Fish models for environmental and biomedical research

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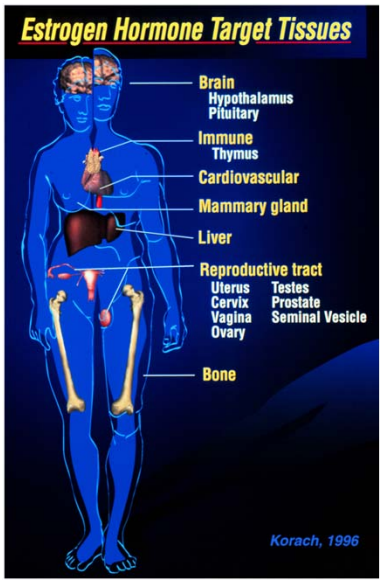
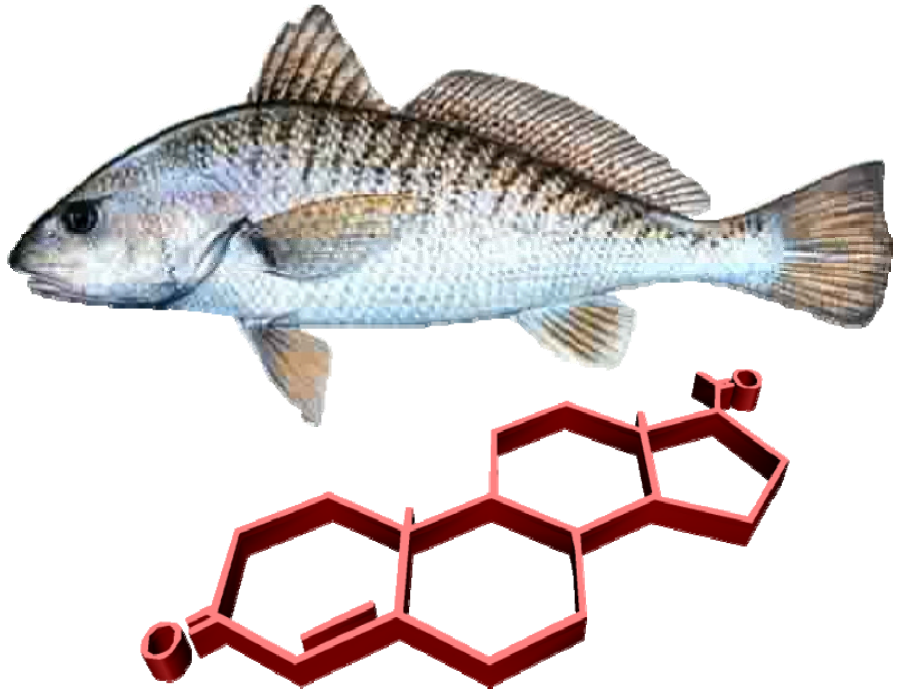
Marine Science



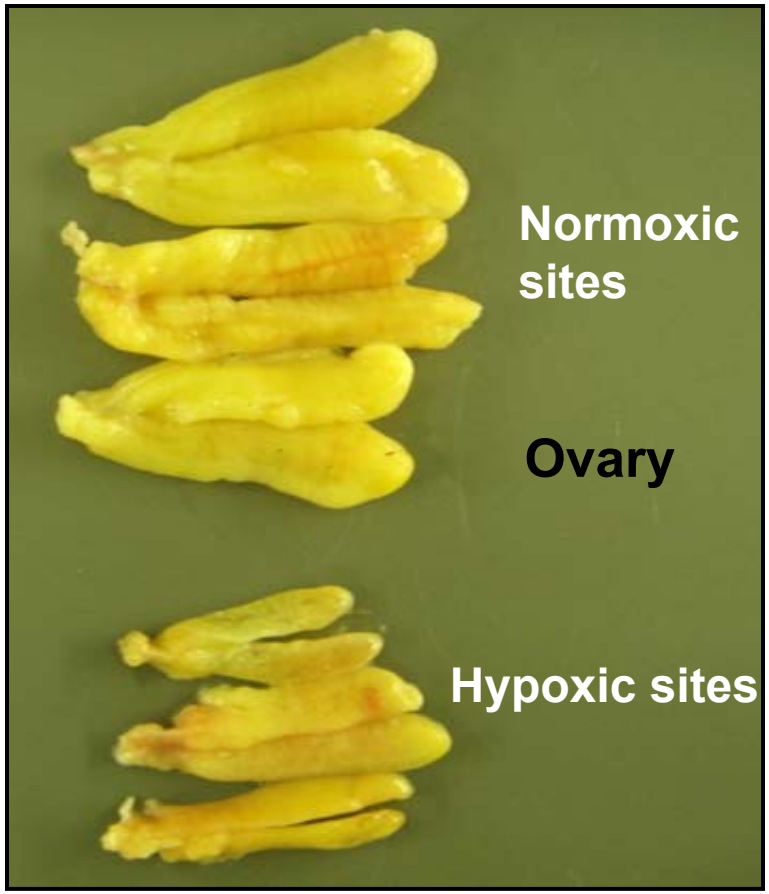


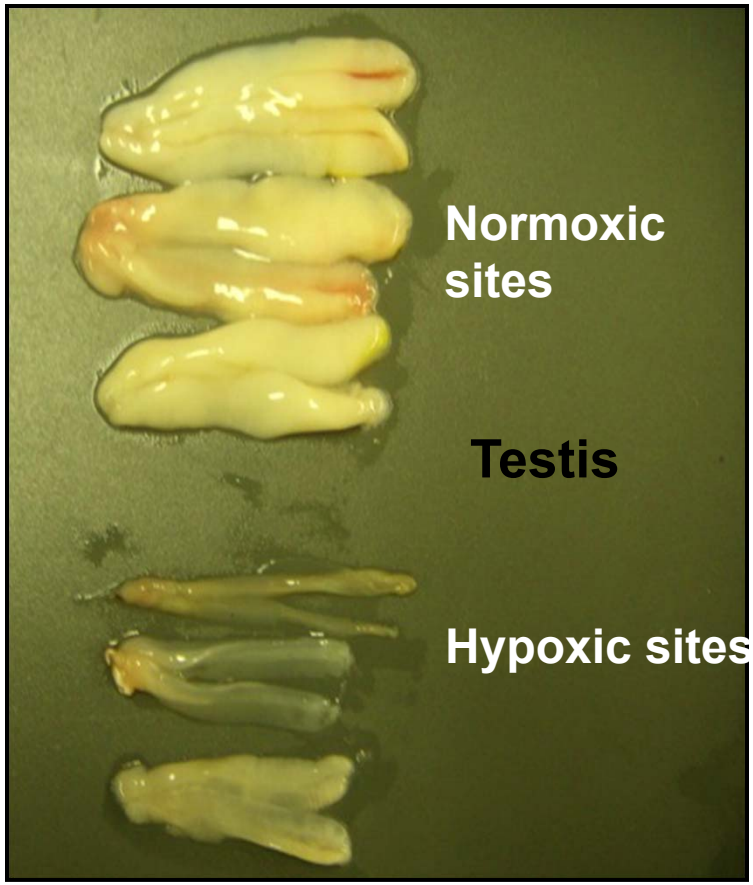
1. Hypoxia

- Hypoxia- state of reduced oxygen availability
- Occurs in:
- Marine and freshwater environments (aquatic hypoxia)
- High altitudes (hypobaric hypoxia)
- Low oxygen work environments –e.g fire-protected rooms (normobaric hypoxia)
- Patients with low blood O2 levels (medical hypoxia)–e.g. preterm birth in neonate, apnea
- Cancer patients- tumor outgrows blood supply (tumor hypoxia)-leads to resistance radio-and chemo-therapy
- Responses to hypoxia:
- through hypoxia inducible factor-HIF
- Brain particularly sensitive to low oxygen levels

Hypoxia in the marine environment

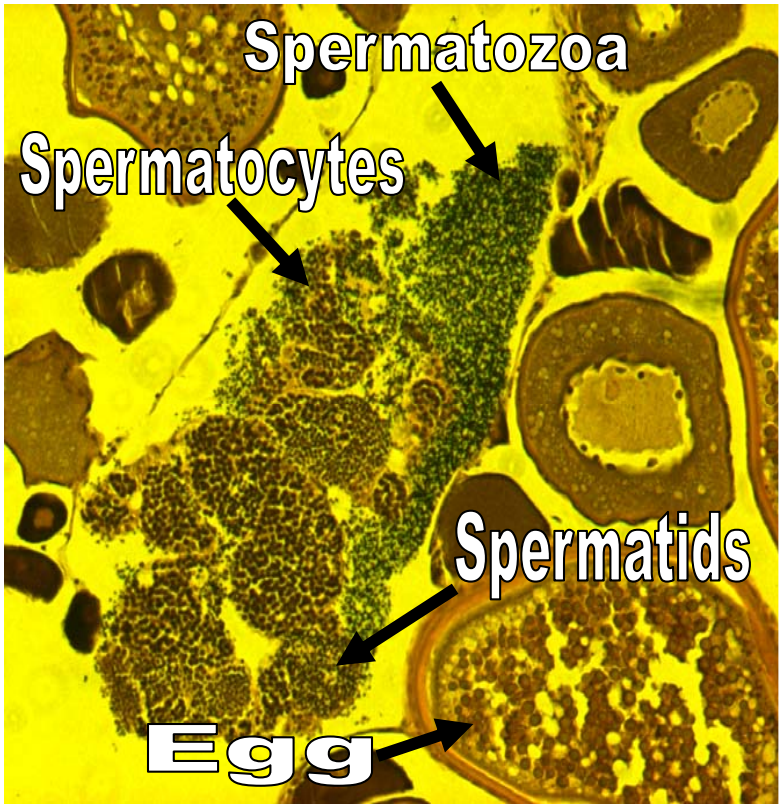
- **Coastal hypoxic regions have tripled in past 30yrs- Major Global Change**
- **Hypoxia in the northern Gulf of Mexico now covers up to 9,000 sq miles each summer.**
- **Causes severe impairment of reproduction in croaker**



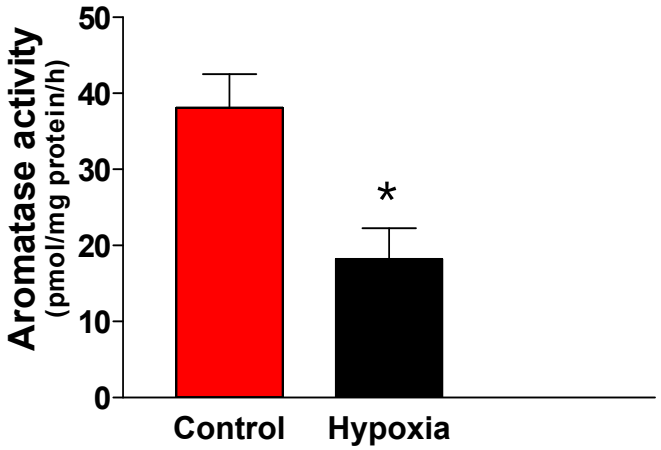


Hypoxia causes ovarian masculinization

ovaries contain sperm

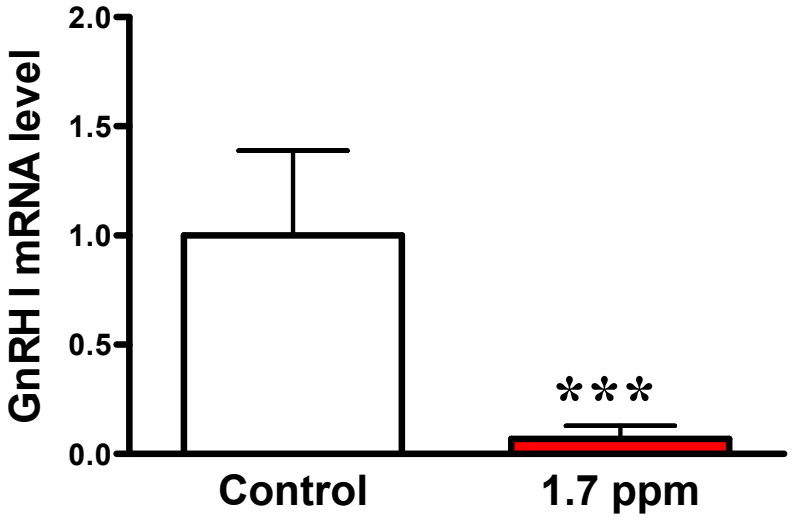


Hypoxia decreases aromatase enzyme activity-causes decline in estrogen levels

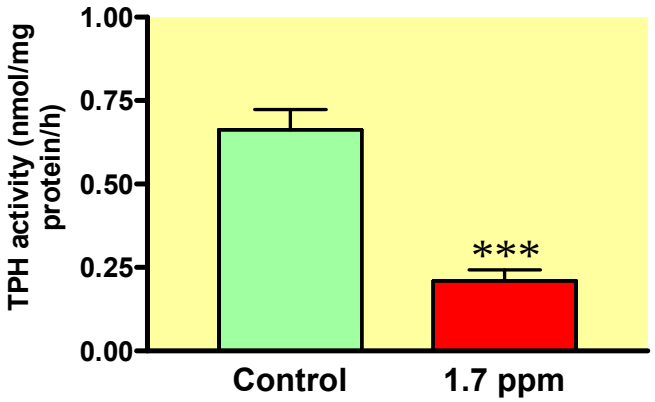


Hypoxia severely impairs reproductive neuroendocrine function through inhibiting serotonin synthesis

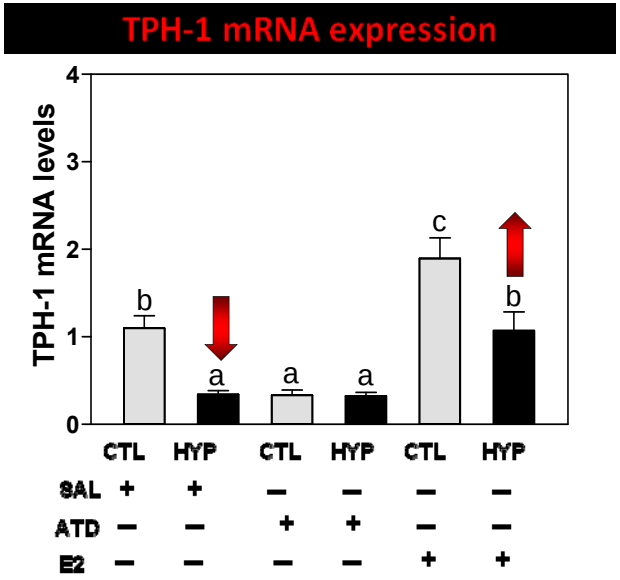
Gonadotropin releasing hormone (GnRH) mRNA decreased

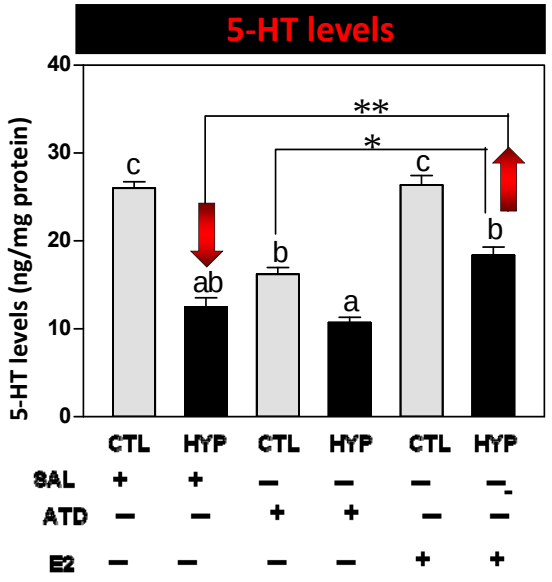


Enzyme that synthesizes serotonin-tryptophan hydroxylase decreased



Tryptophan hydroxylase and serotonin levels restored by estrogen treatment



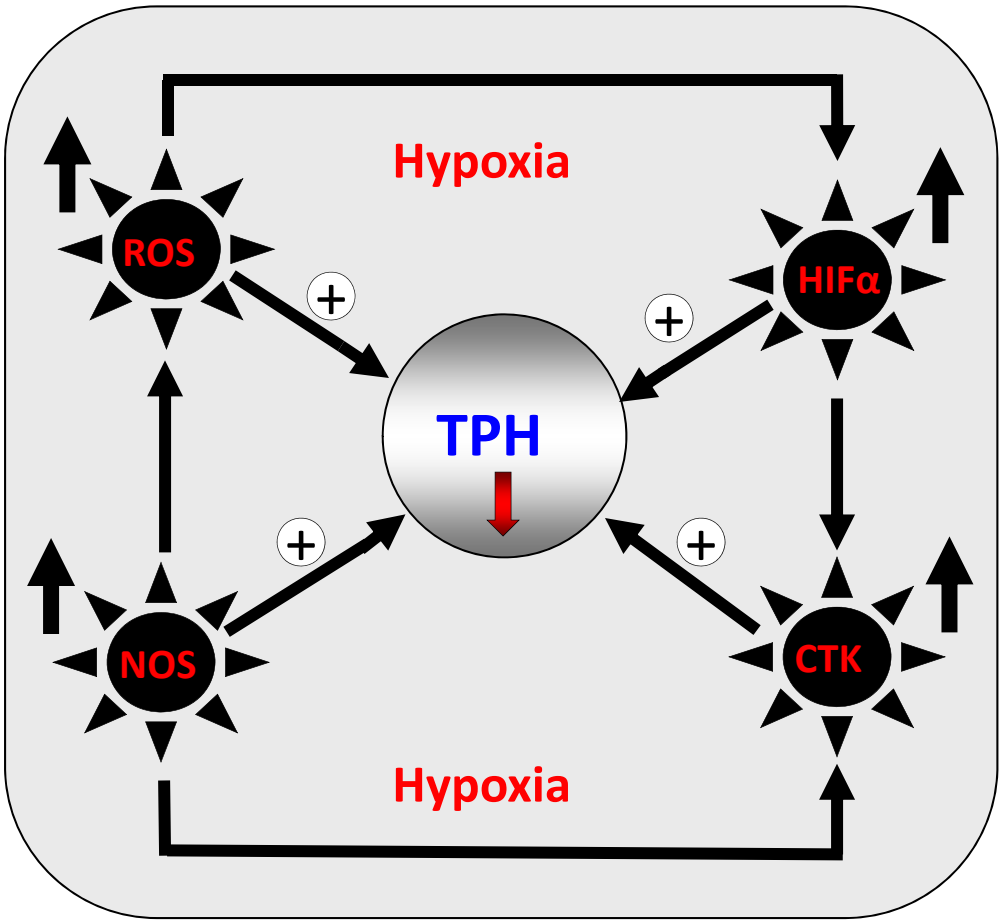


Suggests decrease in aromatase with hypoxia removes protective effect of estrogen on serotonergic functions

2nd mechanism

Reactive Oxygen Species (ROS), *free radicals* ($O2\bullet^-$, H_2O_2)

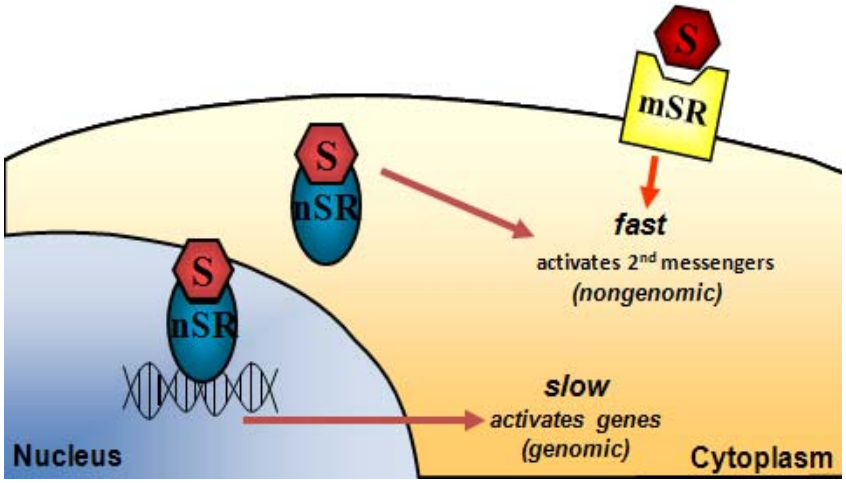
Nitric Oxide Synthase (NOS), *an enzyme*



Hypoxia-Inducible Factor-α (HIF-α), *a transcription factor*

Cytokines (CTK), *a small cell-signaling molecule*

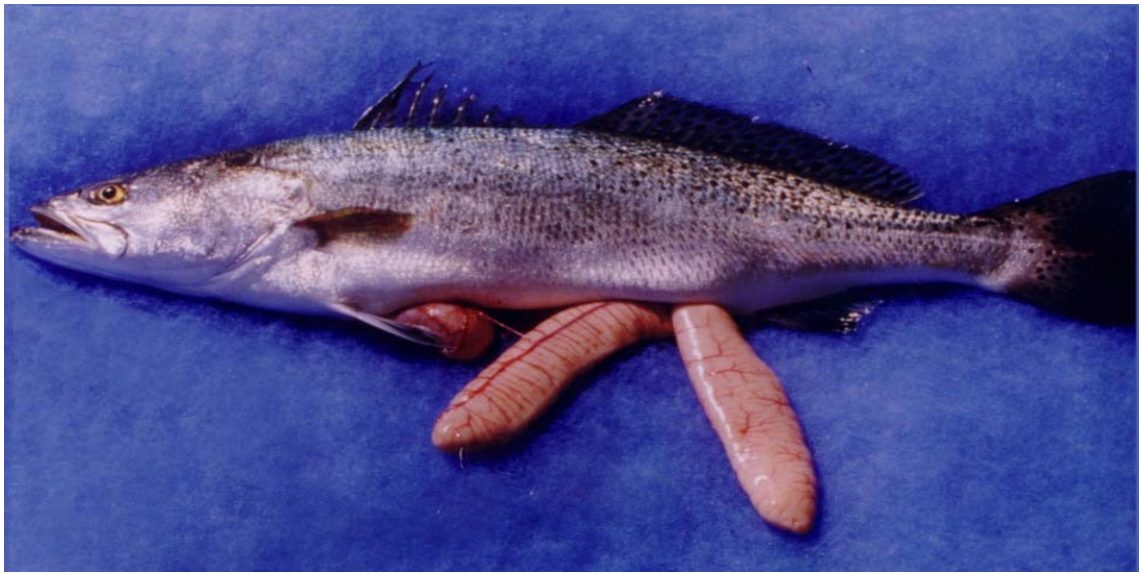
2. Rapid, cell surface-initiated steroid actions through novel 7-8 transmembrane receptors



- Extensive efforts over 25 years to identify membrane steroid receptors unsuccessful
- 3 Novel 7- 8 TM steroid receptors identified on the cell surface in the last 12 years

- **Membrane progestin receptors (mPRs or PAQRs)**
  - Zhu et al. PNAS 2003a,b----first found in fish ovaries
- **G protein-coupled estrogen receptor (GPER or GPR30)**
  - Thomas et al., Endocrinology 2005; Revankar et al., Science 2005
- **Membrane androgen receptor (ZIP9)**
  - Berg et al., Thomas et al., Endocrinology 2014---- first found in fish ovaries

Membrane progestin (mPR) and androgen (ZIP9) receptors first discovered in fish ovaries



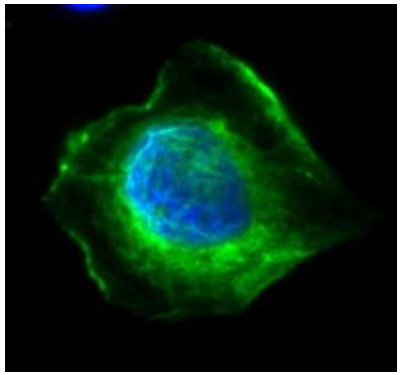
fish ovaries abundant source of receptor- millions of follicles and eggs

● Therefore ideal vertebrate model for identifying ovarian receptors

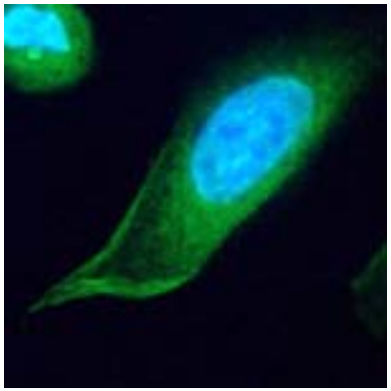
● wide variety of functions identified/proposed in mammals including vascular protection , neuroprotection, sperm motility/fertility, immune functions, breast and prostate cancer.

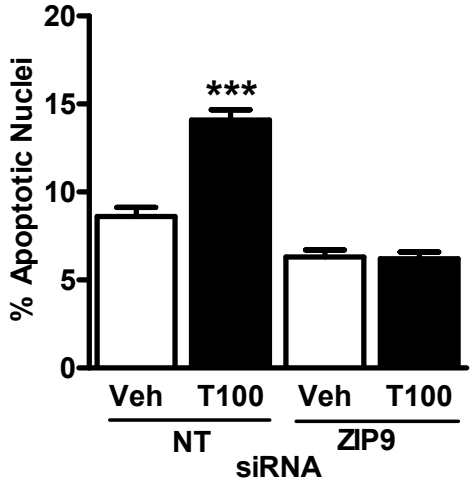
Example: membrane androgen receptor-ZIP9 induces apoptosis of breast and prostate cancer cells

Breast cancer cells



Prostate cancer cells





Testosterone increases cell death through ZIP9 – lost when ZIP9 knocked down

ZIP9 potential therapeutic target for treatment of breast and prostate cancers