



Laboratory of Mouse Molecular Genetics

Meiotic silencing, aneuploidy, genomics, hybrid sterility, *Prdm9*

Jiří Forejt

jiri.forejt@img.cas.cz

Genetic architecture of hybrid male sterility between *Mus m. musculus* and *Mus m. domesticus* subspecies has been analysed on the model of PWD/Ph x C57BL/6 sterile male hybrids. The candidate genes were evaluated by transgenic rescue for the *Hst1* locus and by positional cloning and expression profiling of sorted testicular cells for the *Hstx1* and *Hstx2* loci. We have identified the first vertebrate hybrid sterility locus, the mouse Hybrid sterility 1 [*Hst1*] with *Prdm9* [*Meisetz*], encoding a meiotic histone H3 lysine-4 tri-methyltransferase. Positional cloning was confirmed by hybrid male infertility rescue by using the intact *Prdm9* transgene in bacterial artificial chromosomes with the “fertility” *Hst1^f* allele. Identification of the first vertebrate hybrid sterility gene reveals a role for epigenetics in speciation, and opens a window to a hybrid sterility gene network. We have established a new mouse model of human aneuploidy syndromes. The Ts43H segmental trisomy of proximal 30 MB of mouse chromosome 17 encompasses over 300 protein-coding genes. Chromosome substitution strains C57BL/6.PWD, recently constructed in our laboratory, are used for phenome analysis in collaboration with The Jackson Laboratory, Bar Harbor, Maine, USA [Dr. K.L. Svenson] and for the genetics of gene expression and splicing in a systems genetics project with the Max-Planck-Institute for Molecular Genetics in Berlin [Prof. H. Lehrach]. We study meiotic X-chromosome inactivation by genome-wide expression profiling and by monitoring transcription profiles and histone modifications in meiotic and postmeiotic testicular cells

of carriers of male-sterile autosomal rearrangements and in male-sterile inter-species hybrids.

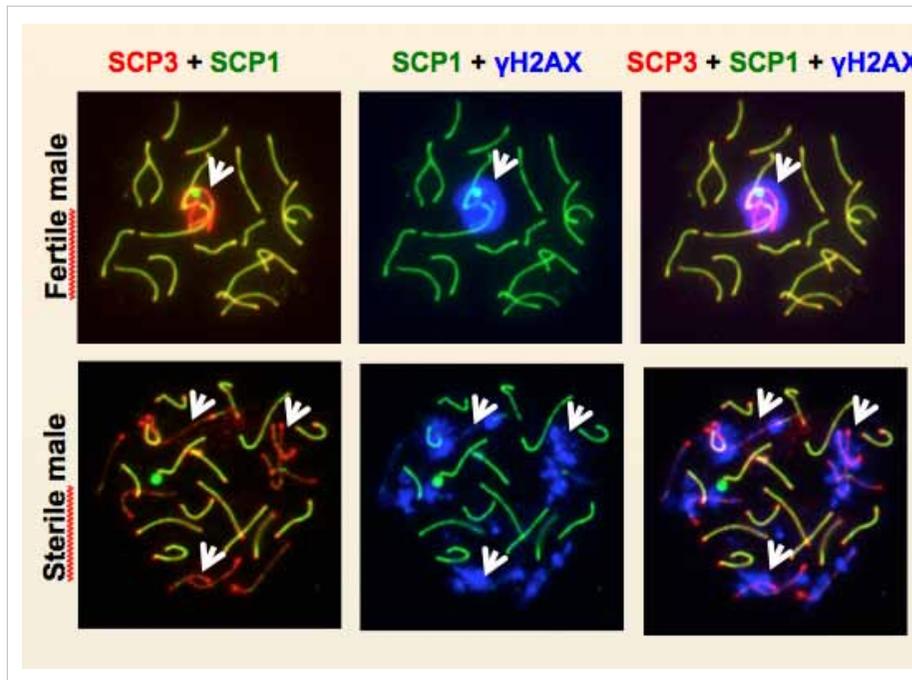


Fig. 1. Pachytene spermatocytes of sterile and fertile hybrids, [PWD x B6]F1 and [B6 x PWD]F1, display unsynapsed autosomes and dislocated histone γ H2AX.



- GA CR, GA301/07/1383 – Gene expression profiling during mouse spermatogenesis: Implications for meiotic sex chromosome inactivation and gene retroduplication, 2007–2009, P. Jansa
- GA CR, GA301/07/1264 – Uncovering regulatory networks in novel mouse models by genetical genomics, 2007–2009, J. Forejt
- GA CR, GAP305/10/1931 – Identification of interactors of the meiotic histone methyltransferase Hybrid sterility 1 [PR-domain 9], 2010–2013, Z. Trachtulec
- AS CR – Premium Academiae, 2007–2013, J. Forejt
- Ministry of Education, Youth and Sports of the Czech Republic, 1M0520 – Center for Applied Genomics, 2005–2011, J. Forejt
- FP6 EU, 37627 ANEUPLOIDY – AnEuploidy: understanding gene dosage imbalance in human health using genetics, functional genomics and systems biology, 2006–2011, J. Forejt



- Homolka D, Ivanek R, Forejt J, Jansa P. Differential expression of non-coding RNAs and continuous evolution of the X chromosome in testicular transcriptome of two mouse species. *PLoS ONE* 2011 6(2): e17198.
- Mihola O, Trachtulec Z, Vleck C, Schimenti JC, Forejt J. A mouse speciation gene encodes a meiotic histone H3 methyltransferase. *Science* 2009 323(5912): 373–375.
- Piálek J, Vyskočilová M, Bimová B, Havelková D, Piálková J, Dufková P, Bencová V, Ďureje L, Albrecht T, Hauffe HC, Macholán M, Munclinger P, Storchová R, Zajícová A, Holáň V, Gregorová S, Forejt J. Development of unique house mouse resources suitable for evolutionary studies of speciation. *J Hered* 2008 99(1): 34–44.
- Gregorová S, Divina P, Storchová R, Trachtulec Z, Fotopulsova V, Svenson KL, Donahue LR, Paigen B, Forejt J. Mouse consomic strains: exploiting genetic divergence between *Mus m. musculus* and *Mus m. domesticus* subspecies. *Genome Res* 2008 18(3): 509–515.
- Trachtulec Z, Vleck C, Mihola O, Gregorová S, Fotopulsova V, Forejt J. Fine haplotype structure of a chromosome 17 region in the laboratory and wild mouse. *Genetics* 2008 178(3): 1777–1784.



From left:
Ondřej Mihola, PhD / Postdoc
David Homolka, MSc / PhD Student
Petr Flachs, MSc / PhD Student
Jana Perlová / Technician
Marta Landíková / Technician
Zdeněk Trachtulec, PhD / Research Fellow
Soňa Gregorová, MSc / Research Fellow
Jiří Forejt, Prof., MD, DSc / Head of Laboratory
Irena Chvátalová, MSc / Research Assistant
Petr Šimeček, PhD / Research Fellow
Hana Vágnerová / Secretary
Petr Jansa, PhD / Research Fellow
Mária Dzúr-Gejdošová, MSc / PhD Student
Tanmoy Bhattacharyya, MSc / PhD Student

Not on the picture:
Radek Blatný, MSc / PhD Student [until 2010]
Vladana Fotopulosová, MSc / Technician [maternity leave]
Štěpán Jeřábek / Diploma Student
Václav John / Diploma Student [until 2010]