

The Male Genital Tract (MGT) : A Physiological Pharmacokinetic Compartment

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The male genital tract (MGT) is a site for infection (HIV), cancer (testicular) and disorders (erectile dysfunction). Since it is part of the male excretory and reproductive system it is also vulnerable to toxic effects of drugs. The MGT is a physiological pharmacokinetic compartment consisting of anatomical (blood-testes barrier) and physiological barriers (expression of drug metabolizing enzymes, efflux & influx transporters) which can significantly influence the penetration of drugs into the disease compartments. The semen is a surrogate for measuring drug concentrations in MGT. The ratio of drug concentration in semen plasma (SP) to blood plasma (BP) (SP/BP) is used as a measure of penetration of drugs into MGT. MGT is included as a compartment in PBPK modelling.

Prostate gland

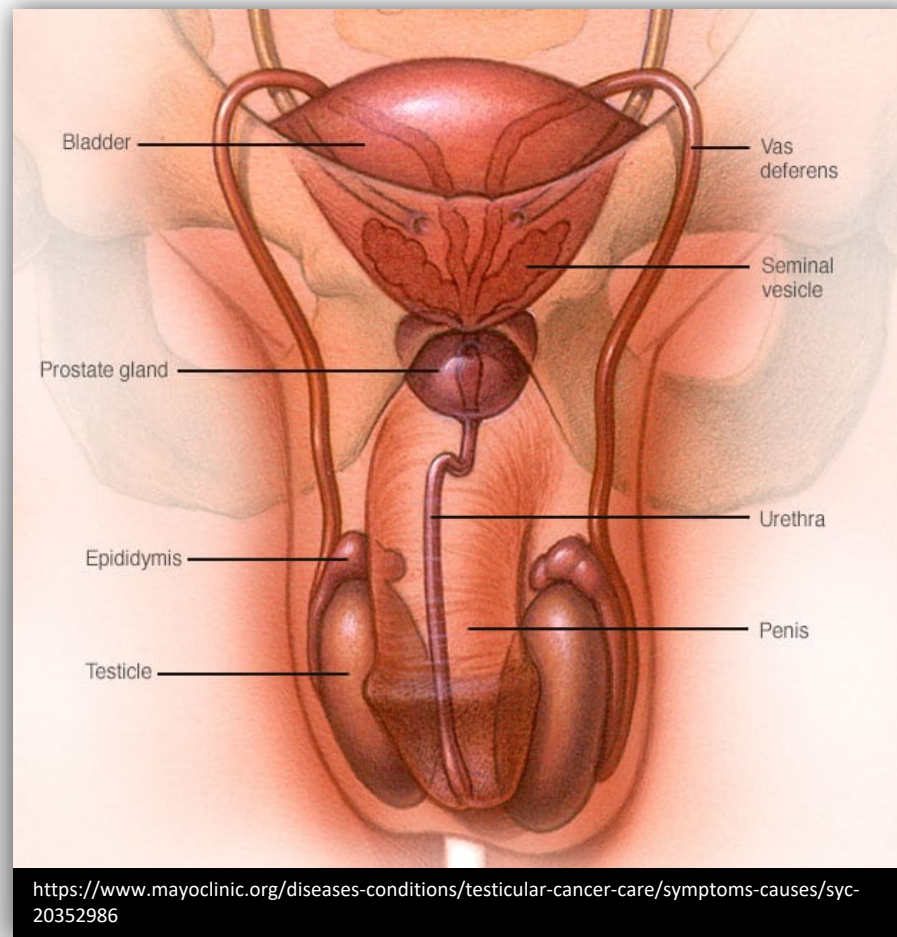
- Phase I DMEs -CYP1A, CYP2C, CYP3A, CYP1B1 isoforms, CYP2D6, CYP4B1.
- Phase II -glutathione S-transferase (GST), UGT families
- Majority of efflux transporters from ABC-transporter family

Epididymis

- Influx transporters -ENT1, ENT2, OAT3, OATP1A4, OCTN2, OCTN3
- Efflux transporters - P-gp, MRP1, MRP5, MRP6, MRP7

Semen

- Surrogate for measuring drug concentrations in MGT
- Semen plasma to Blood Plasma ratio important PK measure in MGT for PK/PD



<https://www.mayoclinic.org/diseases-conditions/testicular-cancer-care/symptoms-causes/syc-20352986>

Seminal Vesicle

- SV epithelium expresses mRNA of 11 ABC-family transporters, 25 solute-linked carrier (SLC)-family transporters & carriers
- MRP1, MRP3, P-gP, BCRP highly expressed on apical membranes. P-gP highly expressed on basolateral membranes to protect SP from toxins and xenobiotics
- SLC-family transporters expressed on basolateral and apical membranes epithelium -support secretory role of seminal vesicles;

Testes

- Blood-testis barrier (BTB) separates testicular blood vessels and the seminiferous tubules. BTB is comprised of Sertoli cells held together by tight junctions
- ABC-family transporters localized on basolateral & apical membranes of Sertoli cells (BCRP, MRPs, and P-gP)
- SLC-family transporters -OATPs, OATs, OCTs, concentrative nucleoside transporters (CNTs), equilibrative nucleoside transporters (ENTs)
- CYP3A4, CYP2D6 found throughout testicular tissue