

“METFORMIN INHIBITS THE GROWTH OF HUMAN CARCINOMA (MCF-7) MAMMOSPHERE CELLS PROMOTED BY ESTROGEN, TCDD and BISPHENOL- A”

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RATIONALE FOR STUDY

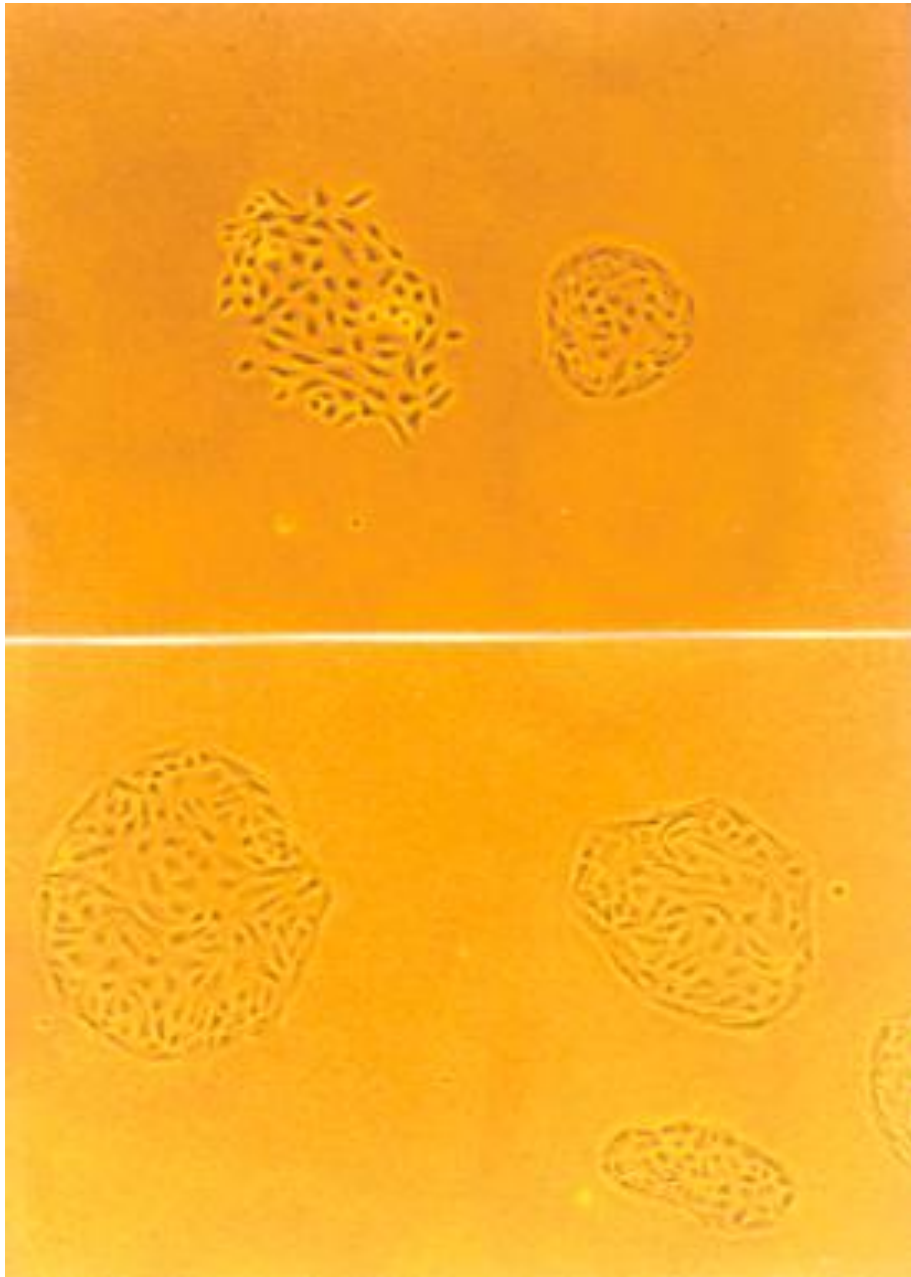
1. **THERE IS A GLOBAL EPIDEMIC OF THE “METABOLIC DISEASES”, DIABETES and CARDIOVASCULAR DISEASE.**
2. **EPIDEMIOLOGICALLY, DIABETES –ASSOCIATED CANCERS, e.g., BREAST, LIVER & PANCREATIC, HVE BEEN SHOWN TO BE REDUCED IN THOSE METFORMIN-TREATED PATIENTS.**
3. **RECENTLY, IN A DANISH EPIDEMIOLOGICAL STUDY, CARDIOVASCULAR DISEASES WERE SIGNIFICANTLY REDUCED IN METFORMIN –TREATED TYPE 2 PATIENTS.**

ERGO,

“CAN METFORMIN , AT NON-CYTOTOXIC CONCENTRATIONS, AFFECT THE GROWTH OF HUMAN ESTROGEN_RECEPTOR POSITIVE, MCF7 CARCINOMA CELLS GROWN in 3-DIMENSION AS “MAMMOSPHERES” and TREATED WITH KNOWN ESTROGENIC TUMOR PROMOTERS?”

ASSUMPTIONS AND HYPOTHESIS

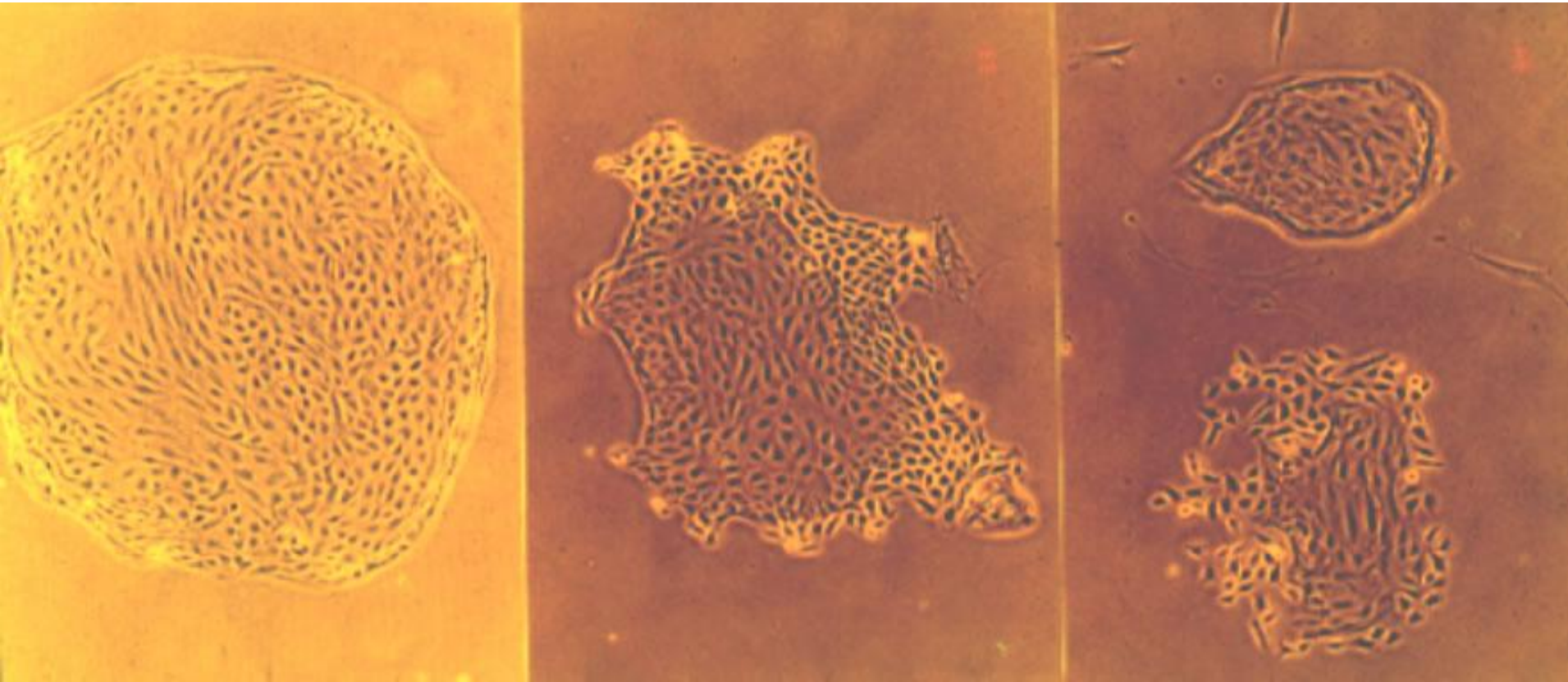
- **ALL CANCERS, SUCH AS HUMAN BREAST CANCERS AND BREAST CANCER CELL LINES, ARE A MIXTURE OF “CANCER STEM CELLS” and “CANCER NON-STEM CELLS”**
- **OCT4 A GENE IS A MOLECULAR MARKER FOR BOTH NORMAL AND CANCER STEM CELLS, BUT NOT “CANCER NON-STEM CELLS”**
- **NORMAL HUMAN BREAST ADULT STEM CELLS EXPRESS OCT4A & ESTROGEN RECEPTOR, BUT NOT CONNEXIN 43, AS DO MCF-7 CELLS.**



**HME-11: Two types
(Type I and Type II)
of normal human
breast epithelial cells**

**Pure cultures of
Type I cells**

Differentiation Pathway of Normal Human Breast Epithelial Cells In Vitro



Type I

Type I–Type II-1

Type I–Type II-1

GJIC in Human Breast Epithelial Cells (HBEC)

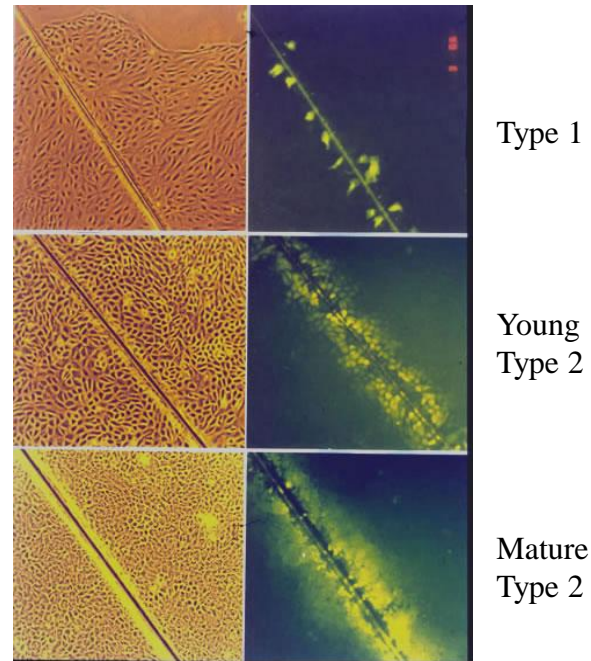


Figure 2. Scrape-loading dye transfer assay (SL/DT) to examine the GJIC in human breast epithelial cells. Type 1 cells were deficient in GJIC (A). Young (B) and mature (C) Type 2 cells were efficient in GJIC. Detail methods were described previously. Lucifer yellow solution was loaded into the cells by making two or three scrape lines on the monolayer with a sharp scalpel. In GJIC-competent cells, Lucifer yellow moves through gap junctions from the primary dye loaded cells to contacting neighboring cells, whereas in GJIC-incompetent cells the dye does not transfer from the primary dye loaded cells to the neighboring cells.

Lobule Type 1 and Organoid Formed in Matrigel



In Vivo

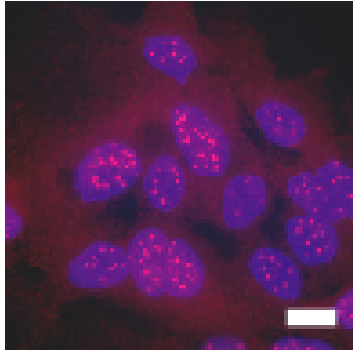


In Vitro

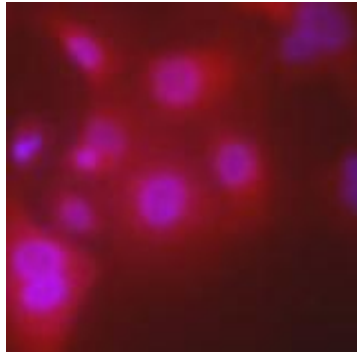


Oct4 expression in human breast stem cells and tumor cell lines

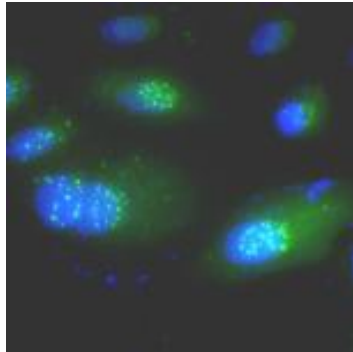
stem cell
(Type 1)



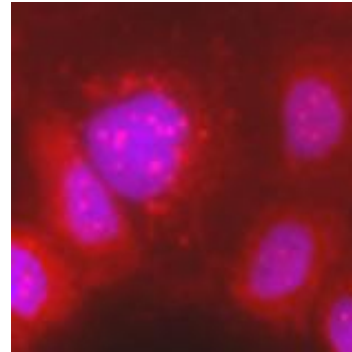
differentiated
(mature type 2)



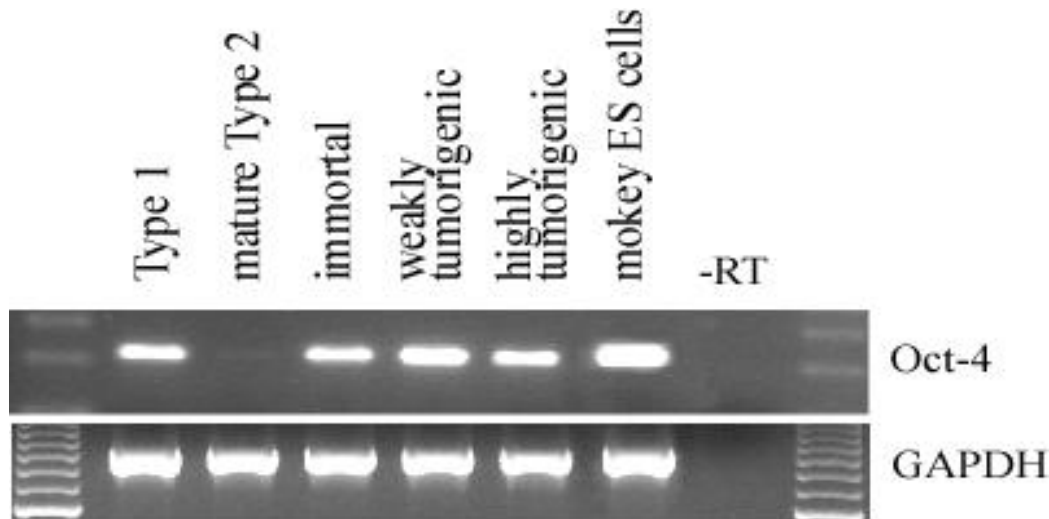
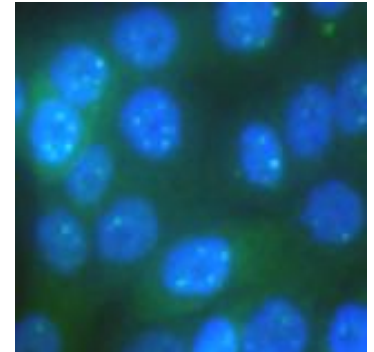
immortal



weakly
tumorigenic

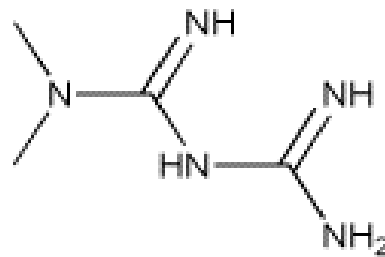
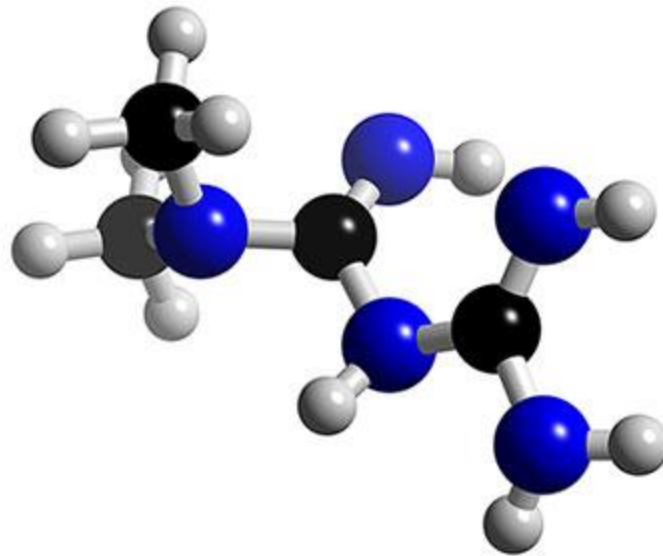


highly
tumorigenic



STRUCTURE OF METFORMIN, a biguanides

Believed to work by inhibiting hepatic glucose production and increasing the sensitivity of peripheral tissues to insulin. It lowers body weight and does not cause hypoglycemia

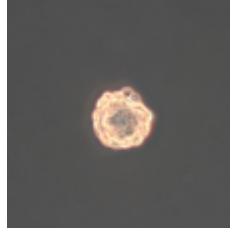


Chemical Formula: $C_4H_{11}N_5$

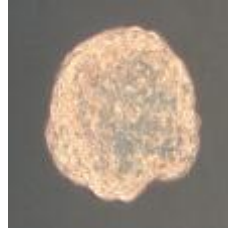
Size of spheres

BREAST TUMOR PROMOTERS

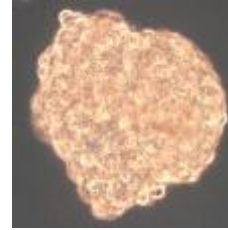
control



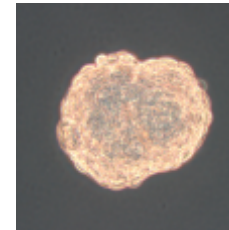
E2



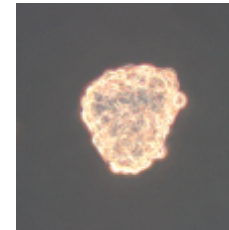
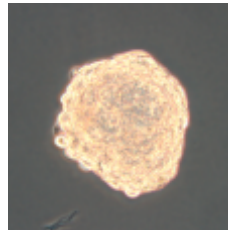
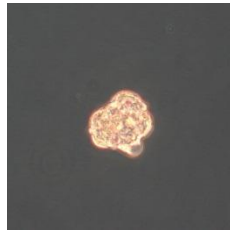
TCDD



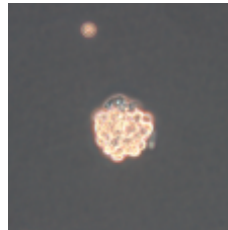
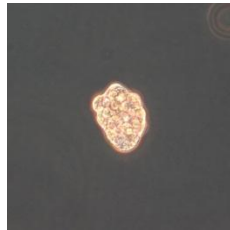
BPA



Non-M



M1



M10

BREAST CHEMOPREVENTIVE AGENTS

NC : Negative control

E2 : 10nM estrogen

TCDD : 100nM

BPA : 10uM

M1 : Metformin 1mM

M10 : Metformin 10mM

CONCLUSION

- **THE ESTROGENIC COMPOUNDS PROMOTED GROWTH OF HUMAN BREAST MAMMOSPHERES CONCENTRATIONS.**
- **METFORMIN INHIBITED THE PROMOTING EFFECTS OF THE ESTROGENIC COMPOUNDS, ALBEIT AT HIGH CONCENTRATIONS IN VITRO.**
- **THERE MIGHT BE SOME PREVENTIVE BENEFIT FROM THE USE OF METFORMIN IN NON- SYMTOMATIC, PRE- DISPOSED AND BREAST CANCER PATIENTS.**