

Reproduction, Development, and Disease (PHSI3010)

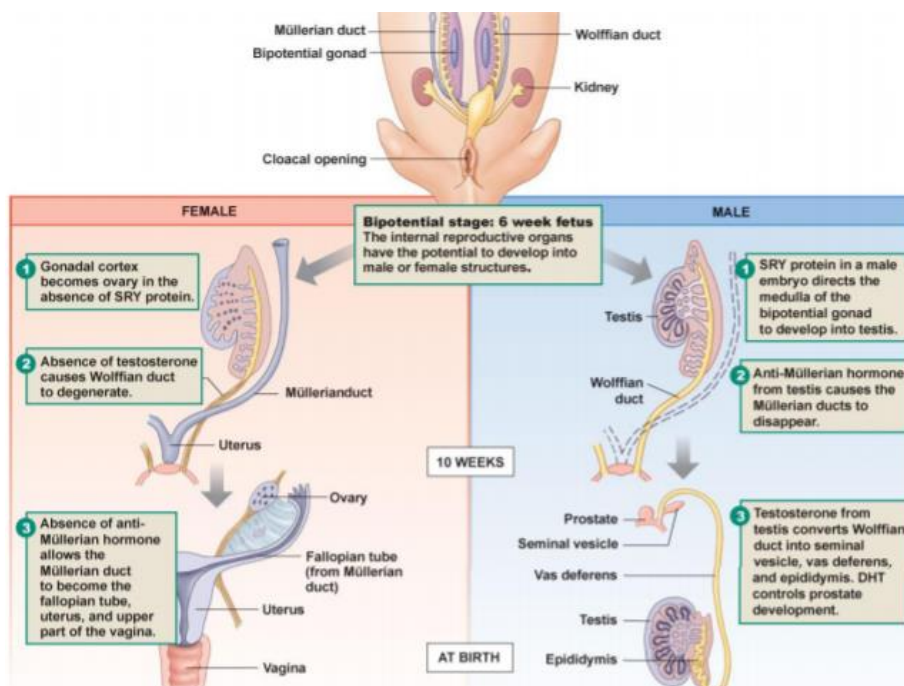
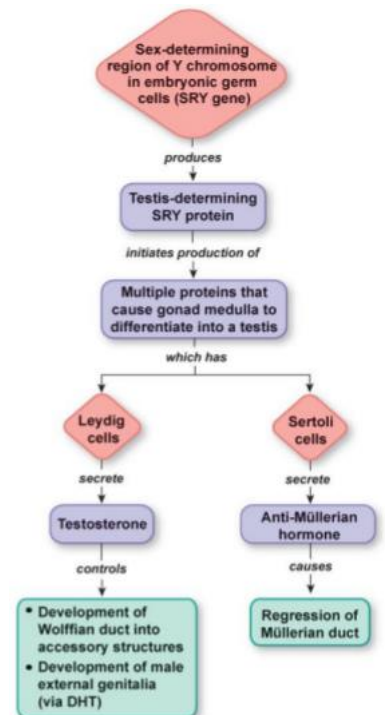
Contents:

- Sexual Reproduction
- Sex Determination
- Mating Systems and Competition
- Testes Development
- Endocrine Regulation in Male Reproduction
- Female Reproduction
- Gametogenesis
- Fertilisation
- Pre-implantation Embryonic Development
- Endocrine Disruption
- Cell Differentiation in Development
- Modelling Development
- The Germ Layers
- Mitochondria
- Metabolism in Development and Cancer
- Brain Development
- Origins of the Heart, Blood, and Vessels
- Pregnancy and Cardiovascular Effects
- Angiogenesis
- Endoderm Development
- Prostate Cancer
- Koala Reproduction
- Cardiovascular Transition
- Preconception Health
- Stillbirth
- Brain Development
- Breast Cancer

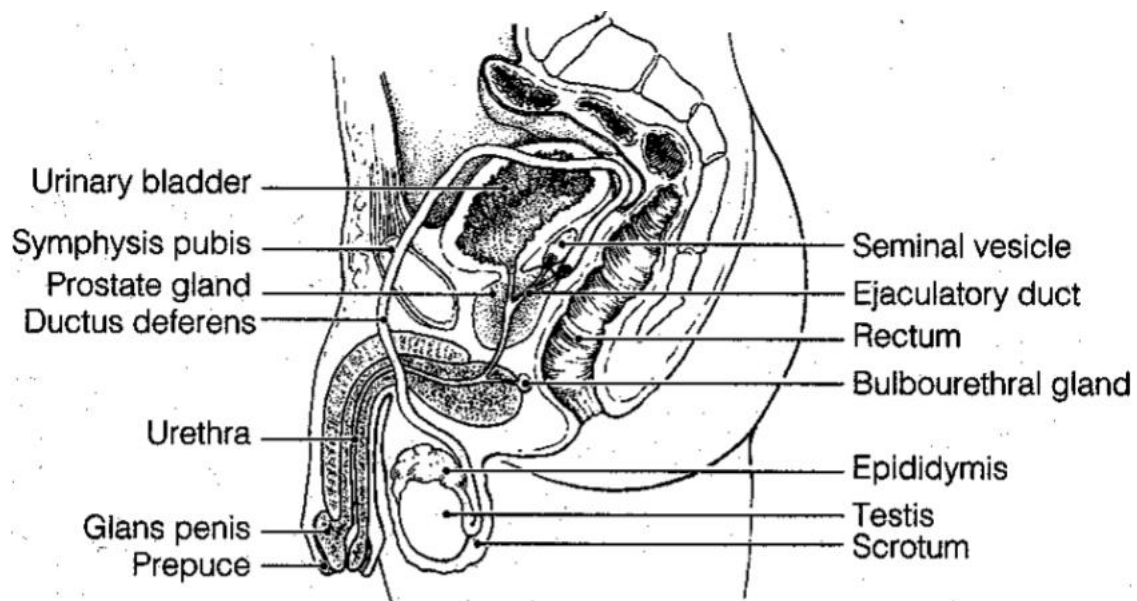
Testes and their development

Determining sex

- We have 22 pairs of autosomes and 1 pair of allosomes (sex chromosomes)
- The **sex determining region in the Y chromosome of germ cells is the SRY gene!**
- With the SRY gene (males):
 - SRY protein will produce more proteins that differentiate gonad medulla into the testis
 - **Leydig cells produce testosterone** for:
 - **Development of Wolffian duct** into accessory structures (seminal vesicle, vas deferens, epididymis)
 - Development of **male external genitalia** (with DHT) and prostate
 - **Sertoli cells produce anti-mullerian hormone with the help of SOX9** for:
 - Regression of mullerian duct
- Without the SRY gene (females):
 - **No SRY protein is produced**
 - **Instead Wnt and Rspo1 are used!!**
 - Gonadal cortex differentiates into the ovary
 - No Leydig cells so no testosterone
 - **Wolffian duct will degenerate**
 - No sertoli cells so no anti-mullerian hormone produced
 - **Mullerian duct develops** into fallopian tube, uterus, upper vagina

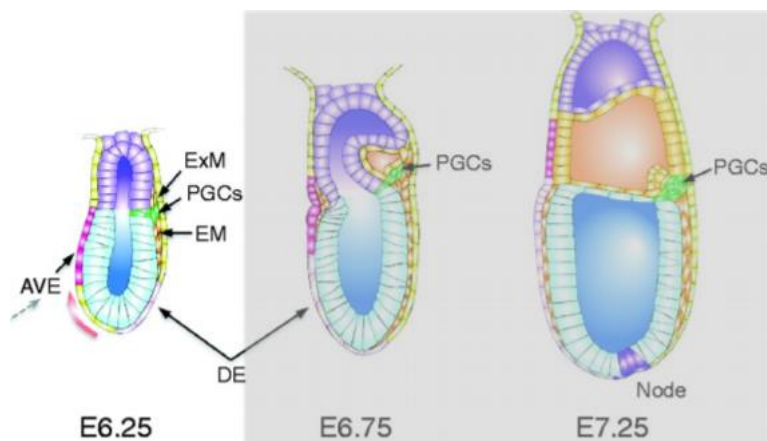


Male reproductive anatomy

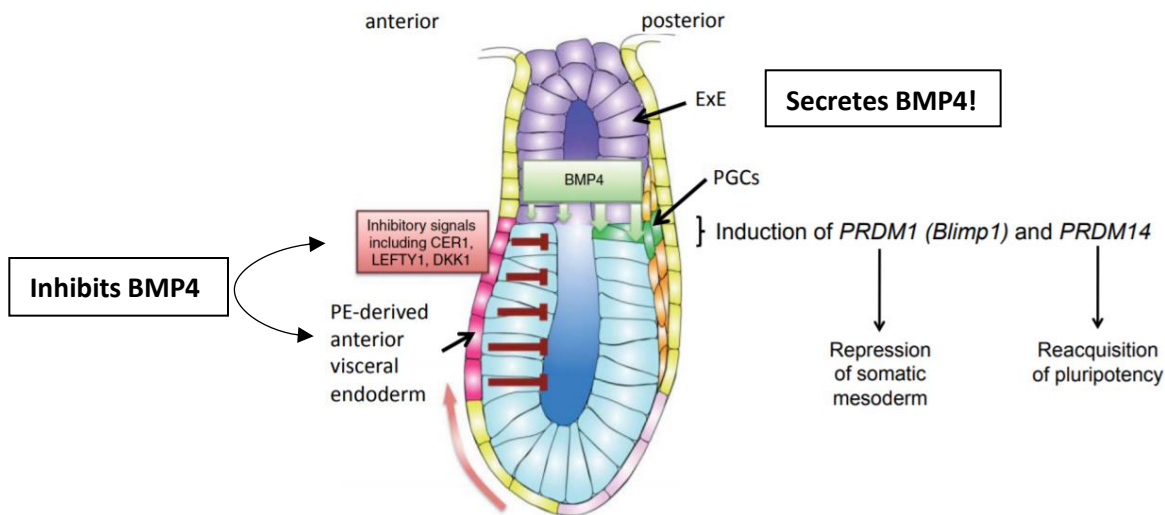


Primordial germ cell (PGC) development

- These are the cells that will develop into the spermatozoa and oocytes
- They arise from the proximal epiblast cells through specification



- Specification
 - **ExE** (extraembryonic ectoderm) will **secrete BMP4**
 - **AVE** (anterior visceral endoderm) will **inhibit BMP4 secretion**
 - There is a **high concentration of BMP4 at the posterior end of the cells**
 - **BMP4 initiates the specification of PGCs**
 - **BMP4 induces PRDM1 (Blimp-1)**
 - Represses somatic mesoderm
 - **BMP4 induces PRDM14**
 - Reacquisition of pluripotency (will allow them to produce many different responses)



- Stages of PGC development:
 - **Proliferation**
 - Undergoes mitosis
 - Increases the number of PGCs
 - **Migration to genital ridge**
 - Directed by chemokines and receptors
 - PGC chemokine receptors include **CXCR4** and **c-Kit**
 - Genital ridge chemokine secretions include **SDF1** and **cKit ligand**
 - Direct the PGC migration to the genital ridge!
 - **Epigenetic reprogramming**

Formation of sex chords (start of testis formation)

- Begins at a **bipotential genital ridge!**
 - **Can go on to form female or male anatomy**
 - **Depends on the presence of the SRY gene!!!**
- Presence of SRY gene **promotes Sox9 expression**
 - Drives the differentiation and proliferation of **sertoli cells**
 - Sertoli cells will produce anti-mullerian hormone
- Lack of SRY gene **promotes Wnt/Rspo1 expression to produce ovaries**
 - Will prevent the development of the mullerian duct into female reproductive anatomy
 - Will prevent the ovarian pathway from developing
- **Sox9 promotes the masculinisation of PGCs**
 - **CYP26B1 inhibits Stra8 to inhibit oocyte meiosis**

Sertoli and Leydig cell development

- **Sertoli cells**
 - Proliferation and differentiation are directed by **Sox9**
 - Will **produce anti-mullerian hormone** to prevent mullerian duct development

- Sertoli cells drive Leydig cell differentiation!
 - Use Dhh (desert hedgehog) and PDGF (platelet-derived growth factor)
- Secrete CYP26B1 (sertoli cell retinoid metabolising protein)
 - Degrade retinoic acid
 - **Stra8 production is inhibited**
 - **Oocyte meiosis is prevented**
 - Leads to irreversible masculinisation of PGCs
- Leydig cells
 - Regulates masculinisation
 - **SF1 (steroidogenic factor 1) induces steroidogenesis**
 - **Testosterone** > Wolffian duct development > male accessory structures
 - **DHT** > development of **external male genitalia**

Retinoic acid is usually stimulated by retinoic acid 8 to produce Stra8. Stra8 is needed to initiate oocyte meiosis (oogenesis) and spermatogial differentiation. Without Stra8, sperm will be azoospermic (non-motile)!

