Fetal alcohol exposures promote the development of aggressive tumors in the endocrine glands

Dipak K. Sarkar, D.Phil., Ph.D.
Endocrine Program
Rutgers, The State University of New Jersey

Alcohol and Cancer Risk

1. A large number of reports now show that alcohol consumption in adult increases the chance of developing certain cancers (e.g., Head and Neck, Esophageal, Liver, Breast, Colorectal). The more alcohol a person consumes, the higher their risk of developing some kinds of cancers.

2. Some case reports suggest that prenatal alcohol exposure increases cancer susceptibility of human offspring (Azouz et al. Pediatr Radiol, 1993; 23:615-616; Becker et al., Wien Klin Wochenschr, 1982; 94:364-5; J. Jorgenson, 2013; Severson et al., Cancer Epidemiol Biomarkers Prev, 1993; 2:433-439; Mongraw-Chaffin et al., Alcohol. 2009; 43:241-5)

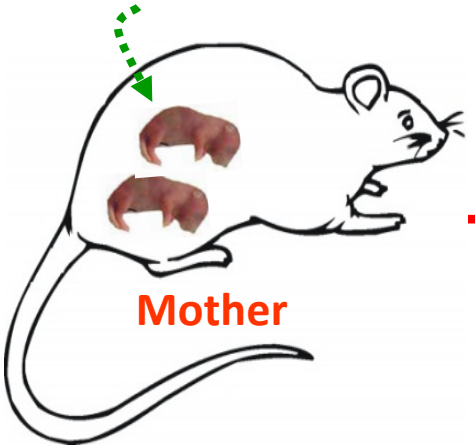
Alcohol exposure *in utero* increases susceptibility to mammary tumorgenesis in rat offspring?

Alcohol-Fed (AF) or

Pair-Fed (PF) or

Rat chow-Fed (AD)

Alcohol (6.7% v/v) or pair-fed liquid diet between ED7-21



Mother

Female offspring (F1)

Study-I

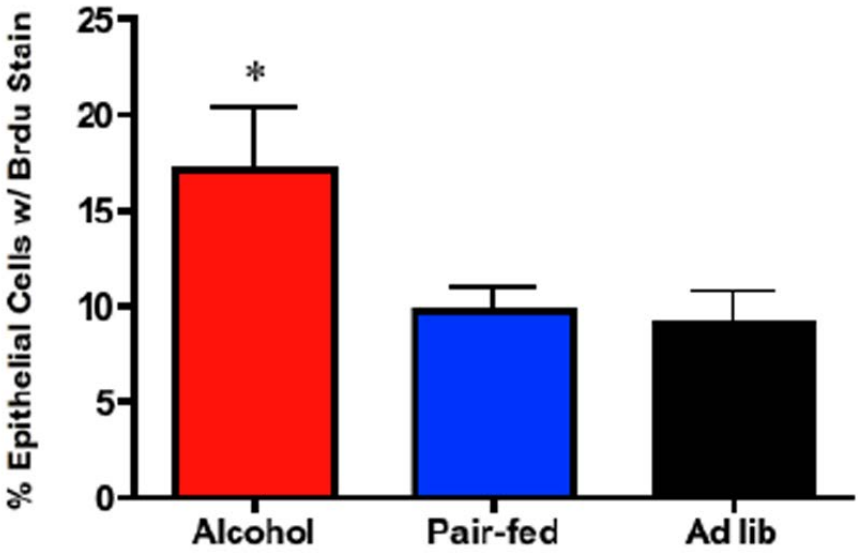
Sacrificed at 1 month of age

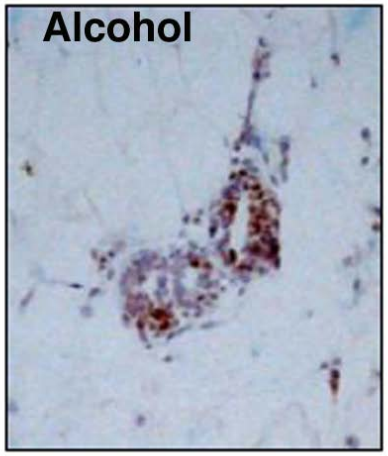
Study-II

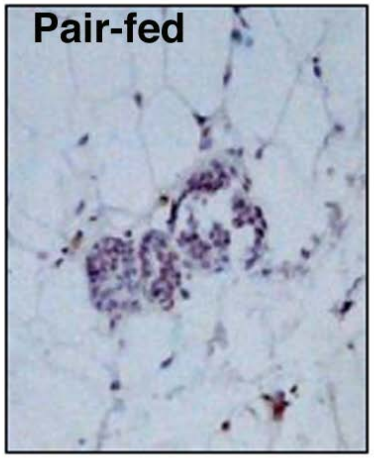
Induction of Mammary Cancer by NMU (50 days of age)

Sacrifice after 4 months

Animals exposed to alcohol *in utero* exhibit increased mammary gland proliferation





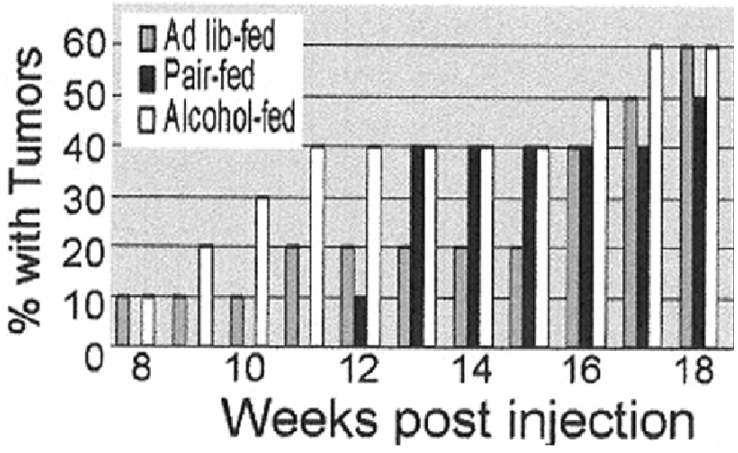


Bromodeoxyuridine incorporation in mammary glands of 20 day old rats exposed to alcohol *in utero*

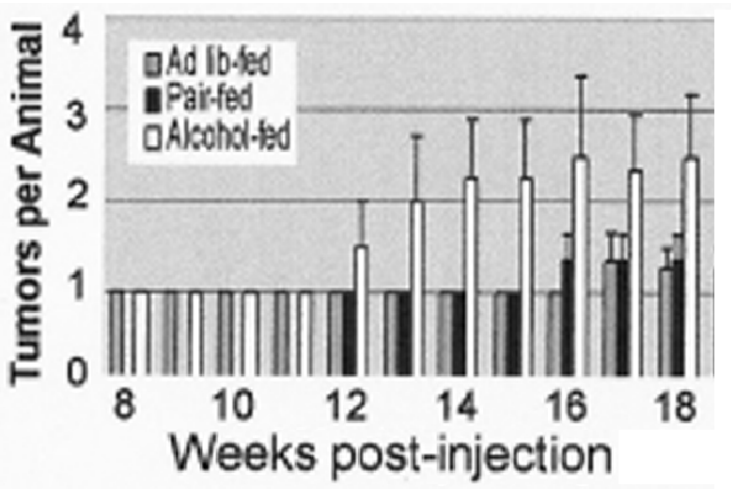
Polanco et al., ACER (2010)

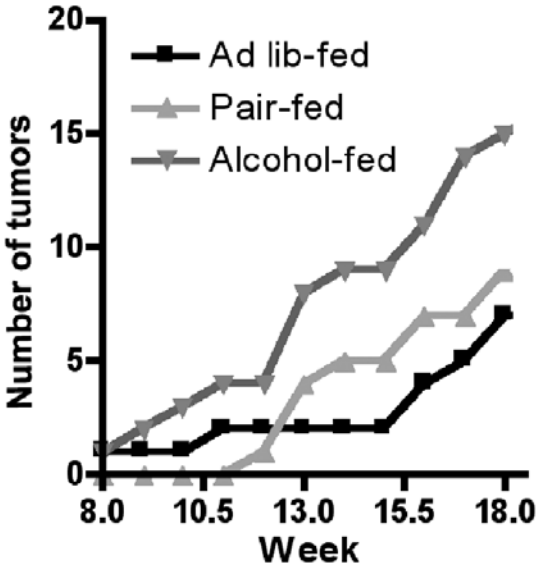
Alcohol exposure in utero increases the risk of developing mammary cancer

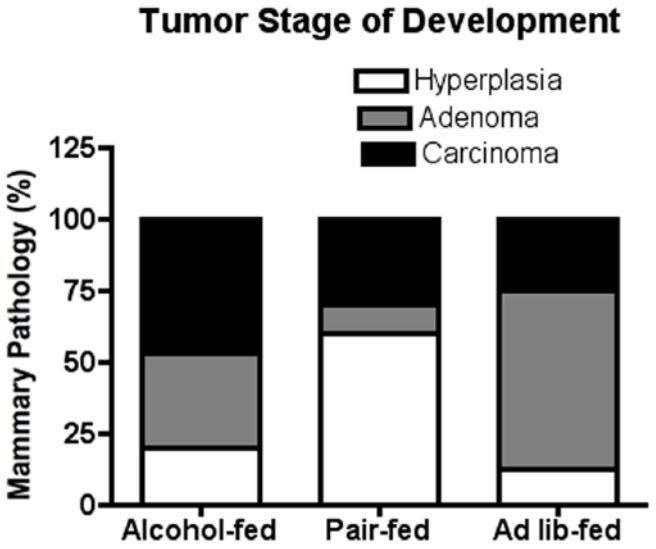
Tumor incidence



Tumor multiplicity

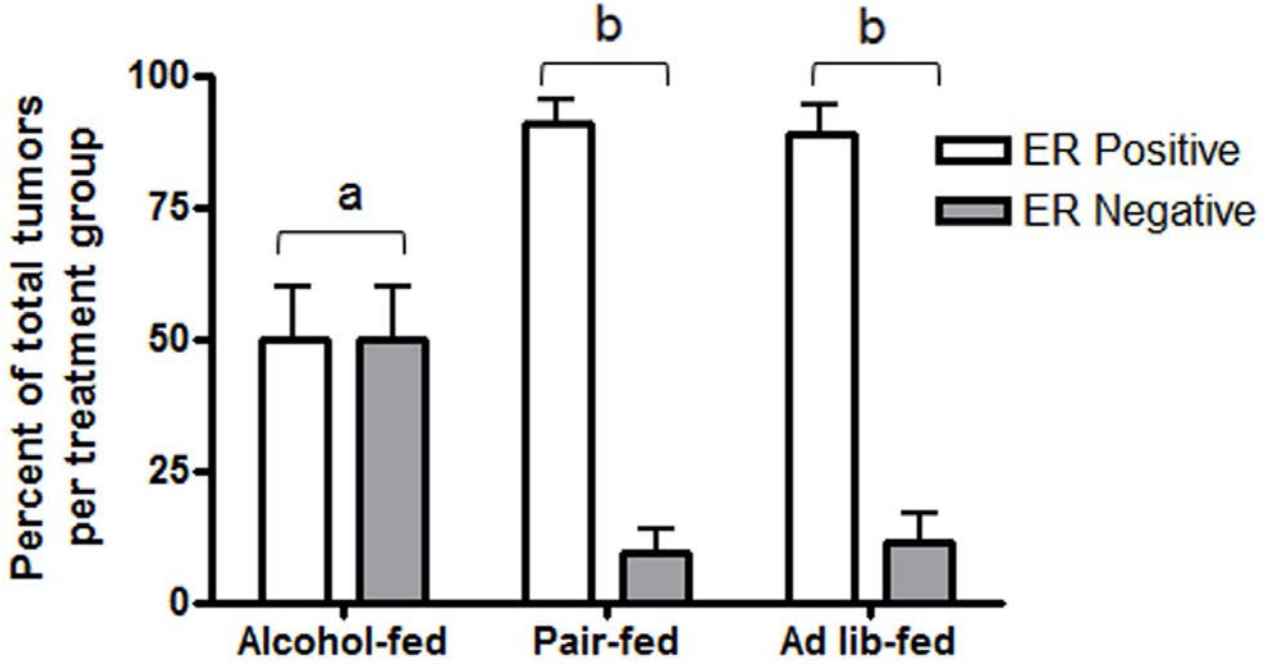




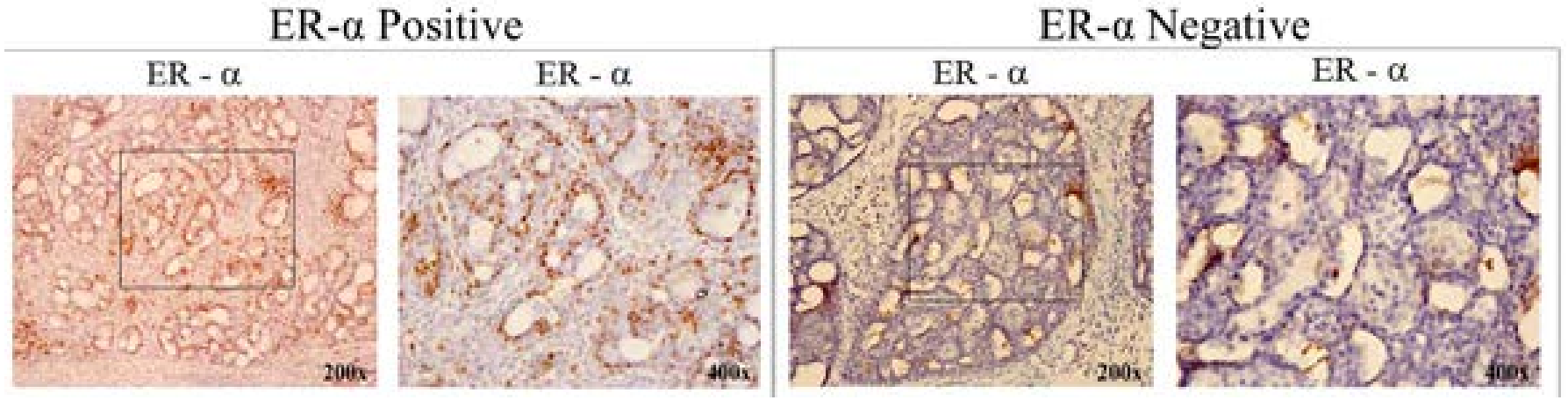


Polanco T, Cohick W, Sarkar DK, 2010, *Alcohol Clin Exp Res* 34:1879-1887.

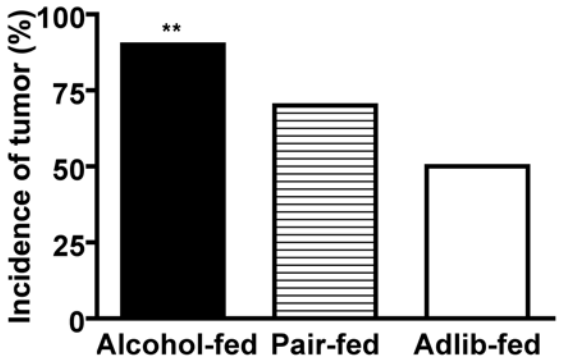
Alcohol exposure *in utero* results in more ER negative mammary tumors following MNU treatment

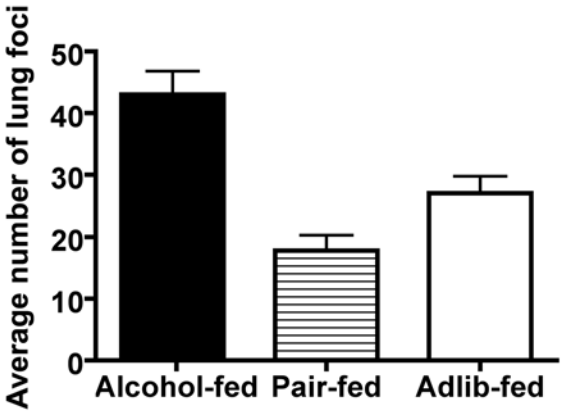


Polanco et al., ACER (2010)

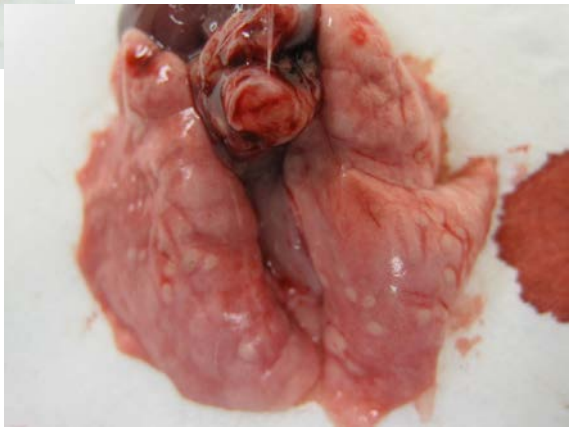


Alcohol exposure *in utero* results in more lung metastasis of mammary tumors cells (MAD B106)

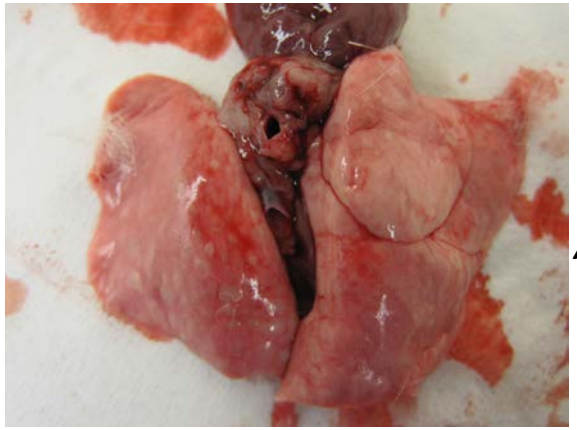




Alcohol-fed



Pair-fed



Ad lib-fed

Zhang et al., ACER, 2016

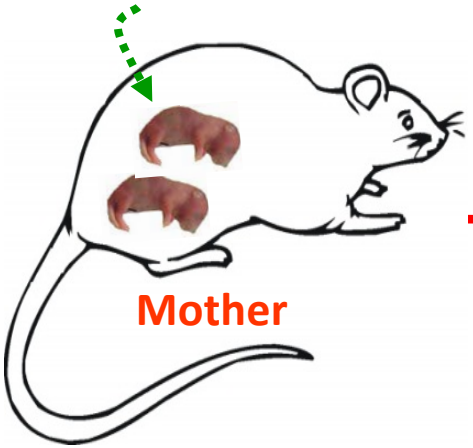
Alcohol exposure *in utero* increases susceptibility to prostate tumorgenesis in rat offspring

Alcohol-Fed (AF) or

Pair-Fed (PF) or

Rat chow-Fed (AD)

Alcohol (6.7% v/v) or pair-fed liquid diet between ED7-21



Mother

Male offspring (F1)

Study-I

Sacrificed at 6 months of age

Study-II

Induction of Prostate Cancer by NMU +T4 (3 months of age)

Sacrifice after 6 months

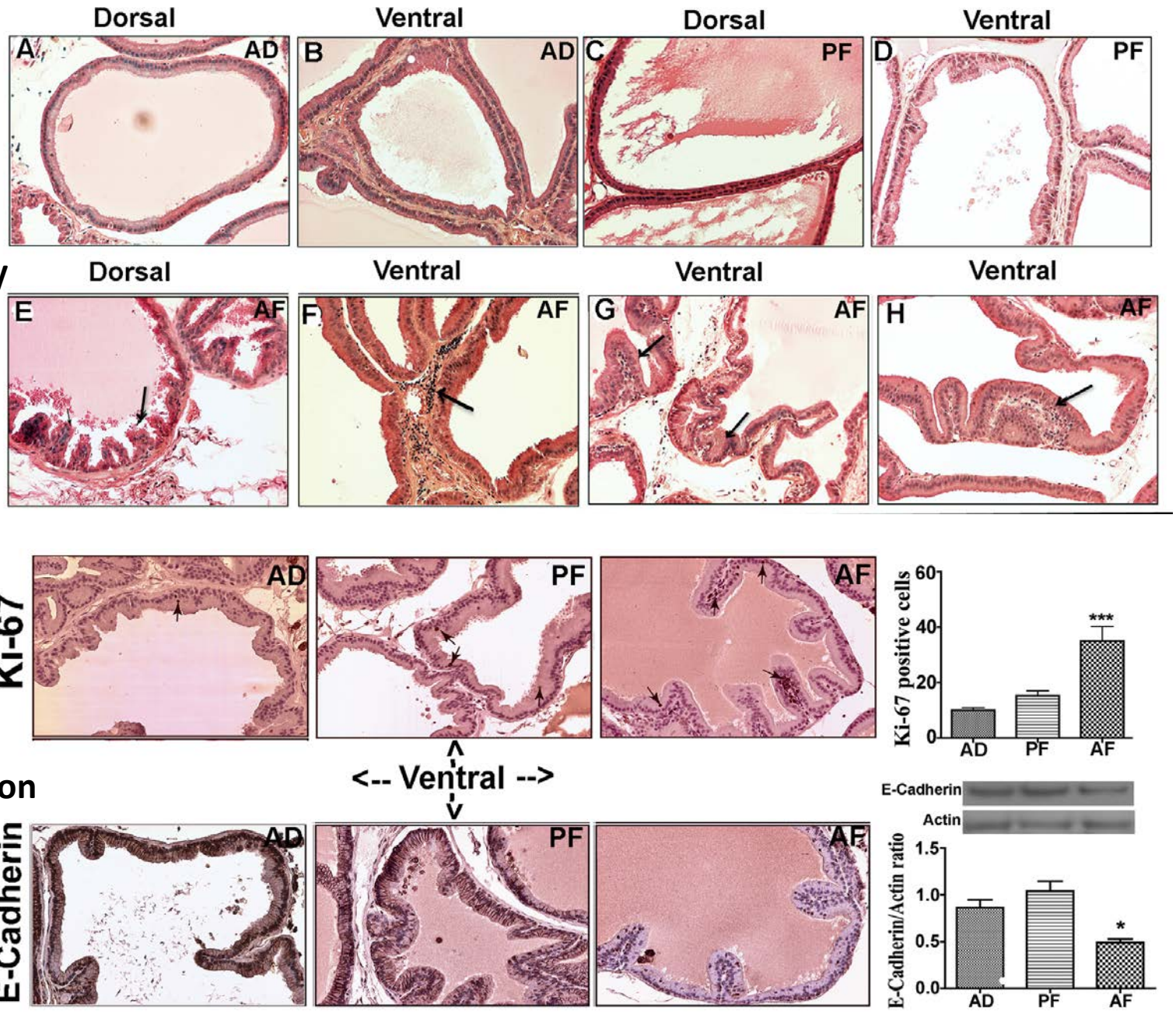
Study-III

Induction of Prostate Cancer by ER-45 +T4 (4 months of age)

Sacrifice after 6 months

Effect of fetal alcohol exposure on prostate histopathology of offspring

Study-I

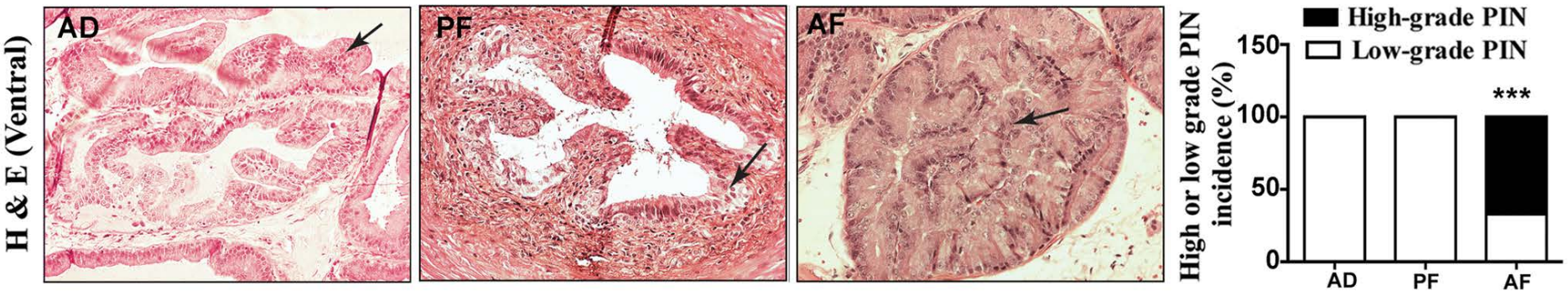


Murugan et al. ACER, 2014

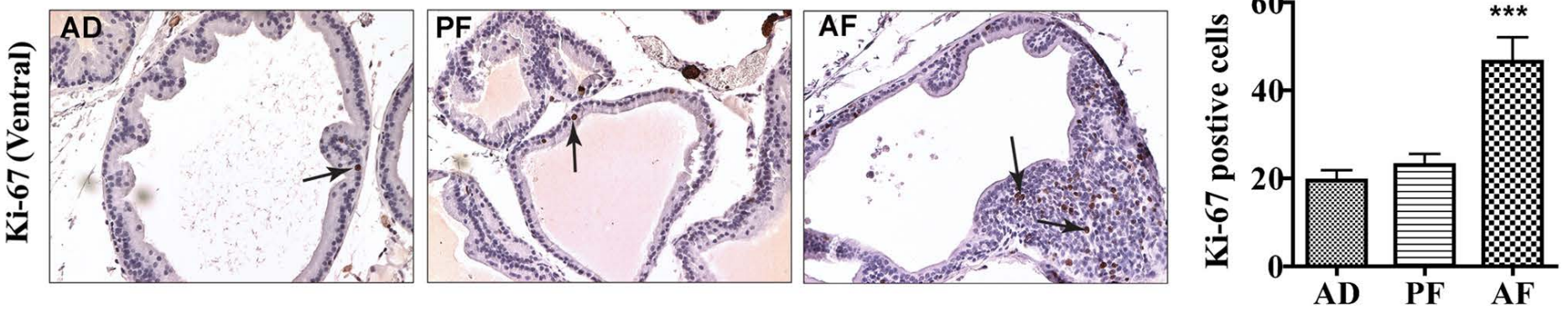
Fetal alcohol exposure and prostate tumorigenesis of rat offspring

Study-II

Histopathological Changes



Expression of cell proliferation marker (ki-67)

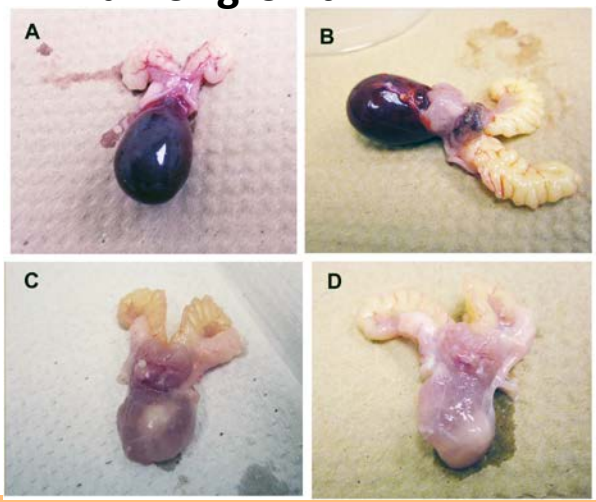


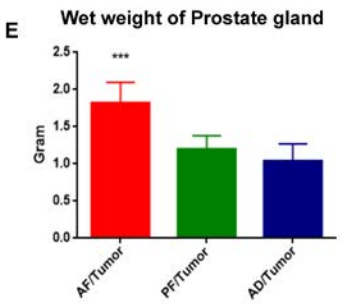
Murugan et al. ACER , 2014

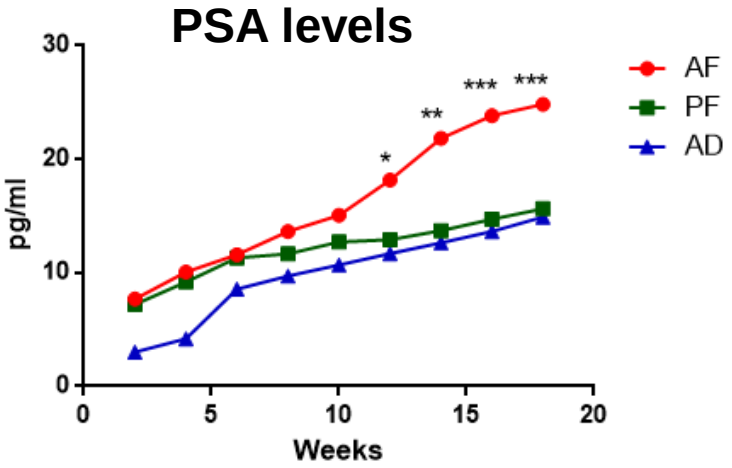
Fetal alcohol exposure and prostate tumorigenesis of rat offspring

Study-III -ER-45 (3.4 mg/kg) + T4 (2 mg/kg)

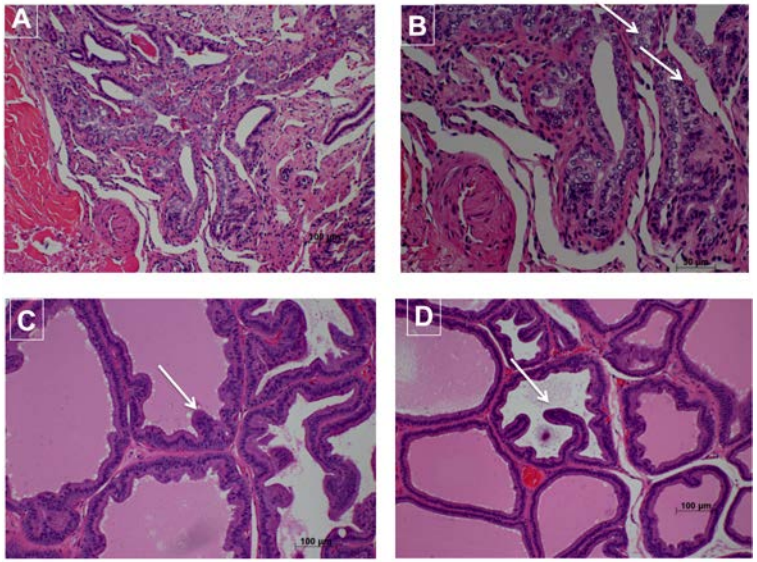
Tumor growth



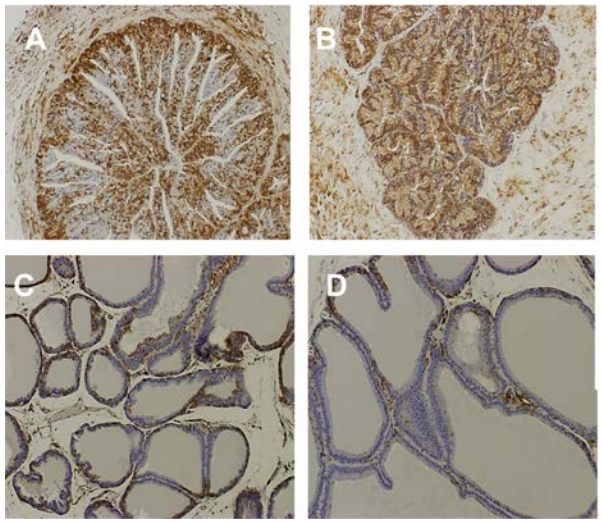


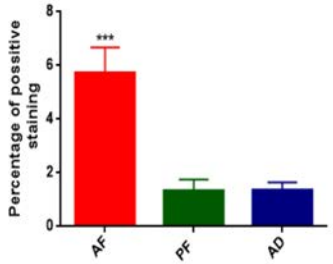


H&E showing hyperchromatic cells



Increased fatty acid synthase





Jabbar et al., unpublished

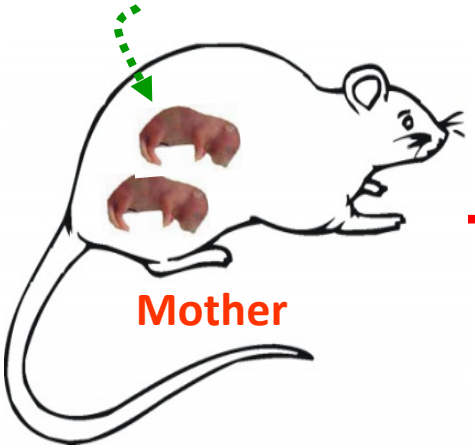
Alcohol exposure *in utero* increases susceptibility to pituitary tumorgenesis in rat offspring

Alcohol-Fed (AF) or

Pair-Fed (PF) or

Rat chow-Fed (AD)

Alcohol (6.7% v/v) or pair-fed liquid diet between ED7-21



Mother

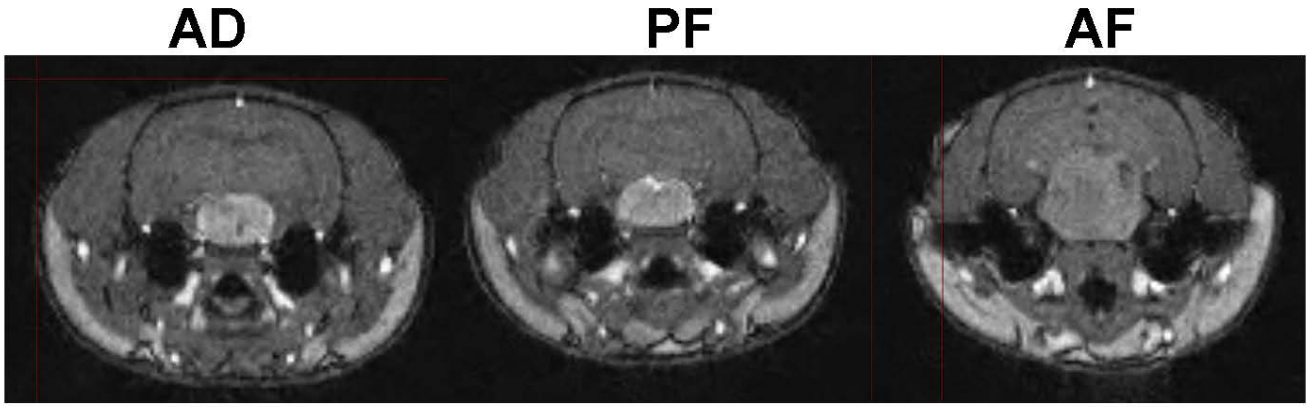
Female offspring (F1)

Treated with estradiol at 3 months of age

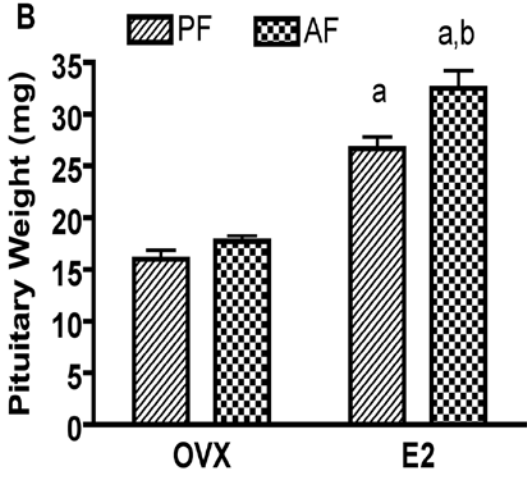
Induction of pituitary adenoma

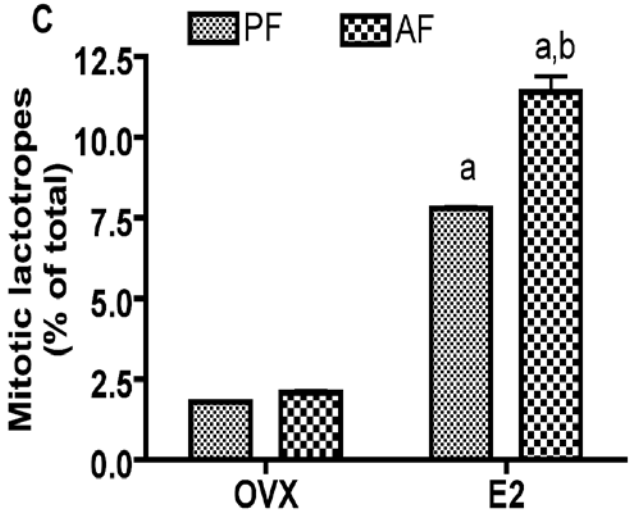
Tumor study at 1-4 months of age

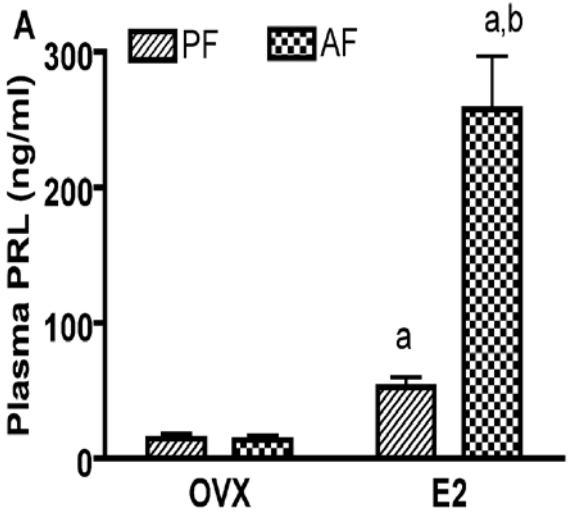
Alcohol exposure *in utero* increases susceptibility to pituitary tumorgenesis in rat offspring

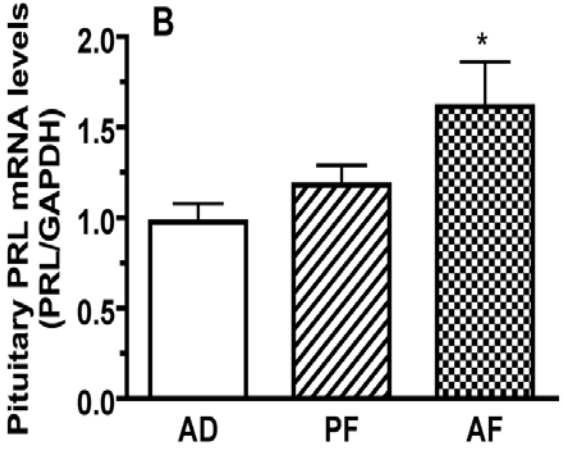


MRI of Pituitary Glands showing volume differences



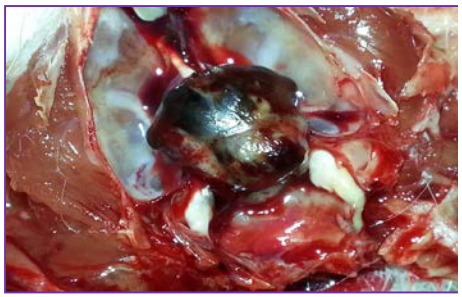


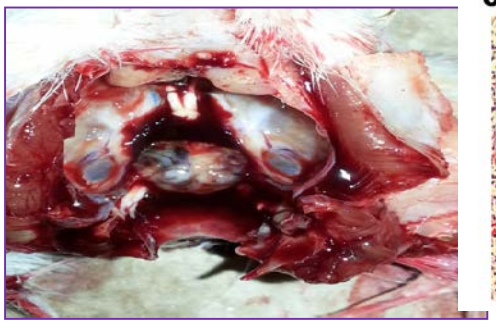


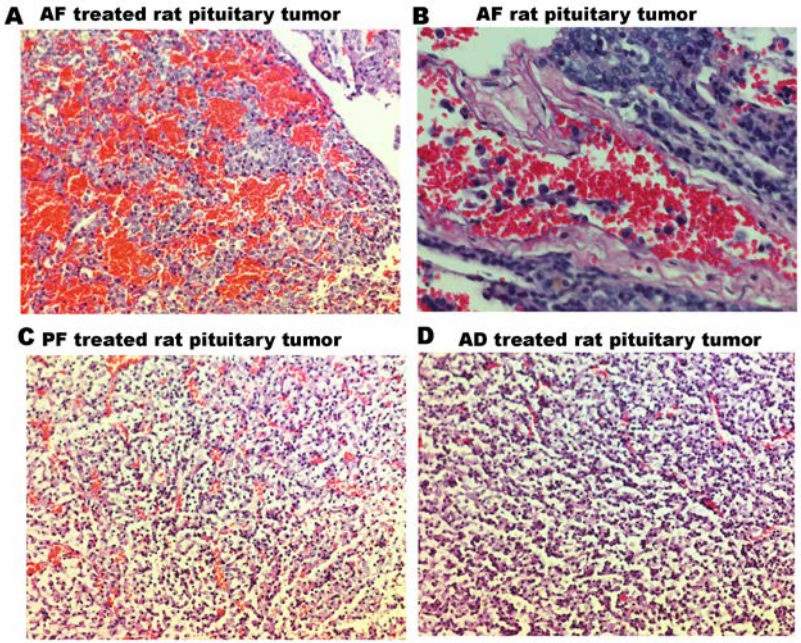


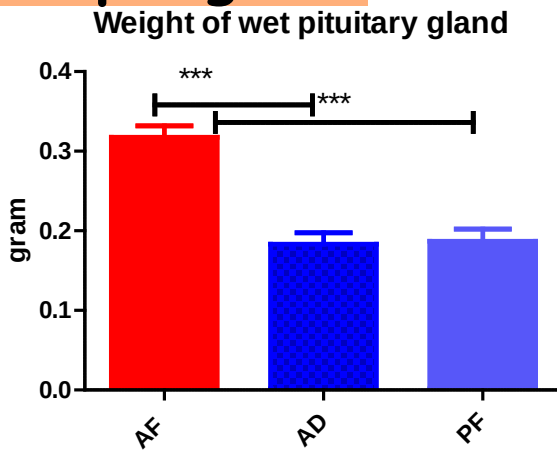
Wynne and Sarkar, Unpublished

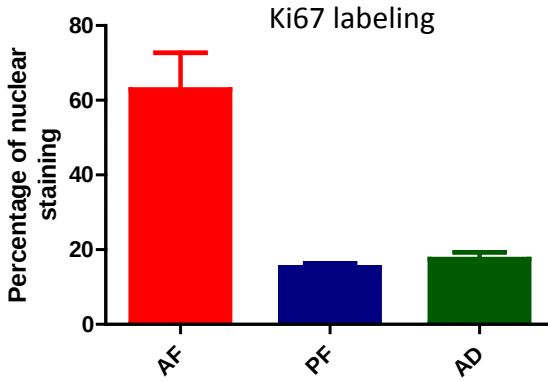
Alcohol exposure *in utero* increases susceptibility to form aggressive pituitary tumors in rat offspring

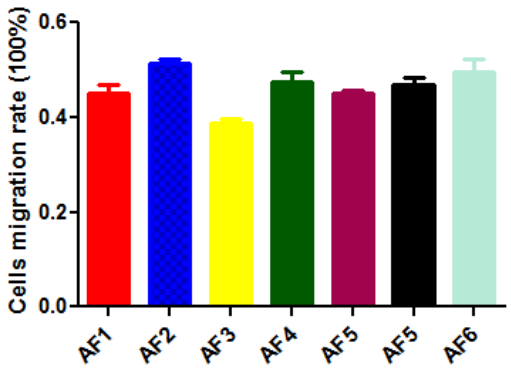


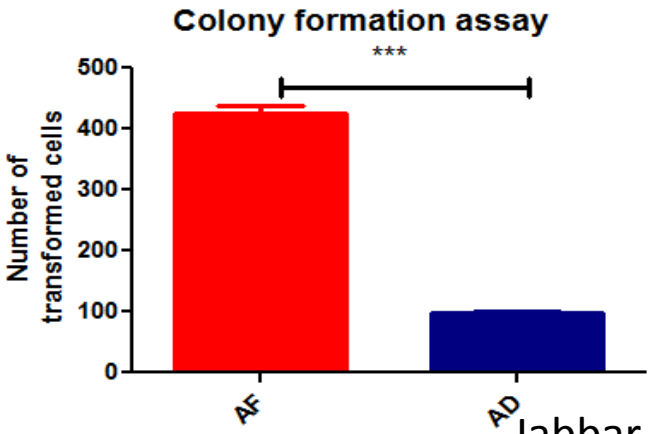


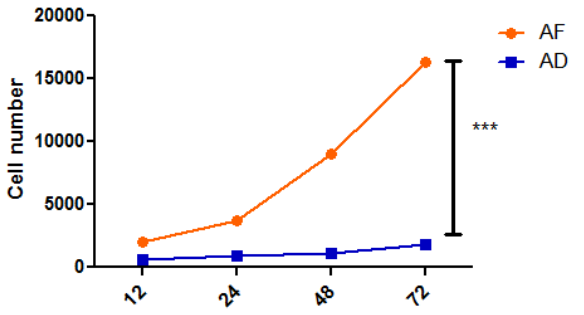






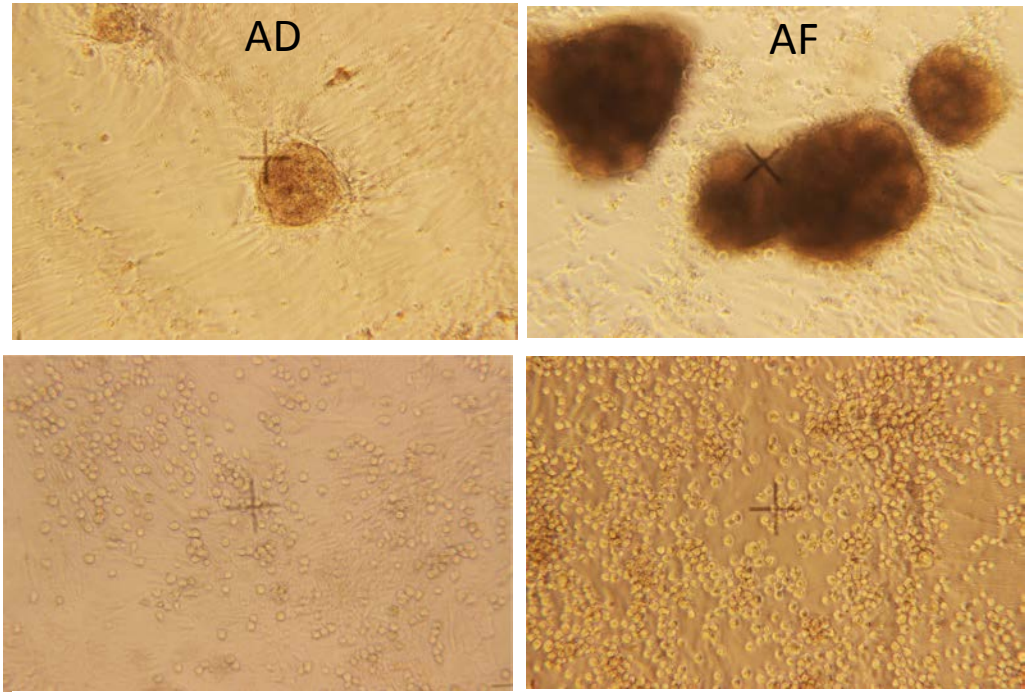




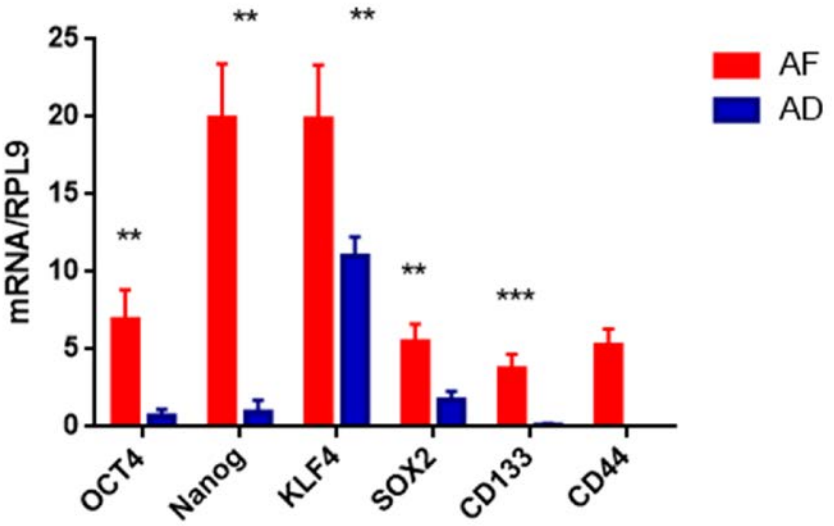


Jabbar and Sarkar, unpublished

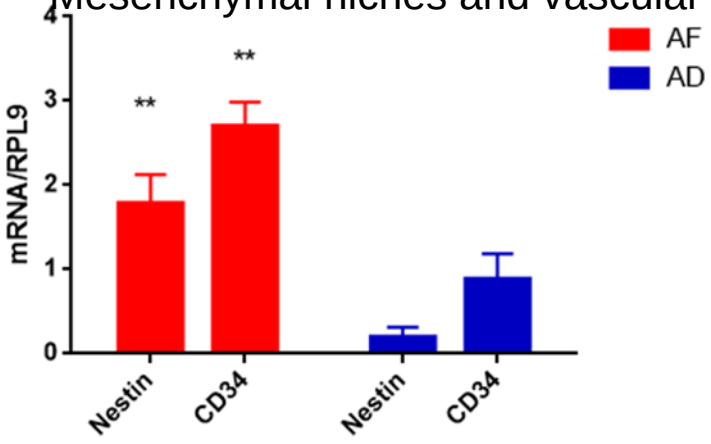
Alcohol exposure *in utero* increases susceptibility to form aggressive pituitary tumors in rat offspring

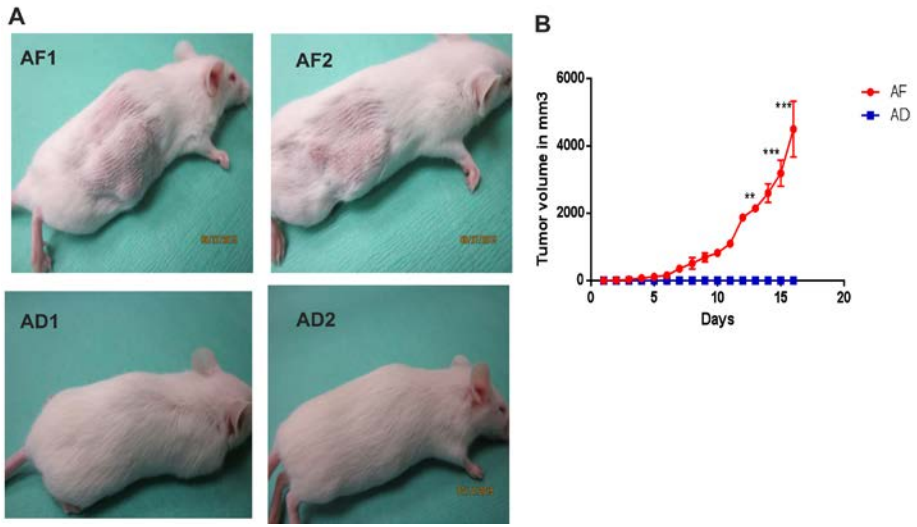


Progenitor mesenchymal cell markers



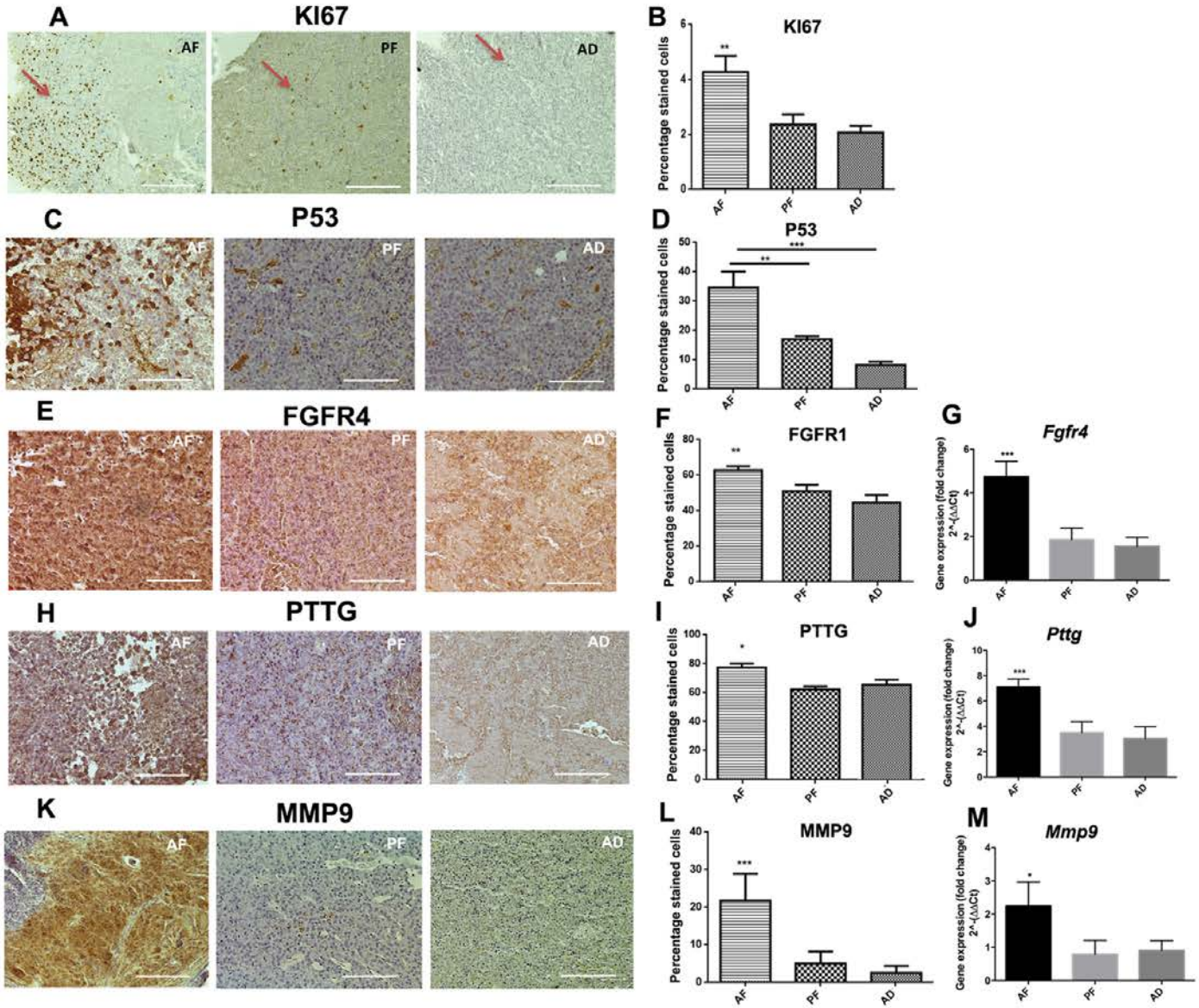
Mesenchymal niches and vascular factors





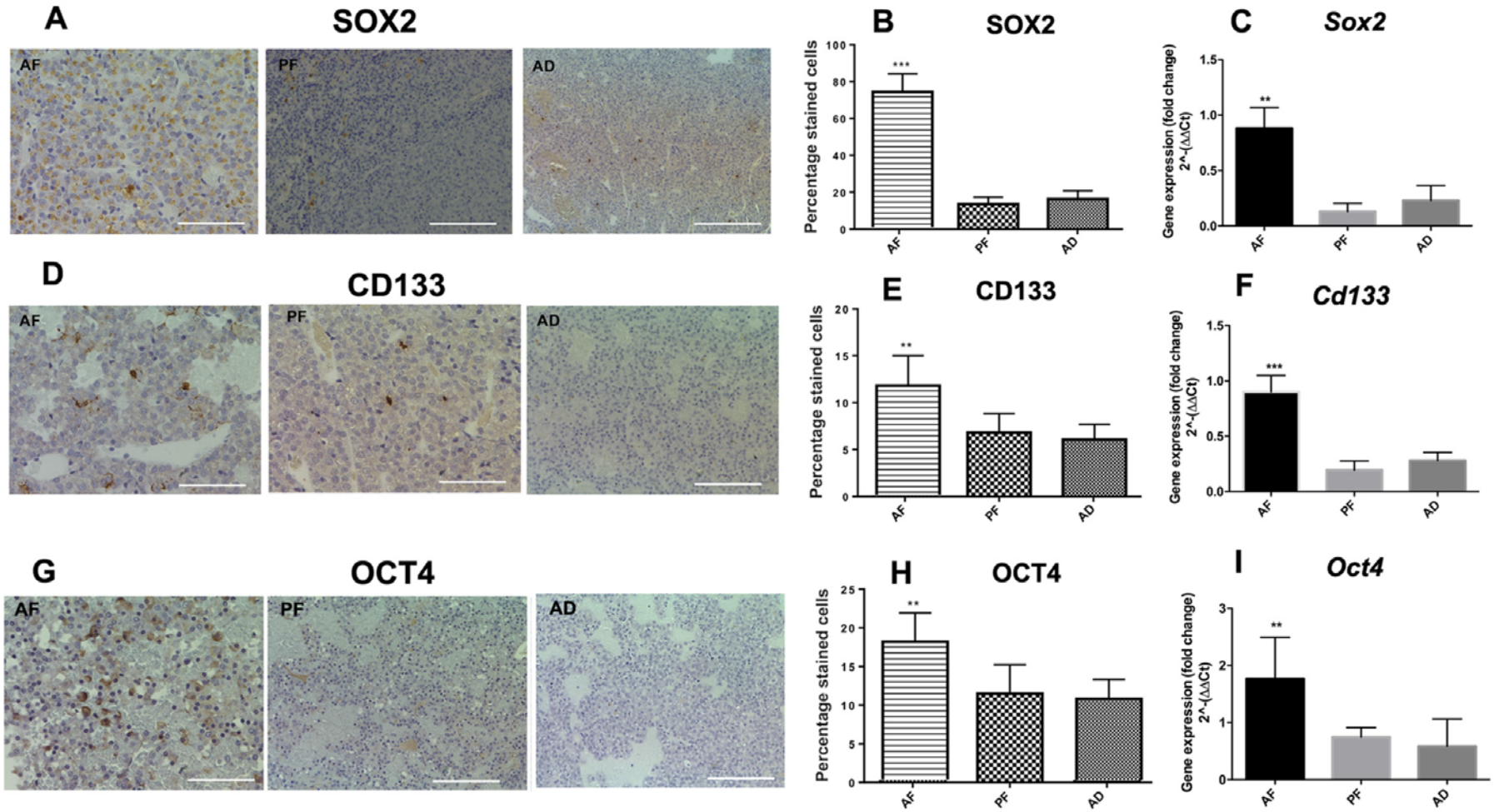
Jabbar and Sarkar, unpublished

Alcohol exposure *in utero* increases susceptibility to form aggressive pituitary tumors in rat offspring



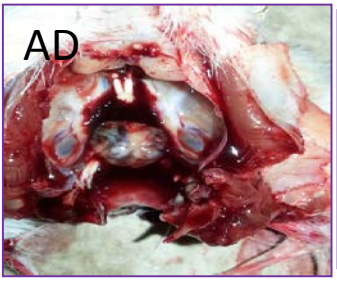
Jabbar et al., Sci Report, 2017

Alcohol exposure *in utero* increases susceptibility to form aggressive pituitary tumors in rat offspring

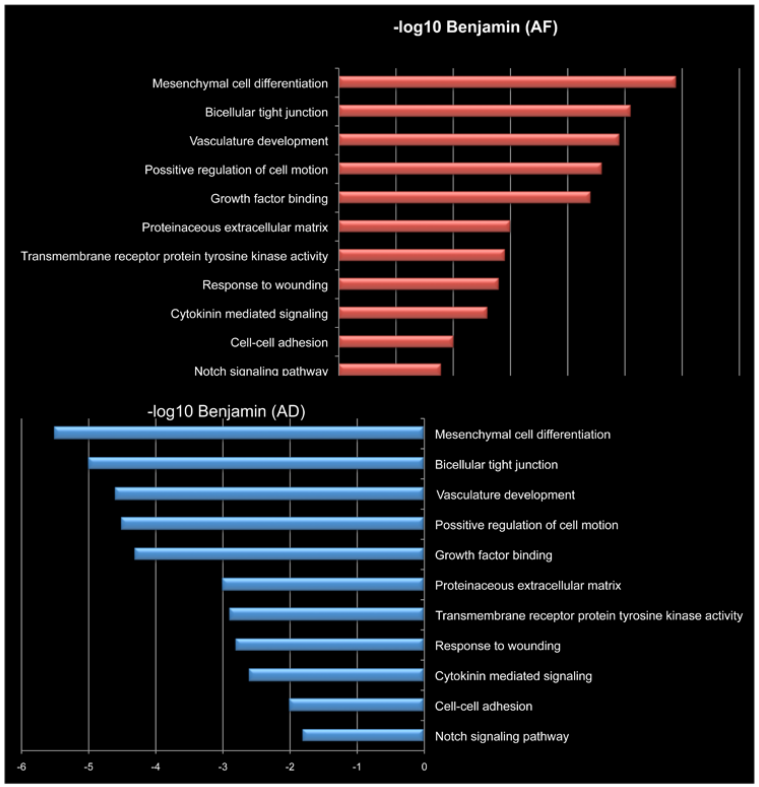


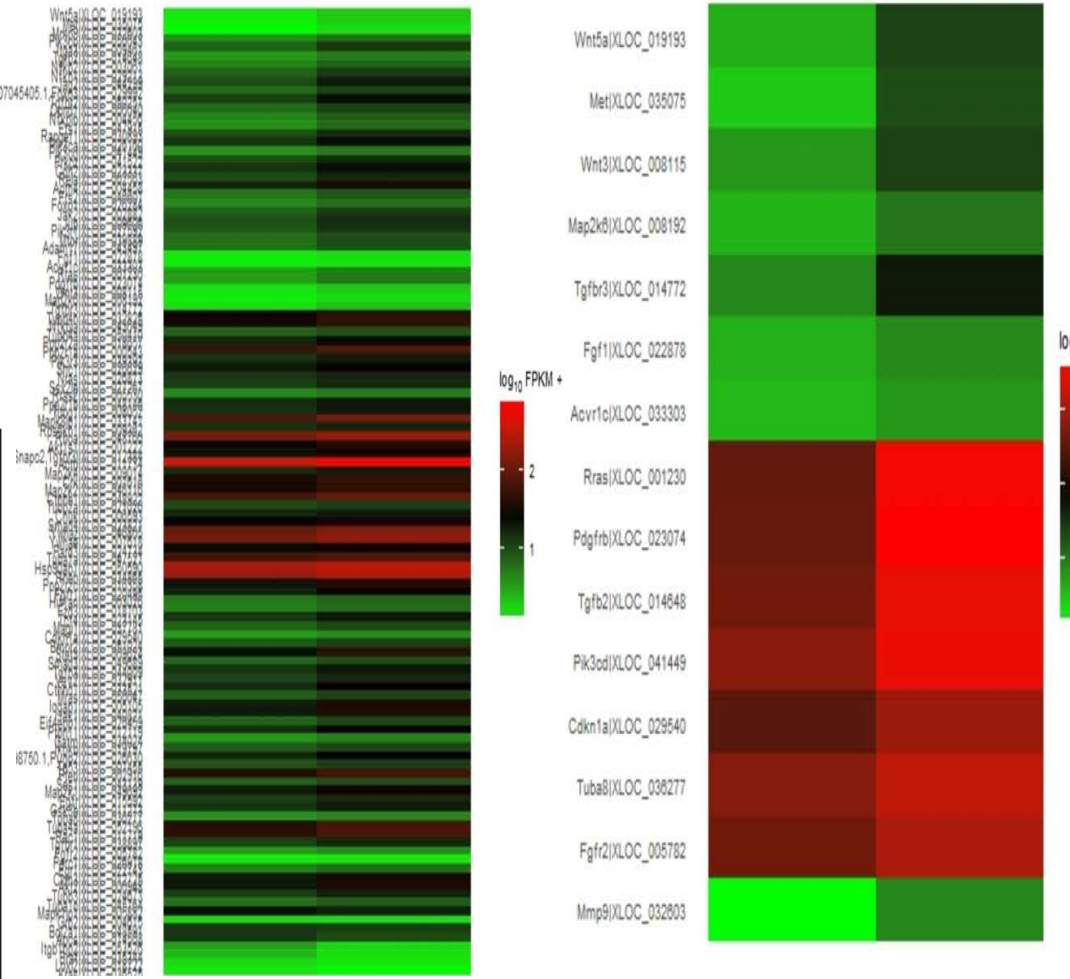
Jabbar et al., Sci Report, 2017

Alcohol exposure *in utero* increases susceptibility to form aggressive pituitary tumors in rat offspring



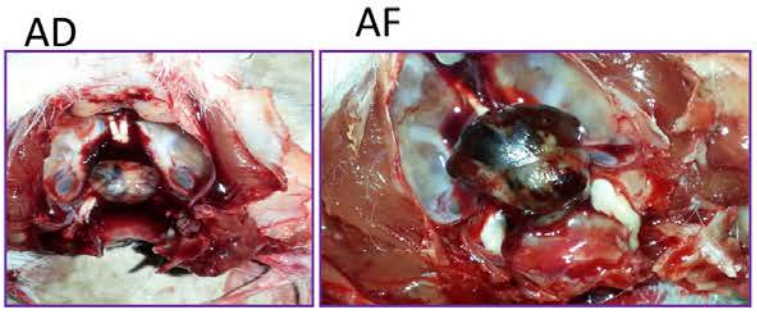
Fetal alcohol exposure increases master transcription factors which control epithelial-to-mesenchymal transition

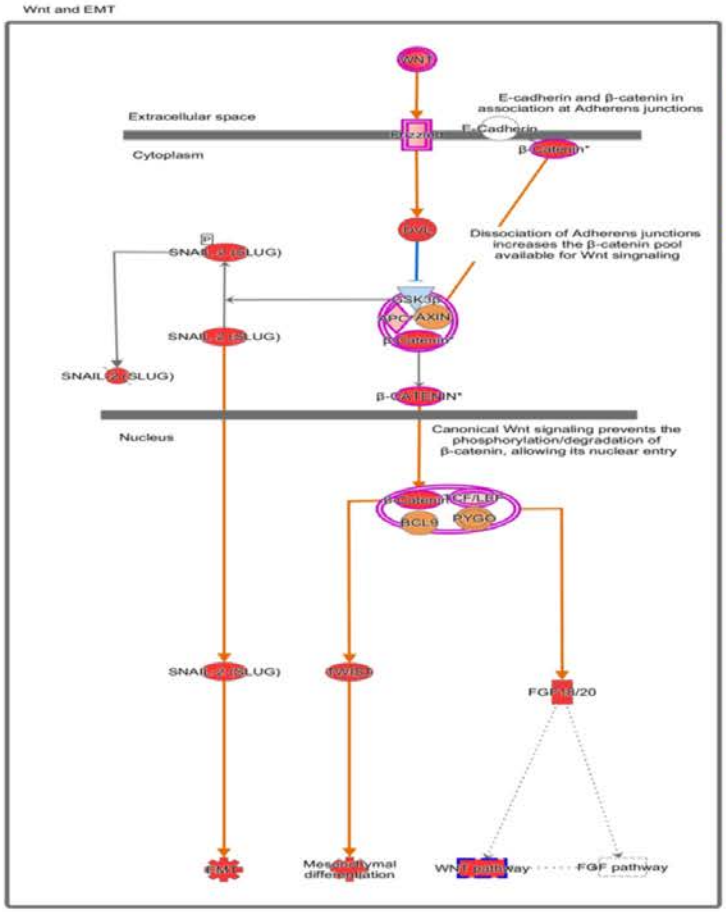


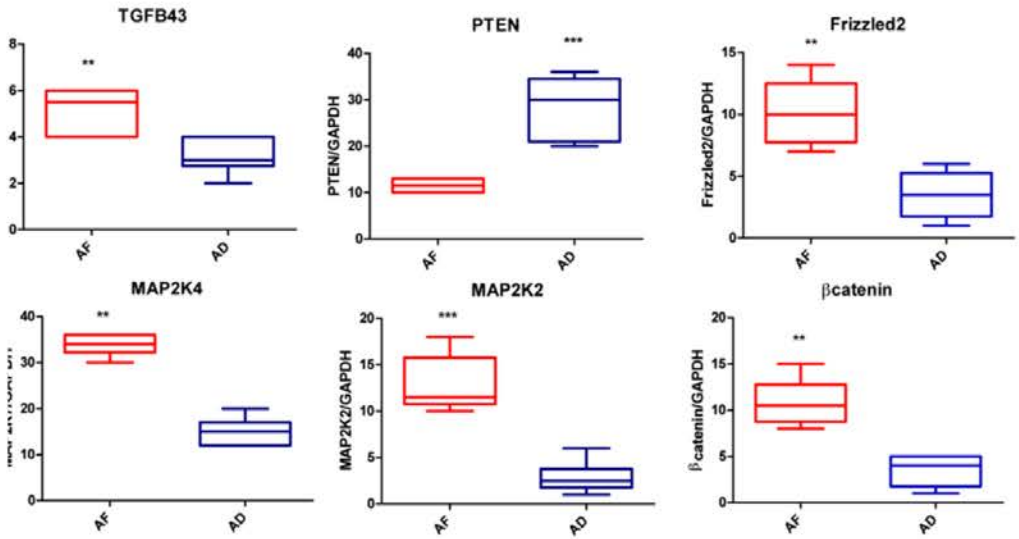


Jabbar and Sarkar, unpublished

Quantitative real-time PCR (qRT-PCR) of rats pituitary tumor tissues demonstrate the activation of Frizzled2/Wnt signaling







Summary and Conclusion

1. These results show that endocrine cells of mammary gland, prostate gland or pituitary gland of fetal alcohol-exposed rats develop hyperplasia (a marker for preneoplasia) during aging and form aggressive tumors following carcinogens challenge
2. Tumor cells of alcohol-fed rats often acquire aggressive and metastatic tumorigenic behaviors, express multipotency stem cell regulators and Wnt signaling genes.
3. Together the data suggest that fetal alcohol exposure programs the endocrine cells to develop aggressive tumors possibly due to increase in stem cell niche within the tumor microenvironment.

Acknowledgements

Fellows and faculty

Sengottuvelan Murugan
Omkaram Gangisetty
Sepide Mojtehedzadeh
Olivia Wynne
Ken Rehul
Wendie Cohick
Kathleen Roberts

Graduate students

Changqing Zhang
Tiffany Polanco
Shaima Jabbar

Funding: R01AA11591; R21 AA024330; F31CA132620