

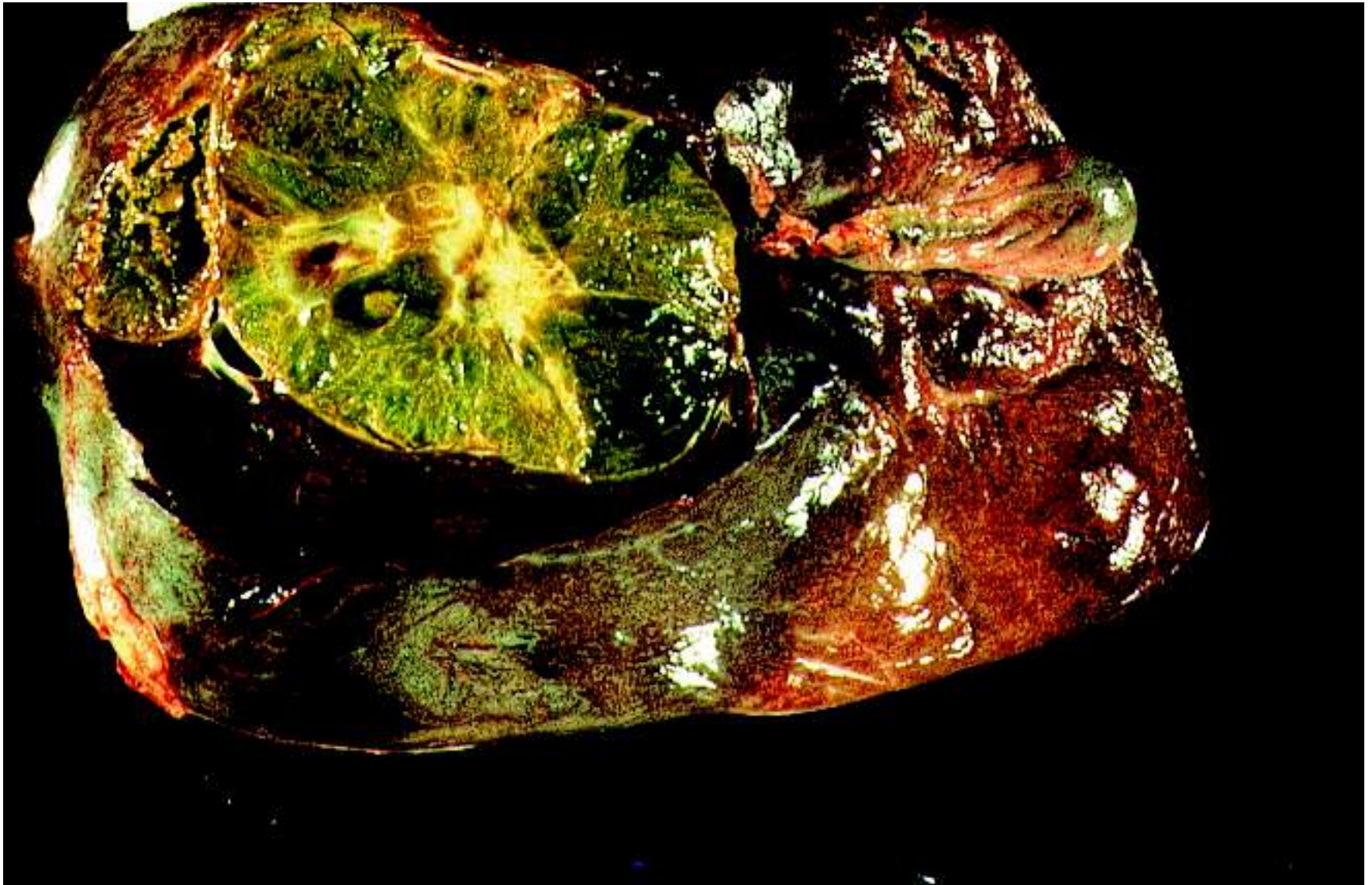
Viral Hepatocarcinogenesis and Signaling Pathways

Jack R. Wands, MD

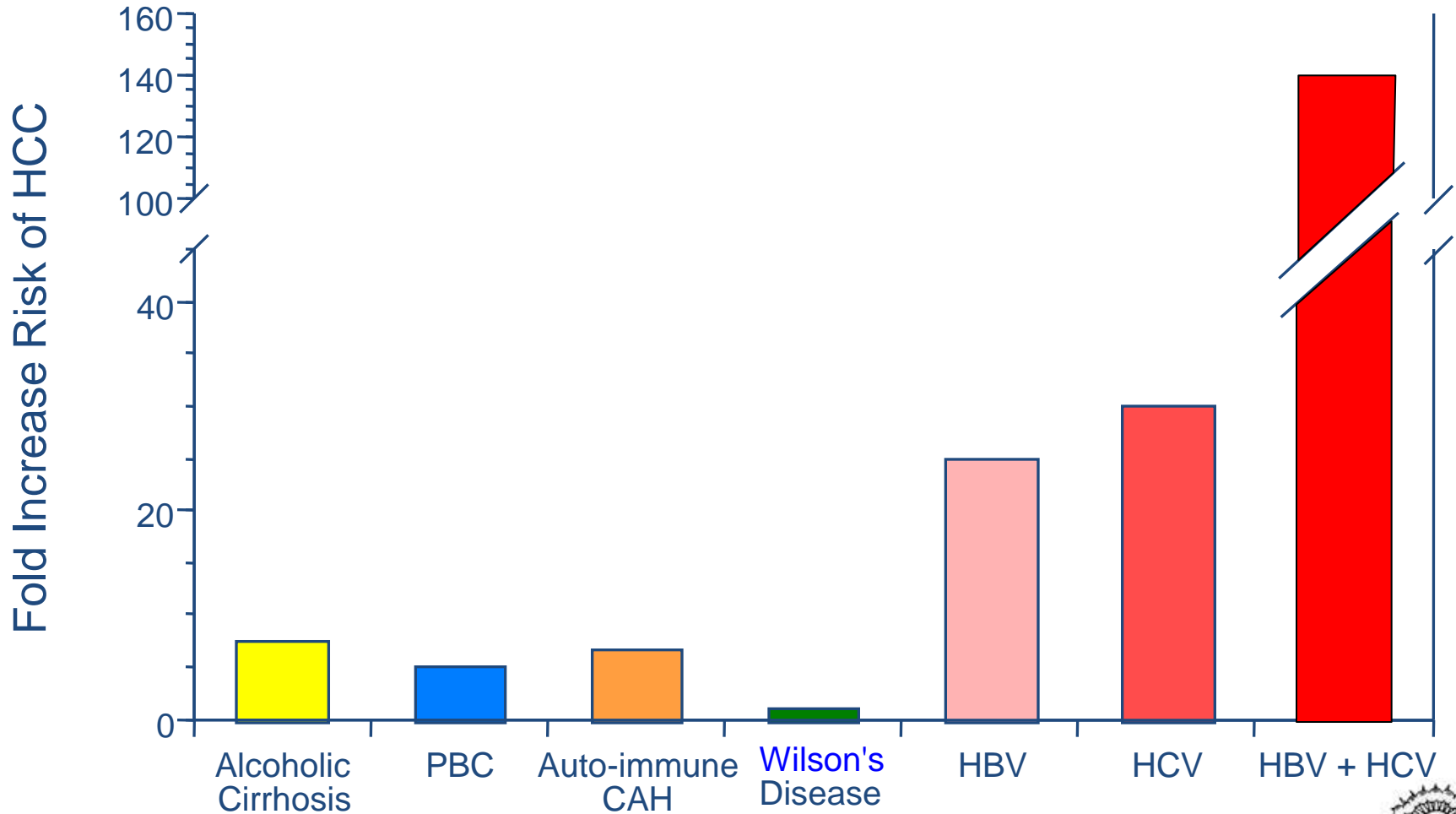
Jeffrey and Kimberly Greenberg - Artemis and Martha Joukowsky, Professor in Gastroenterology and Professor of Medical Sciences, Director, Division of Gastroenterology and Liver Research Center, Brown University

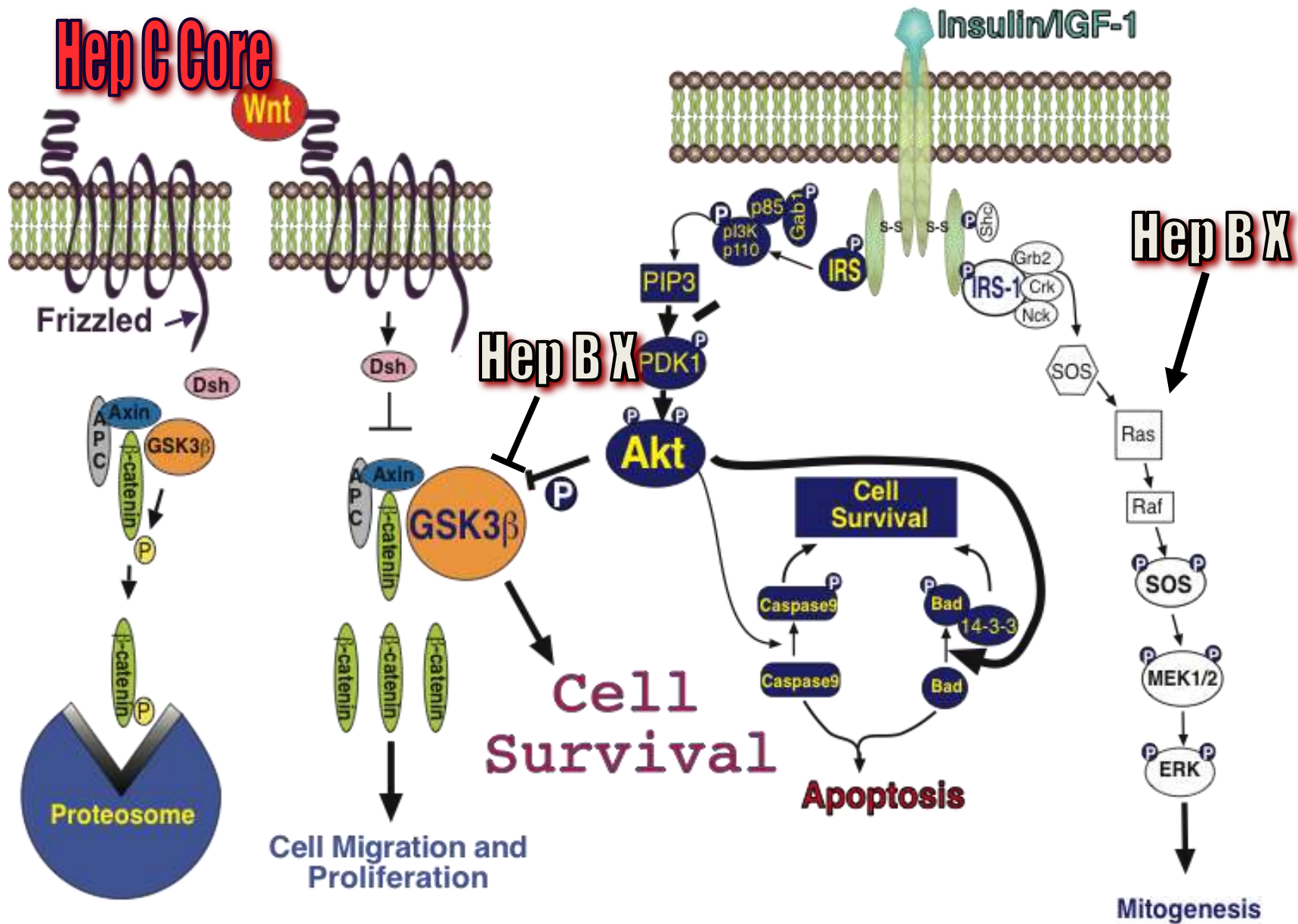


Liver Cancer



Risk of HCC Development





Introduction

- Two signal transduction pathways are activated in over 90% of HBV and HCV related HCC and appear important in the pathogenesis of this disease
- Insulin/IGF/IRS-1/MAPK signaling pathway
- Wnt/Fzd/ β -catenin signaling cascade

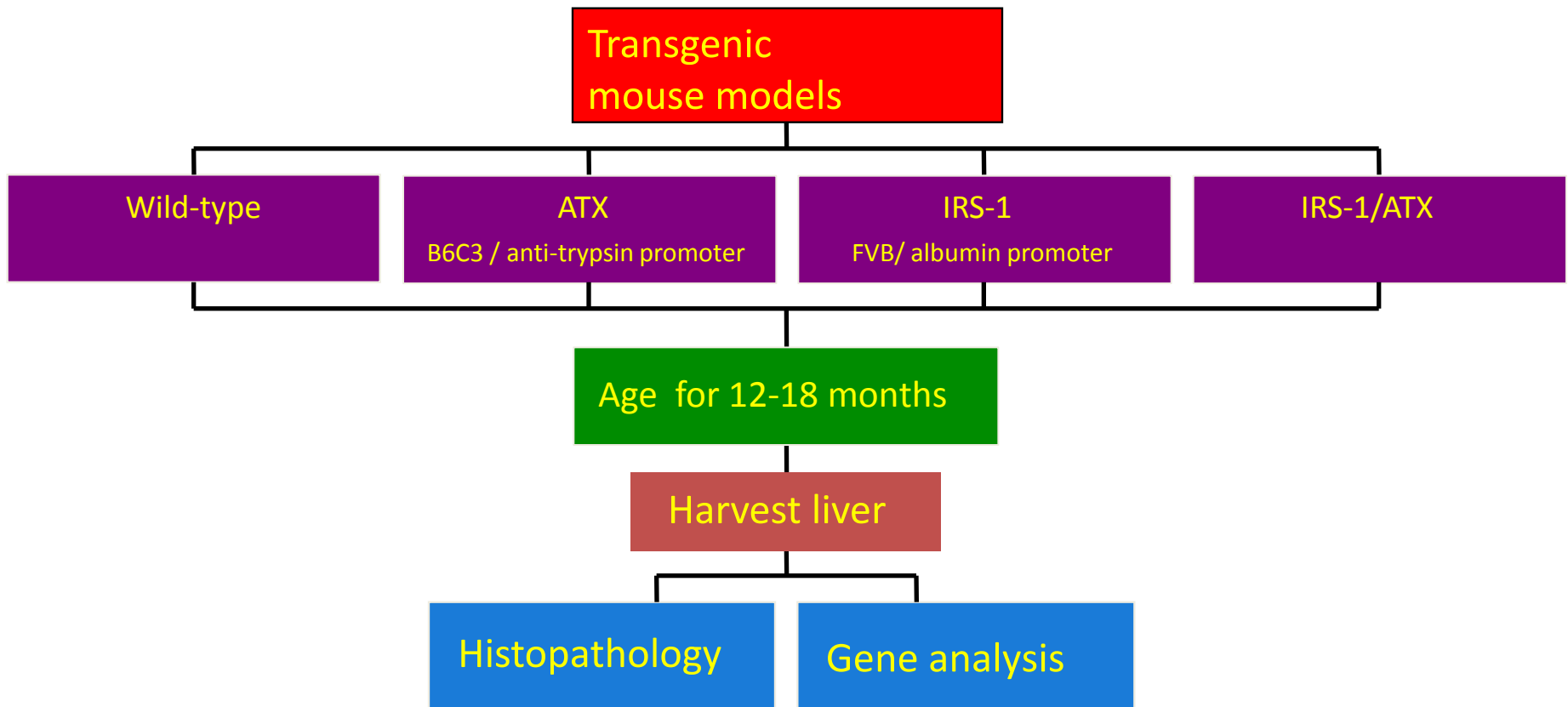


Hypothesis

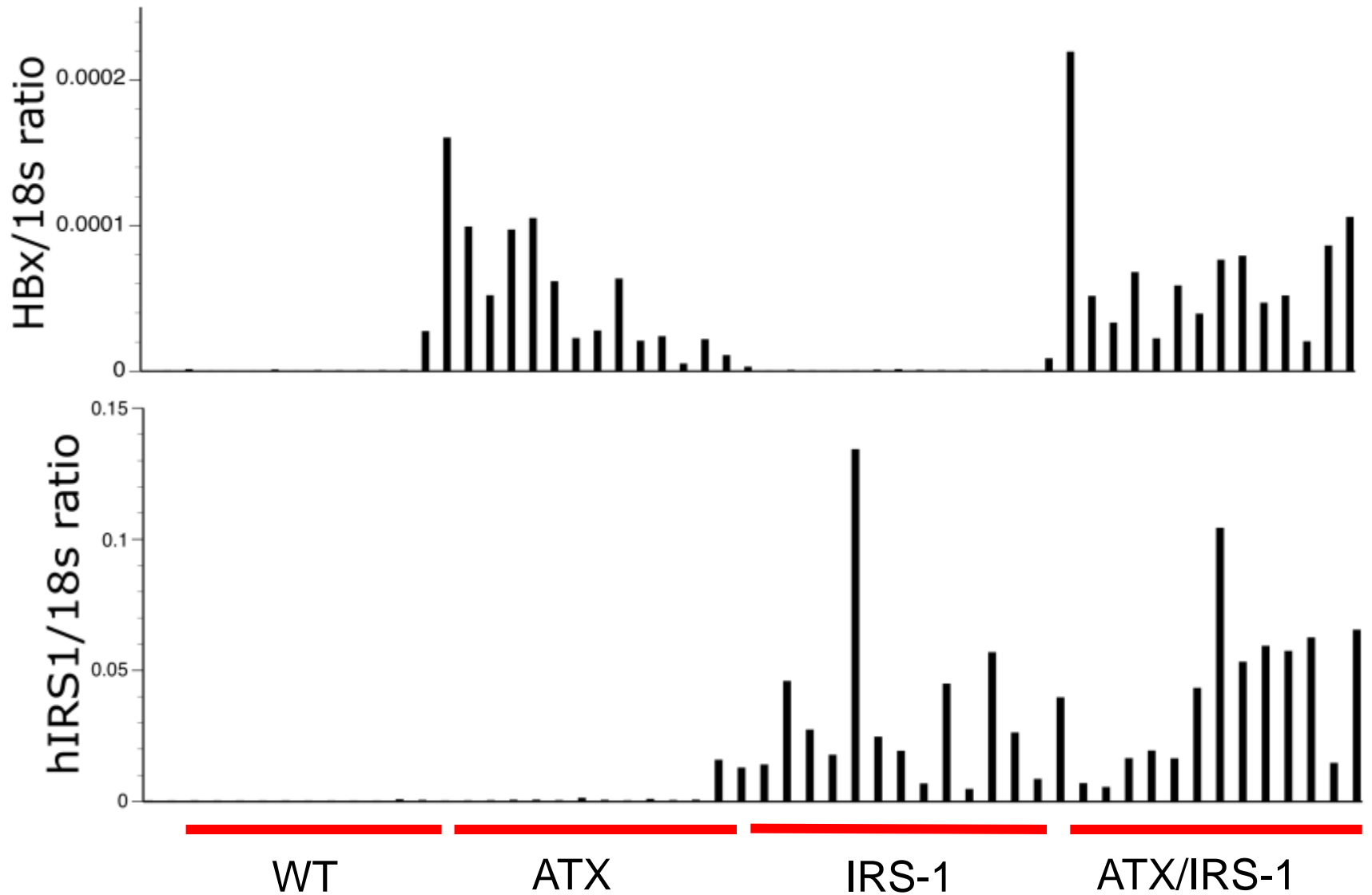
- Develop a transgenic mouse model where the IN/IRS-1/MAPK and the Wnt/ β -Catenin signaling cascades are activated
- Explore if dual pathway activation is necessary and sufficient to transform the mammalian liver



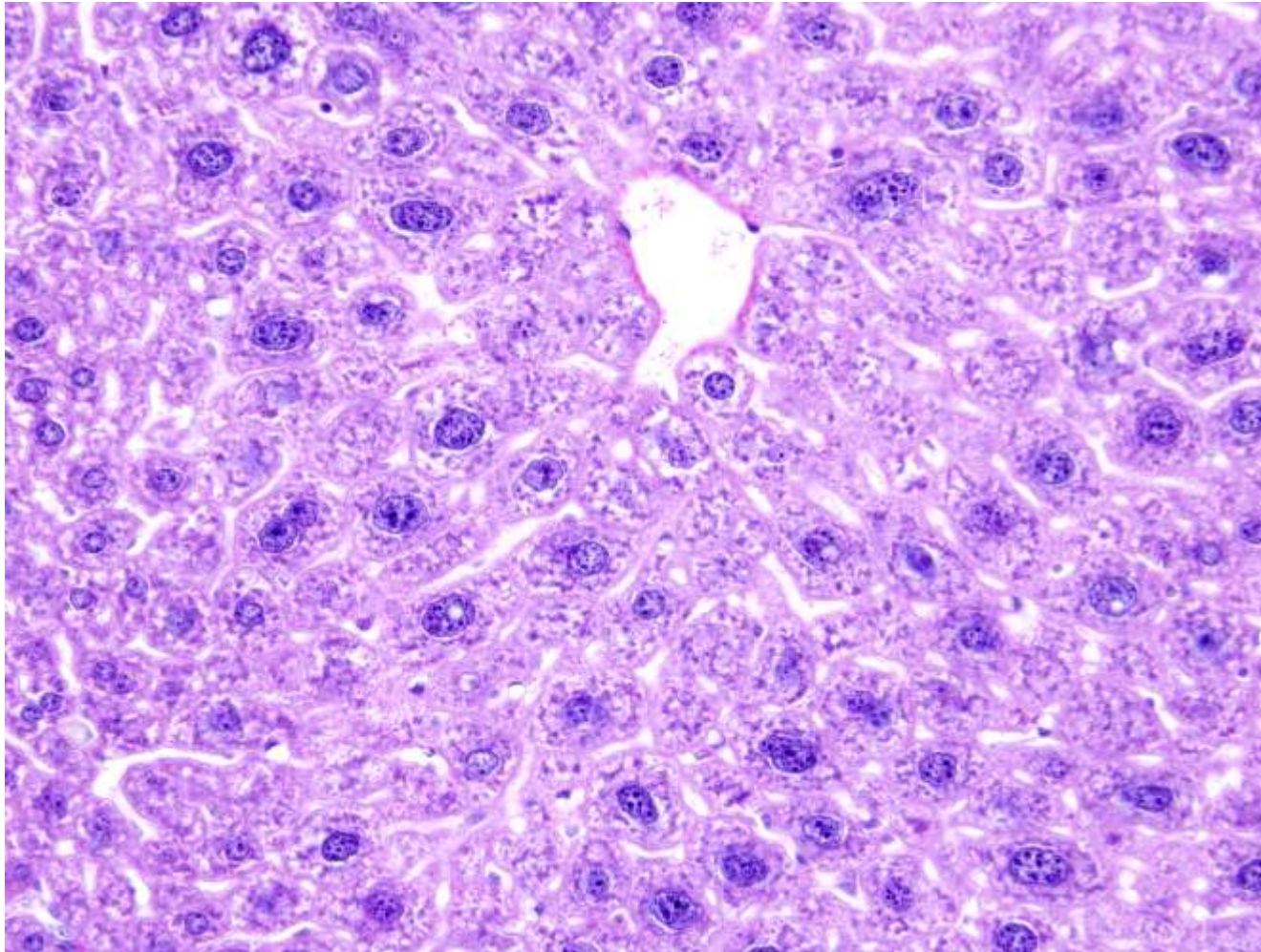
Methods



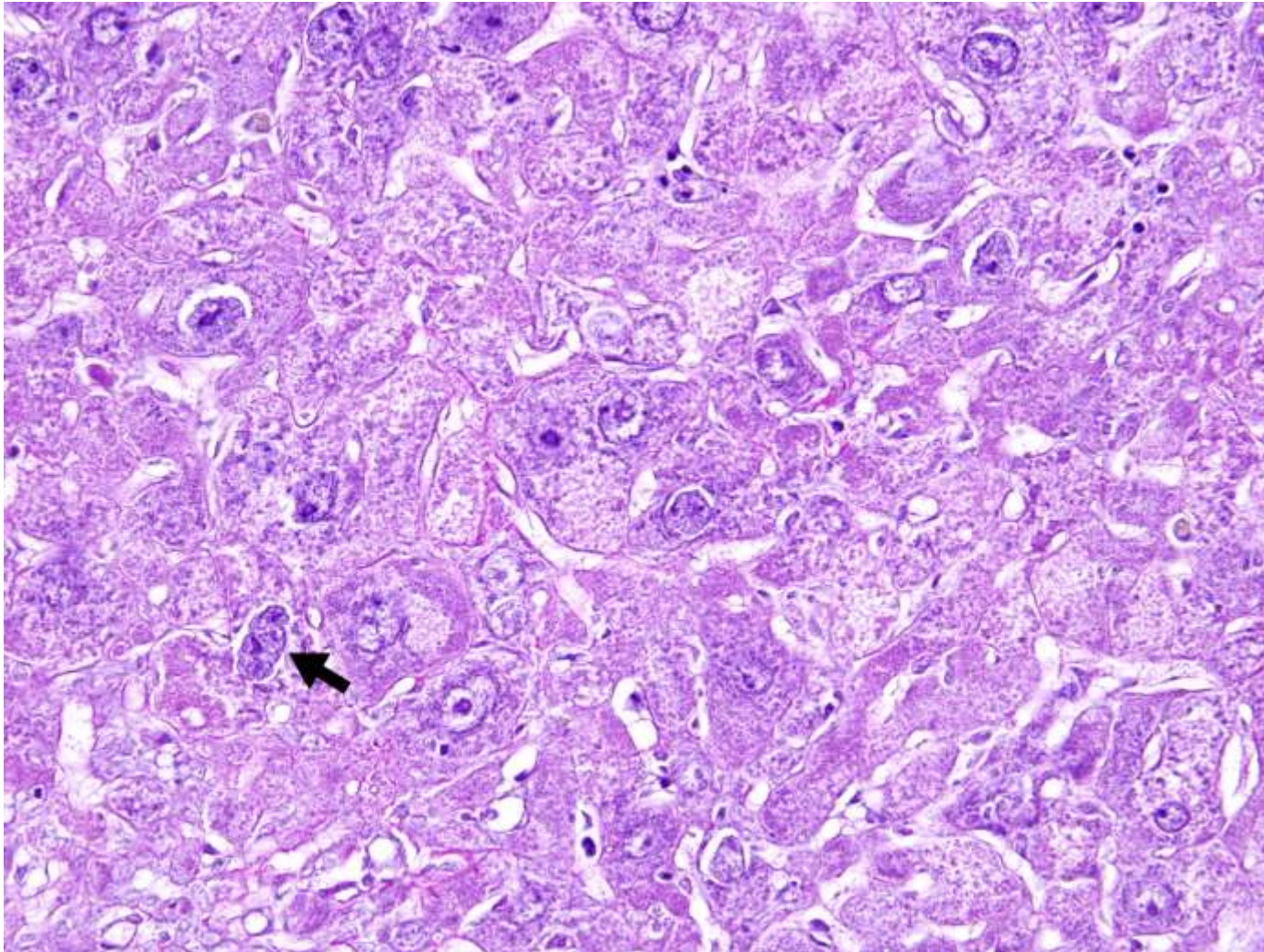
Analysis of Genotypes by RT-PCR



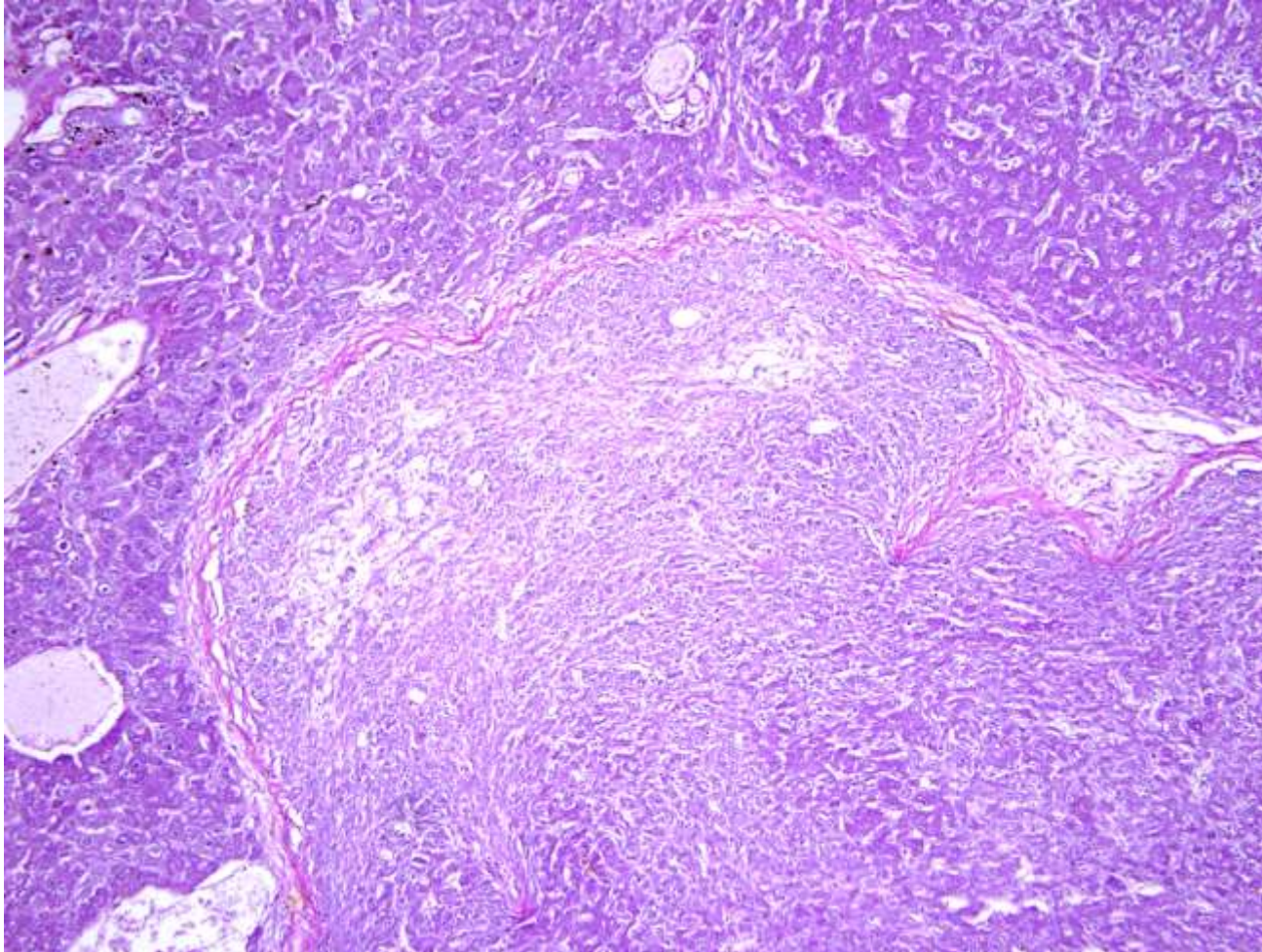
Normal liver from IRS-1/HBx double transgenic mouse at 3 months of age.



Severe hepatic dysplasia in a IRS-1/HBx double transgenic mouse



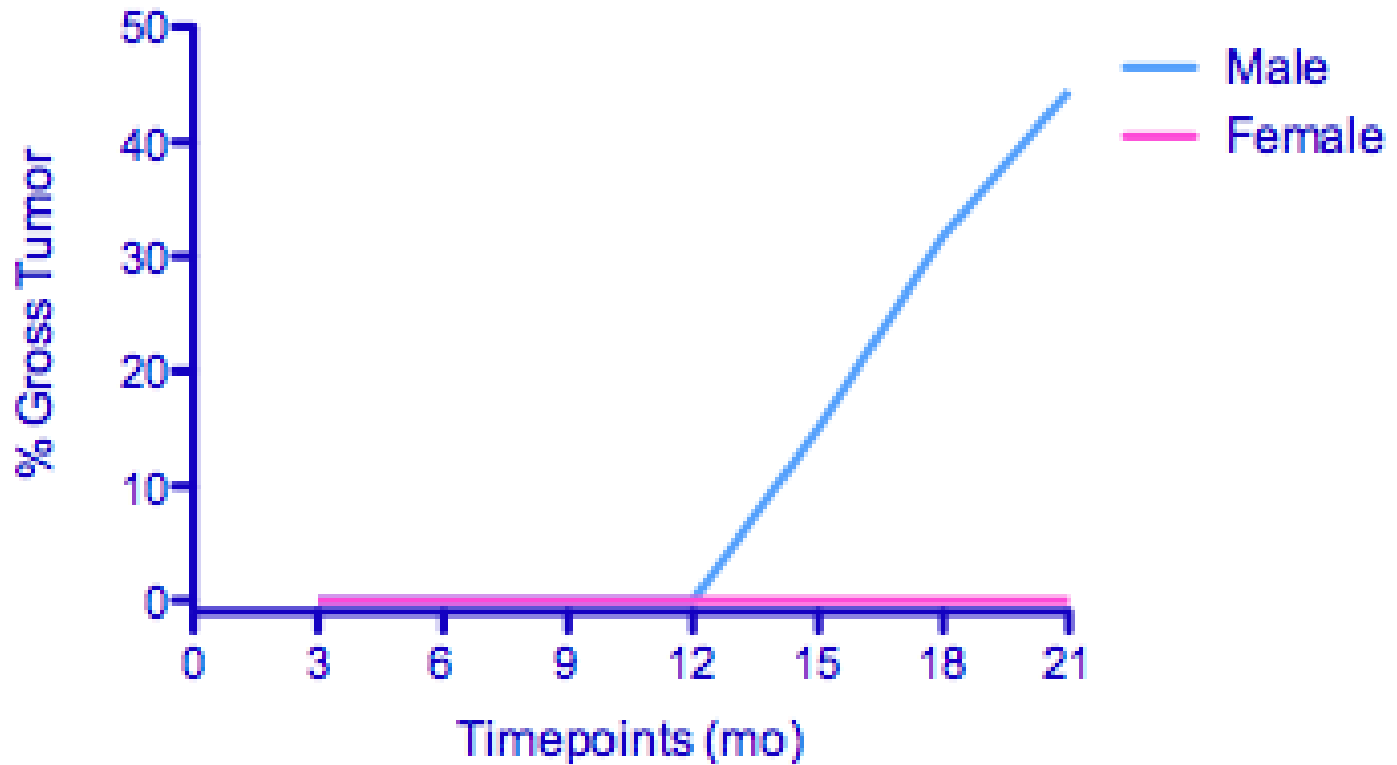
Microscopic HCC tumor in IRS-1/HBx double transgenic mouse



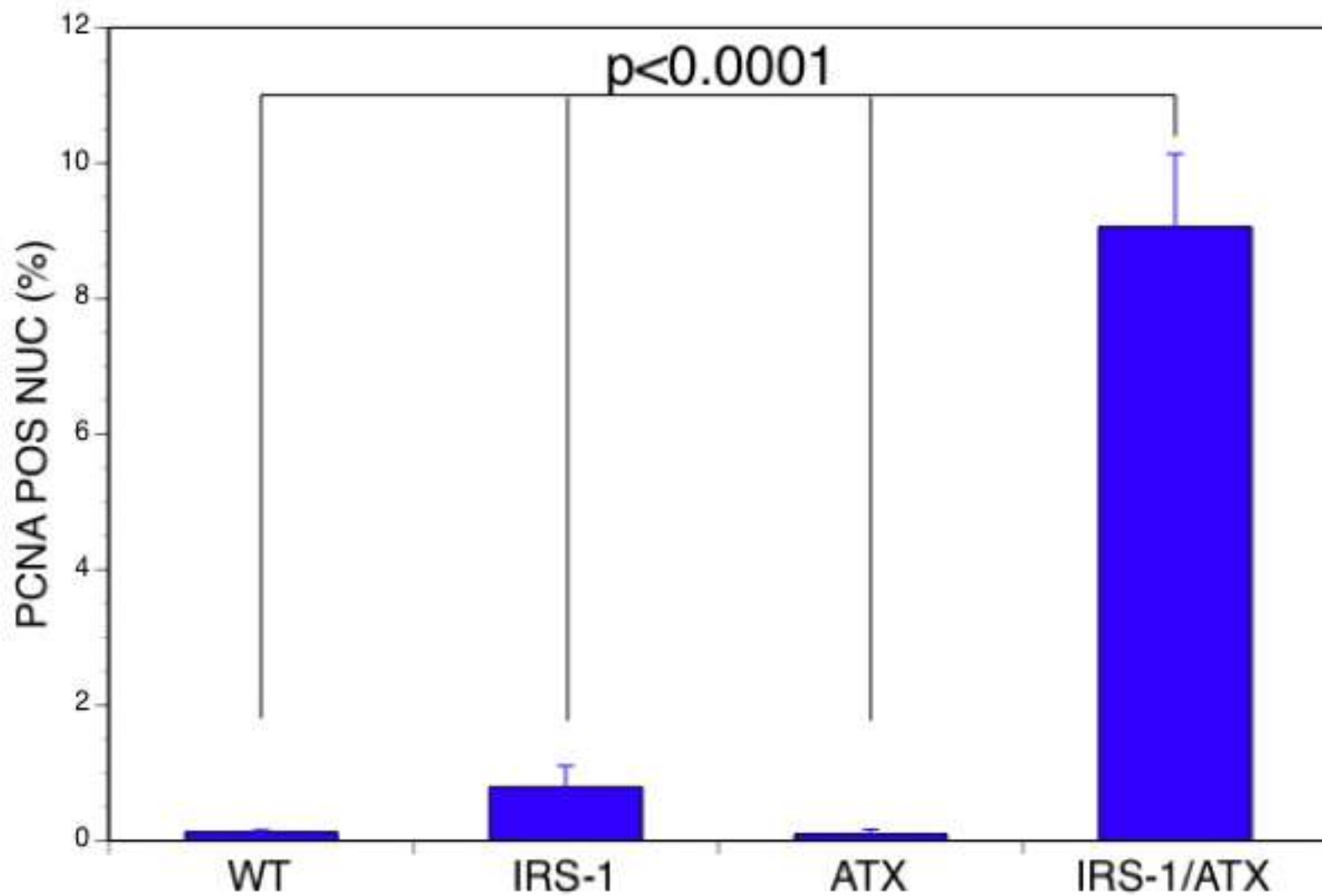
Gross HCC tumor in IRS-1/HBx double transgenic mouse



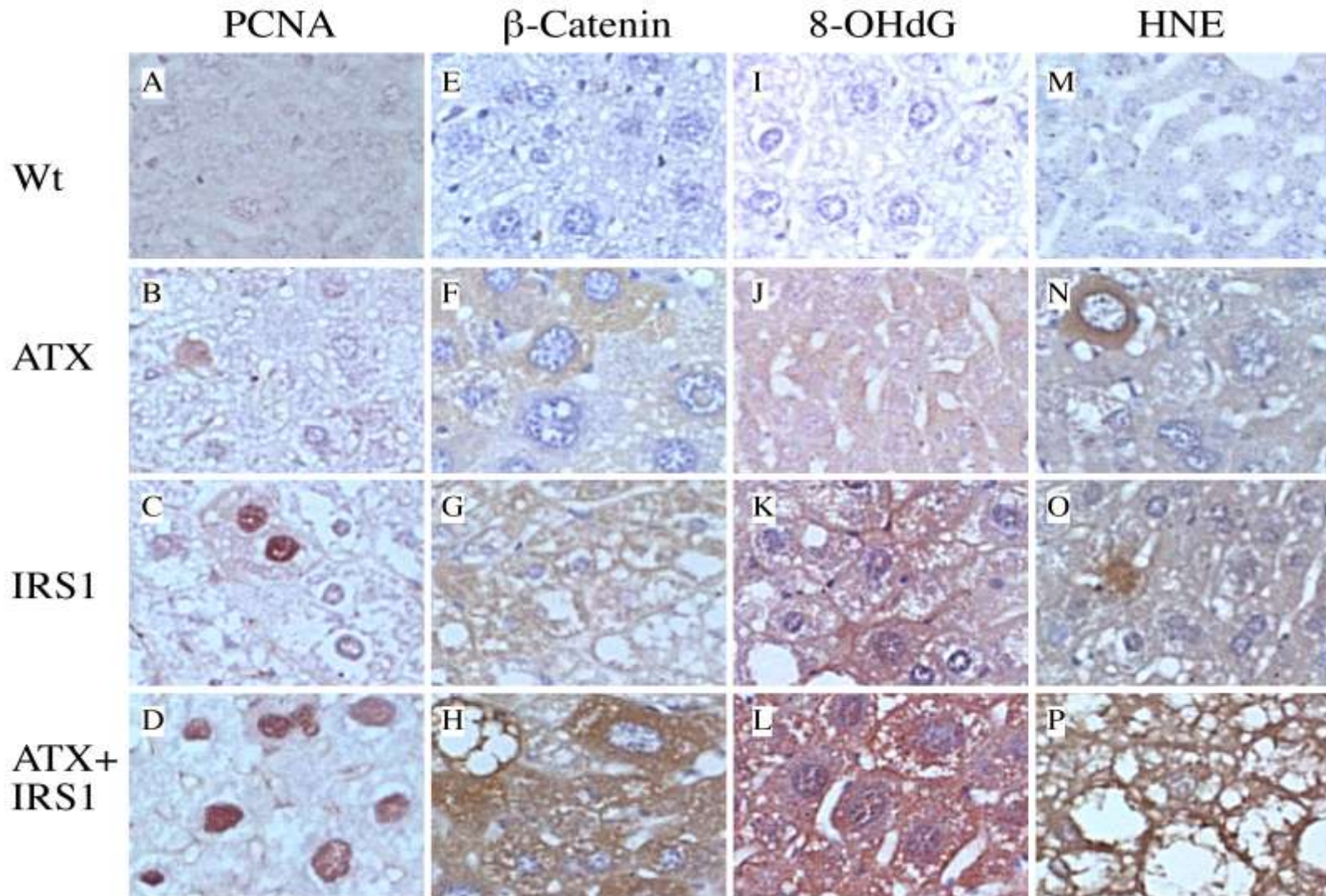
HCC tumor formation in male and female IRS-1/HBx double transgenic mice.



Hepatocyte Proliferation in the Liver of Transgenic Mice at 15 Months of Age

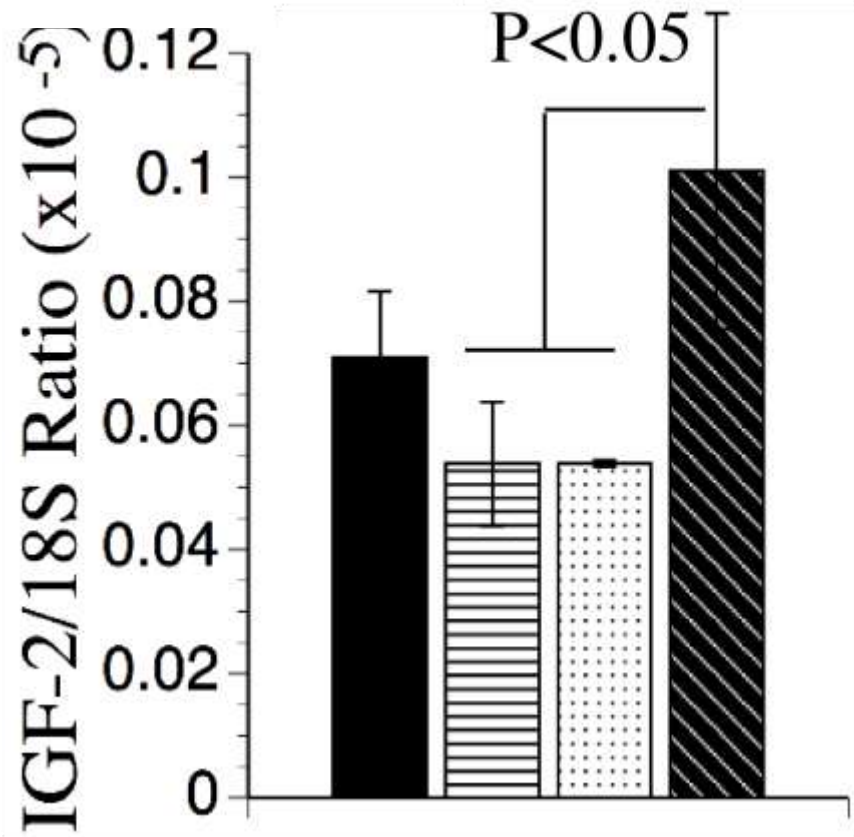
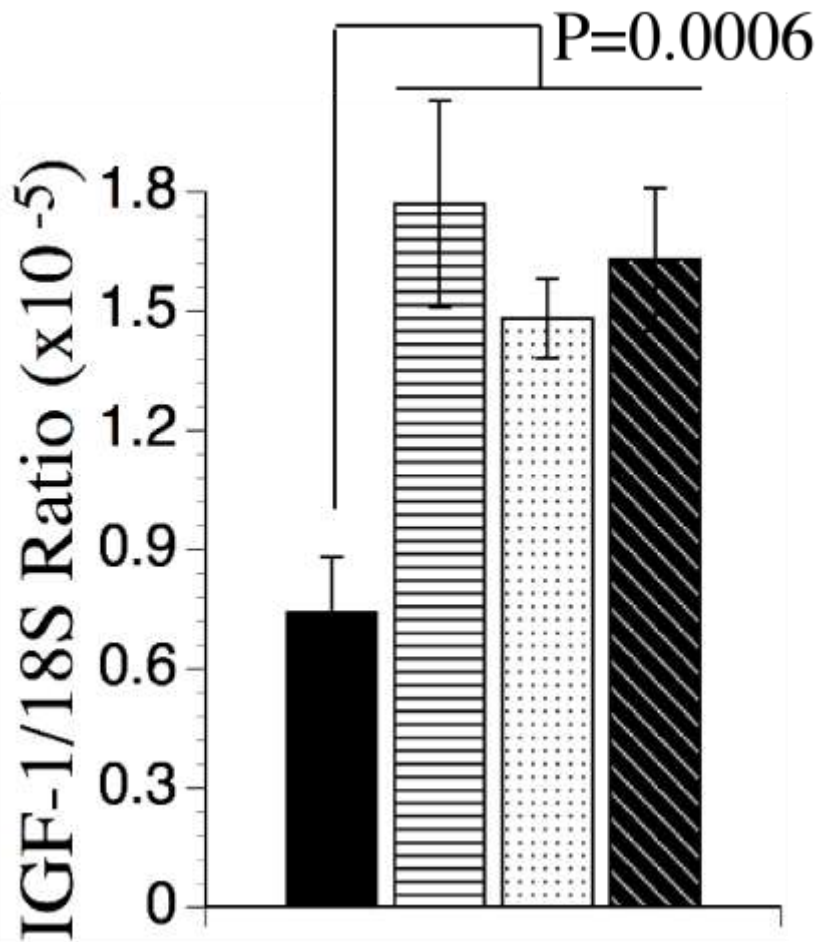


Cell proliferation, β -catenin accumulation, oxidative stress and lipid peroxidation

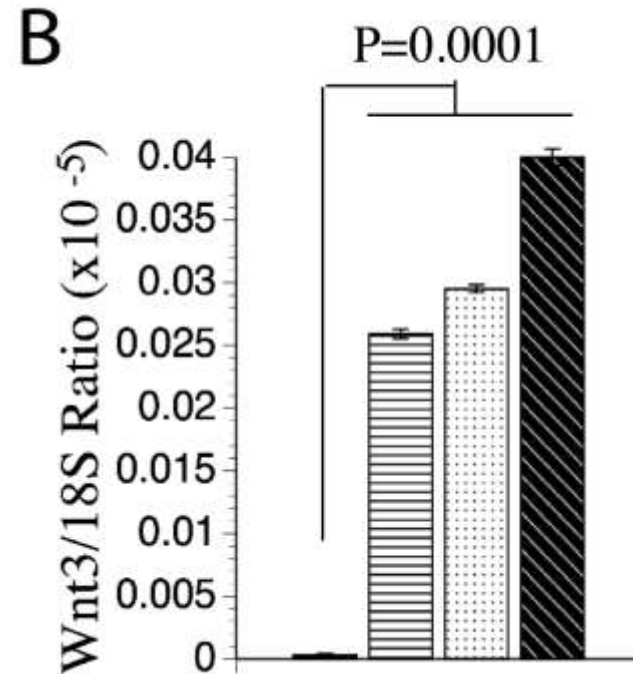
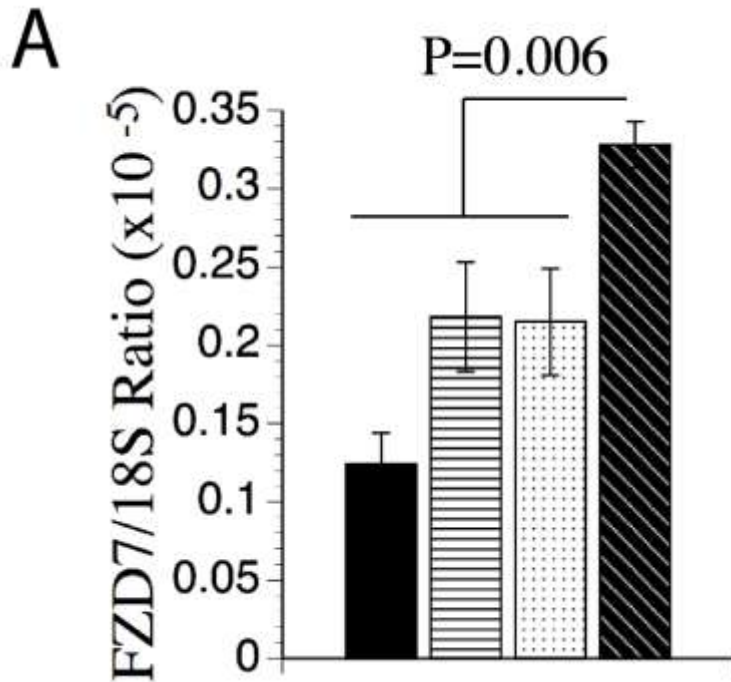


Expression of Insulin Like Growth Factors

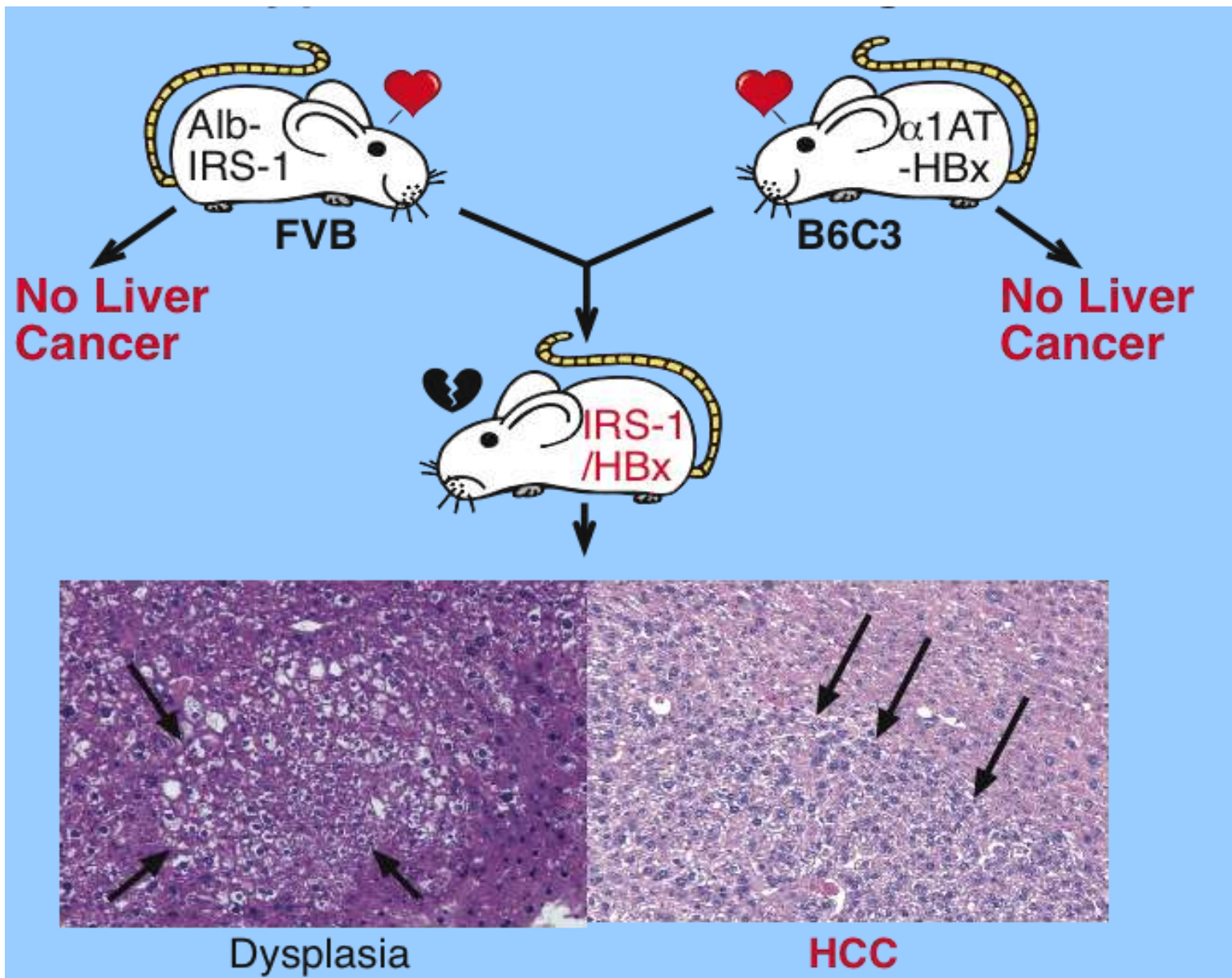
- Wt
- ▨ ATX
- ▩ IRS-1
- ▩ ATX/IRS-1



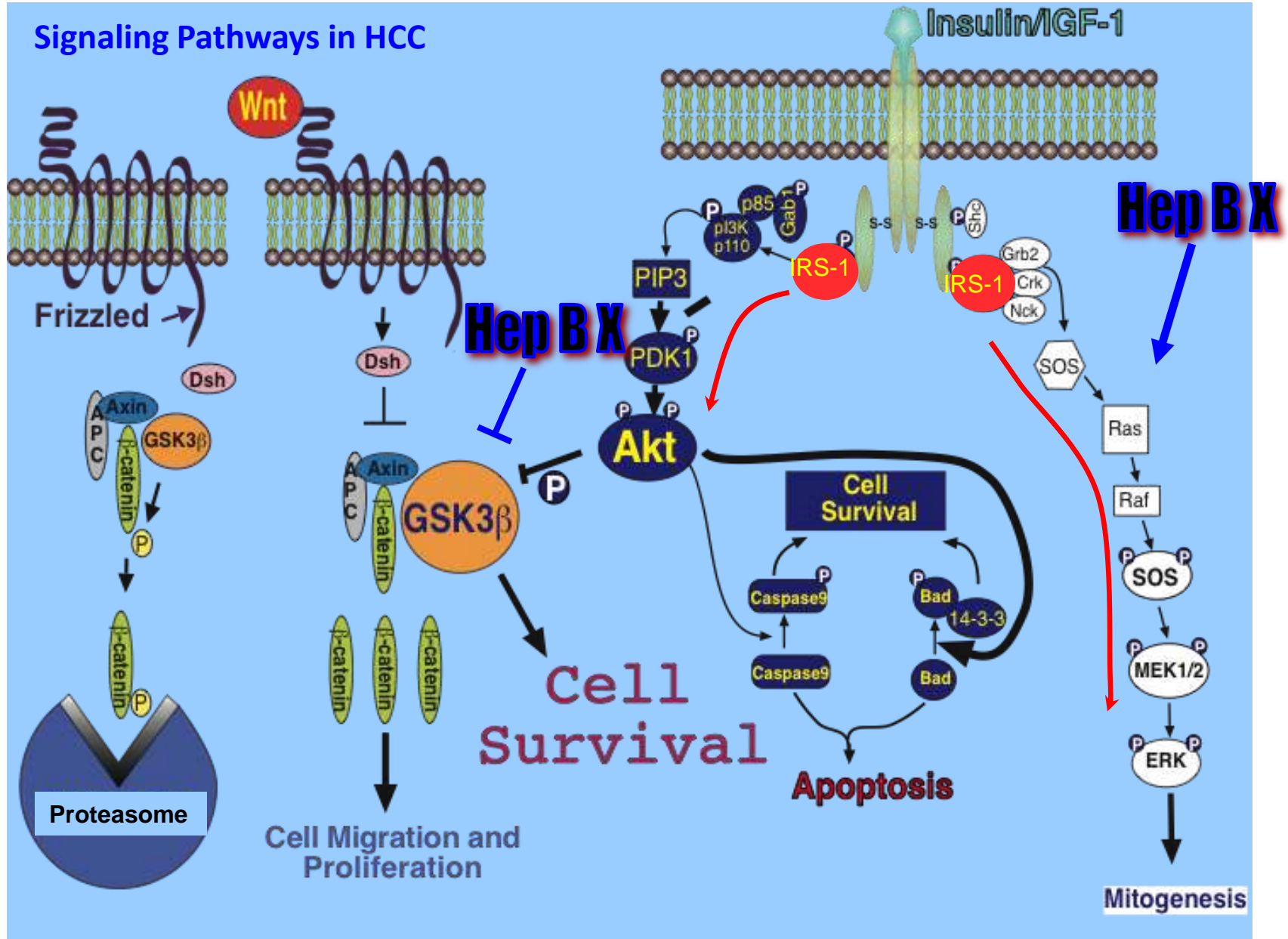
Constitutive Expression mRNA levels of FZD7 and Wnt3 in Transgenic Mice



HBx/IRS-1 Mice Develop HCC



Signaling Pathways in HCC



Summary

- Constitutive over-expression of IRS-1 and HBx promotes hepatocyte dysplasia and HCC
- Activation of the IN/IGF/IRS-1/MAPK and Wnt/ β -catenin signaling cascades is necessary and sufficient to transform mammalian hepatocytes
- The double HBx/IRS-1 transgenic mouse model replicates many of the cellular and molecular abnormalities found in human HCC

Collaborators

Brown University

- ◆ M. Chiara Cantarini
- ◆ Suzanne de la Monte
- ◆ Rolf Carlson
- ◆ Paul Sepe
- ◆ Takashi Meada
- ◆ Seishu Tamaki
- ◆ Fusun Gundogan
- ◆ Ariel Cohen
- ◆ Nitin Roper
- ◆ Costica Aloman
- ◆ Nedim Ince
- ◆ Laurent Lavaissiere

MIT

- Andy Yeung
- Dane Wittrup

South Africa

- Michael Kew

MD Anderson

- Michael Rosenblum

