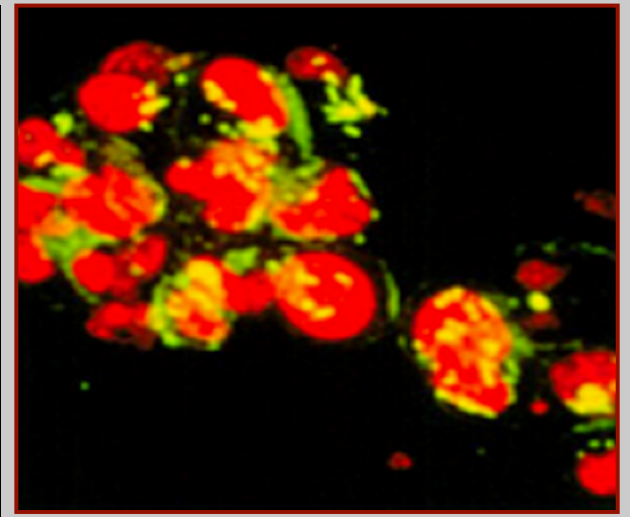
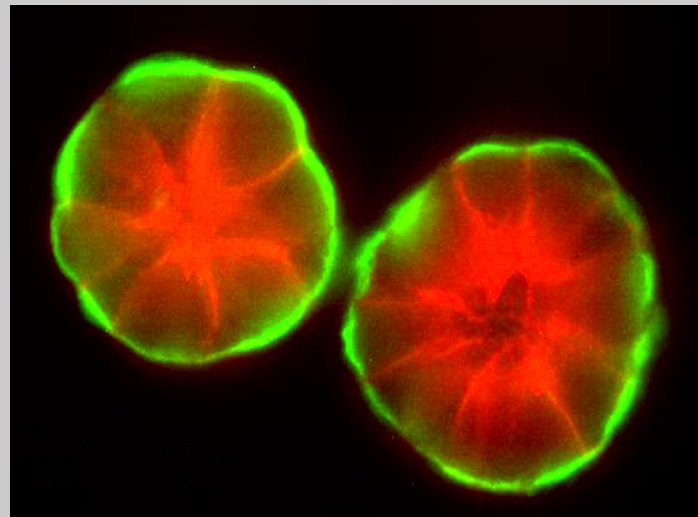




The Importance of Extracellular Matrix (ECM) And Microenvironment in Tissue-Specificity and Breast Cancer

**Mina J. Bissell
Lawrence Berkeley
National Laboratory,
UC Berkeley**

Part I: Half the secret of the cell is outside the cell is inside the cell!

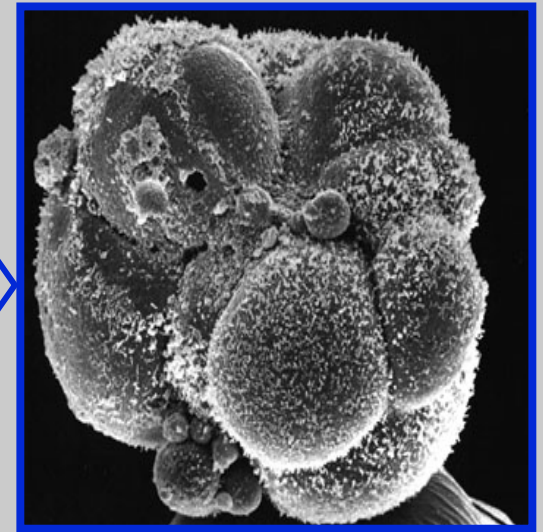


Developmental Biology: The flip side of the cancer coin



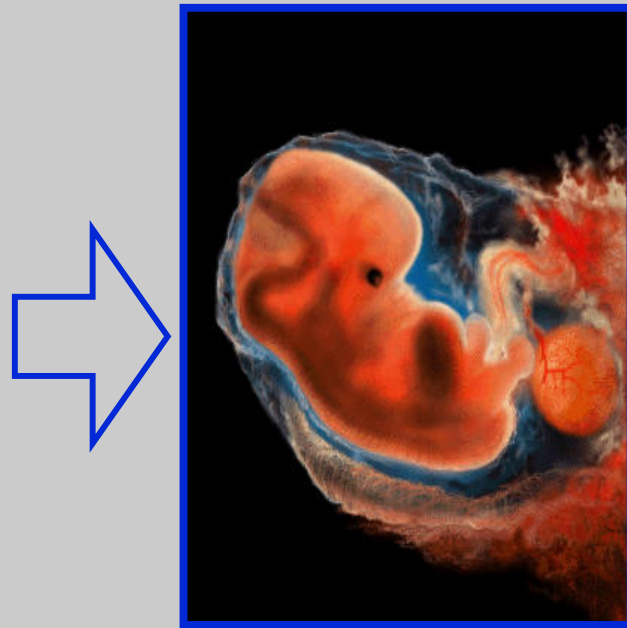
When your mom
and dad met

Developmental Biology: The flip side of the cancer coin



When your mom
and dad met

Developmental Biology: The flip side of the cancer coin



Developmental Biology: The flip side of the cancer coin



Developmental Biology: The flip side of the cancer coin



Have a guess:
How many cells in her body?!

A huge question:

How do 10 -70 trillion
cells, each with the
same genetic
information,
coordinate to make
you, YOU ??!

An 'oncogene' is a gene that
could cause cancer
(Watch Mike Bishop's lecture on
oncogenes in these series).

The first oncogenic virus was
isolated by Rous in 1911 (called
RSV)

It is a chicken virus and forms
ugly tumors when injected into
the wing.

RSV tumor in a chick



RSV expression in the embryo

No tumors!

Dolberg and Bissell, Nature, 1984
Dolberg et al, Science, 1985
Siewke et al. Science, 1990
Stoker et al, JCB, 1990,,
Siewke and Bissell, Critical Reviews in
Carcinogenesis. 1994

Thus context
(i.e. the microenvironment)
determines what even a
potent oncogene can do.

*But what is context
made of??*

Does it signal??

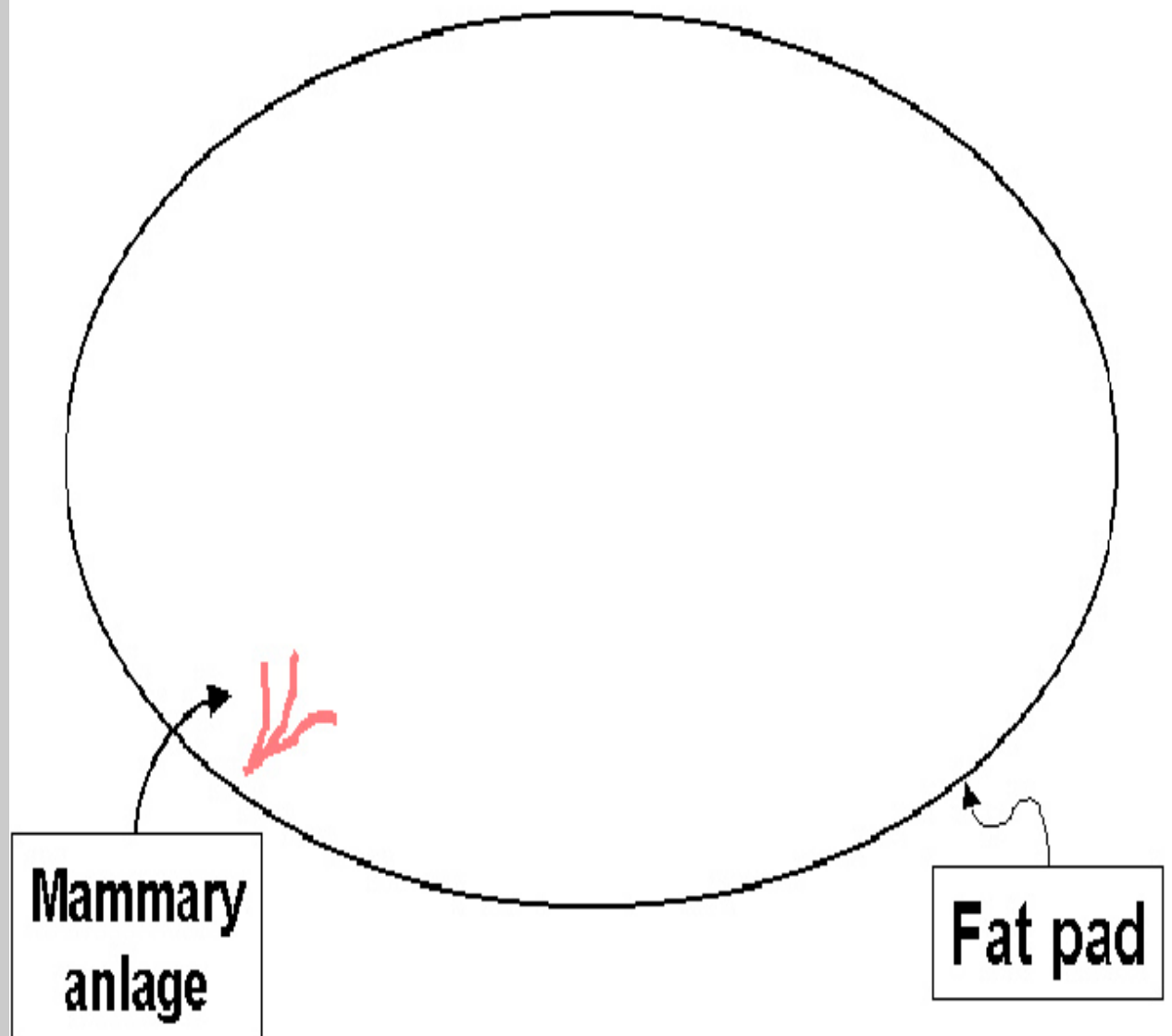
Questions

1. How is tissue specificity maintained?
2. How does one study the problem in mammals, humans?
3. How is the program lost in cancer and aging?
4. How can one use the information for therapy?

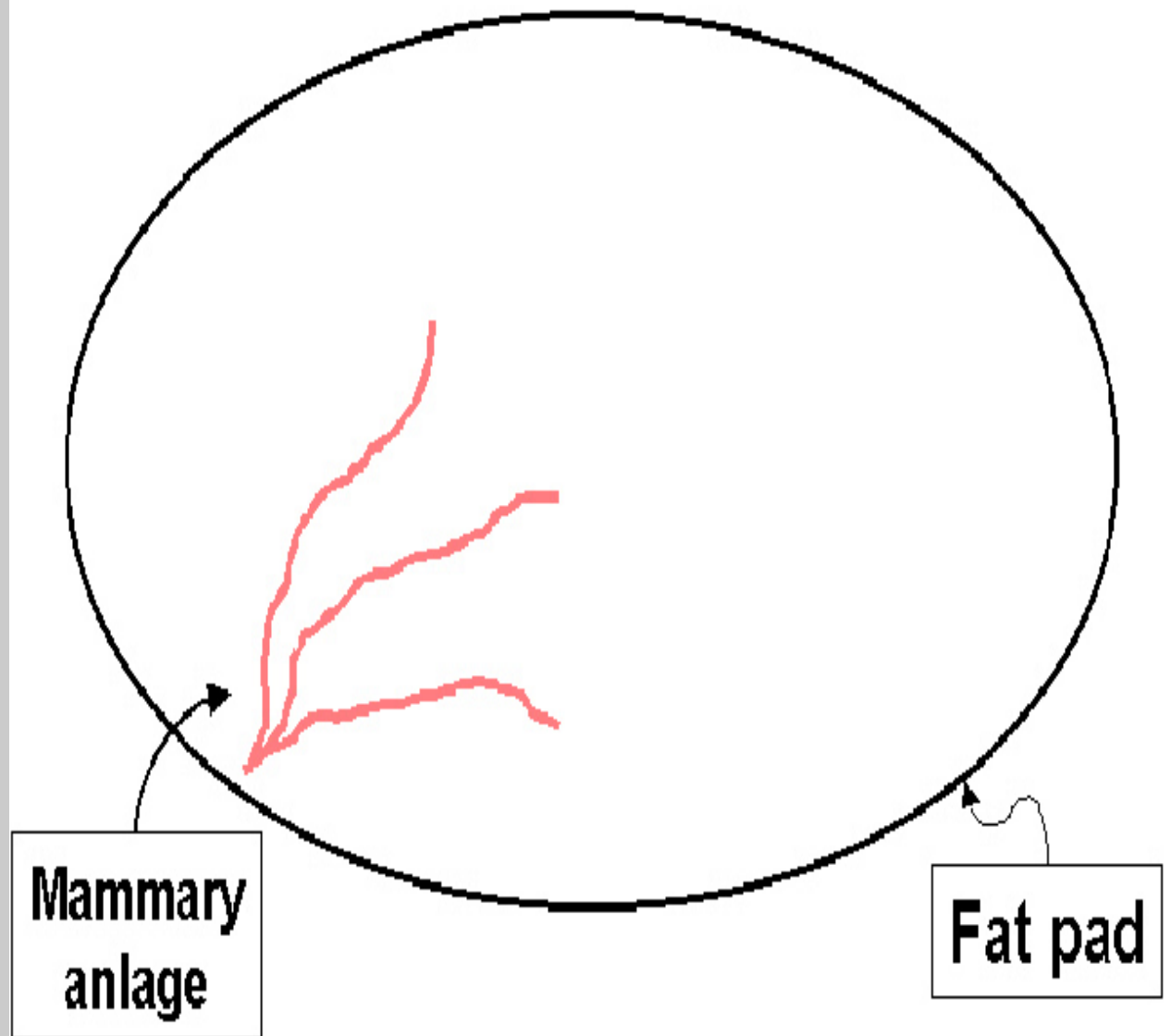
To model mammals,
we turned to using
the mammary gland
as an experimental
“organism”.

It is an
organism within
an organism.

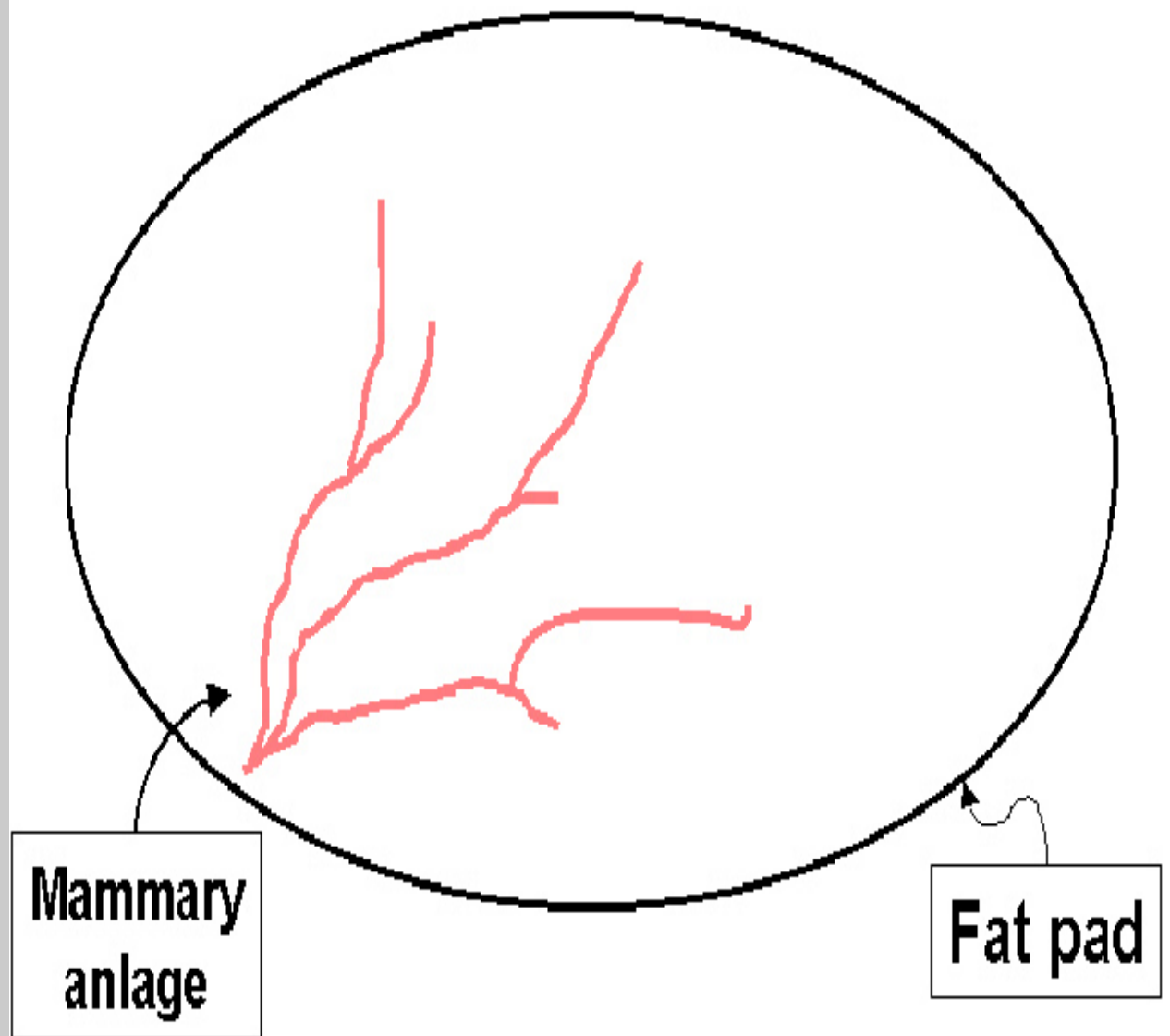
Puberty



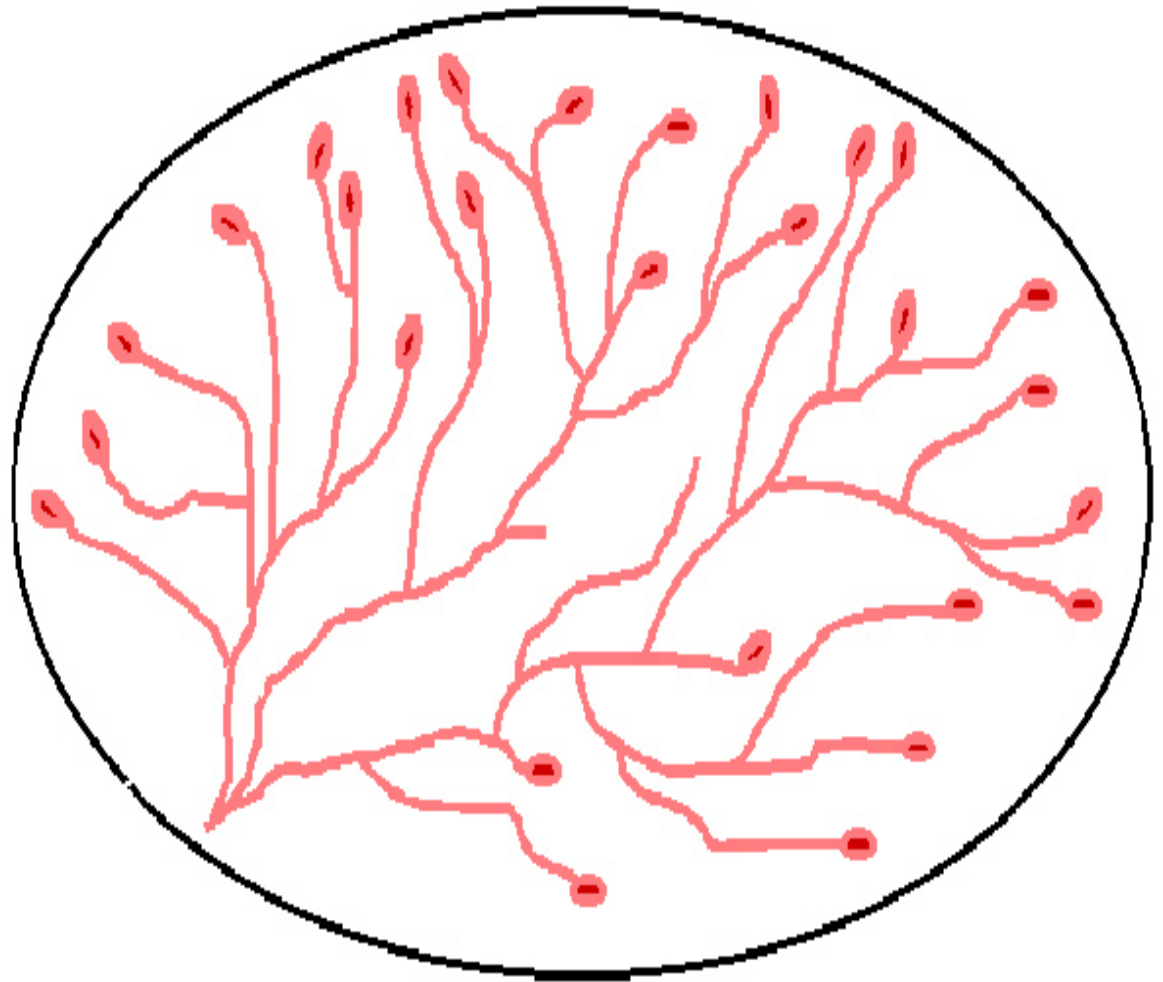
Puberty



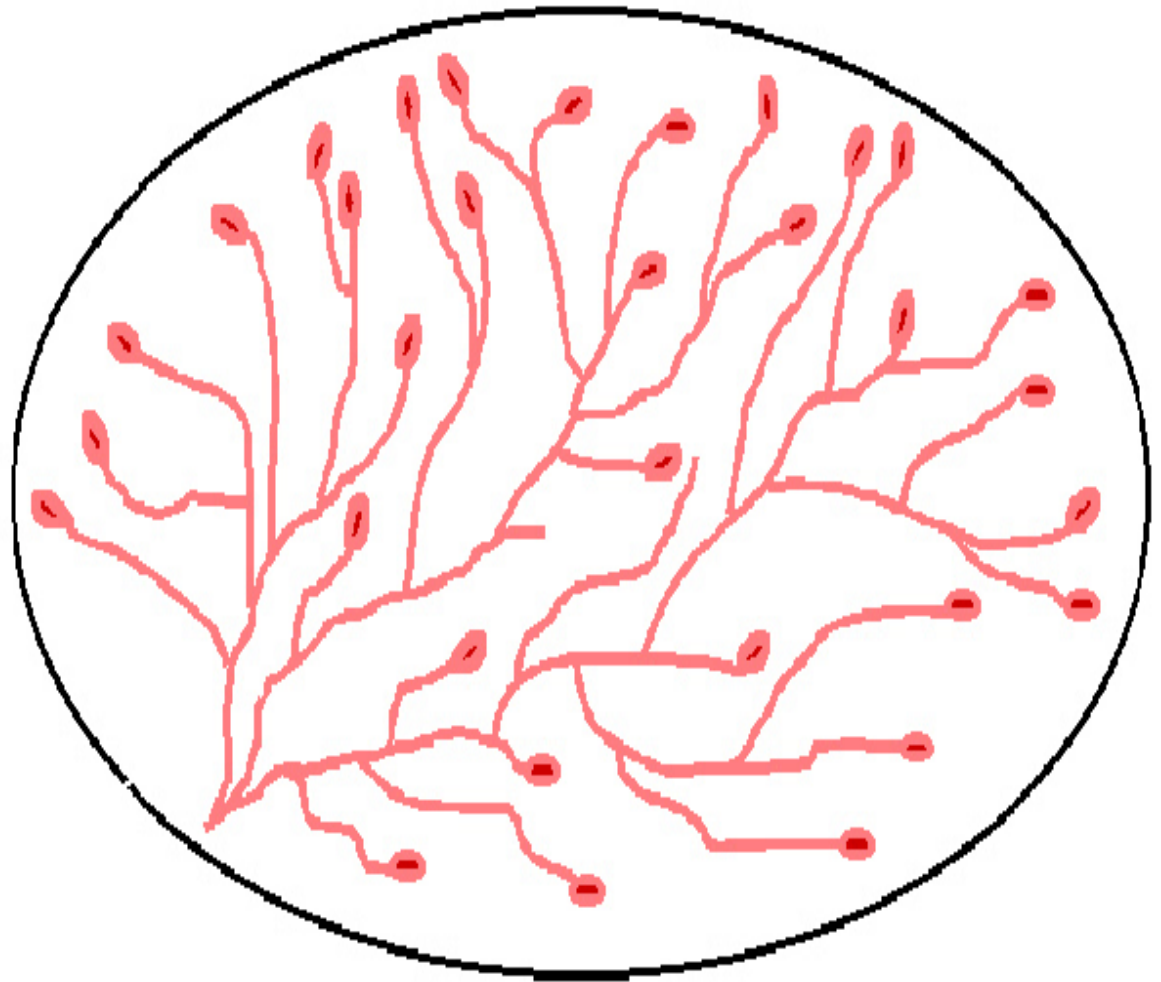
Puberty



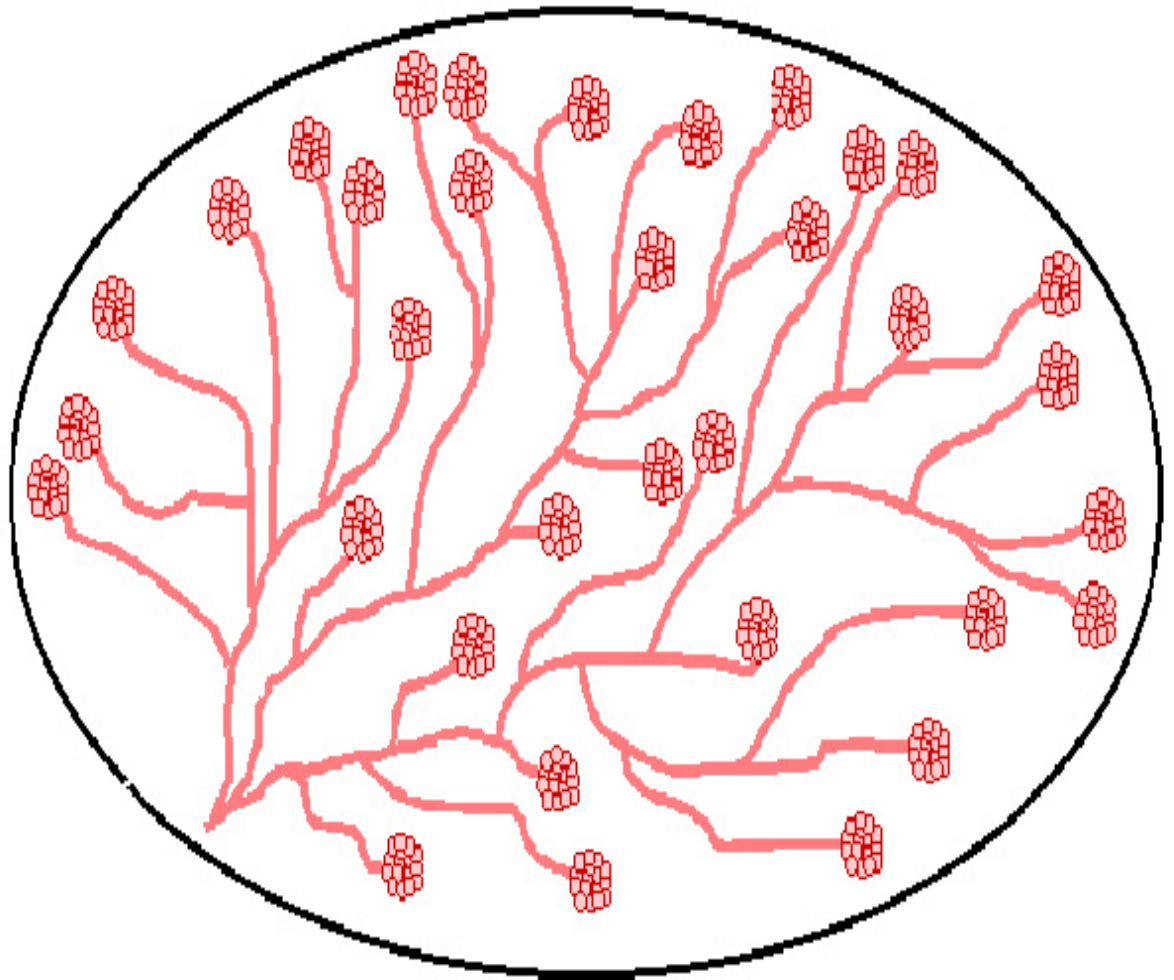
Puberty



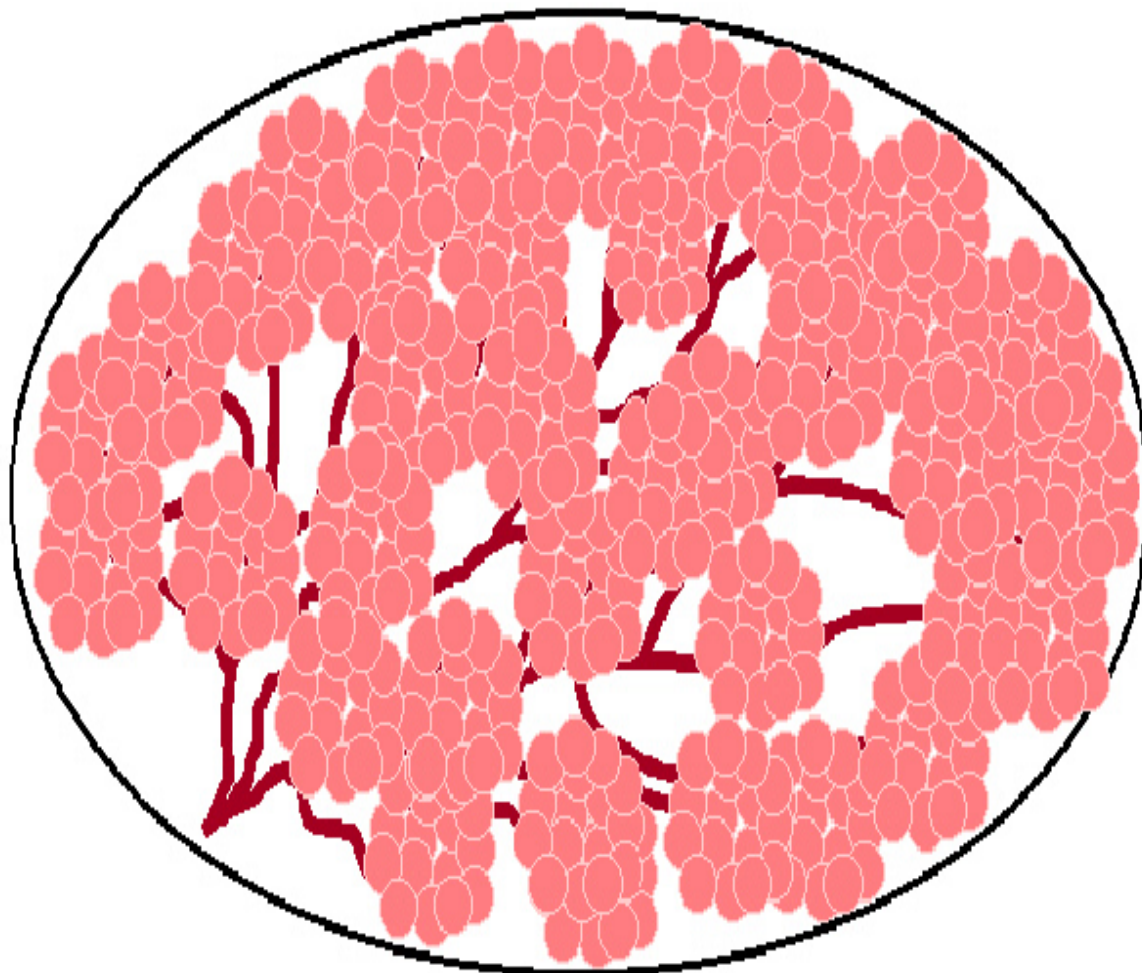
Puberty



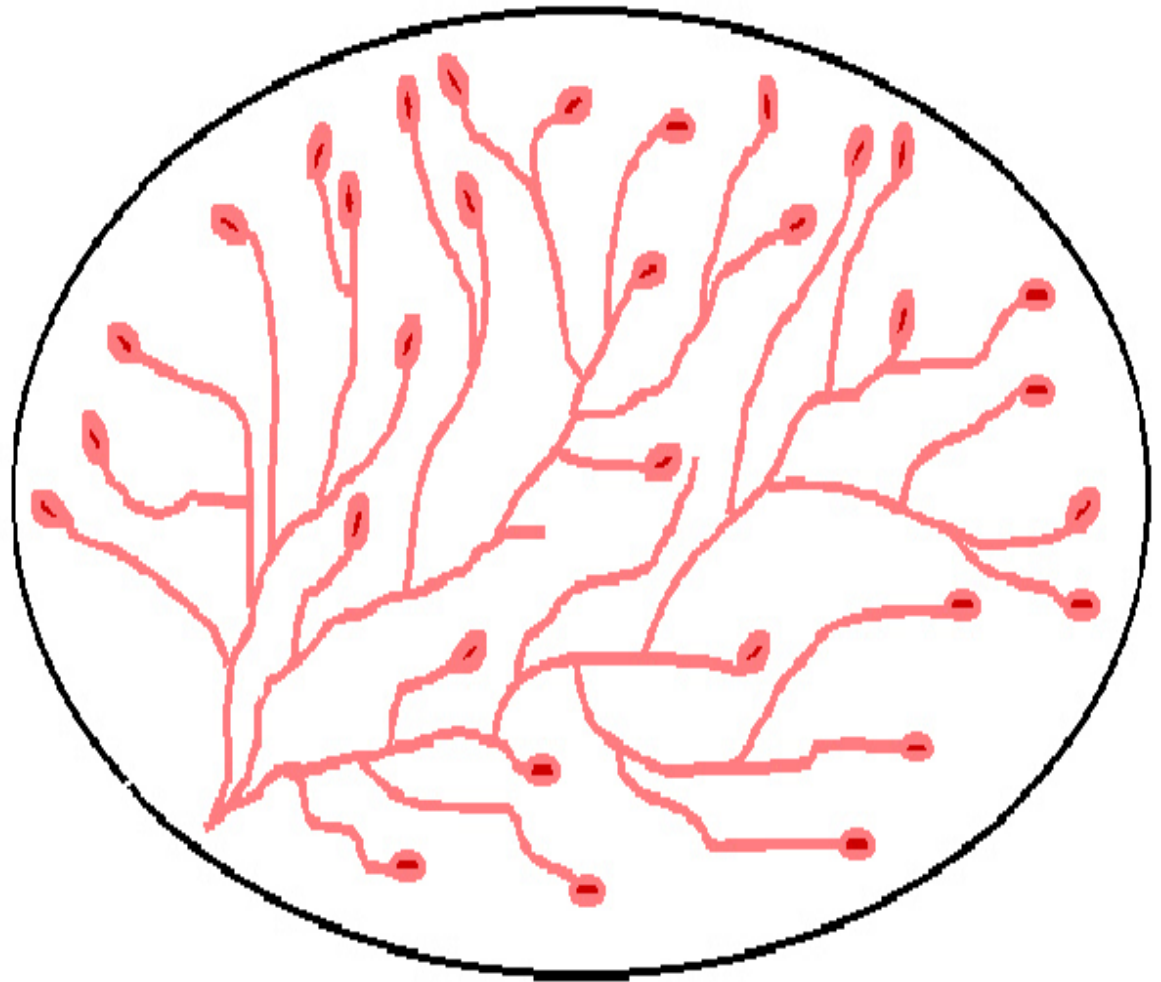
Pregnancy



Lactation

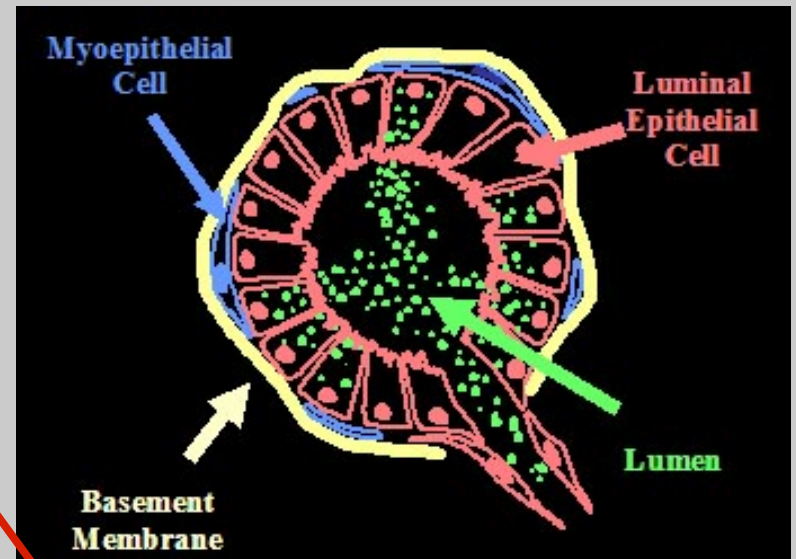
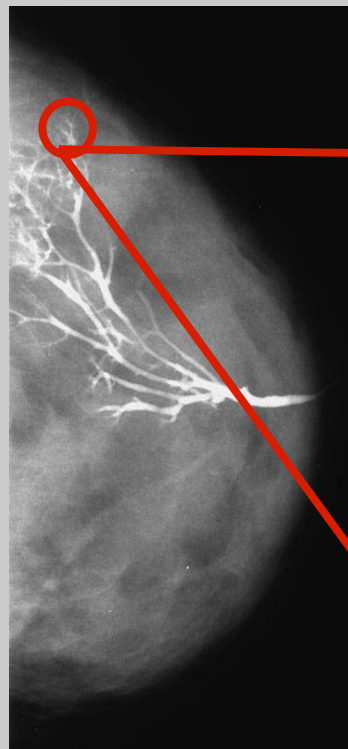


Involution

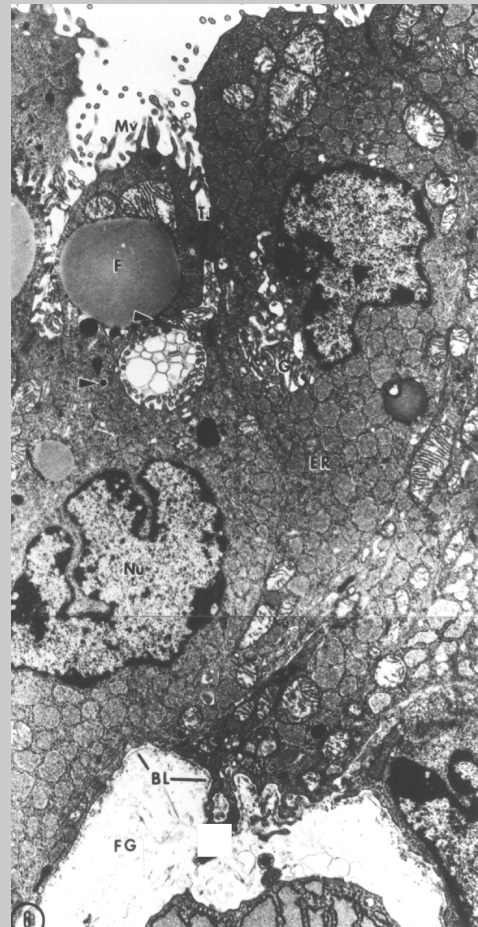


Structure of the mammary gland: Basementmembrane, myoepithelialcells, Luminal cells, 'Lumen'

An ,acinus' is the unit of structure
of the mammary gland

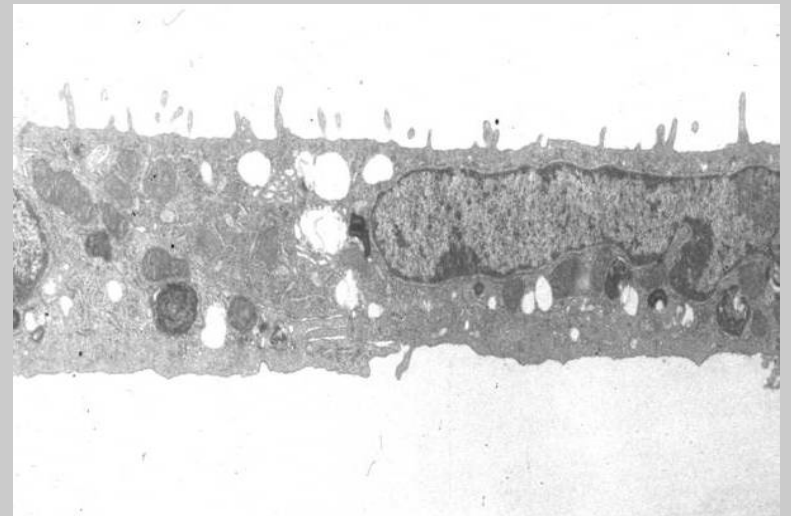


Structural Organization of Mammary Epithelial Cells



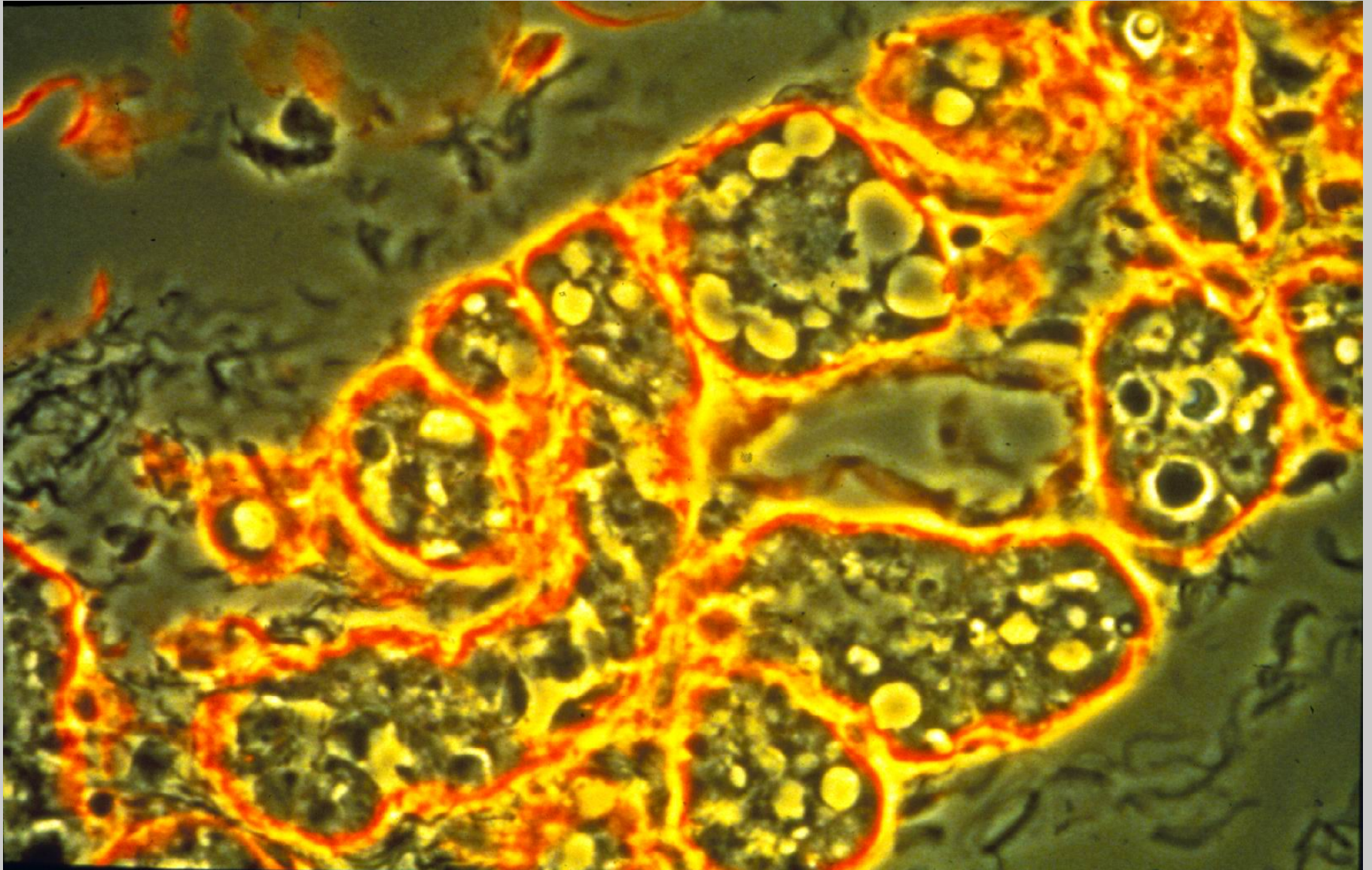
In vivo

(Joanne Emerman)



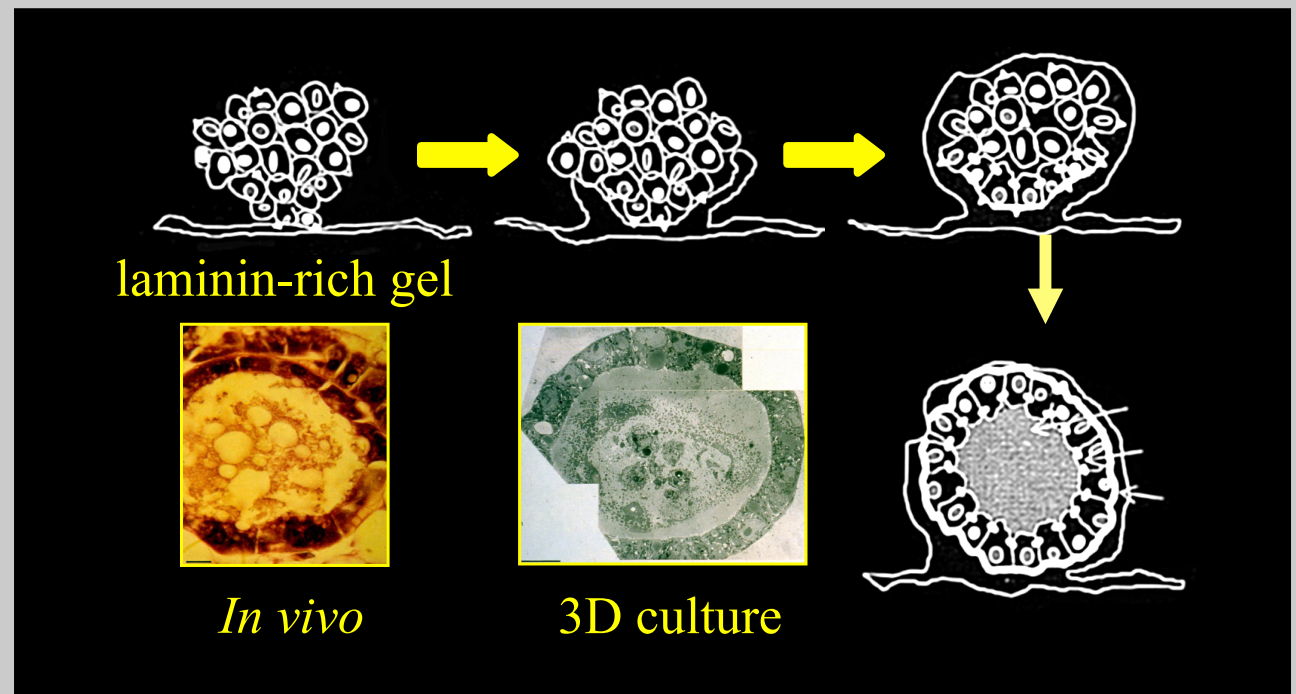
“in vitro”: on tissue
culture plastic

Laminin 111(**red**) staining in mouse mammary gland



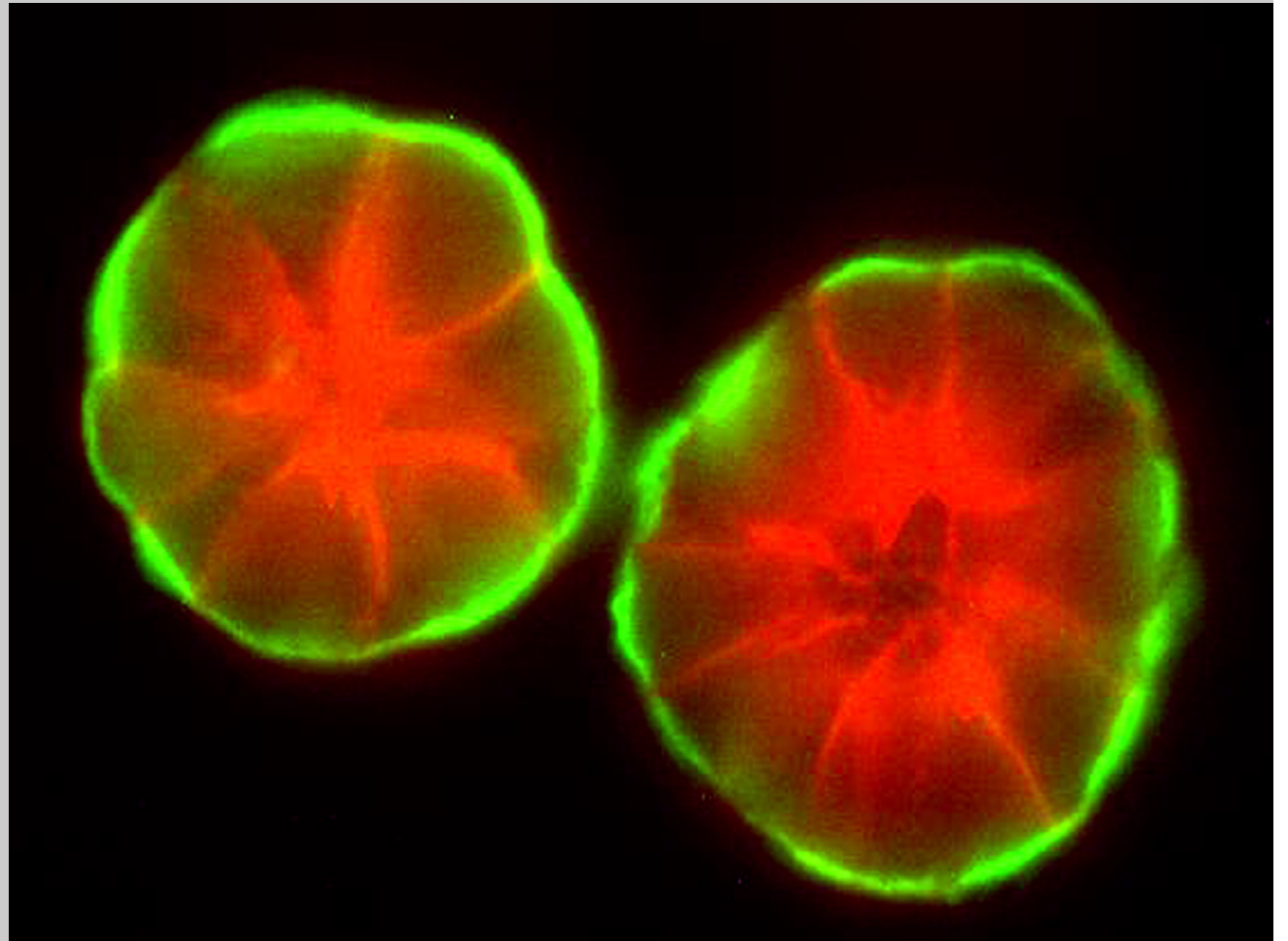
Formation of 'acini' in laminin-rich ECM

Even the sizes of the acini in 3D are similar to those in vivo

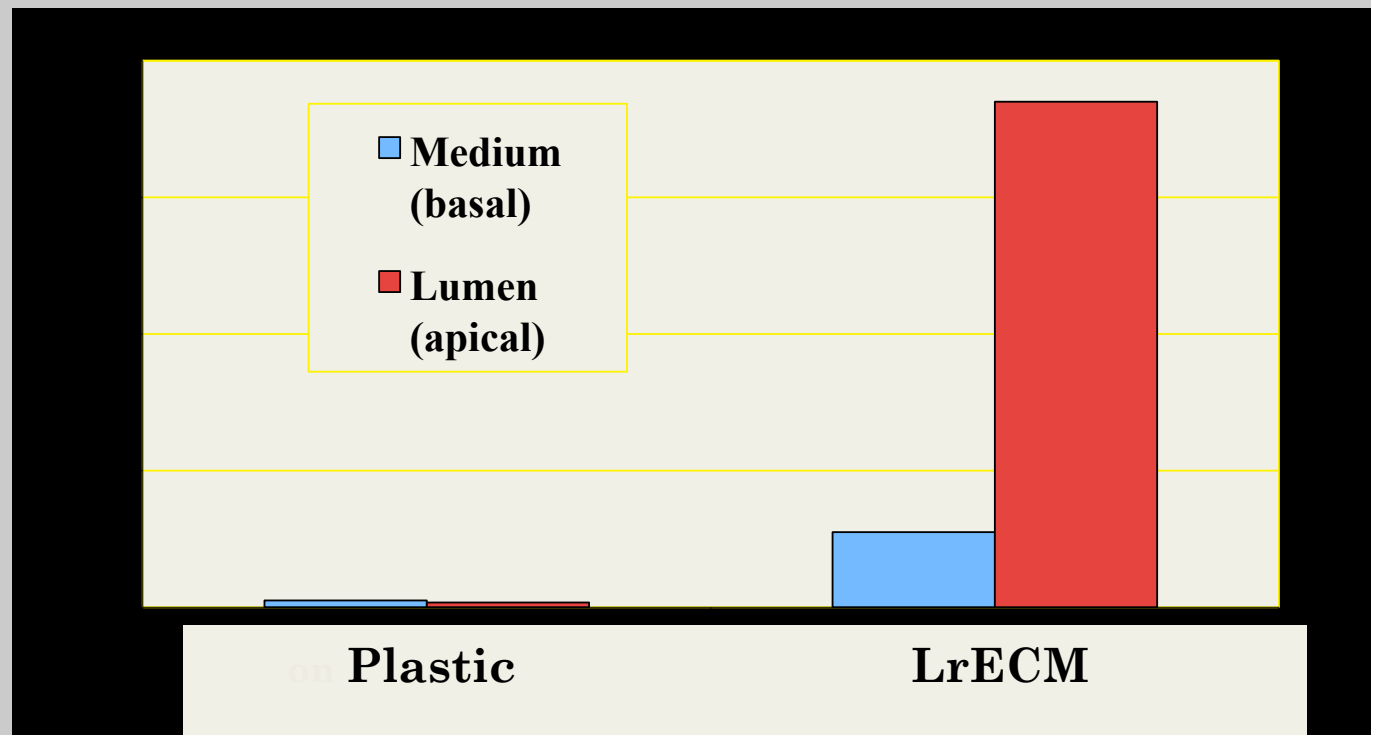


(Barcellos-Hoff et al., *Development*, 1989)

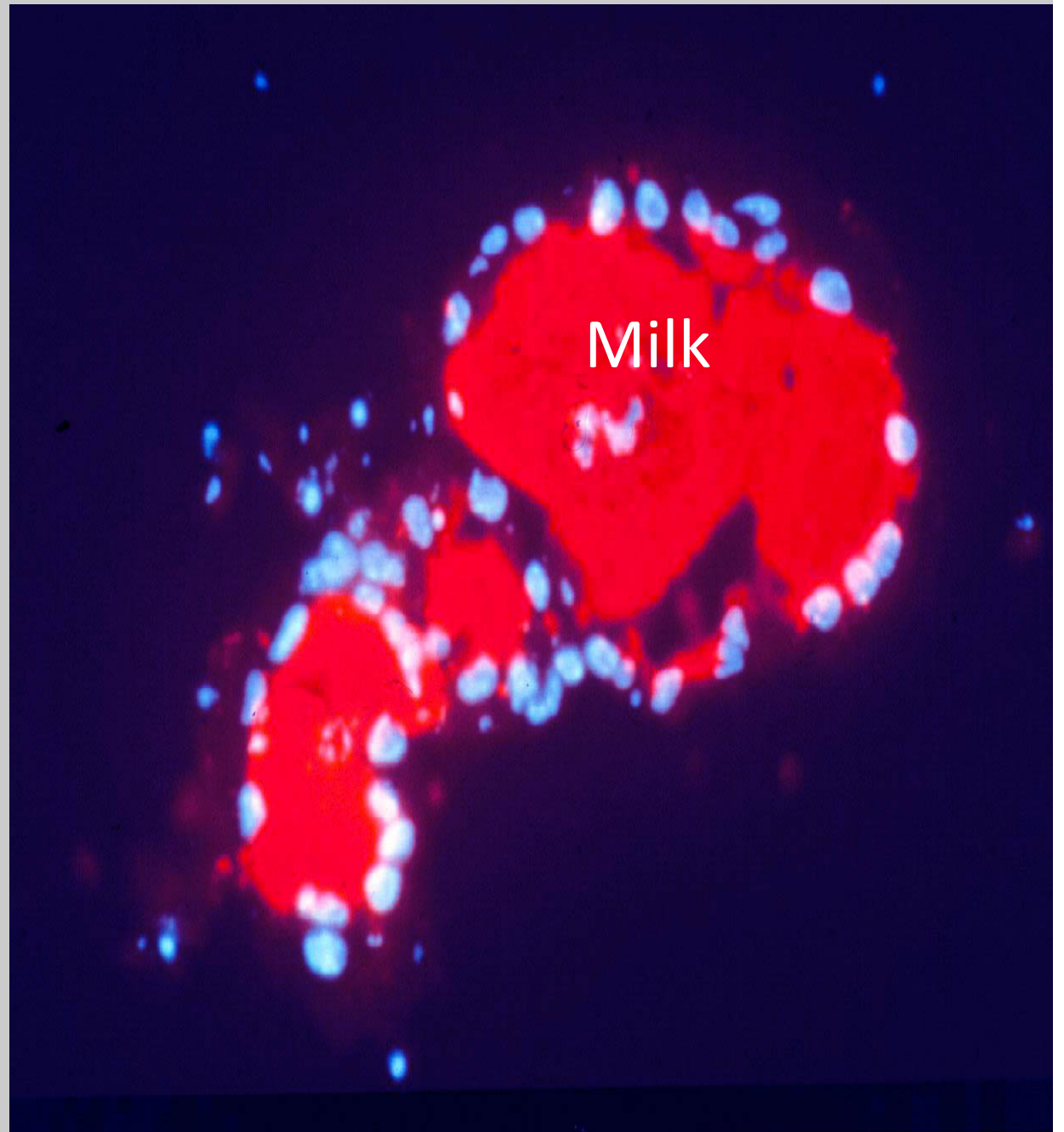
Beautiful mammary gland
units reproduced in 3D!

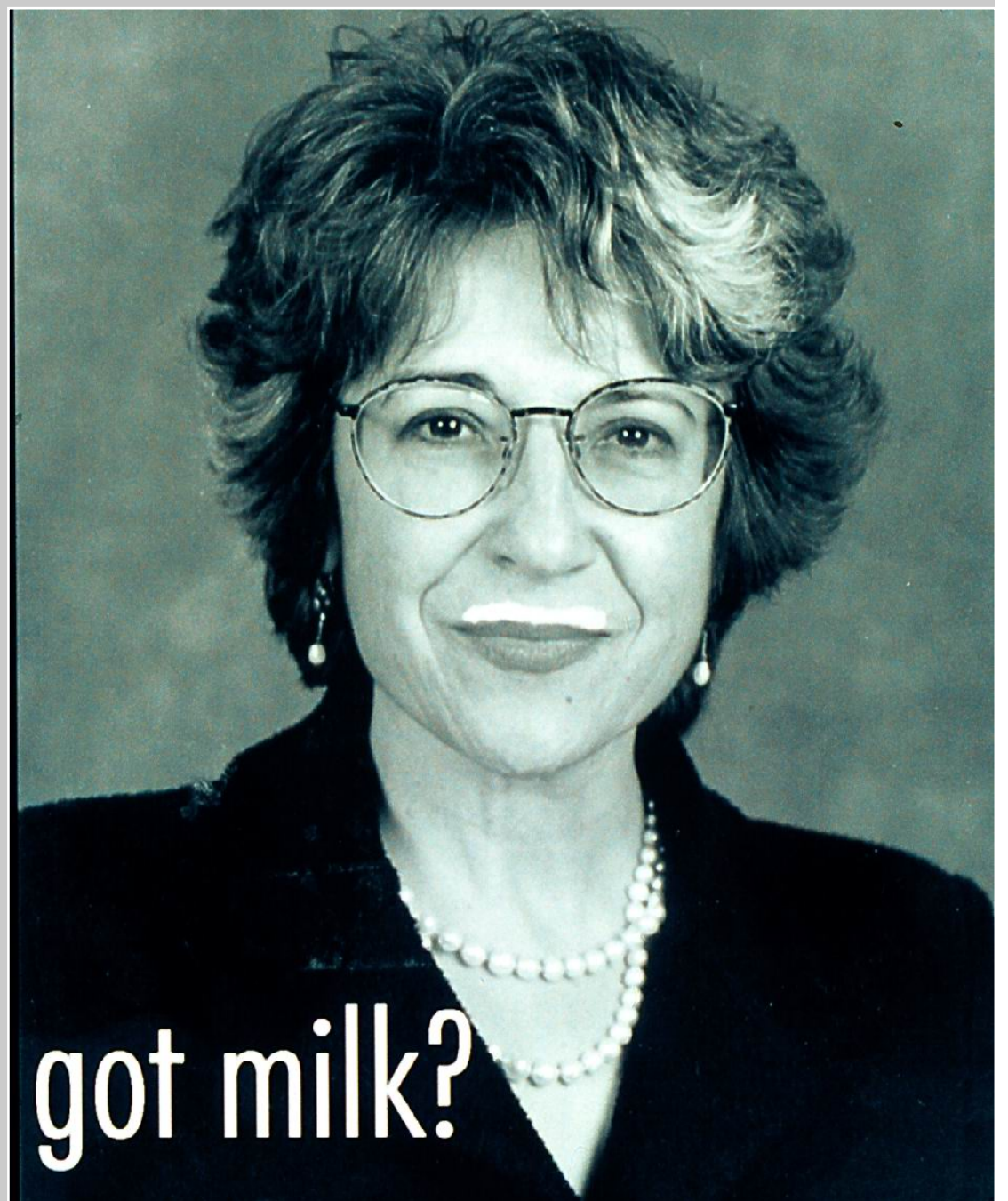


Milk protein/ μ g DNA on plastic and LrECM gels



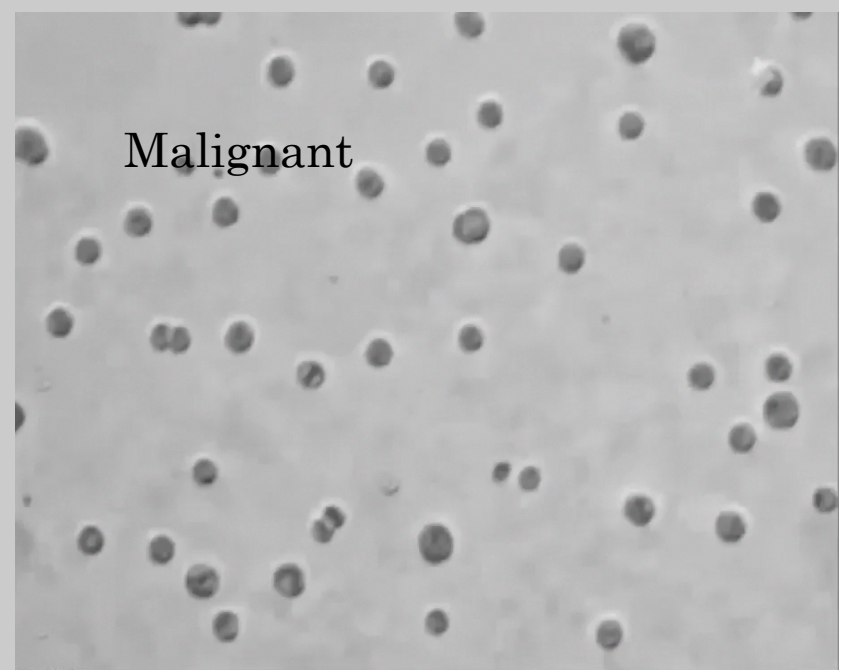
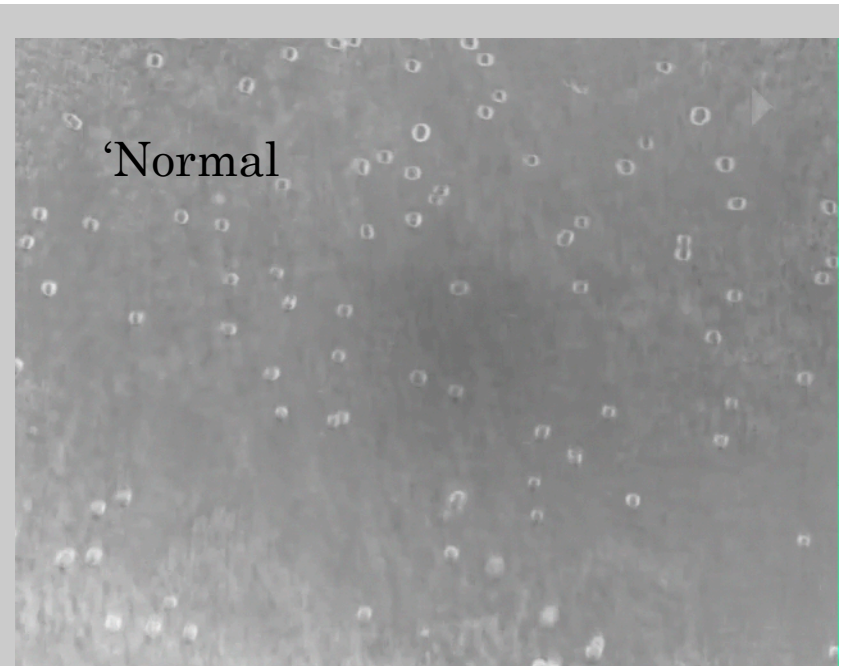
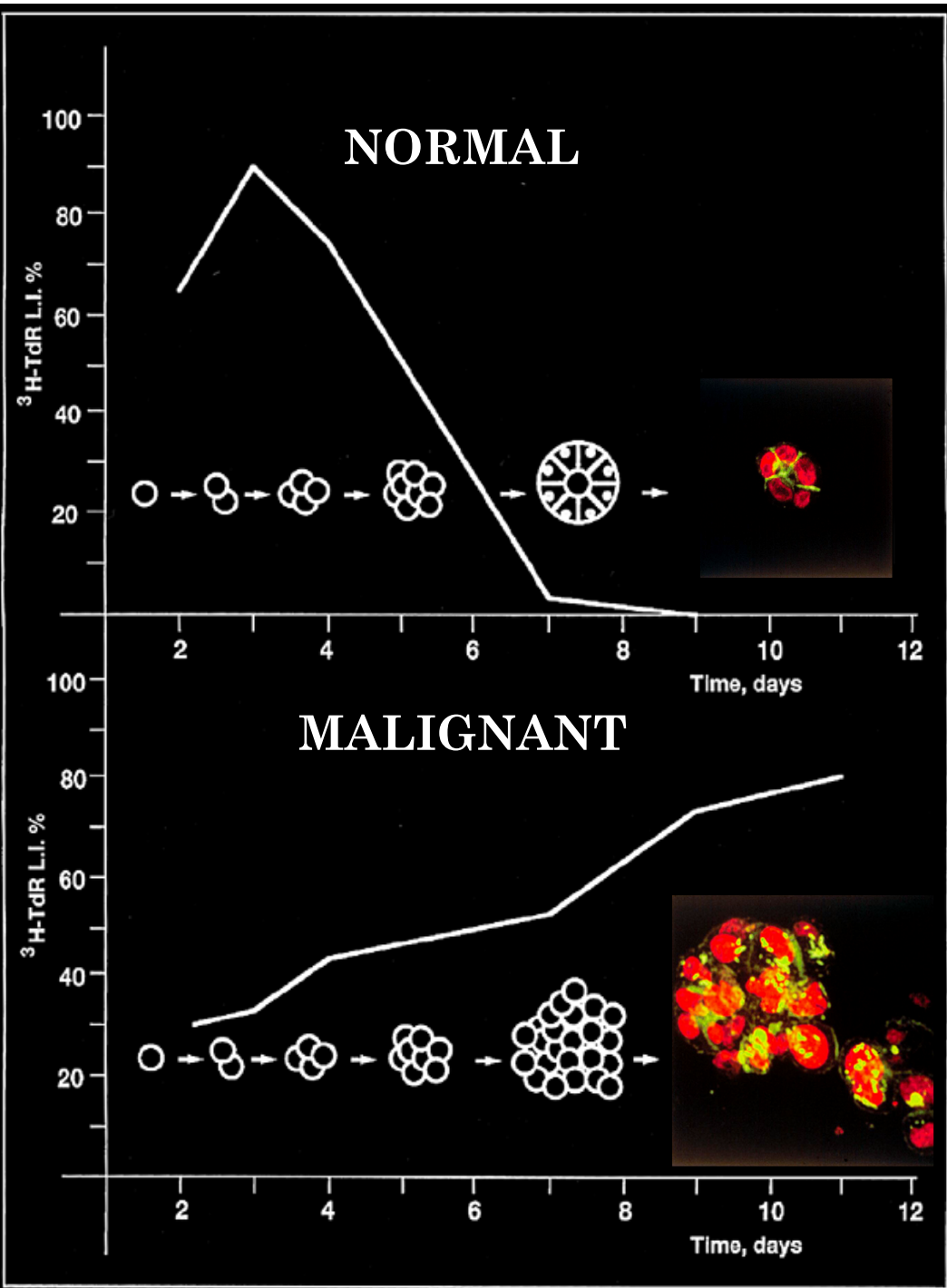
(Lee et al. JCB, 1984)



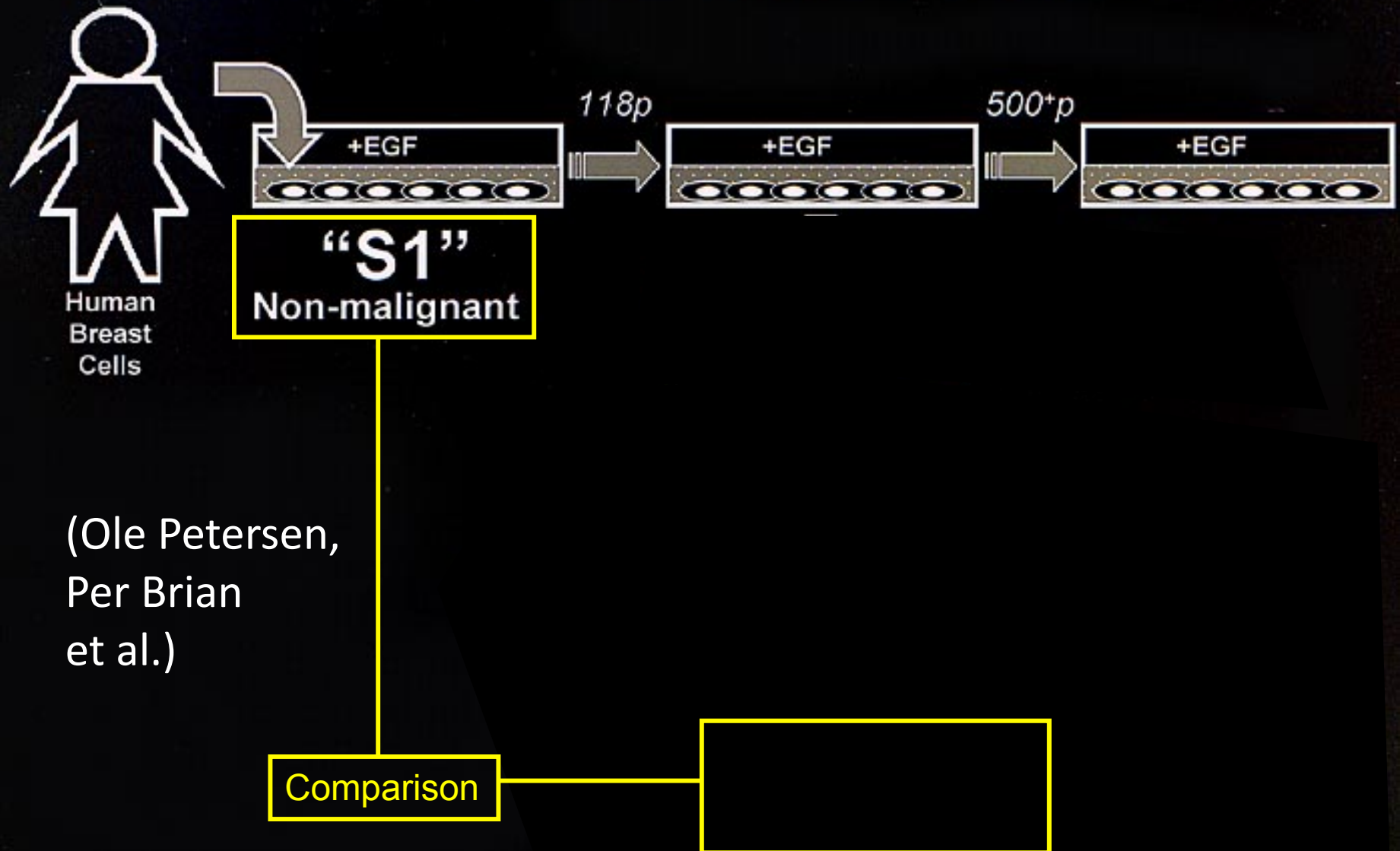


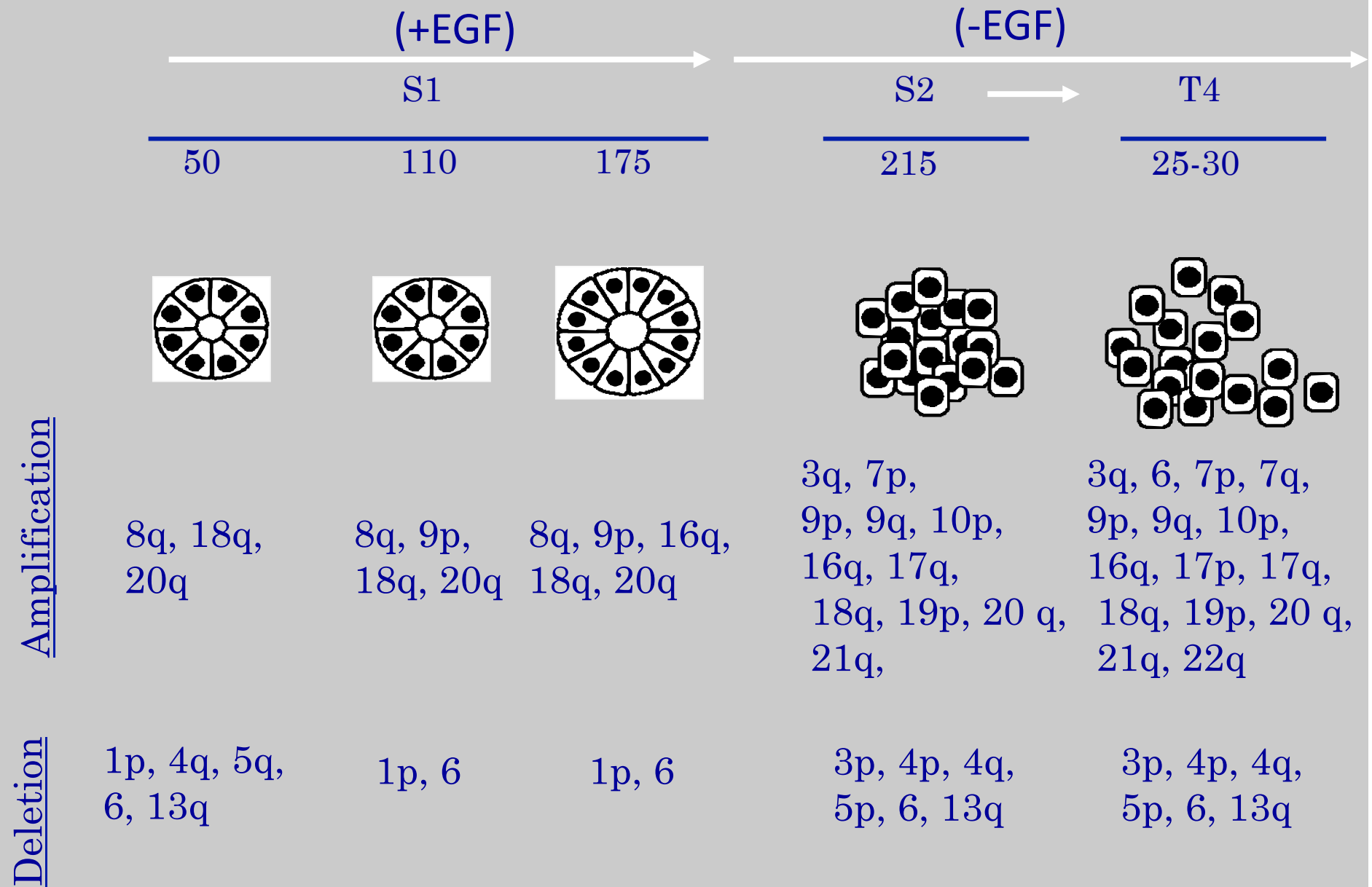
got milk?

**Given that
'normal' cells
remember how
to look in 3D,
could tissue
structure also be
a message
for tumor cells?**



The HMT-3522 Breast Tumor Progression Series





If tissue structure is the message, we can hypothesize:

1. Tumor cells with abnormal genomes should be capable of becoming phenotypically normal if the structure is restored.

2. Destruction of tissue structure by itself could be a carcinogenic event.

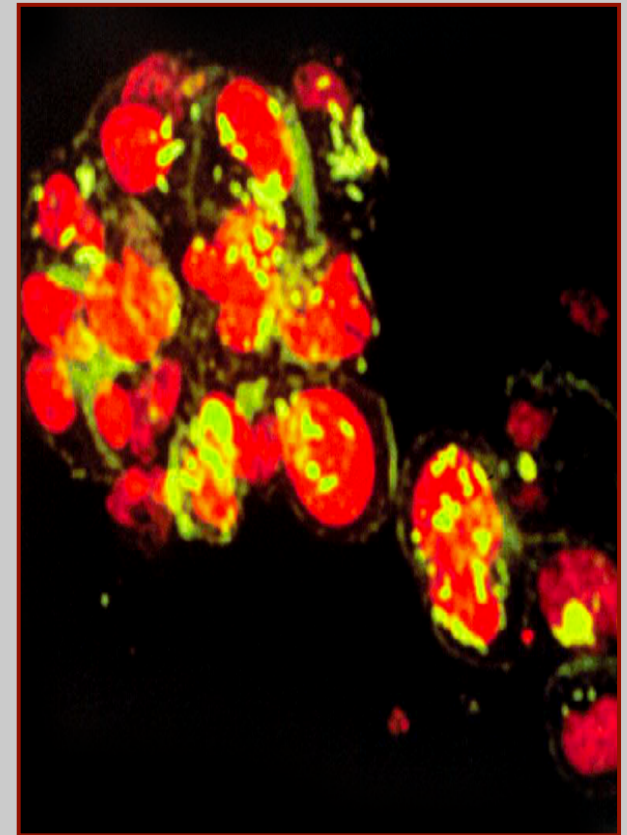
3D assays

“Normal”



Nuclei /red
Actin /green

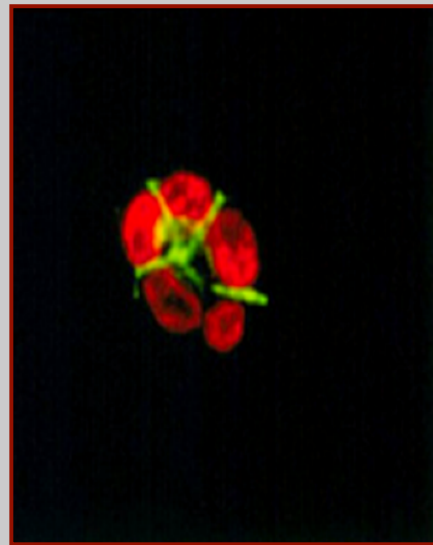
Malignant



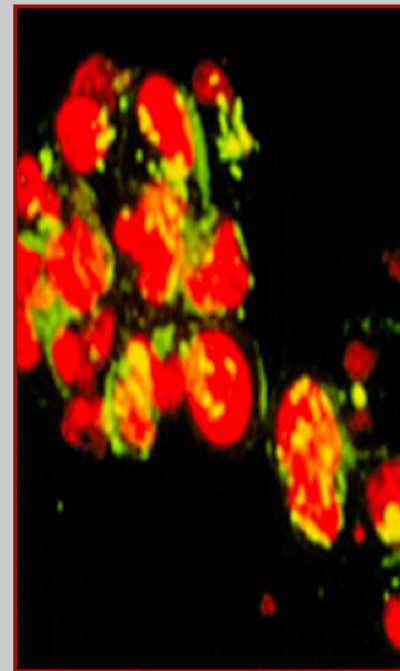
(Petersen..Bissell, PNAS, 1992)

Malignant cells can be reverted biochemically

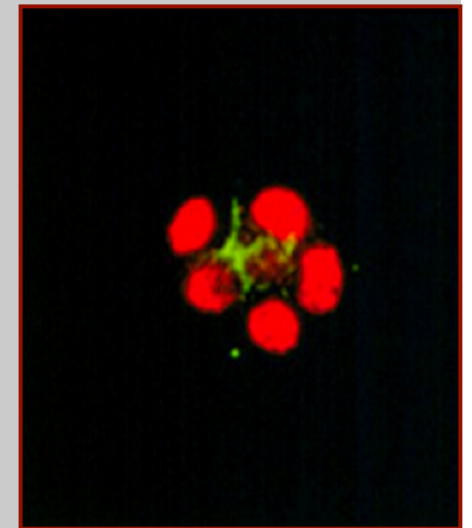
“Normal”



Malignant

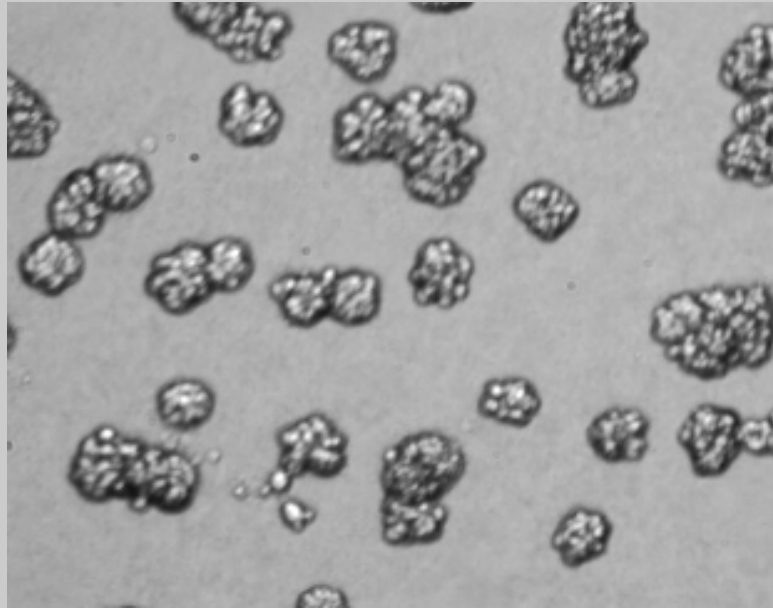


“Reverted”

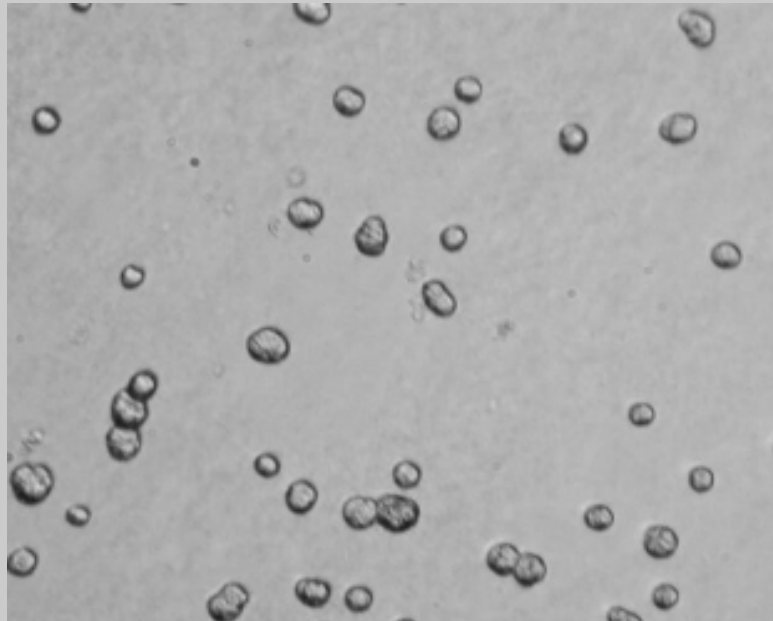


(Weaver et al., JCB, 1997)

EVERY tumor cell gets REVERTED

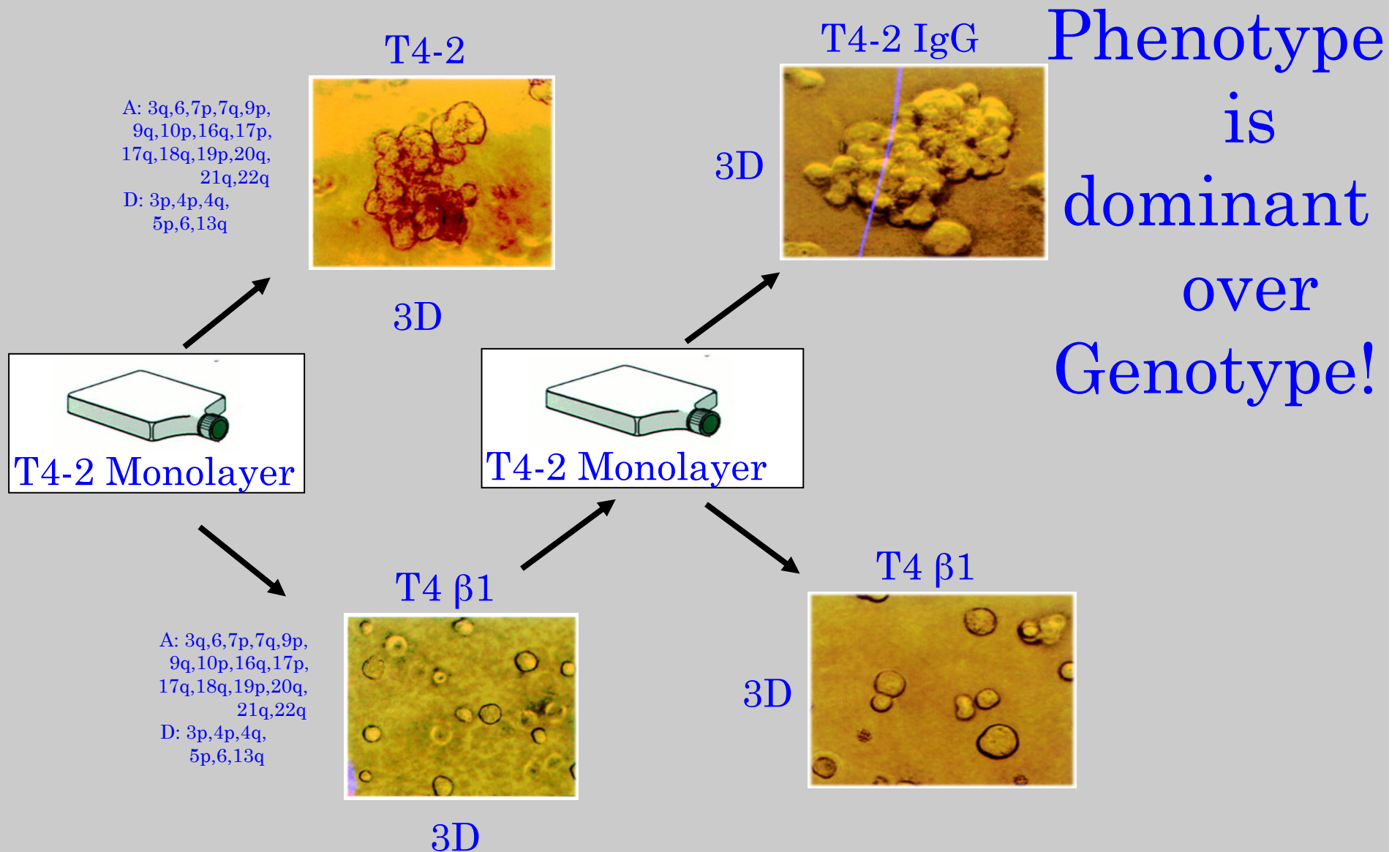


Malignant



“Reverted”
These look exactly
like non-malignant
cells.

Reversion is reversible



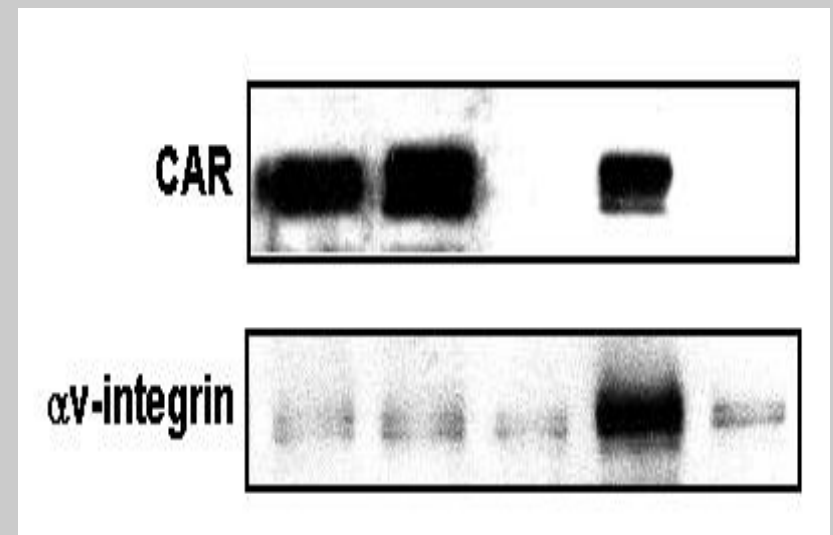
Growth and malignant behavior are regulated at the level of tissue organization.

Tissue organization is dependent on the Extracellular Matrix (ECM)

(Bissell et al. J.Theoretical Biol. 1982)

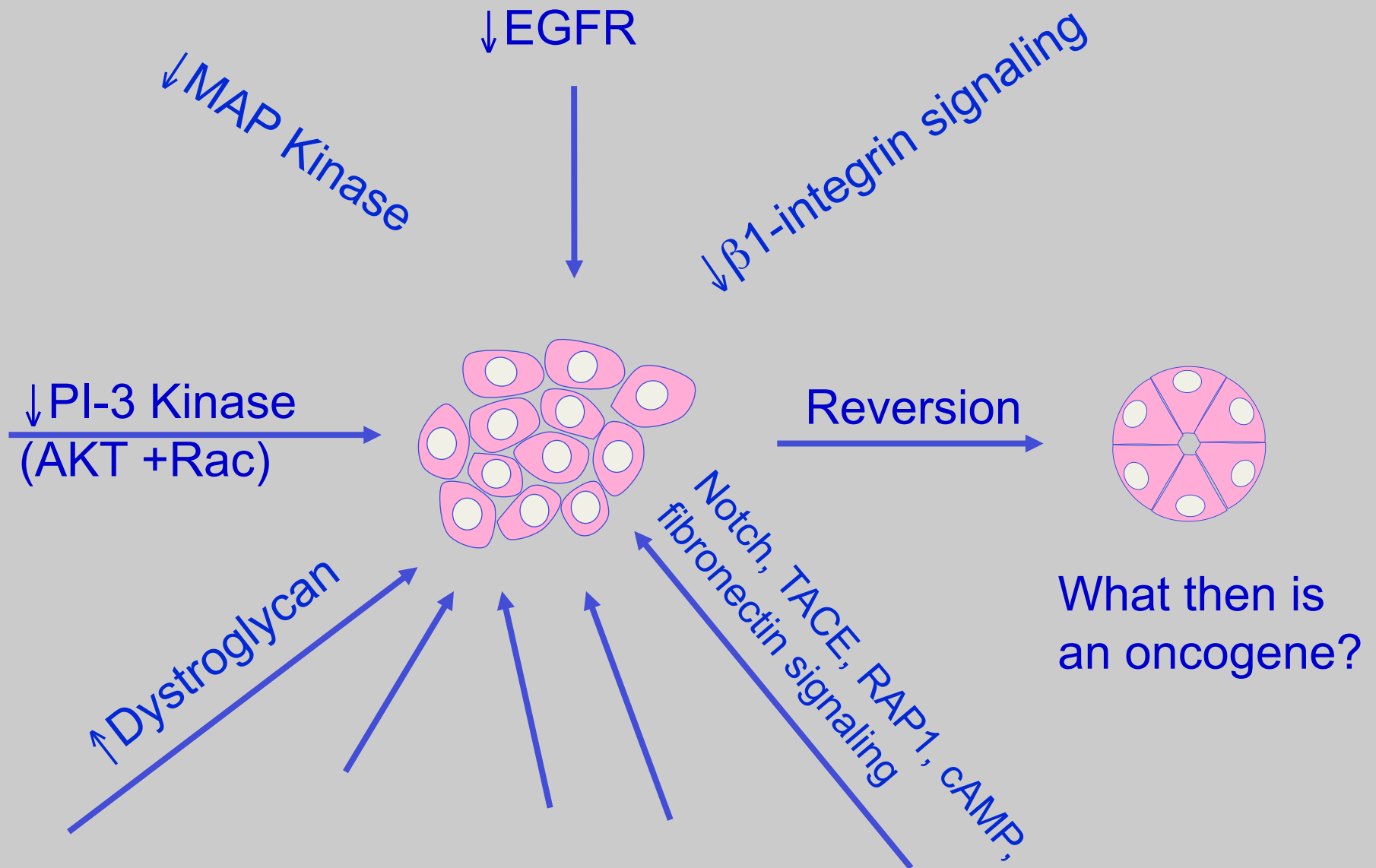
More than 200 publication and reviews from our laboratory on different aspects of these statement since 1995. Please Google us if still skeptical!

Expression of receptors involved in adenovirus infection: **Regulated *only* in 3D**

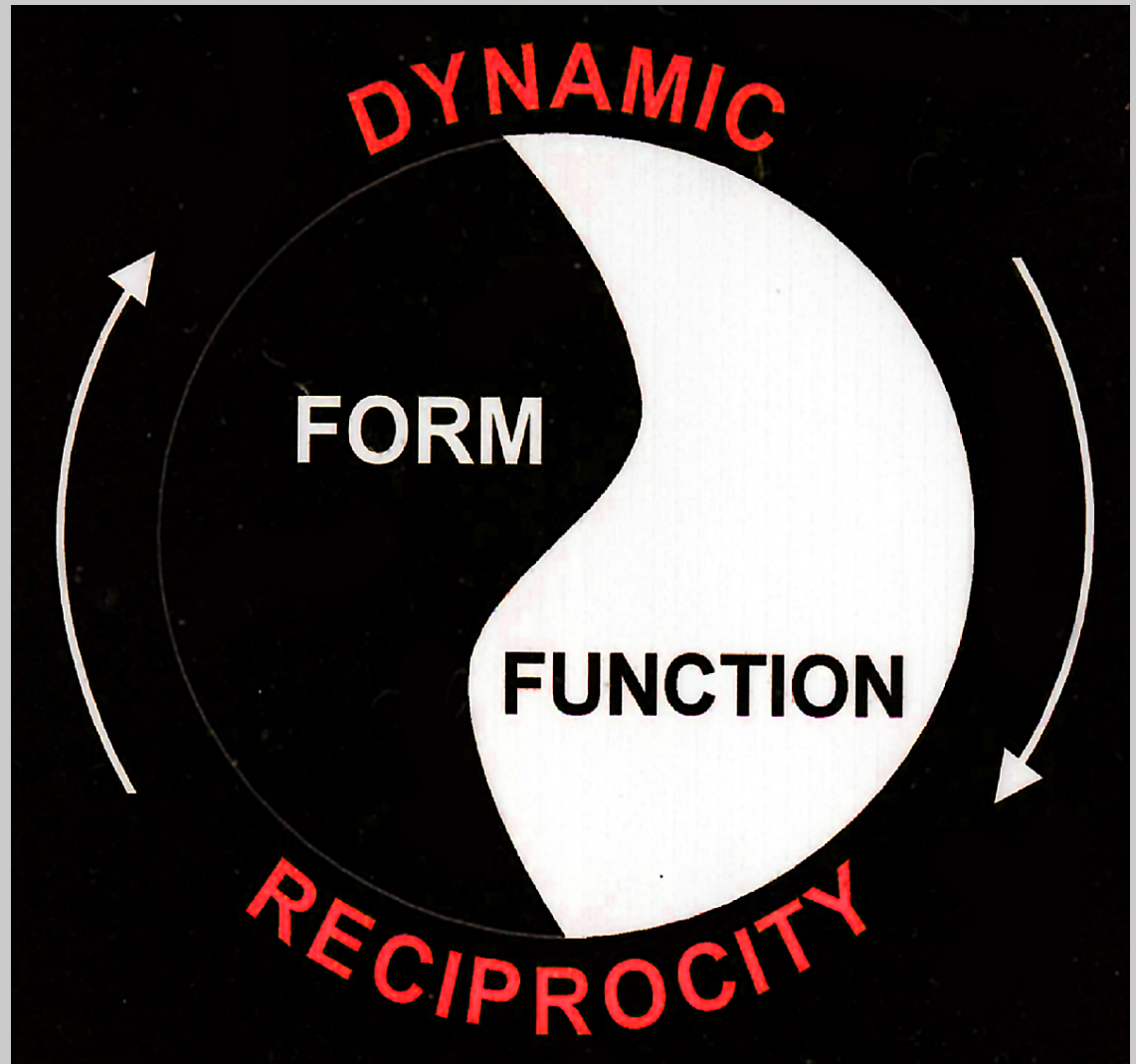


S1 T4 S1 T4 T4R
2D 3D

(Anders, et al, 2003,PNAS)



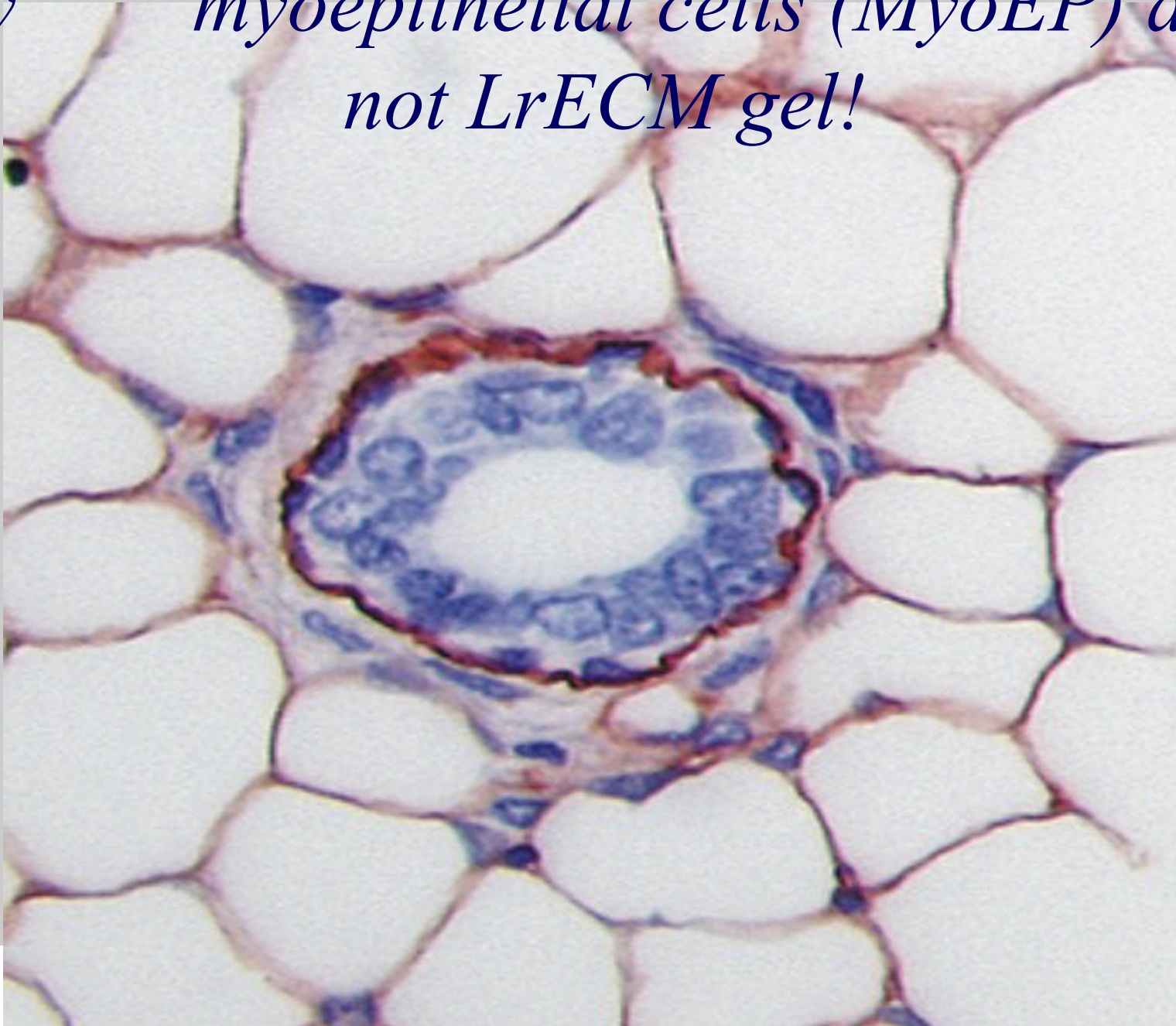
Can also revert metastatic cell lines,
but need two inhibitors together



But what gives the signal to the mammary gland in vivo to tell it to be polar and functional?

What substitutes for laminin-rich gels??

The mammary acinus *in vivo* is surrounded
by *myoepithelial cells (MyoEP)* and
not LrECM gel!



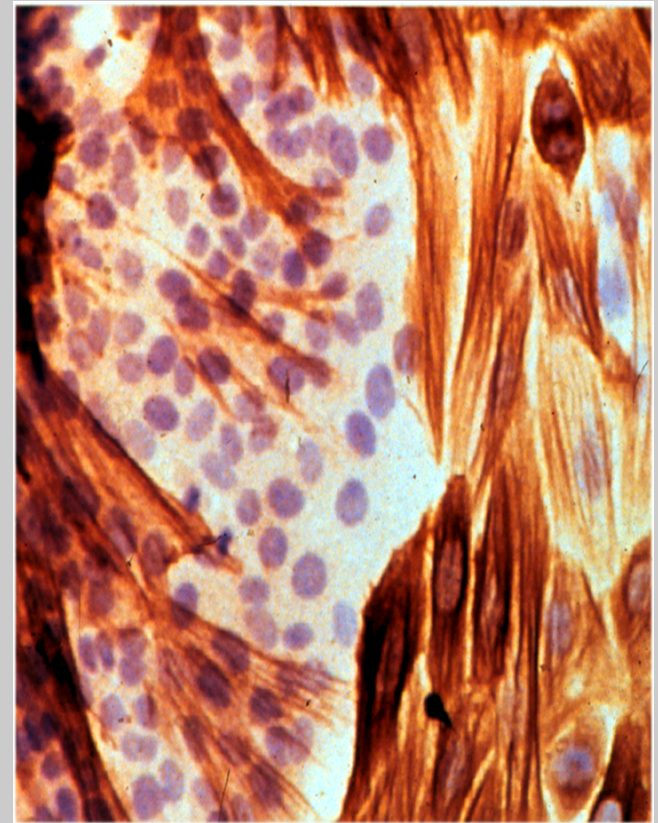
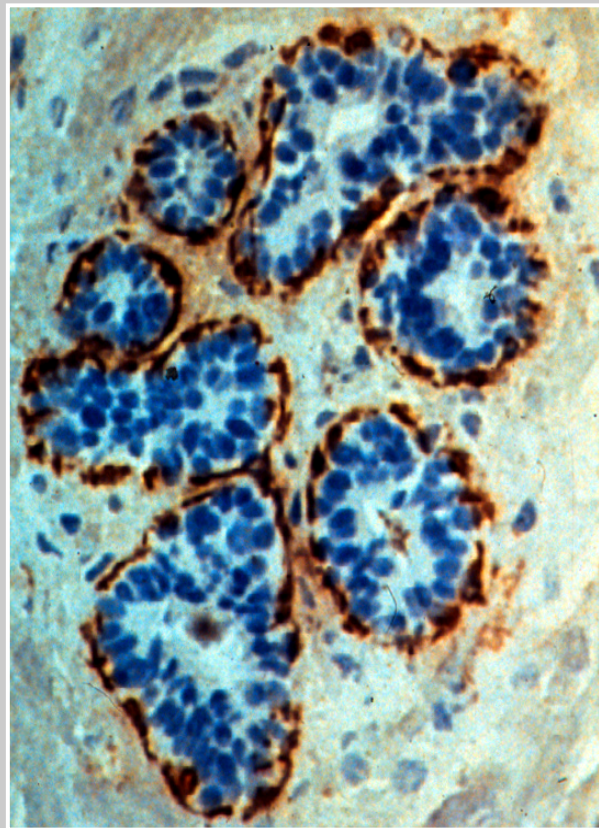
What is the role of myoepithelial cells in vivo?

(Brown highlights

Myoeps)

IN SITU

IN CULTURE



Luminal Epithelial Cells (LEP) in:

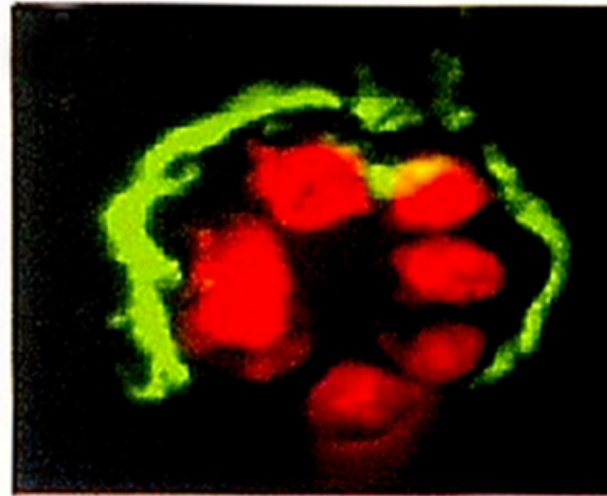
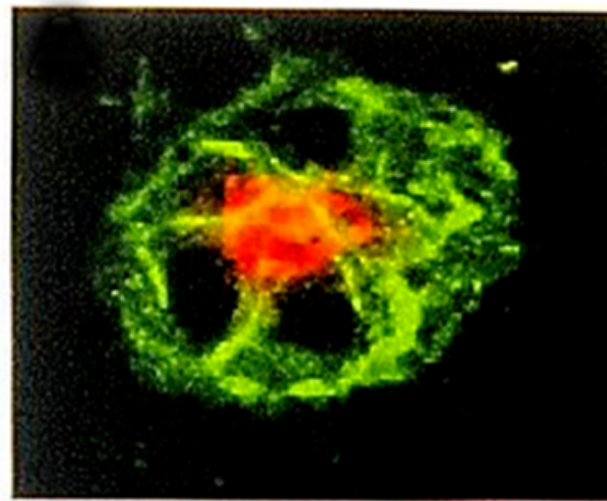
Lr-BM



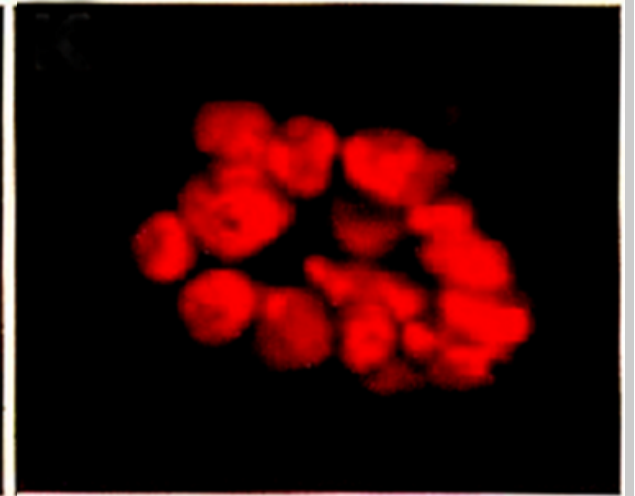
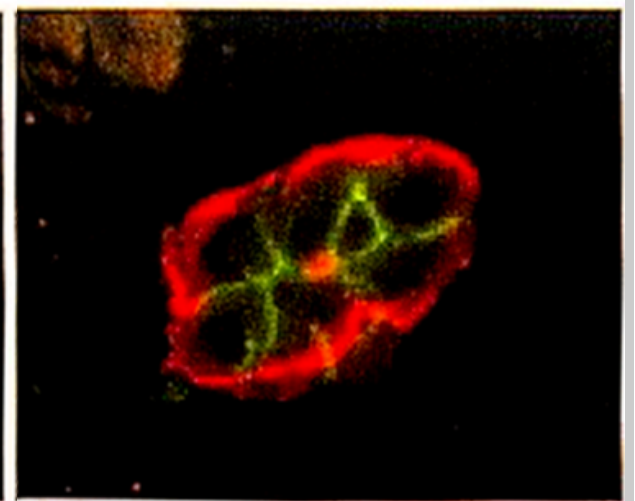
Collagen-I



LEP in rBM



LEP in Col I

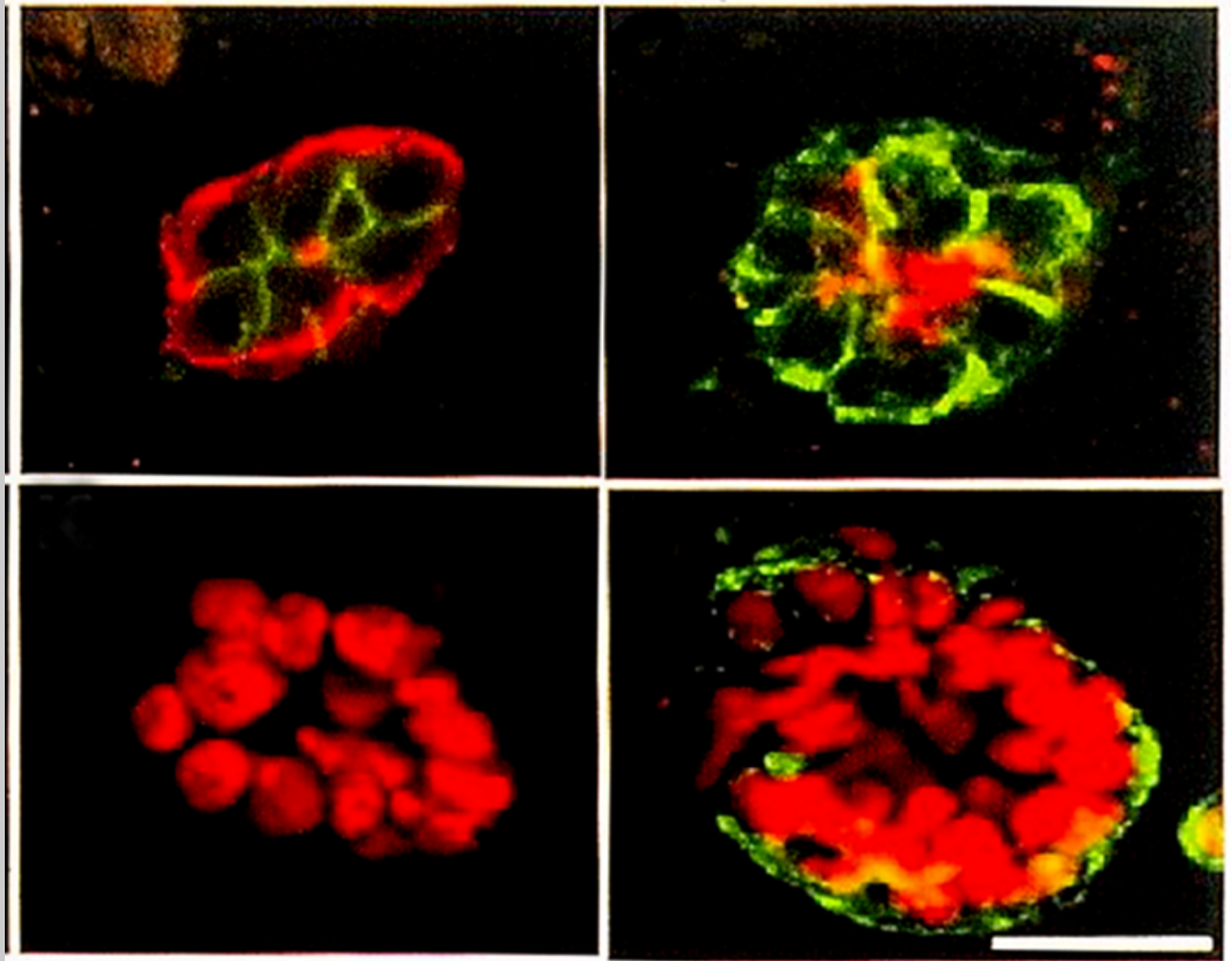


Top row: Sialomucin ESA

Bottom row: Nuclei Collagen IV

LEP in Col I

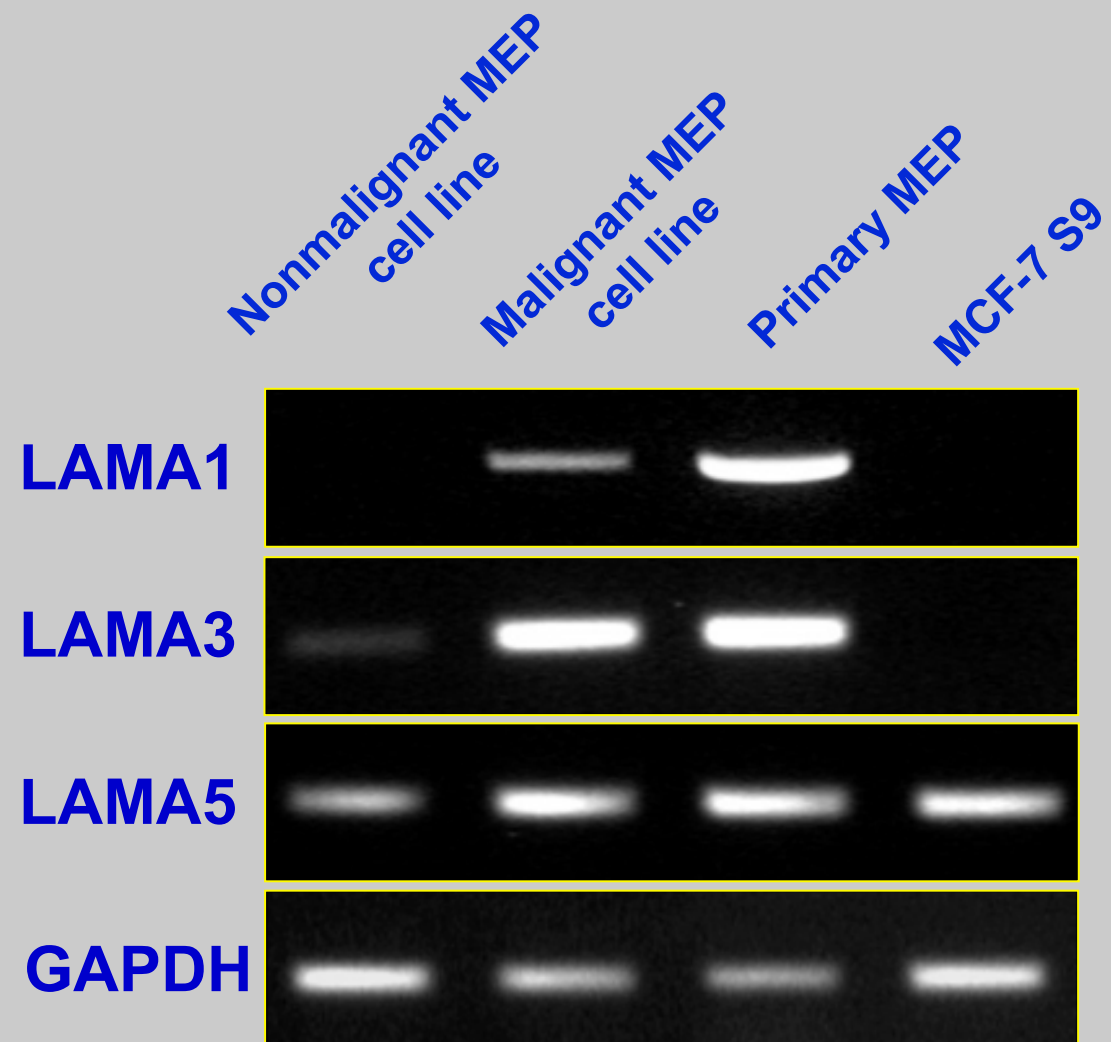
LEP & Myoep



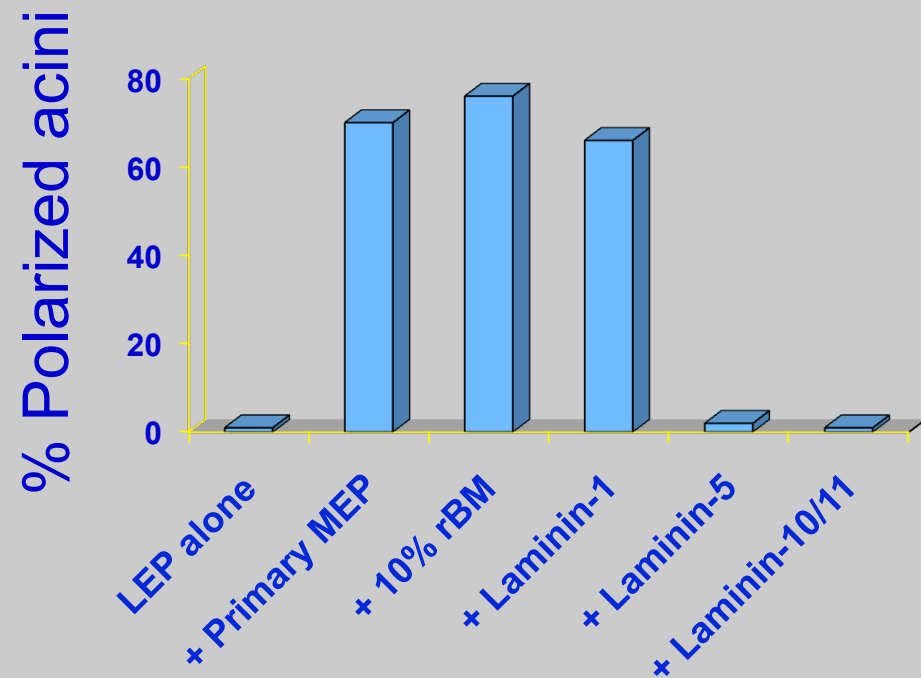
Top row: Sialomucin ESA

Bottom row: Nuclei Collagen IV

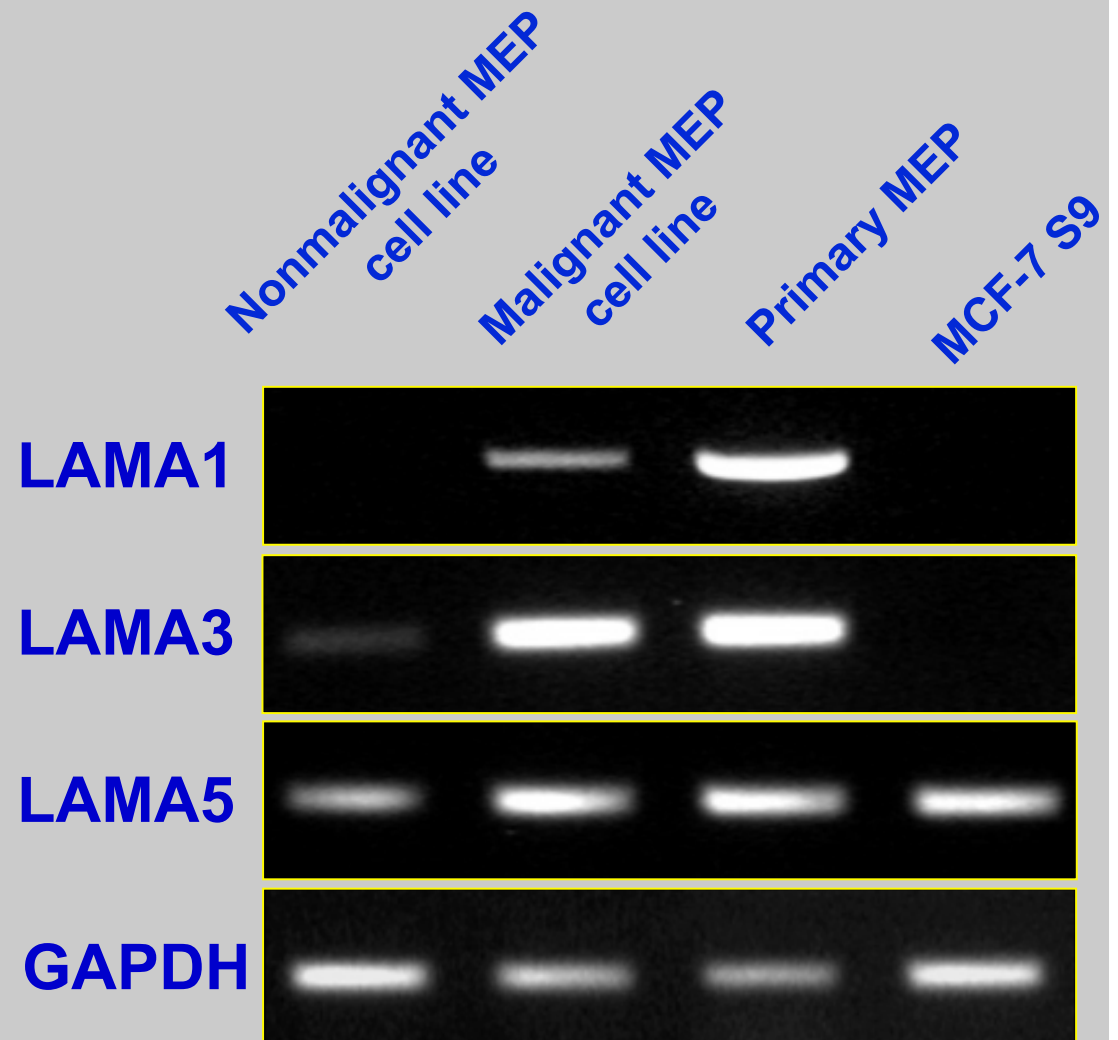
Cancer-derived MEP do not express laminin-A1



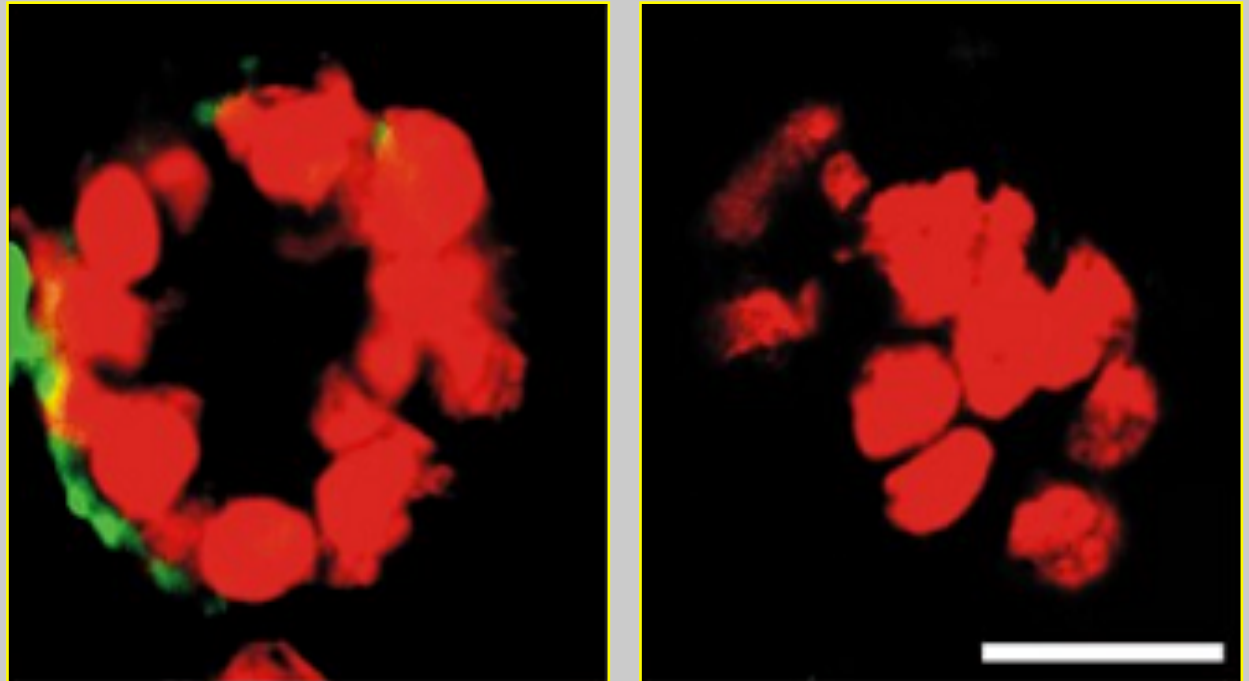
Only laminin-I (Ln-1) can substitute for myoepithelial cells for reversing polarity in collagen gels



Cancer-derived MEP do not express laminin-A1



Cancer derived myoepithelial cells can't re-organize

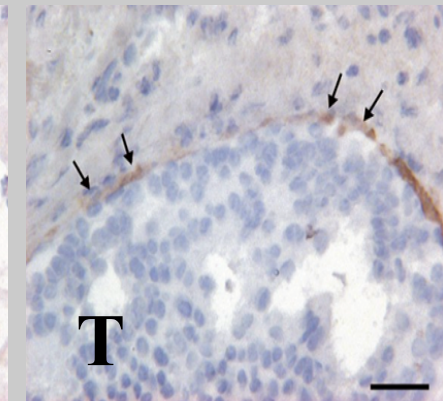
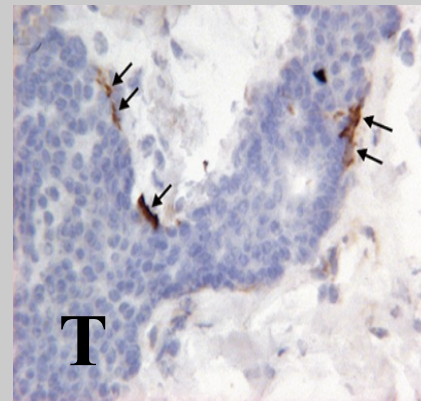
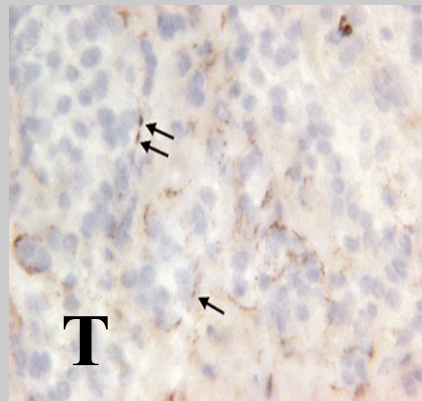
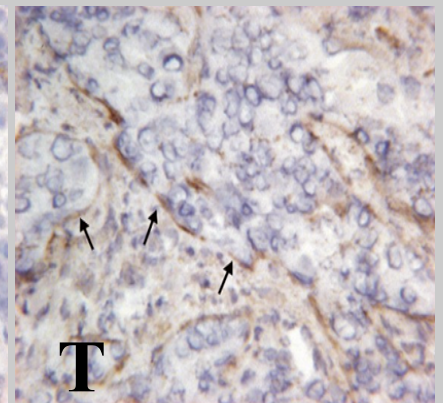
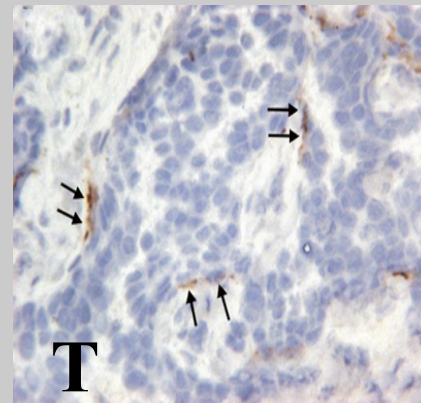
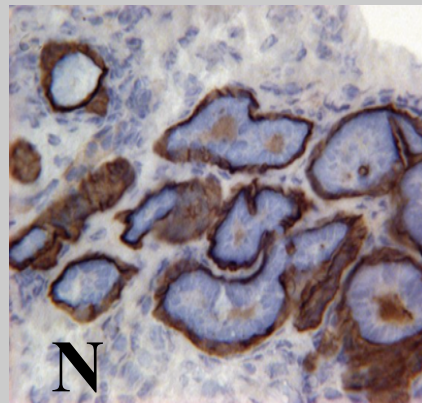


β4-integrin

nuclear stain

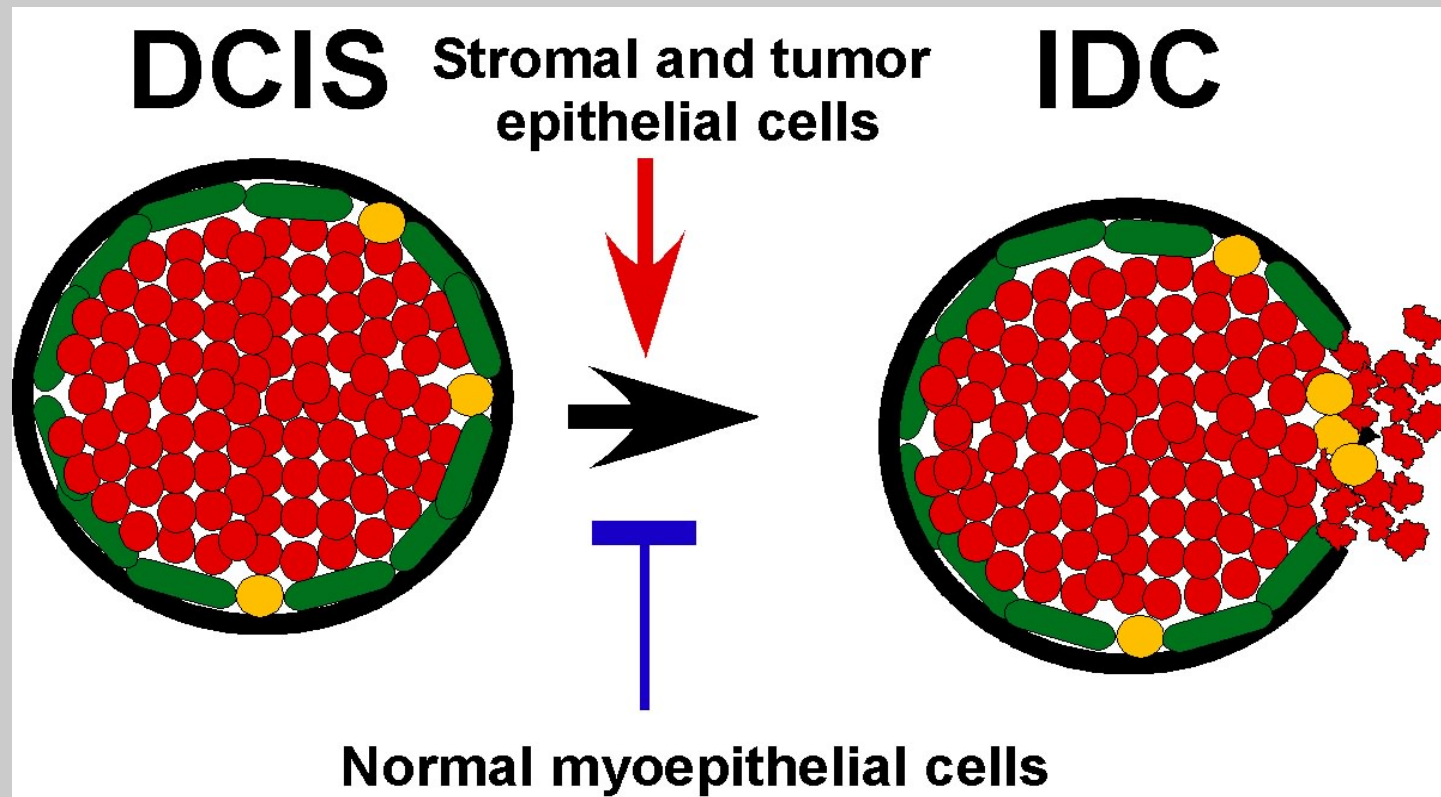
(Gudjonsson, et al. J. Cell Sci, 2002)

Laminin-A1 is reduced in human breast cancer



In situ to invasive carcinoma progression

(only normal myoeps can stop progression)



(Hu...Polyak, Cancer Cell, 2008.)

- 1. Does Loss or aberration of ECM have a functional significance?**
- 2. If so, can it lead to tumor formation?**

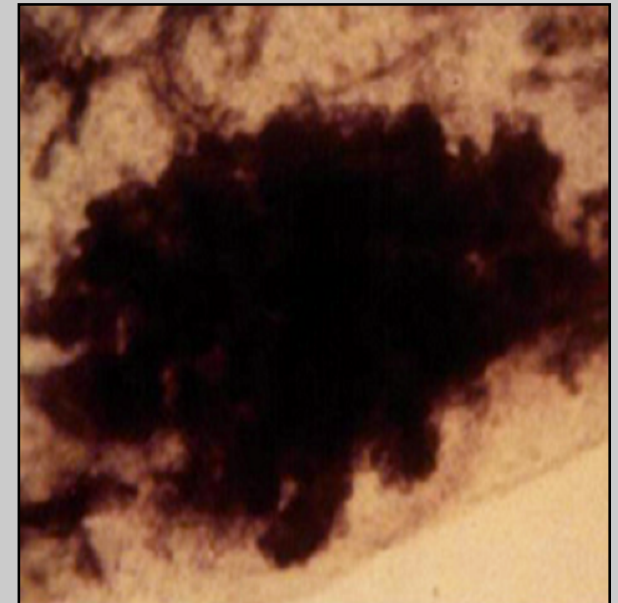
(Sternlicht et al, Cell, 1999; Radisky et al, Nature, 2005)

MMP-3 mice develop mammary tumors as they age

Wild-type



Transgenic



Does MMP 3 select already mutated cells, or does it, by itself, causes genomic instability?

(JCB, 2004)

(E. coli)



Mais ...

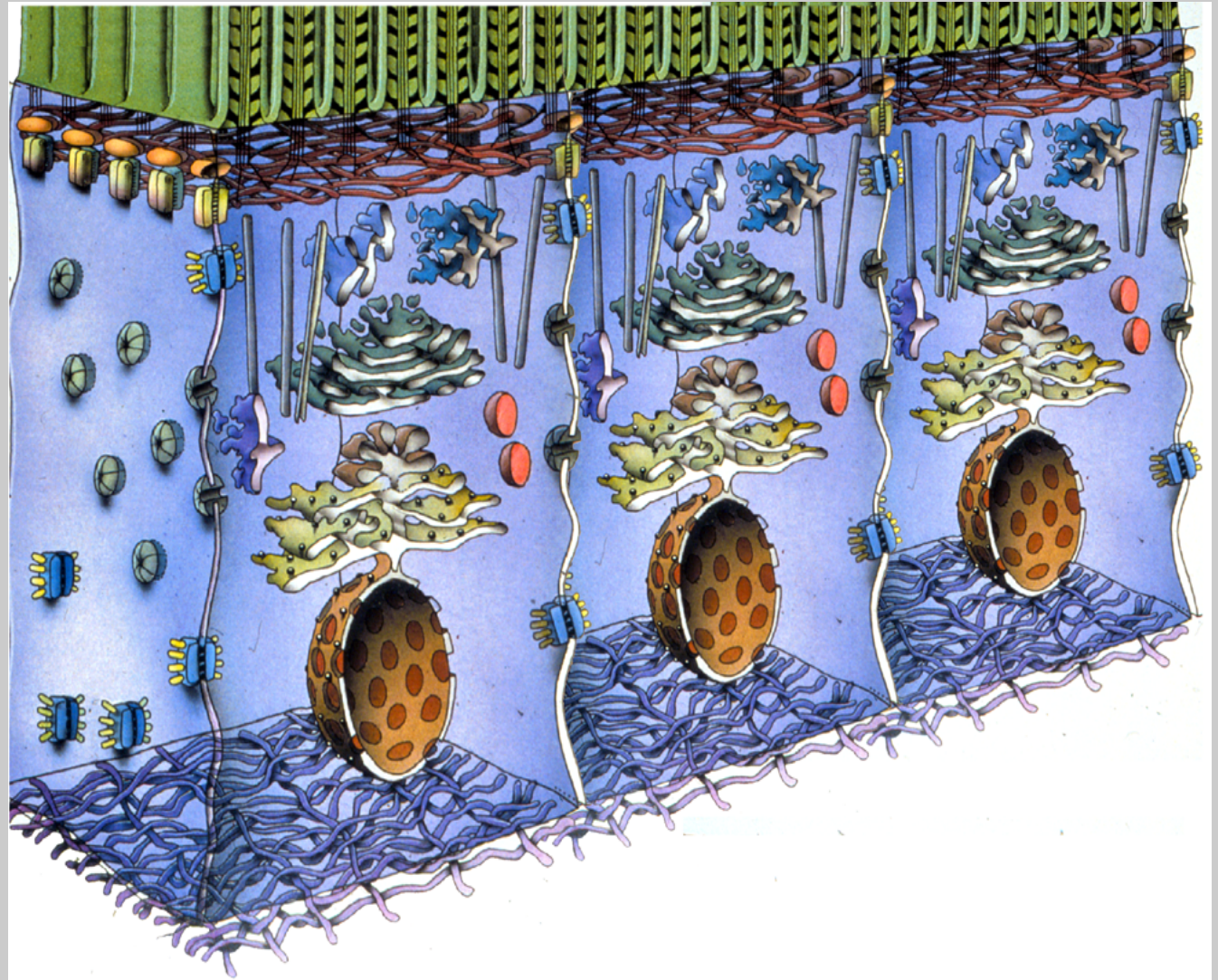
Ce qui est vrai
pour Escherichia, l'est-ce
vraiment pour moi ?

hum ?...



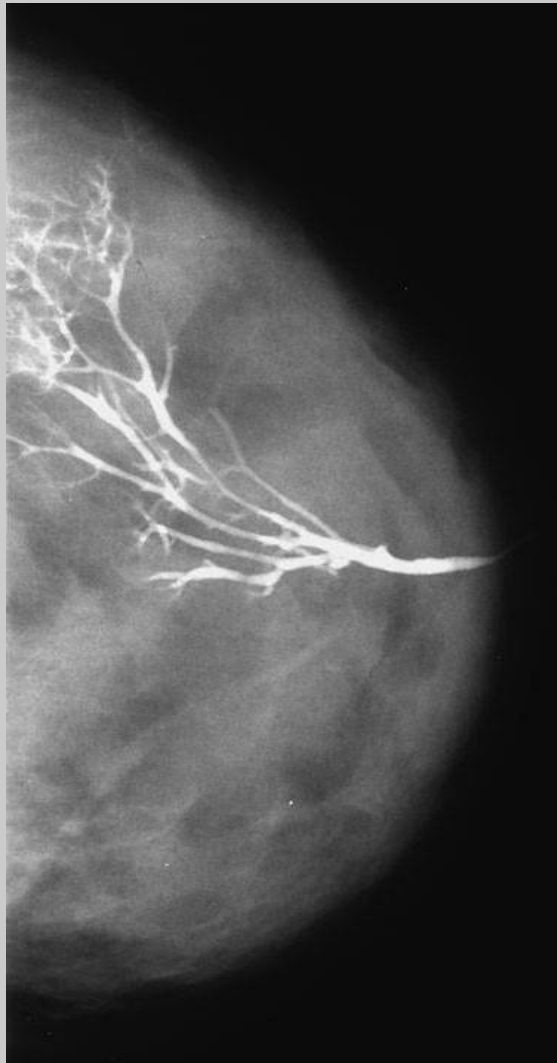
C. J.

When two higher organism cells come together..

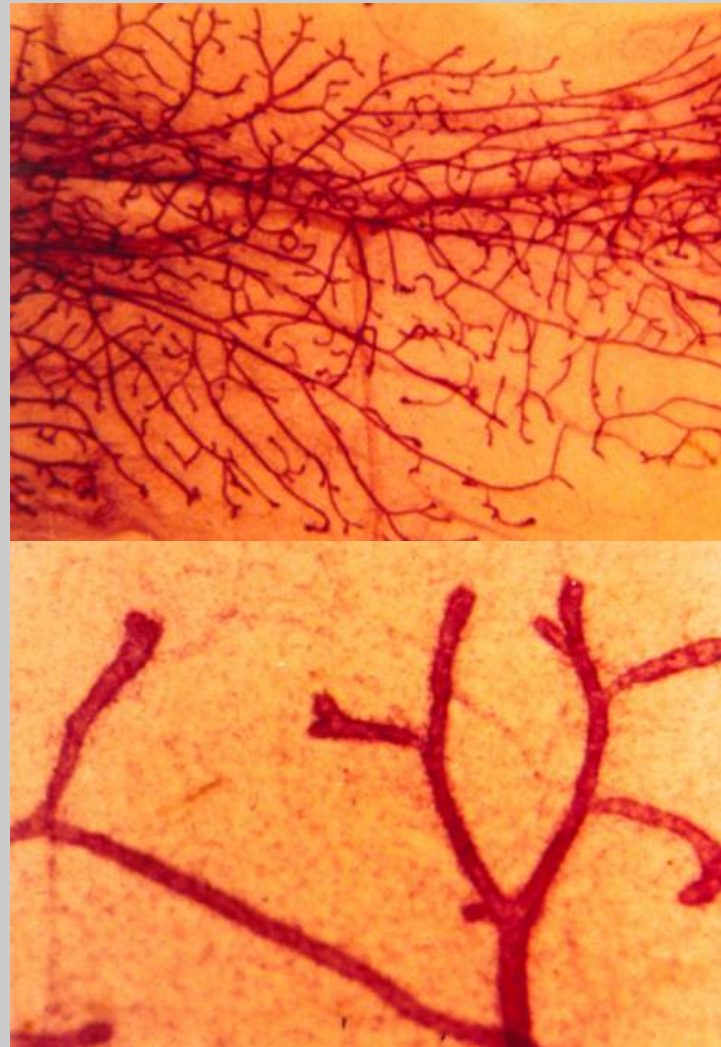


The result is logarithmically different

Invasion into the fat pad: A clue to metastasis?



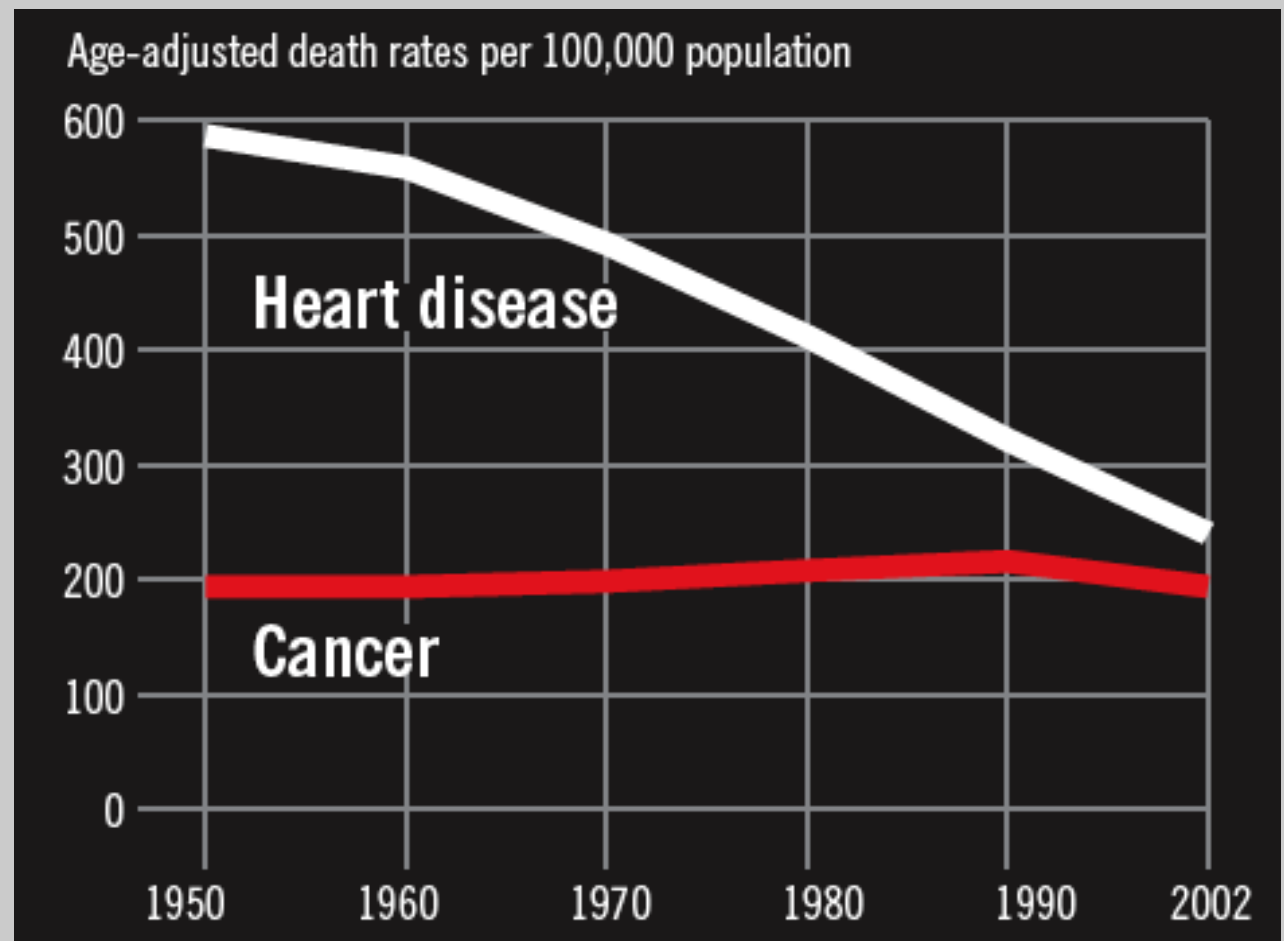
Human



Mouse

New Yorker





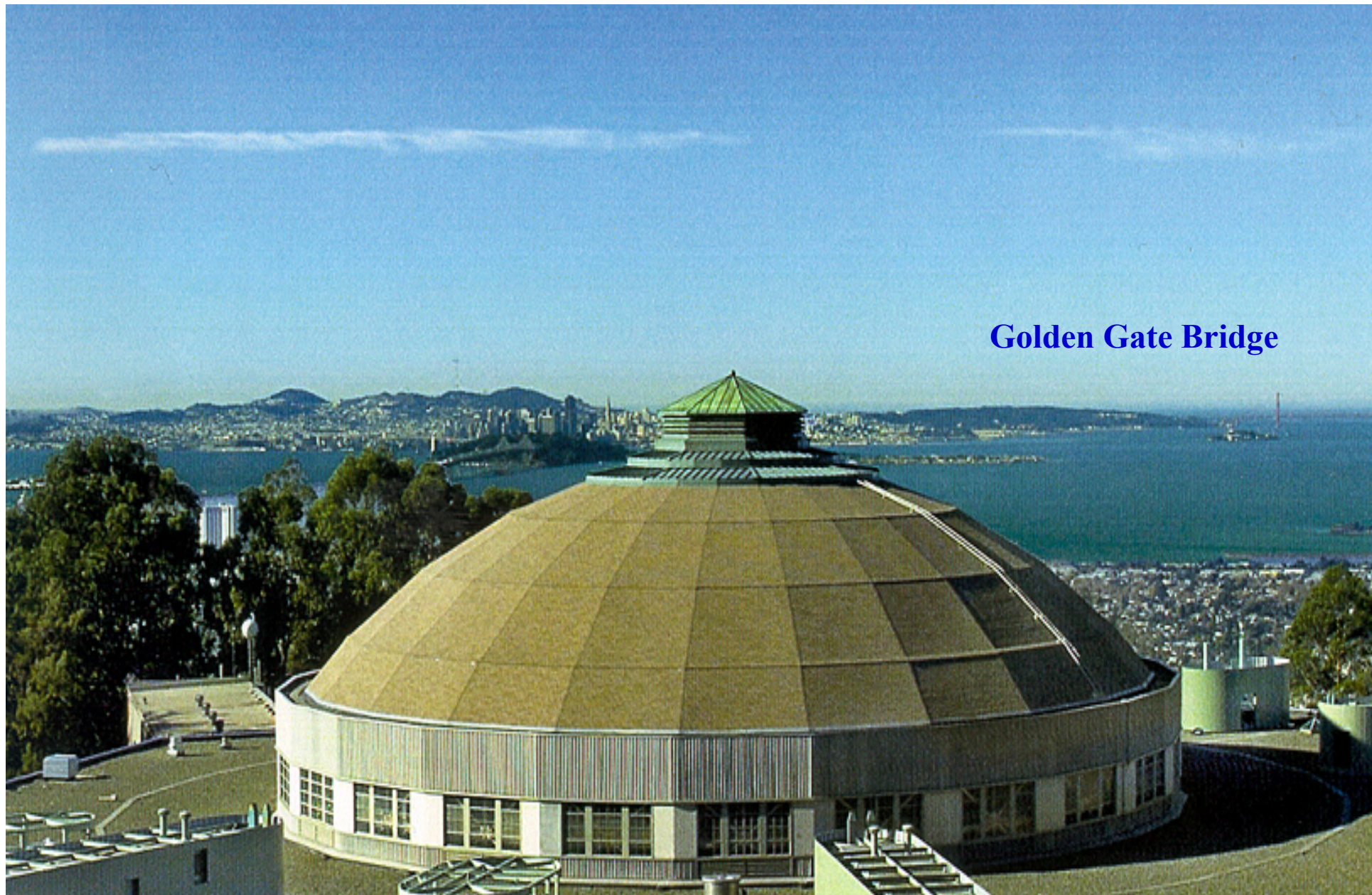
(Clifton Leaf, Fortune Magazine, 2004)



***In memory
of Sonia
Maria
Mueller,
1968- 2003***



Chloe, when she was five



Golden Gate Bridge

**Lawrence Berkeley National Laboratory
The Advanced Light Source**

Bissell Lab





The Human Acinus!

Bissell Lab, In Spring, of 2009