

# “Understanding Complex Mechanisms in Determining Adverse and Beneficial Health Effects With Nutrition/Diets: From Basic Science of Hazard Identification of the Concept of “One Health-One Planet”

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# “A New Paradigm in Understanding the Epigenetic Mechanisms In the Mediterranean Diet: How Sushi, Tofu, Okonomiyaki, Mikans & Green Tea might give Clues to Grilled Tuna, Pasta , Pizza, Cannoli & Vina Rosa !”

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# Objective

**To** understand the fundamental causes of our “global health crises”...i.e., the rise of “metabolic diseases” throughout the world, a comparison between the two “best diets”( e.g., the Mediterranean and Japanese) will be done in order to find an underlying basic mechanism affecting human health.

**Basic** assumption of this brief analysis is that it took the millions of years for our human ancestors to acquire genes via **glacier-speed biological evolution** to adapt to the various environments from which they acquired nutrients for life, which is now on a collision course with the **laser-speed changes in cultural evolution** that is shaping our diets.

**In** just a few decades, because of the Diaspora of people and the Diaspora of foods, together with a reductionalistic approach to solve complex human problems without an integrated “**One Health-One Planet**” strategy, these “metabolic diseases” and deteriorating ecological system will only be exacerbated.

**The** alteration of organ-specific adult stem cells during pregnancy by nutrition/diets is probably the mechanistic basis of chronic diseases later in life (The Barker Hypothesis).



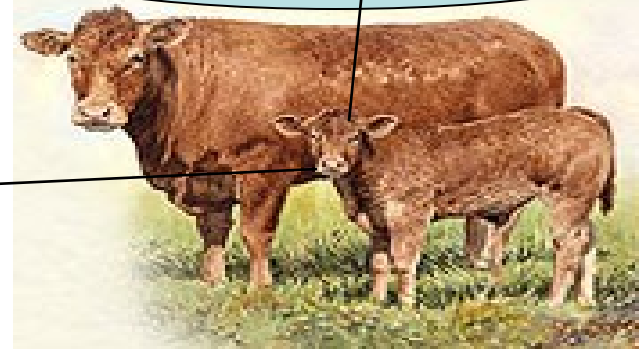
MEDITERRANEAN DIET

JAPANESE DIET



WESTERN DIET

MOM, IS THAT DAD?



## BASIC ASSUMPTIONS

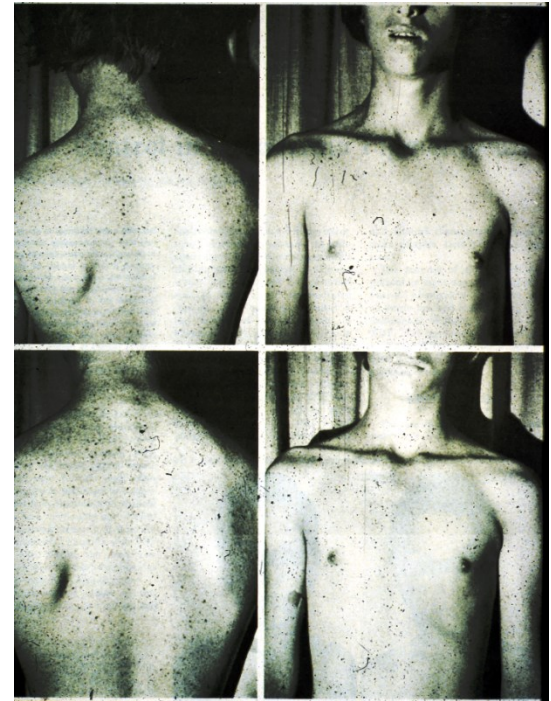
- In order to have a scientific explanation for understanding how nutrition/diets affect human health, one must **understand the fundamental mechanisms of toxicity and how they fit into the prevention of pathogenesis of diseases.**
- There are three fundamental mechanisms of cellular toxicity: **mutagenesis; cytotoxicity and altered gene expression or “epigenetic toxicity”.**
- Although hereditary and somatic mutations of the human genome exist, **genomic mutations are not caused in the critical target cells ( organ-specific adult stem cells) that lead to cancers and other stem cell-related diseases.**
- Mutations are due to either “Errors in DNA Replication” or to “Errors of DNA Replication”. In the case of mutations found in genes of cancer cells, with the exception of most in UV induced skin cancer, they have their origin in **“Bad Luck Mutations” or spontaneous mutations due to errors in DNA replication of stem cells. [ J.Couzin-Frankel, Science 347: 12, 2015; C. Tomasetti & B. Vogelstein. Science 347: 78-80, 2015]**
- Both acute and Chronic Diseases share a common underlying cellular mechanism, namely the modulation of the integrated **Extra-, Intra- and Gap junctional Intercellular Communication.**
- **Chemicals can induce oxidative stress and ROS but these are inducers of either receptor and or receptor -independent Intra- cellular signaling that alters gene expression and gap junctional intercellular communications.**

*“Lasting Biological Effects of Early Influences”*

Rene Dubos, Perspect. Biol. Medicine 12: 479-491, 1969.

**“We resemble our progenitors because we derive from them our genetic endowment; but our genes do not determine traits by which we know a person. They only govern the responses that the person takes to the environmental [or dietary] stimuli. Individuality progressively emerges from these responses.”**

# Genes & Environmental Interactions



Xeroderma Pigmentosum (genetic lack of DNA repair of UV damage in skin cells) predisposes individual to skin cancer only if the skin is exposed to sunlight. Last picture shows two twins who have never been exposed to direct sunlight and they have not developed skin cancer even though they have, genetically, xeroderma pigmentosum.



Bloom's  
Syndrome





## **Down's Syndrome**

**DIASPORA OF HUMANS TO DIFFERENT REGIONS OF FOOD ACQUISITION LED TO BIOLOGICAL EVOLUTION OF GENES TO ADAPT TO CULTURAL EVOLUTIONARY CHANGES IN DIET AND GUT MICROFLORA**



Blubber from seals in frozen environments



Fruits, nuts, jungle meats, fish in the Amazon jungle



Transported dried foods in Machu Picchu



Raw fish, vegetables, Green Tea in **Japan diet**



**Mediterranean Diet** of vegetables, olive oil, pasta, fish, red wine, fruits

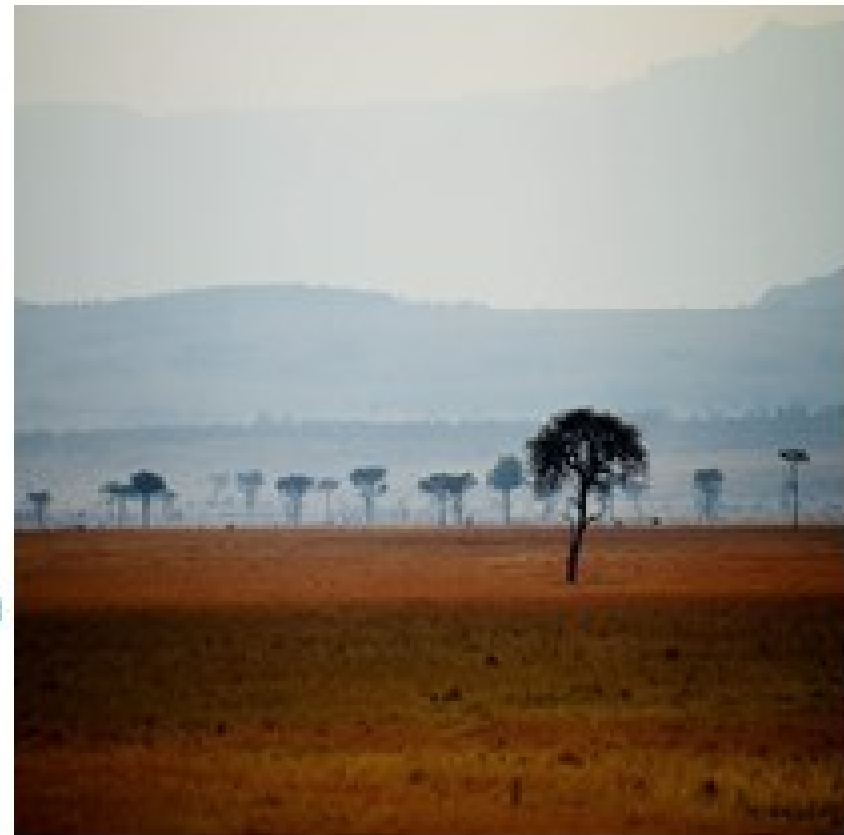


**Western diet** of processed foods of caloric-laden components

## **PRE-Human Diet**

- 1. "Feast or Famine" style of eating**
- 2. Eat what you could eat within walking distance.**
- 3. Eat only during the day**
- 4. Eat only seasonally-available foods**
- 5. Eat grains, nuts, fruits, water-associated animals ( 3-omega fatty acid-rich foods).**
- 6. Ate these foods without grilling.**
- 7. Low caloric intake**

**DIET- THEN**



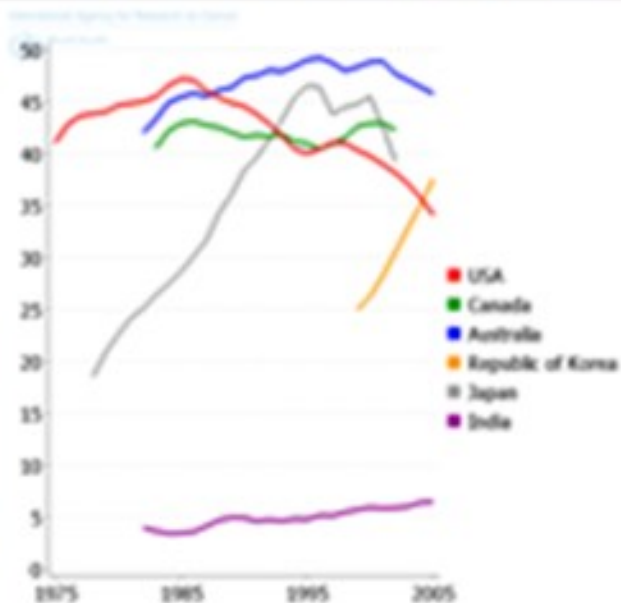
# Modern Diet

- Caloric Unrestricted.
- Foods are processed
- Foods are found year-round
- Eat 24 hours a day.
- Red meat/ grilled or fried
- Use of dietary supplements

DIET-NOW



# GLOBAL DIET & DISEASE



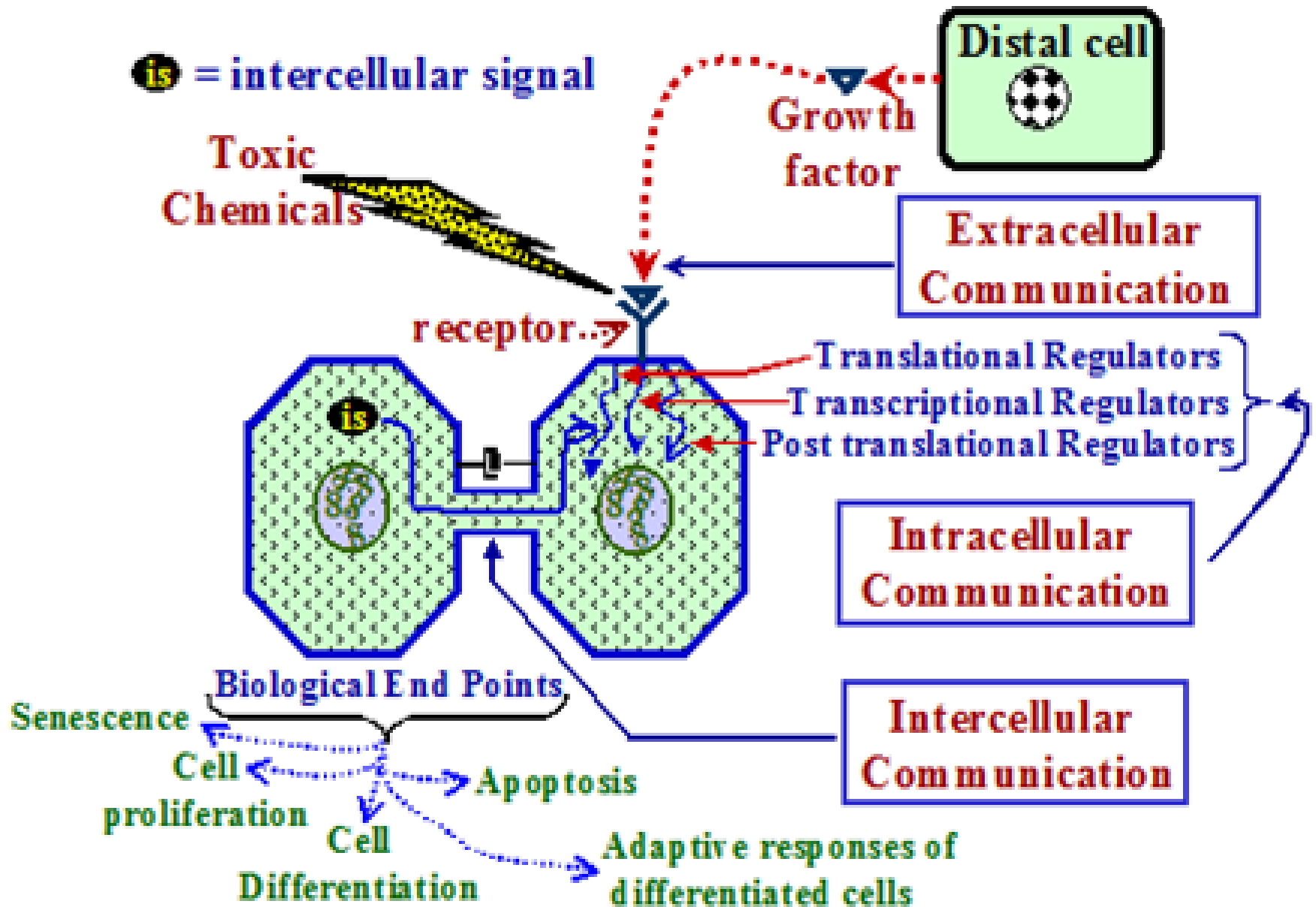
Global Incidence of Colon Cancer

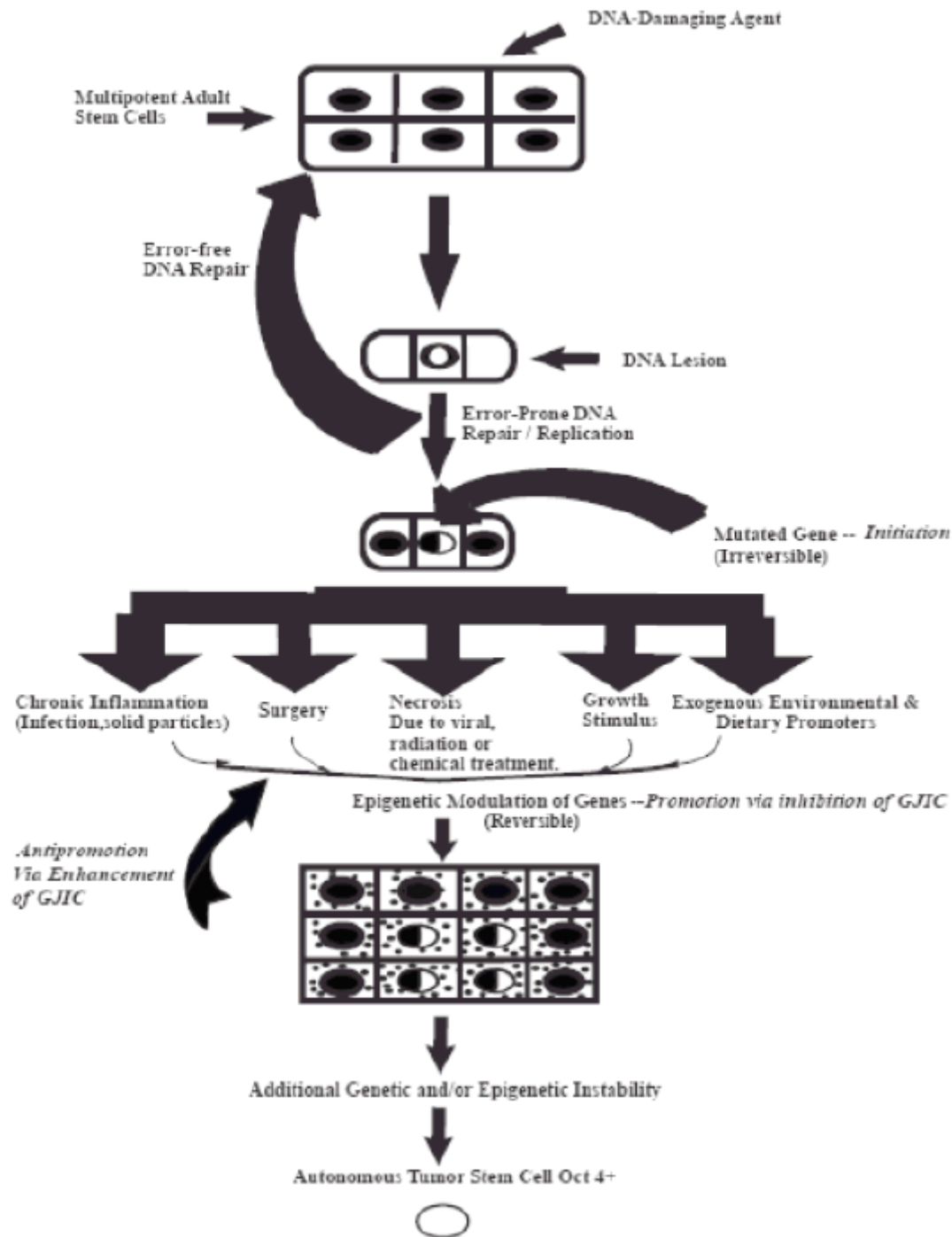




Consequence of Soy-Induced Differentiation of Bone-Stem Cells: BARKER HYPOTHESIS

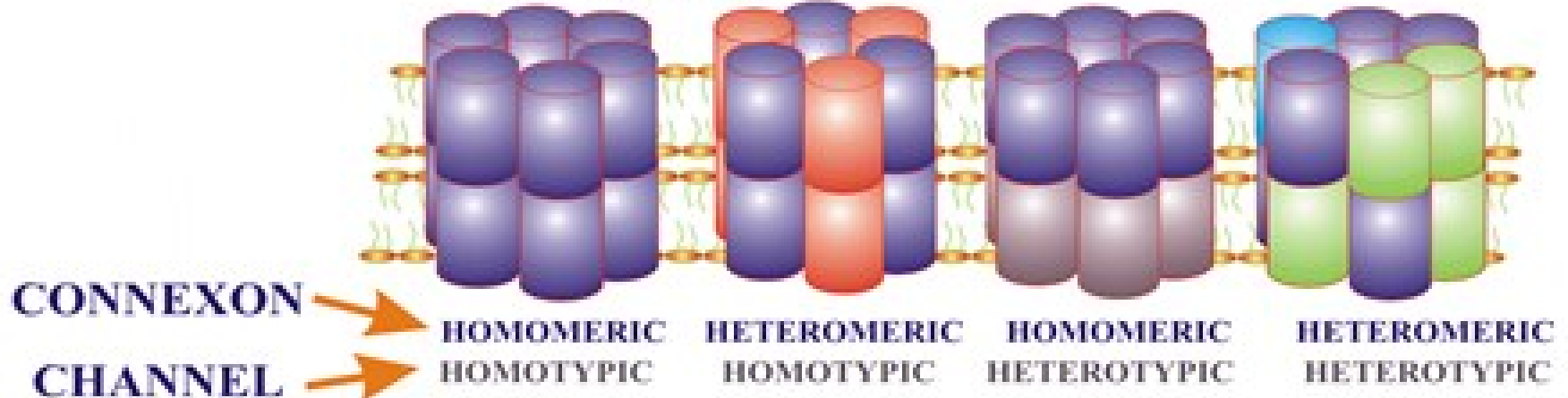
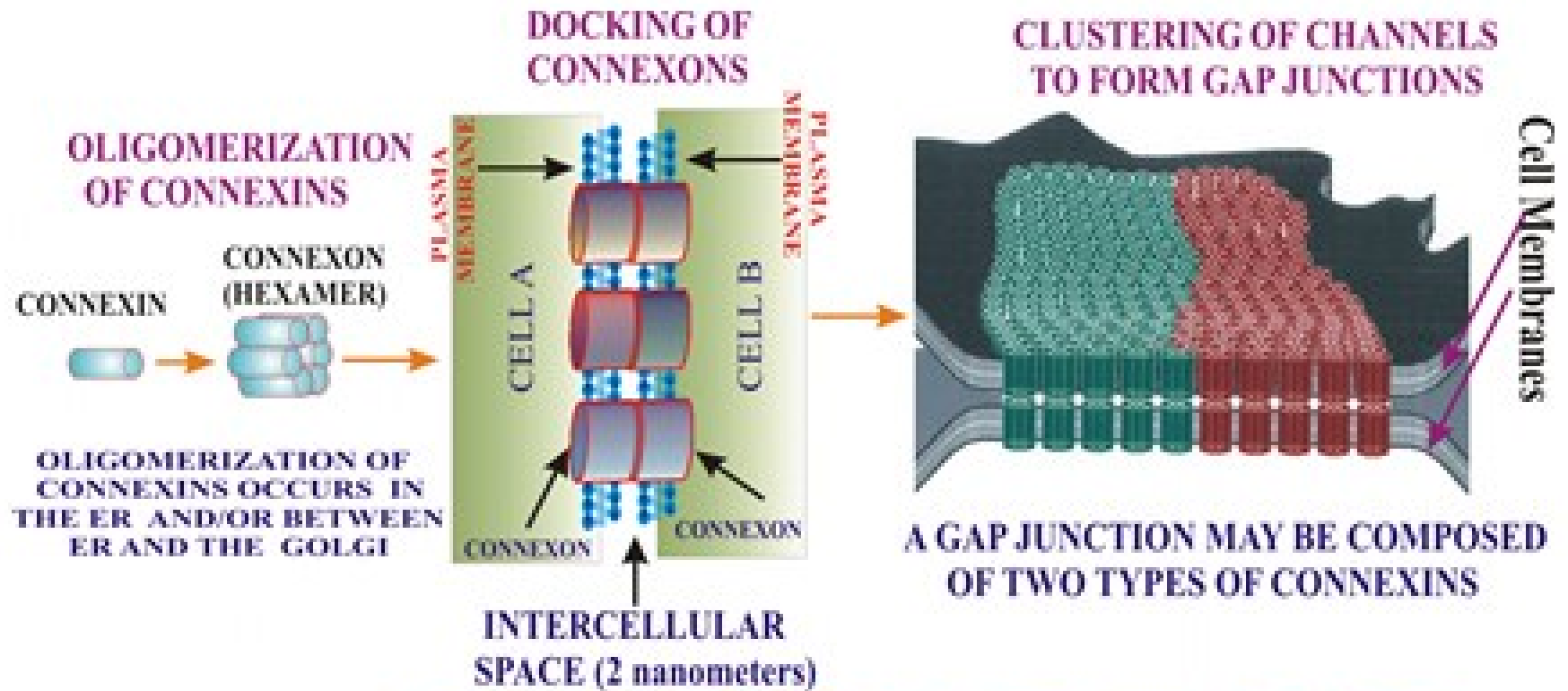
# Gap Junctions in Cellular Homeostasis



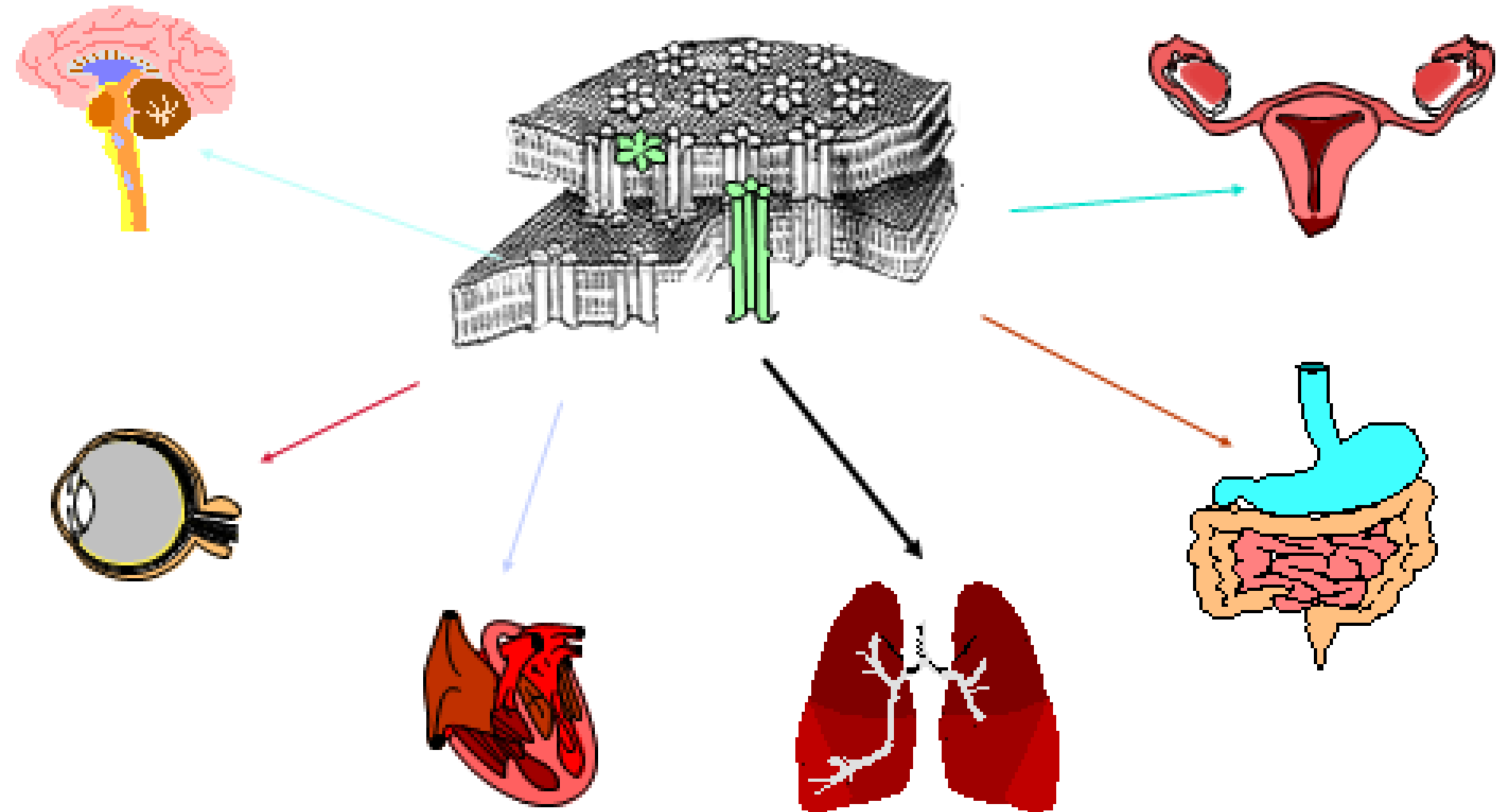




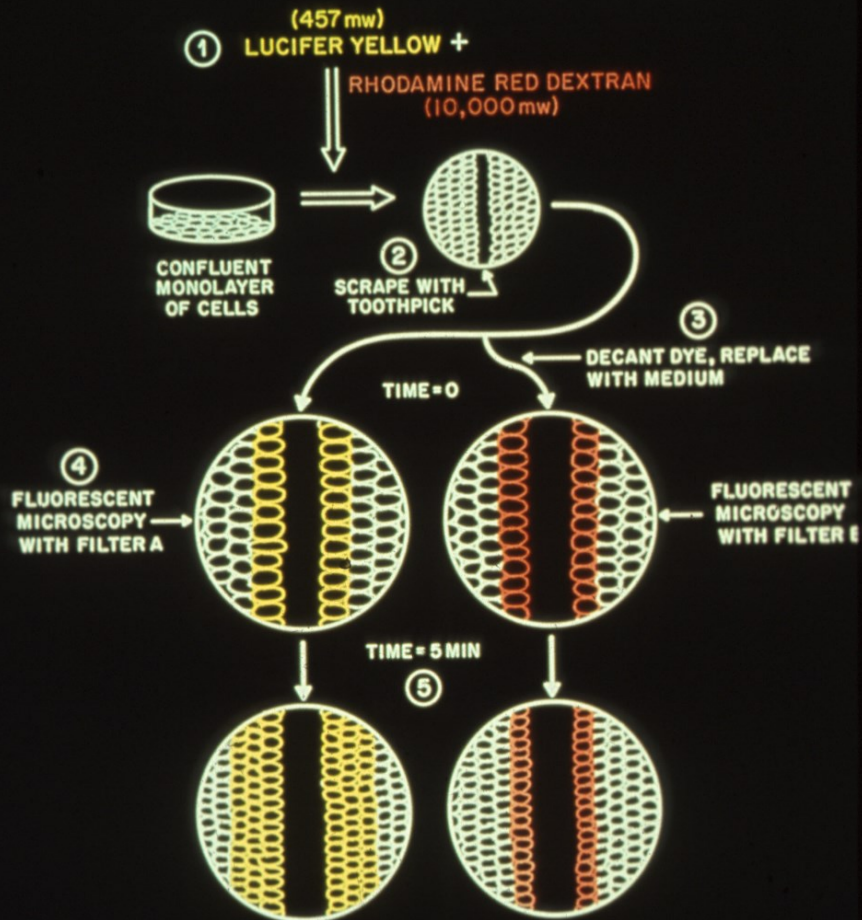
# GENESIS OF GAP JUNCTIONS



# GAP JUNCTION ROLES IN ORGAN HOMEOSTASIS

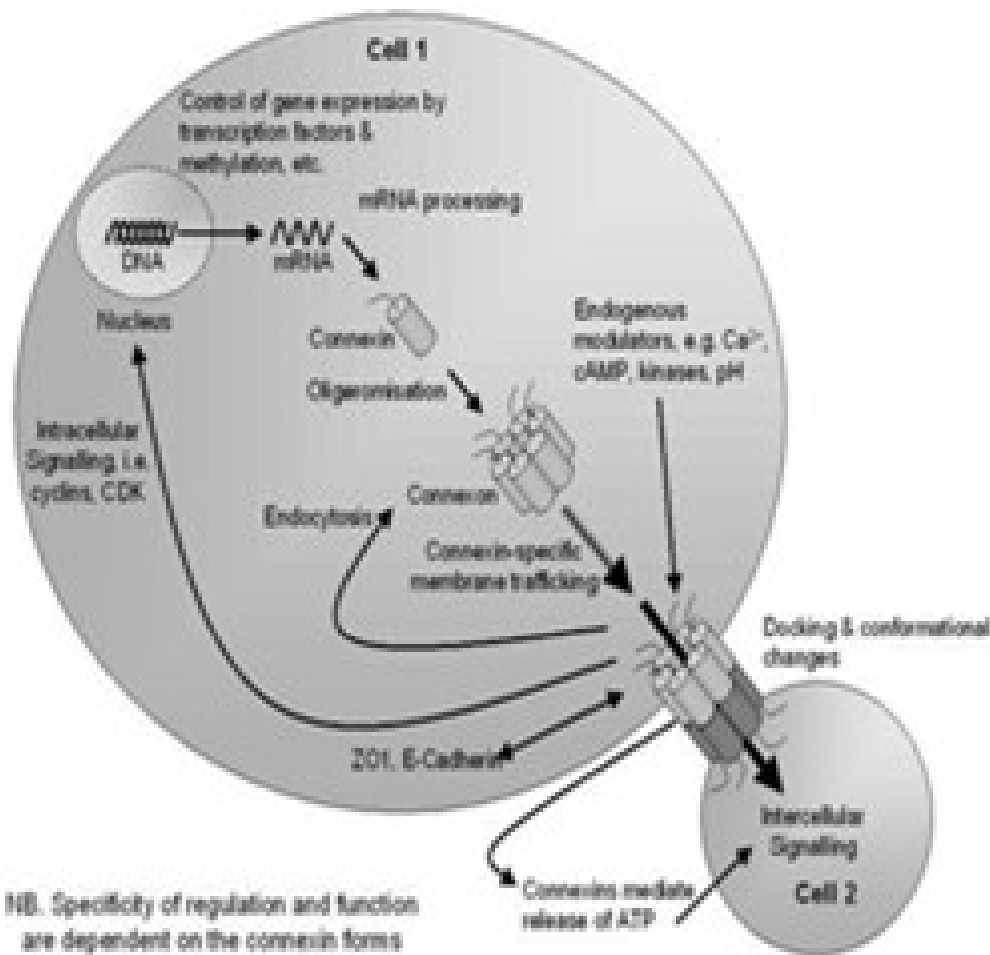


## Scrape Loading / Dye Transfer Technique

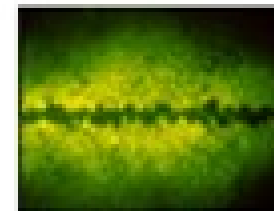


**PRINCIPLE:** If cells have gap junctional communication, Lucifer yellow will diffuse only thru gap junctions, rhodamine red dextran will not.

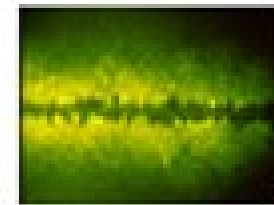
# THE MOLECULAR BIOLOGY OF MODULATED GAP JUNCTIONAL INTERCELLULAR COMMUNICATION



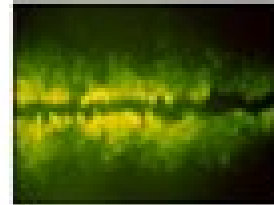
## Scrape Load/Dye Transfer Assay



0 ng/ml TPA



1 ng/ml TPA



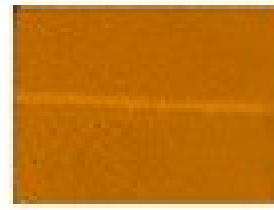
2 ng/ml TPA



4 ng/ml TPA

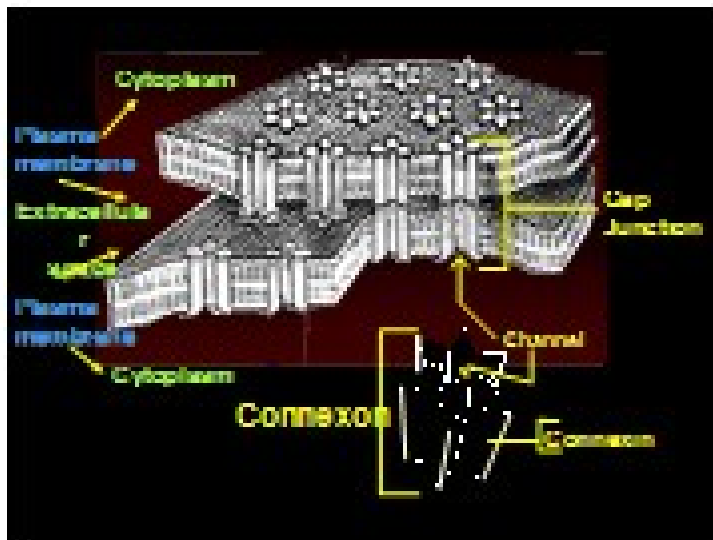


6 ng/ml TPA

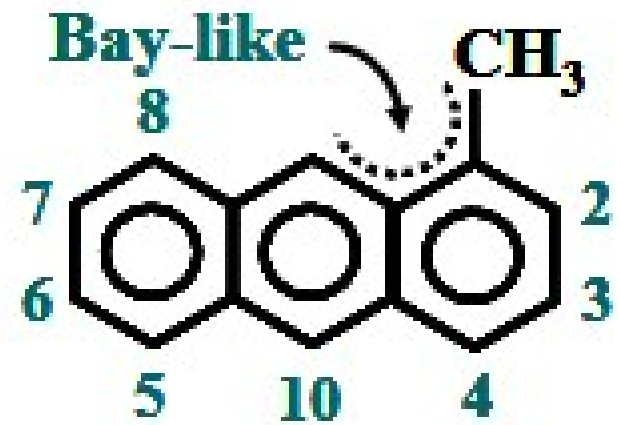
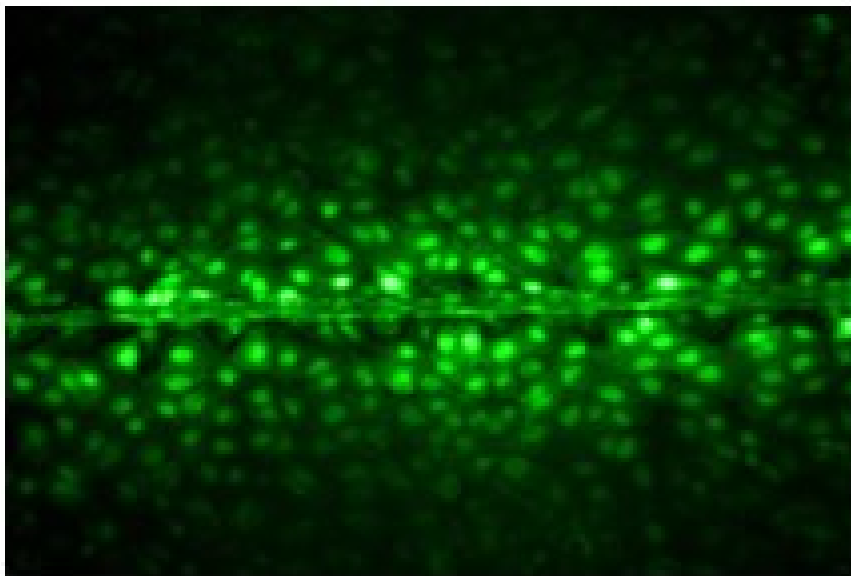


6 ng/ml TPA

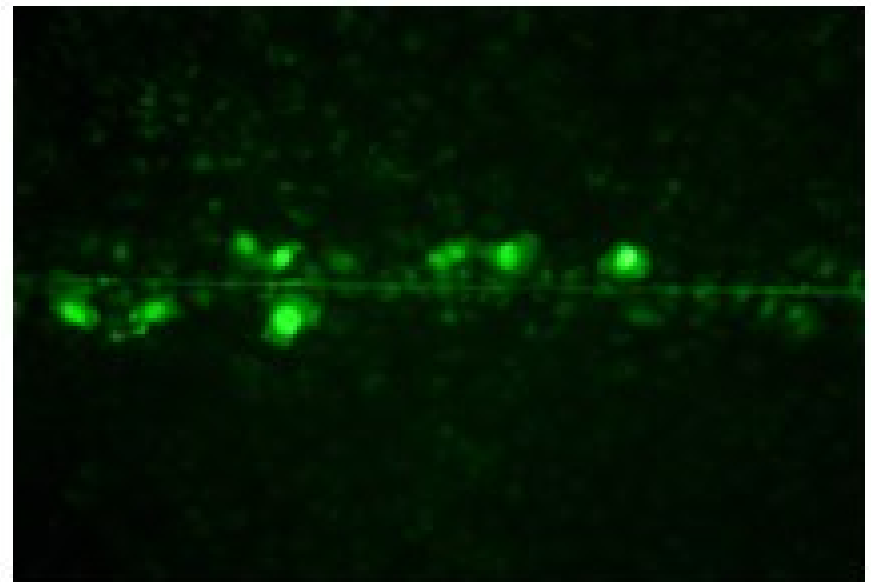
NB. Specificity of regulation and function are dependent on the connexin forms



vehicle



1-methylanthracene



# GJIC as a biomarker of chemopreventive effects

Natural chemopreventive chemicals known to modulate GJIC *in vivo* or *in vitro* (**Leone et al., Phytochem Rev, DOI 10.1007/s11101-012-9235-7 (2012)**)

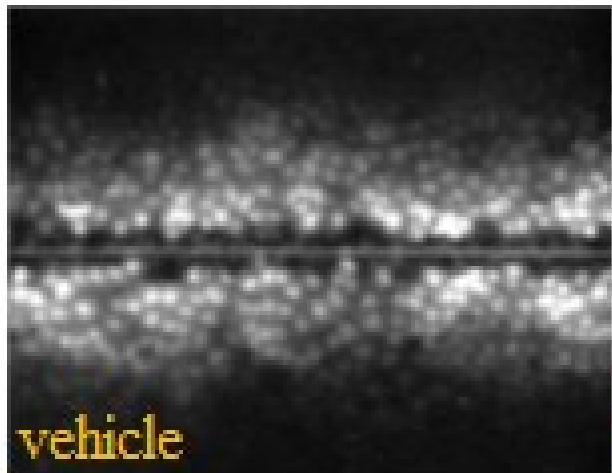
## Chemicals

- alpha- and beta-carotene, lutein, canthaxanthin
- lycopene
- fucoxanthin
- (-)-epigallocatechin-3-gallate (EGCG)
- (-)-epicatechin
- naringenin, apigenin, tangeretin
- genistein, quercetin, resveratrol, pterostillbene, gallic acid
- caffeic acid phenethyl ester
- indole-3-carbinol
- lovastatin
- beta-sitosterol
- ginsenosides

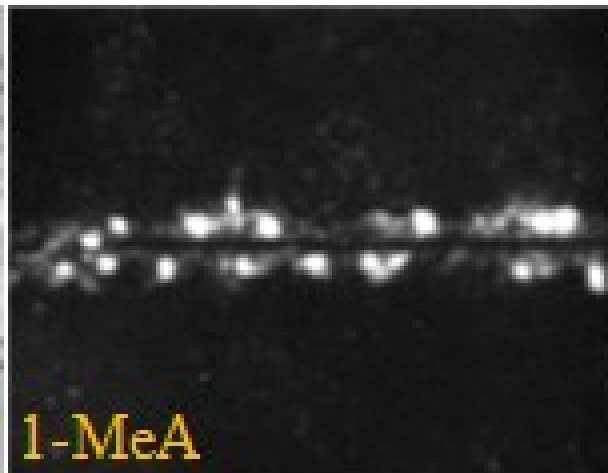
## Extracts

- supercritical-CO<sub>2</sub>-extracted oleoresins from tomato and tomato/grape seed
- cocoa polyphenol extract
- kiwifruit extract
- grape seed extract
- *Petasites japonicus* extract

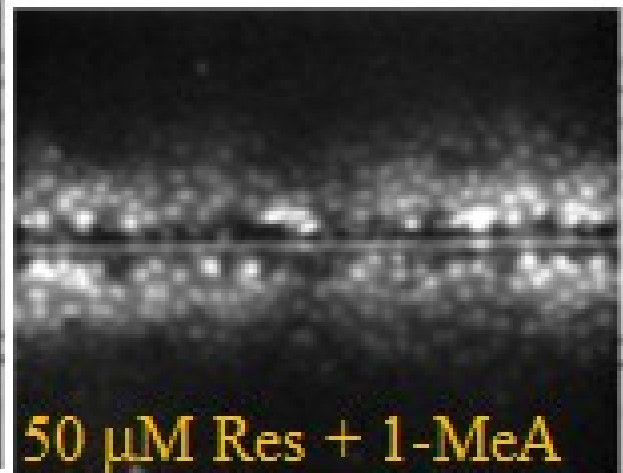
Could be *in vitro* assessment of GJIC a useful tool for identification of chemopreventive effects of chemicals?



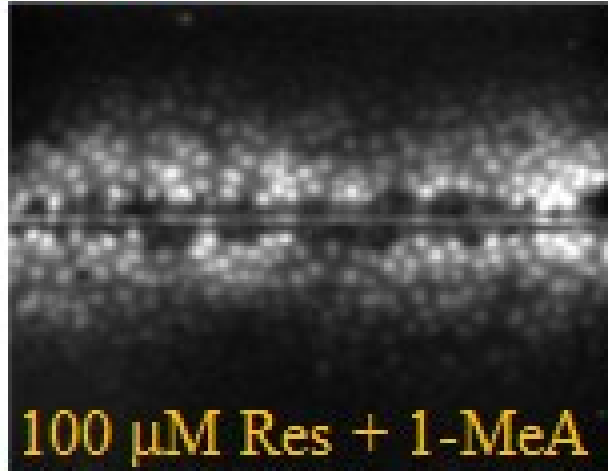
vehicle



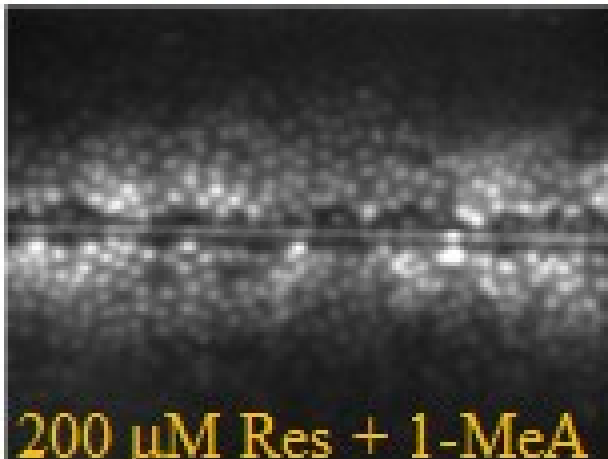
1-MeA



50  $\mu$ M Res + 1-MeA



100  $\mu$ M Res + 1-MeA



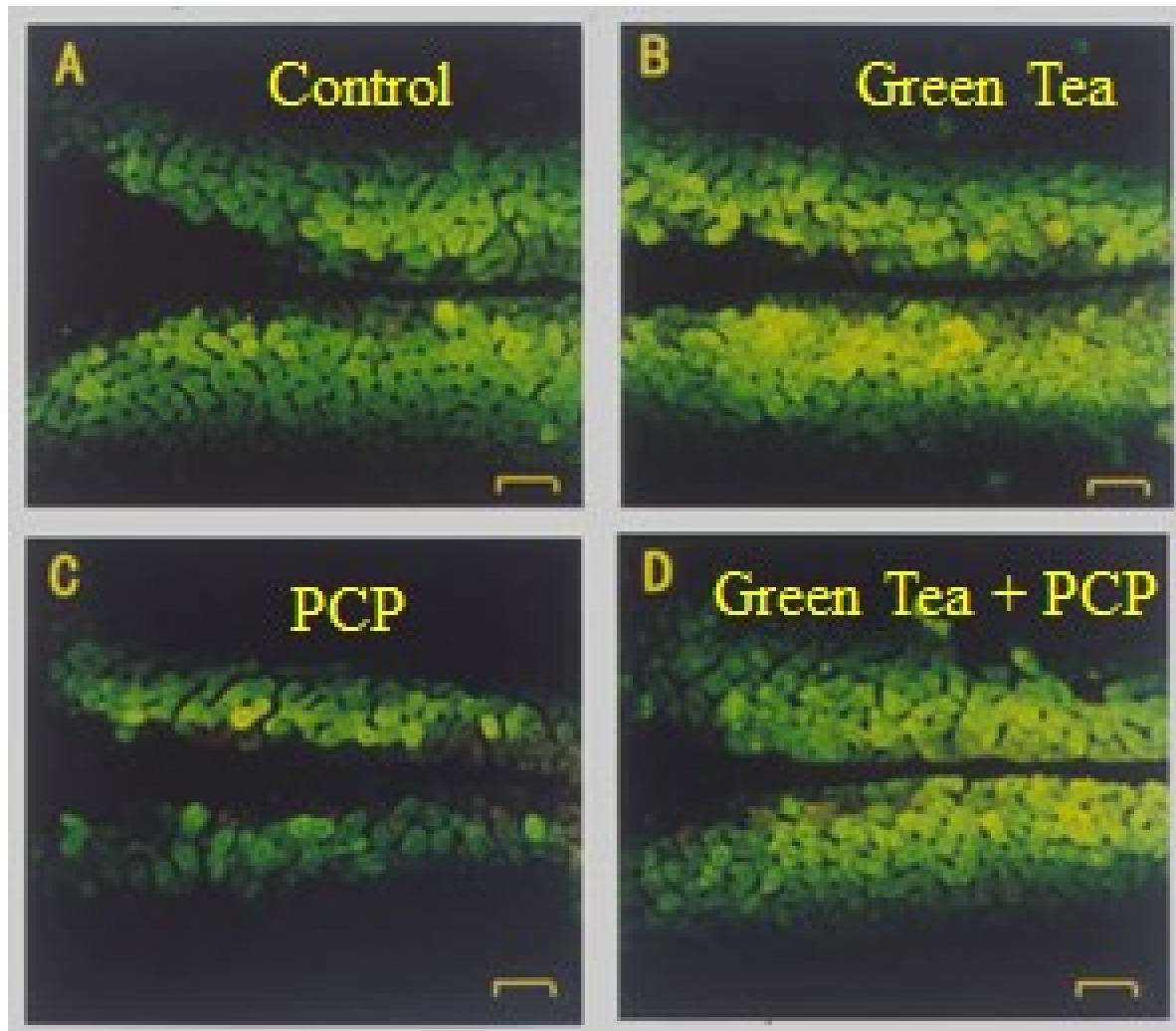
200  $\mu$ M Res + 1-MeA



**Resveratrol is a major antioxidant found in red wine and peanut products.**

**Consumption of 1.5 glasses red wine per day linked to the French Paradox**

# Rat liver in vivo cell-cell communication with and without exposure to PCP +/- green tea



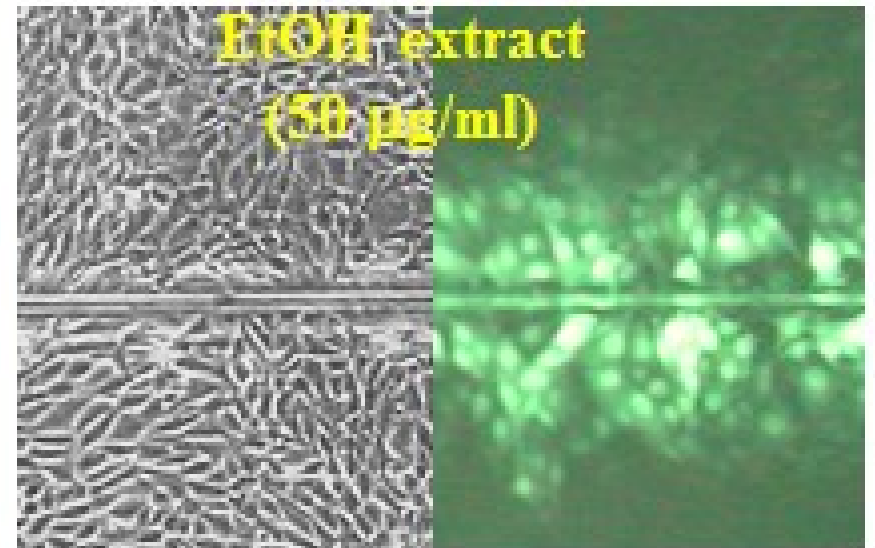
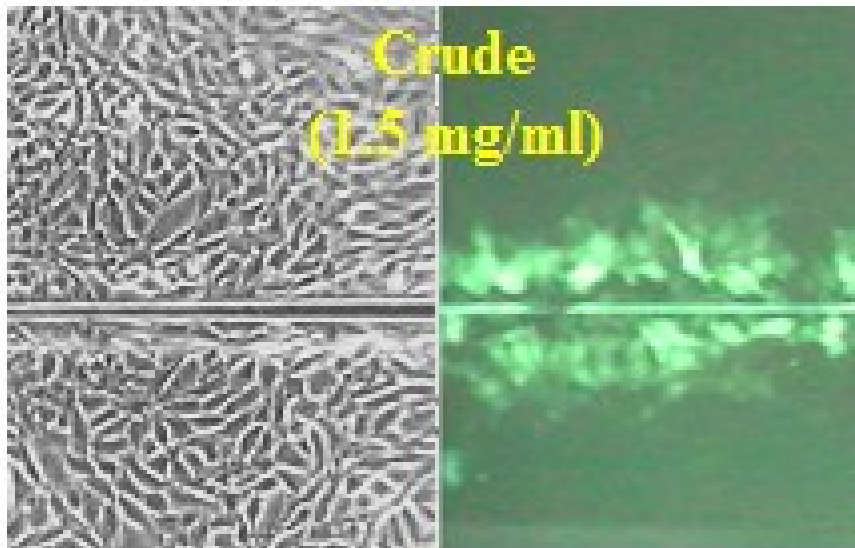
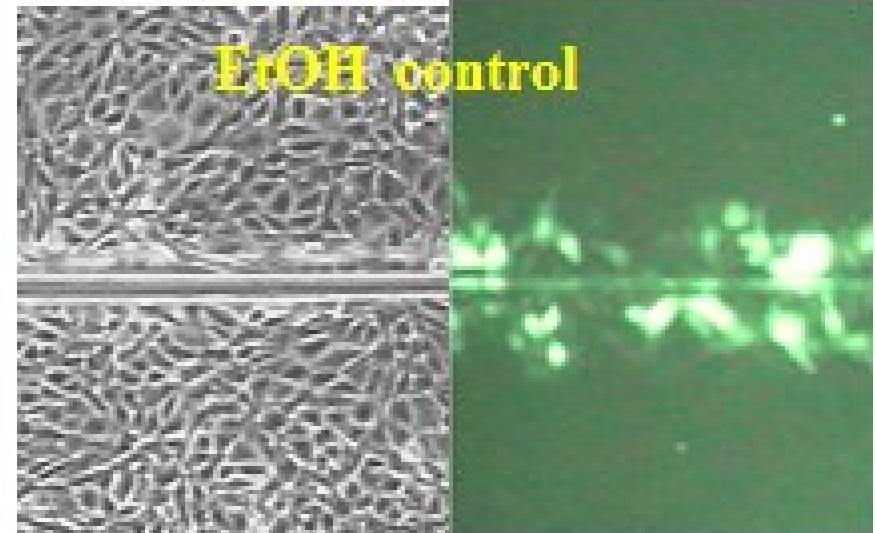
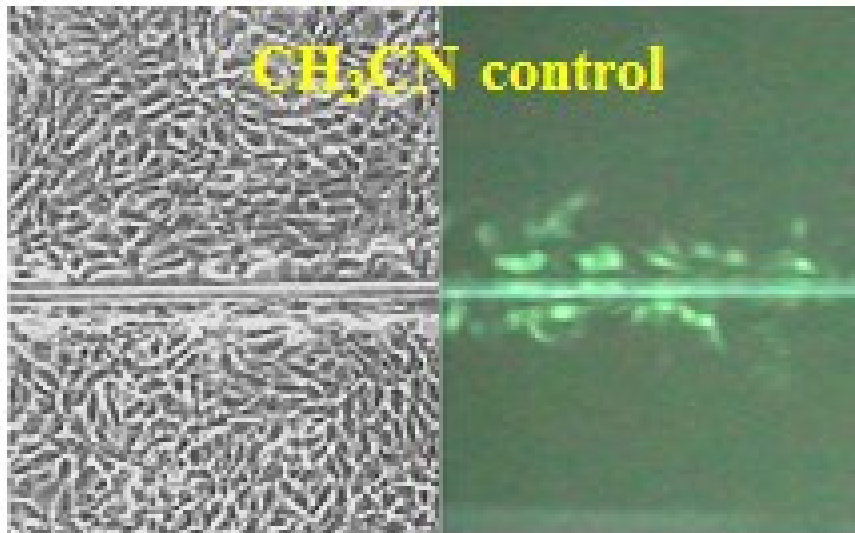


**Hsieh CY, & Chang, C.C. “Stem Cell Differentiation and Reduction as a Potential Mechanism for Chemoprevention of Breast Cancer. Clin Pharm J. 51: 15-30, 1999. [and inducer of osteoporis]**

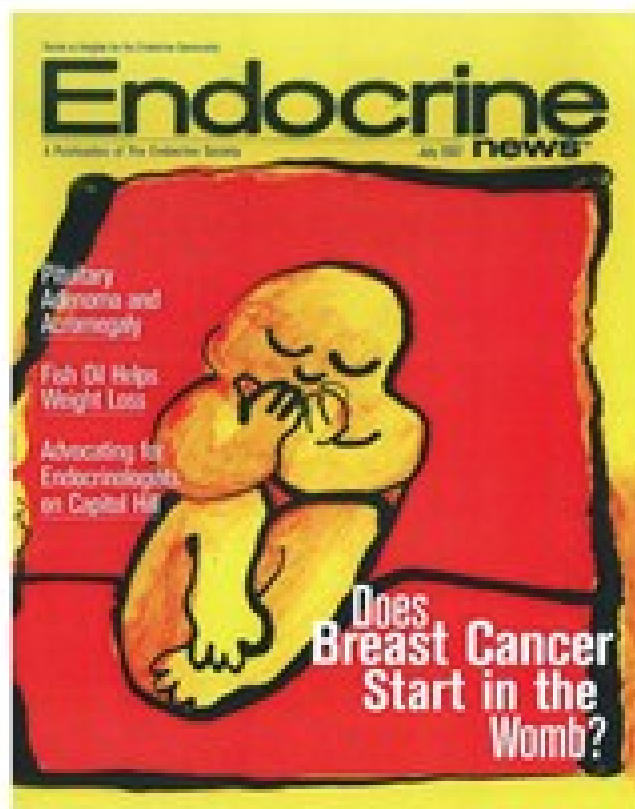
- **Genistein & Bowman-Birk Inhibitor as Bioactive Components of Soy Products**



# Restoration of normal GJIC in WB ras cells grown in psyllium for 48h



# The BARKER HYPOTHESIS: EARLY MODULATION OF ORGAN-SPECIFIC ADULT STEM CELLS CAN ALTER THE RISK TO DISEASES LATER IN LIFE

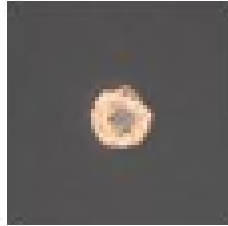


**BARKER HYPOTHESIS:** Adult Diseases are linked to Pre-natal and Early Post-Natal Life.

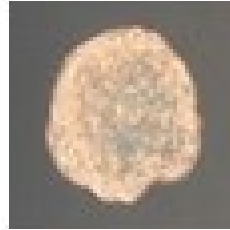
Size of spheres

BREAST TUMOR PROMOTERS

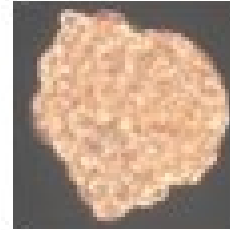
control



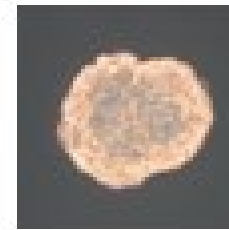
E2



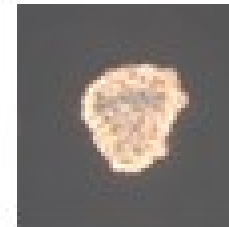
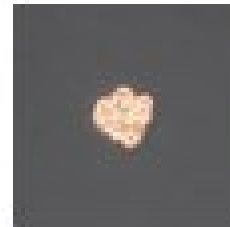
TCDD



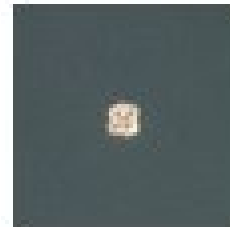
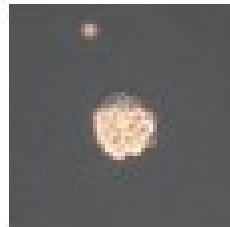
BPA



Non-M



M1



M10

BREAST CHEMOPREVENTIVE AGENTS

NC : Negative control

E2 : 10nM estrogen

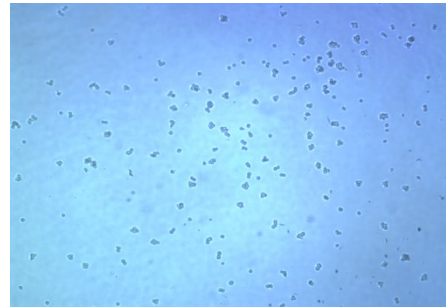
TCDD : 100nM

BPA : 10uM

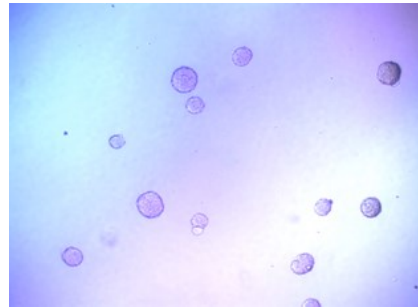
M1 : Metformin 1mM

M10 : Metformin 10mM

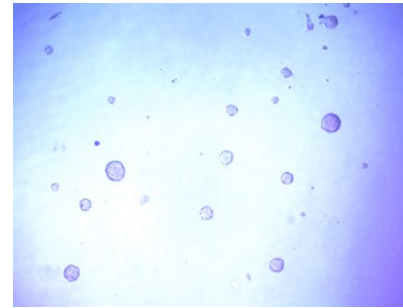
# Melatonin Effects on MCF-7 Mammospheres Treated with Estrogen or BPA



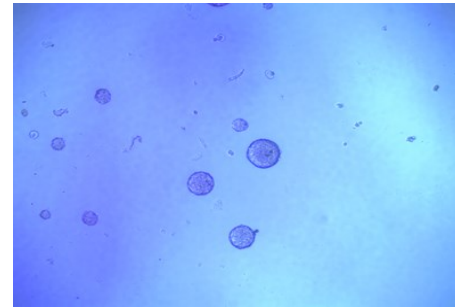
Control, Day 0



Control, Day 6

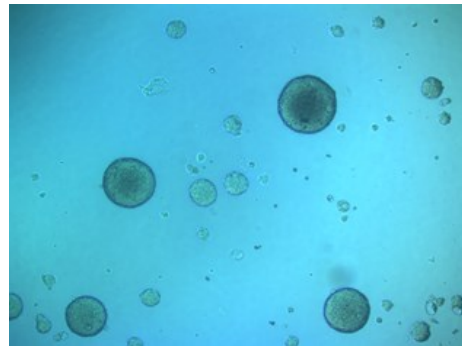


Vehicle ETOH, Day 6

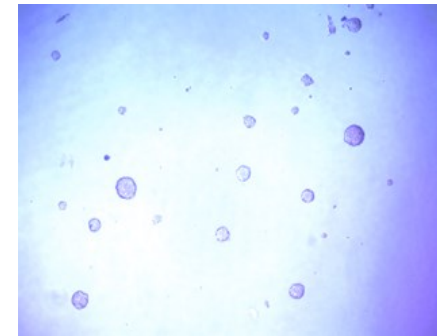


Melatonin, Day 6

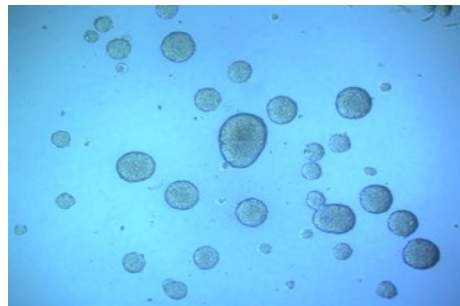
Estrogen, Day 6



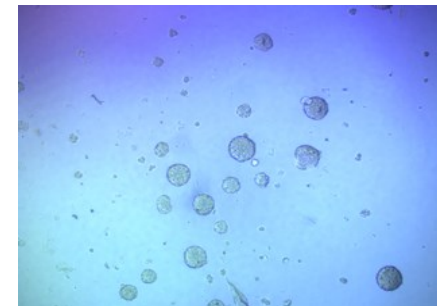
Estrogen +  
Melatonin



BPA, Day 6



BPA + Melatonin

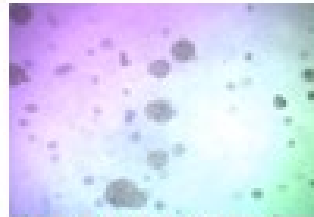


# SOFT AGAR GROWTH OF HUMAN BREAST CANCER STEM CELLS TREATED With TUMOR PROMOTERS & MELATONIN

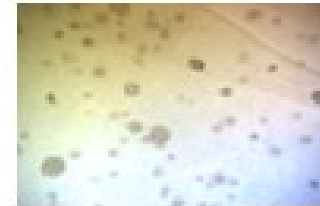
SOFT AGAR GROWTH OF HUMAN BREAST CANCER STEM CELLS TREATED With TUMOR PROMOTERS & MELATONIN



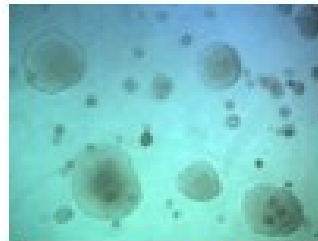
**CONTROL -D ZERO**



**CONTROL -D14**



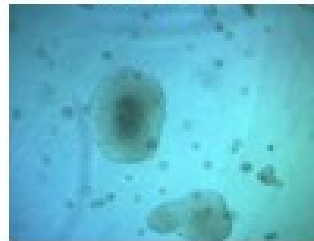
**Melatonin-D14**



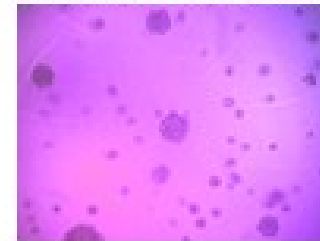
**E2 -D14**



**E2+ Melatonin-D-14**



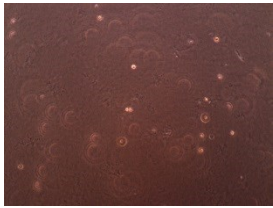
**BPA-D-14**



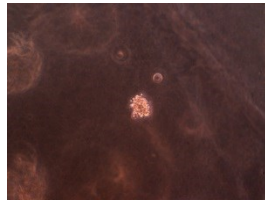
**BPA+Melatonin-D14**

# PANCREATIC CANCER (PANC-1) SOFT AGAR ASSAY WITH METFORMIN

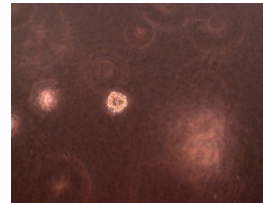
Day 1, Control Panc  
1



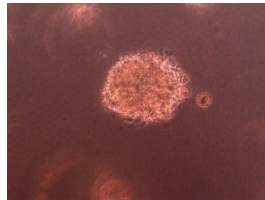
Day 9 control Panc1



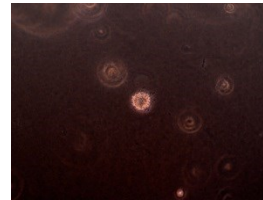
Day 9 Metformin Panc1



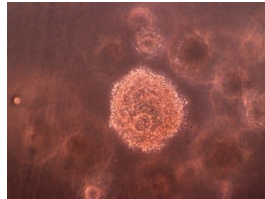
Day 9 BPA



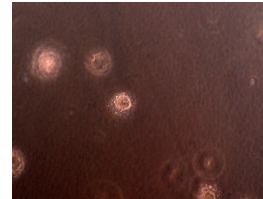
Day 9 BPA+MET



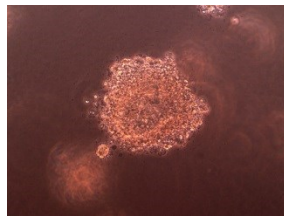
Day 9 1-MA



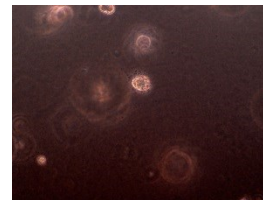
Day 9 1-MA+MET



Day 9 NNK



Day 9 NNK





# CONCLUSIONS



- BOTH THE **QUALITY & QUANTITY** OF ADULT STEM CELLS CAN BE DISRUPTED DURING IN UTERO DEVELOPMENT.
- HUMAN ADULT STEM CELLS ,WHICH ARE **NATURALLY IMMORTAL**, CAN BE BLOCKED FROM TERMINALLY DIFFERENTIATION (**INITIATED**) AND THEN CLONALLY AMPLIFIED (**PROMOTED**) BY HORMONES, INFLAMMATORY CYTOKINES, DIETARY FACTORS AND ENVIRONMENTAL EPIGENETIC CHEMICALS, WHICH REVERSIBLY INHIBIT **GAP JUNCTIONAL INTERCELLULAR COMMUNICATION**.
- THIS DISRUPTION CAN LEAD TO EITHER AN **INCREASE OR DECREASE IN THE RISK** TO CHRONIC DISEASES LATER IN LIFE.
- THE DISRUPTION CAN BE INFLUENCED BY THE INTERACTION OF GENETIC FACTORS WITH ENVIRONMENTAL, DIETARY, PHARMACEUTICAL, MICROBIAL, LIFE STYLE AGENTS DURING PREGNANCY.



“When diet is wrong, medicine  
is of no use. When diet is  
correct, medicine is of no  
need”

Ancient Ayurvedic Proverb