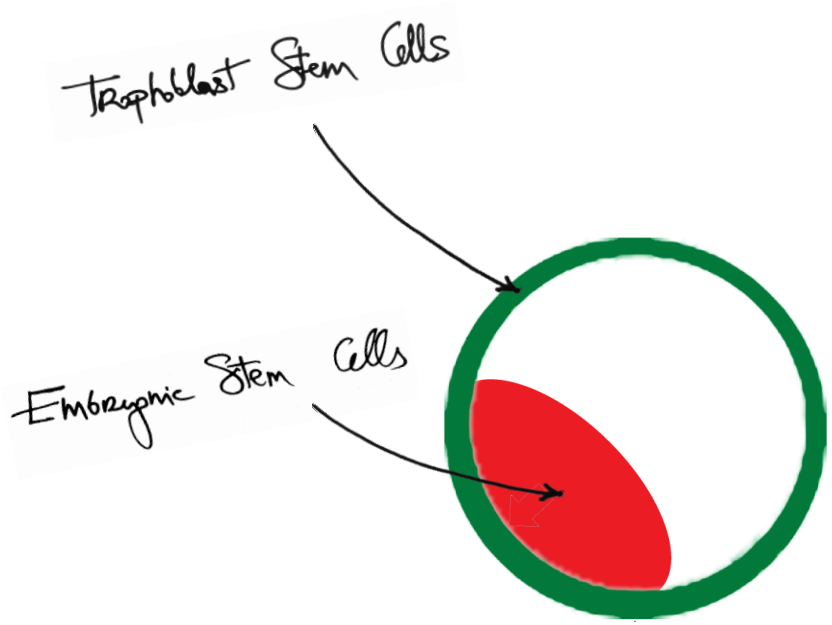
ÖAW AUSTRIAN ACADEMY OF SCIENCES

IMBA Institute of Molecular Biotechnology of the Austrian Academy of Sciences

NRivron

Blastoid: modeling the preimplantation embryo



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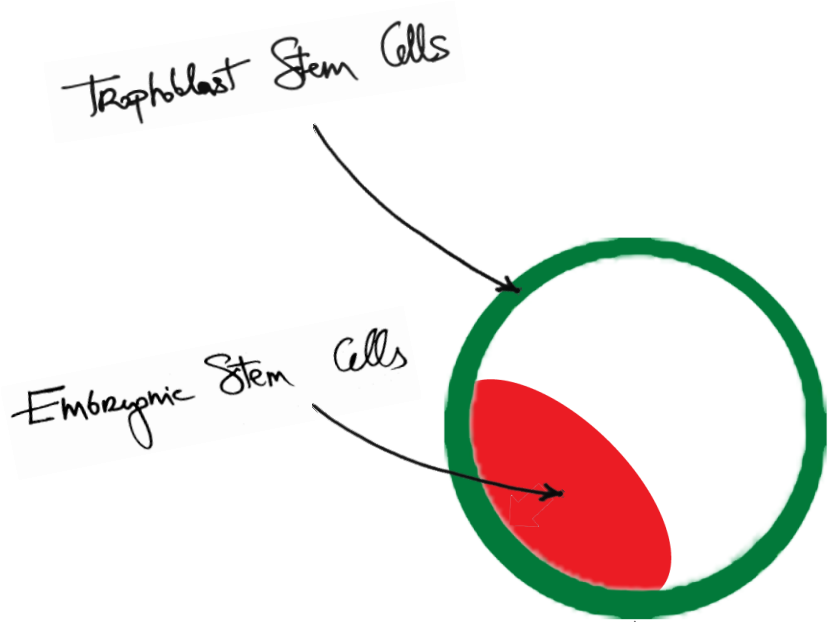
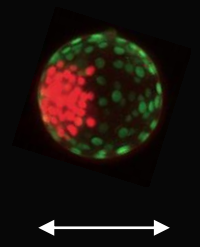
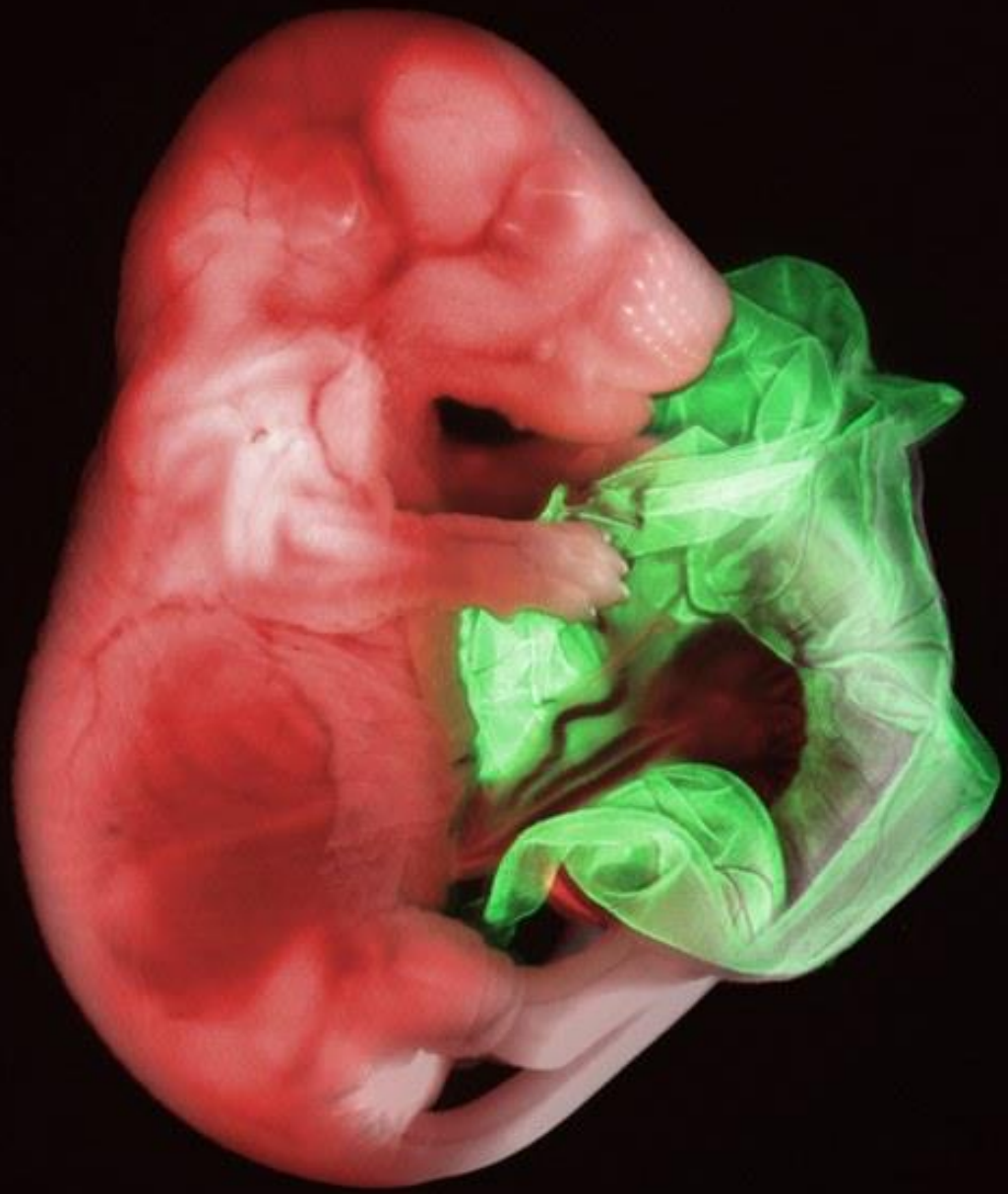


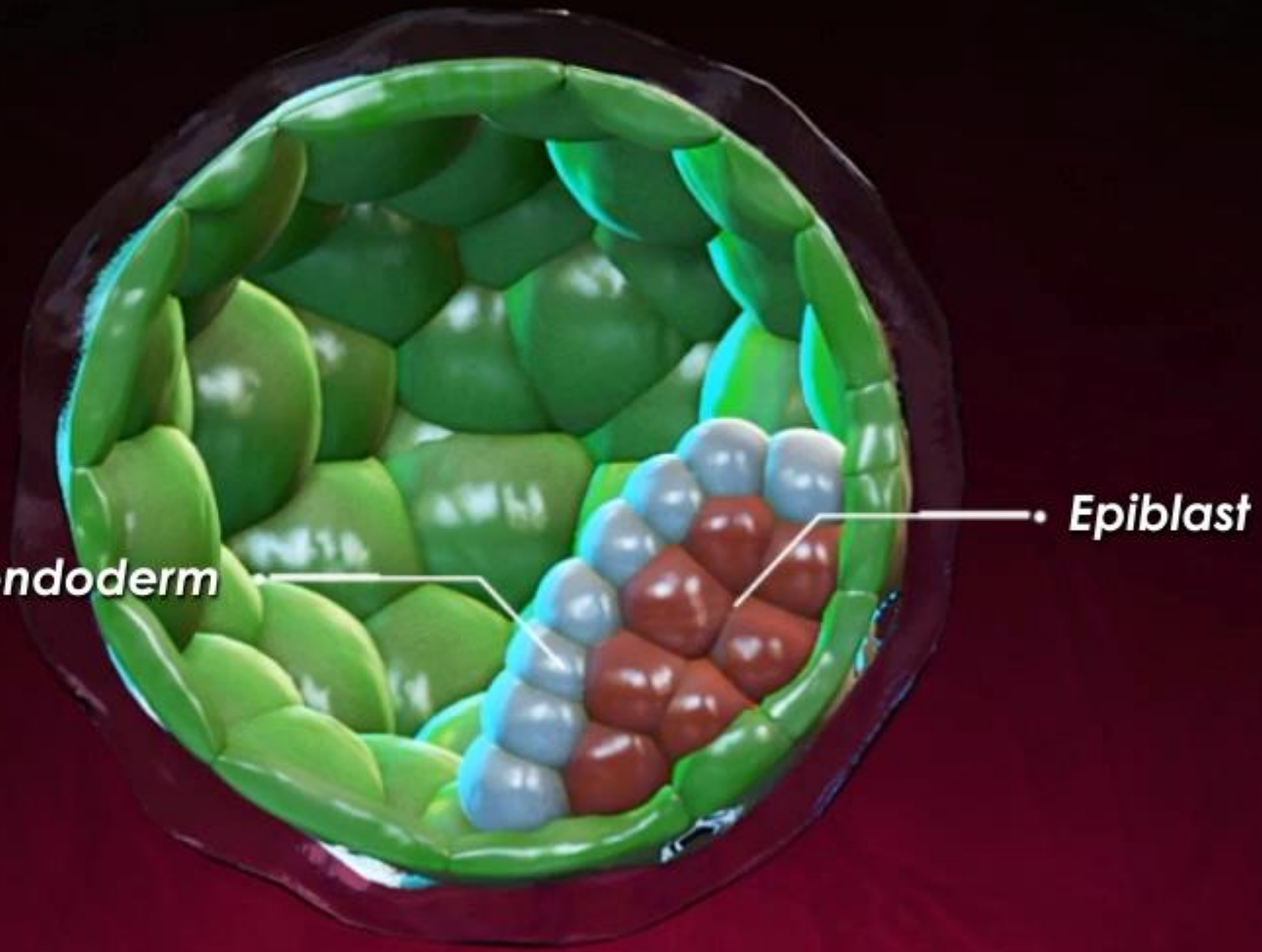
All this work is done using mouse stem cells, not human stem cells.

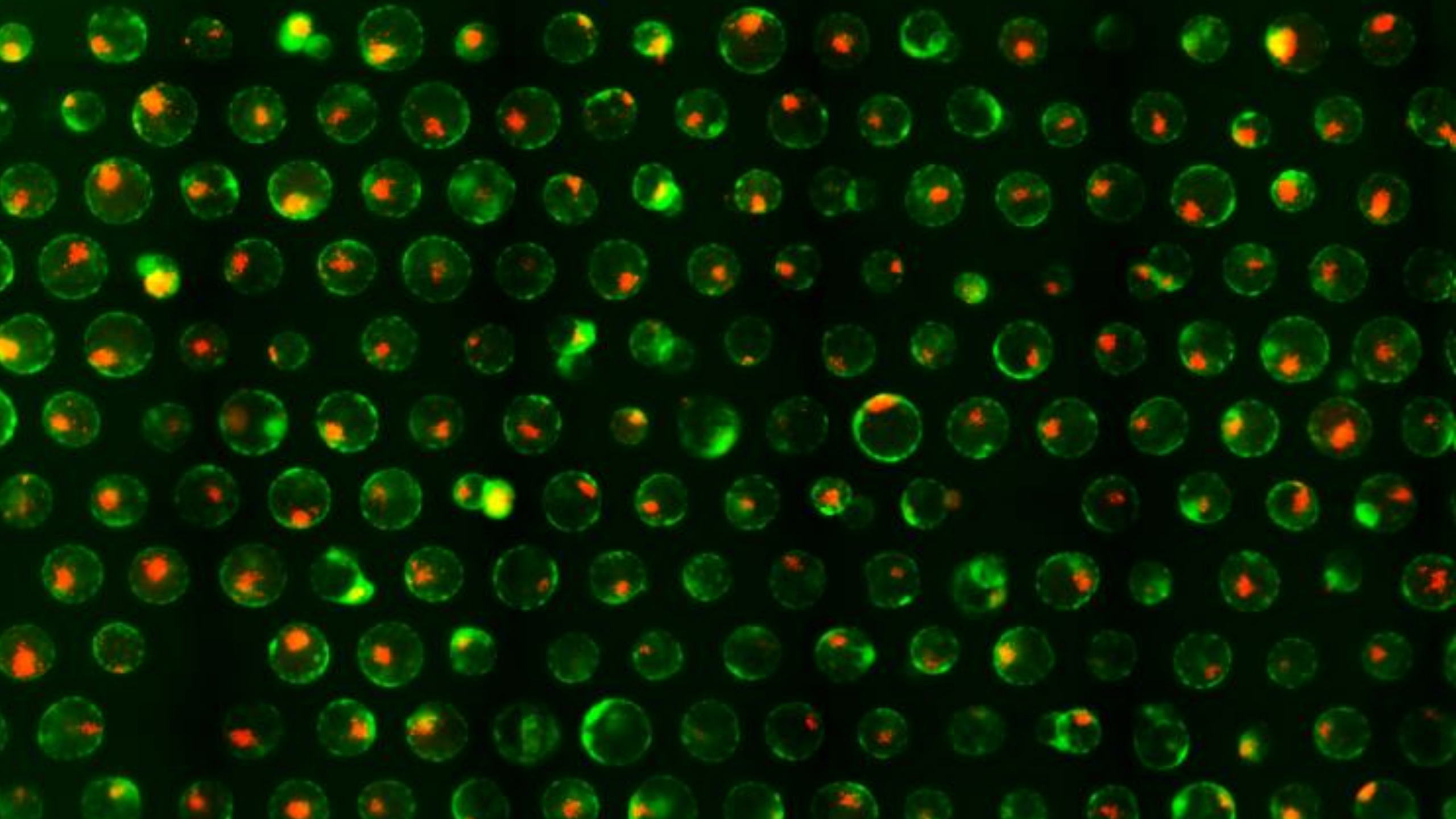


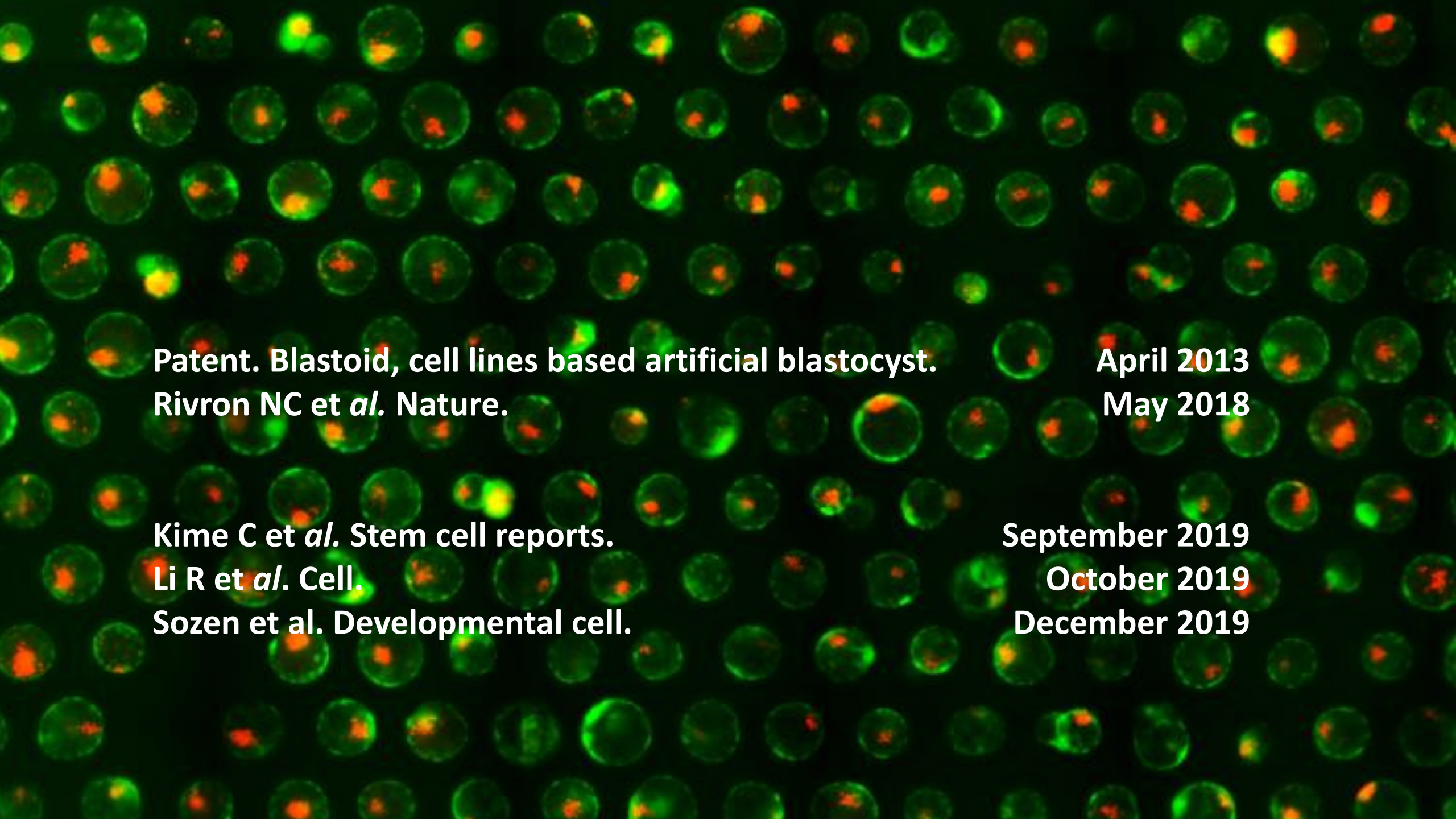
100 micrometers
1/10th of a hair



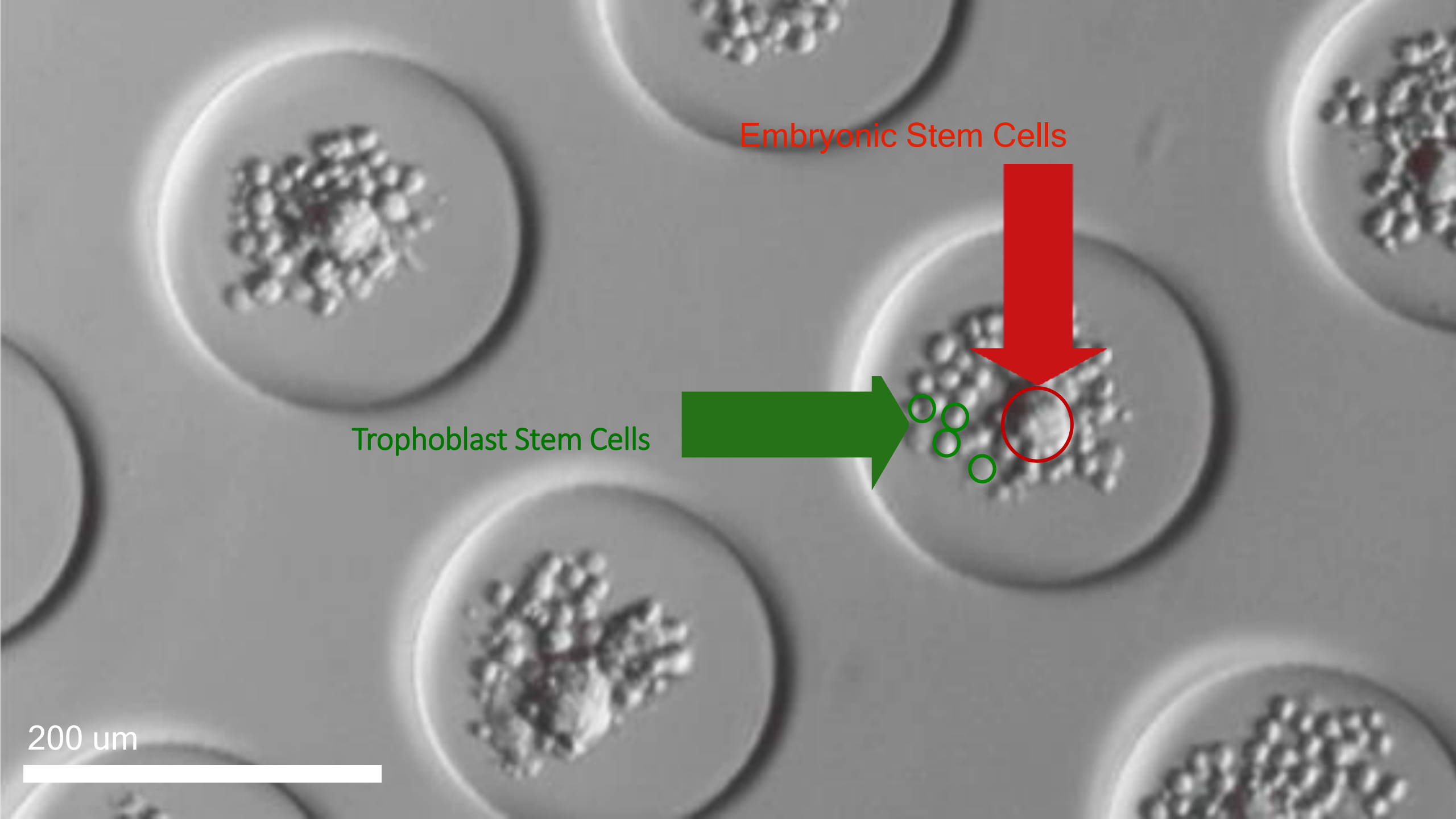
Number of cells = 100
Number of days = 4.5



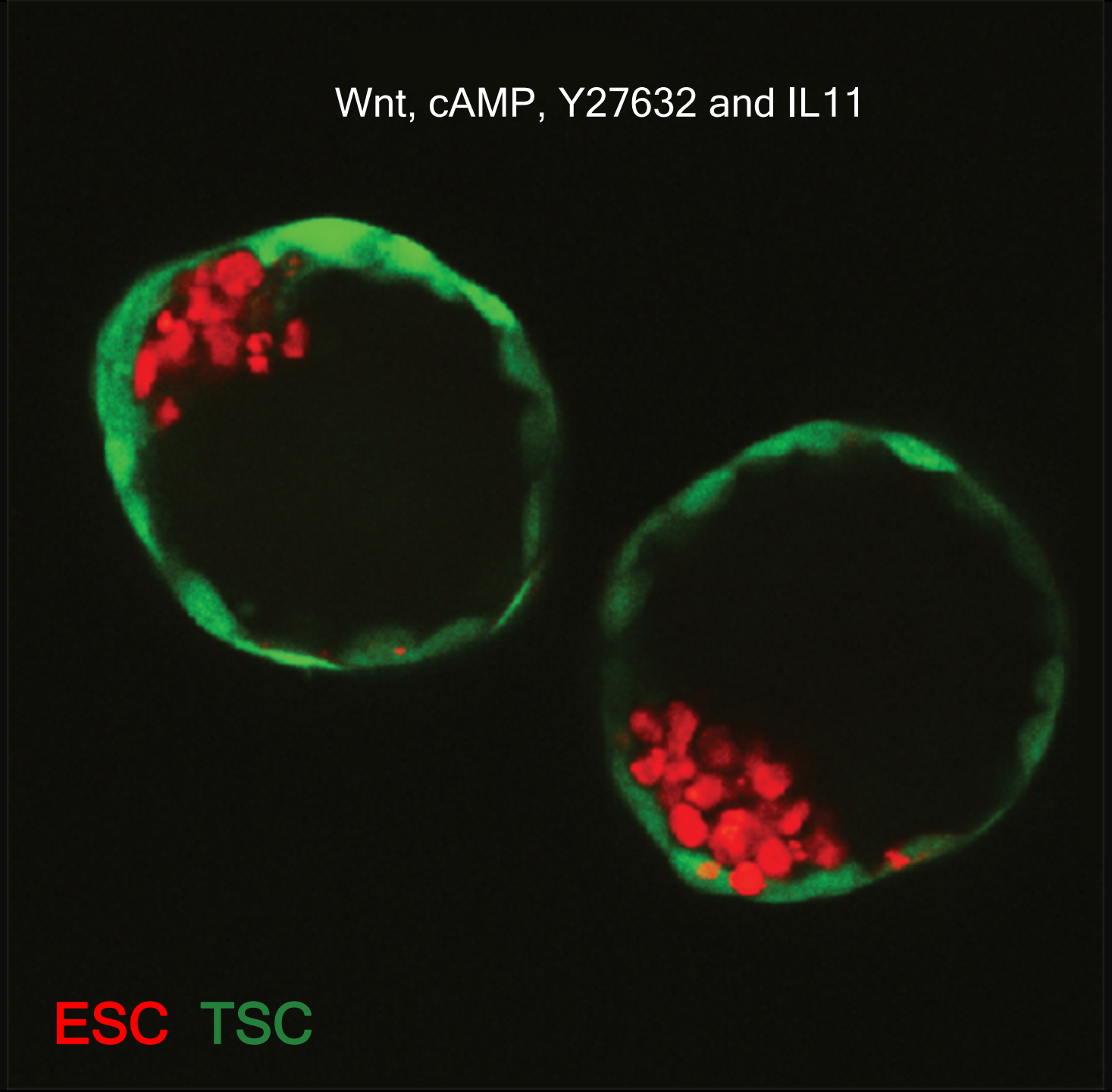




Patent. Blastoid, cell lines based artificial blastocyst.	April 2013
Rivron NC et *al.* Nature.	May 2018
Kime C et *al.* Stem cell reports.	September 2019
Li R et *al*. Cell.	October 2019
Sozen et al. Developmental cell.	December 2019

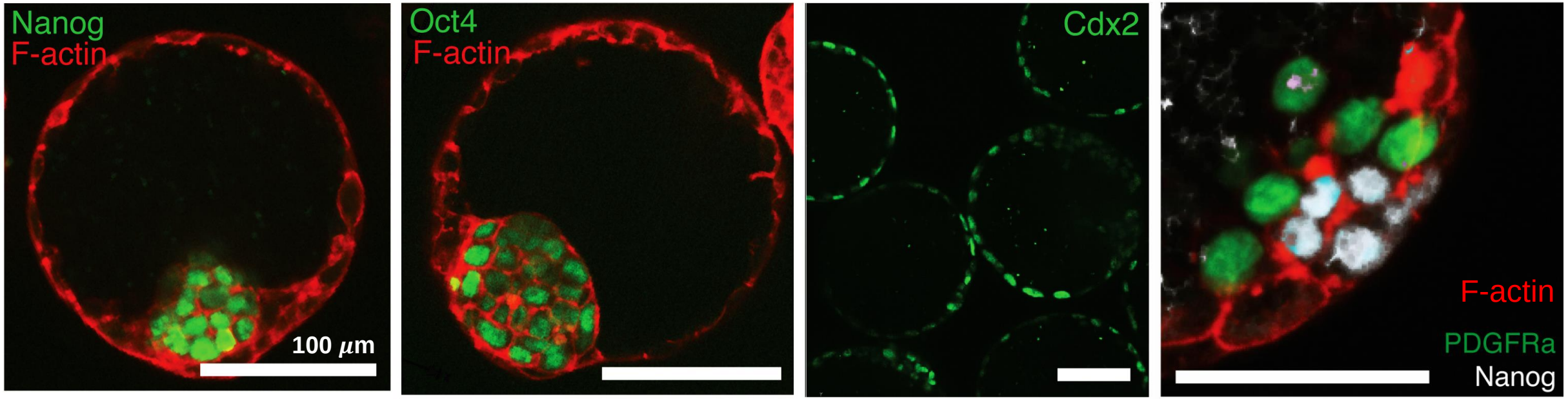

Embryonic Stem Cells
Trophoblast Stem Cells
200 um

Wnt, cAMP, Y27632 and IL11



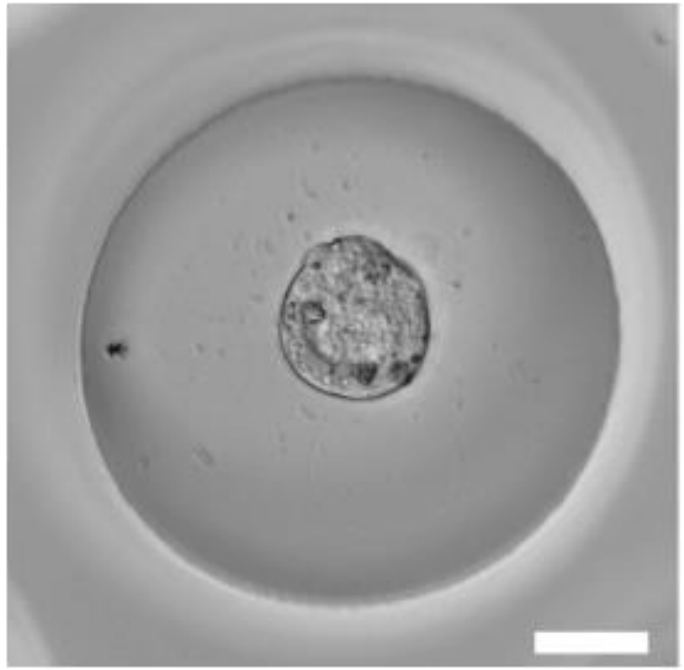
Blastoids make analogs of the 3 cell types forming the blastocyst.

These 3 cell types form the whole organism, meaning placenta, yolk sac, and body.

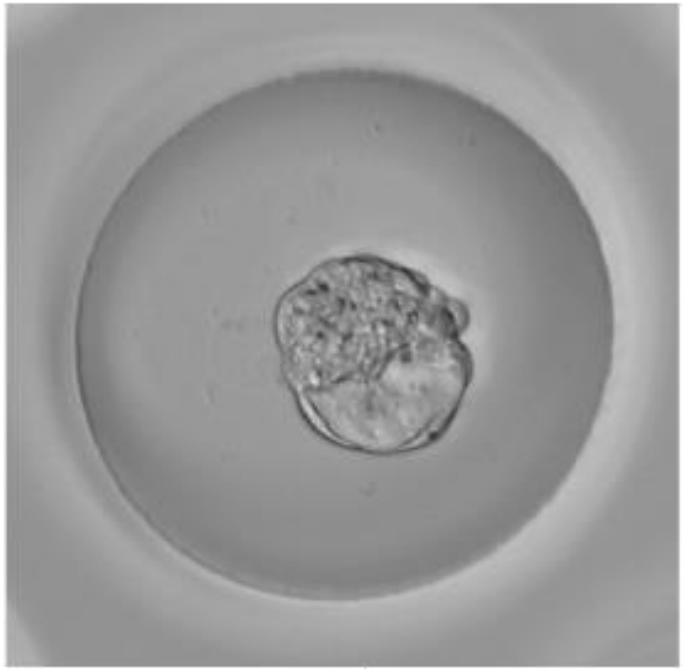


Blastoids are morphologically similar to blastocysts

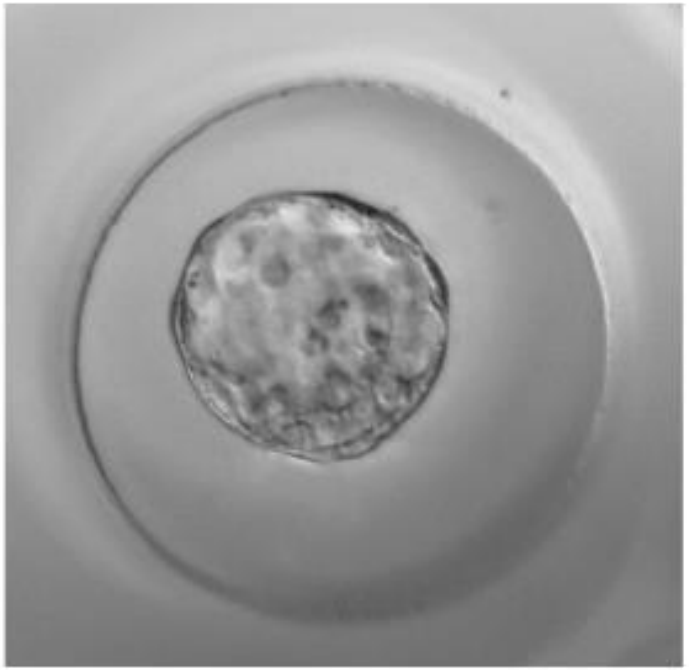
0 hours



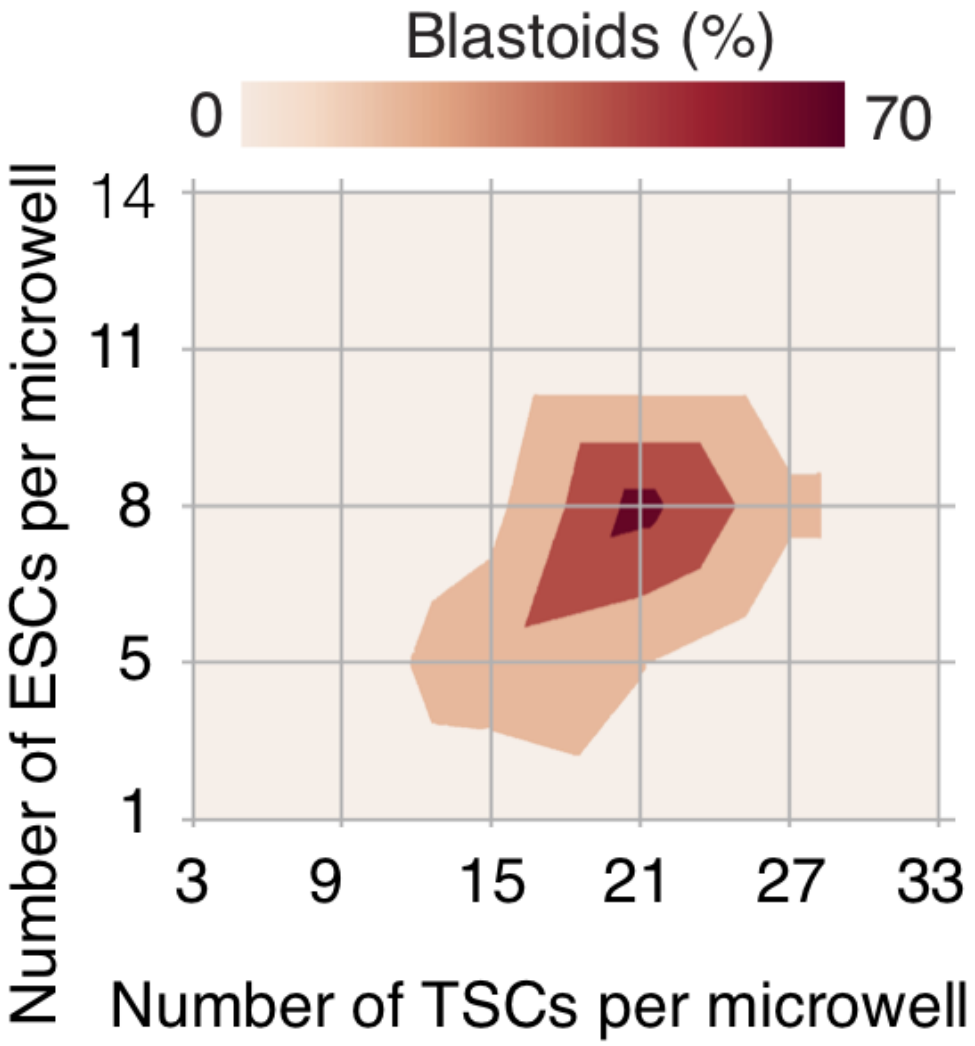
24 hours

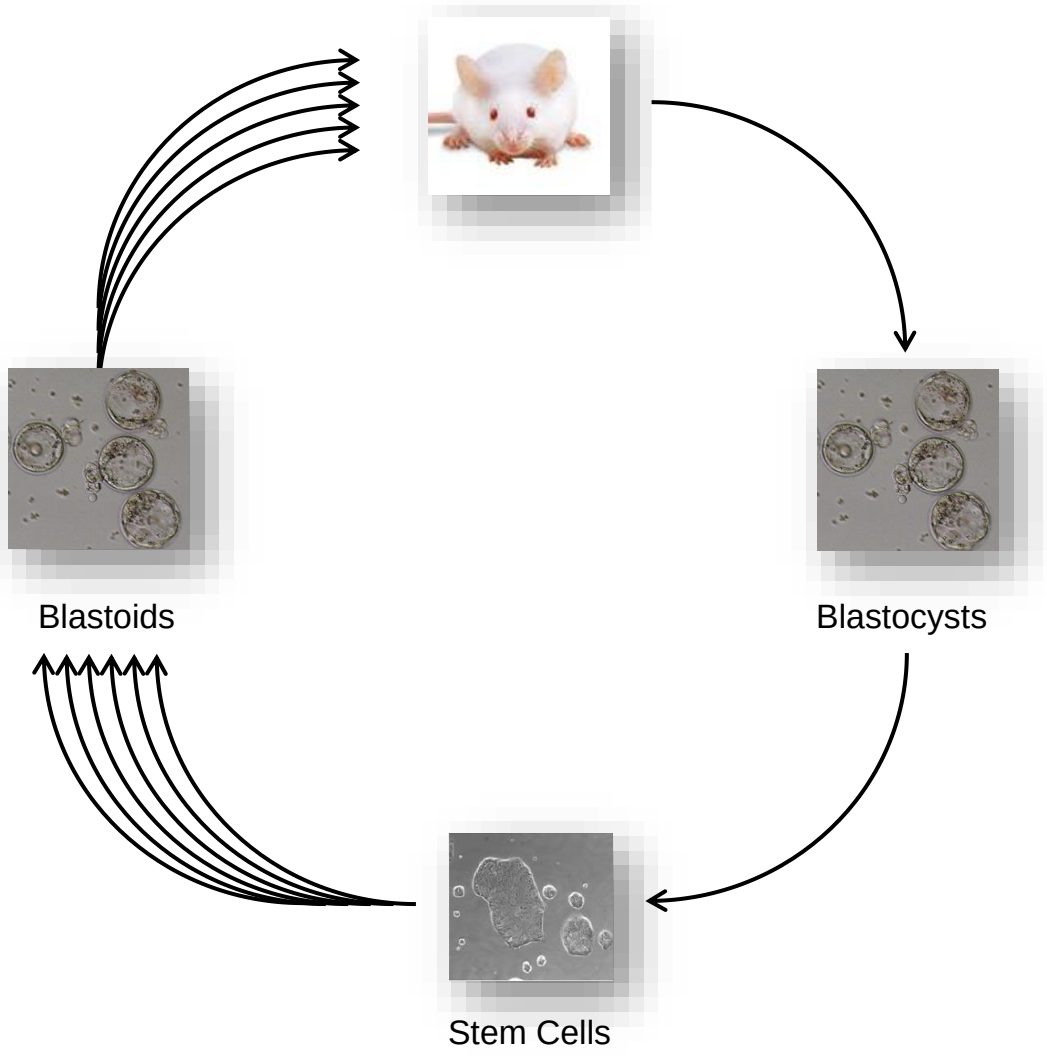


48 hours



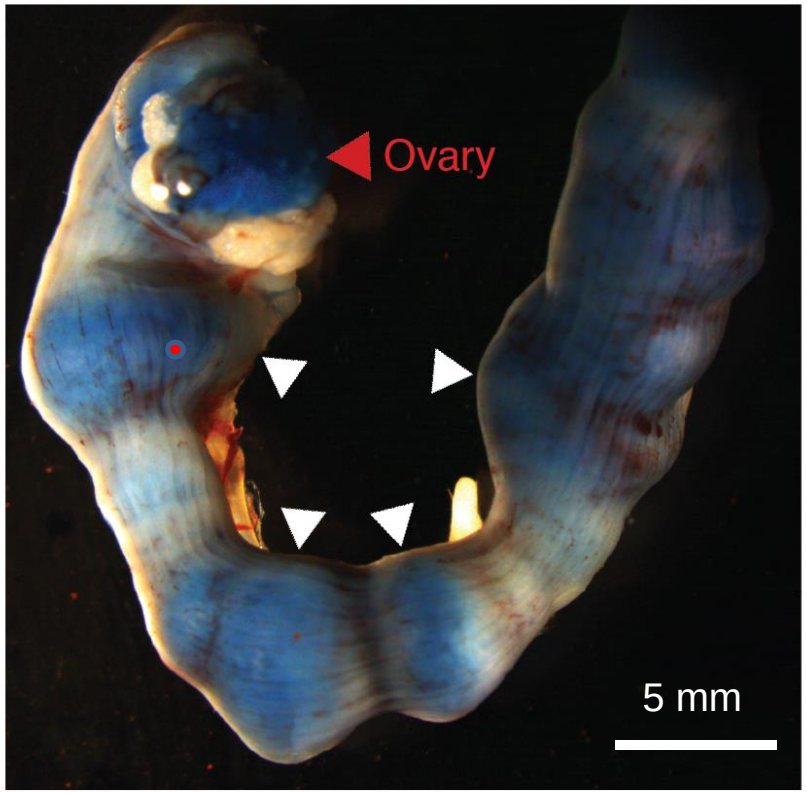
Blastoids form efficiently




Blastoids
Blastocysts
Stem Cells

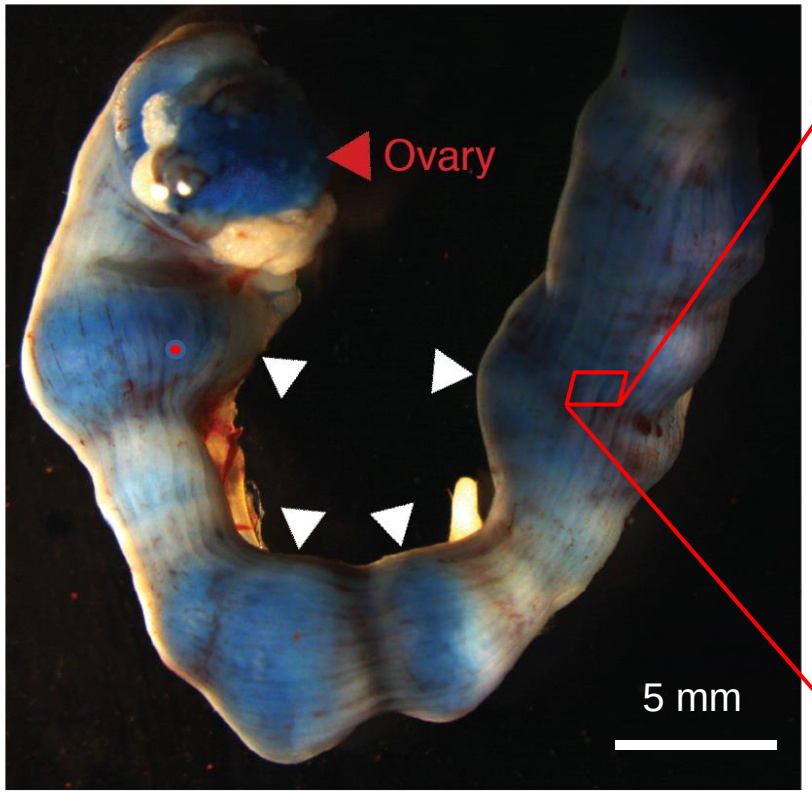
Blastoids initiate implantation and development *in utero*

Local deciduae and irrigation

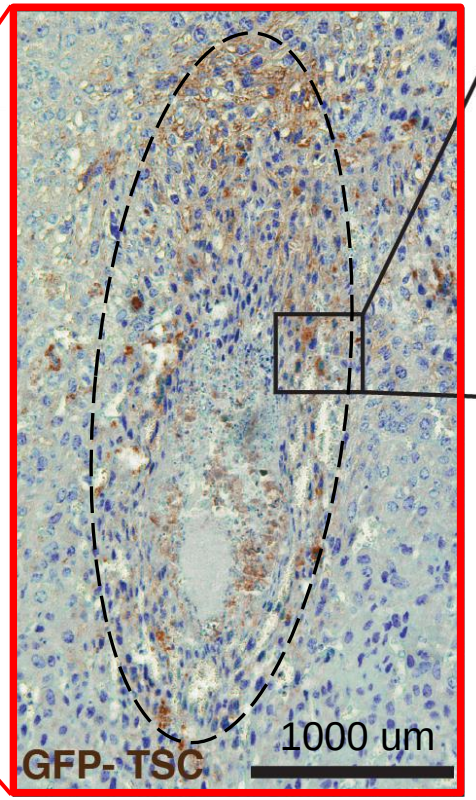


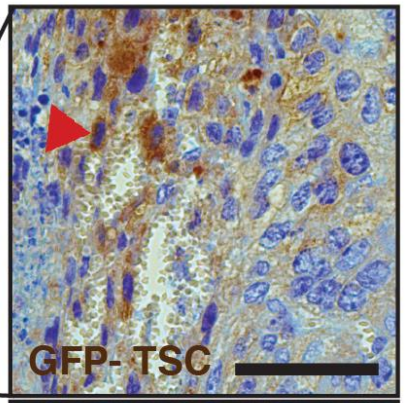
Blastoids initiate implantation and development *in utero*

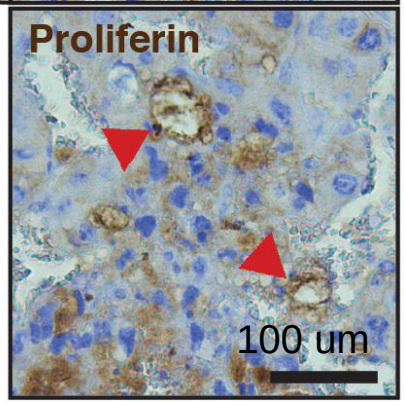
Local deciduae and irrigation



Elongation and anastomosis

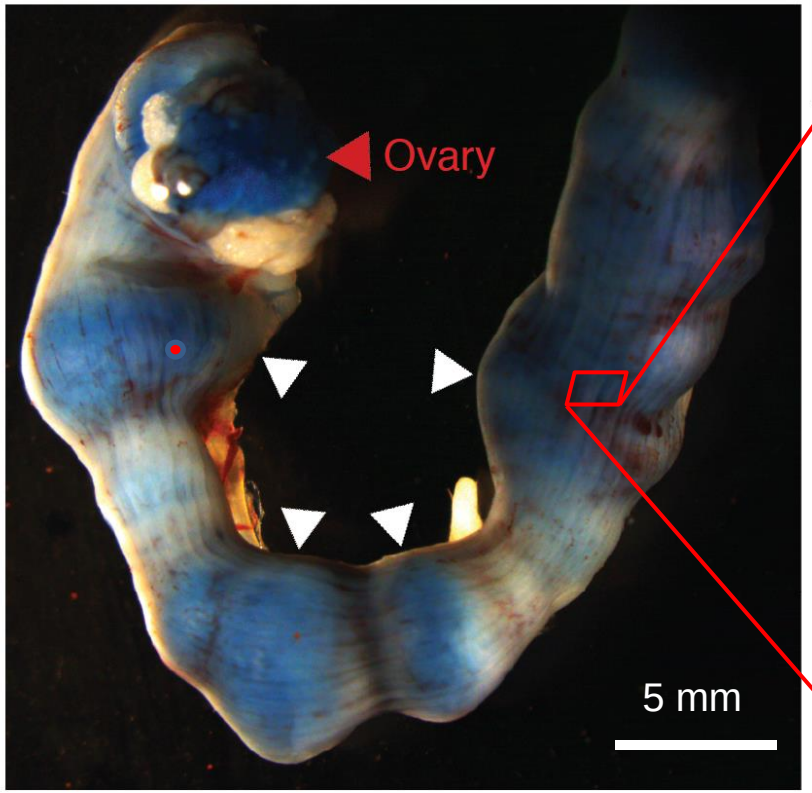




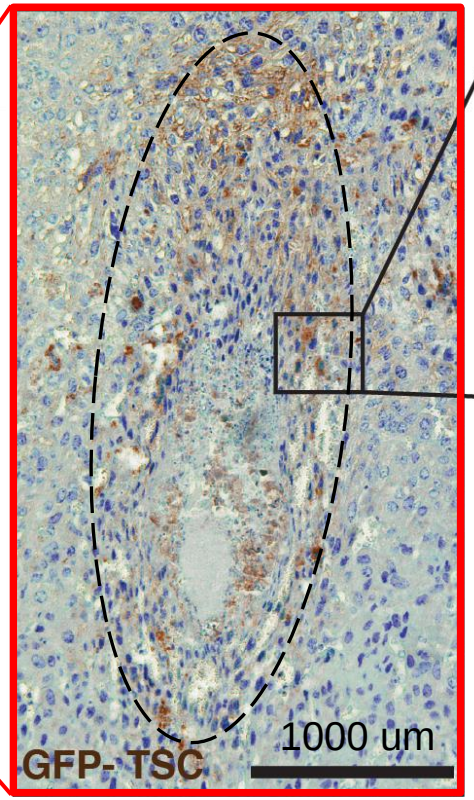


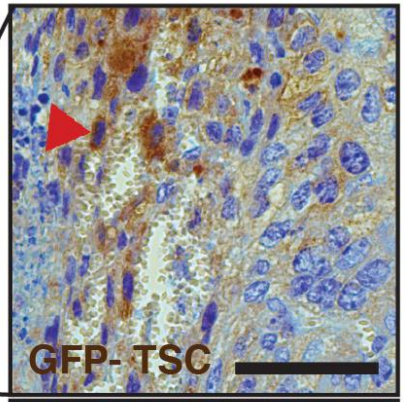
Blastoids initiate implantation and development *in utero*

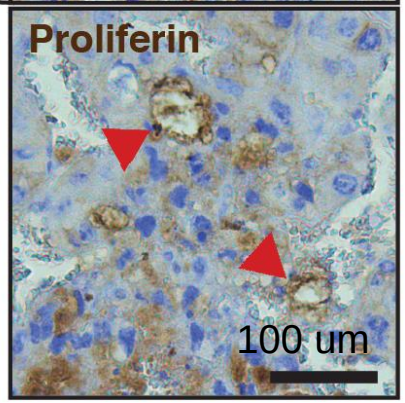
Local deciduae and irrigation



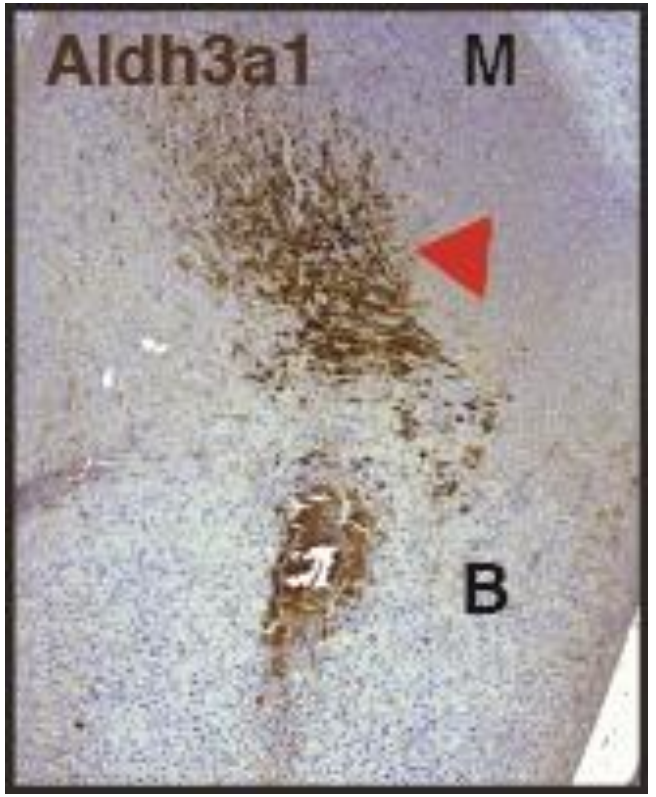
Elongation and anastomosis



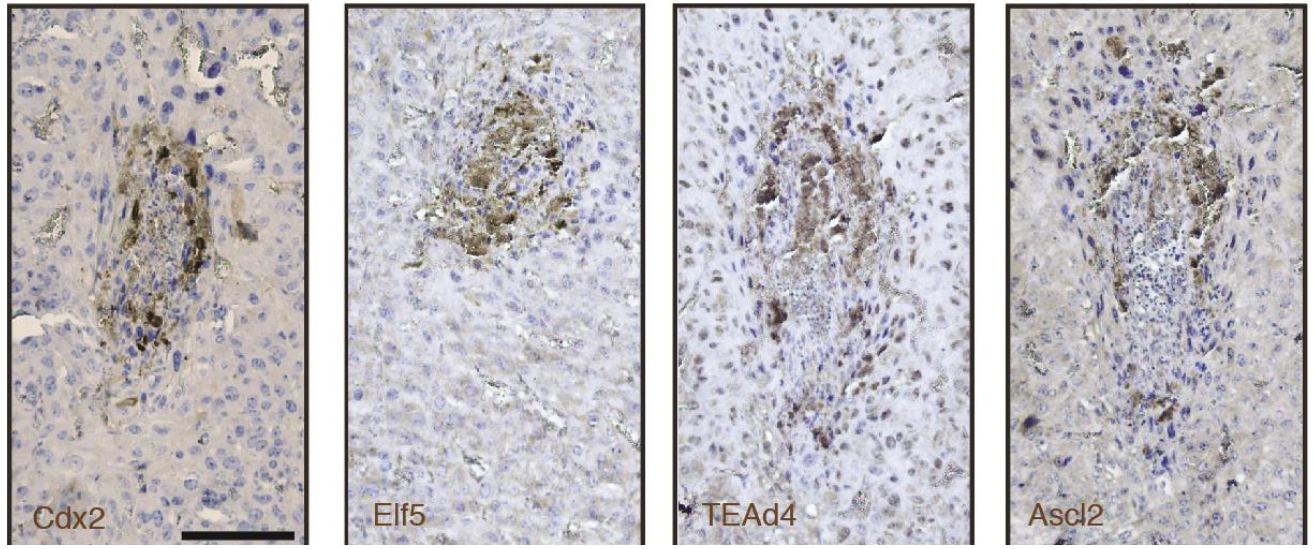




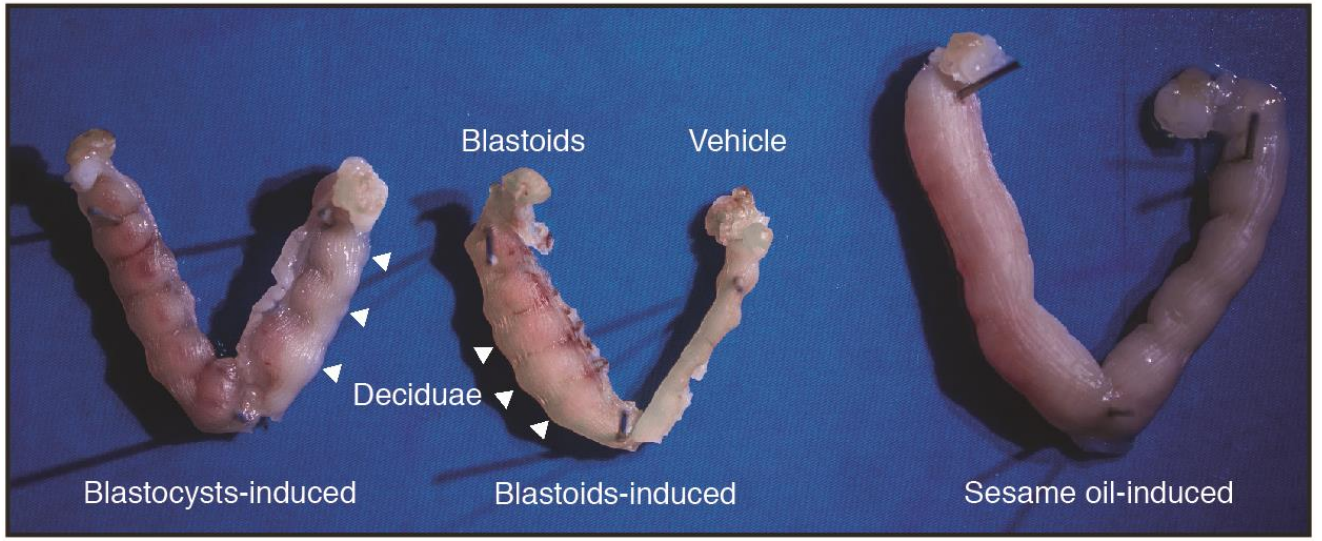
Deciduae are responsive



Blastoids initiate implantation and development *in utero*



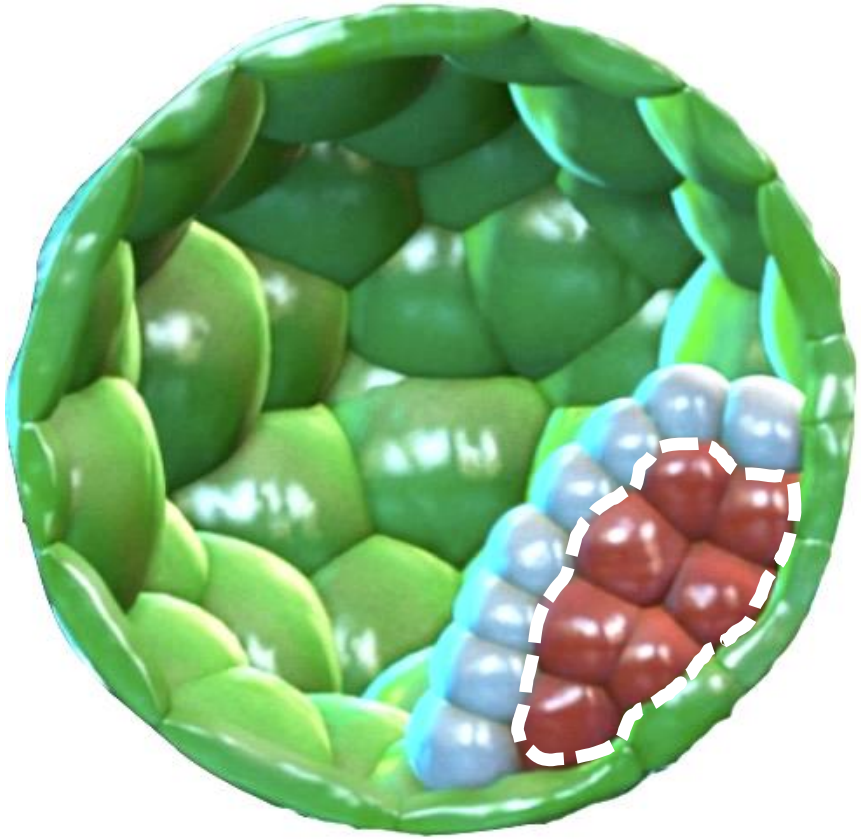
Decidualization produced by blastocysts, blastoids and oil instillation.

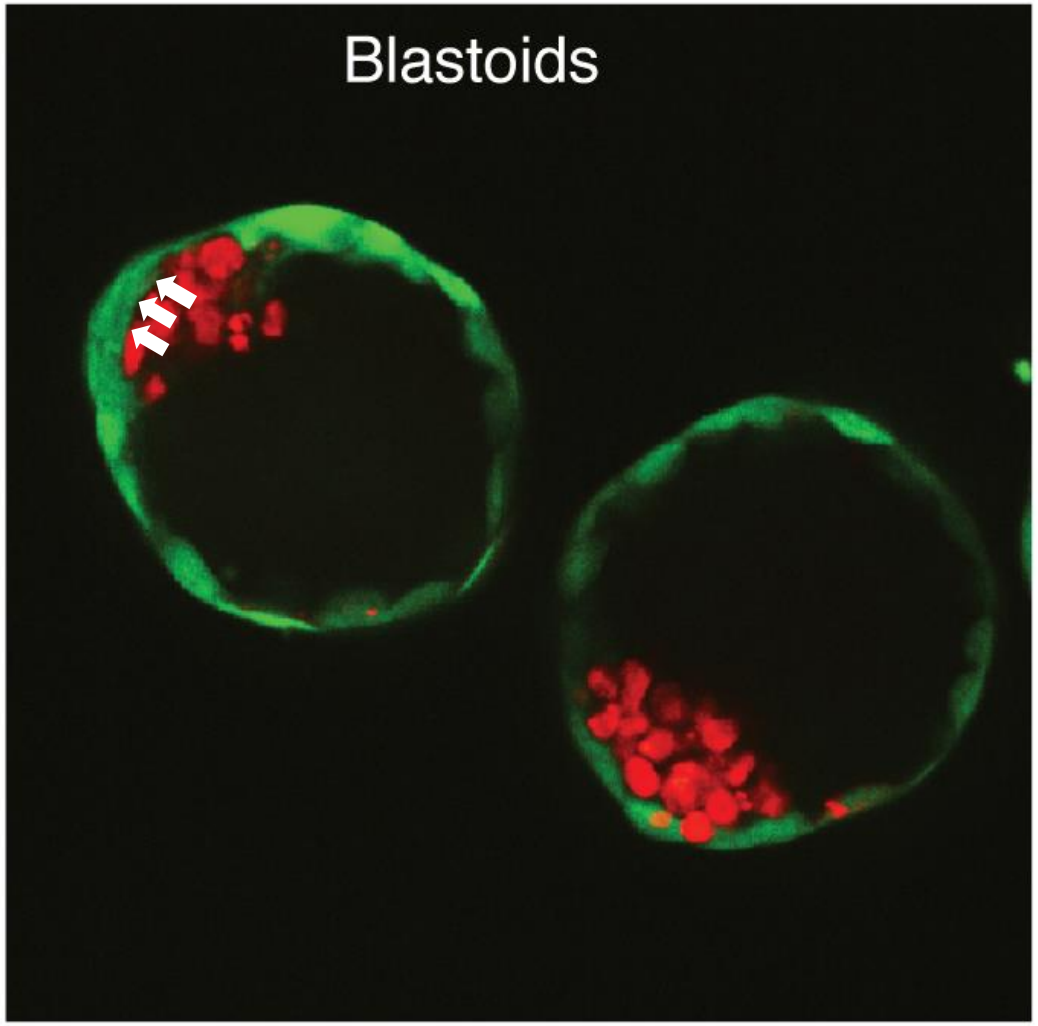


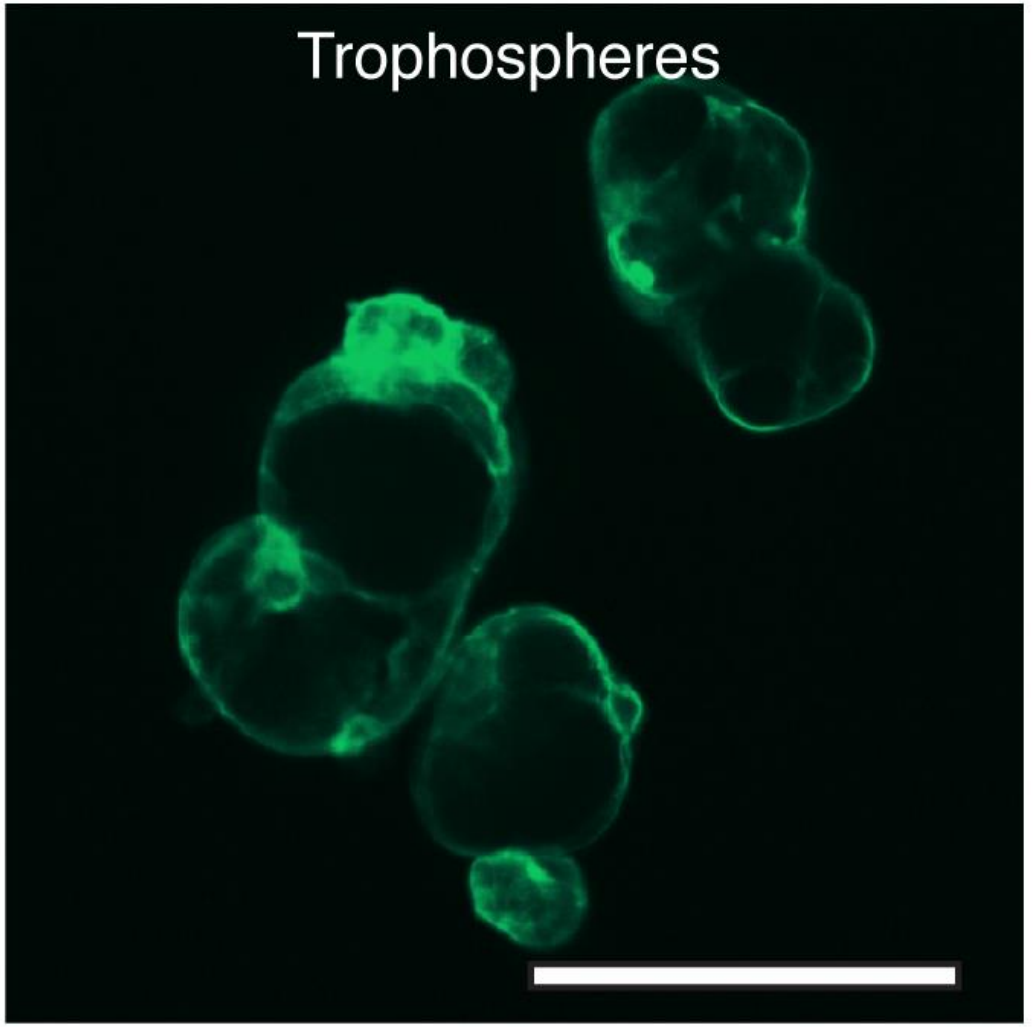
The blastoid

- Blastoids model blastocyst development
- Embryonic / trophoblast communication drive the development
- Blastoid recapitulate aspects of implantation and development *in utero*

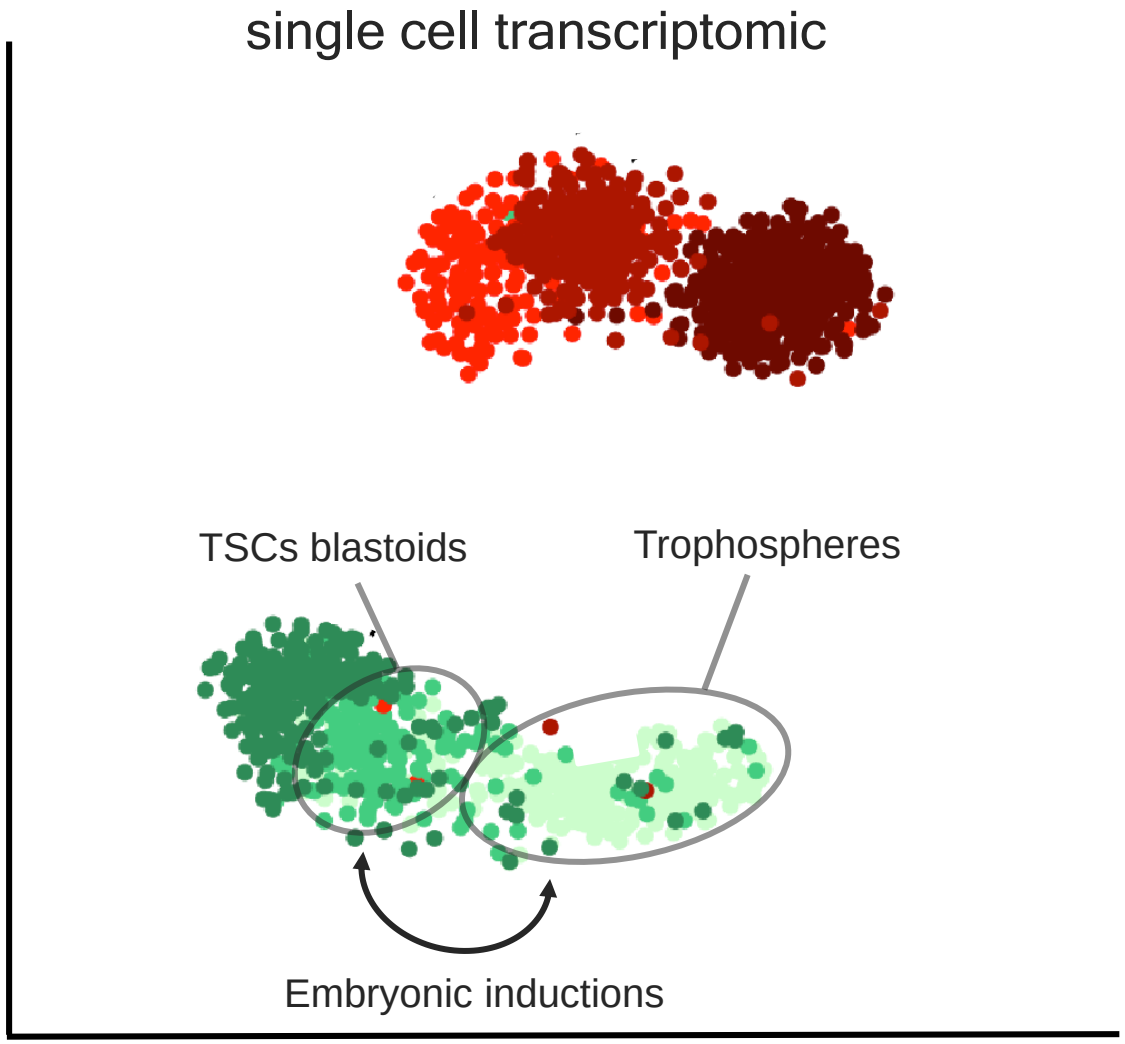
The cooperative life of embryo cells




Blastoids

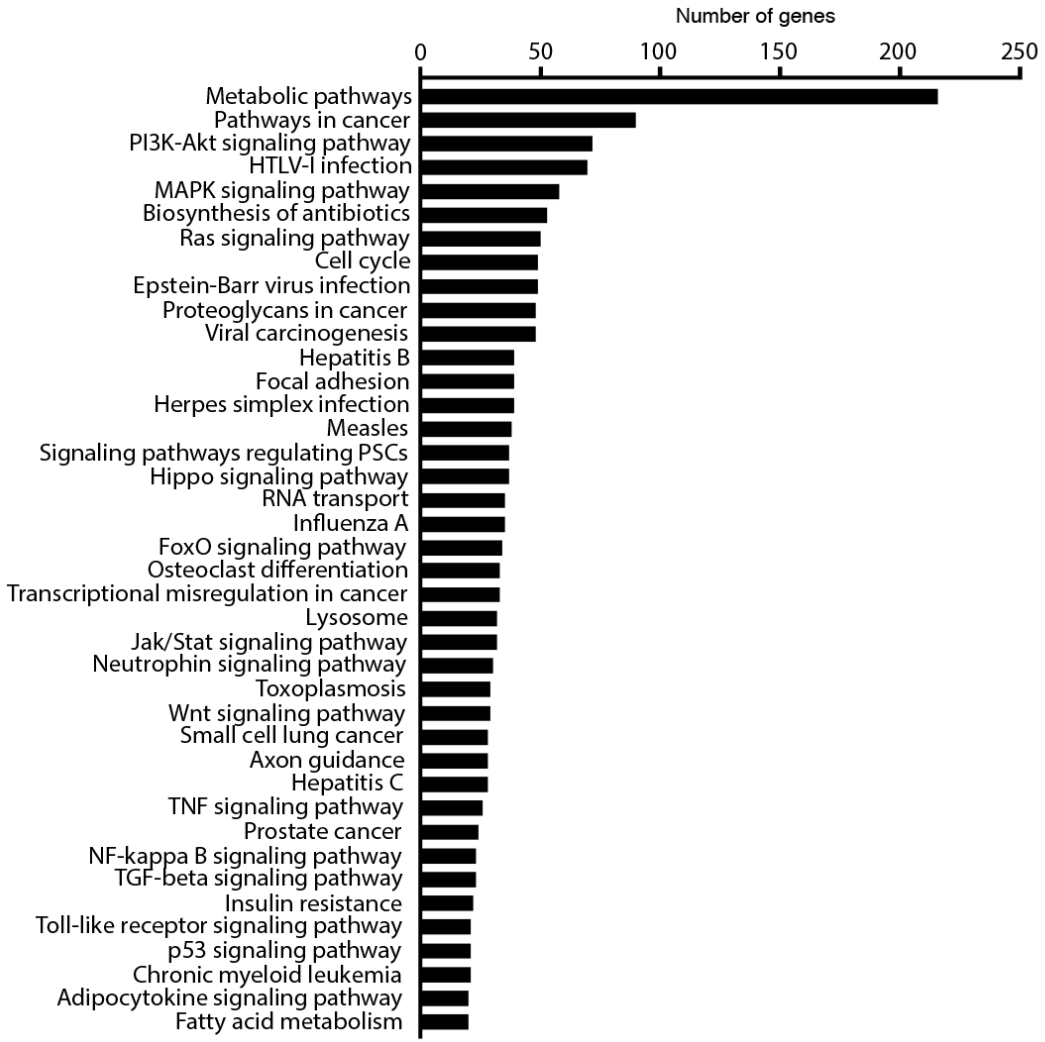

Trophospheres

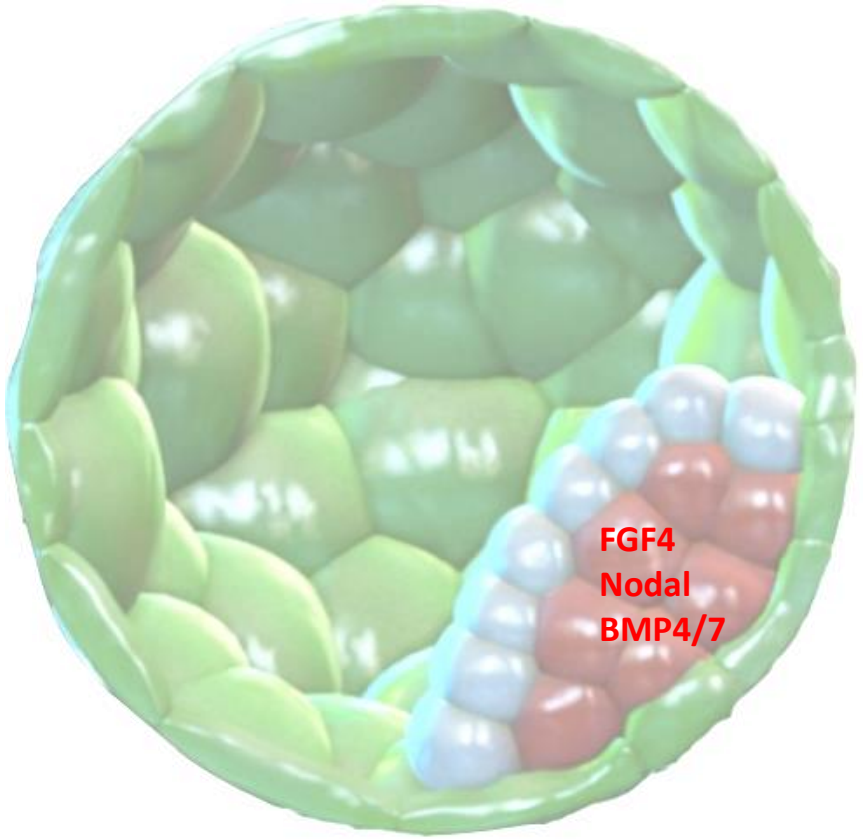
Systematic inventory of embryonic inductions



Systematic inventory of embryonic inductions

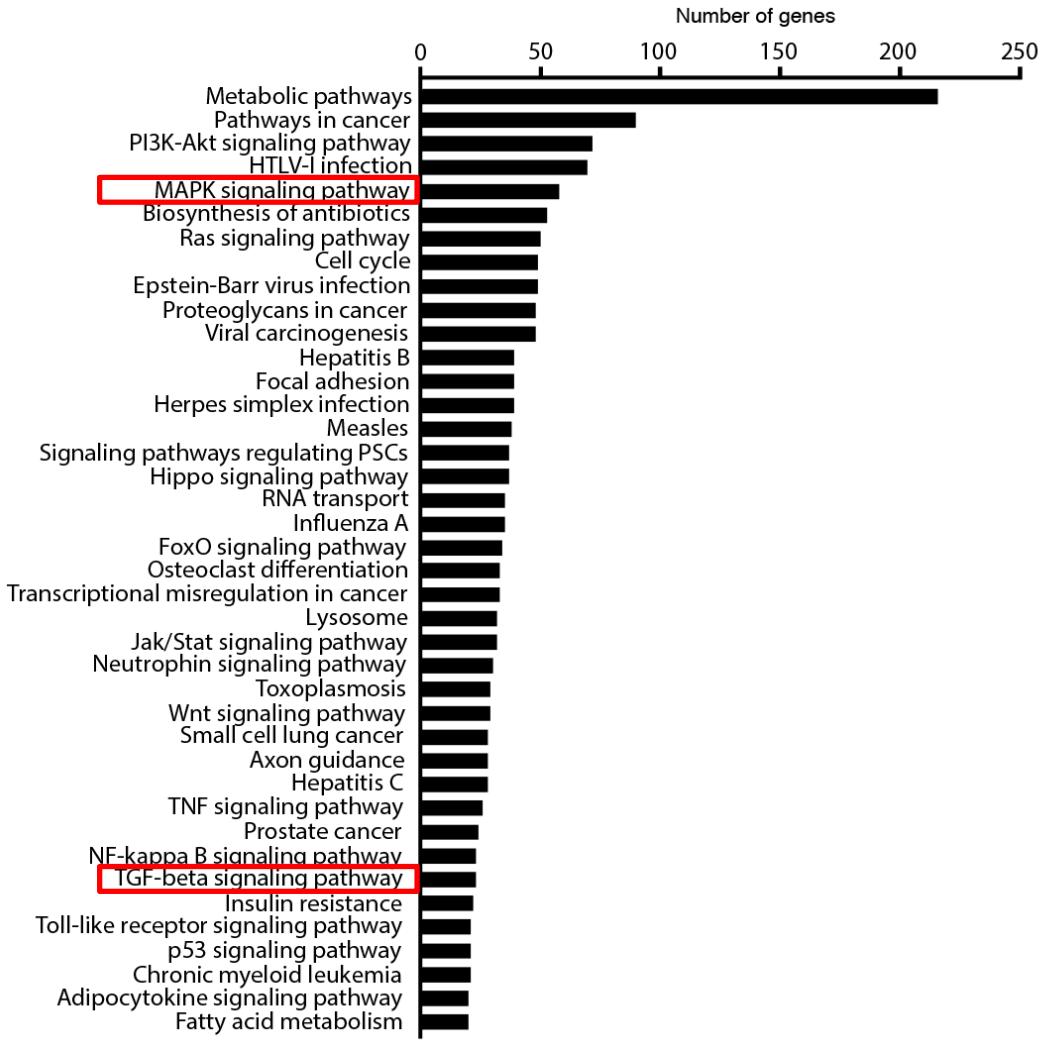
Signaling pathway analysis

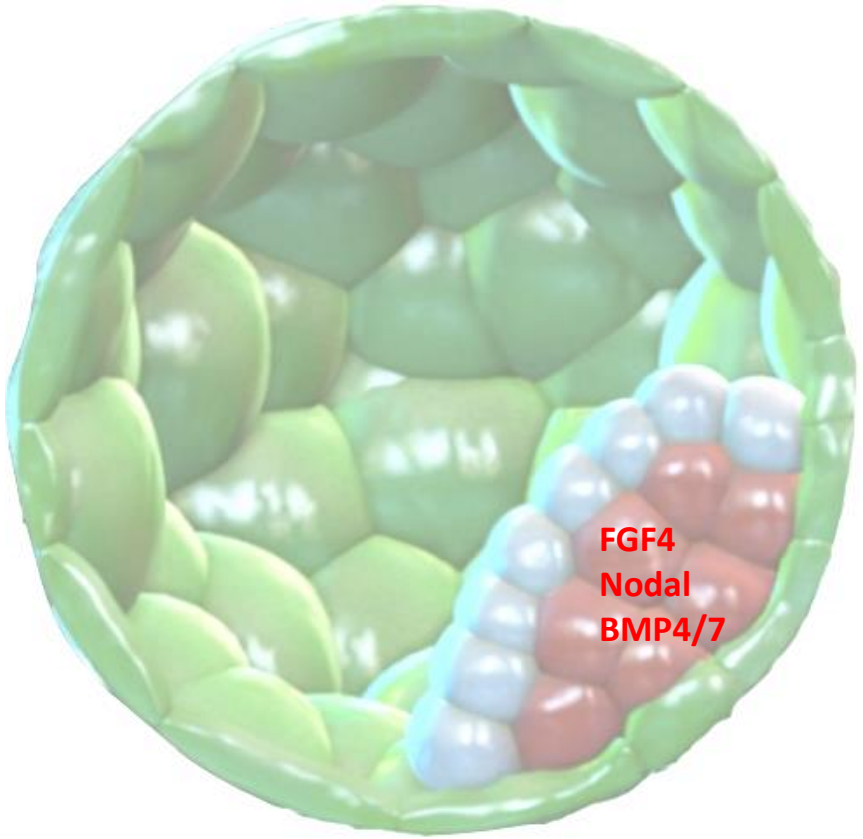




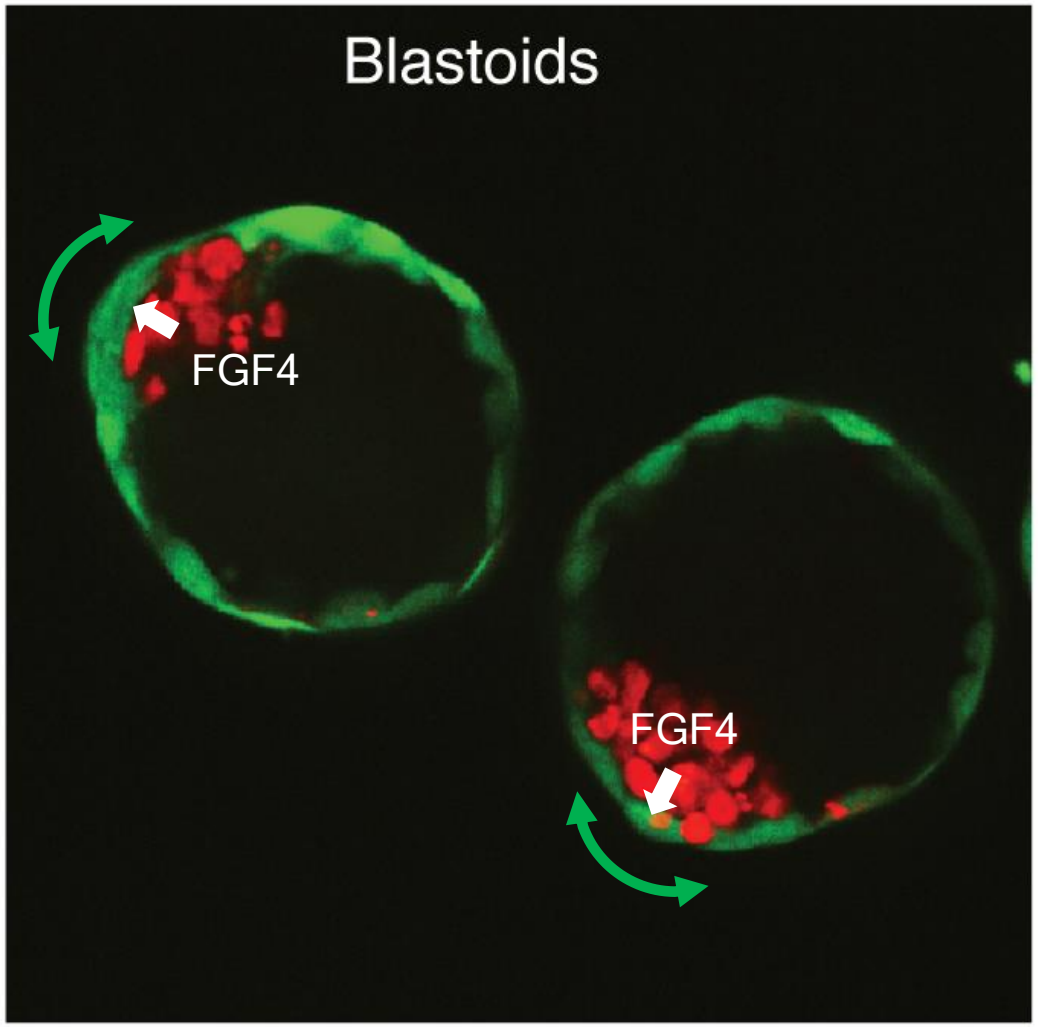
Systematic inventory of embryonic inductions

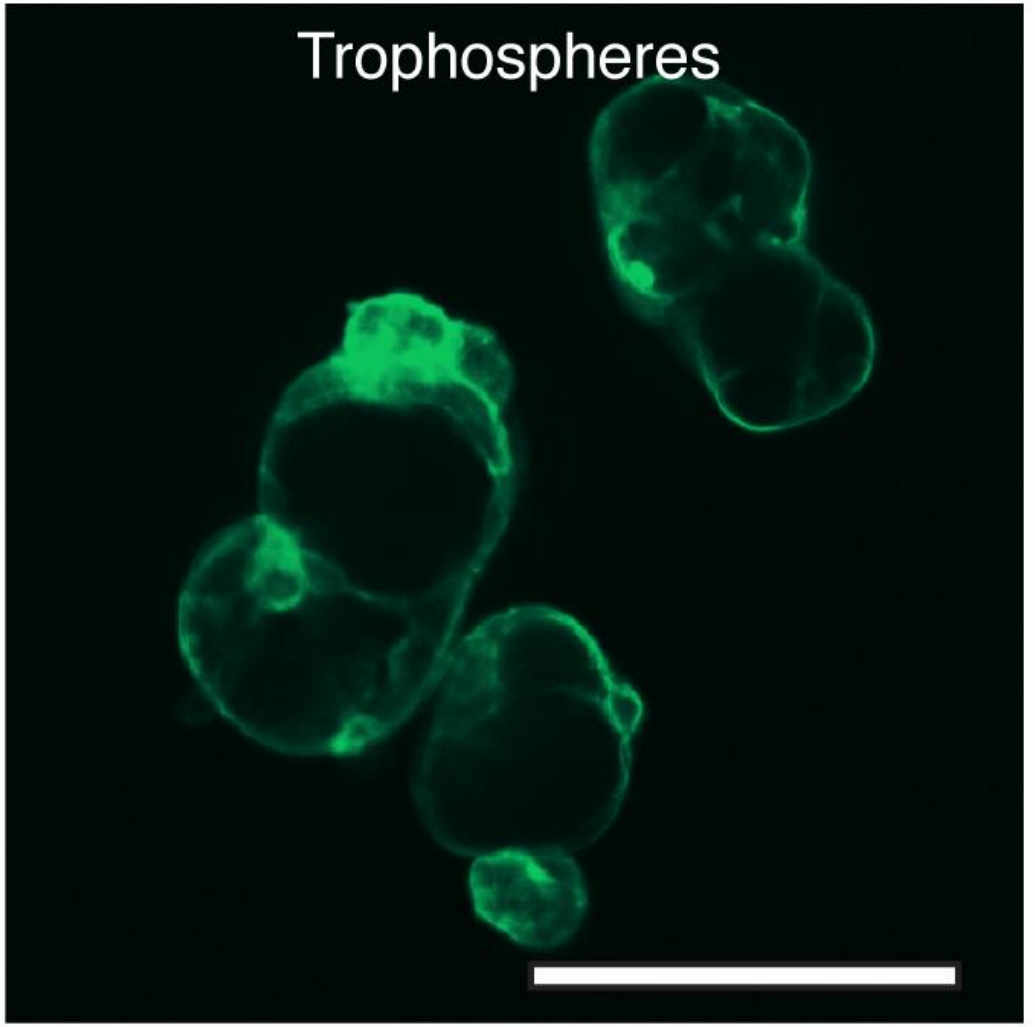
Signaling pathway analysis



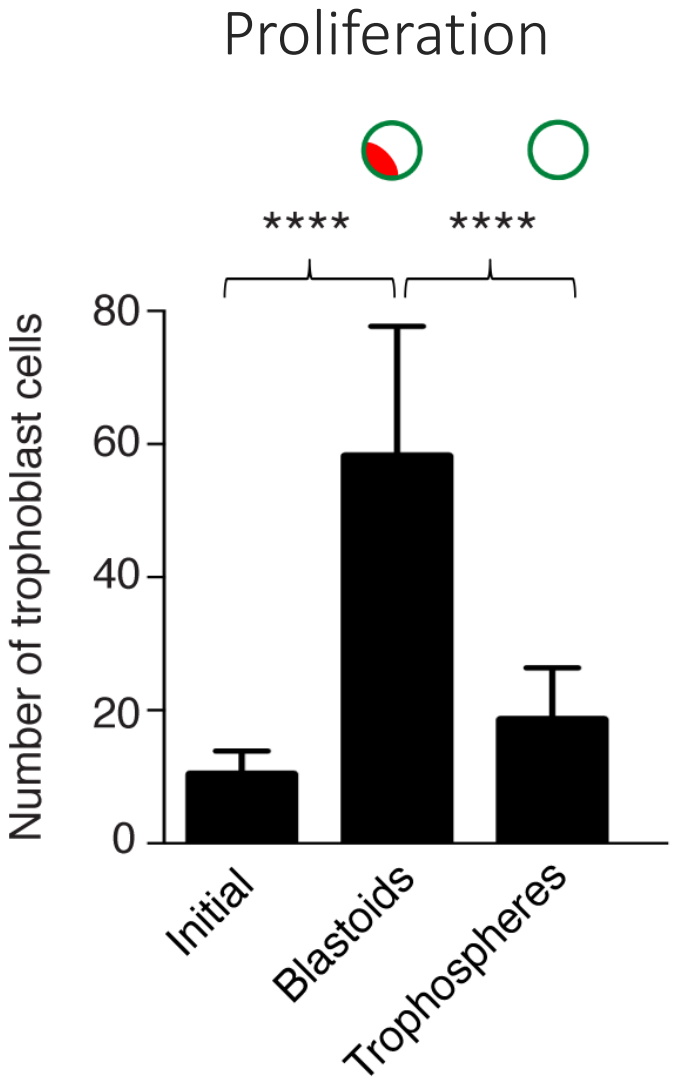


Do embryonic inductions regulate proliferation?

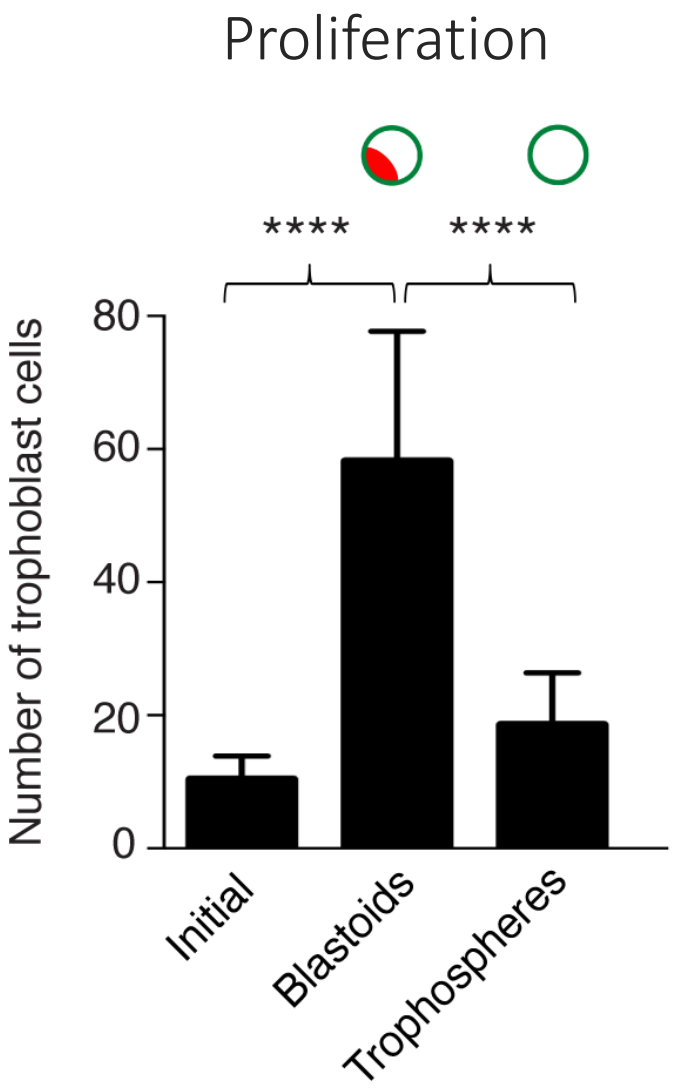


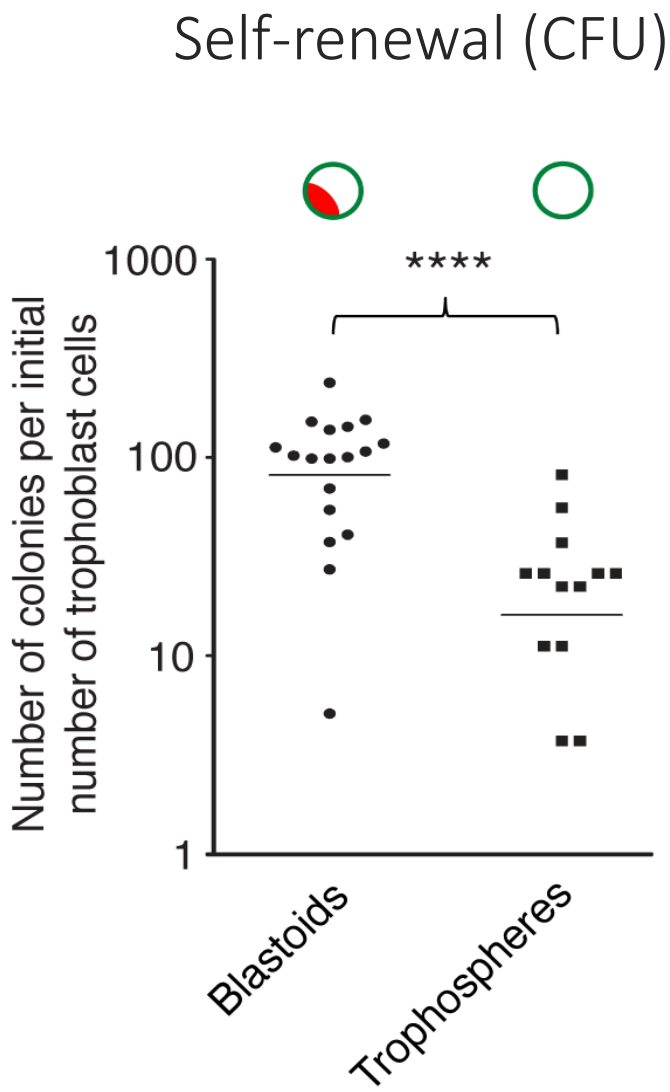


The embryonic cells regulate trophoblast proliferation and self-renewal

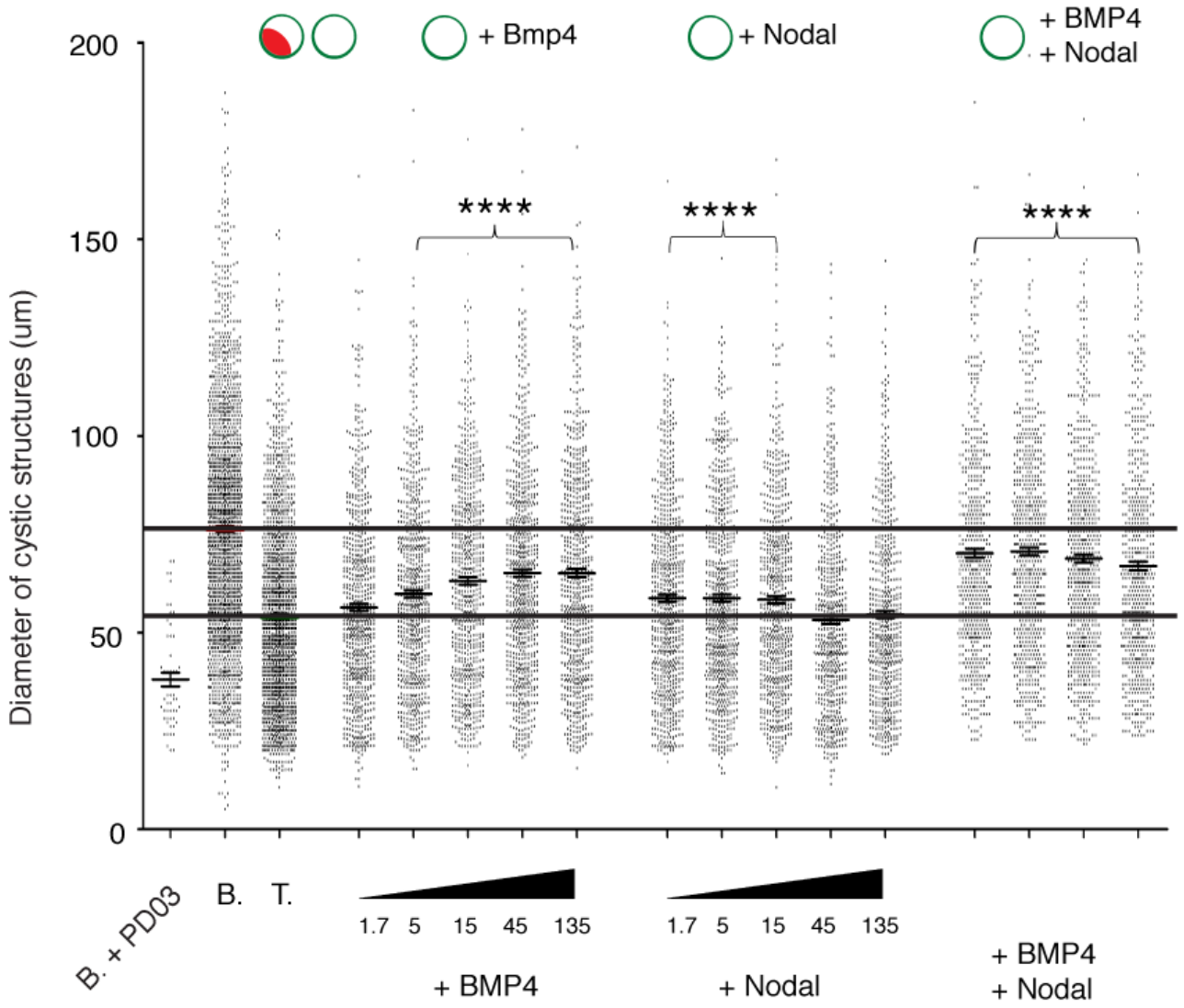


The embryonic cells regulate trophoblast proliferation and self-renewal



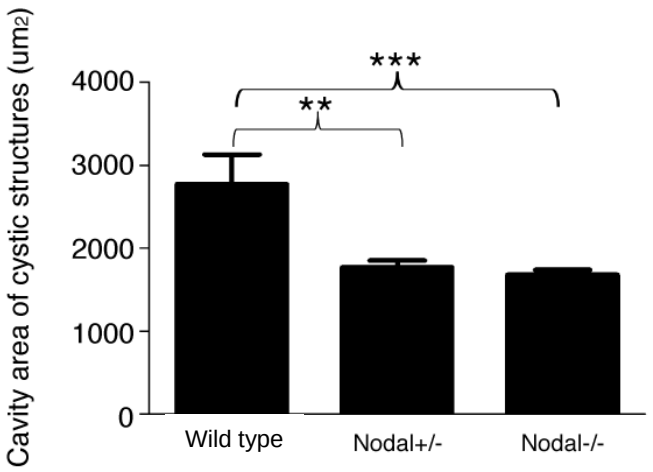


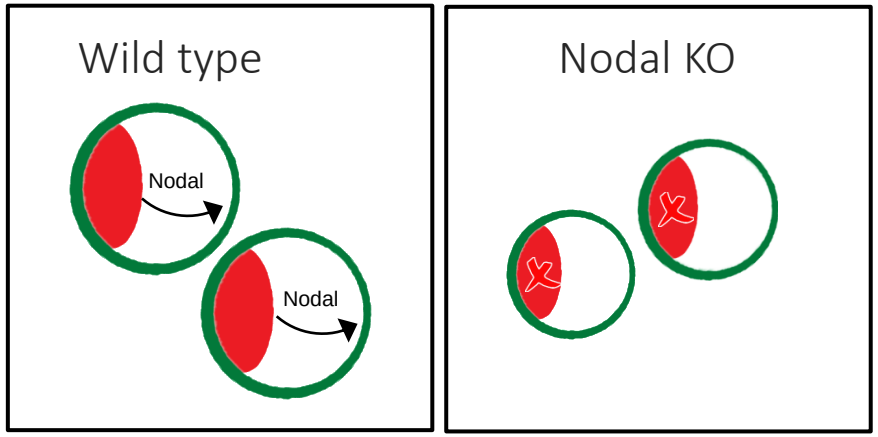
Nodal and Bmp4 induce trophectoderm swelling



Nodal induces trophectoderm swelling

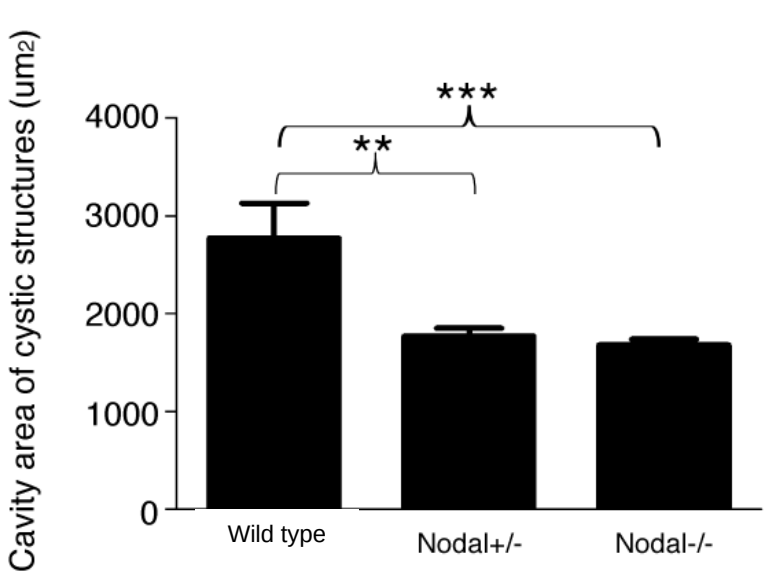
Nodal KO in the ESCs

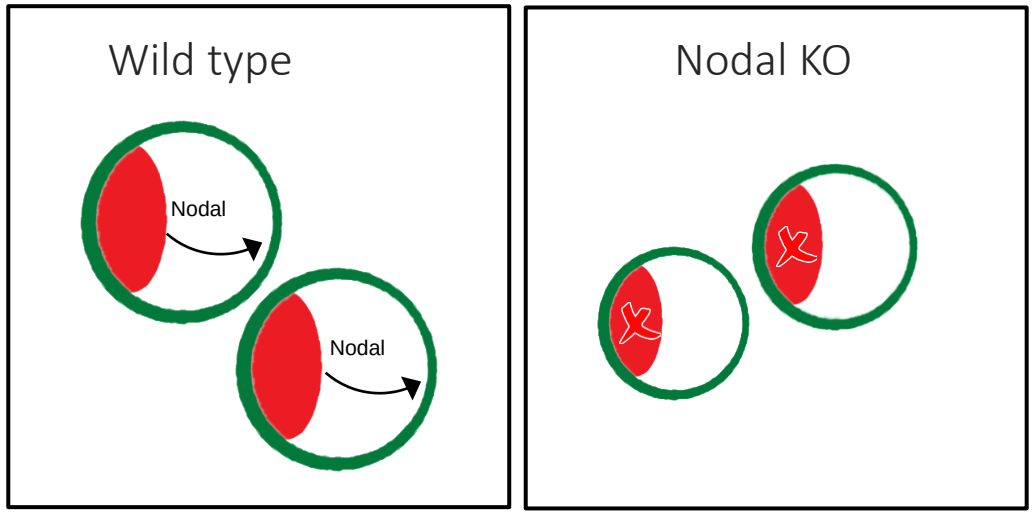




Nodal induces trophectoderm swelling

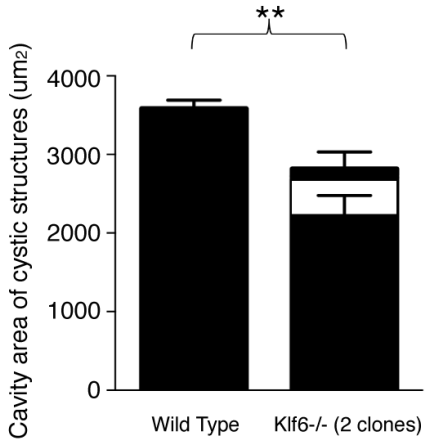
Nodal KO in the ESCs

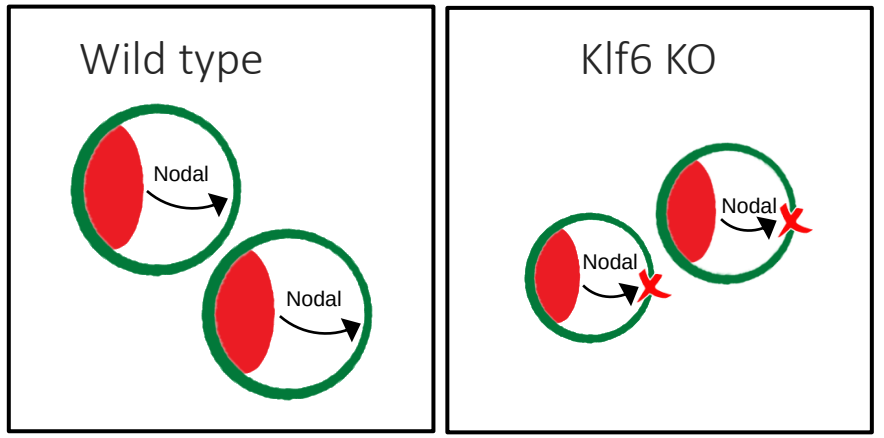




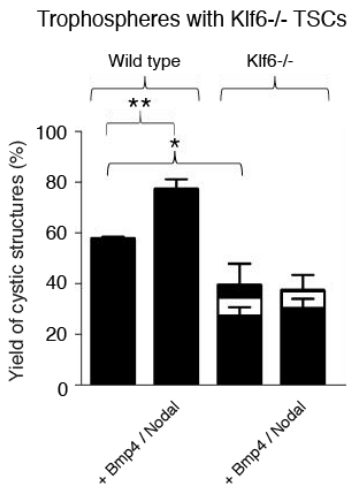
Klf6 regulates trophectoderm swelling

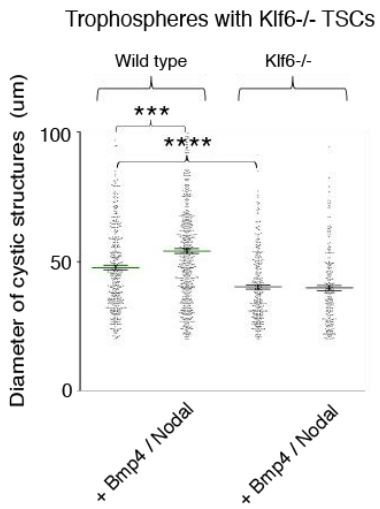
Klf6 KO in the TSCs

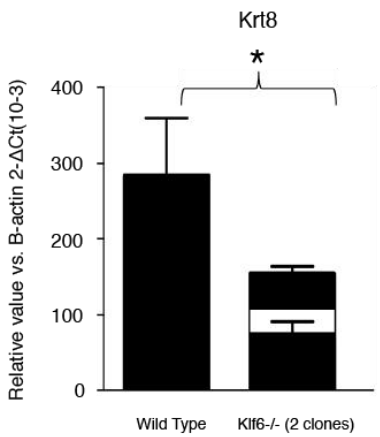




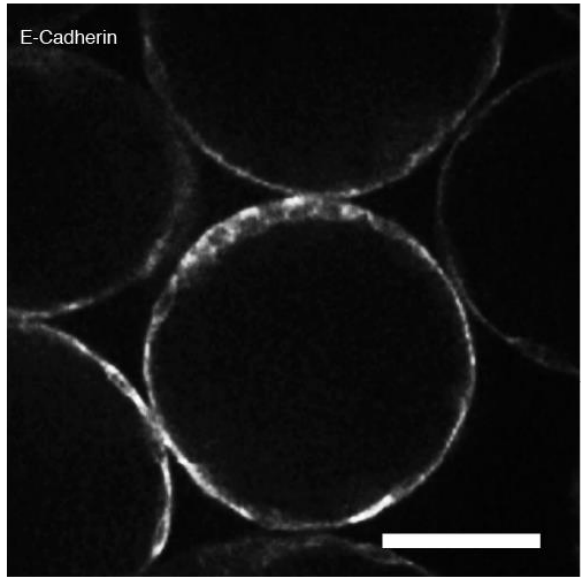
Klf6 regulates trophectoderm swelling



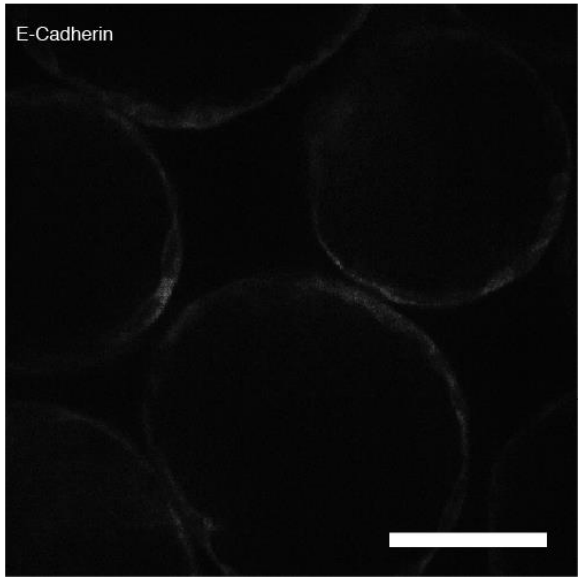




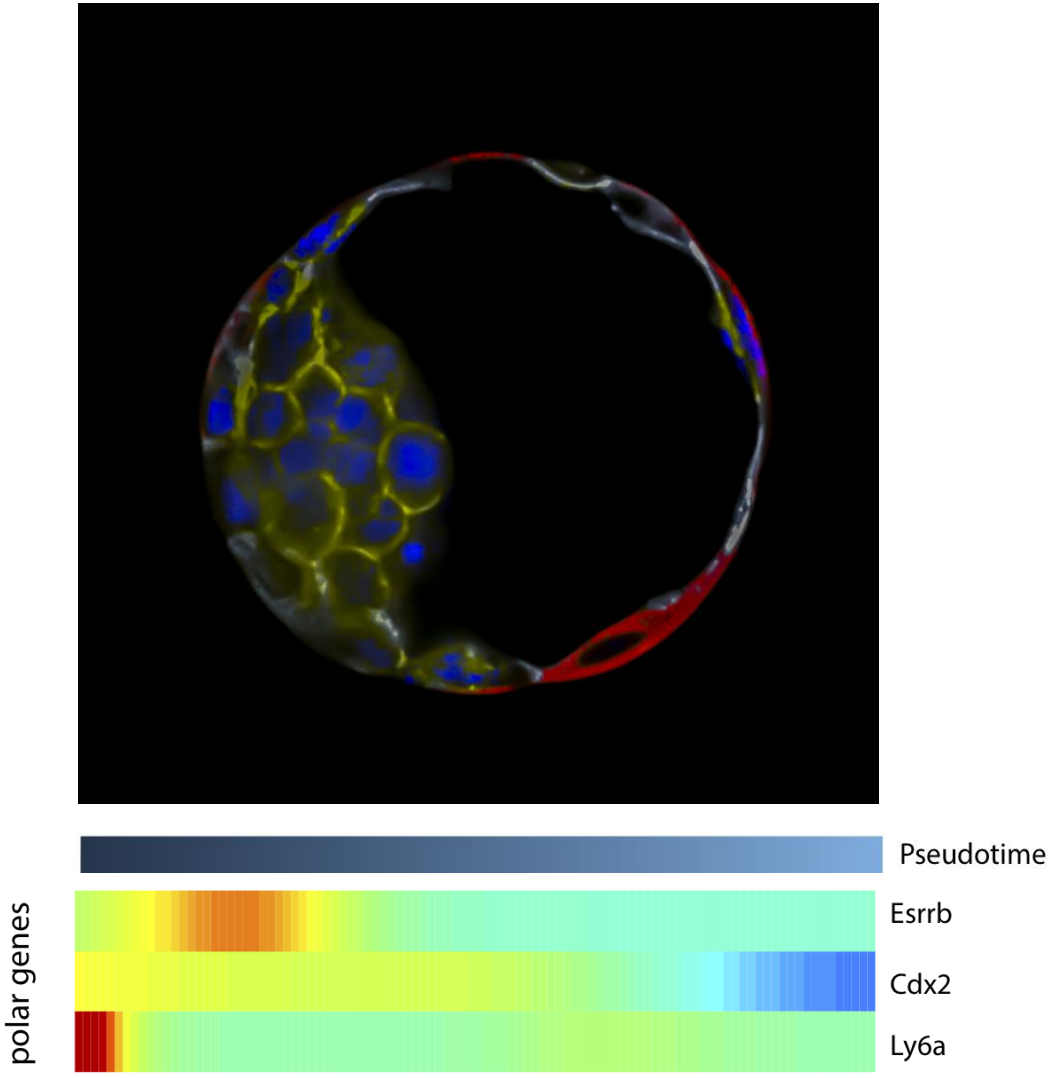
Bastoids with Wild Type TSCs



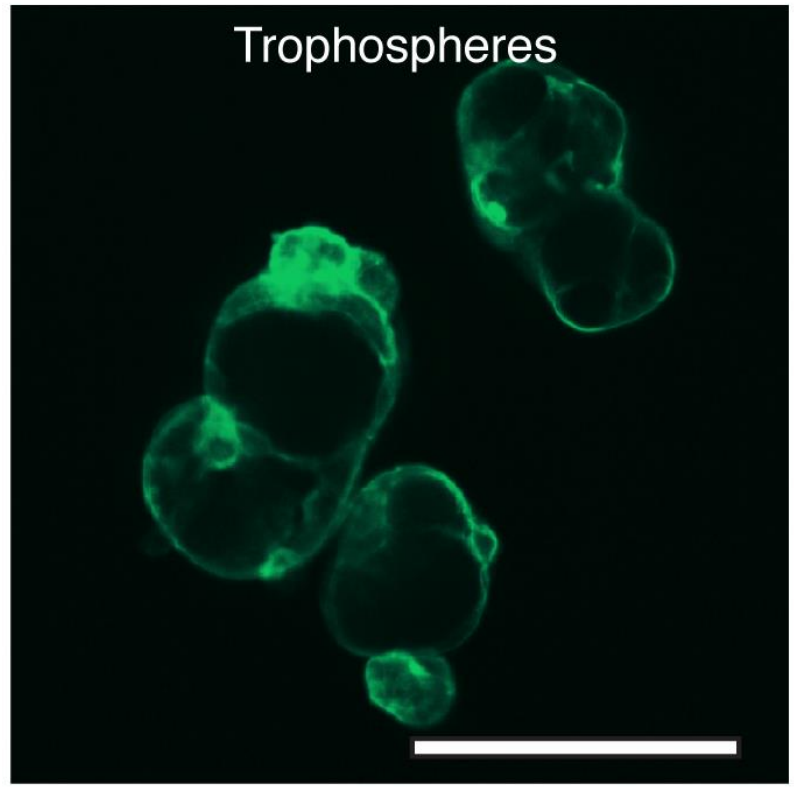
Bastoids with Klf6-/- TSCs



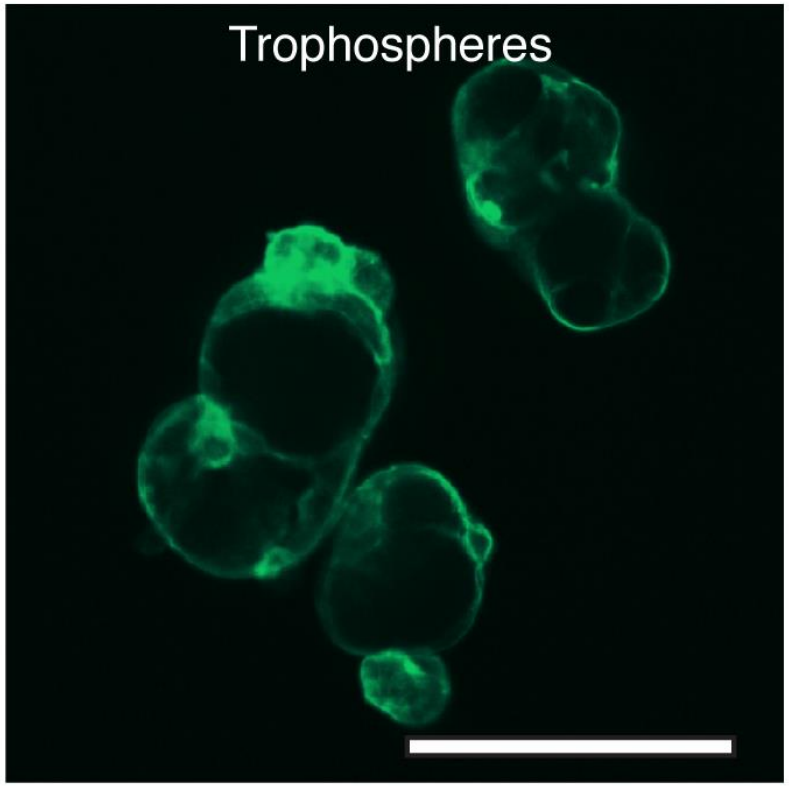
Blastoids form an embryonic-abembryonic axis

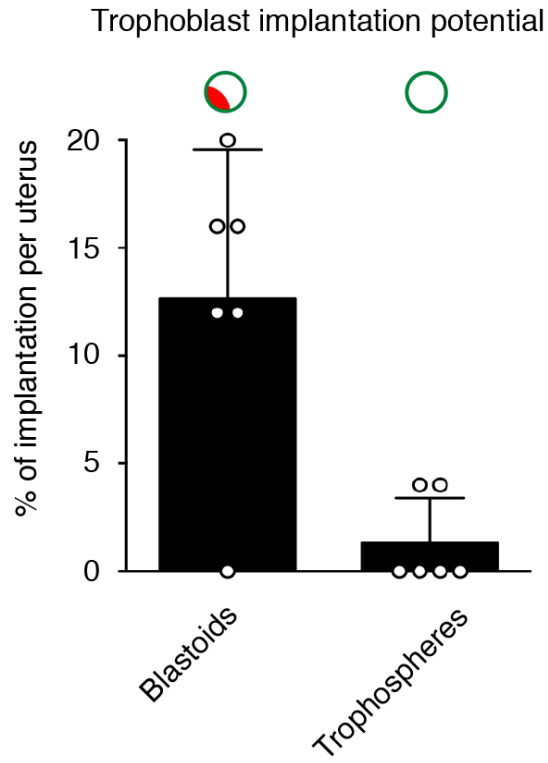



Blastoids


Trophospheres

Embryonic inductions regulate *in utero* implantation

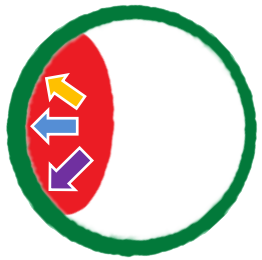




Embryonic signals gate-keep the trophoblasts potential to implant *in utero*

The blastoid

- Blastoids model blastocyst development
- Embryonic / trophoblast communication drive the development
- Blastoid recapitulate aspects of implantation and development *in utero*



Systematic inventory of embryonic inductions

- Maintain trophectoderm core transcription factors / prevent differentiation
- Regulate trophectoderm epithelial morphogenesis
- All together, embryonic inductions maintain the potential to implant

Why embryo models?

The scarcity of **human IVF embryos** makes it very difficult to perform the genetic and drug screens that lie at the heart of biomedical discovery.

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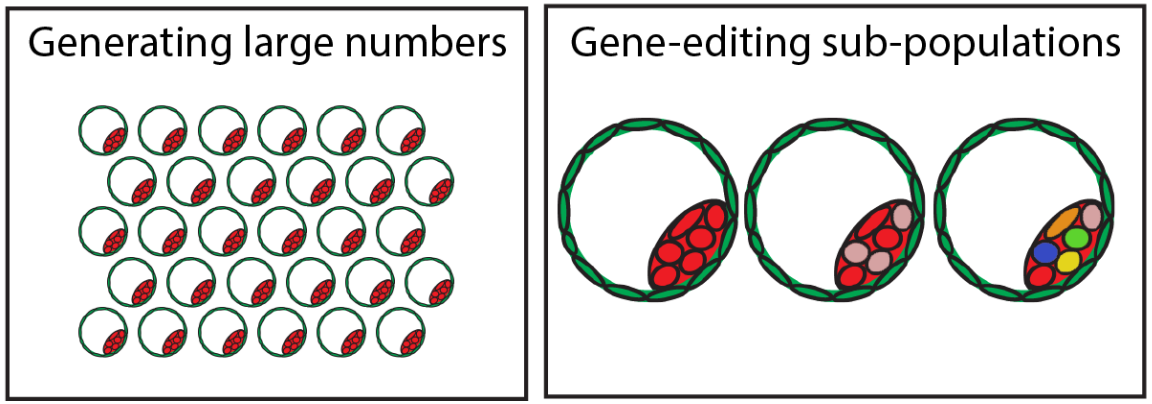

High-throughput genetic and drug screens

Biomedical and drug discoveries

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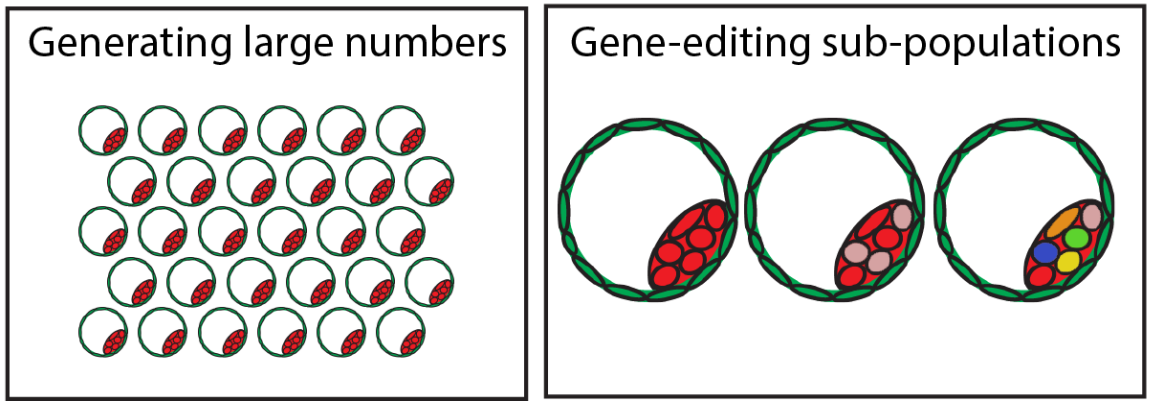

High-throughput genetic and drug screens

Biomedical and drug discoveries

Debate ethics of embryo models from stem cells. Rivron *et al.* **Nature**. 2018
Towards guidelines for research on human embryo models formed from stem cells. Hyun *et al.* **Stem cell reports**. 2020.

Why embryo models?

Treating infertility. Embryo models could give researchers a better understanding of implantation and gastrulation, and lead to better infertility treatments. (It is thought that at least 40% of pregnancies fail by 20 weeks, and that 70% of those that fail do so at implantation[15].)

Improving IVF. Only around 20% of IVF procedures result in a birth[16]. Using stem-cell models, researchers could optimize implantation and minimize cellular abnormalities, such as an aberrant number of chromosomes. As well as safeguarding the health of children conceived *in vitro*, this could reduce the number of procedures.

Designing new contraceptives. Embryo-model work could improve drugs that prevent implantation (as the oral contraceptive pill or intrauterine devices do, in part). Women and health professionals need drugs and devices that are easier to use and that have fewer side effects. Family planning is central to sustainable, global development.

Preventing disease. Subtle cell abnormalities during the first weeks of pregnancy, such as those caused by the use of alcohol or medications, can do damage throughout pregnancy and beyond[17]. They can alter development of the placenta and restrict embryo growth, affecting the baby's birth weight and propensity for chronic diseases (such as those of the heart) decades later[18]. Entities based on stem cells could help researchers to pinpoint the genetic and epigenetic changes involved[18], and assess the effects of diets or drugs[10,16].

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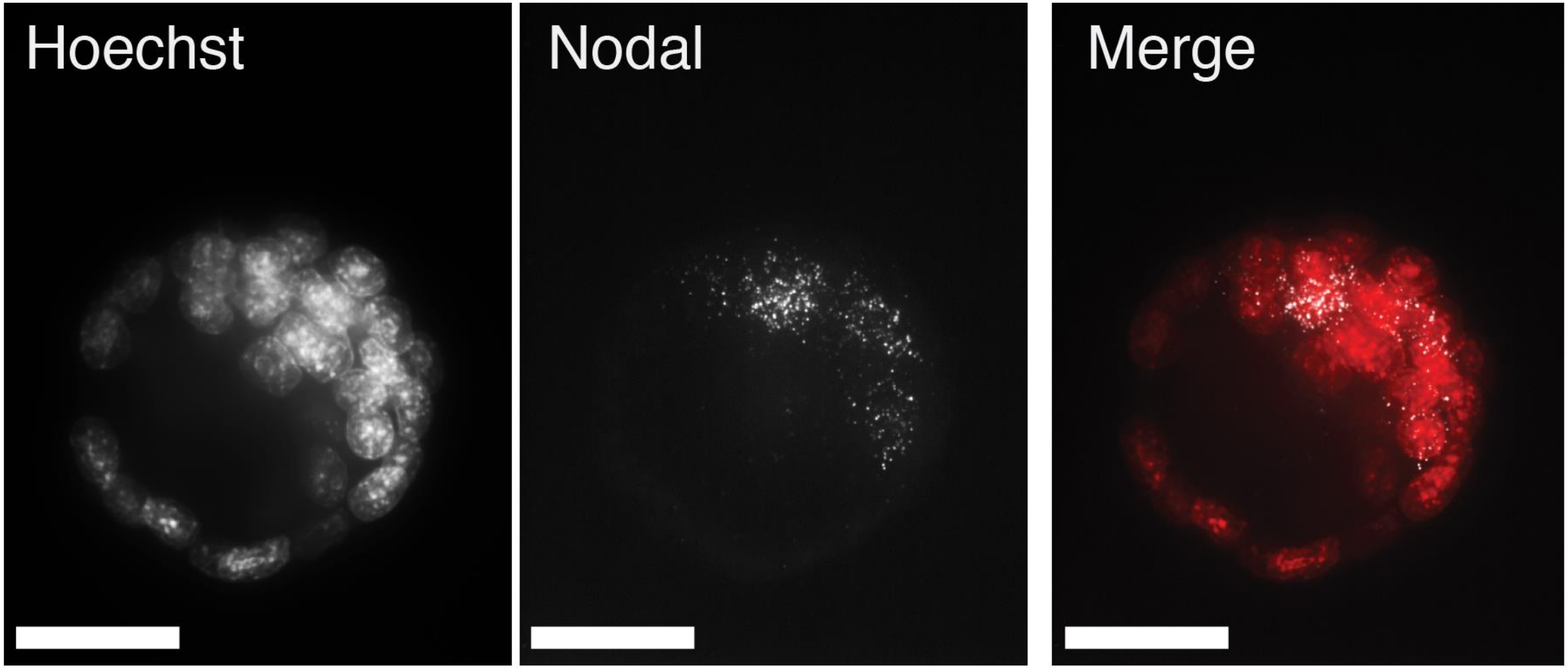
HFSP

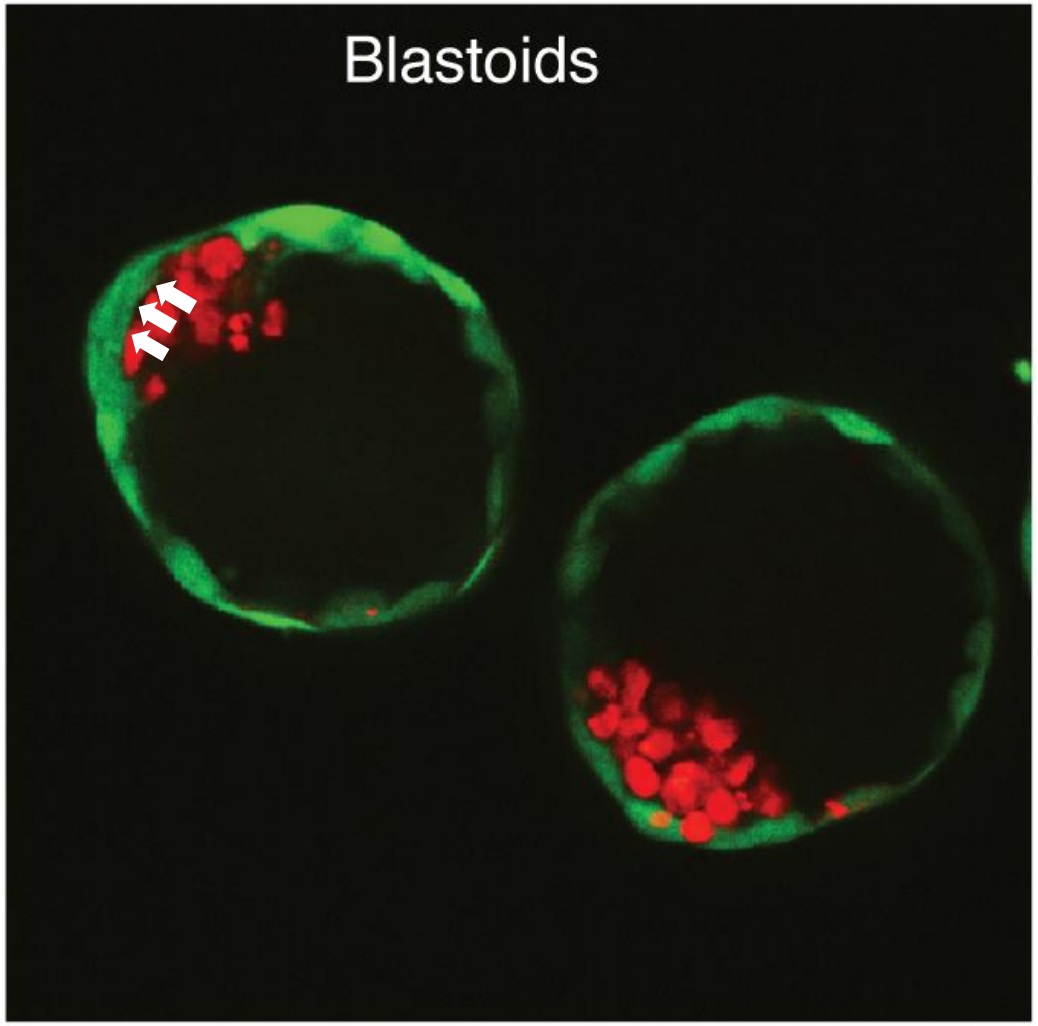
Stem Cell Core Facility

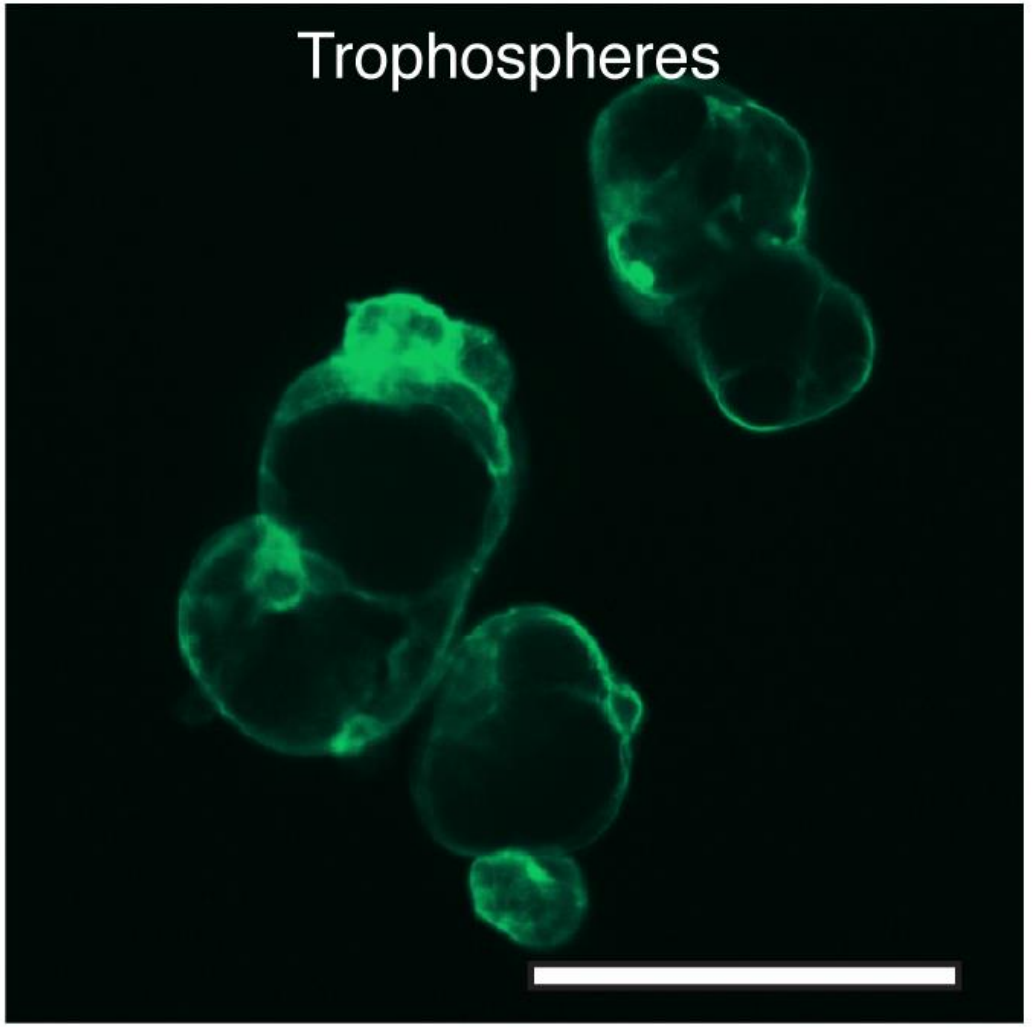
Vienna BioCenter CORE FACILITIES

Nodal is solely expressed in the embryonic cells

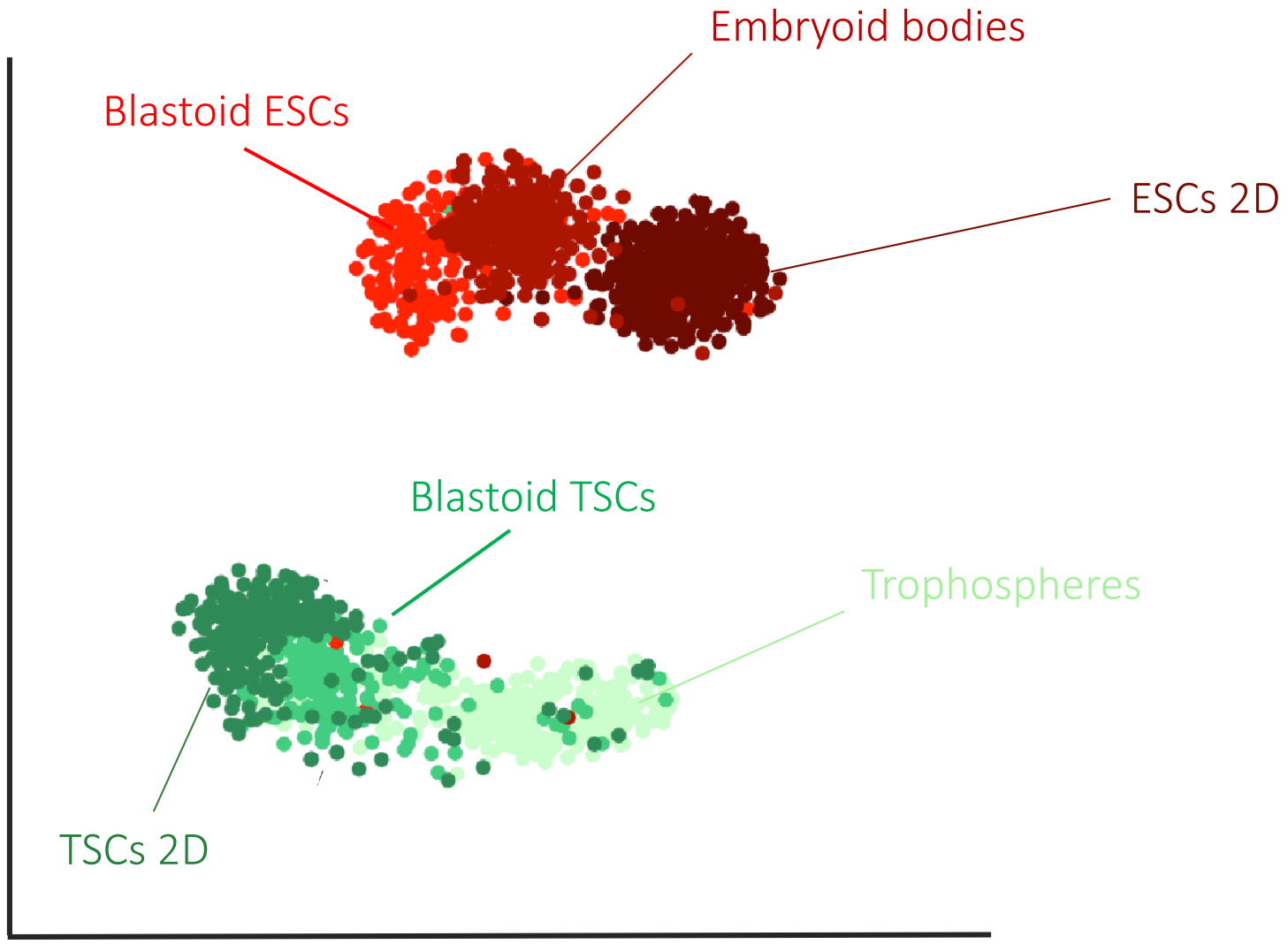
Single molecule FISH in blastocysts




Blastoids


Trophospheres

Compartments communication drives a transcriptome shift



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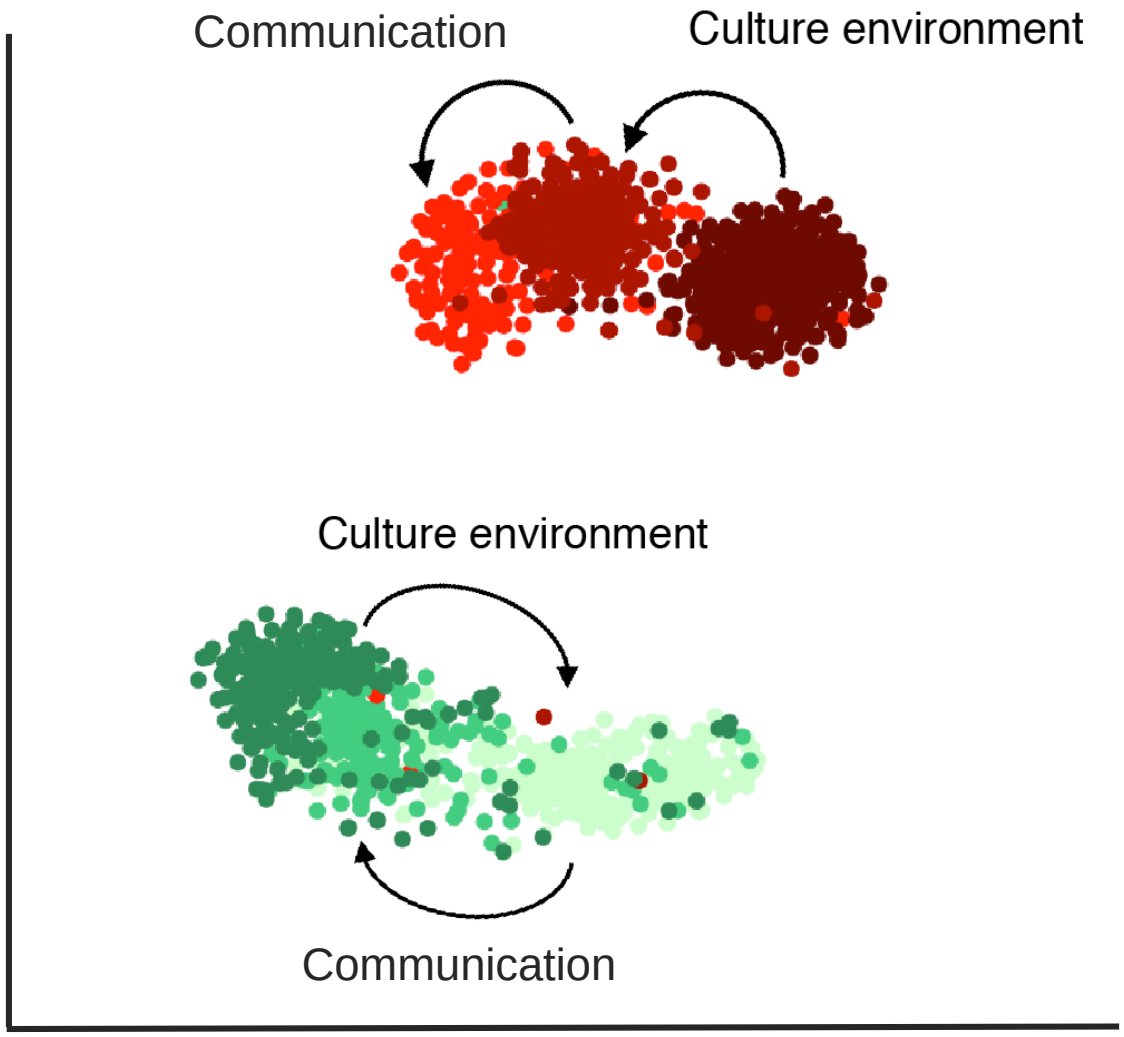
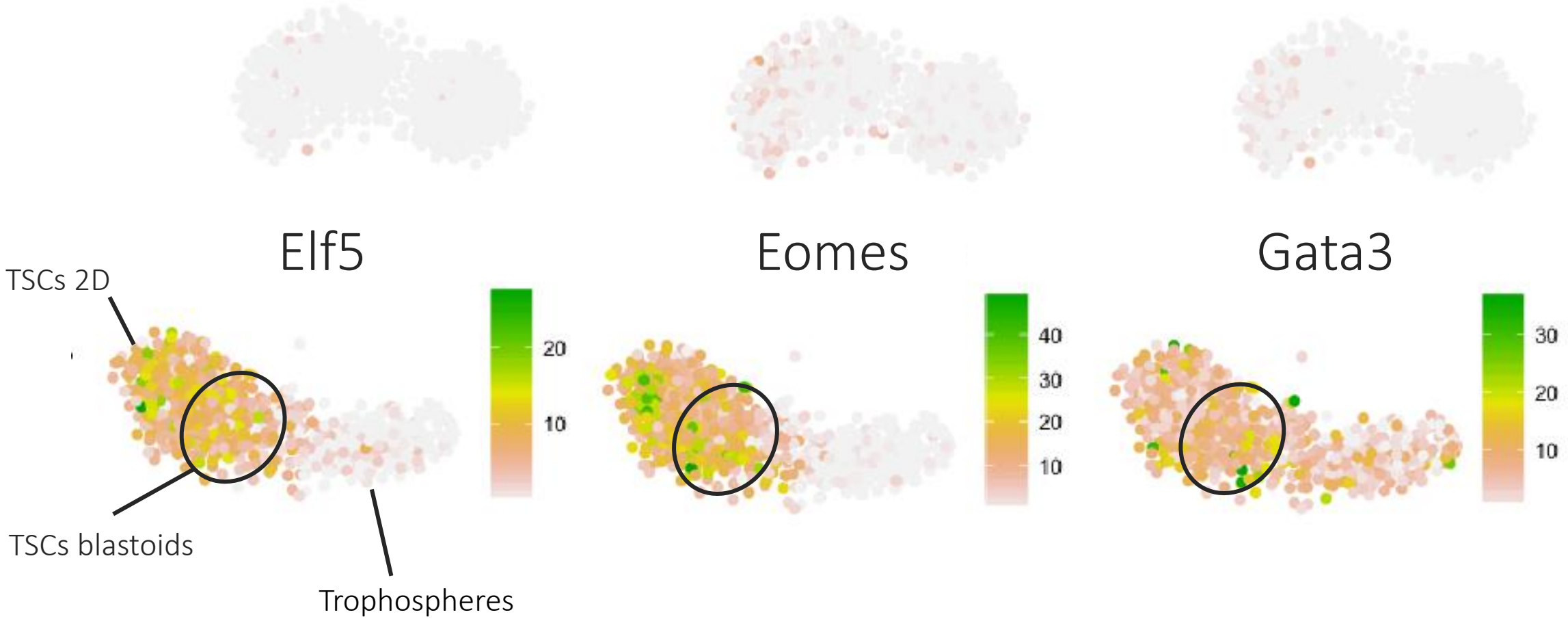


The embryonic cells maintain the trophectoderm TFs



Placental differentiation genes are repressed by the embryonic cells