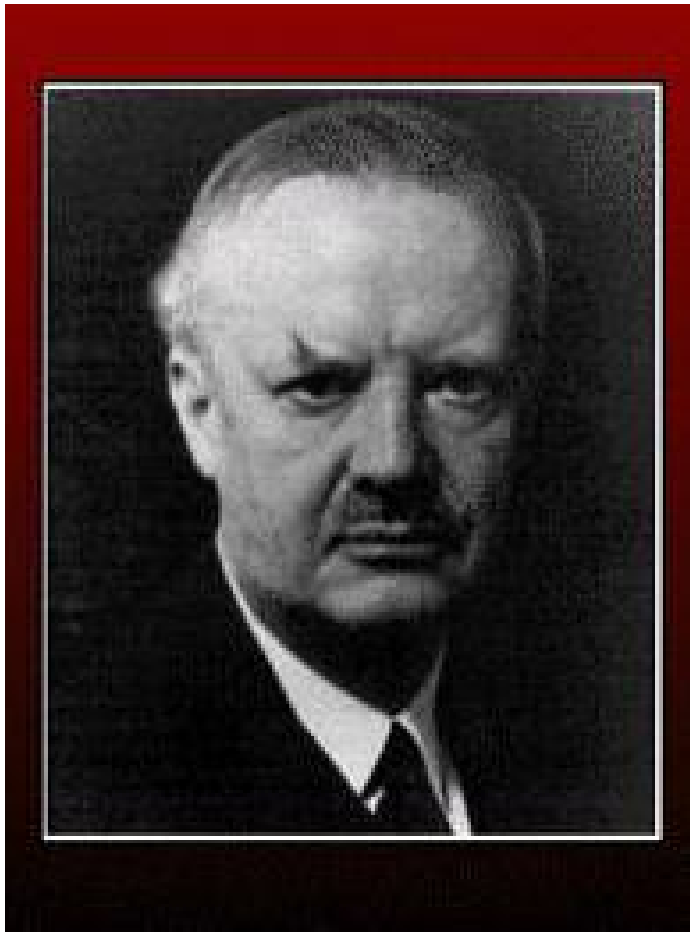
Injection of dominant negative BMPR (DN BMPR) – neural induction

A spanner in the works: inhibitors to modulate pathways vs. evolution of new signaling pathways





Thank you



Hans Spemann (1869-1941)

Hilde Mangold (née Proescholdt) (1898-1924)