Engineered Gene Therapy Vectors Enable Accelerated In Vivo Reproductive Genetics

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Conventional genetic knock-out (KO) animal models have been essential for understanding gene function in fertility. Generating new transgenic models, however, is technically challenging and is time consuming as it requires breeding. Recent large genomics datasets have implicated several transcripts present in reproductive tissues, the experimental testing for their potential role, however is lacking.

We have engineered adeno-associated viruses (AAVs) for gene delivery and editing in the mouse ovary in vivo. We demonstrate that with a single, systemic AAV injection can efficiently edit genes in the ovary and recapitulate known reproductive phenotypes. By targeting Foxl2, Cyp19a1, Esr1, Cyp17a1, Amh, Amhr2, Kitl, Cdkn1b we observe the expected changes in ovarian histology (i.e. somatic sex conversion, cyst formation, stroma over proliferation, accelerated or halted follicle activation), change in blood serum hormone levels, and in fertility assessed by long term mating trials.

This methodology drastically accelerates functional genetics as the production of custom AAV-KO animals requires only a month and additionally also allows for perturbing combinations of genes at the same time. Currently, we are screening a list of candidate transcripts by AAV-KO and assessing their potential role in ovarian follicle development, fertility and ovarian aging.