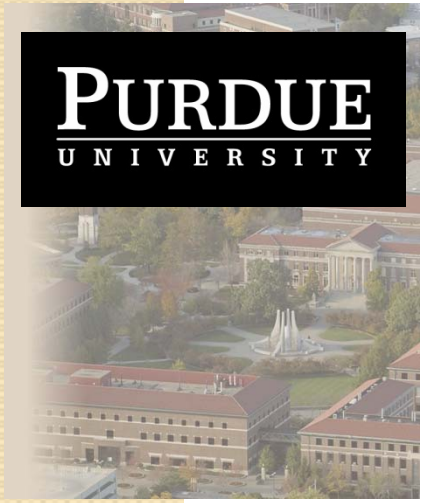
international breast cancer & nutrition
working together for prevention
http://www.purdue.edu/dp/oncological/ibcn.php

Obesity and Energy Metabolism in Breast Cancer Progression Using Molecular Tools



Dorothy Teegarden, Ph.D.

Professor and Associate Dean for Research,

Department of Nutrition Science

College of Health and Human Sciences

Obesity and Cancer

Prospective Study

900,000 men and women

Excess Weight Linked to

16 years

90,000 US Cancer Deaths Annually!

- Uterus
- Kidney
- Esophagus
- Gallbladder
- colon and rectum
- Breast
- Liver
- Pancreas
- Prostate
- Cervix
- Ovary
- Stomach (men)
- Non-Hodgkin Lymphoma
- Multiple Myeloma
- Rectum cancer

Excess body fat may account for ¼ to ½ of the occurrence of many frequent cancers

Calle, E; NEJM 348:1625-1638, 2003; Taubes, Science 335, 2012; IARC, 2002

Postmenopausal Women Obesity is Associated with Increased Risk for Breast Cancer

- Smallest vs largest waist circumference reduces risk by 24%

- Reducing weight reduces risk

Harvie, et al., Obes Rev 2003;4:157-73.
Trentham-Dietz, et al. Cancer Causes Control 2000;11:533-42.
Harvie, et al., Cancer Epidemiol Biomarkers Prev 2005;14:656-61.
Eliassen, et al., JAMA 2006;296:193-201.

Premenopausal Women
Breast Cancer Risk

Reduced risk with increased weight

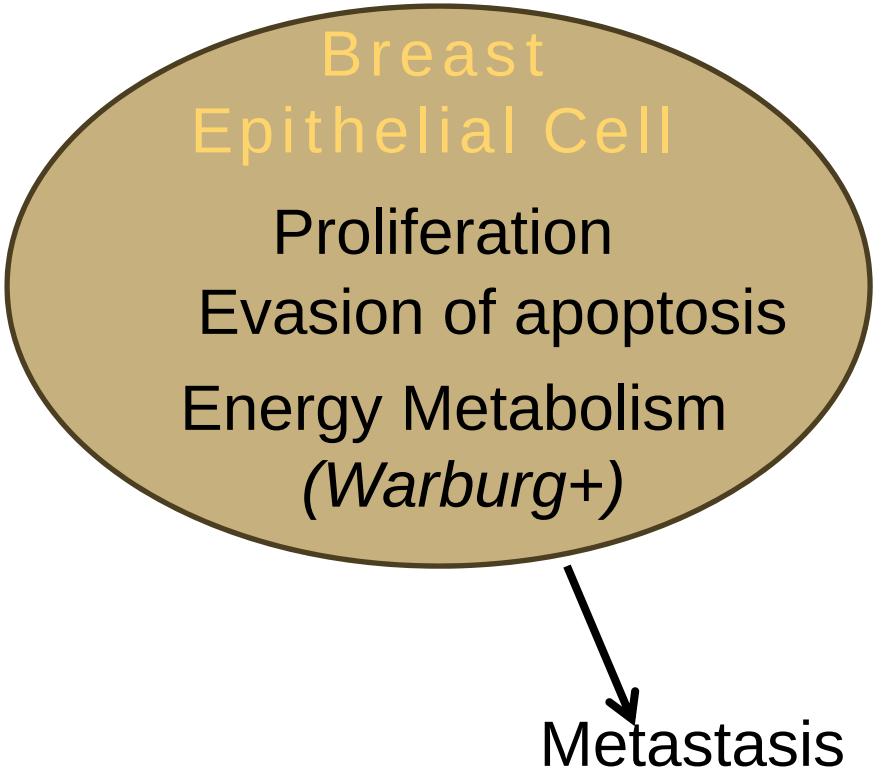
but

obesity in premenopausal is associated with aggressive tumor phenotype

Berstad, et al. Cancer Epidemiol Biomarkers Prev 2010;19:1532-44

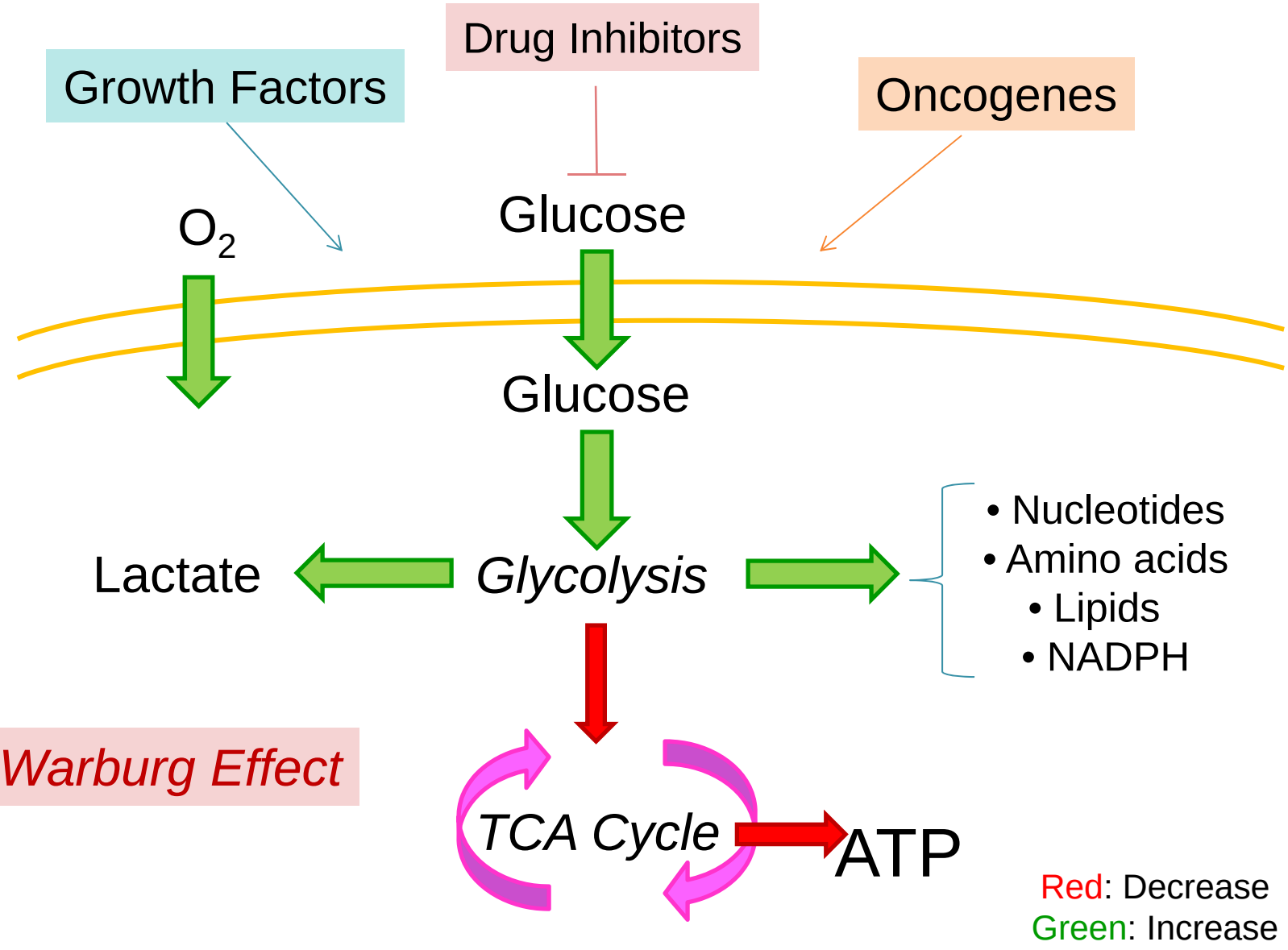
Obesity and Breast Cancer: Global and Complex

Obesity and Energy Metabolism
Mechanistic Links

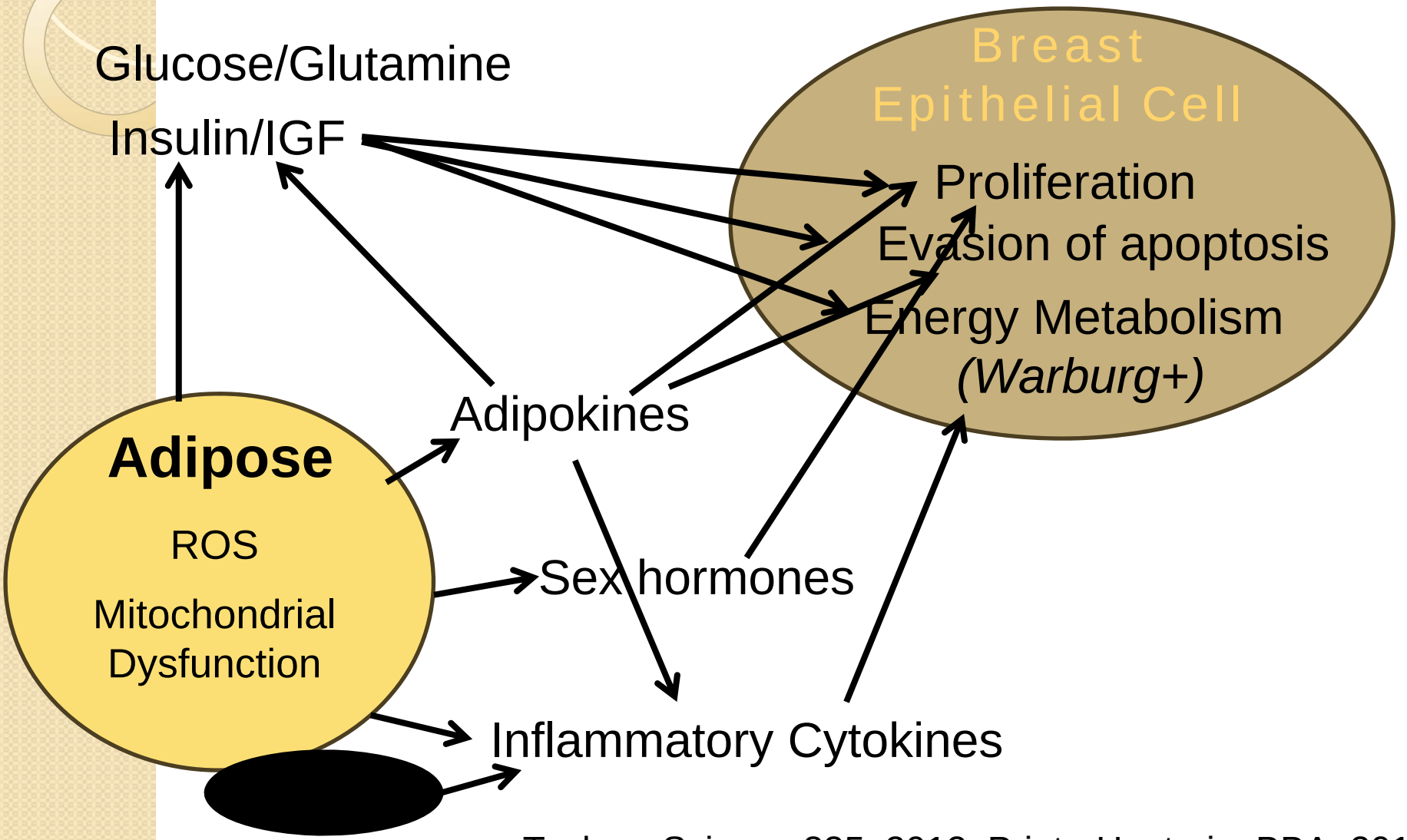


Taubes, Science 335, 2012; Prieto-Hontoria, et al., BBA, 2011;
Yang, H et al., Clin. Exp. Metastasis 22, 2005.

Metabolic Reprogramming in Proliferating and Cancer Cells



Obesity and Energy Metabolism
Mechanistic Links

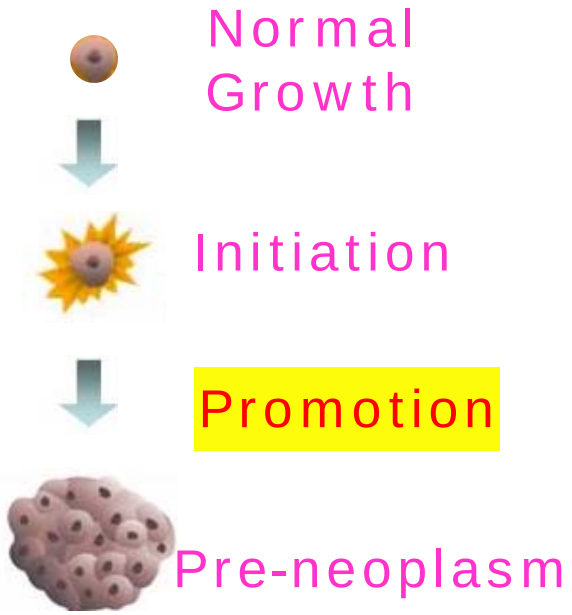


Taubes, Science 335, 2012; Prieto-Hontoria, BBA, 2011

Breast Cancer Prevention and Energy Metabolism *Cell Model*

MCF10A Human Breast Epithelial cells:

- MCF10A cells (untransformed)
- MCF10A-*ras* cells
  (Harvey-*ras* oncogene transfected,
  30% of all cancer)



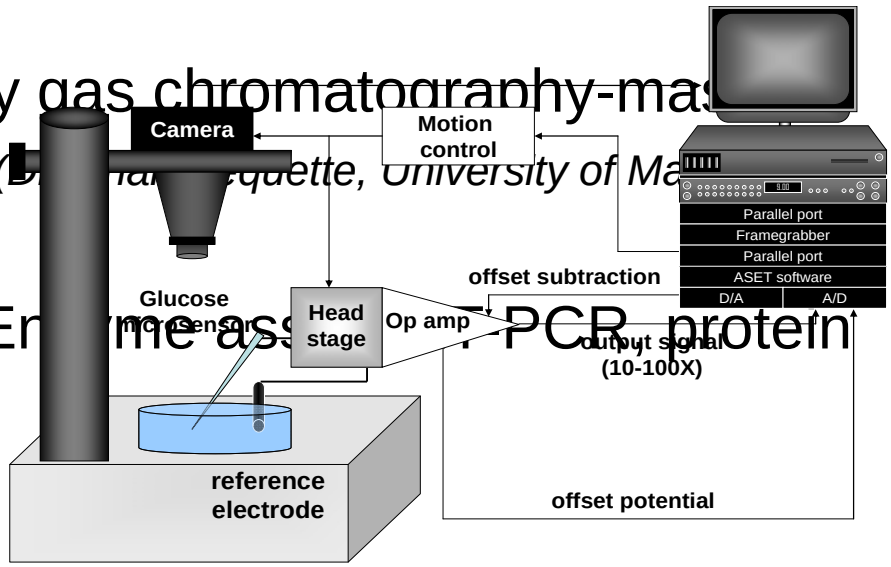
Approaches for Studying Cellular Glucose Metabolism

- Real-time trans-membrane glucose/oxygen flux measurement *(Dr. Marshall Porterfield, Bindley Bioscience Center, Purdue)*
  - Highly sensitive micro biosensor in self-referencing mode
  - Enzyme-based nanoprobe

- Metabolic profiling by nuclear magnetic resonance (NMR) analysis *(Dr. Daniel Raftery, University of Washington)*

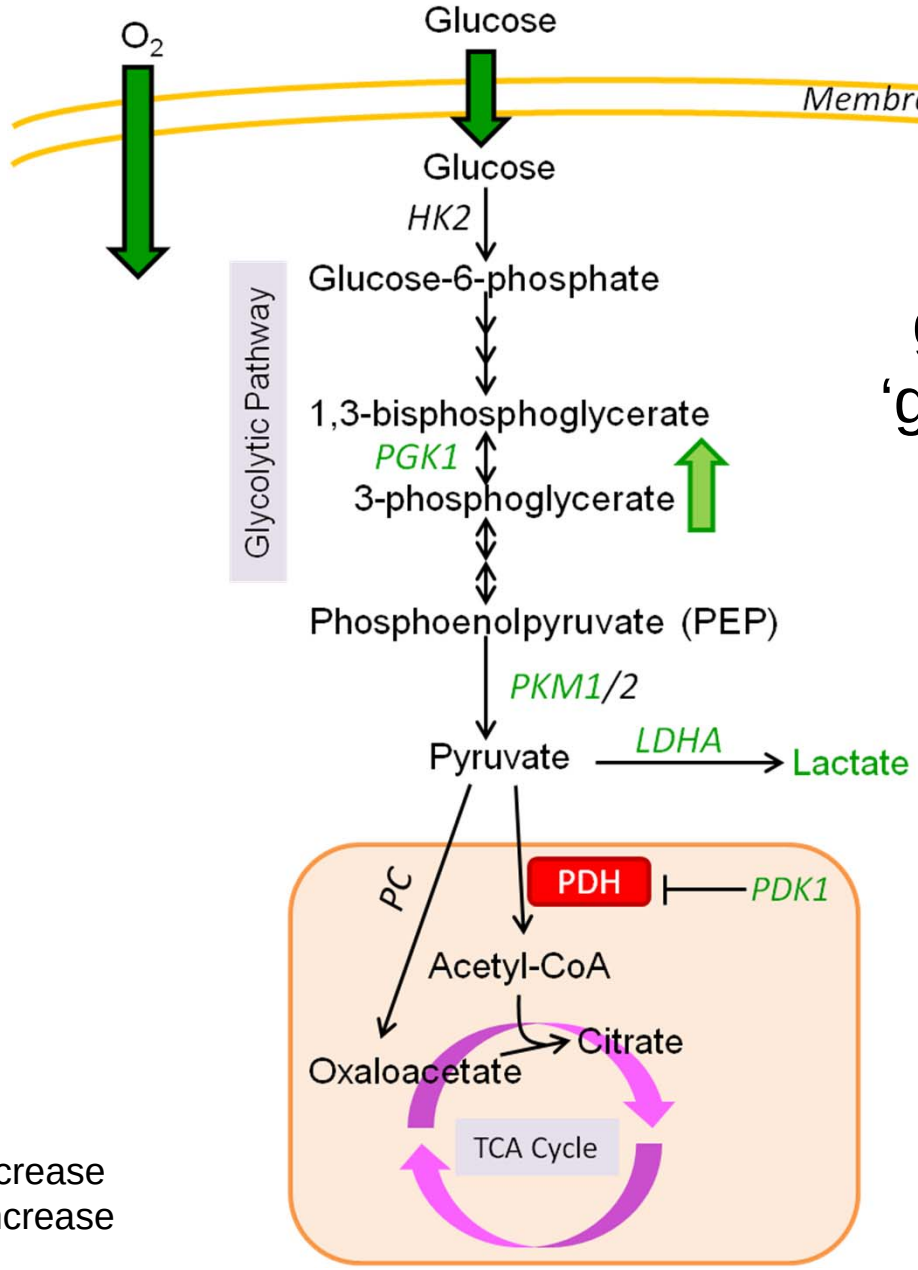
- [$^{13}C_6$]glucose kinetics by gas chromatography-mass spectrometry (GC-MS) *(Dr. [illegible]equette, University of Ma[illegible]*

- Biochemical methods: Enzyme assay, PCR, protein expression, etc.



McLamore et al. *Biosens Bioelectron (2010)*

Alterations in Glucose Metabolism in MCF10A-*ras* cells



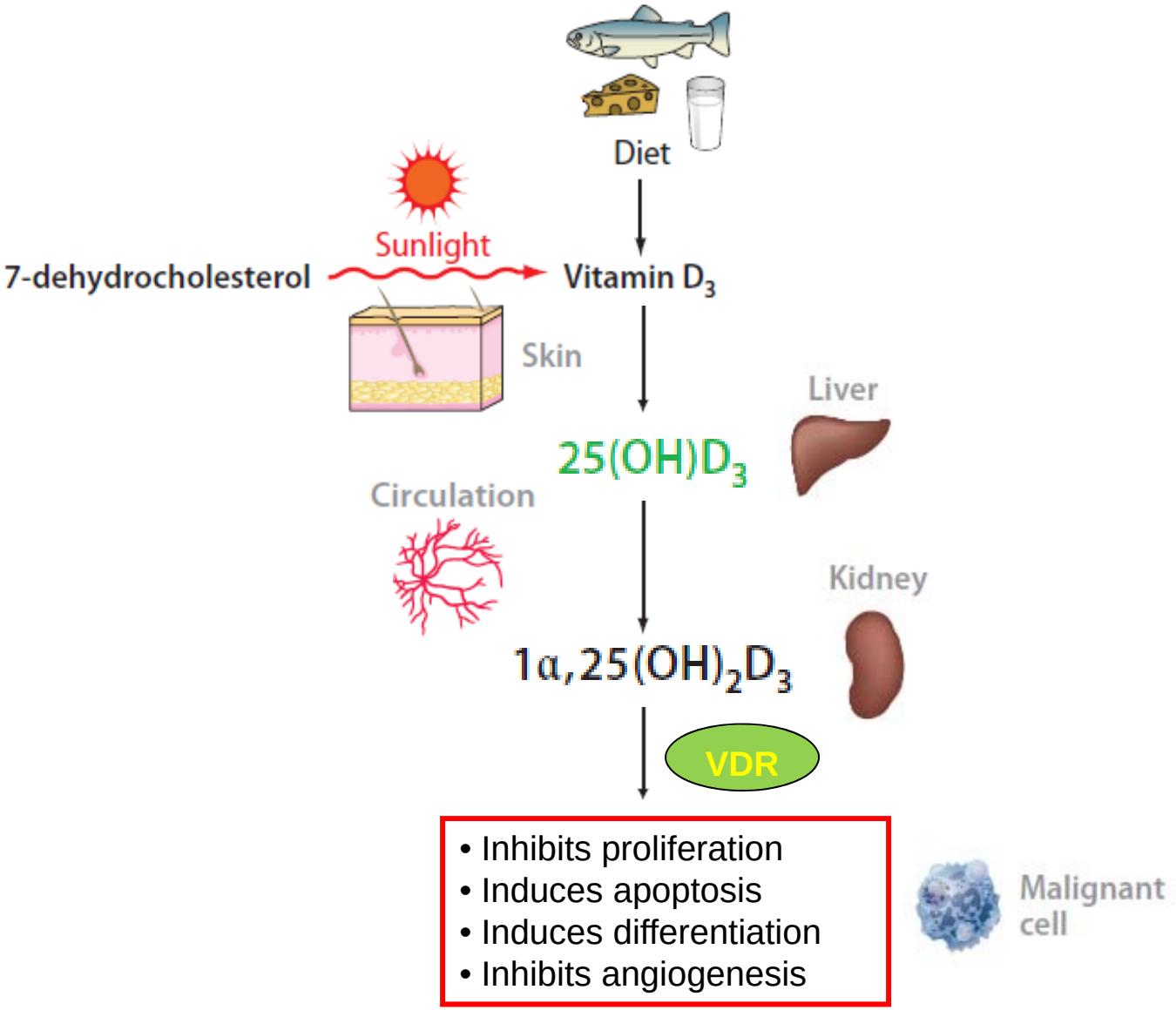
Need for higher glucose levels = 'glucose addiction'

Red: Decrease
Green: Increase

Enzyme Abbreviations:
- HK: Hexokinase
- PGK1: Phosphpglycerate kinase 1
- PKM: Pyruvate kinase
- LDH: Lactate dehydrogenase
- PDH: Pyruvate dehydrogenase
- PDK1: Pyruvate dehydrogenase kinase 1
- PC: Pyruvate carboxylase

Zheng et al. 2013, Mol Carcinog.

Anticancer Effects of Vitamin D

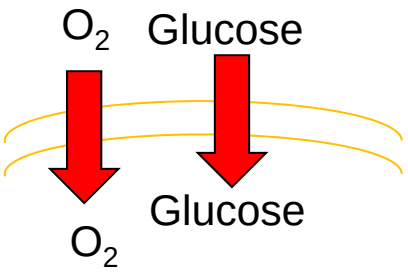


Kirshnan & Feldman, 2011

$1,25(OH)_2D$ Reduces Oxygen Uptake in MCF10A-*ras* Cells

Nanoprobes

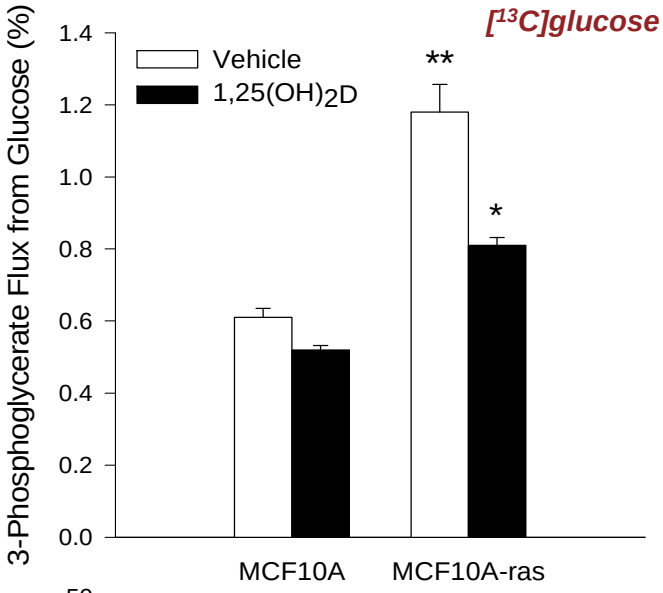
$1,25(OH)_2D$ Reduces Glucose Uptake in Response to Increasing Glucose in MCF10A-*ras* Cells

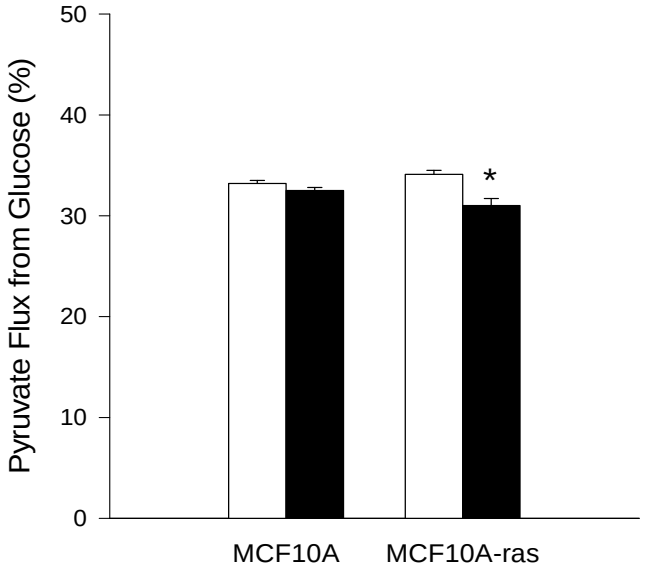


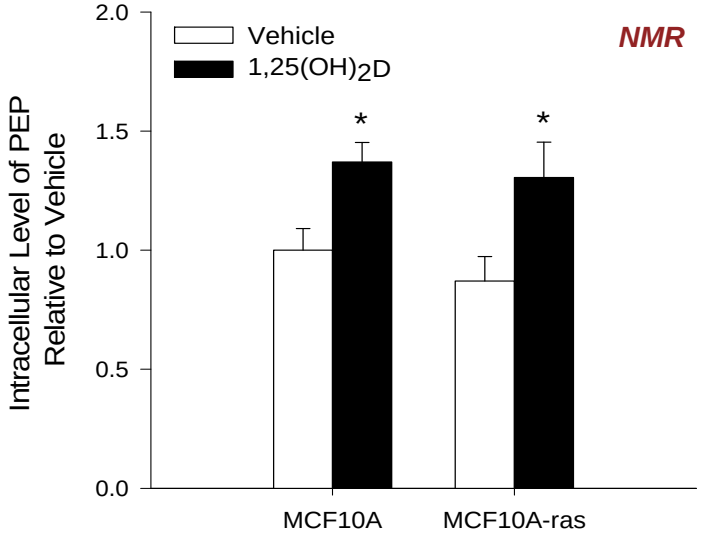
* Statistically significant relative to vehicle of the same cell type, P< 0.05.
** Significant difference between MCF10A-*ras* and MCF10A cells treated with vehicle (P < 0.05).

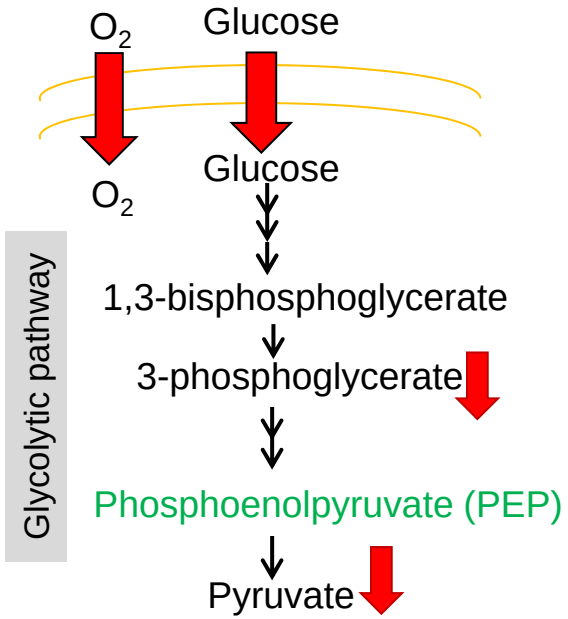
Zheng et al. 2013, JSBMB. 138C:81

1,25(OH)$_2$D Reduces Glycolytic Flux in MCF10A-*ras* Cells





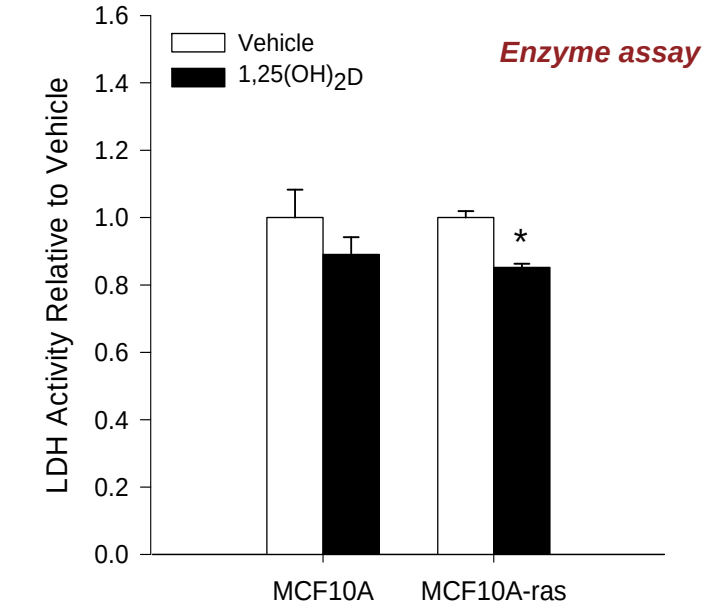


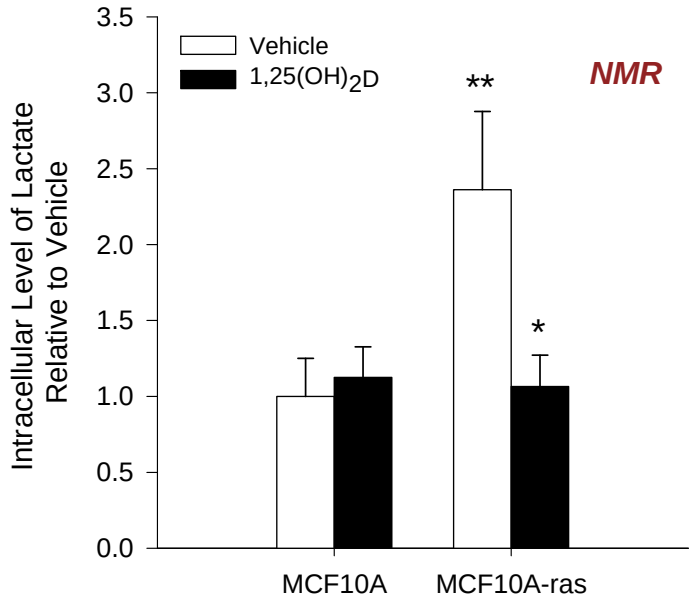


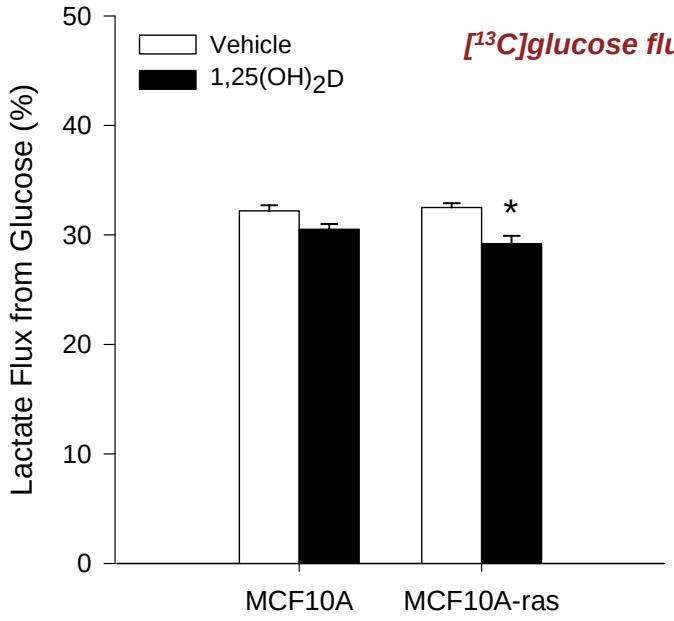
* Statistically significant relative to vehicle of the same cell type, P< 0.05.

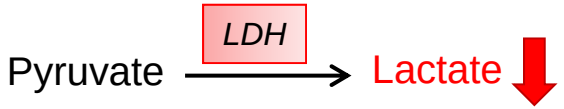
Zheng et al. 2013, JSBMB. 138C:81

1,25(OH)$_2$D Reduces Lactate Production in MCF10A-*ras* Cells







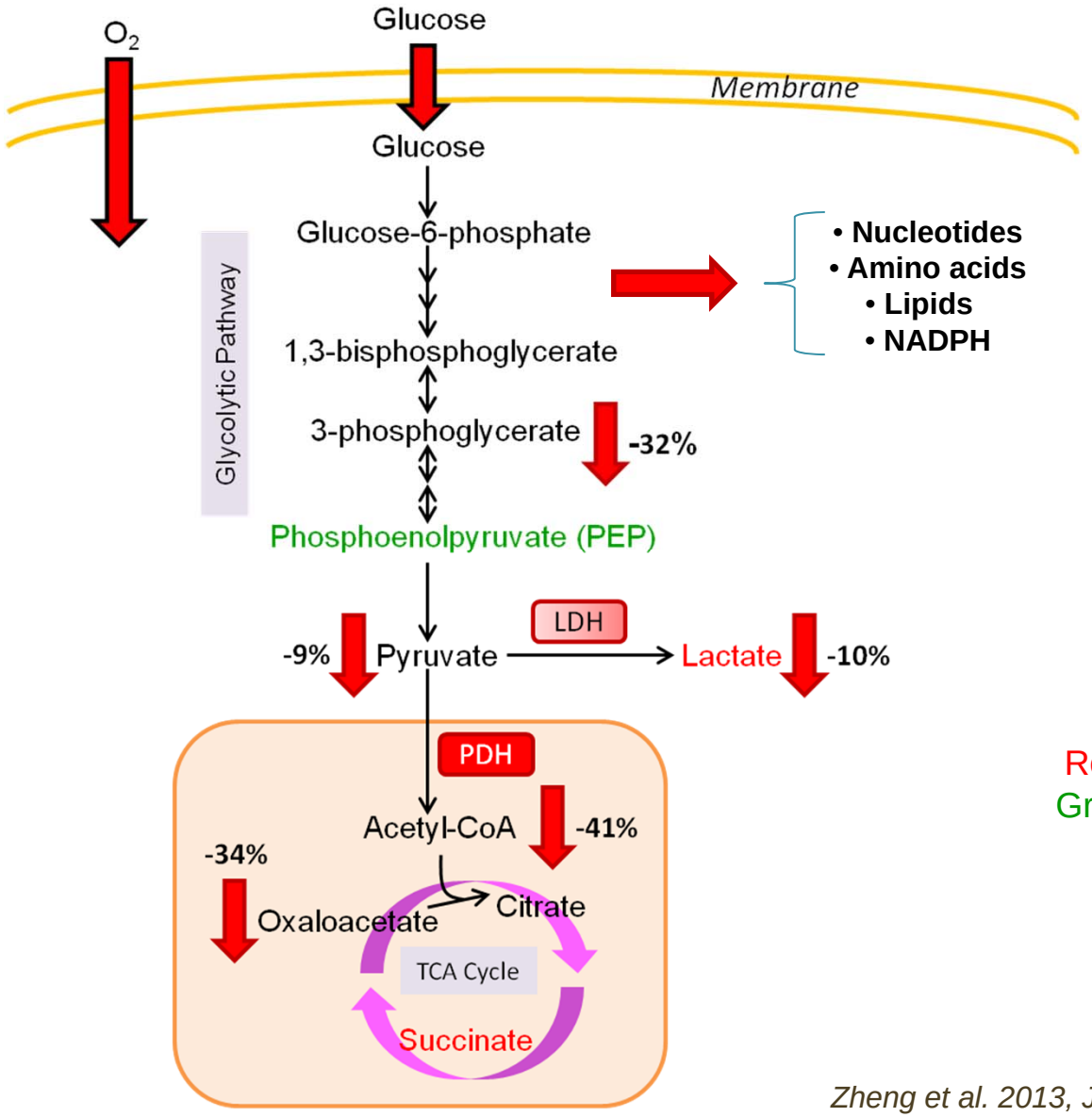


* Statistically significant relative to vehicle of the same cell type, P< 0.05.

** Significant difference between MCF10A-*ras* and MCF10A cells treated with vehicle (P < 0.05).

Zheng et al. 2013, JSBMB. 138C:81

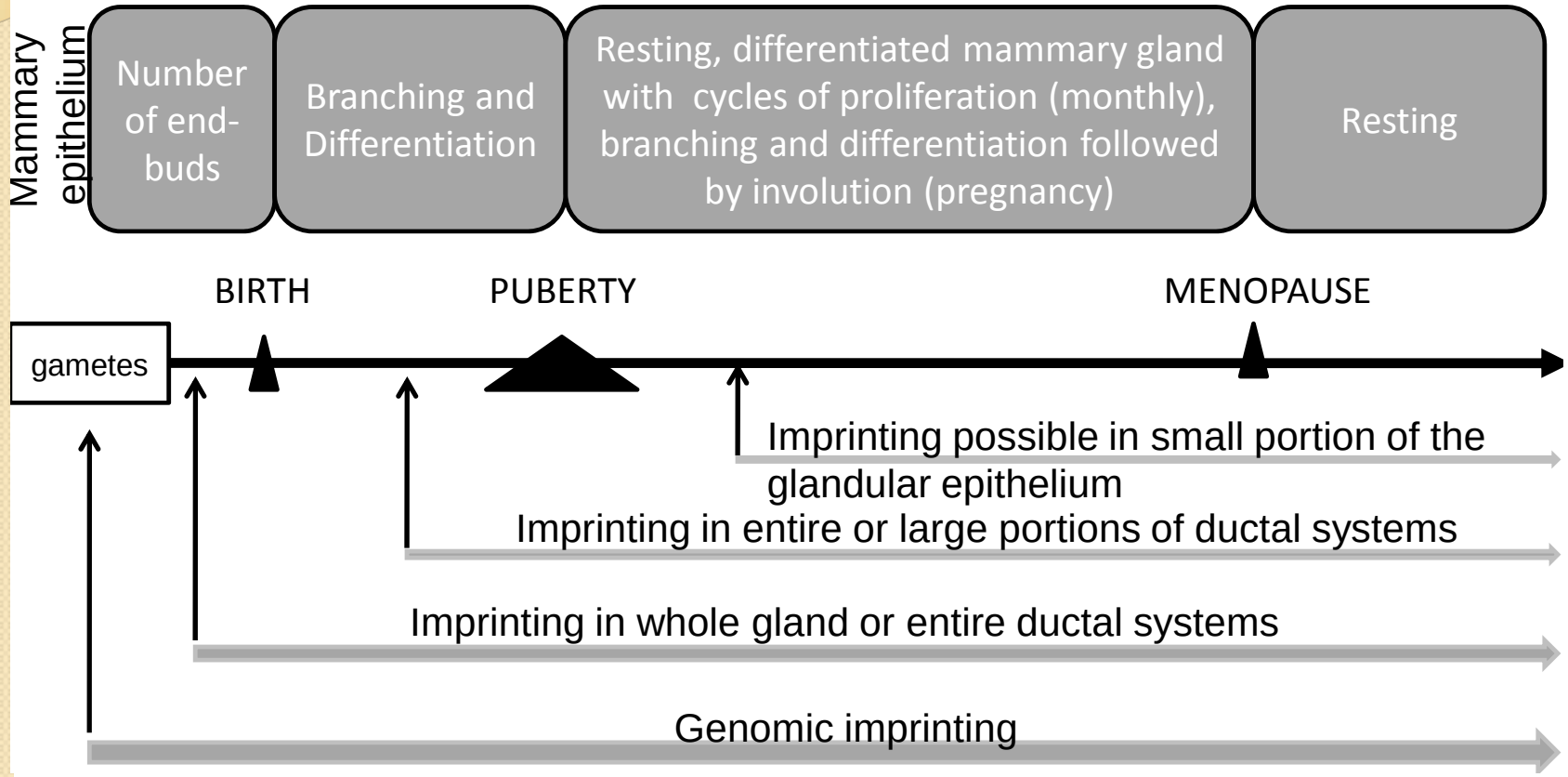
1,25(OH)$_2$D Regulates Glucose Metabolism in MCF10A-*ras* cells



Red: Decrease
Green: Increase

Zheng et al. 2013, JSBMB. 138C:81

Critical Periods of Exposure and Risk of Breast Cancer



Teegarden, Romieu and Leliévre. Nutr Res Rev 25:68, 2012

Maternal Exercise During Pregnancy Reduces Risk of Mammary Tumorigenesis in Rat Offspring

Wei Zheng[1], Ignacio G. Camarillo[2], Leon Clah[2], Xuanzhu Zhou[1], Brienna Larrick[1], Nicole Blaize[3], Emily Breslin[3], Shawn S. Donkin[4], Timothy P. Gavin[3], Sean Newcomer[3] and Dorothy Teegarden[1]

Departments of [1]Nutrition Science, [2]Biological Sciences, [3]Health and Kinesiology, [4]Animal Sciences, Purdue University

April 28, 2014

PURDUE UNIVERSITY

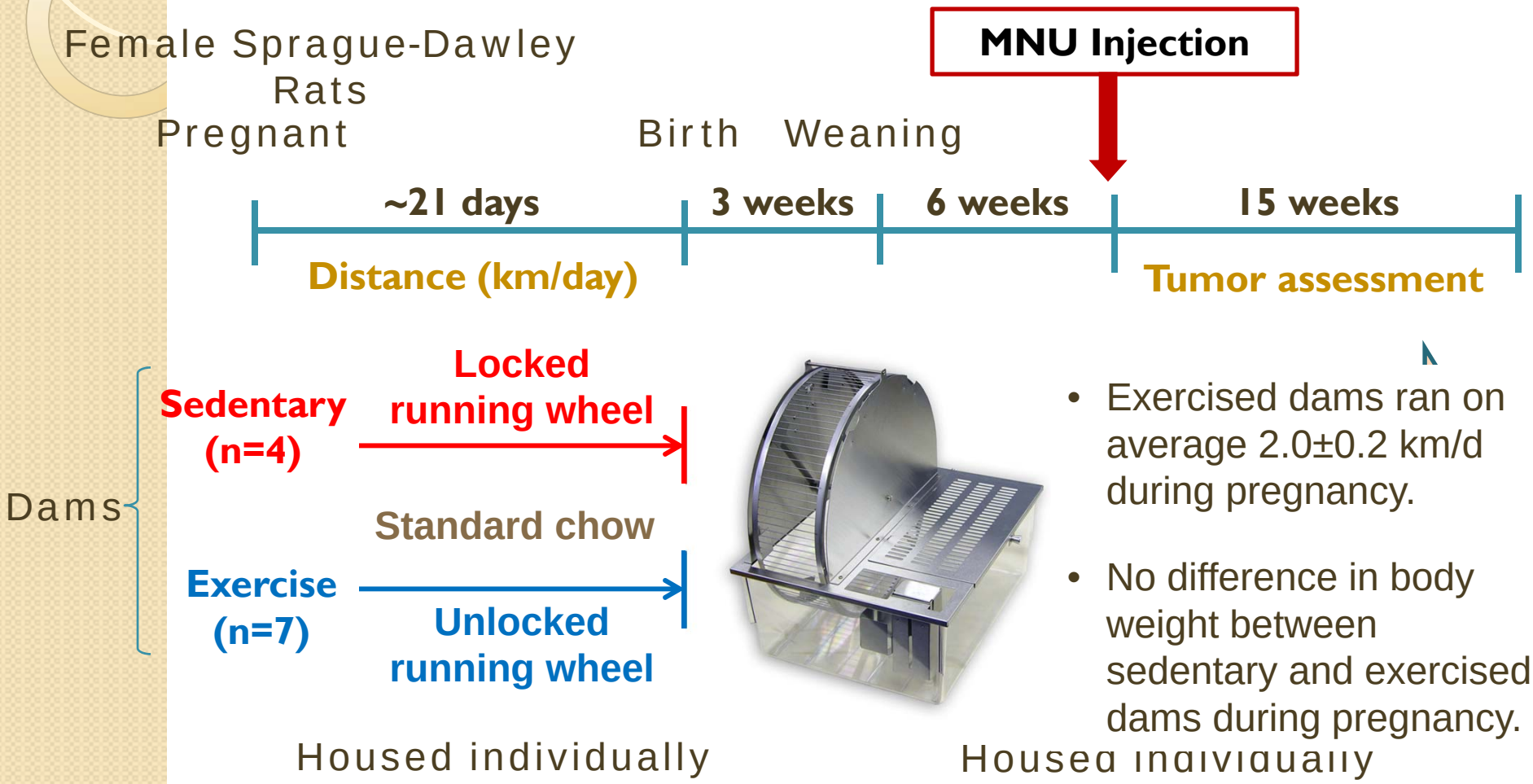
European Journal of Cancer Prevention, in press

Maternal Exercise and Breast Cancer Risk

- Several developmental windows exist when mammary gland is more susceptible to tumorigenesis, including pregnancy and prenatal period (Friedenreich *et al.,* 2001, *Epidemiology*).

- Dietary or behavioral modifications in pregnancy may impact embryonic environment thus the risk of breast cancer in generations of offspring (De Assis et al., 2012, *Nat Commun* ; Cho et al., 2012, *Carcinogenesis*).

Maternal Exercise Impact on Mammary Tumorigenesis in Rat Offspring (pups) *Experimental Design*



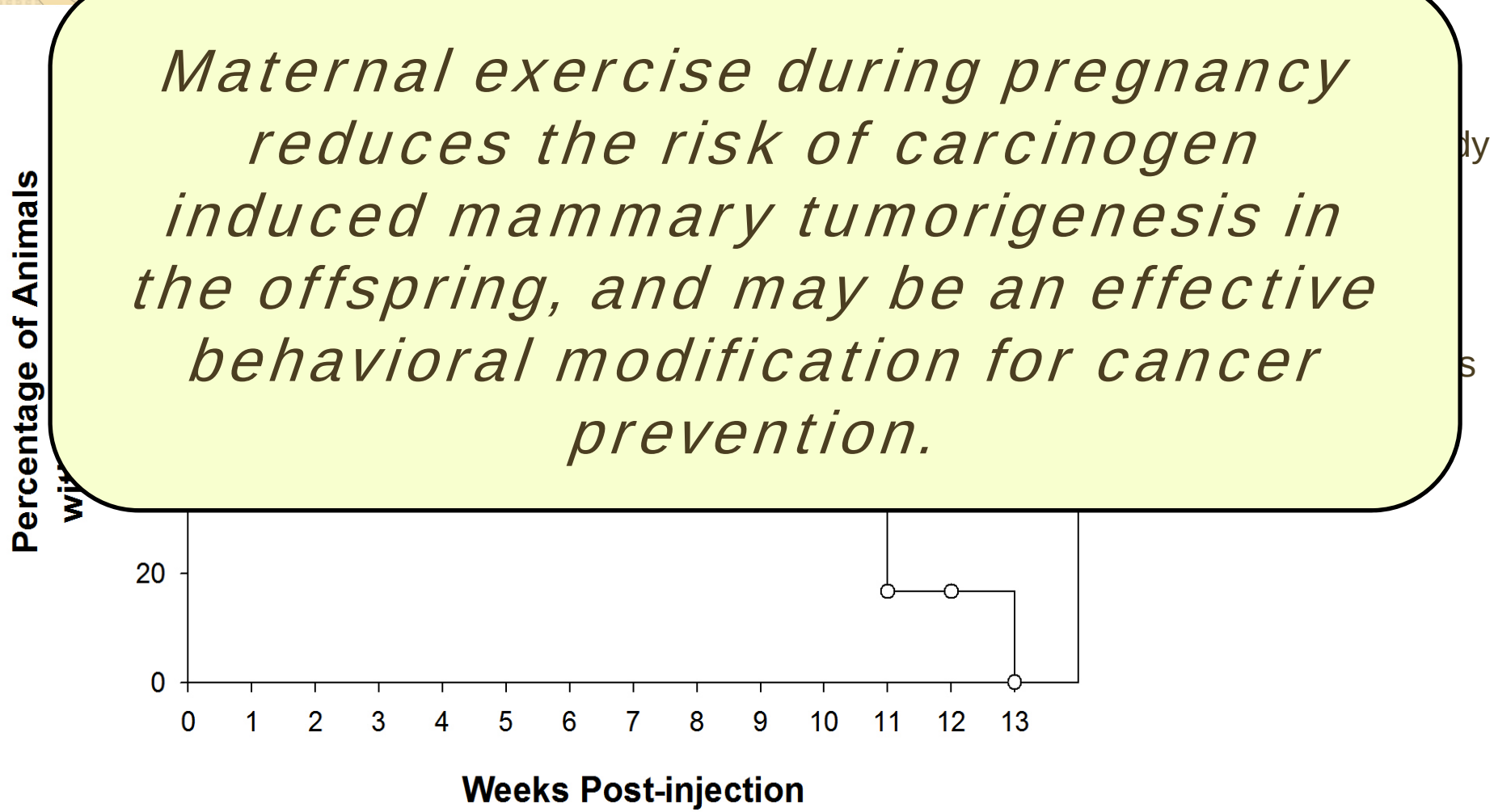
- Exercised dams ran on average 2.0±0.2 km/d during pregnancy.
- No difference in body weight between sedentary and exercised dams during pregnancy.

Camarillo, et al.; *Eur J Cancer Prev. 2014*, *in press.*

Pups

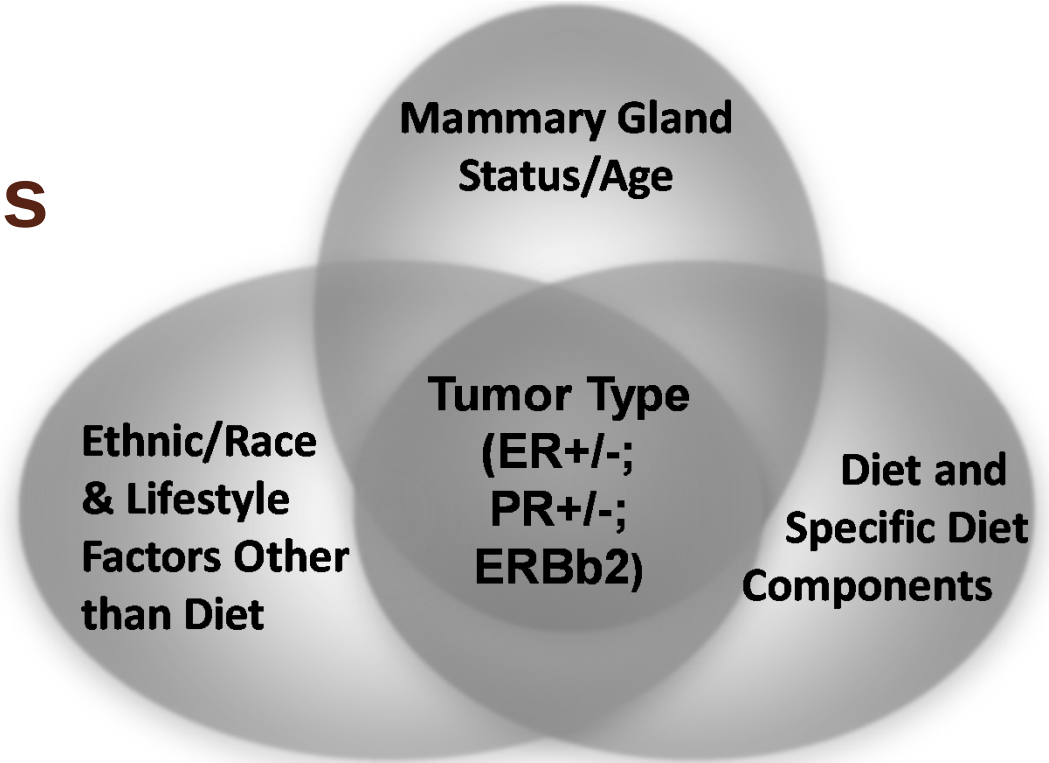
Lower Mammary Tumor Incidence in Pups From Exercised Dams

Maternal exercise during pregnancy reduces the risk of carcinogen induced mammary tumorigenesis in the offspring, and may be an effective behavioral modification for cancer prevention.



Complex Problems

Interdisciplinary, Innovative, Global Solutions



Acknowledgements

NIH R25CA128770

ICTSI NIH/NCRR Grant Number TR000006

NCI CCSG CA23168 to Purdue University Center for Cancer Research

No other disclosures

international breast cancer & nutrition
working together for prevention
http://www.purdue.edu/dp/oncological/ibcn.php

Interdisciplinary
Cancer Prevention
Research Internship Program

PURDUE UNIVERSITY
Discovery Park
ONCOLOGICAL SCIENCES CENTER

INDIANACTSI
Clinical and Translational Sciences Institute

international breast cancer & nutrition
working together for prevention

4th INTERNATIONAL BREAST CANCER PREVENTION SYMPOSIUM:

Genes, the Environment and Breast Cancer Risk

October 16-18, 2014

Purdue University
West Lafayette, IN; USA

WWW.PURDUE.EDU/BREASTCANCER