Diet, metabolic disease and cancers in mouse models

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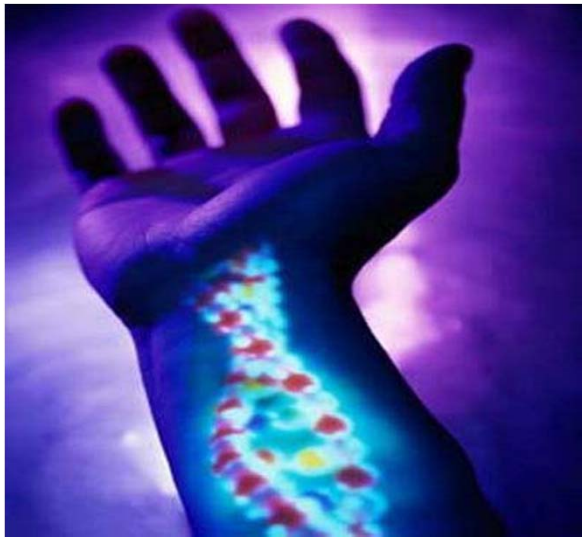
CASE COMPREHENSIVE CANCER CENTER

TREC Transdisciplinary Research on Energetics and Cancer Centers

Cancer risk and metabolic disease



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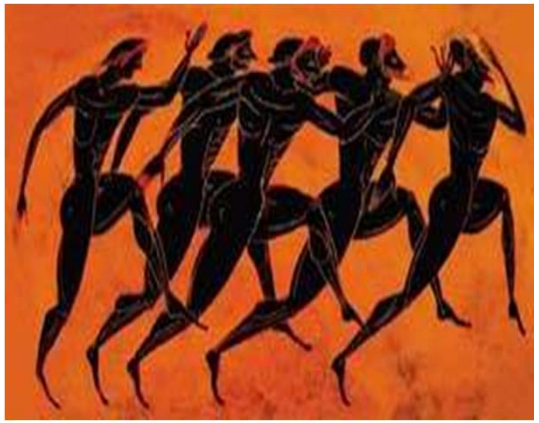

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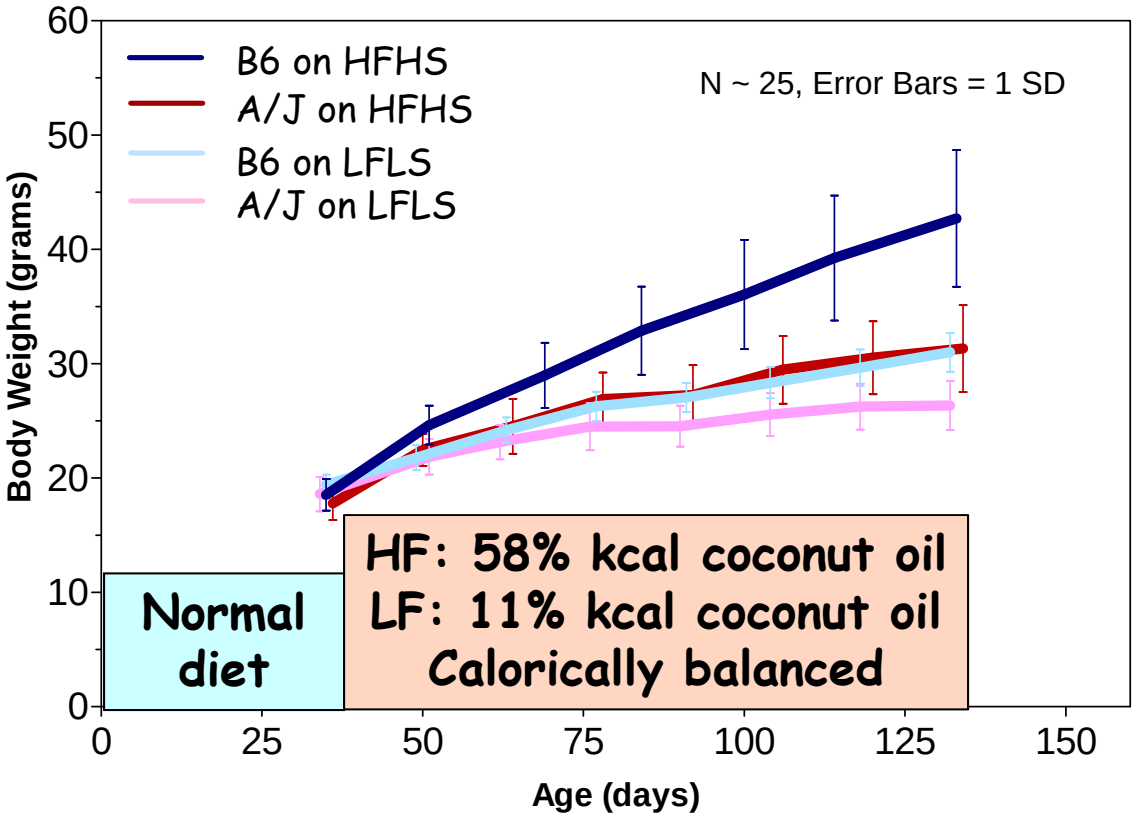
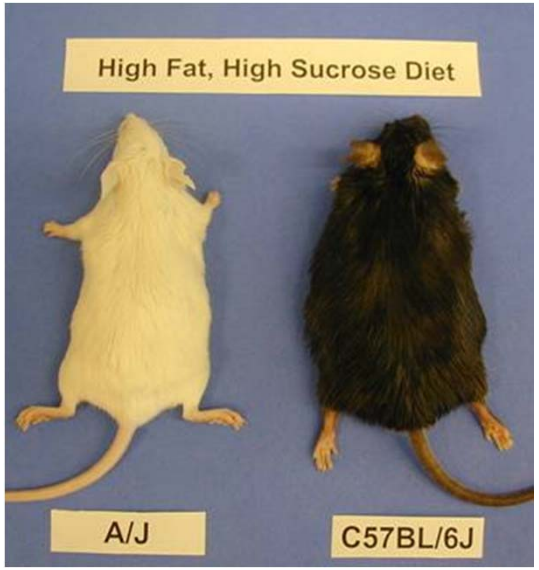
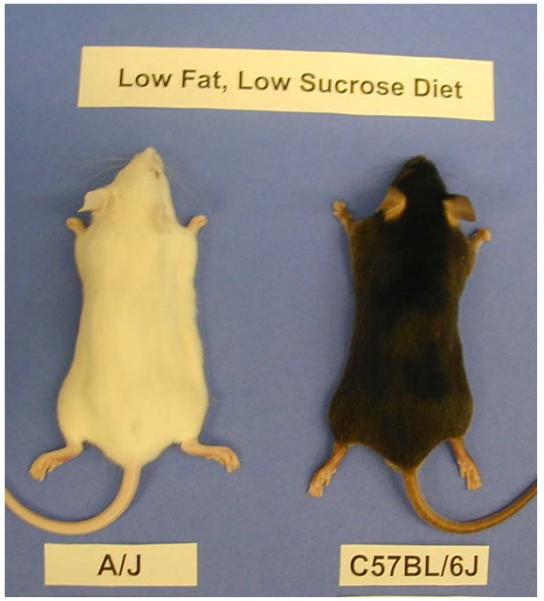
Diet-induced obesity: Gene - diet interactions



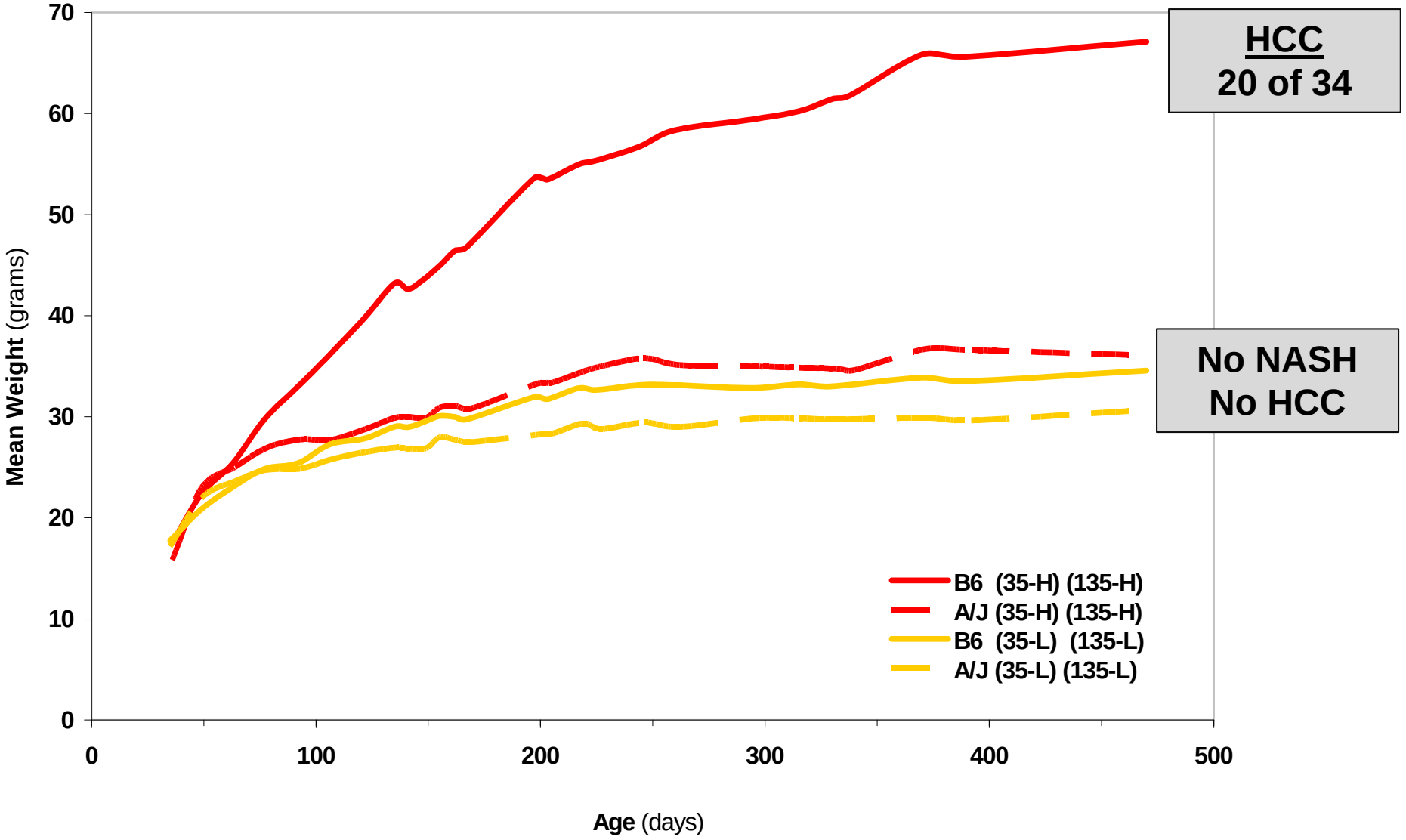


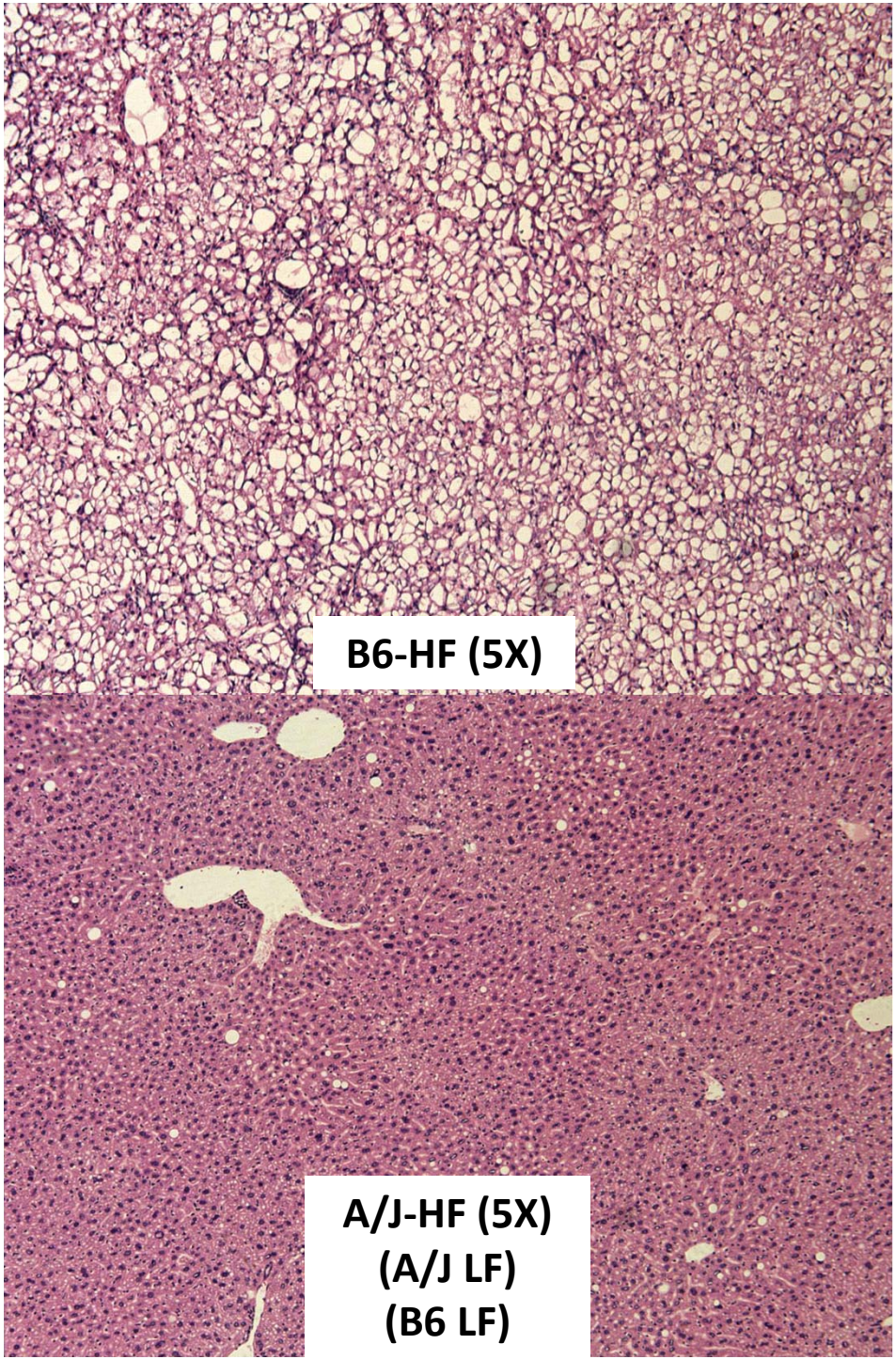


B6 - obese only with a HFHS diet

A/J - lean regardless of diet

Long-term effects of high fat diet





Non-alcoholic steatohepatitis (NASH) in B6 but not A/J mice

-steatosis

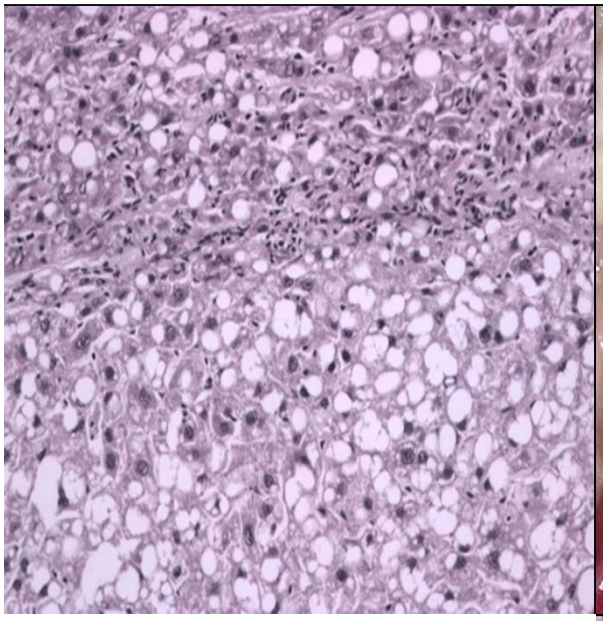
(40% of liver mass is lipid)

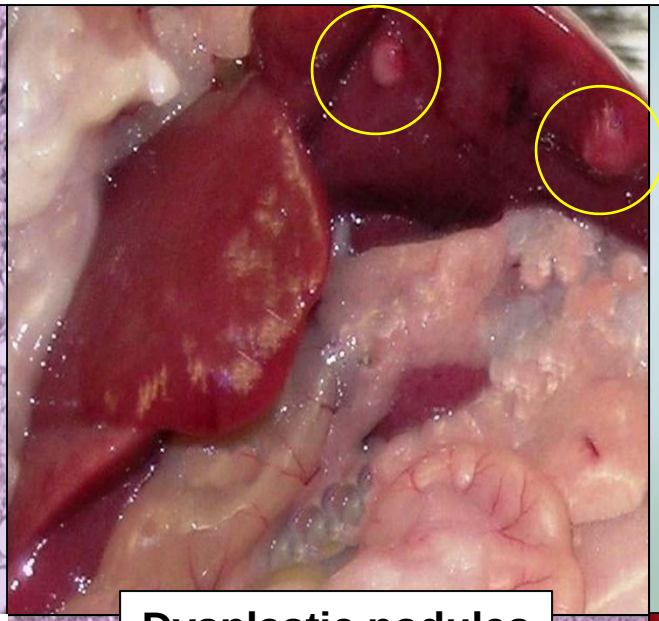
after 100 days on high fat, but not low fat diet

- hepatitis (inflammation)
- fibrosis
- limited cirrhosis

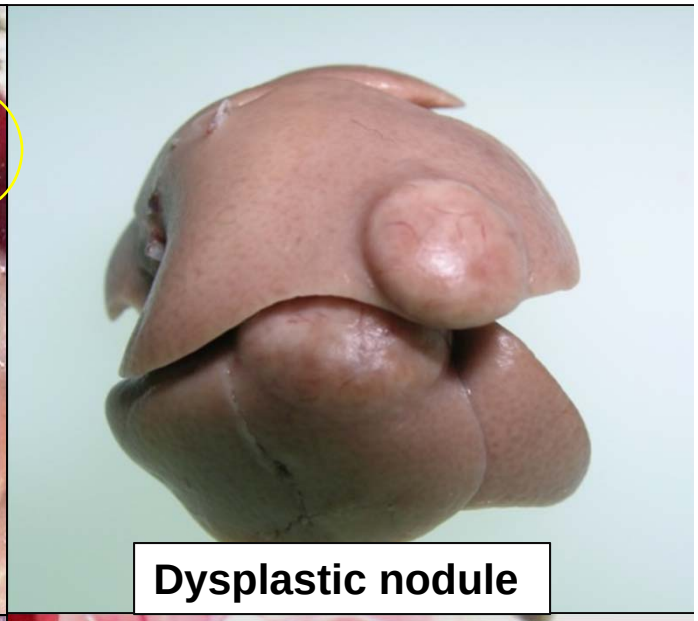
after 400 days

Diet-induced malignant transformation and hepatocellular carcinoma (HCC)



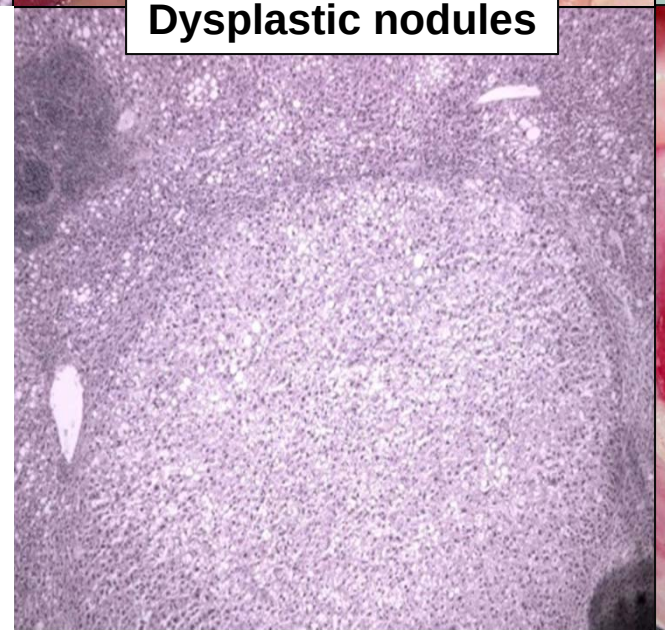


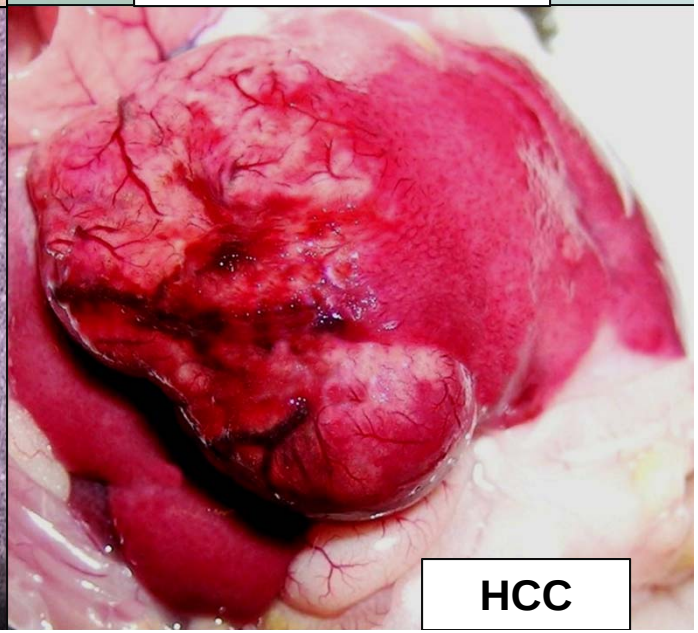
Dysplastic nodules



Dysplastic nodule

Cycles of cell damage, death and regeneration eventually lead to transformation, NASH - the '*fertile soil*' in which transformation occurs





HCC

Hepatocellular carcinoma (HCC)

- 3rd most common cause of cancer death worldwide
- Rapidly growing cause of cancer death in U.S.
- Risk factors:
  1. Hepatitis B or C
  2. Chronic alcohol use

  } ~70% of cases (Ken Tanabe, MGH personal communication)

- Remaining 30% of "unexplained" cases are frequently associated with obesity, diabetes, non-alcoholic steatohepatitis

HCCs in humans and mice

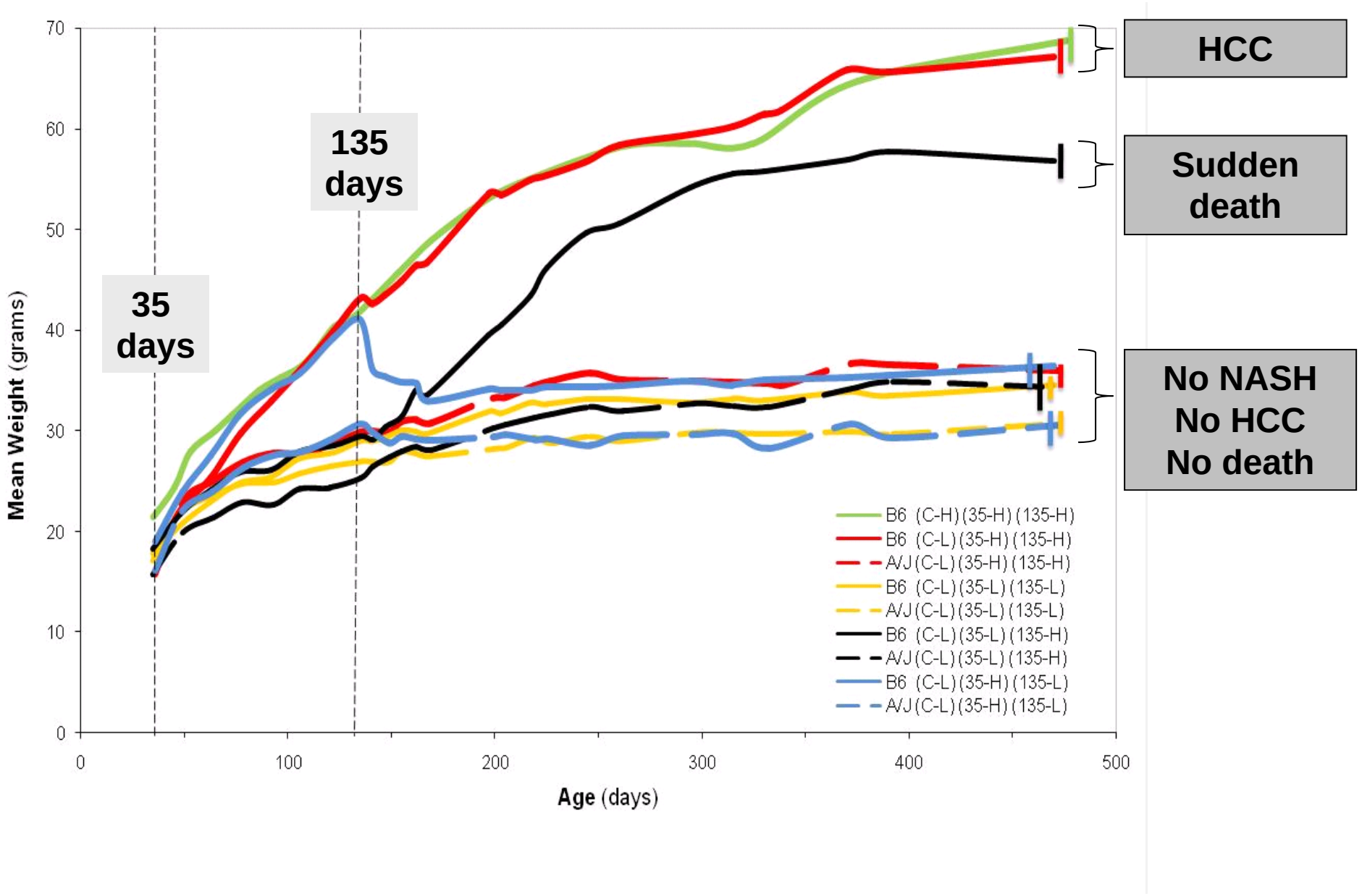
1. Biochemistry
2. Histology
3. mRNA profiles

} **Similar features in humans and mice**

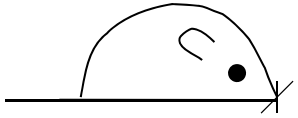
1. Molecular pathways (Myc and NFkB)
2. miRNA profiles (X-linked cluster)
3. Predicted mRNA targets of miRNAs

Liver necrosis, cell death
Liver steatosis
Liver proliferation
Hepatocellular carcinoma
Cardiac degeneration, cell death

Diet-switch prevents HCC



Metabolic Syndrome, NASH, HCC

On High Fat, High Sucrose Diet:	 B6	 A/J
Obesity	✓	X
Hypertension	✓	X
Insulin Resistance	✓	X
Cardiovascular Disease Risk	✓	X
Non-alcoholic steatohepatitis	✓	X
Hepatocellular carcinoma	✓	X
	Genetics of disease	Genetics of health

J. Nadeau and E. Topol, Nat. Genet. 2006; Shao et al. PNAS; JHN et al, in prep

HCC summary

Diet-induced, rather than genetically-engineered or carcinogen-induced

Similar pathology and molecular features

Two pathways in one strain on the same diet

Diet switch reverses outcome

A similar diet modification may have important implications for prevention of HCCs in humans

HCC questions

Genetic control of susceptibility
chromosome substitution strains
(*Singer et al. Science 2004, Shao et al. PNAS 2008*)

Mechanisms of transformation
engineered mutant genes and alternative fats

Diet switch effects
physiological mechanisms

Interventions
drugs and diets

Biomarkers

Eric Lander, Nate Berger, John Lambris,
Mark Daly, Colleen Croniger, Aris Economides,
Ken Tanabe, and Shankar Subramaniam