Trophoblast differentiation from primate pluripotent cells

Conclusions: although further work is warranted, nonhuman primate pluripotent cells are not immediately equivalent to human cells for modeling trophoblast differentiation. Macaque embryos and TS cells may offer enhanced translatability.

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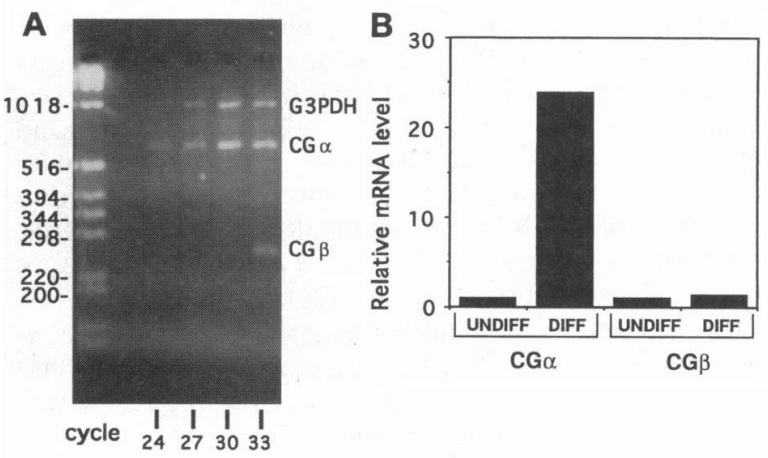
Proc. Natl. Acad. Sci. USA
Vol. 92, pp. 7844–7848, August 1995
Developmental Biology

Isolation of a primate embryonic stem cell line

JAMES A. THOMSON*†, JENNIFER KALISHMAN*, THADDEUS G. GOLOS*, MAUREEN DURNING*, CHARLES P. HARRIS‡, ROBERT A. BECKER*, AND JOHN P. HEARN*§

*The Wisconsin Regional Primate Research Center, §Department of Physiology, School of Medicine, and ‡Cytogenetics Laboratory, State Hygiene Laboratory, University of Wisconsin, 1223 Capitol Court, Madison, WI 53715-1299



Rhesus monkey (and common marmoset) ESC can spontaneously give rise to trophoblasts

Embryonic Stem Cell Lines Derived from Human Blastocysts

James A. Thomson,* Joseph Itskovitz-Eldor, Sander S. Shapiro, Michelle A. Waknitz, Jennifer J. Swiergiel, Vivienne S. Marshall, Jeffrey M. Jones

www.sciencemag.org SCIENCE VOL 282 6 NOVEMBER 1998

Trophoblast formation is also a hallmark of human ESC

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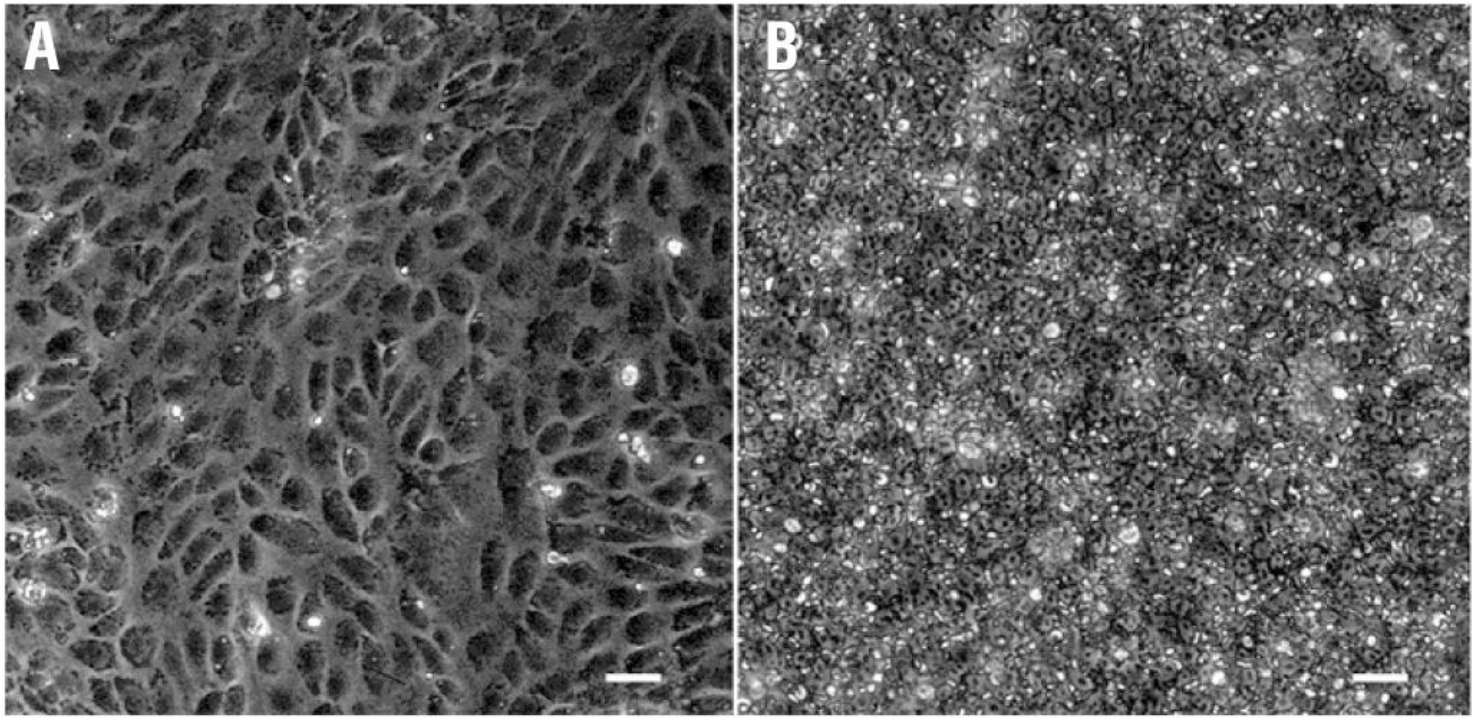
Can human embryonic stem cells provide a system for modeling trophoblast differentiation and placental morphogenesis?

- **Spontaneous differentiation of hES cells to the trophoblast lineage *in vitro* or in teratomas is of low efficiency**

- **Human ES cells can be directed to the trophoblast lineage by extrinsic factors (BMP-4)**



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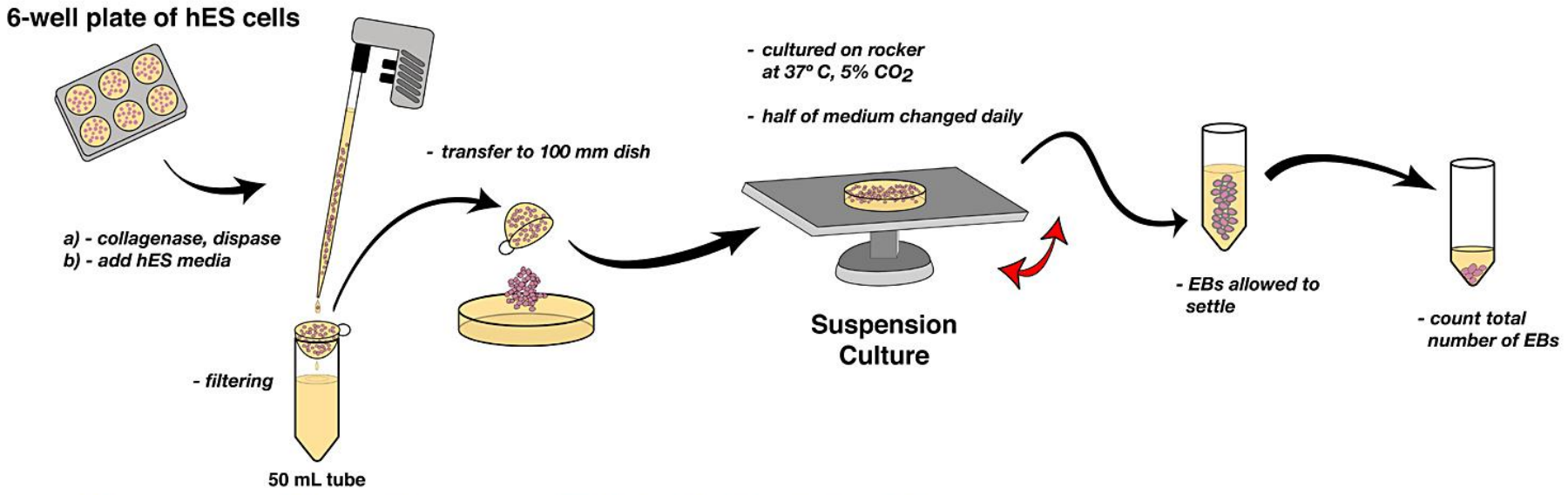
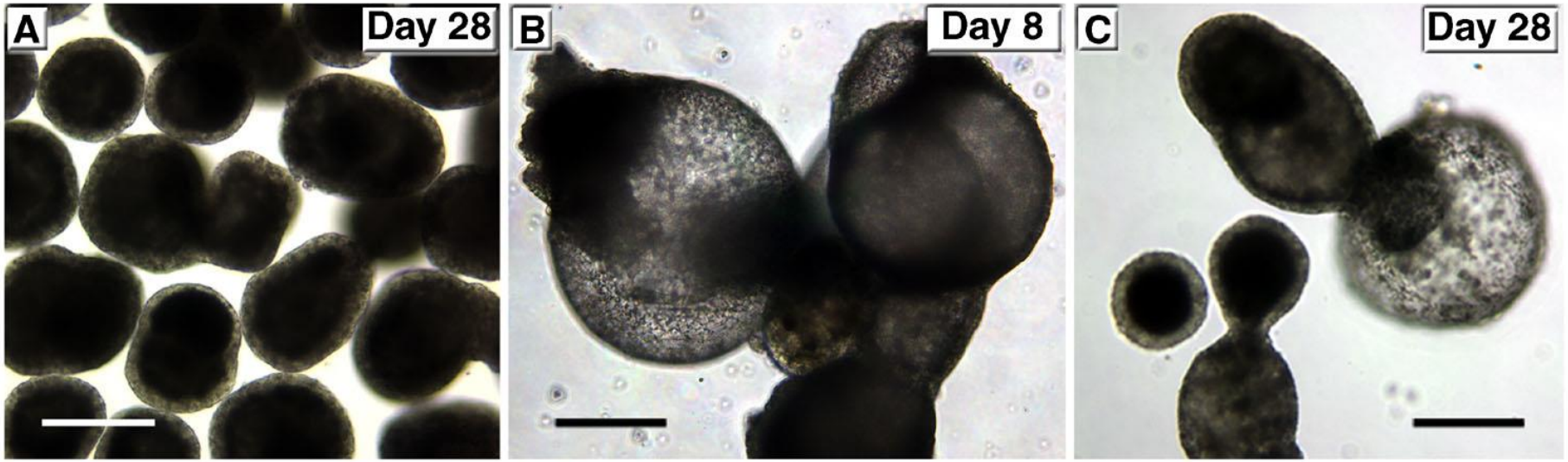
Xu *et al, Nat Biotech* 2002

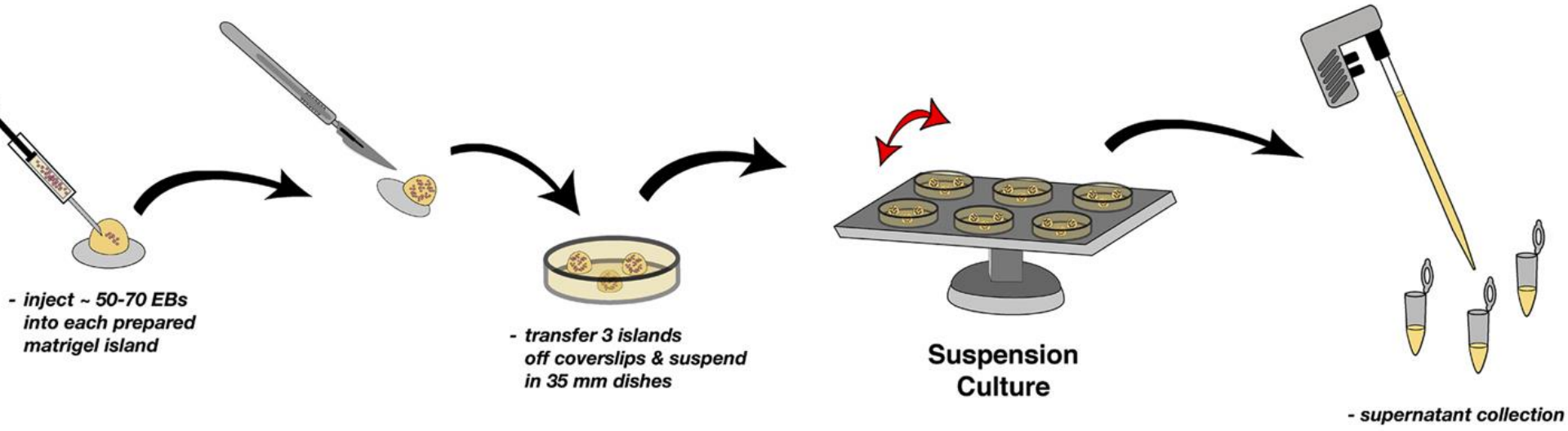
Embryoid body (EB) formation from hESC





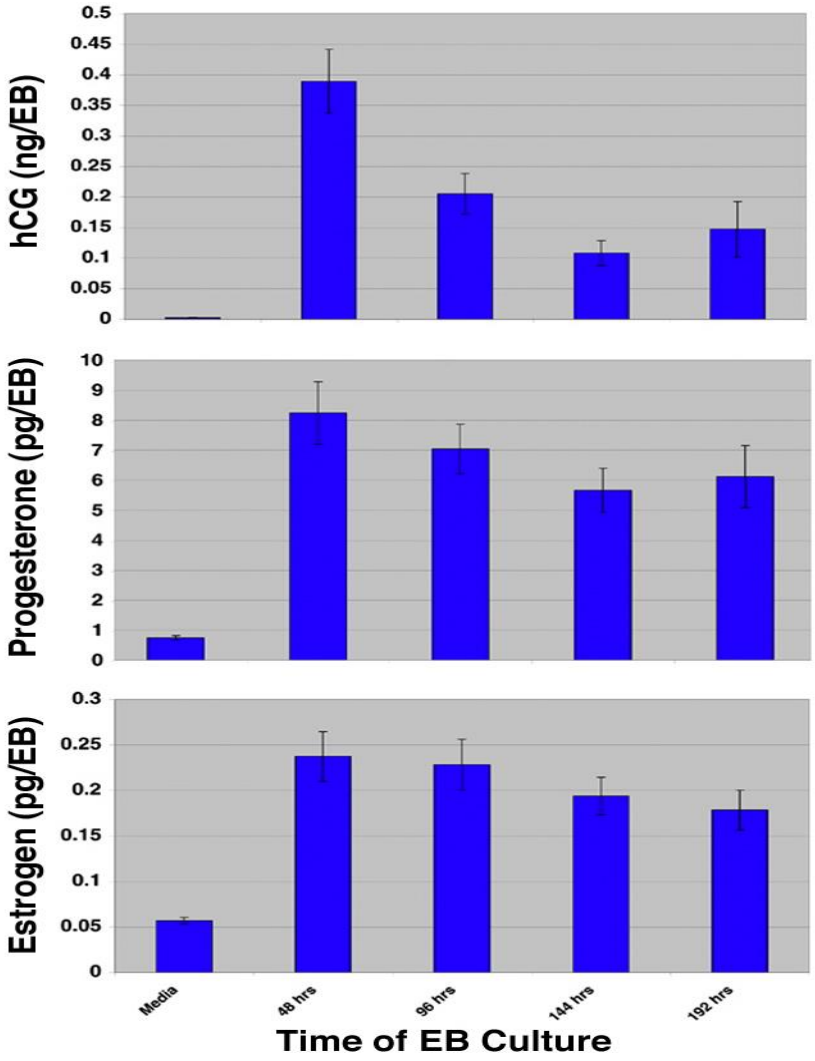
Gerami-Naini *et al*, *Endocrinology* 2004

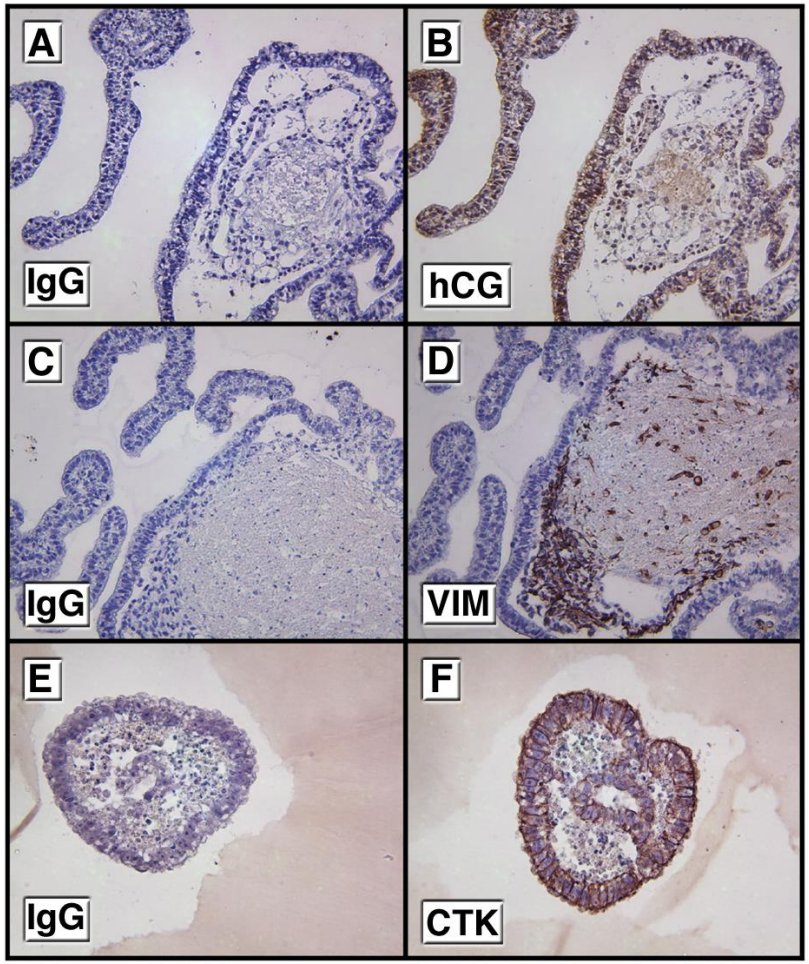
A method for 3-dimensional culture of EBs from hESC in extracellular matrix



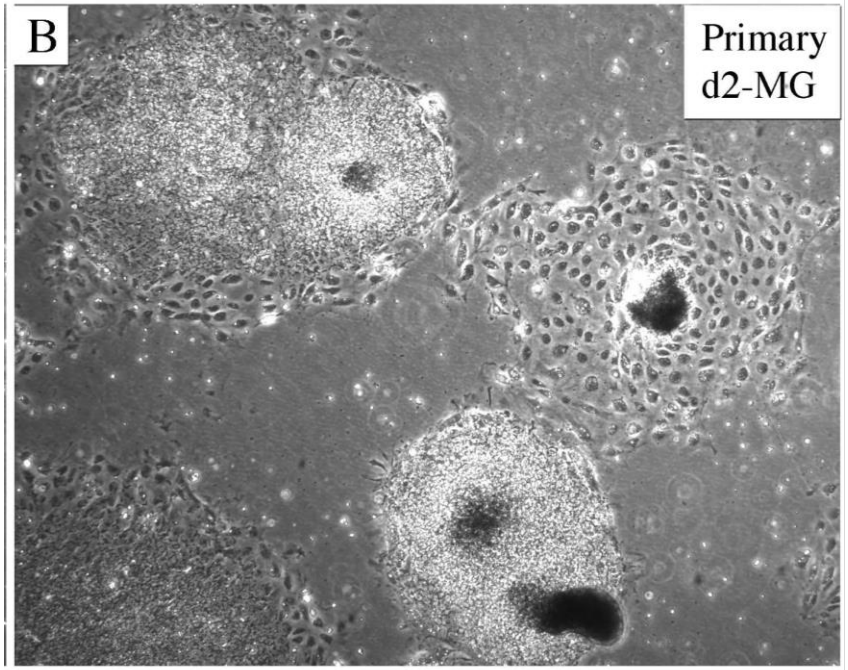
Gerami-Naini *et al*, *Endocrinology* 2004

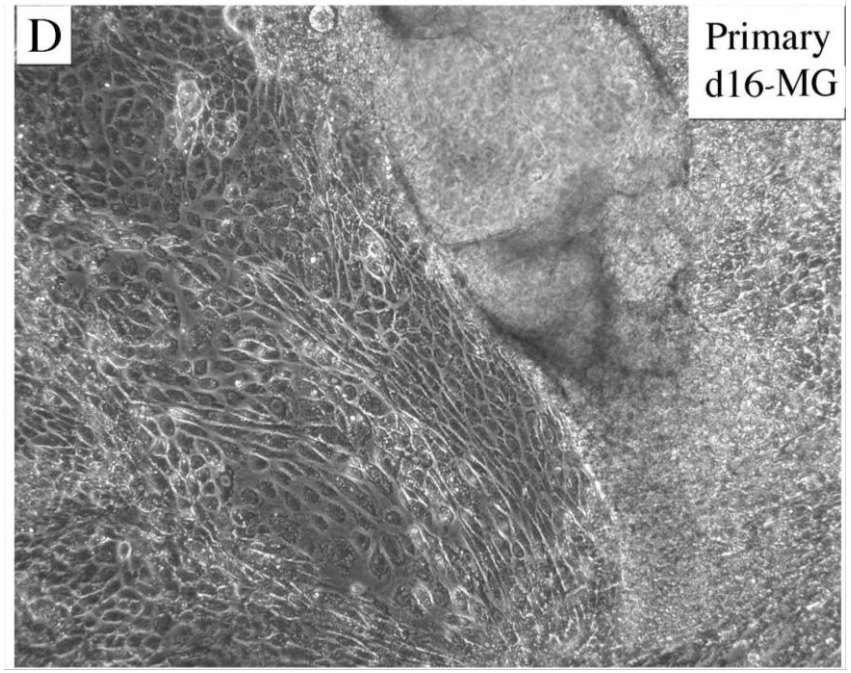
Embryoid bodies in suspension culture secrete protein and steroid hormones characteristic of primate placental function

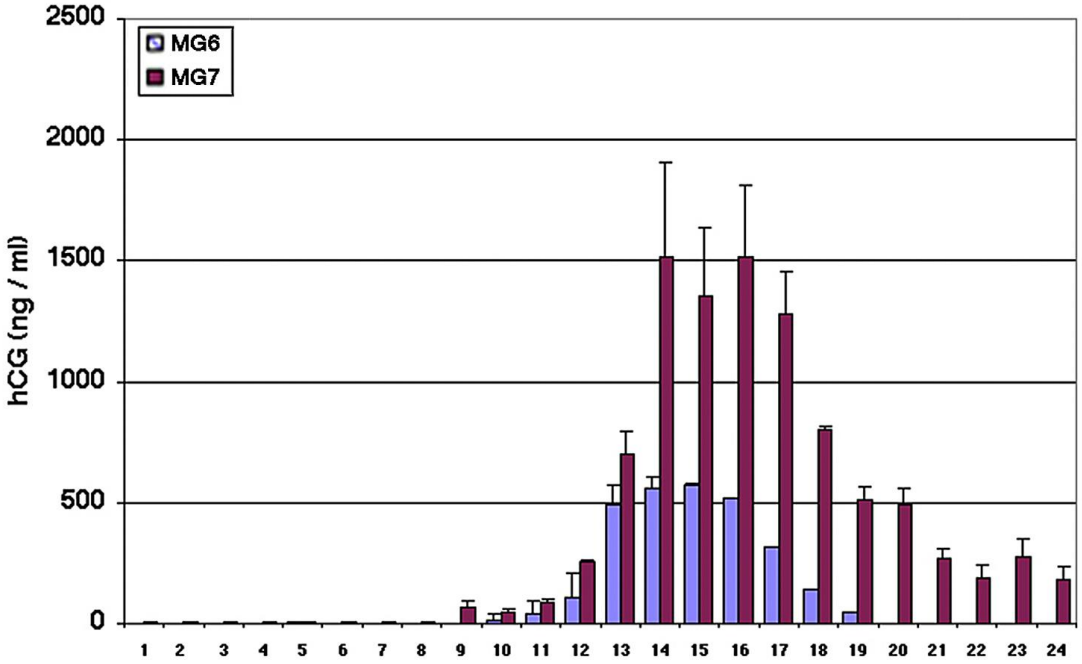




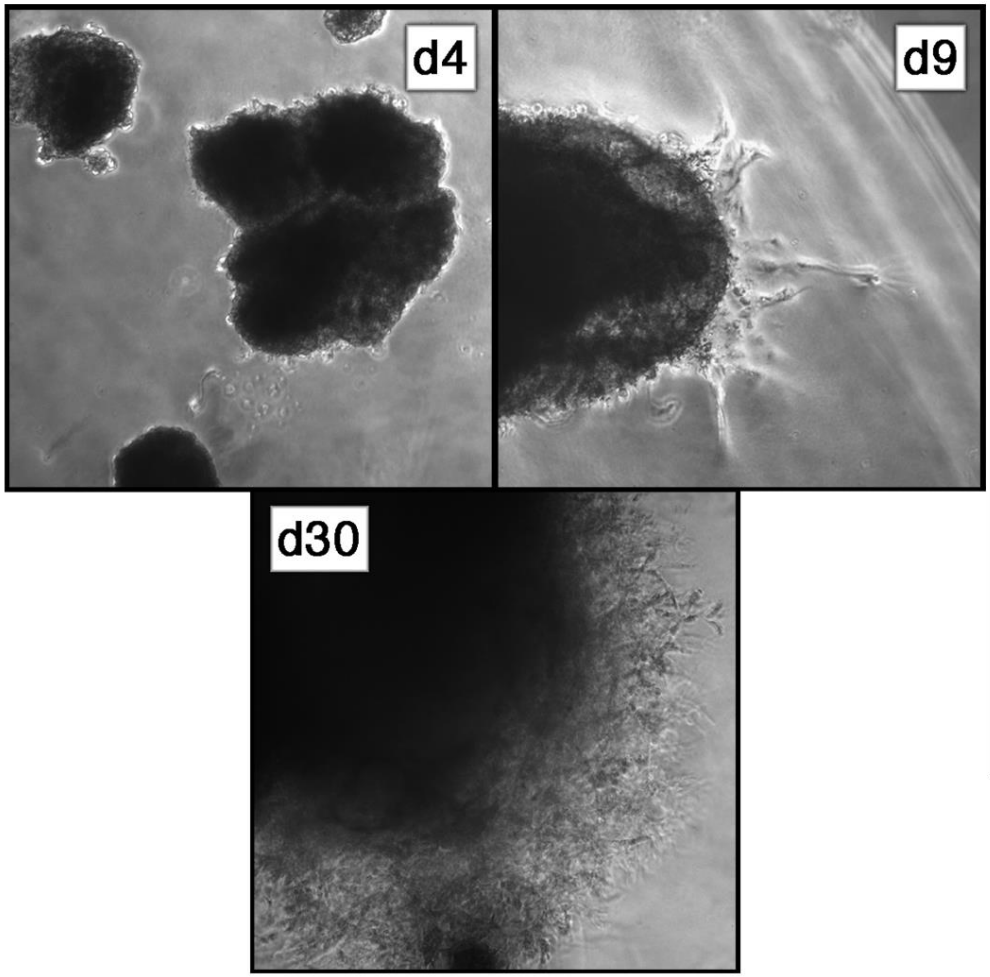
Gerami-Naini *et al*, 2004

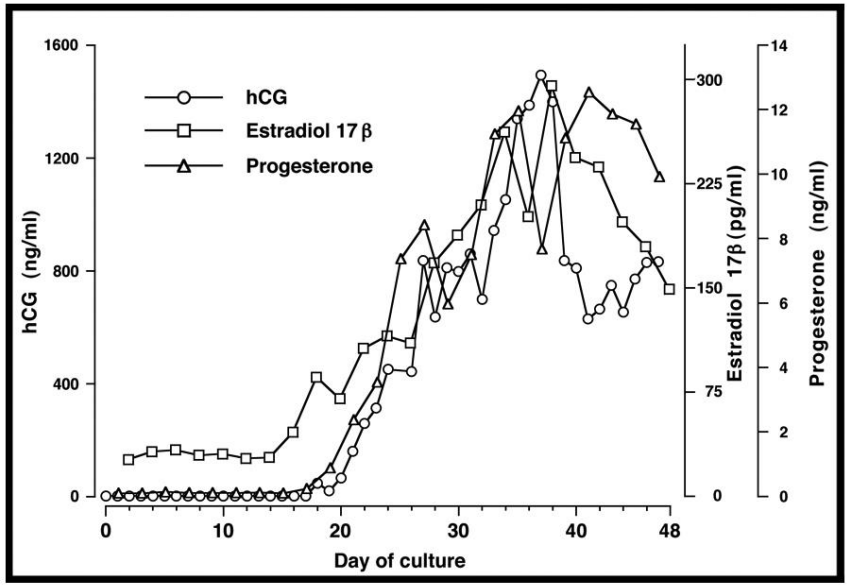






Gerami-Naini *et al*, *Endocrinology* 2004

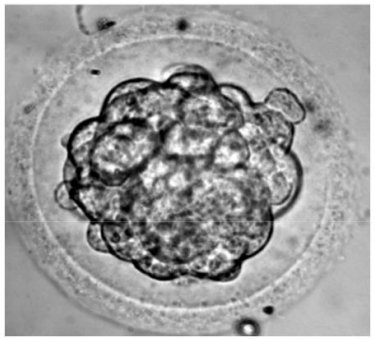


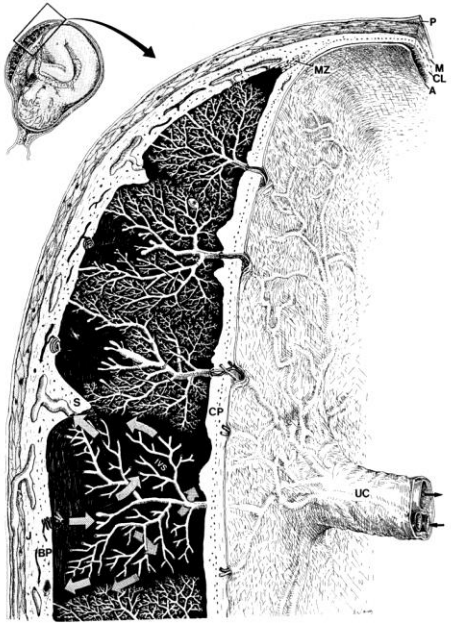


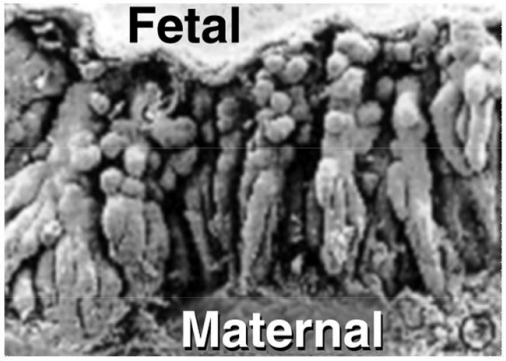
Embryoid bodies growing in a 3-dimensional Matrigel scaffold initiate sustained chorionic gonadotropin and steroid hormone secretion

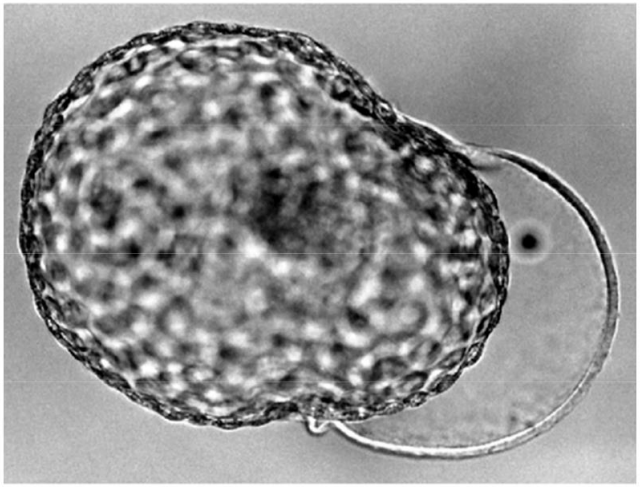
Golos et al Sem Reprod Med 2006

Adaptation of the hESC paradigms to *in vivo* implantation

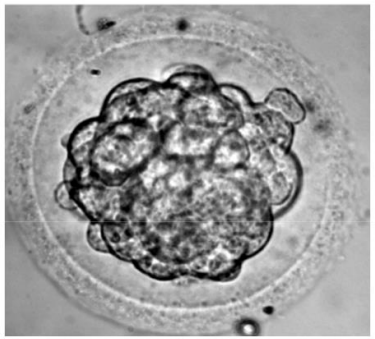


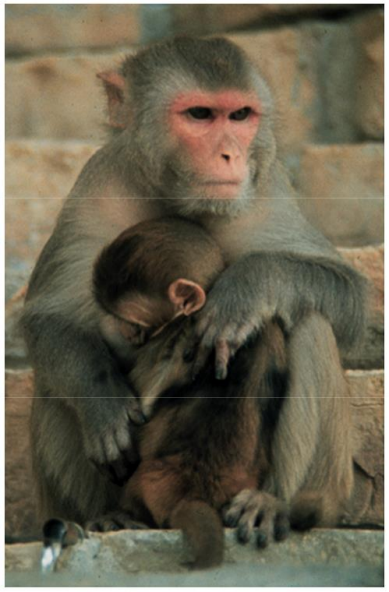


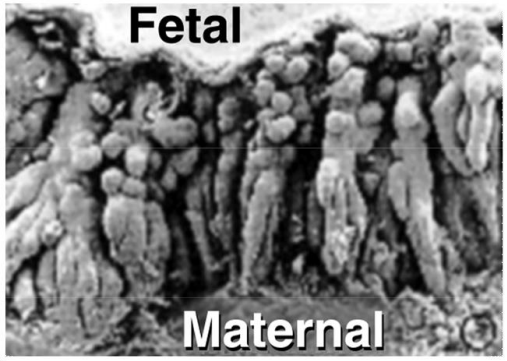


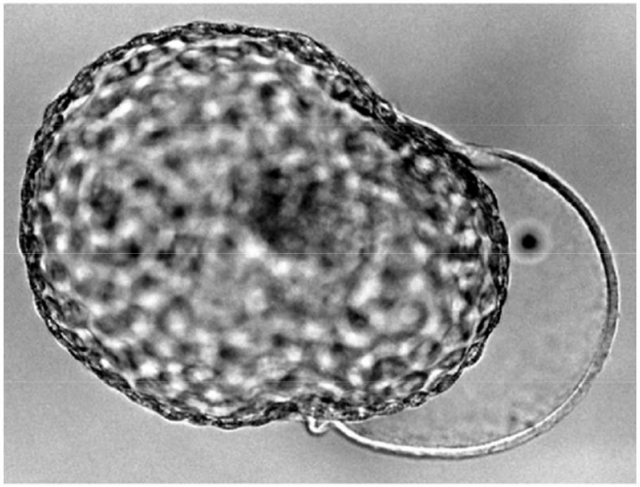


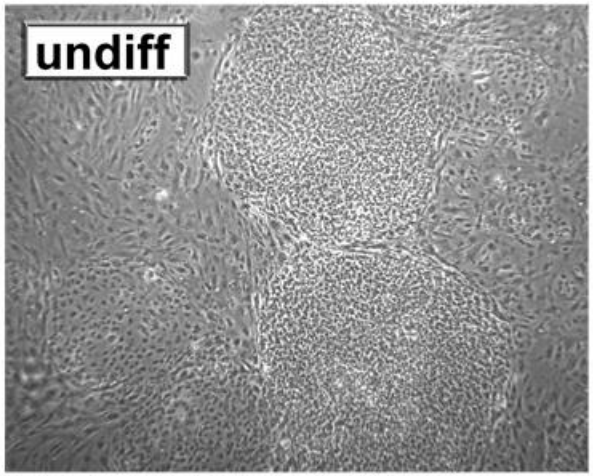
Adaptation of the hESC paradigms to *in vivo* implantation

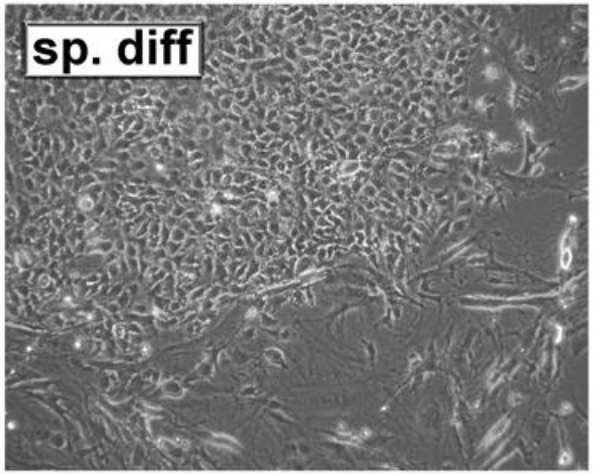


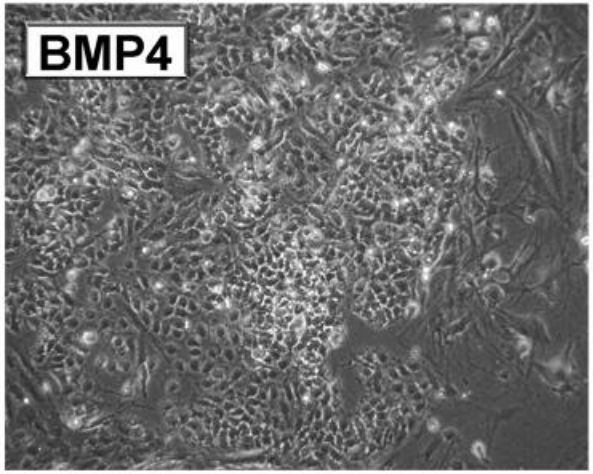






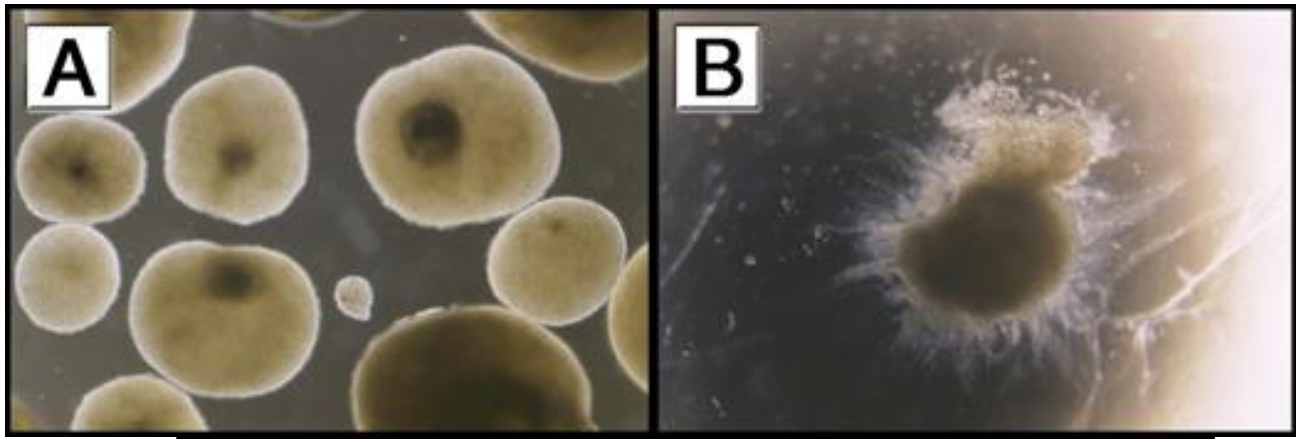


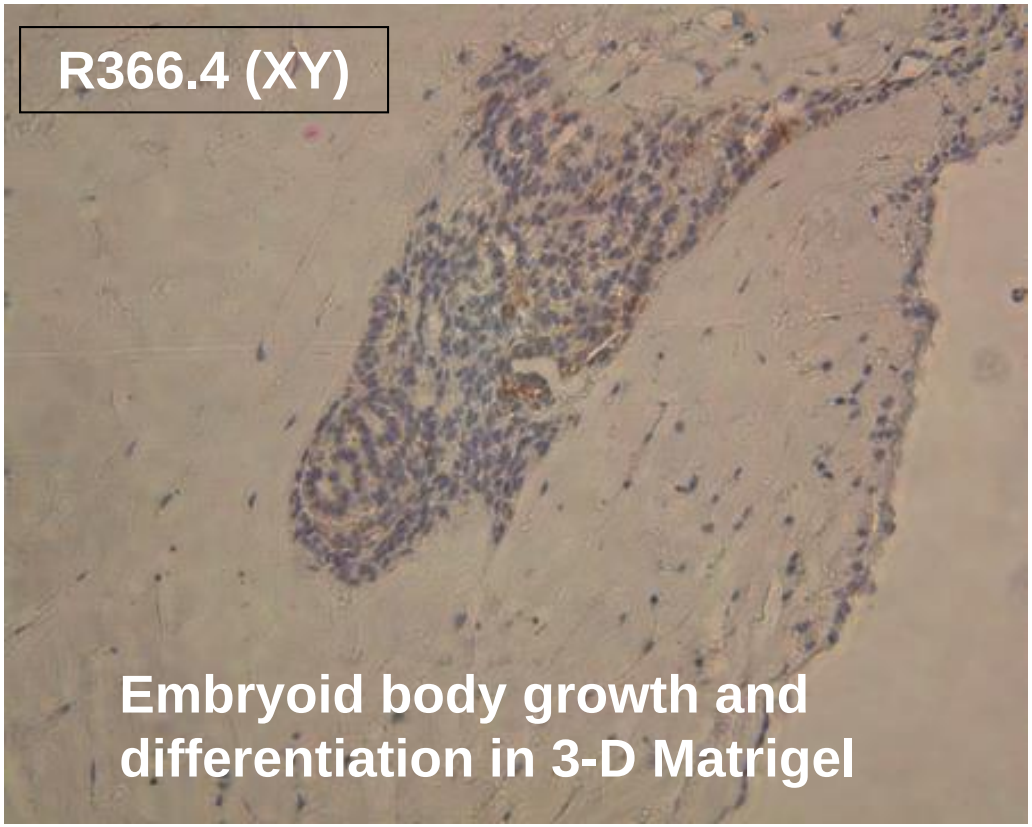




BMP4-induced differentiation

Rhesus ESC and trophoblast differentiation paradigms

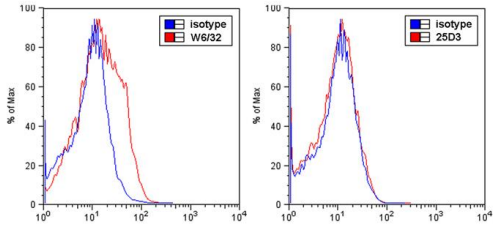




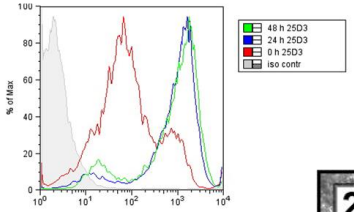
Neither BMP4 nor 2-D or 3-D Matrigel culture stimulated mCG or progesterone secretion.

Cell line	Karyotype	Teratomas	"Mother"	"Father"
R278	42 XY	Yes	R78148	R85098
R366	42 XY	Yes	R78148	R87084
R394	42 XX	Yes	R87097	R83095
R420	42 XX	Yes	R79016	R83095
R456	42 XX	Yes	R79016	R83095

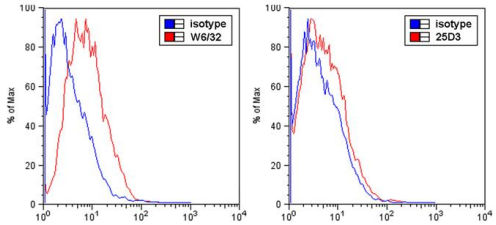
Undifferentiated R366.4



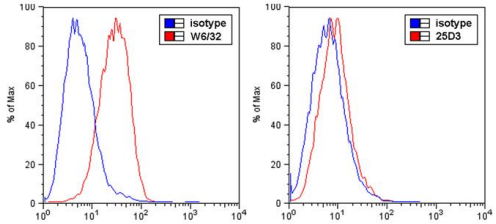
Mamu-AG Trophoblasts



Spontaneously Differentiated R366.4

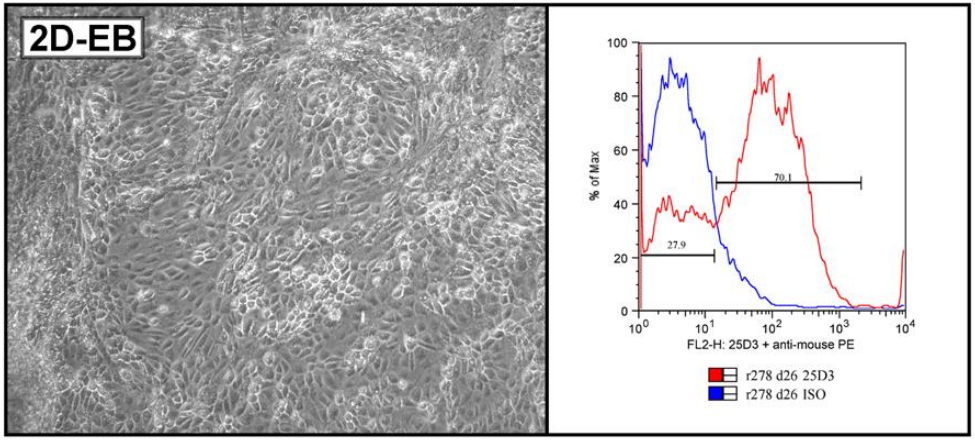


BMP4-Treated R366.4



W6/32 (pan-MHC) | 25D3 (trophoblast specific)

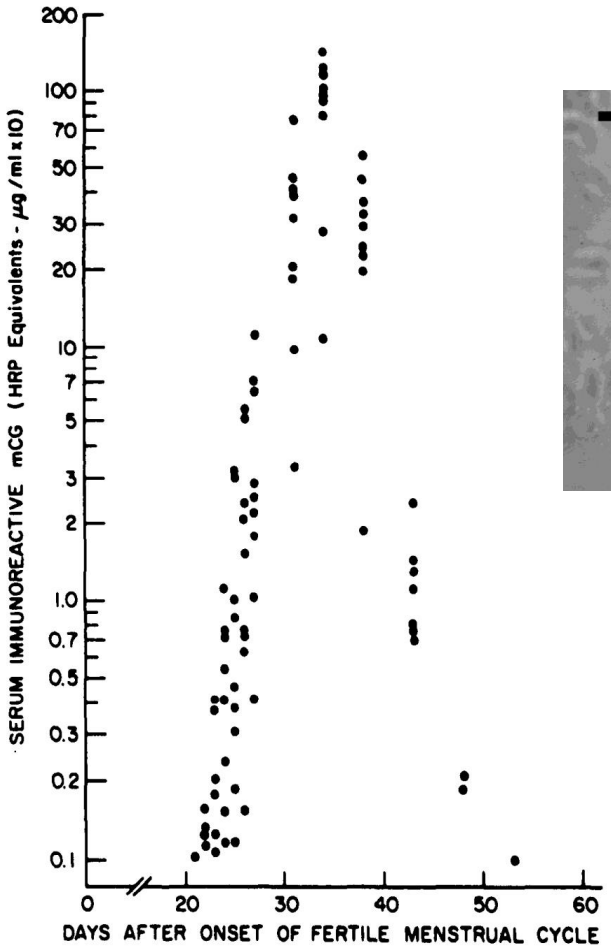
Non-endocrine differentiation?

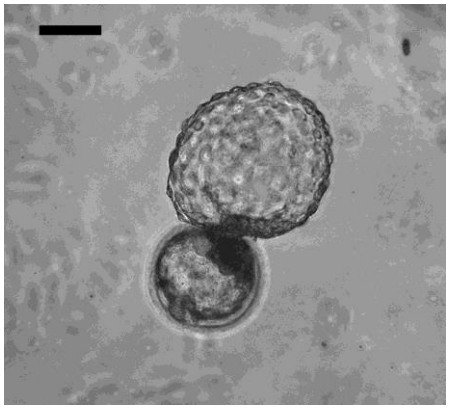


R278.5 ESC outgrowths express placenta-specific Mamu-AG with differentiation in the 2D EB paradigm

Garthwaite, Dambaeva et al, unpublished

Perhaps the macaque placental endocrine profile is not appropriate for these approaches?

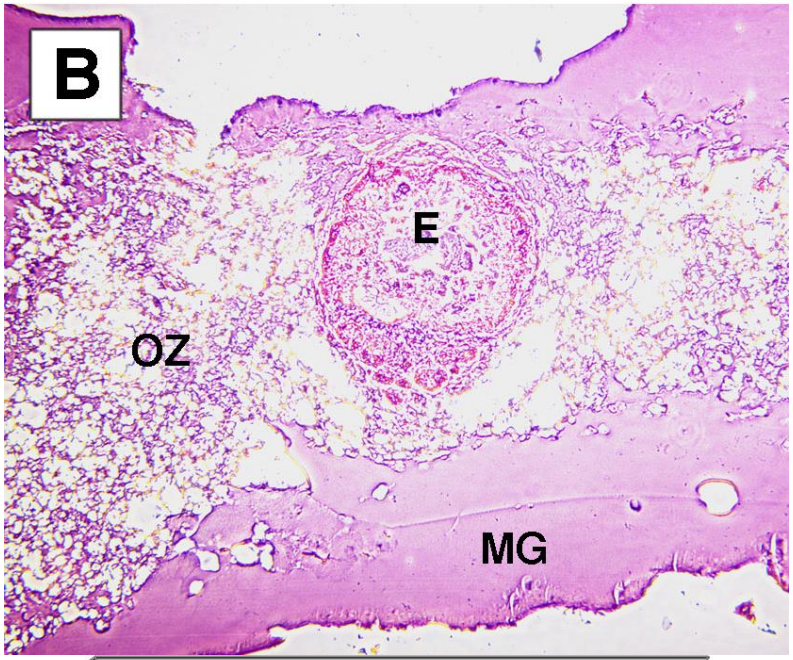


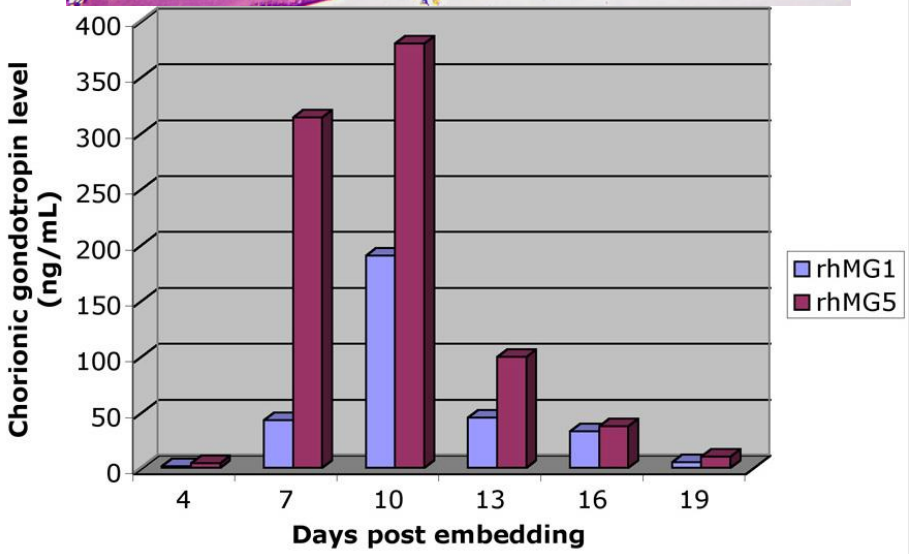


Specific Radioimmunoassay of Chorionic Gonadotropin During Implantation in Rhesus Monkeys

GARY D. HODGEN, WILLIAM W. TULLNER, JUDITH L. VAITUKAITIS, DARRELL N. WARD,* AND GRIFF T. ROSS

JCEM, 1974

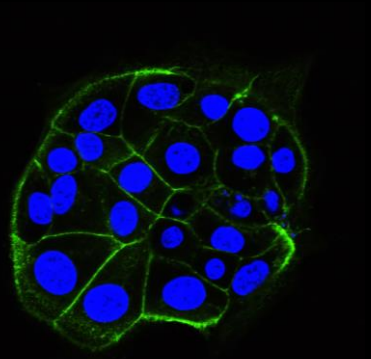




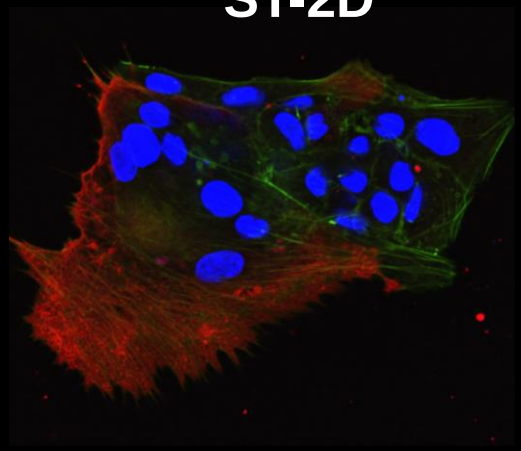
Chang *et al, REB Online* 2018

TSC differentiated to STB secrete mCG

TSC



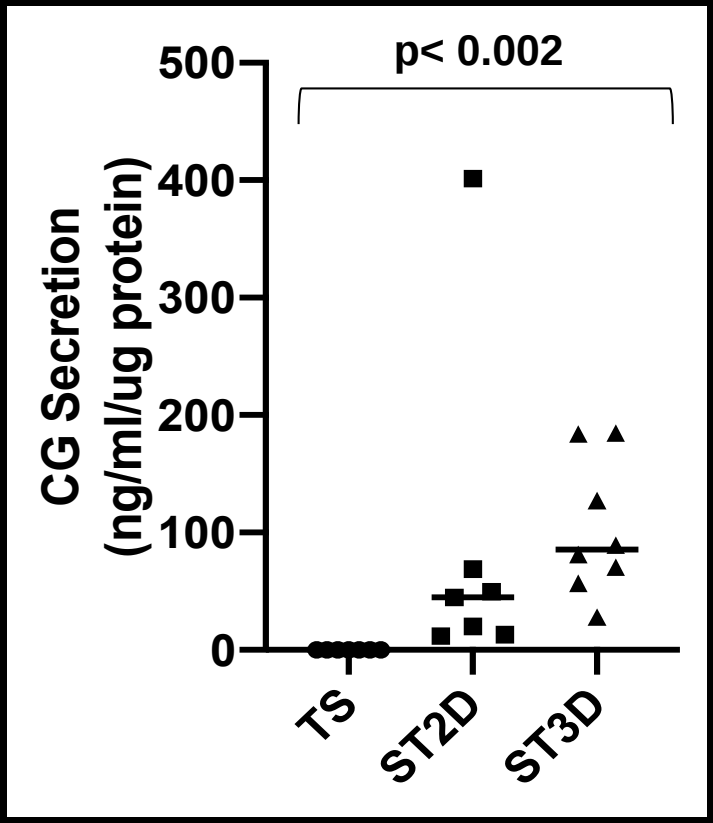
ST-2D



DAPI: Nuclear stain

Phalloidin: F-actin

Monkey Chorionic Gonadotropin



Schmidt *et al*, in preparation

Key questions

How well can nonhuman primate embryo model systems predict the function of systems made with human cells? It depends.

At this time, rhesus pluripotent cells are not transparently equivalent to human cells for trophoblast differentiation.

Differentiation paradigms? Receptor complement? Feeder cells? Trophoblast differentiation niche? maternal factors? genetic background? Organoid aggregates with placental stroma?

Rhesus IVF blastocysts implant in vitro, secrete stereotypical placental hormones, and invasive trophoblasts invade/degrade a Matrigel environment.

Ma *et al,* Science 366:eaax7890, Nov. 15 2019
Niu *et al,* Science 366:eaaw5754, Nov. 15 2019

Rhesus TS cells form mCG-secreting multinuclear STB and putative EVT express placenta-specific MHC I.

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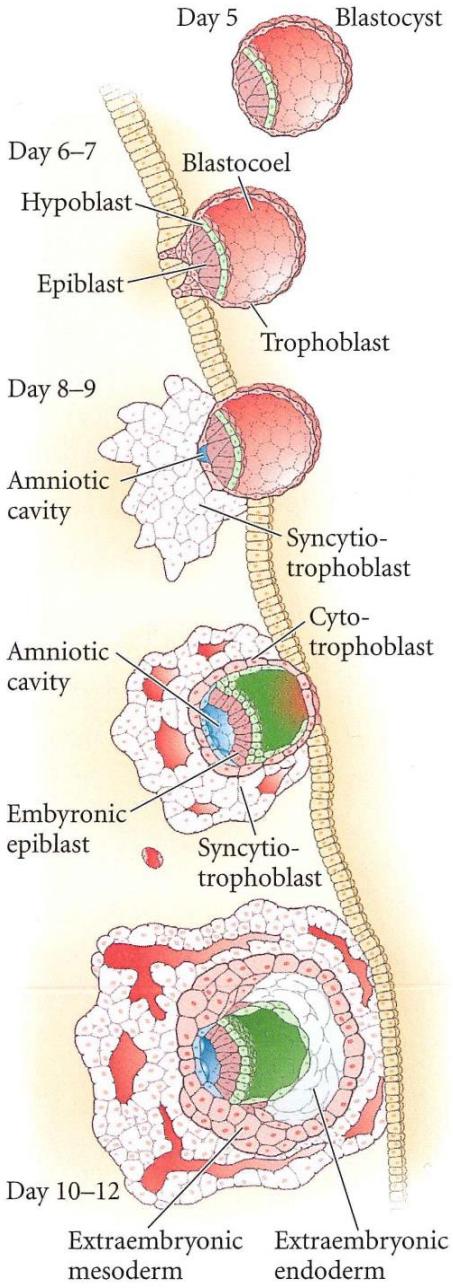
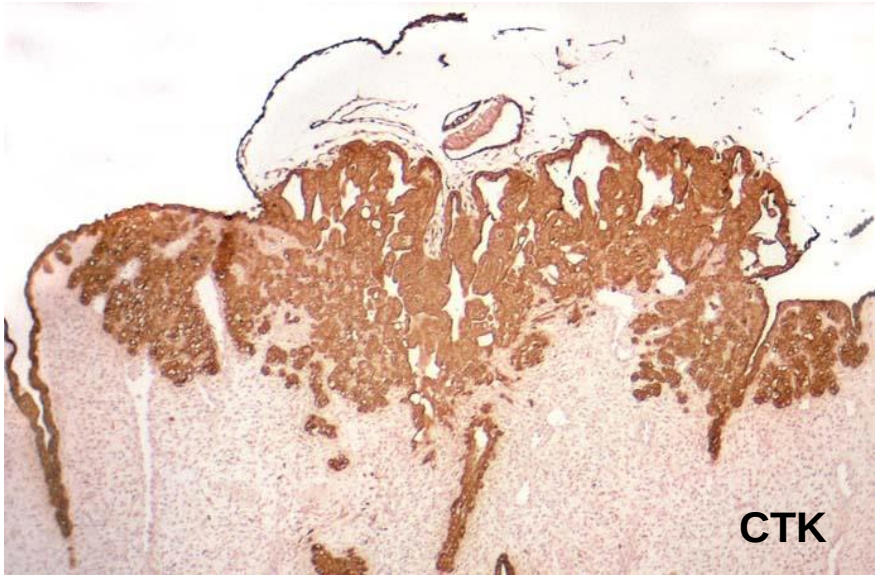
Human implantation



What scientific questions require studying the human embryo?



Day 12 rhesus implantation, courtesy Allen Enders

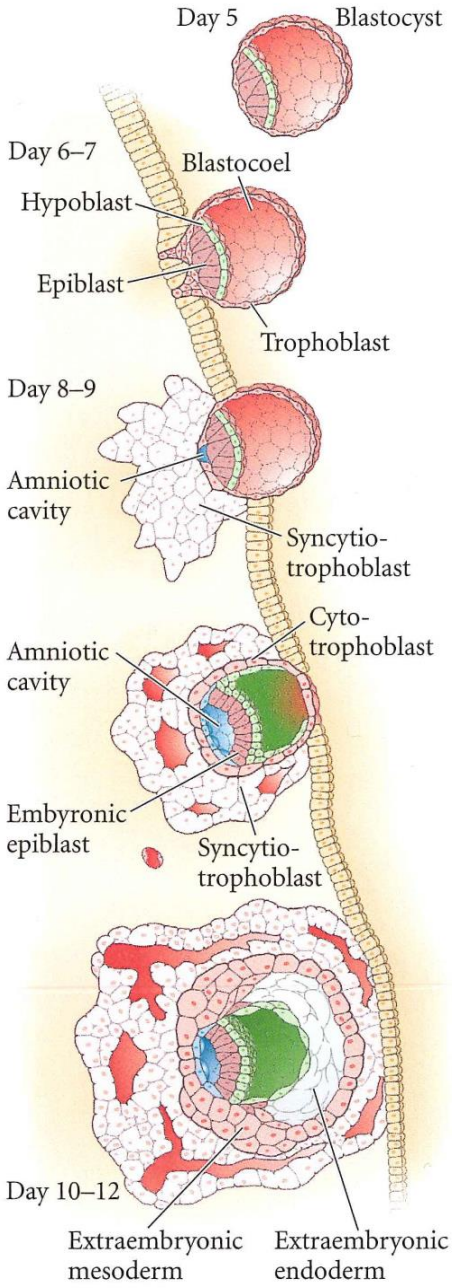
Dynamics of trophoblast differentiation in peri-implantation–stage human embryos

Rachel C. West[a,1], Hao Ming[b,1], Deirdre M. Logsdon[a,1], Jiangwen Sun[c], Sandeep K. Rajput[a], Rebecca A. Kile[a], William B. Schoolcraft[a], R. Michael Roberts[d,e,2], Rebecca L. Krisher[a], Zongliang Jiang[b,2], and Ye Yuan[a,2]

PNAS 116: 22635-44, Nov. 5 2019

What information can be gathered from the peri-implantation period in other species?

Human implantation



The opportunity to interrogate the embryonic events critical for *in vivo* placentation (villous morphogenesis, endovascular tb migration and vessel remodeling) through preimplantation embryo manipulation is the strength of the NHP model.

Enders, Placenta, 2007

What information can be gathered from the peri-implantation period in other species?

Team Placenta at UW-Madison

Ted Golos

- **Maureen Durning, B.S.**
- **Mark Garthwaite, B.S.**
- **Oksana Dovzhenko, M.D.**
- **Behzad Gerami-Naini, Ph.D.**
- **Arthur Chang, Ph.D.**
- **Gennadiy Bondarenko, M.D., Ph.D.**
- **Svetlana Dambaeva, M.D., Ph.D.**
- **Leah Pollastrini, M.S.**
- **Maria Giakoumopoulos, Ph.D.**
- **Greg Wiepz, Ph.D.**
- **Jenna Kropp Schmidt, Ph.D.**

James Thomson, V.M.D., Ph.D.

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Pathology, Animal Care, Precision Medicine, Veterinary and SPI Services.

Bryce Wolfe, Ph.D.

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