Our lab studies how the mammalian sex chromosomes regulate health and disease in women (XX) and men (XY). We achieve our aims using genetic, cell biological, computational, evolutionary and stem cell approaches, and employ eutherian and marsupial mammalian model systems. We have identified mechanisms driving sex chromosome-associated phenotypes and have devised therapeutic approaches to reverse them.

Sex chromosome aneuploidies, including Turner (XO), Klinefelter (XXY) and Jacob (XYY) syndrome, are the most common chromosome abnormalities in humans. Individuals with these conditions are often infertile. We found that early germ cells from Turner and Klinefelter syndrome mice exhibit aberrant X-dosage compensation states, which we
proposed contribute to their infertility phenotypes. We devised the first approach to reverse sex chromosome trisomy-associated infertility. Reprogramming of skin cells from sterile XXY and XYY mice caused loss of the extra sex chromosome. The resulting corrected XY stem cells were converted in vitro into germ cells, which then produced healthy fertile offspring. Reprogramming also corrected trisomy in human XXY and Down syndrome cells. Our work thus identified a novel role for reprogramming as a trisomy therapy.

In individuals with sex chromosome abnormalities, meiotic synapsis between homologues is defective, leading to germ cell loss via ill-defined mechanisms. In early work, we discovered that unsynapsed chromosomes are transcriptionally inactivated, a process we called meiotic silencing. Epigenetic mechanisms underlying meiotic silencing, and its role in infertility, were unclear. We showed that meiotic silencing is mediated by DNA-damage genes Atr and Topbp1, and histone methyltransferase Setdb1. By ablating meiotic silencing, we rescued oocyte loss in XO female mice. We showed that Atr has additional meiotic functions, co-operating with Atm during wild-type meiosis to regulate synopsis and recombination. These findings provided insight into the gonadal phenotypes in patients with mutations in Atr (Seckel syndrome) and Atm (Ataxia Telangiectasia syndrome).

Defective meiotic recombination can cause mutations and aneuploidy in offspring. Germ cells with unresolved recombination intermediates are therefore eliminated by the recombination checkpoint, but how elimination is mediated was not clear. We identified critical functions for BCL-2 pathway members Puma, Noxa and Bax in checkpoint-mediated elimination. Our findings suggest that allelic variants of the BCL-2 pathway may influence the risk of embryonic aneuploidy, and that BCL-2 inhibitors may be of utility in fertility preservation.

Another of our research areas focuses on X-chromosome inactivation, which equalises X-dosage between females and males. X-inactivation defects have been linked to various diseases, including cancer. Using our Monodelphis domestica (opossum) colony, we discovered the marsupial XIST equivalent, RSX and its antisense partner XSR. This work provided a long-sought comparative system with which to understand RNA-mediated chromatin remodelling. We performed the first single-cell RNA-seq analysis of marsupial embryos, identifying lineage-specification and pluripotency factors that are deeply conserved and thus likely to serve critical developmental functions. This study also generated insight into the evolution of imprinted versus random X-inactivation.

**Research outputs**


Single-cell RNA sequencing of embryos can resolve the transcriptional landscape of development at unprecedented resolution, but such studies of mammalian embryos had focused exclusively on placental species. Analysis of mammalian outgroups might identify deeply-conserved lineage specification and pluripotency factors. In this study, we performed the first single-cell RNA-sequencing in a marsupial, which diverged from eutherians 160 million years ago. We identified many critical developmental regulators pre-dating the placental-marsupial separation which are thus likely to be especially important for embryogenesis. Our study has important implications for understanding the high rates of miscarriage in humans and for developing improved conditions for assisted reproduction.

Aneuploidy is remarkably common in human embryos, and most often results from defective recombination in the maternal germ line. There is therefore great interest in determining mechanisms that eliminate recombination-defective oocytes, and how defects in these mechanisms cause chromosome abnormalities in offspring. In this study, we showed that recombination-defective oocytes are eliminated via the BCL-2 pathway components Puma, Noxa and Bax. Our findings raised the possibility that allelic variants of the BCL-2 pathway could influence the risk of embryonic aneuploidy.


Unresolved DNA damage causes chromosome silencing, but how was unclear. We showed that during meiosis, unresolved double-strand breaks induce chromosome silencing via the histone H3-lysine-9 methyltransferase SETDB1. The work provided insight into how cells recognise and repair DNA damage, thereby preserving genome integrity.


Here, we described a technique for reversing infertility in XXY (Klinefelter) and XYY (Jacob) syndrome mice. We showed that reprogramming of fibroblasts from these mice resulted in elimination of the extra sex chromosome, and that resulting XY cells could be converted by in vitro gametogenesis into functional sperm. Reprogramming could also chromosomally correct cells from Down syndrome mice and patients. The work revealed an unexpected role for reprogramming as a form of chromosome therapy.


X-dosage compensation was thought to be essential in all mammalian cell types. In this study, we showed that male and female germ cells exhibit unusual X-dosage compensations states, providing an important exception to this rule. We showed for the first time that sex chromosomally-abnormal germ cells exhibit X-dosage compensation states that are unmatched to their somatic gonadal environment, thereby providing a new potential mechanism for sex chromosome-related infertility.