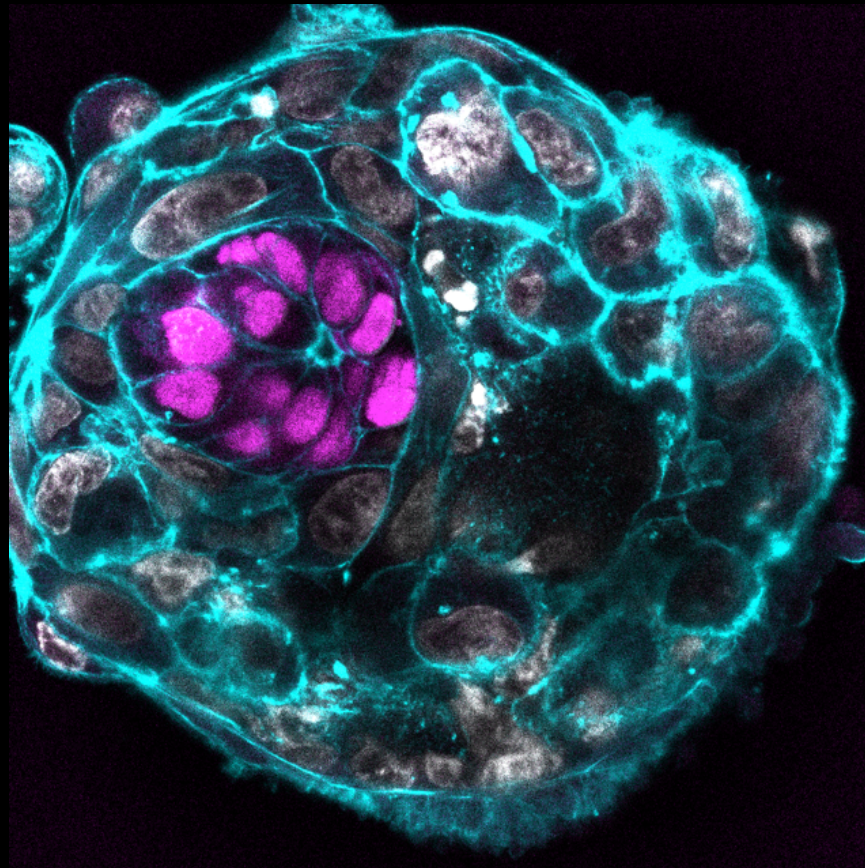


Why it is important to study human development and why it is important to build human embryo models?

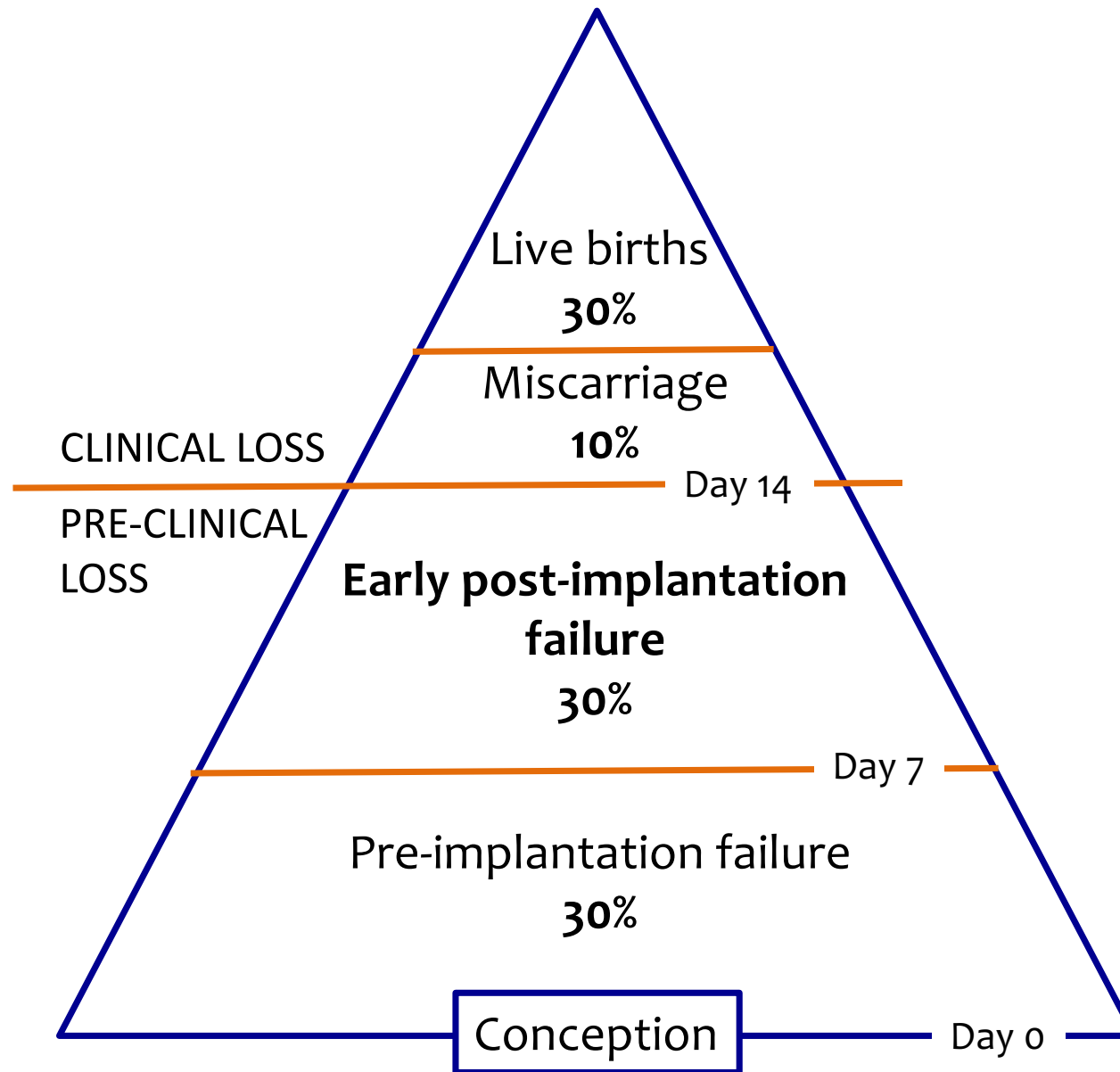


Magdalena Zernicka-Goetz
Caltech, USA and Cambridge, UK

Human Embryo and Stem Cell Meeting

17th January 2020

Human pregnancy loss: When? Why?



The pregnancy loss iceberg

modified from Macklon et al (2002) Human Reproduction

Early post-implantation human embryo development

1. *In vitro* culture of human embryo

- A model system to study early post-implantation development and uncover sequential morphogenetic steps

2. A molecular map of human embryos

- Single cell transcriptomic analysis of post-implantation embryos

3. Aneuploid and mosaic human embryos

- Developmental consequences of specific aneuploidies during post-implantation development

4. 3D stem cell model of development

- A model system to reveal mechanisms of embryo self-organization

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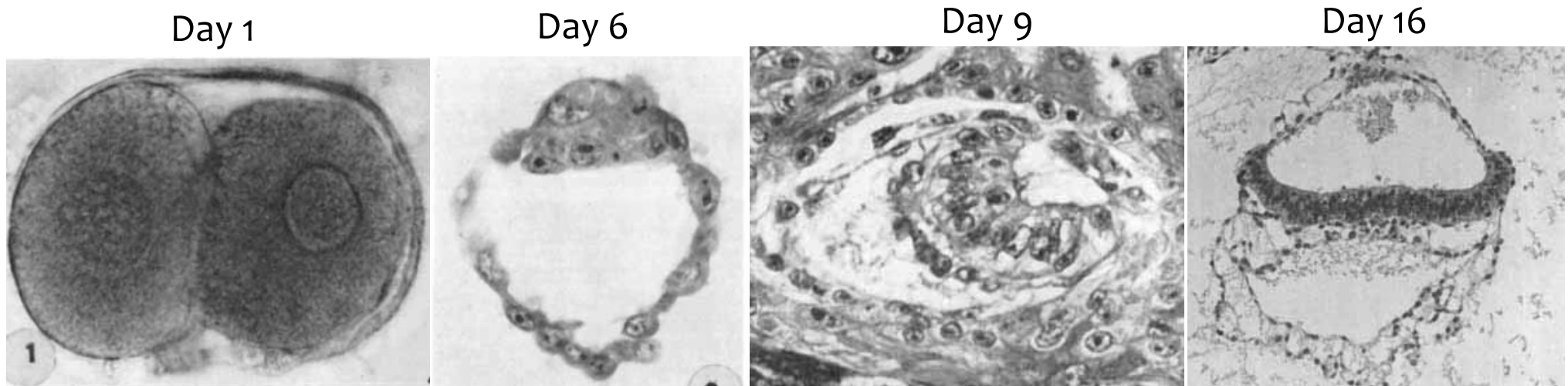
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Human embryo development at implantation: methods to explore the black box of development

- Analysis of embryos developing *in vivo* (Carnegie Institution) after hysterectomy:

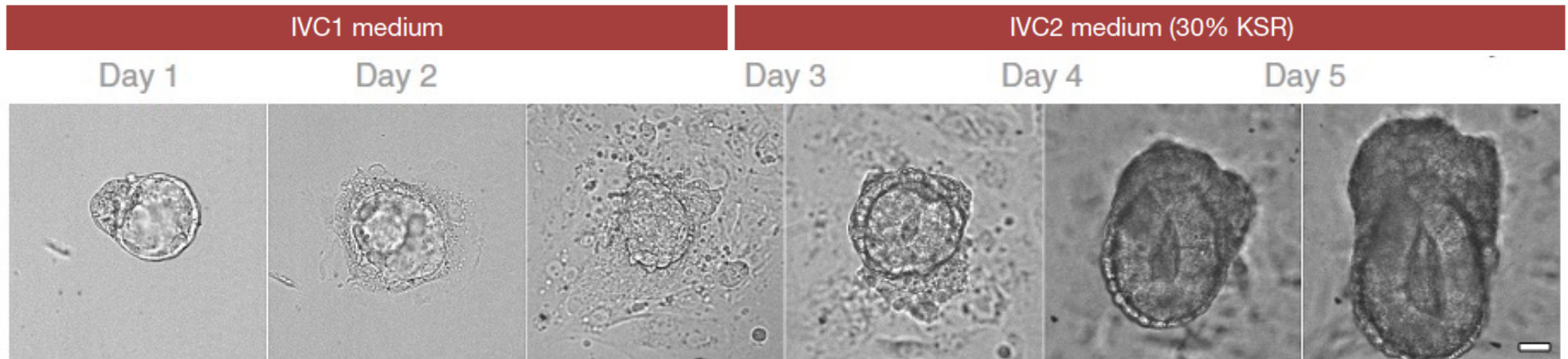


Hertig et al, Am J Anat (1956)

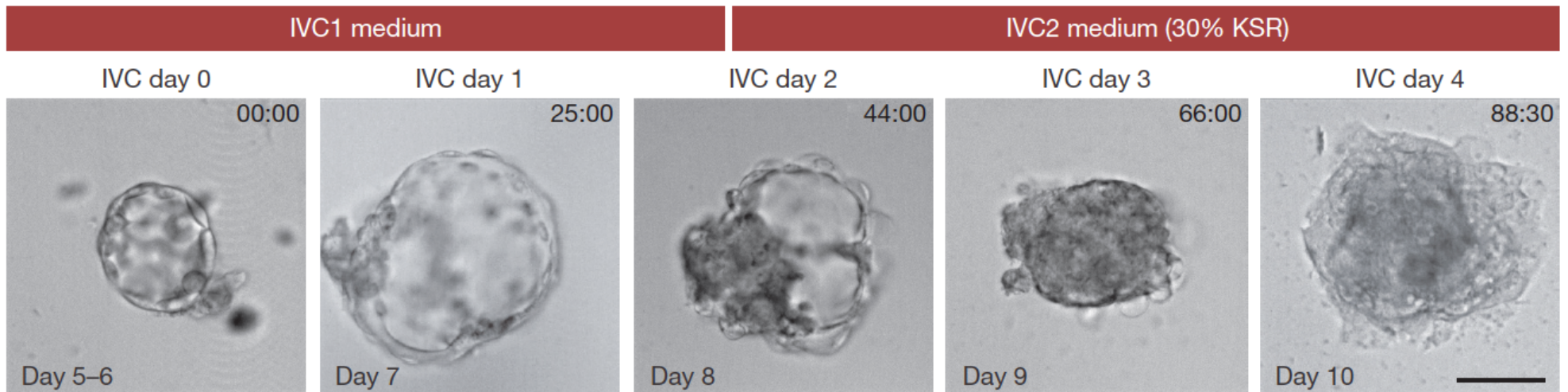
Can we develop an alternative methods – (1) system to culture human embryos beyond day 7 *in vitro* and (2) system to model human development with stem cells?

In vitro culture of mouse embryos beyond implantation

Pre-implantation blastocyst $\xrightarrow{\text{In vitro culture}}$ Post-implantation mouse embryo

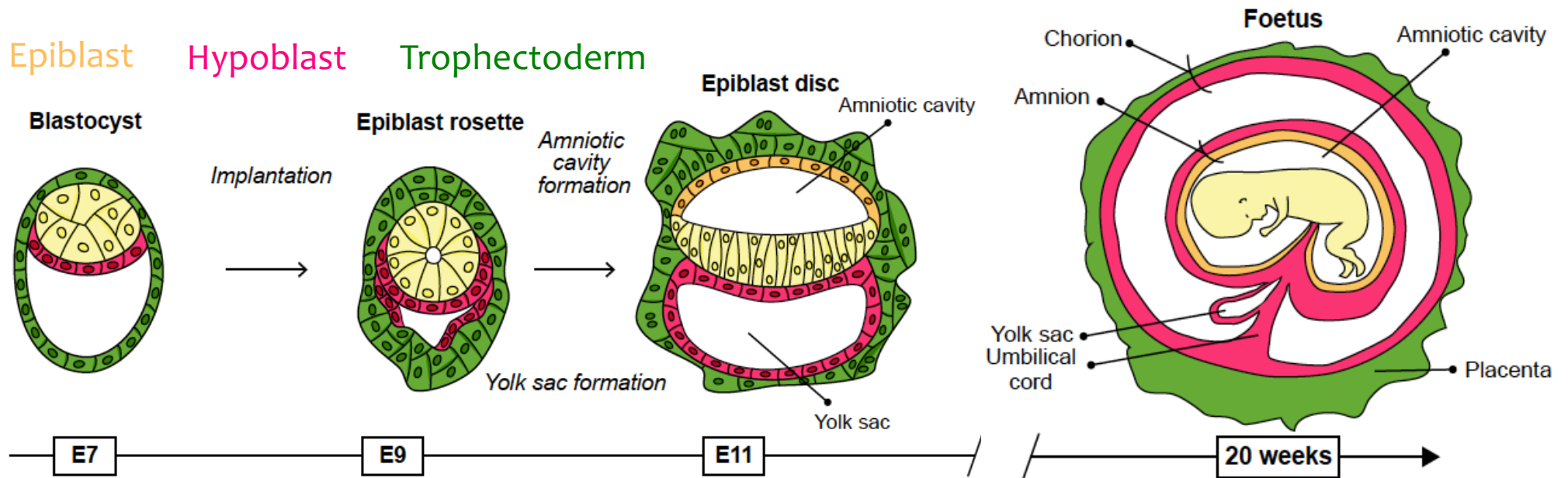


Morris et al (2012) Nat Comm; Bedzhov et al (2014) Nat Prot; Bedzhov et al (2014) Cell



Shahbazi et al (2016) Nat Cell Biol; Deglincerti et al (2016) Nature; Zhou et al (2019) Nature

Post-implantation morphogenesis of the human embryo



Shahbazi et al (2018) Nat Cell Biol

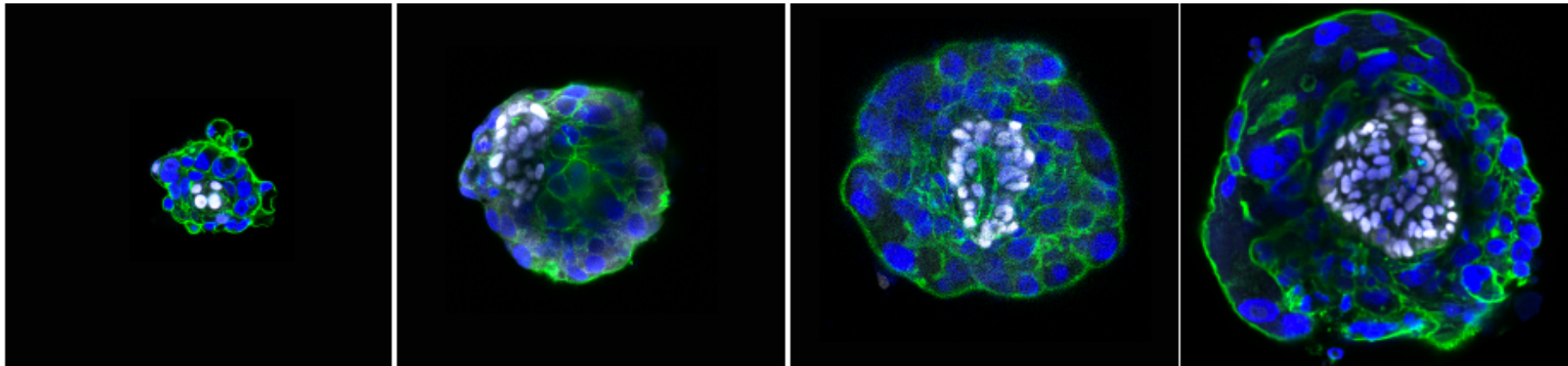
Embryo growth

Day 7-8

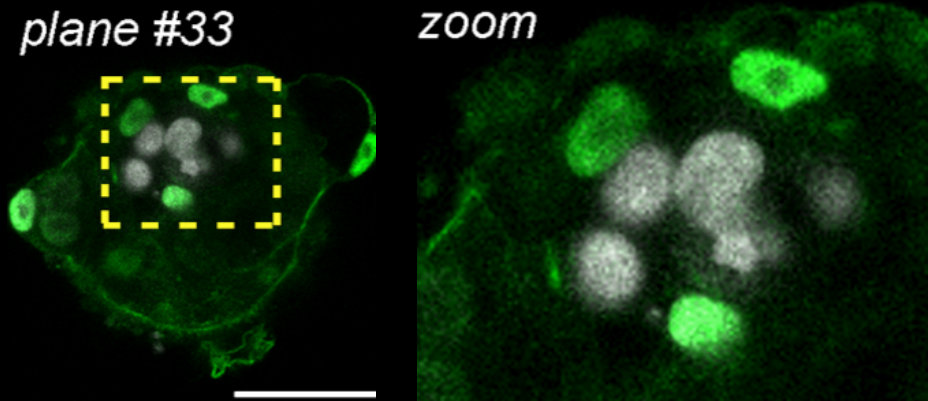
Day 8-9

Day 9-10

Day 10-11



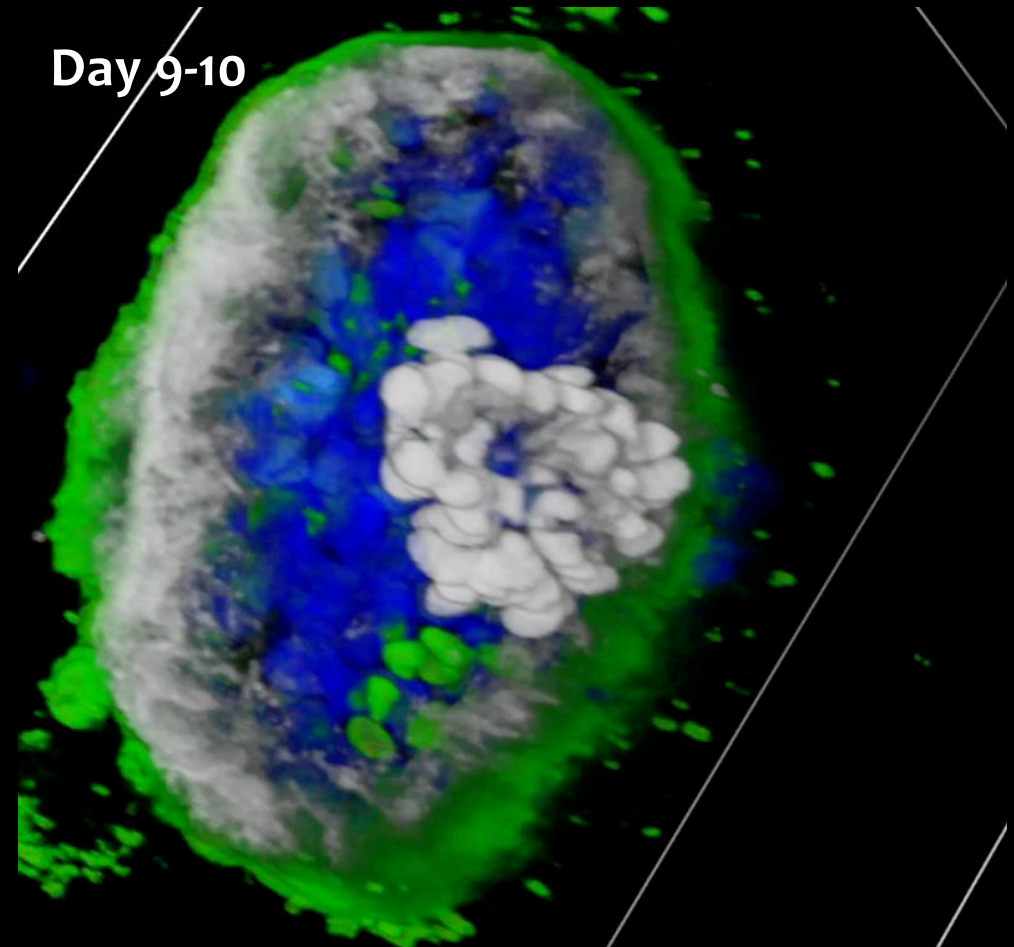
Day 7-8: Segregation of epiblast and hypoblast



Epiblast (OCT4)
Hypoblast (GATA6)



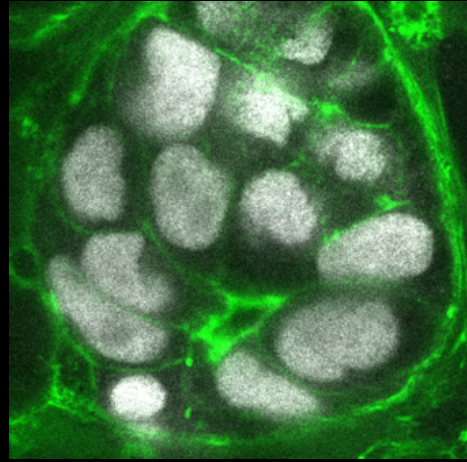
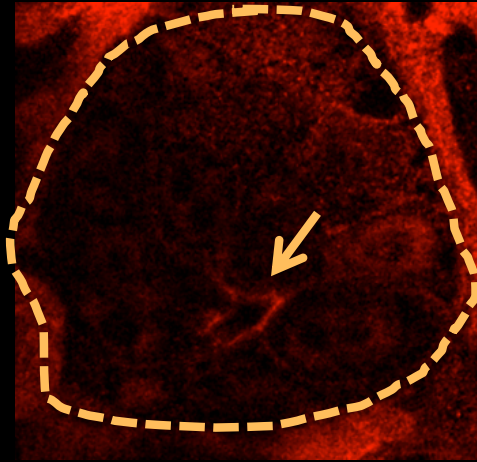
Inner cell mass



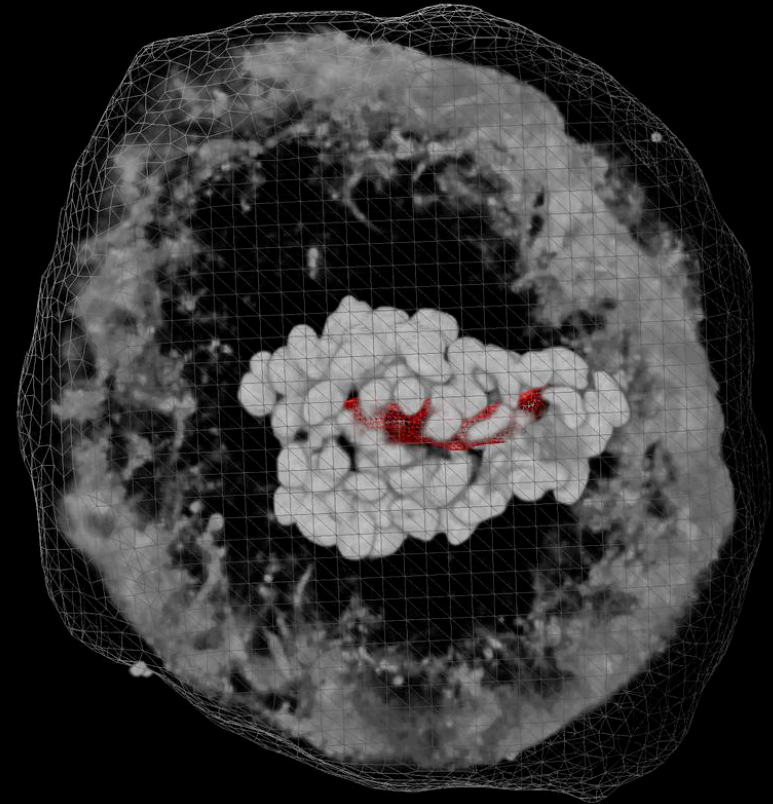
OCT4/GATA6/DAPI

Day 8-9: Amniotic cavity formation

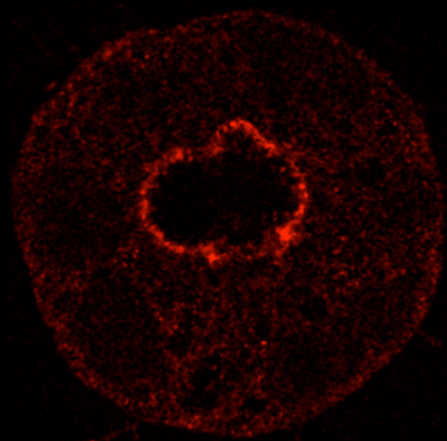
Day 8-9 : human embryo



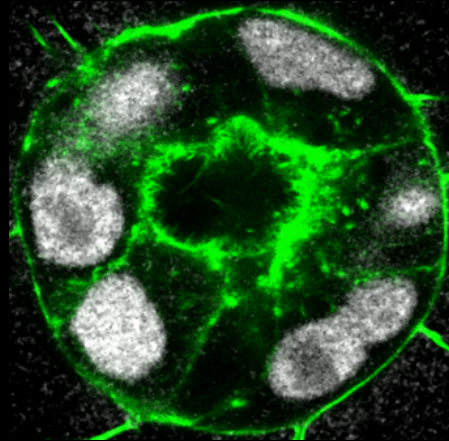
Day 9-10



Human ESCs 3D model: (matrix)



aPKC: apical
polarity complex



OCT4/F-actin

OCT4

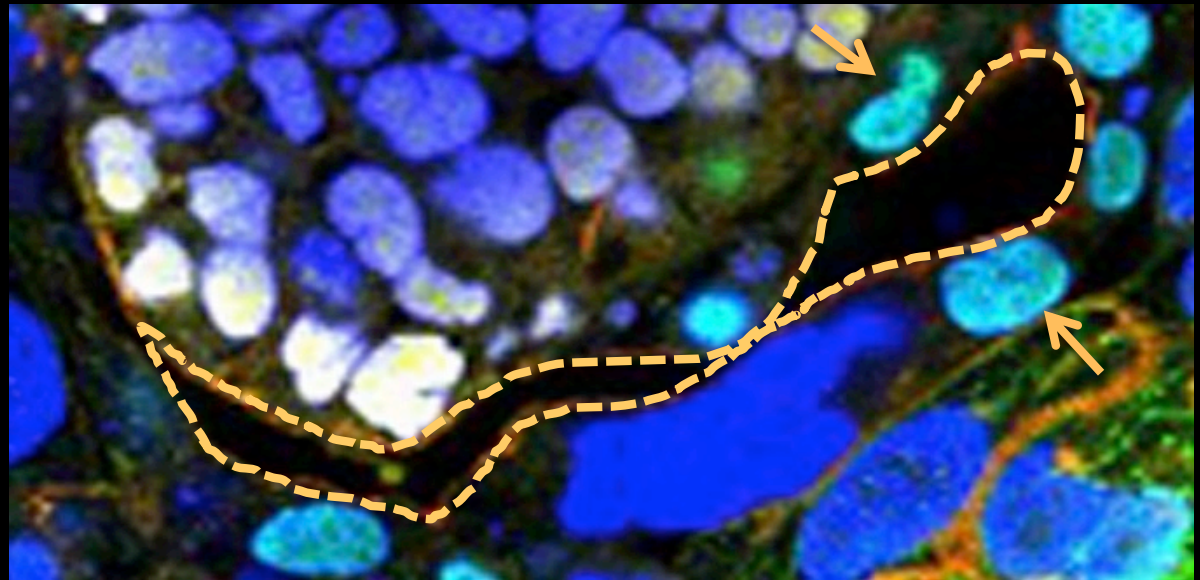
Amniotic cavity

Bedzhov et al (2014) Cell; Shahbazi et al (2017) Nature

Day 10-11: Differentiation of extra-embryonic tissues

Hypoblast

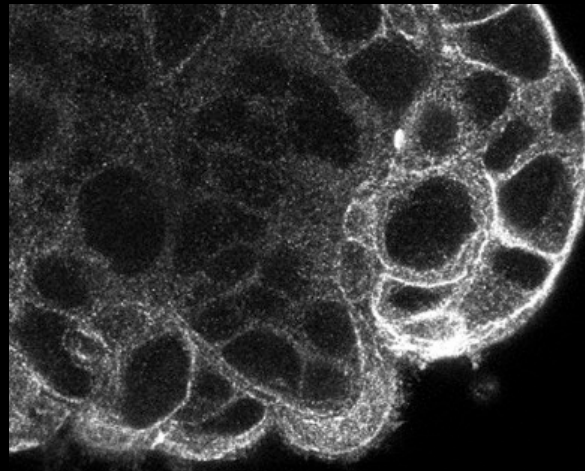
Formation of the prospective yolk sac



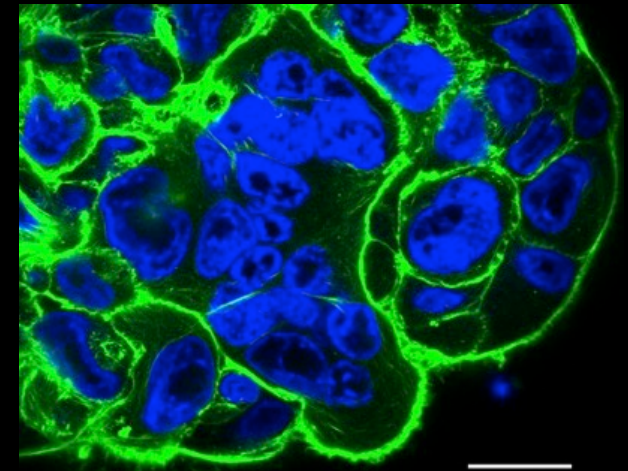
DAPI/GATA6/aPKC/OCT4

Trophoblast

Differentiation into cytotrophoblast and syncytiotrophoblast



Cytokeratin 7: Pan-trophoblast marker



F-actin/DAPI

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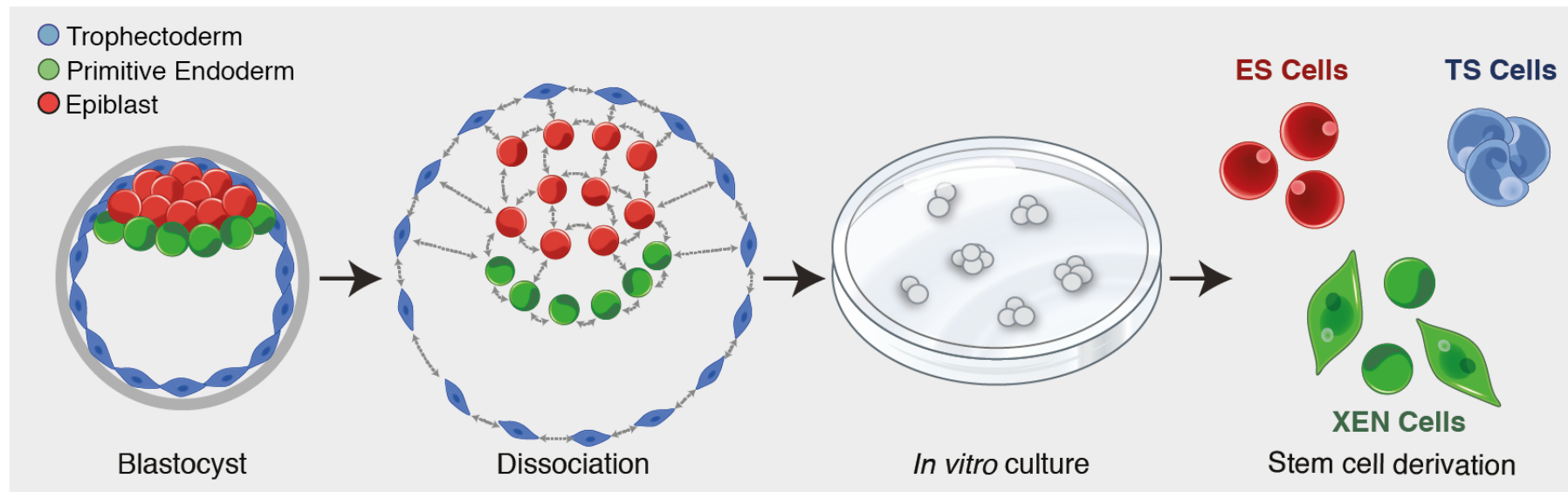
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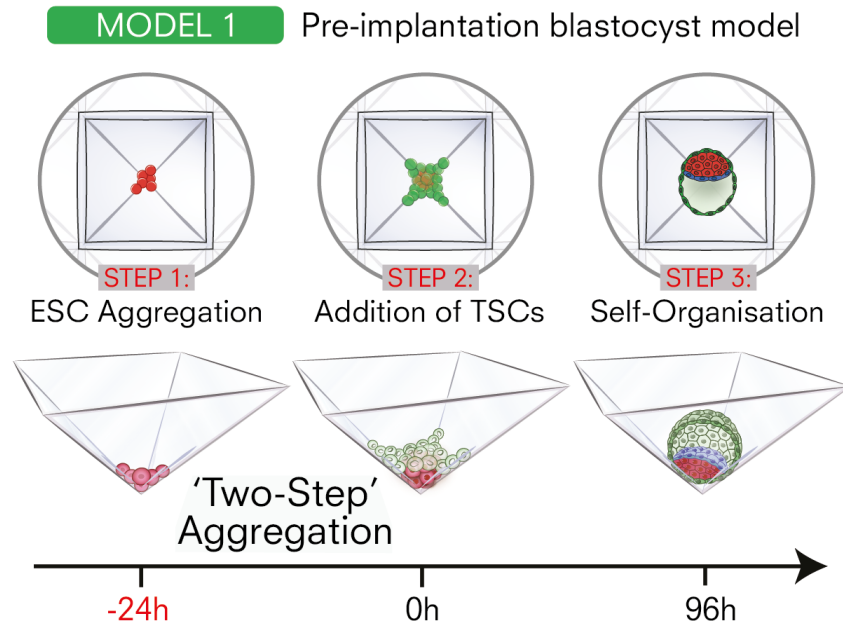
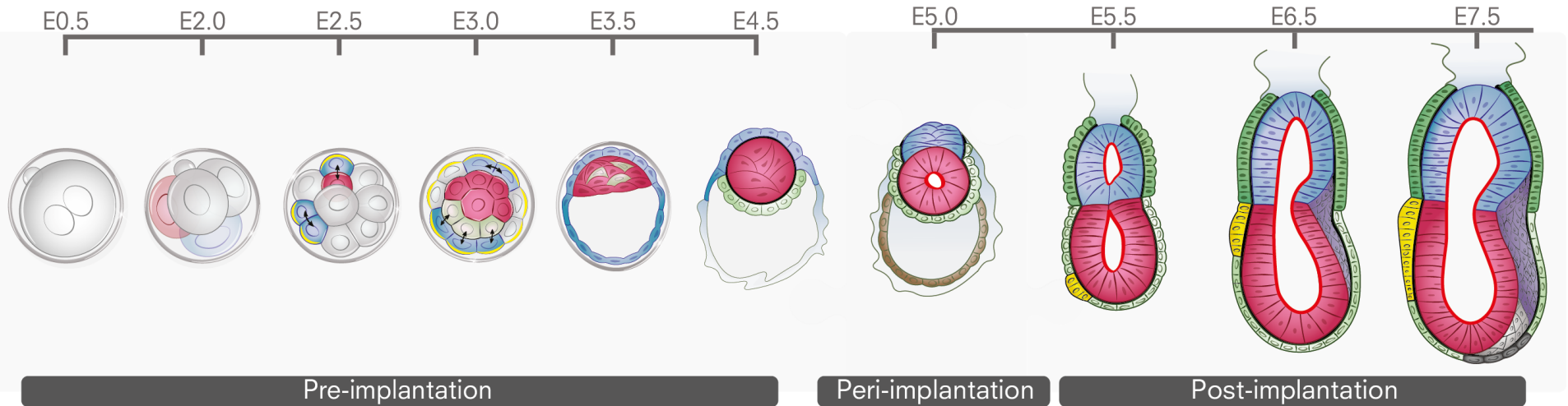
- A model system to reveal mechanisms of embryo self-organization

Can we re-construct mammalian embryos from stem cells for three distinct tissues to bring mechanistic understanding of development

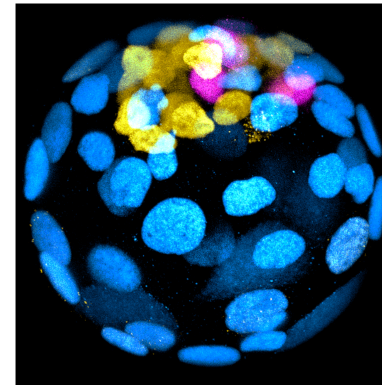
"What I cannot create, I do not understand" Richard Feynman



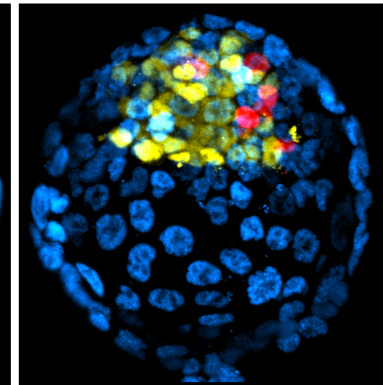
We have developed four 3D stem cell-embryo model systems to generate embryo-like structures



E3.5 Mouse Blastocyst

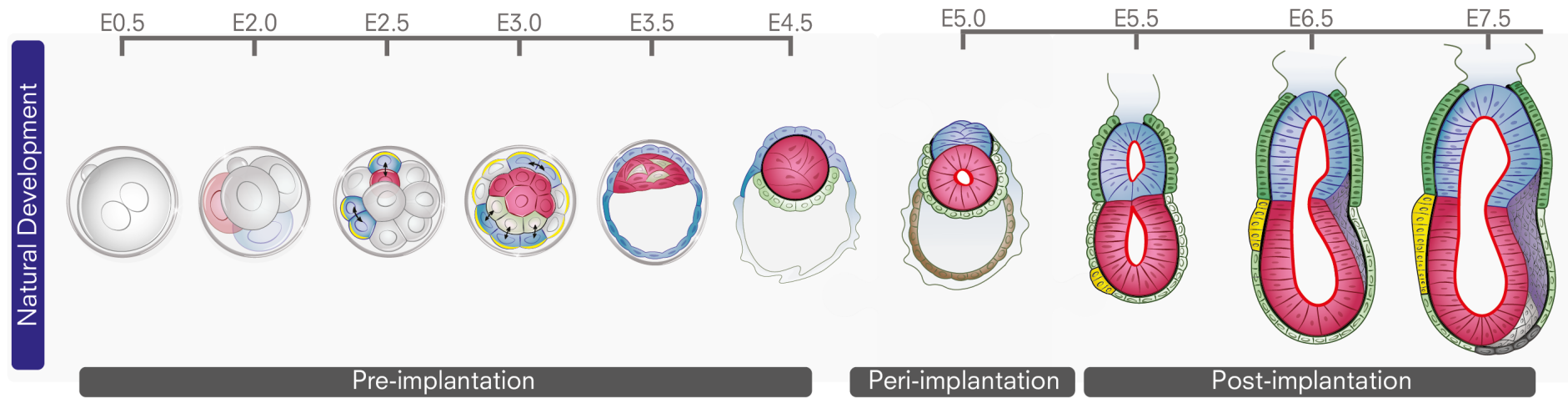


EPS-Blastoid (84h)

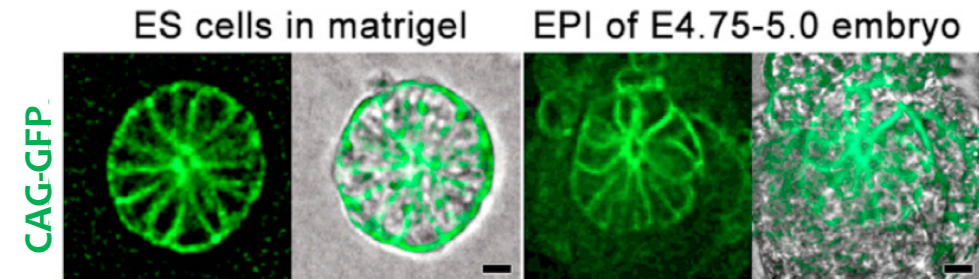
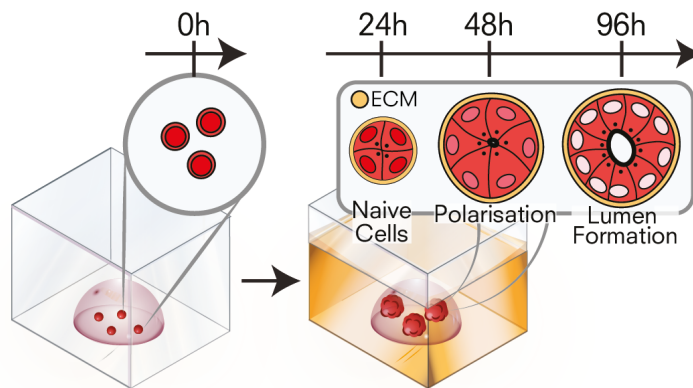


Sozen, Cox et al, (2019) Dev Cell
 Li et al (2019) Cell
 Rivron et al, (2018) Nature

Formation of blastoids having all three cell types: EPI, PE and TE.
 Can induce implantation but don't develop through implantation well ..

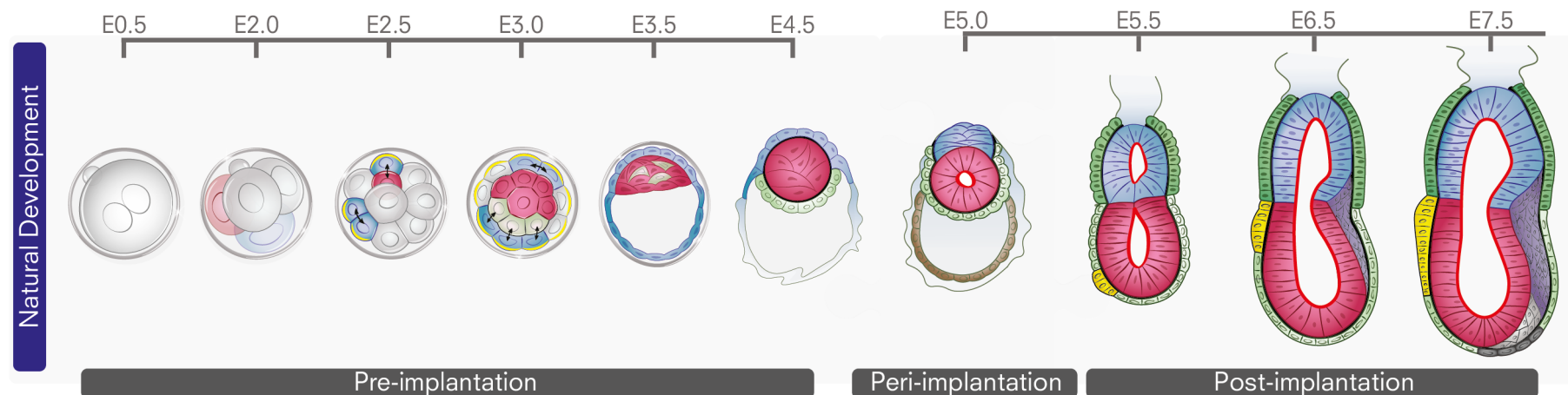


MODEL 2 Peri-implantation epiblast model

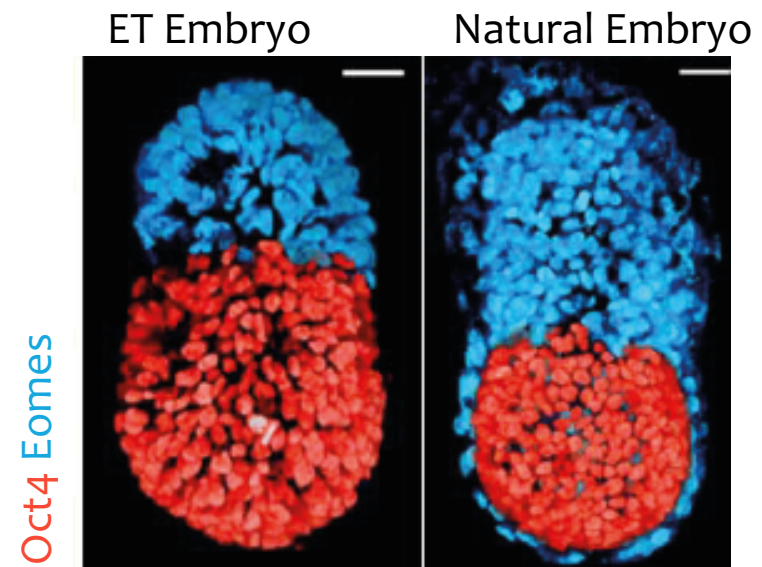
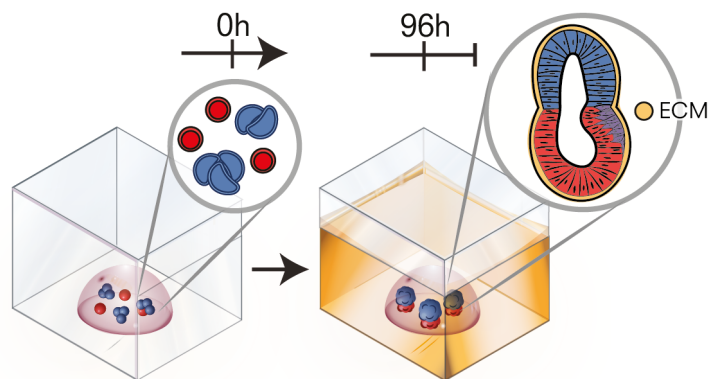


Mouse Bedzhov and Zernicka-Goetz (2014) Cell
Human Shahbazi et al (2017) Nature

- Mechanism behind lumenogenesis in mouse and human
- Interrelationship between different pluripotent states and tissue architecture

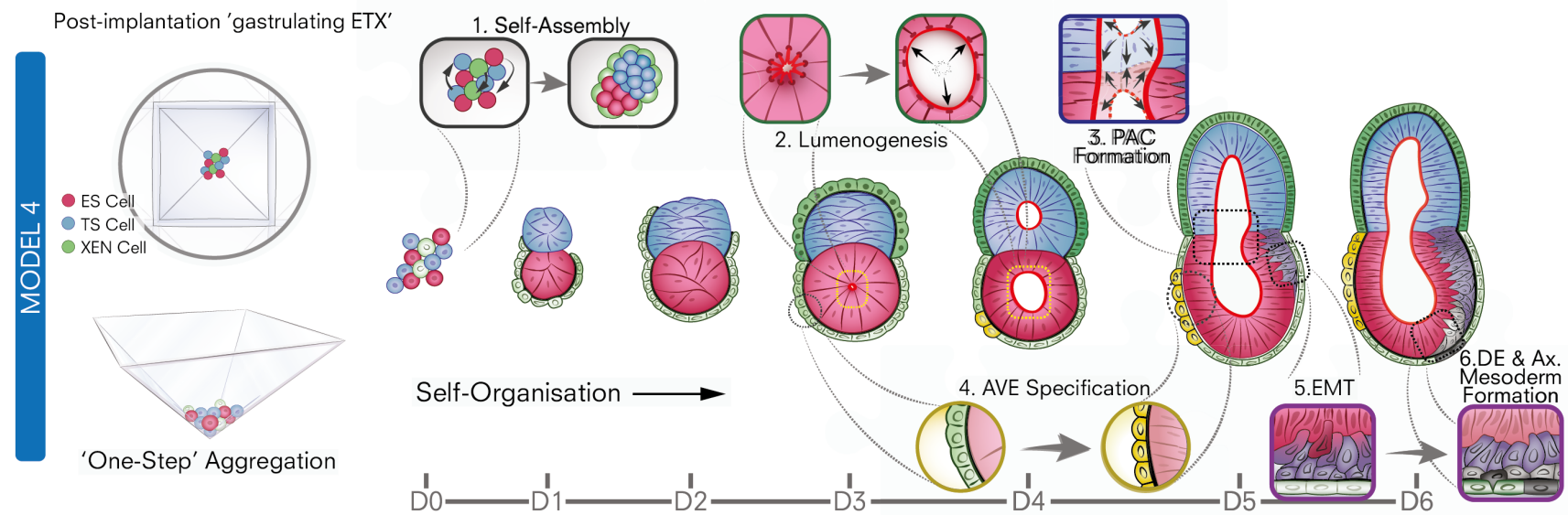
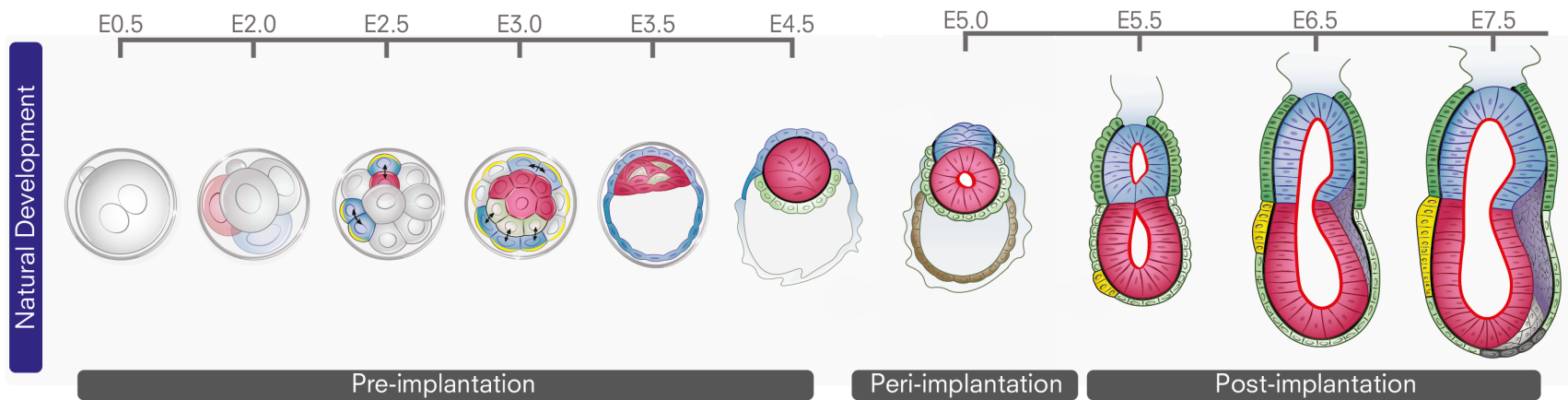


MODEL 3 Post-implantation 'polarising ETS'



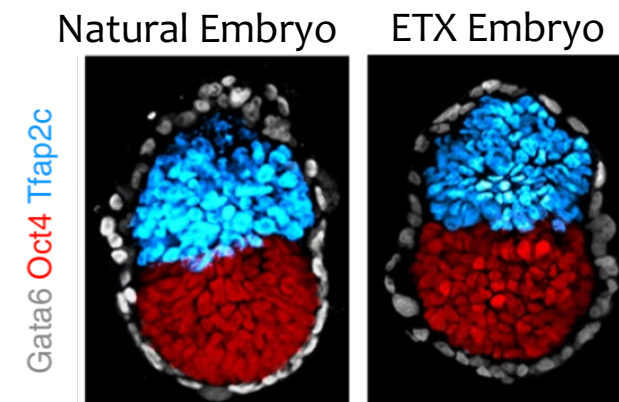
Harrison, Sozen et al (2017) Science

- Mechanism of crosstalk between the embryonic and extra-embryonic compartments to form the pro-amniotic cavity
- Symmetry breaking, Mesoderm specification and PGCs formation does not requires anterior Signaling Center



- How does self-organization work?

Sozen, Amadei, Cox et al (2018) Nature Cell Biol



Human embryo teams



Caltech



Andy Cox

Berna Sozen

Ying Zhang

Tongtong Cui

Dong Yuan Chen



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CAMBRIDGE



Aga Jedrusik

Marta Shahbazi

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Baily Weatherbee

IVI-RMA, US

Emre Seli

Richard Scott

Xin Tao

Tianren Wang

CARE Fertility Clinic, UK

Simon Fishel

Alison Campbell



The SHURL & KAY CURCI
foundation



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