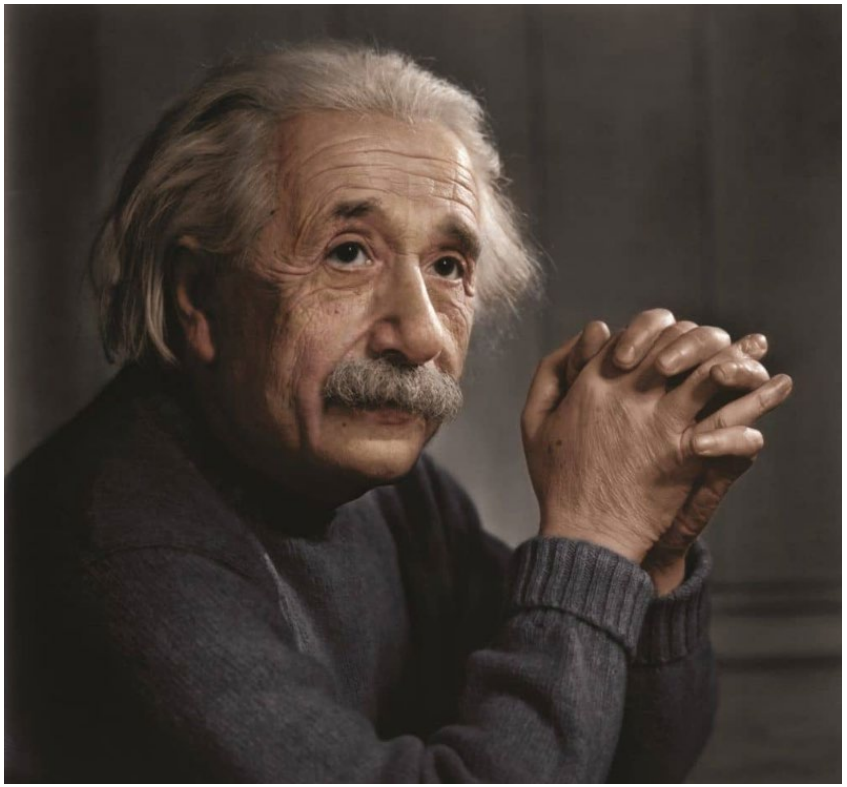
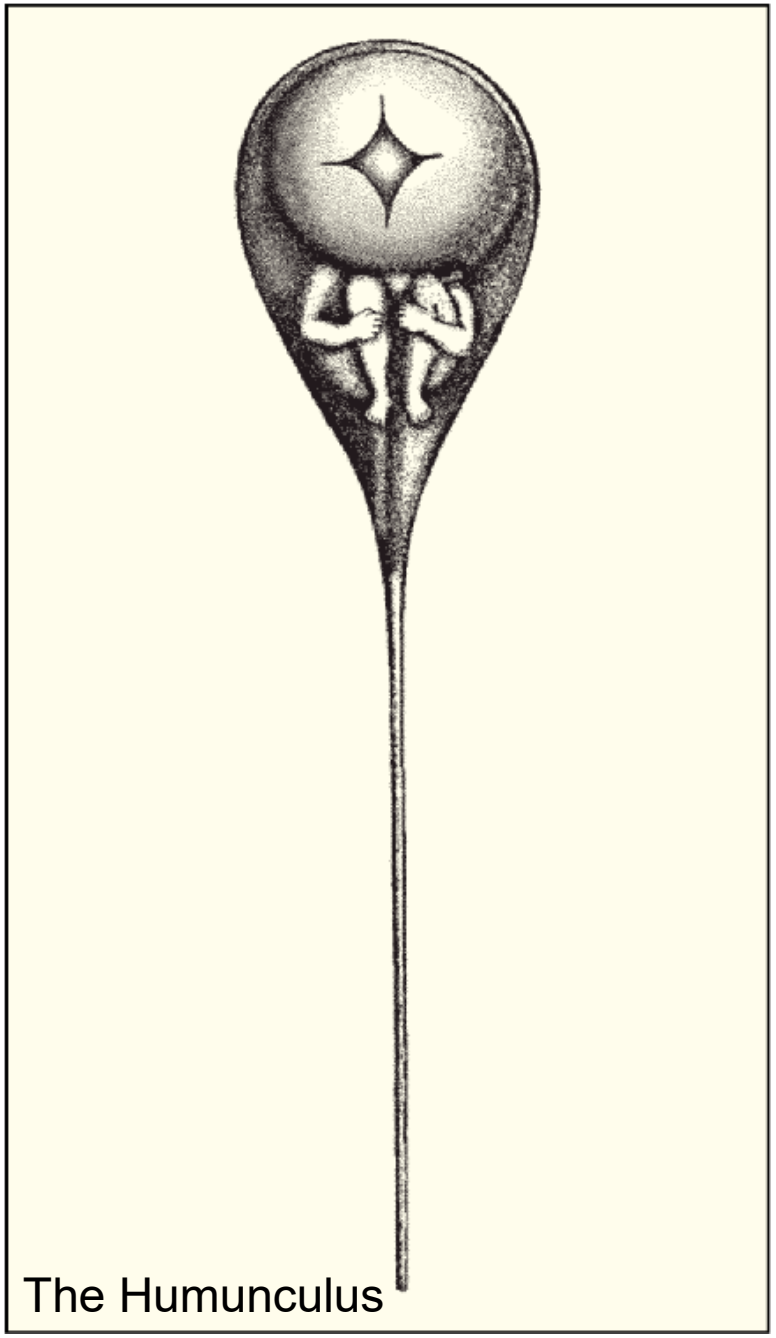

Building
an
embryo
Talk for the Royal Society of Wellington
Peter Pfeffer 21 July 2021

?



(a)

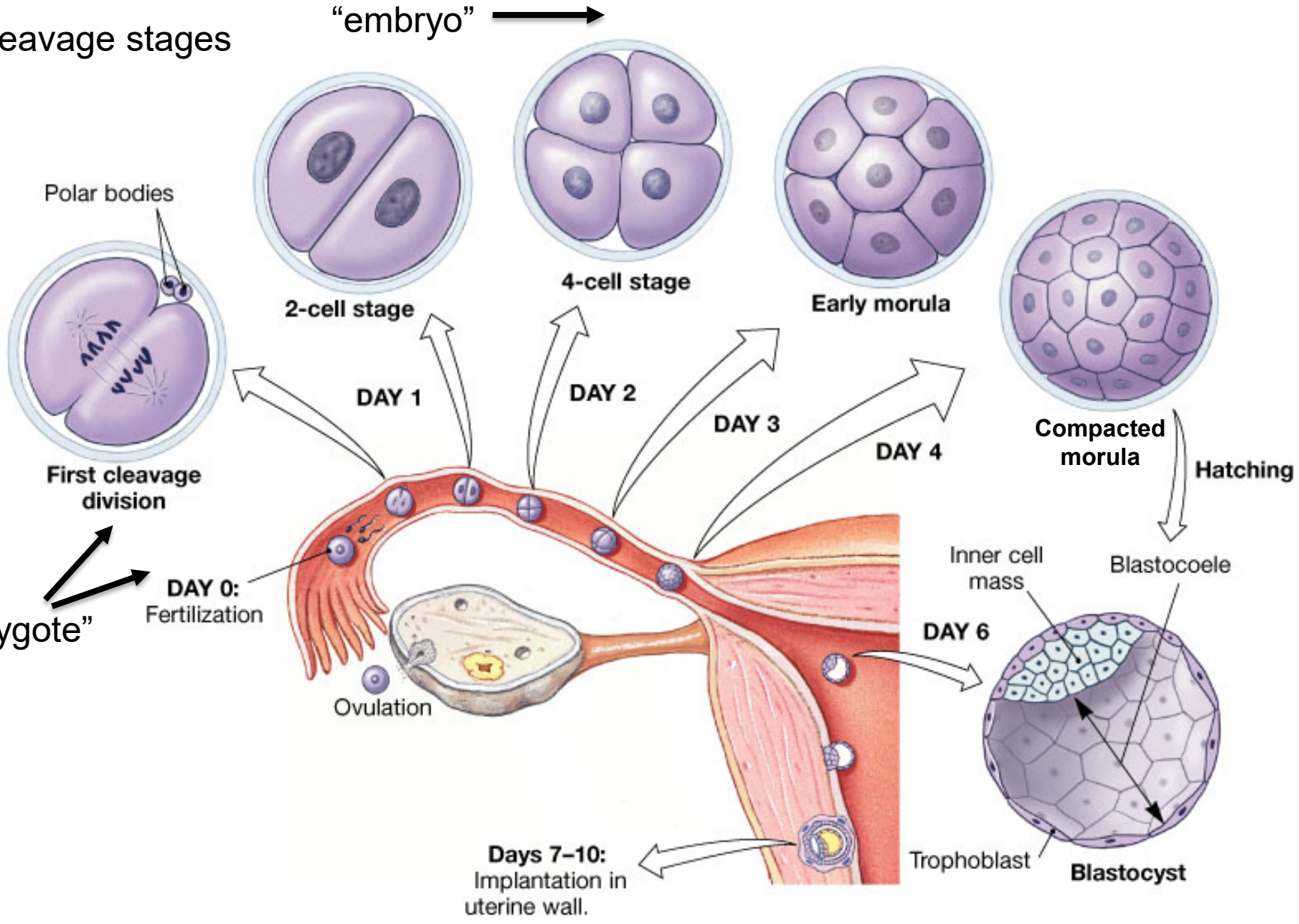


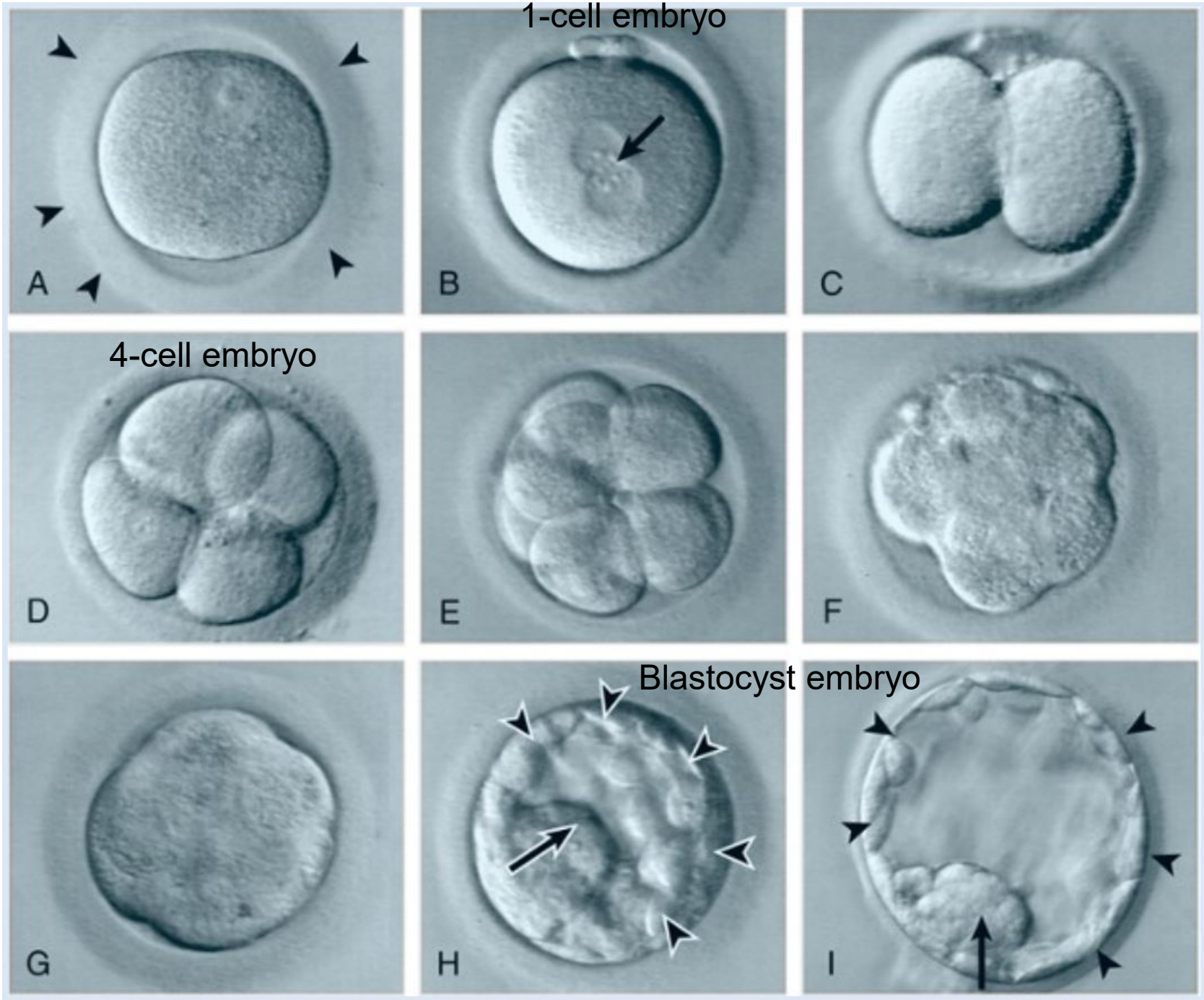
The Humunculus

Epigenesis

New structures arise by progressing through a number of different stages.

Cleavage stages




1-cell embryo
A
B
C
4-cell embryo
D
E
F
Blastocyst embryo
G
H
I


Beyond the blastocyst

Gastrulation

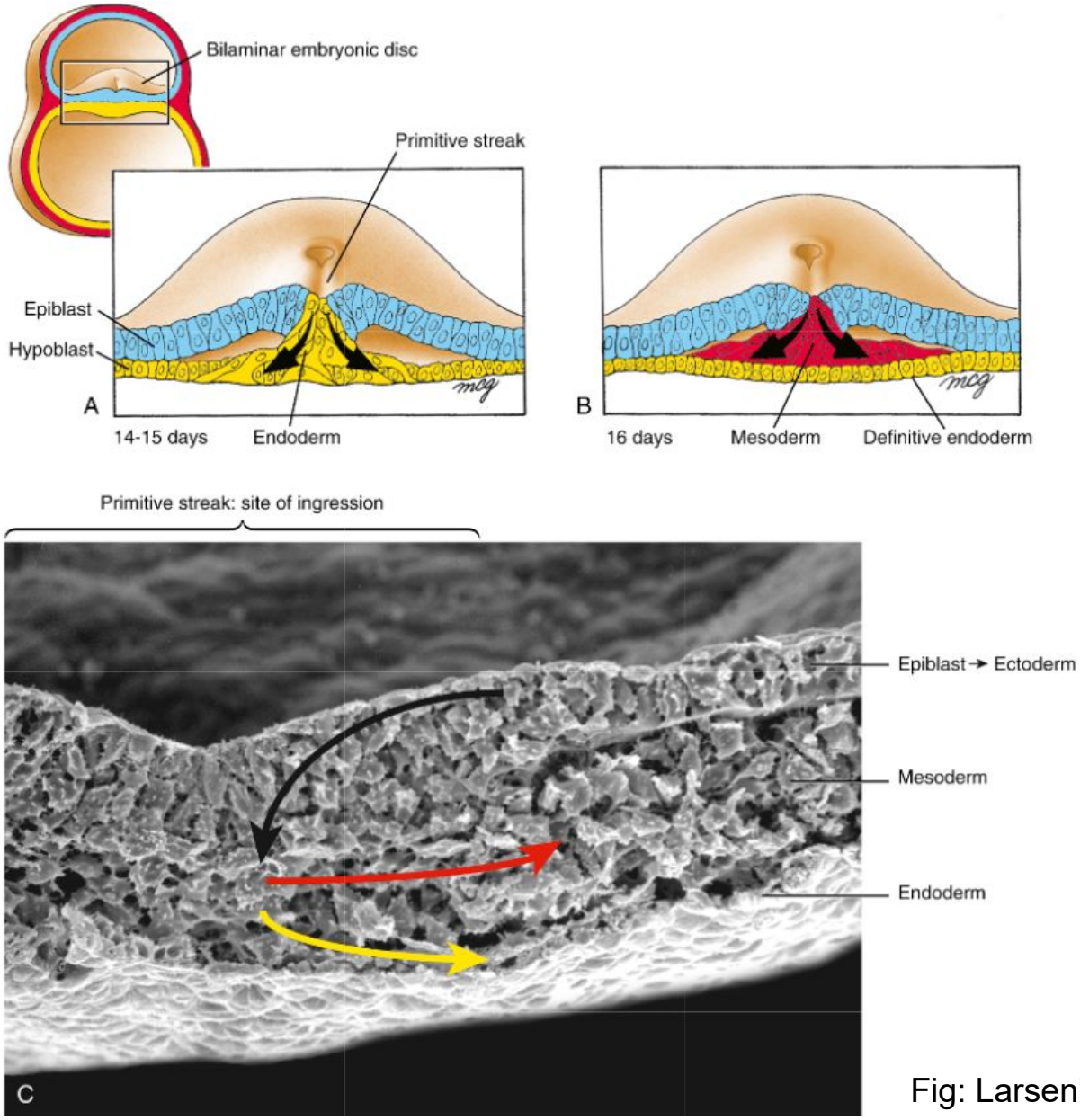
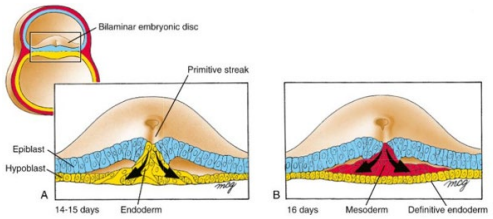


Fig: Larsen's Human Embryology



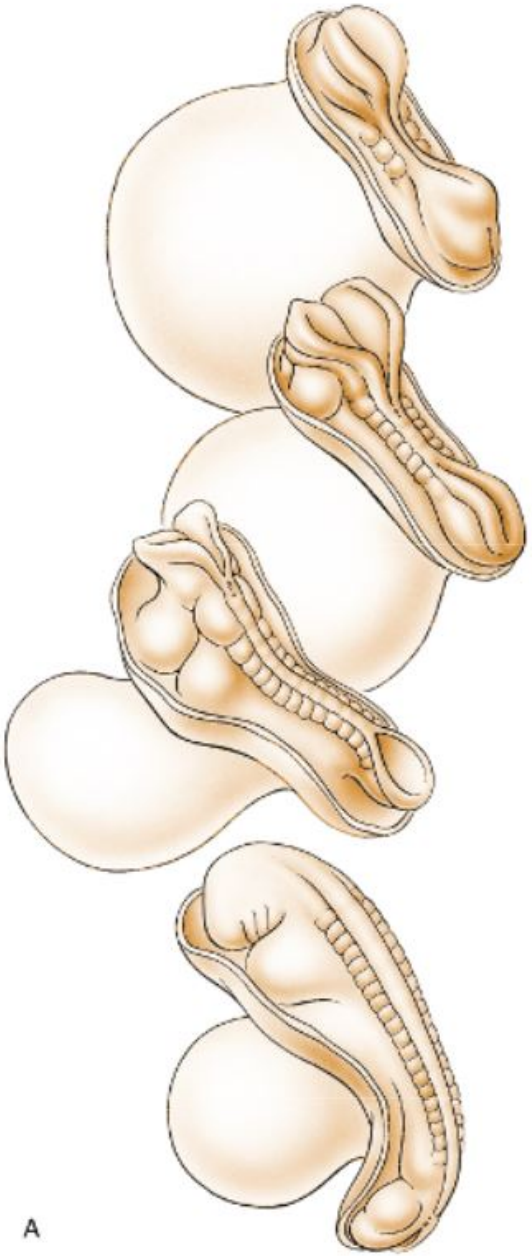
Nervous system

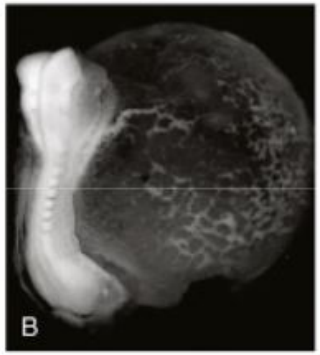
Outer skin

Inner linings

Visceral Organs
Muscle, Skeleton

Carlson: Human embryology and Developmental Biology


A


B


C

Fortification of flour with the B vitamin folic acid

All non-organic wheat flour used for making bread must be fortified with the B vitamin, folic acid, by mid-2023.

8 JULY 2021

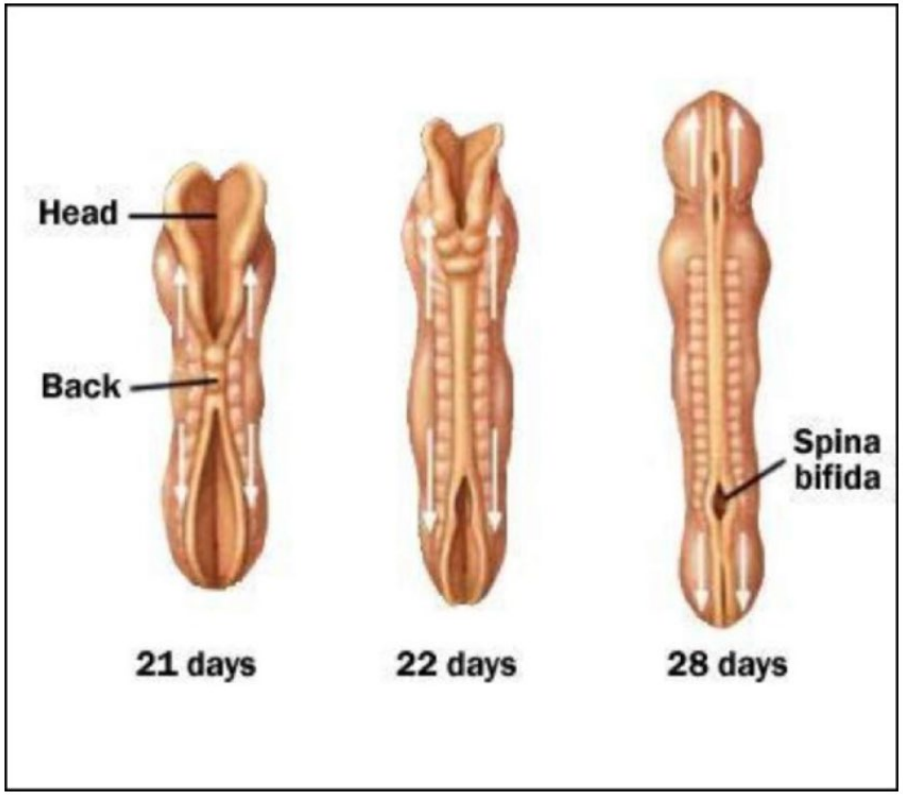
The Government ann
bread making.

This decision aims to
choice. There is a 2-ye

Read the Government

Review of folic acid fo

The health benefits a
and the Royal Society

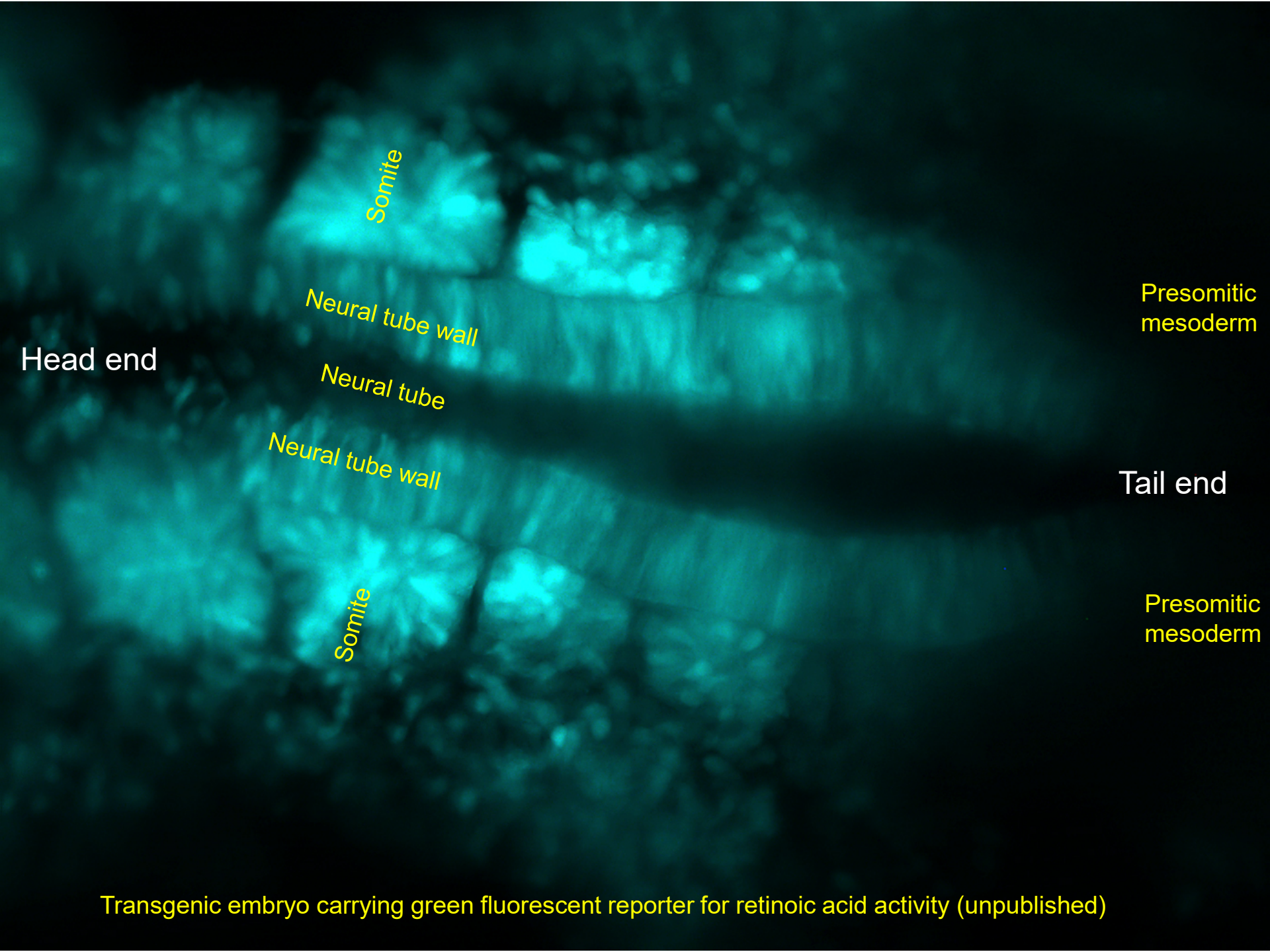


ION

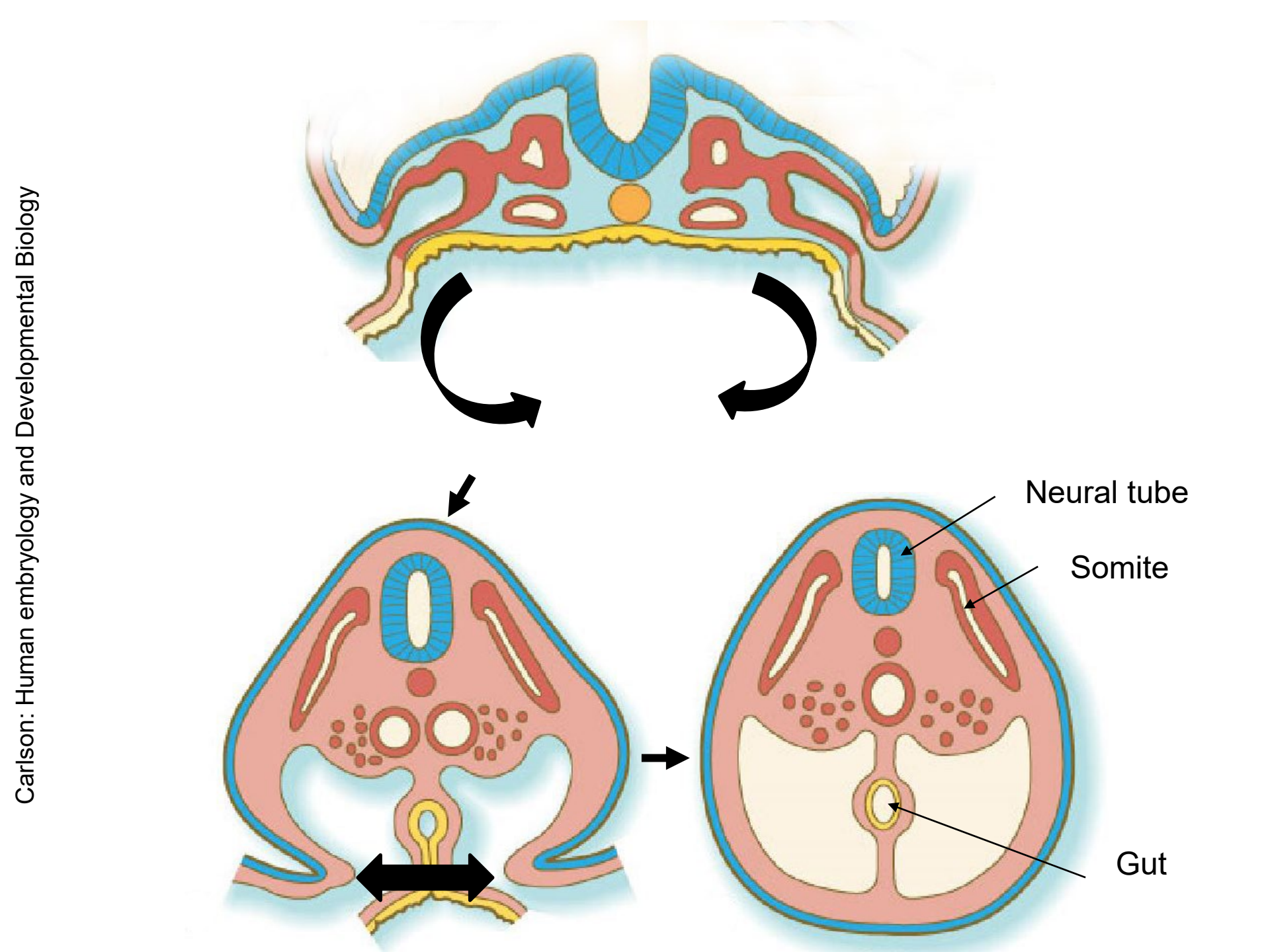
ganic wheat flour used for

effectiveness and consumer
hanges, ending mid-2023.

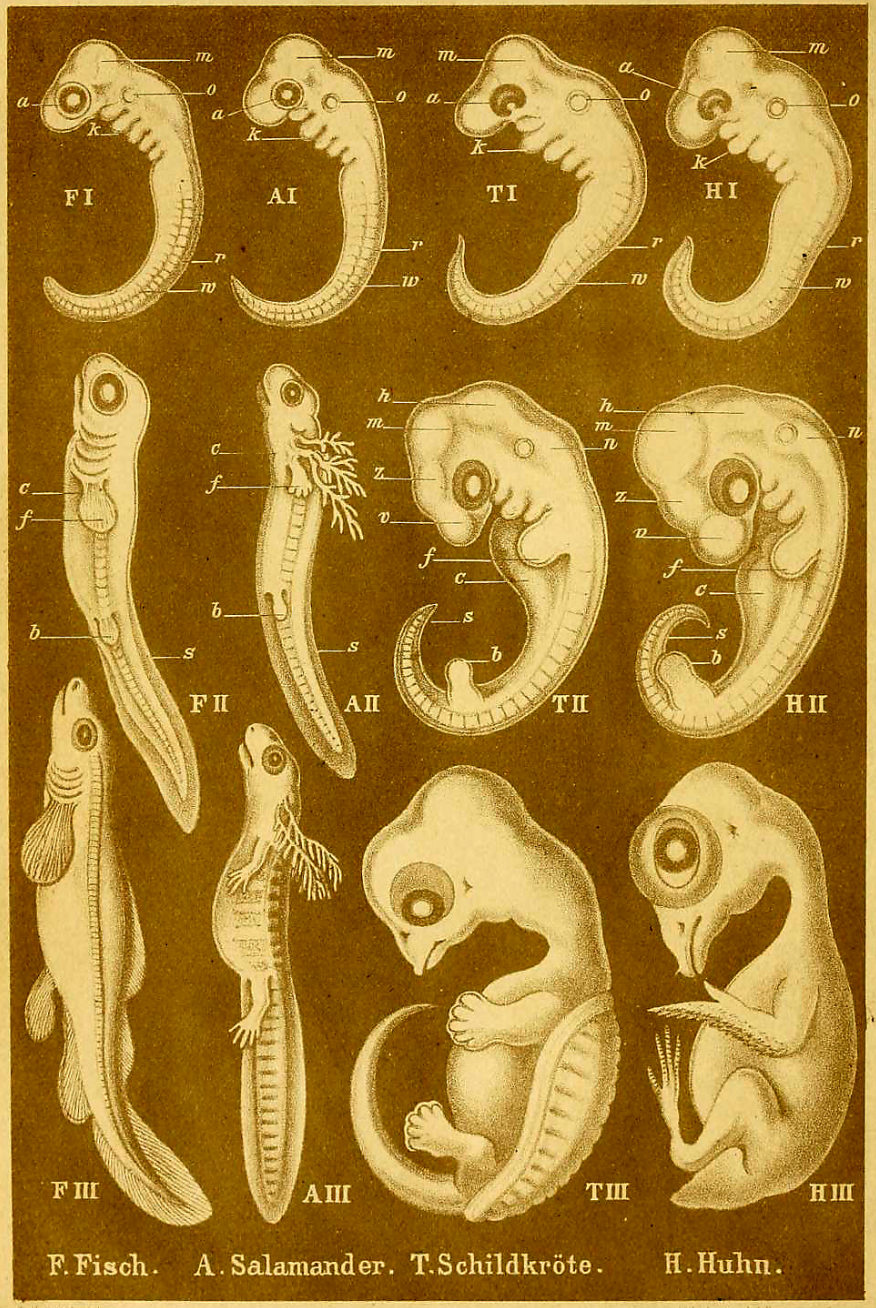
's chief science advisor



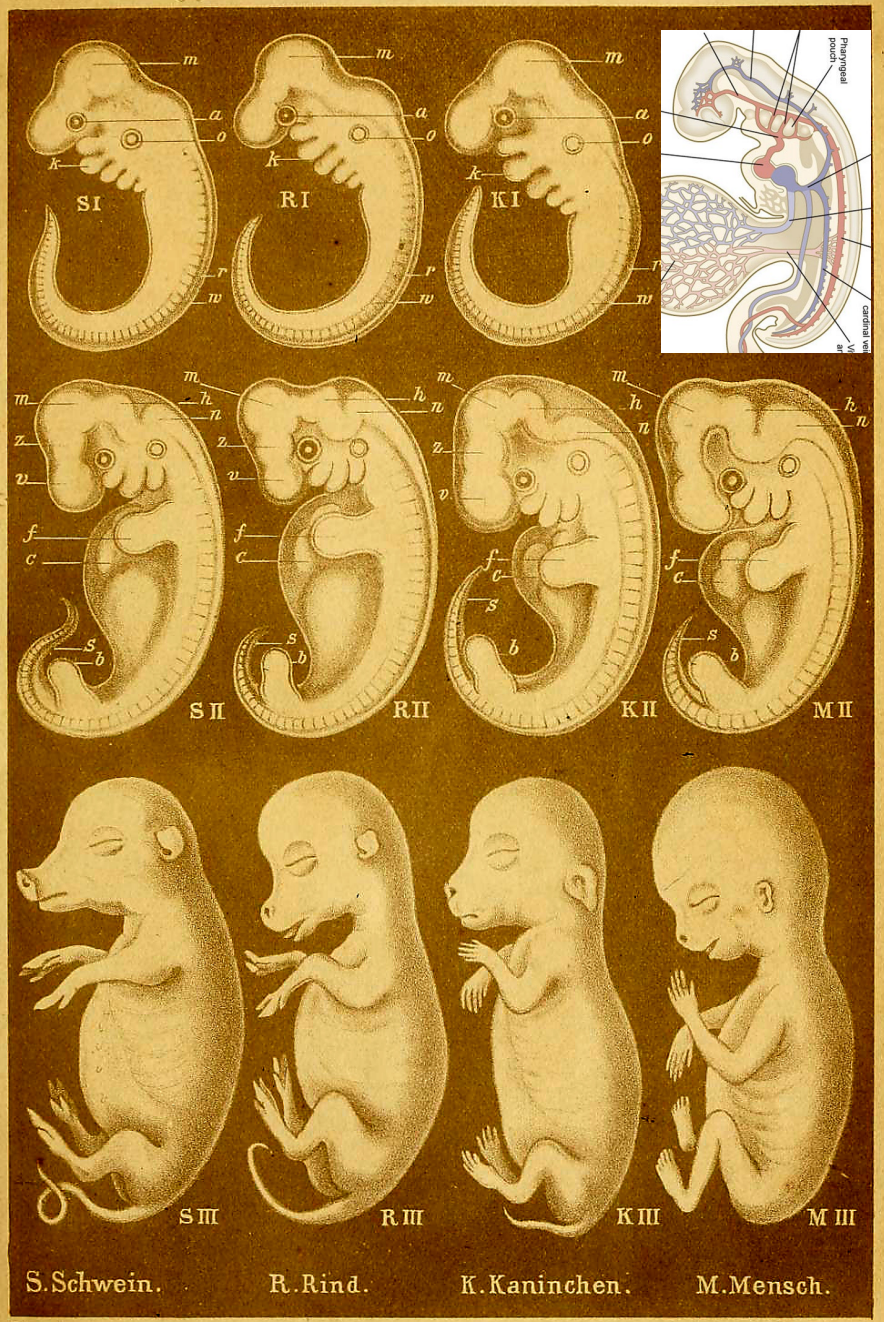
Transgenic embryo carrying green fluorescent reporter for retinoic acid activity (unpublished)



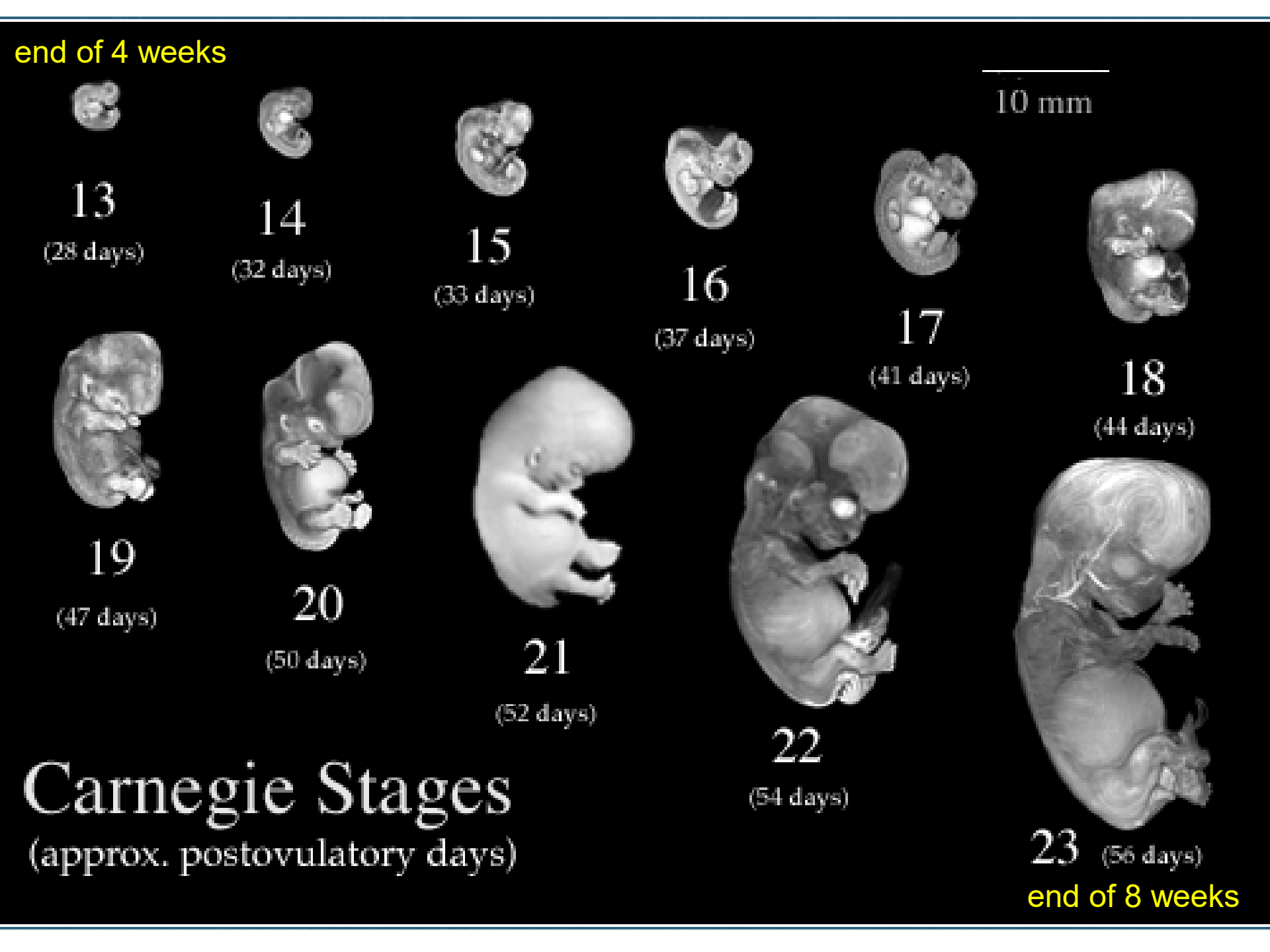
Carlson: Human embryology and Developmental Biology

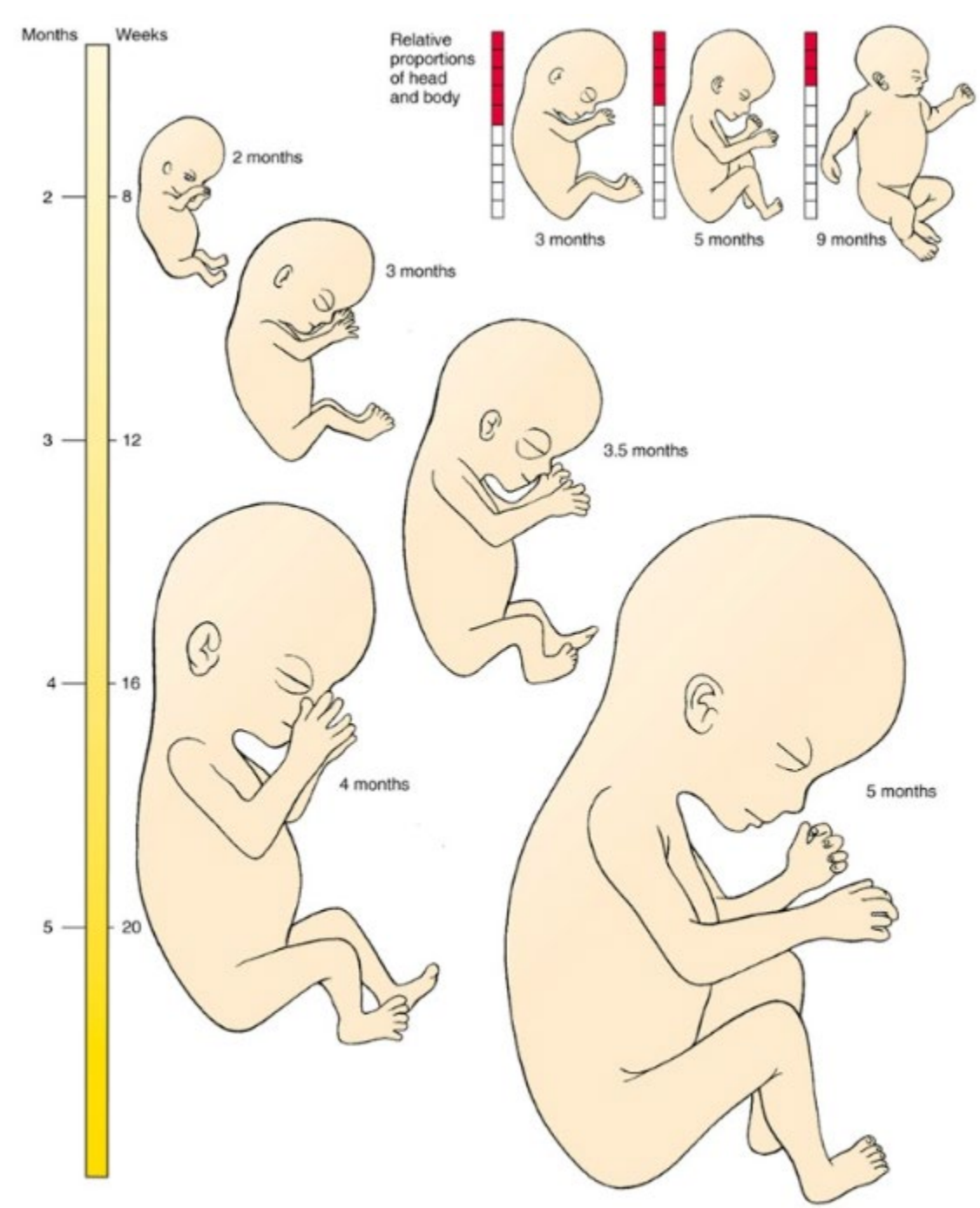


E. Haeckel, del. Lith. Anst. v. J. G. Bach, Leipzig.



E. Haeckel, del. Lith. Anst. v. J. G. Bach, Leipzig.


end of 4 weeks
10 mm
13
(28 days)
14
(32 days)
15
(33 days)
16
(37 days)
17
(41 days)
18
(44 days)
19
(47 days)
20
(50 days)
21
(52 days)
22
(54 days)
23
(56 days)
Carnegie Stages
(approx. postovulatory days)
end of 8 weeks



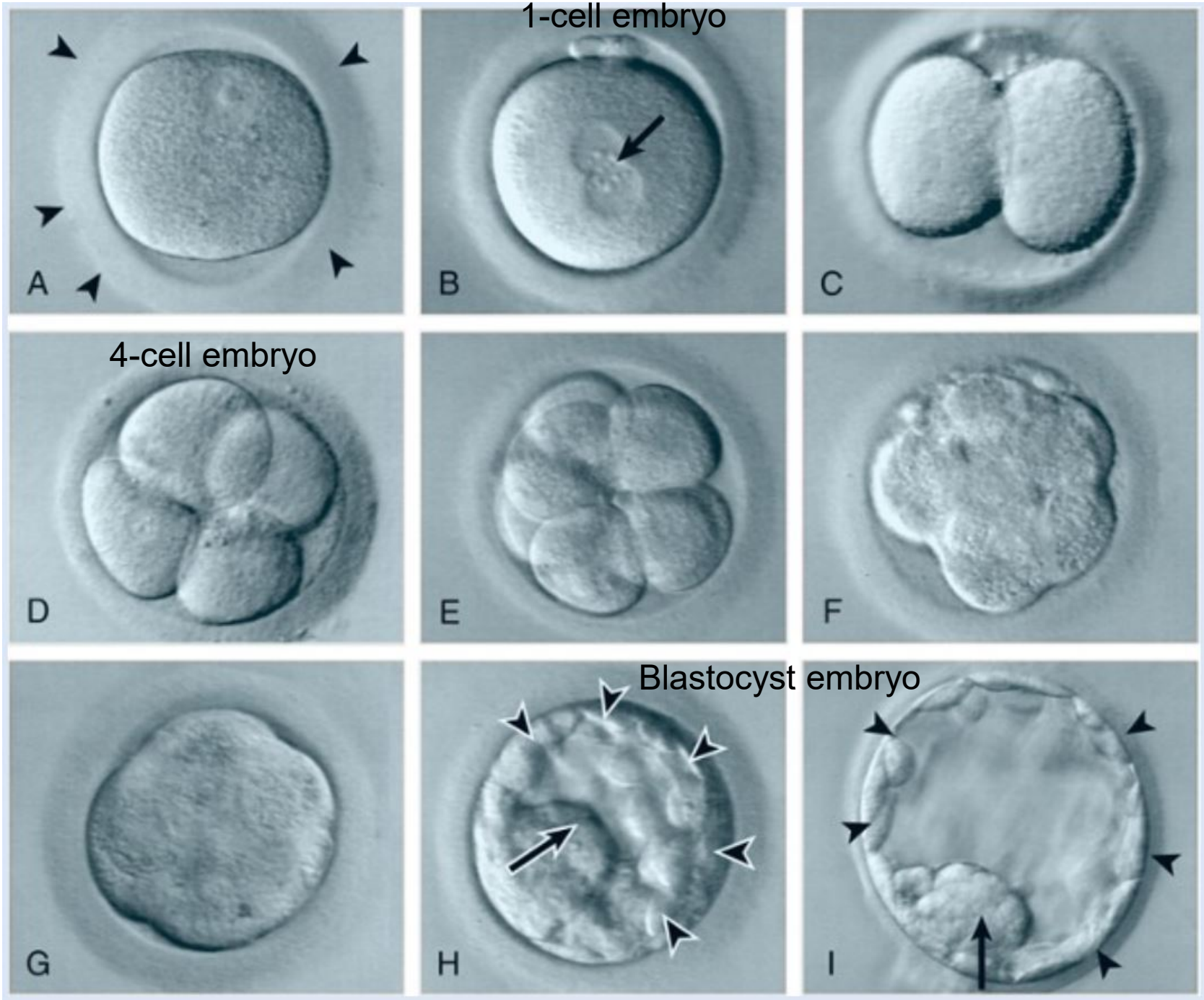
Time line. Fetal development.

The fetal period

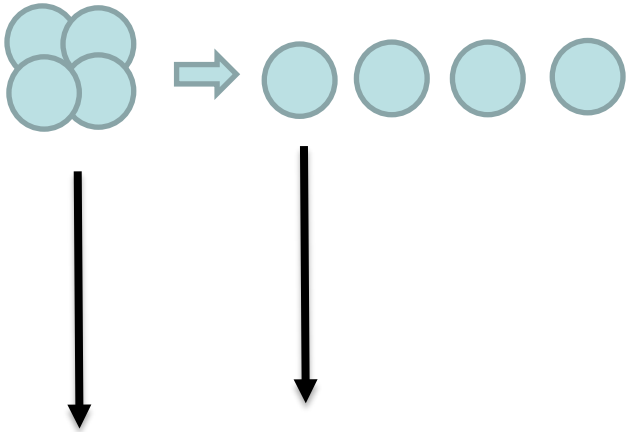
- All organ systems are formed by the end of the eighth week
- Activities of the fetus are growth and organ specialization
- The fetal stage is one of tremendous growth and change in appearance

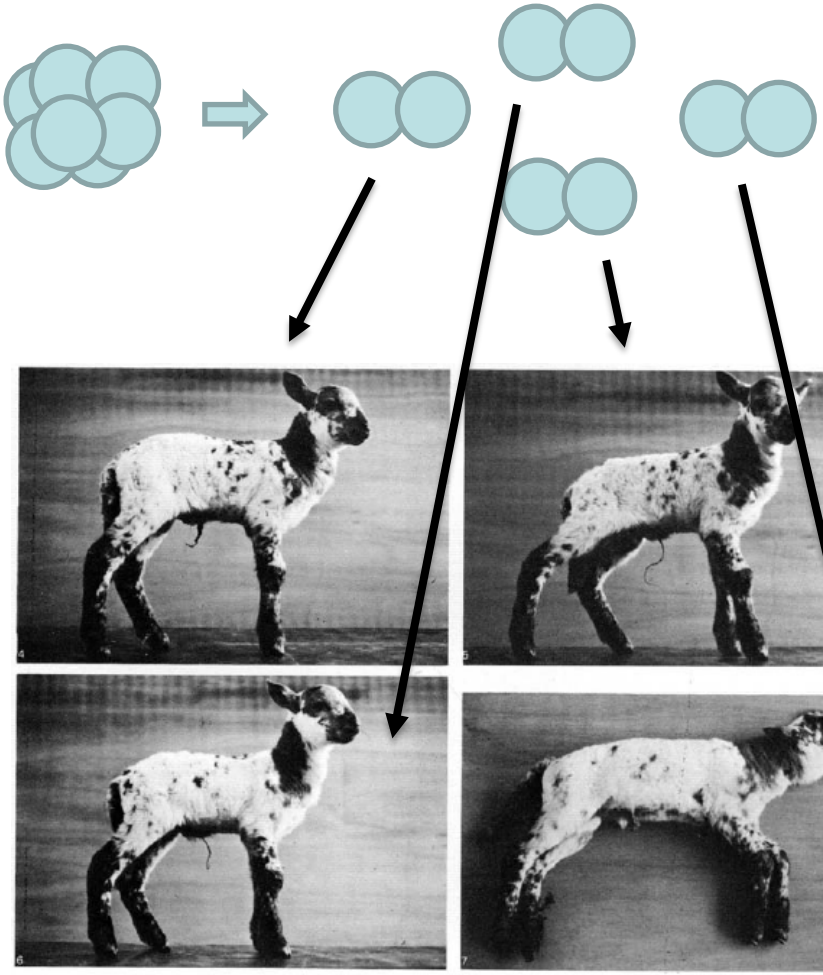
Photo: Peter Chinn


En grève pour défendre nos conditions de travail!
EN GRÈVE
EN GRÈVE
EN GRÈVE
EN GRÈVE


1-cell embryo
A
B
C
4-cell embryo
D
E
F
Blastocyst embryo
G
H
I

All cells from 4-8 cell stages are totipotent





168 S. M. WILLADSEN

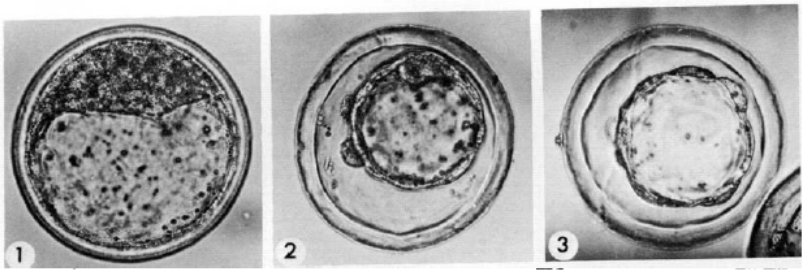
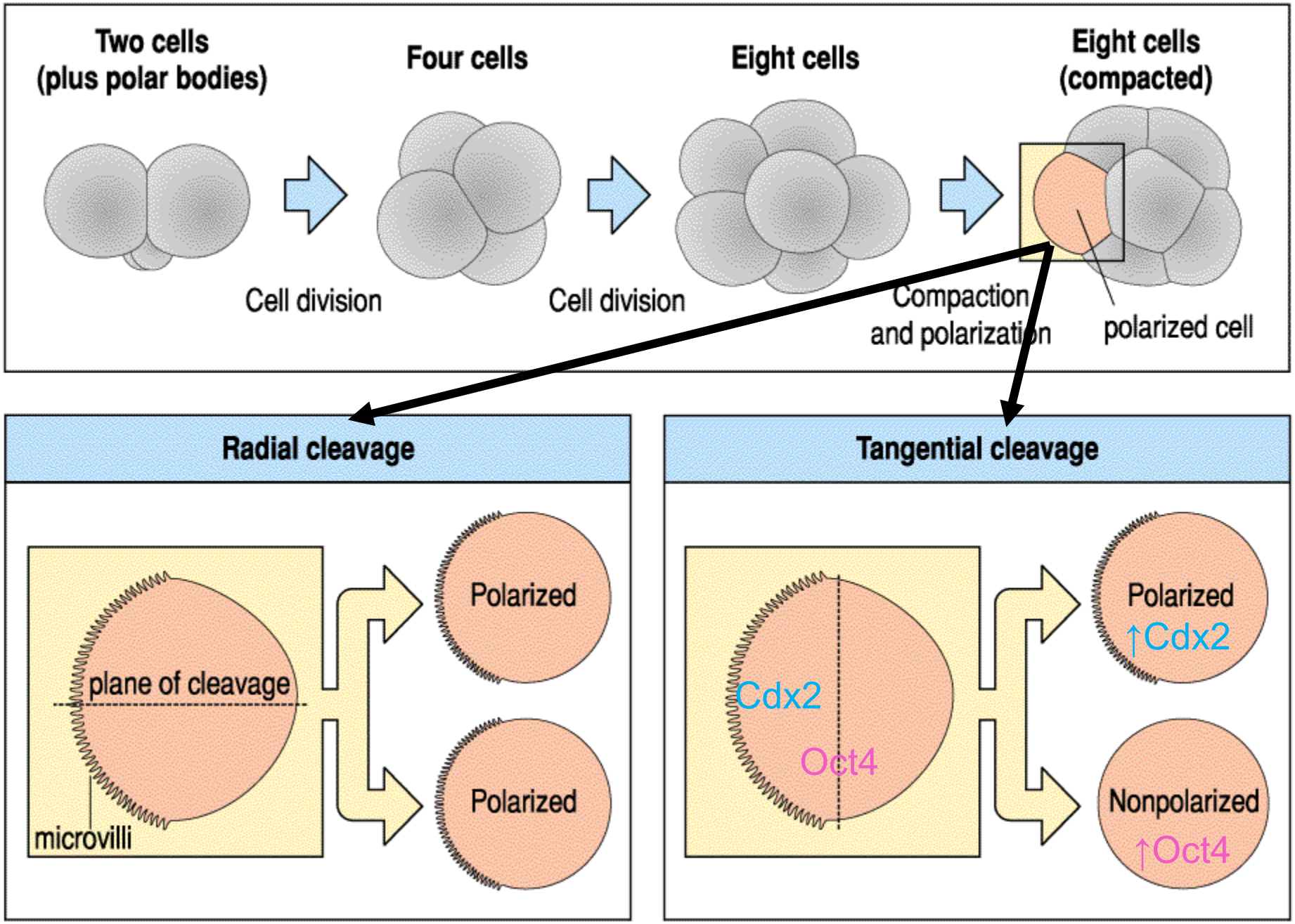


Fig. 1. Normal sheep blastocyst collected on day 7 after onset of oestrus (= Day 0).
Fig. 2. Day-7 blastocyst which developed from a single blastomere of a 4-cell sheep embryo. Note the comparatively small inner cell mass.
Fig. 3. Day-7 vesicular form which developed from a single blastomere of an 8-cell sheep embryo. Note the apparent absence of inner cells.

Figs. 4–7. Monozygotic quadruplet ram lambs, produced from four pairs of blastomeres of an 8-cell embryo. The two lambs in Figs. 4 and 5 were born as twins, and so were the two in Figs. 6 and 7. The dead lamb (Fig. 7) was born alive but trapped in the amnion. This lamb was killed 2 h later, having failed to breathe unaided.

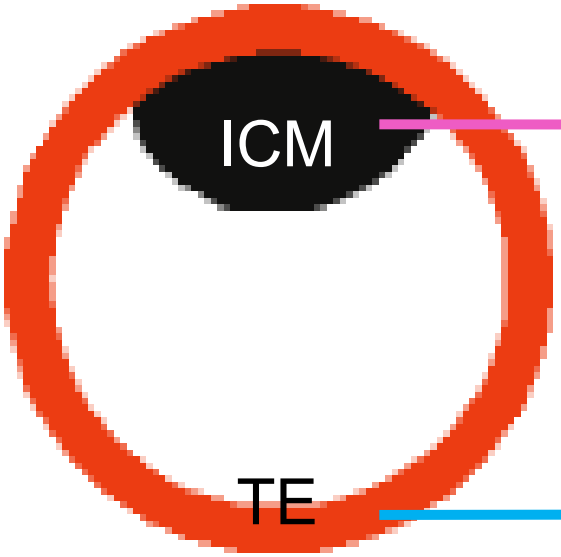
Willadsen, S. M. (1981). The development capacity of blastomeres from 4- and 8-cell sheep embryos. *J Embryol Exp Morphol, 65*, 165-172.

1. Harnessing inherent processes and chance to generate lineage differences


Two cells
(plus polar bodies)
Four cells
Eight cells
Eight cells
(compacted)
Cell division
Cell division
Compaction
and polarization
polarized cell
Radial cleavage
plane of cleavage
microvilli
Polarized
Polarized
Tangential cleavage
Cdx2
Oct4
Polarized
↑Cdx2
Nonpolarized
↑Oct4

Master regulators

Blastocyst



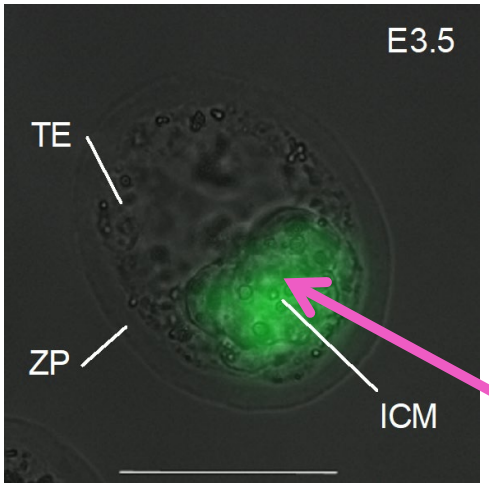
Oct4

Nonpolarized
↑Oct4

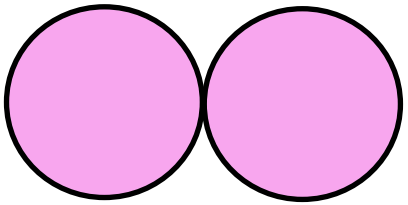
Cdx2

Polarized
↑Cdx2

Mouse embryo



Oct4

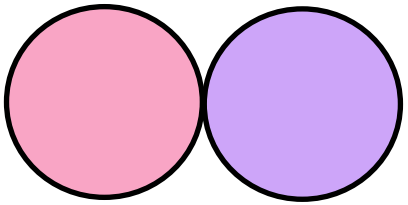


Identity

Gene regulatory network 1 (GRN1)

Oct4
Cdx2

Oct4
Cdx2

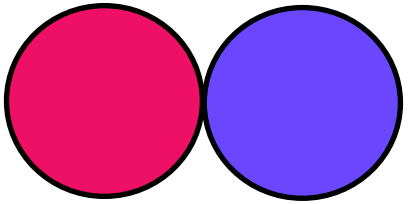


Bias

GRN1 leads to fluctuations in master genes

↑Oct4
Cdx2

↑Cdx2
Oct4

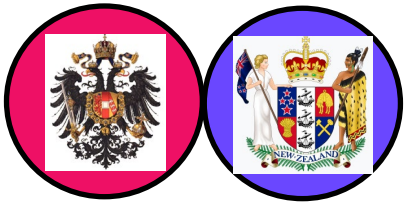


Commitment

Master gene circuitry stabilises bias

Oct4

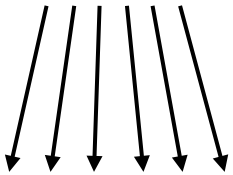
Cdx2



Lineages

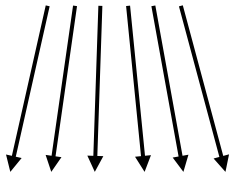
Master gene targets impart new identities (GRN2,3)

Oct4



Embryo-specific genes

Cdx2



Placenta-specific genes


Is the regulatory circuitry
conserved across all mammals?
Theodor Philipsen, 1890

DEVELOPMENTAL BIOLOGY

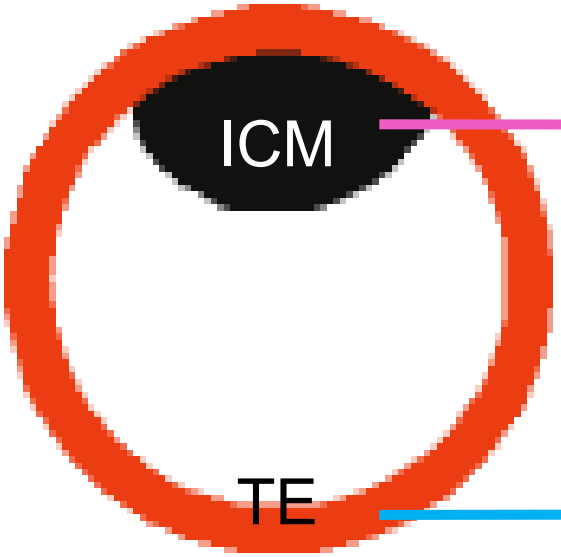
A mouse is not a cow

Early cell-lineage decisions during embryonic development differ between mice and cows. This finding calls for a re-examination of developmental variations across mammals, but does not undermine use of the mouse as a model organism.

Berg DK, Smith CS, Pearton DJ, Wells DN, Broadhurst R, Donnison M, Pfeffer PL. 2011. *Trophectoderm lineage determination in cattle.* **Dev Cell** 20: 244-255.

Master regulators

Blastocyst



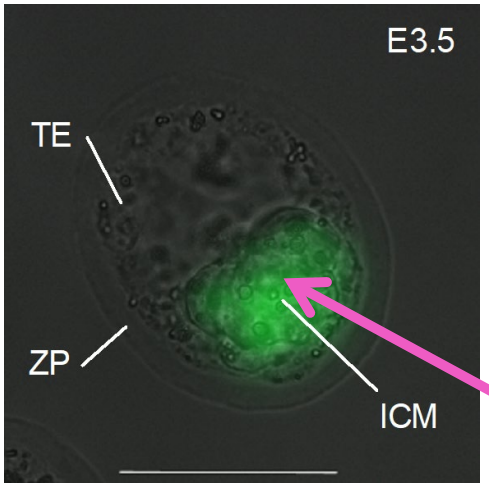
Oct4

Nonpolarized
↑Oct4

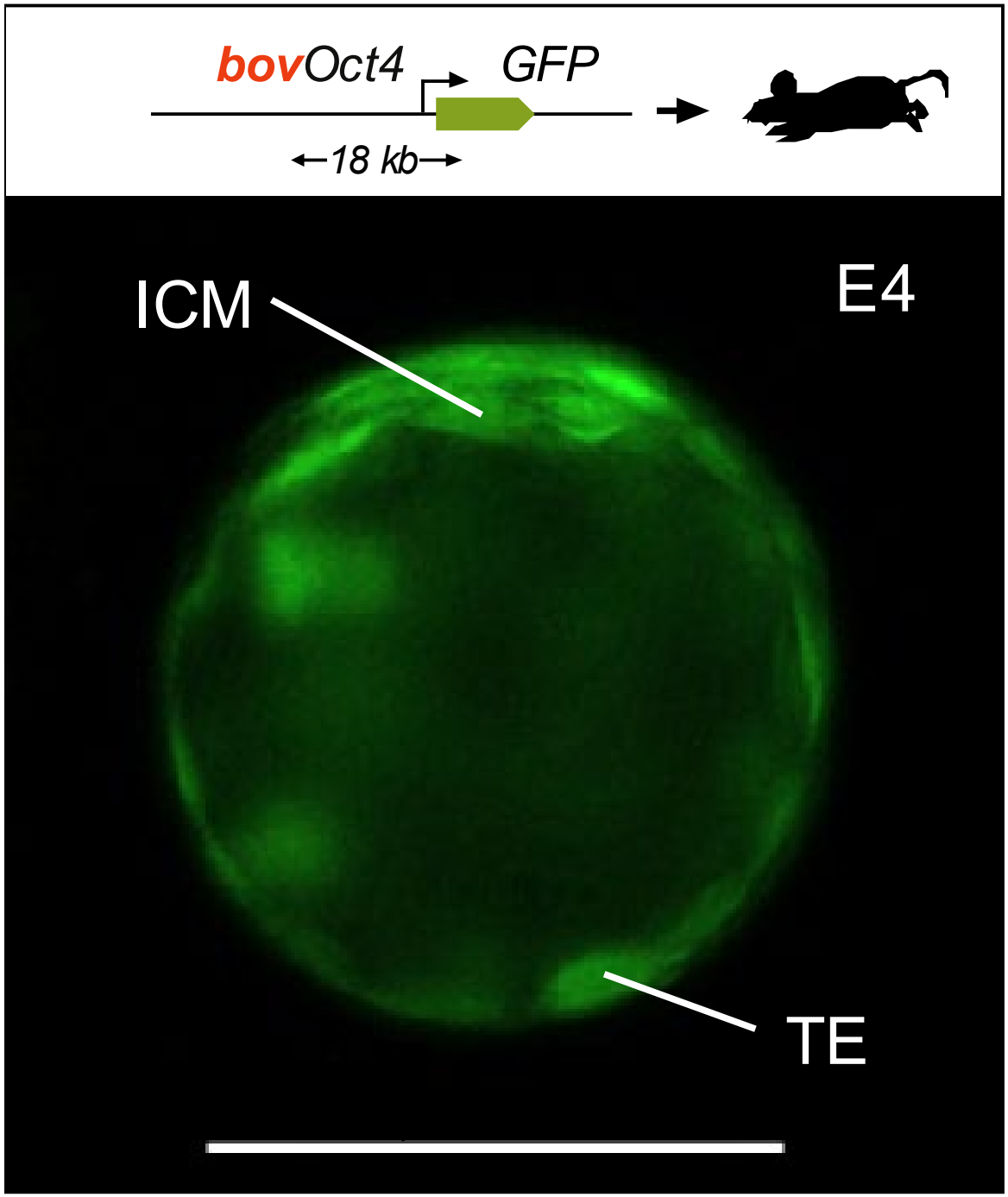
Cdx2

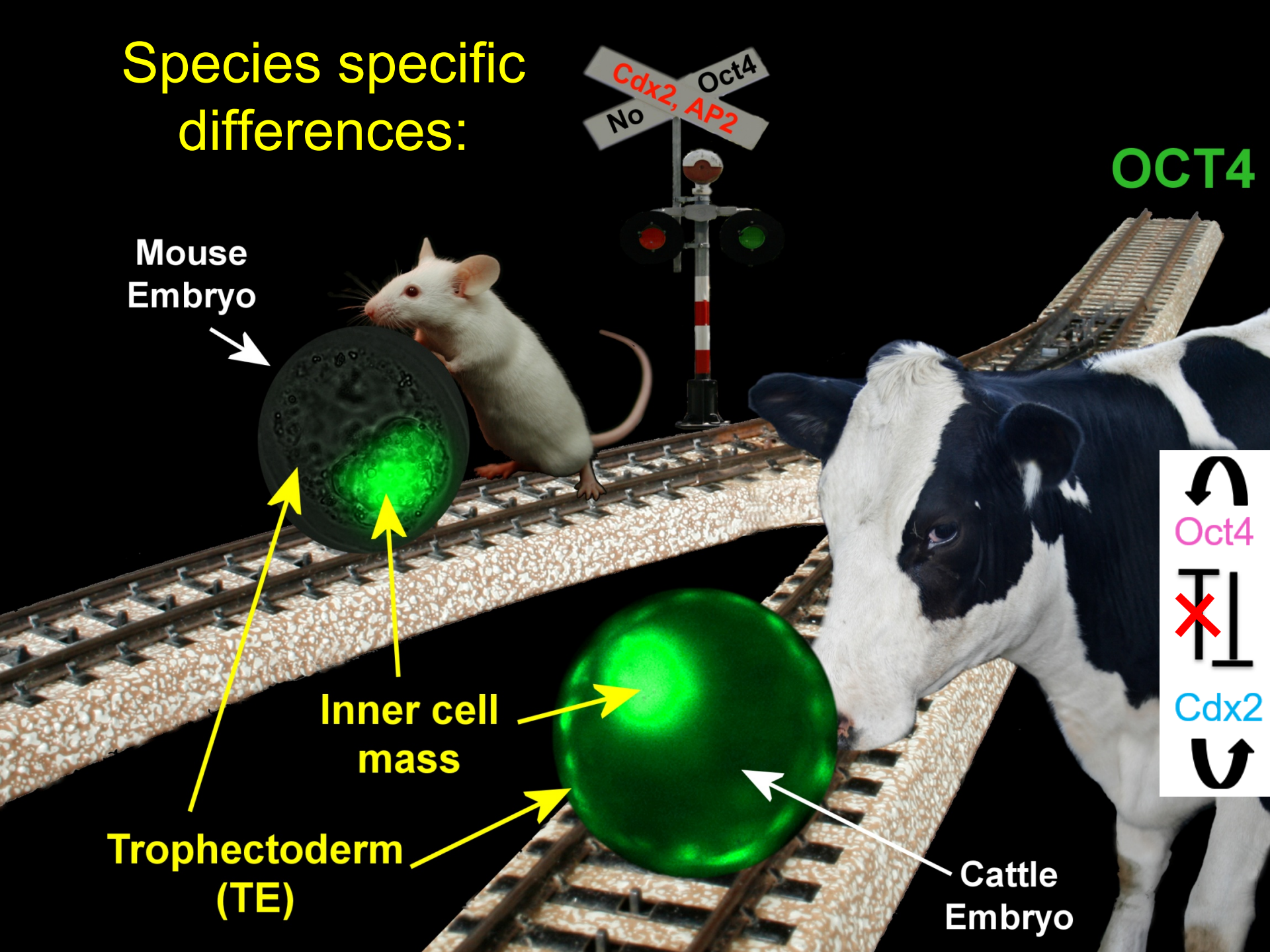
Polarized
↑Cdx2

Mouse embryo

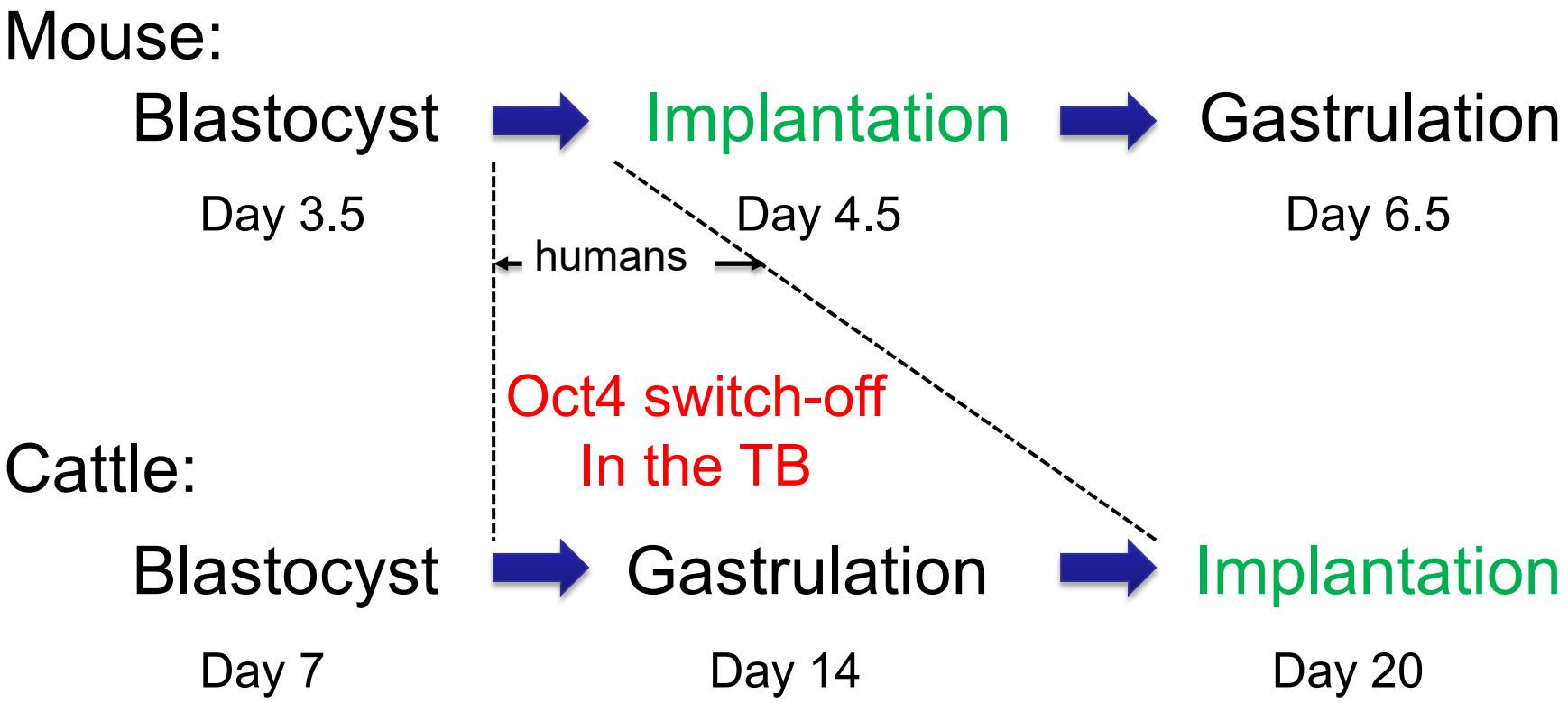


Oct4


bovOct4
GFP
18 kb
ICM
E4
TE


Species specific differences:
Cdx2, AP2
No
Oct4
OCT4
Mouse Embryo
Oct4
Cdx2
Inner cell mass
Trophectoderm (TE)
Cattle Embryo

Not so hasty…..


Mouse:
Blastocyst
Implantation
Gastrulation
Day 3.5
Day 4.5
Day 6.5
humans
Oct4 switch-off
In the TB
Cattle:
Blastocyst
Gastrulation
Implantation
Day 7
Day 14
Day 20

1. Harnessing inherent processes and chance to generate lineage differences

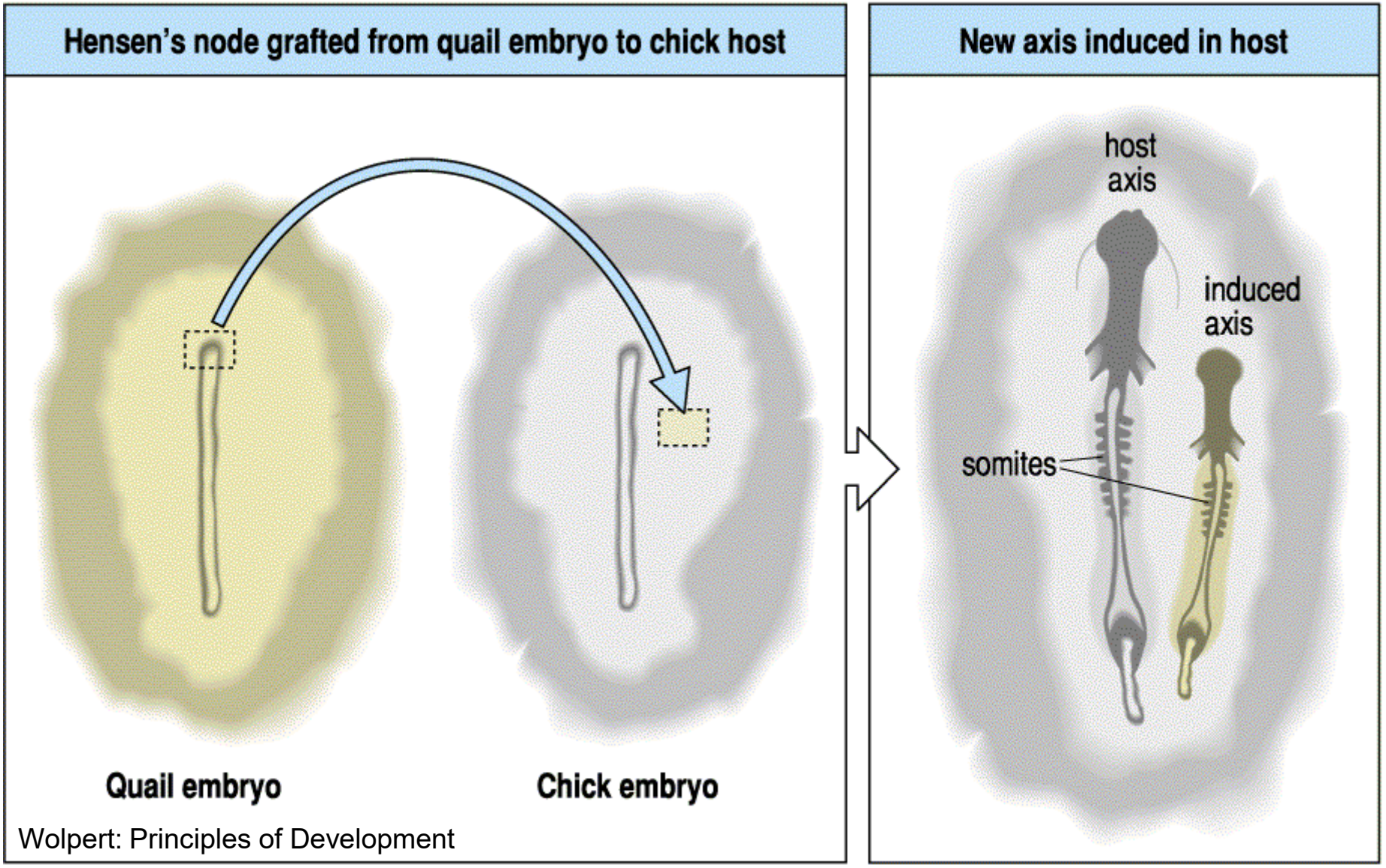
2. Using lineage *boundaries* and *signalling centres* to pattern an embryo

The “organiser”

A piece of the upper blastopore lip of an amphibian embryo undergoing gastrulation exerts an organizing effect on its environment in such a way that, if transplanted to an indifferent region of another embryo, it causes there the formation of a secondary embryonic anlage. Such a piece can therefore be designated as a Organizer.

Hans Spemann

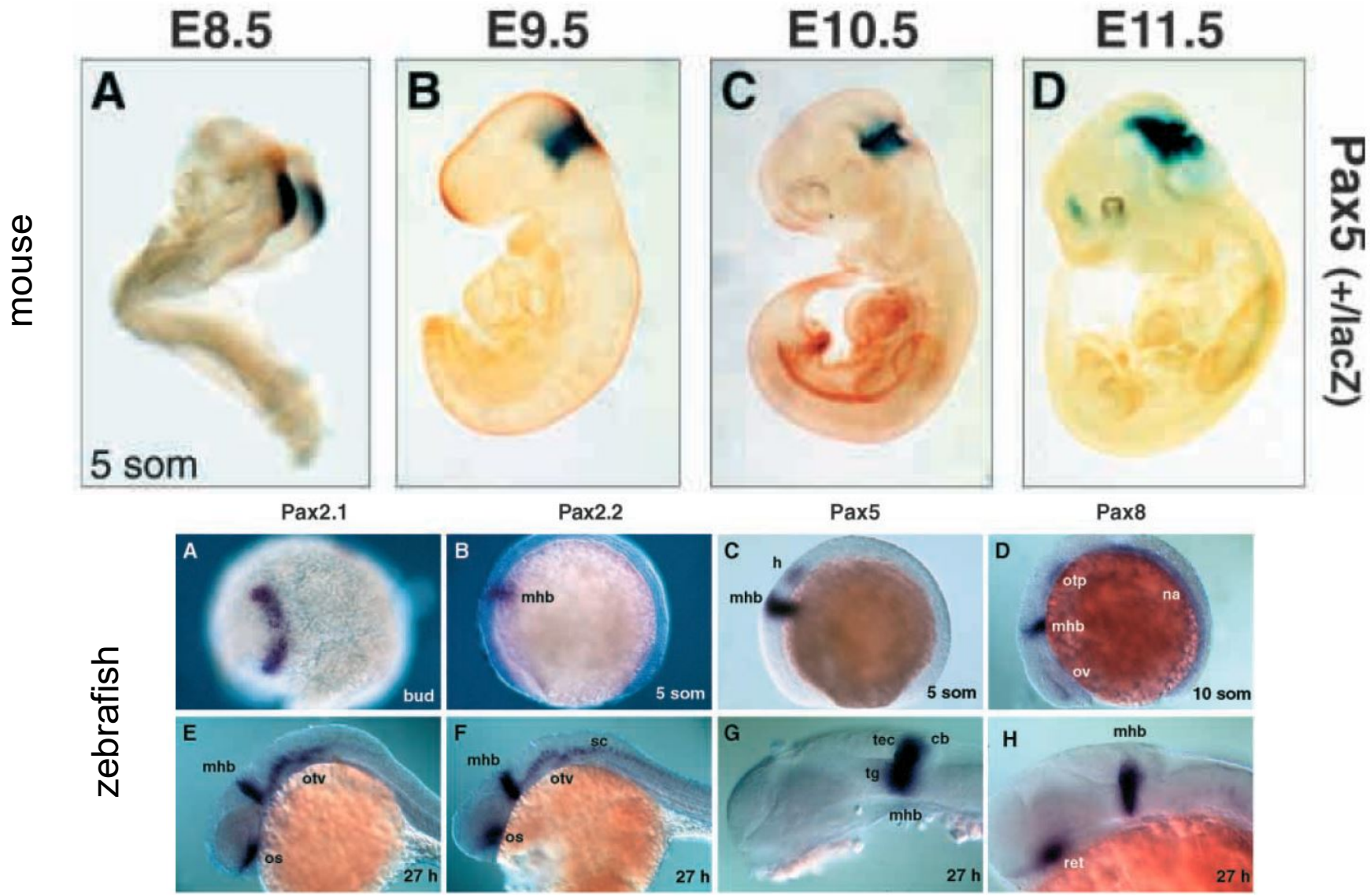
Hilde Mangold



Wolpert: Principles of Development

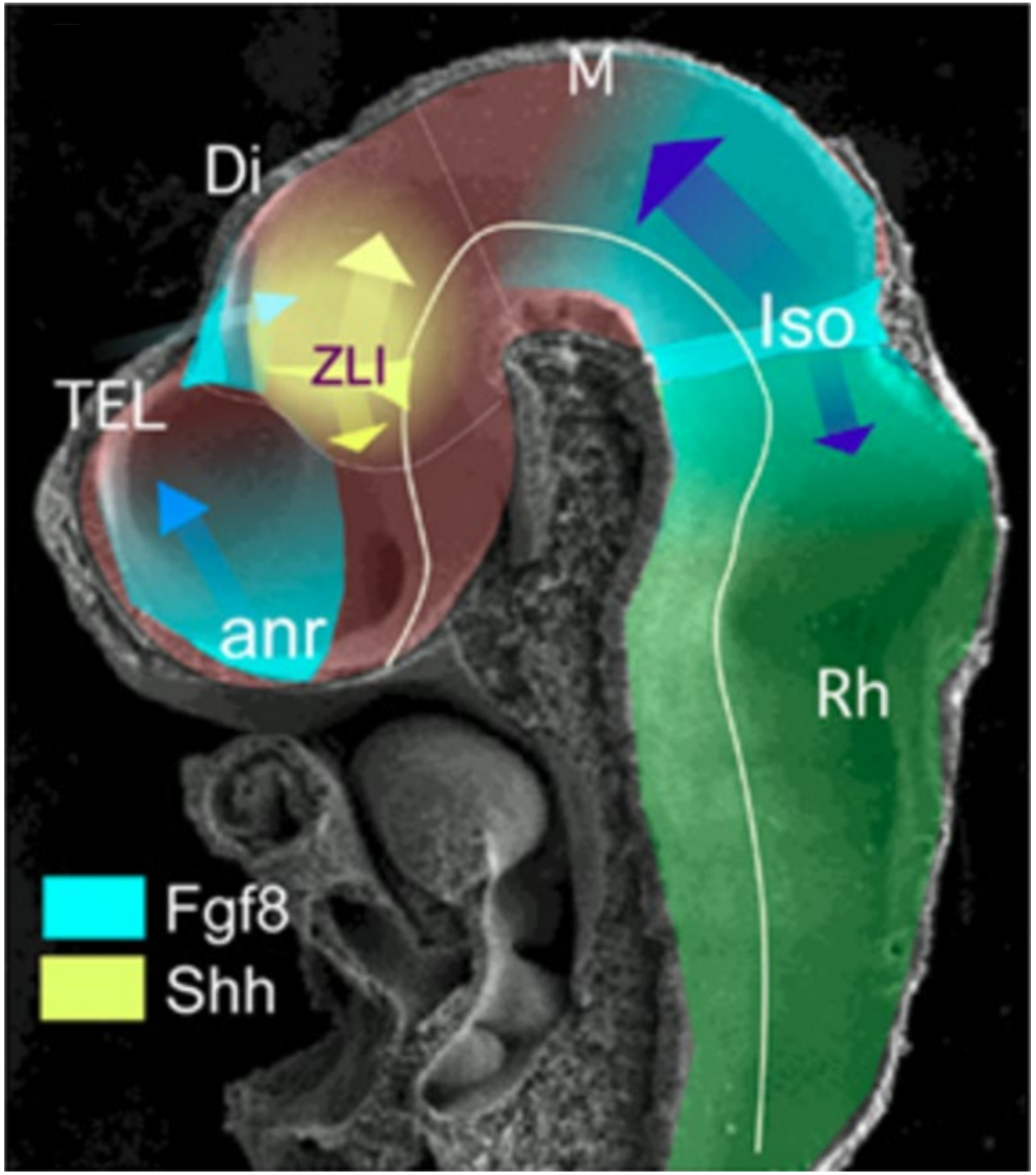
The **Node** is equivalent to the Spemann's organiser in the frog. Also shown in mice, though anterior-most structures are not induced.

The midbrain and hindbrain are separated by an organiser

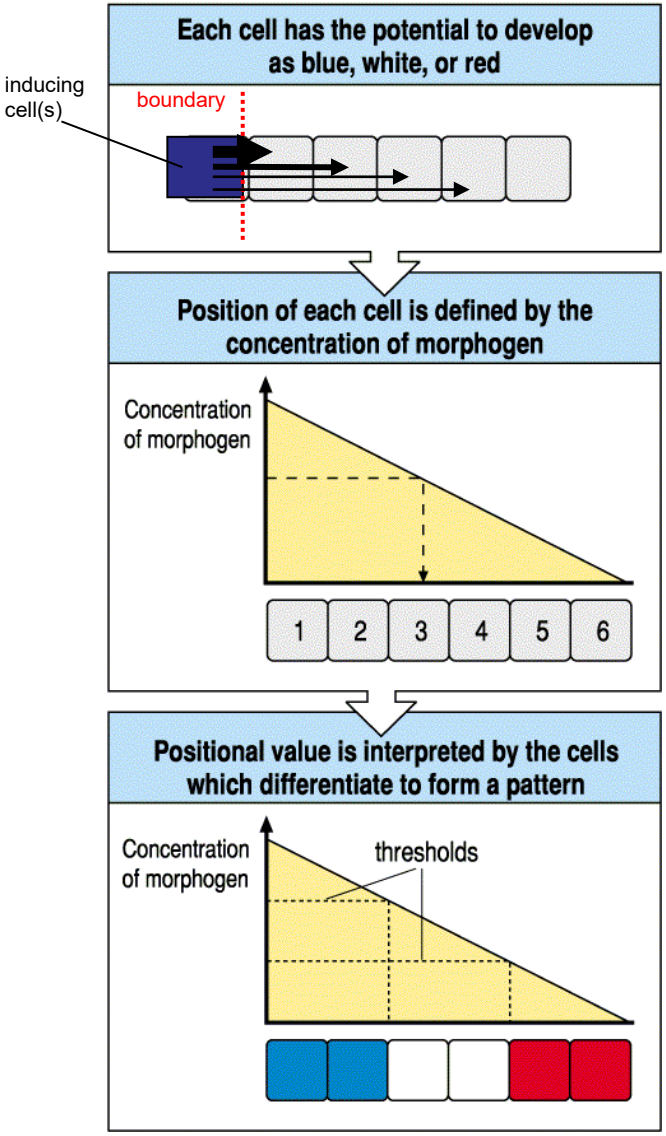


Pfeffer et al., 2002, 2000, 1998, Development 129,307;127,1017; 125,3063.

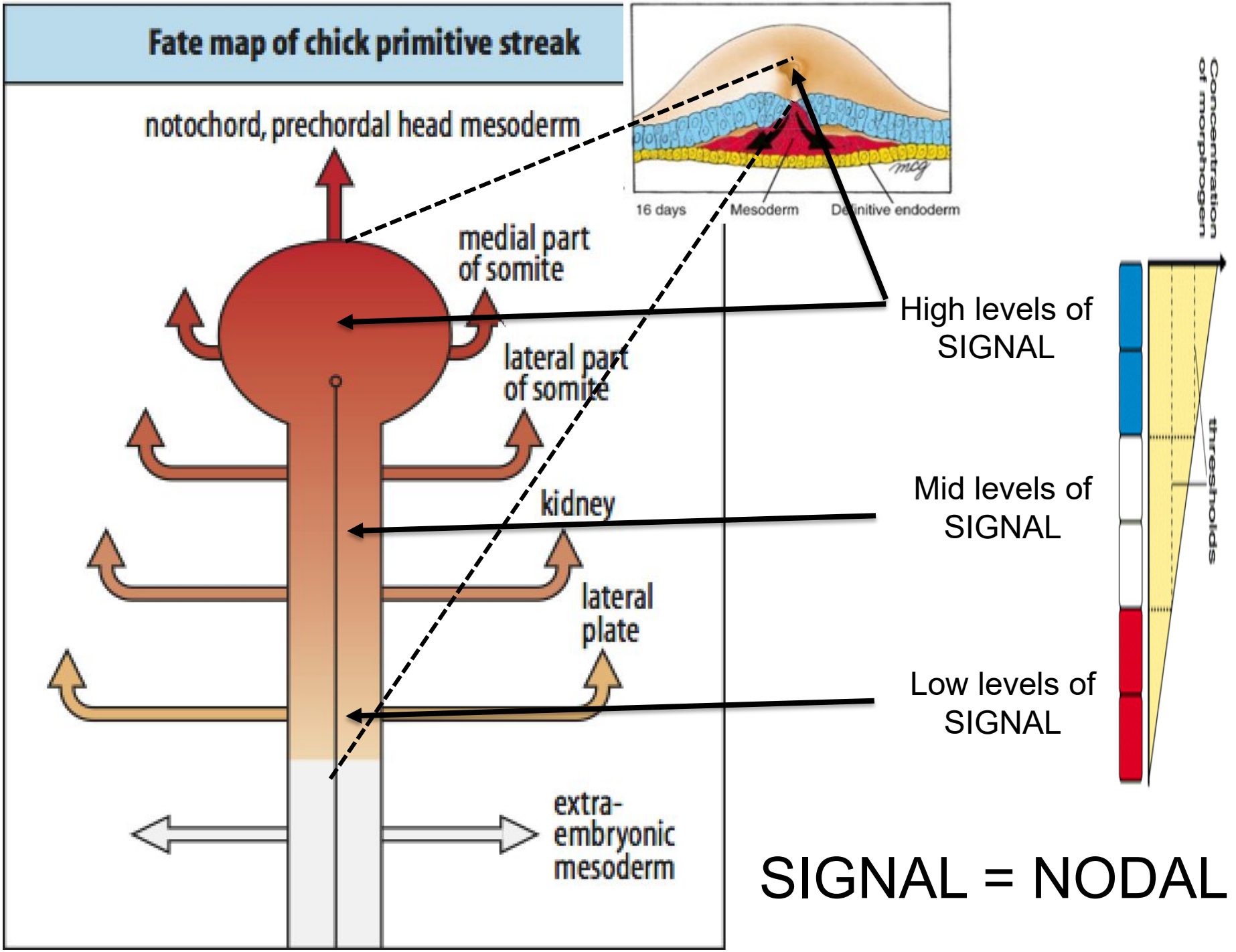
Patterning the brain



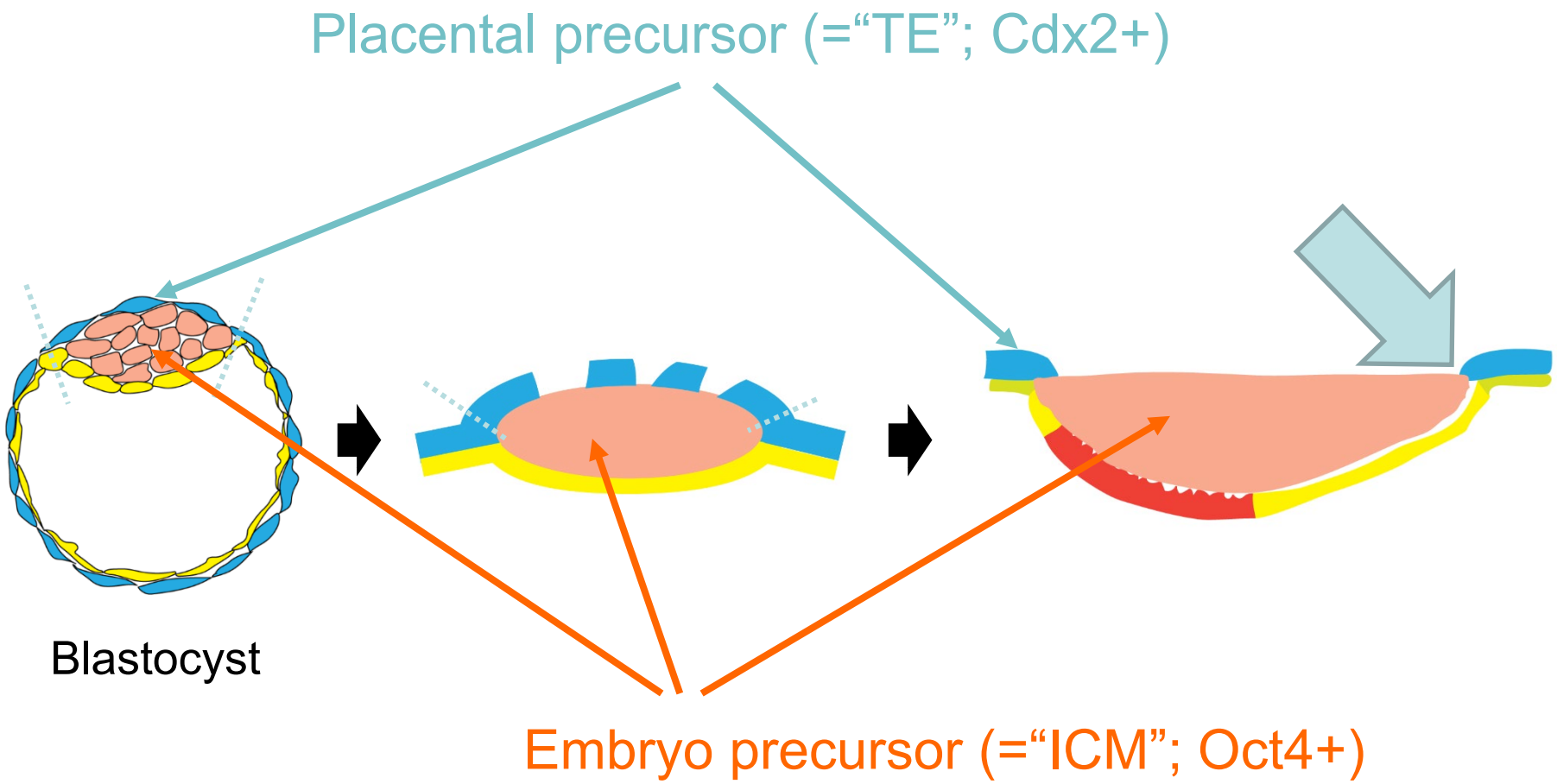
The French flag model of patterning



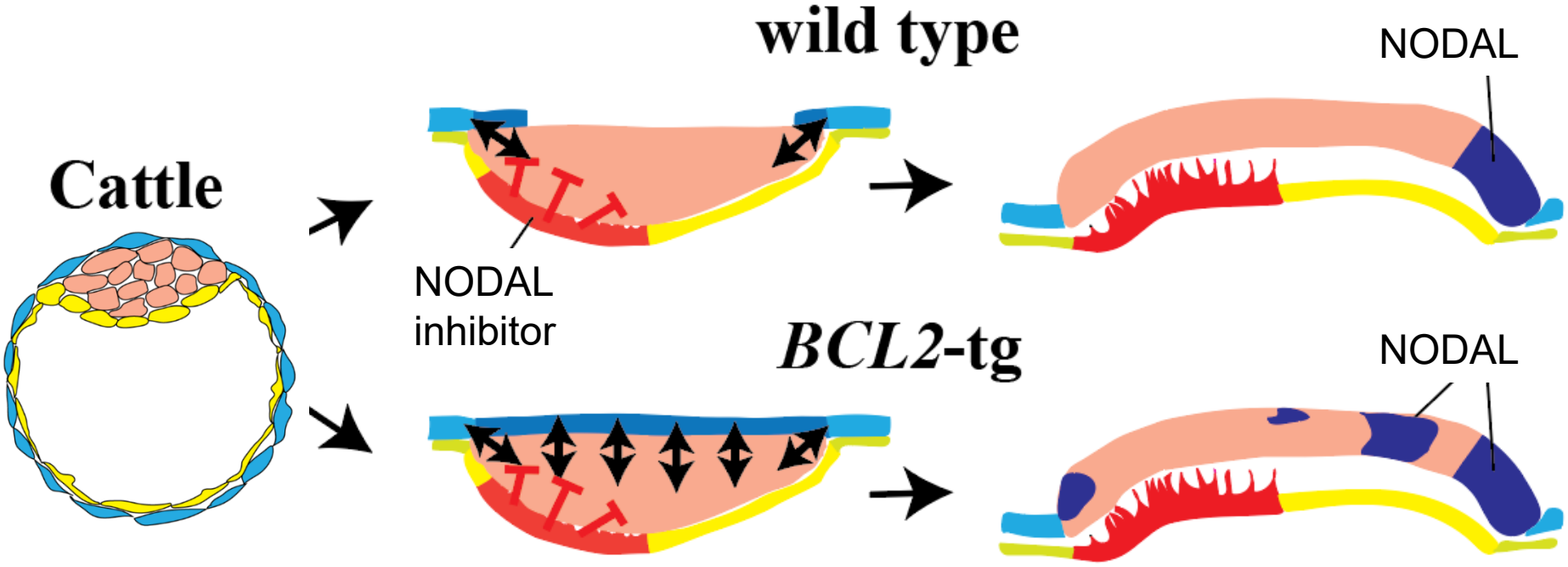
Wolpert, Principles of Development

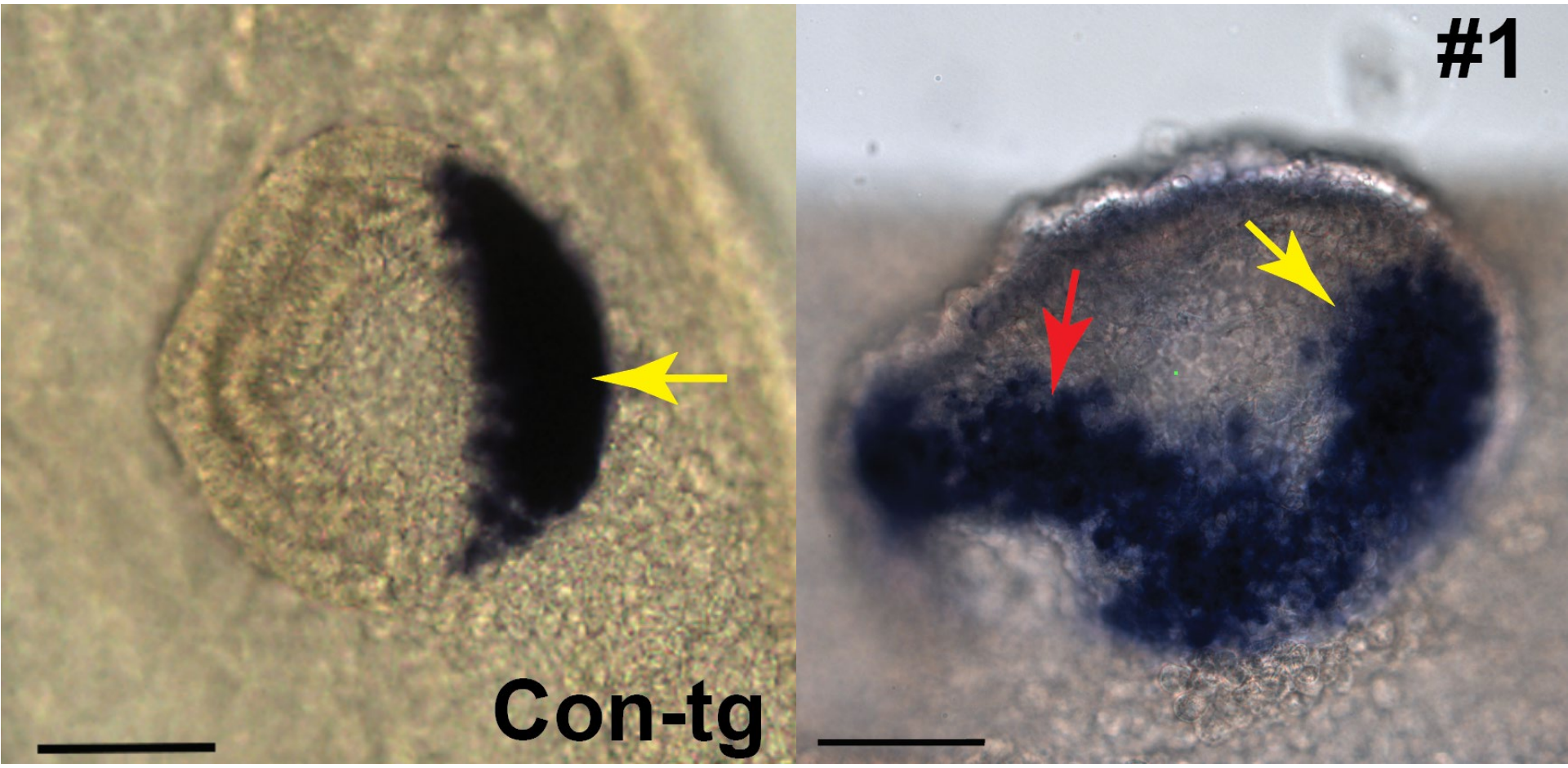

Fate map of chick primitive streak
notochord, prechordal head mesoderm
medial part of somite
lateral part of somite
kidney
lateral plate
extra-embryonic mesoderm
16 days
Mesoderm
Definitive endoderm
High levels of SIGNAL
Mid levels of SIGNAL
Low levels of SIGNAL
Concentration of morphogen
thresholds
SIGNAL = NODAL
Wolpert, Principles of Development

Forming the NODE: The boundary between ICM and TE



Creating a longer border



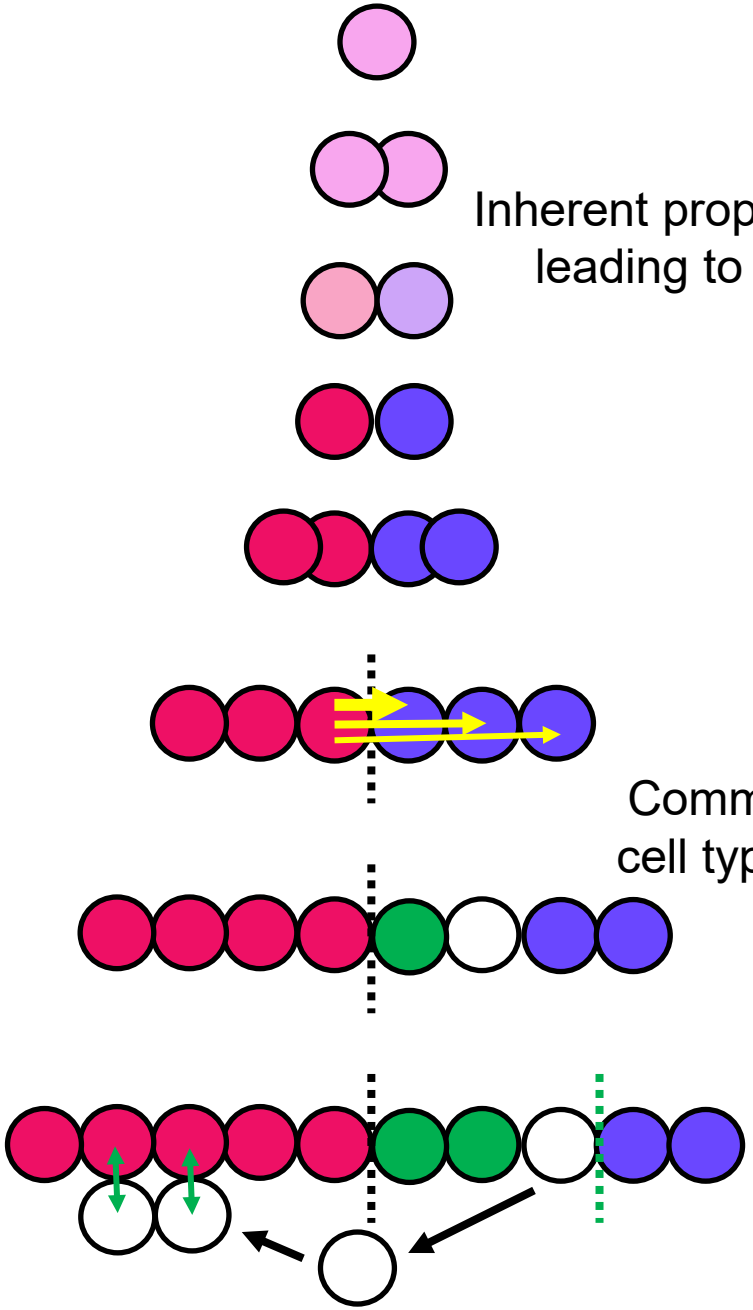


Cattle embryos, top view, stained for gastrulation marker

PhD student Jessica van Leeuwen


Look
but please
don't touch!

Development as a series of successive autonomous steps



Inherent properties of cells
leading to differences

Communication between different
cell types leading to new cell types

Cell migration creating
new possibilities