Obesity, Energy Balance and Cancer: Lessons from Translational Studies

Stephen D. Hursting, PhD, MPH

Professor and Chair
Department of Nutritional Sciences
University of Texas at Austin
and
Professor, Department of Molecular Carcinogenesis
University of Texas MD Anderson Cancer Center

WHAT STARTS HERE CHANGES THE WORLD
THE UNIVERSITY OF TEXAS AT AUSTIN

Disclosure Information

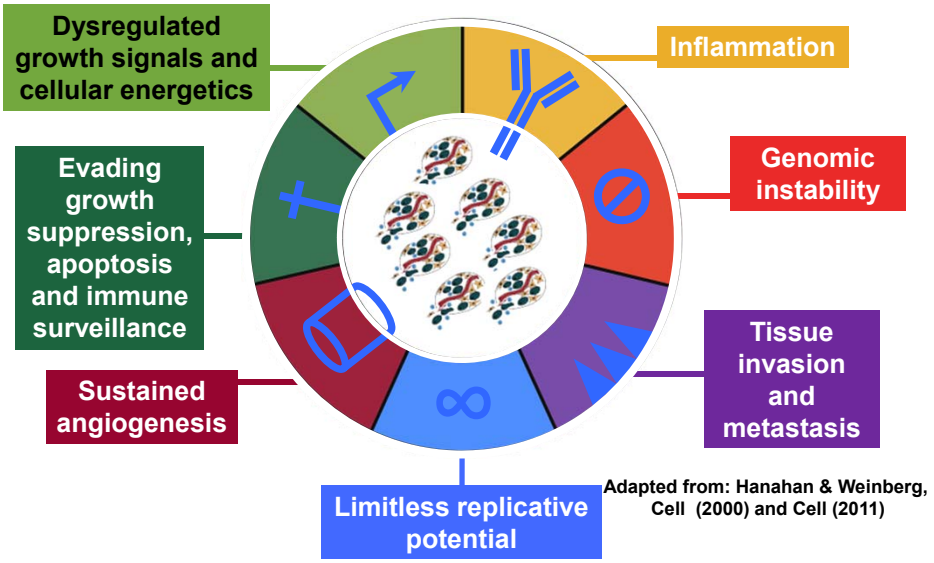
- **I have no financial relationships to disclose**
- **I will discuss a preclinical study using Afinitor® (everolimus, Rad001) and preclinical and off-label clinical studies of Lovaza® (omega-3-acid ethyl esters)**

Today's Presentation

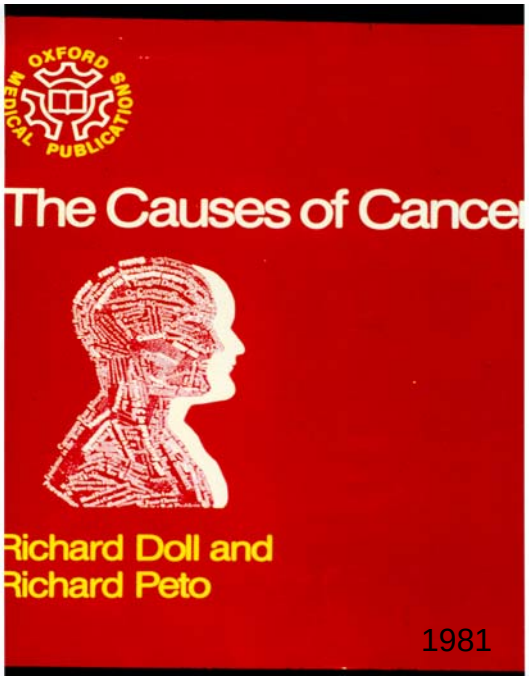
- **The hallmarks of cancer and the scope of the cancer problem**
- **Links between diet, obesity, metabolism and cancer in humans and animals**
- **Where are we today? Diet recommendations (focus on phytochemicals, obesity prevention)**
- **Hot topics in nutrition, obesity and cancer: a focus on mechanisms**
- **Discussion**

Cancer: A Complex Foe

The essential aberrations of cancer



Adapted from: Hanahan & Weinberg, Cell (2000) and Cell (2011)



Factors Contributing to Cancer Risk in the United States

Diet/Obesity: ~35%
Tobacco: ~30%
Occupational and Pollution: ~5%
Infection: ~10%
Other: ~20%

- **Familial**
- **Sunlight / radiation**
- **Alcohol**
- **Long-term exposure to some drugs**

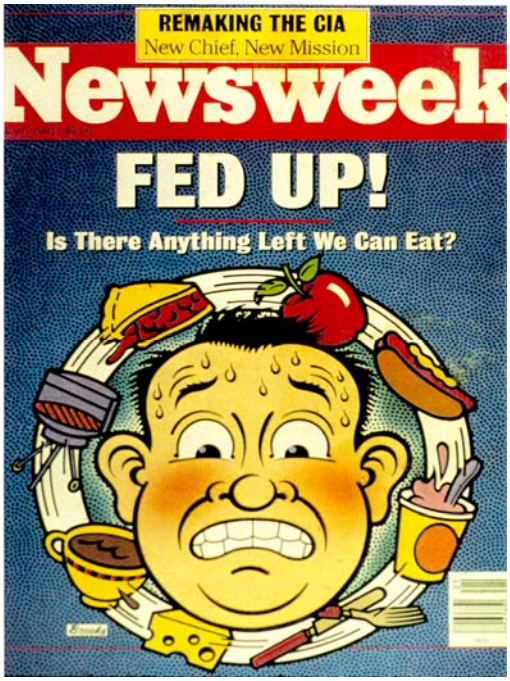
Doll and Peto, 1981

Table 1. Causes of cancer and potential reduction in cancer burden through preventive measures. N/A, not applicable.

Cause*	Percentage of cancer caused	Number of deaths in United States†	Magnitude of possible reduction (%)	Period of time (years)	Evidence example
Smoking	33	188,744	75	10–20	Comparison of lung cancer mortality by state (Fig. 1)
Overweight and obesity	20	114,390	50	2–20	Bariatric surgery and sustained changes in weight and markers (*62*)
Diet	5	28,600	50	5–20	Folate and colorectal cancer (*63*)
Lack of exercise	5	28,600	85	5–20	Adolescent physical activity (*18*)
Occupation	5	28,600	50	20–40	Asbestos workplace regulation (*10*)
Viruses	5	28,600	100	20–40	Liver cancer reduction by vaccine (*22*)
Family history	5	28,600	50	2–10	Bilateral oophorectomy for BRCA1/2 (*34*); aspirin trial for Lynch syndrome (*11*)
Alcohol	3	17,200	50	5–20	Regulation (*64*)
UV and ionizing radiation	2	11,400	50	5–40	Reduced medical exposures (*65*)
Prescription drugs	1	5,720	50	2–10	Hormone therapy–related drop in breast cancer (*66*)
Reproductive factors	3	17,200	0	N/A	N/A
Pollution	2	11,400	0	N/A	N/A
Total potential reduction‡ = 54.5%					

*Adapted from Wolin *et al.* (*67*). †U.S. death estimates from the American Cancer Society (*68*). ‡Defined as sum (percentage caused by modifiable exposure × magnitude of reduction)

Colditz, et al. Applying What We Know to Accelerate Cancer Prevention. *Sci Transl Med*, 2012

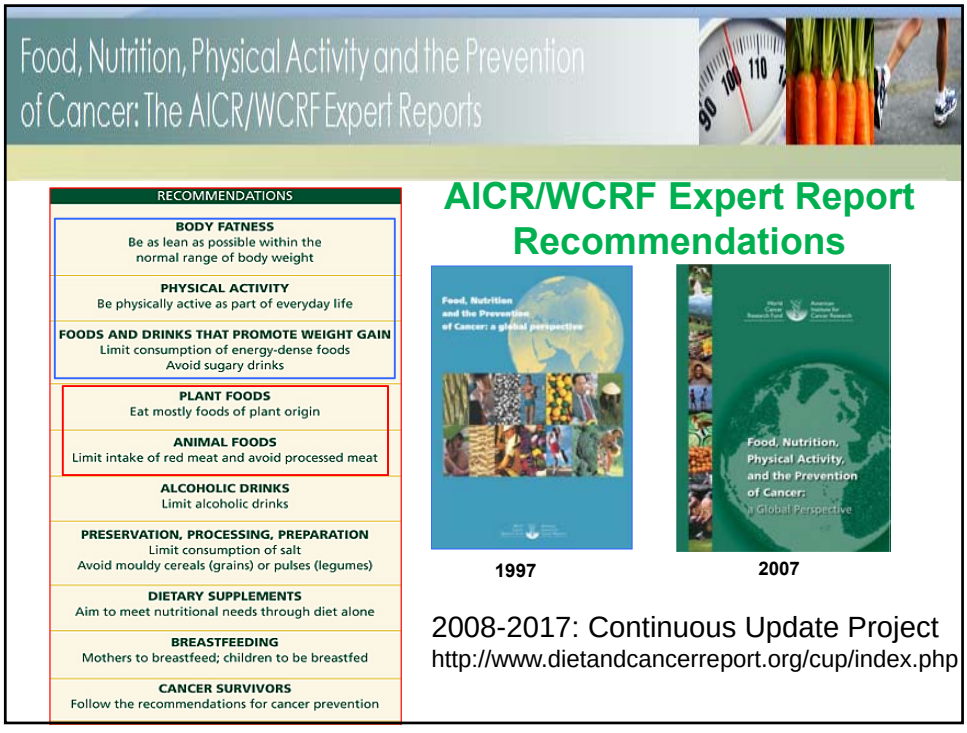


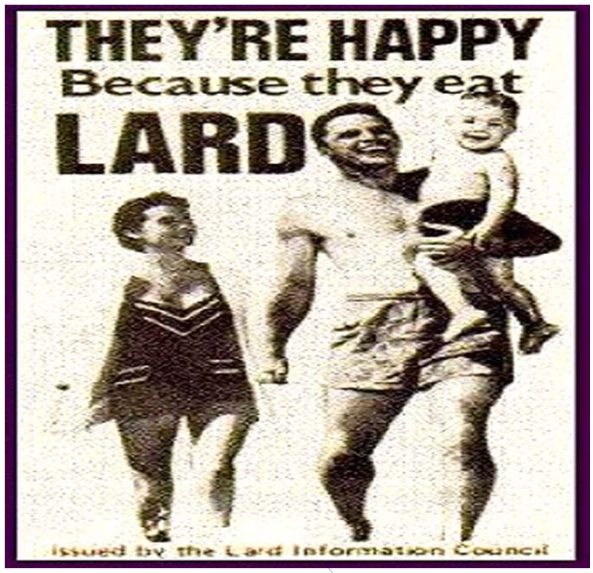
Fatalistic Beliefs about Cancer

- "Almost everything causes cancer…"
  - almost 50% agree or strongly agree
- "There's not much a person can do to prevent cancer…"
  - approximately 25%
- "It's hard to know [which recommendations] to follow…"
  - almost 75%

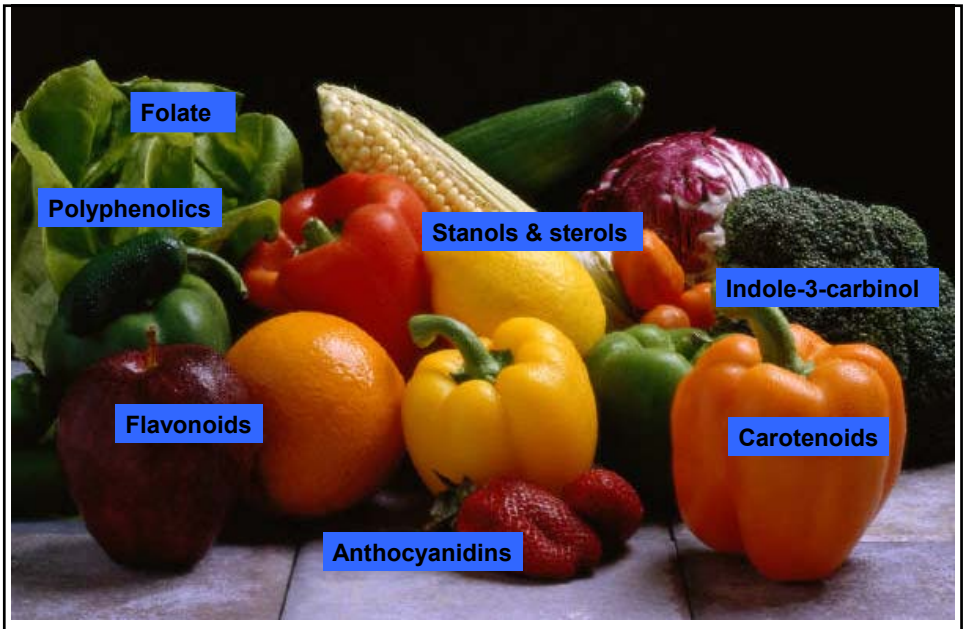
J Niederdeppe, AG Levy, Cancer Epidemiol Biomarkers Prev 2007; 16(5):998-1003

9





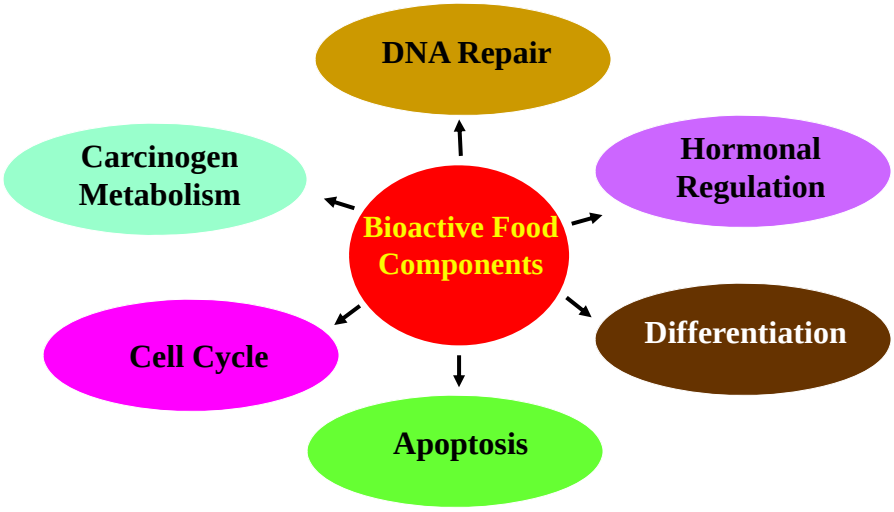
1940's Advertisement from the United Kingdom



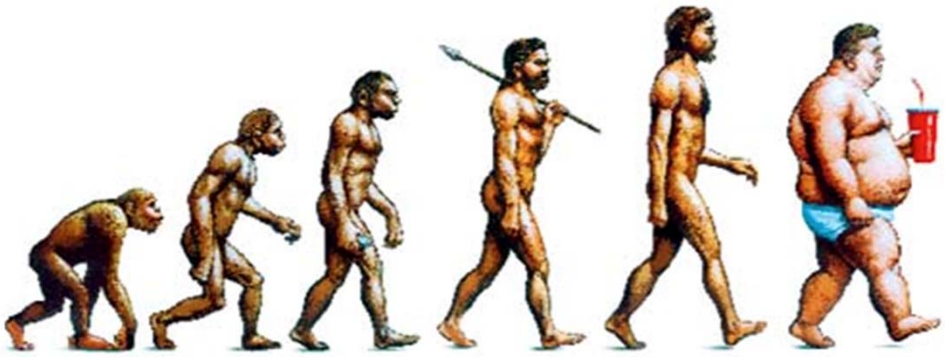
Diets should contain a variety of plant-based foods

WCRF/AICR 2007

Bioactive Food Components Influence Cancer Processes

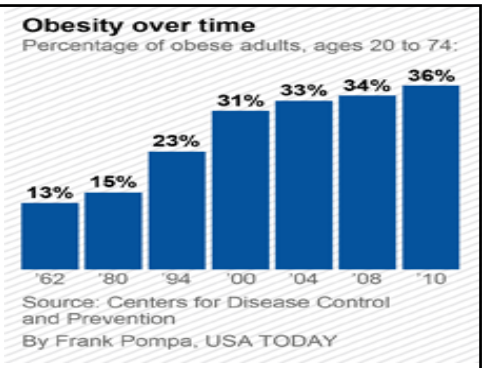


The Shape of Things to Come. The Economist 12/11/03



(http://www.economist.com/displaystory.cfm?story_id=2282754)

The US Obesity Epidemic



Ogden, et al., JAMA 2014:

- 69% of US Adults Overweight or Obese (BMI >25.0 kg/m^2)
- 36% US Adults Obese (BMI >30.0 kg/m^2)
- 6.5% US Adults Extremely Obese (BMI >40.0 kg/m^2)

Metabolic Syndrome

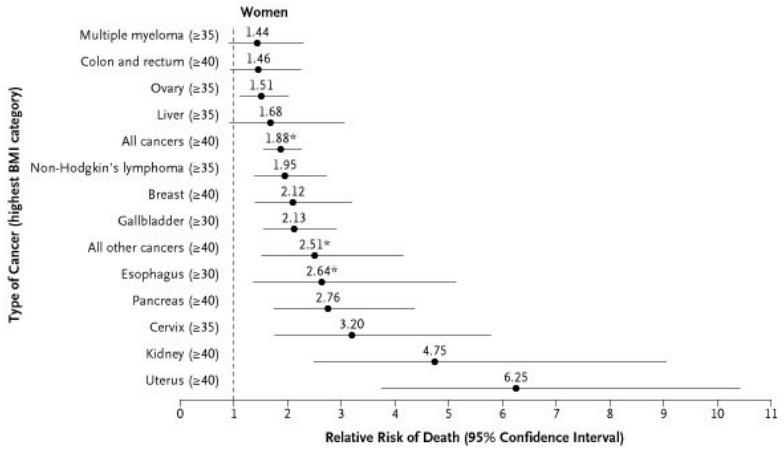
Describes a state of metabolic dysregulation characterized by:

- Insulin resistance, hyperglycemia*
- Dyslipidemia (↑triglycerides*, ↓HDL-C*)
- ↑Waist circumference*
- Hypertension*
- Proinflammatory state (↑cytokines, ↑chemokines)
- Vascular perturbations (↑PAI-1, ↑VEGF)
- Altered adipokines (↑leptin, ↓adiponectin)
- Elevated bioavailable IGF-1 (NHANES)

- **Associated with many types of cancer**
  25% (144K) cancer deaths/year in US caused by overweight/obesity

(Calle, et al., *NEJM* 2003; Colditz, et al. *Science Transl Med*, 2012)

Mortality from Cancer According to BMI for U.S. Women in the ACS Cancer Prevention Study II



Calle, E. et al. N Engl J Med 2003;348:1625-1638

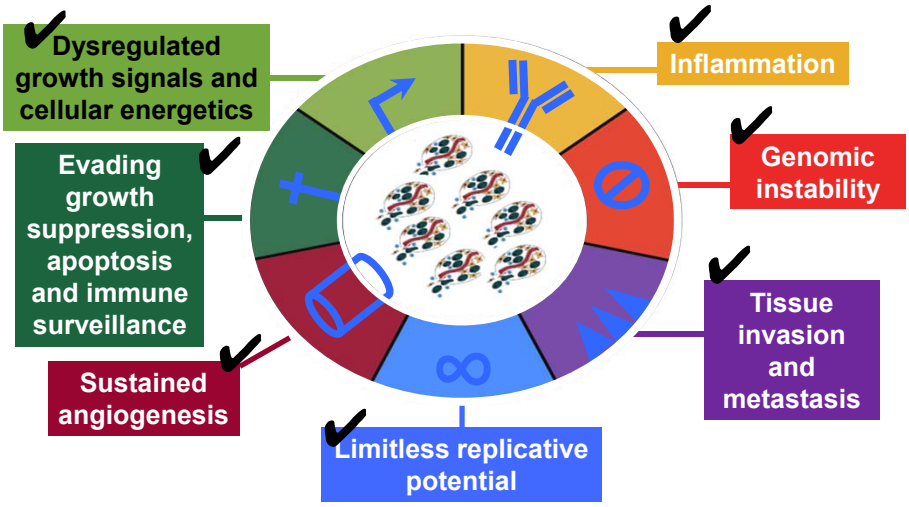
LOOMING QUESTION:

How to Decrease Cancer Risk in the ~710 Million Adults Worldwide Currently Obese?

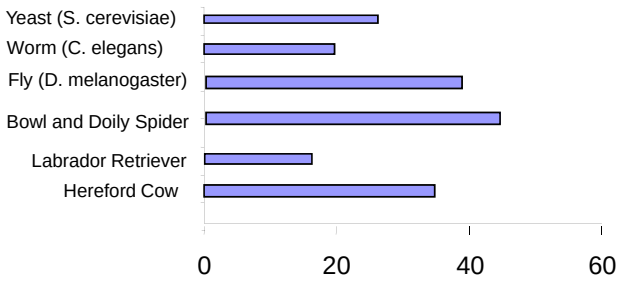
Need a mechanistic approach to identify targets and strategies to break obesity-cancer links

Cancer: A Complex Foe

Obesity, calorie restriction impact each cancer hallmark

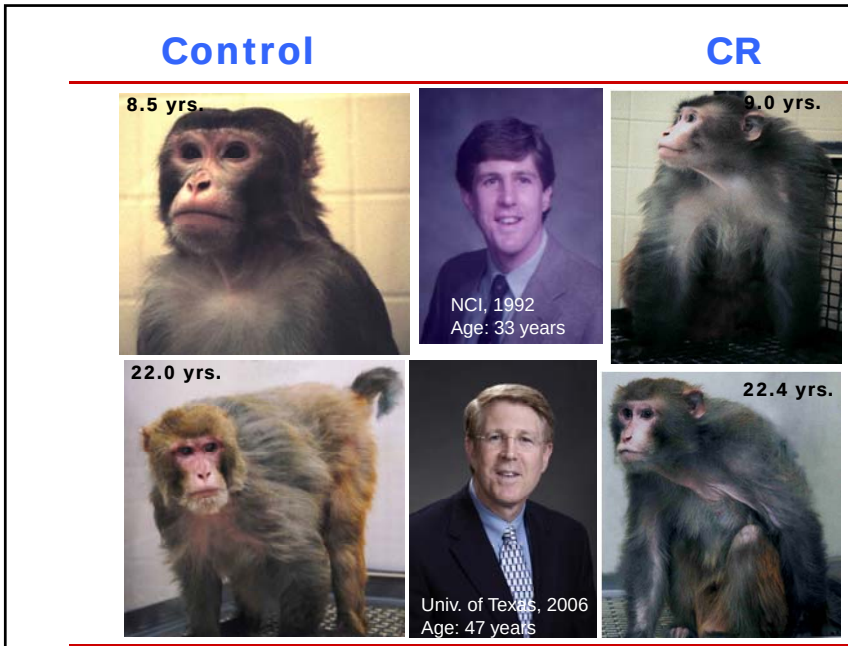


Calorie Restriction (~20%) Extends Lifespan in Multiple Species



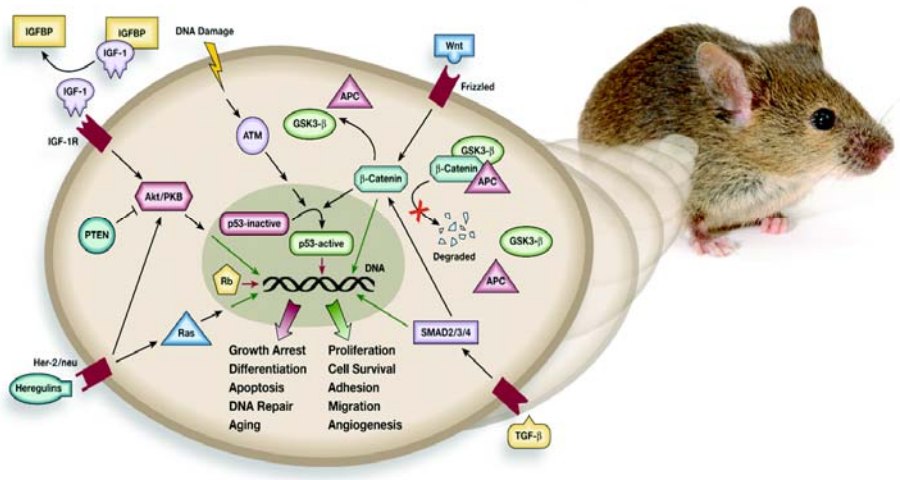
% Increase in Longevity (versus *ad libitum*-fed controls)

Hursting, et al. J Nutr, 2004



Weindruch: U Wisconsin CR Study in Rhesus Monkeys

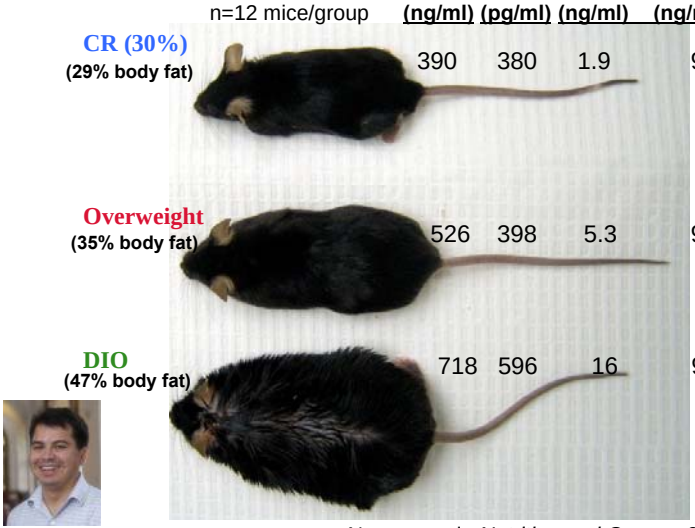
Modeling Energy Balance and Human Cancer in Mice by Altering Key Genes and Pathways



Hursting, et al., *Mutation Res*, 2005

Growth Factor Levels and MMTV-Wnt-1 Mammary Tumor Growth in Lean, Overweight and Obese Mice

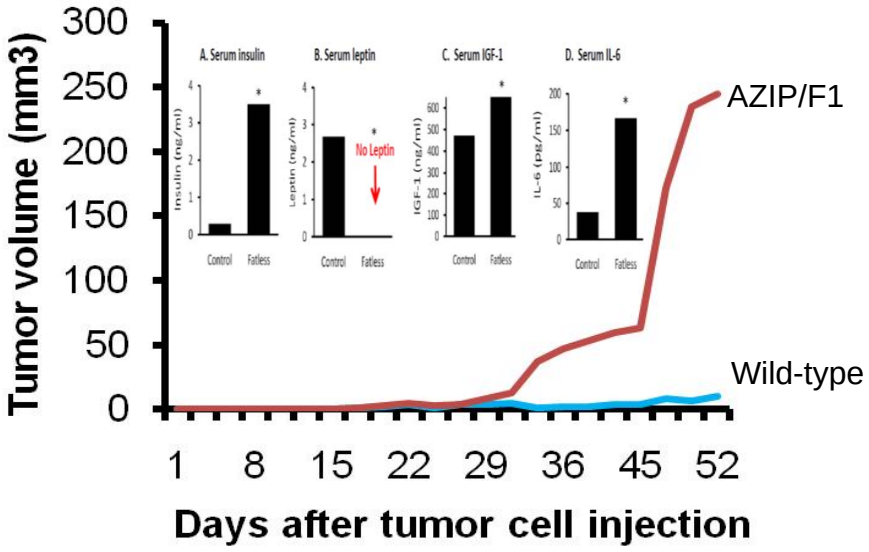
n=12 mice/group	IGF-1 (ng/ml)	Insulin (pg/ml)	Leptin (ng/ml)	Adiponectin (ng/ml)	L/A	Tumor Vol (mm^3)
CR (30%) (29% body fat)	390	380	1.9	9.5	0.2	120
Overweight (35% body fat)	526	398	5.3	9.2	0.6	510
DIO (47% body fat)	718	596	16	9.1	1.8	1485



Dr. Nomeli Nunez

Nunez, et al., *Nutrition and Cancer*, 2007

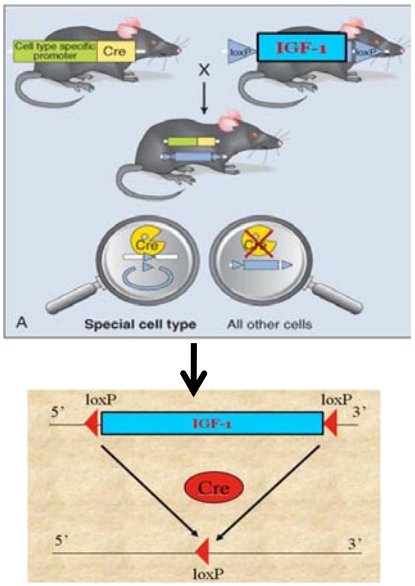
Transplanted Wnt-1 Tumor Growth in AZIP/F-1 (Fatless) Mice Versus Wild-Type Mice

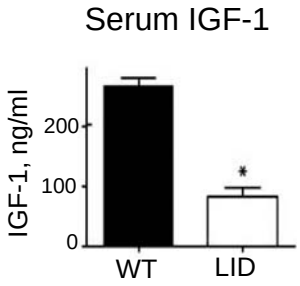


Hursting et al., *Cancer Res*, 2007

Genetic Reduction of Systemic IGF-1

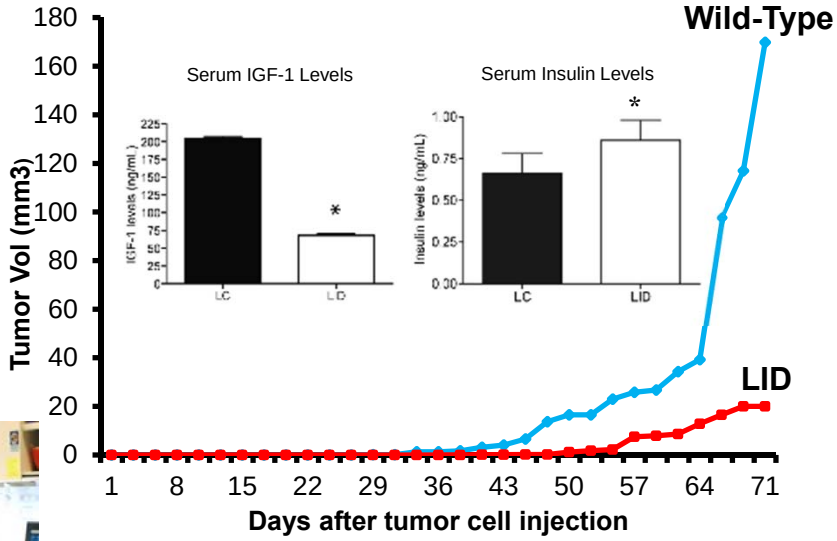
~75% of IGF-1 in serum is produced by liver





Ecuadorians with Laron Syndrome have very low IGF-1 and inflammatory cytokines, increased longevity, and virtually no cancer or diabetes. *NY Times* 2/16/11.

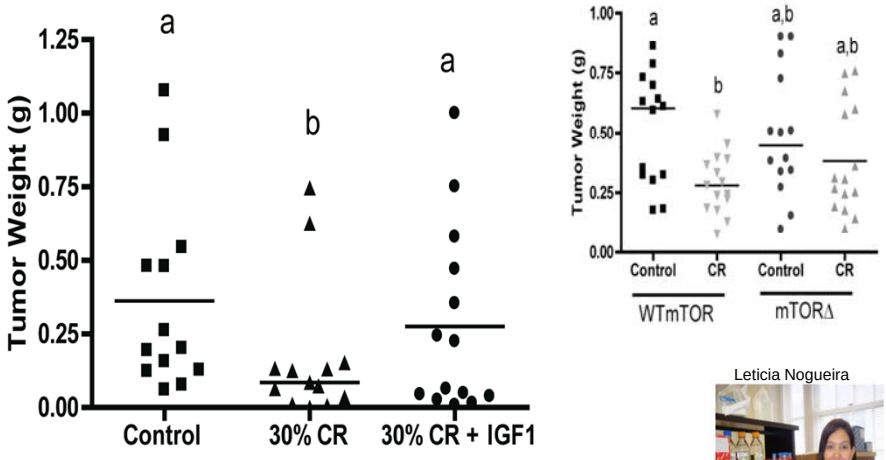
Transplanted Wnt-1 Mammary Tumor Growth in Wild-Type Control and Liver IGF-1 Deficient (LID) Mice



Dr. Nikki Ford

Ford, et al. *Endocrine-Related Cancer*, in press

IGF-1 Infusion or mTOR Activation Impacts Transplanted MMTV-Wnt-1 Mammary Tumor Growth in Calorie Restricted Mice

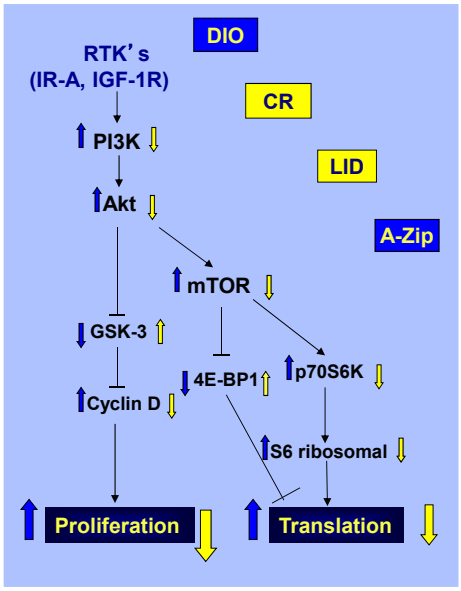


Nogueira et al. *Endocrine-Related Cancer,* 2012

Leticia Nogueira

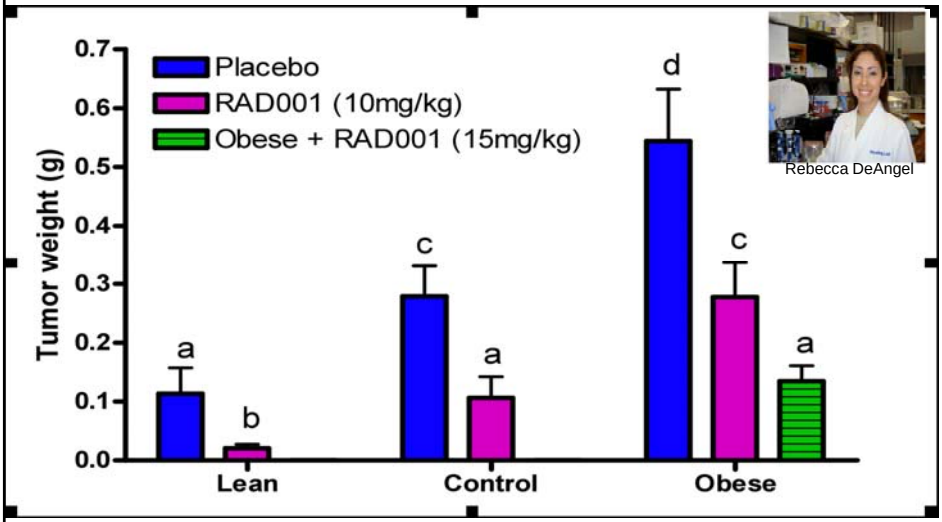
Dietary Energy Balance Modulation of Akt/mTOR Signaling (normal and tumor tissue)

- Skin
- Liver
- Prostate
- Colon
- Pancreas
- Mammary



Hursting, et al., *Cancer Res*, 2007
Moore, et al., *Cancer Prev Res*, 2008;
Olivo-Marston, et al., *Mol Carcinogenesis* 2009
Lashinger, et al, *Cancer Prev Res*, 2011
Blando, et al., *Cancer Prev Res*, 2011
Nogueira, et al, *Endocr Rel Cancer*, 2012
deAngel, et al., *Mol Carcinogenesis*, 2013

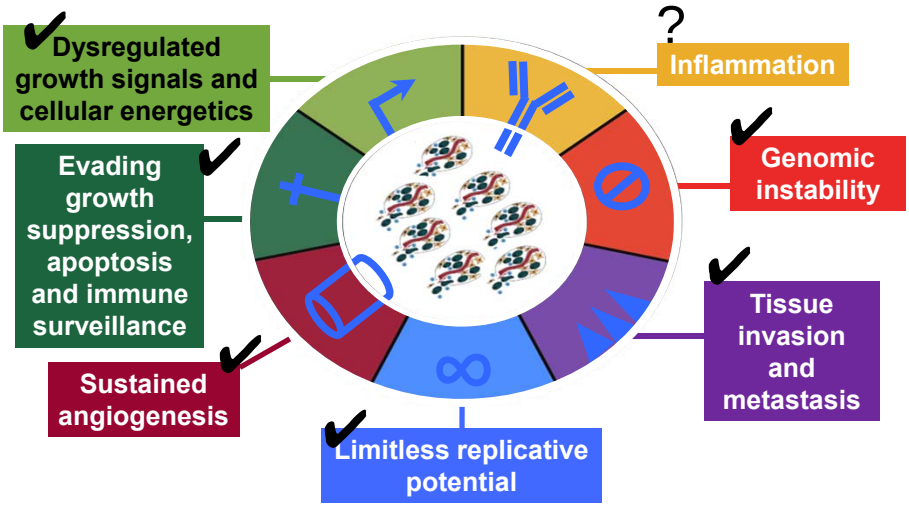
RAD001 (Afinitor®) Inhibits mTOR and Wnt-1 Mammary Tumor Growth in Lean, Control and Obese Mice



DeAngel, et al. *Mol Carcinogenesis*, 2013

Cancer: A Complex Foe

Obesity, CR impact the essential aberrations of cancer



Inflammation and Cancer

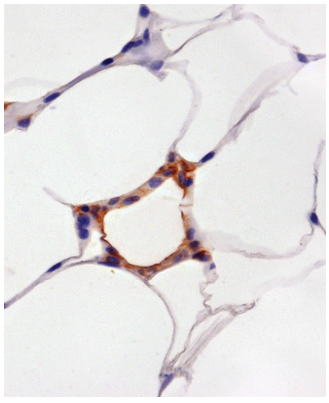
- Malignancies often arise from areas of chronic infection and inflammation

- Chronic inflammatory conditions linked to tumorigenesis include:

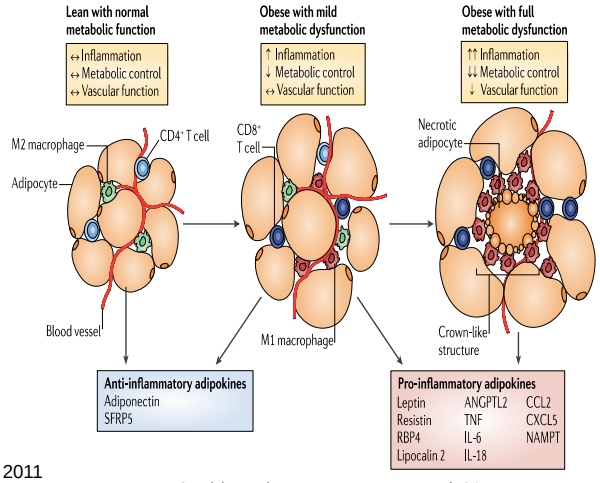
-Gastritis (H. Pylori) – Gastric Cancer
-Cystitis – Bladder Cancer
-Bronchitis – Lung Cancer
-Esophagitis – Esophageal Cancer
-Dermatitis – Skin Cancer
-Ulcerative colitis – Colon Cancer
-Inflammatory bowel disease – Colon Cancer
-Hepatitis (including NASH) – Liver Cancer
-Pancreatitis – Pancreatic Cancer (up to 55-fold increased risk)

Obesity Causes Inflammation in Organs and Visceral Fat

Andrew Dannenberg,
Weill-Cornell Cancer Center



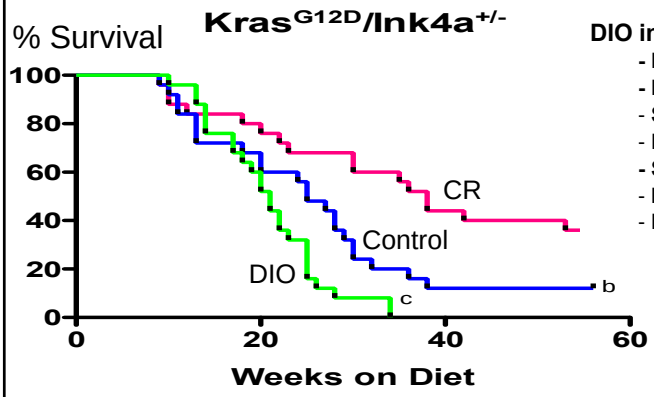
Crown-like Structures (CLS)
(Macrophage/Adipocyte/Epithelial Tumor Cell Interactions)



Subbaramaiah K, et al. *Cancer Prev Res* 2011

Ouchi, et al. *Nature Rev Immunol*, 2011

Dietary Energy Balance Affects Pancreatic Tumor-Free Survival in Kras Ink4a$^{+/-}$ Mice

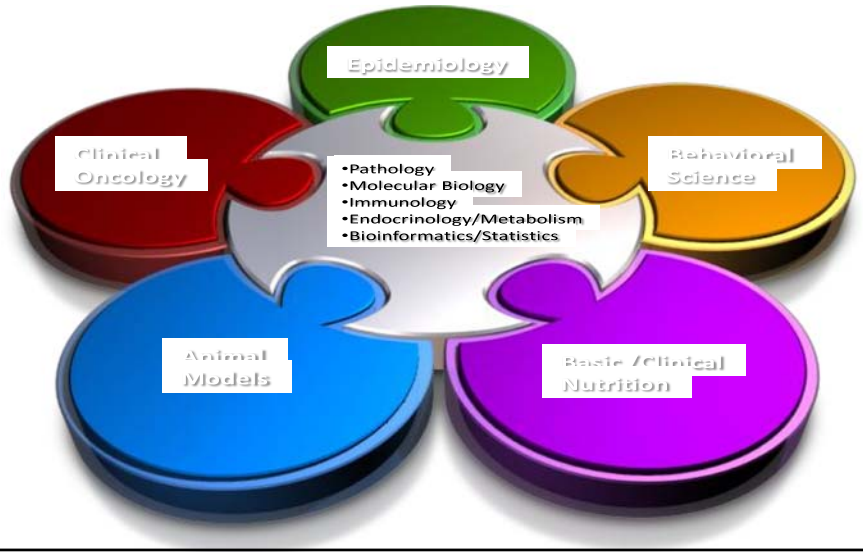


DIO increases, CR decreases:

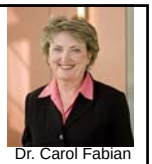
- Pancreatic steatosis
- Pancreatic CLS
- Serum IGF-1 levels
- Leptin:Adpn
- Serum cytokine levels
- IGF-1R/Akt/mTOR signaling
- NF-kB signaling

Lashinger, et al., *Cancer Prev Res* 2013

Energy Balance, Metabolism and Cancer: Transdisciplinary Research Approaches



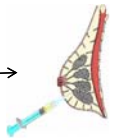
Translational Example 1: CR Pilot Trial in Obese Postmenopausal Women


Dr. Carol Fabian

28 High Risk Women:
BMI >30 kg/m^2
No HRT

→ 
RPFNA

→ 6-month NHLBI Step 1 Diet Regimen →

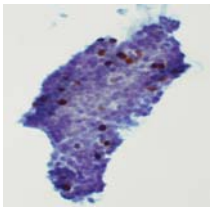

Repeat RPFNA

Response Biomarkers

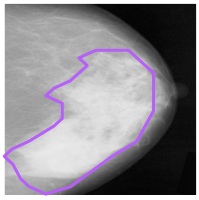
FNA Tissue Markers

RPPA;qRT-PCR; insulin, cytokines, adipokines, E&T, IGF1, IGFBP-3

Proliferation (Ki-67)



Mammographic Breast Density



Serum

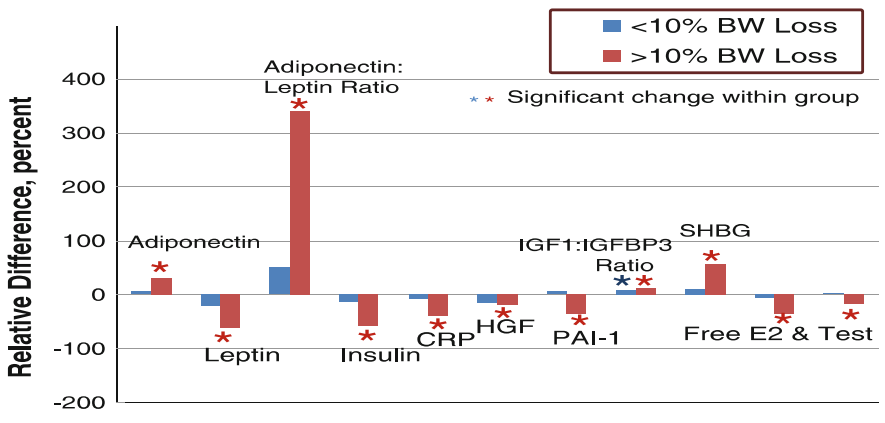
insulin, cytokines, adipokines, E&T, IGF1, IGFBP-3

Breast Cancer Res Treat 2013

Favorable modulation of benign breast tissue and serum risk biomarkers is associated with >10 % weight loss in postmenopausal women

Carol J. Fabian · Bruce F. Kimler · Joseph E. Donnelly · Debra K. Sullivan · Jennifer R. Klemp · Brian K. Petroff · Teresa A. Phillips · Trina Metheny · Sonya Aversman · Hung-wen Yeh · Carola M. Zalles · Gordon B. Mills · Stephen D. Hursting

Change in Serum Biomarkers by Weight Loss Group



Prevention and Epidemiology

2012 Cancer Research

Effects of a Caloric Restriction Weight Loss Diet and Exercise on Inflammatory Biomarkers in Overweight/Obese Postmenopausal Women: A Randomized Controlled Trial

Ikuyo Imayama[1], Cornelia M. Ulrich[2,7], Catherine M. Alfano[8], Chiachi Wang[1], Liren Xiao[1], Mark H. Wener[4], Kristin L. Campbell[9], Catherine Duggan[1], Karen E. Foster-Schubert[5], Angela Kong[10], Caitlin E. Mason[1], Ching-Yun Wang[3,6], George L. Blackburn[11], Carolyn E. Bain[1], Henry J. Thompson[12], and Anne McTiernan[1,5,6]

British Journal of Nutrition, page 1 of 14 doi:10.1017/S0007114513000792

The effect of intermittent energy and carbohydrate restriction *v.* daily energy restriction on weight loss and metabolic disease risk markers in overweight women

Michelle Harvie[1]*, Claire Wright[2], Mary Pegington[1], Debbie McMullan[1], Ellen Mitchell[1], Bronwen Martin[3], Roy G. Cutler[4], Gareth Evans[1], Sigrid Whiteside[5], Stuart Maudsley[4], Simonetta Camandola[3], Rui Wang[3], Olga D. Carlson[3], Josephine M. Egan[3], Mark P. Mattson[4] and Anthony Howell[1]

Changes in Benign Breast Tissue (FNA) Biomarkers After 6-Month Diet and Exercise Intervention in Obese Women

Table 7 Summary of favorable adipocytokine, mRNA, and proteomics changes in benign breast tissue, showing number of paired specimens exhibiting either a decrease or an increase in value

Biomarker (assay method)	Total cohort			Weight loss <10 %			Weight loss >10 %		
	No. Dec	No. Inc	Change over time, *P* value [b]	No. Dec	No. Inc	Change over time. *P* value[b]	No. Dec	No. Inc	Change over time, *P* value[b]
Adiponectin:Leptin Ratio (Luminex)	3	21	**0.003**	2	9	0.16	1	12	**0.011**
pS2 (RT-qPCR)	12	5	**0.035**	2	5	0.40	10	0	**0.005**
CyclinB1 (RPPA; Epitomics 1495-1[a])	16	2	**0.001**	8	1	**0.021**	8	1	**0.011**
Rb pS807-S811 (RPPA; CST 9308[a])	14	4	**0.005**	6	3	0.11	8	1	**0.021**
S6 pS235-S236 (RPPA; CST 2211[a])	14	4	**0.004**	7	2	0.051	7	2	**0.021**

Bold denotes statistically significant results

[a] Antibody source and catalog number: CST Cell Signaling Technology

[b] Wilcoxon signed rank test (2-tailed) assessment of change in values over time (Pre-study to Post-Study)

Fabian, et al. Breast Cancer Res Treat 2013 (epub ahead of print)

Example 2. Integrated Phase II Trial and Animal Studies of Lovaza® (omega-3-acid ethyl esters)

C. Fabian, MD

High-Risk Women

Lovaza (4g/d)

1 yr

Placebo

Serum/Benign Breast Tissue Biomarkers

1. **Response**: Ki-67, cytomorphology
2. **Mechanism**: qRTPCR: ER-genes; miR's
Proteomics: mTOR, MAPK signaling;
Cytokines

Change in Biomarkers

Cancer Endpoint

S. Hursting, PhD, MPH

ER⁻ Mouse Models

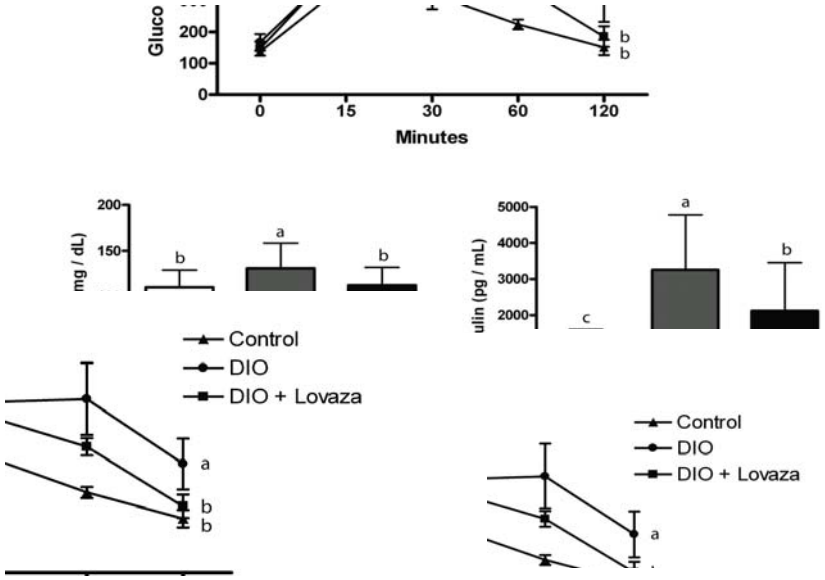
Lovaza (208 mg/kg diet)

3 mos

Placebo

Breast Cancer Research Foundation Grant; Kansas Biomedical Authority Grant

Lovaza Improves Glucose Tolerance and Decreases Serum Insulin and IGF-1 in Obese Mice



Ford, Fabian and Hursting, unpublished

Lovaza Modulates Mammary Inflammation-Related Genes in Obese Mice

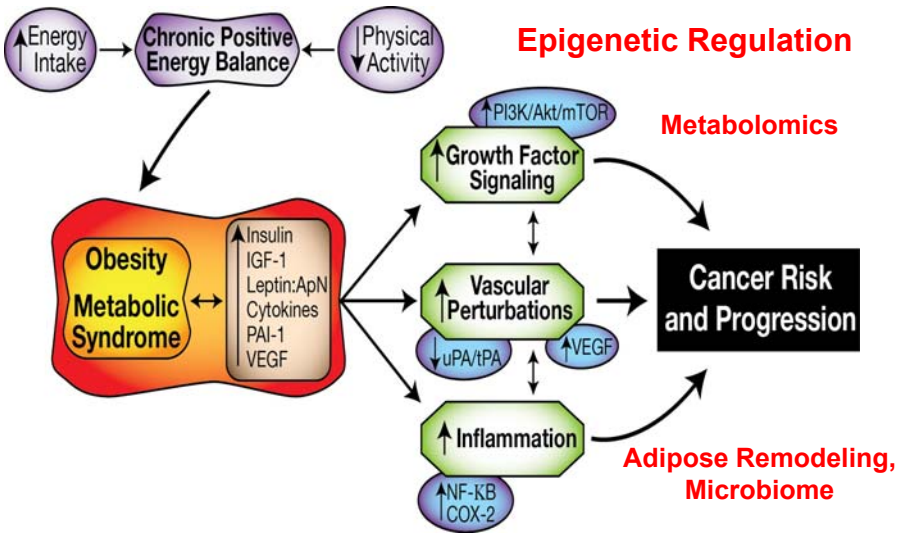
Inflammation-Related Genes	Lovaza® (208 mg/kg)	
10/176 on panel	Fold change (relative to control)	P-value
Interleukin 10 (IL10)	3.9	<0.01
Chemokine (C-X-C motif) ligand 5 (CXCL5)	-2.9	0.04
Chemokine (C-C motif) receptor 3 (CCR3)	-3.2	0.02
Interleukin 3 (IL3)	-4.0	0.01
Interferon alpha 2 (Ifna2)	-5.1	0.03
Interleukin 2 (IL2)	-2.8	<0.01
Chemokine (C-C motif) ligand 2 (CCL2)	-2.0	0.03
Interferon beta 1 (Ifnb1)	-5.2	<0.01
C-reactive protein (CRP)	-2.4	0.04
Epiregulin (Ereg)	-3.6	0.01

Lovaza Ameliorates M-Wnt Mammary Tumor Growth in Obese Mice

!

Ford, Fabian and Hursting, unpublished

Obesity and Cancer: Emerging Mechanistic Targets



S. Hursting and M. Hursting.
Arterioscler Thromb Vasc Biol, 2012

Acknowledgements

University of Texas at Austin

John DiGiovanni, Michele Forman, Nomeli Nunez, Rong Cui

University of Texas-M.D. Anderson Cancer Center

Sue Fischer, Donna Kusewitt, JJ Shen, Powel Brown

Mt. Sinai Medical Center

Derek LeRoith, Shoshana Yakar

National Cancer Institute

Curt Harris, Chuck Vinson, Lyuba Varticovski

Kansas University Medical Center

Carol Fabian, Brian Petroff, Bruce Kimler

UNC-Chapel Hill

Chuck Perou

Weill-Cornell Cancer Center

Andrew Dannenberg

Funding: National Cancer Institute, National Institute of Environmental Health Sciences, American Institute for Cancer Research, Breast Cancer Research Foundation, Susan G. Komen Foundation