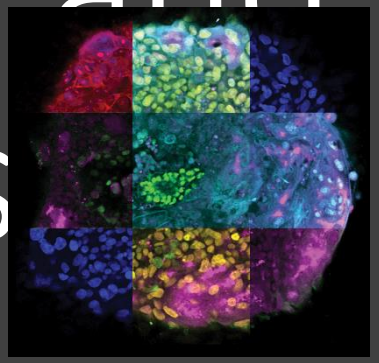
Origin, mechanisms, and clinical consequences of embryo mosicism in humans"



CRB-AAB MAY 18, 2017

David F. Albertini,Ph.D.
Director of Laboratories, Senior Scientist
Center For Human Reproduction

Conflict Statement

Dr. Albertini

Receives income from Springer/Nature Publishing, Inc.

Has stock options in OvaScience, Inc.

Is a member of the EMD Serono speaker bureau

Outline

Origins of chromosomal and non-chromosomal mosaicism are gametic and zygotic

Mechanisms of mosaicism involve perturbations in coordination between cell cycle, cytoskeleton, and chromatin remodeling

Clinical consequences of mosaicism bear on both our ability to detect and make best decisions on behalf of our patients

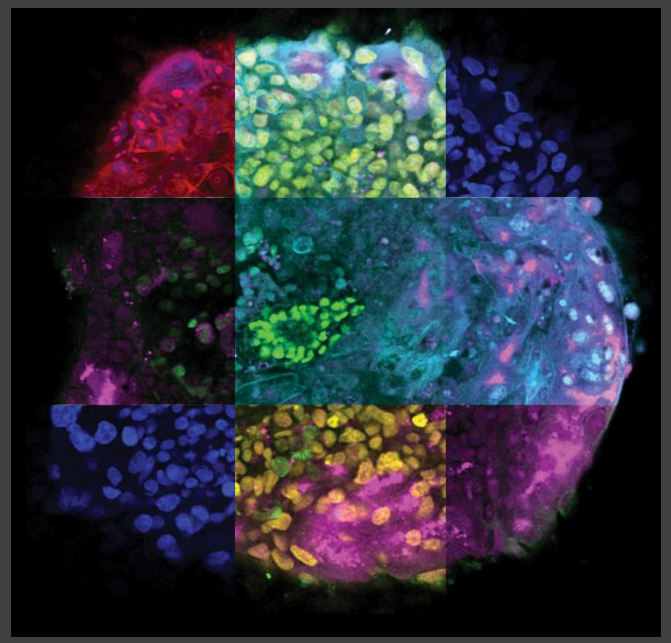
Two Notions About Embryo Quality

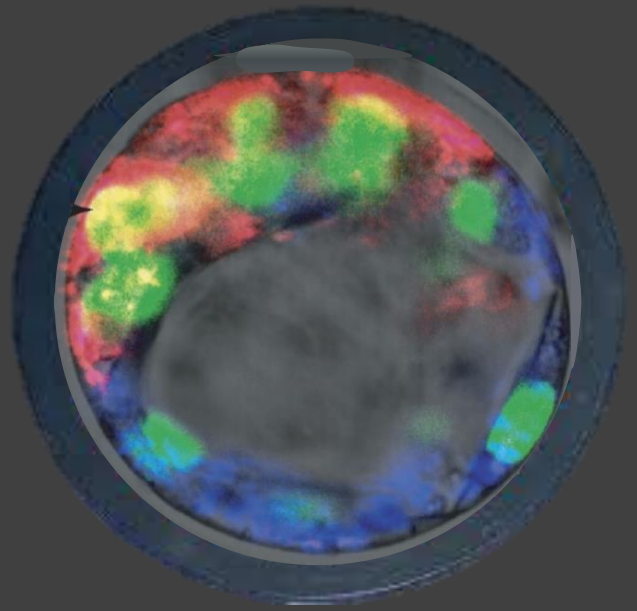
That from fertilization to Blast, the embryo dictates its developmental fate by expressing tangible/observable properties or byproducts reflecting implantation and term development potential

Morphology/Morphokinetics/”omes”/PGD-PGS/Mitochondria…..amongst a cohort, those with potential can be differentiated from those lacking potetial

That a zygote’s developmental potential is determined prior to fertilization, that is inherent to gametes, and in no way manifests during the preimplantation window of development

High quality gametes are few and far between and require pre-selection





Mosaicism

noun mo·sa·ic \mō-ˈzā-ik\

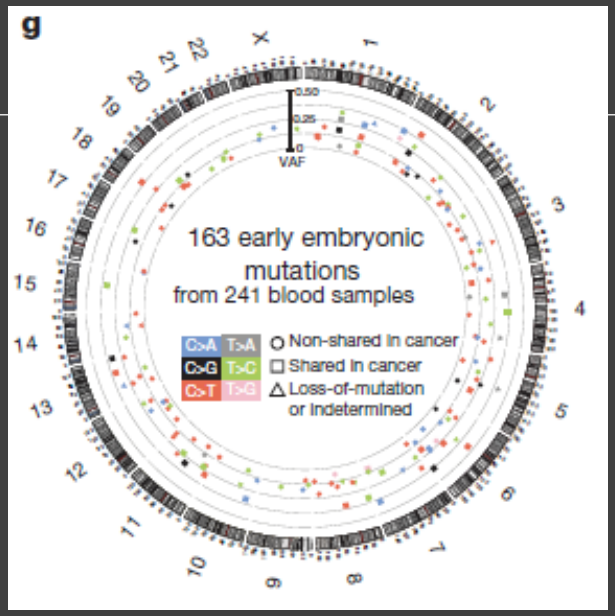
- a decoration on a surface made by pressing small pieces of colored glass or stone into a soft material that then hardens to make pictures or patterns
- the condition of possessing cells of two or more different genetic constitutions

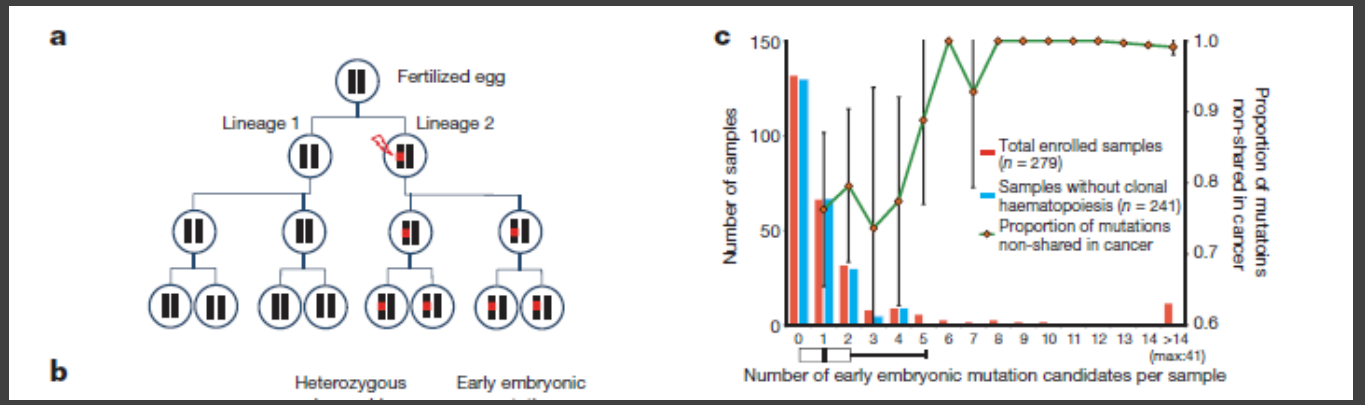
Origins of chromosomal and non-chromosomal mosaicism are gametic and zygotic

doi:10.1038/nature21703

Somatic mutations reveal asymmetric cellular dynamics in the early human embryo

Young Seok Ju[1,2], Inigo Martincorena[1], Moritz Gerstung[1,3], Mia Petljak[1], Ludmil B. Alexandrov[1,4], Raheleh Rahbari[5], David C. Wedge[1,6], Helen R. Davies[1], Manasa Ramakrishna[1], Anthony Fullam[1], Sancha Martin[1], Christopher Alder[1], Nikita Patel[1], Steve Gamble[1], Sarah O'Meara[1], Dilip D. Giri[7], Torril Sauer[8], Sarah E. Pinder[9], Colin A. Purdie[10], Åke Borg[11,12,13], Henk Stunnenberg[14], Marc van de Vijver[15], Benita K. T. Tan[16], Carlos Caldas[17], Andrew Tutt[18,19], Naoto T. Ueno[20], Laura J. van 't Veer[21], John W. M. Martens[22], Christos Sotiriou[23], Stian Knappskog[24,25], Paul N. Span[26], Sunil R. Lakhani[27,28,29], Jórunn Erla Eyfjörd[30], Anne-Lise Børresen-Dale[31,32], Andrea Richardson[33], Alastair M. Thompson[34], Alain Viari[35], Matthew E. Hurles[5], Serena Nik-Zainal[1], Peter J. Campbell[1] & Michael R. Stratton[1]

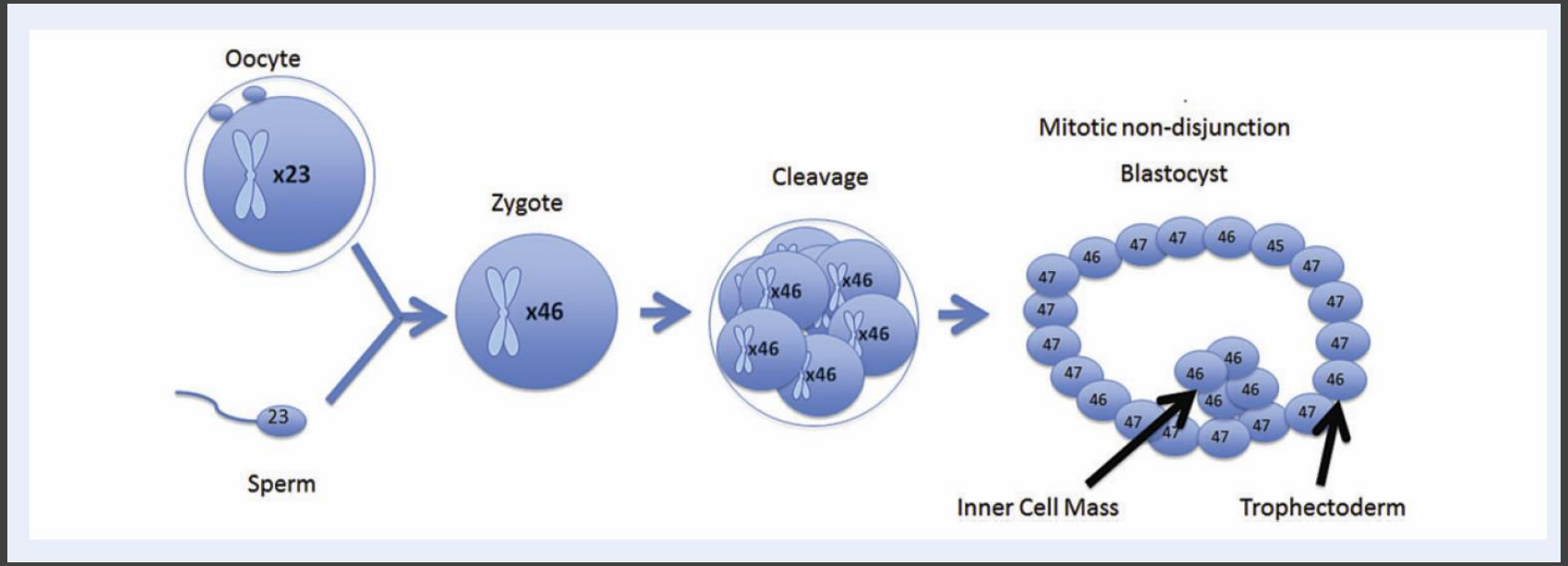




The origin, mechanisms, incidence and clinical consequences of chromosomal mosaicism in humans

Tyl H. Taylor[1,2,*], Susan A. Gitlin[3], Jennifer L. Patrick[1], Jack L. Crain[1], J. Michael Wilson[1], and Darren K. Griffin[2]

[1]Reproductive Endocrinology Associates of Charlotte, 1524 E Morehead St., Charlotte, 28207 NC, USA [2]Department of Biosciences, University of Kent, Canterbury CT2 7NJ, UK [3]Department of Obstetrics and Gynecology, Eastern Virginia Medical School, Jones Institute for Reproductive Medicine, 601 Colley Avenue #316, Norfolk, 23507 VA, USA

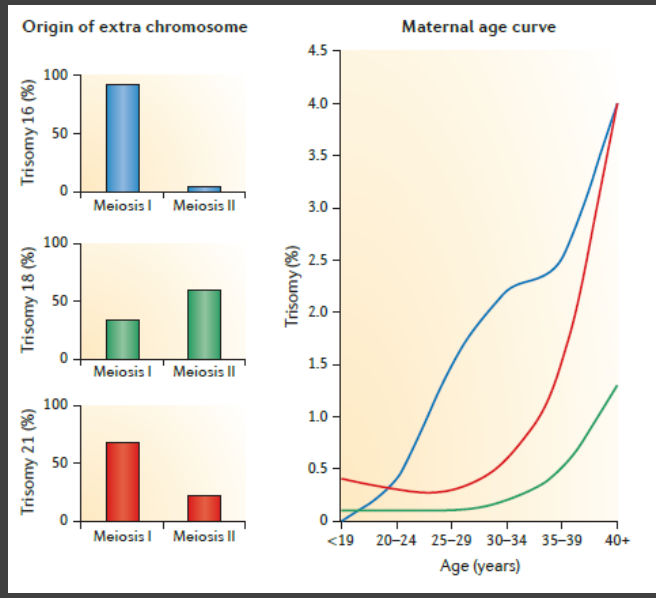


A mitotic error that occurred in the trophectoderm of the blastocyst. The blastocyst is a mosaic; however, the error is isolated to the trophectoderm, while the inner cell mass remains euploid.

Human Reproduction Update, Vol.20, No.4 pp. 571–581, 2014
Advanced Access publication on March 25, 2014 doi:10.1093/humupd/dmu016

Human aneuploidy: mechanisms and new insights into an age-old problem

So I. Nagaoka, Terry J. Hassold and Patricia A. Hunt



Opitz (again)

Am J Med Genet Suppl. 1987;3:93-112.

Western medicine is being sensitized to the enormous extent of prenatal death in humans at a time when such deaths, occurring after the first missed period, involve to an ever increasing degree wanted pregnancies conceived by women with rising mean maternal age, decreasing mean fertility, and ever greater desire and intention to assure a good pregnancy outcome. Available data suggest that about two-thirds of human ova, embryos, and fetuses fail to reach birth or the end of the first year of life, with infant mortality of 1.06%, stillbirth rate of 8/1,000, abortion rate of about 15%, and death rate around the time of implantation estimated at 34%. Based on limited data on sperm, ova aspirated from Graafian follicles in infertile women, direct observation of a few implanting ova, the low rate of human fecundity, and the high failure rate of in vitro fertilization, it seems reasonable to suppose that about 30% of human ova perish at the time of fertilization and before implantation. Most of this prenatal death is attributable to chromosome abnormalities (aneuploidy and polyploidy), estimated to be present at the beginning of development in about half of all human ova or embryos.

Mosaicism is a common thing

Metazoans rely on cell-cell variation and cope with

OPEN ACCESS Freely available online

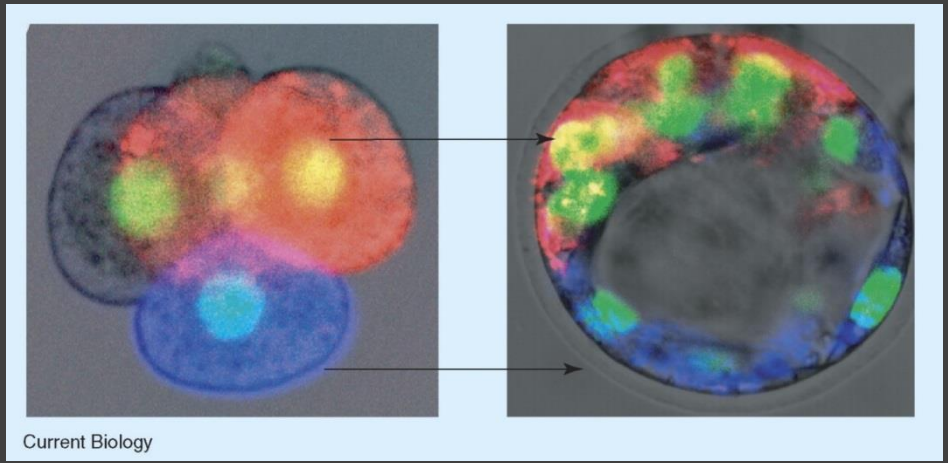
PLoS one

Early Embryonic Chromosome Instability Results in Stable Mosaic Pattern in Human Tissues

Hasmik Mkrtchyan[1], Madeleine Gross[1¤a], Sophie Hinreiner[1¤b], Anna Polytiko[2], Marina Manvelyan[3], Kristin Mrasek[1], Nadezda Kosyakova[1], Elisabeth Ewers[1], Heike Nelle[1], Thomas Liehr[1], Marianne Volleth[4], Anja Weise[1]*

Citation: Mkrtchyan H, Gross M, Hinreiner S, Polytiko A, Manvelyan M, et al. (2010) Early Embryonic Chromosome Instability Results in Stable Mosaic Pattern in Human Tissues. PLoS ONE 5(3): e9591. doi:10.1371/journal.pone.0009591

Mosaicism is the norm not the exception, as is developmental autonomy



LETTER

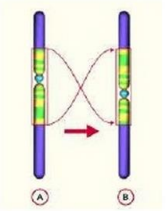
doi:10.1038/nature17948

Self-organization of the *in vitro* attached human embryo

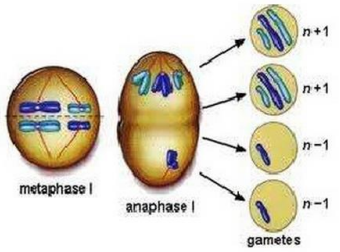
Alessia Deglincerti[1]*, Gist F. Croft[1]*, Lauren N. Pietila[1], Magdalena Zernicka-Goetz[2], Eric D. Siggia[3] & Ali H. Brivanlou[1]

Chromosomal abnormalities

- The inheritance of the parental pathology
  - true inheritance
  (e.g.: parental translocation)



  - Chromosomal nondisjunction during gametogenesis
  (80-85% of causes relate to oocytes
  10-15% - relate to spermatozoa)



- Mitotic errors in the zygote

Critical events during early mammalian development

Get cell cycles in order- finish meiosis and start mitosis-major source of aneuploidies

Erase maternal mRNAs and stockpile maternal proteins (especially TFs for activating embryonic genome)

Orient cell divisions to generate ICM and trophectoderm

Equally distribute organelles (nucleoli, mitochondria, Golgi, centrosomes)

Gametic Contributions

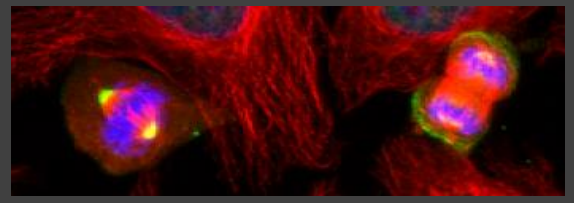
OOCYTE

A haploid genome

Mitochondria

All of the organellar precursors to reconstruct 100 cells in a blastocyst

7 cell cycles worth of cyclins, tubulin (circa 64 mitotic spindles and cleavage furrows)

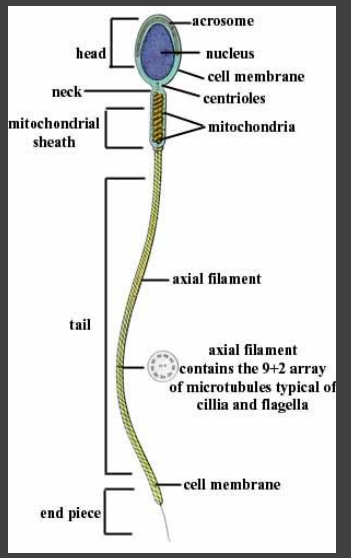


SPERM

A compacted haploid, non-functional genome desperately in need of a makeover

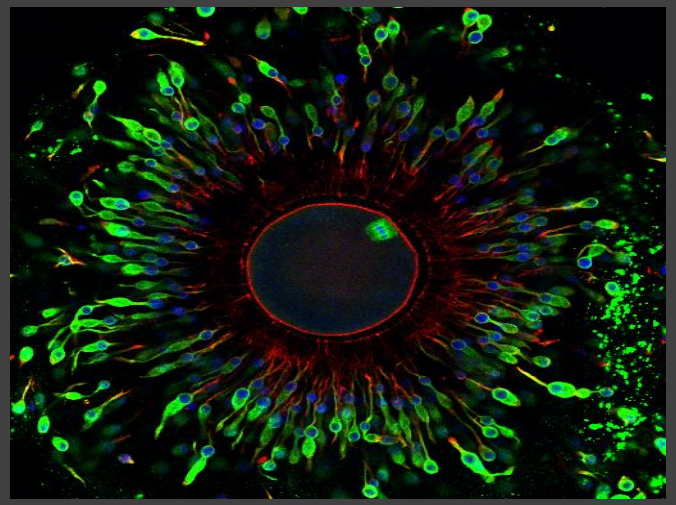
A centrosome

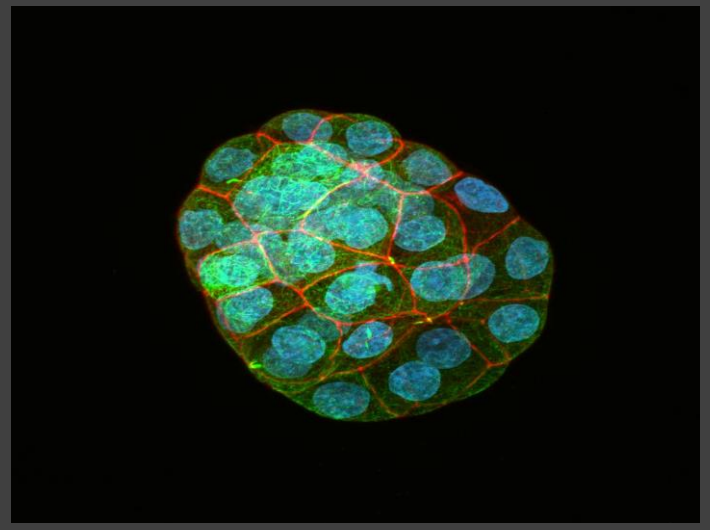
A spark (PLCzeta)



Good Gametes Make Good Embryos

FROM HERE.....TO.....THERE

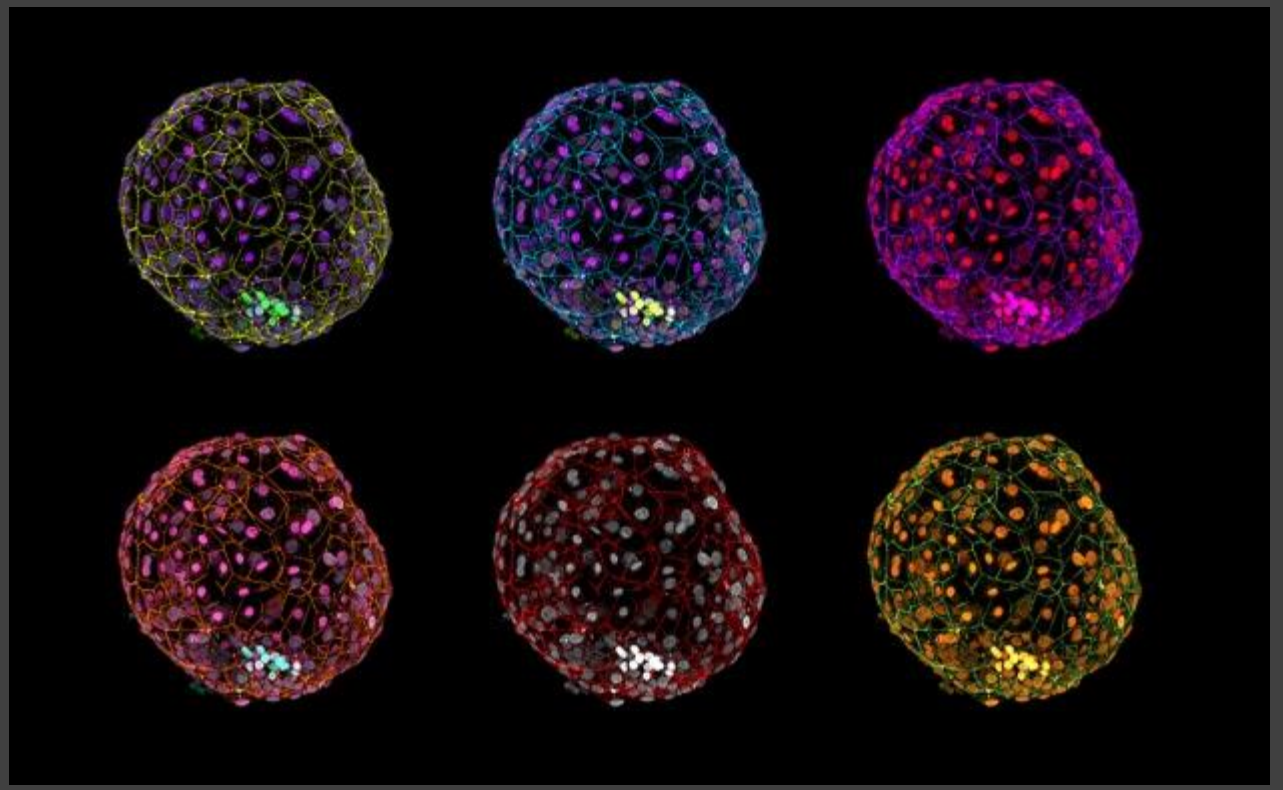




Embryogenesis begins with Oogenesis

Concept emerges that embryogenesis is about carving up the pie!

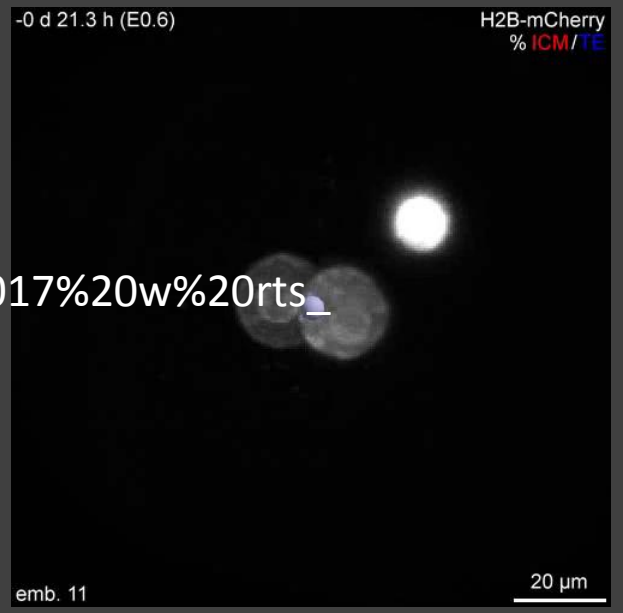
Blastocyst and inner cell mass



Alessia Deglincerti, Gist Croft, and Ali H. Brivanlou

New look at mammalian embryos (Ellenberg, 2016)

https://www.aab.org/images/reg%20form%2017%20w%20rts_rev_4-12-17.pdf



The tip of an iceberg: genetics

Genetics is changing into a very non-mendelian thing

Retains enormous diagnostic potential

May avail molecular nanosurgery for corrective or eradicating lesions

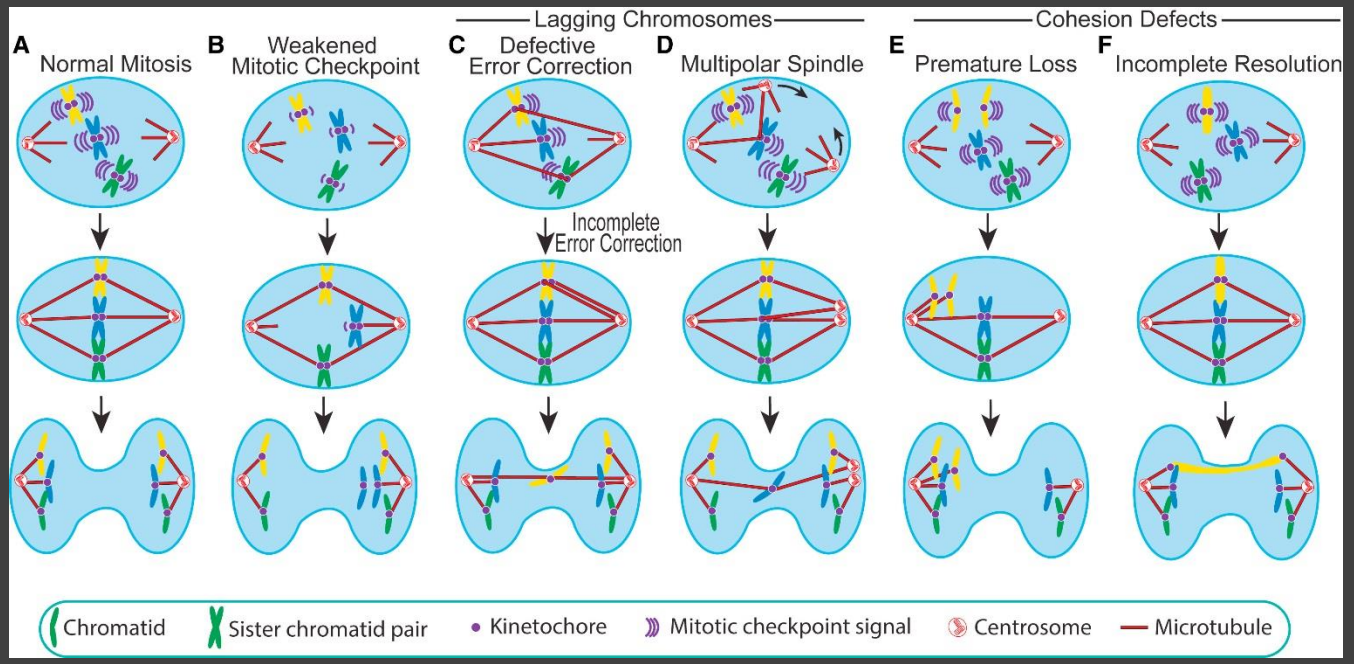
Is dominated presently by phase 3 technology…gene editing

Invading/reshaping practice of ARTs

As are many other entrepreneurs with vivid imaginations and deep pockets to fill

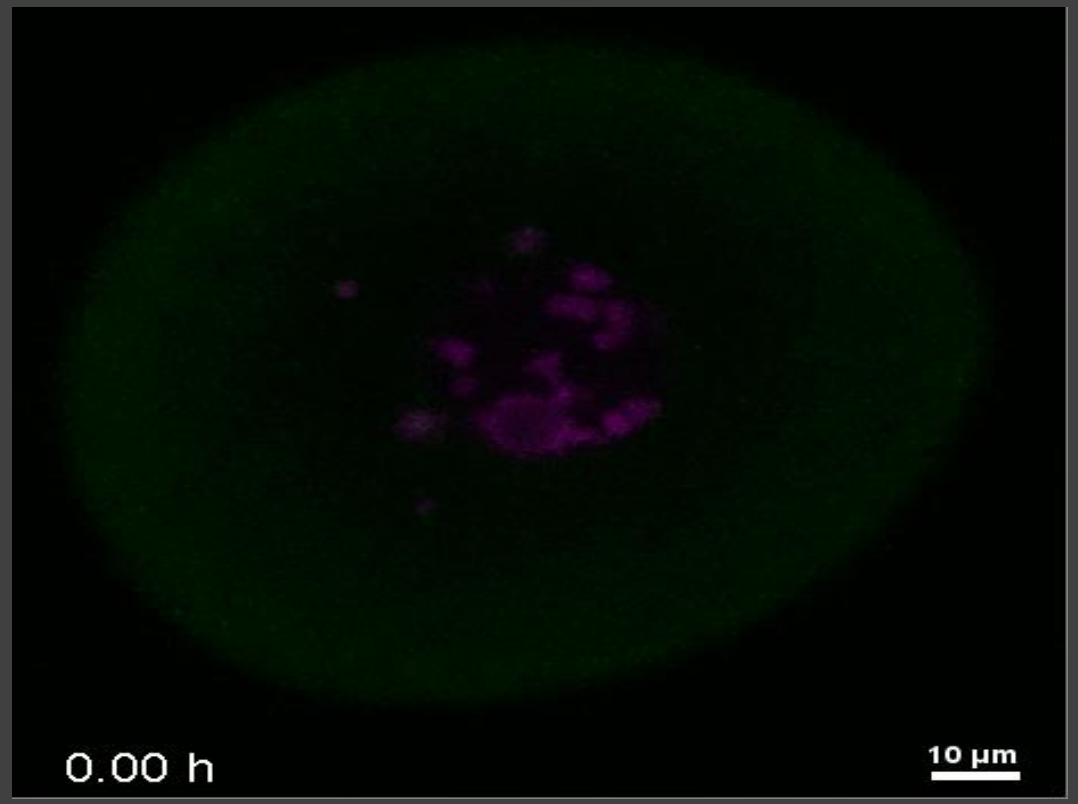
Figure 1

Mechanisms of mosaicism involve perturbations in coordination between cell cycle, cytoskeleton, and chromatin remodeling



Developmental Cell 2016 39, 638-652DOI: (10.1016/j.devcel.2016.10.023)

Genomic instability starts with meiosis I and II in human oocytes

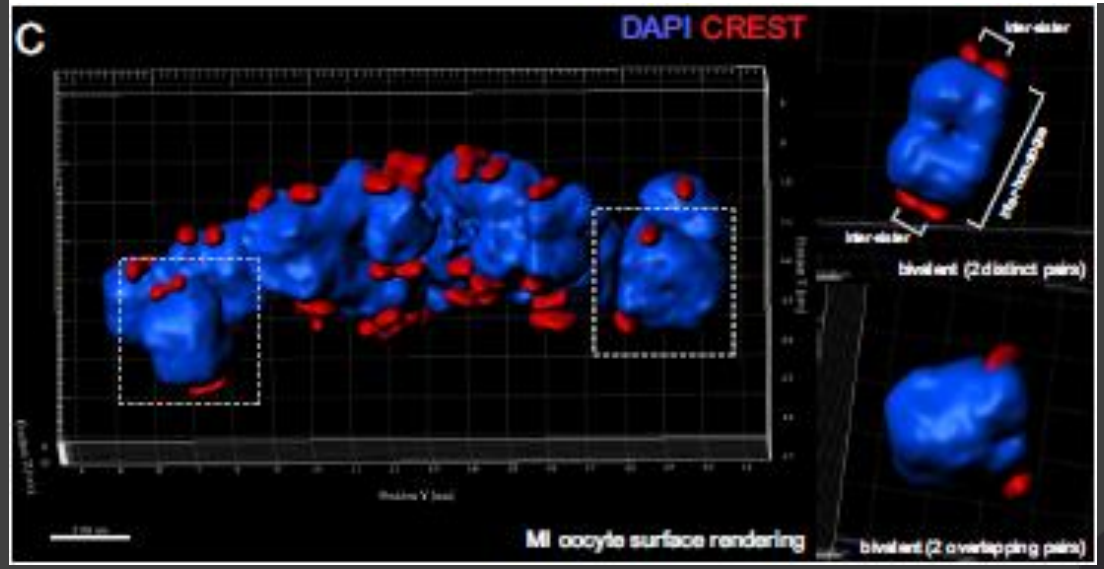


© 2016. Published by The Company of Biologists Ltd | Biology Open (2016) 5, 178-184 doi:10.1242/bio.016394

RESEARCH ARTICLE

Unique geometry of sister kinetochores in human oocytes during meiosis I may explain maternal age-associated increases in chromosomal abnormalities

Jessica Patel[1], Seang Lin Tan[2], Geraldine M. Hartshorne[1,3] and Andrew D. McAinsh[4,*]



Mechanisms Underlying Genomic Instability

weakened spindle checkpoint signaling

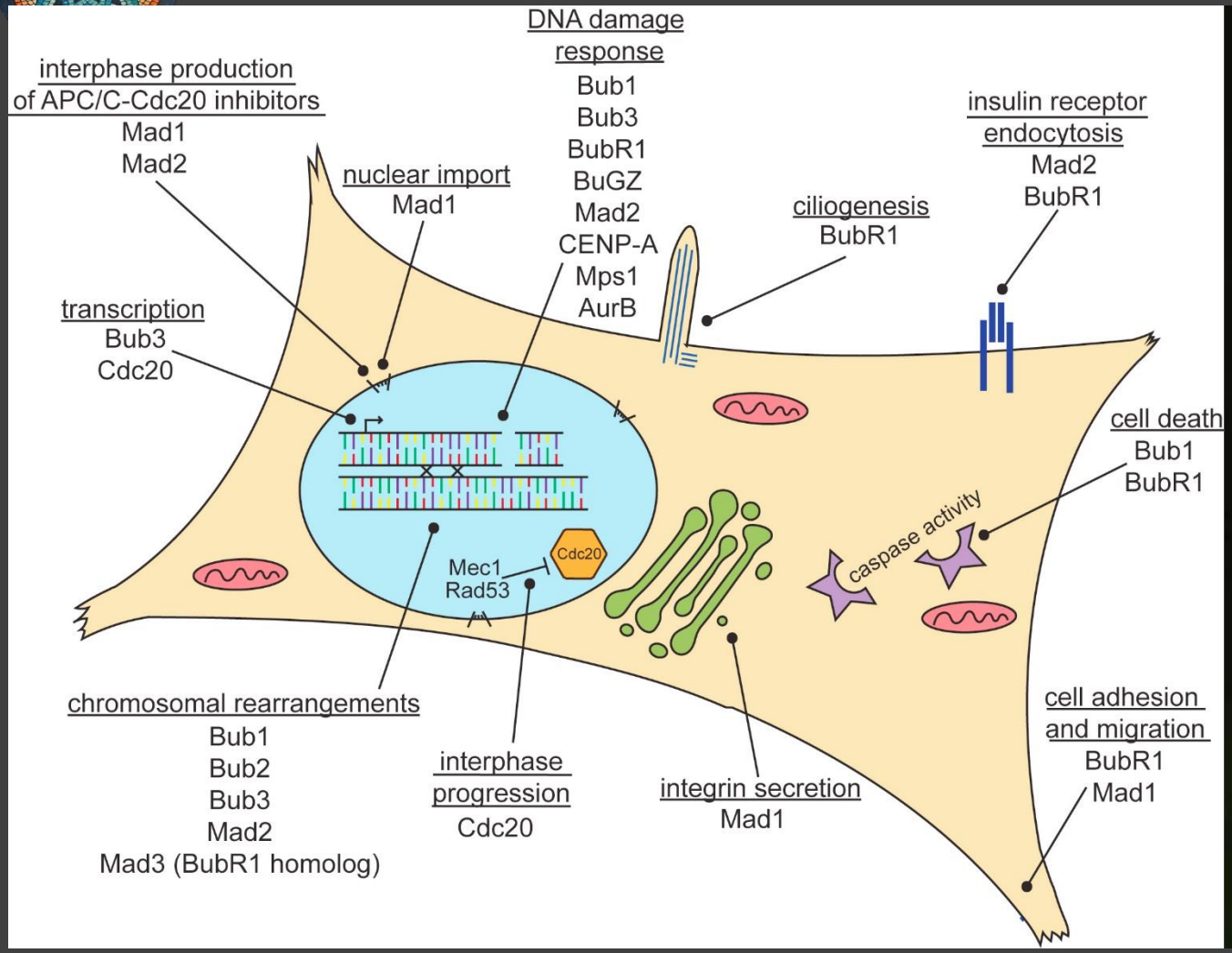
supernumerary centrosomes

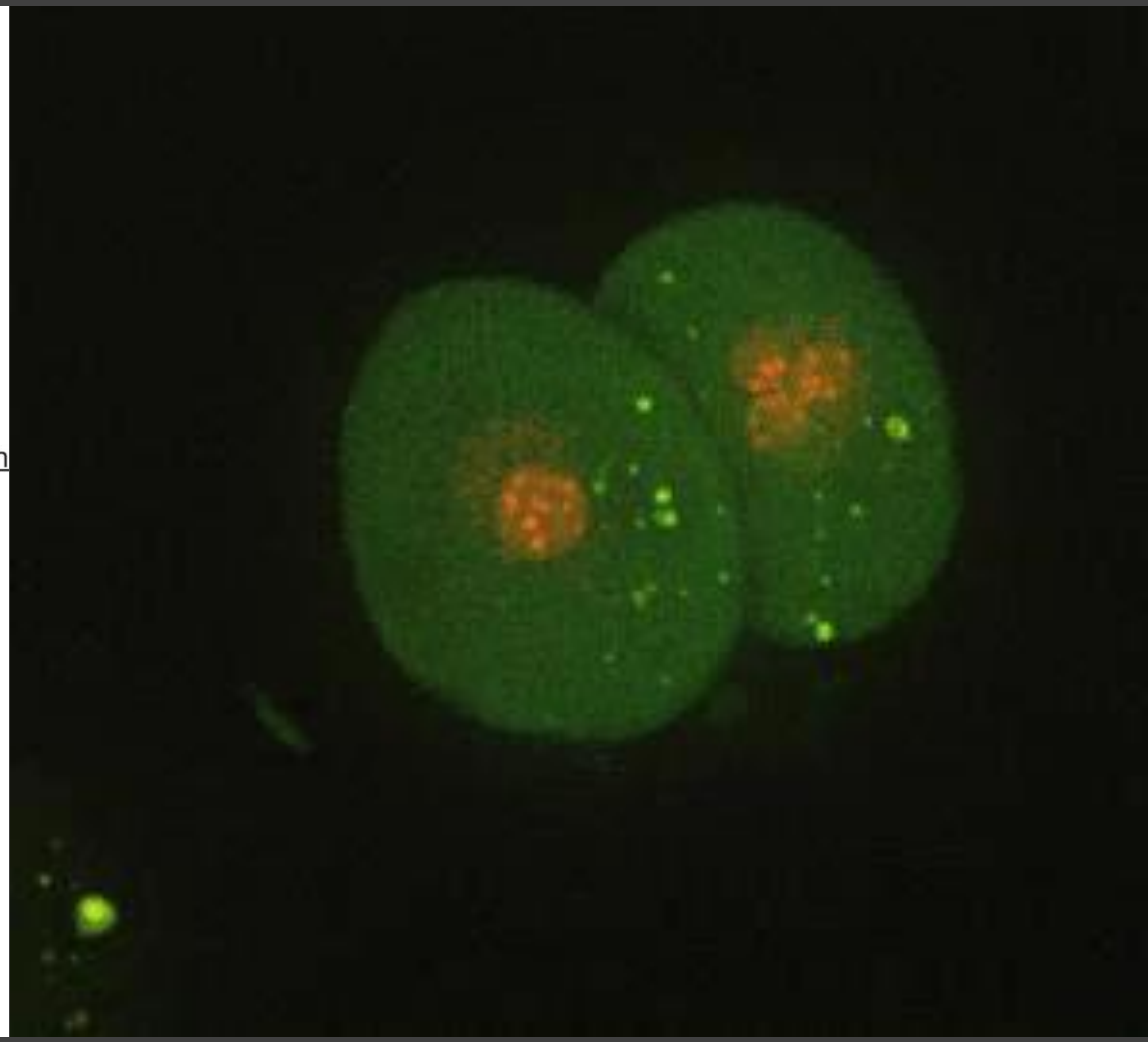
defects in chromatid cohesion

abnormal kinetochore-microtubule attachments

increased spindle microtubule dynamics

Figure 2





Developmental Cell 2016 39, 638-652DOI: (10.1016/j.devcel.2016.10.023)

Strange Cell Cycles

J Assist Reprod Genet (2009) 26:187–195
DOI 10.1007/s10815-009-9306-x

GENETICS

Evidence that human blastomere cleavage is under unique cell cycle control

Ann A. Kiessling · Ritsa Bletsa · Bryan Desmarais · Christina Mara · Kostas Kallianidis · Dimitris Loutradis

Human Reproduction, Vol.0, No.0 pp. 1–12, 2015
doi:10.1093/humrep/dev281

human reproduction ORIGINAL ARTICLE *Embryology*

Human embryos commonly form abnormal nuclei during development: a mechanism of DNA damage, embryonic aneuploidy, and developmental arrest

Daniel H. Kort[1,6,†], Gloryn Chia[2,†], Nathan R. Treff[3], Akemi J. Tanaka[2], Tongji Xing[4], Lauren Bauer Vensand[5], Stephanie Micucci[2], Robert Prosser[1], Roger A. Lobo[1], Mark V. Sauer[1], and Dieter Egli[2,5,*]

Courtesy of Shu Hashimoto and Yoshi Morimoto

Fertil Steril. 2016 Jul;106(1):133-139.e6.
doi: 10.1016/j.fertnstert.2016.03.025.

Multinucleation per se is not always sufficient as a marker of abnormality to decide against transferring human embryos.

Genomic instability is the norm not the exception

© 2015. Published by The Company of Biologists Ltd | Development (2015) 142, 4010-4025 doi:10.1242/dev.122846

STEM CELLS AND REGENERATION

RESEARCH ARTICLE

Human stem cells from single blastomeres reveal pathways of embryonic or trophoblast fate specification

Tamara Zdravkovic[1,2,3,4,5,‡], Kristopher L. Nazor[6,‡], Nicholas Larocque[1,2,3,4,5], Matthew Gormley[1,2,3,4,5], Matthew Donne[1,2,3,7], Nathan Hunkapillar[1,2,3,4,5], Gnanaratnam Giritharan[8], Harold S. Bernstein[4,9], Grace Wei[4,10], Matthias Hebrok[10], Xianmin Zeng[11], Olga Genbacev[1,2,3,4,5], Aras Mattis[4,12], Michael T. McMaster[4,5,13], Ana Krtolica[8,*], Diana Valbuena[14], Carlos Simón[14], Louise C. Laurent[6,15], Jeanne F. Loring[6] and Susan J. Fisher[1,2,3,4,5,7,§]

Clinical consequences of mosaicism bear on both our ability to detect and make best decisions on behalf of our patients

Genetics inMedicine | ORIGINAL RESEARCH ARTICLE

Open

Genome-wide karyomapping accurately identifies the inheritance of single-gene defects in human preimplantation embryos in vitro

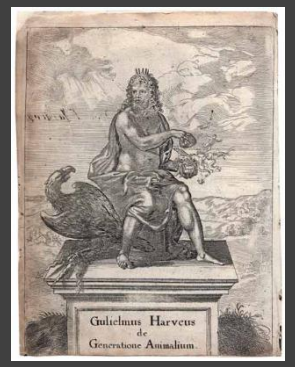
Senthilkumar A. Natesan, MSc, PhD[1], Alex J. Bladon, PhD[1], Serdar Coskun, DVM, PhD[2], Wafa Qubbaj, PhD[2], Renata Prates, BSc[3], Santiago Munne, PhD[3], Edith Coonen, PhD[4,5], Joseph C.F.M. Dreesen, BSc[5,6], Servi J.C. Stevens, PhD[5,6], Aimee D.C. Paulussen, PhD[5,6], Sharyn E. Stock-Myer, PhD[7], Leeanda J. Wilton, BSc, PhD[7], Souraya Jaroudi, PhD[8], Dagan Wells, PhD[8], Anthony P.C. Brown, BSc, PhD[1] and Alan H. Handyside, MA, PhD[1,9]

Am J Med Genet. 1990 Feb;35(2):165-73.

Incidence and timing of pregnancy losses: relevance to evaluating safety of early prenatal diagnosis.

Simpson JL[1].

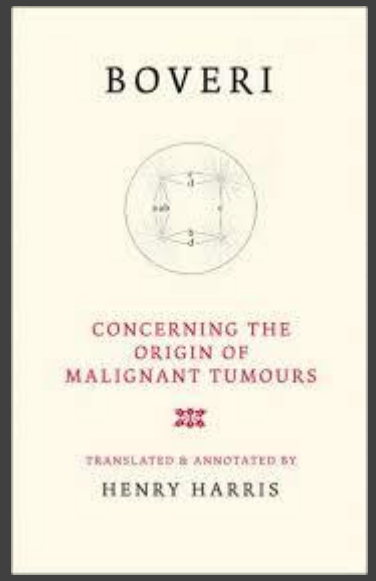
Knowing the frequency and timing of pregnancy loss during normal gestation is integral to evaluating the safety of prenatal diagnostic techniques. That preclinical loss rates are high in humans has long been suspected, but in the past decade new data concerning these losses have become available. Cohort studies indicate that many women who show positive beta-HCG assays never show clinical evidence of pregnancy. Cytogenetic abnormalities have also recently been documented in 20% of ostensibly normal in vitro fertilization embryos. All the above are consistent with the sentinel studies of Hertig and Rock, who showed high frequencies of morphological abnormalities in preimplantation embryos.

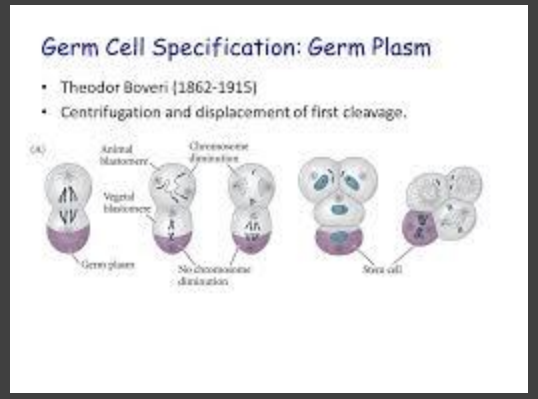


The “imperfections” of early human development

The shortcomings of our technology

Aneuploidy is a bad thing

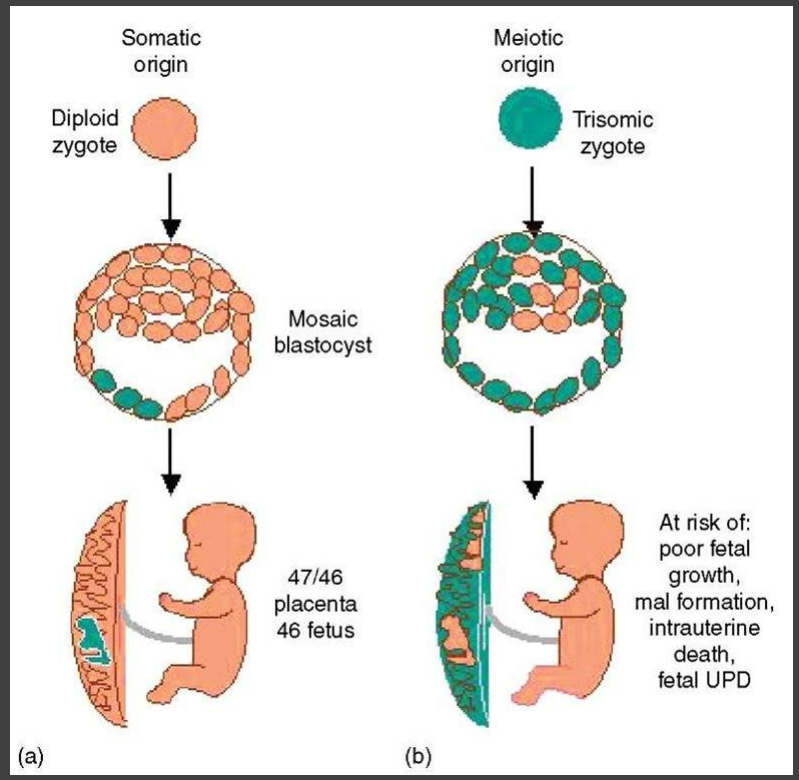




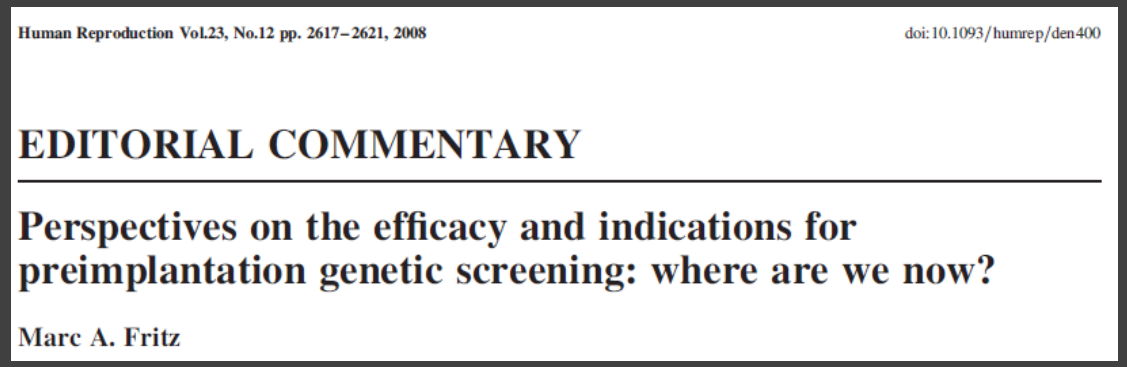
Mosaicism

There is a selective advantage of the normal cell line, thus making it possible for a non-mosaic diploid fetus to result from an abnormal conception.

It is possible to form a baby with entirely (or predominantly) normal cells from only a single diploid cell from the inner cell mass of the blastocyst (Lau et al., 1997; Robinson et al., 2002).



Blastomeres are not created equal!

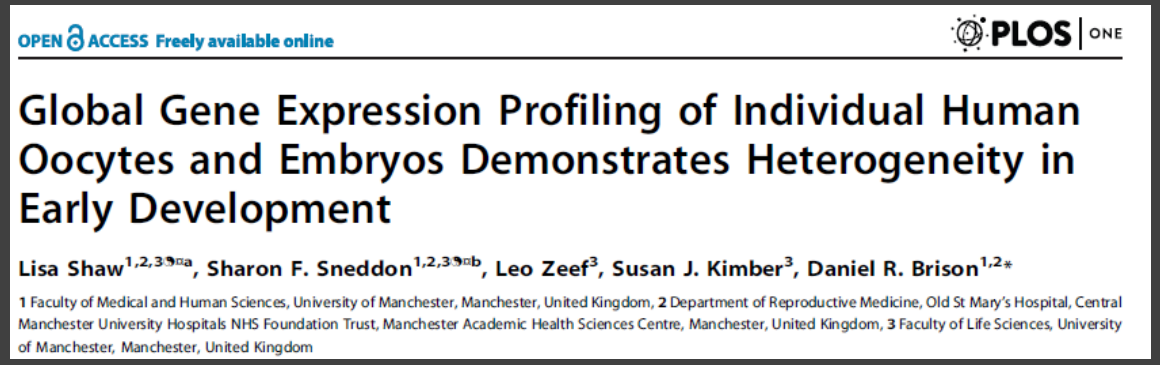


Human Reproduction Vol.23, No.12 pp. 2617–2621, 2008 doi:10.1093/humrep/den400

EDITORIAL COMMENTARY

Perspectives on the efficacy and indications for preimplantation genetic screening: where are we now?

Marc A. Fritz



OPEN ACCESS Freely available online PLOS ONE

Global Gene Expression Profiling of Individual Human Oocytes and Embryos Demonstrates Heterogeneity in Early Development

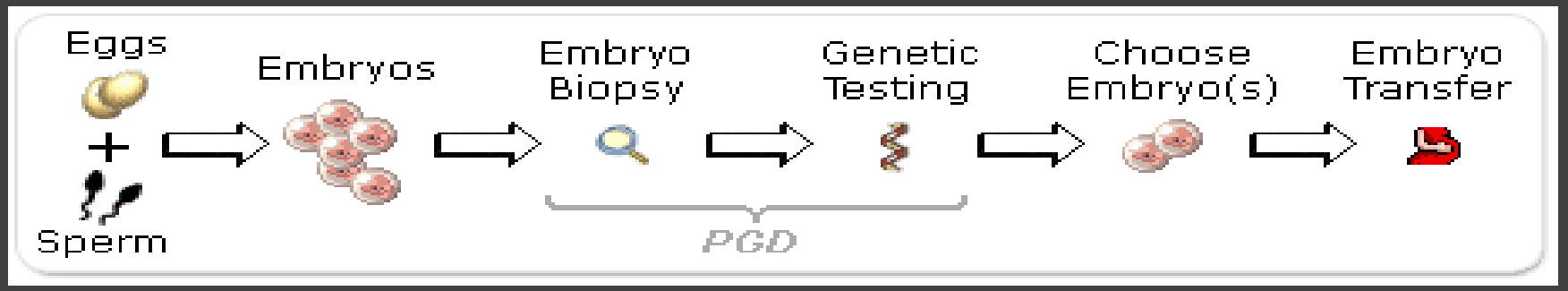
Lisa Shaw[1,2,3¤a], Sharon F. Sneddon[1,2,3¤b], Leo Zeef[3], Susan J. Kimber[3], Daniel R. Brison[1,2*]

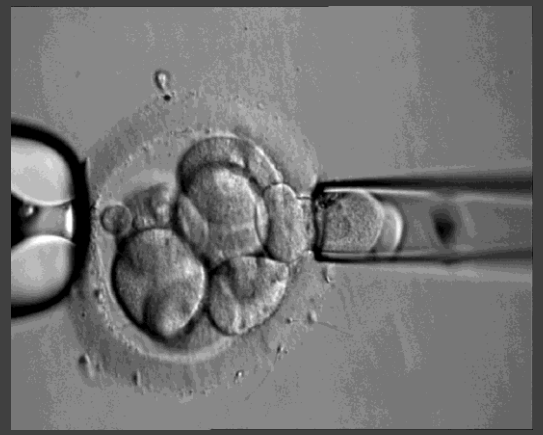
1 Faculty of Medical and Human Sciences, University of Manchester, Manchester, United Kingdom, 2 Department of Reproductive Medicine, Old St Mary's Hospital, Central Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Sciences Centre, Manchester, United Kingdom, 3 Faculty of Life Sciences, University of Manchester, Manchester, United Kingdom

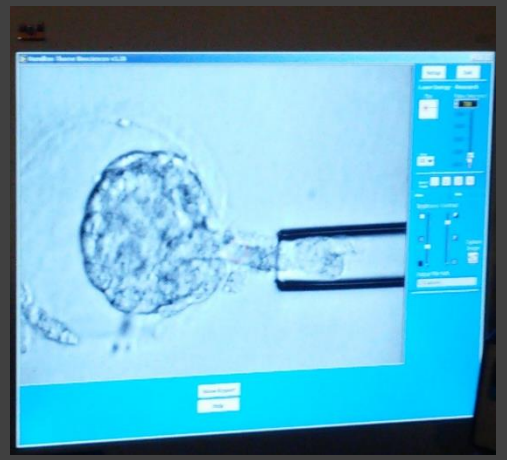
Post-provocateuring…….

Preimplantation Diagnosis

Preimplantation diagnosis

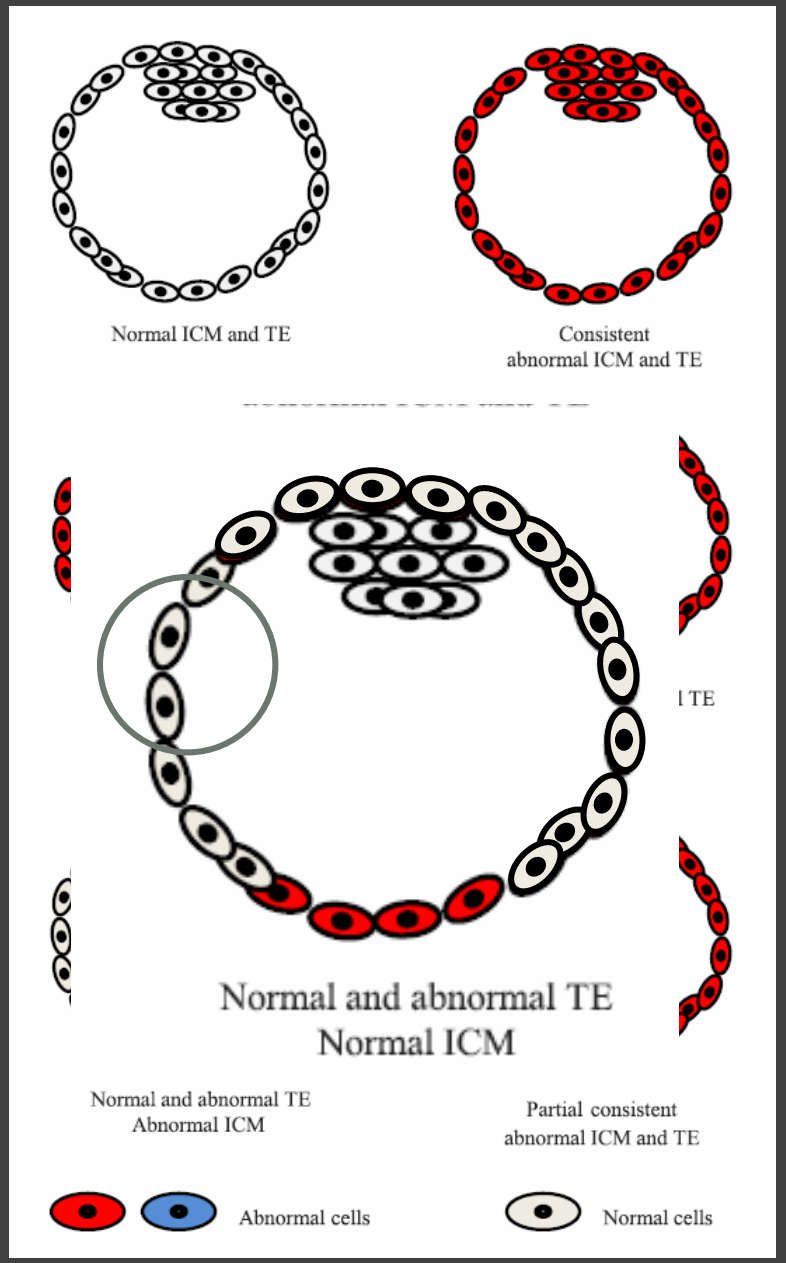






DNA Microarray Reveals That High Proportions of Human Blastocysts from Women of Advanced Maternal Age Are Aneuploid and Mosaic

- high proportions of aneuploid blastocysts (69.2%)
- including aneuploid TE and euploid ICM, inconsistent anomalies between ICM and TE, or euploid TE cells and aneuploid ICM in the same blastocyst.
- Biopsy from TE in blastocysts does not exactly predict the chromosomal information in ICM if the embryos are aneuploid.
- Some mosaic blastocysts have euploid ICM%



Liu et al. BIOLOGY OF REPRODUCTION (2012) 87(6):148, 1–9

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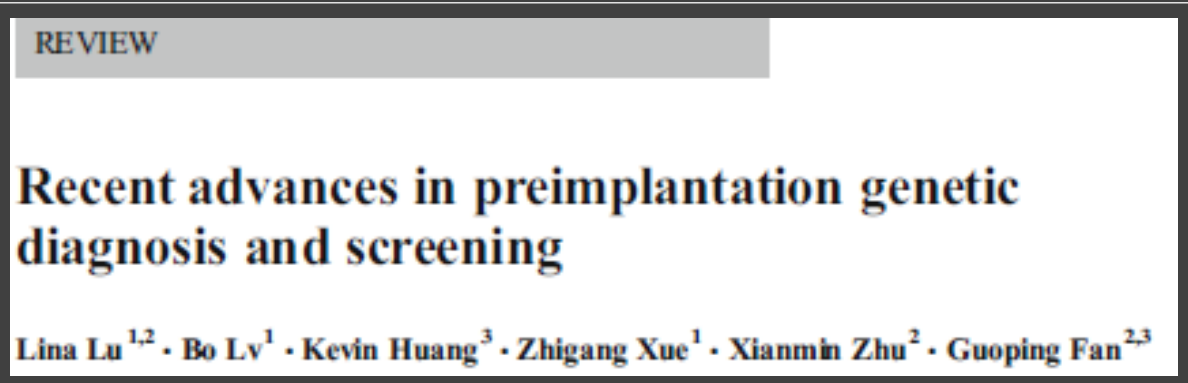


REVIEW

Recent advances in preimplantation genetic diagnosis and screening

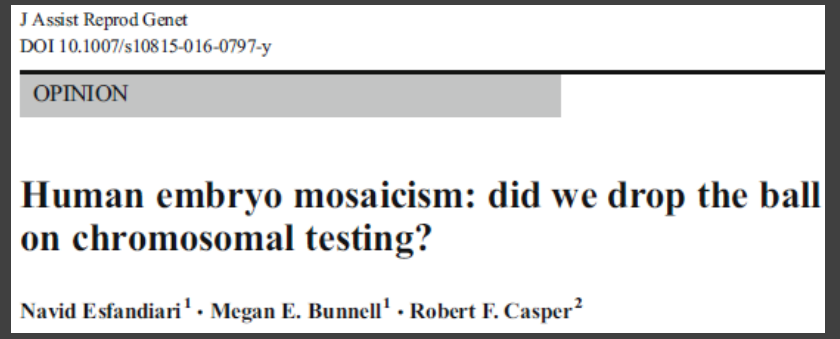
Lina Lu[1,2] · Bo Lv[1] · Kevin Huang[3] · Zhigang Xue[1] · Xianmin Zhu[2] · Guoping Fan[2,3]

J Assist Reprod Genet
DOI 10.1007/s10815-016-0766-5

GENETICS

Reanalysis of human blastocysts with different molecular genetic screening platforms reveals significant discordance in ploidy status

Drew V. Tortoriello[1] · Molina Dayal[1] · Zeki Beyhan[1] · Tahsin Yakut[2] · Levent Keskintepe[1,2]



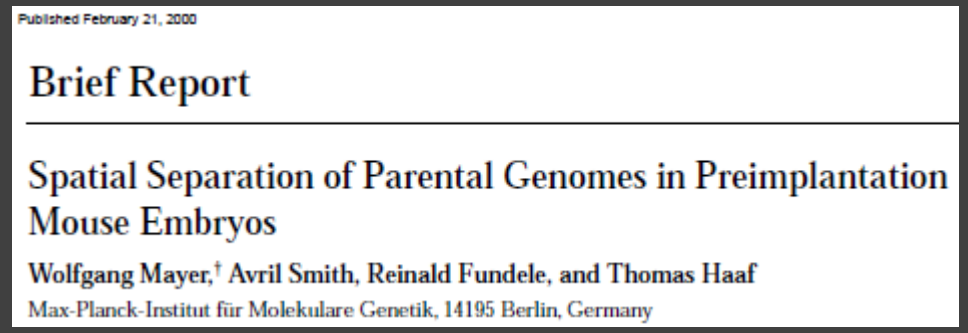
J Assist Reprod Genet
DOI 10.1007/s10815-016-0797-y

OPINION

Human embryo mosaicism: did we drop the ball on chromosomal testing?

Navid Esfandiari[1] · Megan E. Bunnell[1] · Robert F. Casper[2]

Early influences

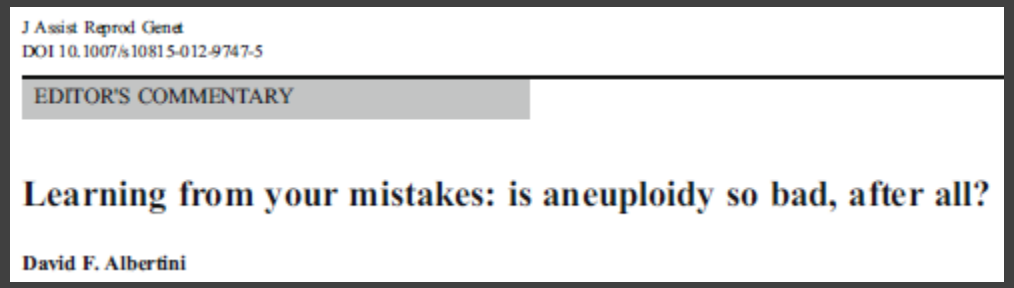


Published February 21, 2000

Brief Report

Spatial Separation of Parental Genomes in Preimplantation Mouse Embryos

Wolfgang Mayer,† Avril Smith, Reinald Fundele, and Thomas Haaf
Max-Planck-Institut für Molekulare Genetik, 14195 Berlin, Germany



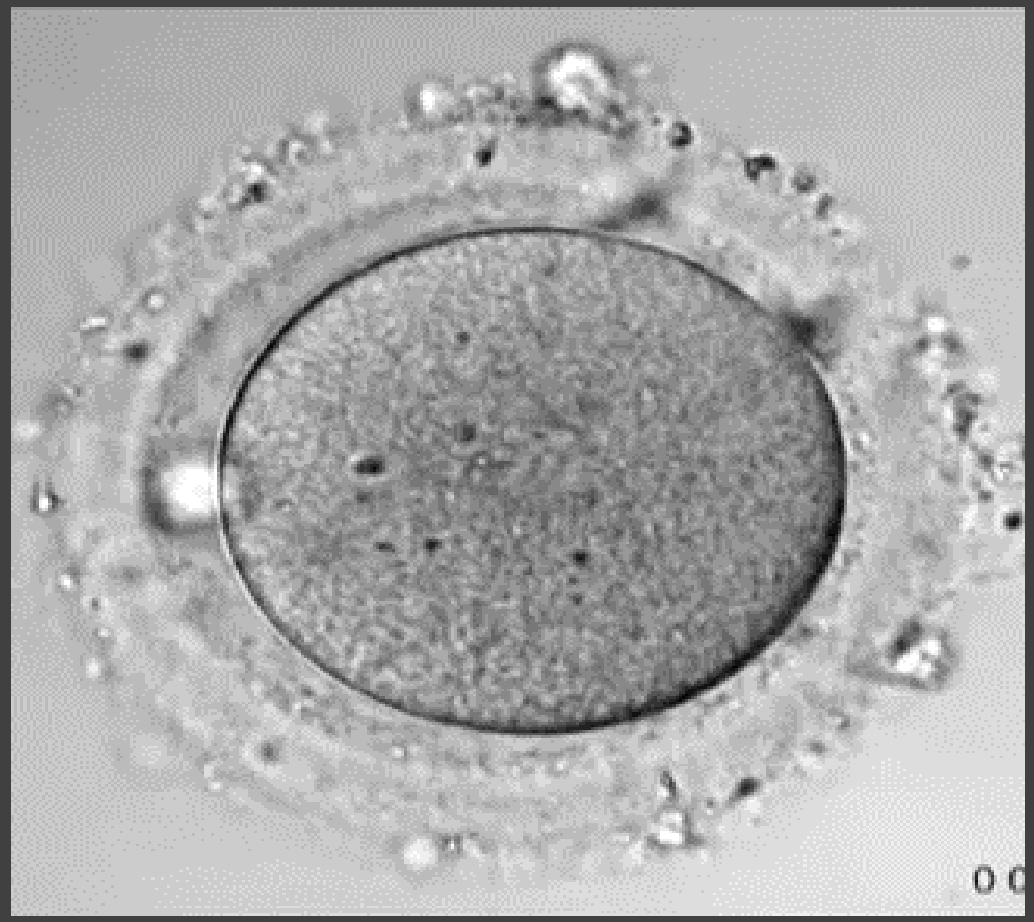
J Assist Reprod Genet
DOI 10.1007/s10815-012-9747-5

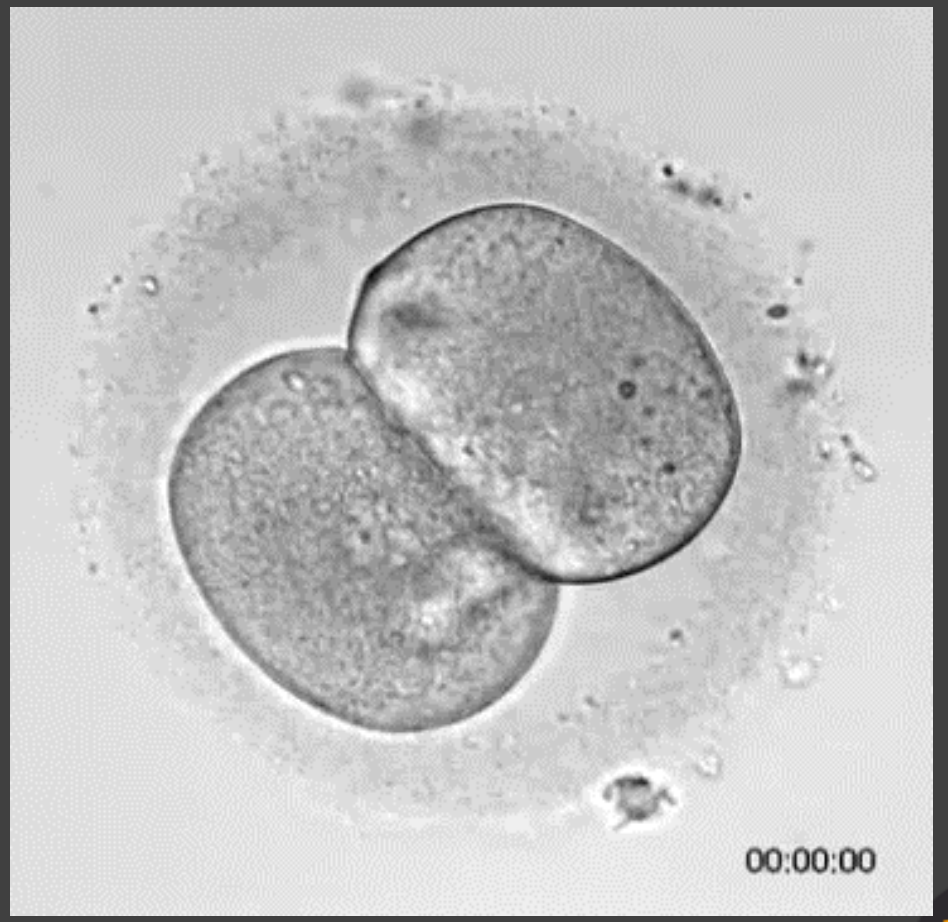
EDITOR'S COMMENTARY

Learning from your mistakes: is aneuploidy so bad, after all?

David F. Albertini

More than morphokinetics (Prof. Wolfe)





Greco et al., 2015 NEJM

Healthy Babies after Intrauterine Transfer of Mosaic Aneuploid Blastocysts

N ENGL J MED 373;21 NEJM.ORG NOVEMBER 19, 2015

The New England Journal of Medicine

Original Article

The Effect of Prolonged Culture of Chromosomally Abnormal Human Embryos on The Rate of Diploid Cells

Conclusion: Although mosaicism is frequently observed in blastocysts, the prolonged single culture of blastocysts does not seem to increase the rate of normal cells.

26:567–578 Published by Cold Spring Harbor Laboratory Press; ISSN 1088-9051/16; www.genome.org

Human Molecular Genetics, 2008, Vol. 17, Review Issue 1 **R10–R15**
doi:10.1093/hmg/ddn170

Aneuploidy and early human embryo development

Gayane Ambartsumyan[1,5] and Amander T. Clark[1,2,3,4,*]

[1]Department of Molecular Cell and Developmental Biology, [2]Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research, [3]Molecular Biology Institute, [4]Jonsson Comprehensive Cancer Center and [5]Department of Obstetrics and Gynecology, University of California, Los Angeles, CA 90095, USA

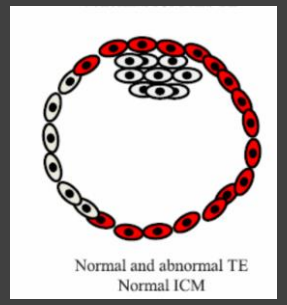
Research

Zygotes segregate entire parental genomes in distinct blastomere lineages causing cleavage-stage chimerism and mixoploidy

Aspasia Destouni,[1,8] Masoud Zamani Esteki,[2,8] Maaike Catteeuw,[3] Olga Tšuiko,[1,4] Eftychia Dimitriadou,[1] Katrien Smits,[3] Ants Kurg,[4] Andres Salumets,[5,6] Ann Van Soom,[3] Thierry Voet,[2,7,9] and Joris R. Vermeesch[1,9]

Preimplantation Genetic Diagnosis - Aneuploidy

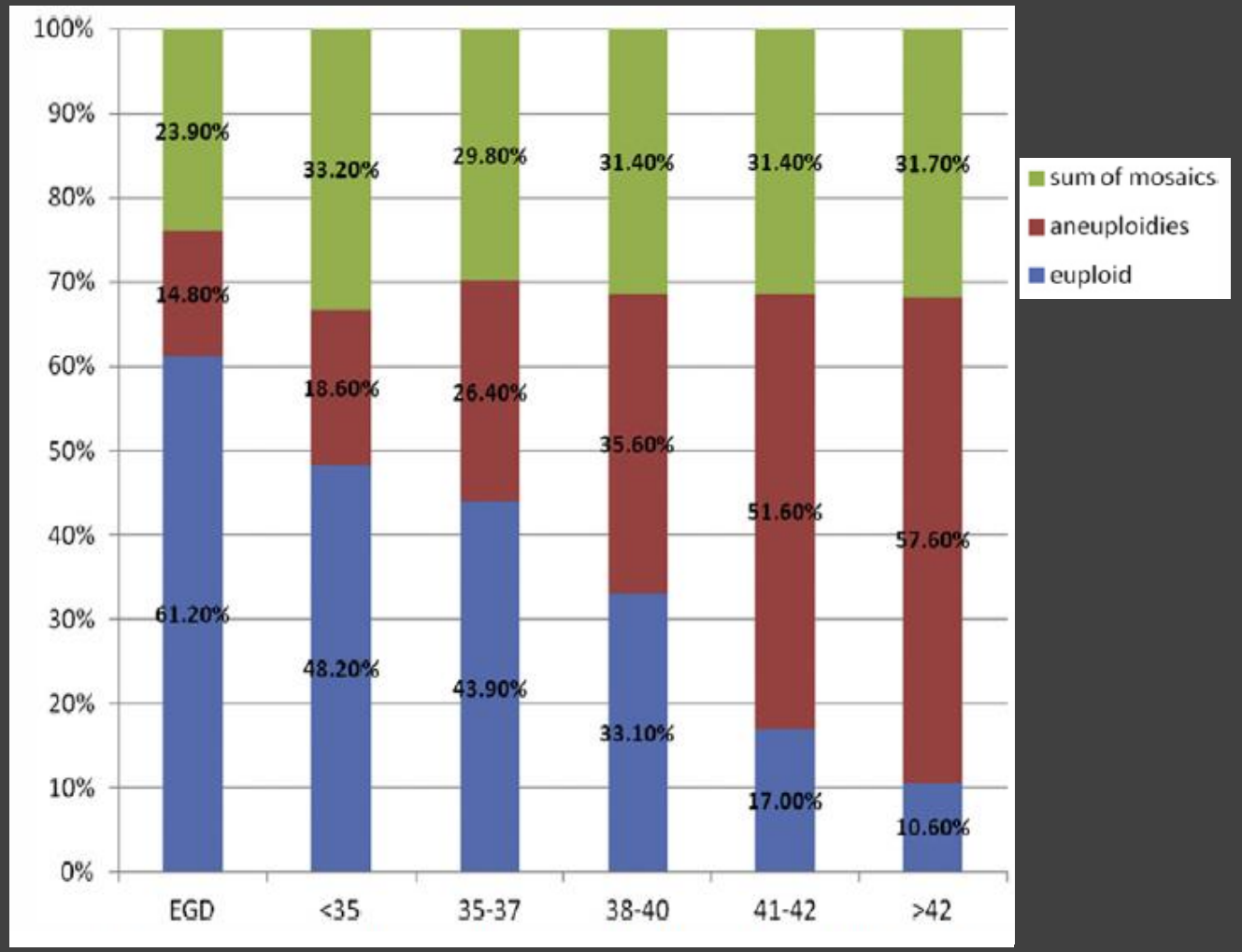
"In the absence of any fully euploid biopsies the transfer of mosaics, which may have appeared aneuploid using less sensitive methods, will sometimes result in a viable pregnancy."



Munne, Grifo and Wells. *Mosaicism: "survival of the fittest" versus "no embryo left behind"* Fertility and Sterility 2016

http://dx.doi.org/10.1016/j.fertnstert.2016.01.016

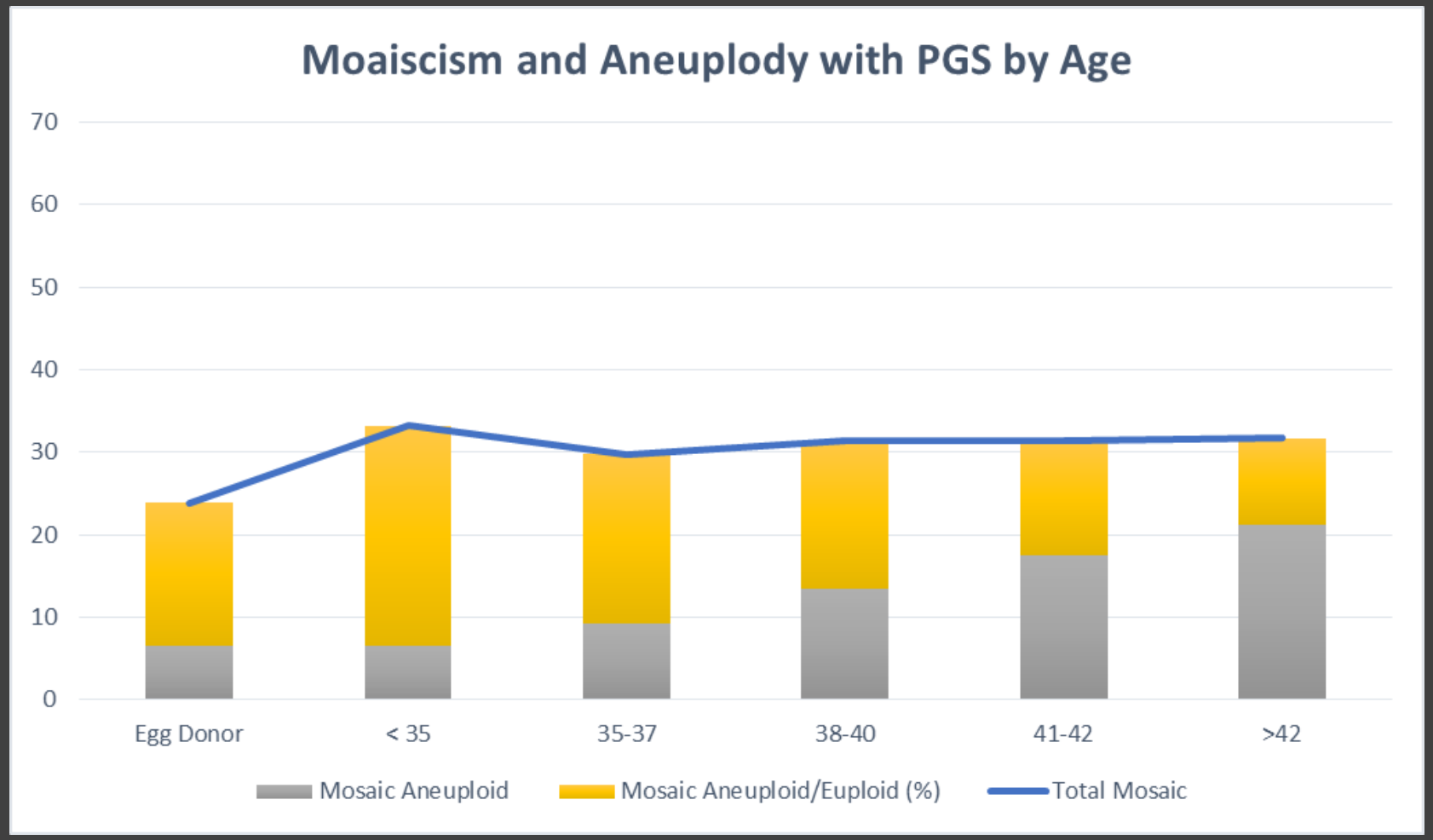
NEXT GENERATION SEQUENCING (NGS) FOR PREIMPLANTATION GENETIC SCREENING (PGS) DISCOVERS MOSAICISM IS INDEPENDENT OF AGE. Tomas Escudero, Lia Ribustello, Marina Sumarroca, Santiago Munne. Reprogenetics A Cooper Surgical Company, Livingston, NJ, USA.



ARTICLE · FEBRUARY 2016

DOI: 10.1016/j.fertnstert.2015.12.066

Percentages of mosaic, aneuploid and euploid embryos by age groups.



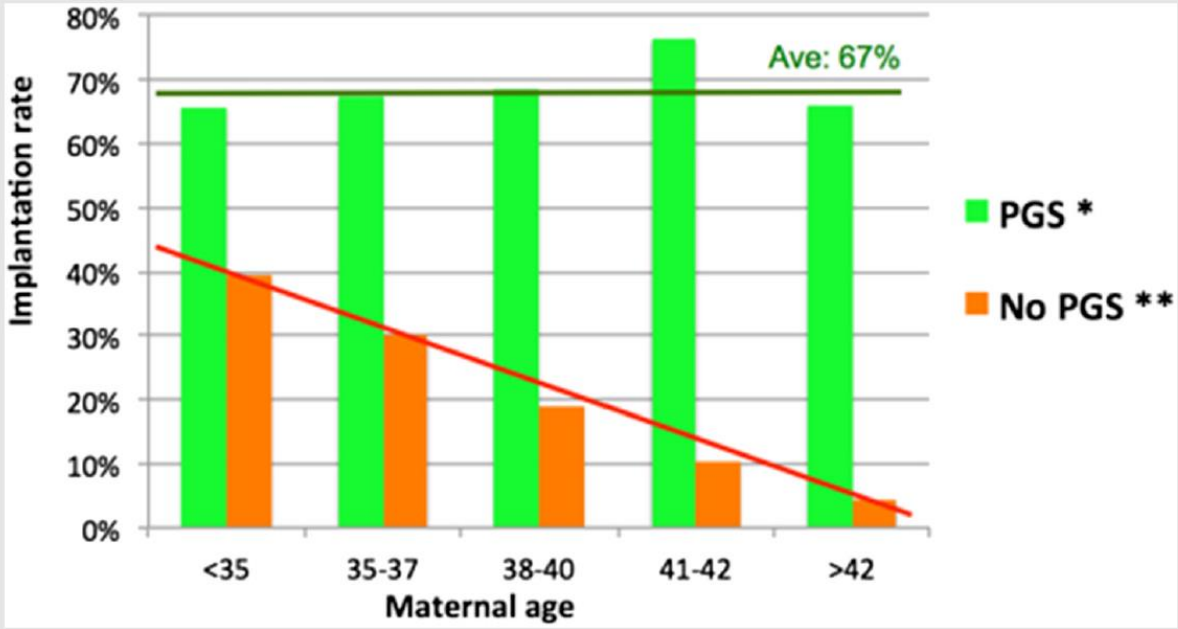
Munne et al. http://dx.doi.org/10.1016/j.fertnstert.2016.01.016

CONCEPTIONS

Santiago Munné, Ph.D.
James Grifo, M.D., Ph.D.
Dagan Wells, Ph.D.

Mosaicism: "survival of the fittest" versus "no embryo left behind"

FIGURE 1



Implantation rates after transfer of euploid embryos are independent of maternal age. * 2,532 cycles of PGD-A by aCGH with known outcome to 8/2015 from Harton et al. (2) and unpublished data; ** 2013 SART data.

Munné. Conceptions. Fertil Steril 2016.

embryo A2-A4 and D8-D11

Comparison of Lab Results

- Only 2/11 (18.2%) of embryos demonstrated within laboratory congruent results between both laboratory evaluations.
- 4/11 (36.4%) of embryos, on repeat assessment were found to be normal 46, XX or 46, XY embryos.

Table 1. Comparison of embryo ploidy between two PGS 2.0 assessments

Embryo ID	Biopsy #	Original PGS analysis (all embryos reported as abnormal)	Repeat PGS analysis (multiple biopsies)
A1	1	45,XY, -18	Normal 46,XX
A2	1	Complex aneuploid	XY, +10, -18q
A3	2		XY, +11, +16, -21
A4	3		XX, -3q
A5	1	46,XY, +3, -11, +15, -14	XX, -2
A6	2		Normal 46XX
A7	3		45,XY, -18
A8	4		Normal 46,XX
B1	1	46,XY, +3, -11	45,XY, -14
B2	2		45,XY, -14
B3	3		45,XY, -14
B4	4		45,XY, -14
B5	1	47,XY, +19	47,XY, +3
B6	2		47,XY, +3
B7	3		47,XY, +3
B8	4		Normal 46,XY
C1	1	45,XX, -1	Normal 46,XX
C2	2		Normal 46,XX
C3	3		Normal 46,XX
C4	1	47,XY, +19	Normal 46,XY
C5	2		Normal 46,XY
C6	3		Normal 46,XY
C7	1	47,XY, +19	Normal 46,XY
C8	2		Normal 46,XY
C9	3		Normal 46,XY
C10	4		Normal 46,XY
D1	1	Complex aneuploid	Normal 46,XY
D2	2		47, +18
D3	1	Complex aneuploid	47XY, +8q, -15, +16
D4	2		46,XY, -15, +16
D5	3		46,XY, -15, +16
D6	4		46,XY, -15, +16
D7	5		46,XY, -15, +16
D8	1	46,XX, +14, -15	46,XX, +14, -15
D9	2		46,XX, +14, -15
D10	3		46,XX, +14, -15
D11	4		46,XX, +14, -15

White and shaded areas represent individual embryos.

Characteristics of Aneuploid embryos which implanted

Patient	N Embryos transferred	PGS Result	Outcome
1	1	43, XY, -13, -15, -18	Normal birth, 46, XY
2	1	45, XY, -21	Normal birth, 46, XY
3	2	45, XY, -21 46, XX	Normal birth, 46, XY
4	2	Partial 47,XX,17p11.2-pter 45, XY, -22	Normal birth, 46, XX
5	2	47, XY, +22 Partial 45,XY,-1plar-p36,12	Normal birth 46, XY
6	1	45, XY, -21	Chemical pregnancy

Table 1. Clinical Outcomes of Single Mosaic Blastocysts Transferred.*

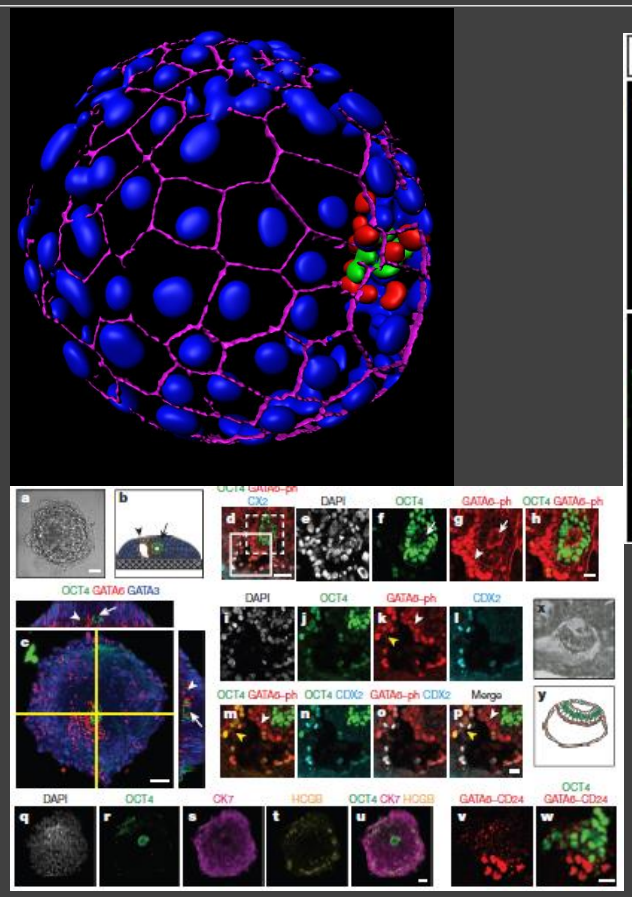
Patient No.	Chromosomal Constitution	Mosaicism†	Karyotype‡	Clinical Outcome
		percent		
1	arr(4)x1,(10)x1	40	46,XX	Baby healthy at birth
2	arr(6)x1,(15)x1	50	46,XX	Baby healthy at birth
3	arr(2)x1	40	46,XX	Baby healthy at birth
4	arr(2)x1	35	46,XY	Baby healthy at birth
5	arr(5)x1	50	46,XX	Baby healthy at birth
6	arr(5)x1,(7)x1	40	46,XX	Baby healthy at birth
7	arr(11)x1,(20)x3,(21)x3	30	NA	No pregnancy
8	arr(1)x1,(6)x3,(10)x3,(12)x3,(13)x3,(14)x3,(21)x3	50	NA	No pregnancy
9	arr(3)x1,(10)x3,(21)x3	35	NA	No pregnancy
10	arr(1)x3	50	NA	Biochemical pregnancy§
11	arr 9p21.2q34.3(26,609,645-140,499,771)x3	45	NA	Biochemical pregnancy§
12	arr(15)x3	30	NA	No pregnancy
13	arr(18)x1	50	NA	No pregnancy
14	arr(18)x1	50	NA	No pregnancy
15	arr(18)x1	40	NA	No pregnancy
16	arr(4)x1	50	NA	No pregnancy
17	arr(5)x3	40	NA	No pregnancy
18	arr 10q21.3q26.3(67,216,644-134,326,648)x3	50	NA	No pregnancy

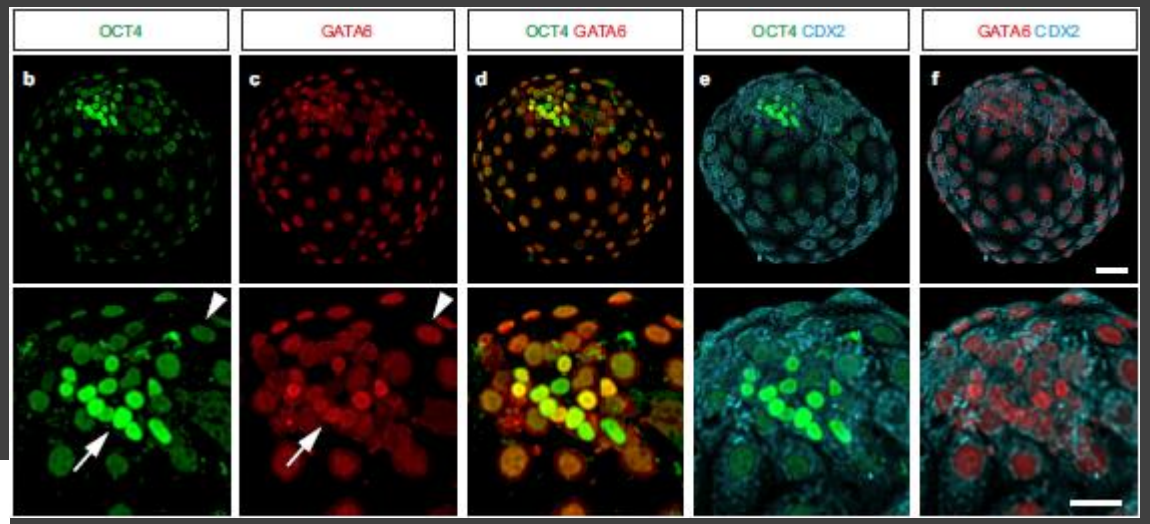
* NA denotes not available.
† The approximate percentage of aneuploid cells in the transferred blastocyst is listed (see the Supplementary Appendix).
‡ The karyotype was determined by means of chorionic-villus sampling.
§ Biochemical pregnancy was defined by the presence of a low peak in levels of the beta subunit of human chorionic gonadotropin (β-hCG) (<100 mIU per milliliter), a rapid decrease in the urinary or serum β-hCG concentration, and no substantial delay in the onset of the next menstrual period, but with no detection of an identifiable pregnancy by means of ultrasonographic examination.

Greco and Minasi, N Engl J Med 2015;373:2089-90.

Very different from mouse and macaque

New look at human embryos



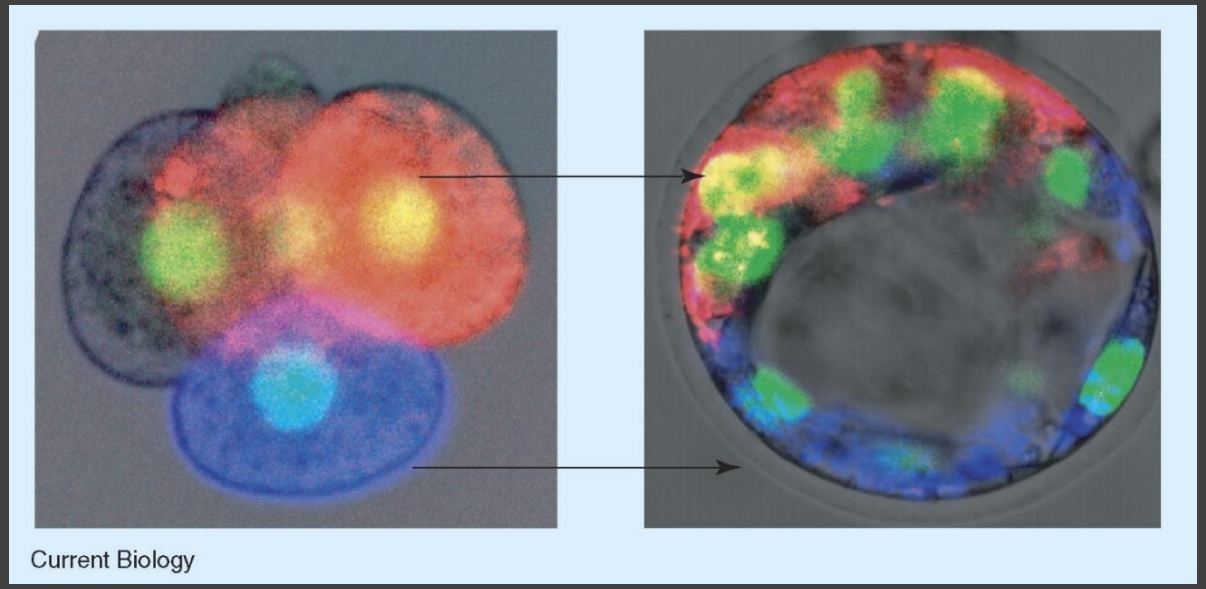


Nature. 2016 Aug 24;537(7618):57-62. doi: 10.1038/nature19096. [Epub ahead of print]

A developmental coordinate of pluripotency among mice, monkeys and humans.

Nakamura T[1,2], Okamoto I[1,2], Sasaki K[1,2], Yabuta Y[1,2], Iwatani C[3], Tsuchiya H[3], Seita Y[3], Nakamura S[3], Yamamoto T[4,5,6], Saitou M[1,2,4,5].

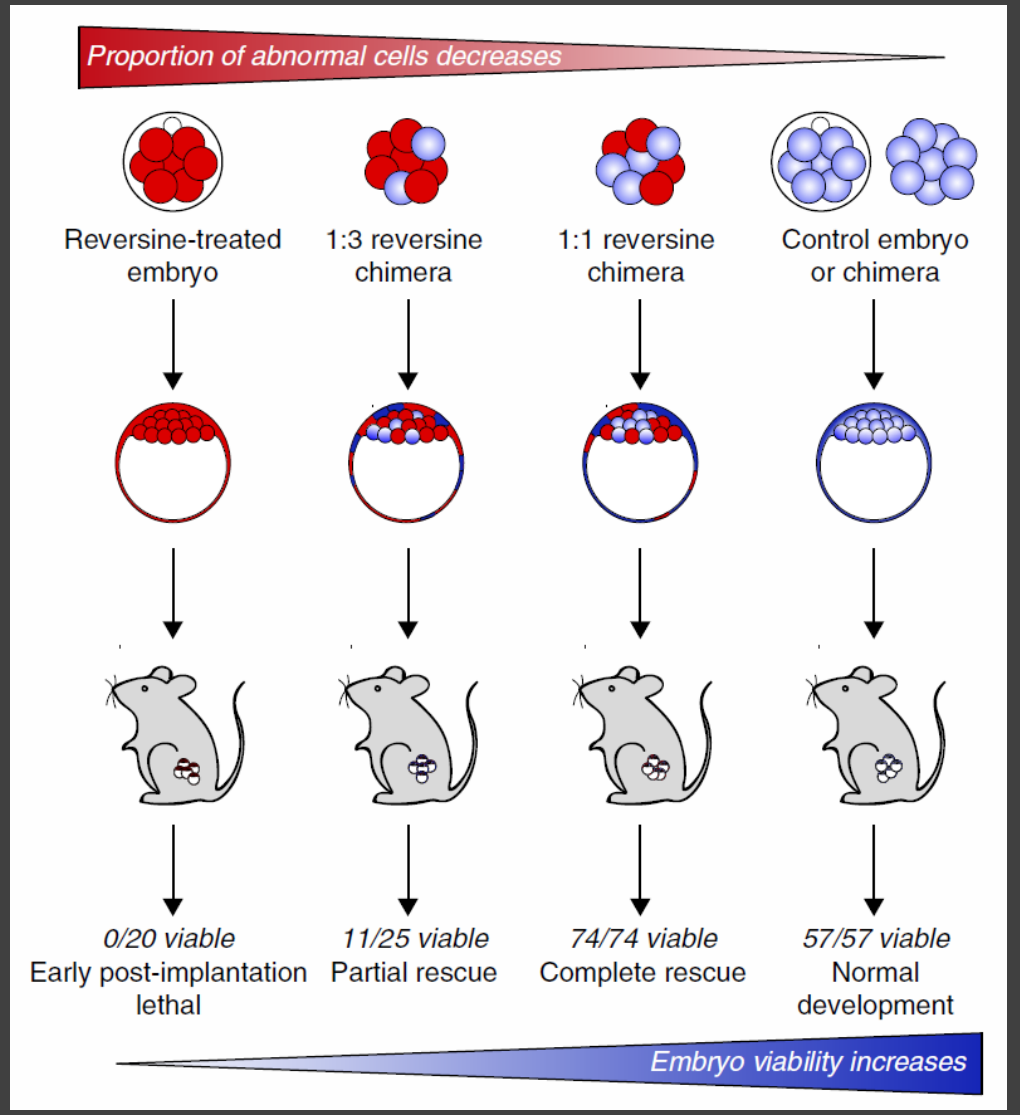
Four cell mouse embryo contributes to different areas of the blastocyst



Current Biology Volume 16, Issue 7, pR236–R239, 4 April 2006

Effects of pre-implantation chromosome mosaicism on embryo development and survival

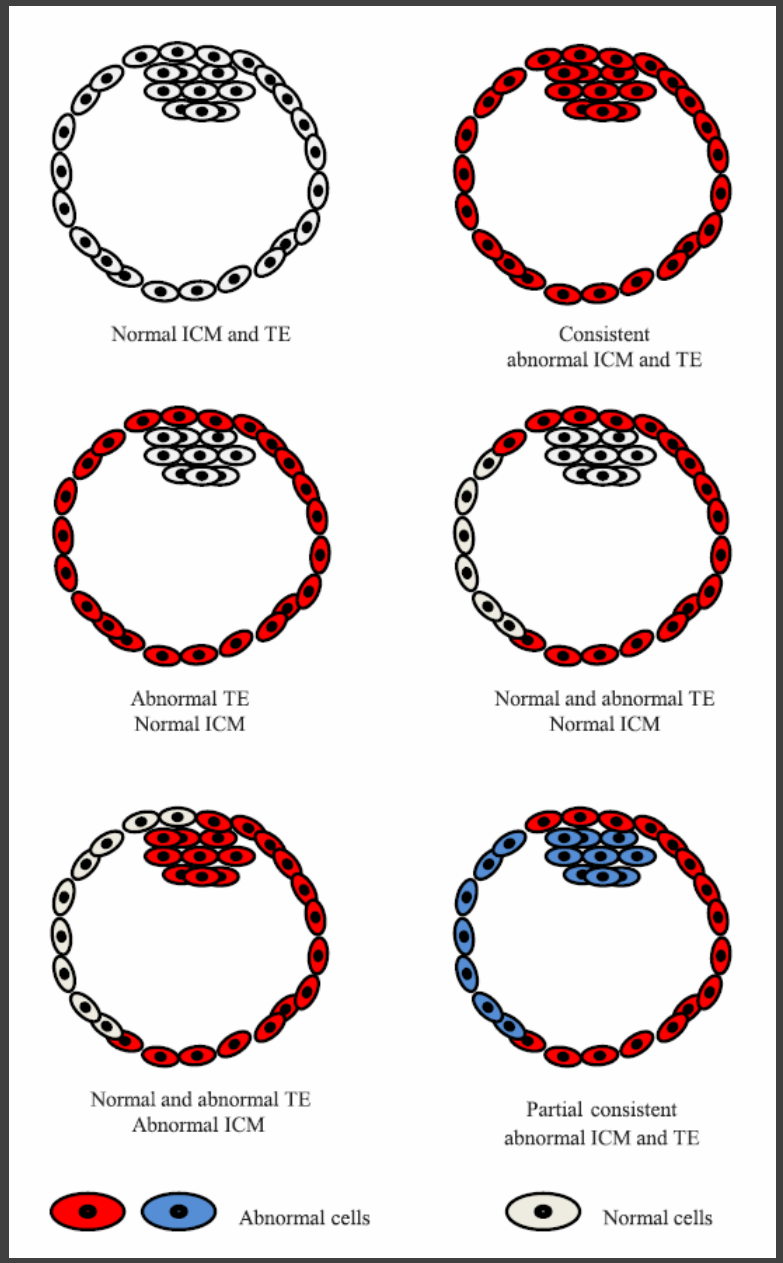
Reversine-treated embryos formed blastocysts but failed to develop past implantation. Increasing the proportion of control blastomeres in the embryo rescued the lethal phenotype. Numbers represent the viability of early postimplantation embryos that had successfully implanted.



Bolton et al. NATURE COMMUNICATIONS | 7:11165 | DOI: 10.1038/ncomms11165 |www.nature.com/naturecommunications

DNA Microarray Reveals That High Proportions of Human Blastocysts from Women of Advanced Maternal Age Are Aneuploid and Mosaic

- high proportions of aneuploid blastocysts (69.2%)
- including aneuploid TE and euploid ICM, inconsistent anomalies between ICM and TE, or euploid TE cells and aneuploid ICM in the same blastocyst.
- Biopsy from TE in blastocysts does not exactly predict the chromosomal information in ICM if the embryos are aneuploid.
- Some mosaic blastocysts have euploid ICM%



Liu et al. BIOLOGY OF REPRODUCTION (2012) 87(6):148, 1–9

Summary

Origins of mosaicism are both gametic and zygotic, influenced by age and ARTs

Mechanisms of mosaicism involve perturbations during gametogenesis and early embryogenesis as a result of alterations in cell cycle checkpoints

Clinical consequences of mosaicism are rooted in controversies as wide ranging as technicalities in detection and the likelihood that embryos that could have developed to term are instead being discarded

CHR Staff

(* Visiting Scientists)

David F Albertini, PhD
David H Barad, MS, MD
Ali Brivanlou, PhD, MD*
Sarah Darmon, PhD, MS
Norbert Gleicher, MD
Vitaly A Kushnir, MD
Emanuela Lazzaroni-Tealdi, MS
Qi (Vicky) Wang, PhD
Nico Santiquet, PhD
Andrea Weghofer, PhD, MS, MBA, MD*
Yan-Guang Wu, PhD*

And our patients

Affiliates

University of Rochester School of Medicine and Dentistry:
Aritro Sen, PhD

Rockefeller University:
Gist Croft, PhD
Ali Brivanlou, PhD, MD

Videos courtesy of
Jean-Philippe Wolf
Shu Hashimoto
Yoshi Morimoto