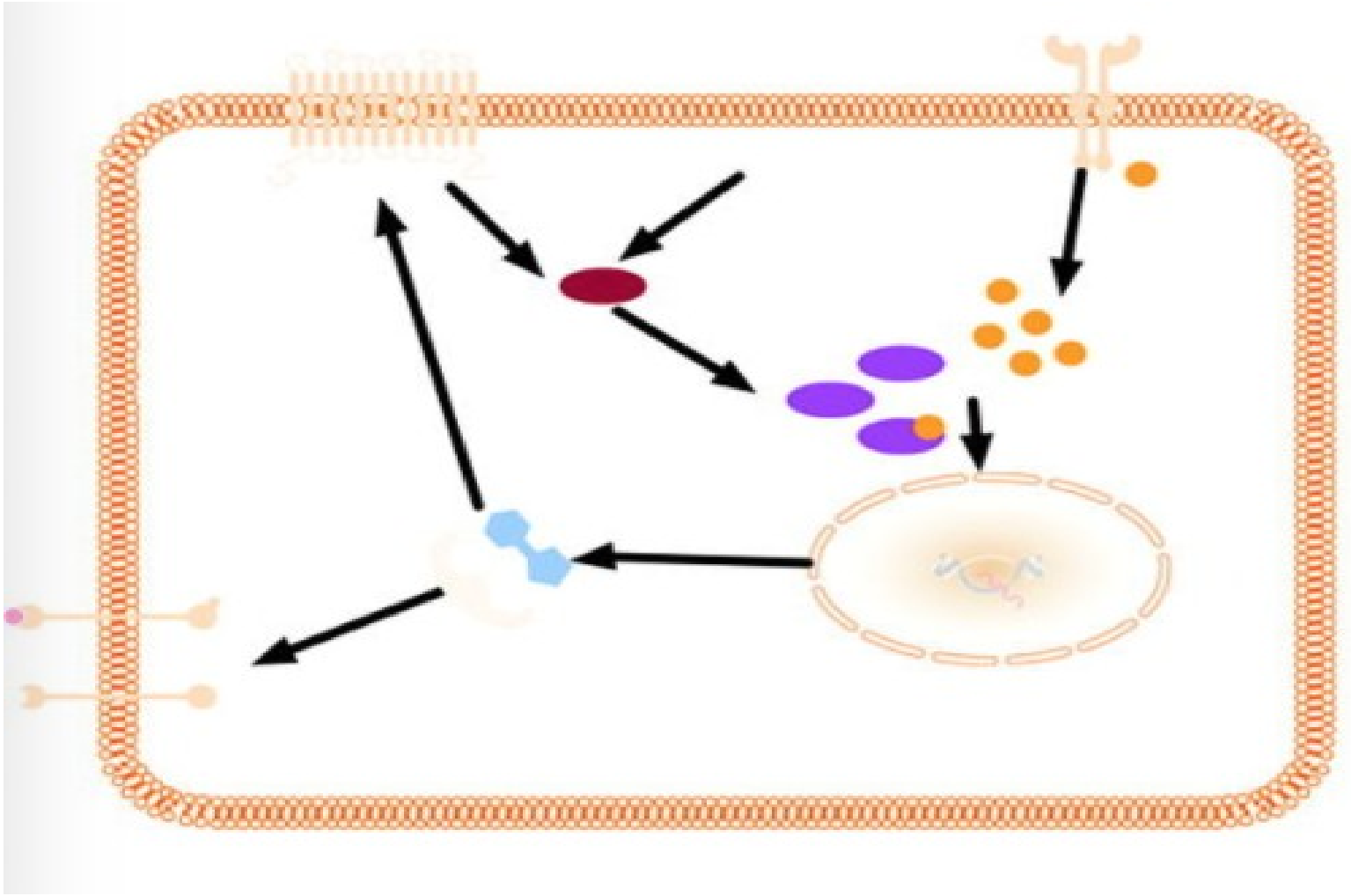
Information processing in living cells: mapping a logic gate to a gene regulation event.

Tilmann Wurtz, independent scholar

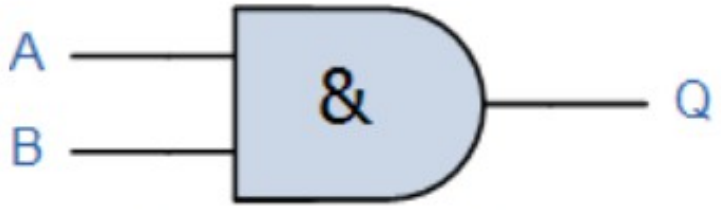
A cell with interacting elements



The signal processing network

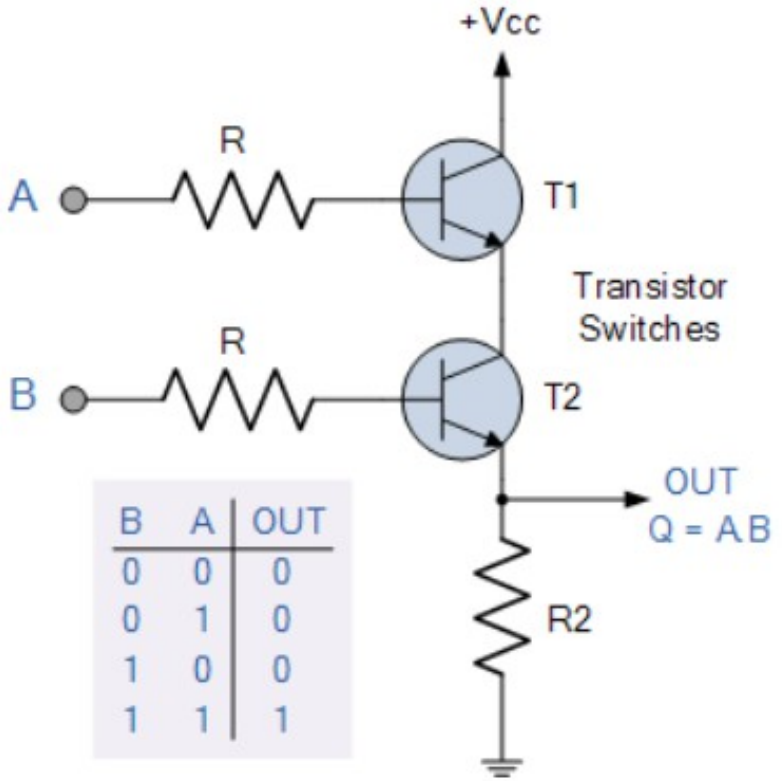
- Many receptors receive signals
- Signals are propagated by signaling chains
- Signaling chains interact (crosstalk)
- Signal propagation is in essence binary
- The combined signal chains constitute a information processing system
- Hypothesis: logic gates contribute to signal processing in cells

AND gate – symbol, switches and truth table



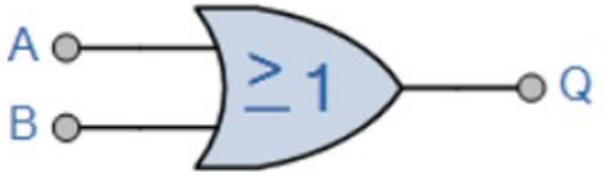
2-input AND Gate

Boolean Expression Q = A.B

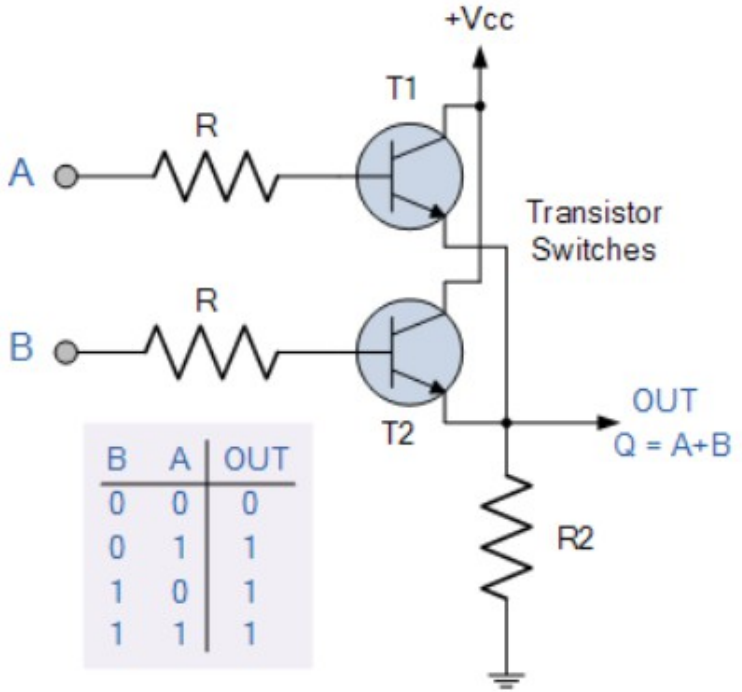


B	A	OUT
0	0	0
0	1	0
1	0	0
1	1	1

OR gate – symbol, switches and truth table



2-input OR Gate



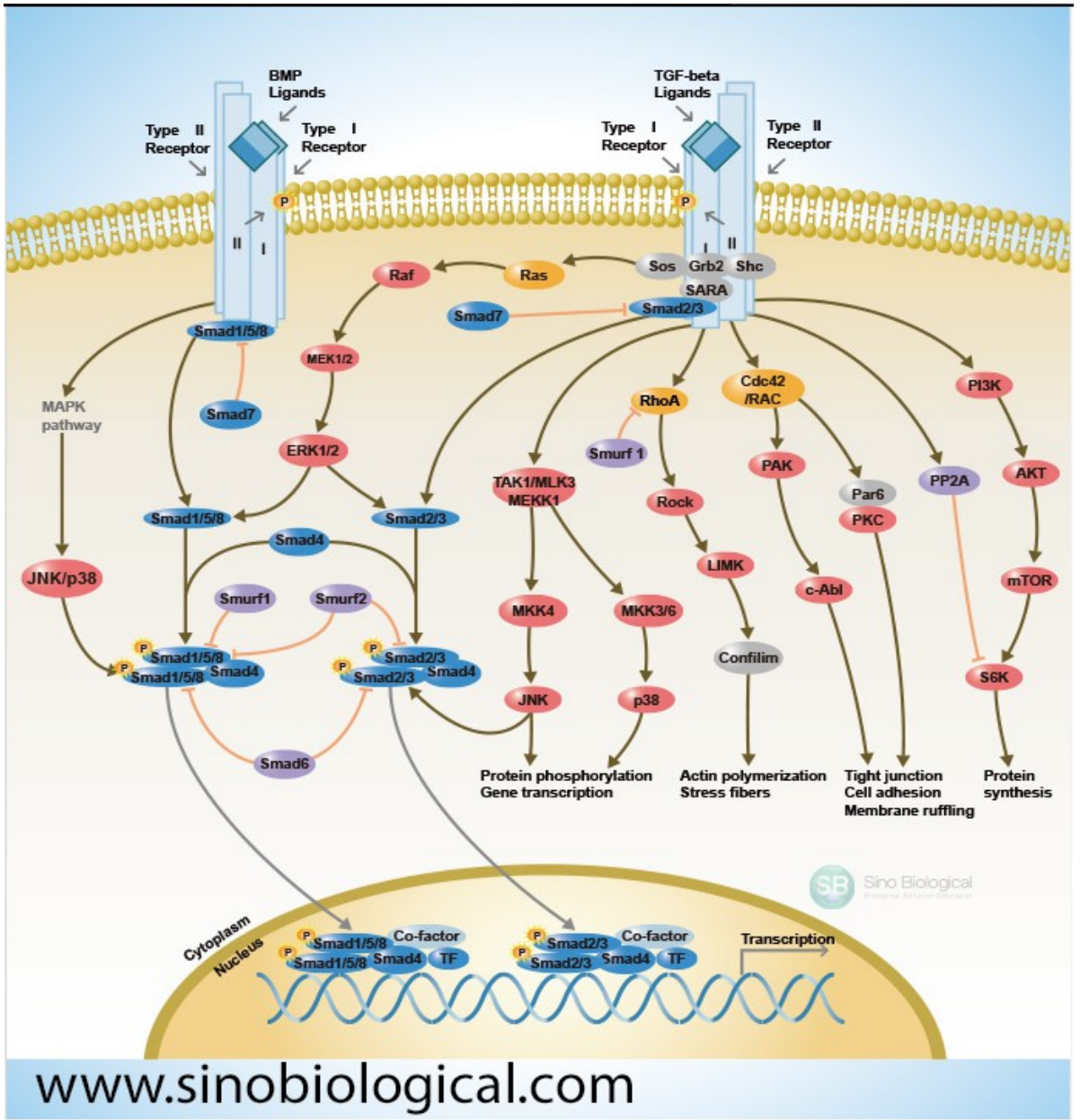
B	A	OUT
0	0	0
0	1	1
1	0	1
1	1	1

Boolean Expression **Q = A+B**

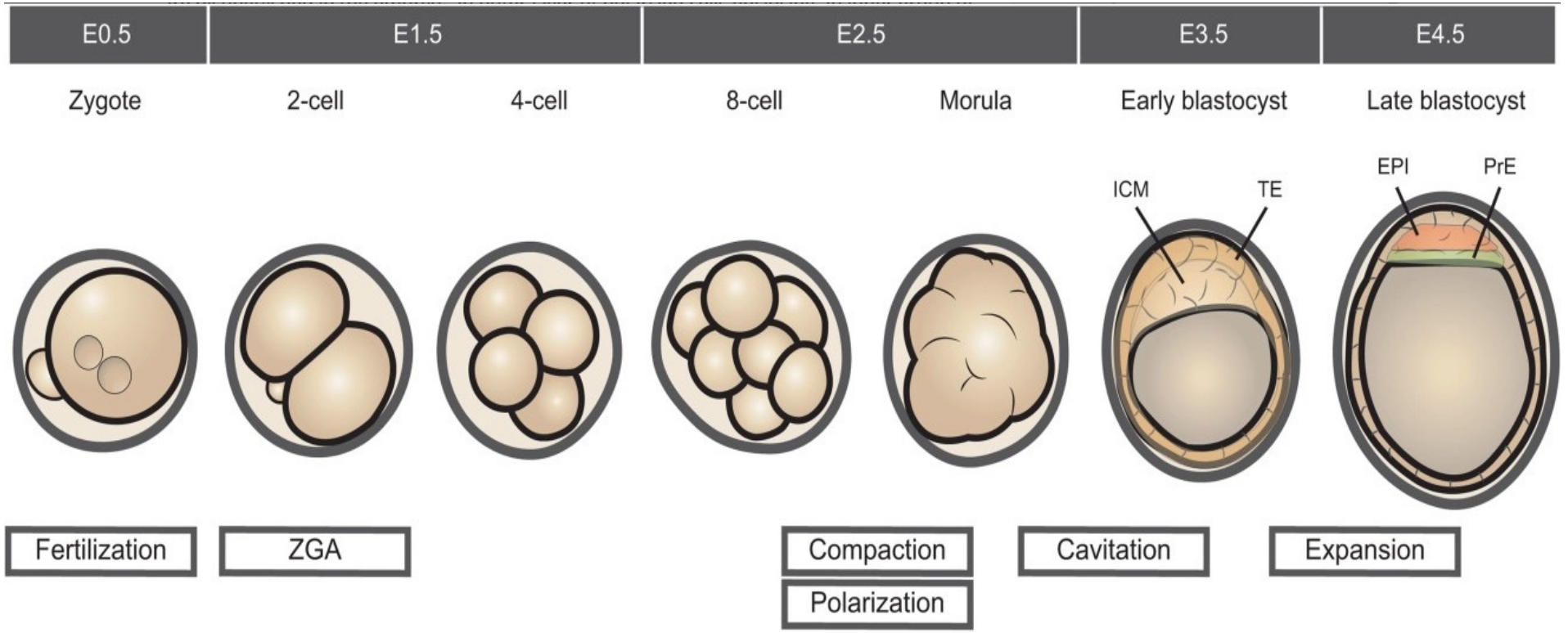
If signal chain components are elements of logic gates, they should:

- be integrated in a logic gate structure
- be part of a network
- be implicated in biological decision making
- help interpretation of experimental findings
- contribute to testable models

Signaling by BMP and TGF-beta

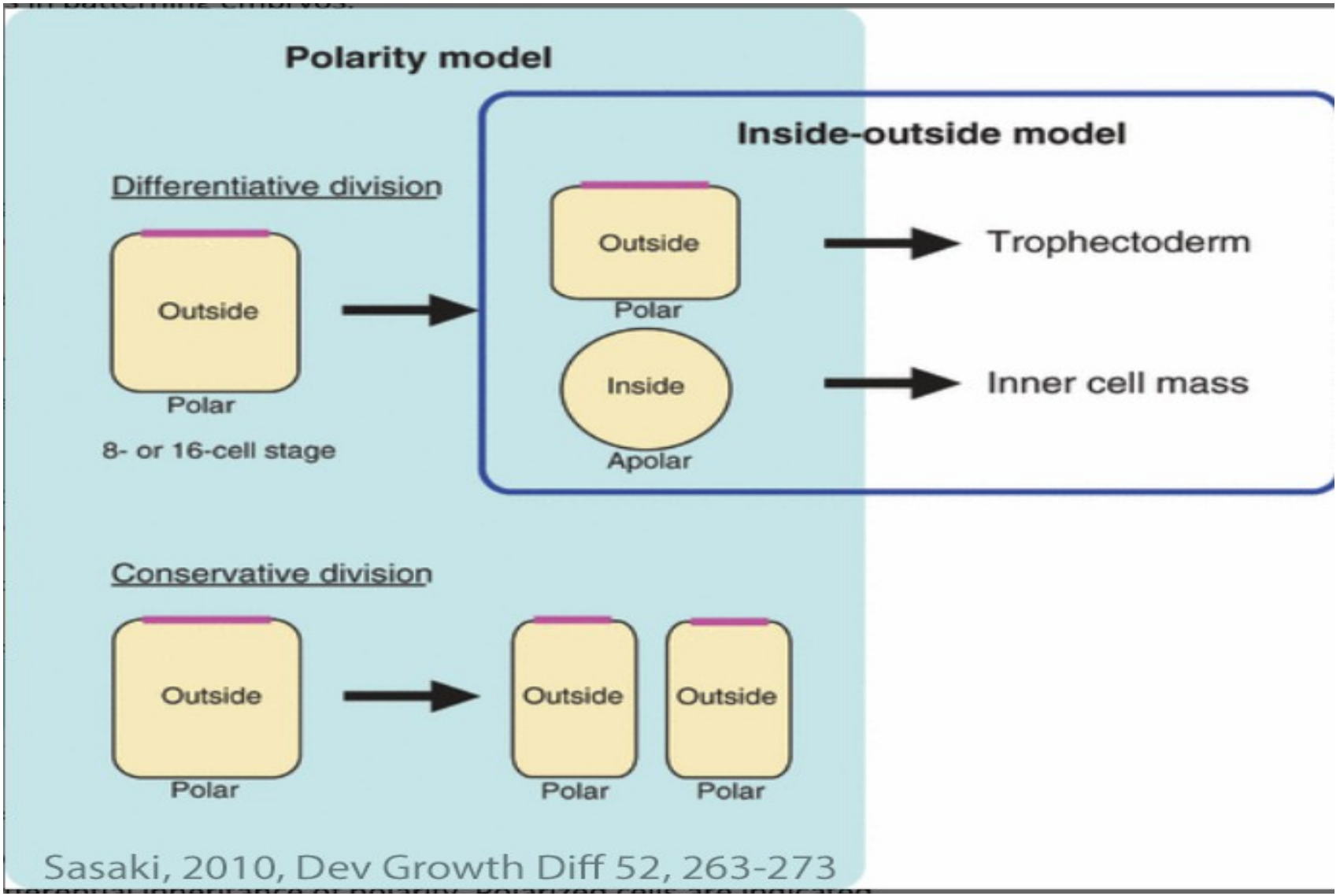


Early mammalian embryo

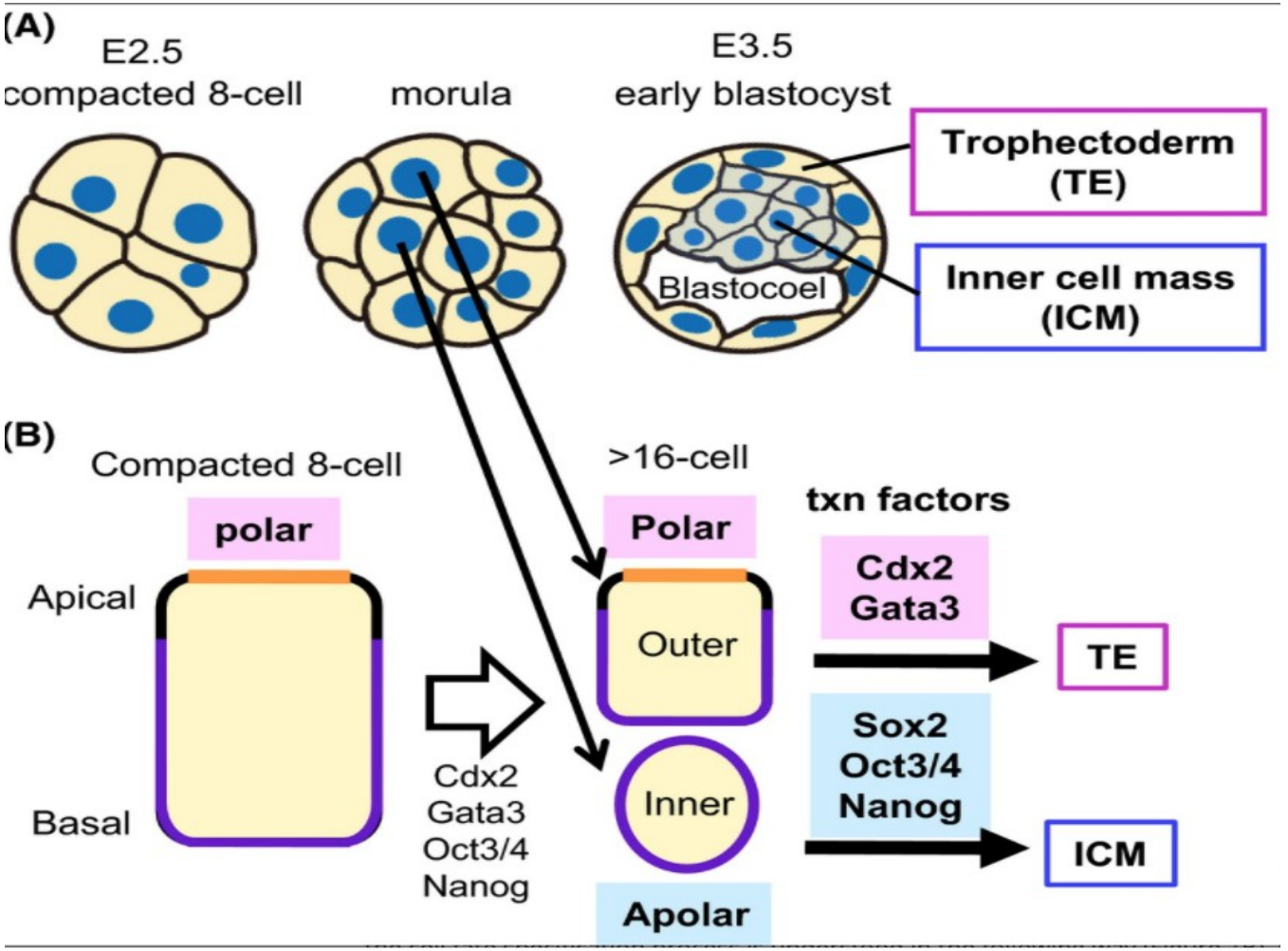


S. Menchero et al., Dev Dyn 2017, 246, 245-261

Differentiation TE – ICM in early embryos

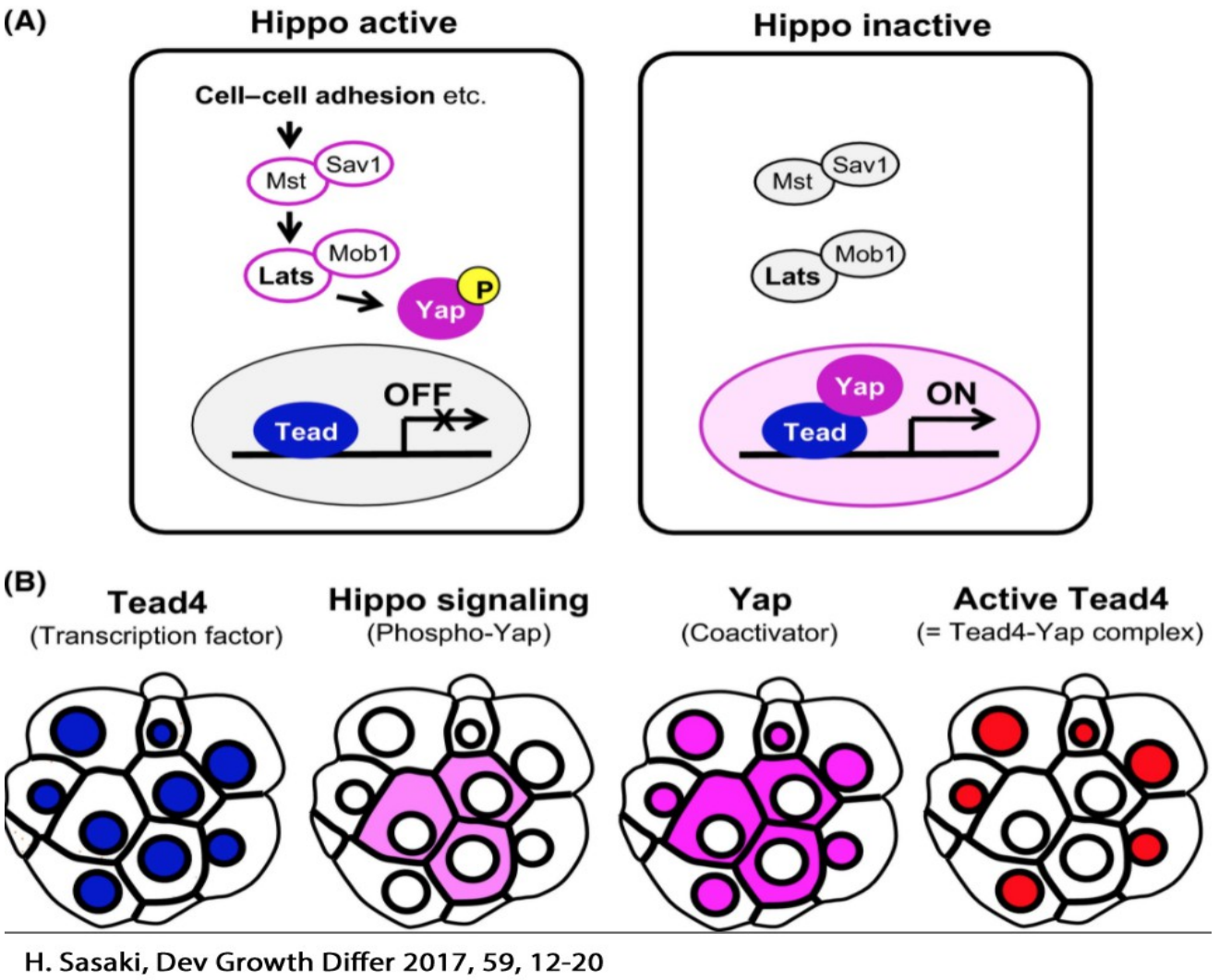


Differentiation TE - ICM in early embryos



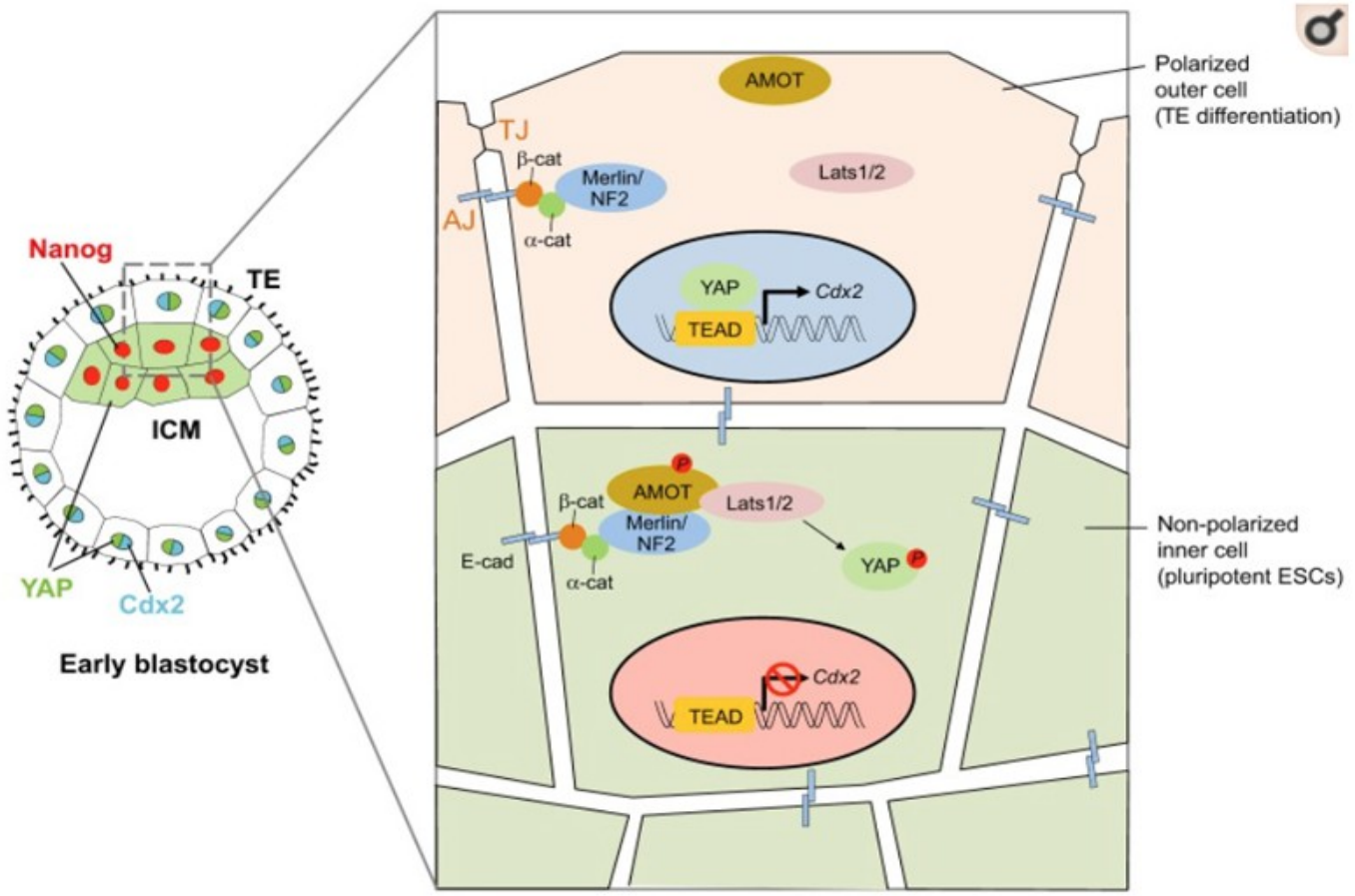
H. Sasaki, Dev Growth Differ 2017, 59, 12-20

The HIPPO pathway in early embryos



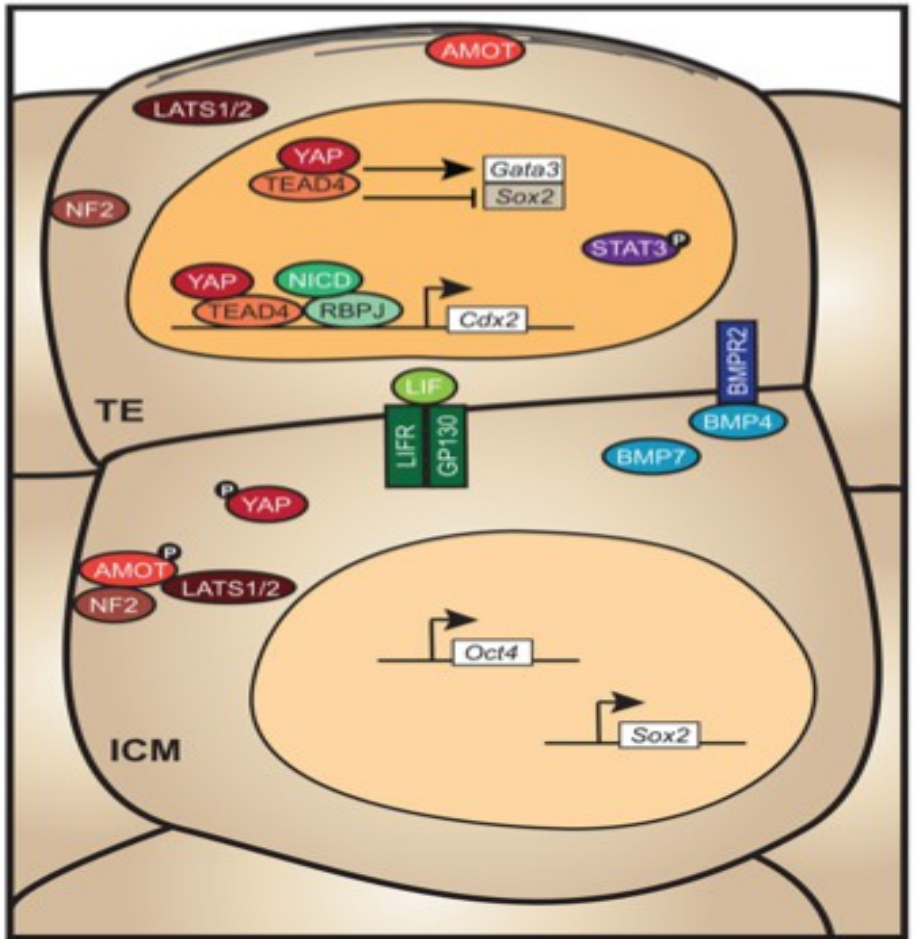
H. Sasaki, Dev Growth Differ 2017, 59, 12-20

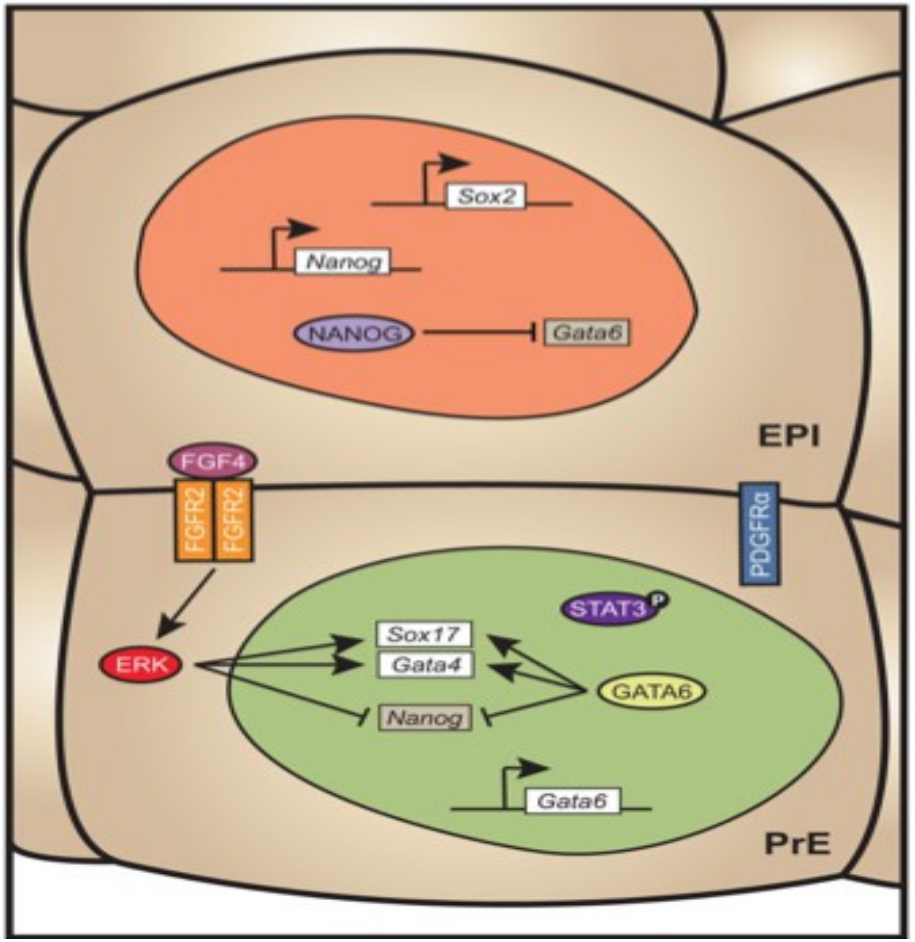
Polarity regulates CDX2 via YAP



Gumbiner, Kim, 2014 J Cell Science 127, 709-717

Polarity (YAP) plus position (NICD) sensing



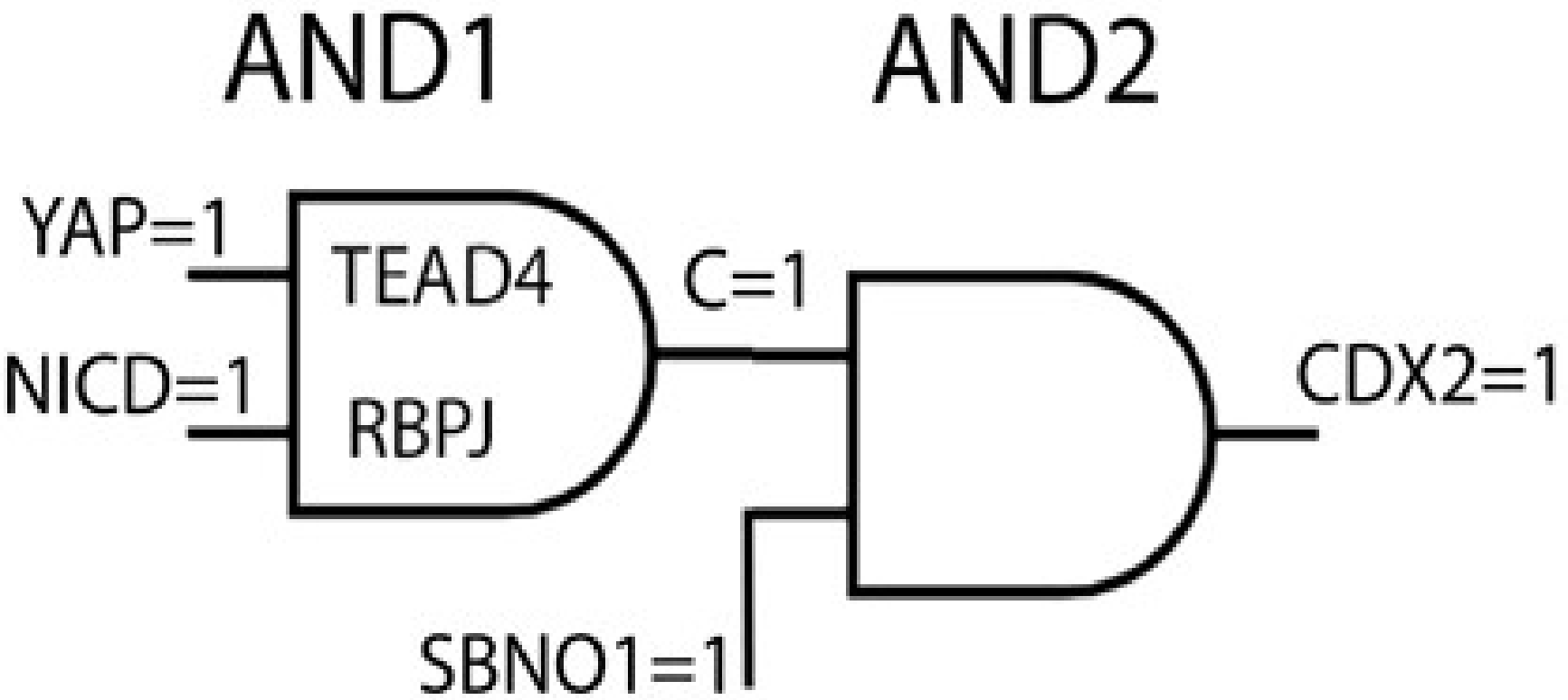


Menchero et al., Dev Dyn 246, 245-261 (2017)

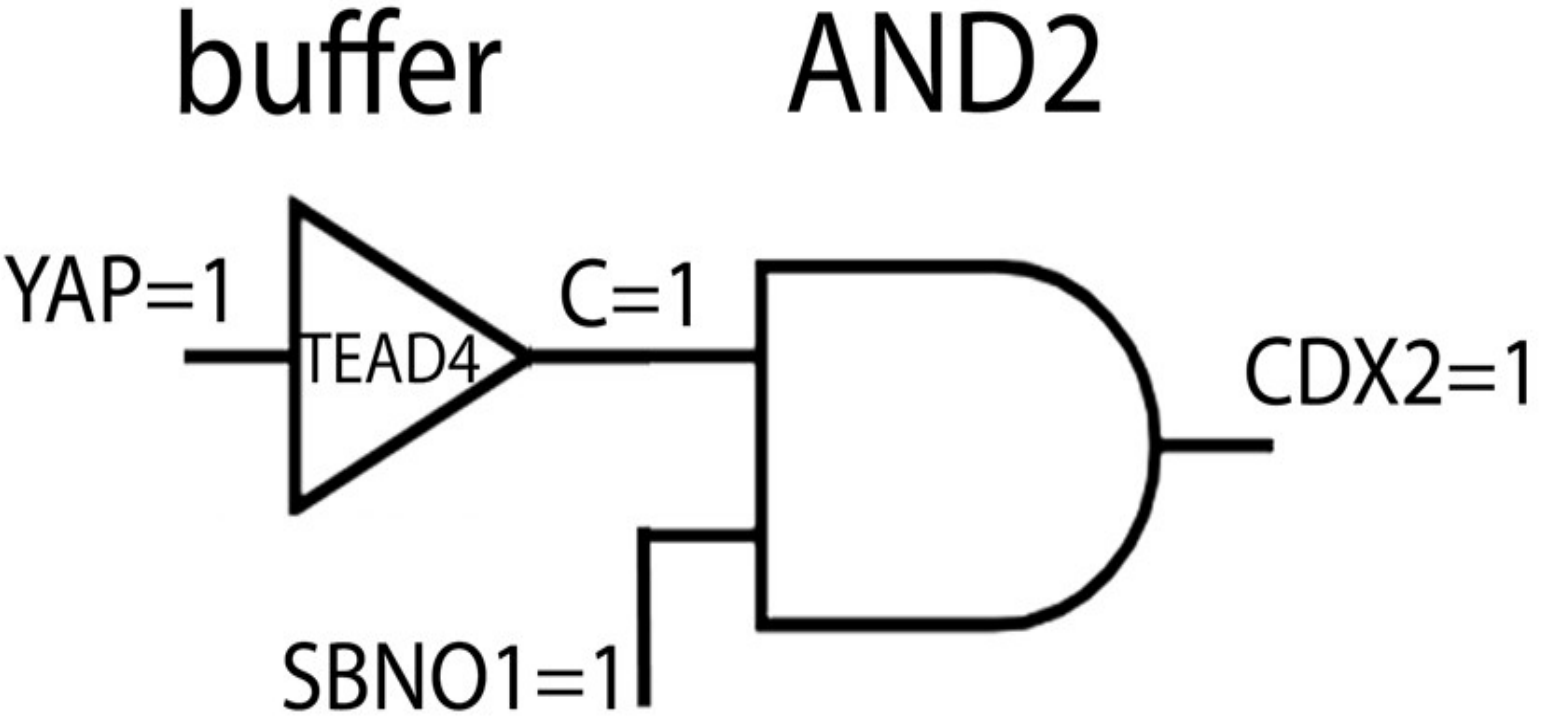
NOTCH in TE differentiation

- Elevated presence of NOTCH in TE cells
- NOTCH can rescue CDX2 expression in TEAD4 null mutants in an artificial construct
- But: RBPJ null mutant mice develop to mid-gestation, arguing against a NOTCH involvement
- The contradiction is resolved by the gate model, because absence of RBPJ converts the AND gate to a buffer gate

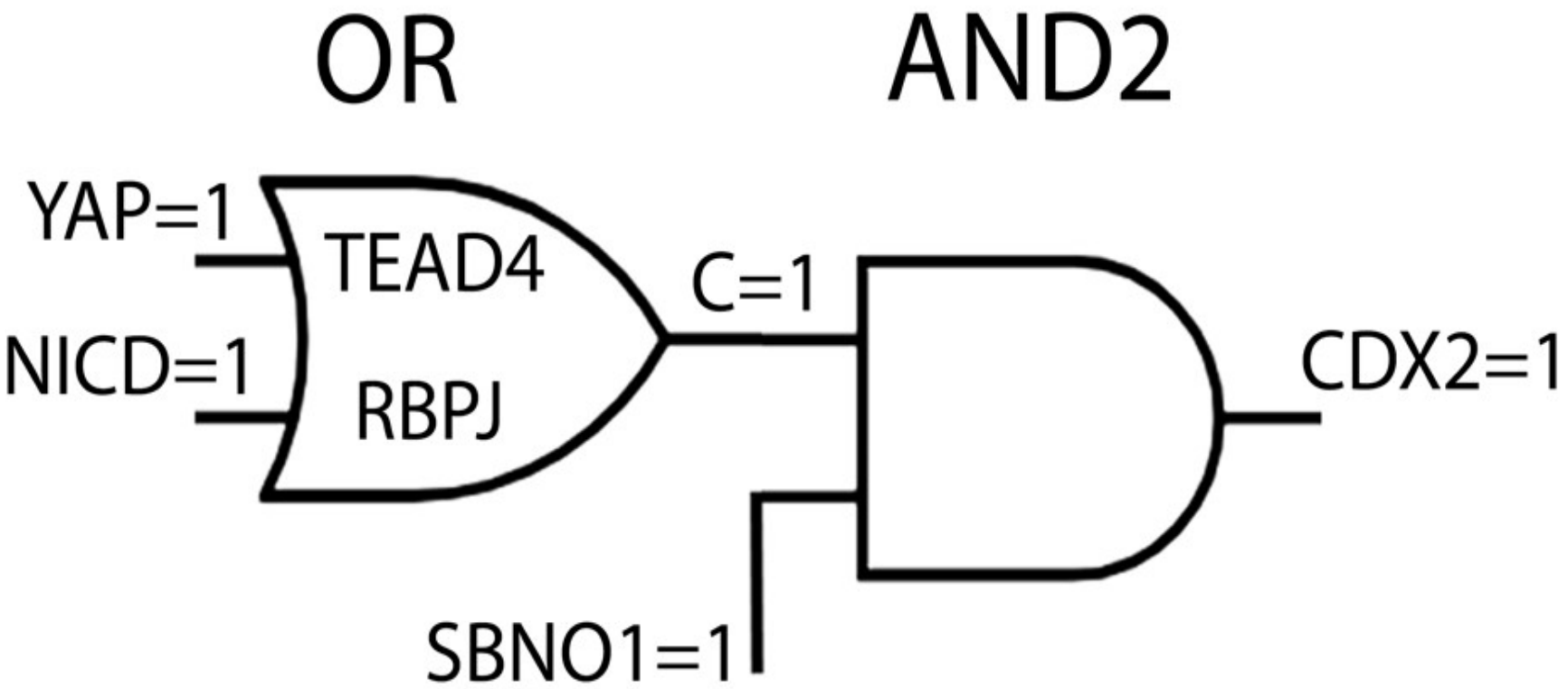
TE enhancer of gene CDX2 as two AND gates



TE enhancer of gene CDX2 as buffer plus AND gates with RBPJ absent



TE enhancer of gene CDX2 as OR plus AND gates

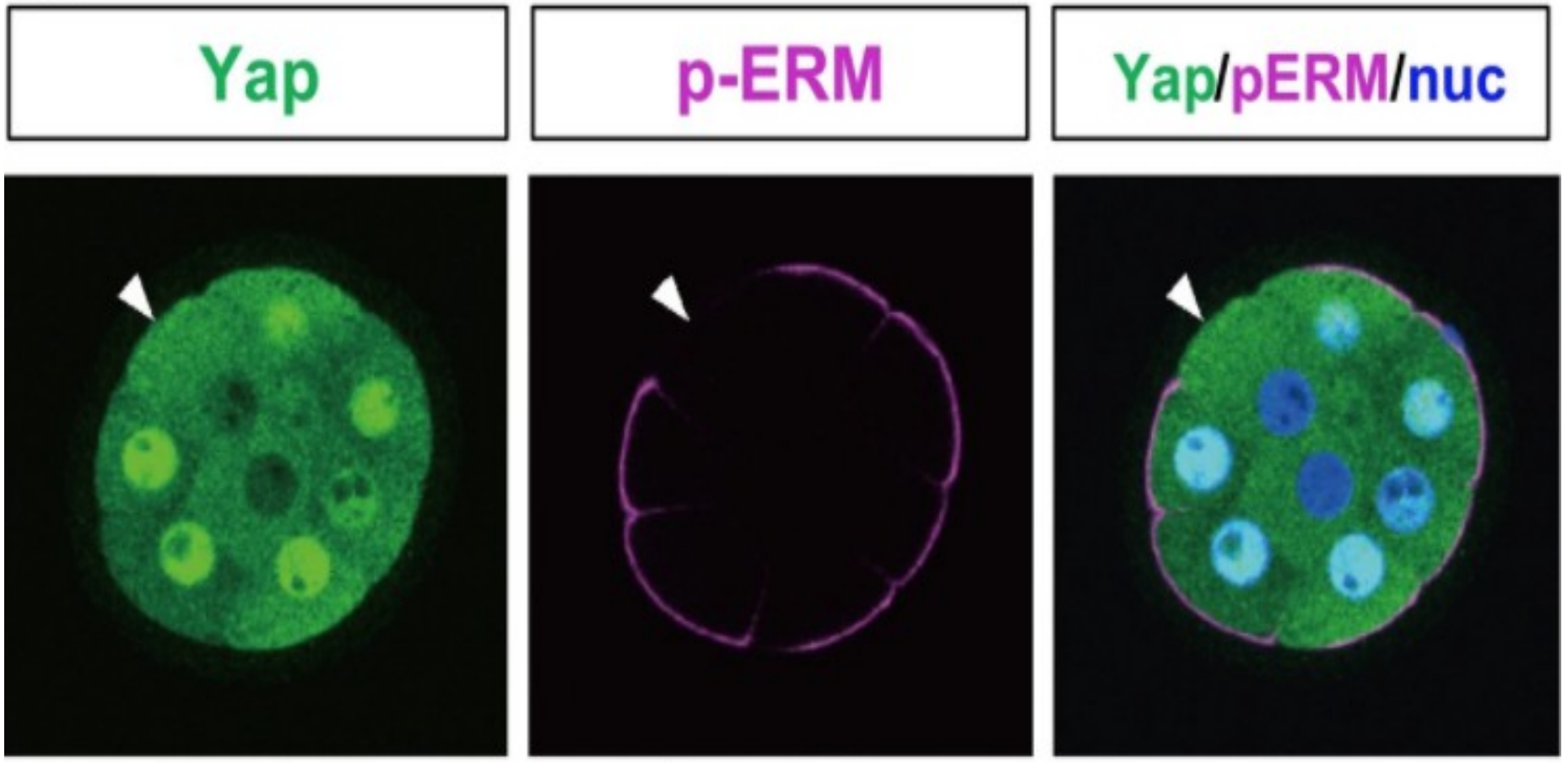


Discrimination between AND and OR gate

- So far, either YAP or NICD may suffice for CDX2 induction. Also an OR gate would be converted to a buffer gate without RBPJ.
- Single cells are observed at the embryo surface that are HIPPO active. They develop into ICM and do not induce CDX2.
- These cells indicate that both YAP and NICD are needed for CDX2 induction (AND gate).

  No YAP – no CDX2 induction

Peripheral cell with inactive YAP signaling



Sasaki,H 2017 Dev Growth Diff 59, 12-20

Summary

- YAP and NICD are integrated in a logic gate-structure and part of a network.
- They induce transcription of CDX2, a key event in TE – ICM differentiation.
- The AND gate model can explain NICD and YAP cooperation plus the RBPJ null phenotype.
- The AND gate model can be tested: it predicts that CDX2 induction is lost after abrogation of either NICD or YAP. The alternative, an OR gate, would require suppression of both factors.