

Dissecting the Obesity-Cancer Link: Mechanistic Insights from Animal Models

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

Today's Presentation

- **Links between obesity, energy balance and cancer in animal models**
- **Lessons from studies in mice regarding molecular targets and strategies for breaking the obesity-cancer link**
 - **Calorie Restriction**
 - **Diet- and Genetically-Induced Obesity**
 - **Physical Activity**
 - **Calorie Restriction Mimetics**
(mTOR/IGF-1R inhibitors; bioactive food components)

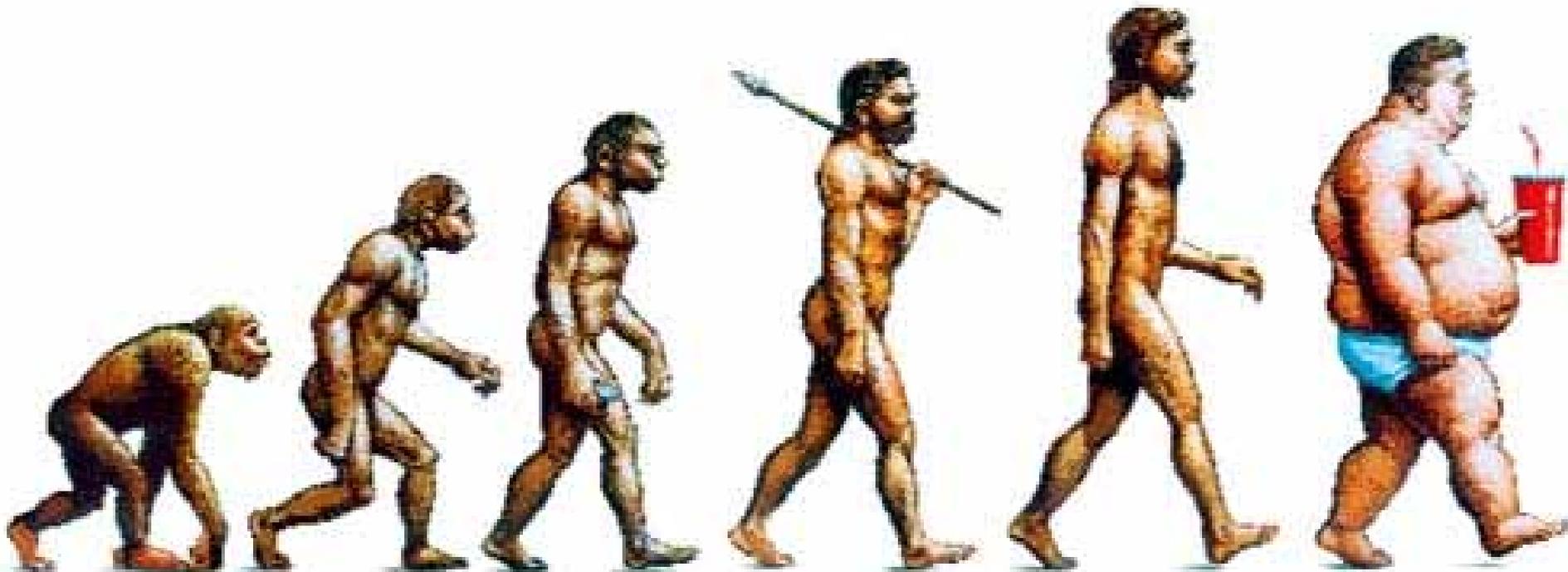
Disclosure Information

Stephen D. Hursting

I have no financial relationships to disclose.

**I will discuss an experiment using Rad001
(Everolimus) in my presentation.**

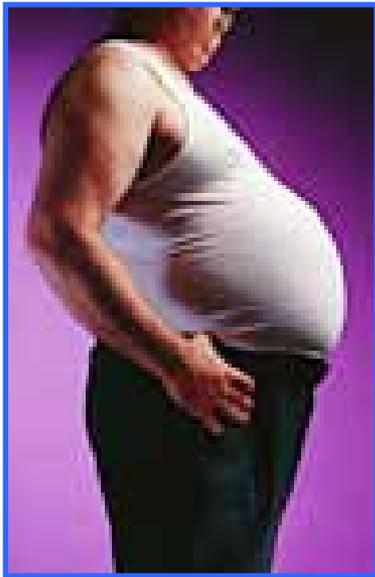
The Shape of Things to Come. The Economist 12/11/03



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

Metabolic Syndrome

Describes a state of metabolic dysregulation characterized by:



- § Insulin resistance
- § Elevated bioavailable IGF-1
- § Pro-inflammatory state (elevated CRP, cytokines)
- § Altered adipokines (elevated leptin)
- § Pro-coagulant changes
- § Dyslipidemia (hypertriglyceridemia)

§ **Associated with many types of cancer**

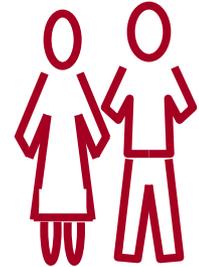
(Calle, et al., *NEJM* 2003: 14% of cancer deaths in men; 20% in women due to overweight/obesity)

Energy Balance and Cancer Prevention



Energy in

- Amount
- Type
- Pattern

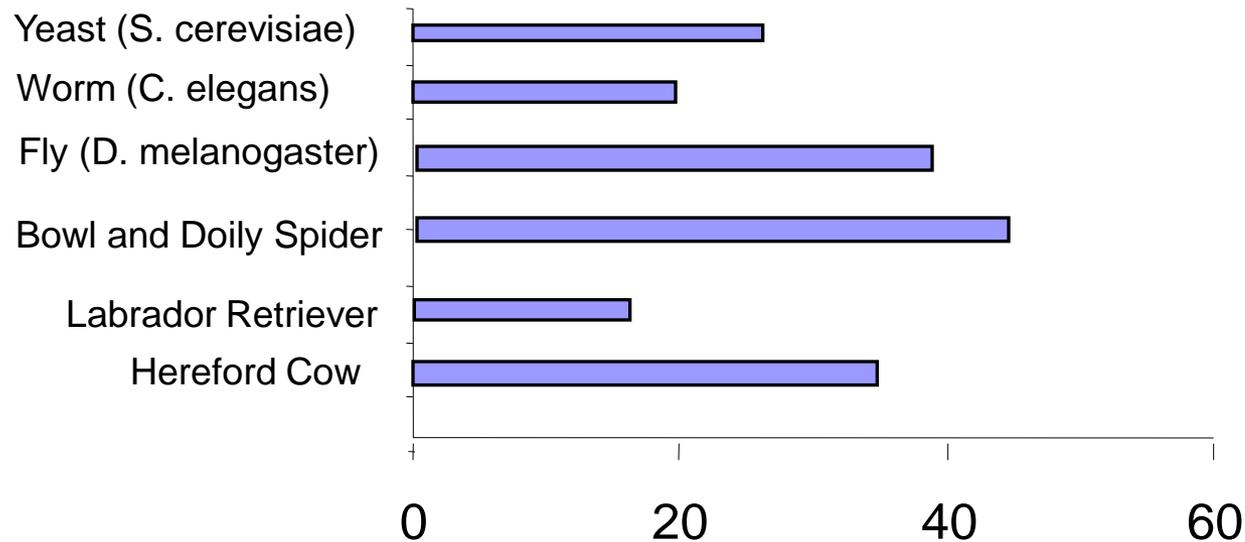


Energy out

- Physical Activity
- Routine Metabolism
- Thermoregulation
- Growth
- Storage

Energy
Balance:
kcal in = kcal out

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



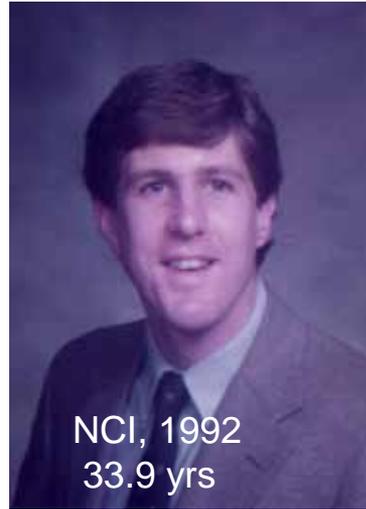
% Increase in Longevity (versus *ad libitum*-fed controls)

Control

?

CR

8.5 yrs.



9.0 yrs.



22.0 yrs.



22.4 yrs.



81125

81010

Weindruch: CR Study in Rhesus Monkeys (Colman, et al., *Science* 2009)

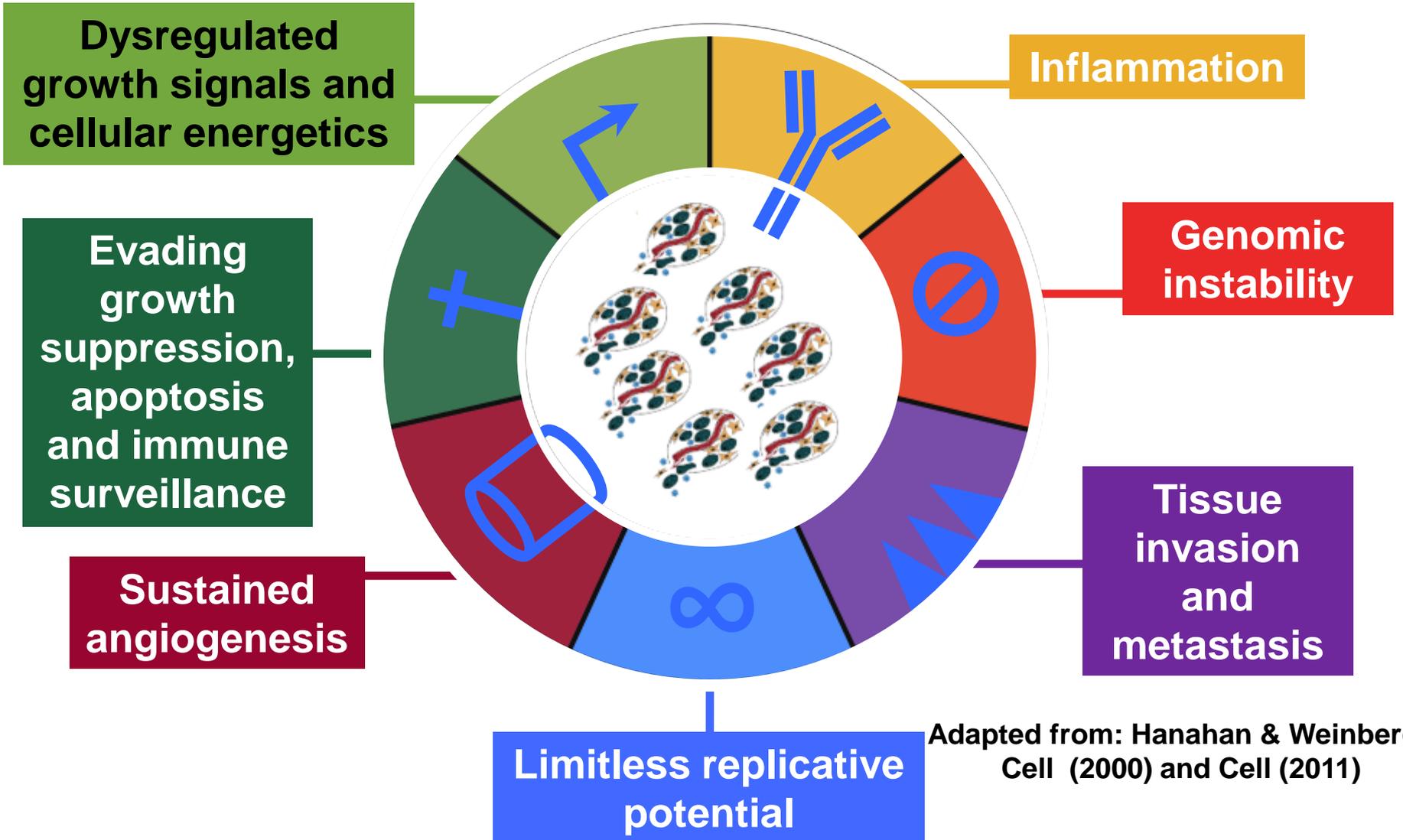
Calorie Restriction Inhibits Spontaneous Tumorigenesis in Multiple Model Systems

<u>Experimental System</u>		Degree of Calorie Restriction	Ratio of incidence in AL/CR
Tumor (spontaneous)	Animals		
Mammary	DBA mice	33%	44
	MMTV-neu TG	30%	3.7
	MMTV-Wnt-1 TG	30%	9.1
	Wistar rats	20%	5.0
Liver	C3H mice	33%	44
	Swiss mice	20%	7
Leukemia	AK mice	25%	6.5
	F344 rats	25%	9.3
Skin	CD1	40%	6.1
	Sencar mice	40%	2.5
	Wistar rats	20%	6
Pituitary	Wistar rats	20%	1.7
	Swiss mice	20%	7
	H:NMRI mice	20%	4.1
Pancreas	COBS rats	30%	4
	K-ras x Ink4A mice	30%	7.3
	K5-COX-2 TG mice	30%	5.5
Testes	F344 rats	40%	1.7

Adapted from: Hursting and Kari, *Mut Res*, 1999

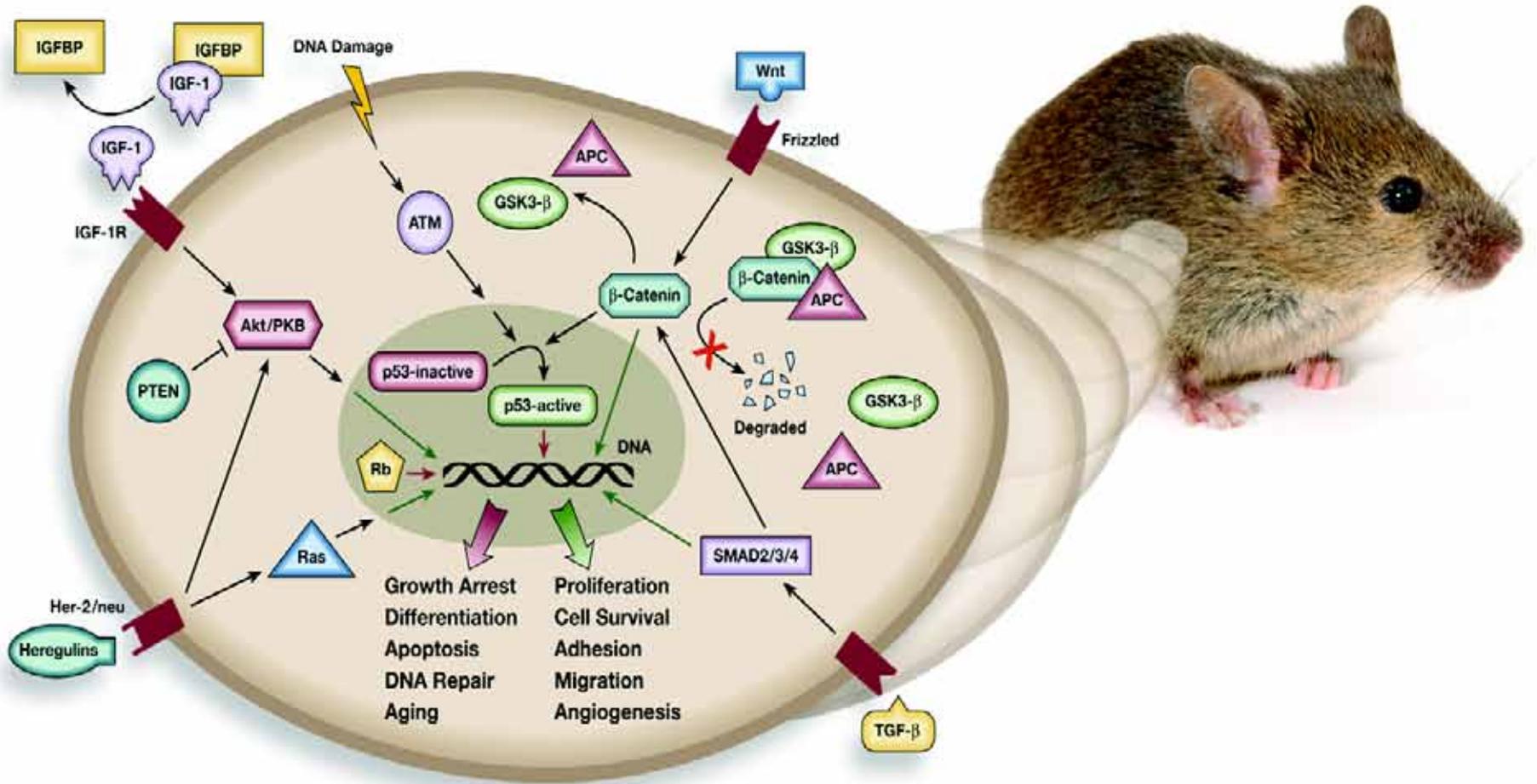
Cancer: A Complex Foe

The essential aberrations of cancer



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

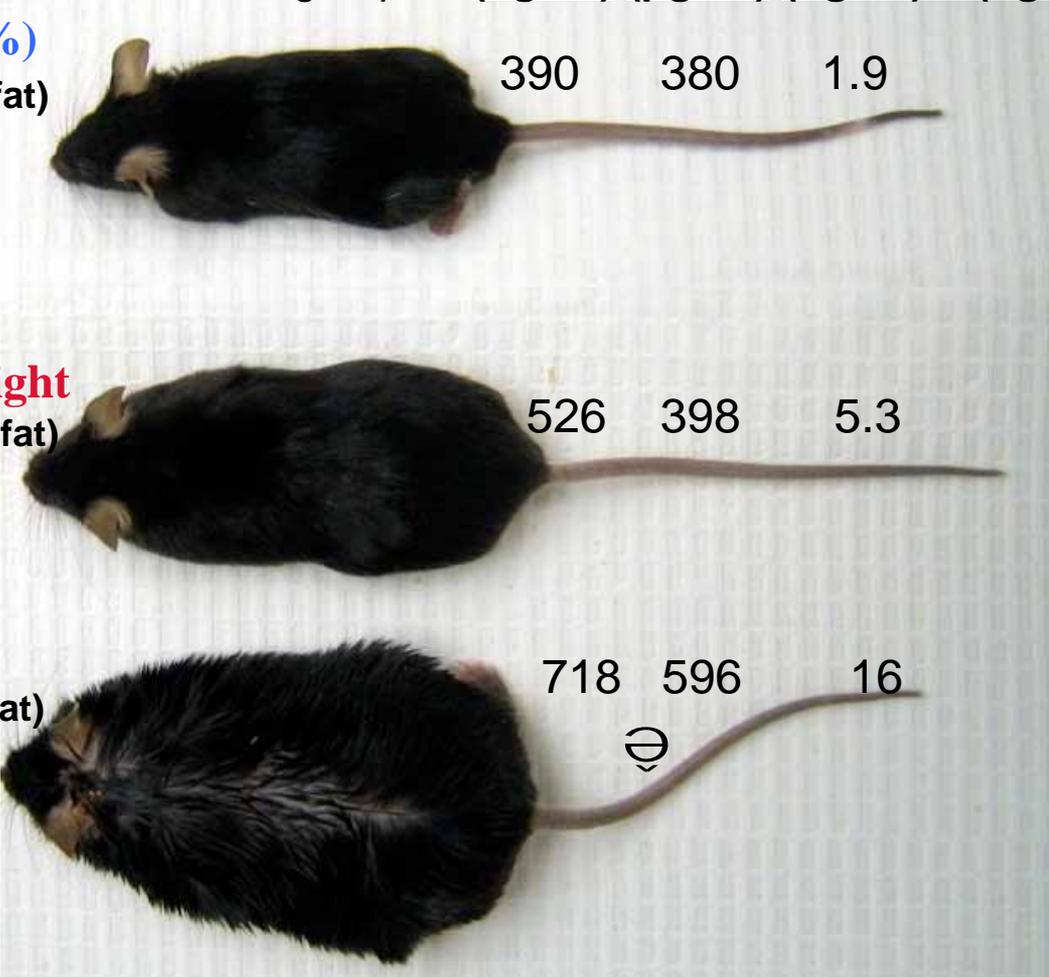
Modeling Energy Balance and Human Cancer in Mice by Altering Key Genes and Pathways



Growth Factor Levels and MMTV-Wnt-1 TG Mammary Tumor Growth in CR, Overweight and Diet-Induced Obese (DIO) Mice

	\hat{e}	\hat{e}	\hat{e}	\hat{e}	\hat{e}	\hat{e}
	IGF-1	Insulin	Leptin	Adiponectin	L/A	Tumor Vol
	(ng/ml)	(pg/ml)	(ng/ml)	(ng/ml)		(mm ³)
CR (30%) (29% body fat)	390	380	1.9	9.4	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
		\ominus			\ominus	\ominus

n=12 mice/group

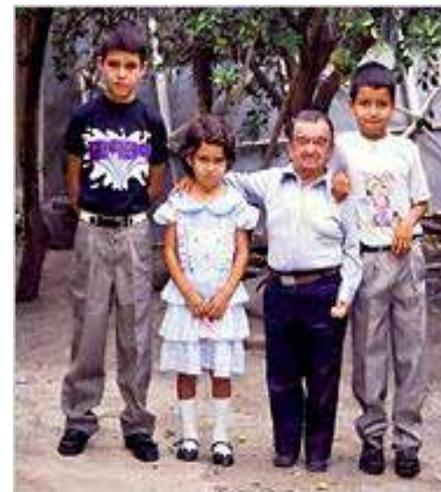
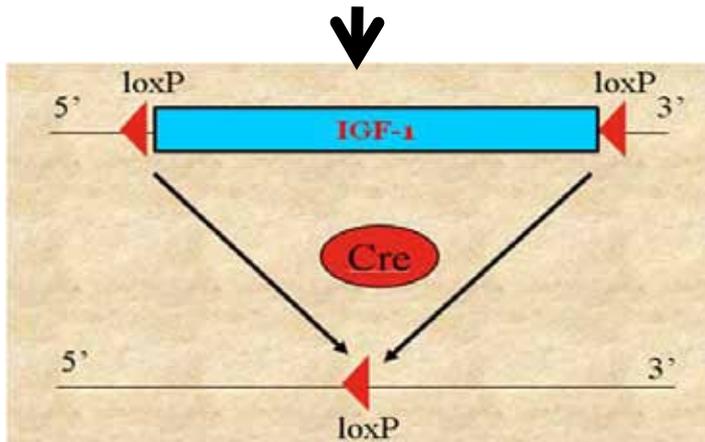
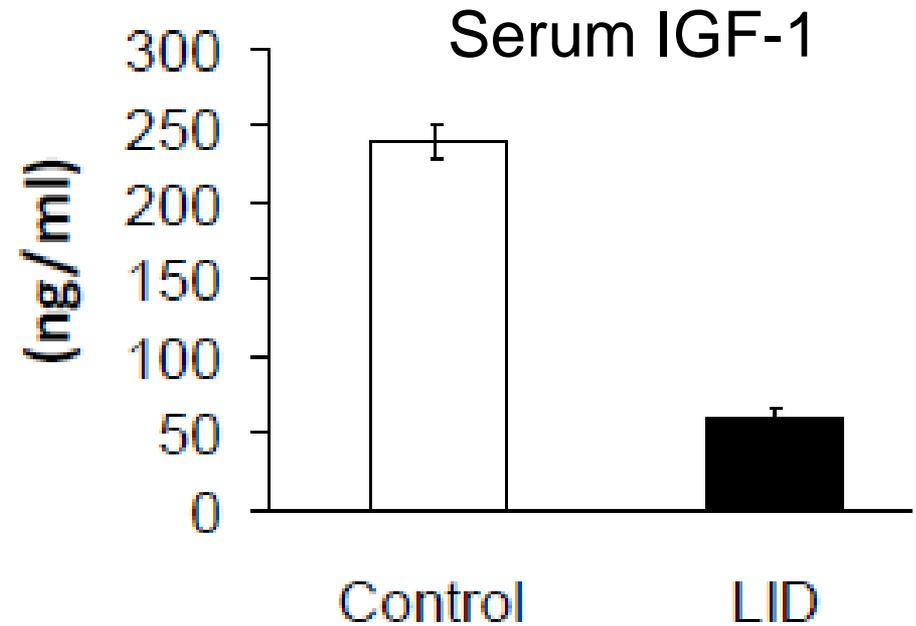
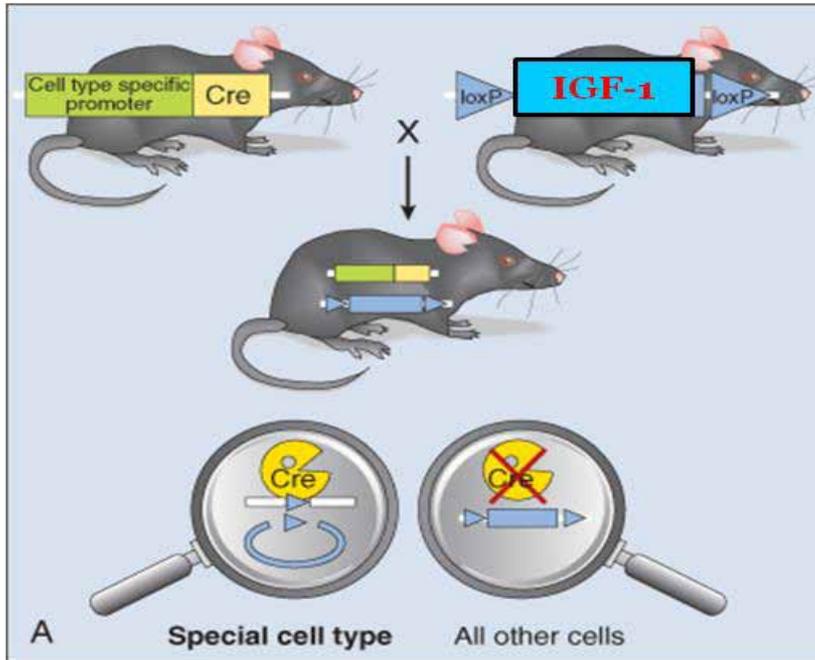



Dr. Nomeli Nunez

Adapted from: Nunez, et al., *Nutrition and Cancer*, 2007

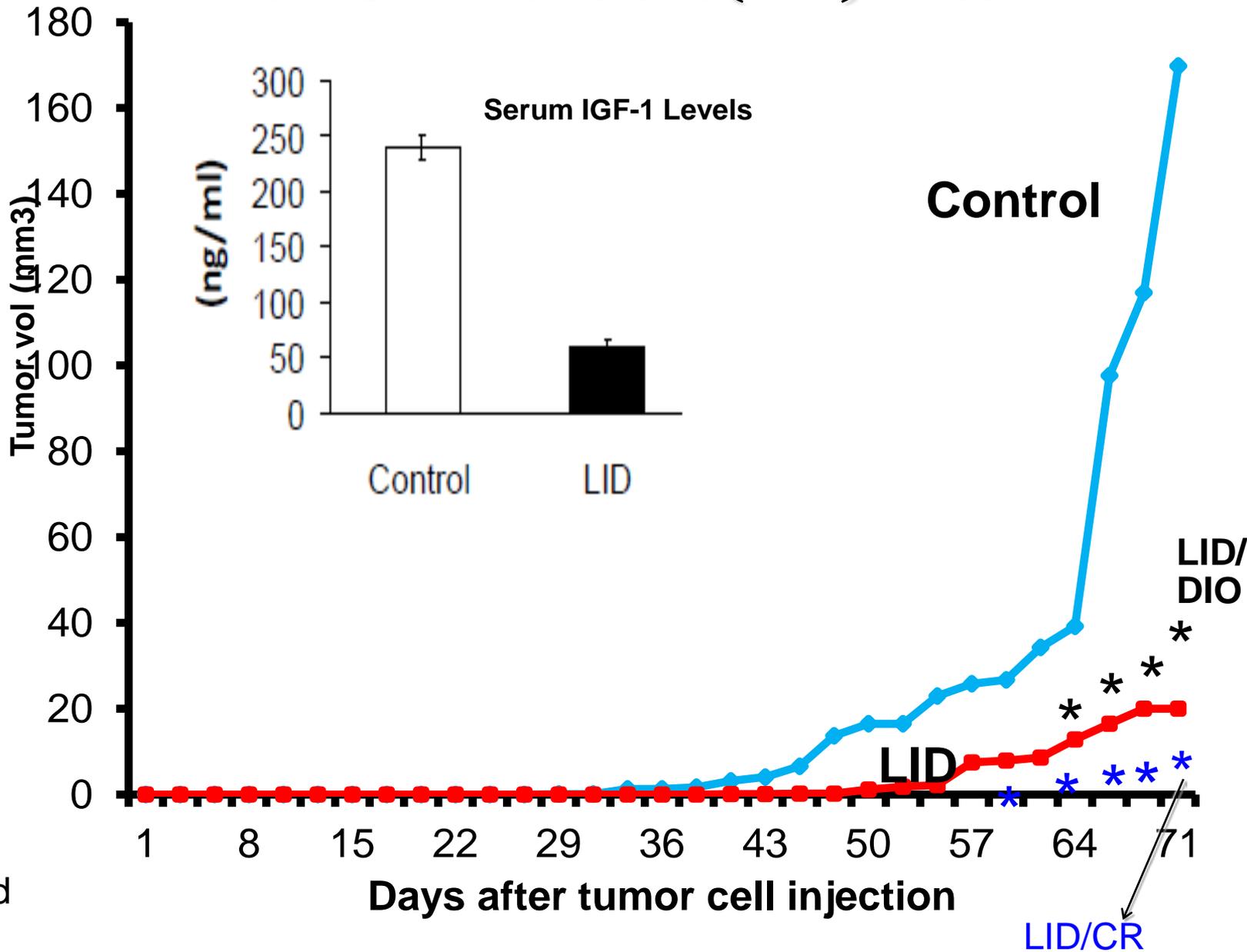
Genetic Reduction of Systemic IGF-1

~75% of IGF-1 in serum -- liver



Ecuadorians with Laron Syndrome Have Very Low IGF-1, Increased Longevity, and Virtually No Cancer or Diabetes. *NY Times* 2/16/11.

Mammary Tumor Growth in Control and Liver IGF-1 Deficient (LID) Mice



Dr. Nikki Ford

Diabetic A-Zip/F-1 Mice Lack WAT But Display Increased Susceptibility to Mammary and Skin Carcinogenesis



A-ZIP/F-1

A-ZIP/F-1

Wild type

Serum:

- é Insulin, IGF-1
- é Cytokines
- ê Adipokines

Tissue:

- é pAkt
- é pmTOR

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;

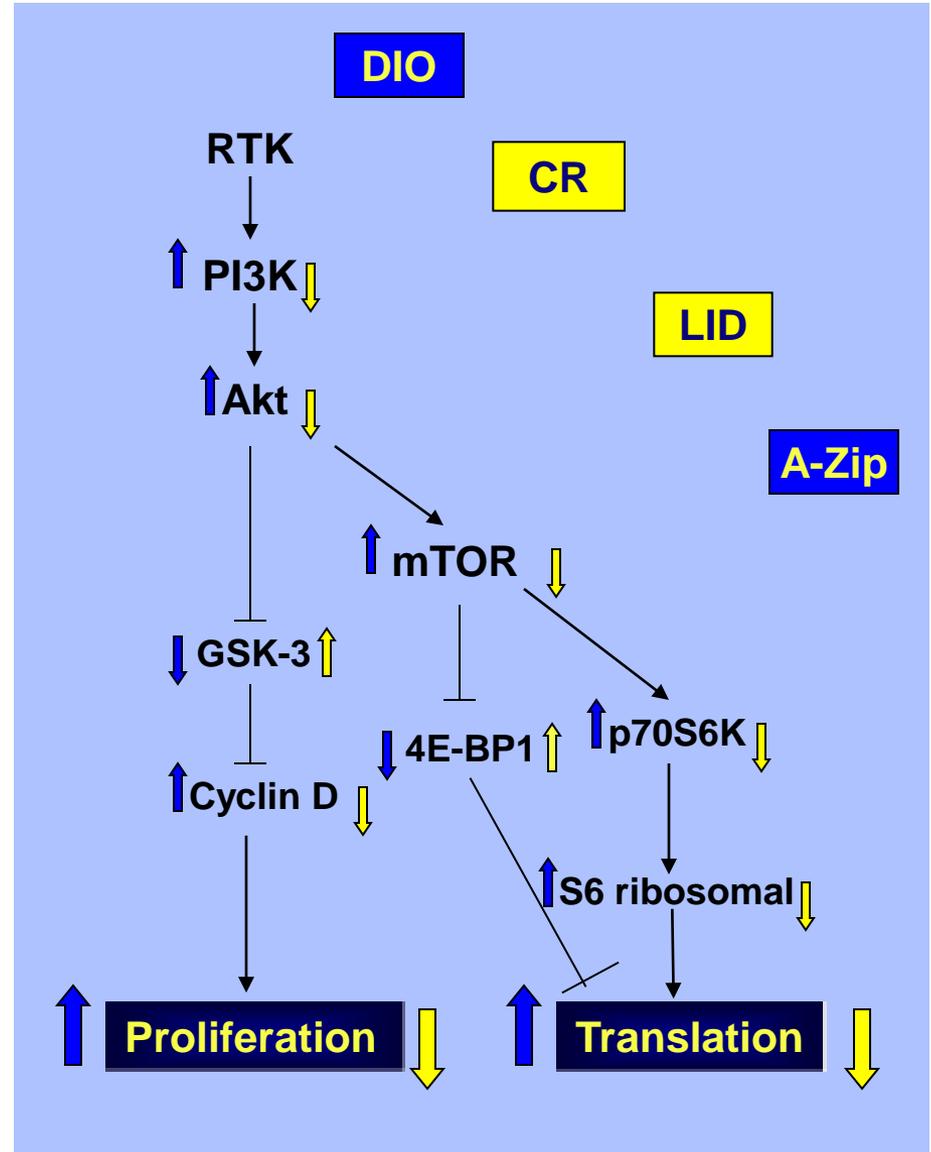
Olivo-Marston, et al., *Mol Carcinogenesis* 2009

Lashinger, et al, *Cancer Prev Res*, 2011

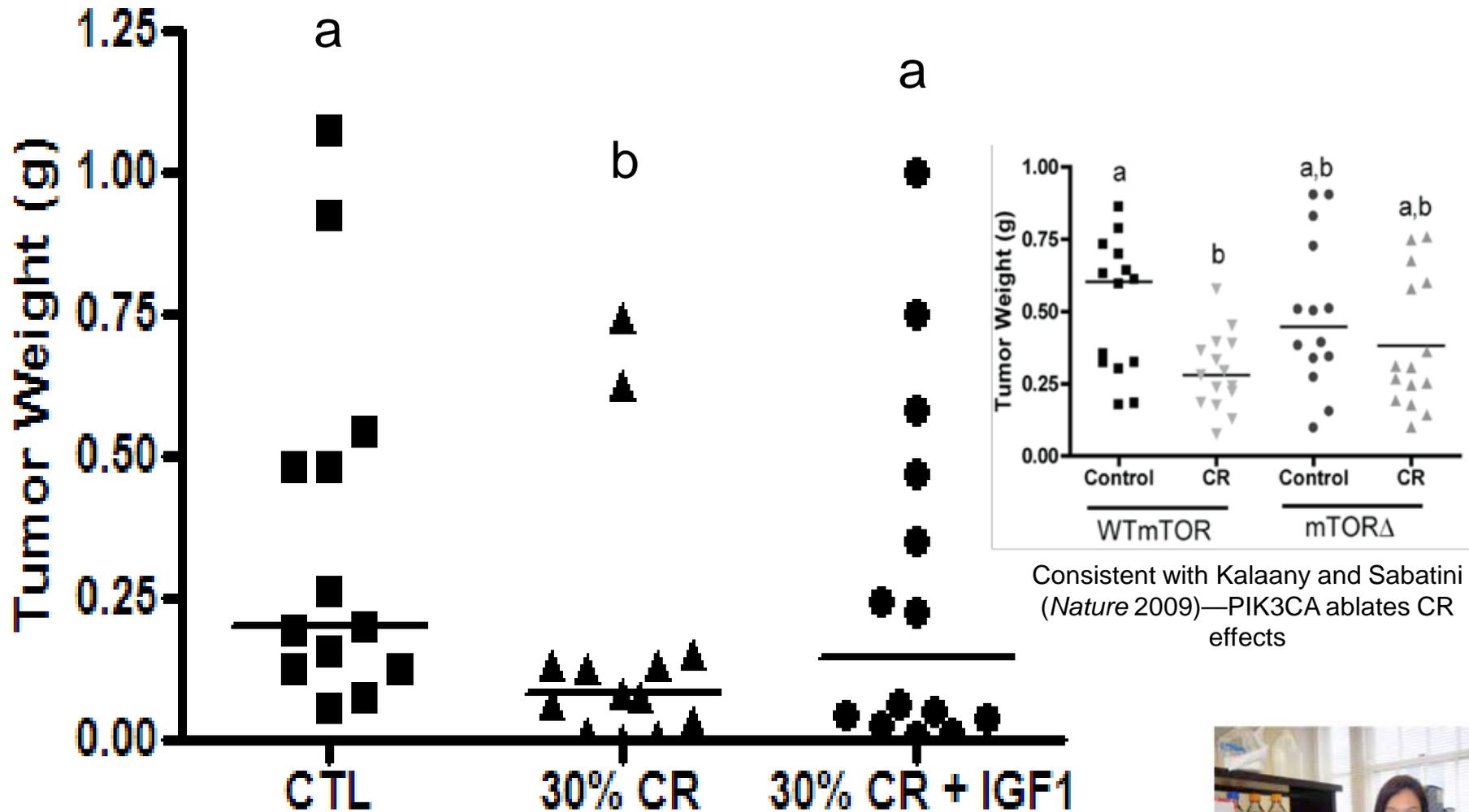
Blando, et al., *Cancer Prev Res*, 2011

Nogueira, et al, *Endocr Rel Cancer*, 2011 in press

deAngel, et al., *Mol Carcinogenesis*, in press

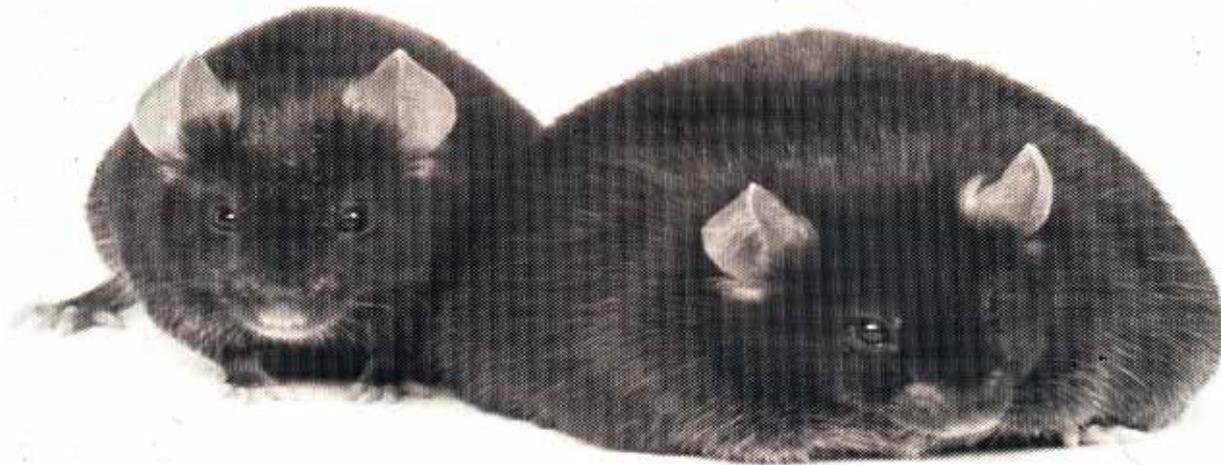


The Effect of IGF-1 Infusion on Growth of Orthotopically Transplanted MMTV-Wnt-1 Mammary Tumors in Calorie Restricted Mice



Phenotypes of Genetically Obese *db/db* and *ob/ob* Mice

- Morbid obesity - early onset
- Hyperphagic –2X the intake of controls
- Hyperglycemic
- Hyperinsulinemic, but low IGF-1 and HMW adiponectin
- *db/db*: Hyperleptinemic/leptin resistant - mutant leptin receptor
- *ob/ob*: Hypoleptinemic; no circulating WT leptin



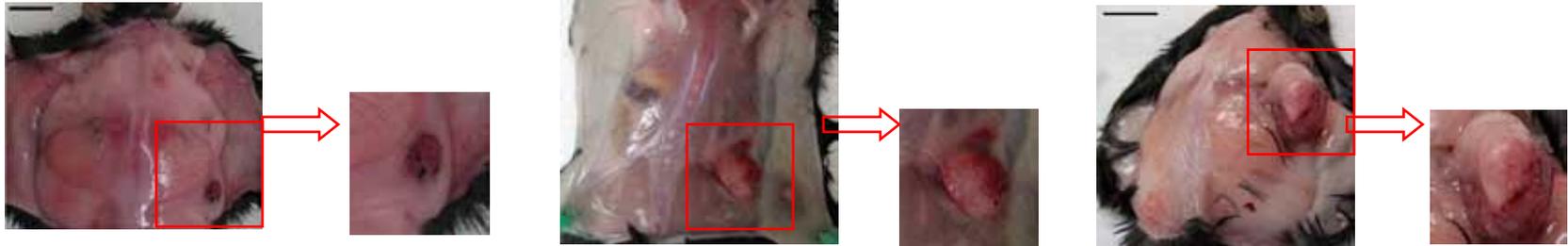
Wnt-1 Mammary Tumor Growth Is Increased in *db/db* Mice but Suppressed in *ob/ob* Mice



ob/ob

WT

db/db



Insulin:

ééé

è

ééé

IGF-1:

ê

è

ê

L/A:

ê

è

ééé

Tumor Wt (g)

0.21 ± 0.07

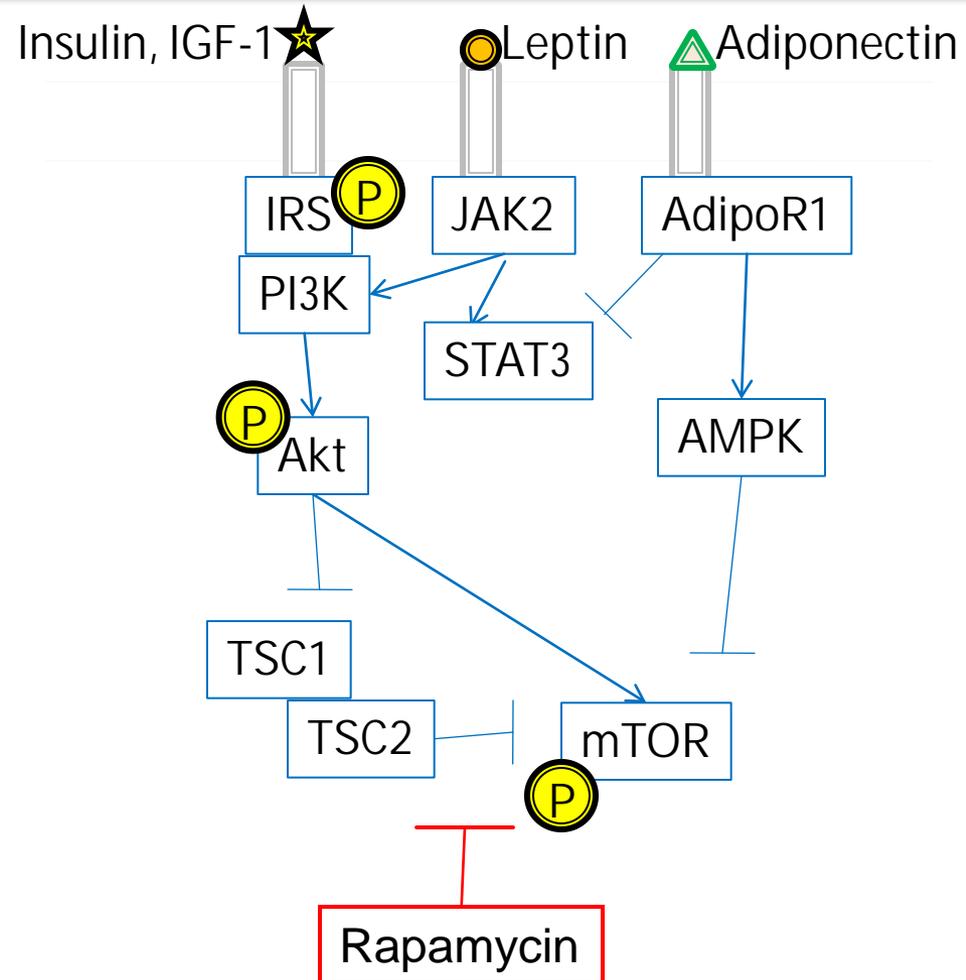
0.62 ± 0.13

1.68 ± 0.33

Converging Signaling Pathways

Obesity/Insulin Resistance

- ↑ Insulin
- ↑ IGF-1
- ↑ Leptin
- ↓ Adiponectin

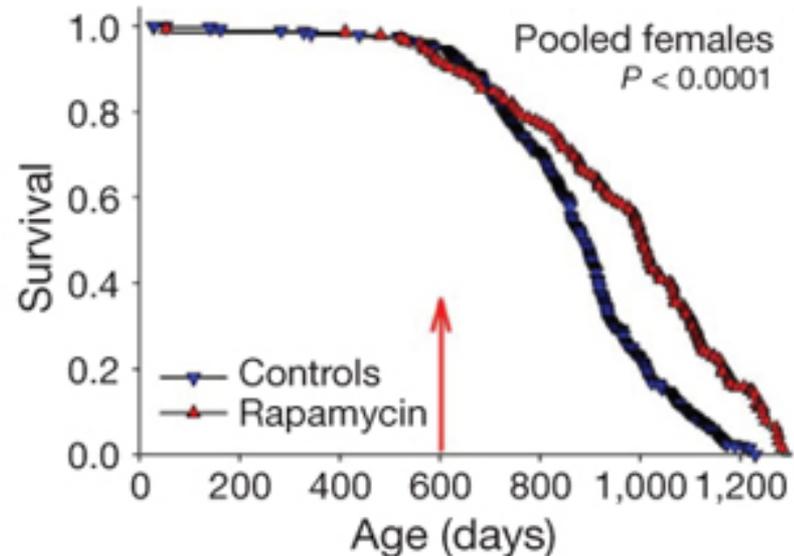
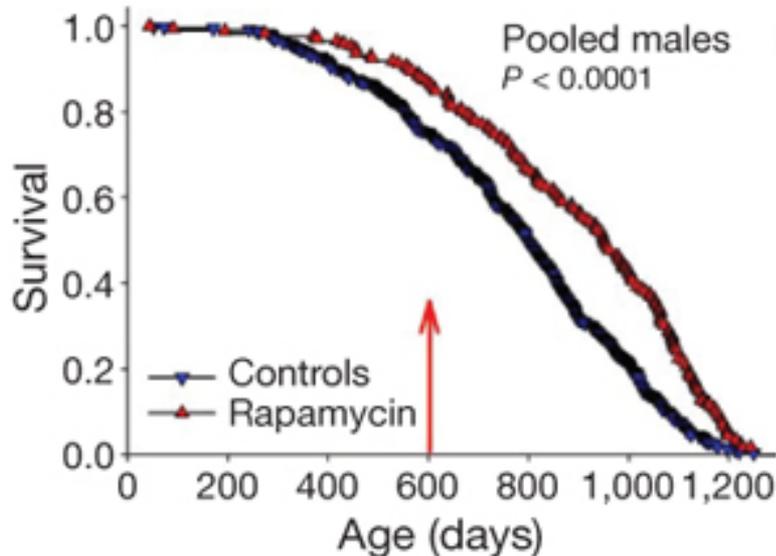


LETTERS

Rapamycin fed late in life extends lifespan in genetically heterogeneous mice

David E. Harrison^{1*}, Randy Strong^{2*}, Zelton Dave Sharp³, James F. Nelson⁴, Clinton M. Astle¹, Kevin Flurkey¹, Nancy L. Nadon⁵, J. Erby Wilkinson⁶, Krystyna Frenkel⁷, Christy S. Carter⁸{, Marco Pahor⁸{, Martin A. Javors⁹, Elizabeth Fernandez² & Richard A. Miller^{10*}

Survival plots for male and female mice, comparing control mice to those fed rapamycin (2.4 mg/kg/day) in the diet starting at 600 days of age, pooling across the three test sites.



CR and Rapamycin (but not Treadmill Exercise) Reverse the Effects of DIO on Transplanted Wnt-1 Tumor Growth

n=15 mice/group

Tumor Weight (mg)

- Rapamycin + Rapamycin

CR



61 ± 19

Not done

Treadmill Exercise



347 ± 211

Not done



394 ± 243

92 ± 23

DIO



Mouse Models of Physical Activity and Carcinogenesis

Motorized Treadmill



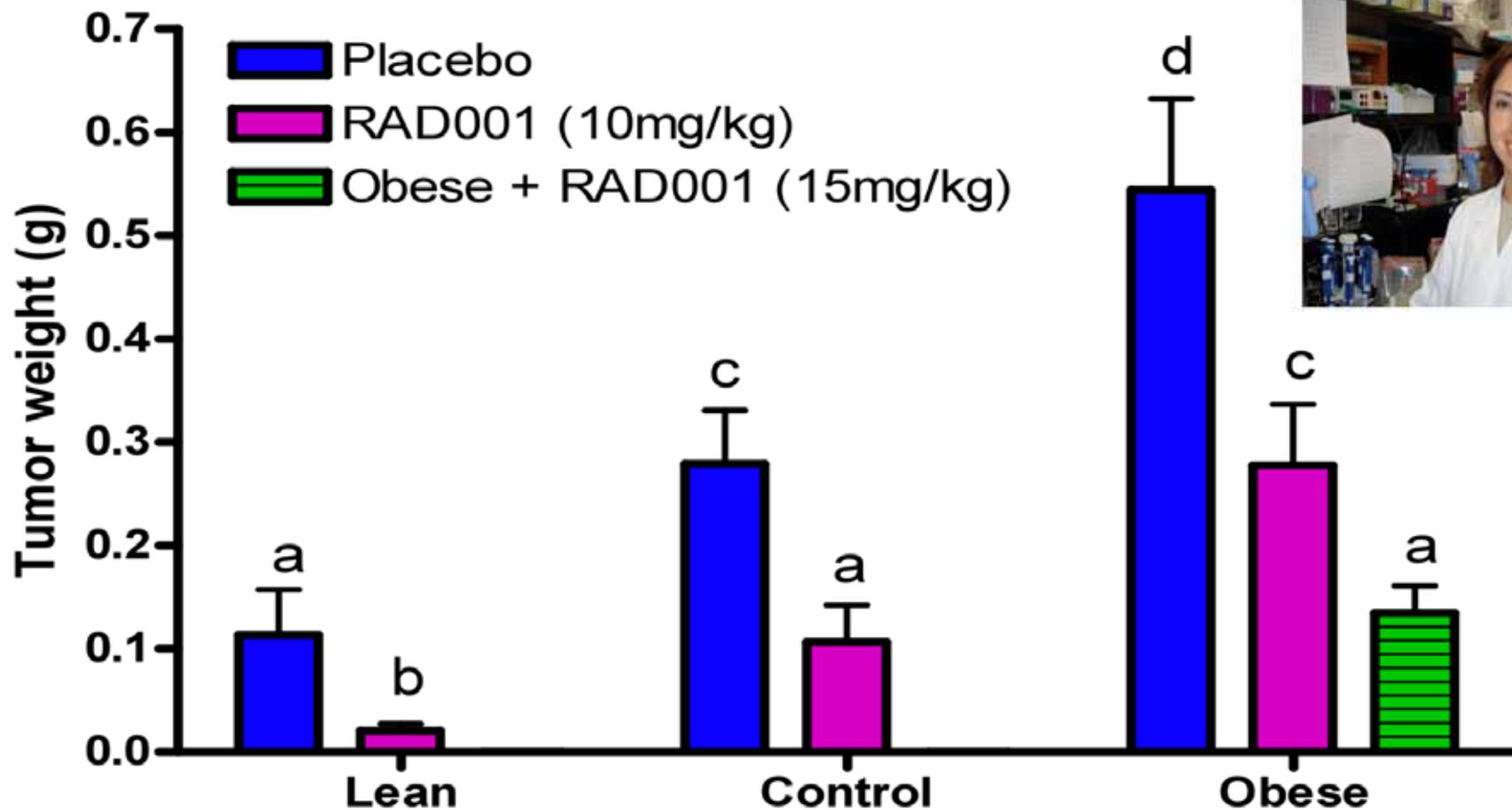
Voluntary Running Wheel



CR, Voluntary Wheel Running Decreases Polyp Formation in *APC*^{min} Mice

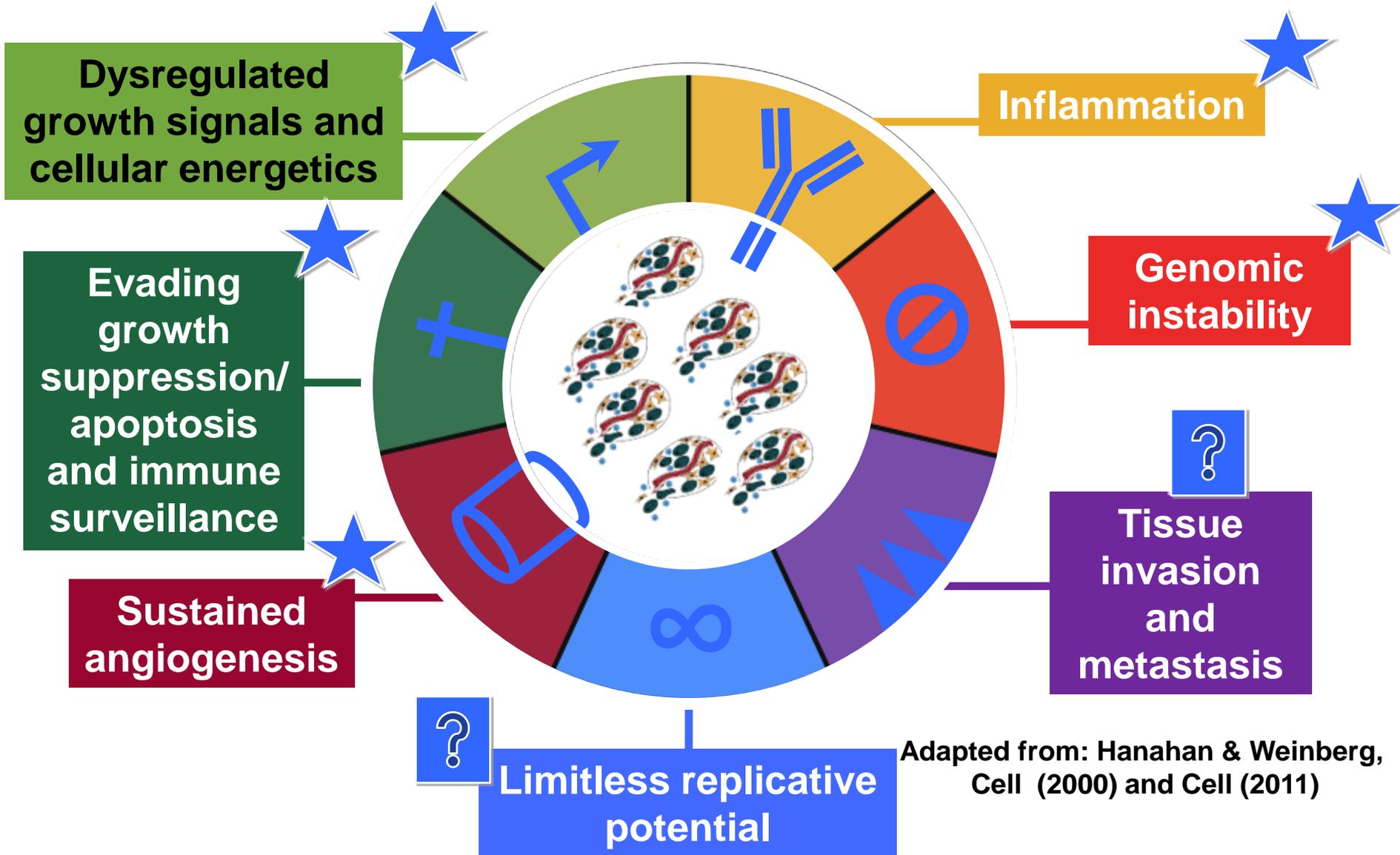
<u>Treatment</u>	<u>Total Polyps (SE)</u>	<u>Polyps > 2mm (SE)</u>	<u>Survival 100 days</u>
Control (n=20)	26.2 (2) ^a	20.3 (1.8) ^a	62% ^a
Wheel (n=21)	21.2 (2.3) ^b	14.2 (2) ^b	100% ^b
CR (n=20)	3.8 (0.6) ^c	1.1 (0.4) ^c	100% ^b

The mTOR Inhibitor RAD001 (Everolimus) Inhibits Wnt-1 Mammary Tumor Growth in Lean, Control and Obese Mice



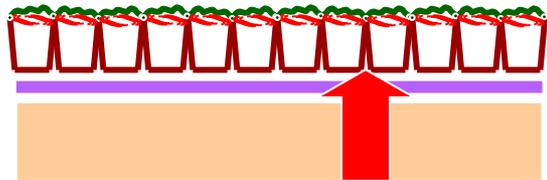
Cancer: A Complex Foe

Energy balance impacts the essential aberrations of cancer

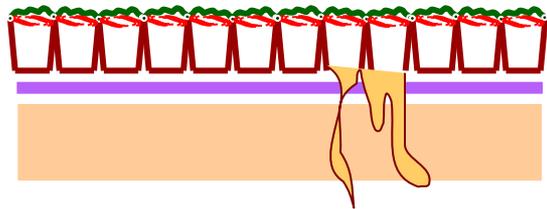


Adapted from: Hanahan & Weinberg, Cell (2000) and Cell (2011)

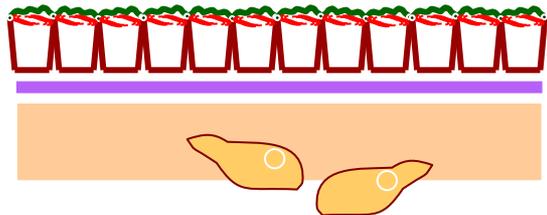
Dynamics of epithelial tissues: epithelial-mesenchymal transition (EMT)



Specific epithelial cells receive signals to differentiate



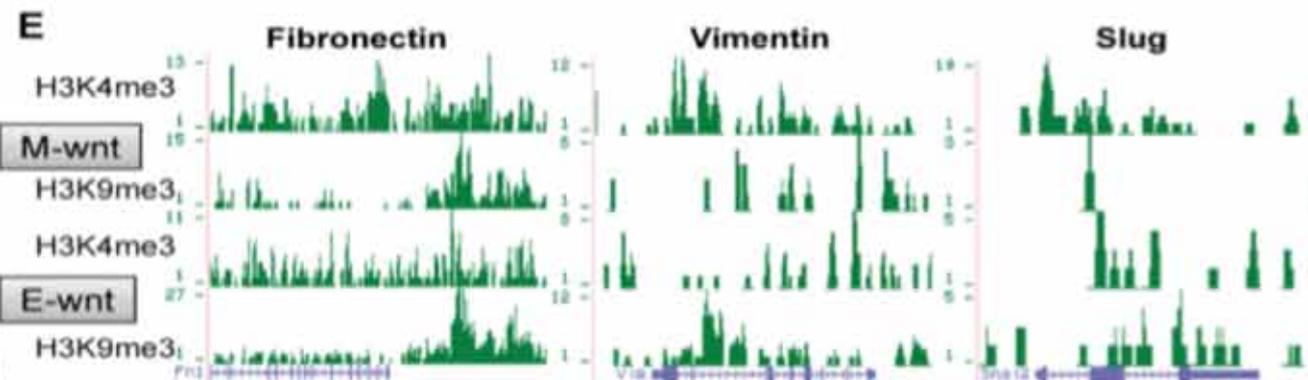
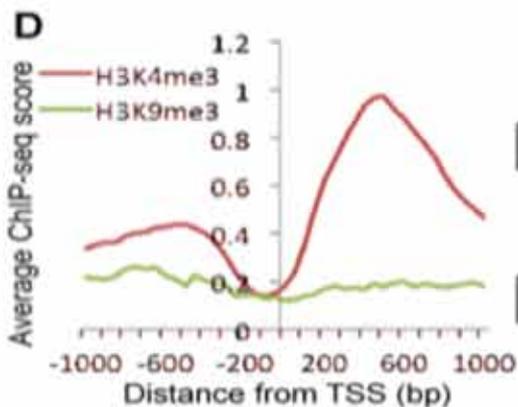
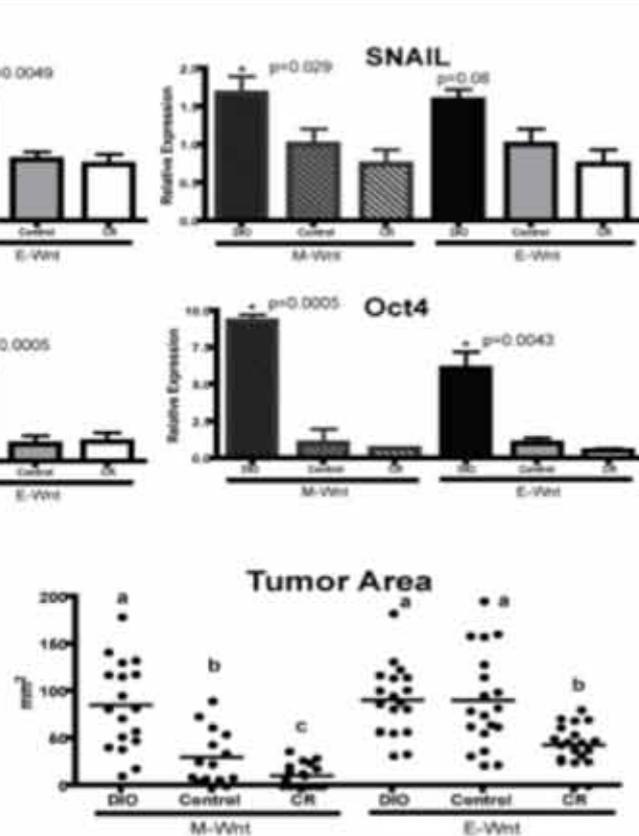
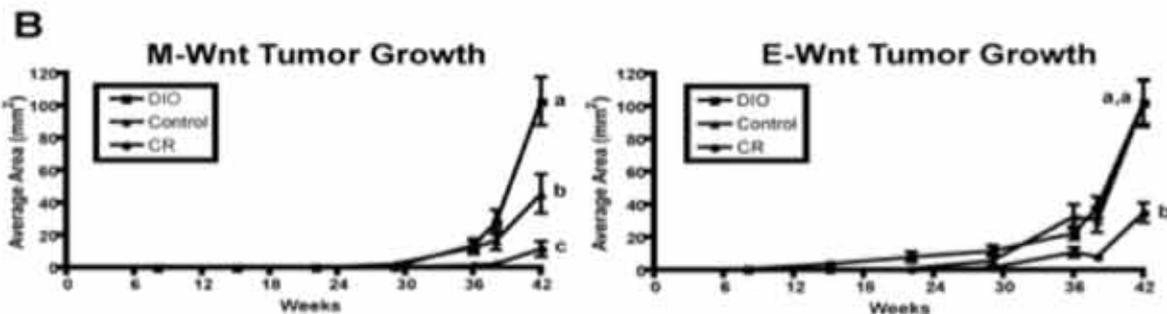
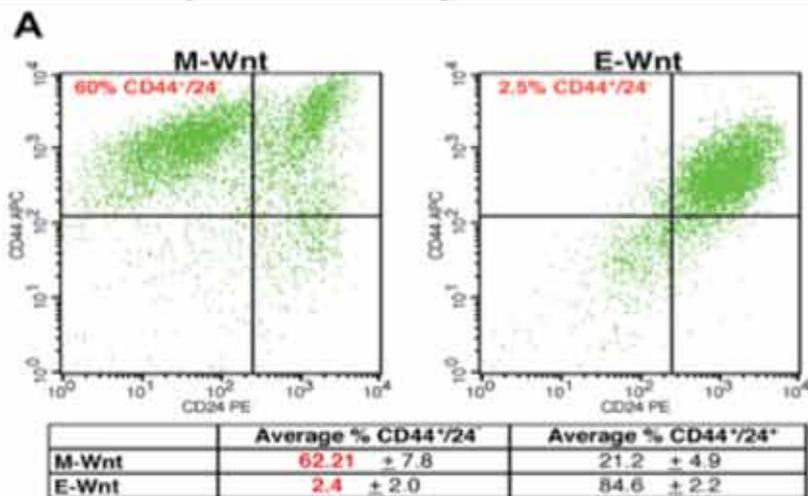
Cells protrude out of epithelium, disassemble cell-cell junctions



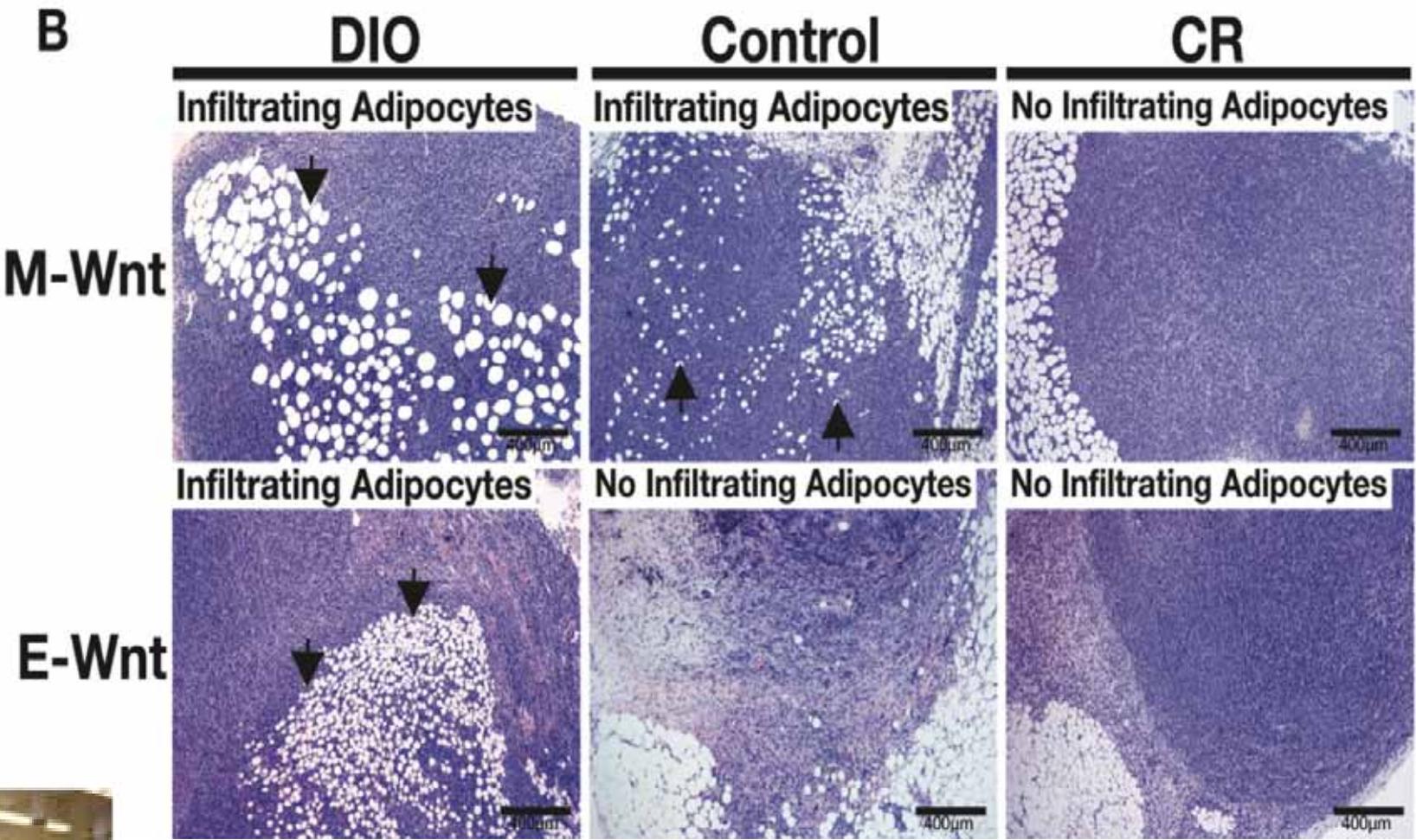
Cells become 'mesenchymal' (invasive and migratory) and then differentiate to a new cell type in another location.

Does Obesity Promote EMT? Enrich Breast Cancer Stem Cells?

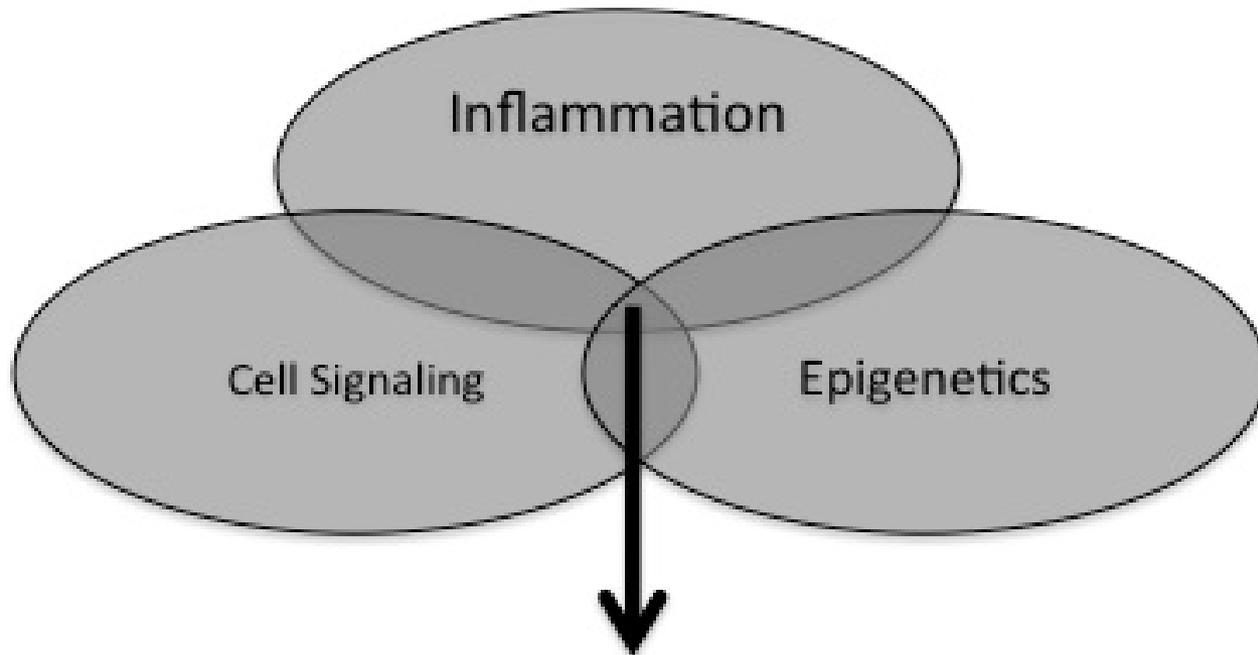
Effects of Energy Balance on M-Wnt (Claudin-low) and E-Wnt (Basal-like) Mammary Tumors and EMT Markers (Dunlap, et al., *Cancer Res*, submitted)



Energy Balance Modulates Adipocyte/Tumor Cell Interactions in M-Wnt (Claudin-low) Mammary Tumor Cells



Targets and Pathways for Intervention



Breaking the Obesity Cancer Link



Karrie
Wheatley

Jason
Goldberg

Alison
Harvey

Lauri
Lashinger

Susan
Perkins

[Person in center back row]

Leticia
Nogueira

Rebecca
DeAngel

Sarah
Dunlap

Audrey
Rasmussen

Lauren
Malone

Hunting Lab

Hunting Lab

Hunting Lab

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National Cancer Institute

Lyuba Varticovski, Chuck Vinson, Curtis Harris

Cleveland Clinic/Case Western

Ofer Reizes

University of Kansas Medical Center

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