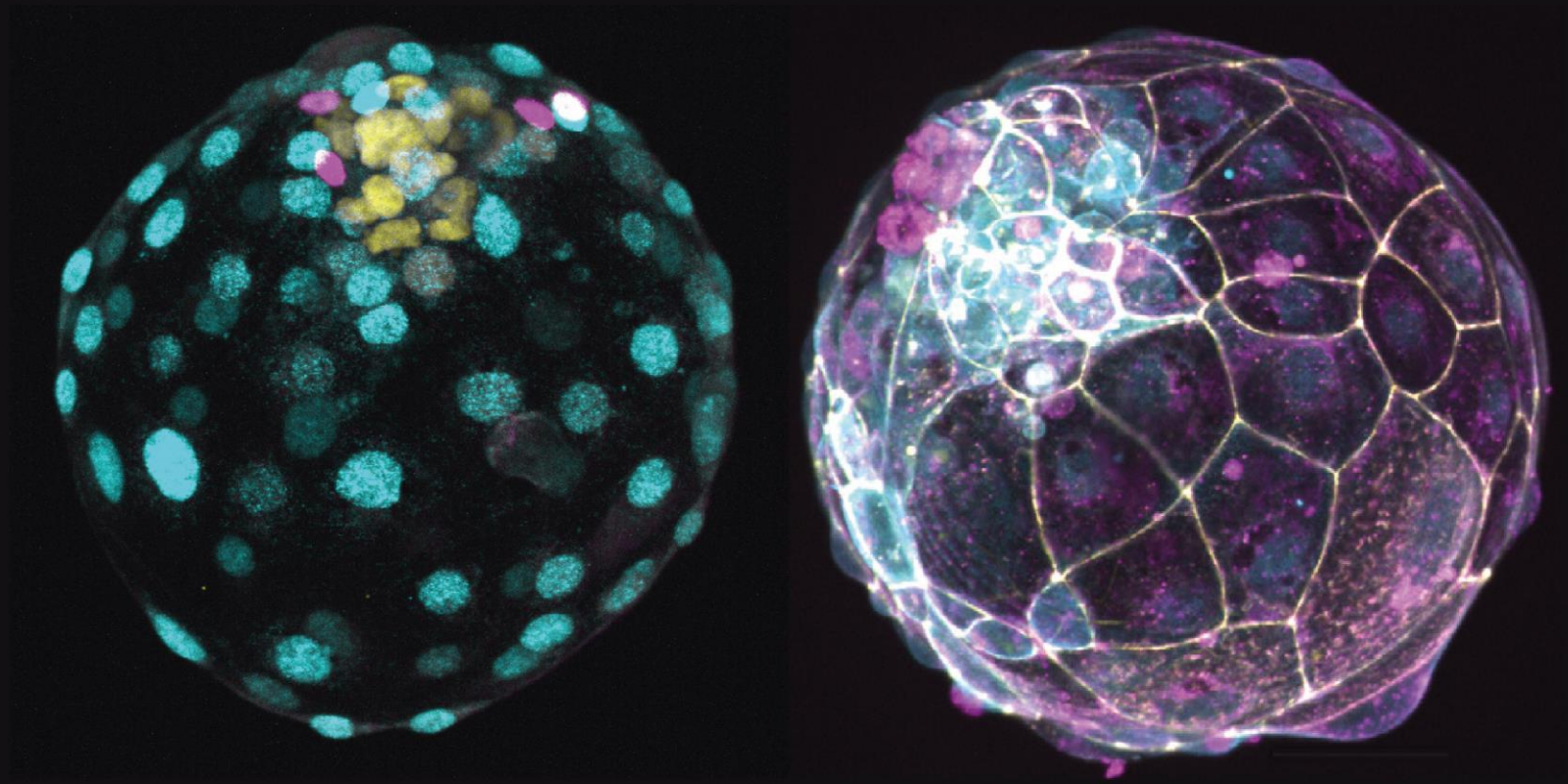
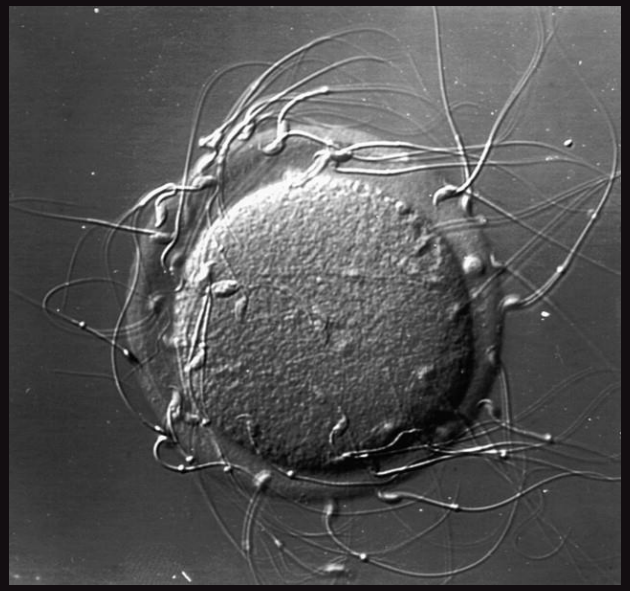
Embryo models formed from stem cells



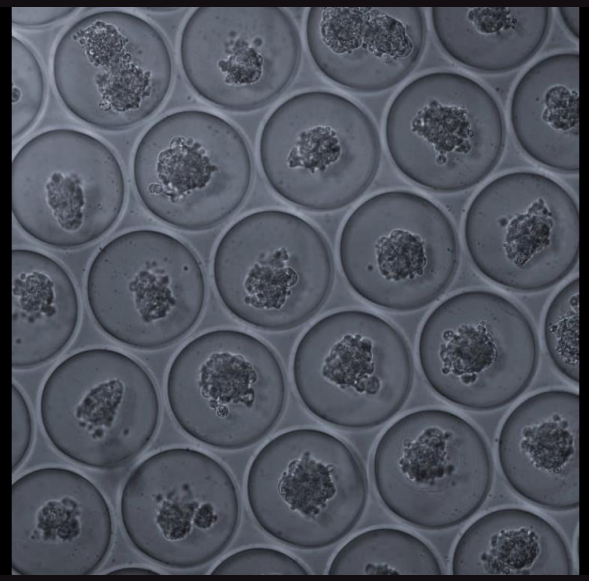
3 paths to forming embryos

Fertilization

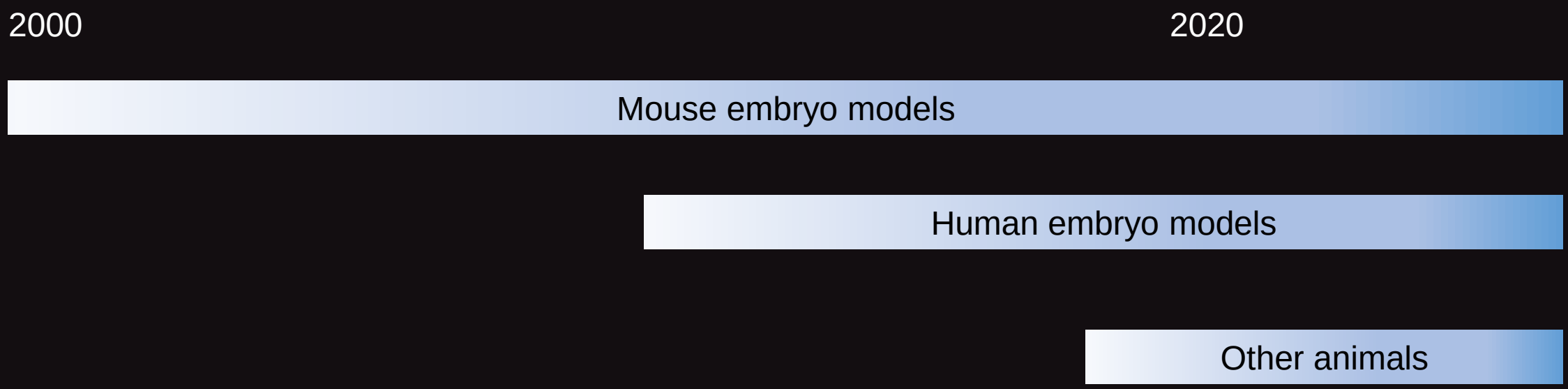


Somatic cell nuclear transfer

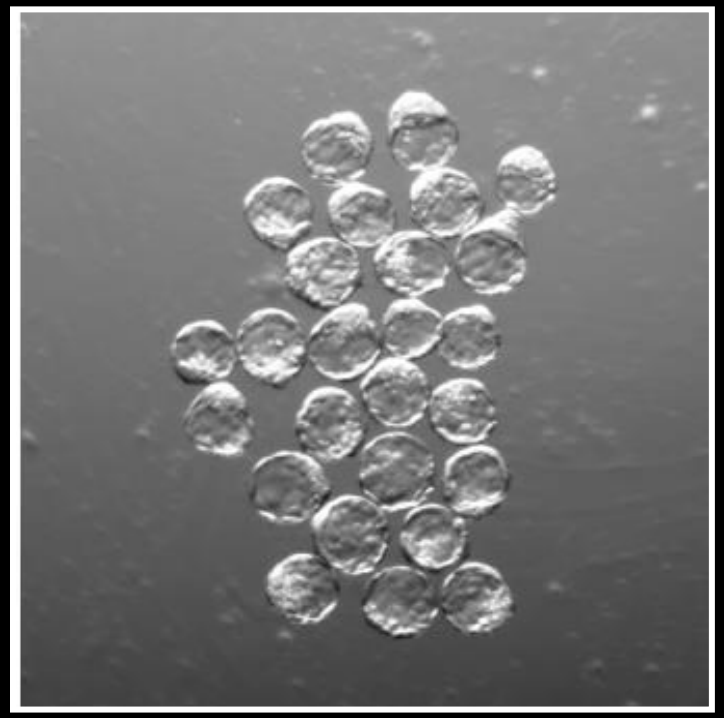
Self-organization of stem cells

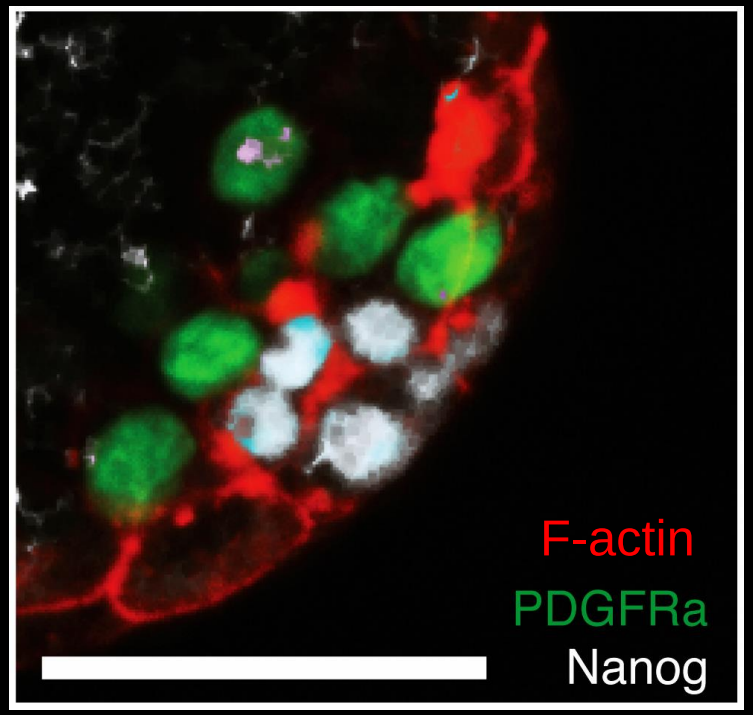


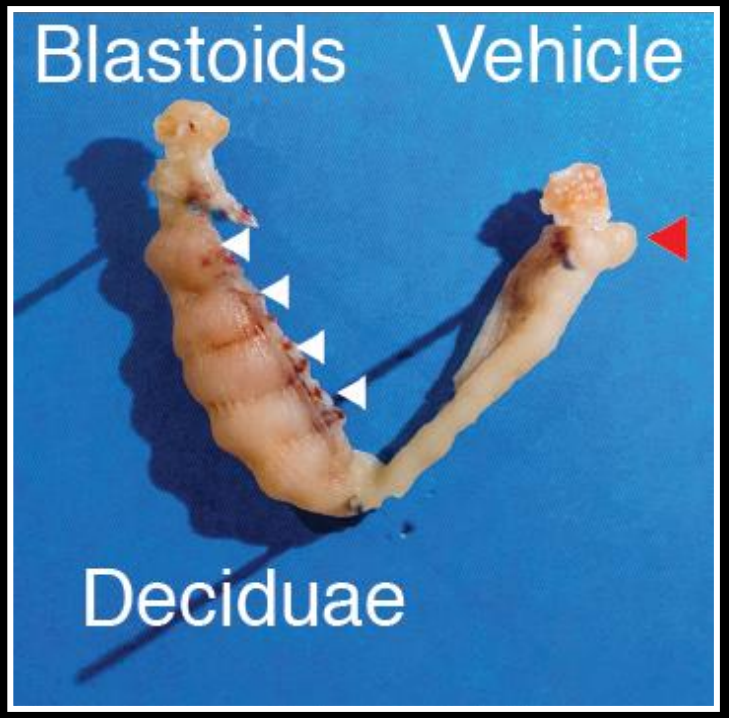
Embryo models: a gradual formation over time



Mouse blastoids model the whole conceptus and uterus implantation

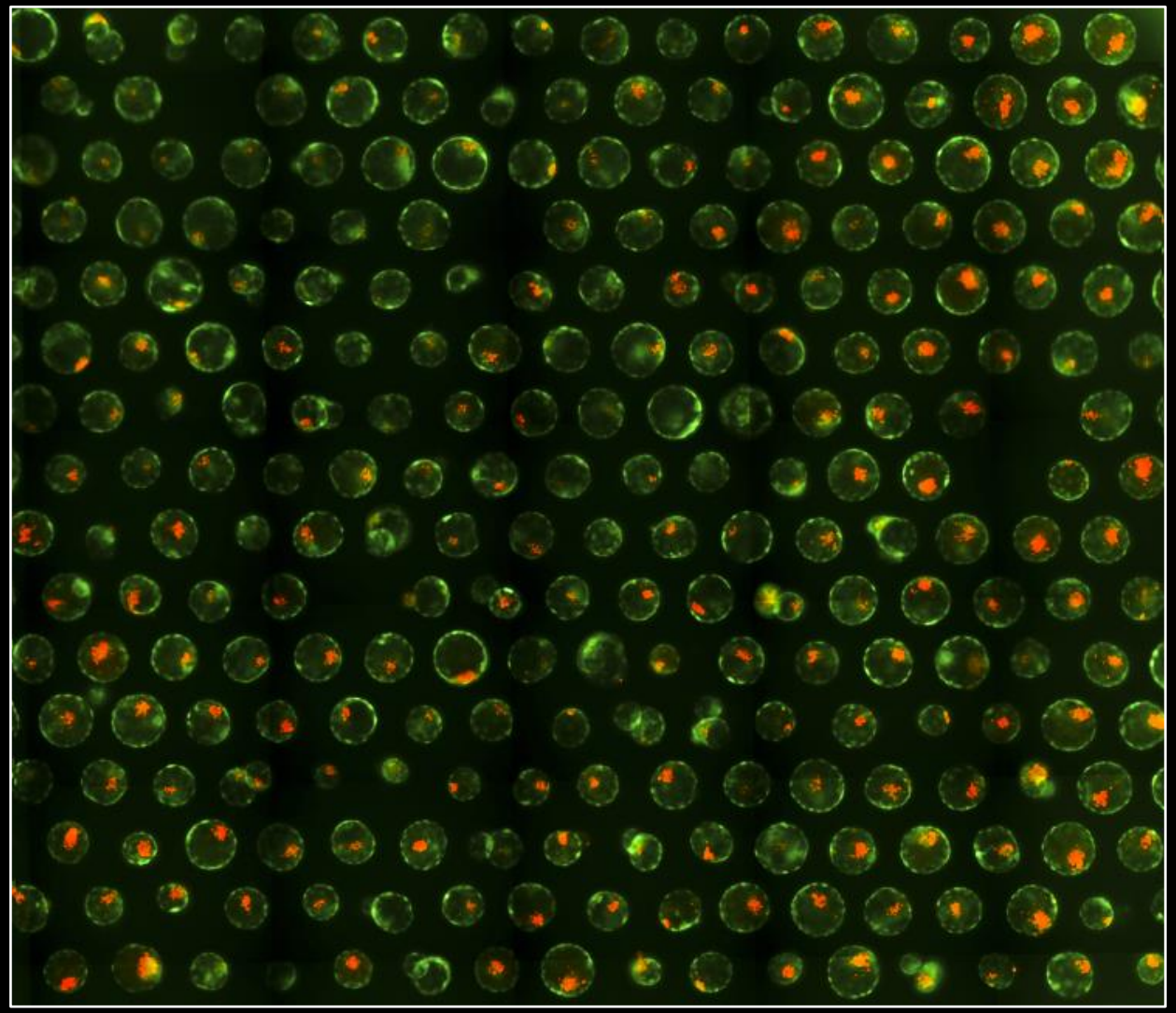






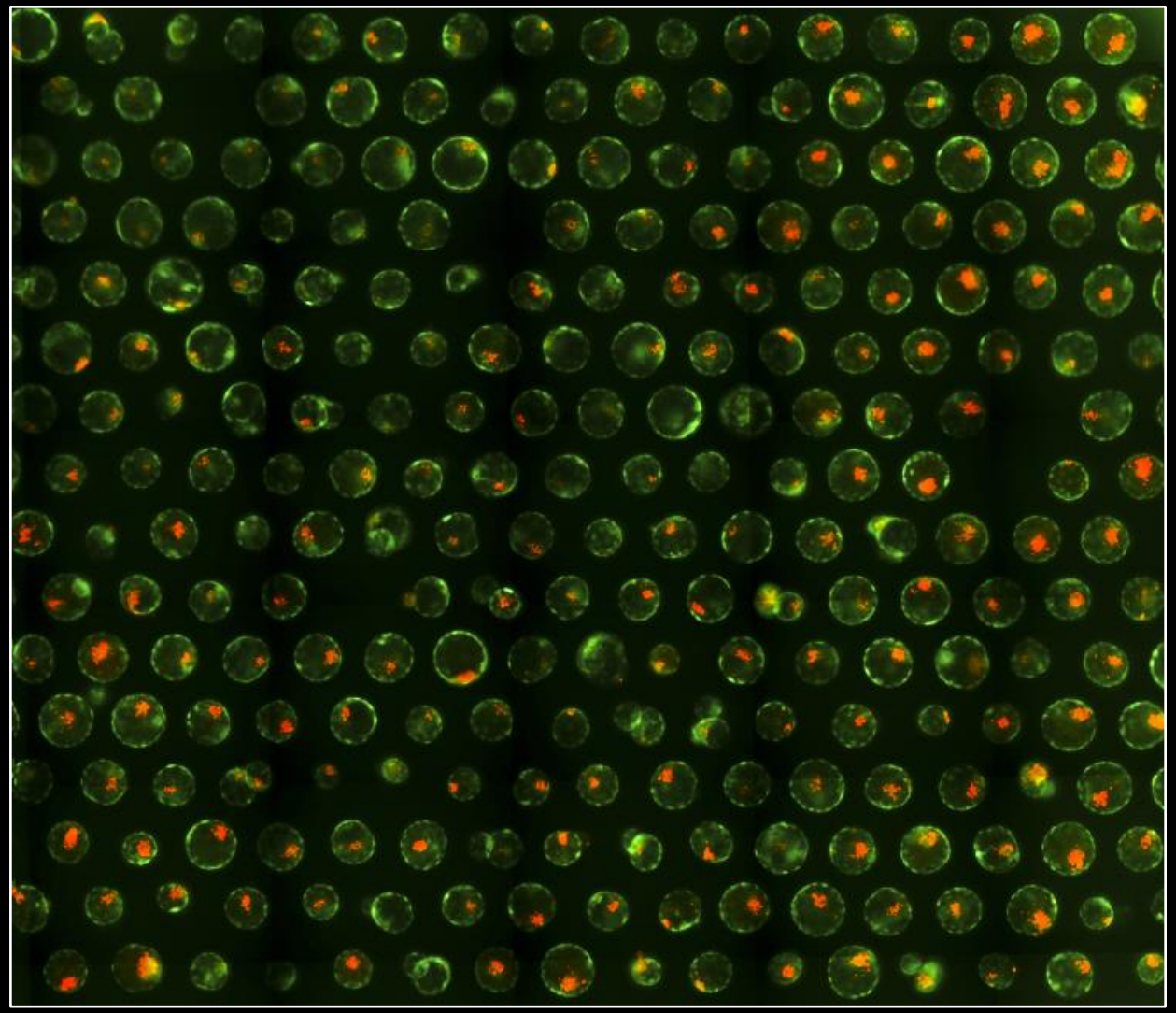
Nature- 2018

Mouse blastoids can be generated in infinite numbers



Nature- 2018

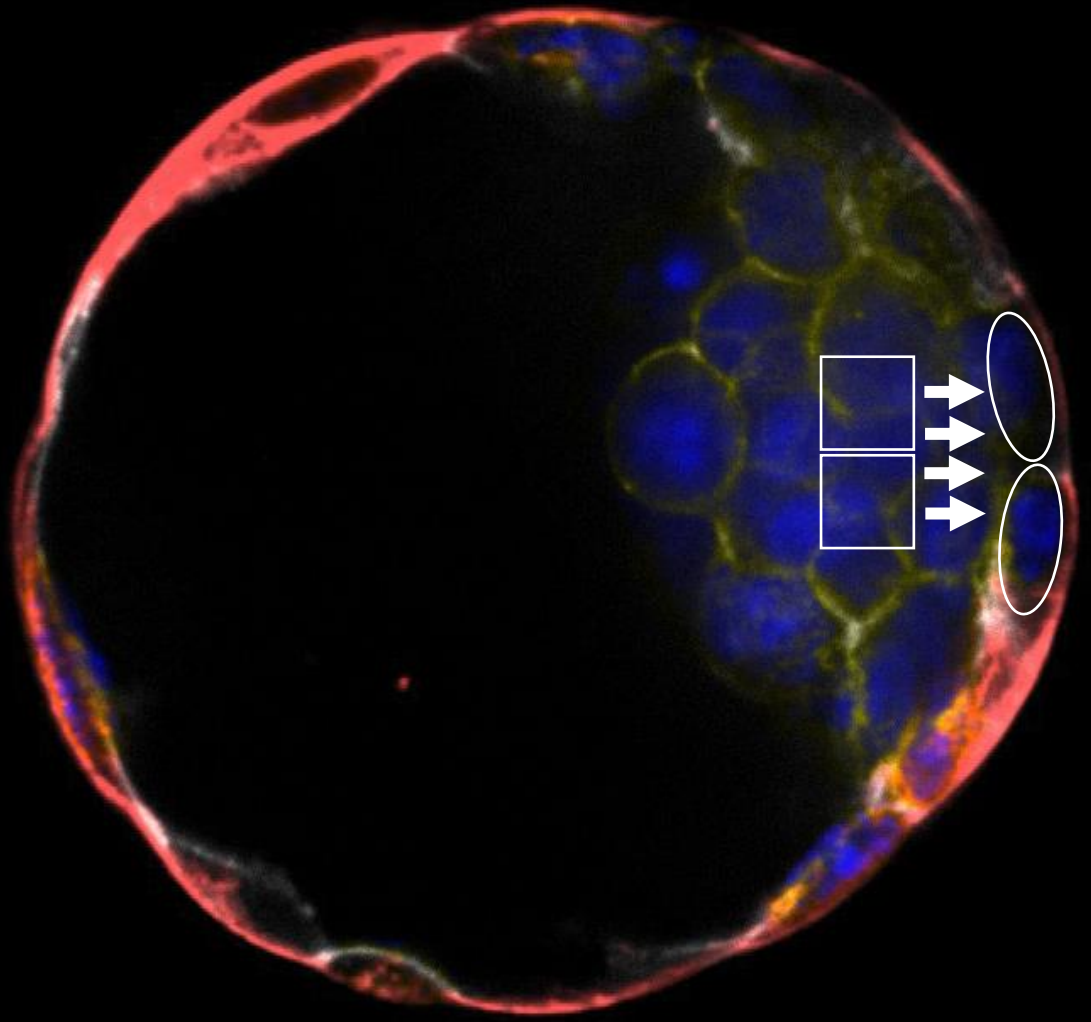
Mouse blastoids can be generated in infinite numbers



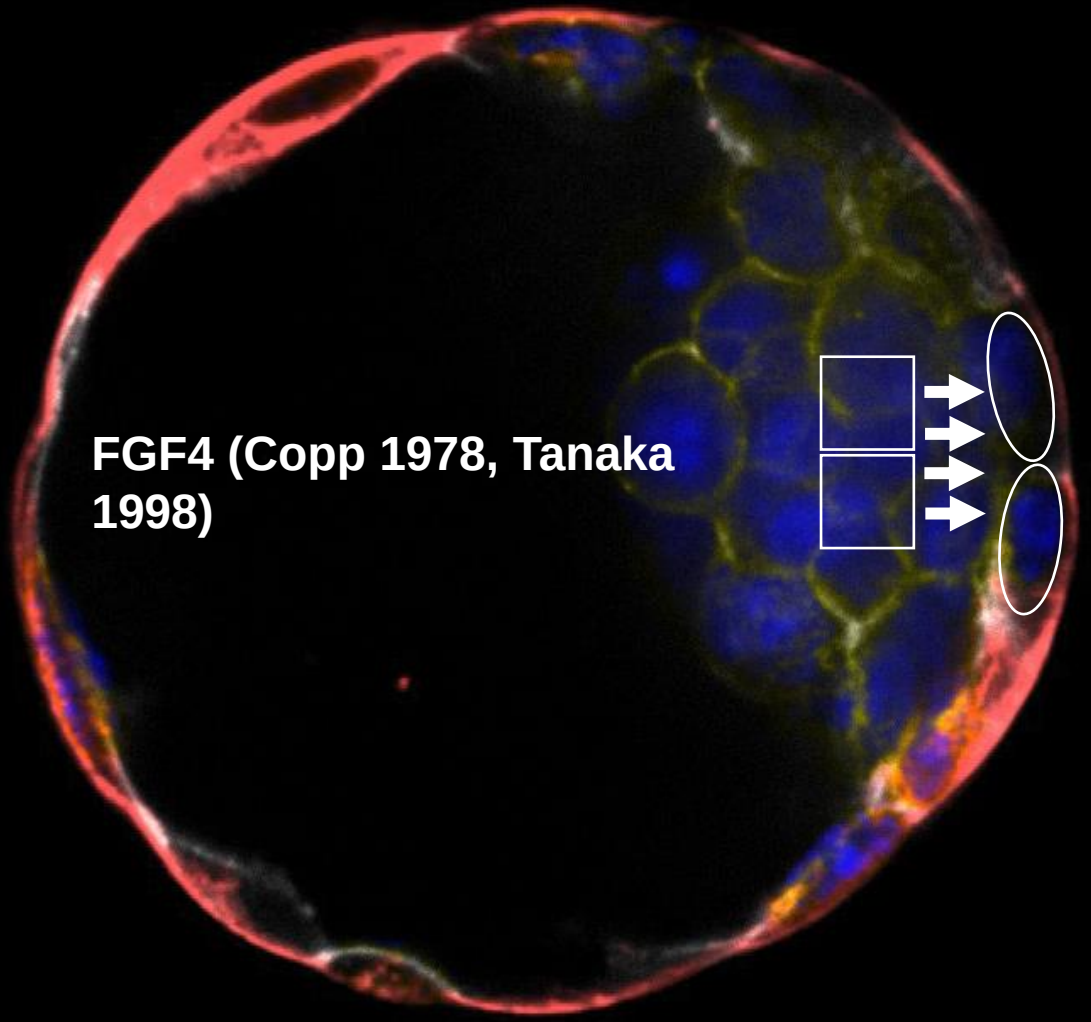
- Optimization of IVF media
- Toxicity test for IVF media and devices
- Optimizing blastocyst vitrification/thawing
- Training on manipulation in IVF clinics
- Drug screens and drug development

Nature- 2018

Embryonic inductions for positional information



Embryonic inductions for positional information

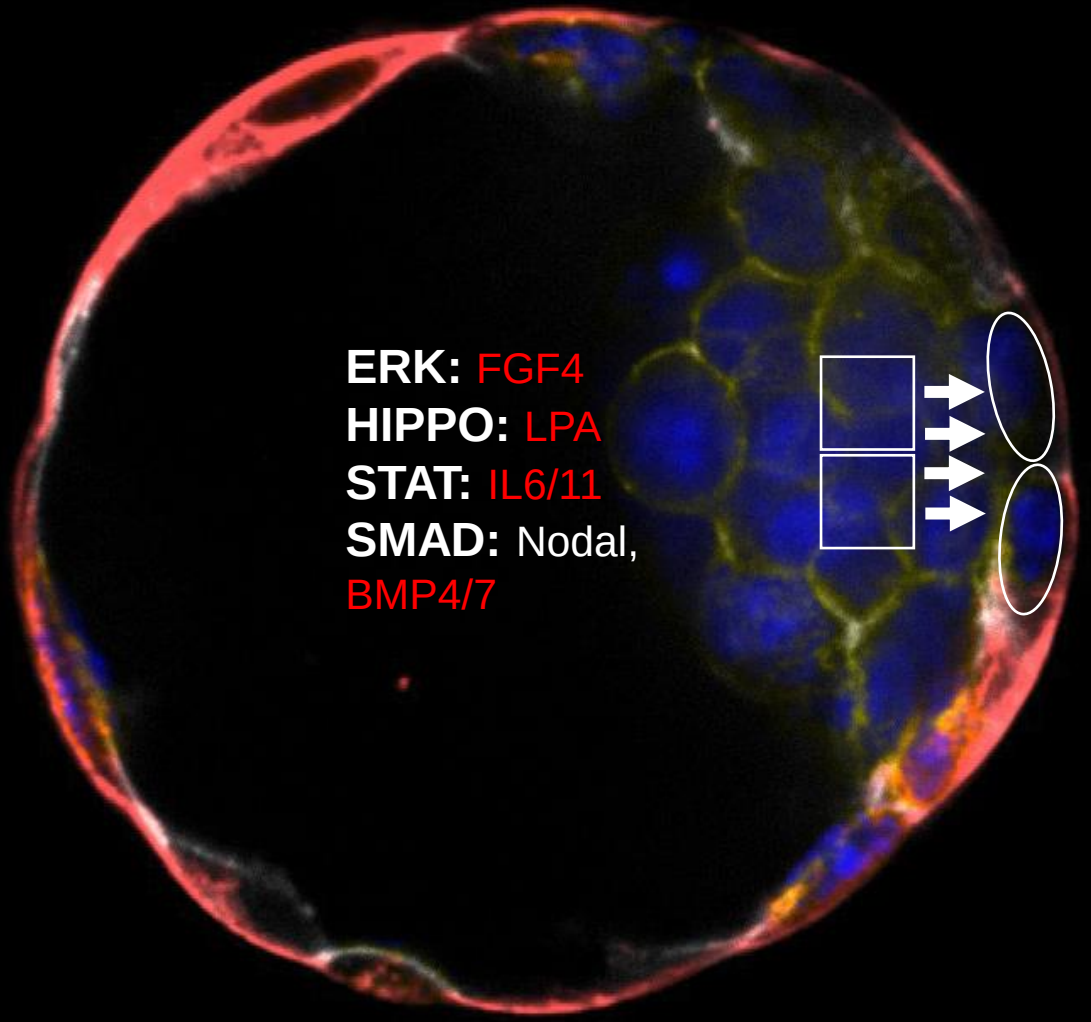


FGF4 (Copp 1978, Tanaka 1998)

Proliferation

1978 - PMID: 744943
1998 - PMID: 9851926

Embryonic inductions for positional information



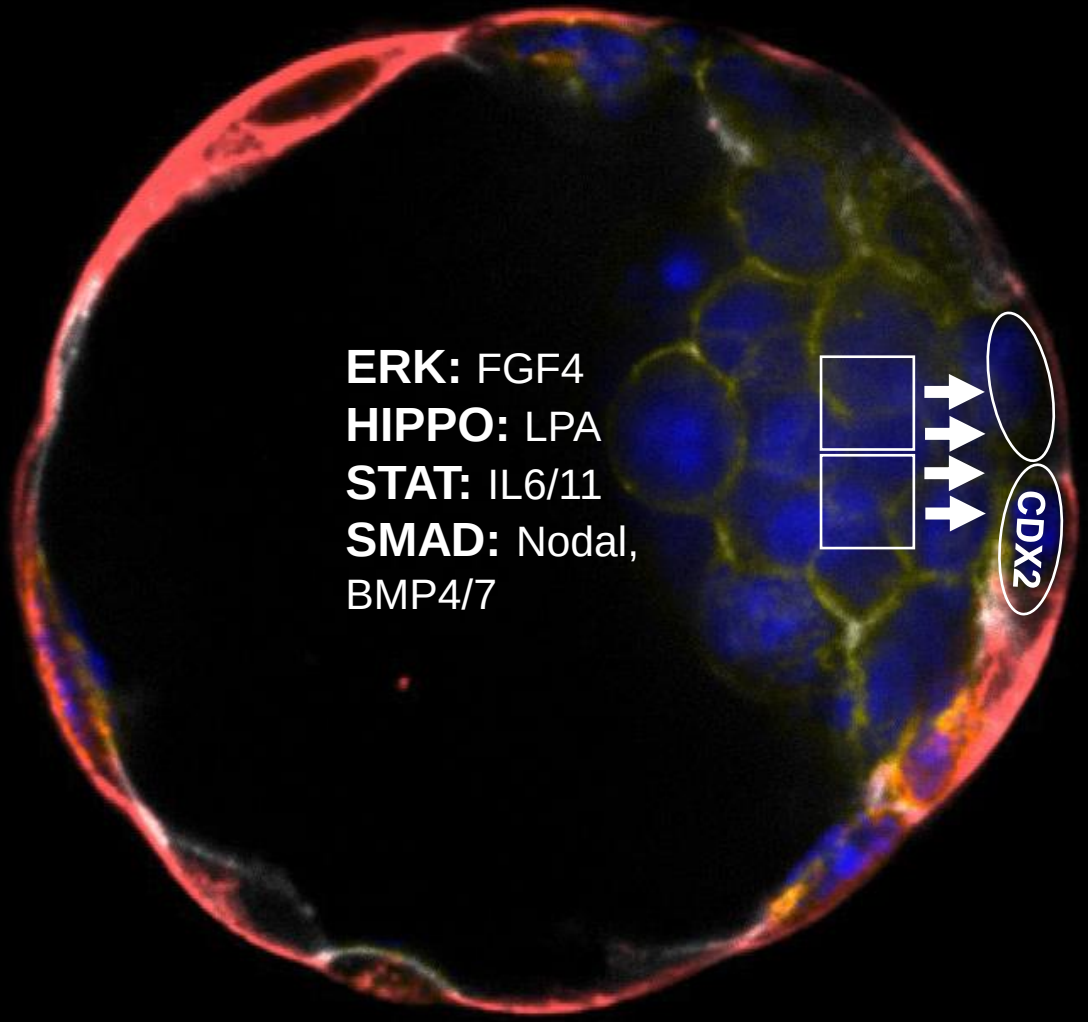
ERK: FGF4
HIPPO: LPA
STAT: IL6/11
SMAD: Nodal, BMP4/7

Proliferation
Self-renewal

Growth

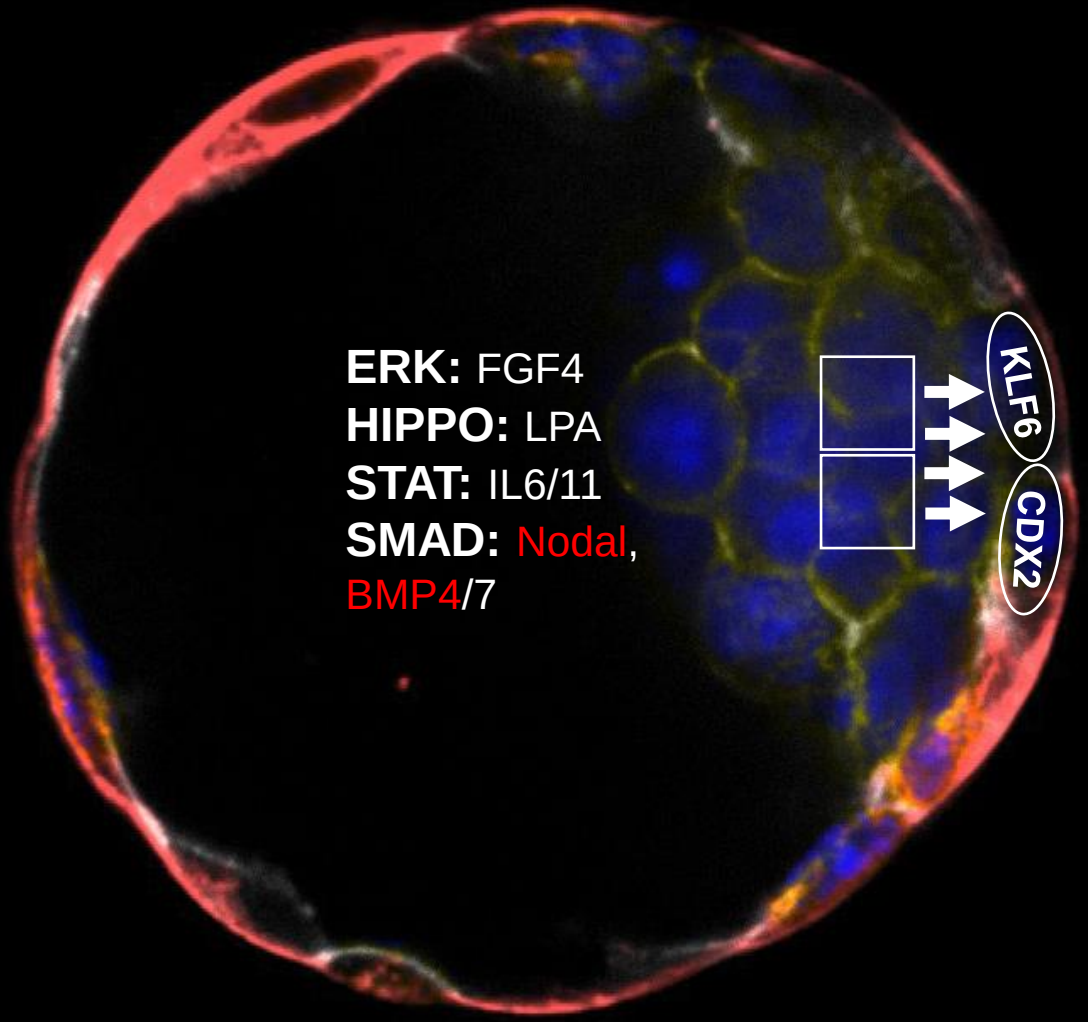
Nature – 2018
Cell Stem Cell - 2022

Embryonic inductions for positional information



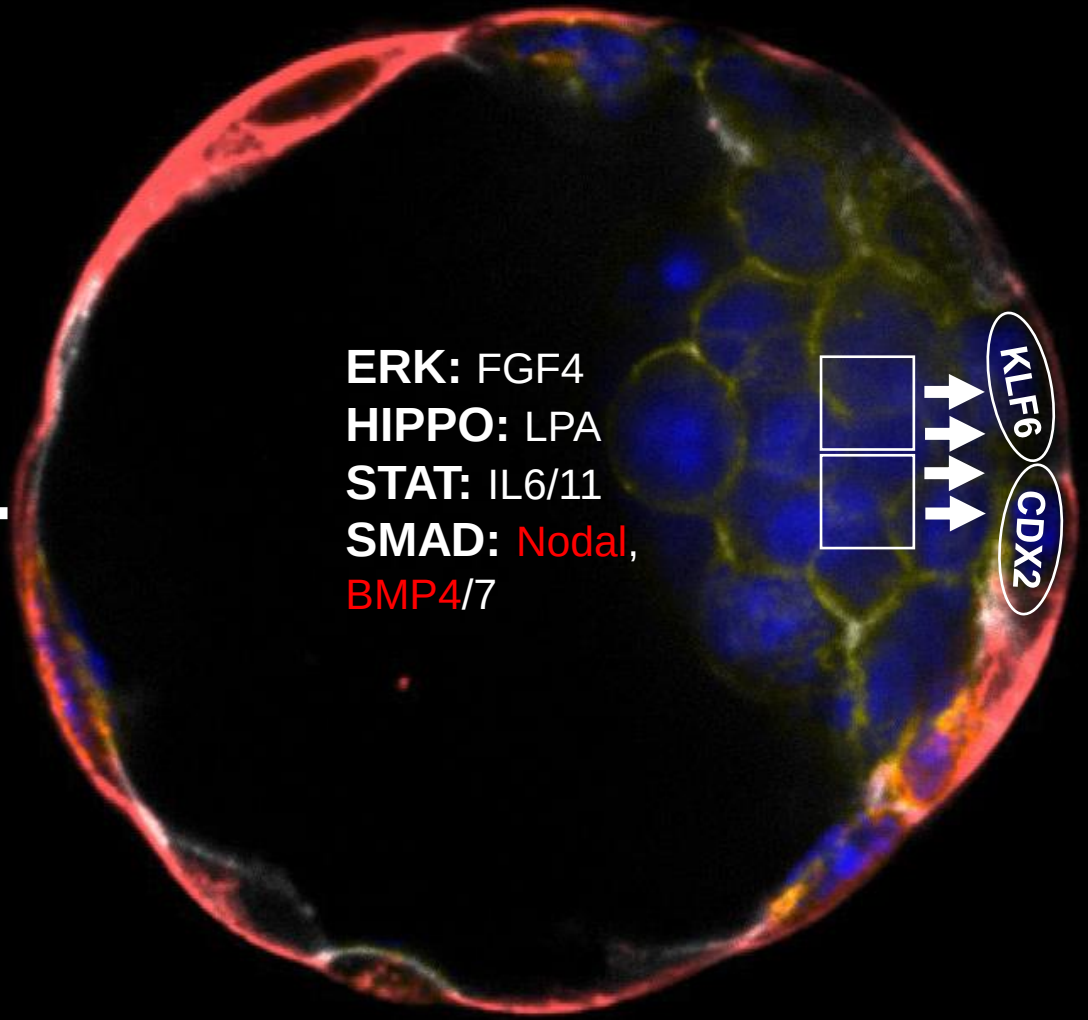
Nature – 2018
Cell Stem Cell - 2022

Embryonic inductions for positional information



Nature – 2018
Cell Stem Cell - 2022

Embryonic inductions for positional information



Adhesion

ERK: FGF4
HIPPO: LPA
STAT: IL6/11
SMAD: Nodal, BMP4/7

KLF6

CDX2

Proliferation
Self-renewal

Secretion (Wnt6/7b)

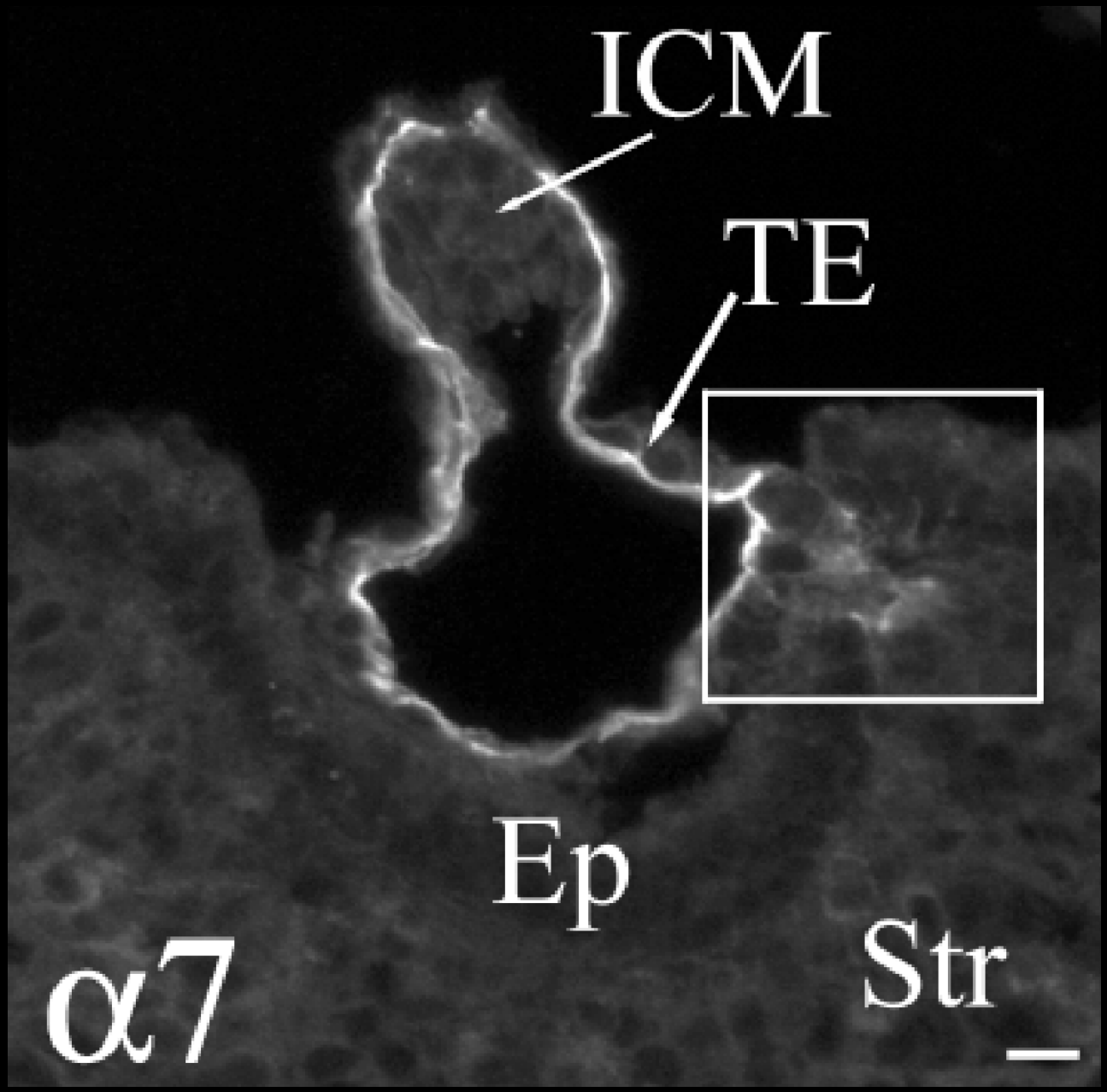
Epithelial morphogenesis

Growth

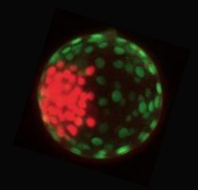
Uterus instruction

Patterning

Nature – 2018
Cell Stem Cell - 2022



2001 - PMID: 11784026



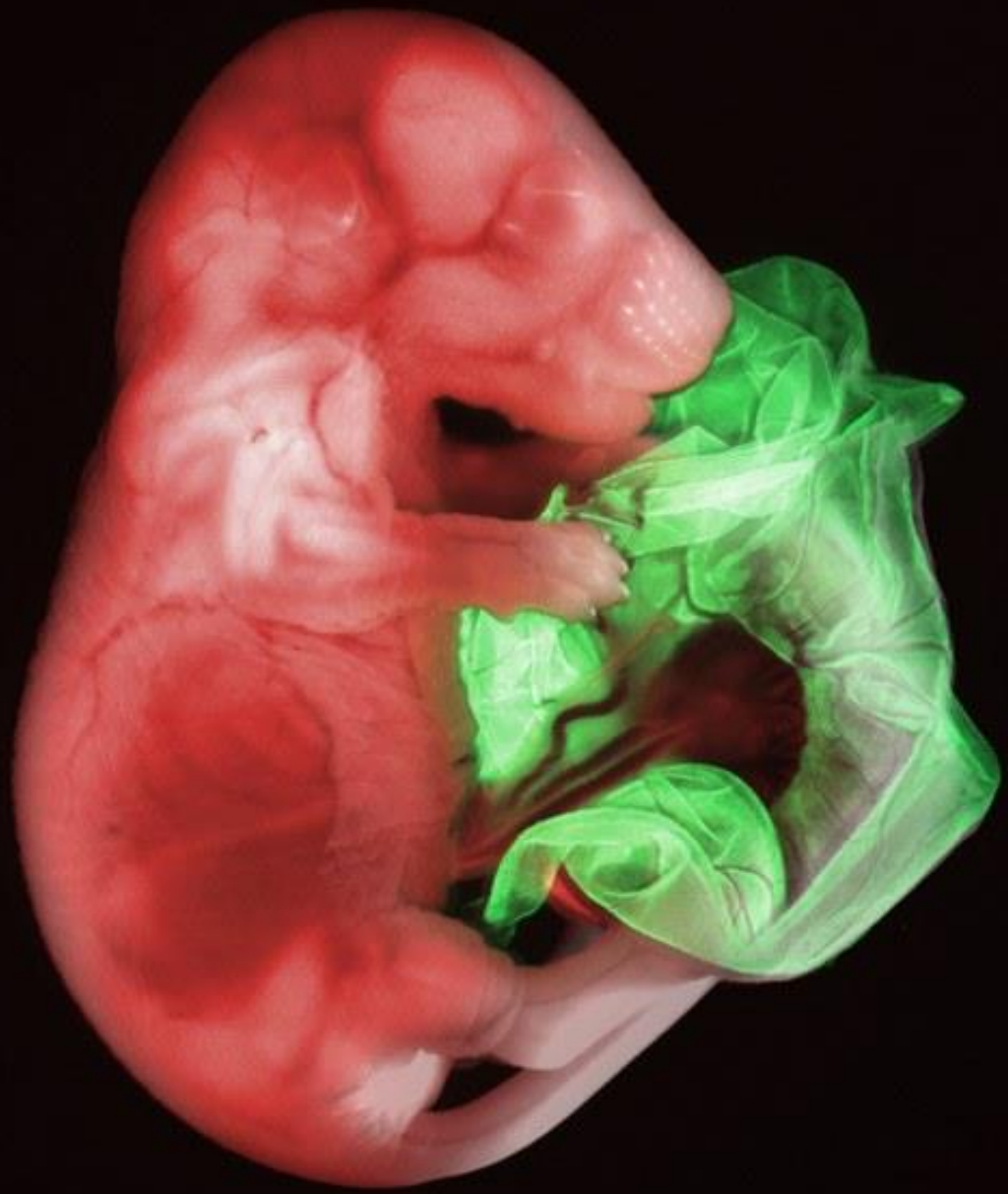
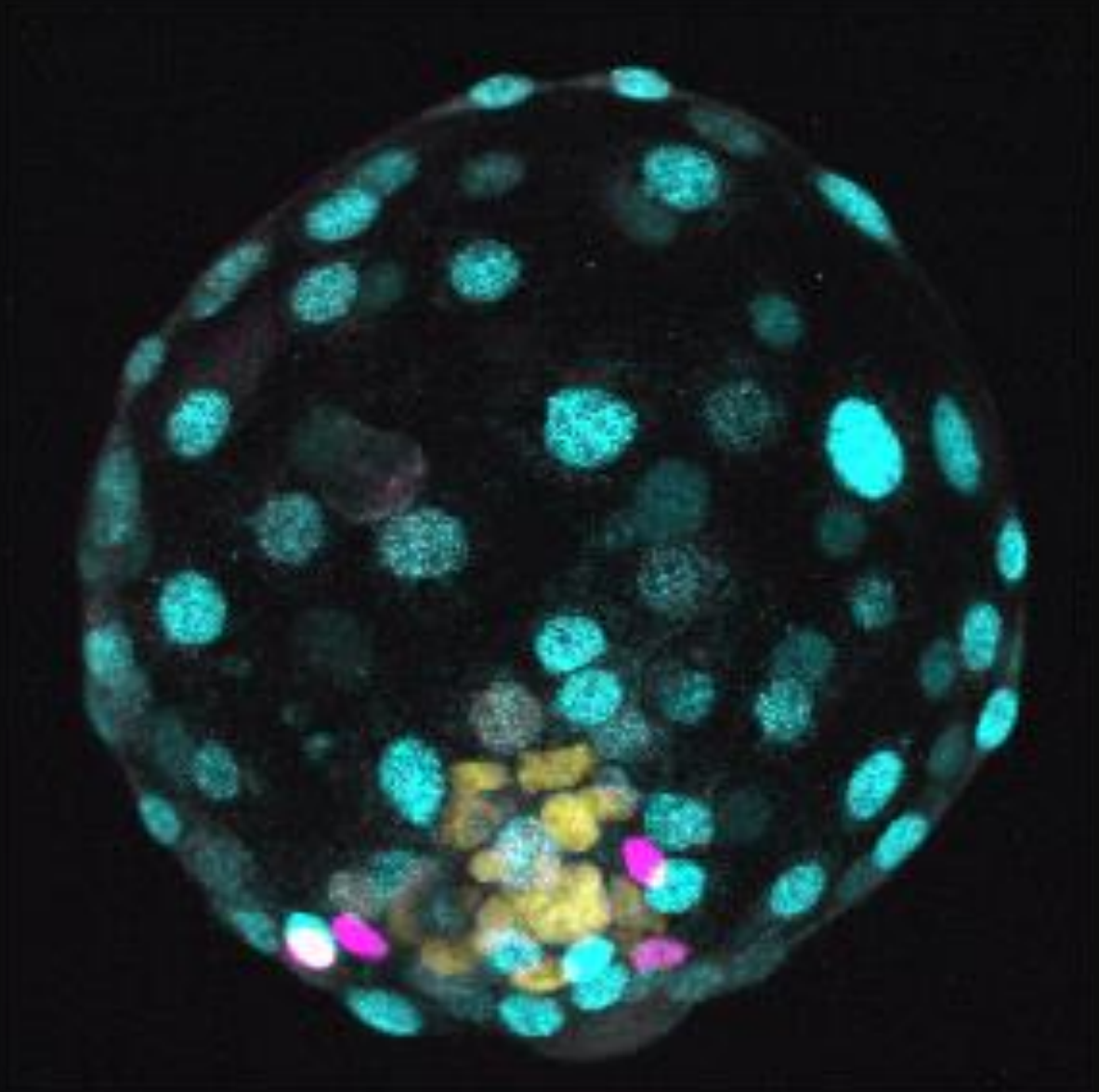


Photo by Gloria

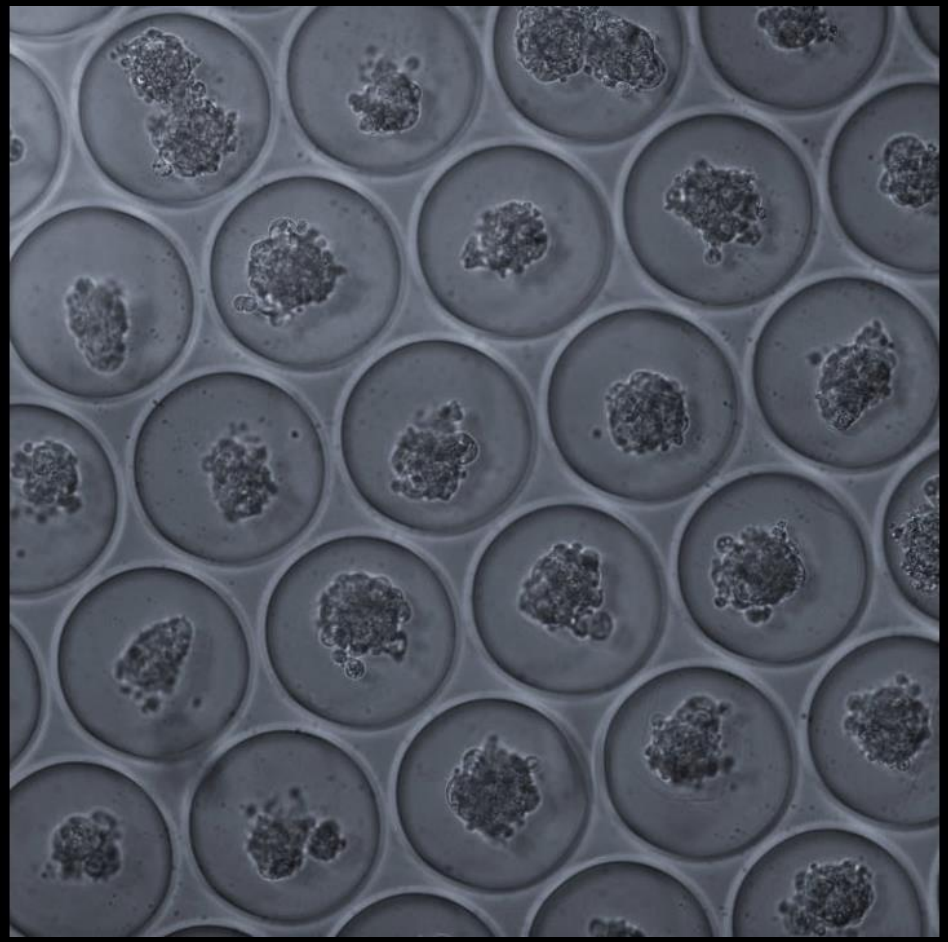
Human blastoids



PXGL hPSCs triply inhibited (Hippo/ERK/TGFb) efficiently form blastoids

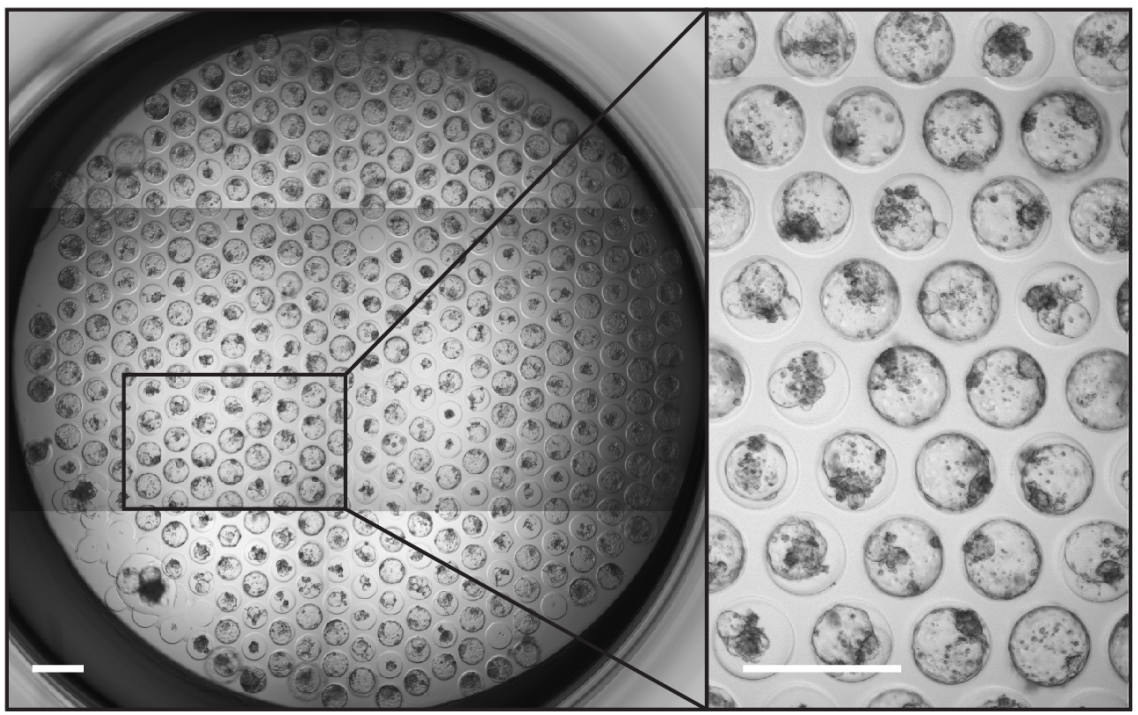
Two essential parameters:

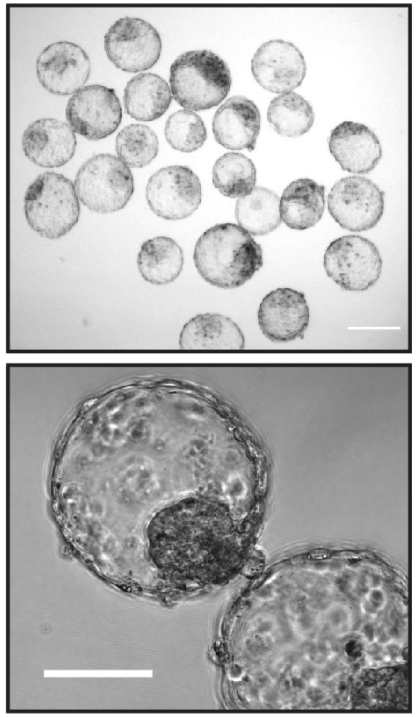
– Starting with the earliest possible cell state: PXGL hPSCs culture (2017 - PMID: 28765214)
– Stimulating cells adequately: ERK/TGFb inhibition (2013 - PMID: 23493551) + Hippo inhibition (2019 - **PMID: 35803228)**

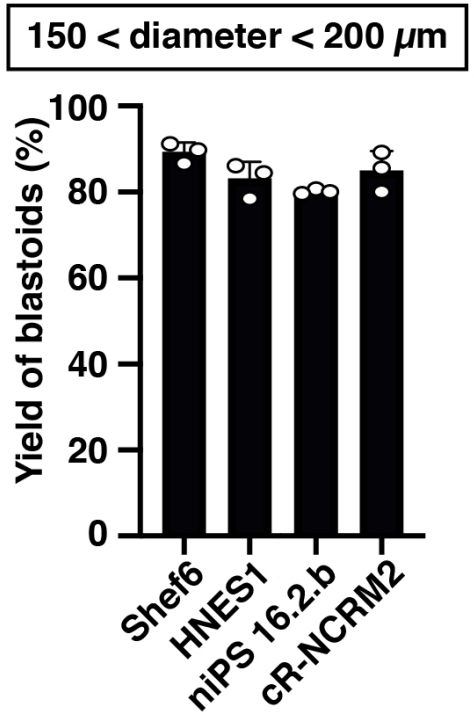


Nature - 2021

Human blastoids form with high efficiency (~80%)



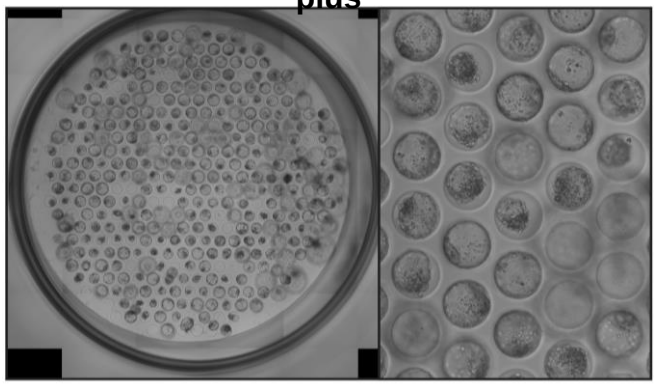




Nature - 2021

Human blastoids form with high efficiency (~80%) in IVF medium

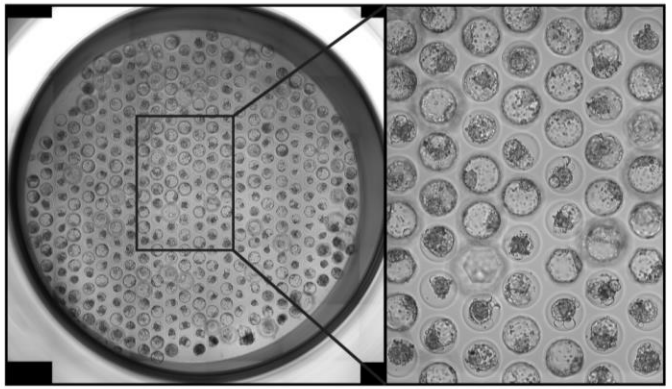
Blastoids in IVF medium Vitrolife G2-plus



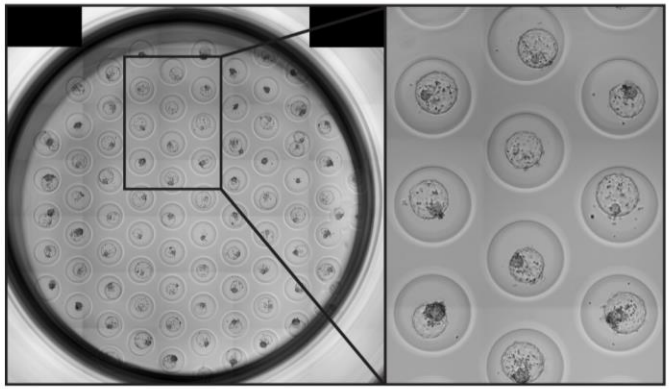
Blastoids also form in:

- Continuous Single Culture-NX from Fujifilm,
- ORIGIO® Sequential Blast™ from CooperSurgical Fertility

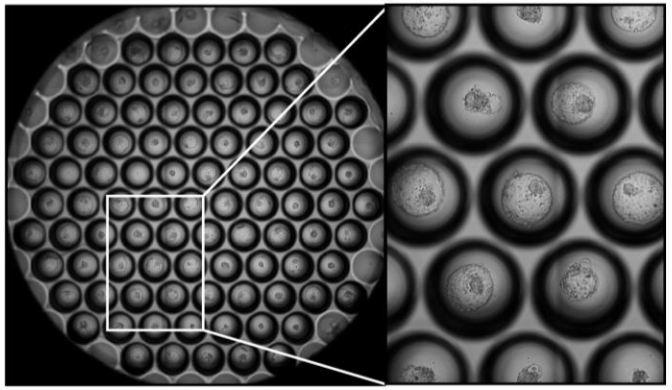
Hydrogel microwell plate- 200 μM



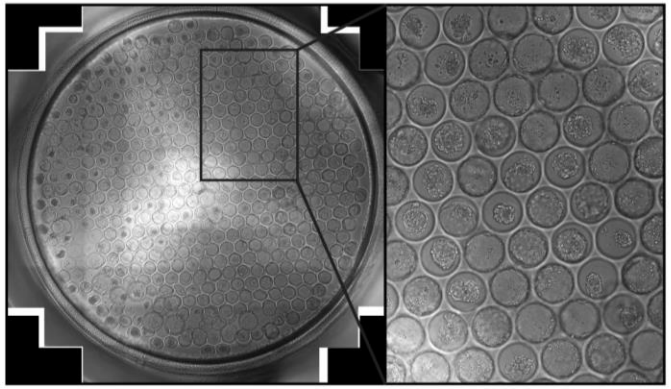
Hydrogel microwell plate- 400 μM



Elplasia from Corning

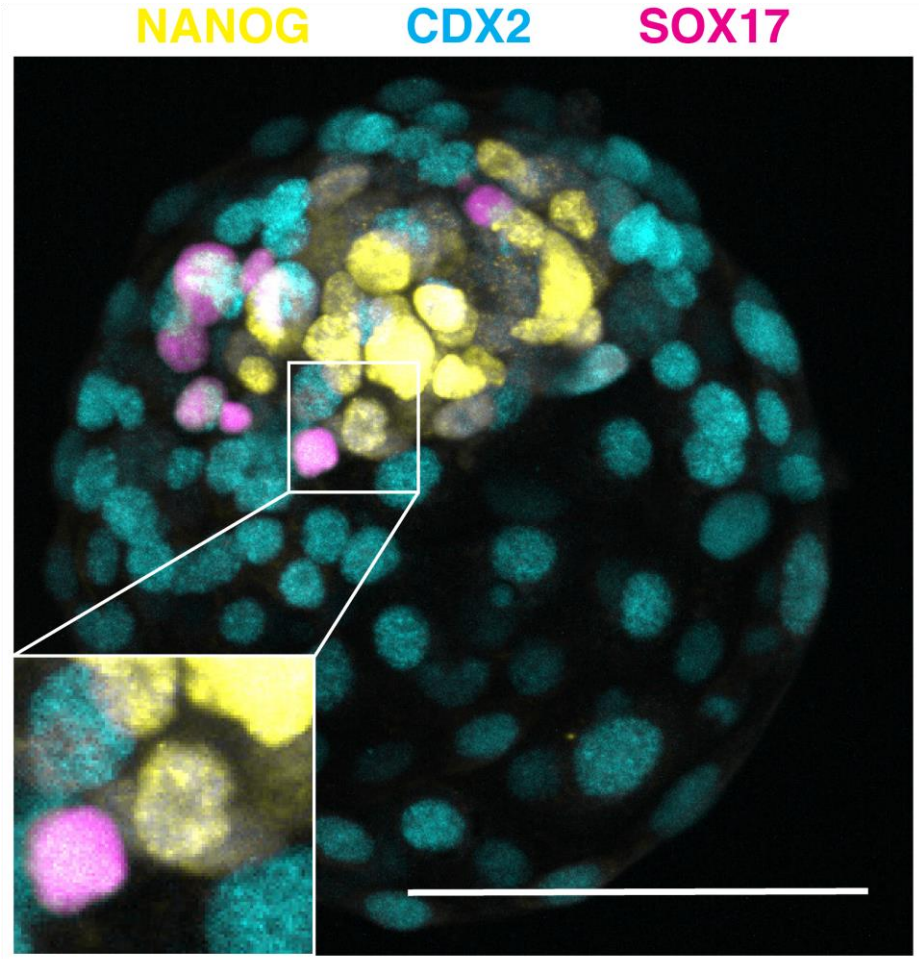


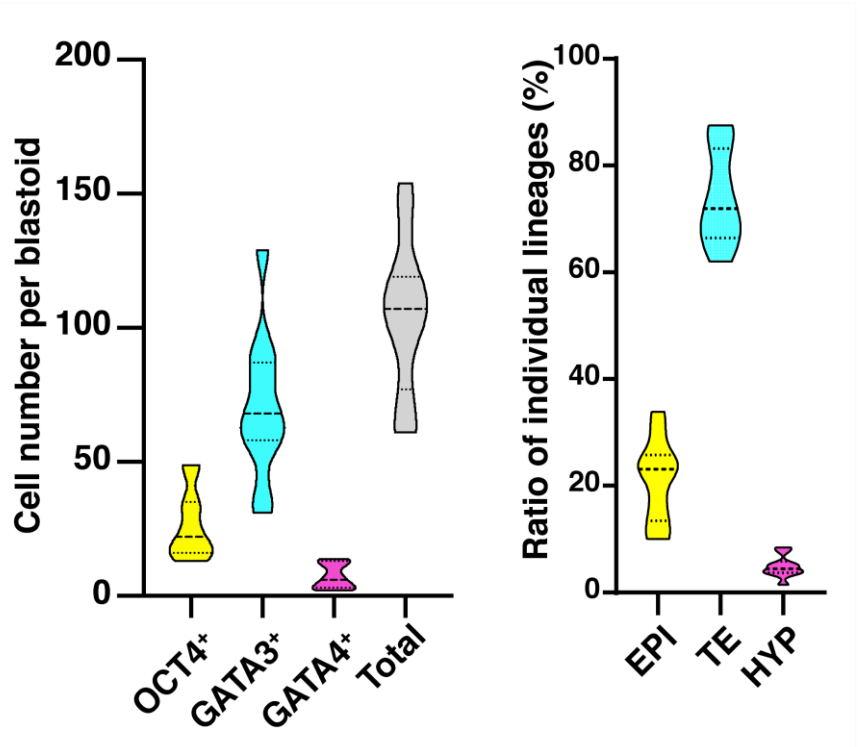
Gri3D from Sun Bioscience



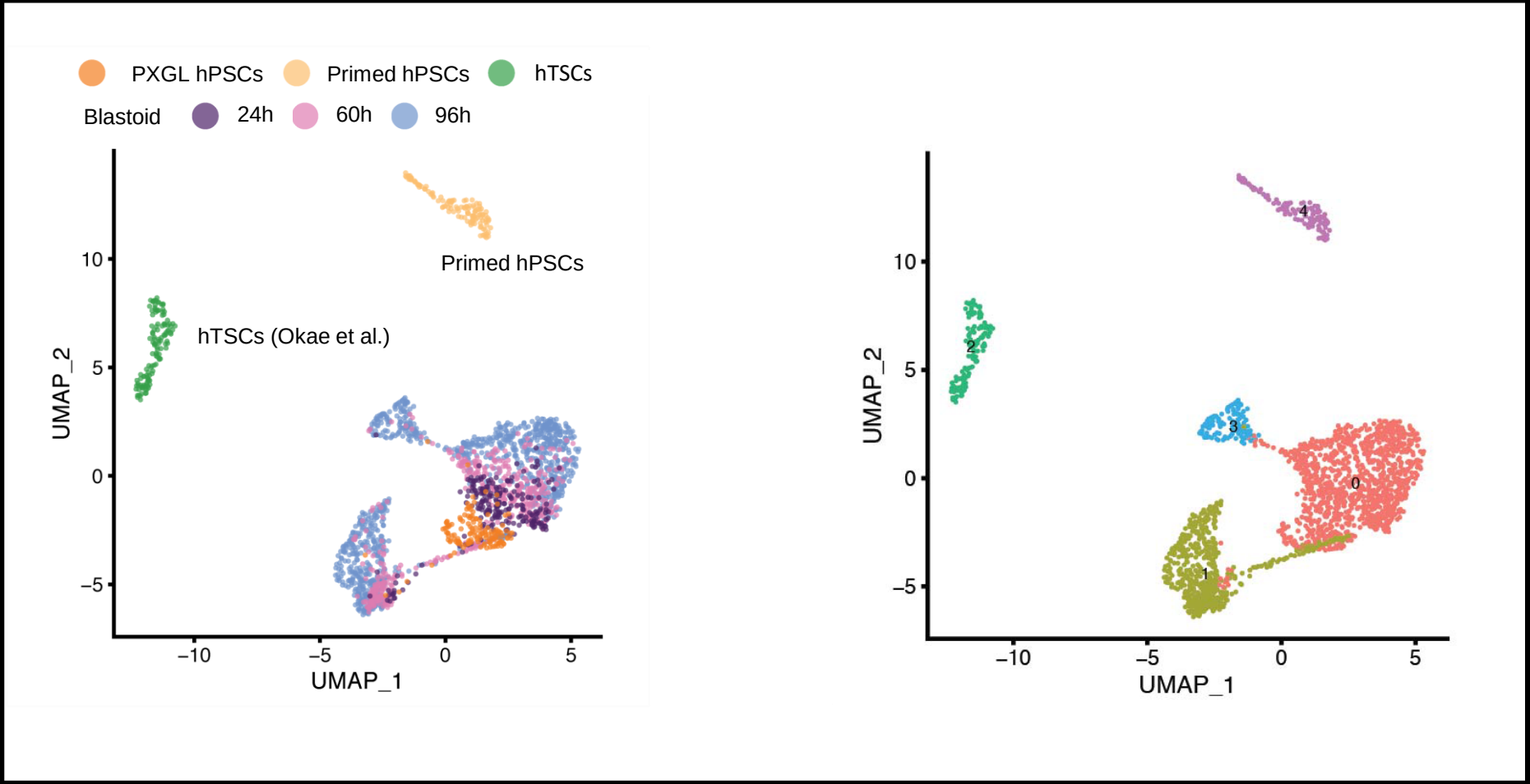
Nature Protocol - 2022

Human blastoids self-organize the three founding lineages

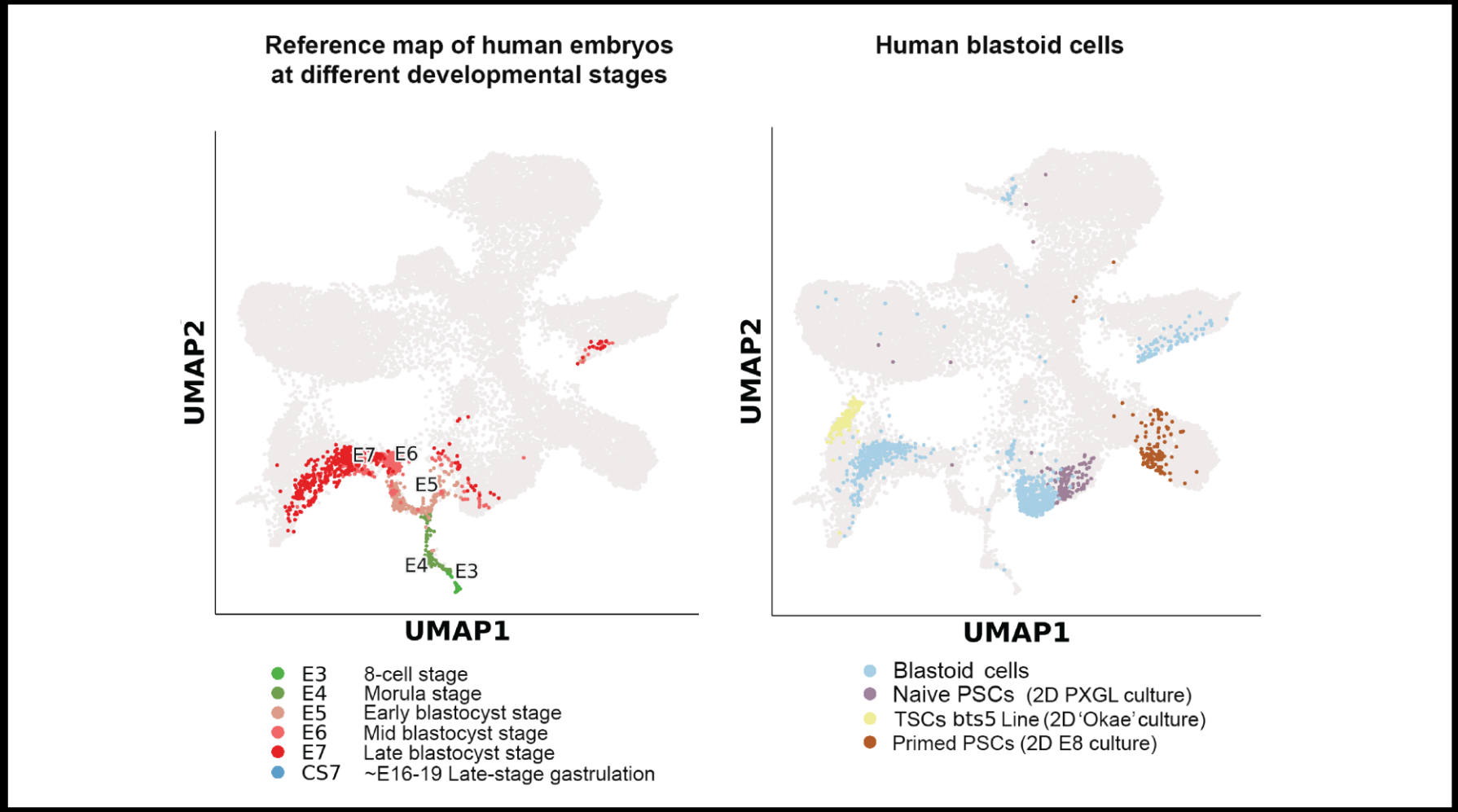




Human blastoids sequentially form the three founding lineages

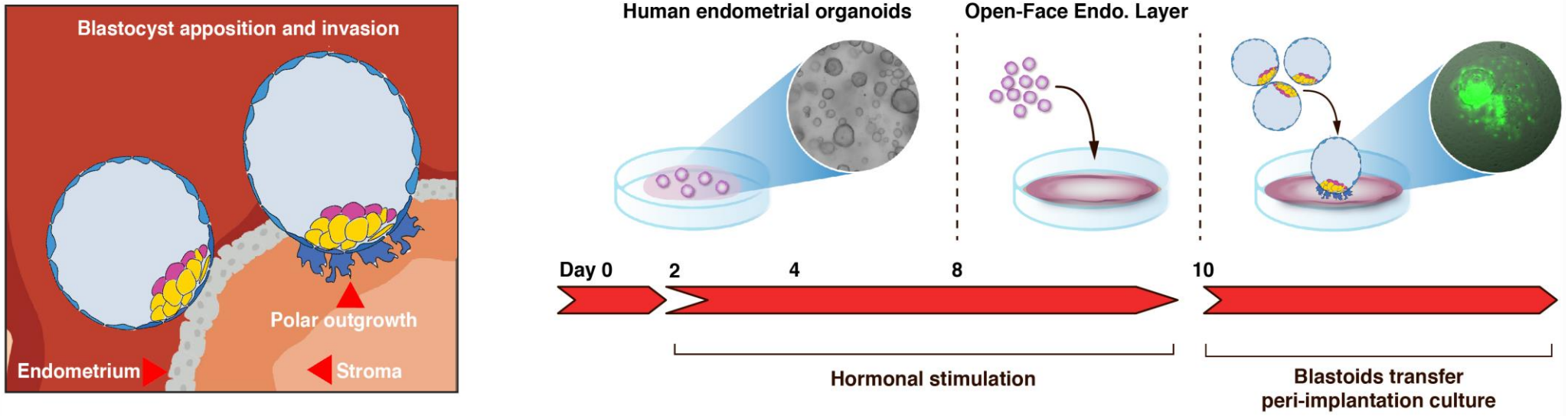


Human blastoids form the 3 transcriptional analogs of the blastocyst stage

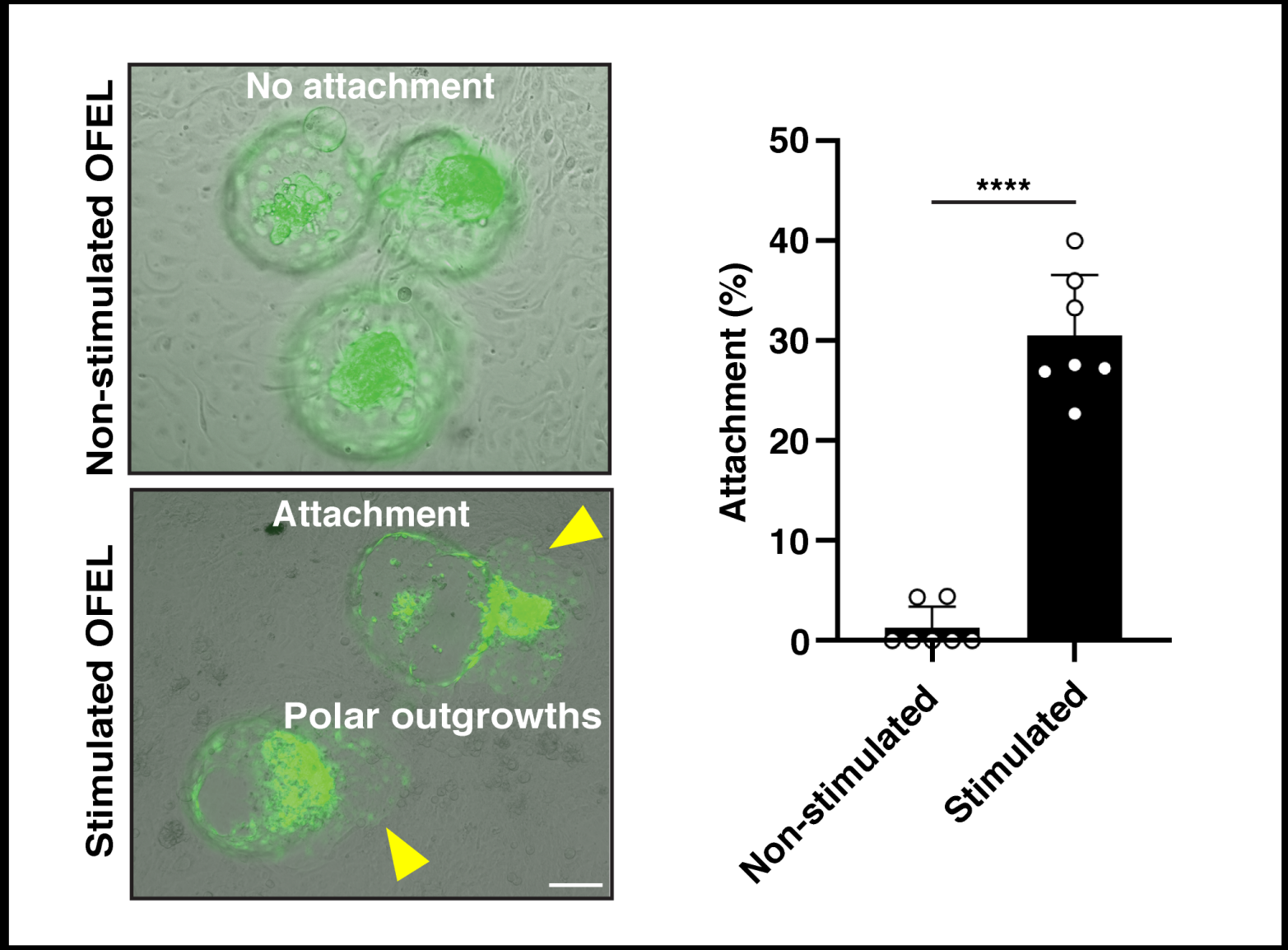


https://petropoulos-lanner-labs.clintec.ki.se - **2021 - Biorxiv:** 442980v2

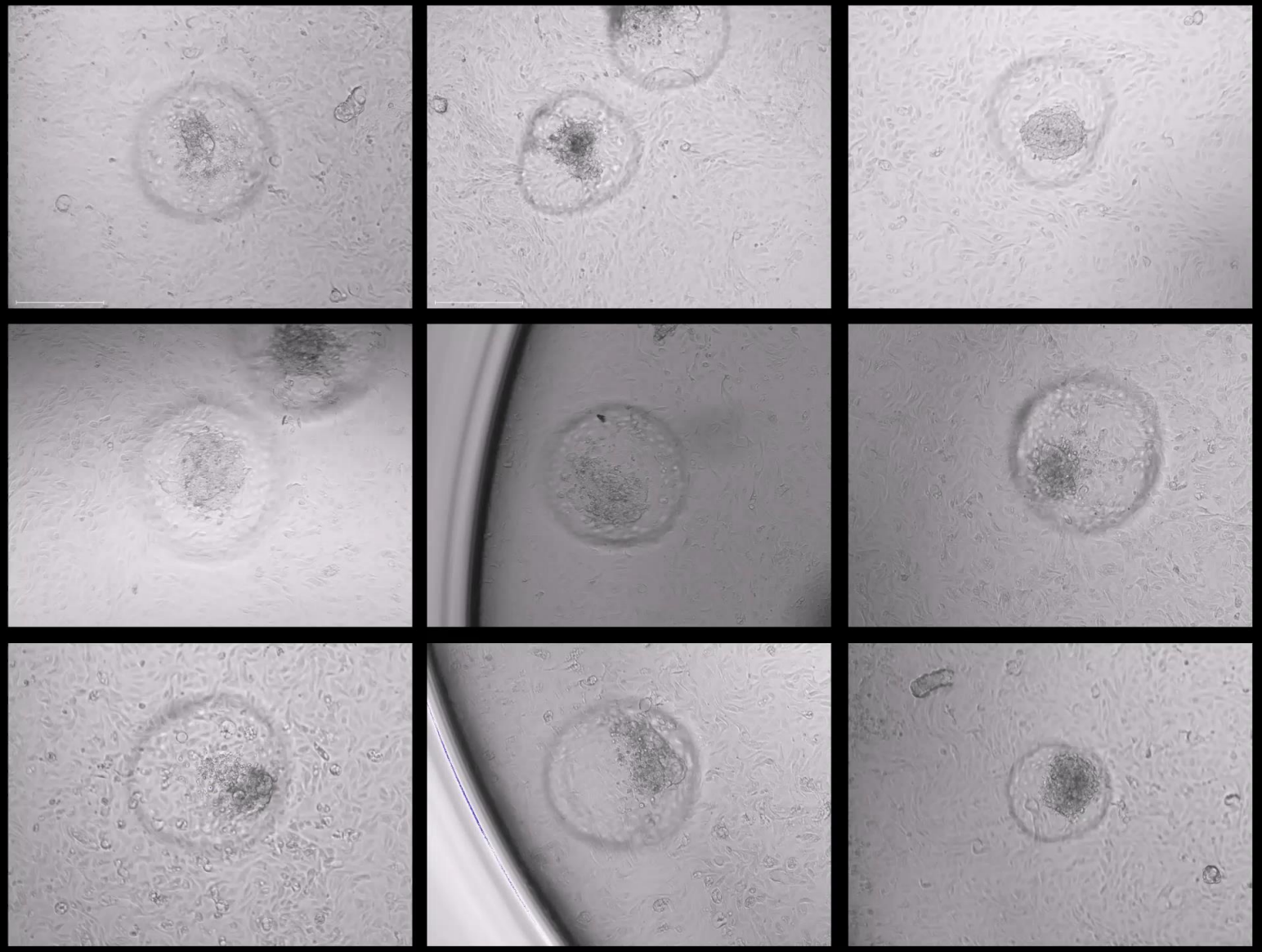
Can blastoids model implantation *in vitro* ?



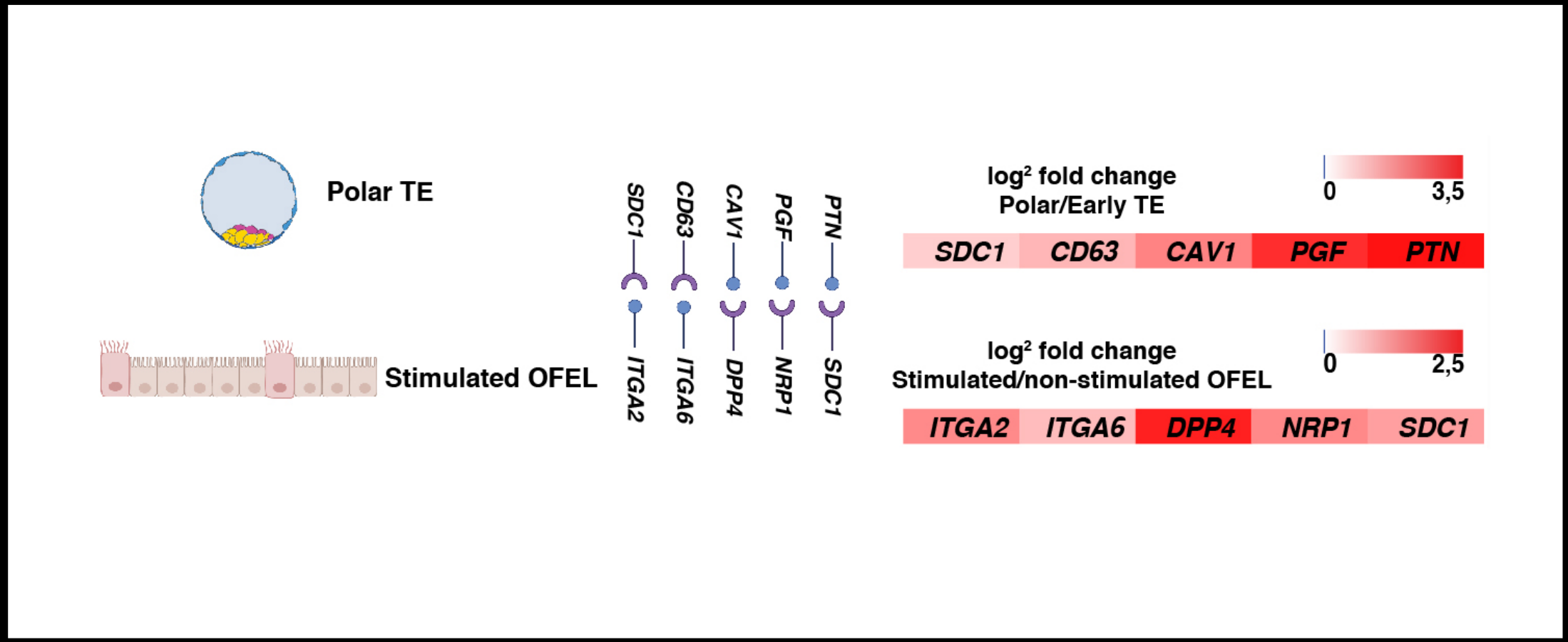
Human blastoids only attach to hormonally-stimulated endometrial cells



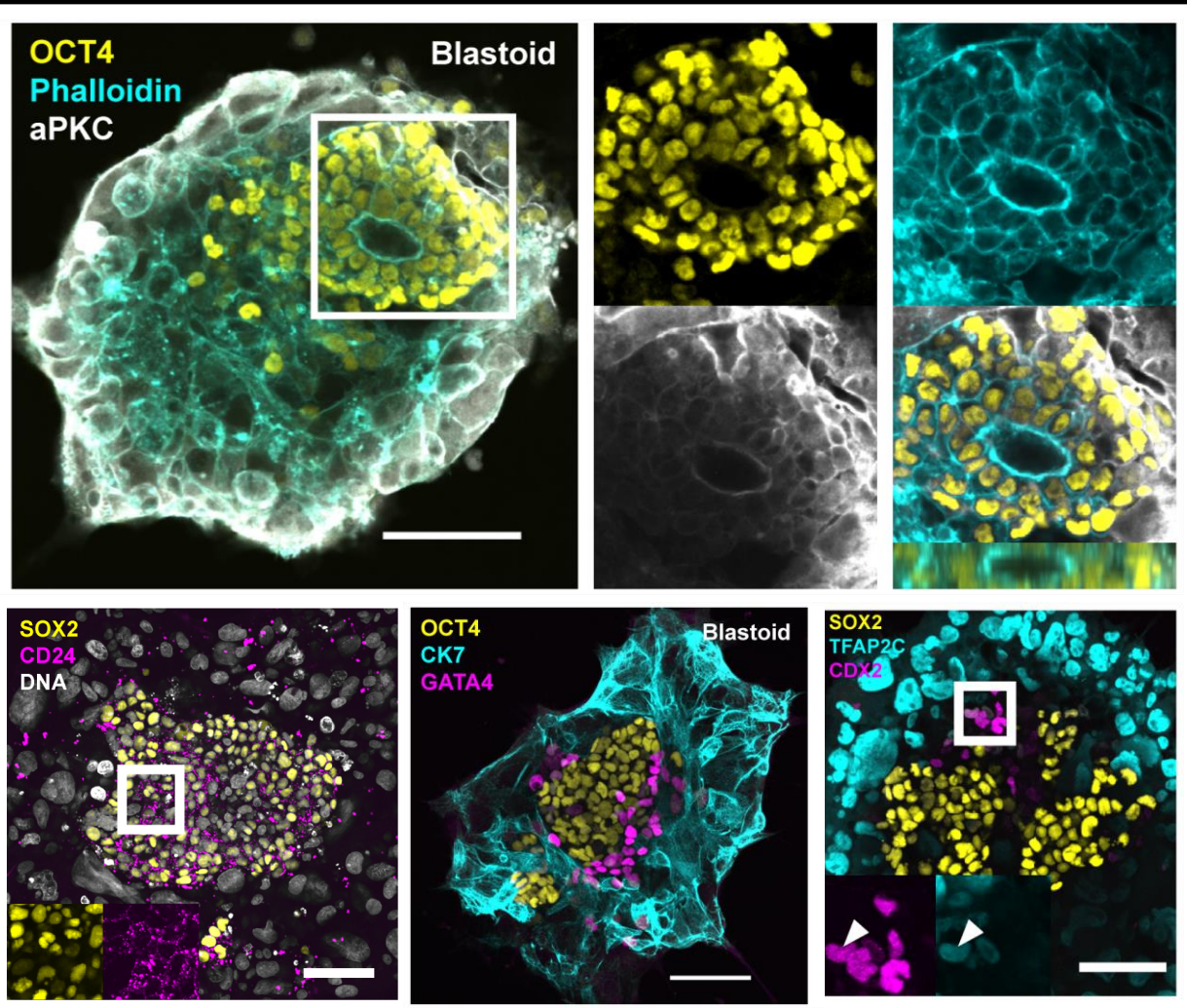
Human blastoids attach to endometrial cells via the polar side

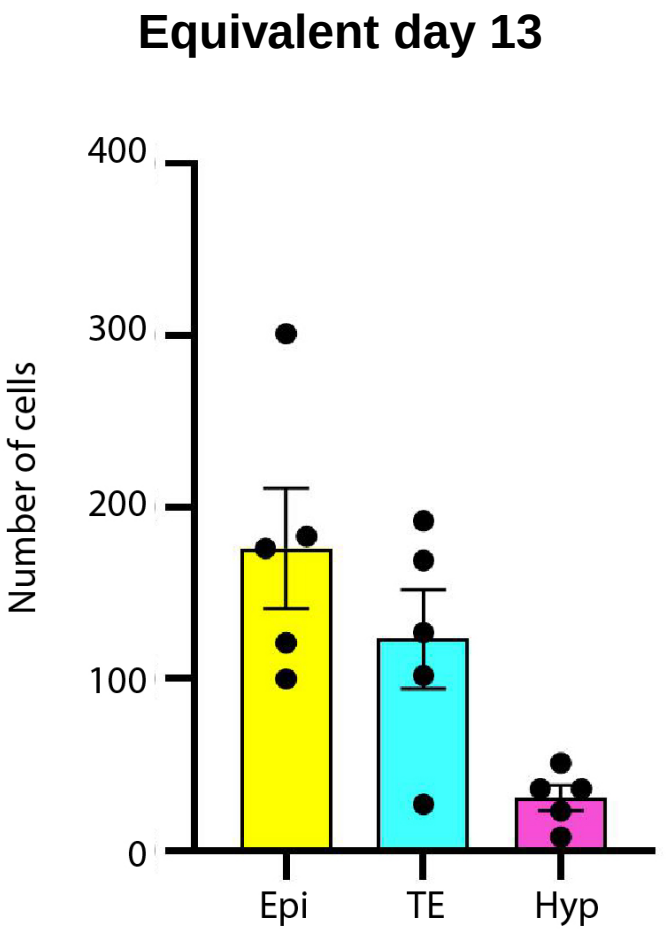


Epiblast induces polar trophoblast maturation to gatekeep endometrium interactions



Human blastoids lineages progress although they do not organize





Opportunities for clinical translation

1. Treating infertility.

It is estimated that at least 40% of pregnancies end before 20 weeks of gestation, with 70% of those failing around implantation. An improved understanding of early embryogenesis could inform on therapeutic strategies to improve infertility treatments.

2. Improving IVF.

Only about 20% of IVF procedures result in a birth. Understanding early embryogenesis could instruct on ways to optimize the implantation of IVF embryos while minimizing cellular abnormalities. This could reduce the number of IVF procedures while ensuring the health of children.

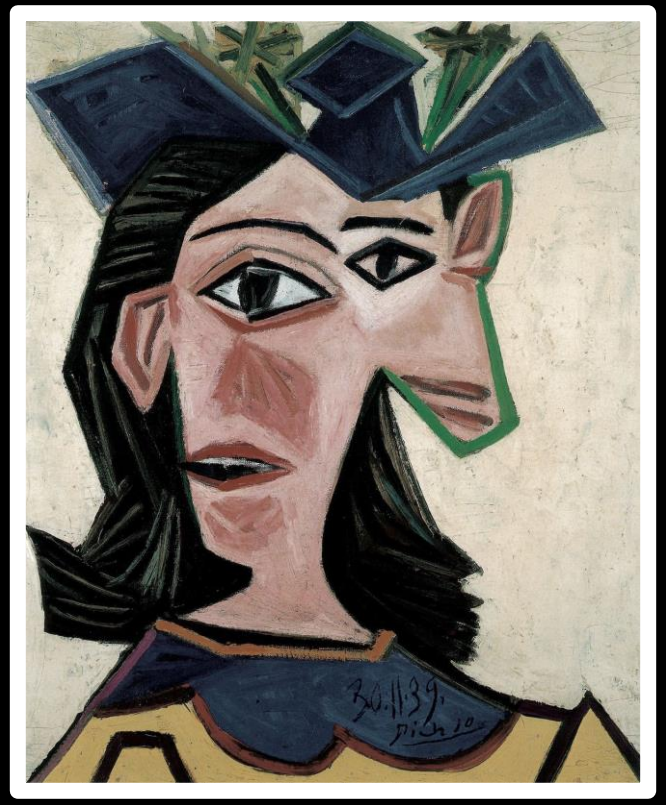
3. Advancing family planning.

The ability for women to control pregnancy is critical to sustainable, global development and to improve gender equality. Knowledge about early embryogenesis could lead to the development of effective contraceptive strategies with fewer side effects.

PMID: 33979590 PMID: 30542177 PMID: 31951813 PMID: 33979599

Ethics for human blastoids

Blastoids are rudimentary, different from embryos, and cannot form an organism.



The 2021 ISSCR guidelines propose ethical oversight for human blastoid research.

PMID: 28494856 | PMID: 30542177 | PMID: 31951813 | PMID: 32715543 | PMID: 32712668 | PMID: 31741321 | PMID: 34048690 | PMID: 33792755

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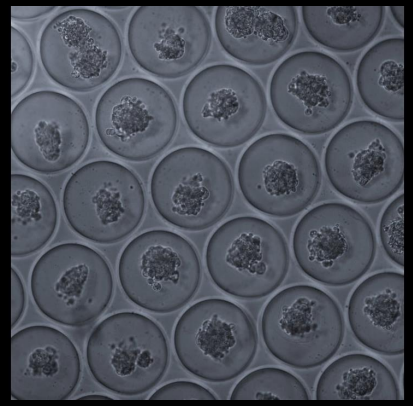
IMBA Institute of Molecular Biotechnology of the Austrian Academy of Sciences

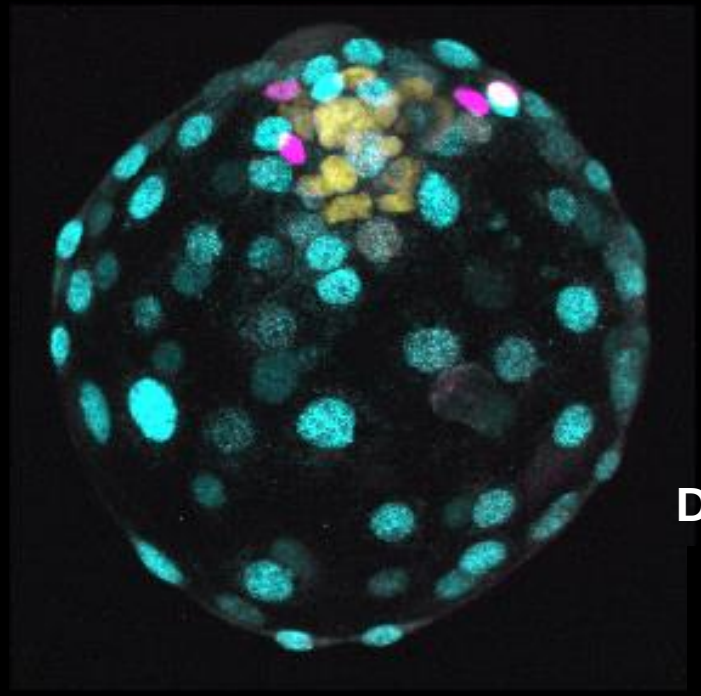
HFSP

erc European Research Council Established by the European Commission

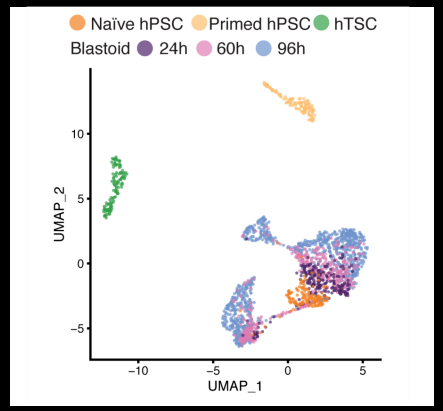
Four basic criteria

Efficient morphogenesis

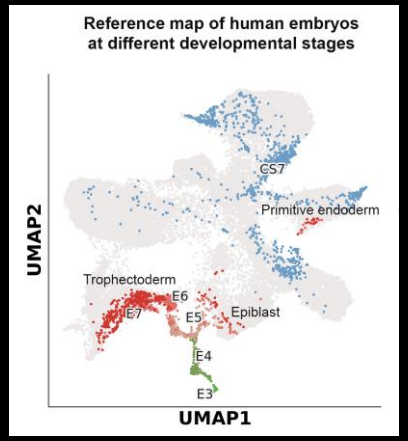




Timing and sequence of lineage specification



Blastocyst-like transciptome



Directional attachment to endometrial cells