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TOP3A is required for the maintenance of the ovarian follicular reserve and oocyte quality

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Background

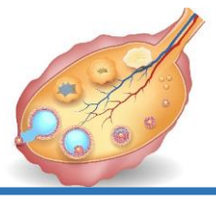
- Several lines of evidence from budding yeast, plants and flies suggest that TOP3A is critical for quality control in oocytes:
  - ——repair of meiotic DNA double strand breaks;
  - ——repair of DNA damage arising from exogenous stressors;
  - ——maintenance of mitochondrial DNA (mtDNA).
- The role of TOP3A in the oocytes of higher vertebrates has never been established.

Aim

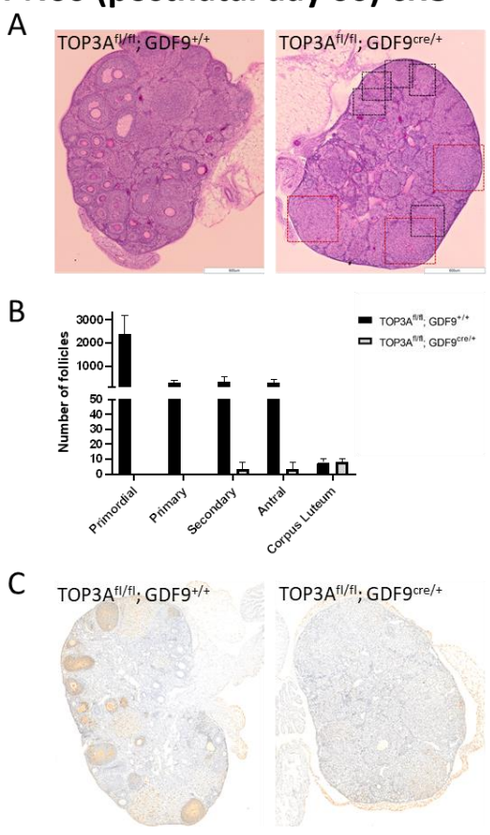
- To investigate the role of TOP3A in mammalian oocytes.

Methods

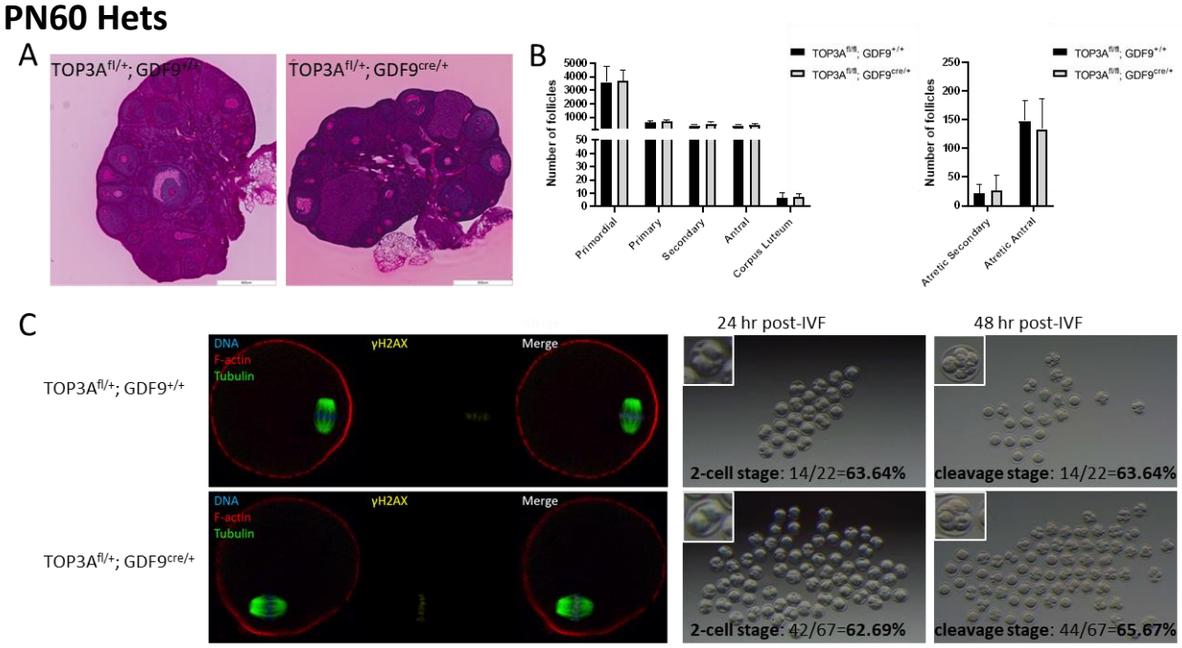
- Generation of novel mouse models with conditional loss of TOP3A in oocytes (**cKO**).
- Analysis (n=6 mice/genotype/age):
  - ——ovarian morphology;
  - ——follicle number;
  - ——apoptosis (TUNEL);
  - ——Top3a mRNA expression;
  - ——oocyte morphology;
  - ——fertilisation rate;
  - ——mtDNA copy number;
  - ——ATP level.



PN60 (postnatal day 60) cKO



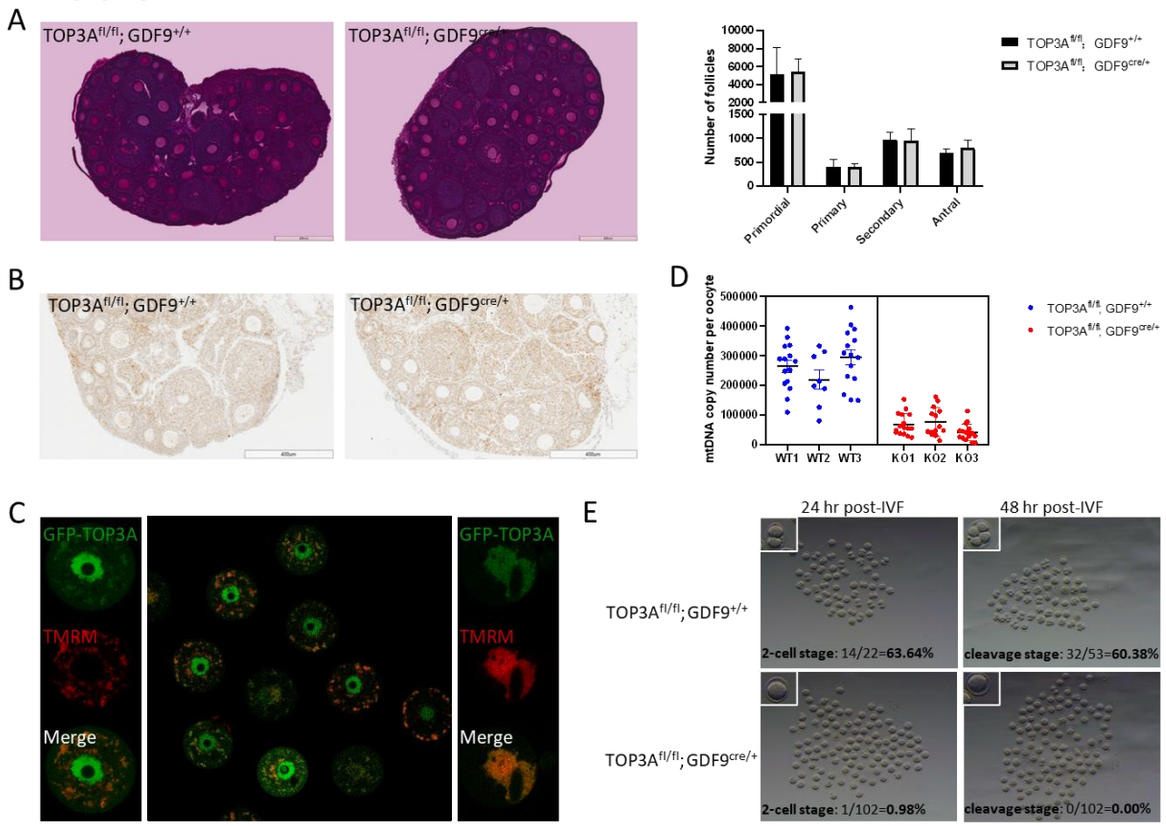
PN60 Hets



Results from adult mice:

- **Follicle numbers**——dramatic **depletion** of follicles in adult **cKO** mice; **normal** in **Hets**.
- **Oocyte quality**——**normal** oocyte morphology and fertilization rate in adult **Hets**.

PN20 cKO



Results from prepubertal mice:

- **Follicle numbers**——**similar** between **prepubertal** WT and cKO mice.
- ***Top3a* mRNA** (*in situ hybridization*)—— expressed by oocytes within primordial, primary, secondary and antral follicles, while absent in cKO oocytes.
- **TOP3A protein** (GFP-tagged)—— **colocalizes with mitochondria** during oocyte maturation.
- **mtDNA copy number**——dramatically **reduced** in TOP3A-cKO oocytes.
- **Oocyte quality**——almost all oocytes from TOP3A-cKO mice **failed** to progress beyond **fertilization**.

Significance

- First evidences the critical role of TOP3A for mammalian oocytes.