THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Cancer & Evolution Symposium, Oct 14-16

The Giant Cells: Toward Unification of Embryogenesis, Cancer, and Evolution

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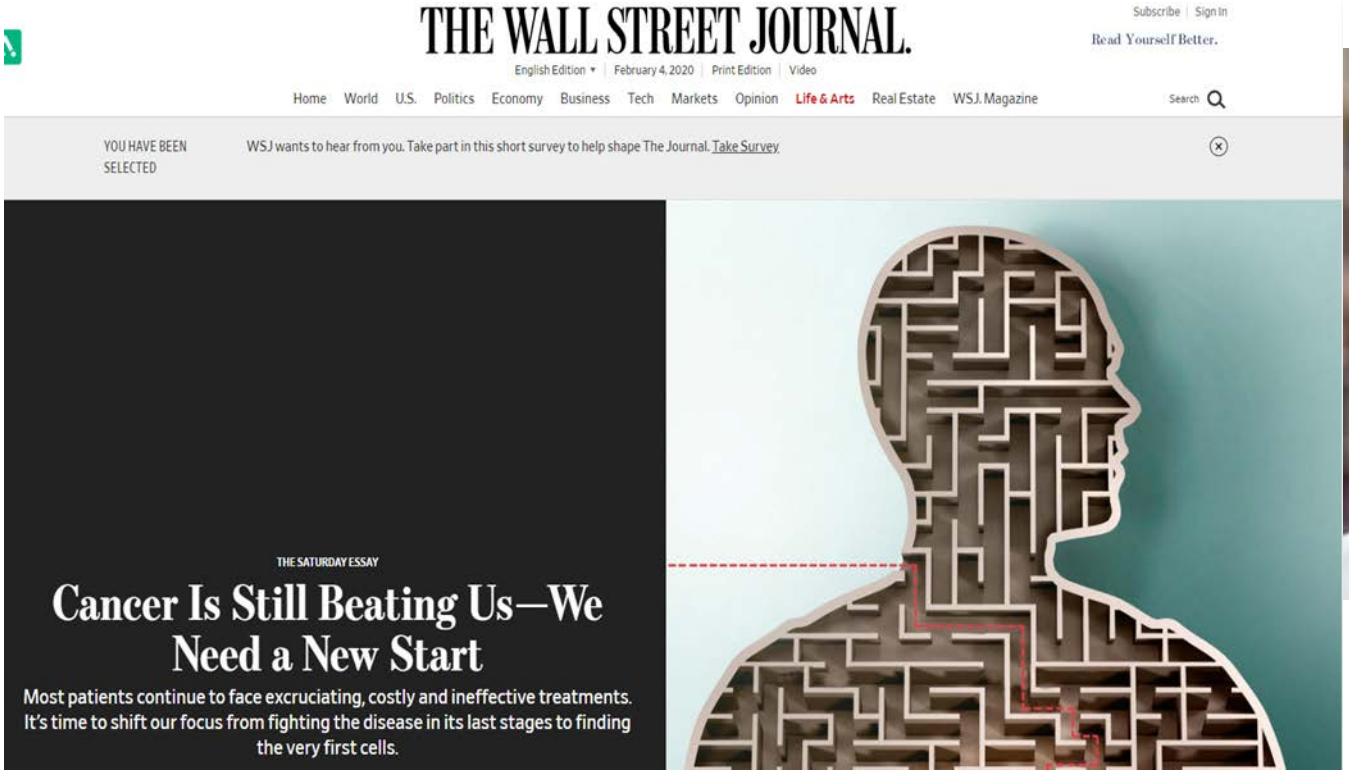
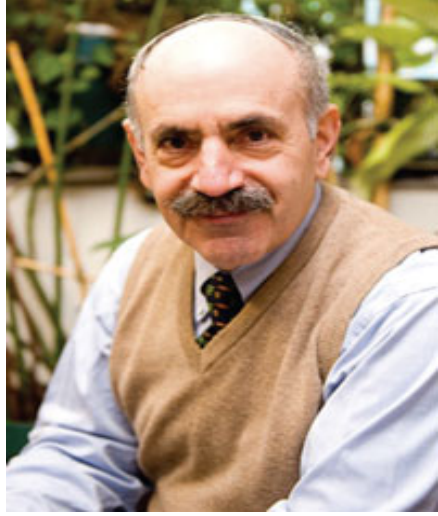
Professor, Department of Anatomic Pathology



Dr. Azra Raza

We have not made much progress in the past 50 years won't advance much more in another 50 if we insist on the same-old same-old, all of us in the biomedical research need to descent from our high horse and humbly admit where we have been wrong" .....

"Cancer is not linear--it is completely non-linear. It lives in the science of chaos"!



Leading Edge
Essay

Coming Full Circle—From Endless Complexity to Simplicity and Back Again

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http://dx.doi.org/10.1016/j.cell.2014.03.004

We lack the conceptual paradigms and computational strategies for dealing with this complexity.

What has been wrong ?
What could be right?
How to move forward?

Fundamental question in life and cancer?

- What is human life?
- What is cancer?
- Is cancer a life or a cluster of mutated cell?

19th century scientist

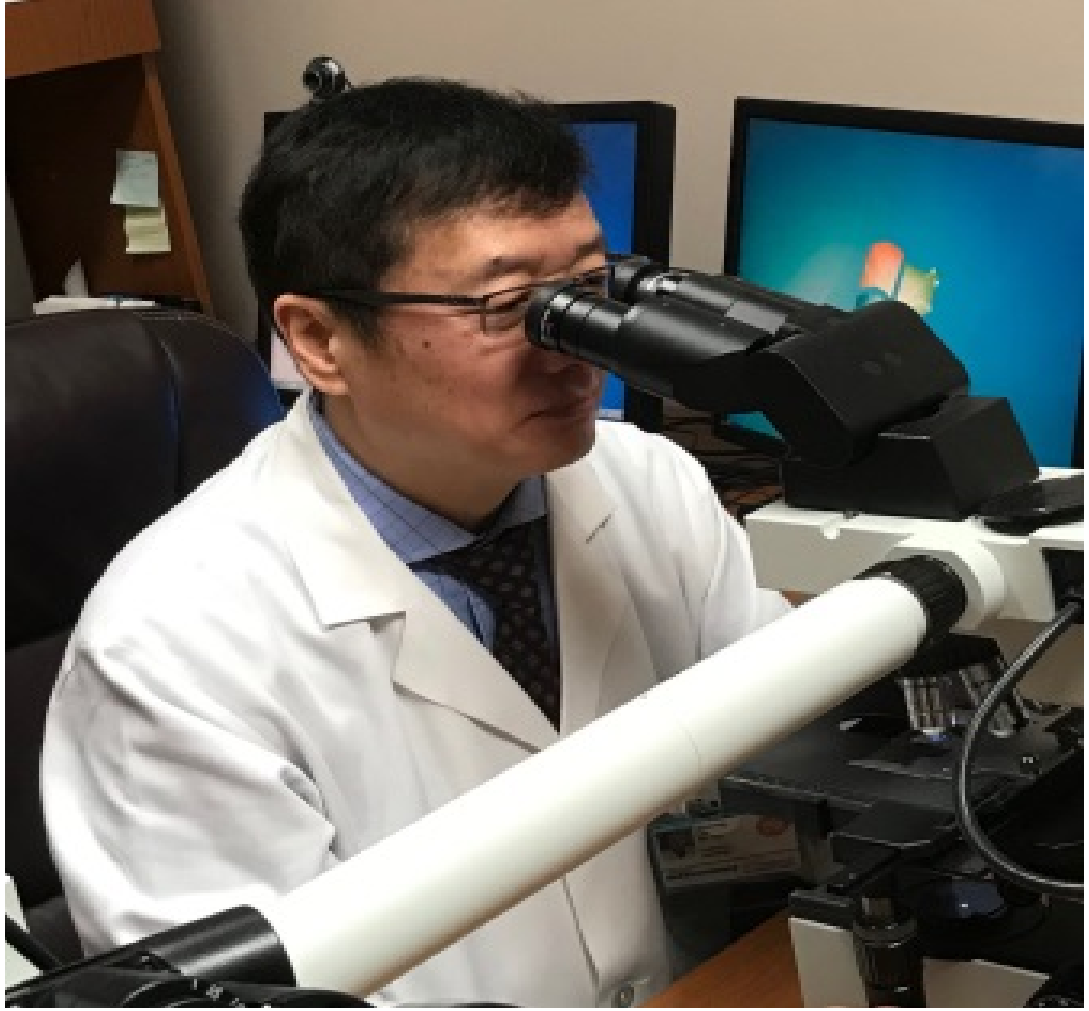
I must find the explanation for this phenomenon in order to truly understand Nature...

Curiosity driven, Darwinian approach

21st century scientist

I must get the result that fits my narrative so I can get my paper into Nature..

Molecular driven- Mechanism

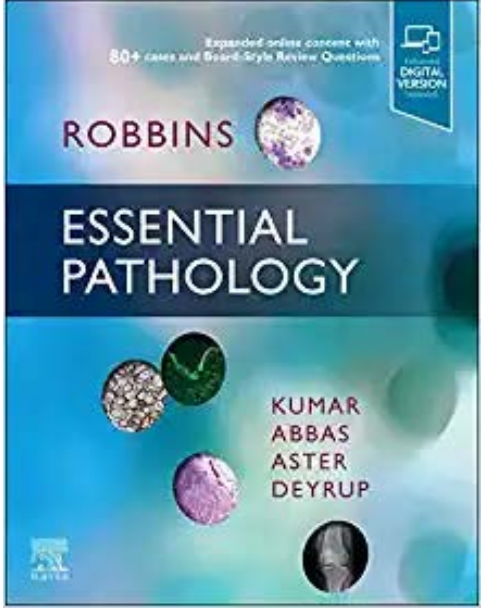


Cancer is Defined by Microscopic Criteria by Pathologists

Nothing is more important to the individual with a tumor than being told “it is benign”

Benign **Malignant (cancer)**

Differences Between Benign and Malignant Tumors



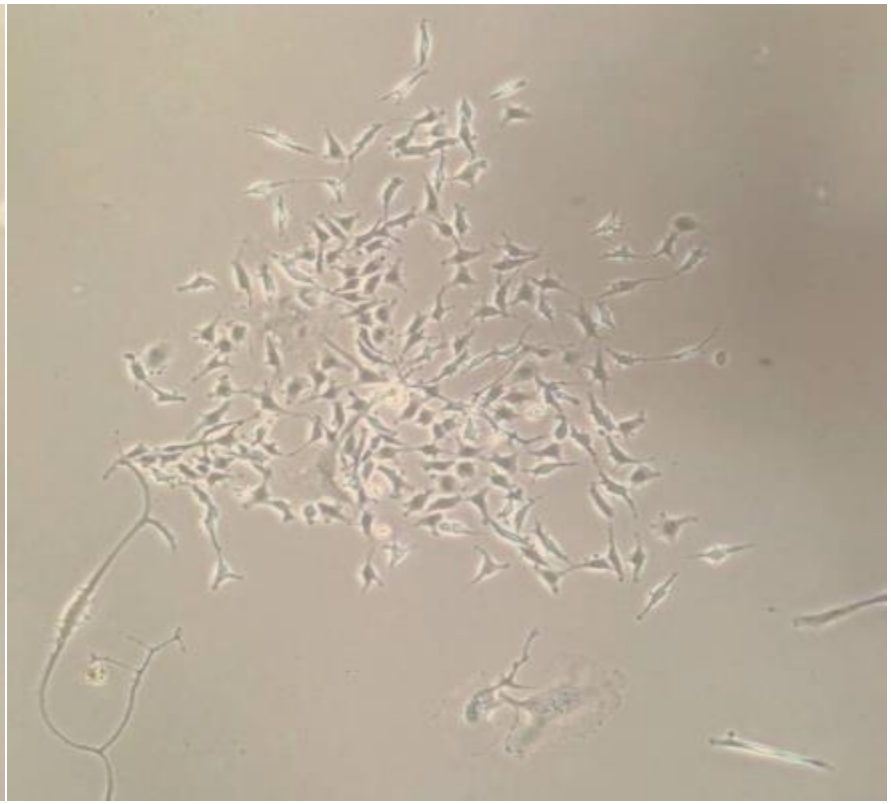
- **Level of Differentiation** (Tissue immaturity)
- **Nuclear grade** (Nuclear atypia, size variation, and tumor giant cells)

Any viable theory of cancer must be able to explain the benign and malignant phenotypes observed by pathologists

- Tumor size has nothing to with malignancy – measurement of tumor size as endpoint will fail the patients

Polyploid Giant Cancer Cells (PGCCs) Can Grow back

(Hey Ovarian Cancer Cell Line, 09/22/2010)



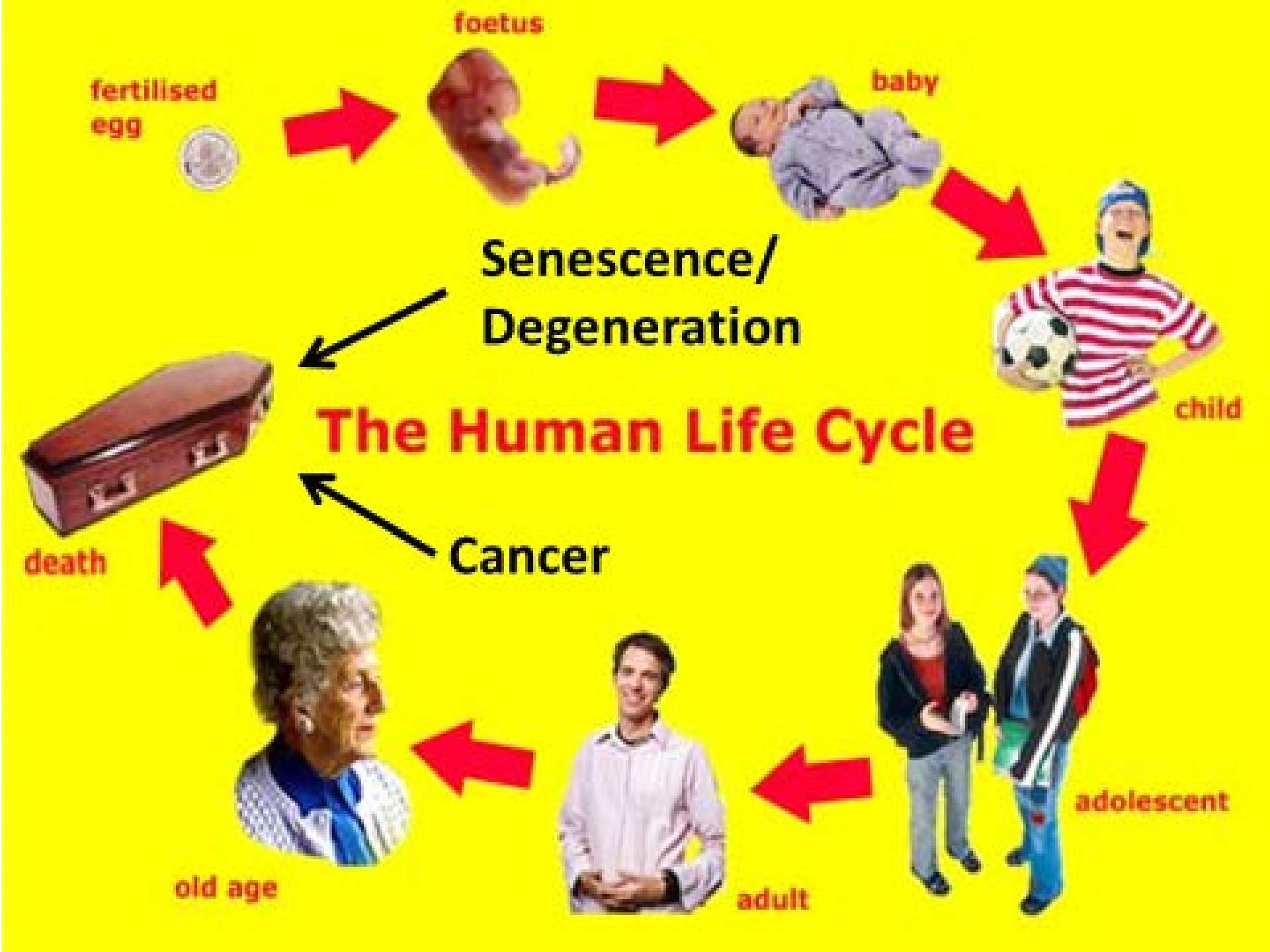
450 μM $CoCl_2$

1 Month Later

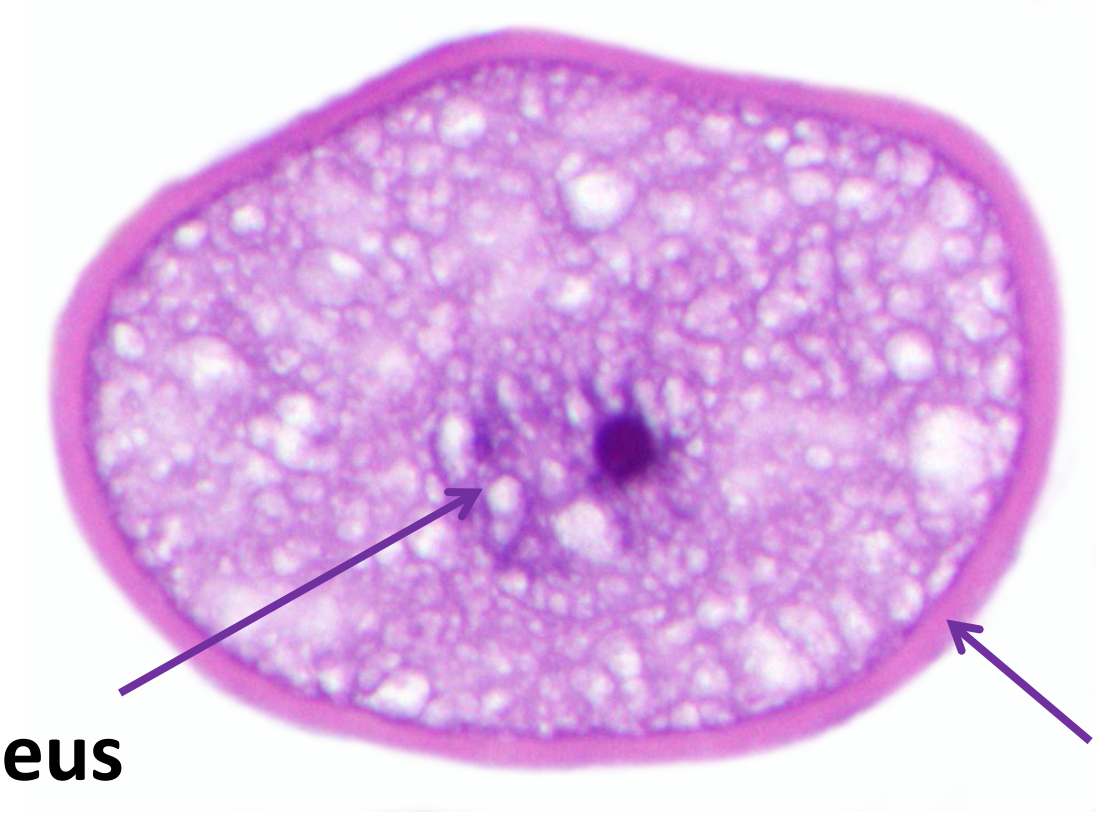
Dogma

Polyploid giant cancer cells (PGCCs) are believed to be non-dividing and degenerating cells (trash cells, >100 years)

The Human Life Cycle



Life Starts with a Giant Cell (largest human cell)

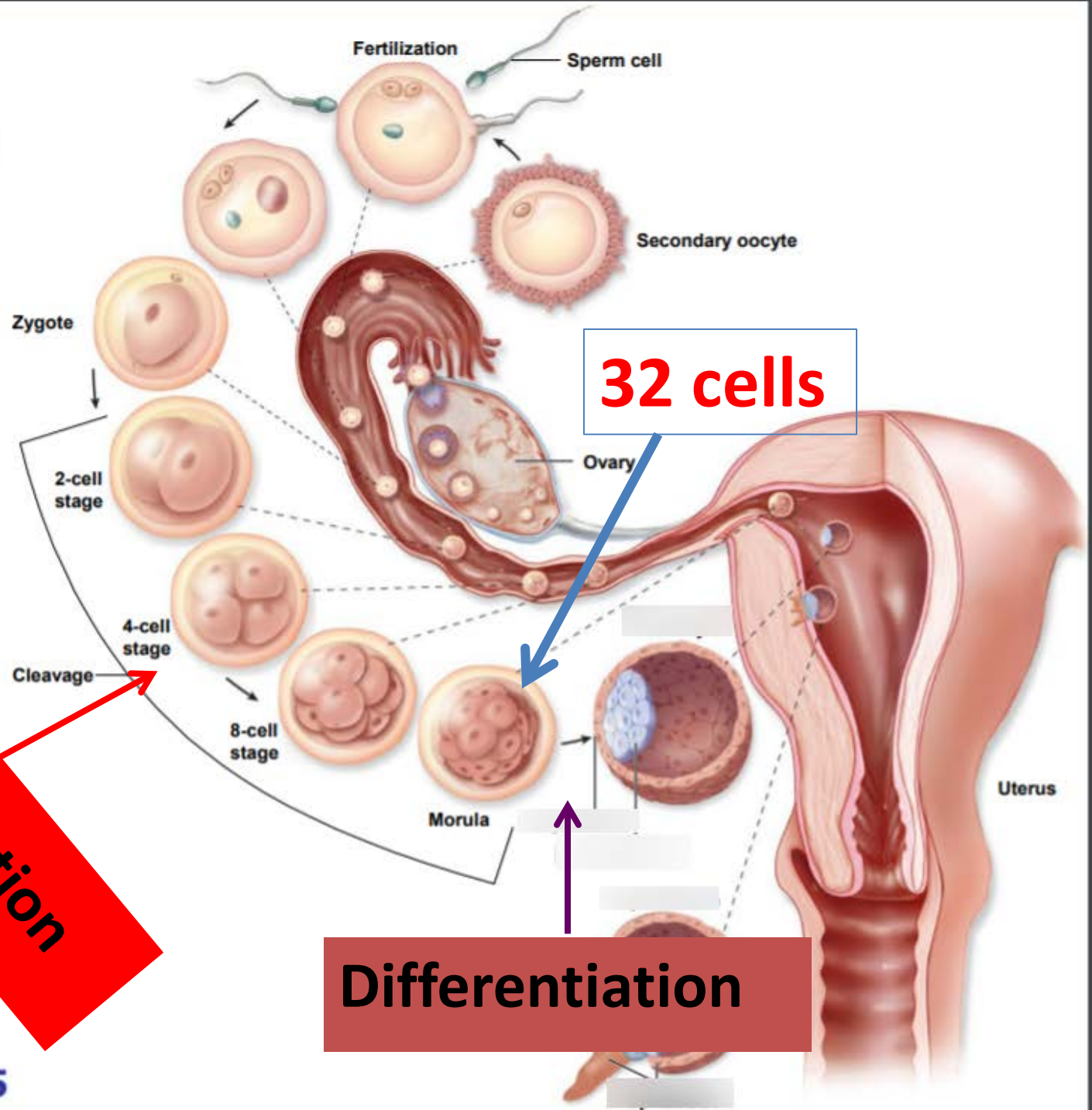


Nucleus

Zona Pellucida

160 uM (Normal cells 10-12 um)
4,000,000 um3 vs 3,000 um3
(Hela cell)

Pre-Embryonic Period (Weeks 1-2)



32 cells

Dedifferentiation

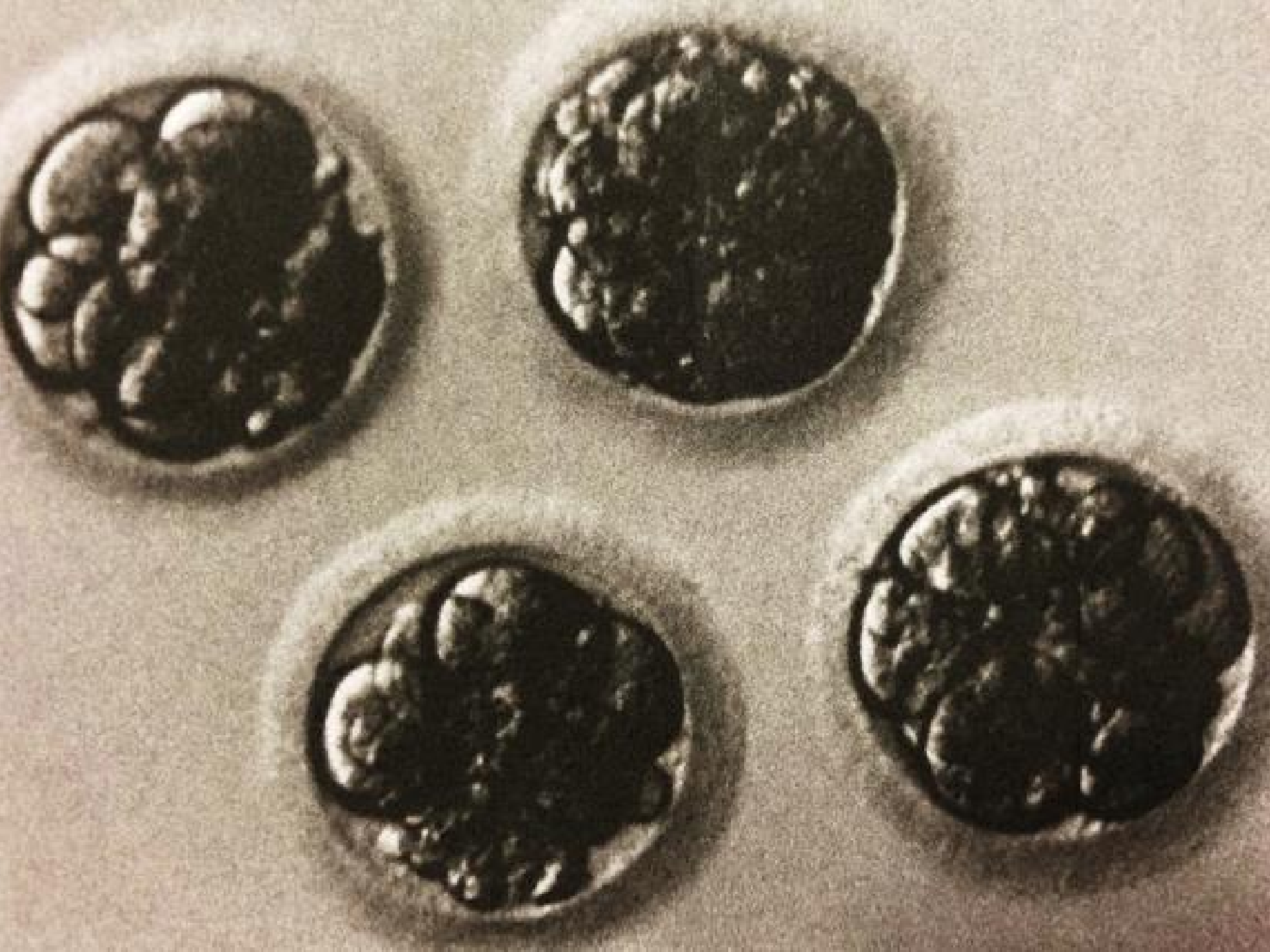
Differentiation

page 64, figure 3.5

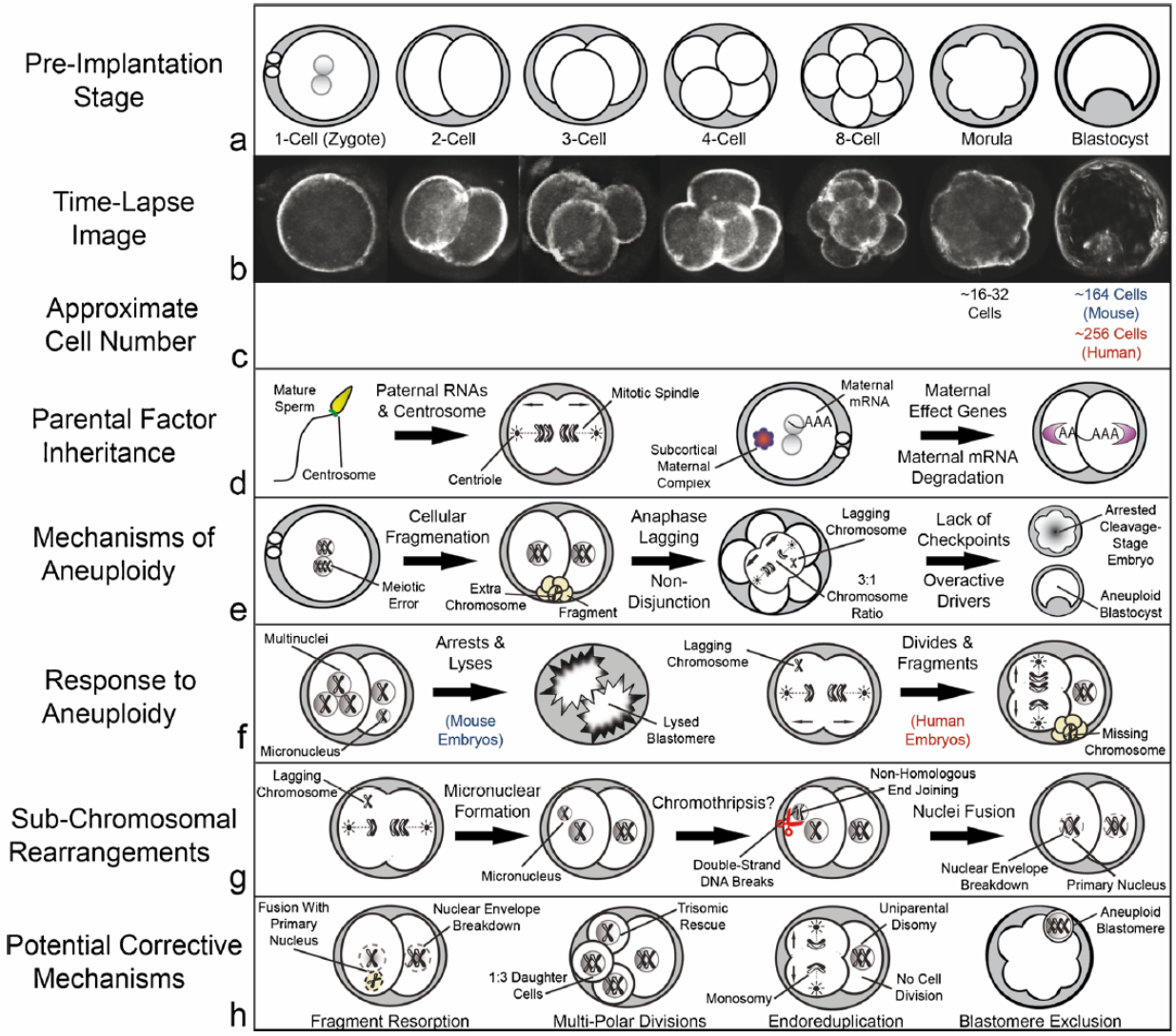
Life Code (Cleavage)

$$2^5 = 32$$

2, 4, 8, 16, 32



Embryonic Chaos in Human



Lack of Cell Cycle Checkpoint

Mosaicism

Atypical Cell Division

Cellular Fragmentation

Sub-chromosomal instability

Micro-nucleation

Chromothripsis

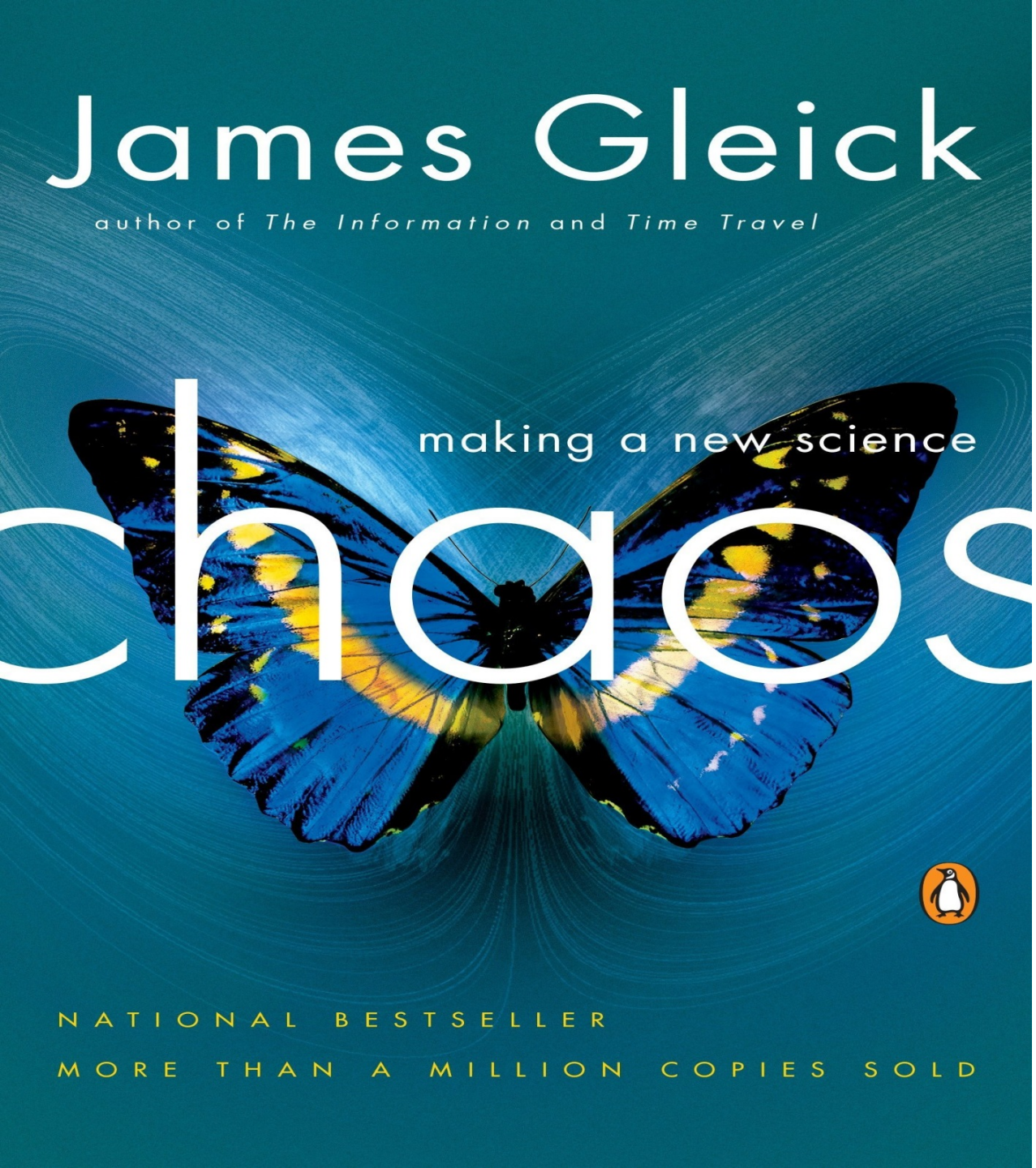
Daughtry and Chavez, 2016

Chaos in Early Human Embryo

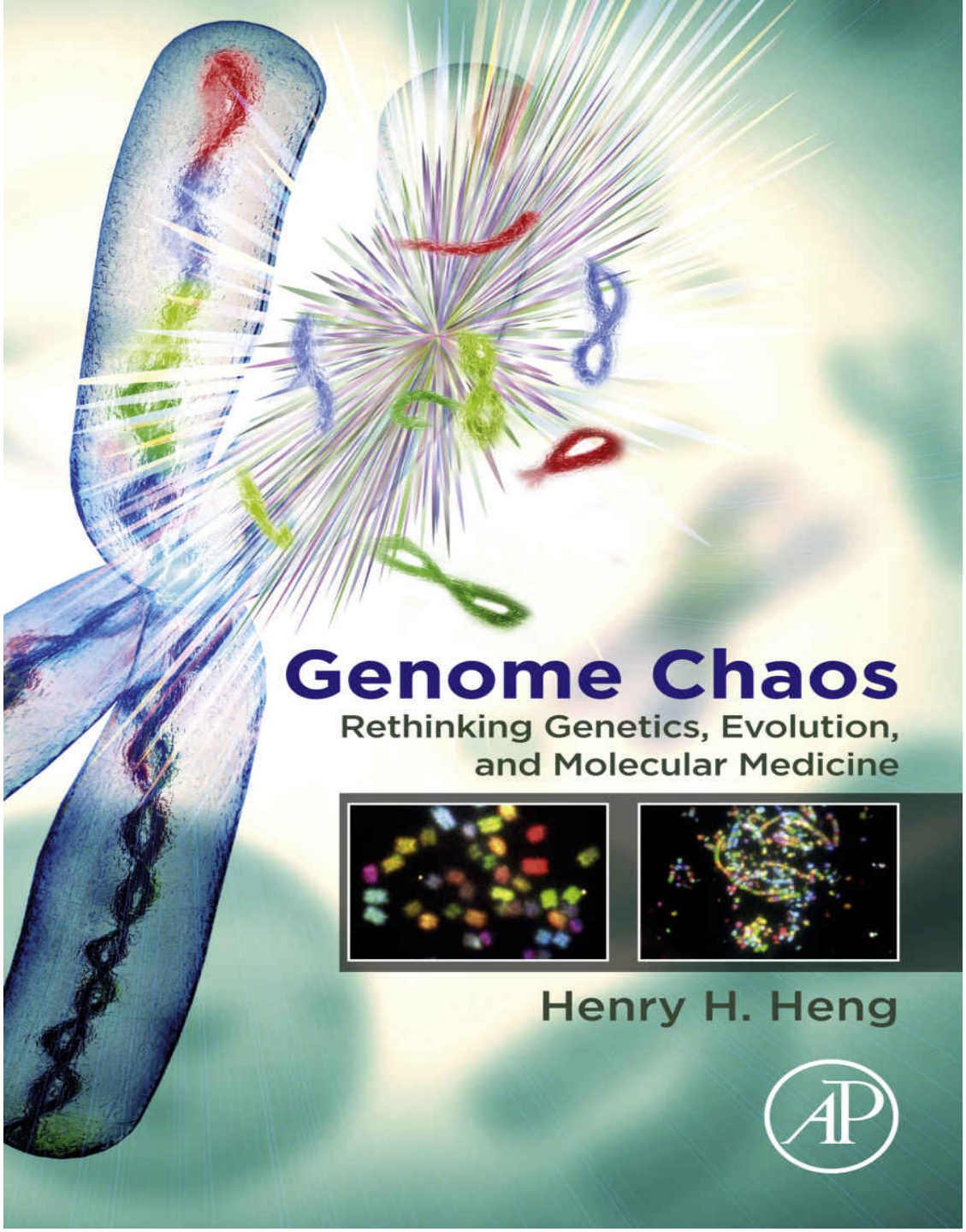
“It's amazing that any of us has made it this far, let alone that and of our children are healthy”.

Ledbetter DH, Nature Medicine 15, 490 - 491 (2009)

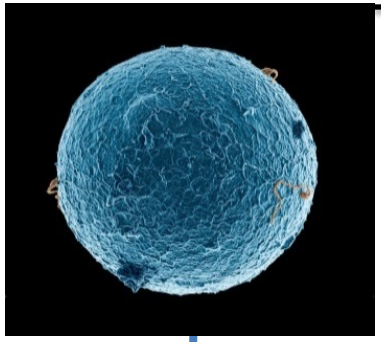
Chromosome instability is common in human cleavage-stage embryos. Vanneste et al., Nature Medicine 15 (577-583), 2009



Chaos Theory: Extremely sensitive to initial stimulus: Non-linear mechanism to create a new order from a disorder

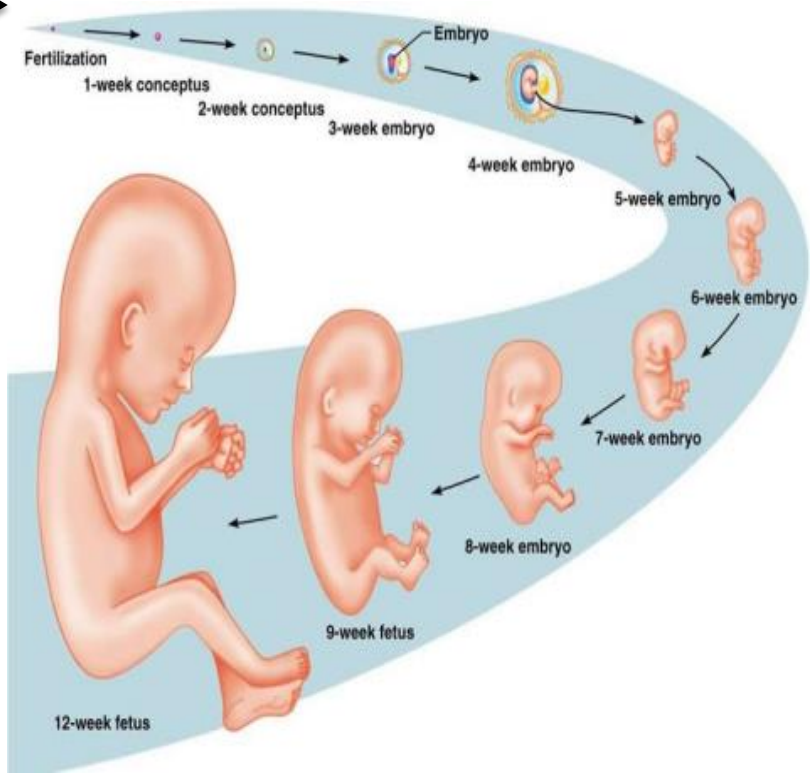

Genome Chaos
Rethinking Genetics, Evolution, and Molecular Medicine
Henry H. Heng
AP

Tumors are a spectrum of diseases along development (Barry Pierce)



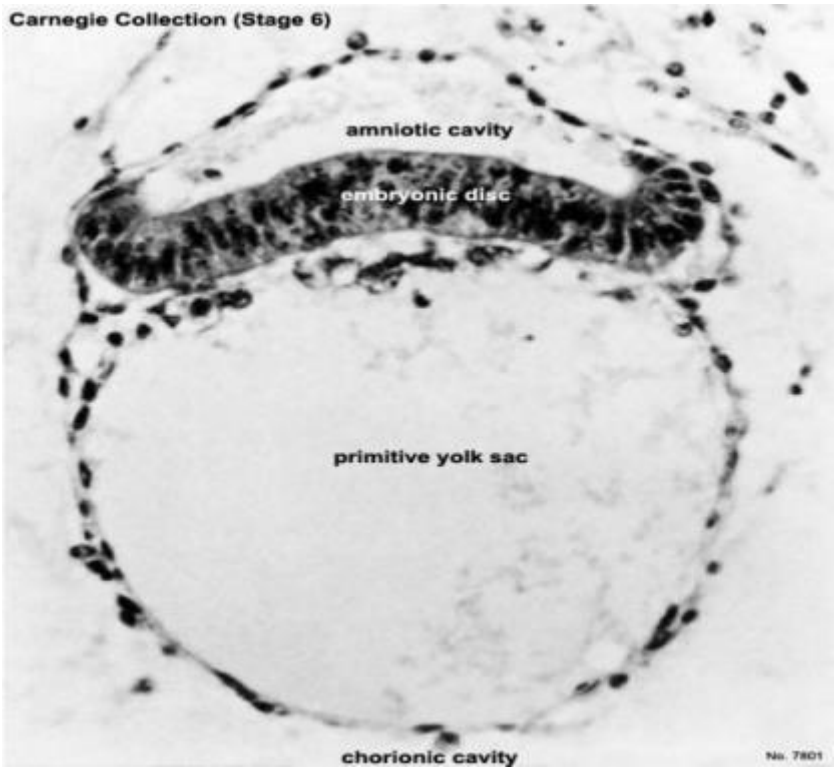
Uterus
Embryonic development

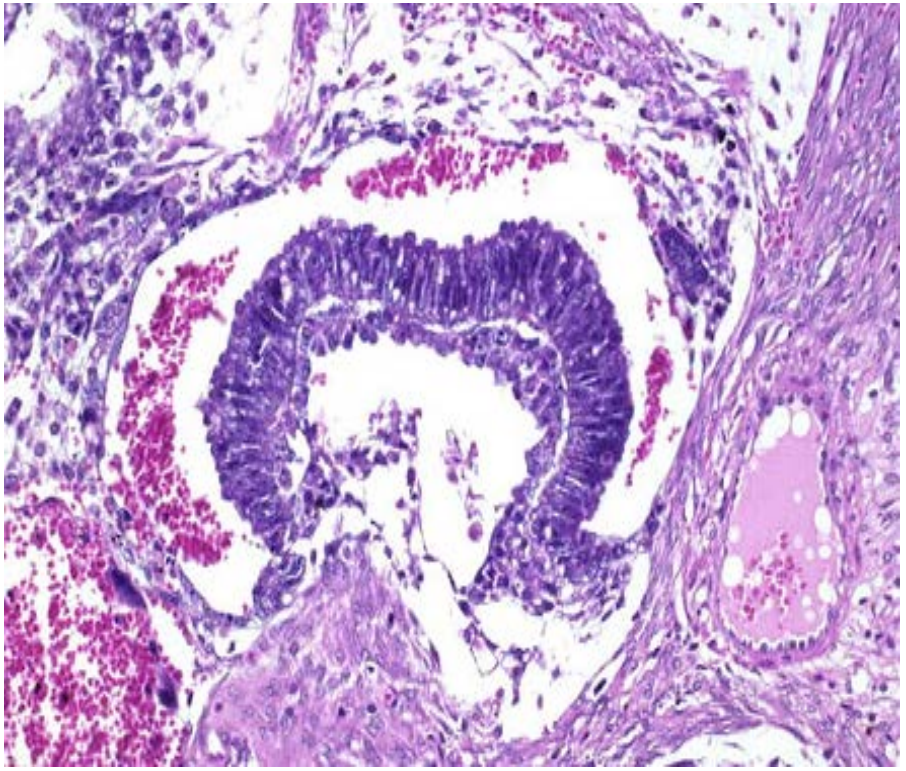
Ovary/Testis
Parthenogenesis



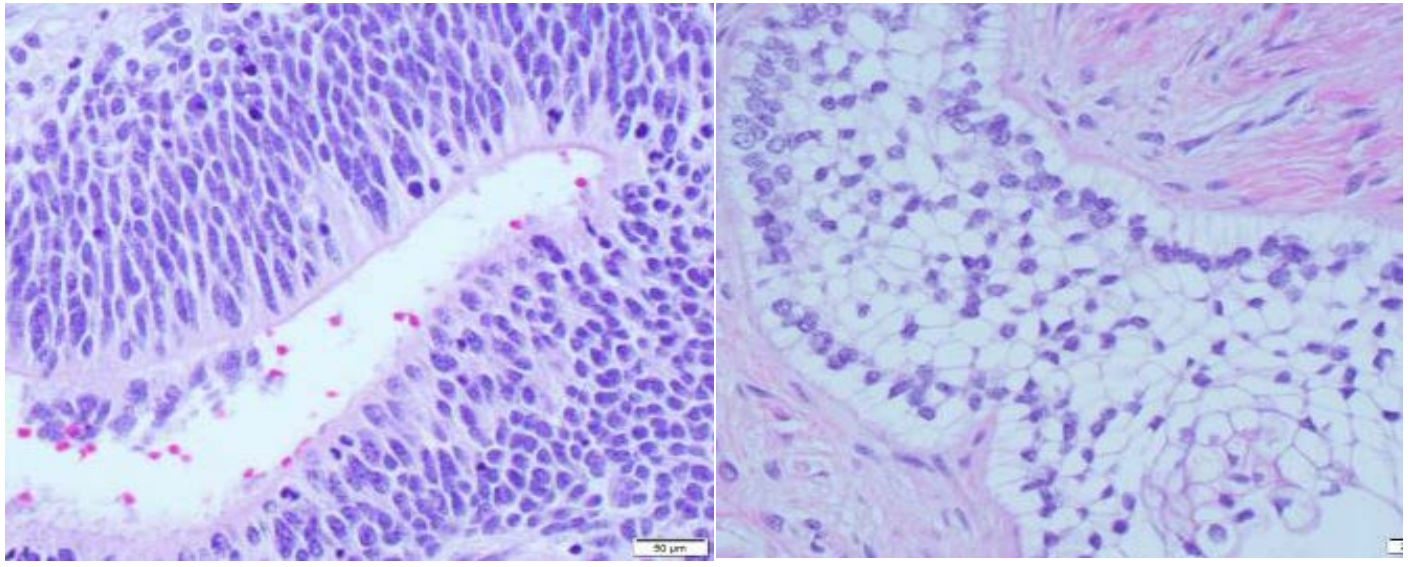
Dev-Arrested Tumors: First Cancer Cell(s) are defined by amount of embryonic tissue (Quantity)

Bilaminar disk stage: Polyembryoma

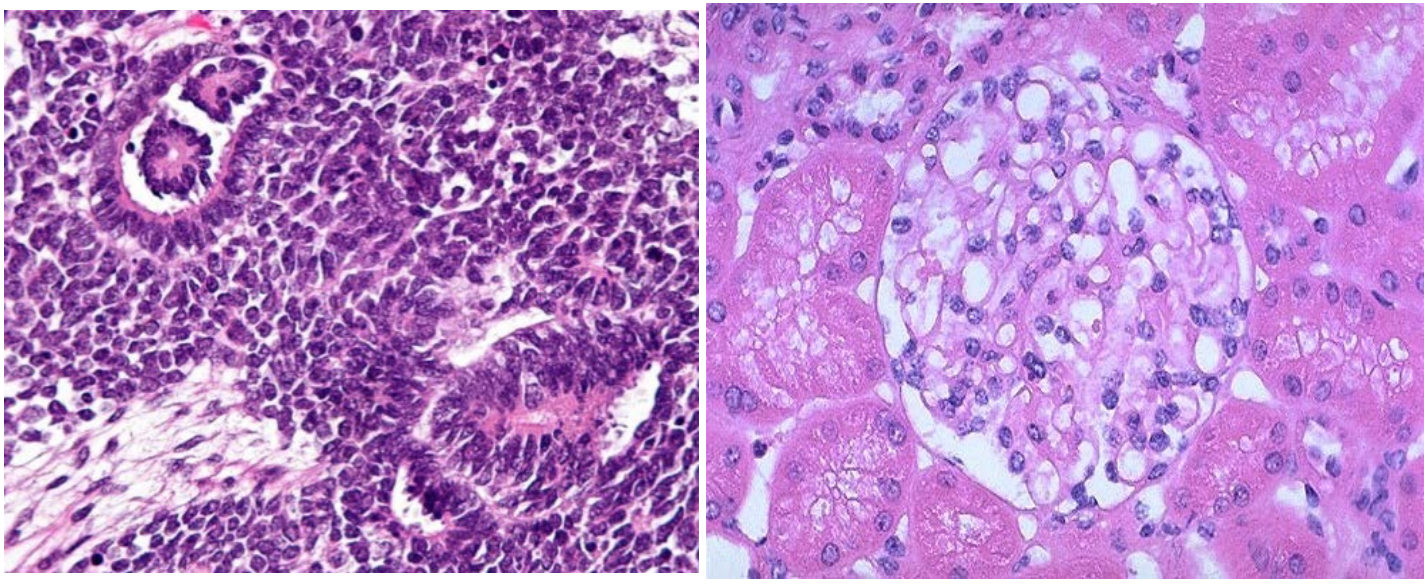




Gastrulation stage: Immature teratoma



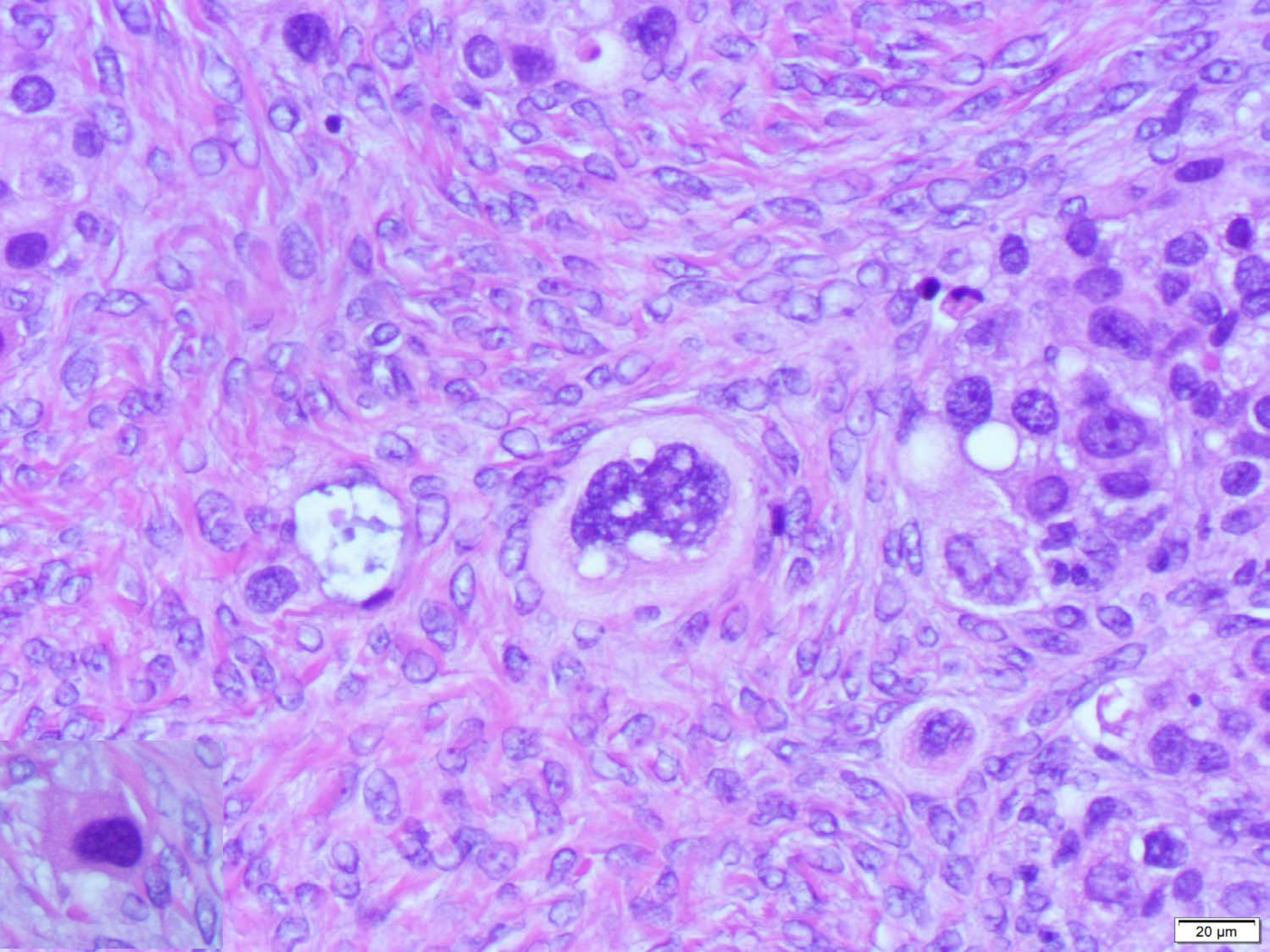
Organ developmental stage: Wilms tumor



Somatic-derived first cancer cells are defined by nuclear grade (quality)

Atypia, increased N/C ratio, pleomorphism, PGCCs

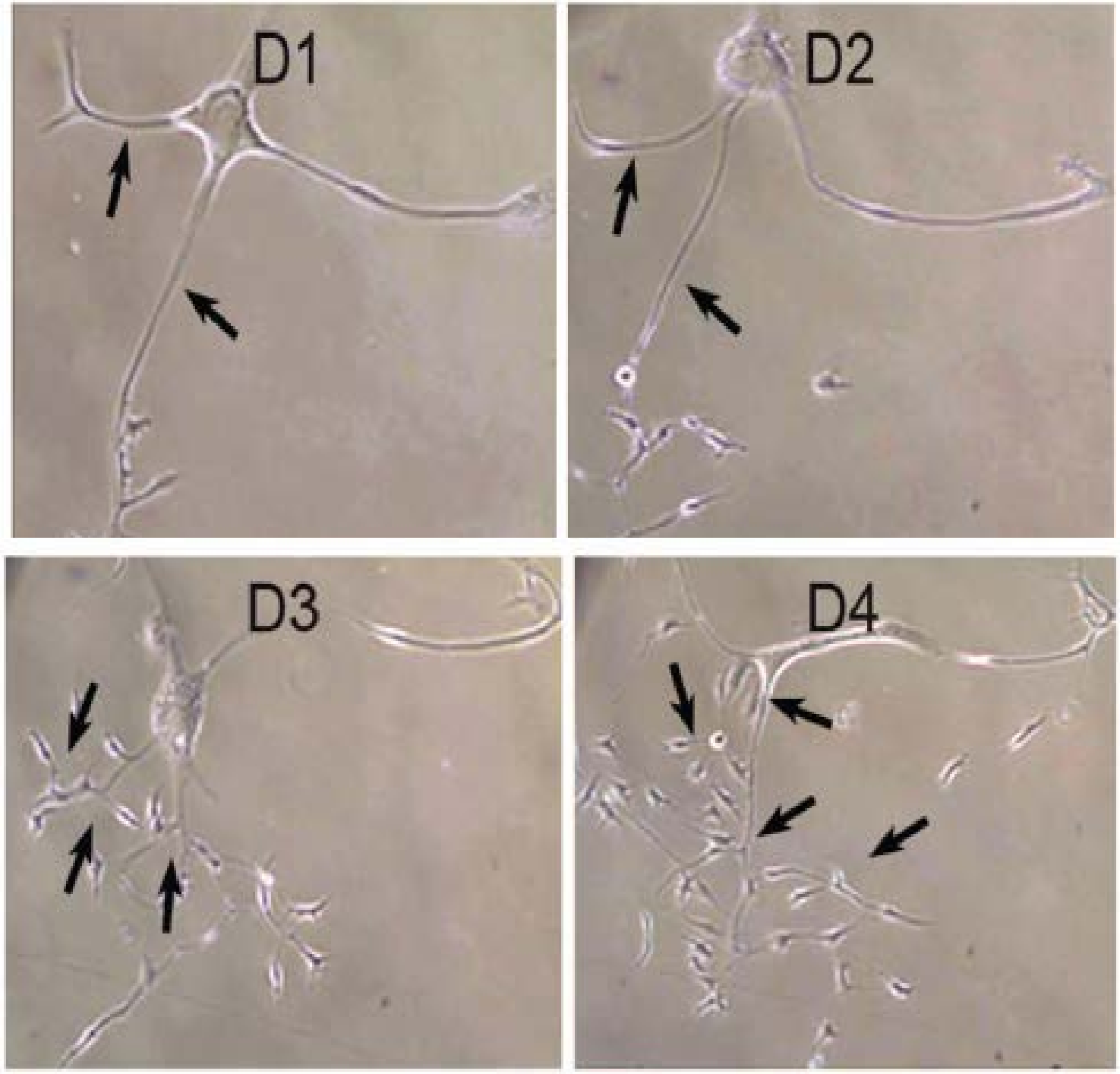
-Quality of Cells: Born to be bad

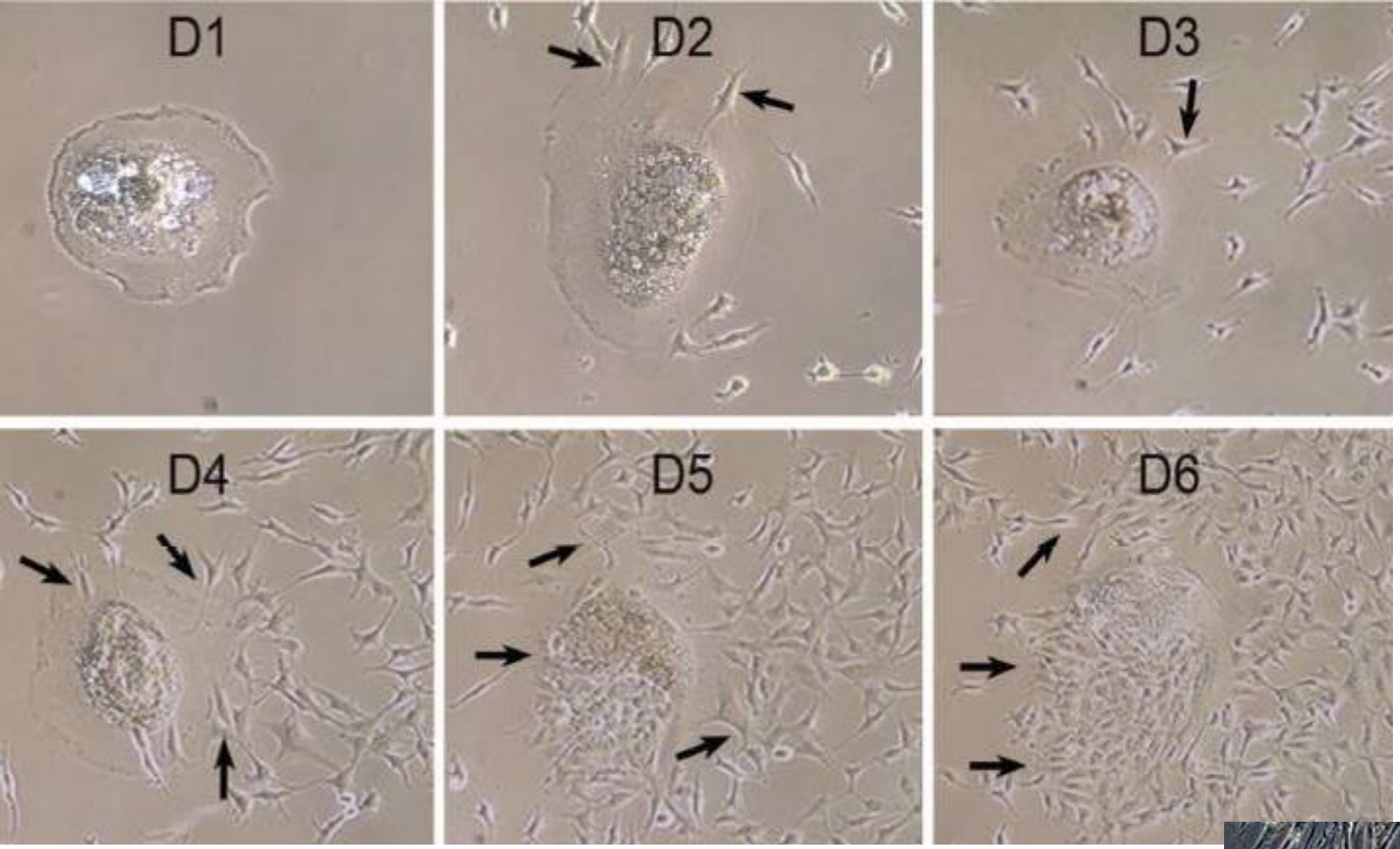

20 µm

#1. Could the initiation of high grade cancer go through a reproductive process similar to that of human embryo?

#2. Could be the giant cell a somatic equivalent of an “egg”?

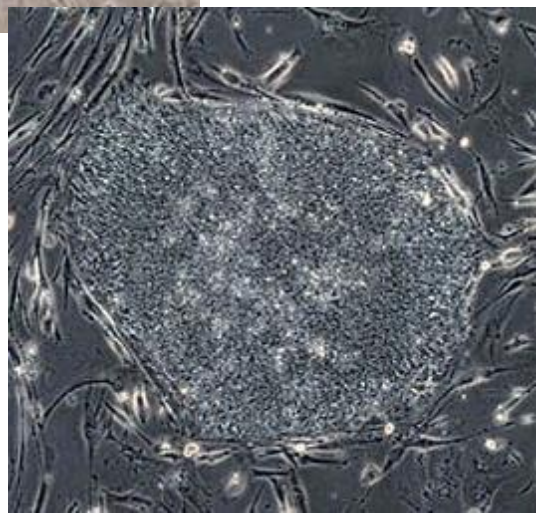
Unexpected finding #1: Primitive cell division


D1
D2
D3
D4

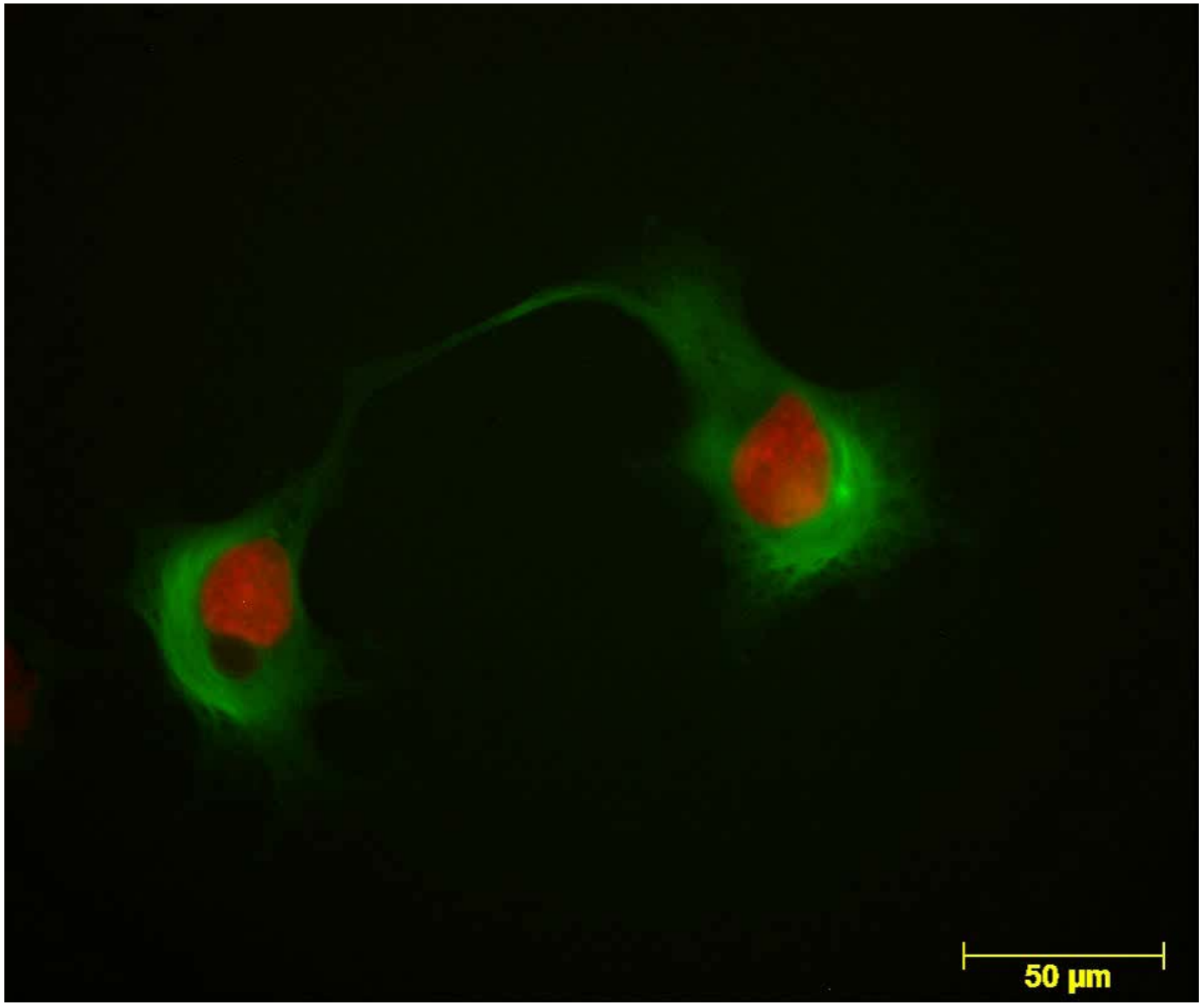


PGCCs

Human Embryonic Stem Cells

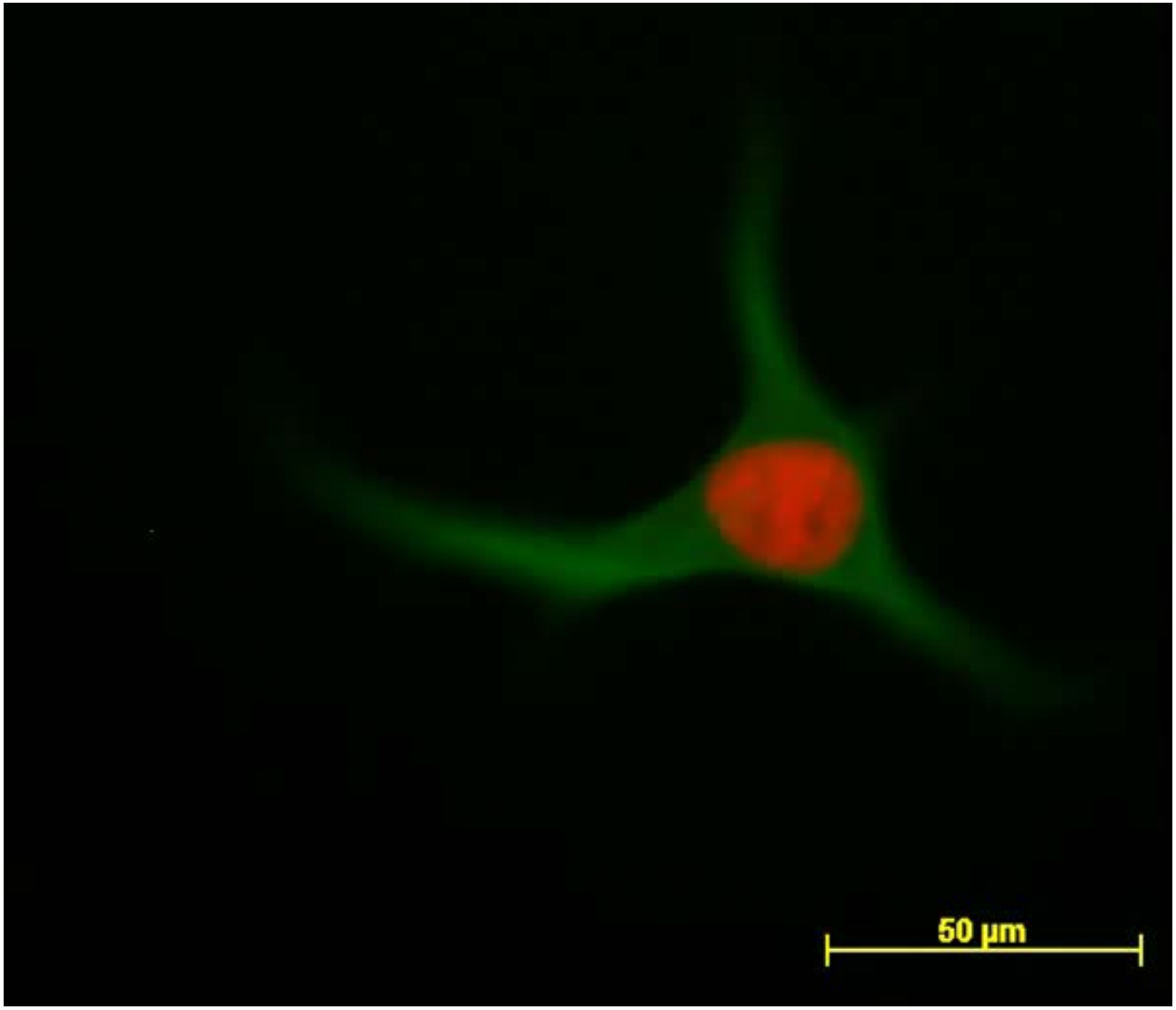


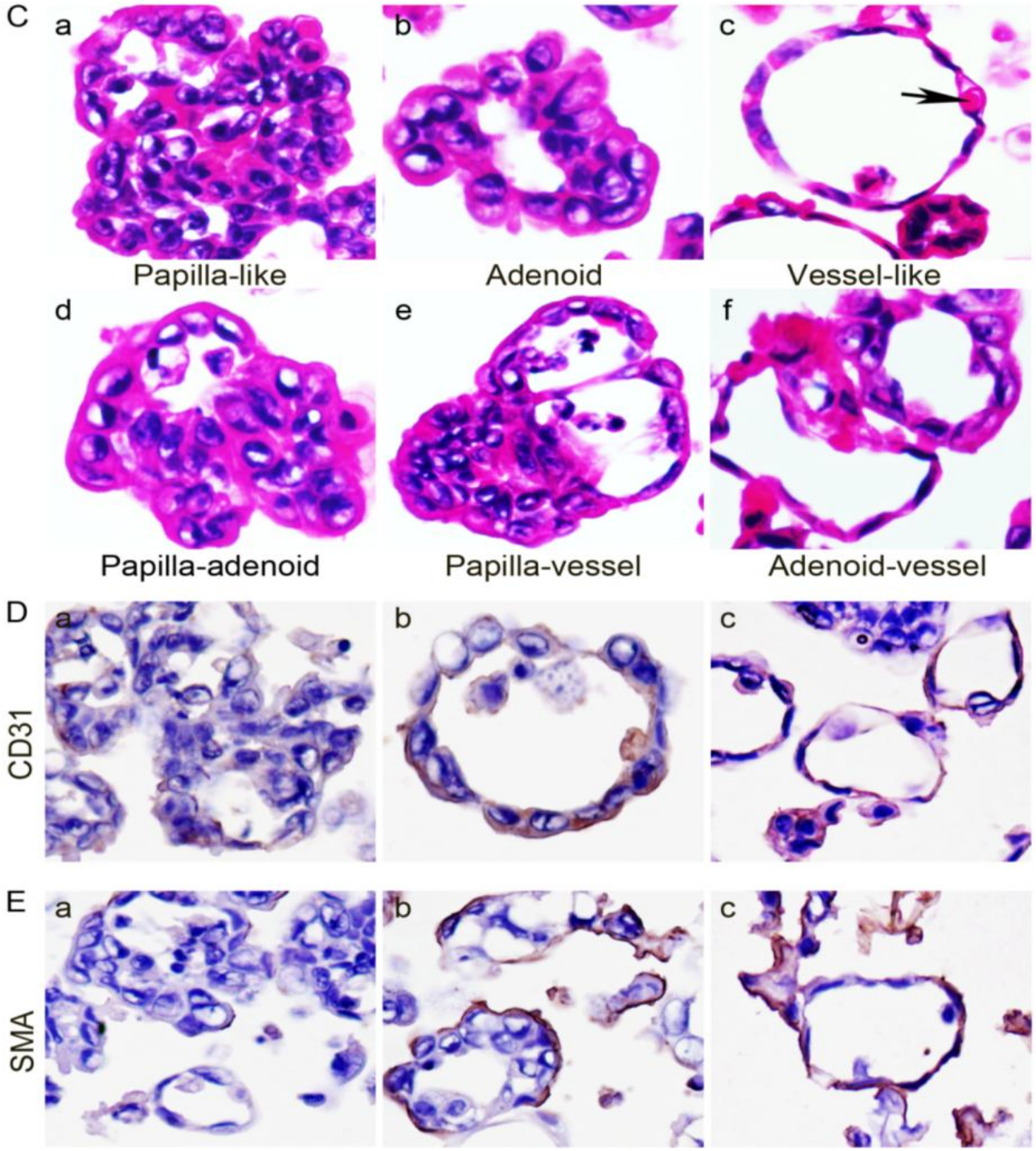
Budding from Binucleated PGCC (amitosis)



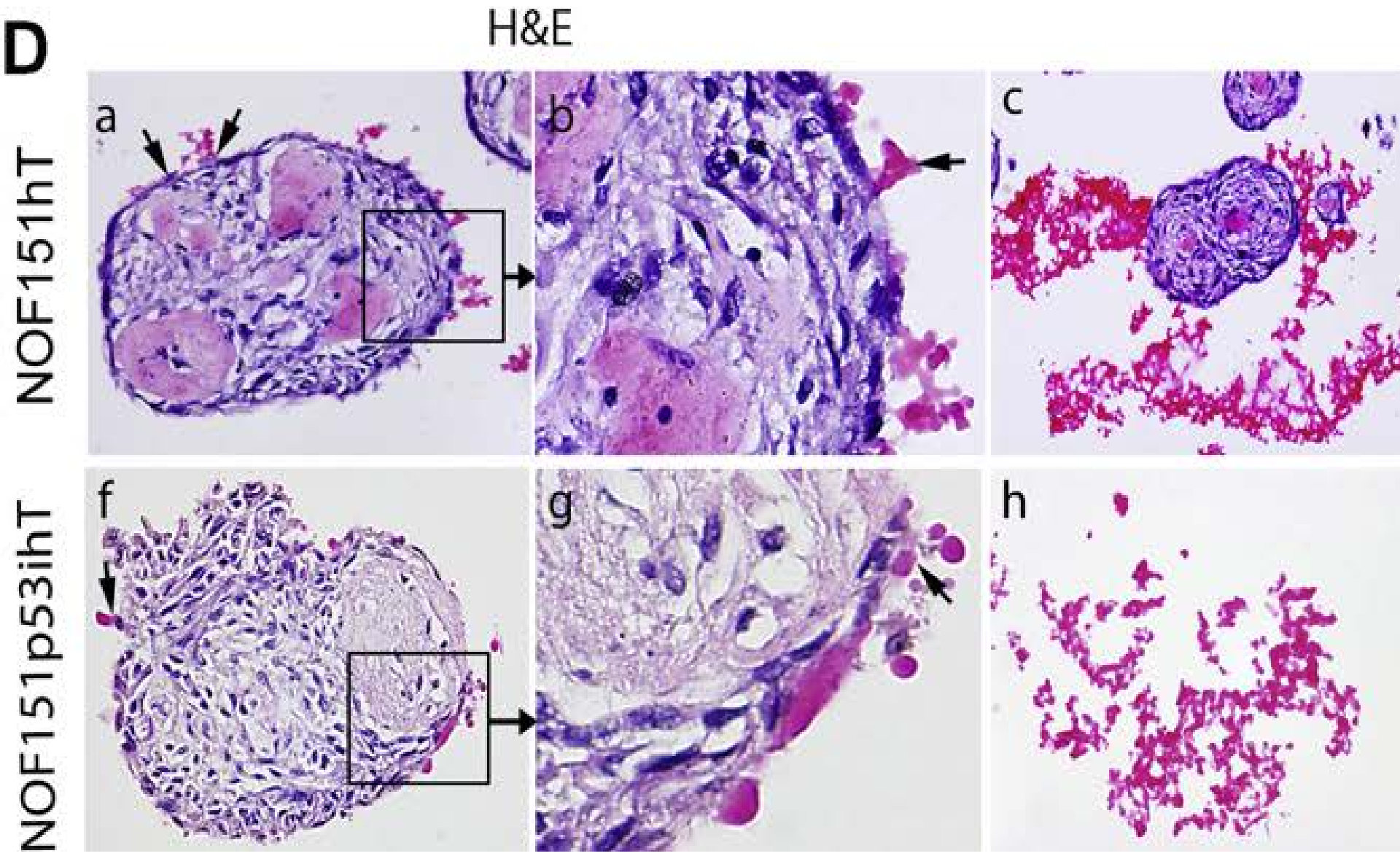
Unexpected finding #2: A tissue morphology code

Big Bang Division of a Giant Cell: The Origin of Tissue



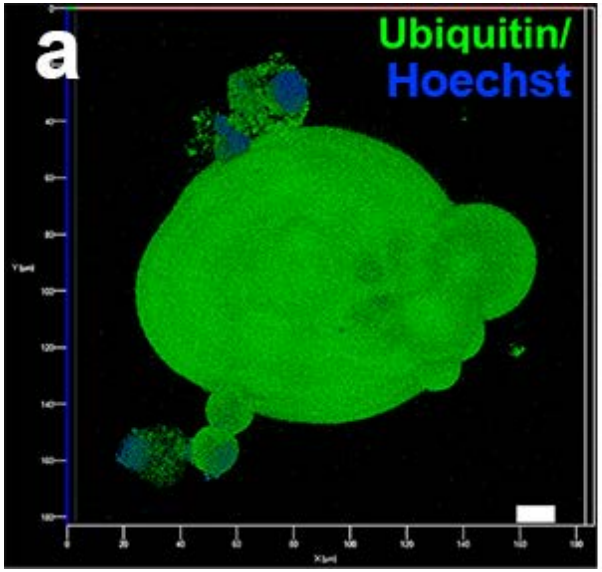


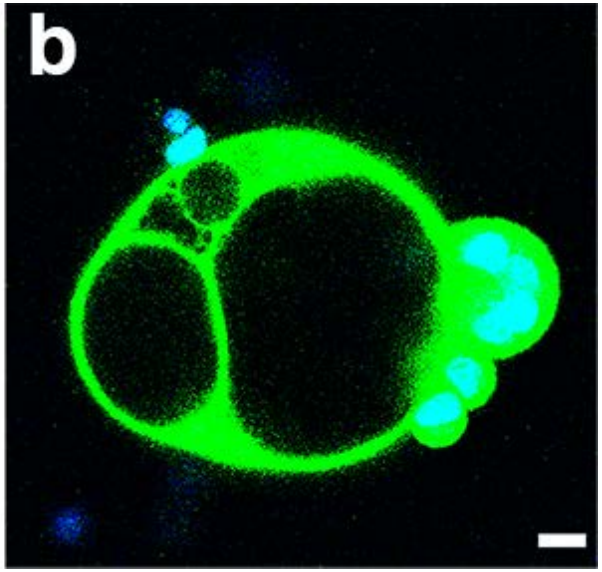
Zhang et al,
I J Cancer, 2013



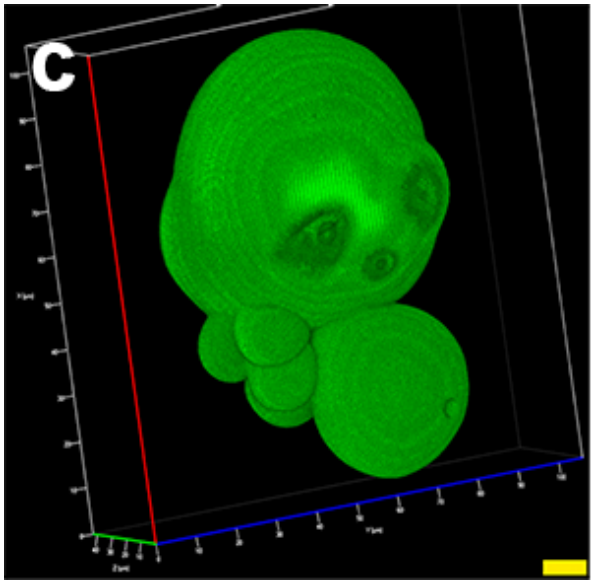
Zhang S. et al, 2013, Cancer Lett

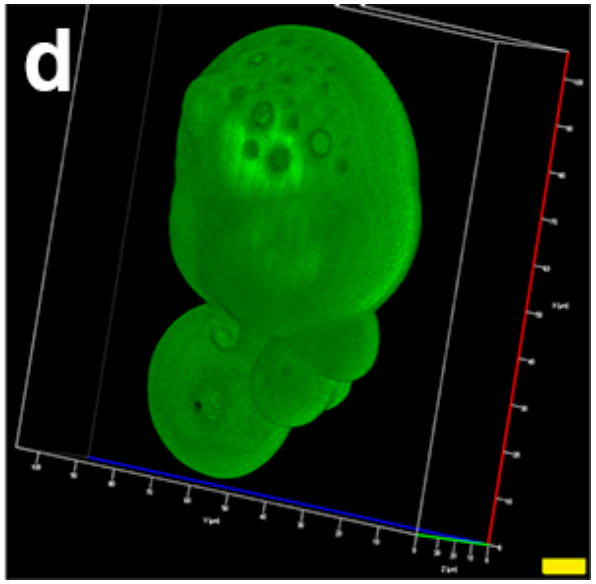
Unexpected finding #3: A mechanism to generate germ tumors





Blastocyst-like

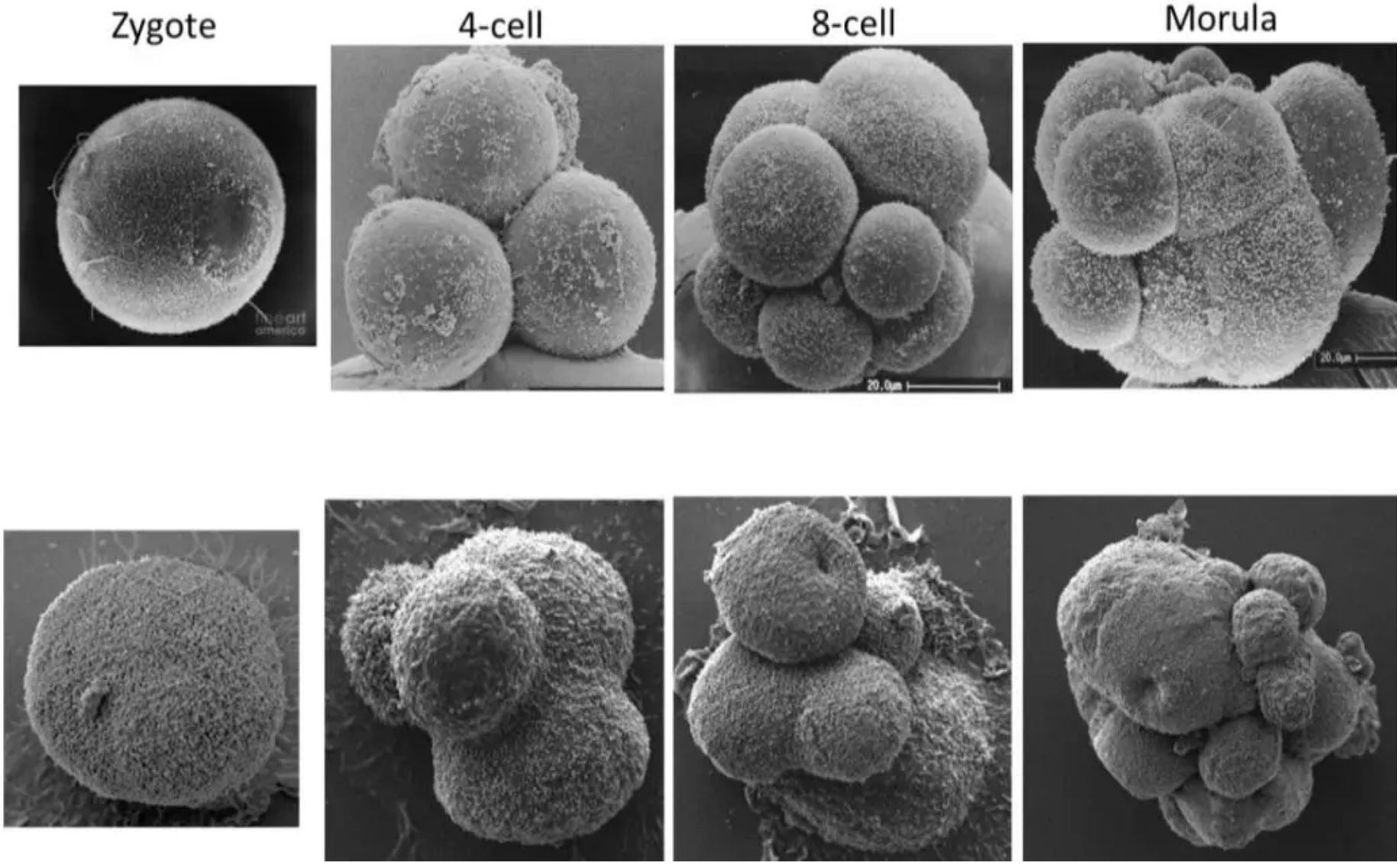




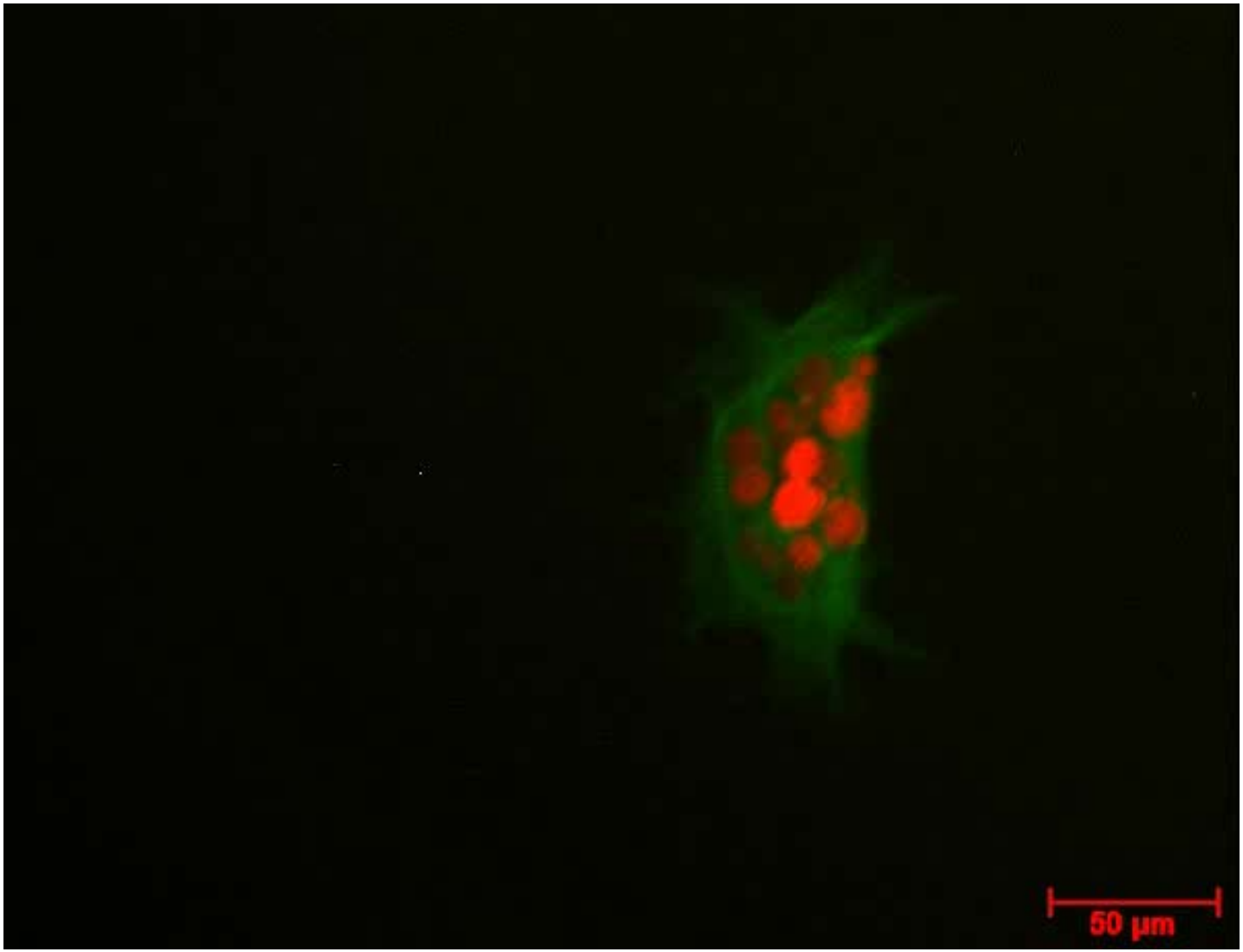
Disfigured blastocyst

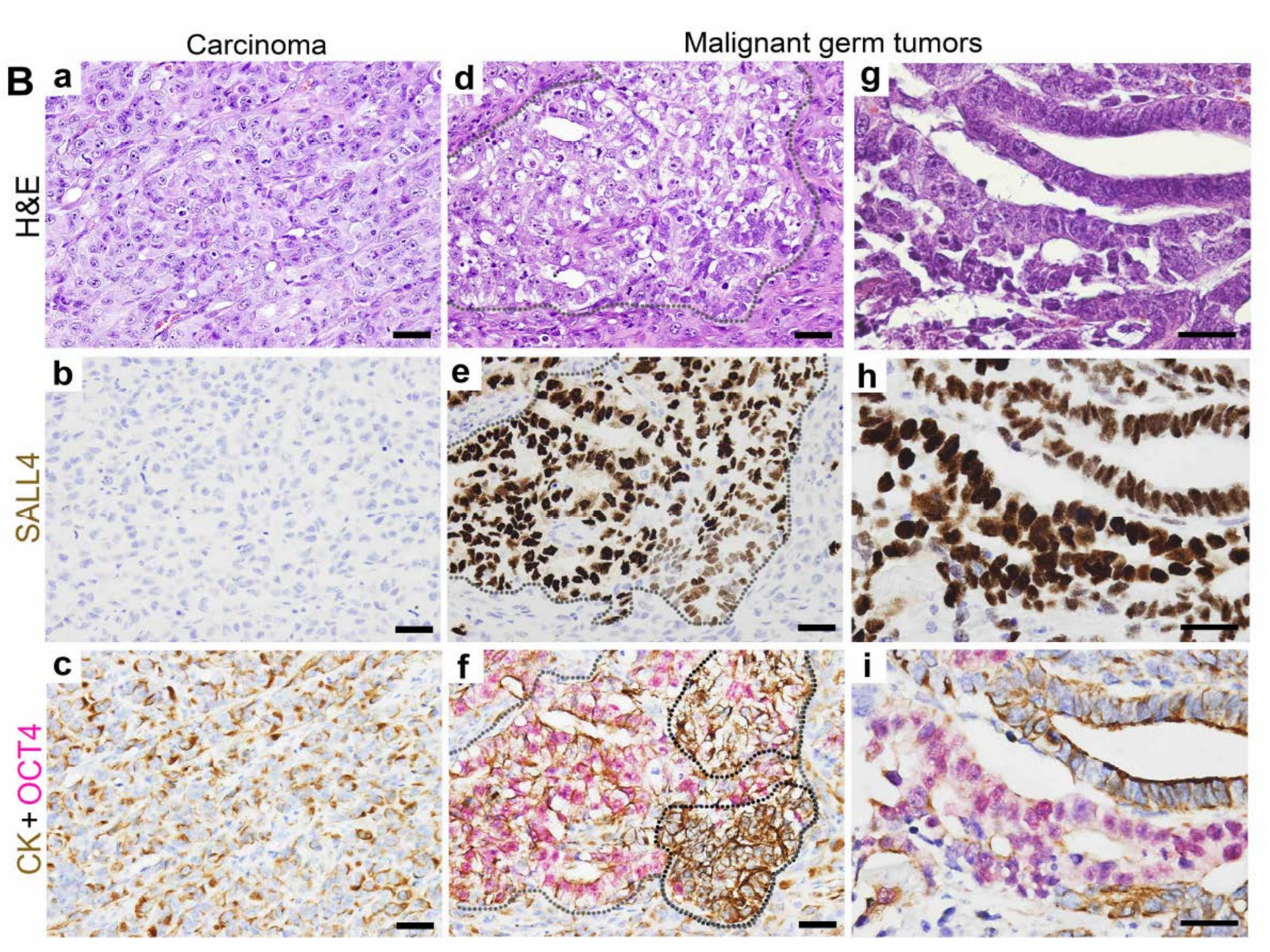
Human early embryo

PGCC



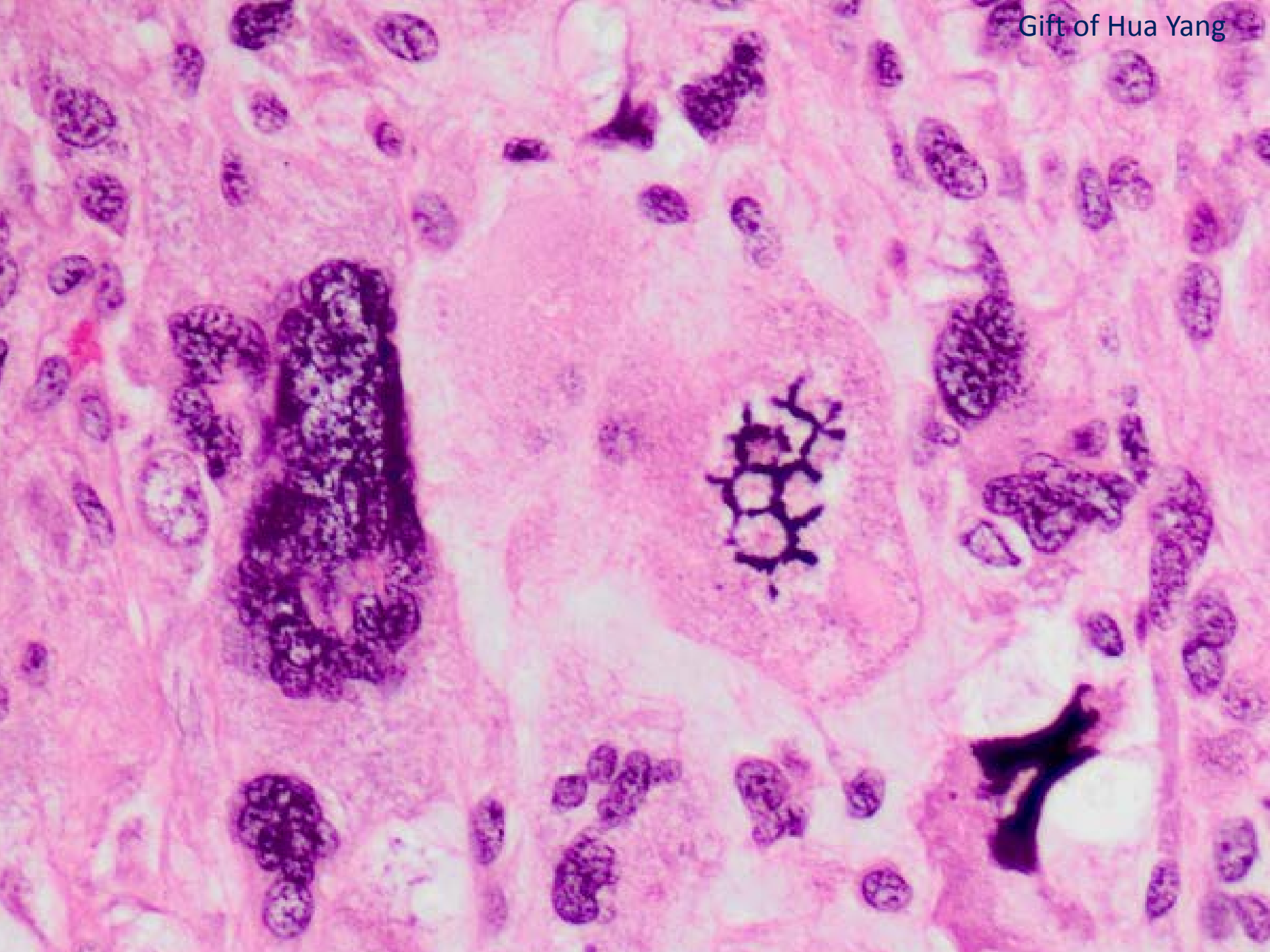
Morula-like Multinucleated PGCC

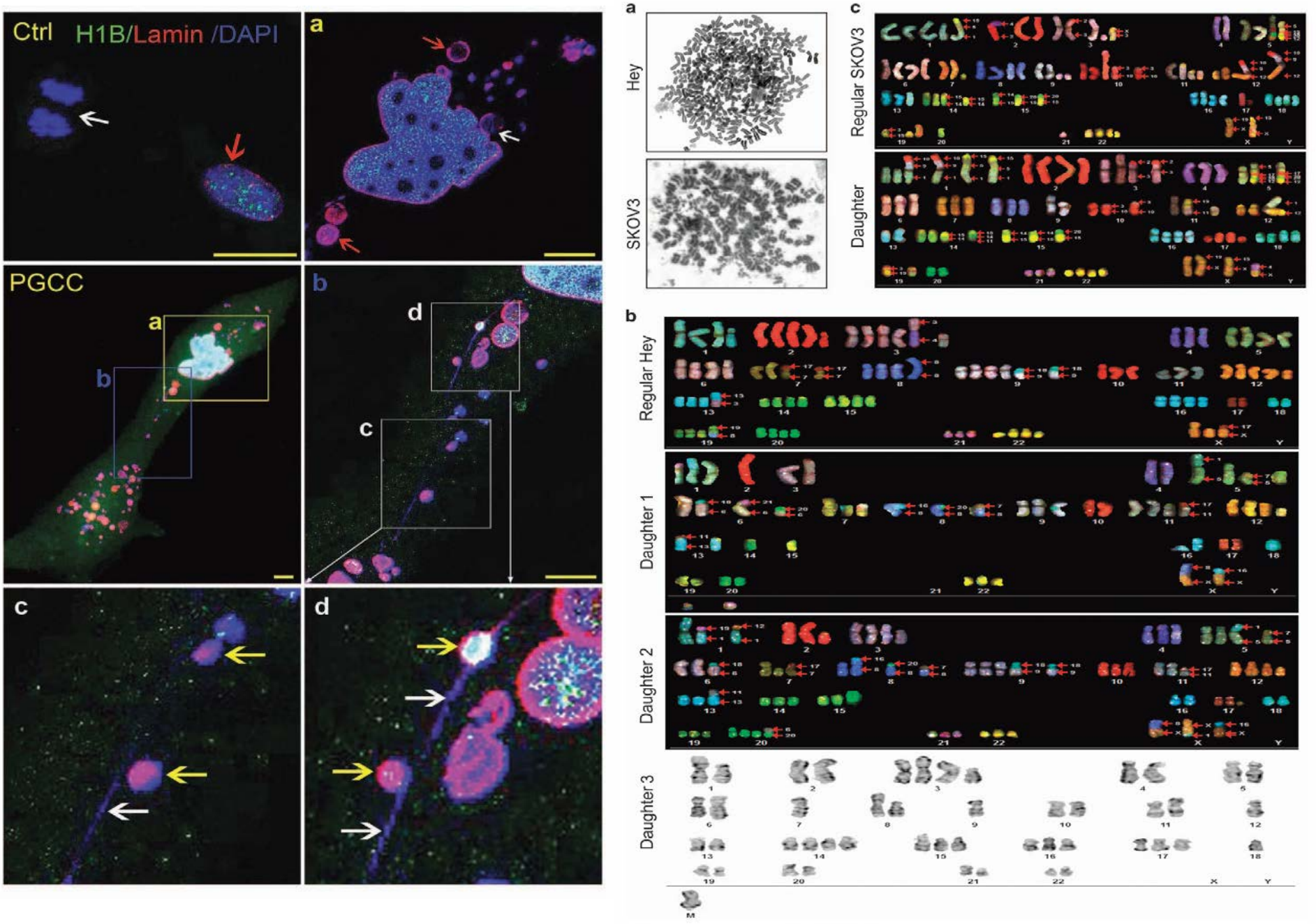



Carcinoma
Malignant germ tumors
B
a
d
g
H&E
b
e
h
SALL4
c
f
i
CK + OCT4

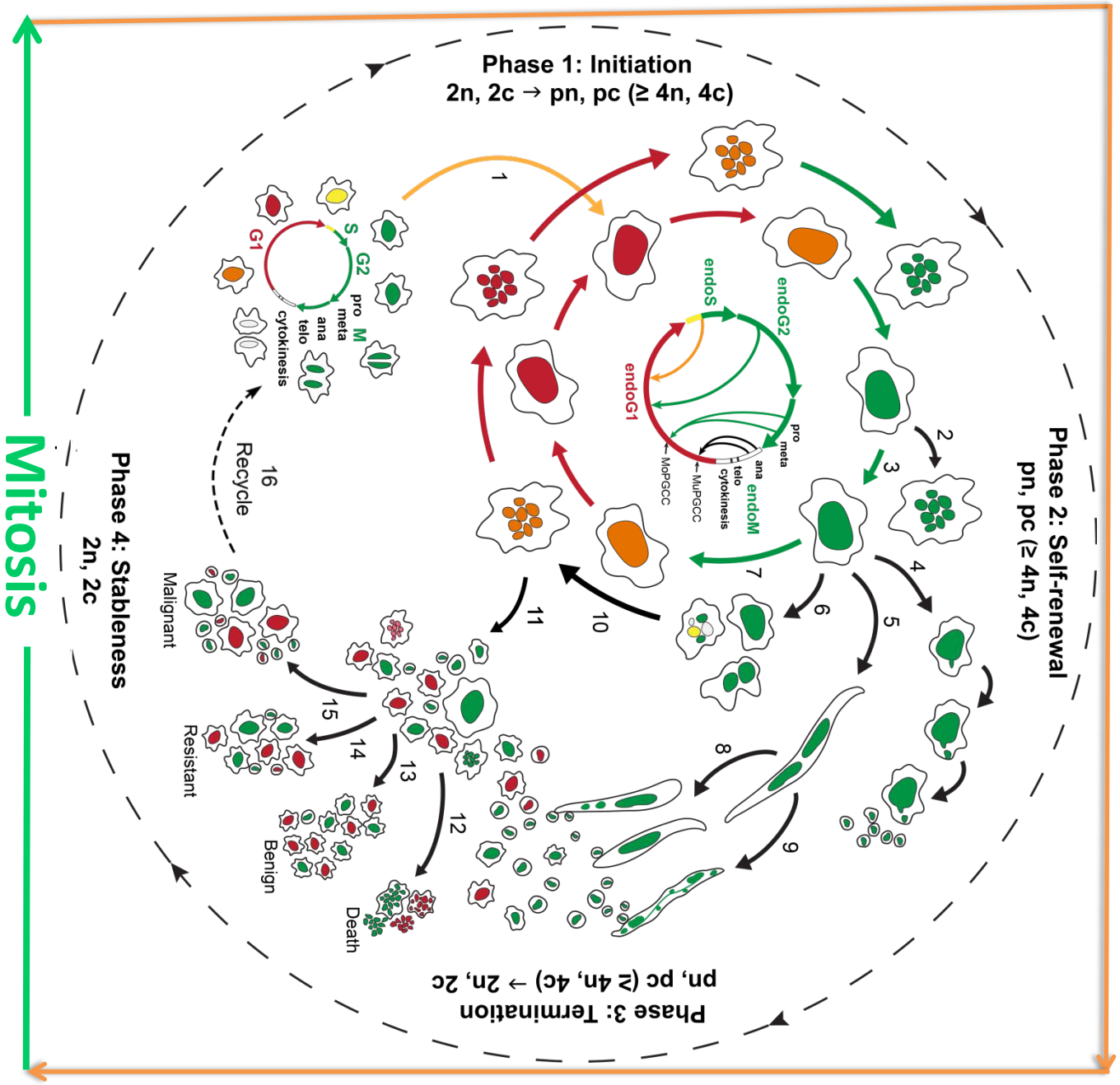
Unexpected finding #4

Mechanism of whole genomic reorganization: Genomic Chaos (Henry Heng)


Gift of Hua Yang


Ctrl
H1B/Lamin /DAPI
a
PGCC
a
b
b
d
c
c
d
a
Hey
SKOV3
c
Regular SKOV3
Daughter
b
Regular Hey
Daughter 1
Daughter 2
Daughter 3

The Giant Cell Life Cycle



Amitosis: no spindle/
no nuclear membrane breakdown

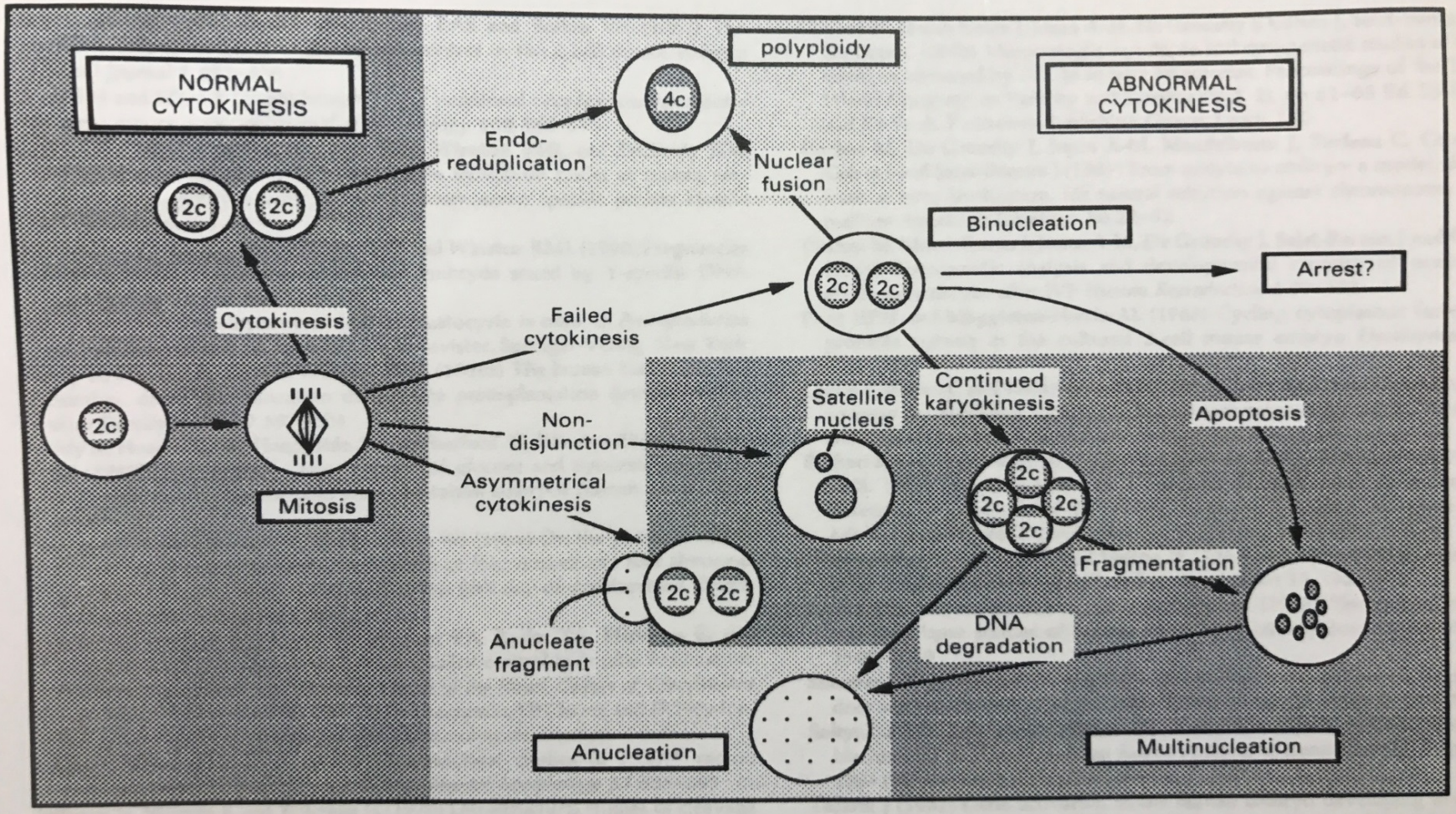


Fig. 6. Hypothetical model demonstrating the possible inter-relationships among binucleate, anucleate, multinucleate and polyploid blastomeres in human preimplantation embryos. 2c: two-cell; 4c: four-cell.

Blastomere Growth and Division: Hardy, 1993, J reproduction and Fertility (McClintock)

Giant Ovum Pathway

Egg (+/- sperm)

↓

Cleavage (Chaos)

↓

Dedifferentiation

↓

Differentiation/Arrest
(embryonic tissue)

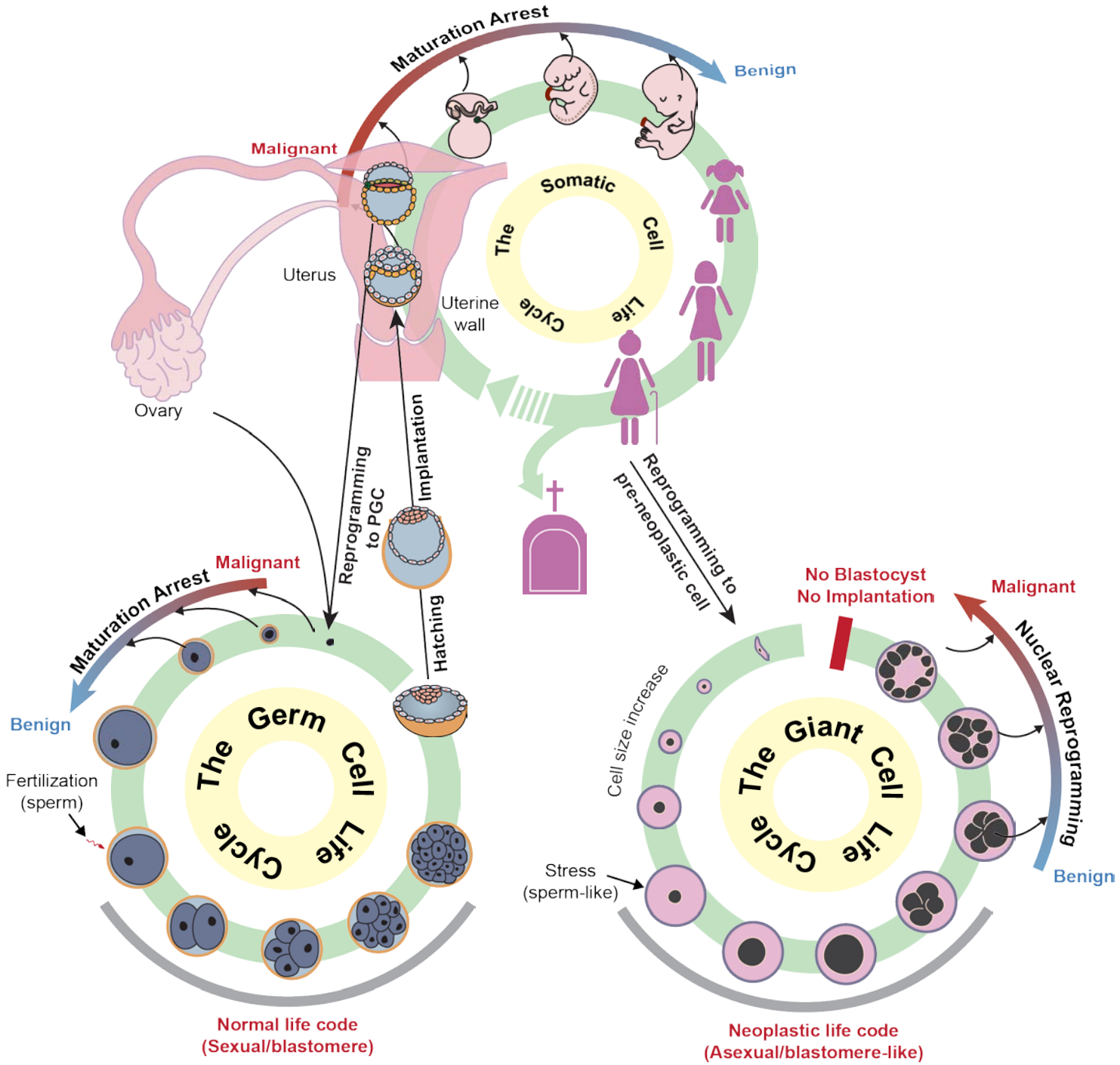
Senescent Giant Cell Pathway

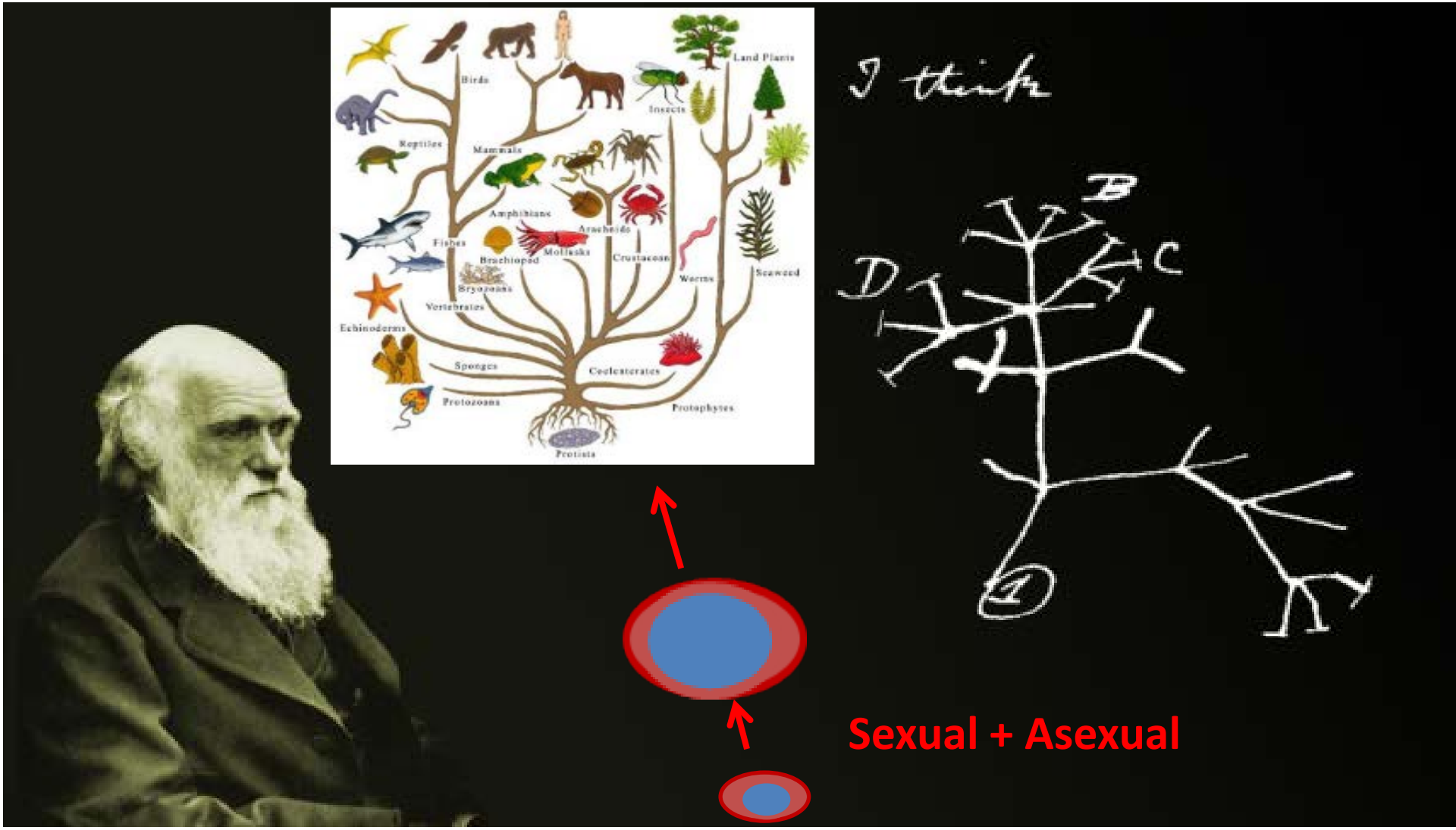
Aging somatic cells

Endoreplication (Chaos)

Dedifferentiation

Arrest (undiff tumors)


Maturation Arrest
Benign
Malignant
The Somatic Cell Life Cycle
Uterus
Uterine wall
Ovary
Reprogramming to PGC
Implantation
Hatching
Reprogramming to pre-neoplastic cell
Maturation Arrest
Malignant
Benign
The Germ Cell Life Cycle
Fertilization (sperm)
Normal life code (Sexual/blastomere)
No Blastocyst No Implantation
Malignant
Nuclear Reprogramming
Benign
Cell size increase
The Giant Cell Life Cycle
Stress (sperm-like)
Neoplastic life code (Asexual/blastomere-like)



The Origin of Species: "Polyploidy allows quick whole genomic reorganization in response to environmental stress and allows a punctuated macro-evolution for new species"

First Cell in Life: The Giant Cells

Oncogene (2014) **33,** 116–128

www.nature.com/onc

ORIGINAL ARTICLE

Generation of cancer stem-like cells through the formation of polyploid giant cancer cells

S Zhang[1,2], I Mercado-Uribe[1], Z Xing[1], B Sun[3], J Kuang[4] and J Liu[1]

OPEN

Citation: Oncogenesis (2016) **5**, e281; doi:10.1038/oncsis.2016.75

www.nature.com/oncsis

ORIGINAL ARTICLE

Linking genomic reorganization to tumor initiation via the giant cell cycle

N Niu[1], J Zhang[1], N Zhang[1], I Mercado-Uribe[1], F Tao[1], Z Han[2], S Pathak[3], AS Multani[3], J Kuang[4], J Yao[2], RC Bast[4], AK Sood[5], M-C Hung[2,6] and J Liu[1,2]

OPEN

Oncogene (2017), 1–14

www.nature.com/onc

ORIGINAL ARTICLE

Dedifferentiation into blastomere-like cancer stem cells via formation of polyploid giant cancer cells

N Niu, I Mercado-Uribe and J Liu

Seminars in Cancer Biology xxx (2018) xxx-xxx

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The dualistic origin of human tumors

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Review

The "life code": A theory that unifies the human life cycle and the origin of human tumors

Jinsong Liu

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IN BOTT