

Increased Risk of Cancer in Obesity and Type 2 Diabetes

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Disclosures

- Consultant :

- Merck
- Bristol Myers Squibb
- Astrazeneca
- Sanofi-Aventis

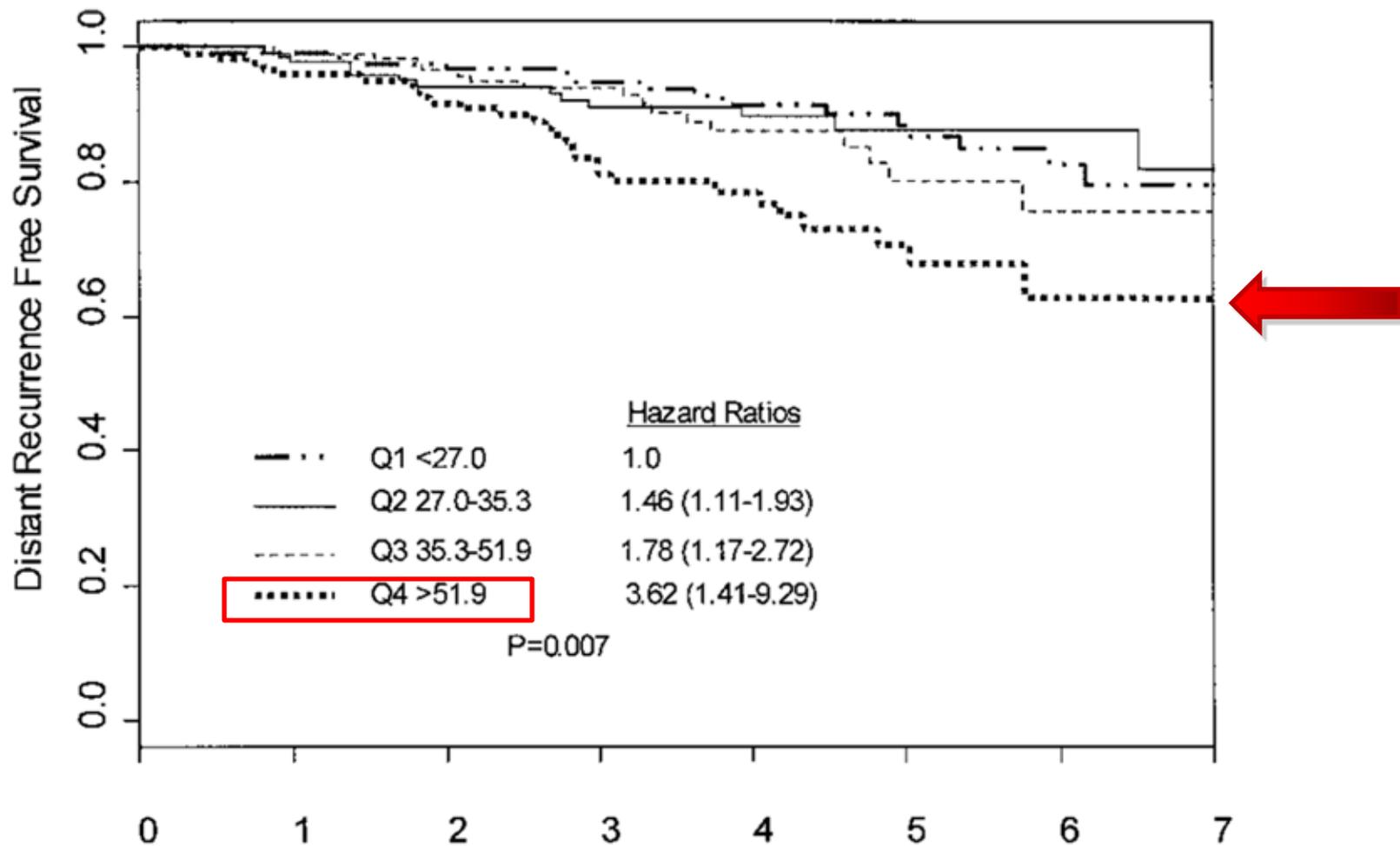
Grant Support:

Merck
Sanofi
Novartis

Order:

1. Epidemiology
2. Animal model
3. Mechanisms

Breast Cancer and Endogenous Insulin Levels



Does Bariatric Surgery Affect Mortality?

University of Utah, 2007

- Retrospective cohort study
 - 9949 gastric bypass patients
 - 9628 severely obese driver's license applicants (BMI ≥ 35 kg/m²)

Does Bariatric Surgery Affect Mortality?

	Surgery Group (#/10,000 person-yr)	Control Group (#/10,000 person-yr)
All causes of death	37.2	61.1
CV disease	8.5	19.3
Diabetes	0.3	3.5
Cancer	5.4	15
Other disease	11.4	17
Non-disease causes		
Accident	3.7	2.7
Poisoning	1.9	0.6
Suicide	2.7	1.2

Historical - 1910

A Statistical Study in Cancer Death-Rates

Cancer and Diabetes,

Both diseases have very much the same age distribution. (2) They stand almost alone as being on the increase, while other causes of death show declining rates. (3) The aetiology of both diseases is obscure. (4) Both being diseases of old age ...

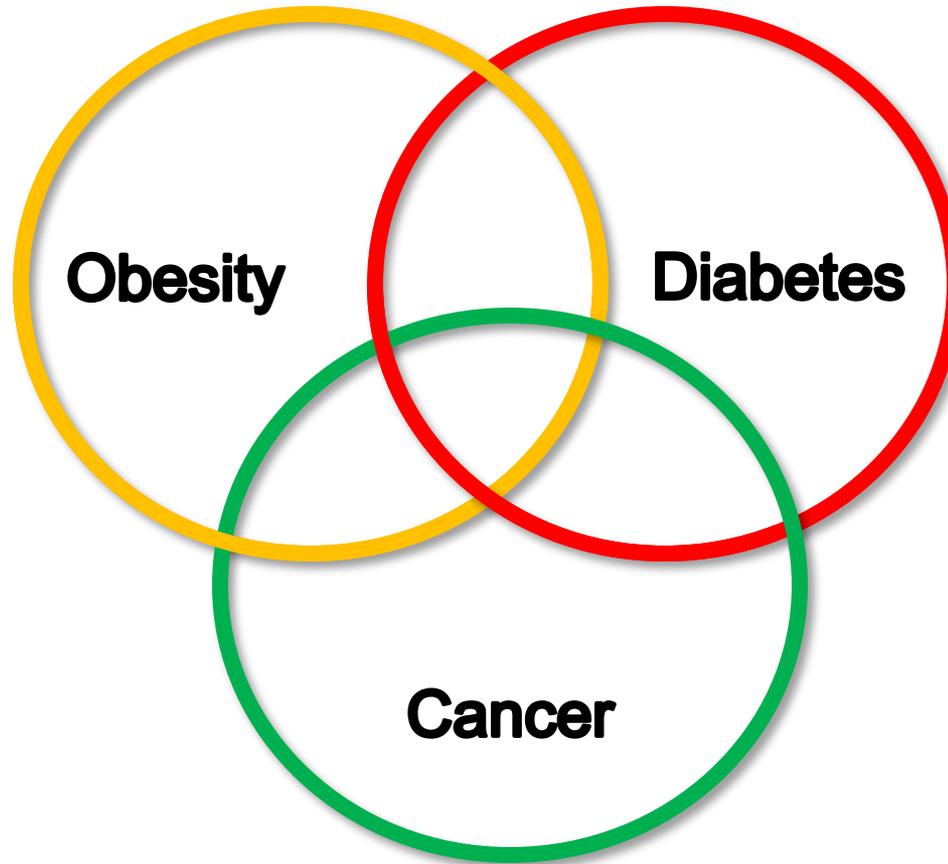
... If there were a common factor in the causation of the dual increase a correlation between these diseases might be discovered.

If there was a common factor in the causation of the dual increase.....

**Today we know that the risk of cancer in diabetes goes from $<1/10$ to $\sim 1/6$
Diabetes care 2011**

How Can Obesity and Diabetes Affect Breast Cancer Development?

Nutrients
IGF-I
Leptin
Adiponectin
Cytokines
Chemokines

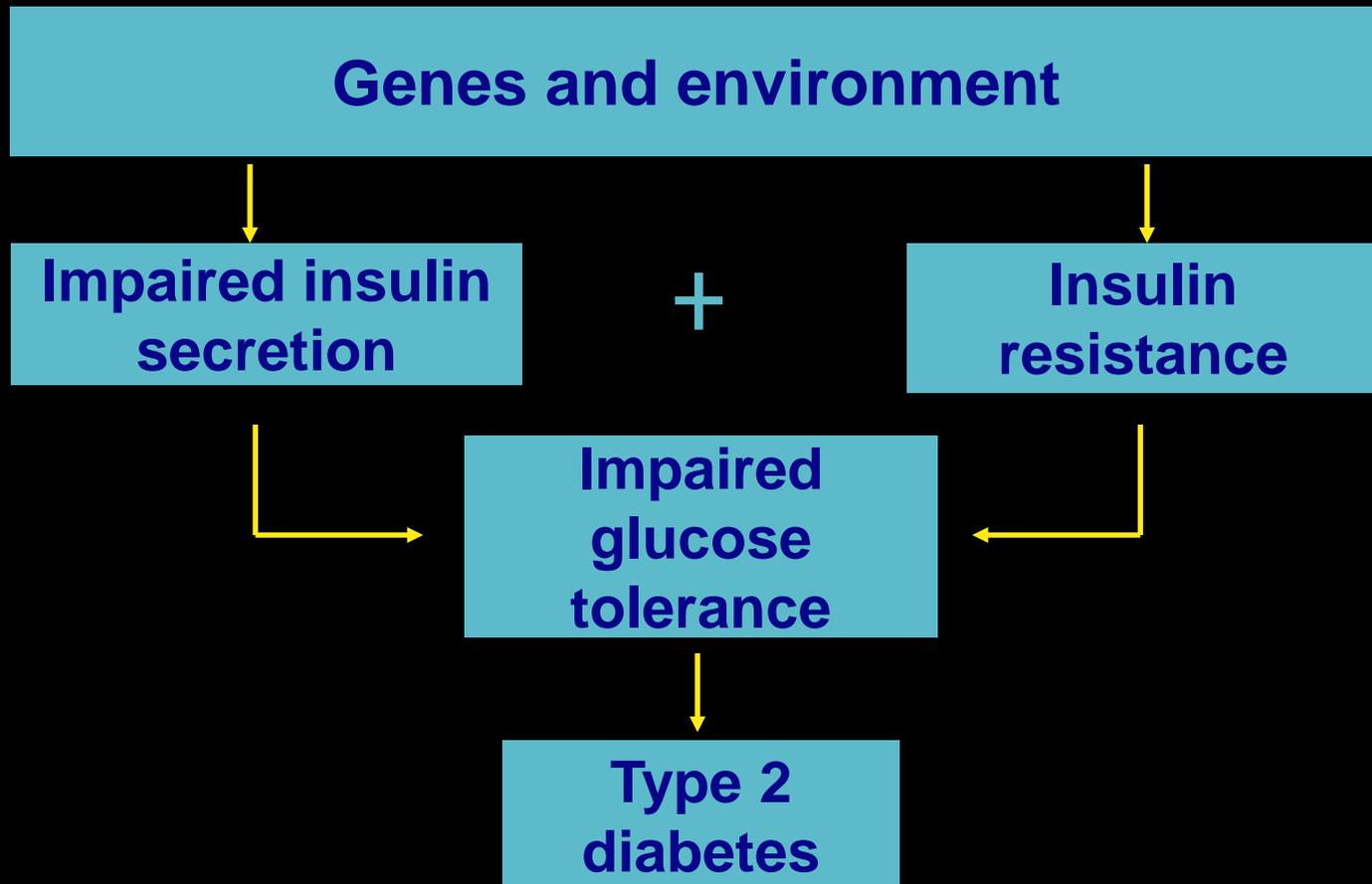


Hyperinsulinemia
Hyperglycemia
Hyperlipidemia

A Mouse Model of Type 2 Diabetes

Etiology of Type 2 Diabetes

Impaired Insulin Secretion and Insulin Resistance



Animal Model of Insulin Resistance

IGF-I/insulin
receptor
hybrids in
muscle

Insulin resistance in adipocytes

Insulin resistance
in liver

Muscle Insulin
Resistance

Increased lipolysis
in visceral fat

Increased
gluconeogenesis
in liver

Increased fatty acids

Fatty acid
oxidation

β cell
compensation

Increased glucose output

Impaired
glucose tolerance

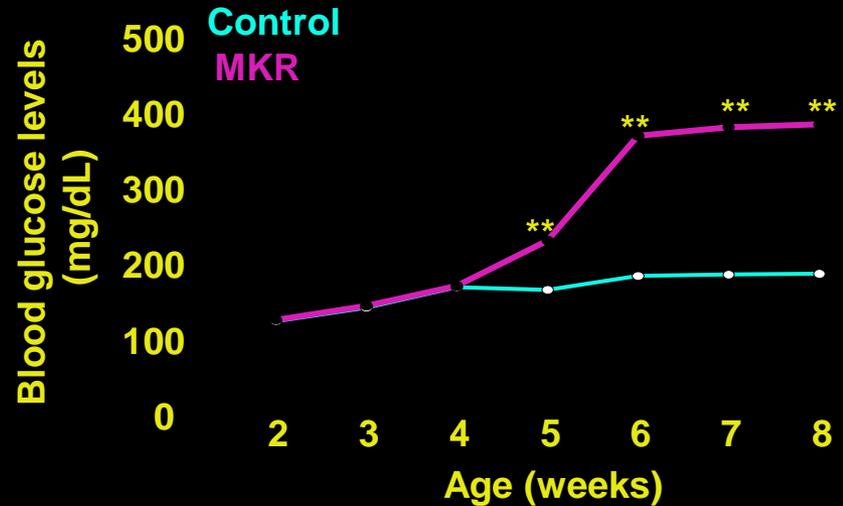
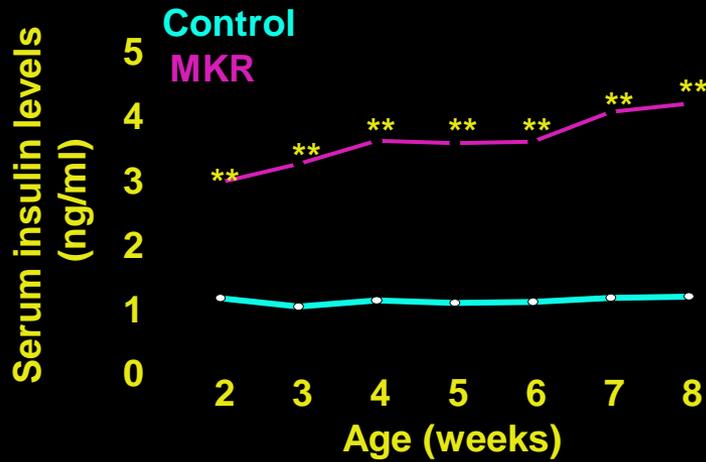
β cell
decompensation

Loss of 1st phase
insulin secretion

Type 2 Diabetes

Non-Obese

Metabolic Characteristics of MKR Mice



3 weeks GTT

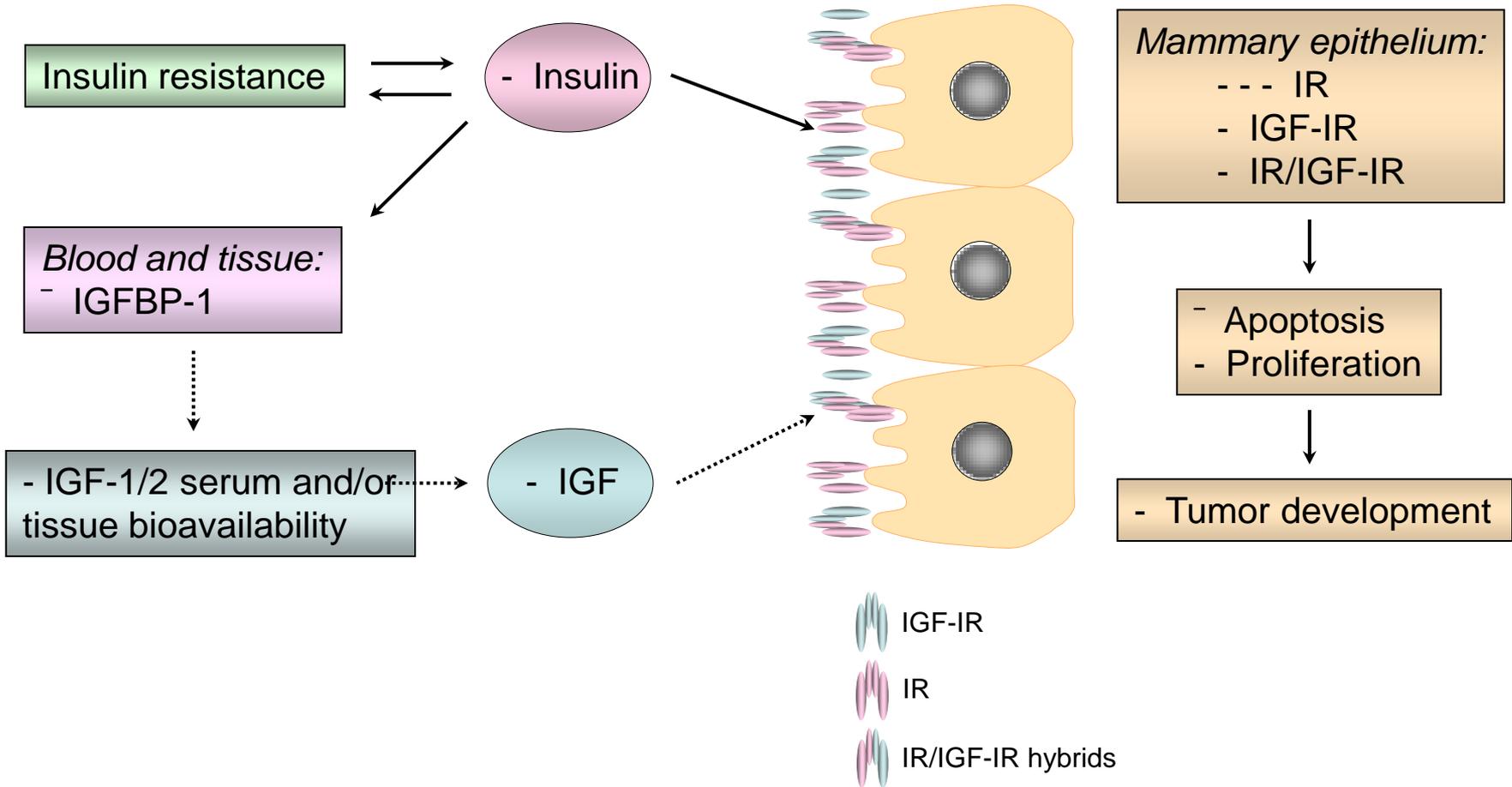


8 weeks GTT

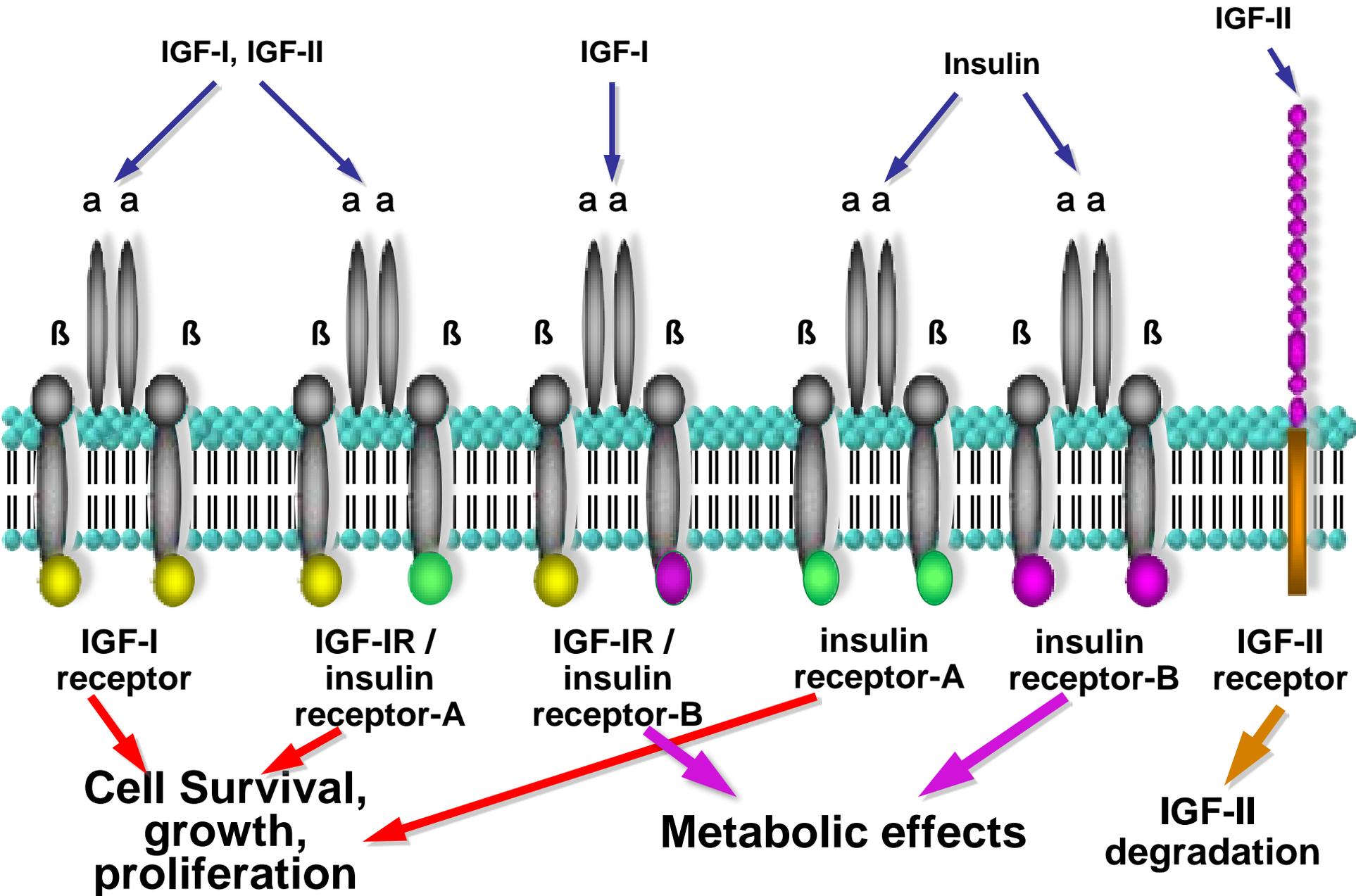


Metabolic Abnormalities in MKR Mice

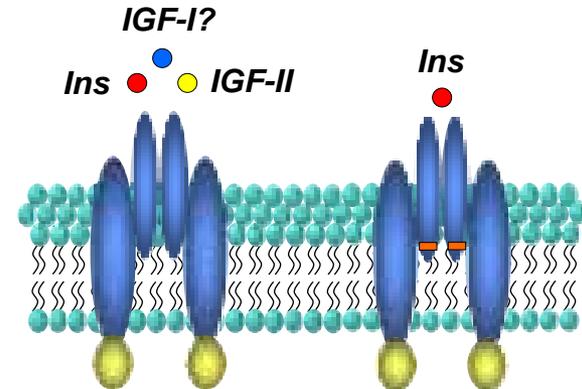
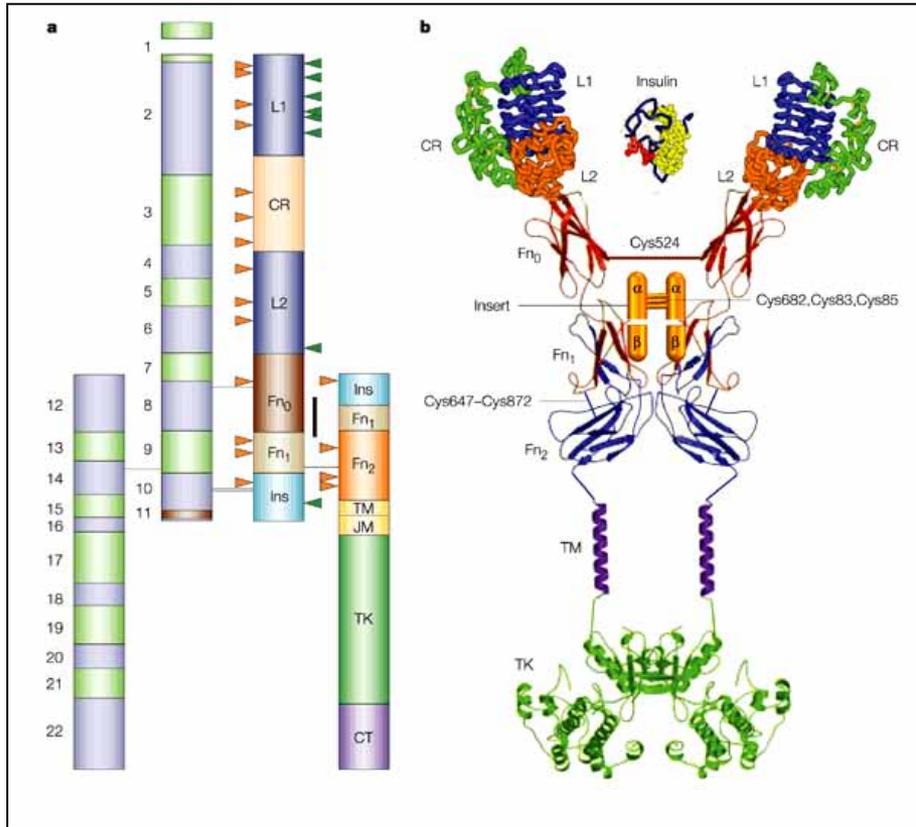
	Males	Females
Hyperglycemia	++	-
Hyperinsulinemia	+++	+++
Insulin resistance	+++	+++
Hyperlipidemia	++	-
Obesity	-	-



IR and IGF-IR Receptors



Insulin Receptor Isoforms



IR-A

IR-B

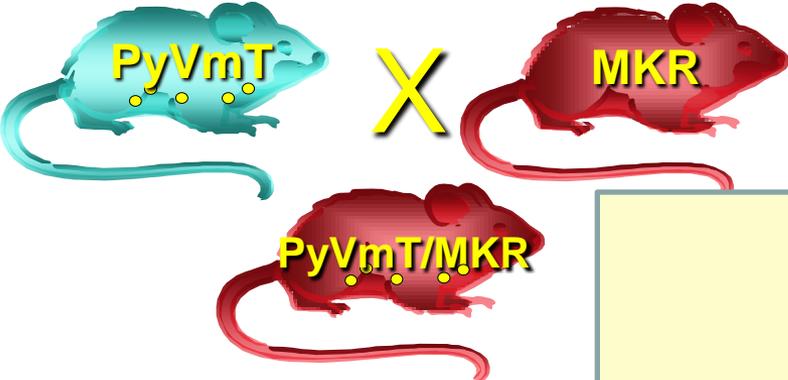
Metabolic
and mitogenic
effects

Metabolic
effects

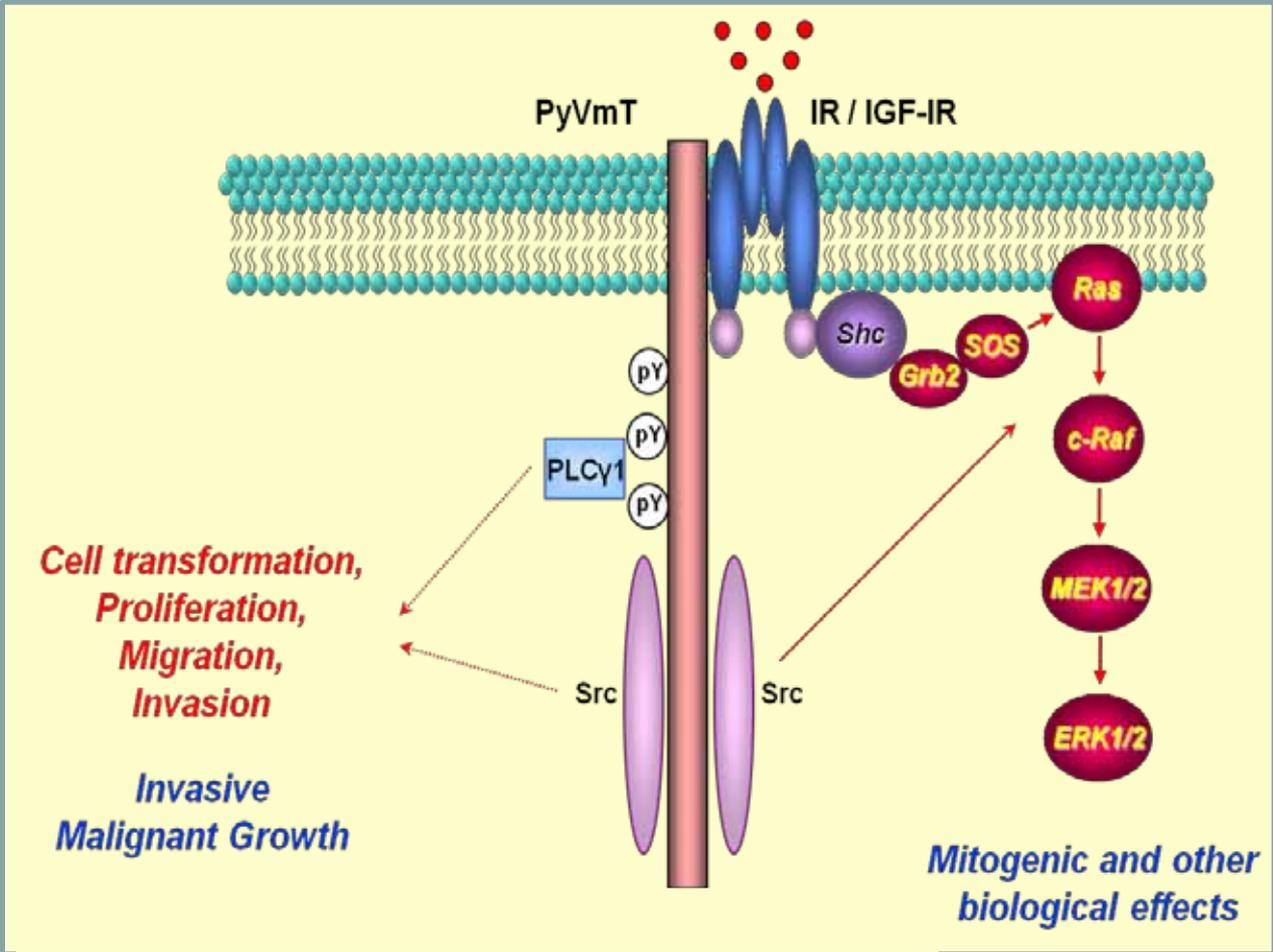
High levels of expression
in fetal and neoplastic
tissues

Mouse Models of Breast Cancer

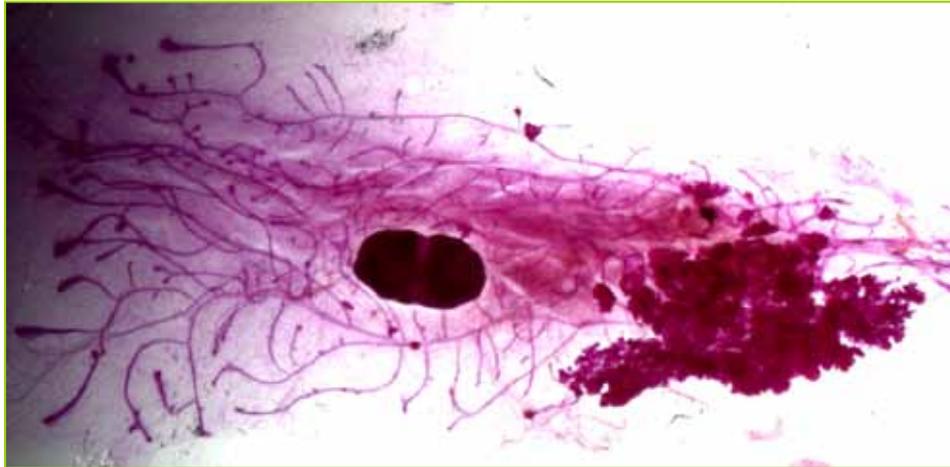
Transgenic Model



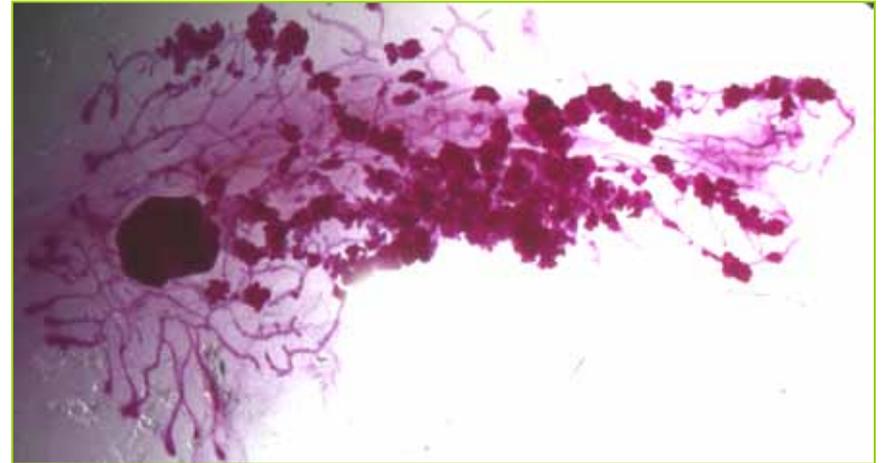
Polyoma Middle T Ag
(PyVmT)



Transgenic Model: Early Stages of Mammary Tumorigenesis



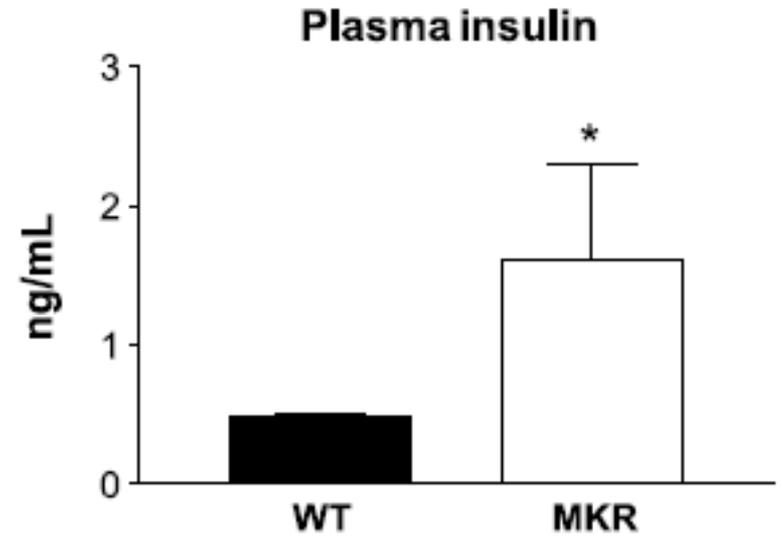
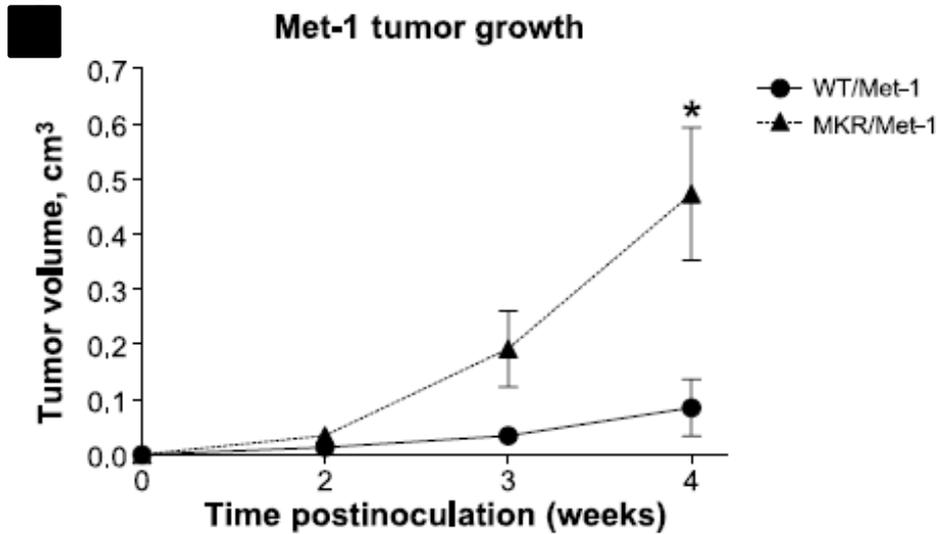
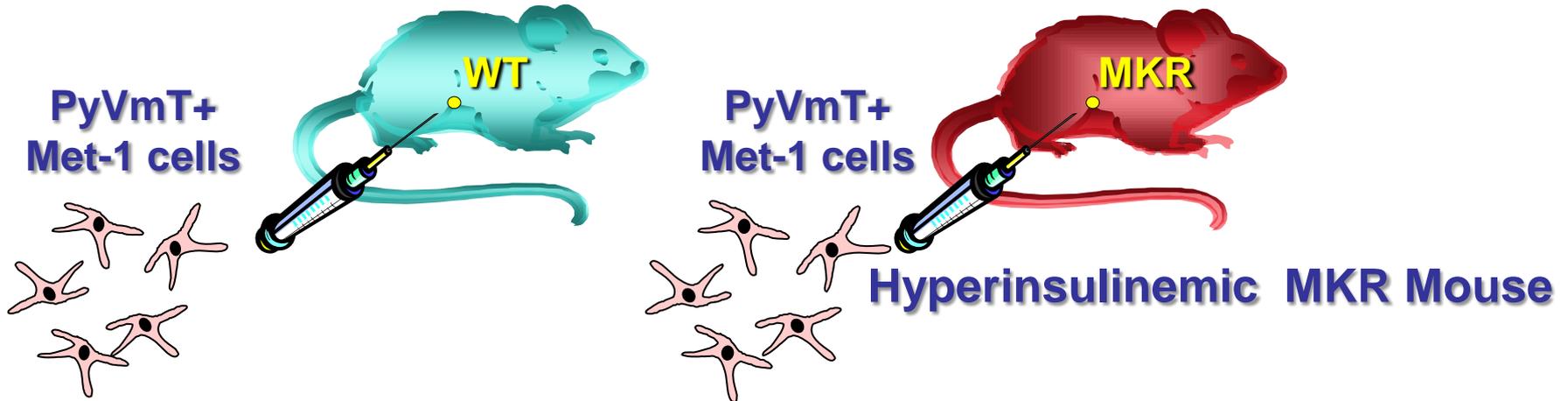
PyVmT at 6 weeks



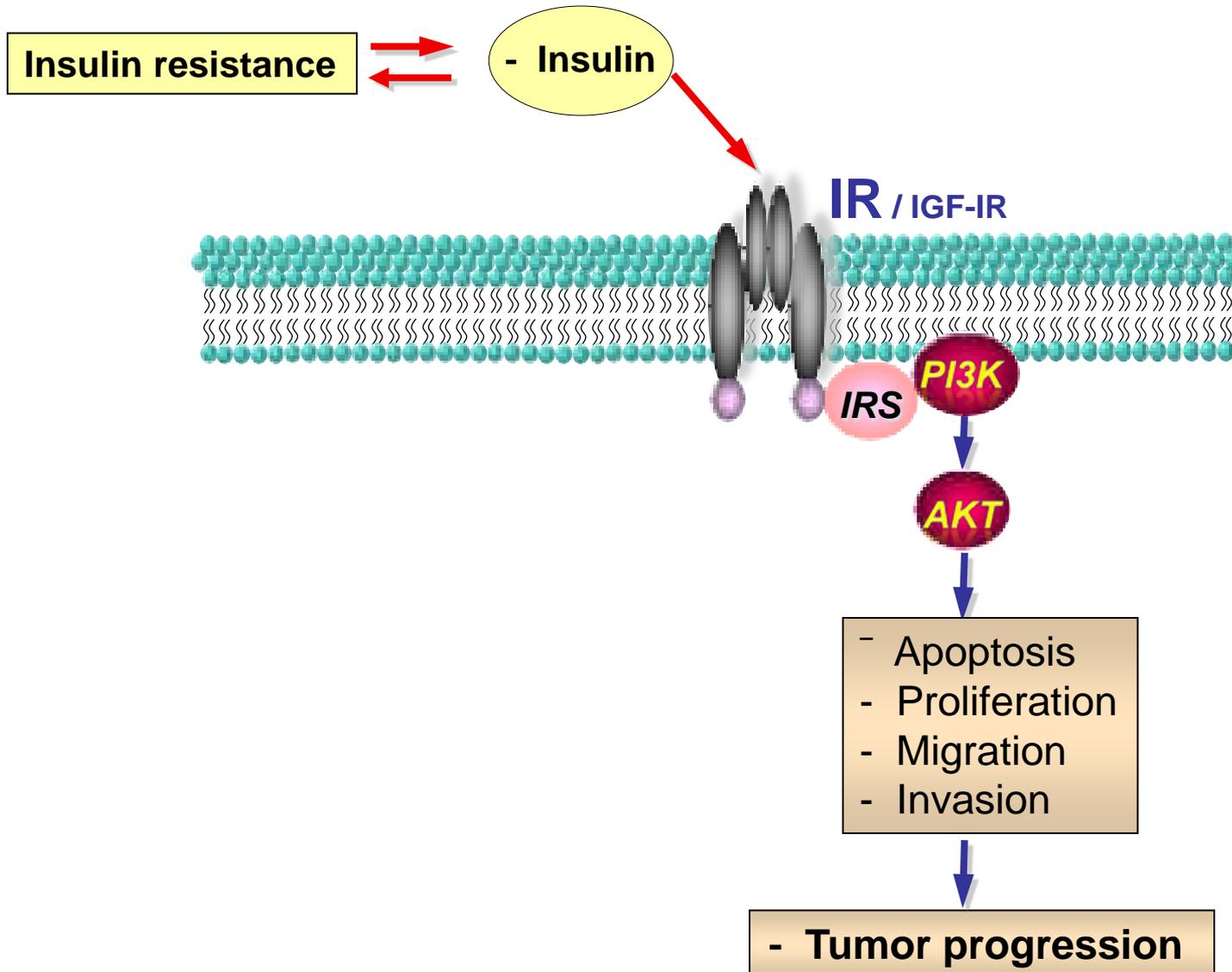
PyVmT/MKR at 6 weeks

**Polyoma Middle T Ag
(PyVmT)**

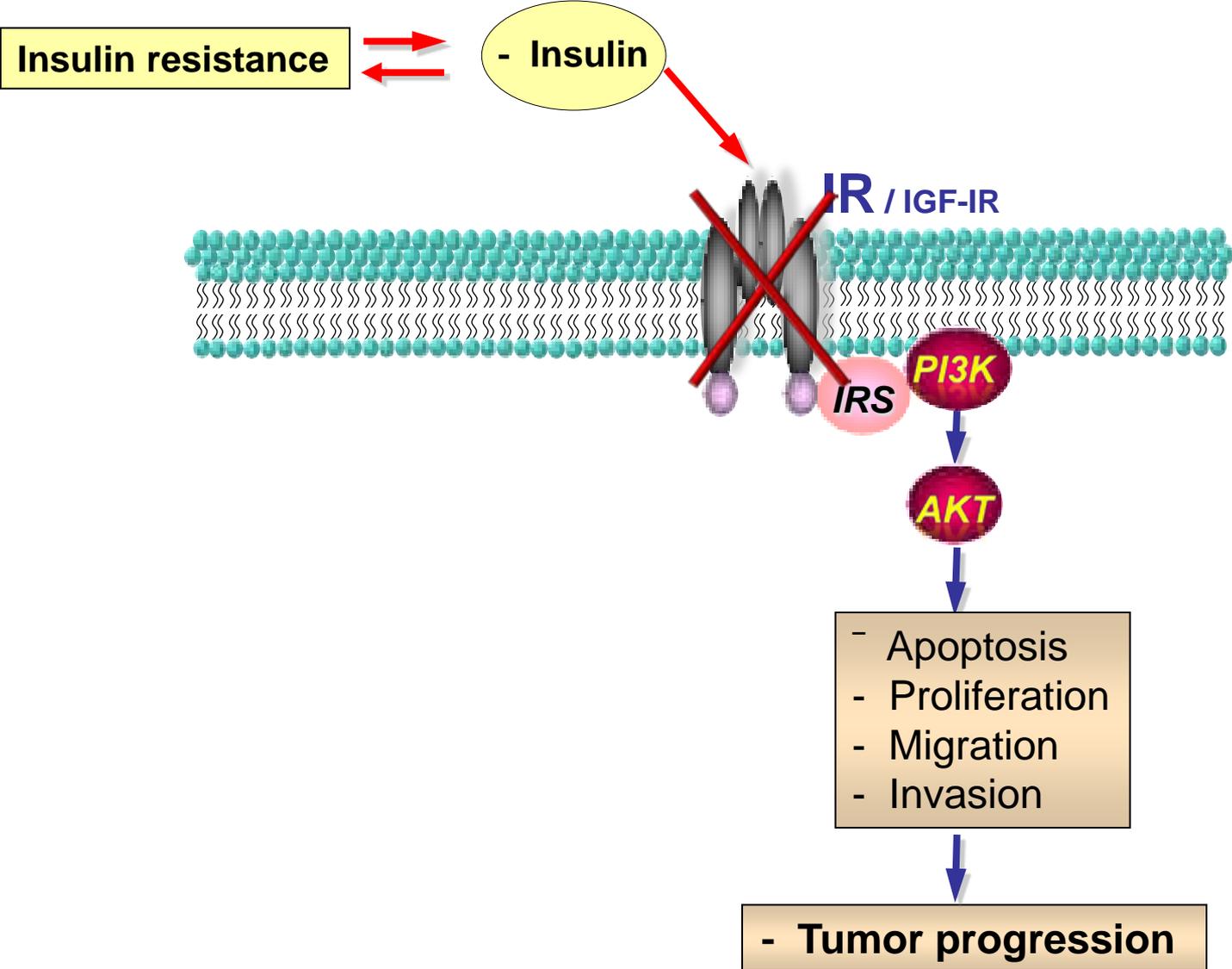
Orthograft Model



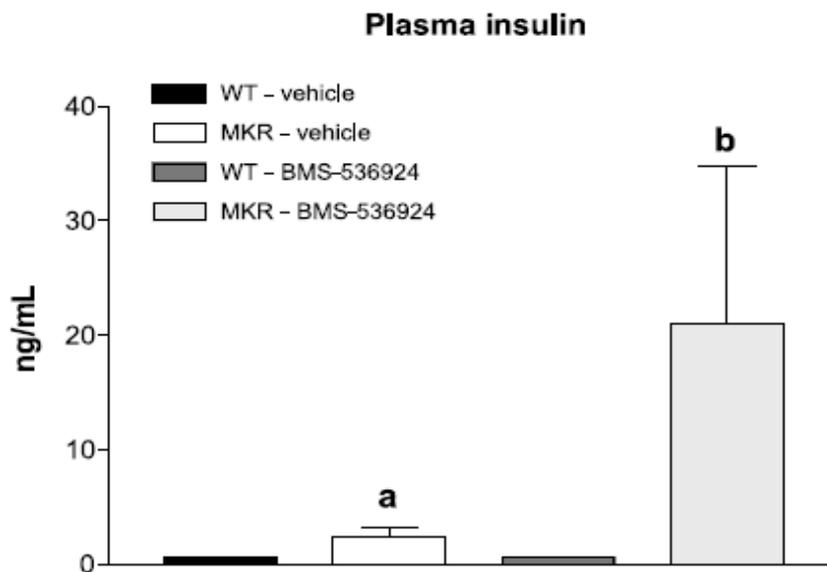
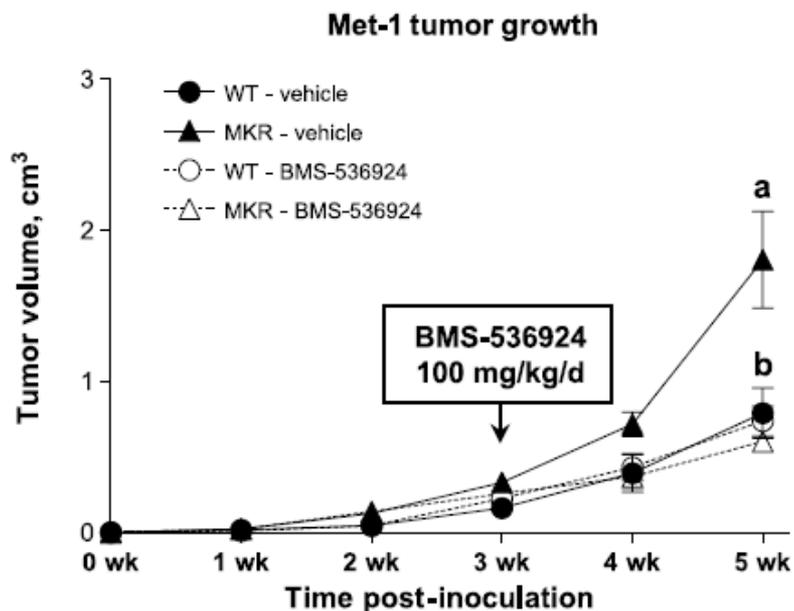
Molecular Mechanisms Underlying Tumor-Promoting Activity in T2DM



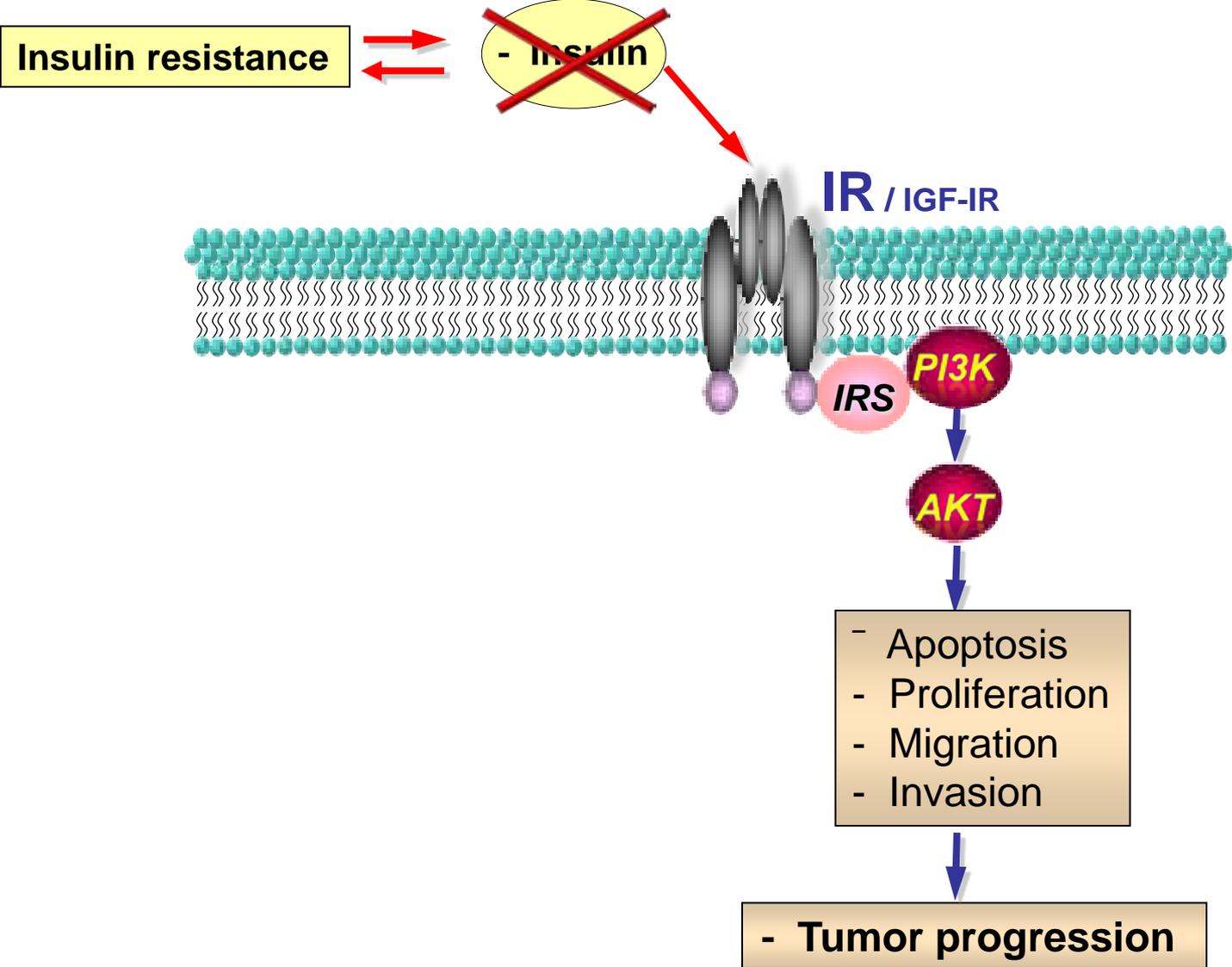
Strategies to Reduce Tumor-Promoting Activity in T2DM



Reduction of Mammary Tumors Using a Tyrosine Kinase Inhibitor, Despite the Marked Hyperinsulinemia

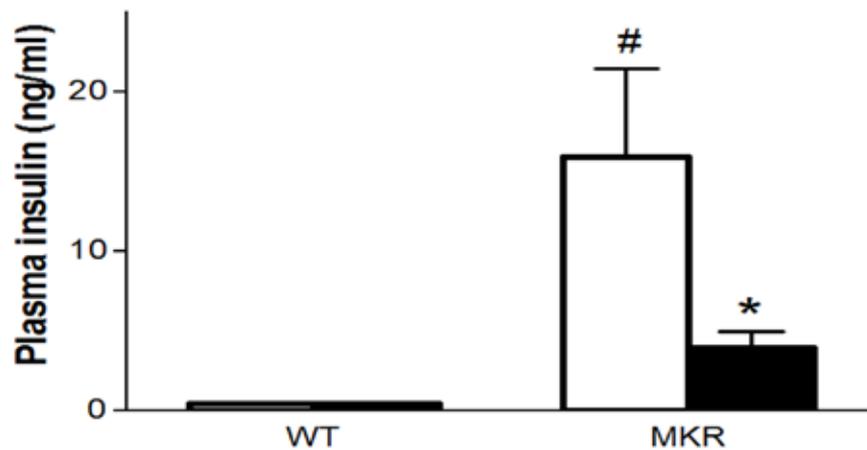
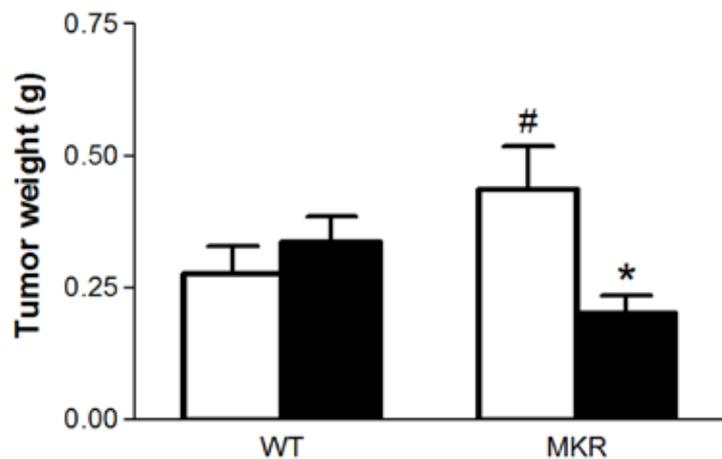
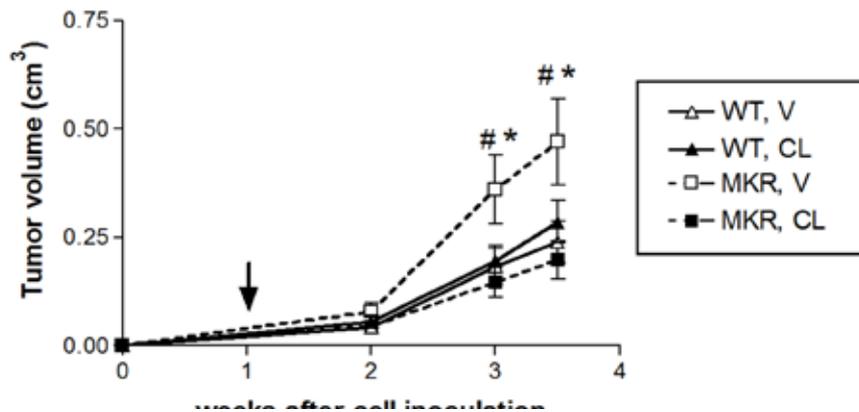
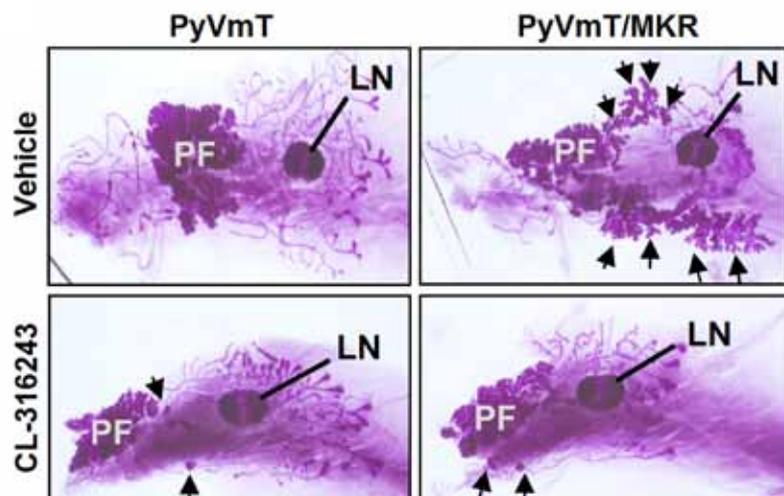


Strategies to Reduce Tumor-Promoting Activity in T2DM



Reduction of Mammary Tumors Associated with a Reduction in the Hyperinsulinemia

A



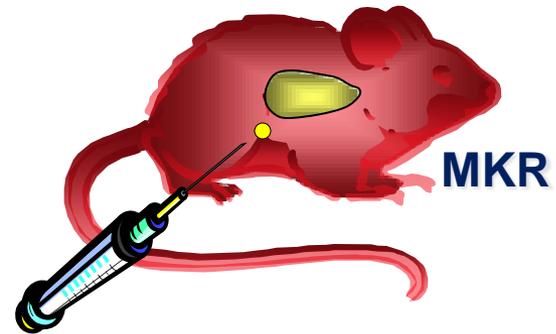
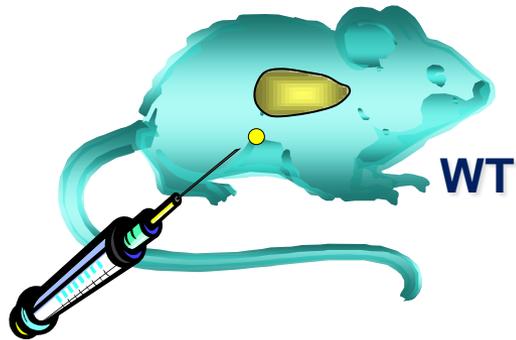
PyVmT Oncogene Expressing Cells

Metastases

- Metastases were measured both by in vivo imaging of c-myc (Mvt1)-induced tumors; cells were transfected with luciferase expression vector.

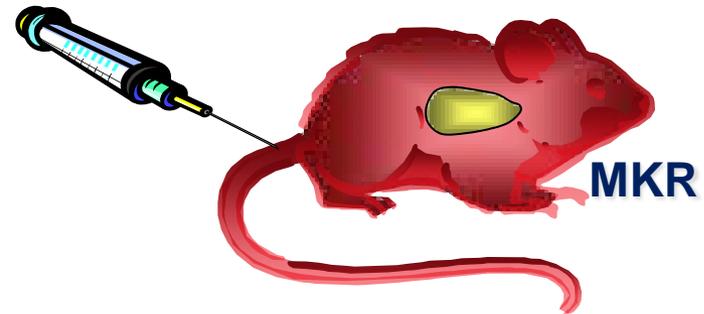
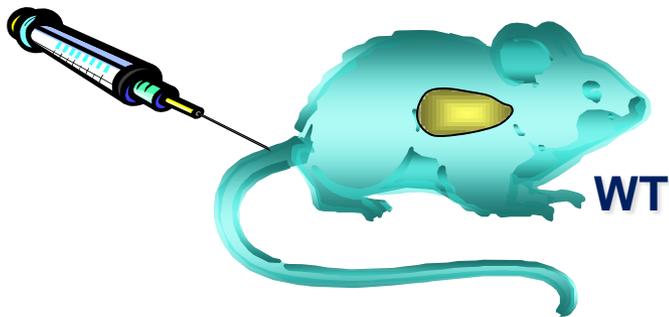
Xenograft Model

Orthotopic Inoculation of Mvt-1 Cells



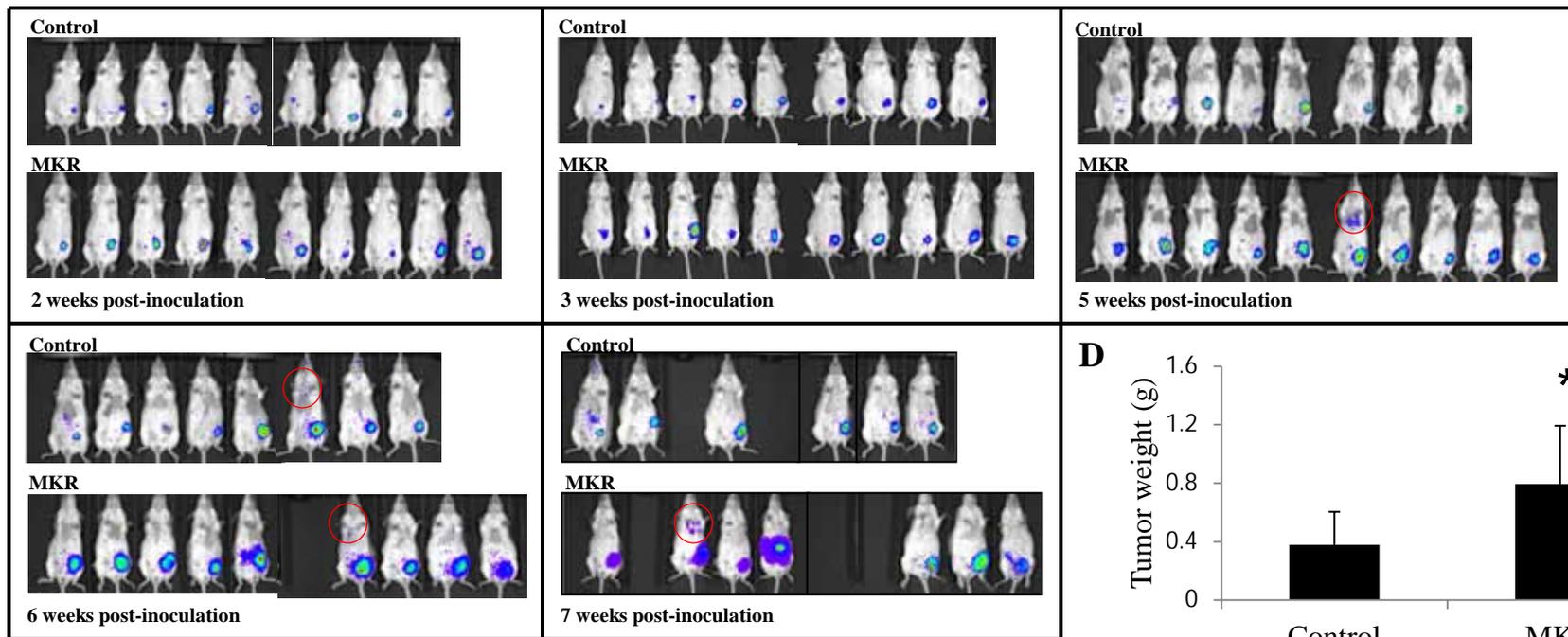
Monitoring of primary tumor formation and development of pulmonary metastases

Heterotopic Inoculation of Mvt-1 Cells

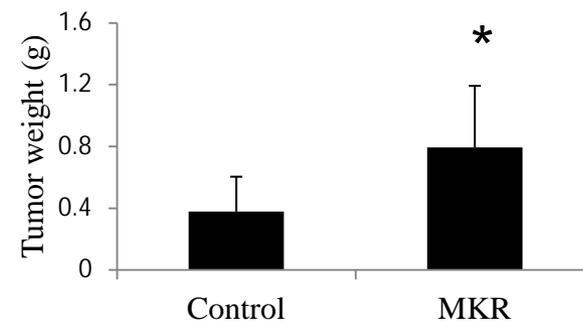


Monitoring of pulmonary metastases in mice devoid of primary tumors

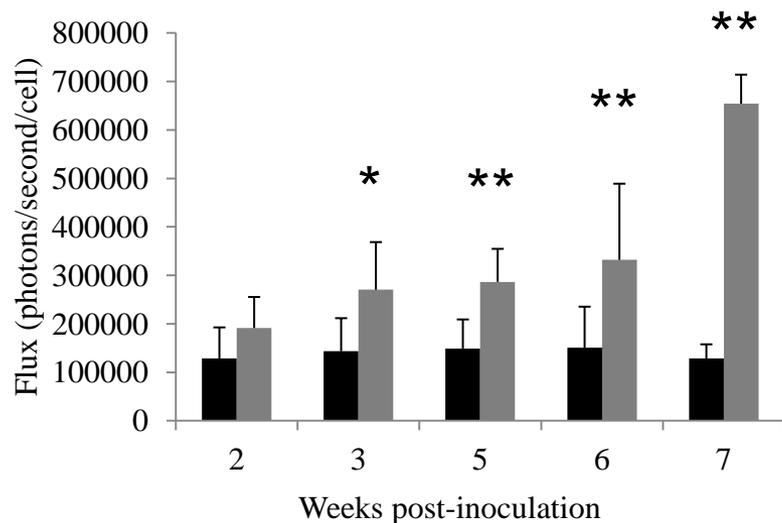
A



D



B



C

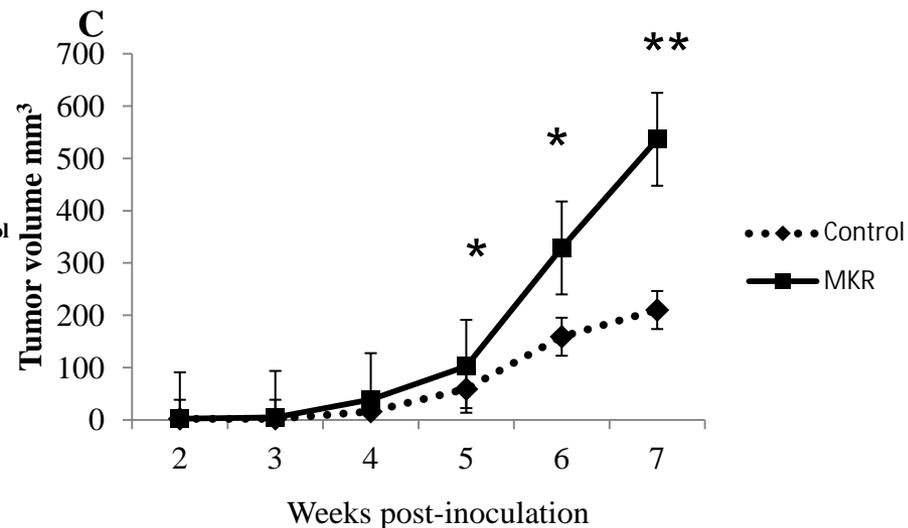
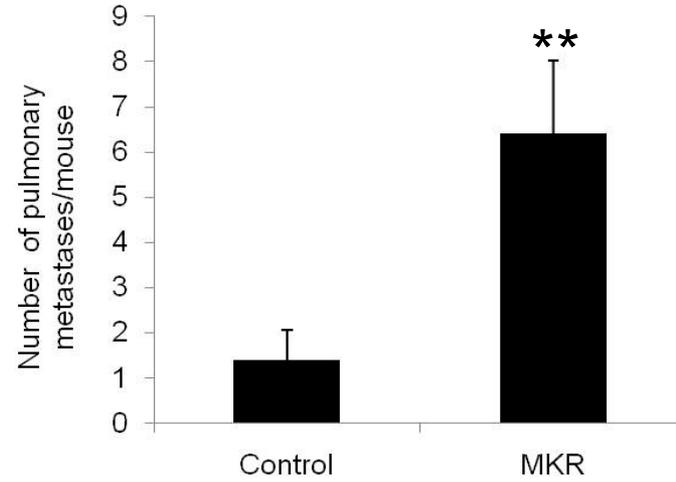


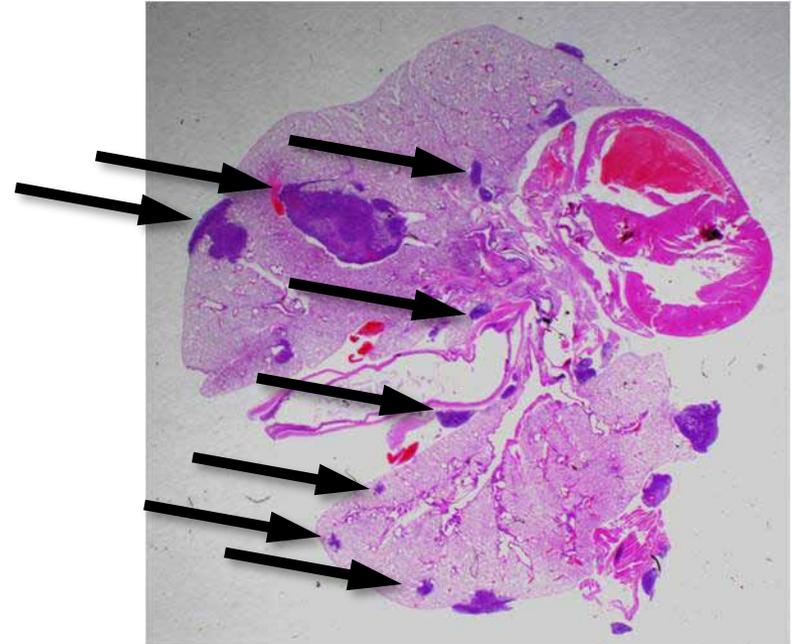
Figure 2

Metastases



Control

MKR



To determine whether the increased metastases in MKR hyperinsulinemic mice was due to larger tumors, we removed tumors when still small (at different stages; earlier in MKR than WT controls).

After recovery from survival surgery, mice were followed for another few weeks and then lung metastases quantified.

Results: The increased metastases in MKR mice occurred whether from small or larger tumors.

Finally, the reduction in hyperinsulinemia reduced metastases.

Conclusions: Hyperinsulinemia maybe the direct cause for increased metastases.

