Findings of the Independent Academic *Prostate* Studies in CLARITY-BPA

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Early-life BPA Exposure Increases Prostate Cancer Susceptibility

BPA (10 μg/kg BW)

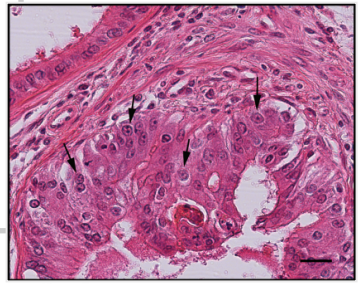
Birth

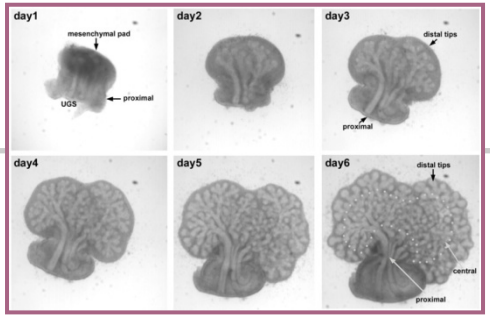
Puberty

No PCa

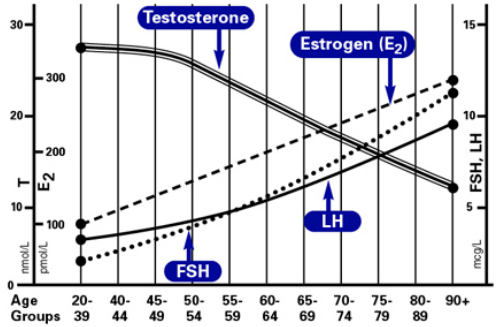
Adult Estrogen

↑ PCa incidence



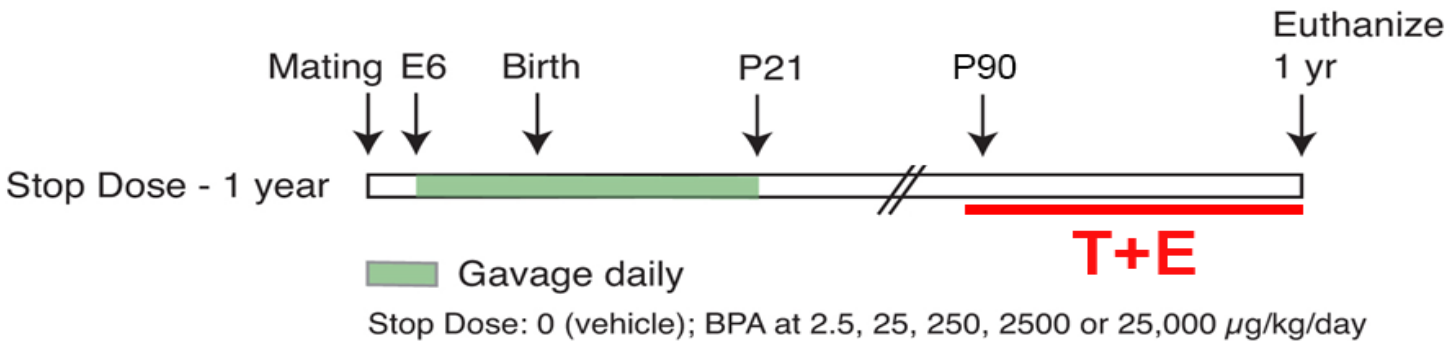


↑ E/T in aging men

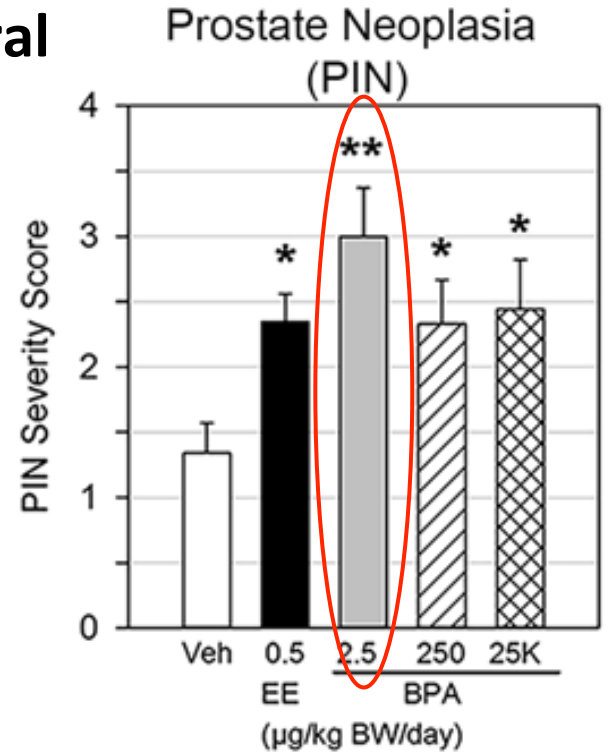


Ho, et al, *Cancer Research*, 2006; Prins, et al, *Repro Toxicology*, 2011; Prins et al, *Environ Health Perspectives*, 2017

CLARITY-BPA: Prostate Independent Study: Prins laboratory



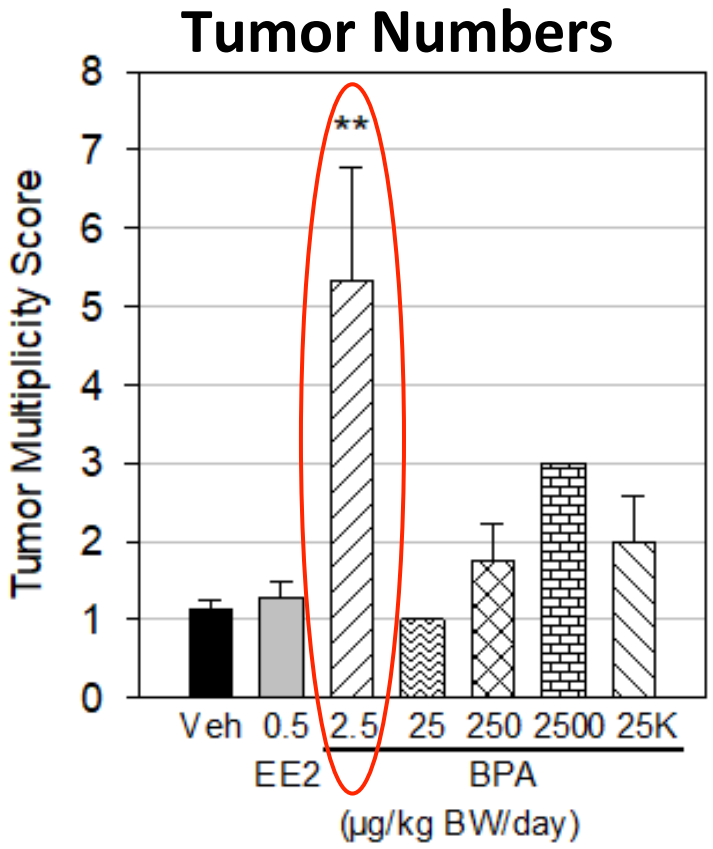
Dorsolateral Prostate

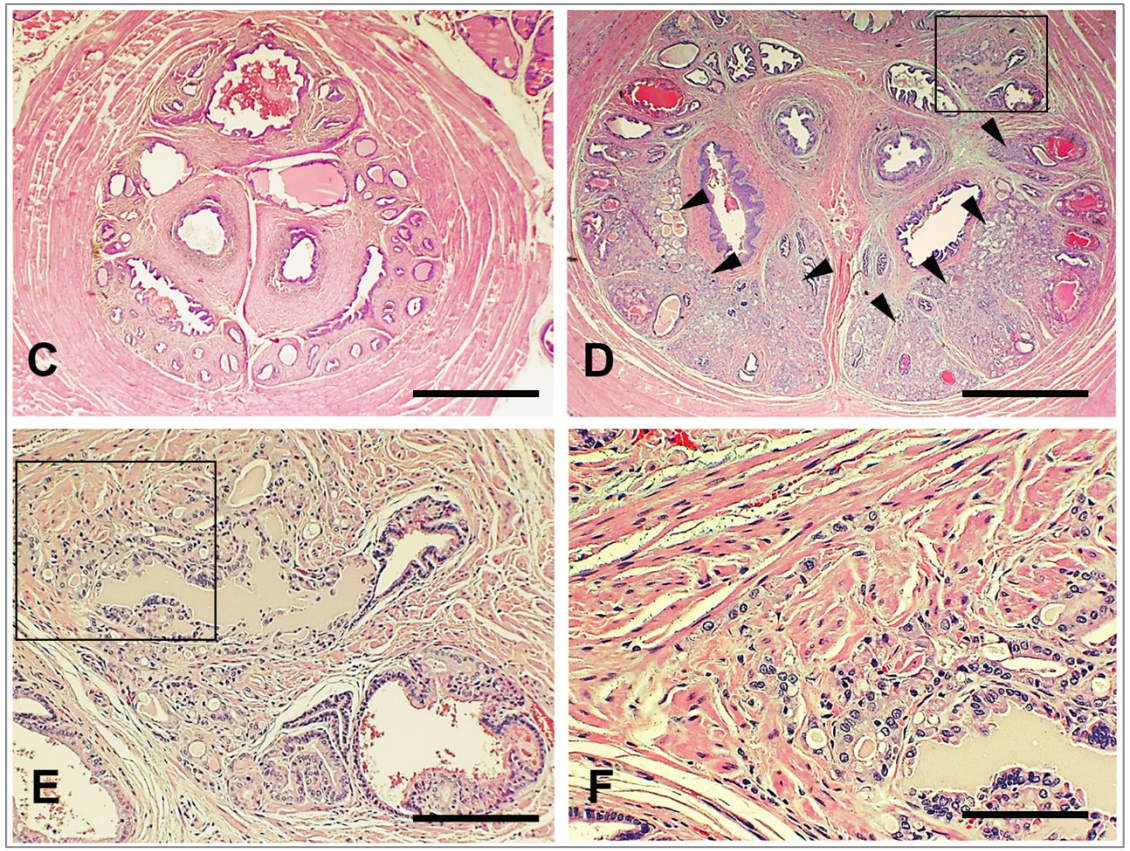


SUMMARY

- Repeated previous findings:
  - Increased prostate cancer risk
  - Greatest effect at lowest BPA dose
    i.e. *2.5 μg/kg BPA*

Low-dose BPA increased E_2-induced adenocarcinoma multiplicity

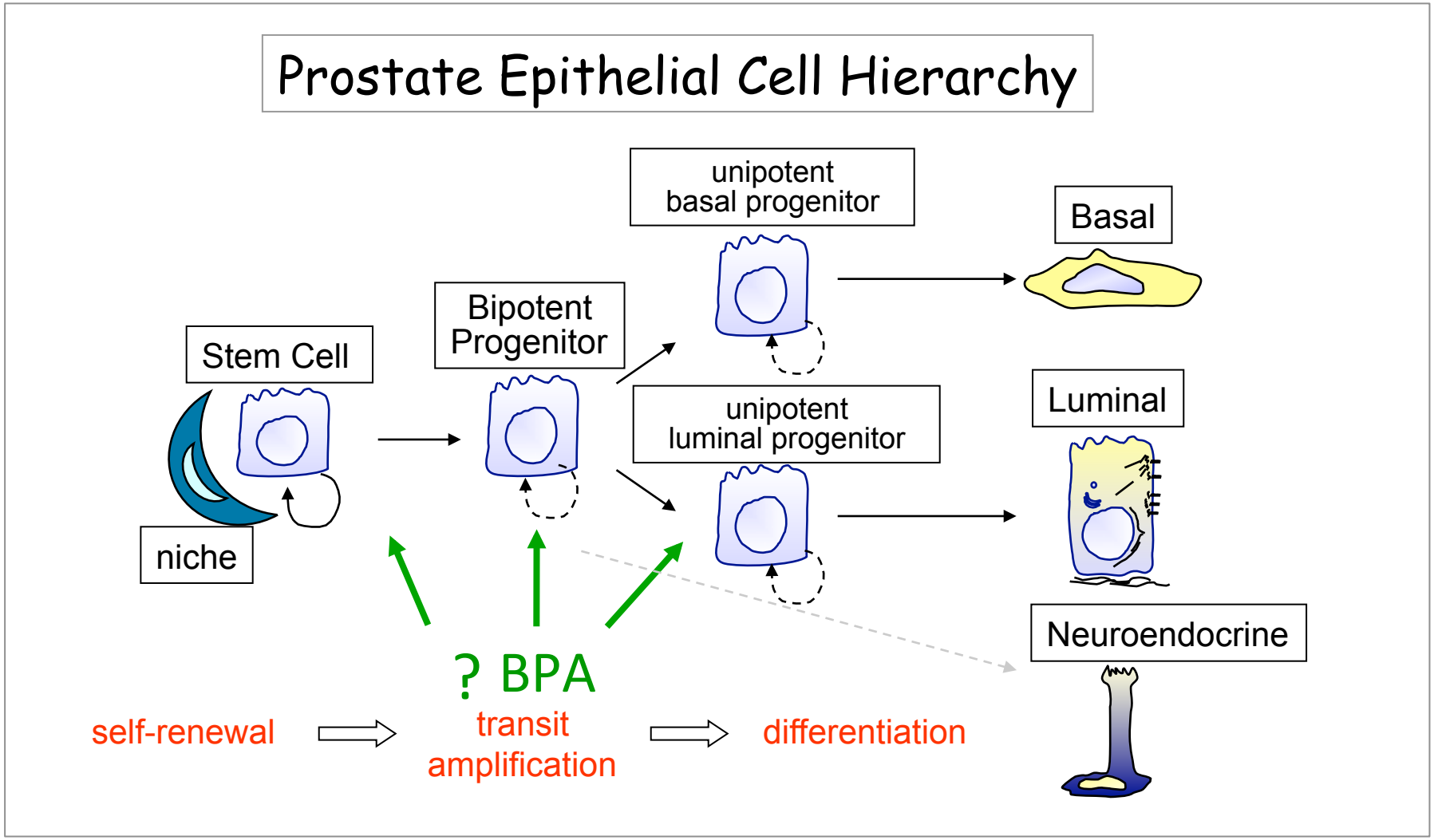




Dorso-Lateral Prostate Ducts:

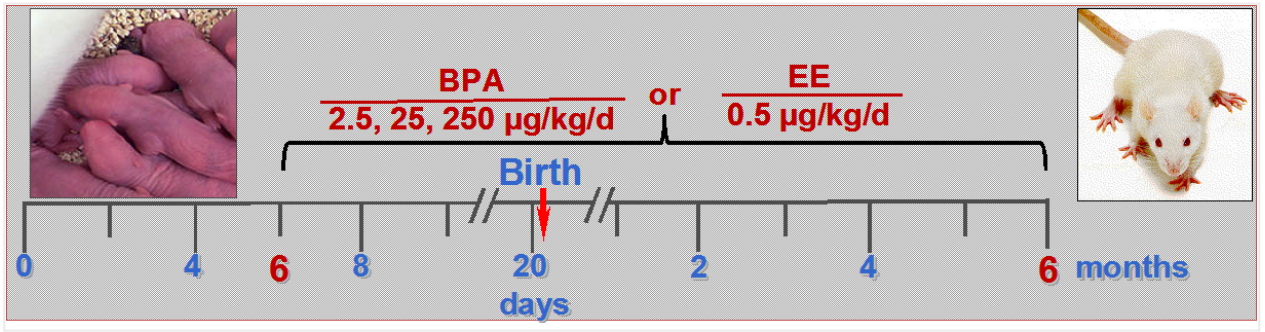
- Increased *multiplicity* of ductal adenocarcinoma in 2.5µg BPA (P<0.01 vs Vehicle).
  Trending for higher doses; borderline significance in parametric analysis.

How might early-life BPA exposure affect prostate cancer susceptibility later in life, long after BPA is cleared from the body?

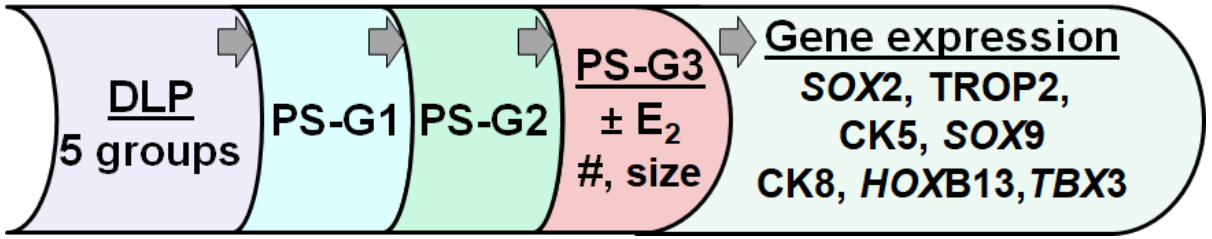


CLARITY-BPA: ***Examined the stem and progenitor cells from BPA-exposed rat prostates***

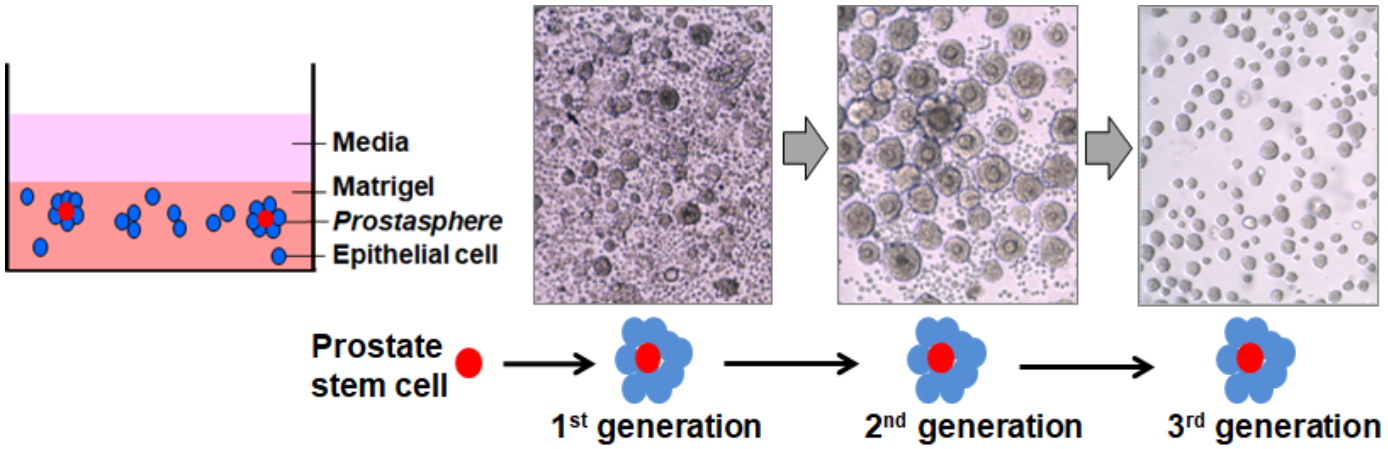
Animal Tx at FDA-NCTR



Workflow at UIC

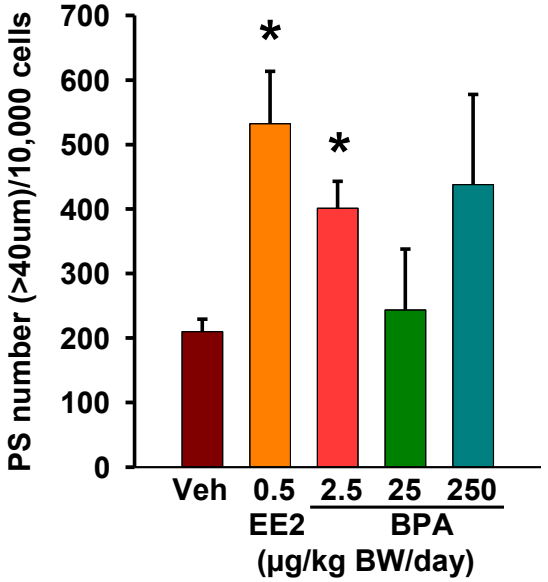


Prostasphere (PS) Assay and Passage

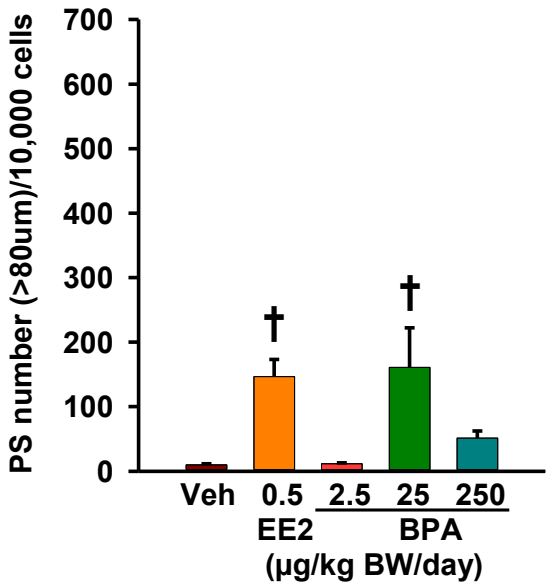


Chronic exposure to low-dose BPA *increased* prostate stem cell numbers and progenitor cell proliferation

Passage 3 – Total PS

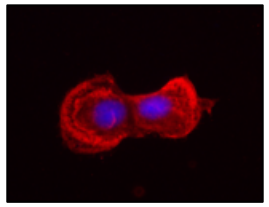


Passage 3 – PS > 80 µM



Representative of stem cell number

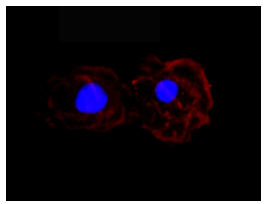
↓



Symmetric
Self-renewal

Representative of progenitor cell proliferation

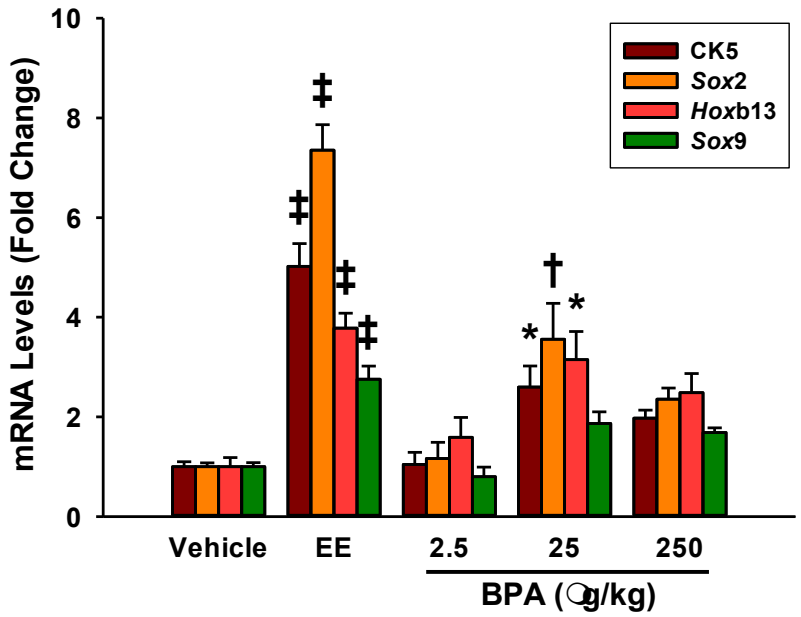
↓



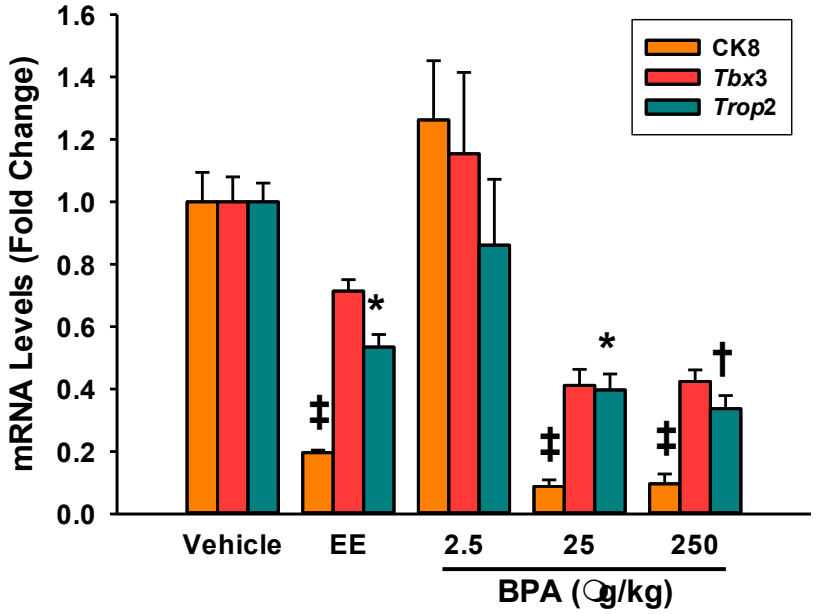
Symmetric
Committed division

Chronic low-dose EE and BPA (25 and 250 μg/kg) exposures alter progenitor cell lineage commitment

Basal Progenitor Pattern

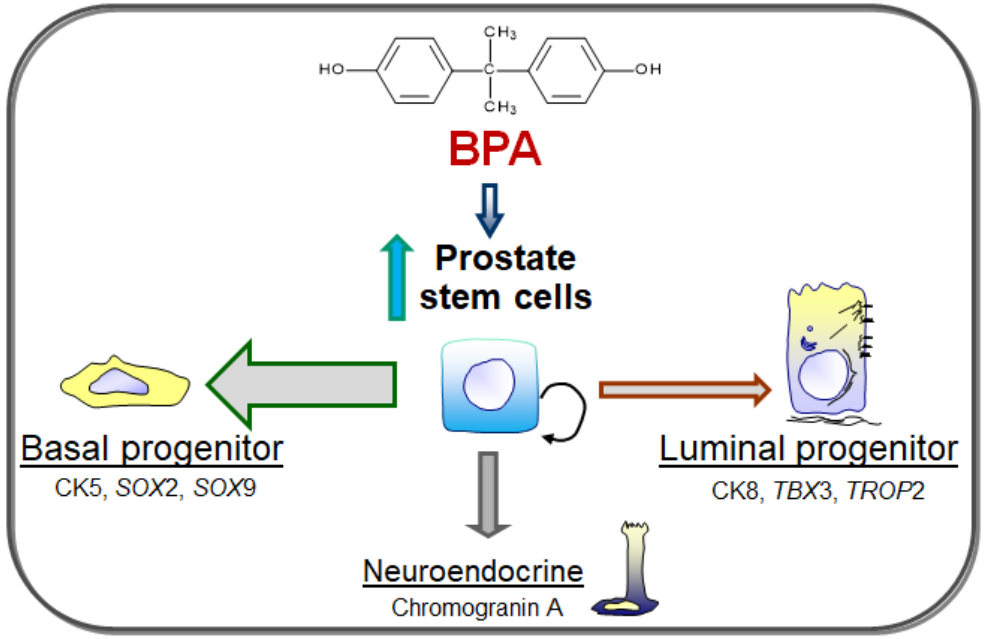


Luminal Progenitor Pattern



See a shift towards *increased* basal progenitor lineage at the expense of *decreased* luminal progenitor lineage

CLARITY-BPA Prostate Study: Summary Model



➢ **How might the stem cell changes influence PCa susceptibility?**

- Cancer risk is highly correlated to # normal stem cell divisions in most tissues, *including prostate.*
  (Tomasetti & Vogelstein, *Science*, 2015, 2017)
- Tumor initiating cells for human PCa are largely localized to basal cell population.
  (Goldstein et al, Science, 2010)

➢ *Propose*: Chronic *in vivo* low-dose BPA exposures ↑ prostate stem cell numbers and altered lineage commitment underpinning an increased carcinogenic risk with aging

Prins et al, *Environ Health Perspectives* Nov;126(11):117001, 2018