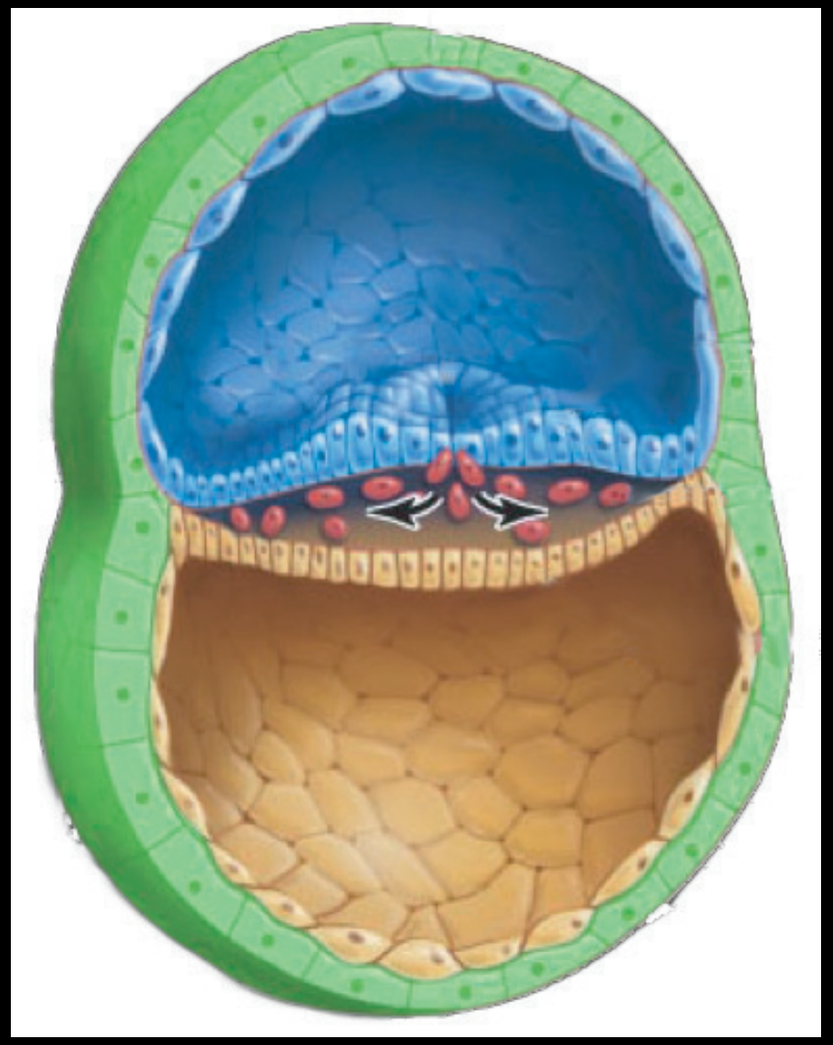
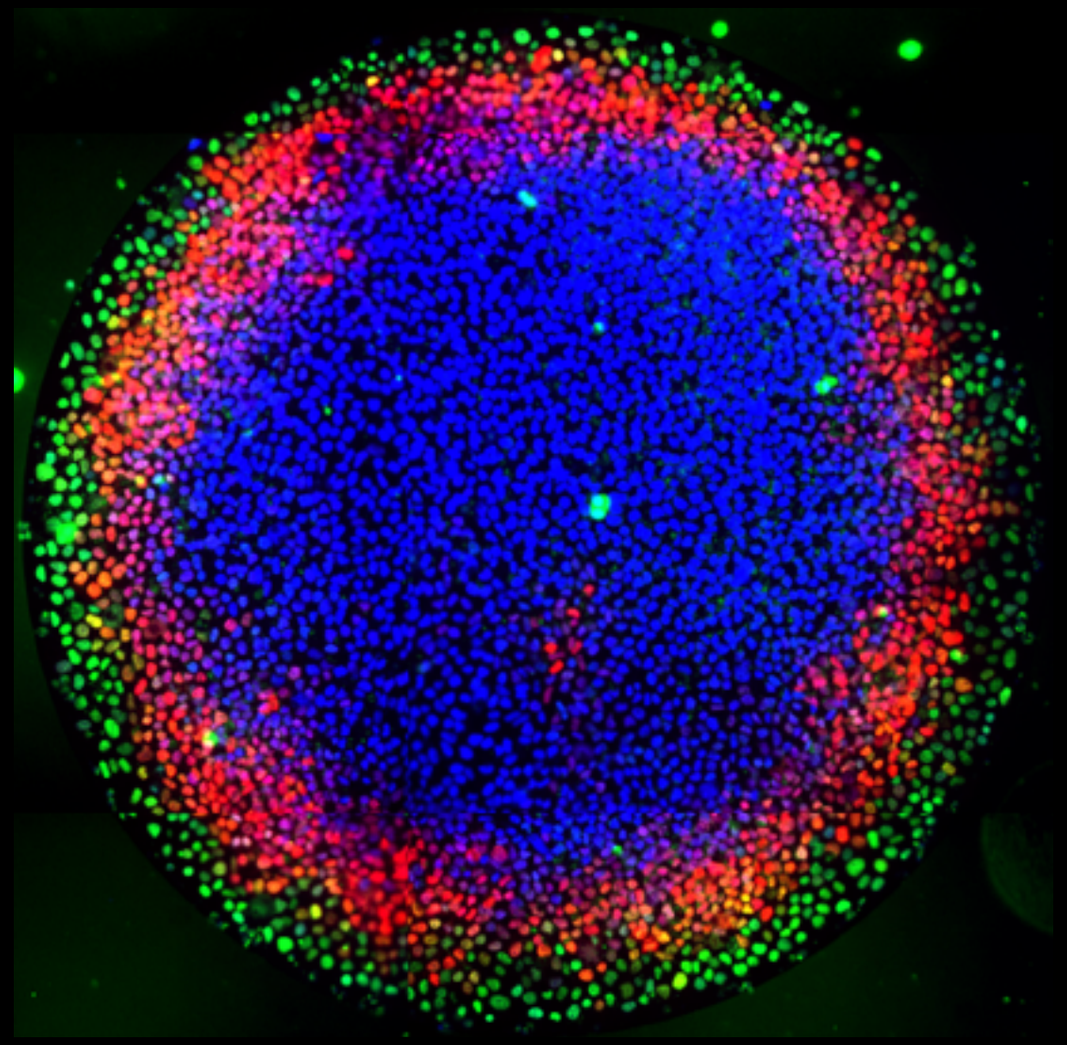
Mammalian development and embryonic stem cells



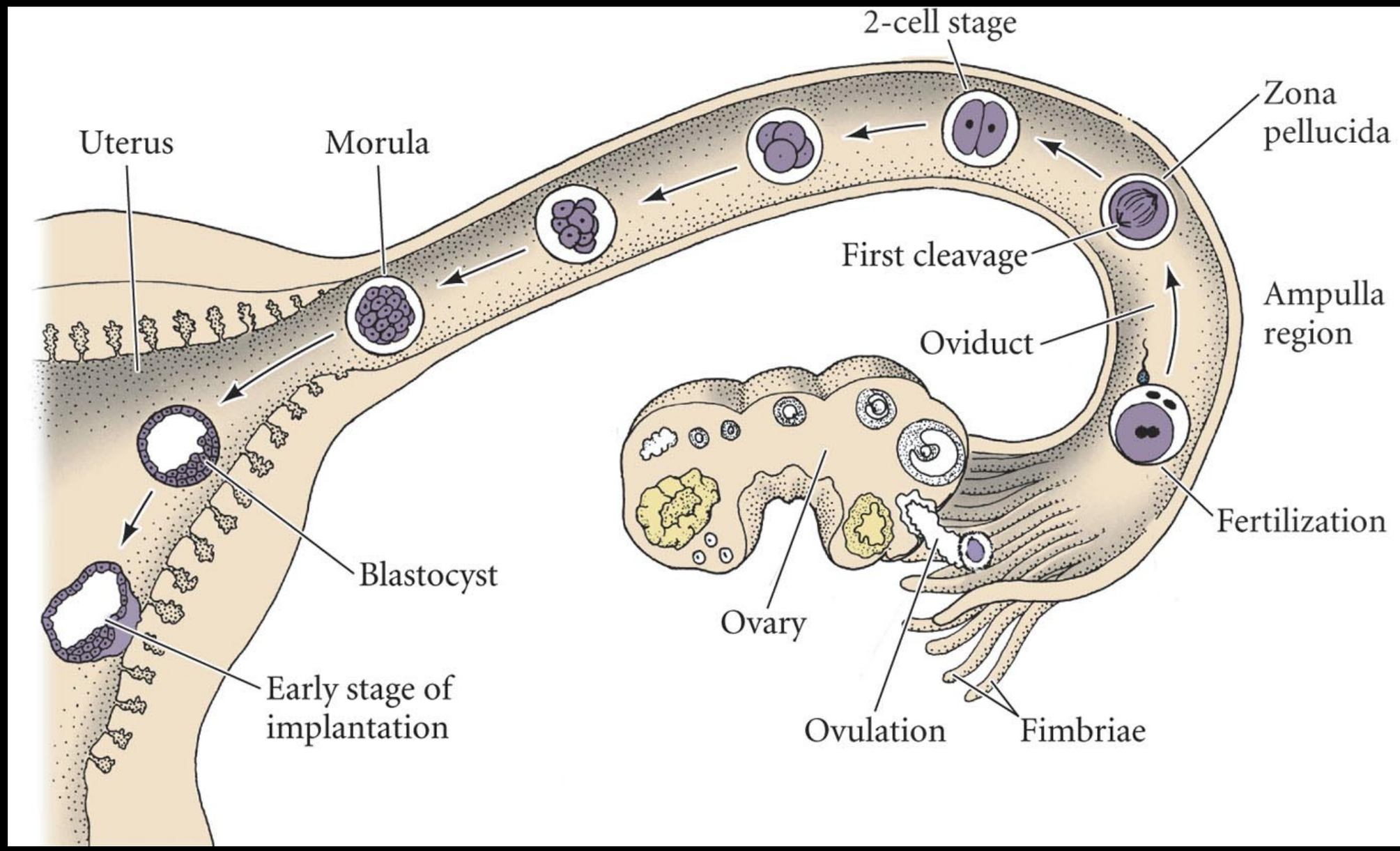


Aryeh Warmflash

KITP - morpho16

7/29/16

Early mammalian development



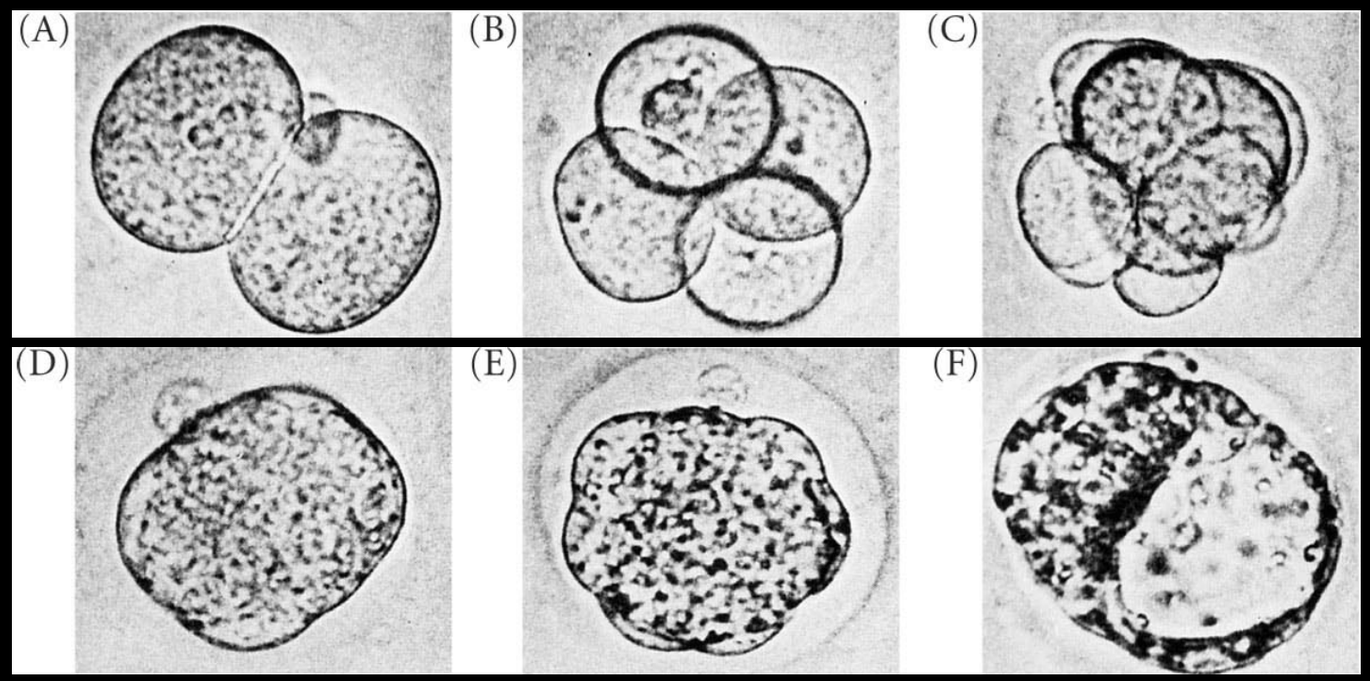
Early cleavage stages

<u>Unique nature of mammalian cleavage</u>

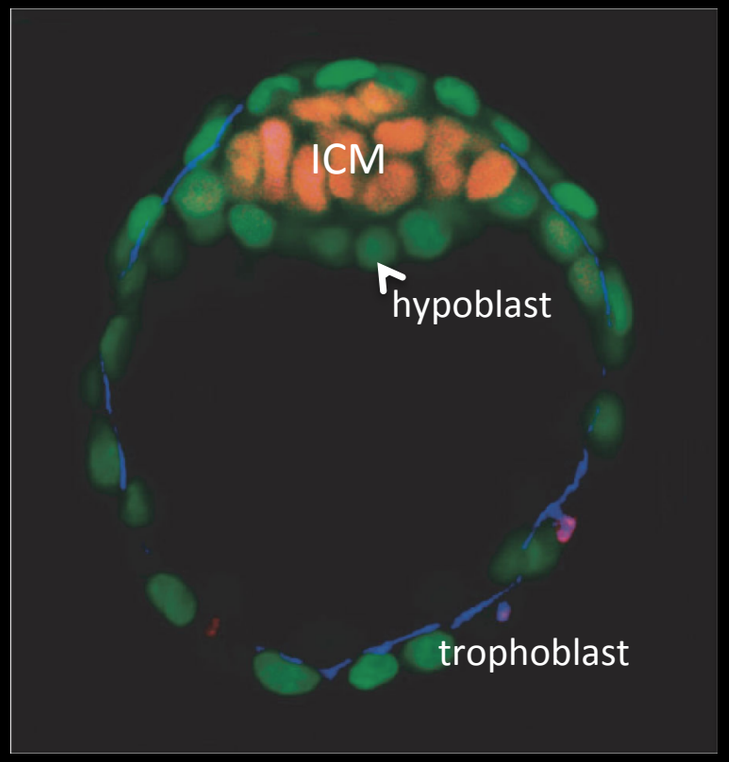
-Cleavages are slow (12-24 hrs apart).

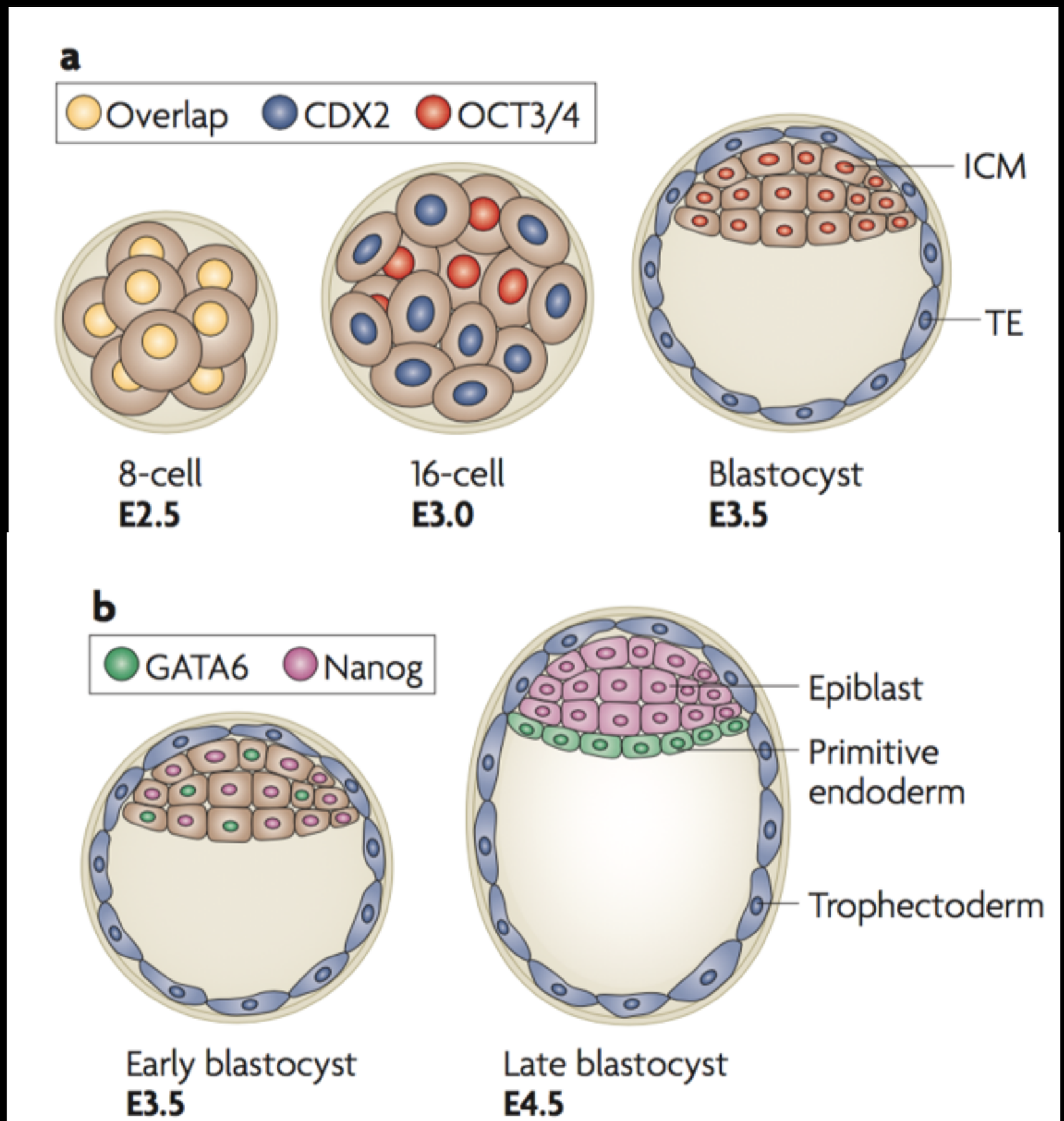
-Zygotic genome is activated early (2-4 cell stage).

-Lack of maternally generated prepattern



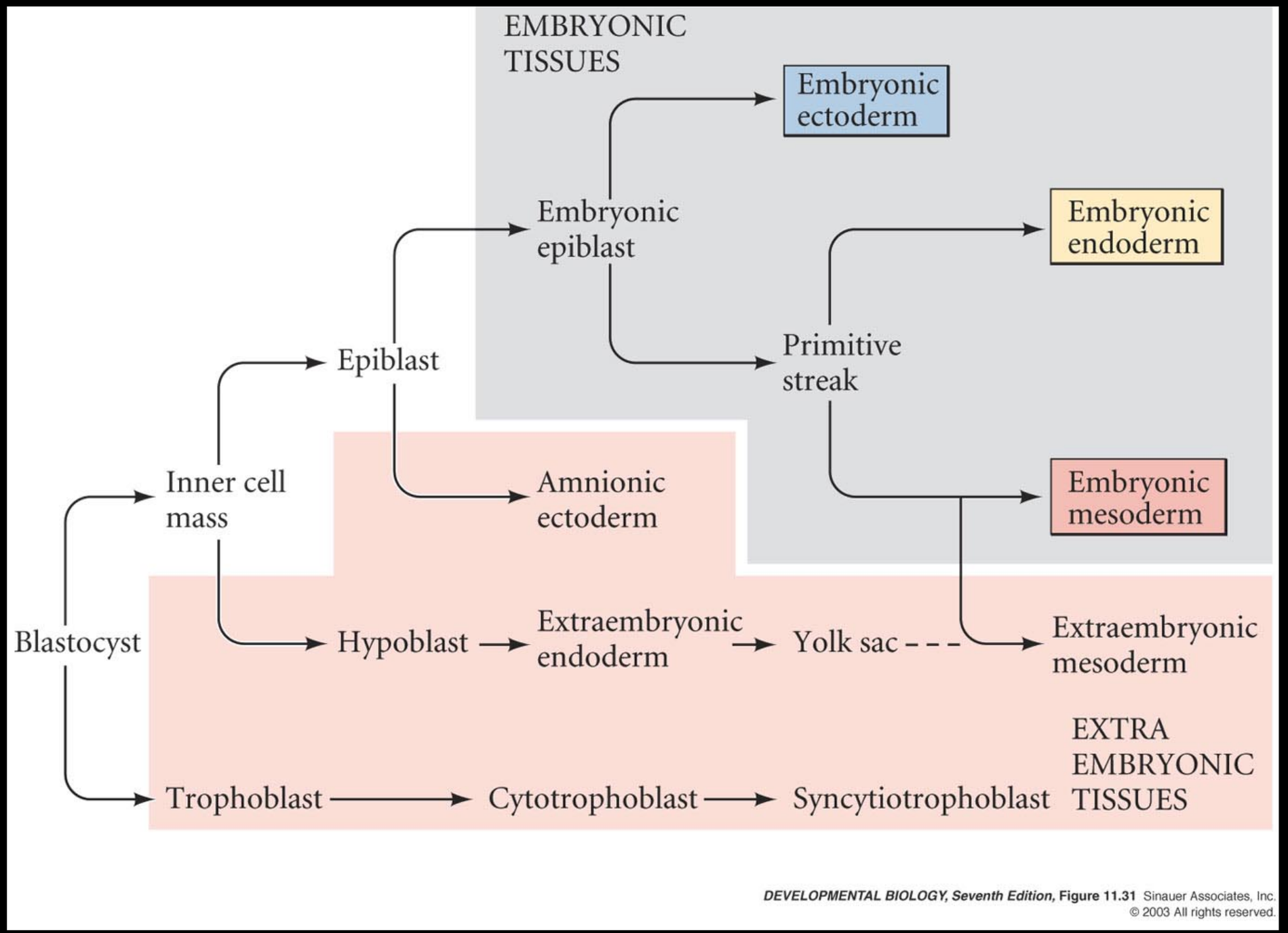
Pregastrulation development





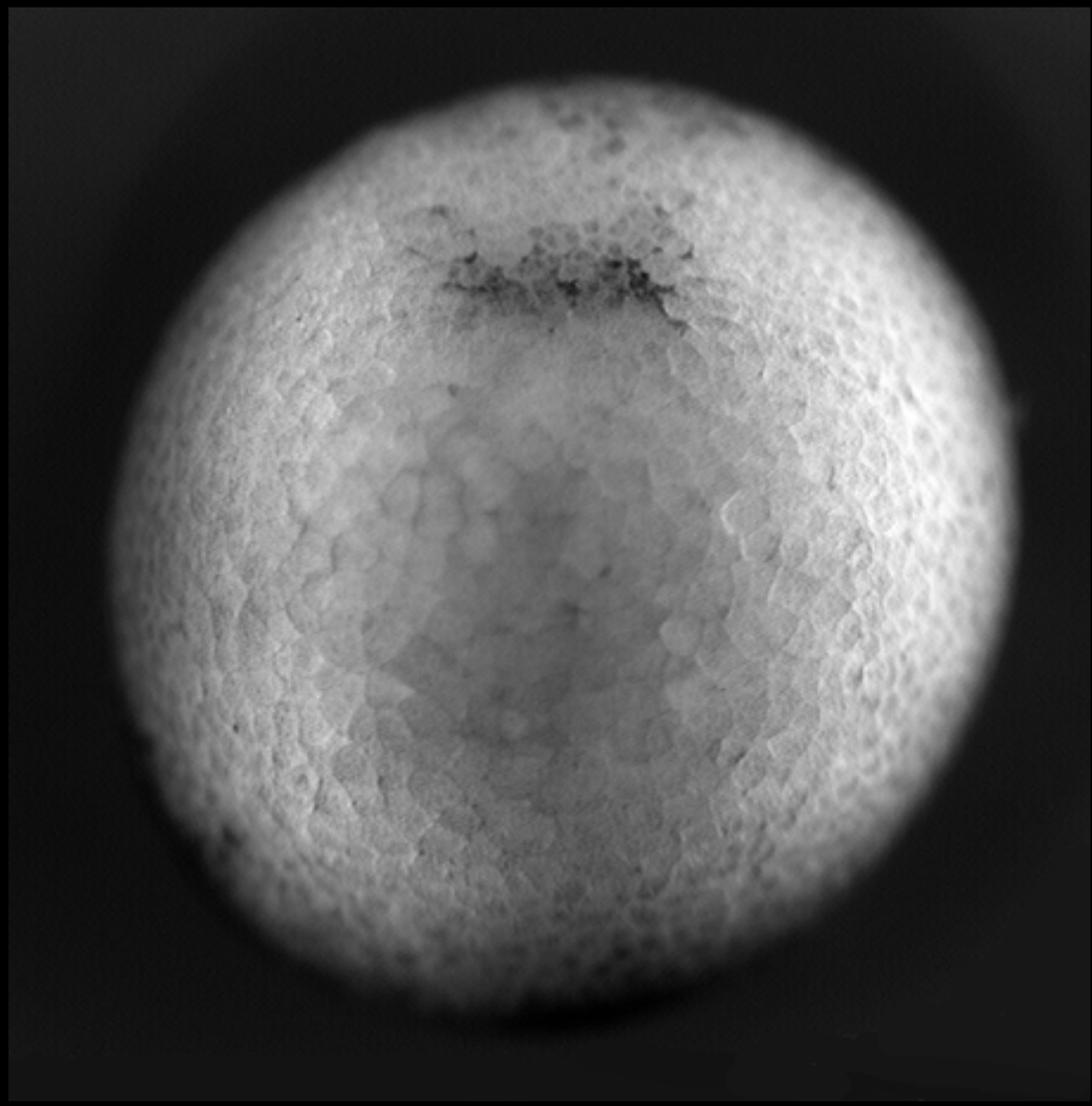
Arnold & Robertson
Nat Rev Mol Cell Biol 2009

Summary of lineage decisions in the mammalian embryo



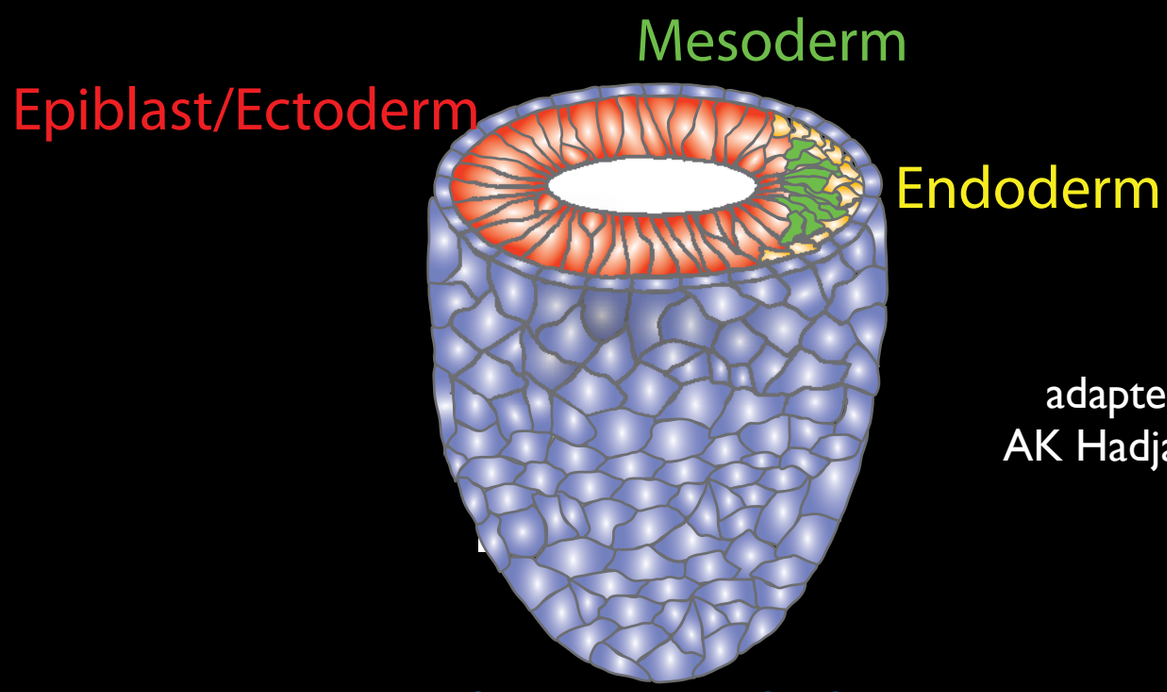
DEVELOPMENTAL BIOLOGY, Seventh Edition, **Figure 11.31** Sinauer Associates, Inc.

Gastrulation

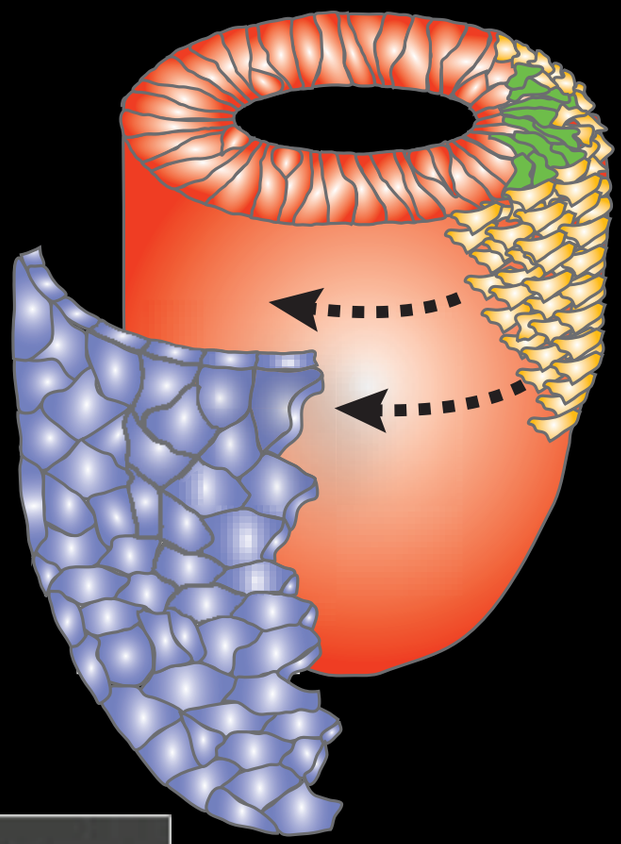


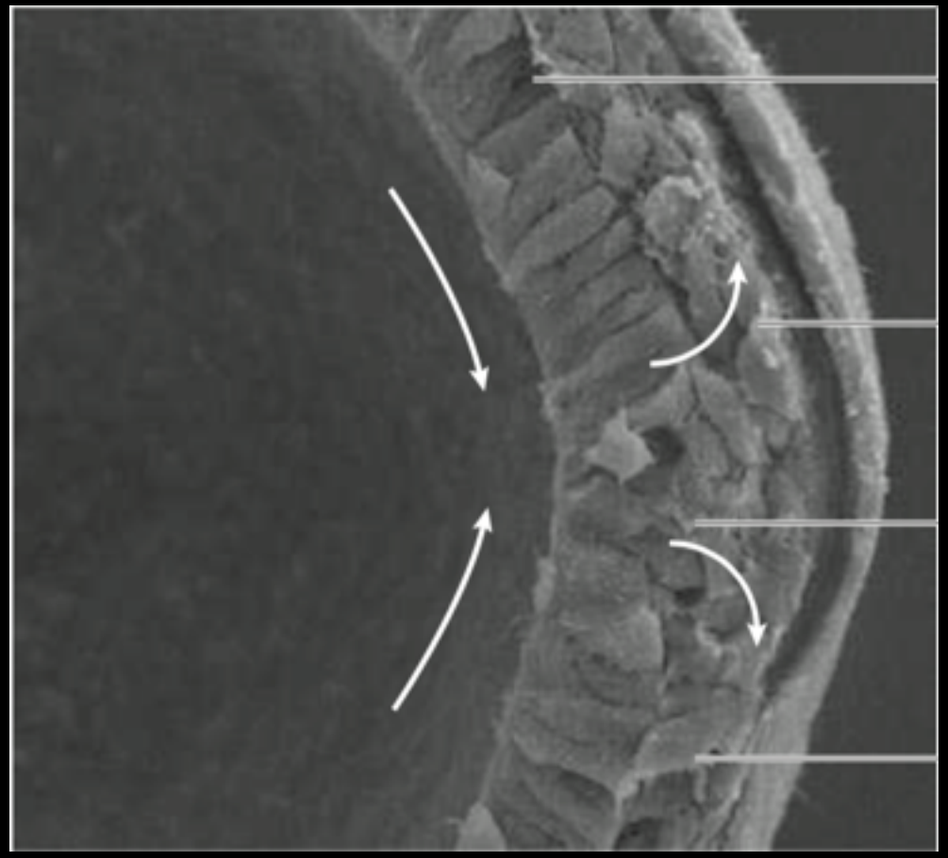
D Shook

Gastrulation - creating the three germ layers



adapted from
AK Hadjantonakis

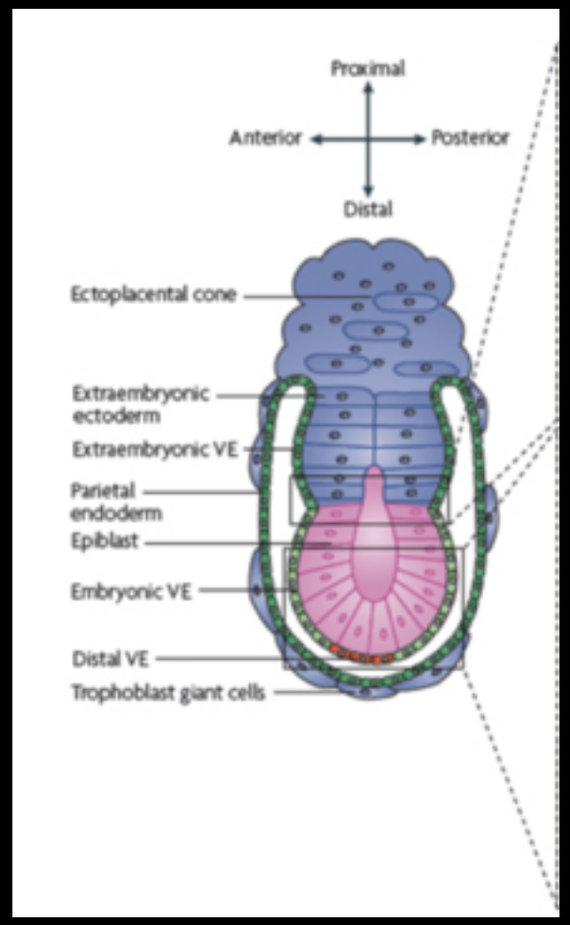


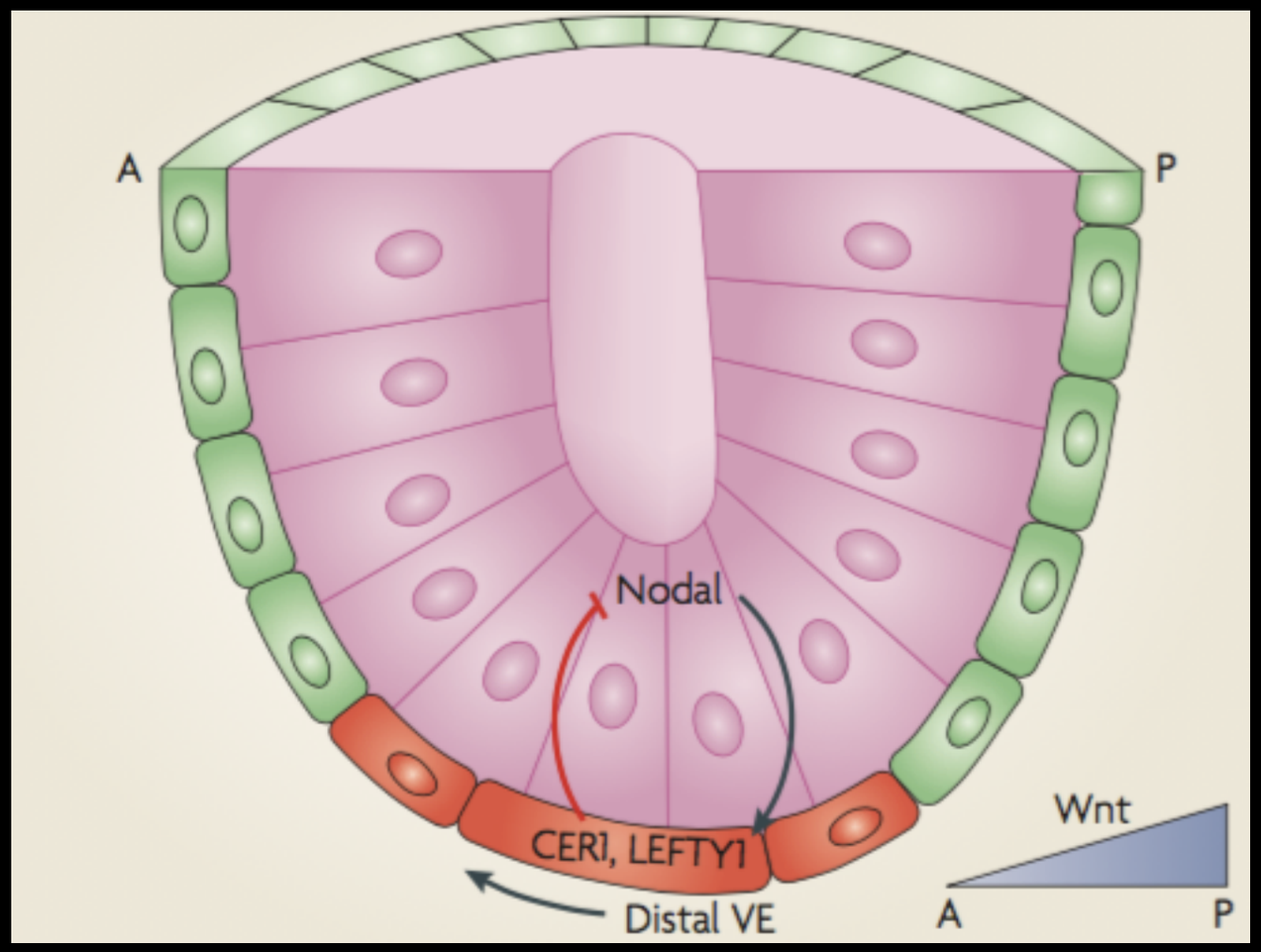


Arnold & Robertson
Nat Rev Mol Cell Biol 2009

Molecular basis of gastrulation

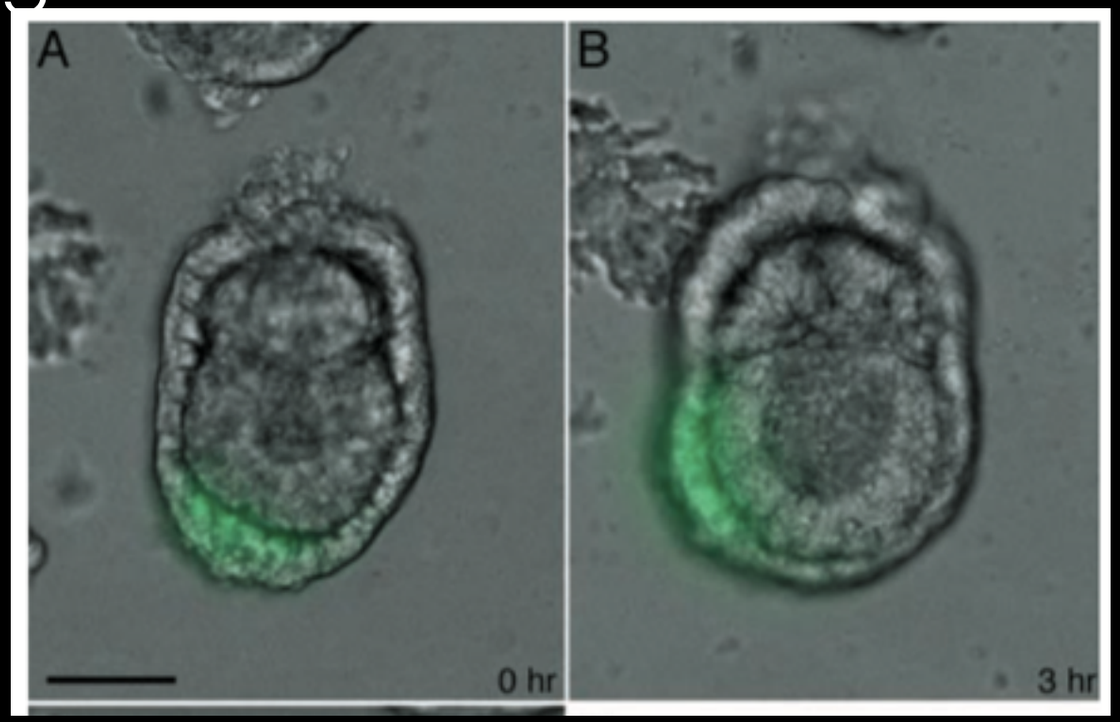
1. Nodal induces its own inhibitors at the distal tip of the embryo in the distal visceral endoderm (DVE).





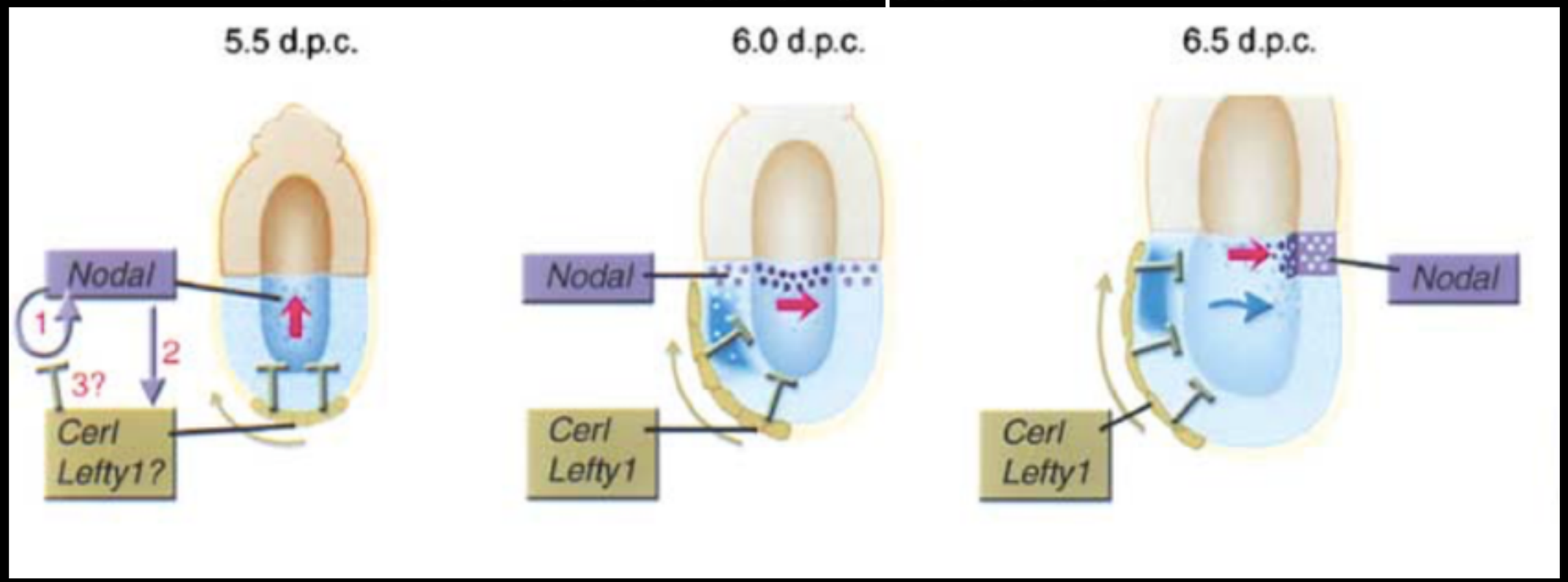
Arnold & Robertson
Nat Rev Mol Cell Biol 2009

2. DVE migrates to the anterior side

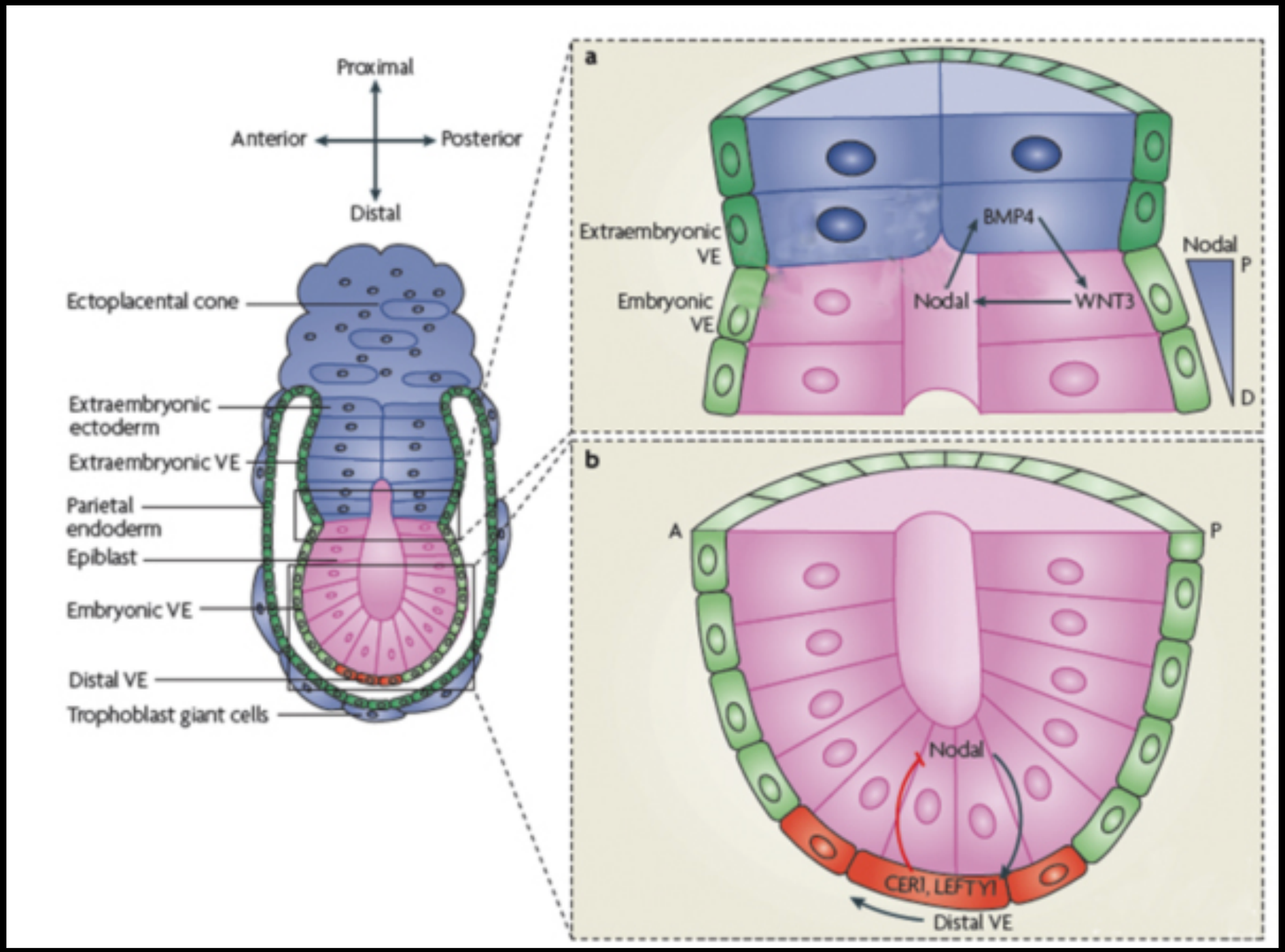


Srinivas et al Development 2004

3. Presence of inhibitors on the anterior side causes restriction of Nodal to the posterior



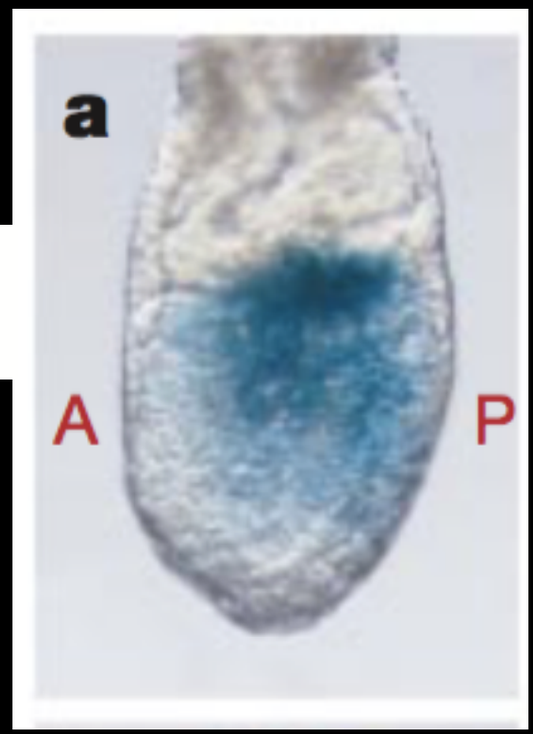
4. A positive feedback loop of three signaling pathways maintains posterior/distal expression and is necessary for gastrulation



Issues with this model

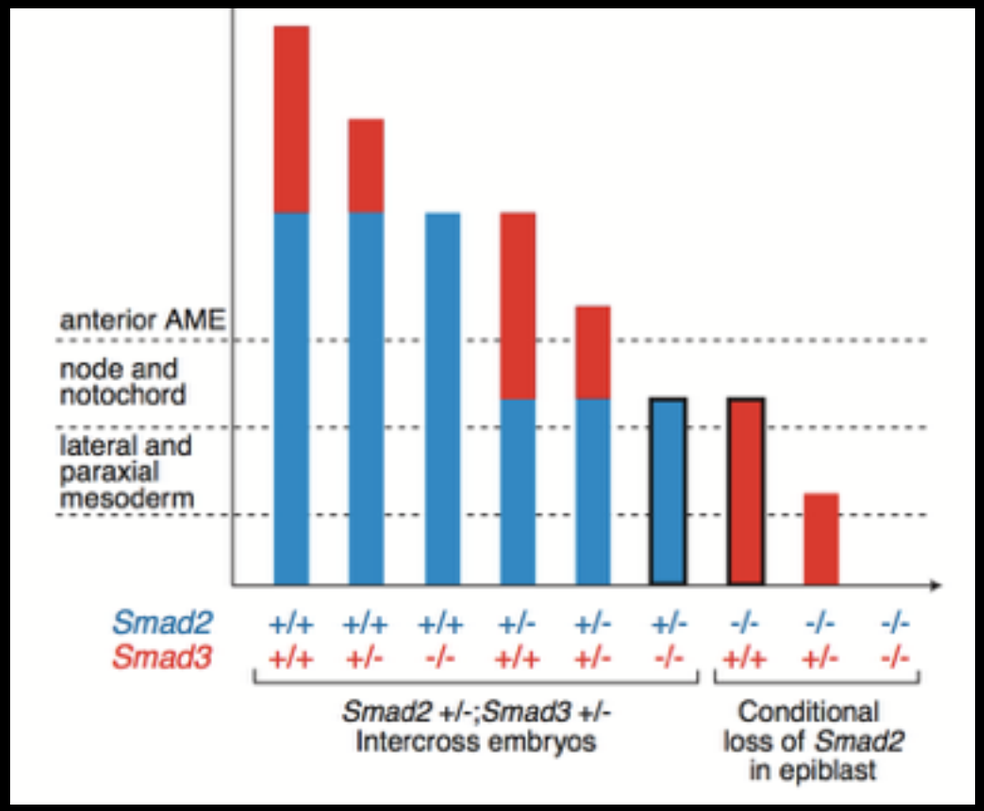
1. State of the data

Nodal^{lacZ} reporter allele



Brennan et al Nature 2001

-Most of our evidence is indirect from genetic knockouts



Dunn et al Development 2004

2. Do we really understand how Nodal works

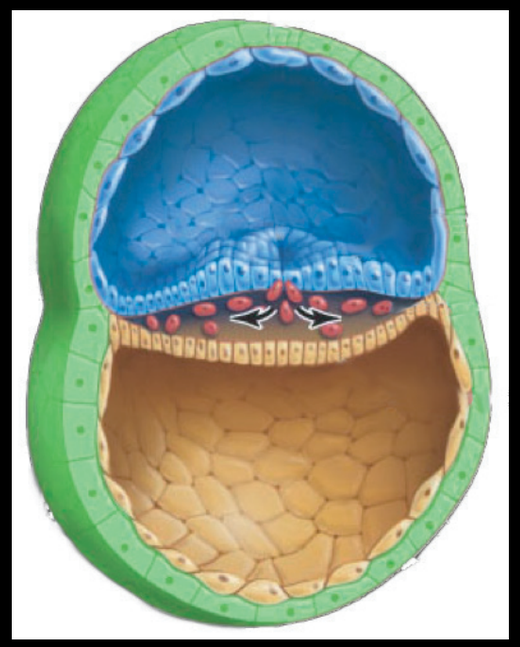
A. Are expression patterns consistent with function?
-How does it induce the DVE at the distal tip, if it is in a PD gradient

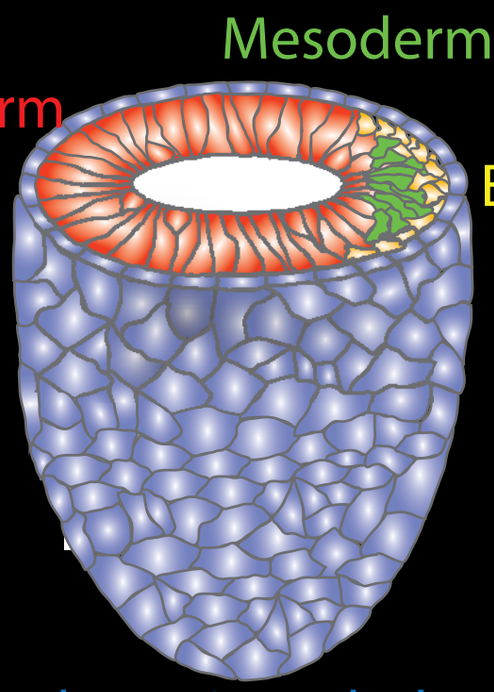
-Nodal is expressed throughout the epiblast prior to gastrulation

B. Does Nodal RNA —> Nodal protein —> Activity? We have no data

C. Nodal gradient must be dynamic, how do cells interpret changing signals

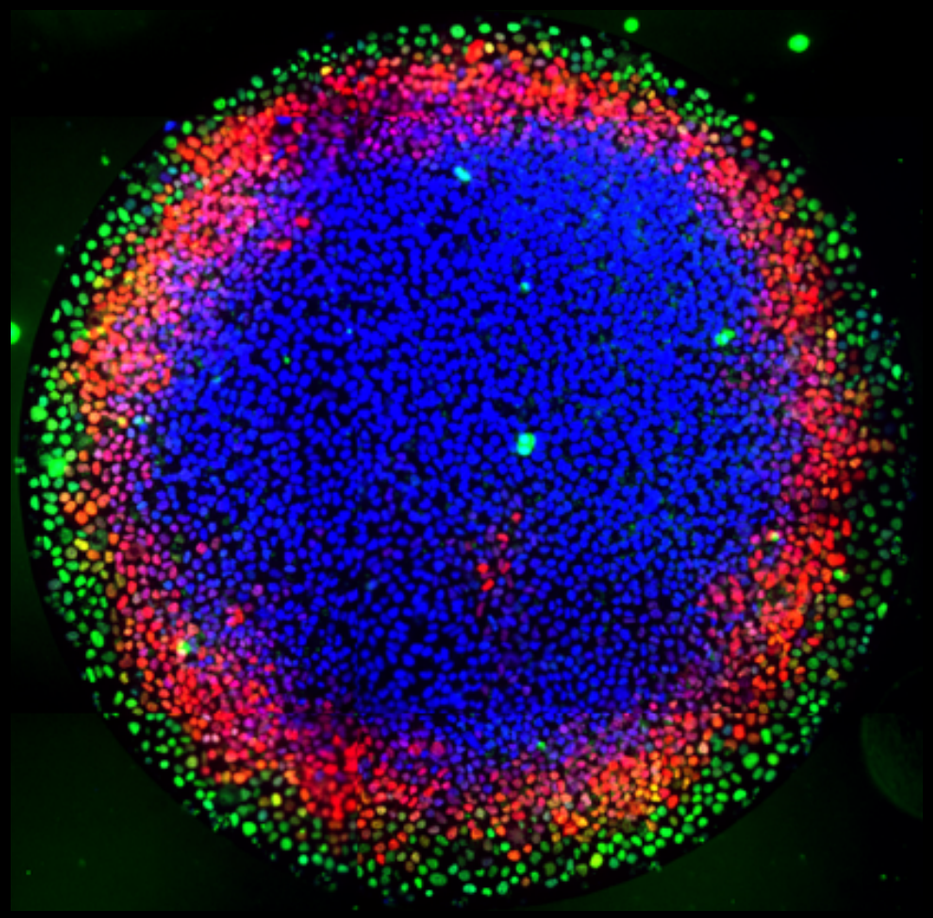
D. Human ≠ Mouse !!



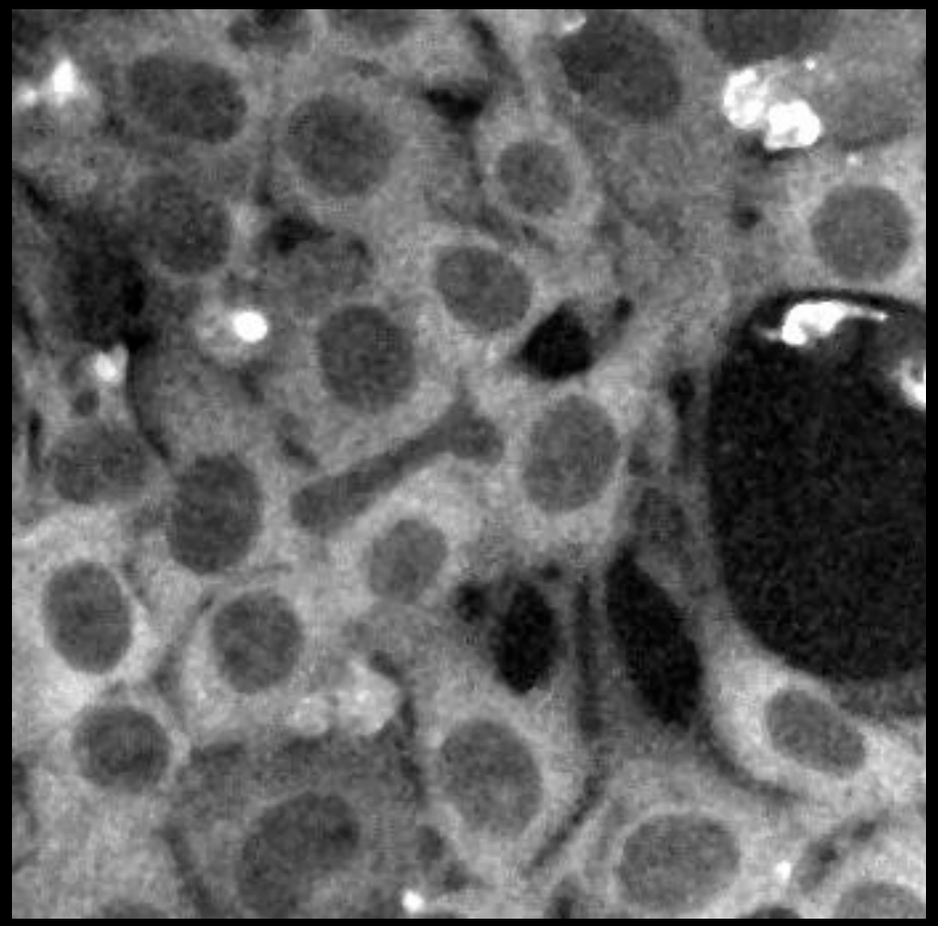


What can we do in cell culture

Make patterns

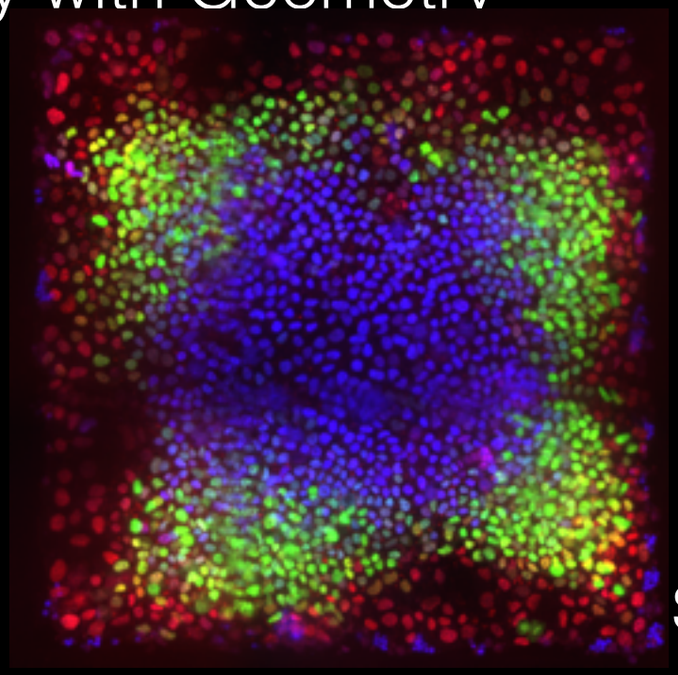


Study dynamics



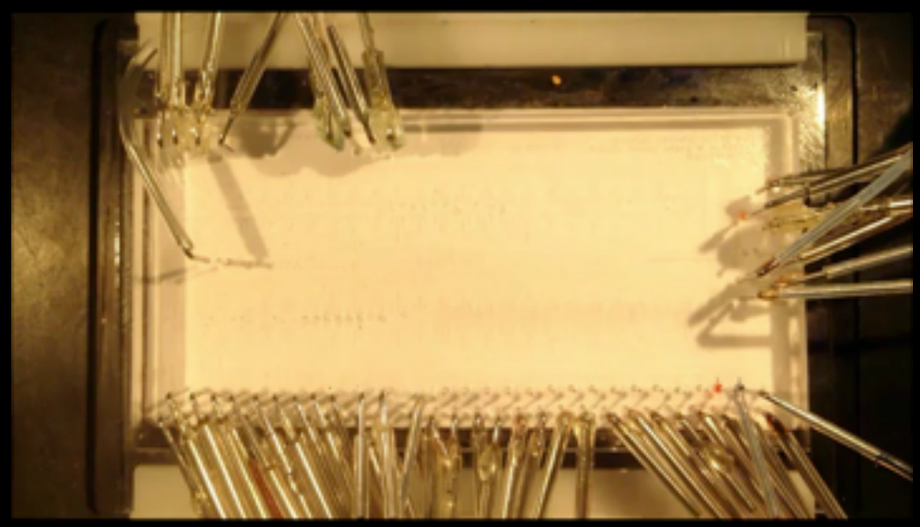
I Heemskerk

Play with Geometry



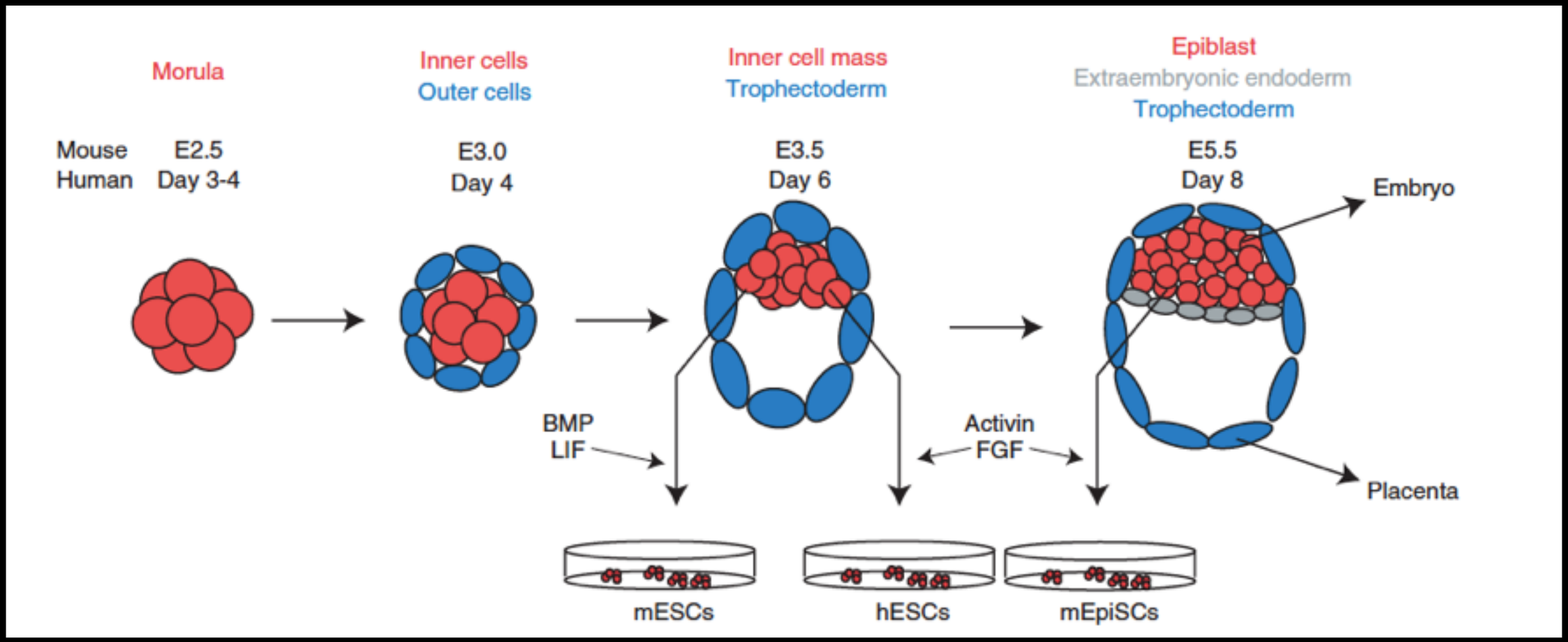
S Chhabra

Modulate dynamics



B Sorre

Stem cells come from early embryos

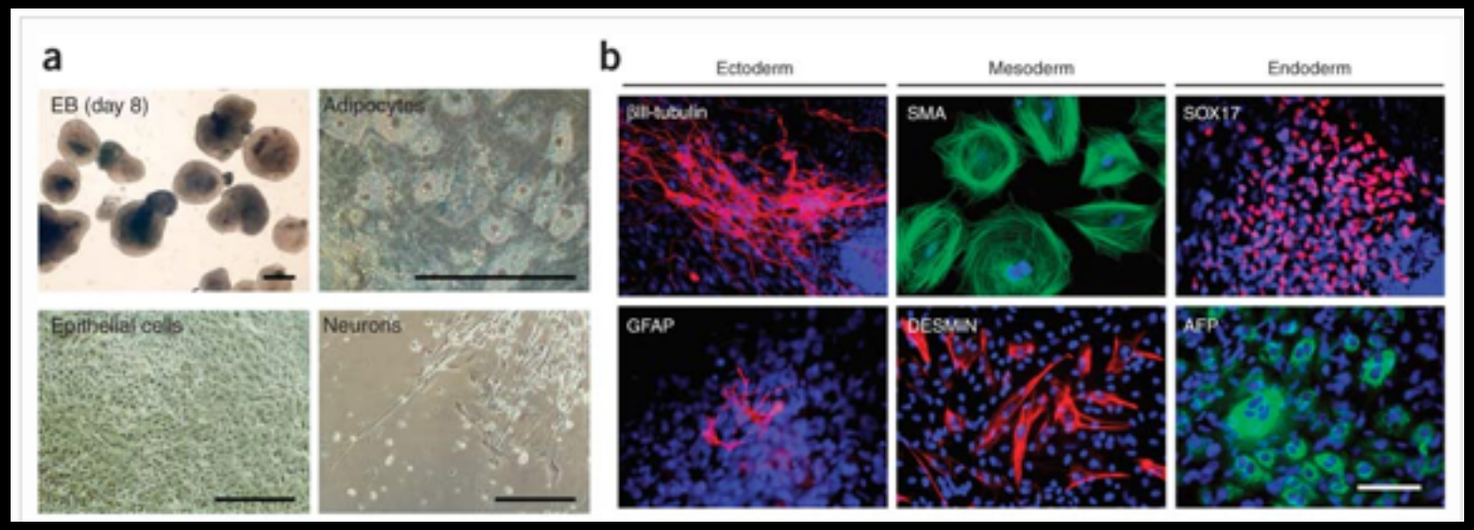


Note mESCs and hESCs come from the embryos at same stage but represent different stages of development

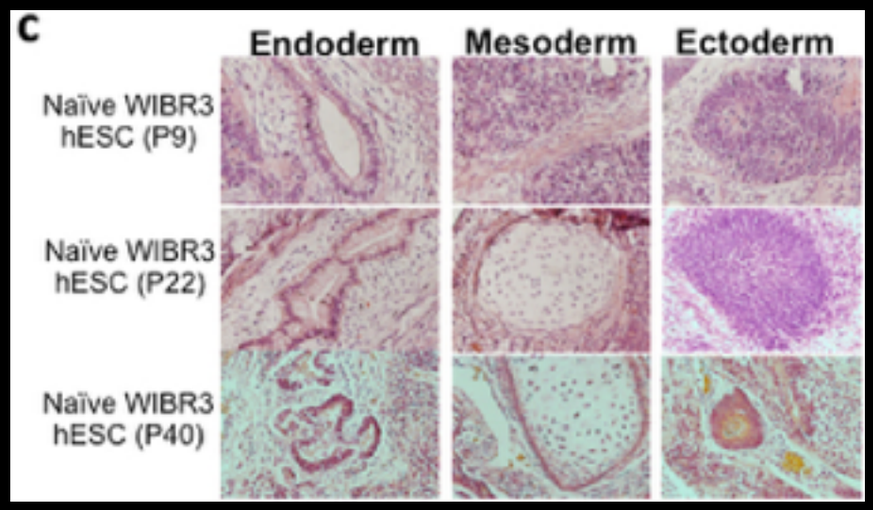
We are able to do this because of the unique features of early mammalian embryogenesis

How can we tell if cells are pluripotent?

1. Embryoid body formation



2. Teratoma formation

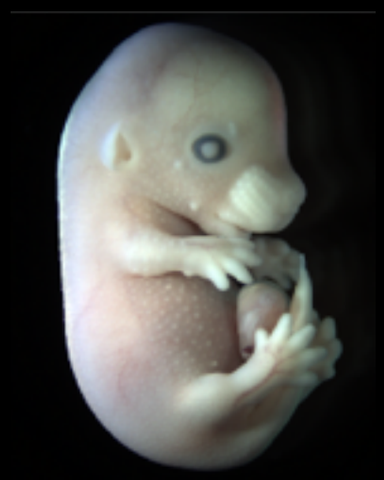


3. tetraploid complementation

Hybrid vigor, fetal overgrowth, and viability of mice derived by nuclear cloning and tetraploid embryo complementation

Kevin Eggan*†, Hidenori Akutsu‡, Janet Loring*, Laurie Jackson-Grusby*, Martina Klemm*, William M. Rideout 3rd*, Ryuzo Yanagimachi‡, and Rudolf Jaenisch*†§

*Whitehead Institute for Biomedical Research and †Department of Biology, Massachusetts Institute of Technology, 9 Cambridge Center, Cambridge, MA 02142; and ‡Institute for Biogenesis Research and Department of Anatomy and Reproductive Biology, John A. Burns School of Medicine, University of Hawaii, Honolulu, HI 96822



ICM-like stem cells

PNAS 1981

Proc. Natl. Acad. Sci. USA
Vol. 78, No. 12, pp. 7634–7638, December 1981
Developmental Biology

Isolation of a pluripotent cell line from early mouse embryos cultured in medium conditioned by teratocarcinoma stem cells

(embryonic stem cells/inner cell masses/differentiation *in vitro*/embryonal carcinoma cells/growth factors)

GAIL R. MARTIN

Department of Anatomy, University of California, San Francisco, California 94143

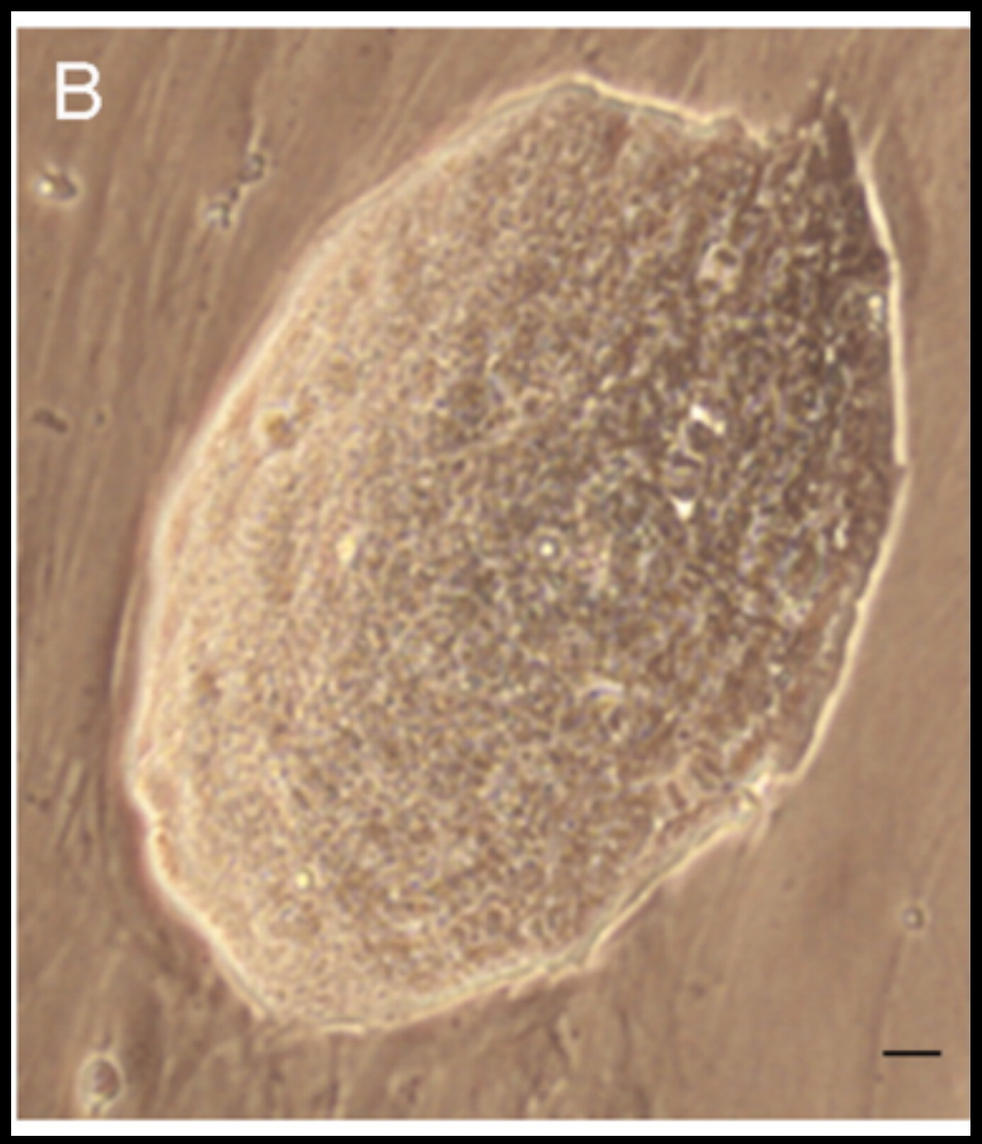
Communicated by J. Michael Bishop, September 14, 1981

Nature 1981

Establishment in culture of pluripotential cells from mouse embryos

M. J. Evans* & M. H. Kaufman†

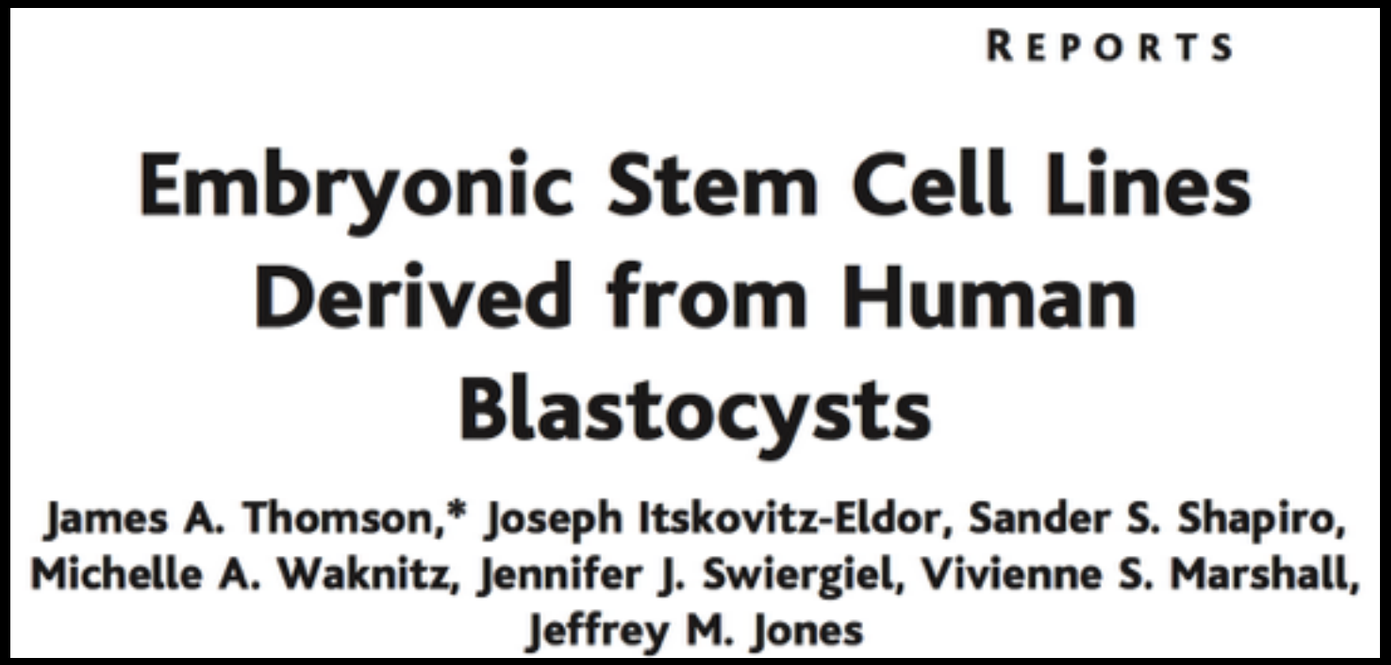
Departments of Genetics* and Anatomy†, University of Cambridge, Downing Street, Cambridge CB2 3EH, UK



mouse embryonic stem cells on a feeder layer

Grow in piled up balls of cells that mimic the ICM in vivo.

Epiblast-like stem cells

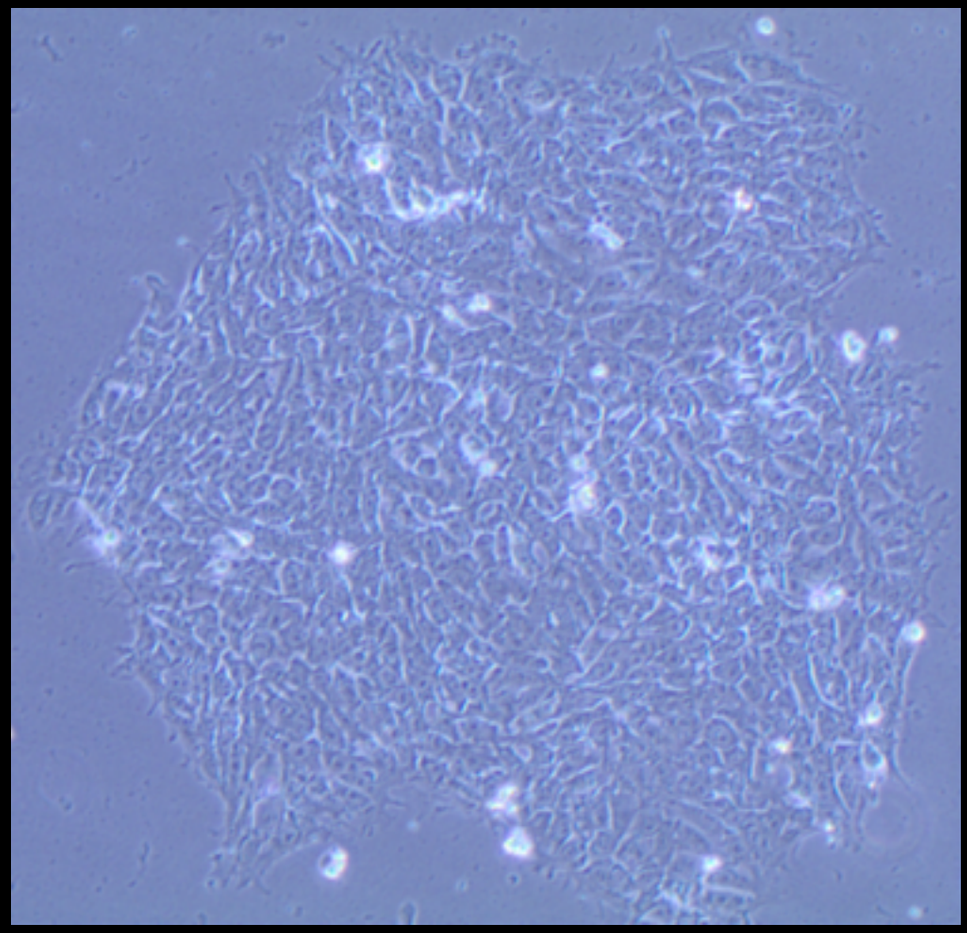


REPORTS

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

Science 1998



Human embryonic stem cell colony

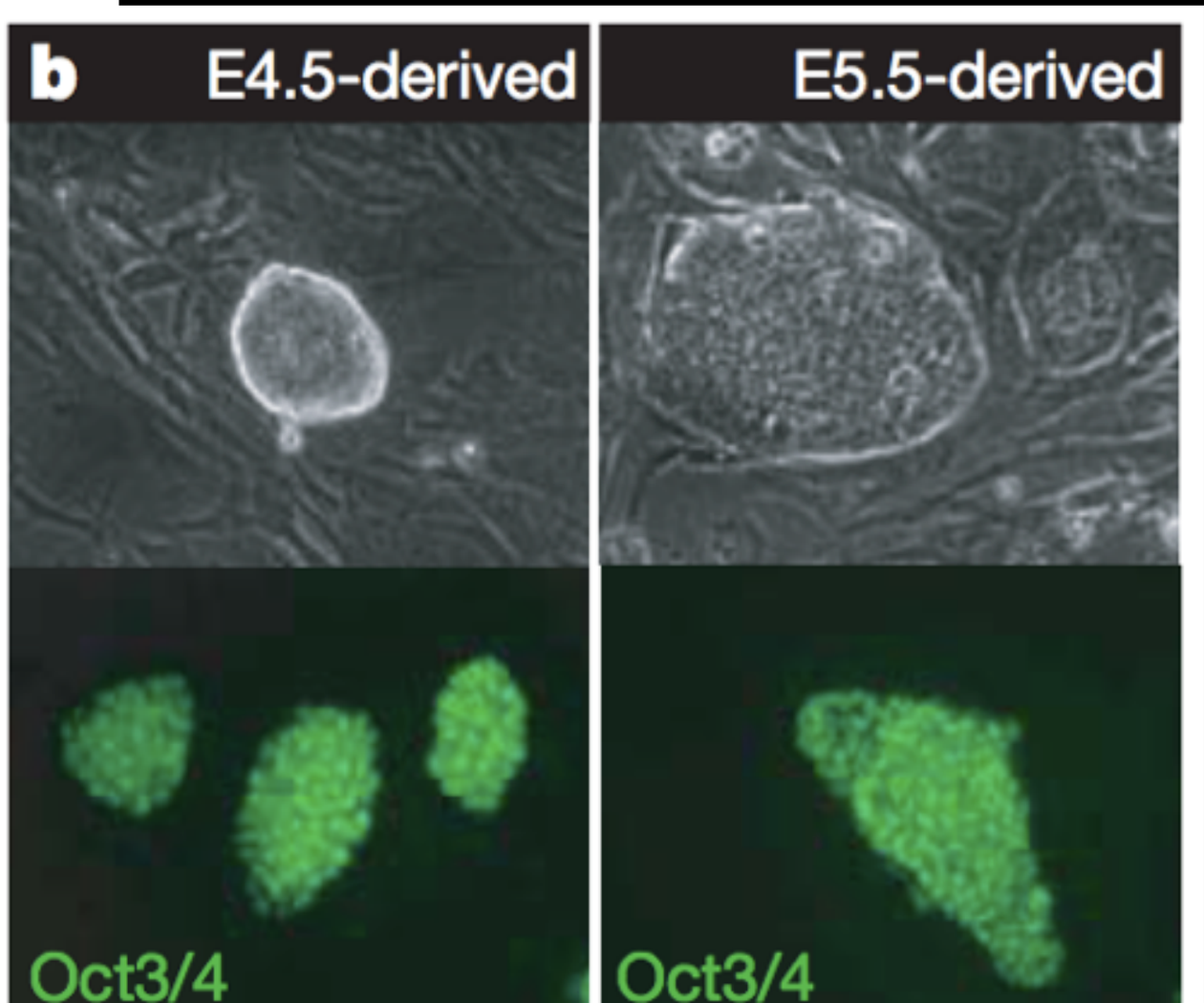
Stem cells lines can be derived from the mouse epiblast that resemble hESCs

LETTERS

New cell lines from mouse epiblast share defining features with human embryonic stem cells

Derivation of pluripotent epiblast stem cells from mammalian embryos

I. Gabrielle M. Brons[1], Lucy E. Smithers[2], Matthew W. B. Trotter[2], Peter Rugg-Gunn[1]†, Bowen Sun[1], Susana M. Chuva de Sousa Lopes[3], Sarah K. Howlett[4], Amanda Clarkson[5], Lars Ahrlund-Richter[6], Roger A. Pedersen[1] & Ludovic Vallier[1]



Properties of hESCs and mESCs

TABLE 2 | Comparison of mESCs, mEpiSCs with hESCs. Many Features of mESCs, mEpiSCs, and hESCs Have Been Evaluated Singly and In Parallel. A Summary of Key Characteristics is Provided Here. For Additional Information, See Refs 25, 26, 28, and 29

	mESCs	hESCs	mEpiSCs
Morphology	Rounded	Flattened	Flattened
Single cell survival	Good	Poor	Poor
Potency	All embryonic fates	All embryonic fates	All embryonic fates
Signaling inputs	BMP, LIF	Activin, FGF	Activin, FGF
Embryoid body formation	Yes	Yes	Yes
Teratoma formation	Yes	Yes	Yes
Tetraploid complementation	Yes	N/A	No
X inactivation	No	Yes	Yes

hESC, human embryonic stem cell; mESC, mouse embryonic stem cell; mEpiSC, mouse epiblast stem cell.

Complex manipulations can force hESCs to revert to an ICM-like state

LETTER

doi:10.1038/nature12745

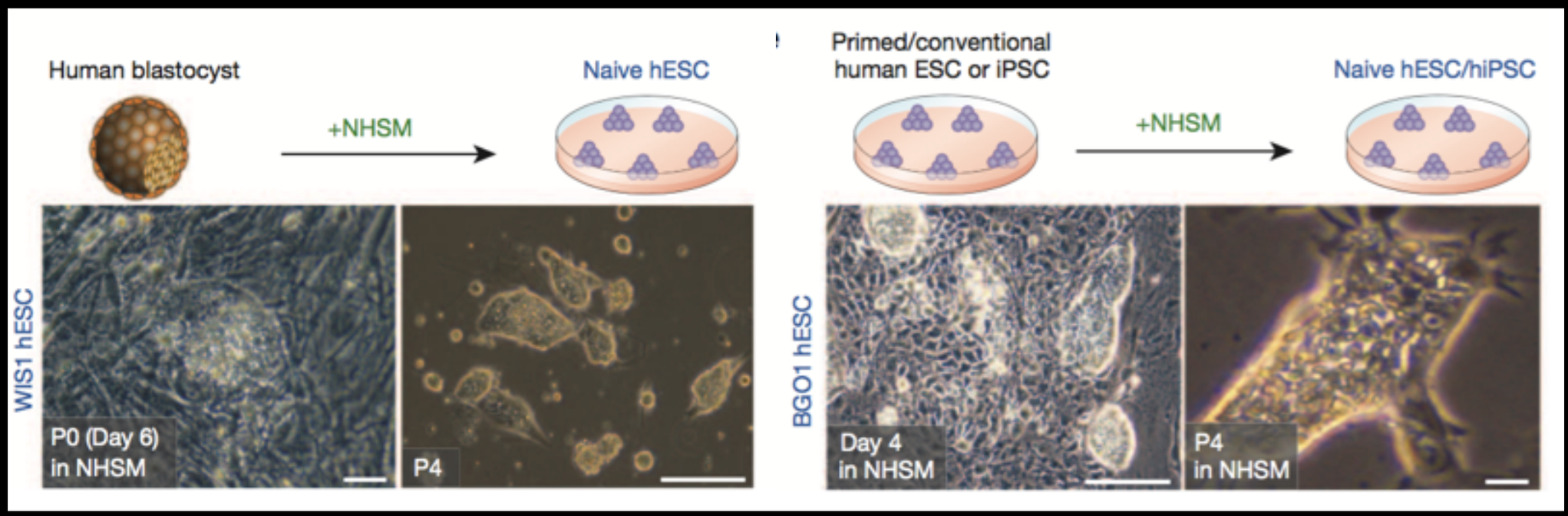
Derivation of novel human ground state naive pluripotent stem cells

Ohad Gafni[1]*, Leehee Weinberger[1]*, Abed AlFatah Mansour[1]*, Yair S. Manor[1]*, Elad Chomsky[1,2,3]*, Dalit Ben-Yosef[4,5], Yael Kalma[4], Sergey Viukov[1], Itay Maza[1], Asaf Zviran[1], Yoach Rais[1], Zohar Shipony[2,3], Zohar Mukamel[2,3], Vladislav Krupalnik[1], Mirie Zerbib[1], Shay Geula[1], Inbal Caspi[1], Dan Schneir[1], Tamar Shwartz[4], Shlomit Gilad[6], Daniela Amann-Zalcenstein[6], Sima Benjamin[6], Ido Amit[7], Amos Tanay[2,3], Rada Massarwa[1], Noa Novershtern[1] & Jacob H. Hanna[1]

NHSM

Essential components:
LIF (20 ng ml^{-1})
TGFβ1 (1 ng ml^{-1})
FGF2 (8 ng ml^{-1})
ERK1/2i (PD0325901 1 μM)
GSK3βi (CHIR99021 3 μM)
JNKi (SP600125 10 μM)
p38i (SB203580 10 μM)

Optimizing components:
ROCKi (Y-27632 5 μM)
PKCi (Go6983 5 μM)

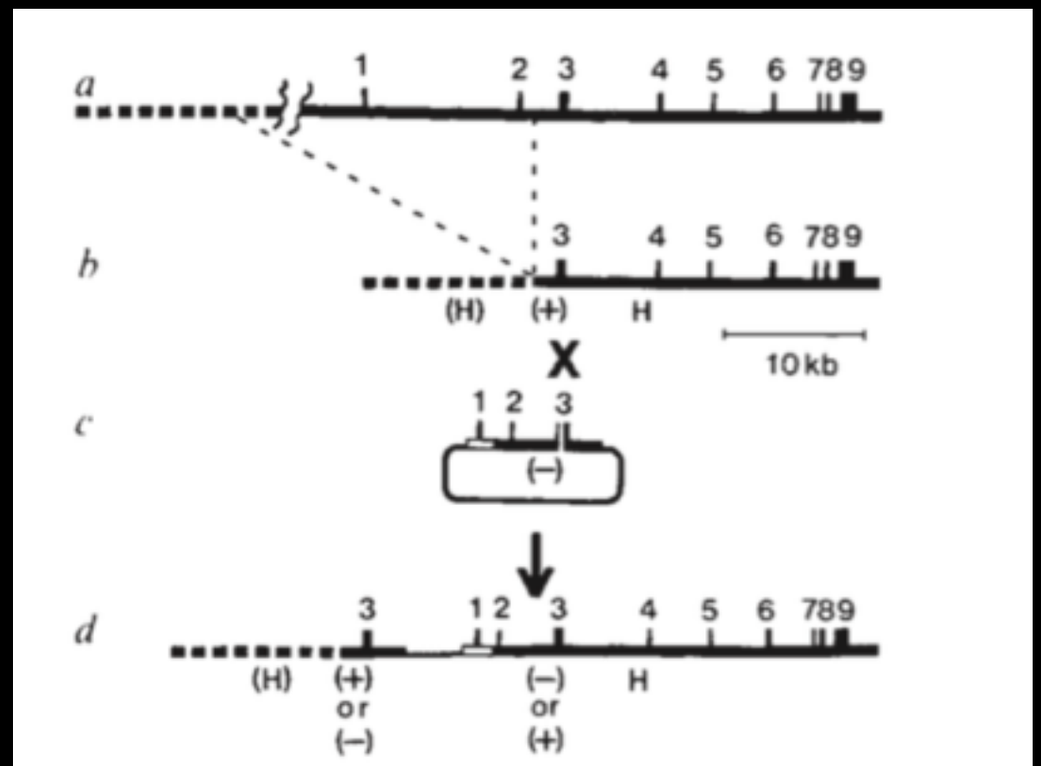


Stem cells enabled a revolution in studying mammalian development

Targetted correction of a mutant HPRT gene in mouse embryonic stem cells

Thomas Doetschman*, Ronald G. Gregg*, Nobuyo Maeda*, Martin L. Hooper†, David W. Melton‡, Simon Thompson‡ & Oliver Smithies*§

* Laboratory of Genetics, University of Wisconsin, Madison, Wisconsin 53706, USA
† Department of Pathology, University of Edinburgh, Teviot Place, Edinburgh EH8 9AG, UK
‡ Department of Molecular Biology, University of Edinburgh, Mayfield Road, Edinburgh EH9 3JR, UK

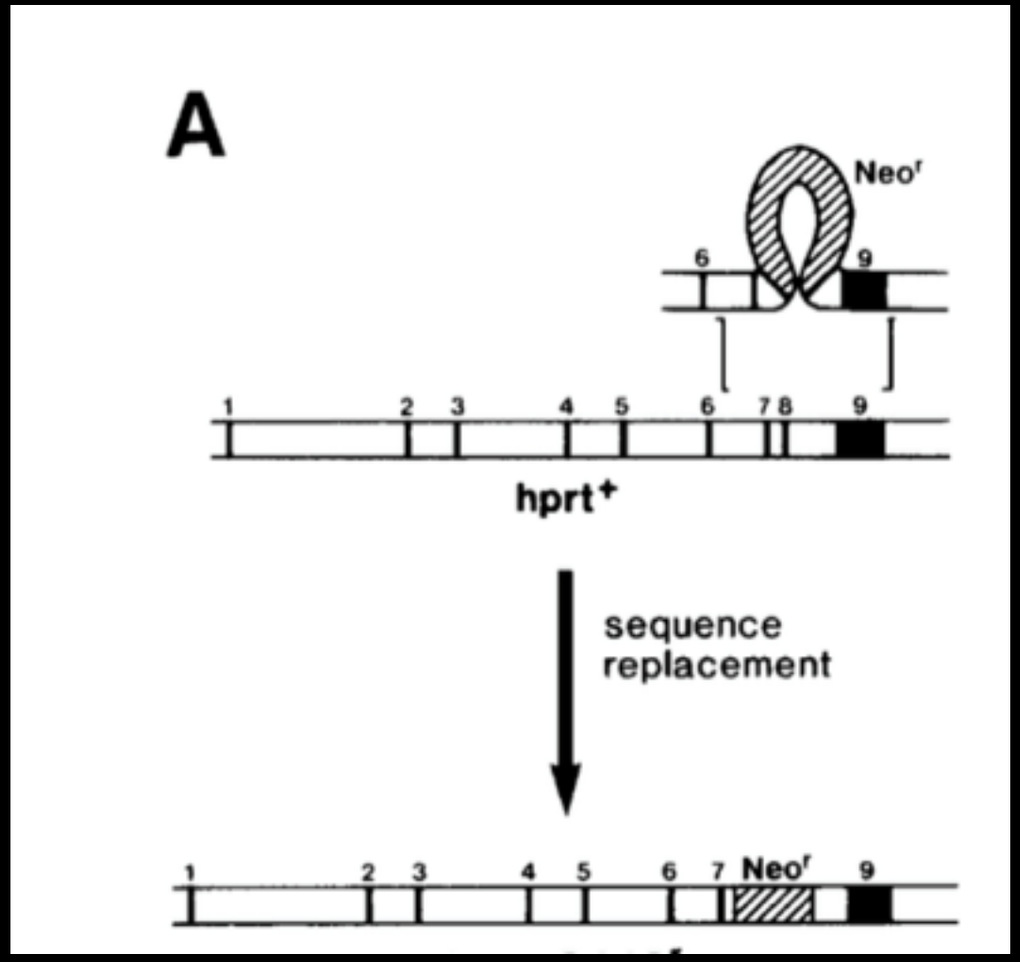


Nature 1985

Cell, Vol. 51, 503–512, November 6, 1987, Copyright © 1987 by Cell Press

Site-Directed Mutagenesis by Gene Targeting in Mouse Embryo-Derived Stem Cells

Kirk R. Thomas and Mario R. Capecchi
Department of Biology
University of Utah
Salt Lake City, Utah 84112



homologous chromosomal sequence
entail incorrect repair of a heteroduple
the newly introduced DNA and the cog
sequence (Thomas and Capecchi, 198
methods has its own advantages. The

targeting experiments. It is hoped that this combination of using ES cells as the recipient cell line and site-specific mutagenesis achieved by gene targeting will provide the means for generating mice of any desired genotype. An advantage of this scenario is that the first generation chimera will usually be heterozygous for the targeted mutation and that subsequent breeding can be used to generate the homozygous animal. Thus, only one of the two loci need be inactivated, and recessive lethals can be maintained as heterozygotes. If successful, this technology will be used in the future to dissect the developmental pathway of the mouse as well as to generate mouse models for human genetic diseases.

1989: the first transgenic mice

Targeted disruption of the murine *int-1* proto-oncogene resulting in severe abnormalities in midbrain and cerebellar development

Kirk R. Thomas & Mario R. Capecchi*

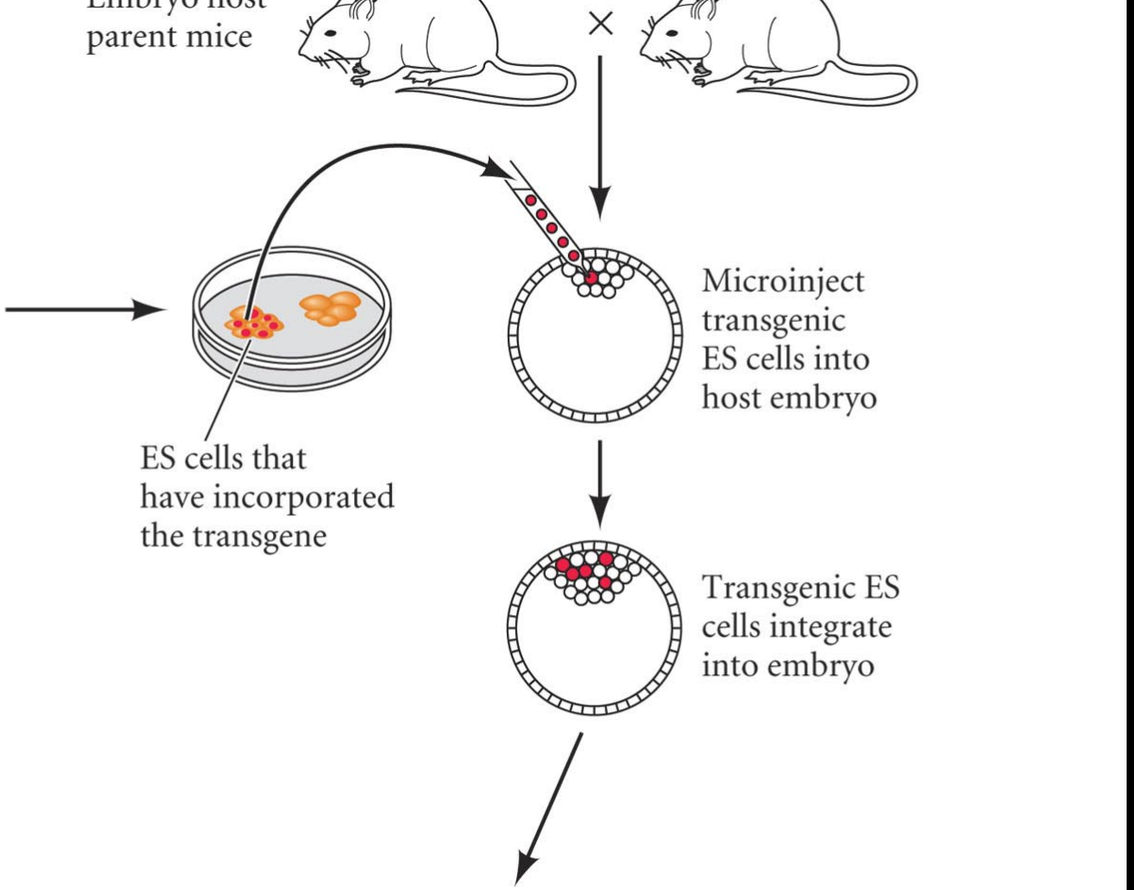
Howard Hughes Medical Institute, Department of Biology and Human Genetics, Salt Lake City, Utah 84112, USA

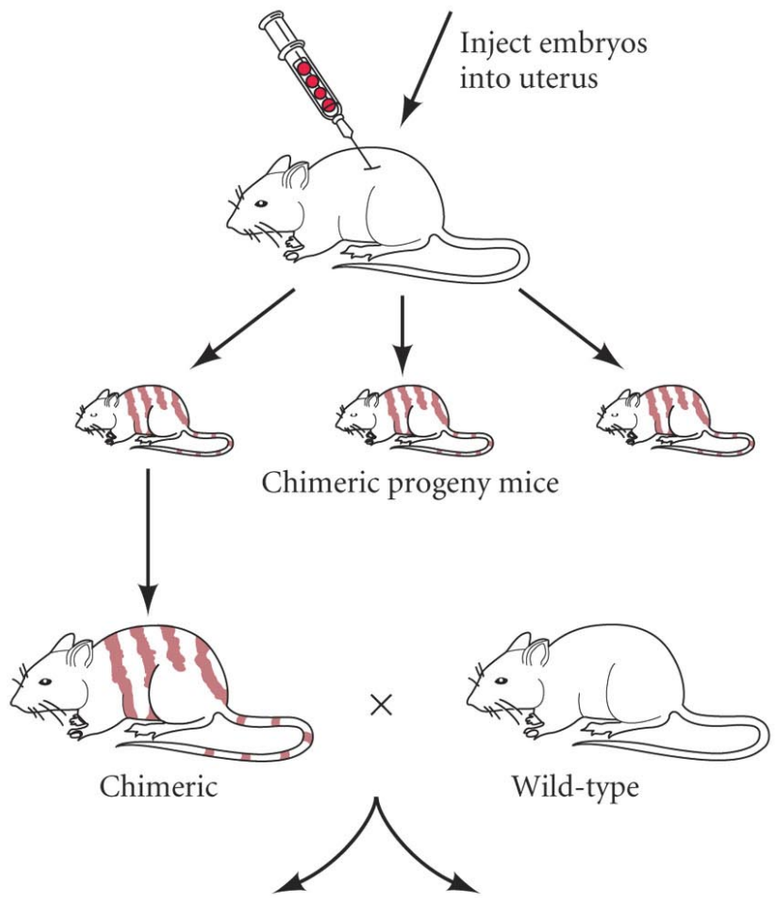
Germ-line transmission of a disrupted β_2-microglobulin gene produced by homologous recombination in embryonic stem cells

Maarten Zijlstra*, En Li*, Fereydoun Sajjadi†, Suresh Subramani† & Rudolf Jaenisch*

* Whitehead Institute for Biomedical Research, Nine Cambridge Center, and Department of Biology, Massachusetts Institute of Technology, Cambridge, Massachusetts 02142, USA
† Department of Biology, University of California, B-022 Bonner Hall, San Diego, La Jolla, California 92093, USA

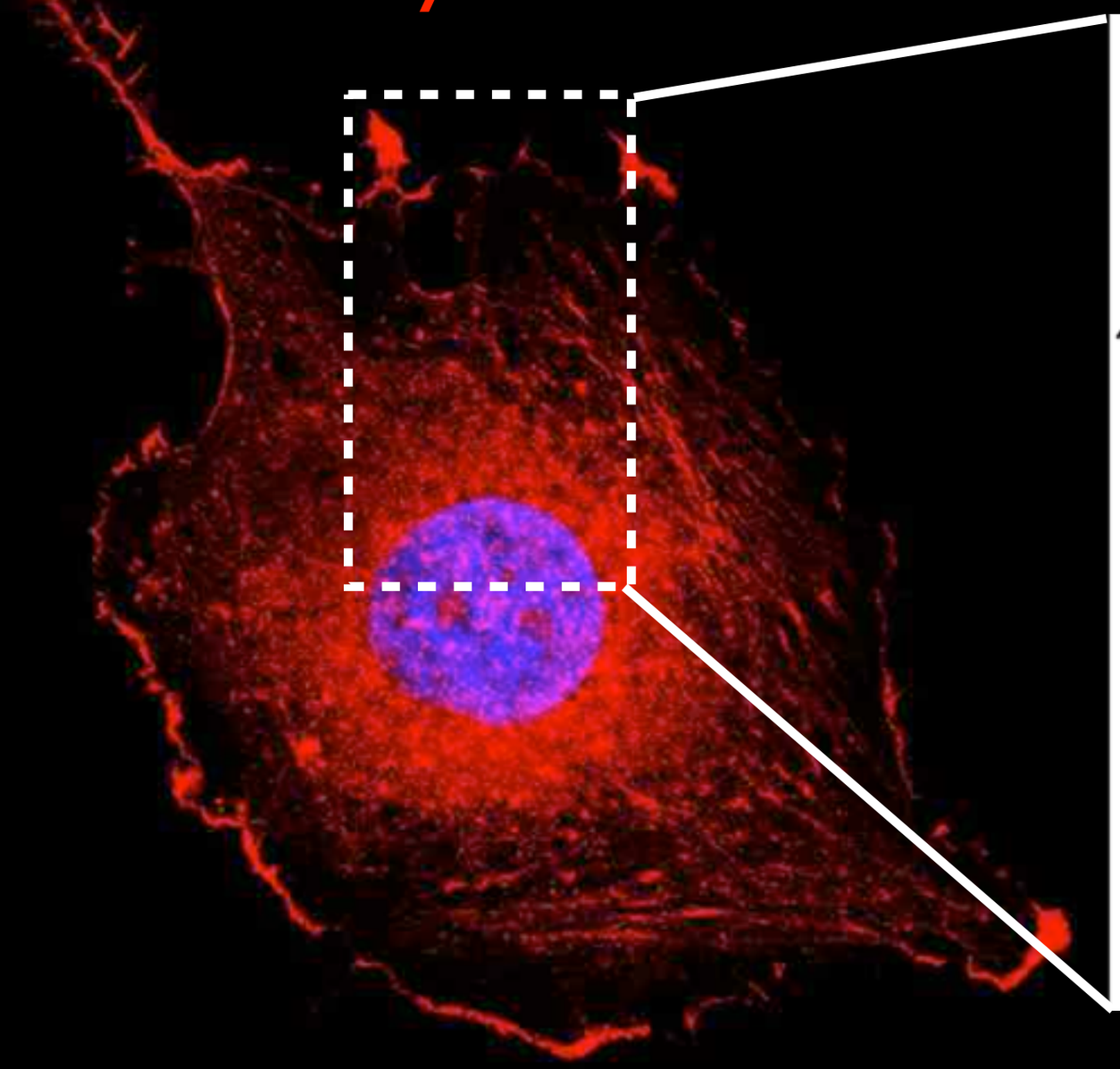
to Mario R. Capecchi, Sir Martin J. Evans and Oliver Smithies "for their discoveries of principles for introducing specific gene modifications in mice by the use of embryonic stem cells".

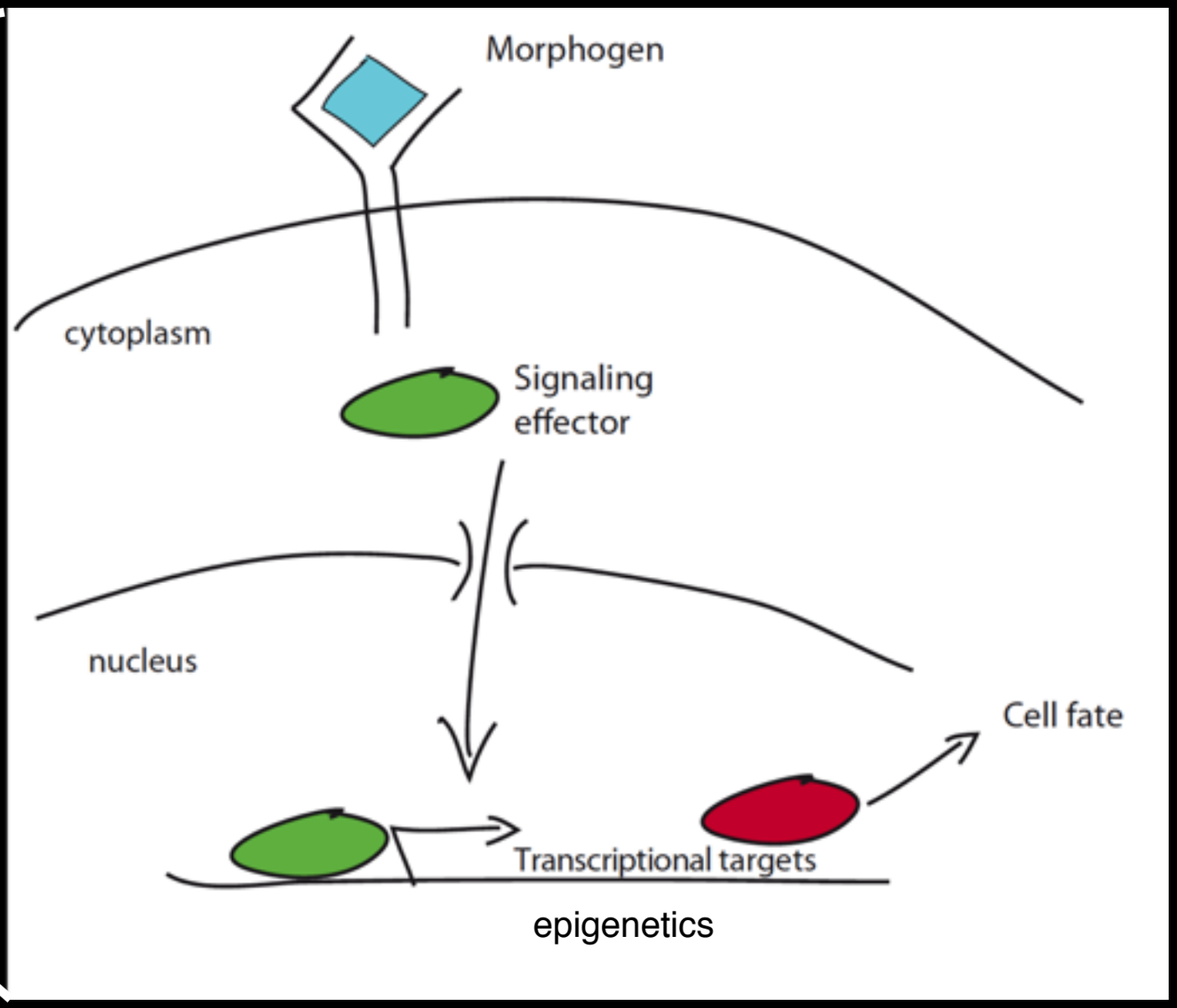




Hierarchy of regulation

DNA/Cytoskelton





epigenetics

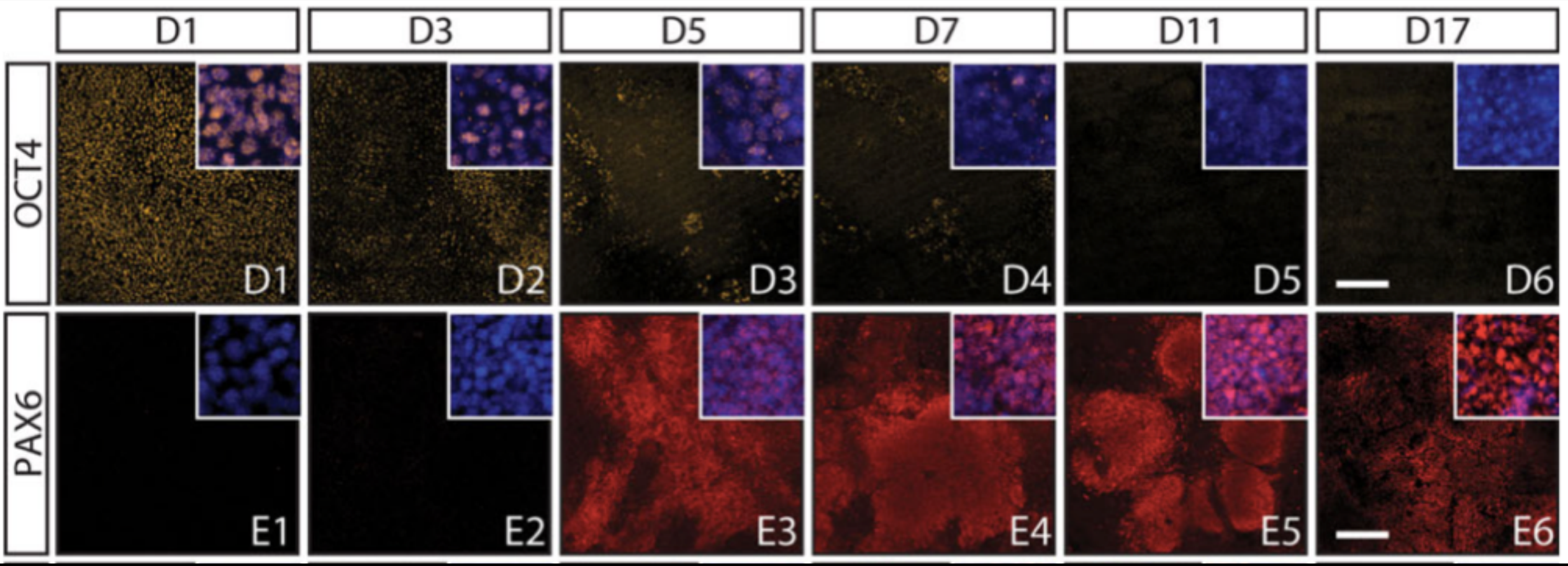
If all signals are removed from stem cells, they differentiate to neurons

Highly efficient neural conversion of human ES and iPS cells by dual inhibition of SMAD signaling

Stuart M Chambers[1], Christopher A Fasano[1], Eirini P Papapetrou[2], Mark Tomishima[1,2], Michel Sadelain[2,3] & Lorenz Studer[1,2,4]

SMAD7 Directly Converts Human Embryonic Stem Cells to Telencephalic Fate by a Default Mechanism

Mohammad Zeeshan Ozair, Scott Noggle, Aryeh Warmflash, Joanna Ela Krzyspiak, Ali H. Brivanlou

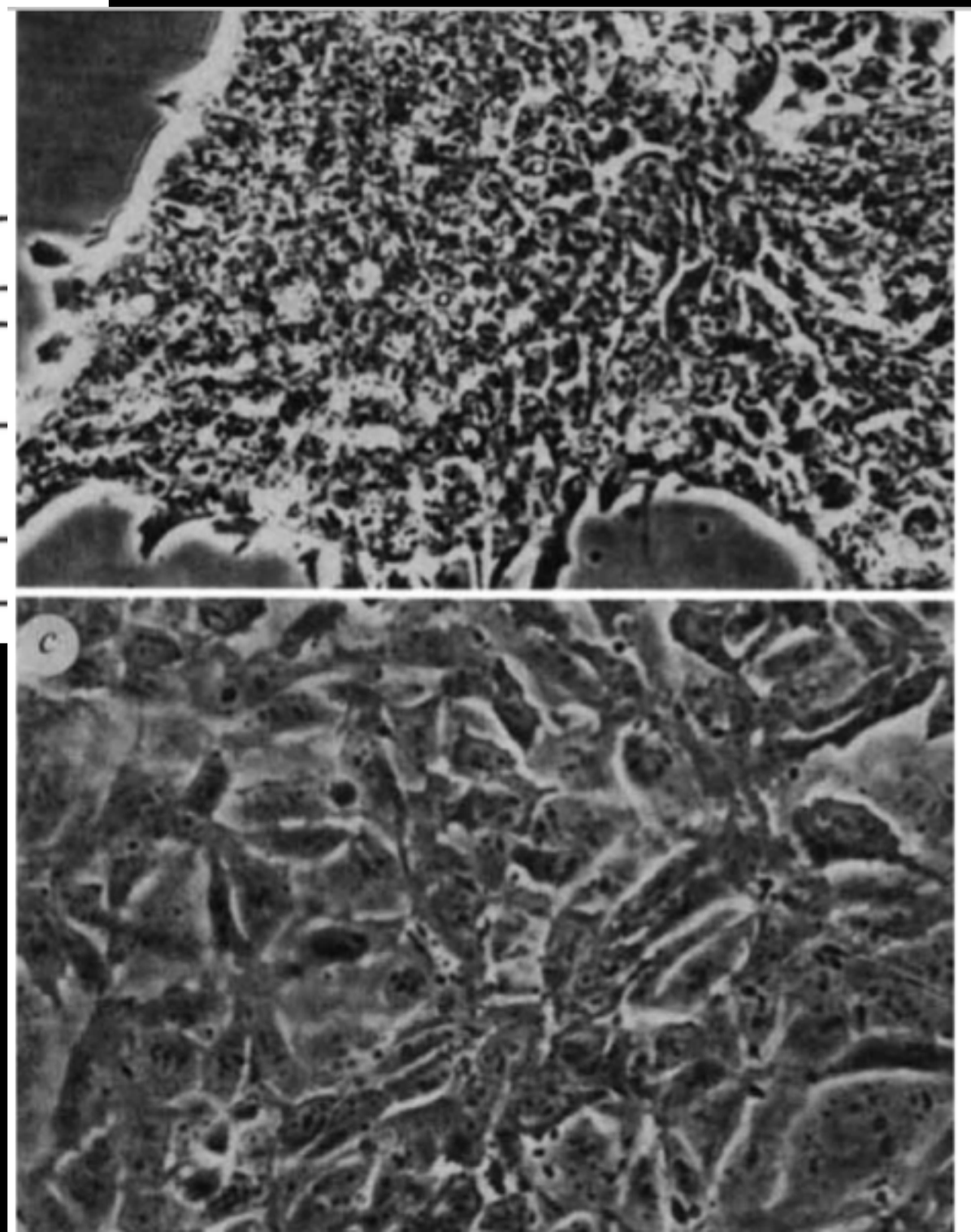


Signaling requirements of stem cells

Inhibition of pluripotential embryonic stem cell differentiation by purified polypeptides

Austin G. Smith*, John K. Heath*†, Deborah D. Donaldson‡, Gordon G. Wong‡, J. Moreau§, Mark Stahl‡ & David Rogers‡

* Department of Biochemistry, University of Oxford, South Parks Road, Oxford OX1 3QU, UK
‡ Genetics Institute, 87 Cambridge Park Drive, Cambridge, Boston, Massachusetts 02140, USA
§ INSERM U211, 1 Rue Gaston-Veil, 44035 Nantes, Cedex France

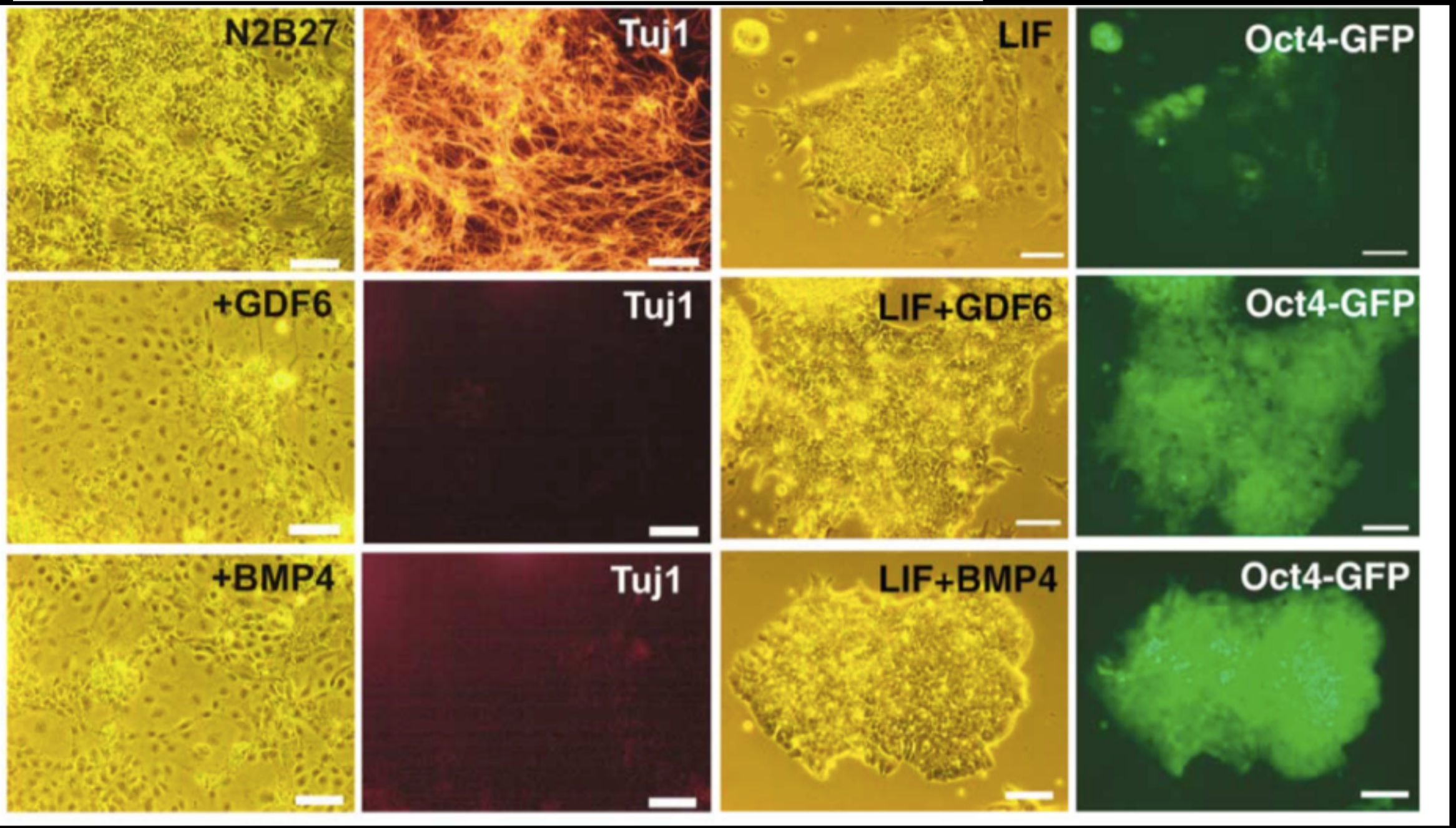


LIF was the first cytokine identified to maintain pluripotency and allowed the growth of mESCs without CM or feeders but they still needed serum. What was the other signal?

BMP can serve as the second signal

Cell, Vol. 115, 281–292, October 31, 2003, Copyright ©2003 by Cell Press

BMP Induction of Id Proteins Suppresses Differentiation and Sustains Embryonic Stem Cell Self-Renewal in Collaboration with STAT3



The stem cell state can also be maintained by suppression of differentiation pathways

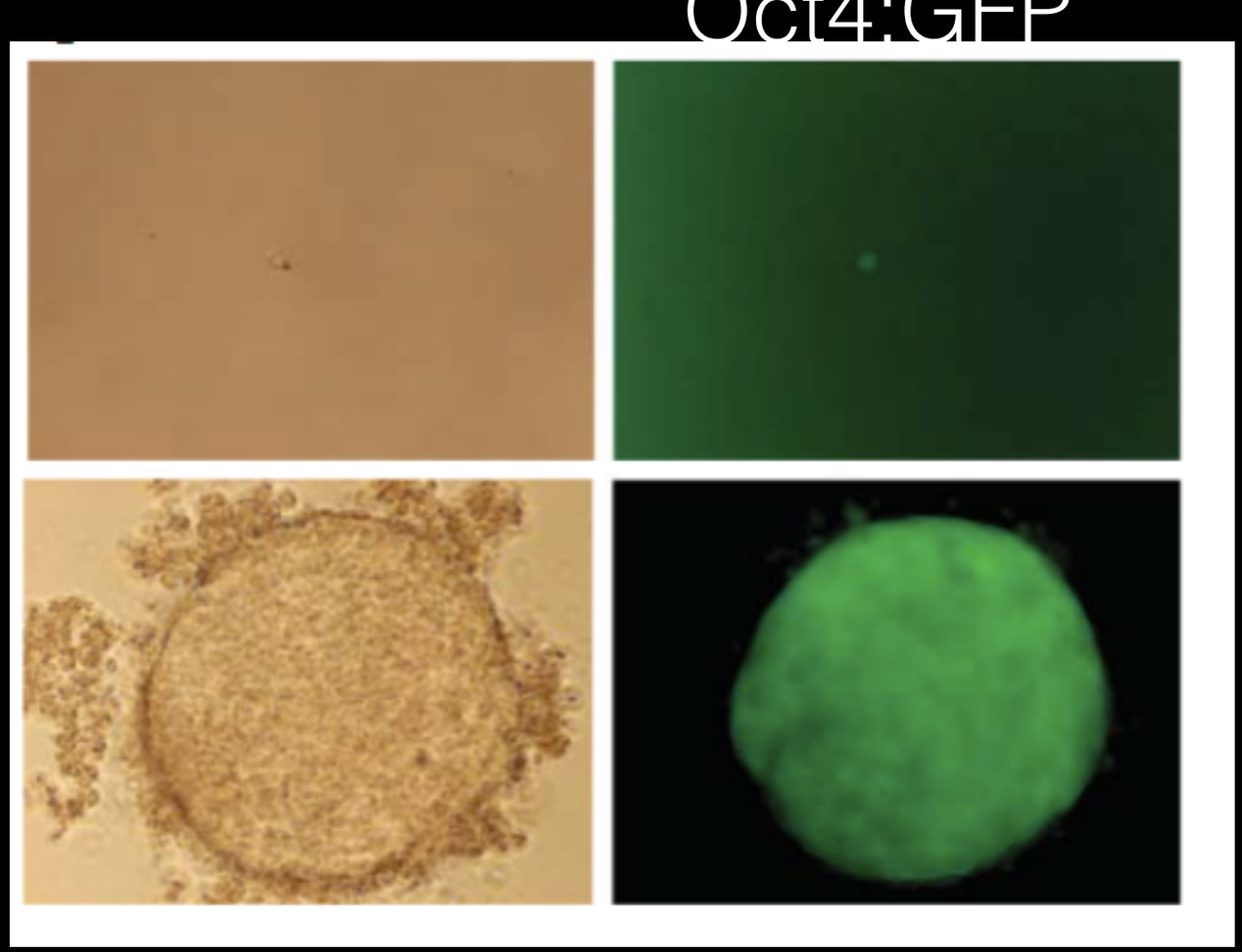
LETTERS

The ground state of embryonic stem cell self-renewal

Qi-Long Ying[1], Jason Wray[2], Jennifer Nichols[2], Laura Batlle-Morera[2], Bradley Doble[3], James Woodgett[4], Philip Cohen[5] & Austin Smith[2]

Inhibition of:
-FGFR
-MEK1/2
-GSK3beta

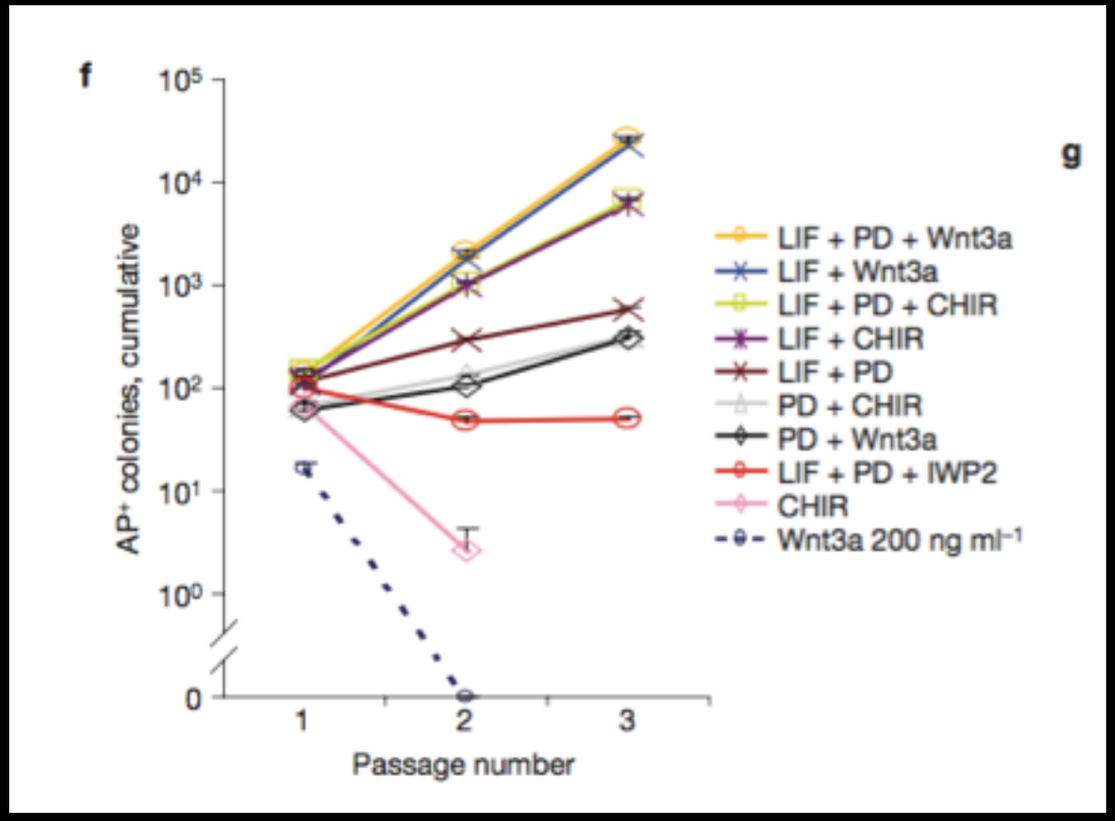
But is GSK3beta inhibition really suppressing a differentiation signal?



Effect of GSK3beta inhibition is equivalent to Wnt stimulation

Embryonic stem cells require Wnt proteins to prevent differentiation to epiblast stem cells

Derk ten Berge[1,2,4], Dorota Kurek[1], Tim Blauwkamp[2], Wouter Koole[2], Alex Maas[3], Elif Eroglu[2], Ronald K. Siu[2] and Roel Nusse[2]

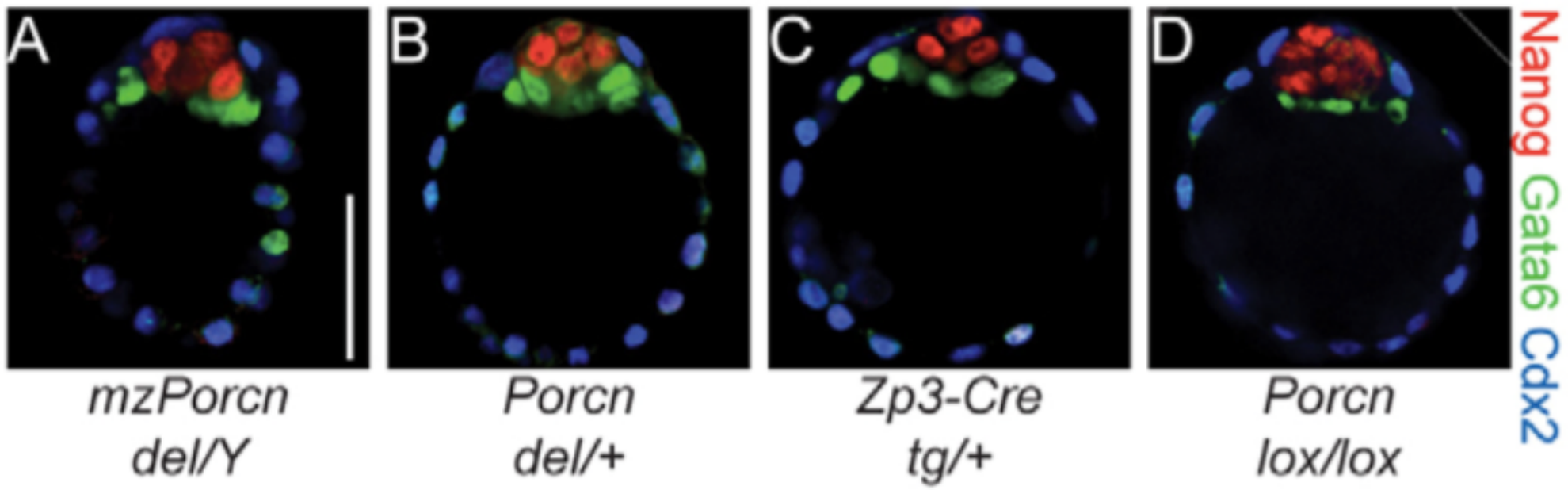


Caution: There can be discrepancies between cell culture and the embryo.

Development 140, 2961-2971 (2013) doi:10.1242/dev.094458

Porcn-dependent Wnt signaling is not required prior to mouse gastrulation

Steffen Biechele[1,2], Katie Cockburn[1,2], Fredrik Lanner[1,*], Brian J. Cox[1,‡] and Janet Rossant[1,2,§]



Completely different signals maintain the pluripotent state of human embryonic stem cells

Activin/Nodal and FGF pathways cooperate to maintain pluripotency of human embryonic stem cells

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Accepted 20 June 2005
Journal of Cell Science 118, 4495-4509 Published by The Company of Biologists 2005
doi:10.1242/jcs.02553

TGFβ/activin/nodal signaling is necessary for the maintenance of pluripotency in human embryonic stem cells

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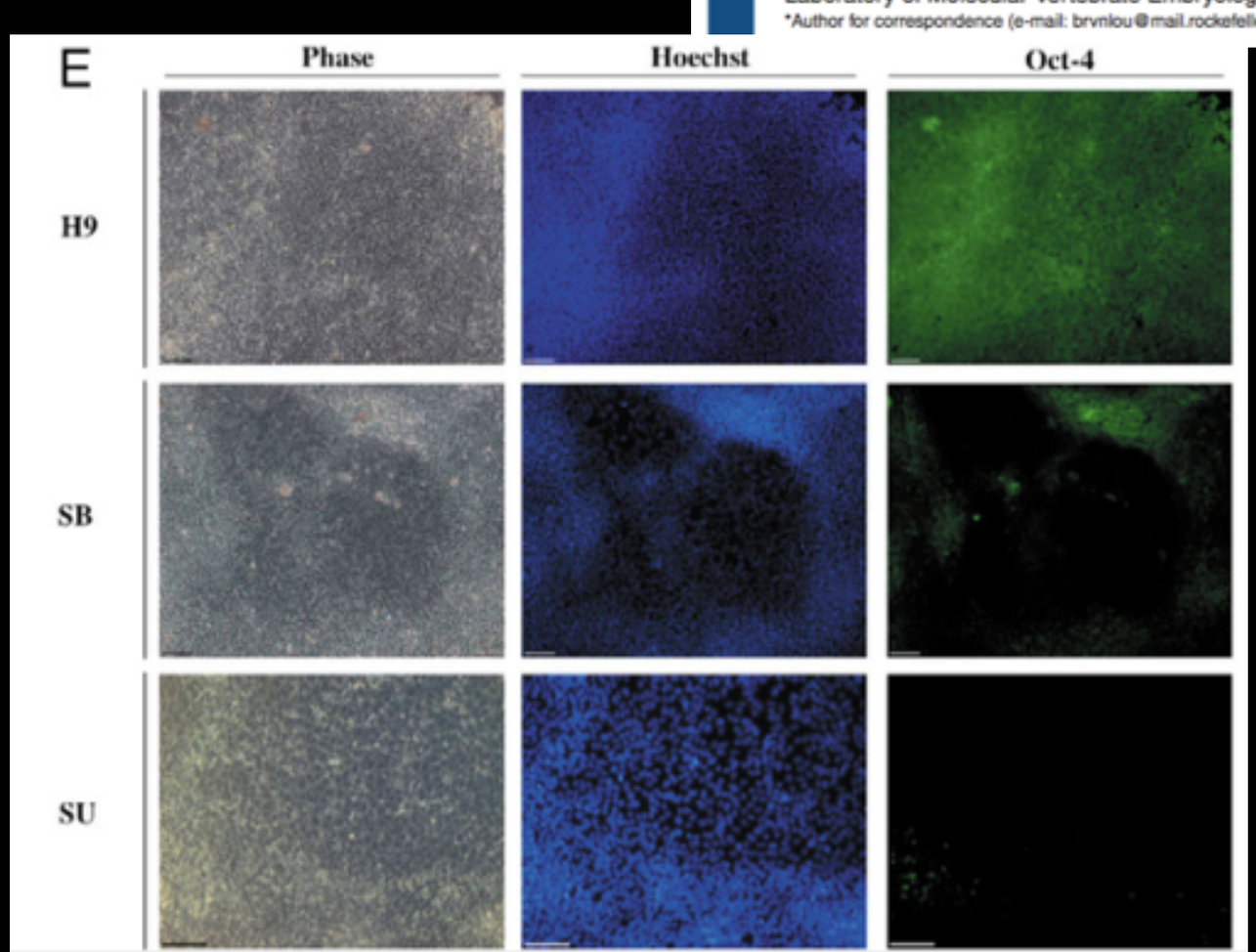
Laboratory of Molecular Vertebrate Embryology, The Rockefeller University, 1230 York Avenue, New York, NY 10021, USA

*Author for correspondence (e-mail: brvnlou@mail.rockefeller.edu)



Signaling in stem cells: summary

TABLE 1 | Signaling Pathways Involved in the Maintenance of Pluripotency. Table Summarizing Properties of Pathways that Play a Role in Maintaining Pluripotency Either in mESCs or hESCs

Pathway	LIF	BMP	Activin/Nodal	FGF	Wnt
Receptor	gp130	Alk2/3/6	Alk4/5/7	FGF-R	LRP5/6
Signal transducer	Stat3	Smad1/5/8	Smad2/3	MEK/ERK	β-catenin
Promotes pluripotency in mESCs?	+	+	−	−	+
Promotes pluripotency in hESCs?	−	−	+	+	+

hESC, human embryonic stem cell; mESC, mouse embryonic stem cell.

Transcriptional networks in stem cells

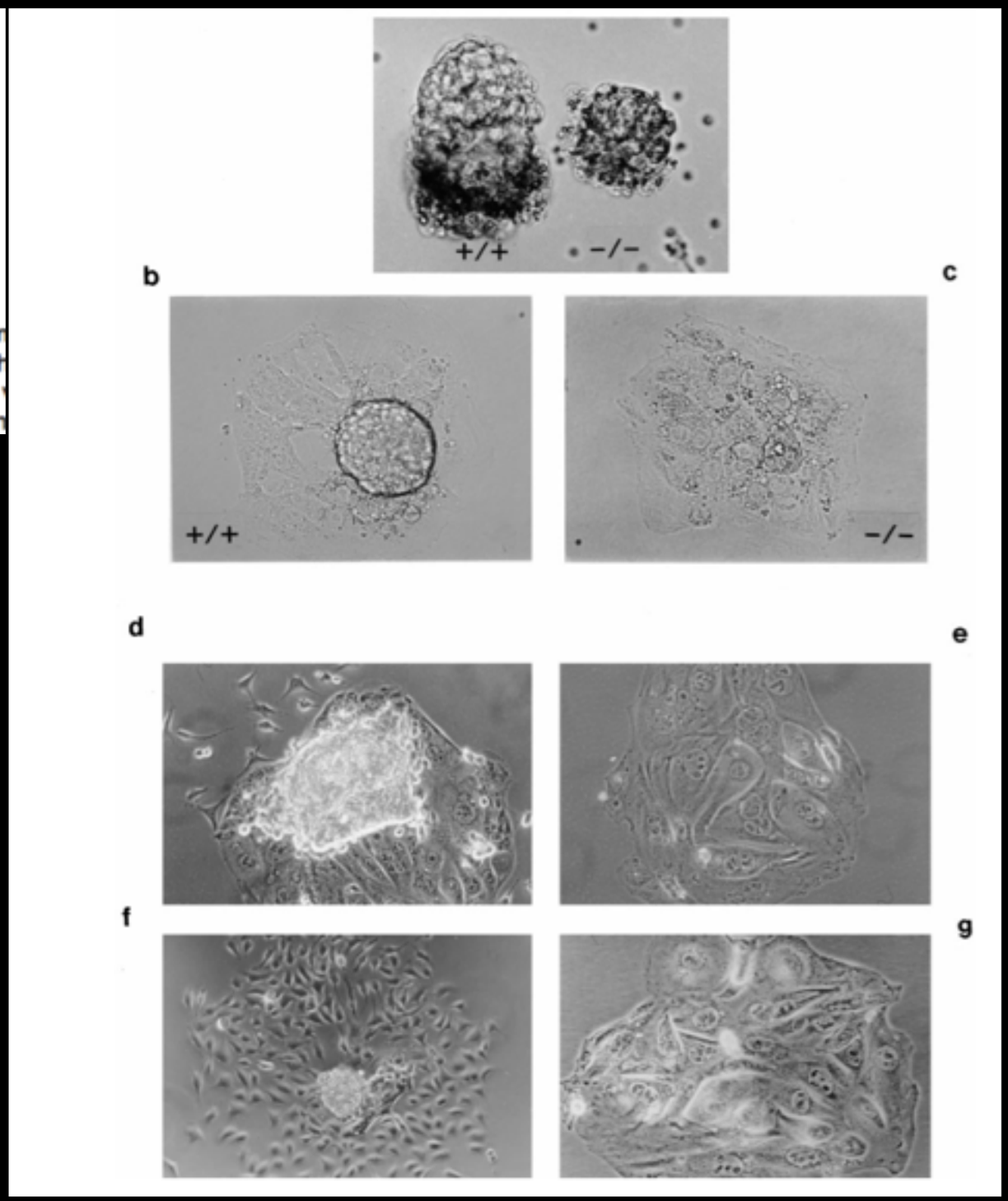
What genes maintain pluripotency in vivo and in vitro?

Cell, Vol. 95, 379–391, October 30, 1998, Copyright ©1998 by Cell Press

Formation of Pluripotent Stem Cells in the Mammalian Embryo Depends on the POU Transcription Factor Oct4

Jennifer Nichols,* Branko Zevnik,*§
Konstantinos Anastassiadis,† Hitoshi Niwa,*‖
Daniela Klewe-Nebenius,* Ian Chambers,*
Hans Schöler,† and Austin Smith*‡

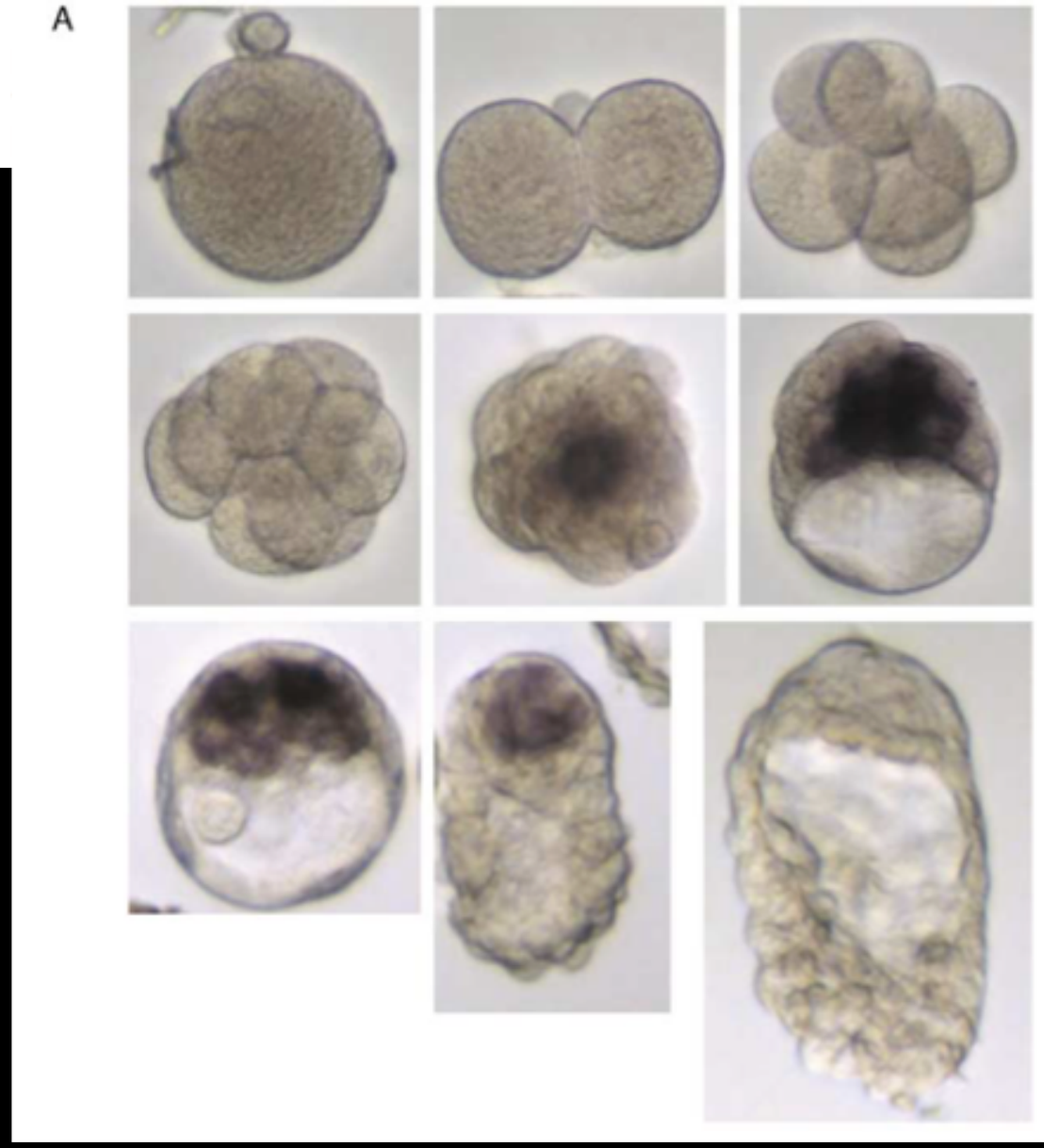
cell types, including germ
sor the epiblast are high
tions that can adjust to
major alterations in cell n

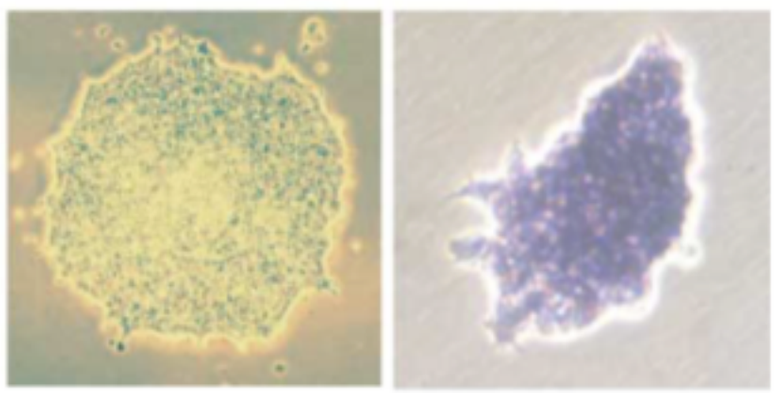


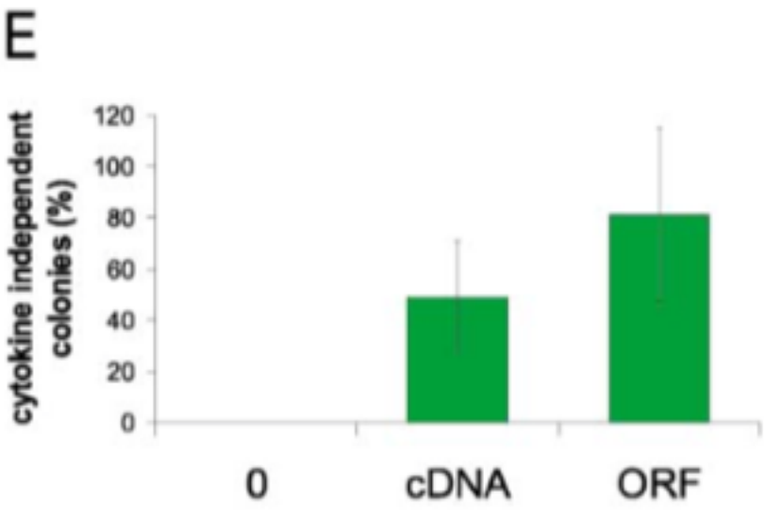
Cell, Vol. 113, 643–655, May 30, 2003, Copyright ©2003 by Cell Press

Functional Expression Cloning of Nanog, a Pluripotency Sustaining Factor in Embryonic Stem Cells

Ian Chambers,* Douglas Colby, Morag Robertson, Jennifer Nichols, Sonia Lee, Susan Tweedie, and Austin Smith

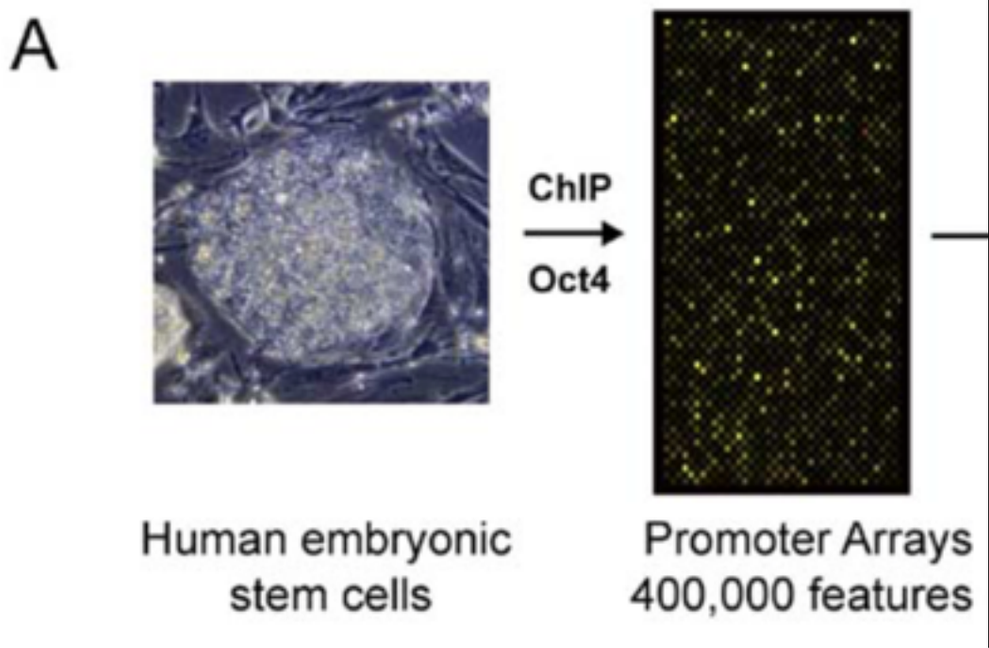


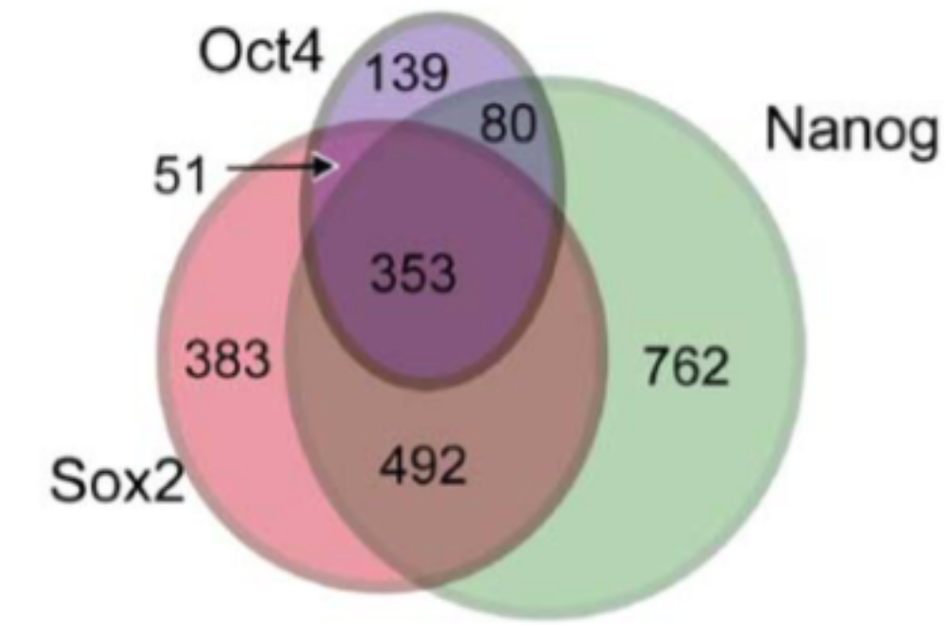


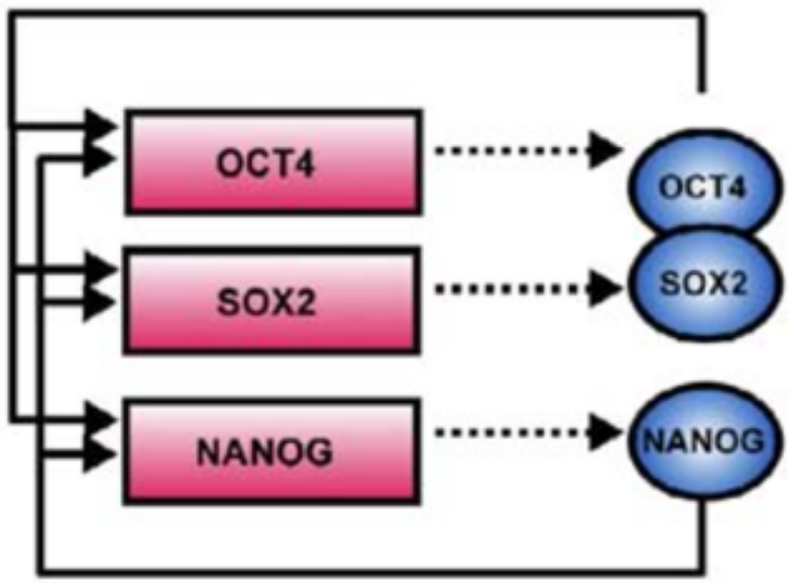


Core Transcriptional Regulatory Circuitry in Human Embryonic Stem Cells

Laurie A. Boyer,[1,6] Tong Ihn Lee,[1,6] Megan F. Cole,[1,2]
Sarah E. Johnstone,[1,2] Stuart S. Levine,[1]
Jacob P. Zucker,[3] Matthew G. Guenther,[1]
Roshan M. Kumar,[1] Heather L. Murray,[1]
Richard G. Jenner,[1] David K. Gifford,[1,4,5]
Douglas A. Melton,[3,5] Rudolf Jaenisch,[1,2]
and Richard A. Young[1,2,5,*]







Relationship between pluripotency and differentiation

A Precarious Balance: Pluripotency Factors as Lineage Specifiers

Kyle M. Loh[1,*] and Bing Lim[1,2,*]
[1]Genome Institute of Singapore, Stem Cell & Developmental Biology Group, Singapore 138672, Singapore
[2]Harvard Medical School, Department of Medicine and Beth Israel Deaconess Medical Center, Division of Hematology/Oncology, Boston, MA 02115, USA
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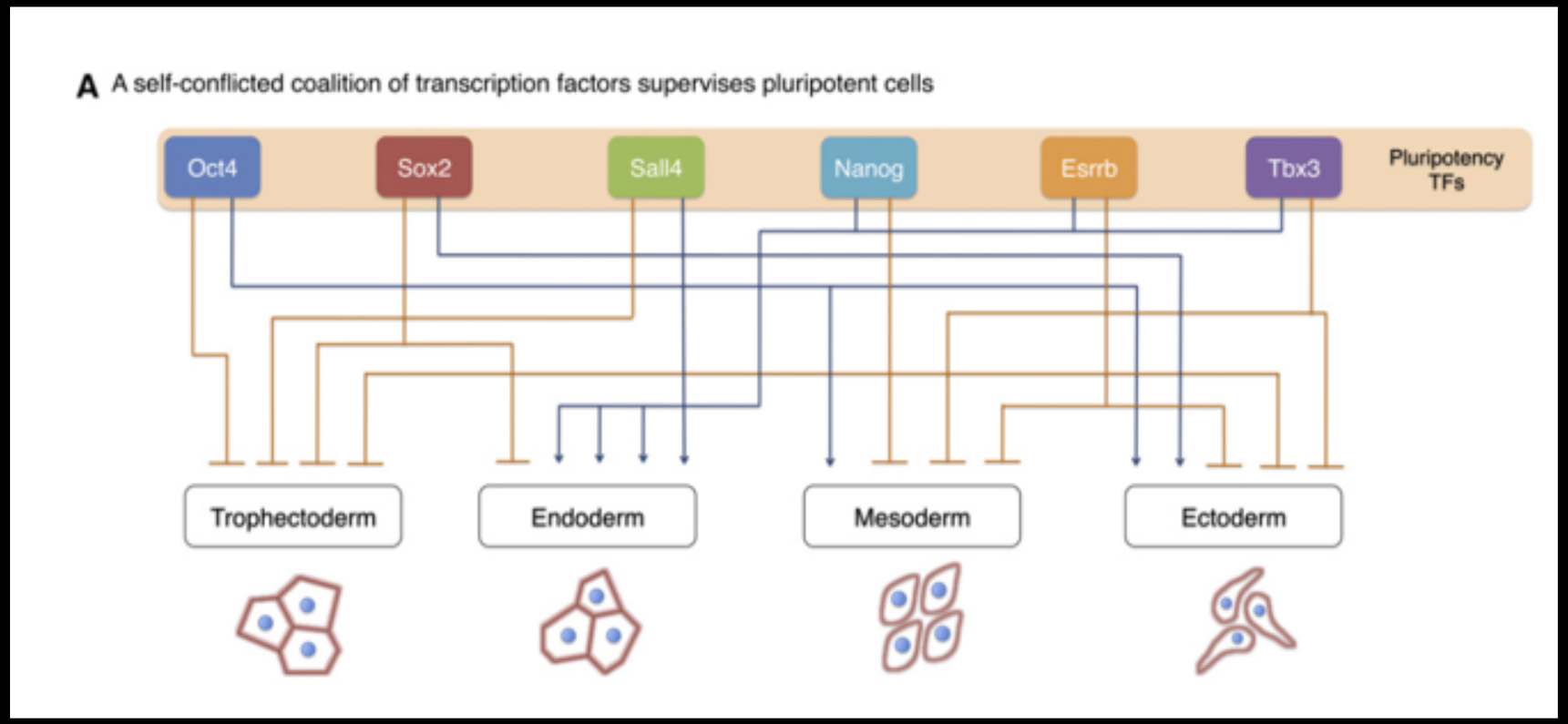
DOI 10.1016/j.stem.2011.03.013

Pluripotency genes have complex and opposing relationships with differentiated fates



How do cells exit the pluripotent state?

Pluripotency Factors in Embryonic Stem Cells Regulate Differentiation into Germ Layers

Matt Thomson,[1,2,3] Siyuan John Liu,[1,6] Ling-Nan Zou,[1,3] Zack Smith,[4] Alexander Meissner,[3,4] and Sharad Ramanathan[1,2,3,5,6,*]
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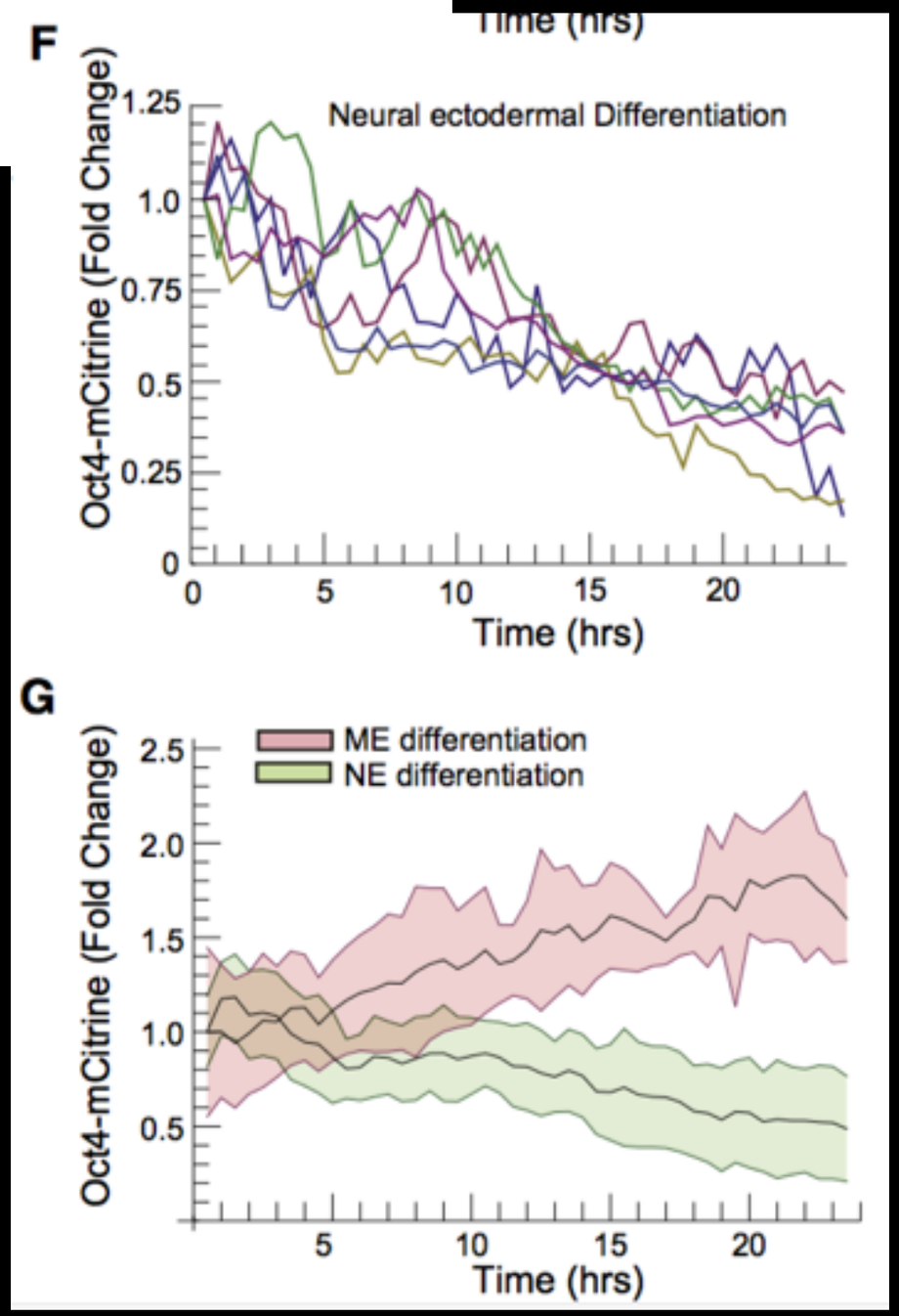
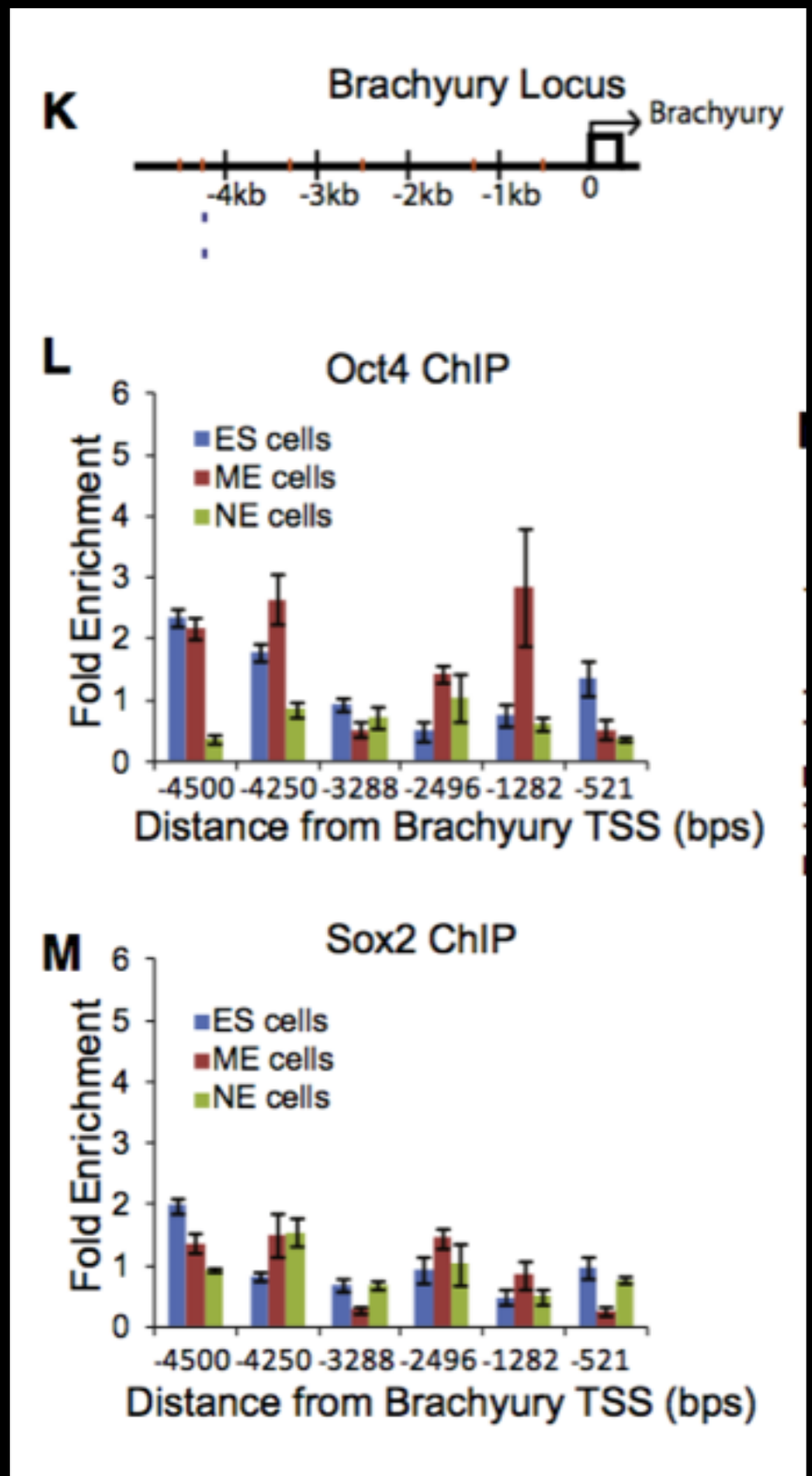
[2]Biophysics Program
[3]Harvard Stem Cell Institute
[4]Department of Stem Cell and Regenerative Biology
[5]School of Engineering and Applied Sciences
[6]Department of Molecular and Cellular Biology
Harvard University, Cambridge, MA 02138, USA





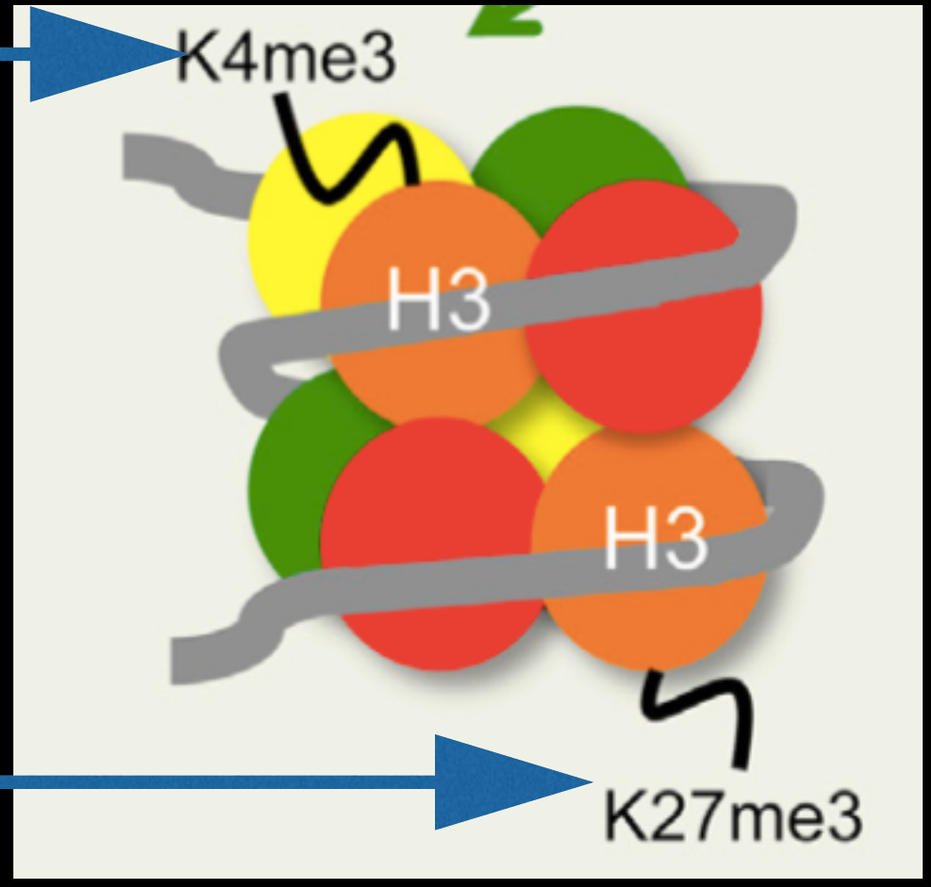
Epigenetics in stem cells

A Bivalent Chromatin Structure Marks Key Developmental Genes in Embryonic Stem Cells

Bradley E. Bernstein,[1,2,3,*] Tarjei S. Mikkelsen,[3,4] Xiaohui Xie,[3] Michael Kamal,[3] Dana J. Huebert,[1] James Cuff,[3] Ben Fry,[3] Alex Meissner,[5] Marius Wernig,[5] Kathrin Plath,[5] Rudolf Jaenisch,[5] Alexandre Wagschal,[6] Robert Feil,[6] Stuart L. Schreiber,[3,7] and Eric S. Lander[3,5]

Repressive

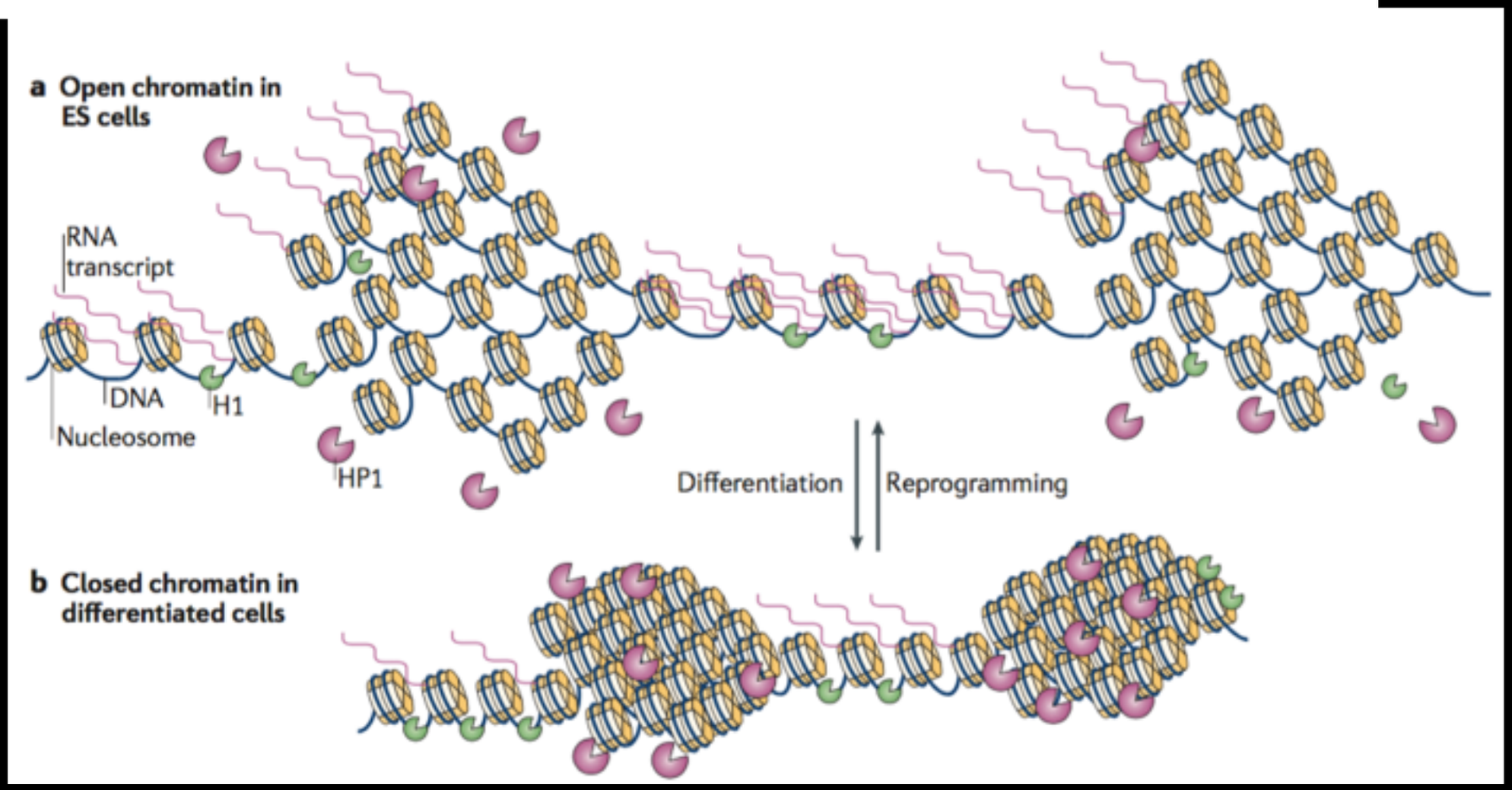
Activating



Global Chromatin Architecture Reflects Pluripotency and Lineage Commitment in the Early Mouse Embryo

Kashif Ahmed[1☯], Hesam Dehghani[2☯], Peter Rugg-Gunn[3], Eden Fussner[1], Janet Rossant[3], David P. Bazett-Jones[1*]

1 Genetics and Genome Biology Program, The Hospital for Sick Children, Toronto, Ontario, Canada, **2** Department of Physiology, School of Veterinary Medicine and Institute of Biotechnology, Ferdowsi University of Mashhad, Mashhad, Iran, **3** Developmental and Stem Cell Biology Program, The Hospital for Sick Children, Toronto, Ontario, Canada



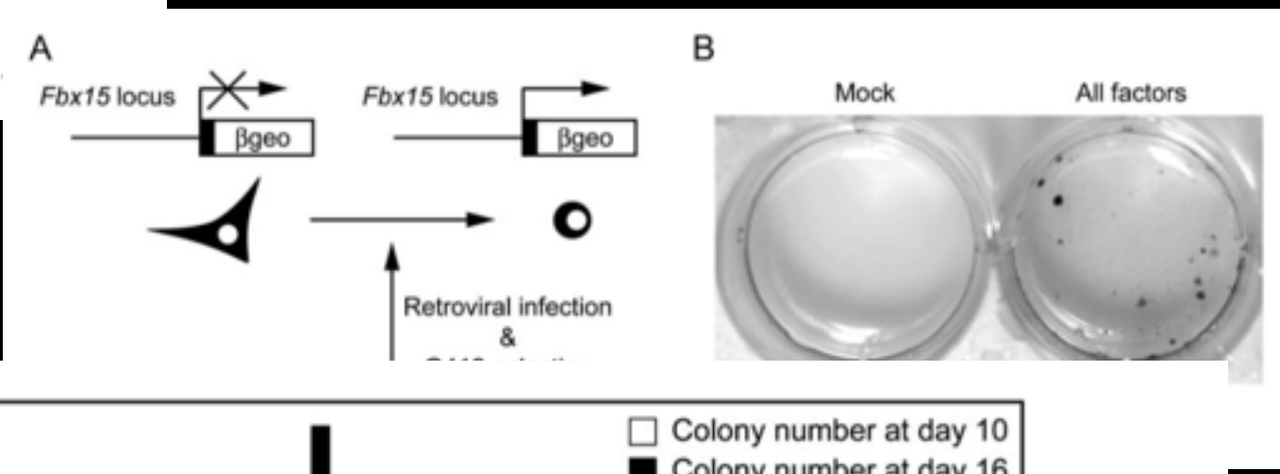
Global Transcription in Pluripotent Embryonic Stem Cells

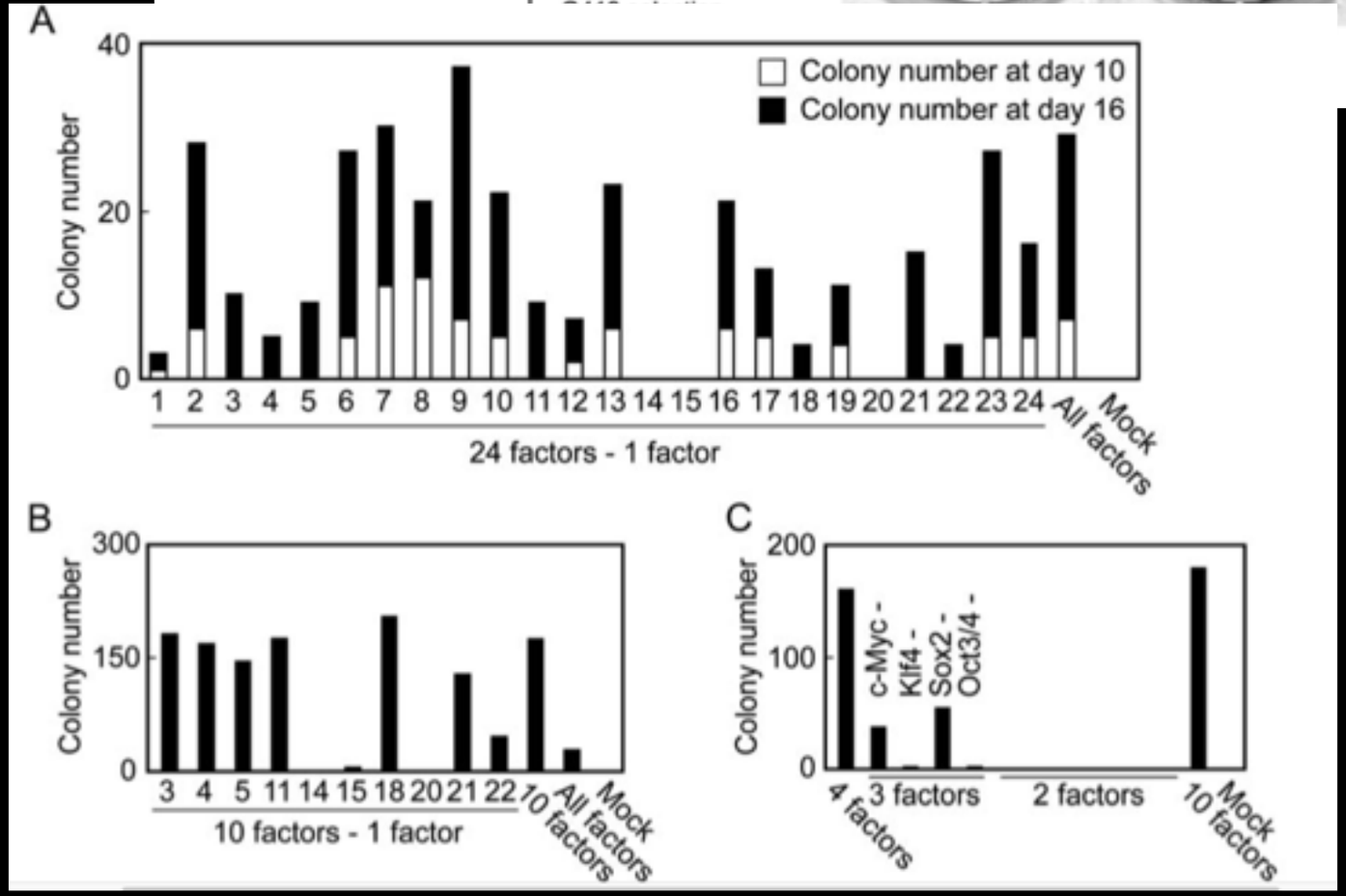
Sol Efroni,[1,8] Radharani Duttagupta,[2] Jill Cheng,[2,10] Hesam Dehghani,[3,11] Daniel J. Hoeppner,[4] Chandravanu Dash,[5] David P. Bazett-Jones,[3] Stuart Le Grice,[5] Ronald D.G. McKay,[4] Kenneth H. Buetow,[1] Thomas R. Gingeras,[2] Tom Misteli,[7,9,*] and Eran Meshorer[6,8,9,*]

Differentiated cells can be reprogrammed to the pluripotent state

Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors

Kazutoshi Takahashi[1] and Shinya Yamanaka[1,2,*]
[1] Department of Stem Cell Biology, Institute for Frontier Medical Sciences, Kyoto University, Kyoto 606-8507,
[2] CREST, Japan Science and Technology Agency, Kawaguchi 332-0012, Japan





To Gurdon and Yamanaka

"For the discovery that mature cells

can be reprogrammed
to become pluripotent"

SCNT can be done in human cells as well.

Human Embryonic Stem Cells Derived by Somatic Cell Nuclear Transfer

Masahito Tachibana,[1] Paula Amato,[2] Michelle Sparman,[1] Nuria Marti Gutierrez,[1] Rebecca Tippner-Hedges,[1] Hong Ma,[1] Eunju Kang,[1] Alimujiang Fulati,[1] Hyo-Sang Lee,[1,6] Hathaitip Sritanaudomchai,[3] Keith Masterson,[2] Janine Larson,[2] Deborah Eaton,[2] Karen Sadler-Fredd,[2] David Battaglia,[2] David Lee,[2] Diana Wu,[2] Jeffrey Jensen,[1,4] Phillip Patton,[2] Sumita Gokhale,[5] Richard L. Stouffer,[1,2] Don Wolf,[1] and Shoukhrat Mitalipov[1,2,*]

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*Correspondence: mitalipo@ohsu.edu

Substates of the pluripotent state

Regulated Fluctuations in Nanog Expression Mediate Cell Fate Decisions in Embryonic Stem Cells

Tibor Kalmar[1☯], Chea Lim[1☯], Penelope Hayward[1☯], Silvia Muñoz-Descalzo[1], Jennifer Nichols[2], Jordi Garcia-Ojalvo[3], Alfonso Martinez Arias[1*]

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Single-Cell Gene Expression Profiles Define Self-Renewing, Pluripotent, and Lineage Primed States of Human Pluripotent Stem Cells

Shelley R. Hough,[1,2] Matthew Thornton,[1] Elizabeth Mason,[4] Jessica C. Mar,[3] Christine A. Wells,[4] and Martin F. Pera[1,5,*]

[1]Eli and Edythe Broad Center for Regenerative Medicine and Stem Cell Research, Keck School of Medicine, University of Southern California, Los Angeles, CA 90089, USA
[2]University of Melbourne, Melbourne, 3010 VIC, Australia
[3]Department of Systems and Computational Biology and Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY 10461, USA
[4]Australian Institute for Bioengineering and Nanotechnology, University of Queensland, Brisbane, 4072 QLD, Australia
[5]University of Melbourne, Walter and Eliza Hall Institute of Medical Research, Florey Institute of Neuroscience and Mental Health, Melbourne, 3010 VIC, Australia

Dynamic Heterogeneity and DNA Methylation in Embryonic Stem Cells

Zakary S. Singer,[1,7] John Yong,[2,7] Julia Tischler,[6] Jamie A. Hackett,[6] Alphan Altinok,[2,3] M. Azim Surani,[6] Long Cai,[4] and Michael B. Elowitz[5,*]

[1]Computation and Neural Systems
[2]Division of Biology
[3]Biological Network Modeling Center
[4]Program in Biochemistry and Molecular Biophysics and Division of Chemistry and Chemical Engineering
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California Institute of Technology, Pasadena, CA 91125, USA
[6]The Wellcome Trust/Cancer Research UK Gurdon Institute, The Henry Wellcome Building of Cancer and Developmental Biology, University of Cambridge, Tennis Court Road, Cambridge CB2 1QN, UK
[7]Co-first author

The cell cycle and differentiation

The Cell-Cycle State of Stem Cells Determines Cell Fate Propensity

Siim Pauklin[1,*] and Ludovic Vallier[1,2,*]
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Department of Surgery, University of Cambridge, Cambridge CB2 0SZ, UK
[2]Wellcome Trust Sanger Institute, Hinxton, Cambridge CB10 1SA, UK
*Correspondence: sp579@cam.ac.uk (S.P.), lv225@cam.ac.uk (L.V.)
http://dx.doi.org/10.1016/j.cell.2013.08.031

Cell-Cycle Control of Developmentally Regulated Transcription Factors Accounts for Heterogeneity in Human Pluripotent Cells

Amar M. Singh,[1] James Chappell,[1] Robert Trost,[1] Li Lin,[2] Tao Wang,[2] Jie Tang,[1] Hao Wu,[3] Shaying Zhao,[1] Peng Jin,[2] and Stephen Dalton[1,*]
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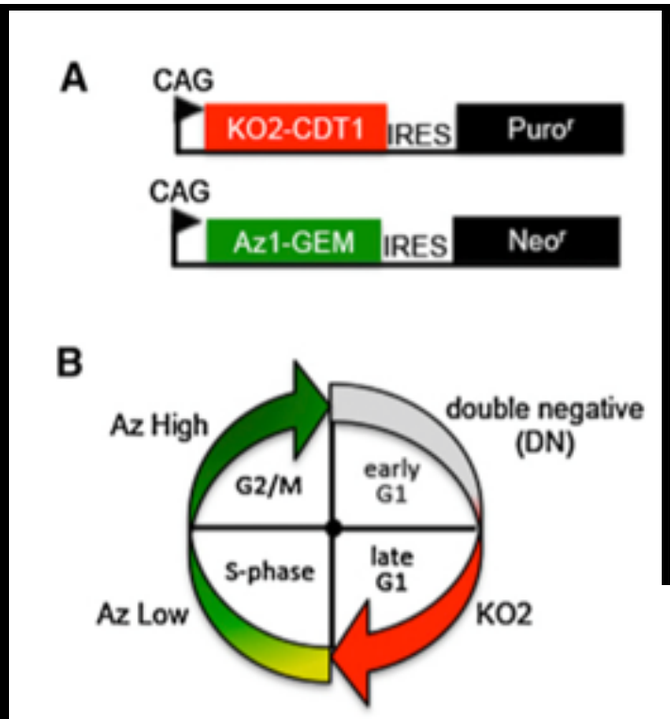
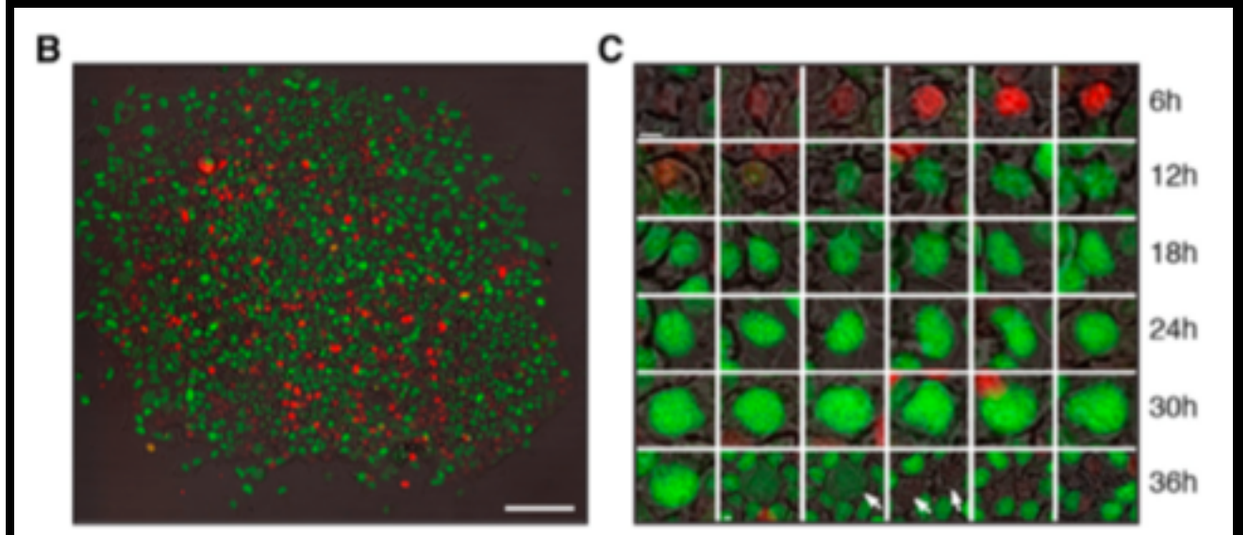
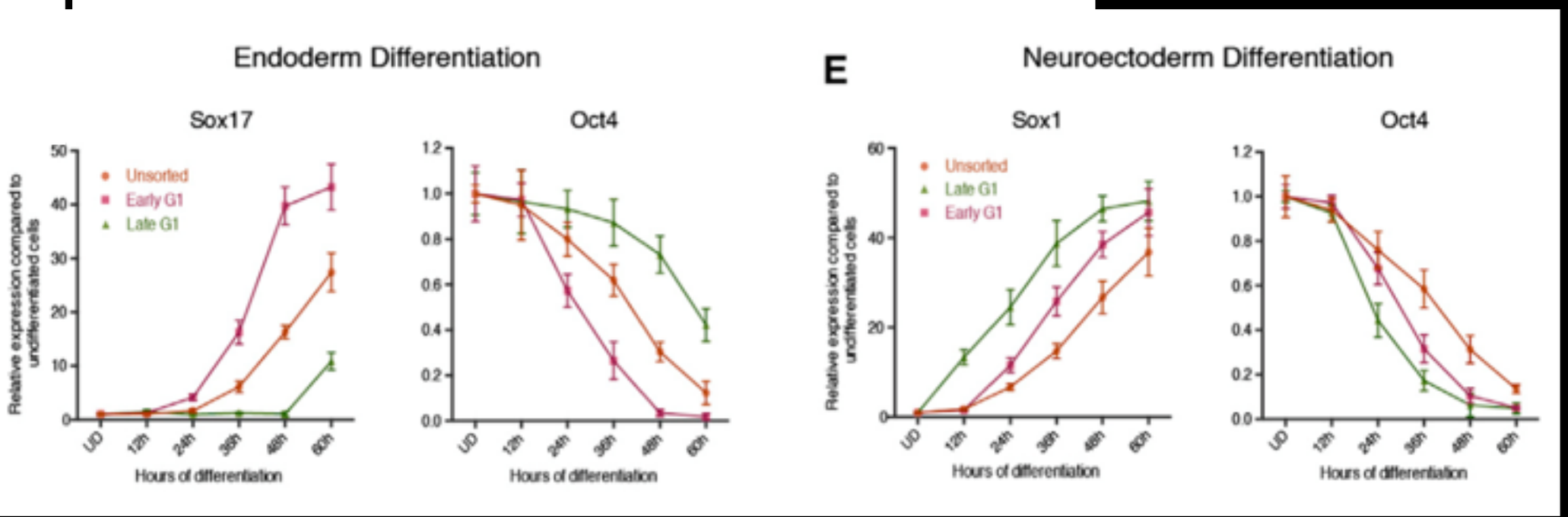
[3]Department of Biostatistics and Bioinformatics, Emory University, 1518 Clifton Road, Atlanta, GA 30322, USA
*Correspondence: sdalton@uga.edu
http://dx.doi.org/10.1016/j.stemcr.2013.10.009







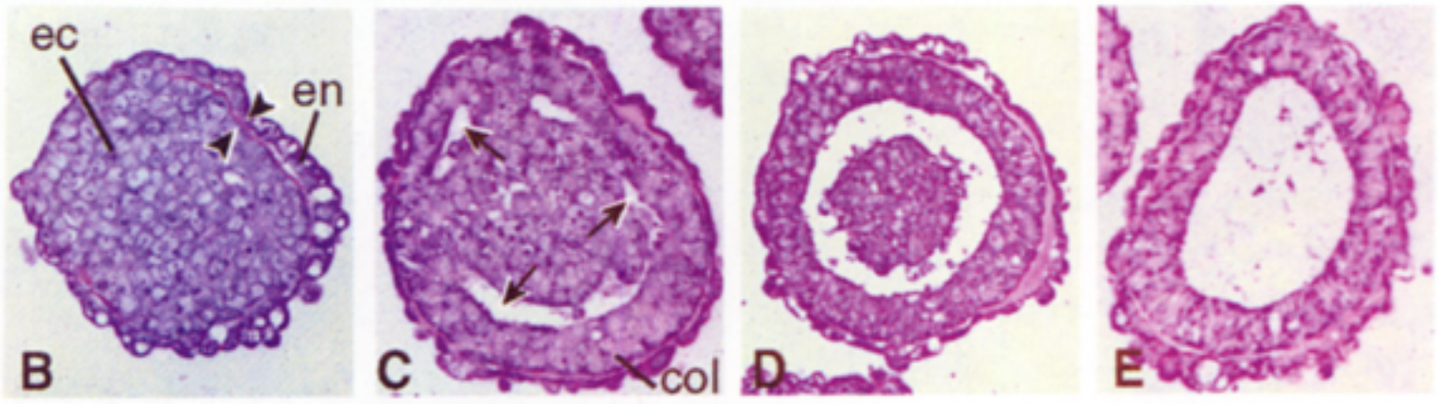
Understanding early development with stem cells

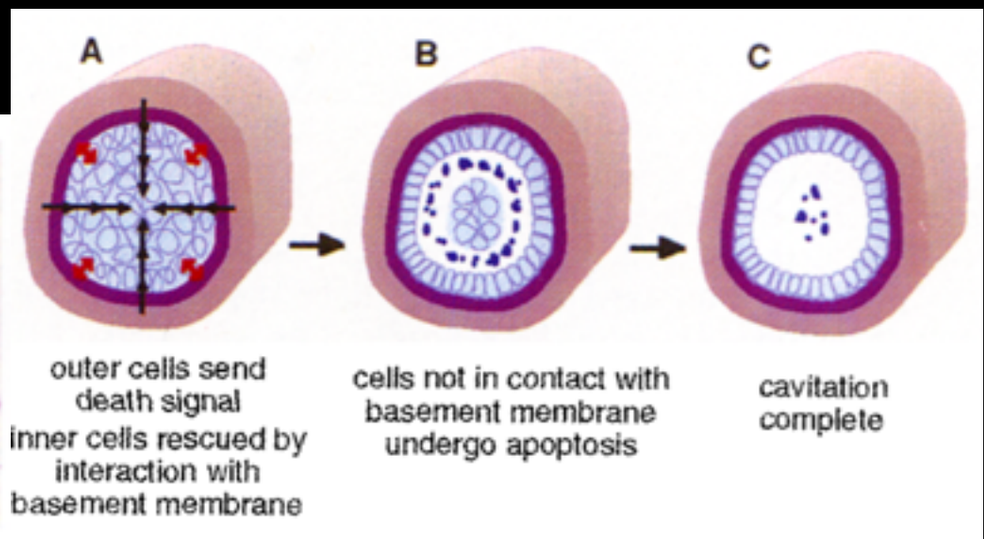
Cell, Vol. 83, 279–287, October 20, 1995, Copyright © 1995 by Cell Press

Signals for Death and Survival: A Two-Step Mechanism for Cavitation in the Vertebrate Embryo

Electra Coucouvanis and Gail R. Martin

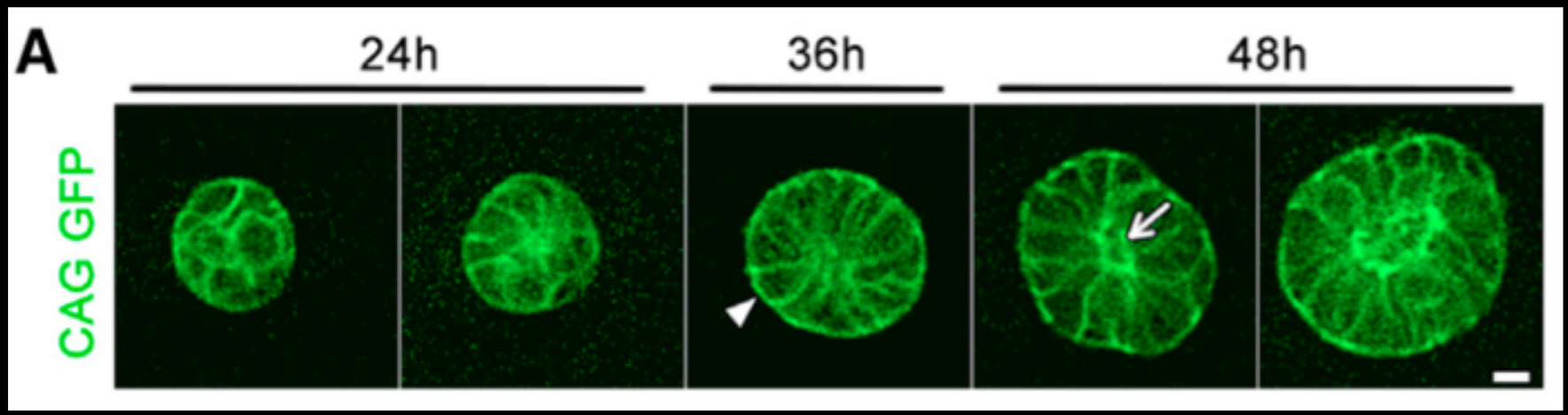
cells had been docum





Self-Organizing Properties of Mouse Pluripotent Cells Initiate Morphogenesis upon Implantation

Ivan Bedzhov[1,2] and Magdalena Zernicka-Goetz[1,2,*]



Studying patterning with stem cells

RESEARCH ARTICLE STEM CELLS AND REGENERATION

Symmetry breaking, germ layer specification and axial organisation in aggregates of mouse embryonic stem cells

Susanne C. van den Brink[1,*], Peter Baillie-Johnson[1,*], Tina Balayo[1], Anna-Katerina Hadjantonakis[2], Sonja Nowotschin[2], David A. Turner[1] and Alfonso Martinez Arias[1,‡]

Wnt Signaling Mediates Self-Organization and Axis Formation in Embryoid Bodies

Derk ten Berge,[1,2,3,*] Wouter Koole,[1,2,3] Christophe Fuerer,[1,2] Matt Fish,[1,2] Elif Eroglu,[1,2] and Roel Nusse[1,2,*]
[1]Howard Hughes Medical Institute
[2]Department of Developmental Biology
Stanford University School of Medicine, Stanford, CA 94305, USA
[3]These authors contributed equally to this work
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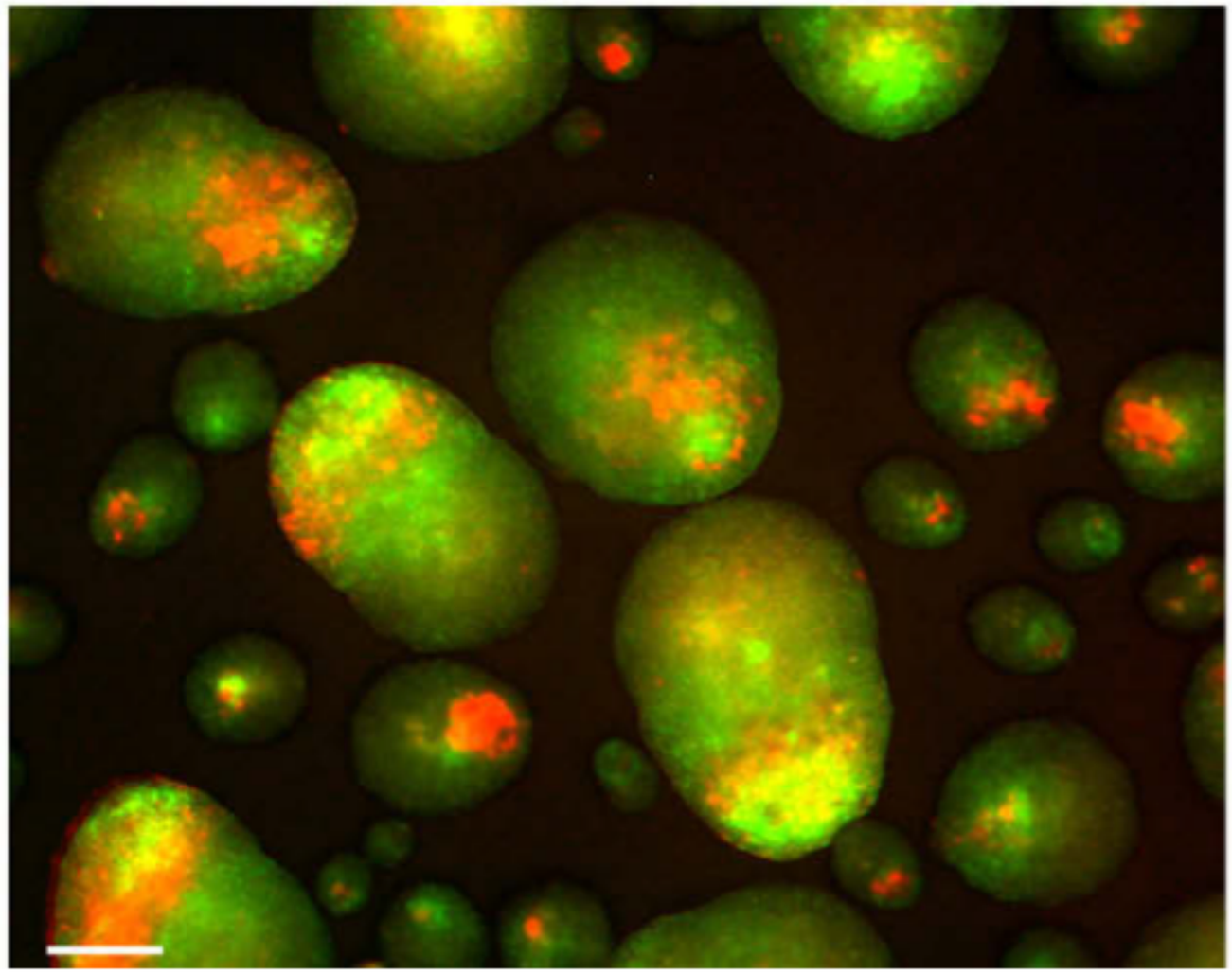
DOI 10.1016/j.stem.2008.09.013

Bry-GFP;7xTCF-mCherry



Spatial patterning in hESCs

A method to recapitulate early embryonic spatial patterning in human embryonic stem cells

Aryeh Warmflash[1–3], Benoit Sorre[1–3], Fred Etoc[1,2], Eric D Siggia[1] & Ali H Brivanlou[2]