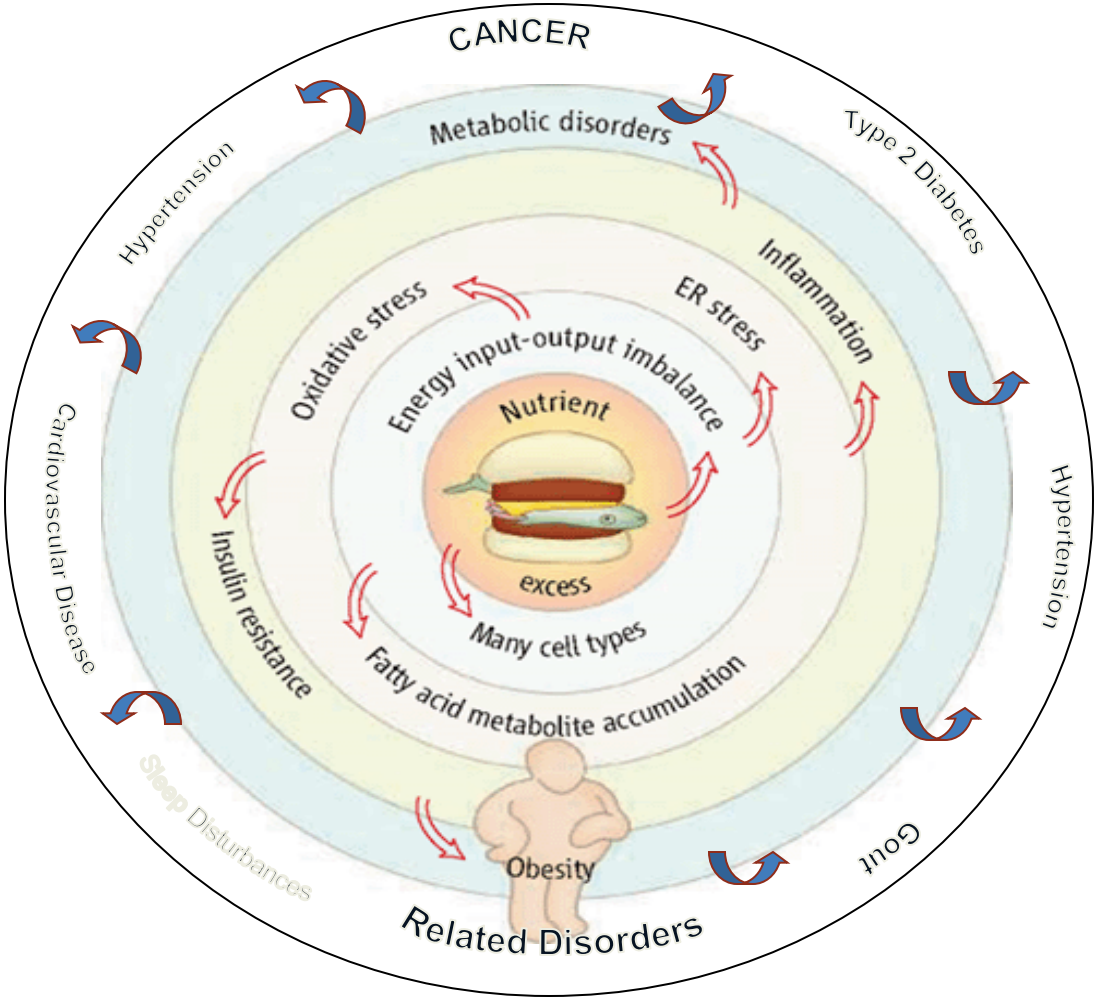
The Role of Obesity in Cancer Survival and Recurrence: A Workshop Hosted by the IOM National Cancer Policy Forum

October 31 - November 1, 2011
Washington, DC

Overview of Mechanisms by Which Obesity May Influence Cancer Progression
"Focus on Dietary Fat"

Nathan A. Berger, M.D.
CWRU Distinguished University Professor
Hanna Payne Professor of Experimental Medicine
Professor, Medicine, Biochemistry, Genetics and Oncology
Director, Center for Science, Health & Society
Case Western Reserve University

An Integrative View of Obesity



Common Responses to Nutrient Excess

Adapted from BE Wise, F Kim, MW Schwartz, Science 318:928-929 (2007).

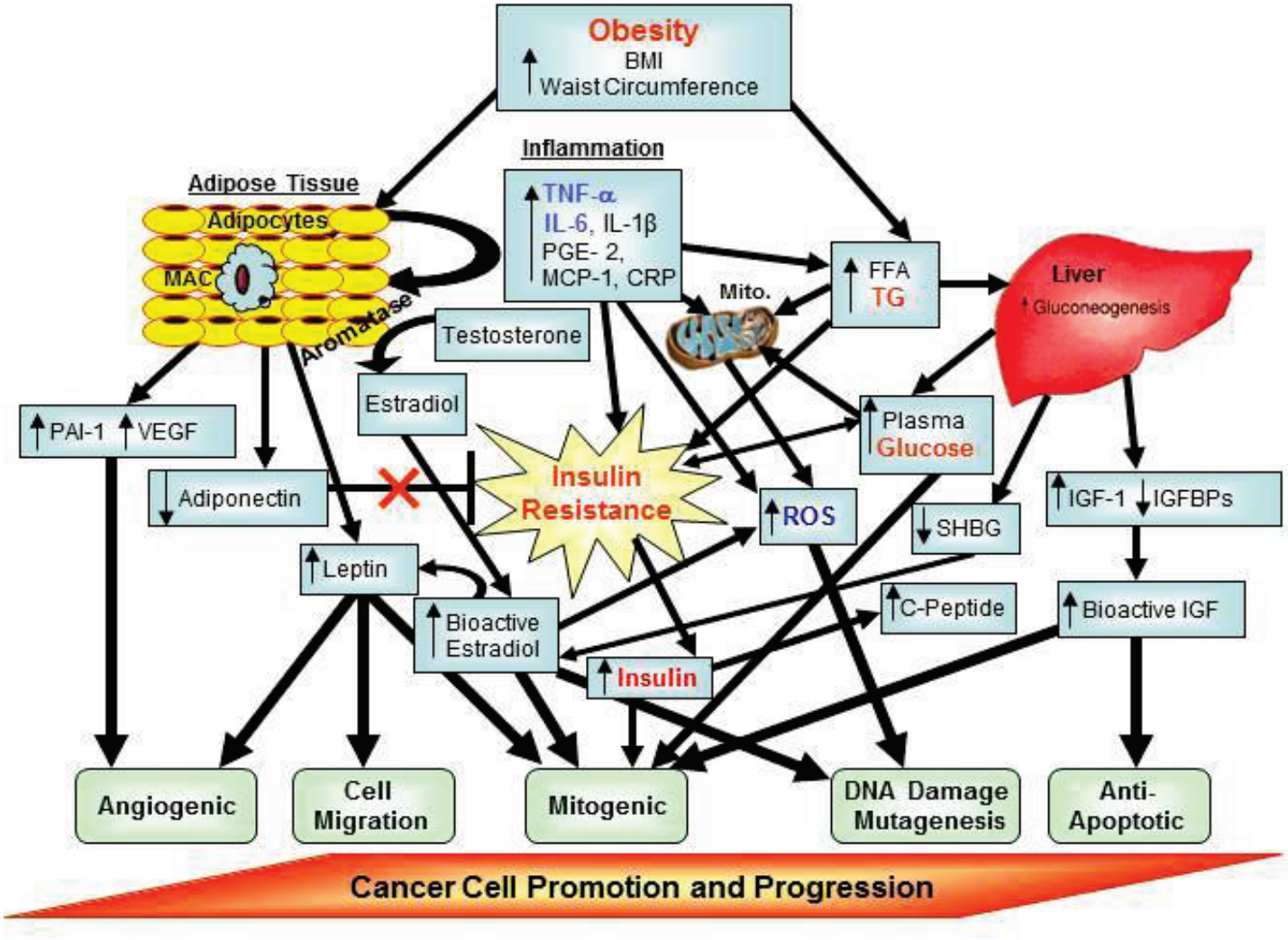
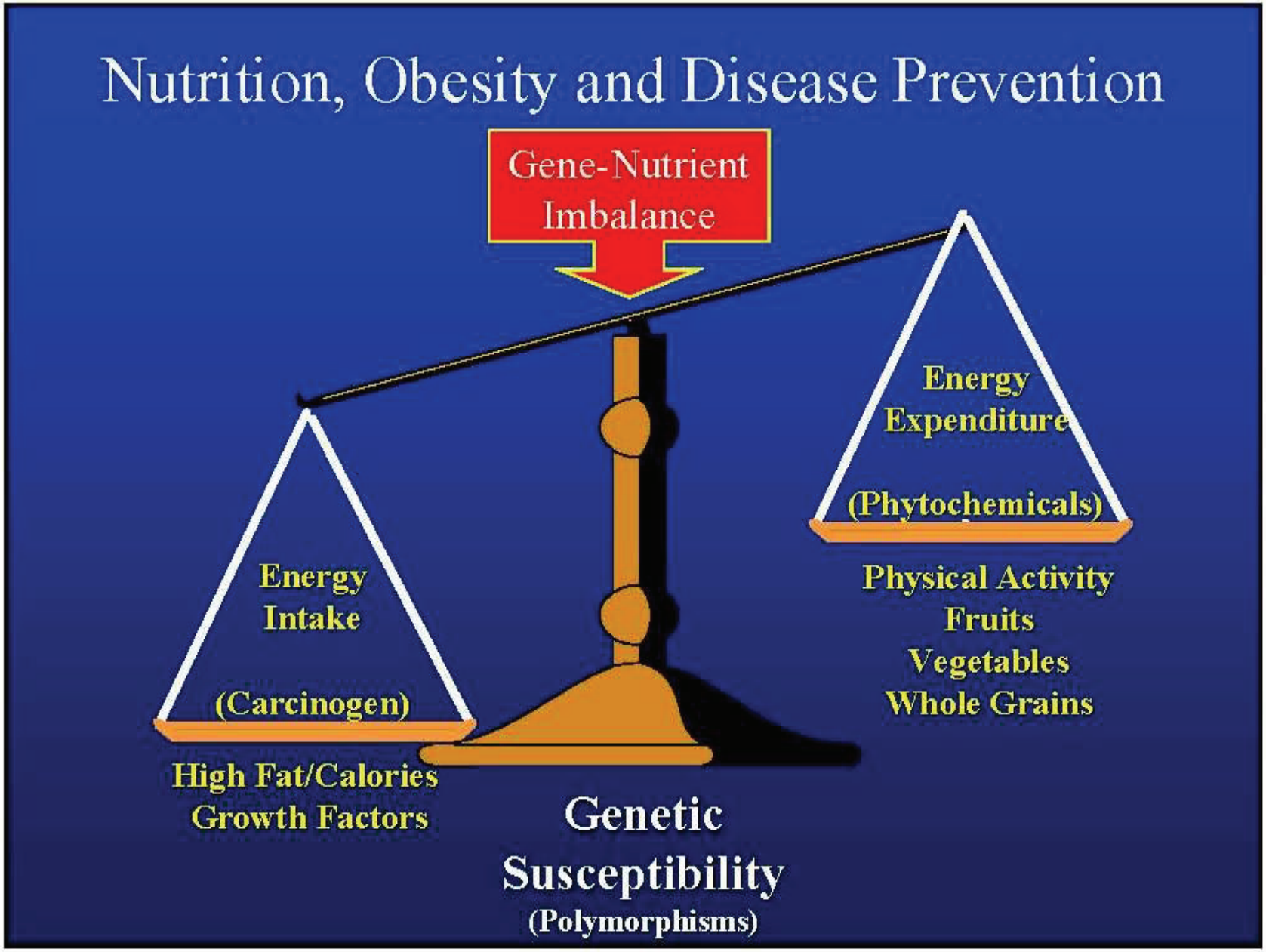


Figure 1. Putative Factors Involved in Obesity-Related Carcinogenesis. Factors denoted in bold red text are core features in the Metabolic Syndrome. Factors dented in bold blue text are additional features that may also be components of the Metabolic Syndrome. MAC=macrophages; TG = triglycerides; Mito.= mitochondria.

Adapted from Nock NL, Berger NA. Obesity and Cancer: Overview of Mechanism, in Cancer and Energy Balance, Epidemiology and Overview, editor - NA Berger, Springer, 2010.



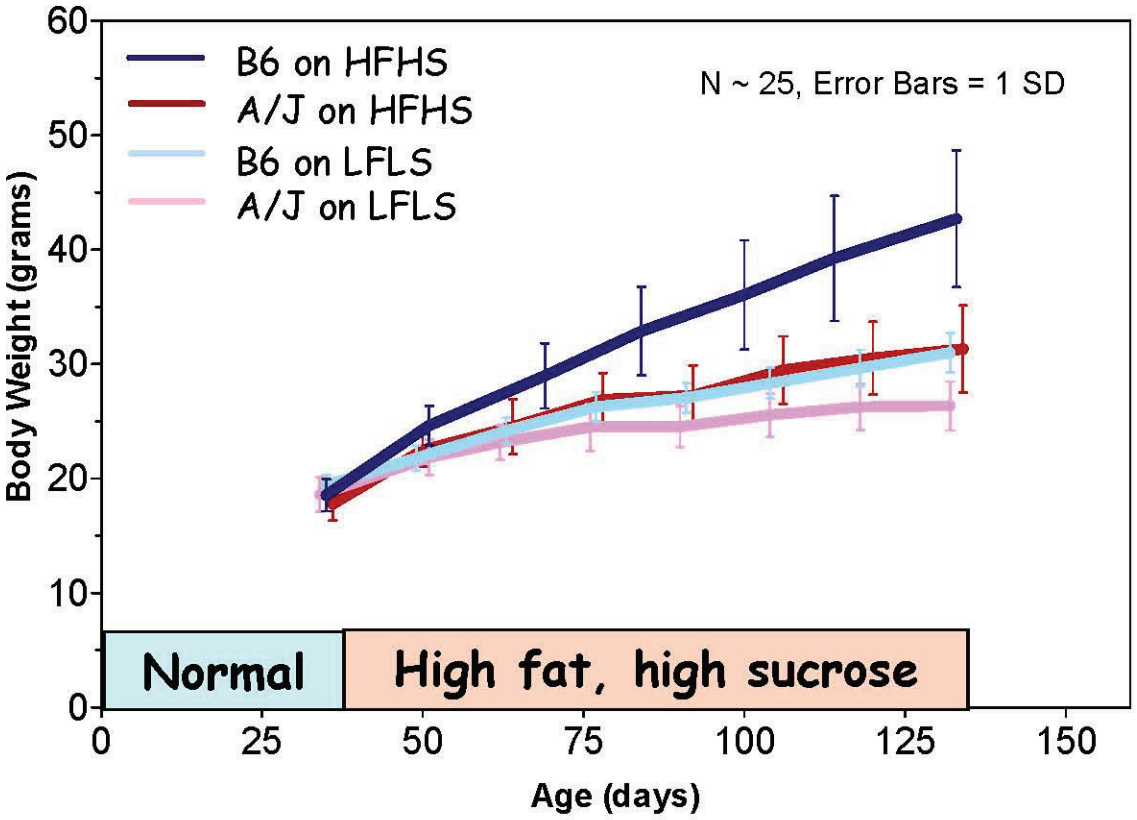
From Sharon Ross, Ph.D., NCI

Questions

- What are the independent contributions of diet and obesity to intestinal neoplasia?
- Are all dietary fats created equal?
- Can diet modulate inflammatory pathways in intestinal neoplasia?

Diet-induced obesity:

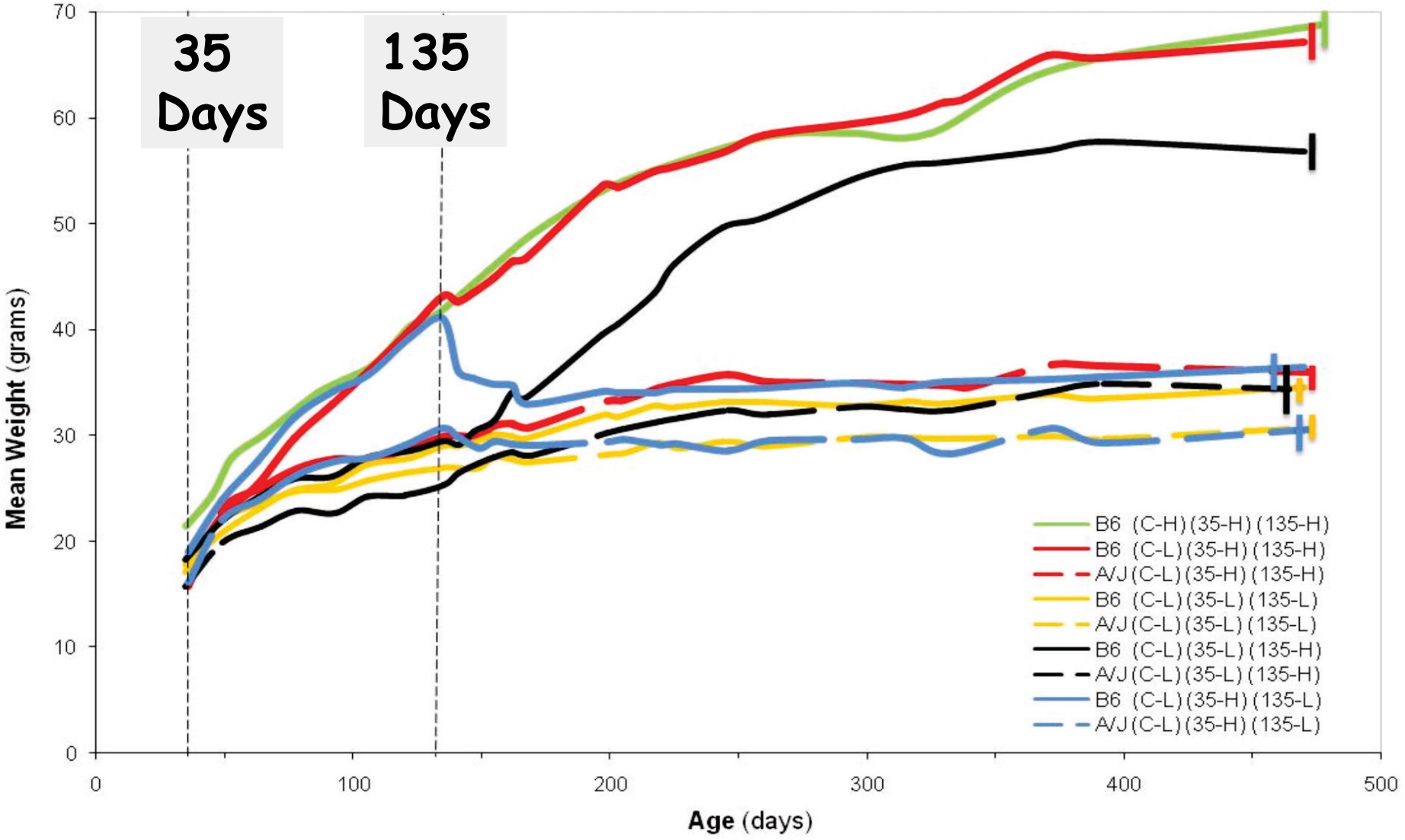
Gene-environment interactions



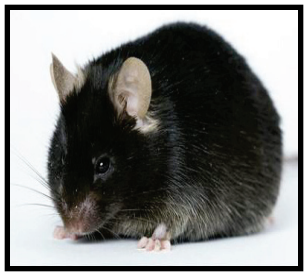
B6 is obese only with a HFHS diet

A/J is lean regardless of diet

Diet-induced obesity in B6 and A/J mice

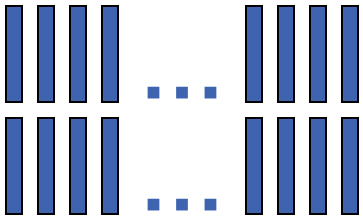


Creation of the consomic strains

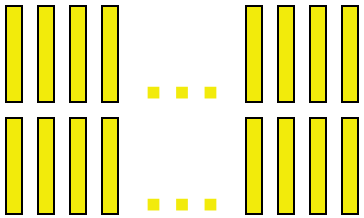


B6-Host

(Susceptible to Diet-Induced Obesity)

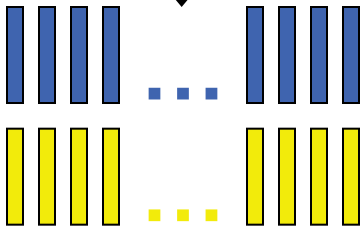


X



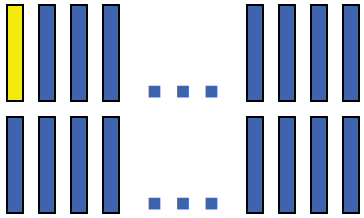
A/J-Donor

(Resistant to Diet-Induced Obesity)

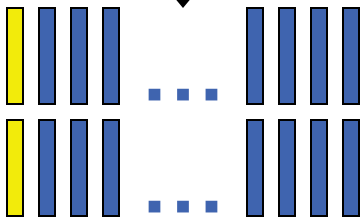


F1 Generation

Backcross for 10 generations



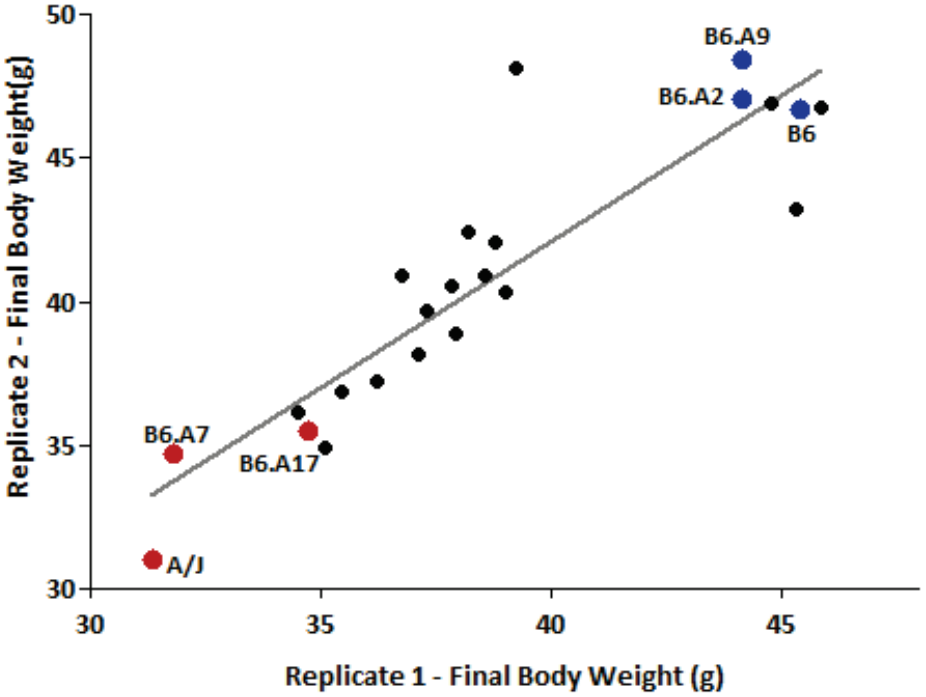
Heterosomic for the desired chromosome



Completed consomic strain

Singer JB *et al. Science:* 304; 445-448 (2004)

CSSs, models of obesity resistance



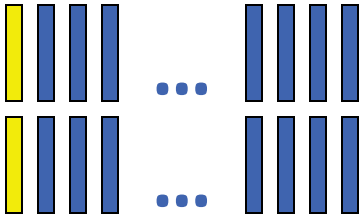
Unpublished data from David Sinasac, Ph.D. and Annie Hill-Baskin

- Chromosome Substitution Strains (CSSs) created by substituting chromosome from donor strain to host strain
- Mimic complexity of human obesity
  - 5% obesity cases are monogenic (i.e. leptin)
- **Obesity-susceptible (B6.A2, B6.A9) and obesity-resistant (B6.A7, B6.A17) chosen for studies**

Creation of consomic-congenic strains

Consomic

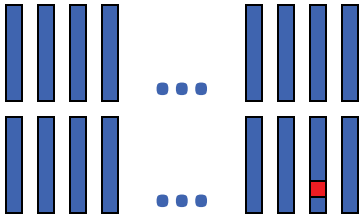
B6.A CSS Chromosome 1 (B6.A1)

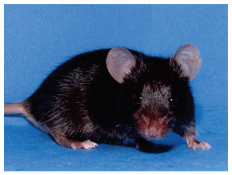


X

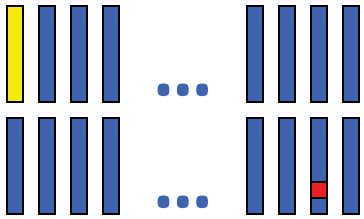
Congenic

B6.Apc$^{min/+}$ heterozygote



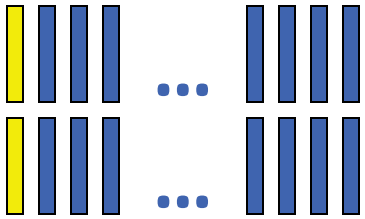


F1 Progeny



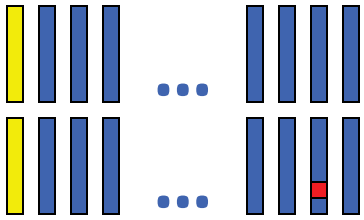
Apc $^{min/+}$ F1 Progeny

X

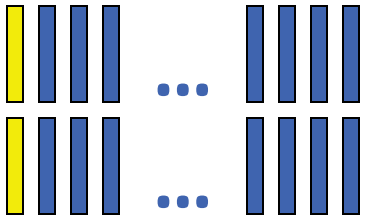


B6.A1

Completed consomic-congenic



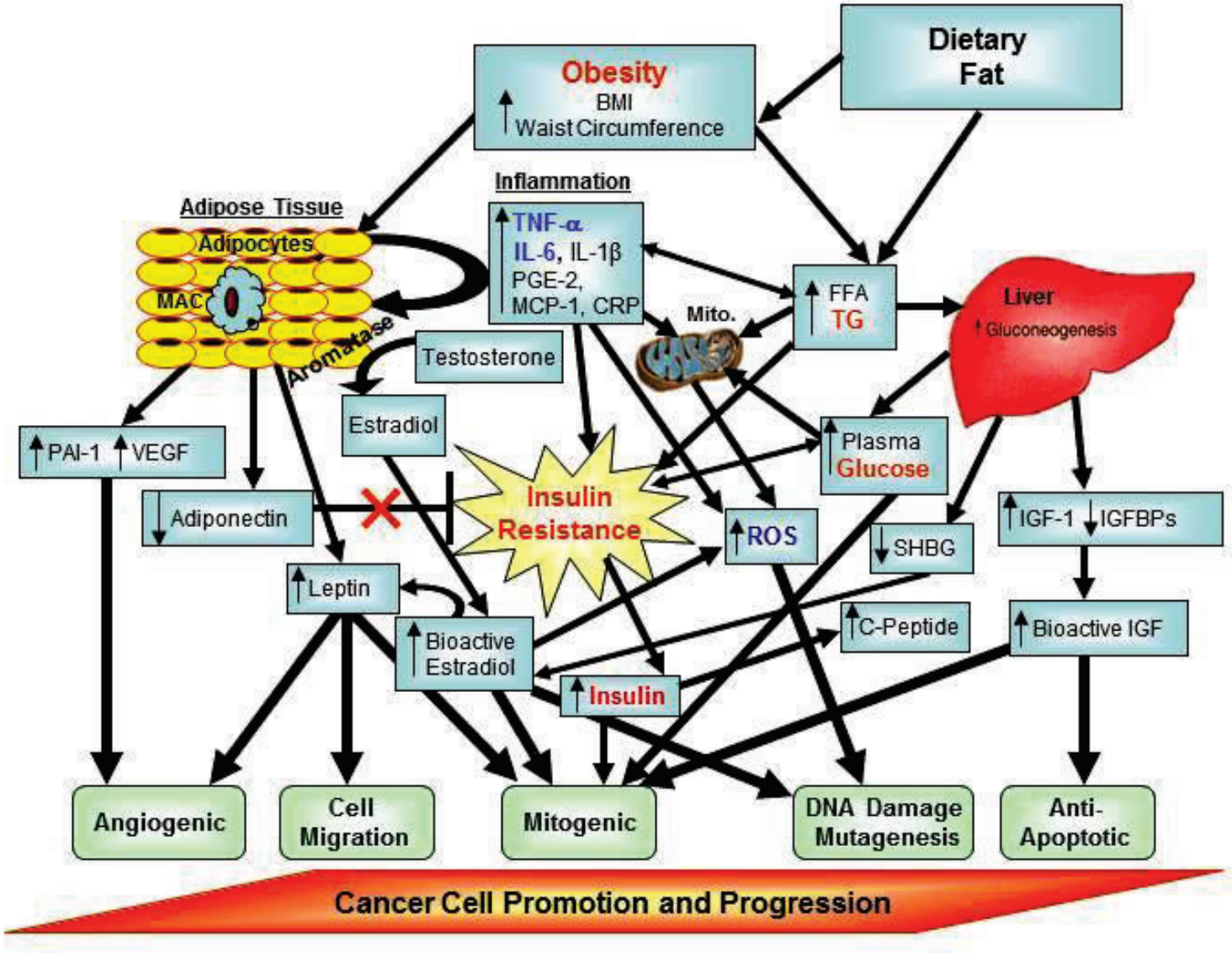
A1.APC



B6.A1

Summary

- Diets high in saturated fat and omega-6 fatty acids increase polyp number and burden in $APC^{min/+}$ mice after 30 days and 60 days on diet
- High Fat Diets activate inflammatory pathways
- CSSs made it possible to dissect diet from obesity
- All strains, including non obese strains, fed a HF diet show increases in polyp number and burden
- High Fat diet stimulates cancer progression, independent of obesity or diabetes



Adapted from Nock NL, Berger NA. Obesity and Cancer: Overview of Mechanism, in Cancer and Energy Balance, Epidemiology and Overview, editor - NA Berger, Springer, 2010.

Case Comprehensive Cancer Center

Mouse Models Program for Studies of Aging, Energy Balance and Cancer

Investigators

Nathan A. Berger, MD
Richard Hanson, PhD
Parvin Hakimi
Guangbin Luo, PhD
Sanford Markowitz, MD, PhD
Joseph Nadeau, PhD
James Swain, PhD
Gemma Casadesus, PhD
Ofer Reizes, PhD
Annie Baskin-Hill
Stephanie Doerner
Jason Heaney, PhD
Michael Green
C.K. Qu, MD, PhD
William Qu

Grant Support

U54 CA116867
P20 CA102736
P30 CA-43703
RO1 DK058620
RO1 DK025541
RO1 DK025541
RR0 012305

Case Western Reserve University | Case Comprehensive Cancer Center

TREC Transdisciplinary Research on Energetics and Cancer Centers