Cleavage stage and cell division kinetics

Thorir Hardarson, PhD.

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Possible conflict of interest

NO

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Kinetics?

WIKIPEDIA

Greek: κίνησις "kinesis", *movement* or *to move*

i.e. Cleavage rate (of embryos)

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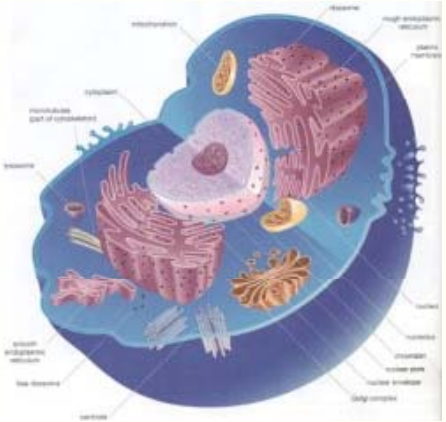
Cleavage rate then…?



Cleavage rate = Cell division rate

Cell division is the process by which a parent cell divides into two or more daughter cells, *i.e. mitosis.*

A human being's body experiences about 10,000 trillion cell divisions in a lifetime

Before division can occur, the chromosomes must be replicated, and the duplicated genome separated cleanly between cells.

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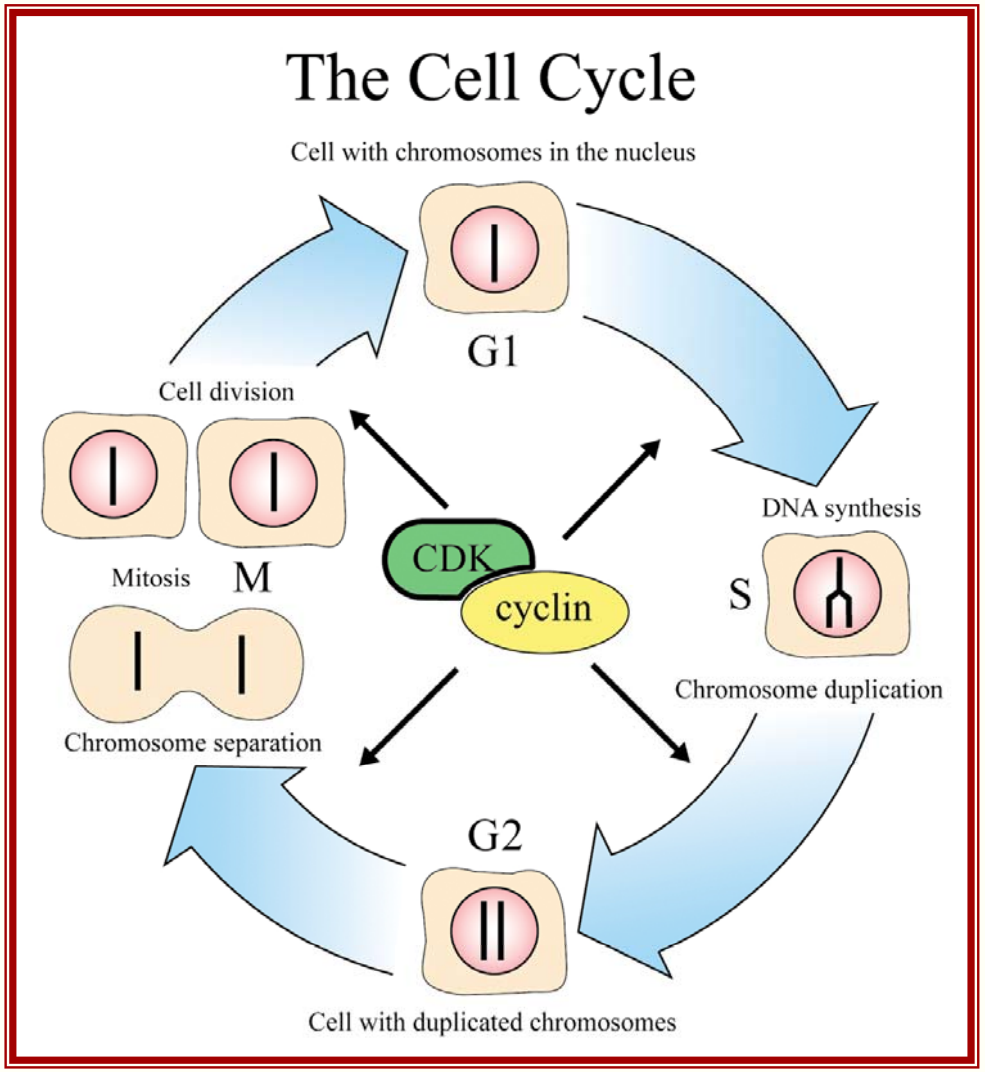

The Nobel Prize in Physiology or Medicine 2001

Leland H. Hartwell, Tim Hunt, Sir Paul Nurse

For their discoveries of "key regulators of the cell cycle"

”Start-Genes”
“Checkpoints”
“CDK” (Cyclin dependent kinase)
“Cyclins, (proteins that regulate CDK)

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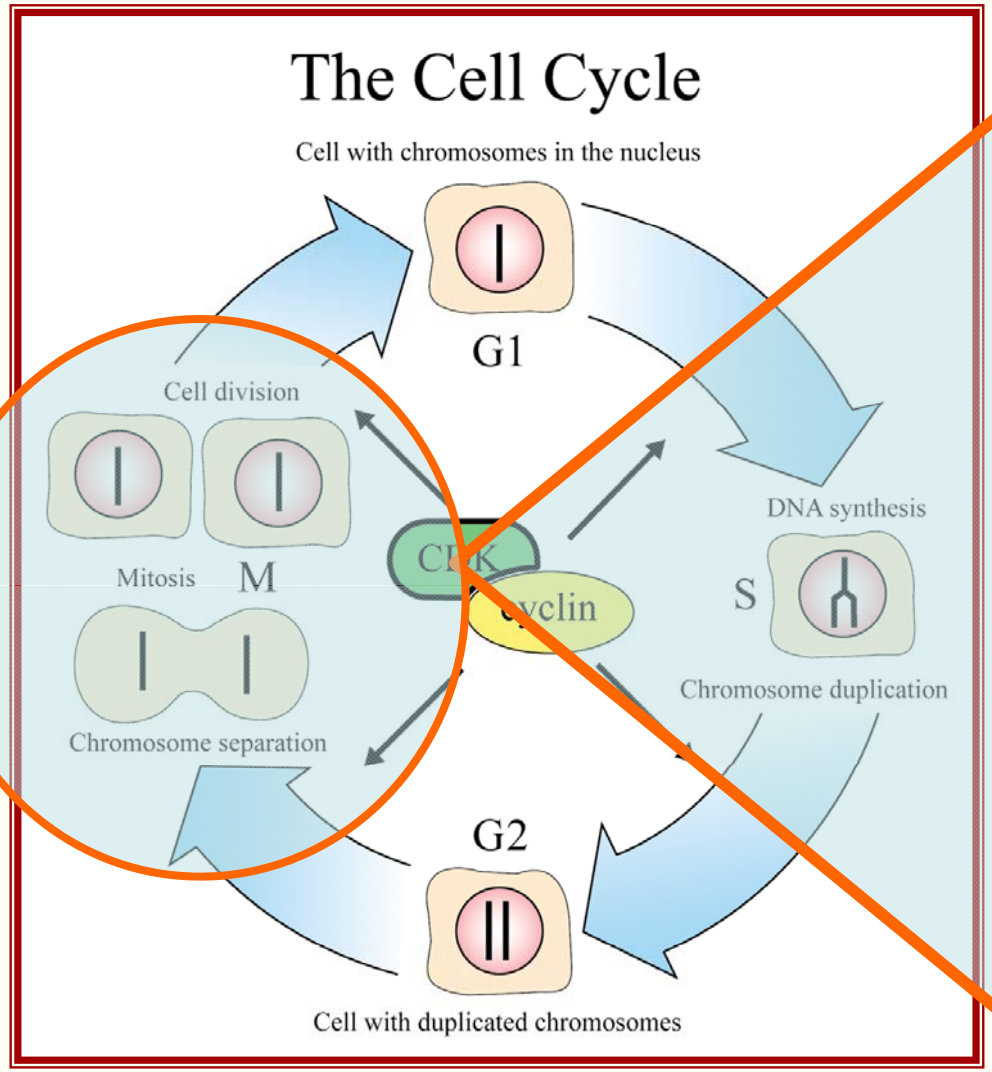
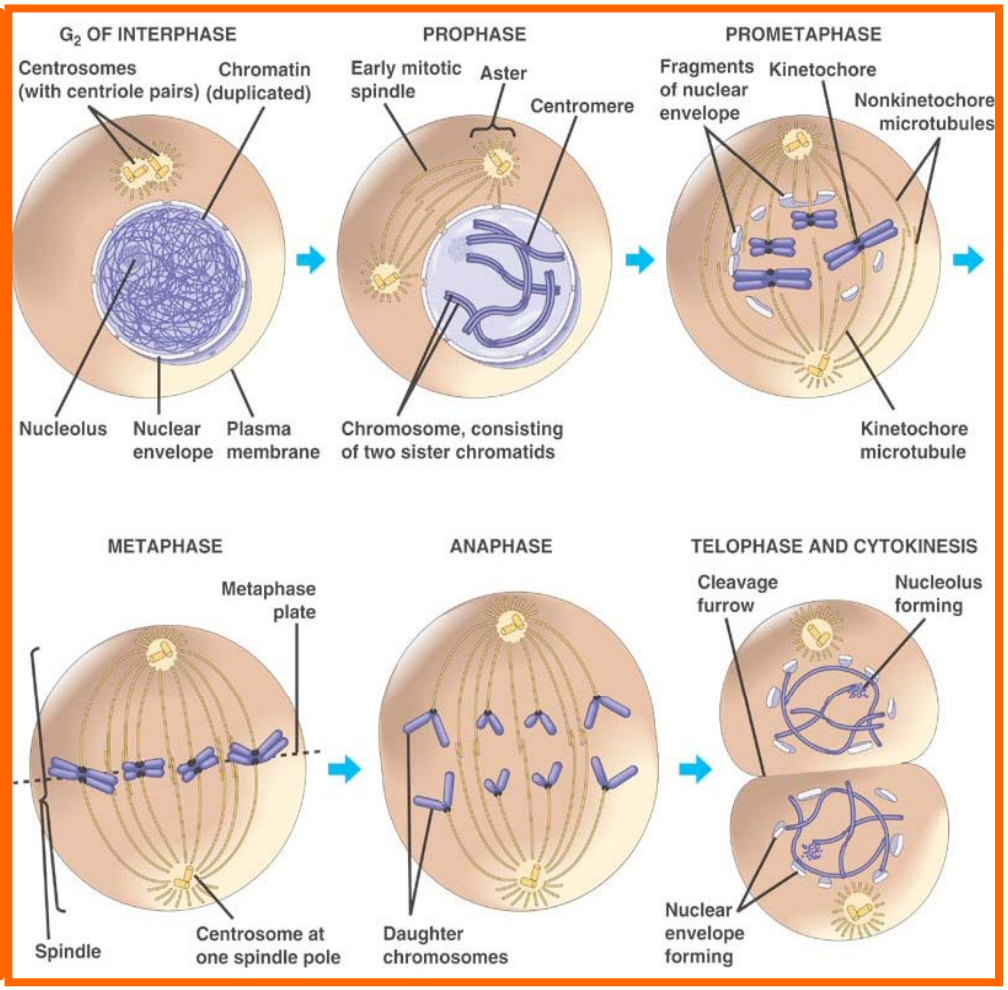


Mitosis



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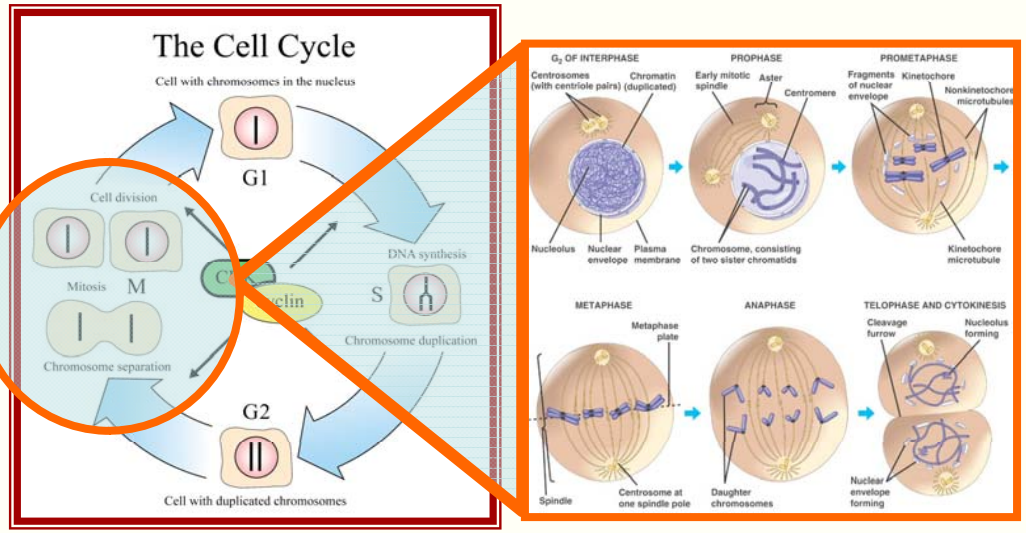
Cell cycle control

Hundred of genes and macromolecules involved
Checkpoints of DNA damage and order of cell cycle events

Hundred of genes and macromolecules involved
Checkpoints of DNA damage and order of cell cycle events



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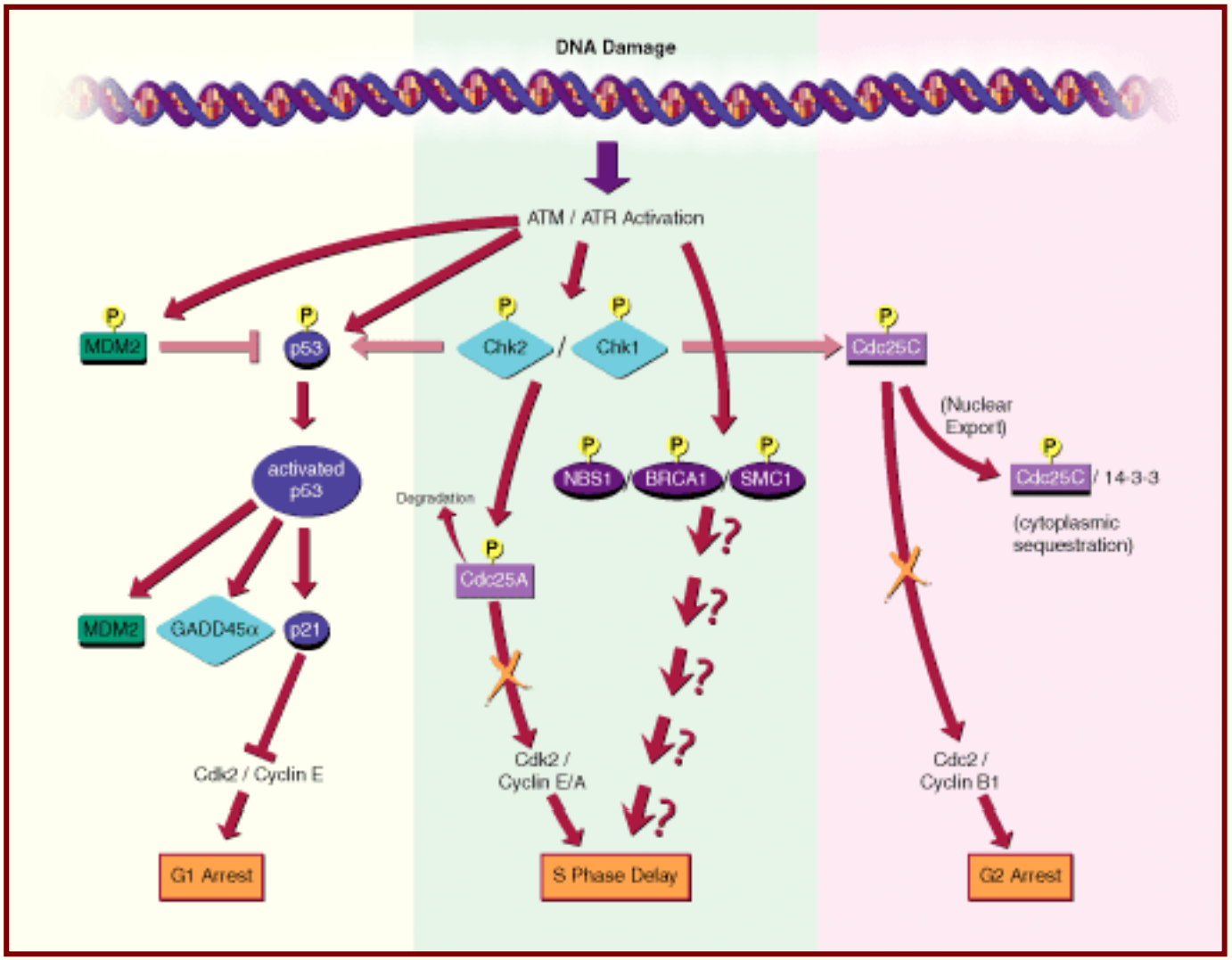
Cell cycle checkpoints



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So…

For all living eukaryotic organisms it is essential that the different phases of the cell cycle are precisely coordinated.

The phases must follow in correct order, and one phase must be completed before the next phase can begin. Errors in this coordination may lead to chromosomal alterations.

Chromosomes or parts of chromosomes may be lost, rearranged or distributed unequally between the two daughter cells, often seen in cancer cells.

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Checkpoints in oocytes

Human Reproduction Update, Vol.14, No.2 pp. 143–158, 2008
doi:10.1093/humupd/dmm043
Advance Access publication December 14, 2007

Meiosis in oocytes: predisposition to aneuploidy and its increased incidence with age

Keith T. Jones[1]

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High chromosomal aberration rates in the human oocyte/embryo

*Has evolution **favored** low fecundity in humans?*

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Fertil. Steril. 2011

The relationship between blastocyst morphology, chromosomal abnormality, and embryo gender

Samer Alfarawati, M.S.[a,b] *Elpida Fragouli, Ph.D.,*[a,b] *Pere Colls, Ph.D.,*[c] *John Stevens, M.S.,*[d] *Cristina Gutiérrez-Mateo, Ph.D.,*[c] *William B. Schoolcraft, M.D.,*[d] *Mandy G. Katz-Jaffe, Ph.D.,*[d] *and Dagan Wells, Ph.D., F.R.C.Path.*[a,b]

Existing, but weak correlation between morphology and chr. Abnorm.

Supports earlier findings at all developmental stages

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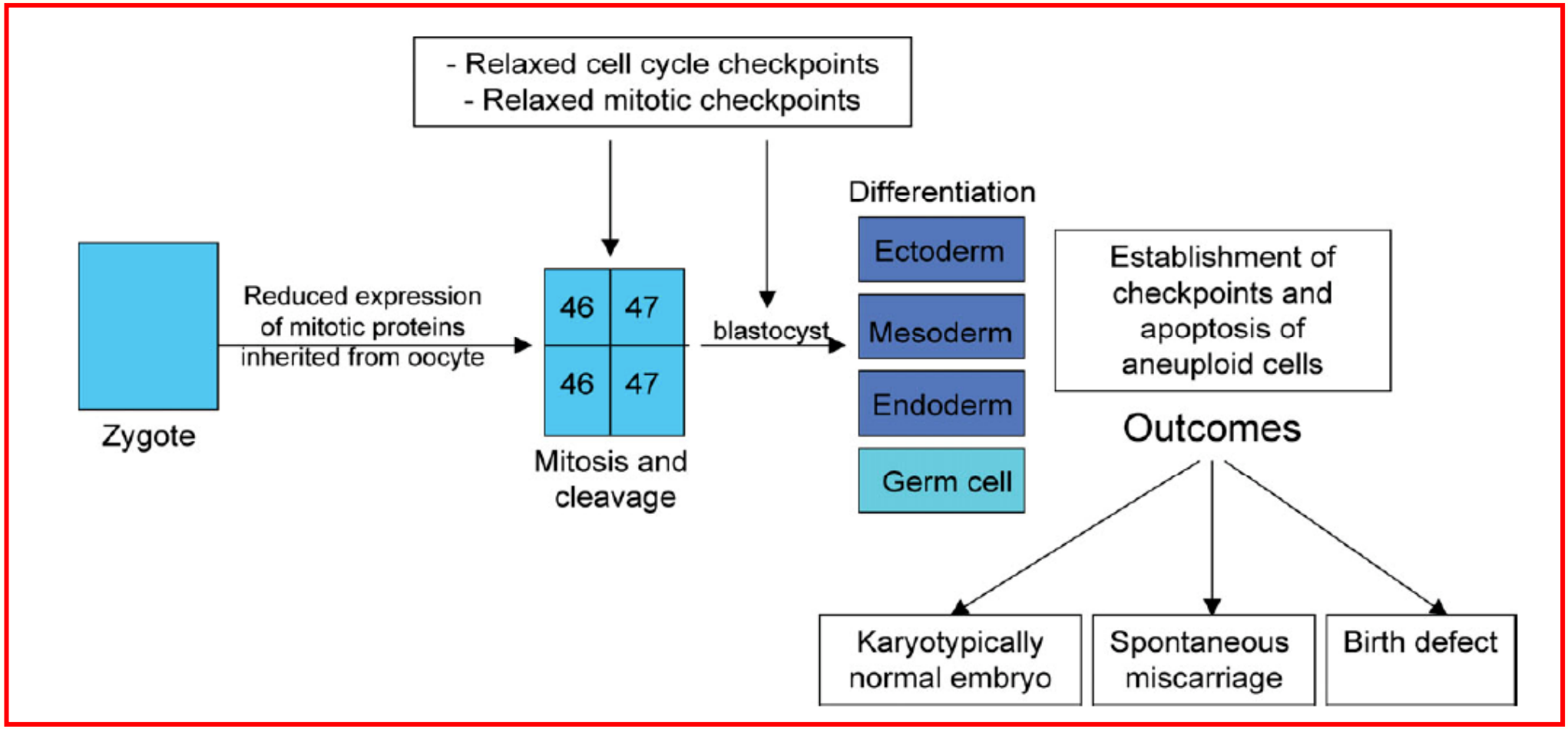
Human Molecular Genetics, 2008, Vol. 17, Review Issue 1 **R10–R15**
doi:10.1093/hmg/ddn170

Aneuploidy and early human embryo development

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



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More parameters affecting cleavage rate

Metabolism

Cytoskeleton – spindle …

Laboratory conditions

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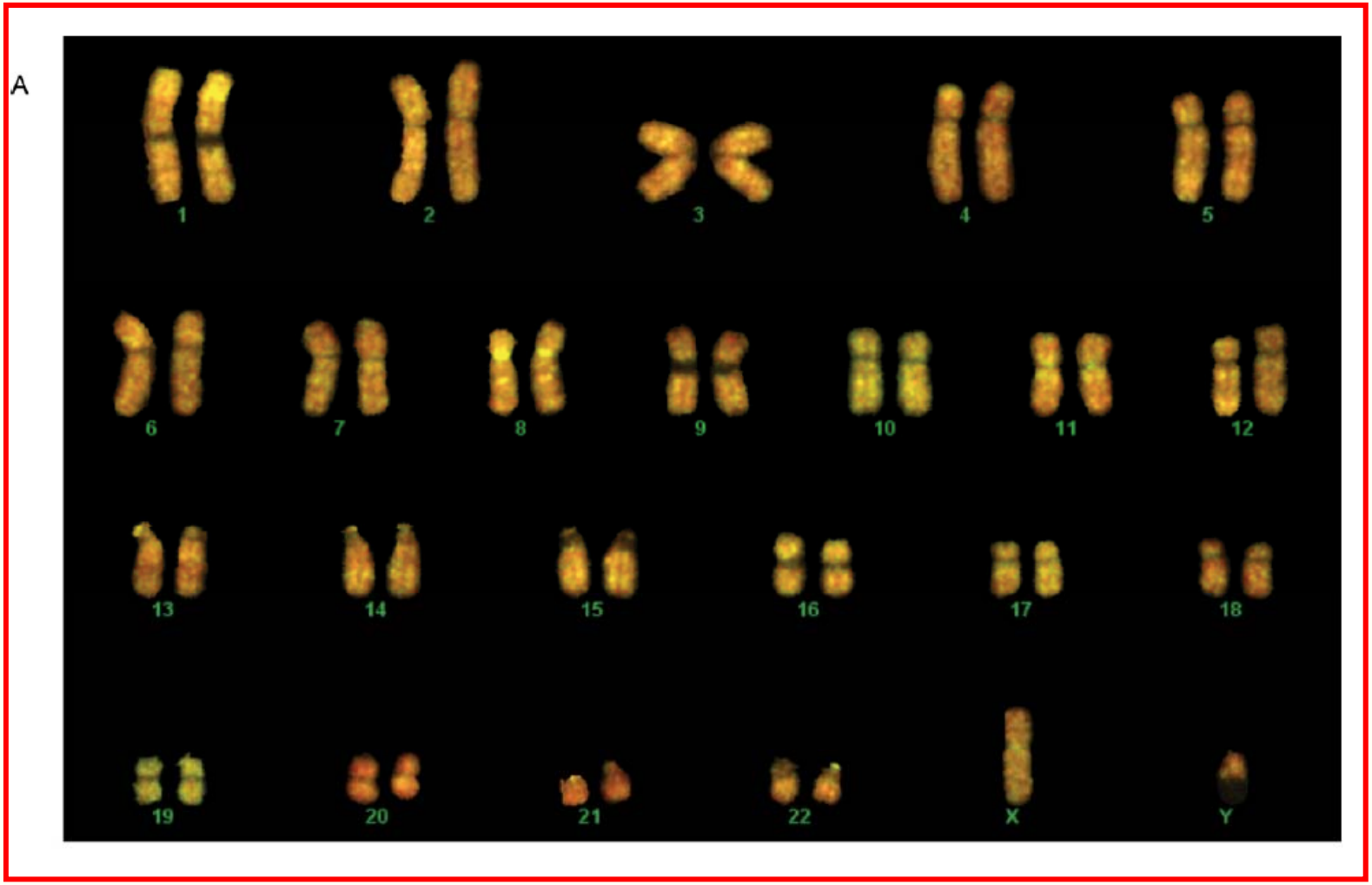
Molecular Human Reproduction Vol.14, No.12 pp. 703–710, 2008
Advance Access publication on November 28, 2008
doi:10.1093/molehr/gan062

NEW RESEARCH HORIZON

Use of comprehensive chromosomal screening for embryo assessment: microarrays and CGH

Dagan Wells[1,2,3], Samer Alfarawati[1] and Elpida Fragouli[1]



Molecular Human Reproduction Vol.14, No.12 pp. 667–672, 2008
Advance Access publication on November 19, 2008 doi:10.1093/mole

NEW RESEARCH HORIZON

Metabolism of the viable mammalian embryo: quietness revisited

Henry J. Leese[1,4], Christoph G. Baumann[1], Daniel R. Brison[2], Tom G. McEvoy[3] and Roger G. Sturmey[1]

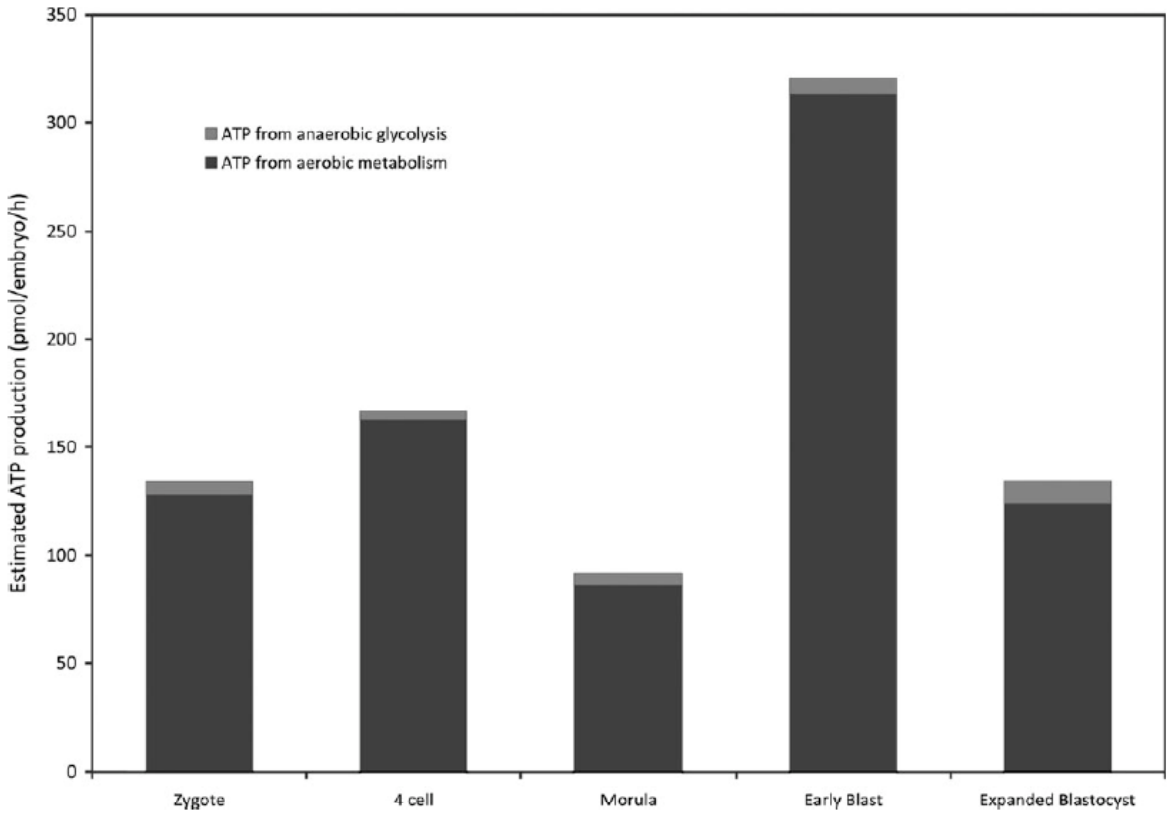
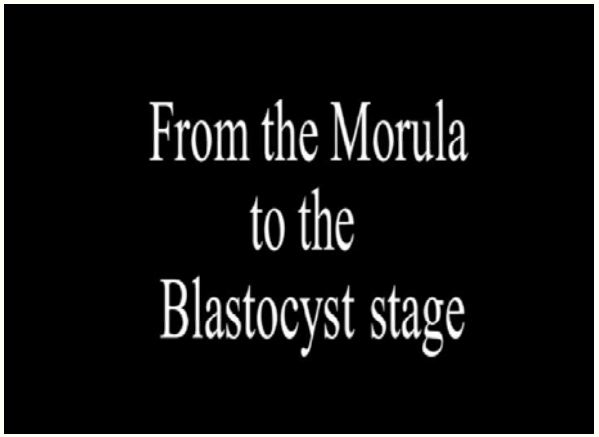


Figure 1: ATP production by *in vitro*-derived porcine embryos calculated from lactate production and oxygen consumption. There is a characteristic shift in the metabolic profile of early porcine embryos, with an increase in the amount of ATP produced but the relative contribution from glycolysis is minimal. The methods used in generating these data are described in Sturmey and Leese (2003).

Using kinetics to predict fate



Will we be able to use cleavage rate and/or pattern to accurately predict the implantation potential of the embryo?

Will we be able to detect all the subtle changes in the embryos that do grow nicely but will not implant (deselect) or vice versa (select)?

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Current landmarks

Early cleavage/syngamy

4 cell on day 2

8 cell on day 3

Expanded blastocyst (>3) on day 5

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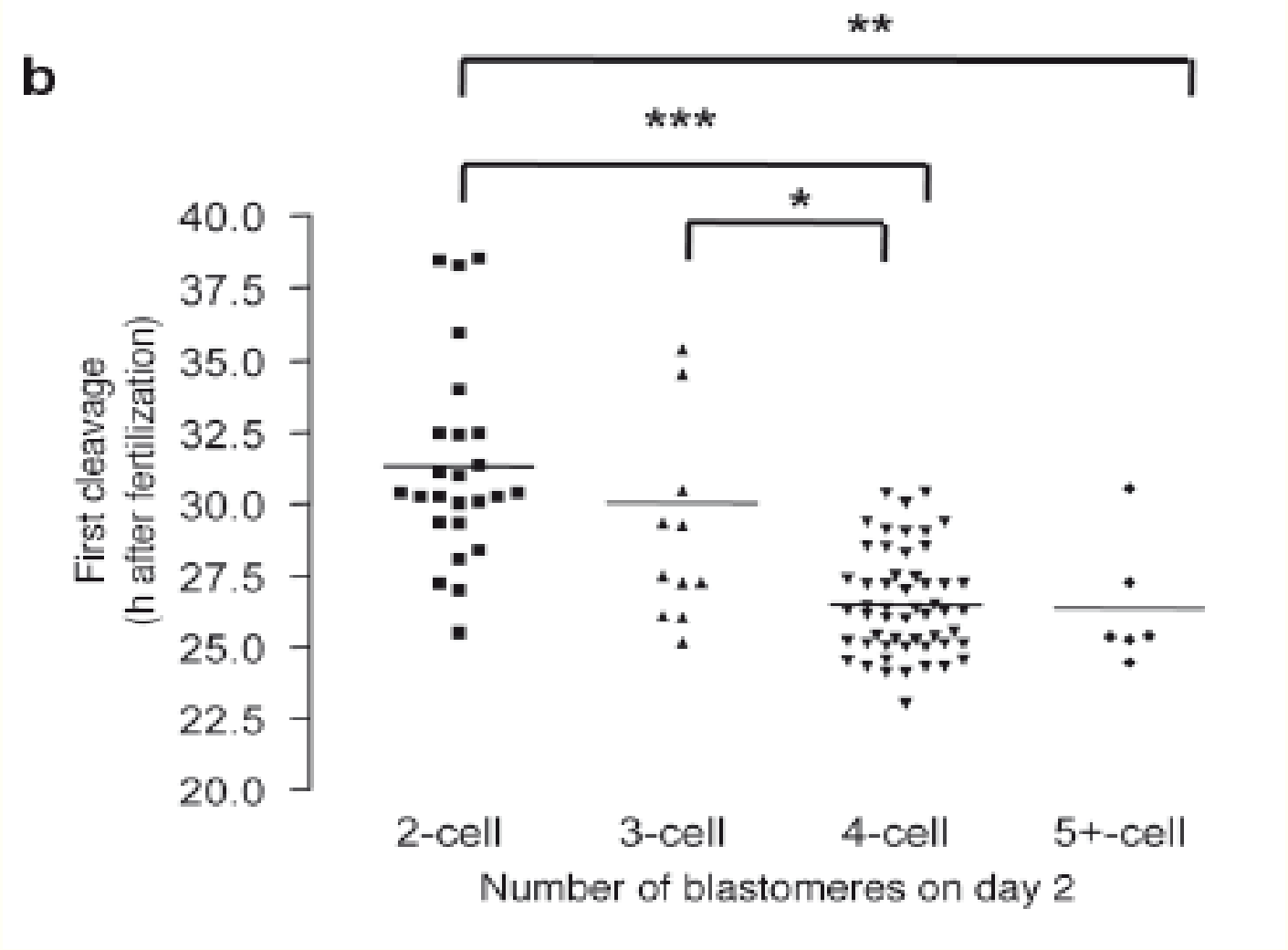
Embryo kinetics

Individualize embryo scoring?



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Lemmen *et al.* 2008 RBM Online

Cleavage pattern analysis

nature biotechnology

Non-invasive imaging of human embryos before embryonic genome activation predicts development to the blastocyst stage

Connie C Wong[1,2,7], Kevin E Loewke[1–3,6,7], Nancy L Bossert[4], Barry Behr[2], Christopher J De Jonge[4], Thomas M Baer[5] & Renee A Reijo Pera[1,2]

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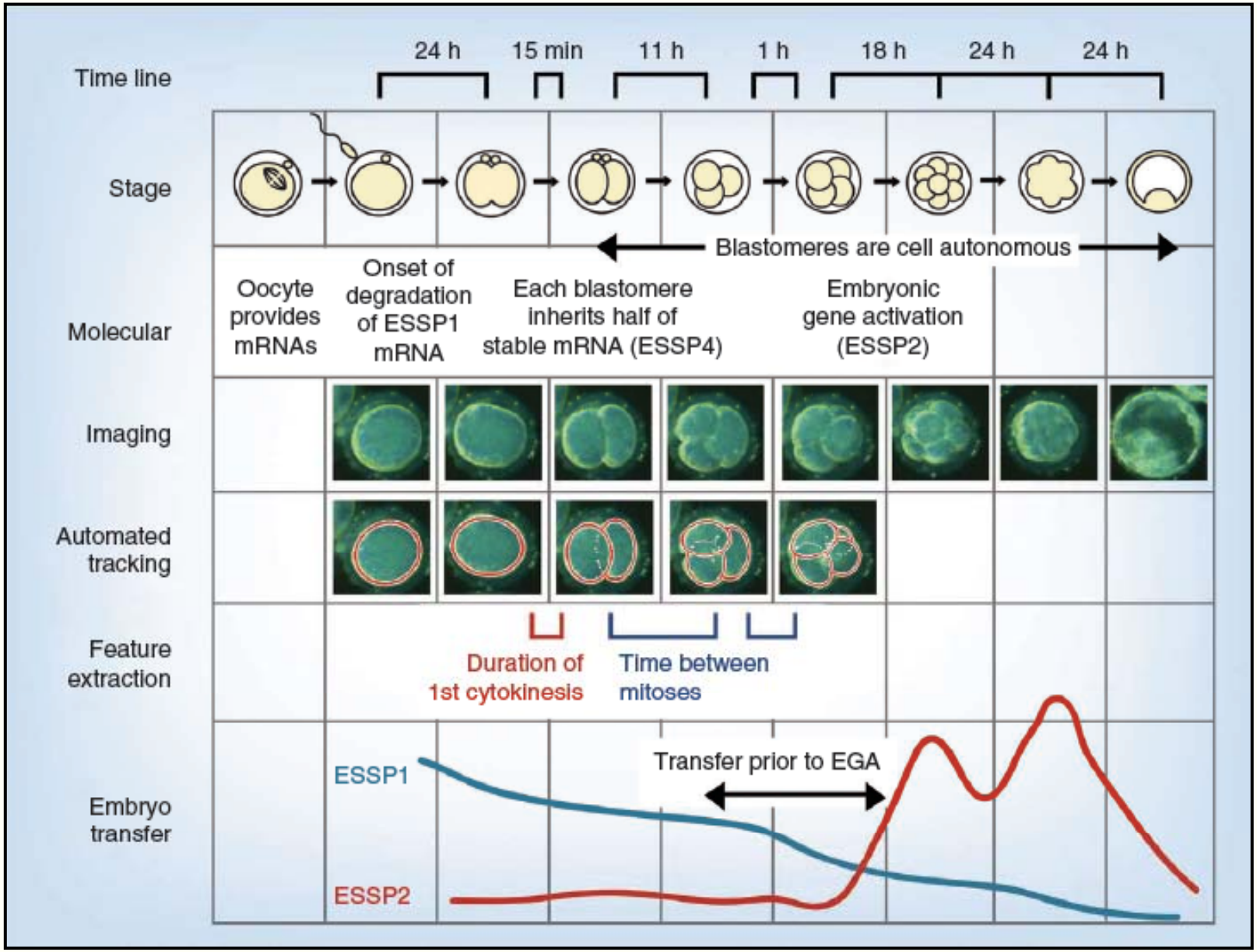

Cleavage pattern analysis

ASRM 2010

[V-6] CLINICAL USE OF TIME-LAPSE MICROSCOPY TO EVALUATE PRE-IMPLANTATION EMBRYO DEVELOPMENT.

M. Meseguer, K. S. Pedersen, J. Herrero, M. Cruz, A. Tejera, N. B. Ramsing

[P-193] LINKING SUCCESSFUL IMPLANTATION WITH THE EXACT TIMING OF CELL DIVISION EVENTS OBTAINED BY TIME-LAPSE SYSTEM IN THE EMBRYOSCOPE.

J. Herrero, T. Alberto, N. B. Ramsing, M. J. De los Santos, L. Escrich, M. Meseguer

RESULTS:

Implantation within the time-range for each variable

Event	PN formation	PN fading*	1st division*	2nd division*	3rd division*
Range (h)	7.8 - 11.1	22.3 - 25.8	24.4 - 28.2	35.3 - 40.6	36.0 - 41.6
Implanted (%)	20	29.5	28.8	23.2	29.7
N	32	47	46	37	47

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Time-lapse

Enables you to observe changes otherwise missed

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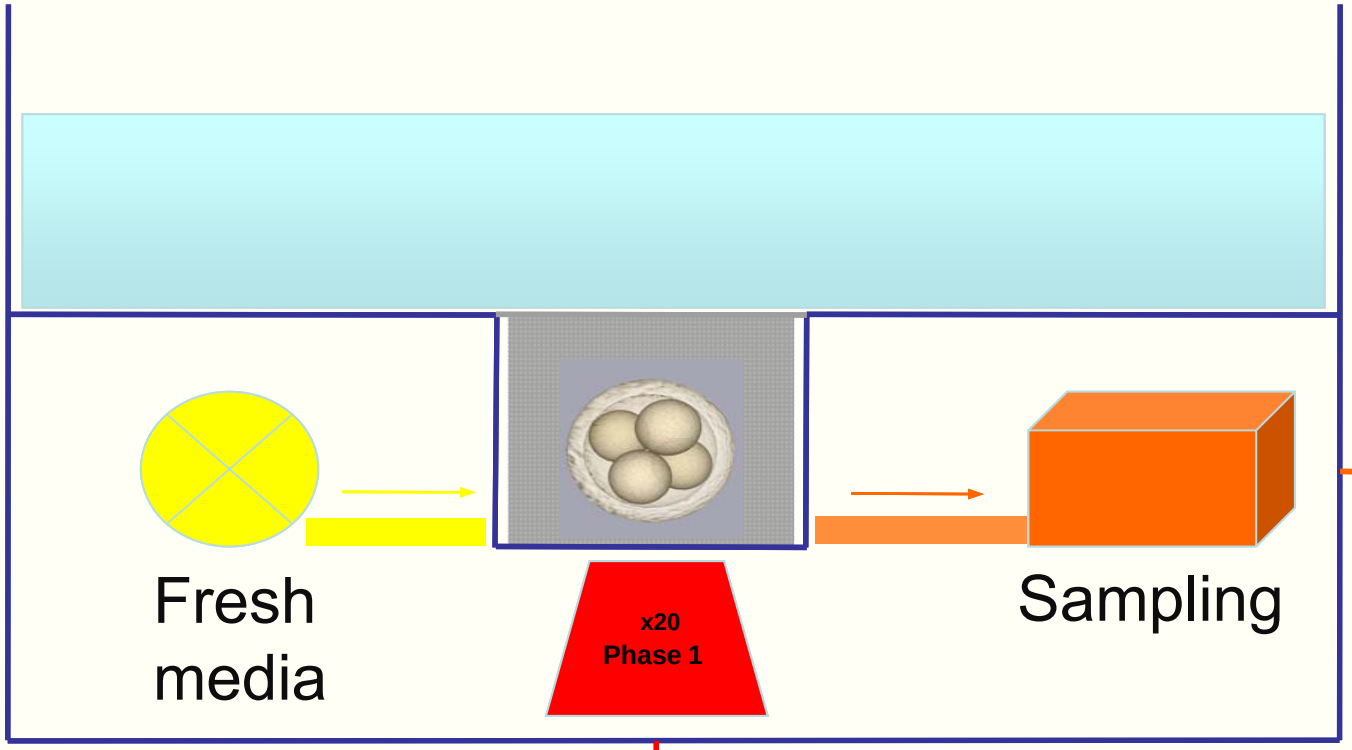
Future of embryology?



Indirect analyses:
- Metabolomics
- Protein metabolism
- Gene analysis
- Chromosomal analysis?
- …more to come!!

Contineous morphological recordings

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