The genomic timeline of testicular germ cell tumour (TGCT)

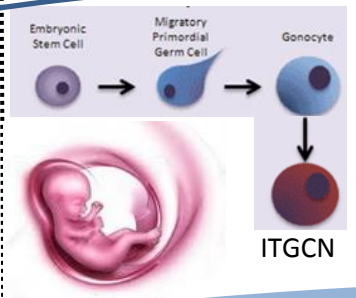
Features

Pre-cancer: TGCT predisposition

-FRR of TGCT is high (4 to 8 fold)
- 49% of all TGCT risk is inherited
- Susceptibility is highly polygenic
- Pathways implicated: *KIT* signalling, male germ cell development, sex determination, genomic integrity

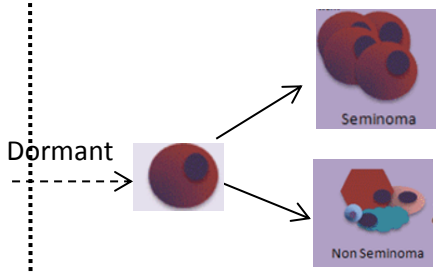
Precursor state: tumour origin

- TGCTs can arise from a non-invasive precursor lesion, called ITGCN
- ITGCN likely forms during fetal development
- ITGCN has high expression of OCT3/4 & NANOG
- ITGCN is malignant equivalent of PGC



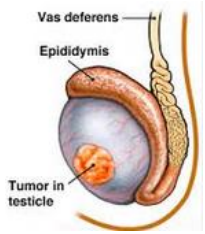
Progression to cancer: tumour subtypes

- ITGCN lies dormant until puberty
- Following puberty ITGCN cells begin to proliferate, due to hormonal influences
- i(12p) likely acts as a triggering event, causing invasive growth
- ITGCN transforms to either seminoma / non-seminoma tumour histologies



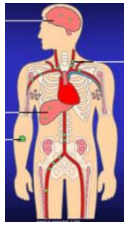
Presentation with malignant tumour

- TGCTs have a low rate of somatic mutations
- *KIT* and *KRAS* are most frequent driver genes
- wt *p53* retained
- High level of i(12p) - hallmark CNV
- seminoma = m*KIT*, hyper-triploid
- non-seminona = wt*KIT*, hypo-triploid



Post-treatment: platinum resistance

- TGCTs are typically platinum-sensitive with high >95% 5-year survival.
- Small minority are resistant to platinum
- Mechanisms of platinum resistance are poorly understood but may include DNA repair genes, *p53* activity and methylation patterns



Post-cancer: long term survivorship issues

- TGCT survivors can experience a number of platinum-based side effects: neurotoxicity, hypogonadism, infertility, increased risk cardiovascular disease and secondary cancer.
- Certain germline polymorphisms, e.g. variants in *GSTP1*, increase patient risk

Time: Pre-conception → Fetal development → Post natal development ⇢ Post pubertal development ⇢ Early adulthood ⇢ Late adulthood