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Background: Germ cell tumours (GCTs) are cancers of the testis, ovary and extragonadal sites that occur in infants, children, adolescents and adults. Post-pubertal (type II) malignant GCTs may present as seminoma, non-seminoma or mixed histologies. In contrast, pre-pubertal (type I) GCTs are limited to (benign) teratoma and (malignant) yolk sac tumour (YST). Epidemiological and molecular data have shown that pre- and post-pubertal GCTs arise by distinct mechanisms. Dedicated studies of the genomic landscape of type I and II GCT in children and adolescents are lacking.
Material and methods: We performed whole-exome sequencing, panel-based deep sequencing, copy-number analysis, RNASeq and methylations analysis on a clinically annotated cohort of GCTs from patients aged 0–24 years. We complemented the genomic analysis with functional studies in human cells and zebrafish models.
Results: Activation of the WNT pathway by somatic mutation, copy-number alteration, and differential promoter methylation is a prominent feature of GCTs in children and adolescents, and is associated with poor clinical outcomes. Significantly, we find that small molecule WNT inhibitors can suppress GCT cells both *in vitro* and *in vivo* in zebrafish models. These results highlight the distinctive mechanisms underlying the development of childhood and adolescent GCTs and provide a foundation for future efforts to develop targeted therapies for these cancers.

GCT-25 The avian embryo as a new patient-derived xenograft model to explore germ cell tumour aetiology, heterogeneity and therapeutic screening

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Background: Gonadal and extragonadal germ-cell-tumours (GCTs) arise from pluripotent primordial-germ-cells (PGCs). The aetiology of extragonadal GCT and metastasis is still debated, mainly because of lack of suitable models recapitulating GCT pathogenesis, including i*n vivo* patient-driven analyses of tumour migration/chemosensitivity. Our main objective was to develop an avian Patient-Derived Xenograft (PDX) system, to reproduce GCT heterogeneity/clinical features.
Methods: Based on previous experiments on neuroblastoma, we conceived an avian model of GCTs in which tumorigenesis is driven in HH25 chick embryos either in gonadal site by grafting GCTs in the migration path of PGCs, or in extragonadal brain site. We set up the technique with NCC-IT and Tera2 GCT cell lines with extension to 3 GCT patient samples, harvested from fresh surgical resections and preserved in DMSO freezing medium: one mediastinal yolk-sac tumour in a 6-year-old patient and two metastatic testicular mixed GCT (in 16- and 15-year-old patients).
Results: Cell lines grafted in the PGC migration path formed visible tumours in avian primitive gonads 5 days after engraftment while grafts in the developing brain permitted the replication of secondary foci in 2 days. Similar graft experiments on GCT patient samples confirmed a rapid and highly reproducible tumour intake in the embryo for both paradigms. Intravenous injection of 5.1 mg/kg cisplatin into embryos grafted with patient samples reduced tumour volume of these avian replicas of cisplatin-responding patients within 48 h. Our GCT avian model opens exciting possibilities ranging from the study of GCT aetiology to the evaluation of novel drug/combination efficacy on patient-derived material.

Ovarian GCTs Including Teratoma

GCT-26 Survival outcomes and long-term follow-up in children treated for ovarian nonseminomatous germ cell tumours in the French TGM-95 study

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Background: To analyze characteristics and outcomes with actualized very-long-term follow-up data from patients treated for ovarian non seminomatous germ-cell-tumours (NS-GCT).
Methods: Children (≤18 years) treated for ovarian NS-GCT in 1995–2005 in France and Belgium were included in TGM-95. Patients with localized, completely-resected tumours (FIGO-stage IA) had no adjuvant treatment (low-risk, LR). Patients with advanced-stage (FIGO-stage ≥IC) received 3–5 VBP cycles (vinblastin-bleomycin-cisplatinum) in intermediate-risk disease (IR: FIGO-stage IC-II-III and AFP<15,000 ng/ml) or 4–6 VIP (etoposide-ifosfamide-cisplatinum) in high-risk (HiR: metastatic and/or AFP ≥ 15,000 ng/ml).
Results: Seventy-seven patients were included (median age = 12 years, 43 pure yolk-sac tumour; 34 mixed NS-GCT). Primary surgery was performed in 55/77 cases. Fourteen patients were LR (12 stage IA, 2 retrospectively stage IC), 26 IR (12 stage IC, 12 stage II-III, 2 not-available) and 37 HiR (8 metastatic, 29 loco-regionally advanced). After a median follow-up of 13 years, 9 events (including 5 relapses/bilateralizations and 2 secondary acute-myeloid-leukemias) and 6 deaths occurred. All relapses/bilateralizations occurred in LR (n = 4, including the 2 retrospectively-stage-IC) and IR groups (n = 1), within 2 years post-diagnosis. Five-year EFS and OS were 89% (95%CI = 80–95%)