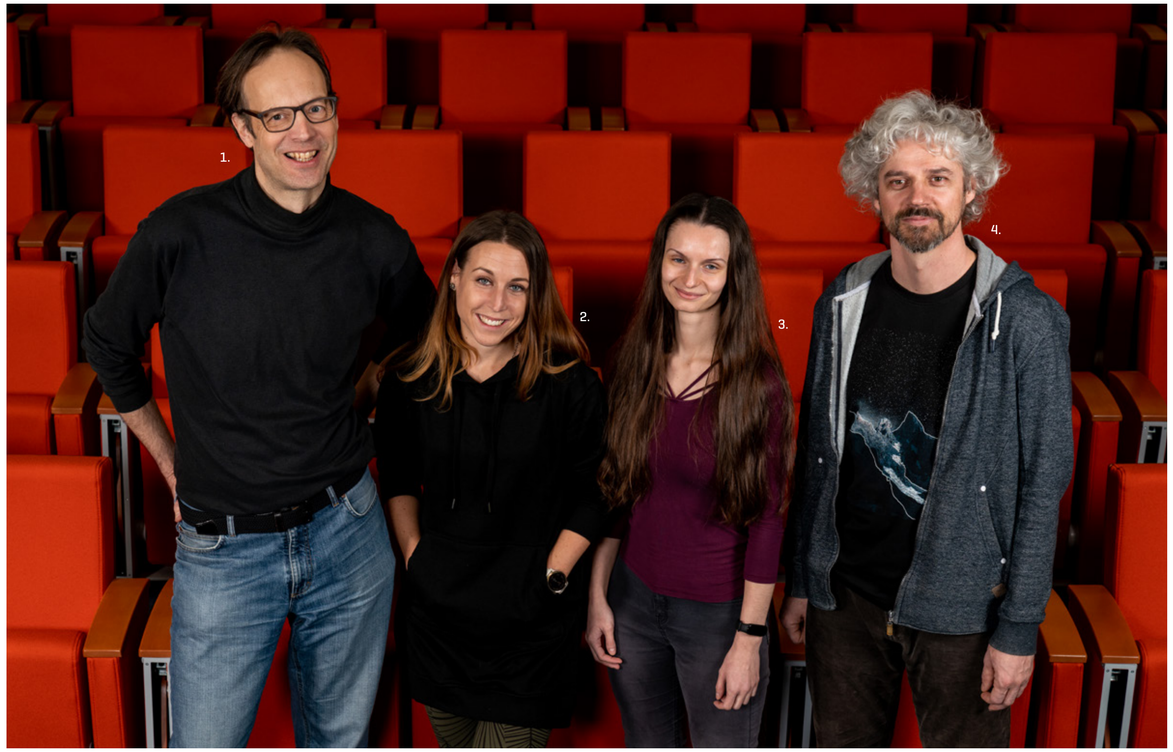
LABORATORY OF

MECHANISMS OF GERM CELL DEVELOPMENT

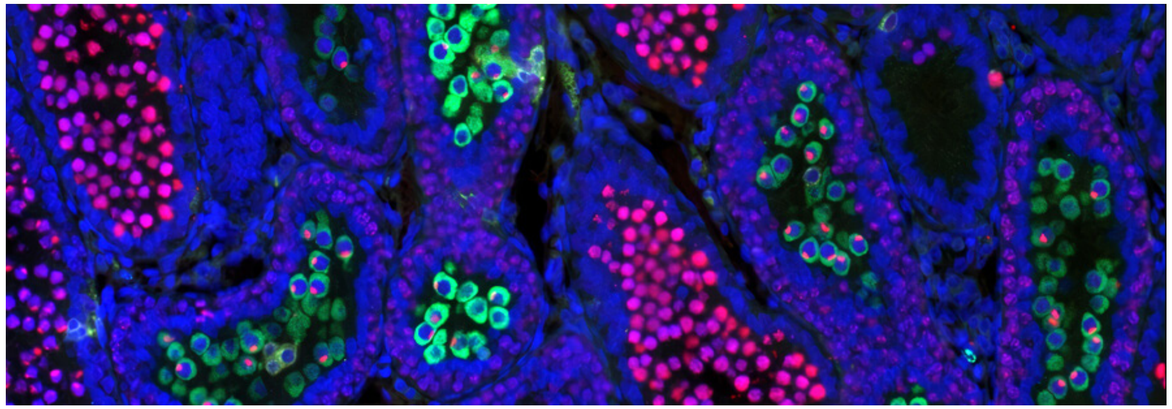
Fertility, meiosis, spermatogenesis, oogenesis, PRDM9, reproductive age

Zdeněk Trachtulec



In the picture: 1. Trachtulec Zdeněk | 2. Tůmová Lucie | 3. Pírková Daniela | 4. Mihola Ondřej

Our society faces new challenges, including the increased age of parents and decreasing sperm quality and quantity, which need to be addressed by the fertility research. Mammalian fertility depends on meiotic recombination (the repair of self-inflicted DNA breaks to crossovers). The sites of recombination hotspots (RHS) are determined by DNA-binding meiotic histone-3-methyltransferase PRDM9. Genetic inactivation of *Prdm9* causes complete meiotic arrest in both sexes of the C57BL/6J (B6) mouse; the reason for the arrest and subsequent sterility has been thought to be the relocation of RHS to promoters. However, dogs or birds carry RHS in promoters and yet do not require PRDM9 for fertility. To resolve this discrepancy, we prepared additional *Prdm9*-deficient rodents. In contrast to the B6 mouse, some mouse and rat males lacking PRDM9 were able to produce sperm and some even offspring, despite RHS in promoters. We predicted that these males with rescued fertility could have more efficient DNA repair of relocated RHS. Indeed, we found a positive correlation between the number of crossovers and sperm presence in *Prdm9*-deficient rodent males. In line with this result, we also found that *Prdm9* is important for quantity, motility and structure of sperm in semifertile mouse hybrids. This sperm amount and quality was affected by the level of expression of a proteasomal subunit; the levels of proteasomal subunits are also changed in the sperm of infertile men. We assume that drugs inducing elevated DNA repair targeted into the testes of some human infertility patients could increase crossover rate and lead to functional sperm. Mutations in the human gene encoding PRDM9 have been implicated in Premature Ovarian Insufficiency (POI), a common subfertility disorder reducing reproductive age. Our rat females lacking PRDM9 also display shortened reproductive age. We uncovered a possible mechanism linking POI in mothers with aneuploidy (which includes Down syndrome) in offspring. This link could be non-homologous meiotic synapsis, which causes DNA repair with decreased crossover rate followed by aberrant segregation of chromosomes leading to aneuploid eggs with abnormal chromosome numbers. Our animals thus represent excellent models of the currently important infertility disorders occurring in both men and women.



Cross-sections of 22-day-old rat testes with labelled DNA (blue), a nuclear protein of less advanced sperm precursors (red), and a cytoplasmic protein of more advanced sperm precursors (green) visualized by fluorescence microscopy. Comparing sections from control and mutant testes revealed delayed meiotic progression in mutant males.
Photo: O. Mihola

Selected publications:

1. Kusari F, Mihola O, Schimenti JC, Trachtulec Z*: Meiotic epigenetic factor PRDM9 impacts sperm quality of hybrid mice. Reproduction 2020 160(1): 53-64.
2. Mihola O*, Kobets T, Krivankova K, Linhartova E, Gasic S, Schimenti JC, Trachtulec Z: Copy-number variation introduced by long transgenes compromises mouse male fertility independently of pachytene checkpoints. Chromosoma 2020 129(1): 69-82.
3. Mihola O, Landa V, Pratto F, Brick K, Kobets T, Kusari F, Gasic S, Smagulova F, Grey C, Flachs P, Gergelits V, Tresnak K, Silhavy J, Mlejnek P, Camerini-Otero RD, Pravenec M, Petukhova GV, Trachtulec Z*: Rat PRDM9 shapes recombination landscapes, duration of meiosis, gametogenesis, and age of fertility. BMC Biol 2021 19(1): 86.
4. Gasic S, Mihola O, Trachtulec Z*: *Prdm9* deficiency of rat oocytes causes synapsis among non-homologous chromosomes and aneuploidy. Mamm Genome 2022 33(4): 590-605.