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Review

Minutes of the 14th European Workshop on Molecular and Cellular Endocrinology of the Testis

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The concept of the European Testis Workshops evolved from smaller national and bilateral workshops within Europe and the 1st European Testis Workshop took place in Geilo, Norway in 1980. There are no statutes, no written rules, no society, no president and no elections behind the ETWs. There is just a self-appointed "Permanent Committee" of eight European researchers dedicated to the testis as their research focus. Each of them organizes an ETW at the beginning and again at the end of his/her term in the committee and hands the torch over to a successor from the same country or region. In recent years, the old and the new members have organized their last and first ETW together. This guarantees a smooth transition and a constant rejuvenation of the Permanent Committee.

The 7th ETW was the first to be held in Germany and took place in 1992 at the legendary Castle Elmau. The 14th ETW was also supposed to be held there. Everything was prepared for that event, when Castle Elmau burned down in August 2005—not only a disaster for the owners and the guests, but especially for the ETW. In a frantic search for alternatives Hotel Sankt Georg in Bad Aibling was identified as a possible substitute venue.

The 14th ETW convened in Bad Aibling, in southern Bavaria, Germany from 22 to 26 April 2006 and was organized by Eberhard Nieschlag and Jörg Gromoll, both from the Institute of Reproductive Medicine of the University of Münster, Germany. Over 220 participants from 14 different European countries, as well as participants from North and South America, Australia, Iran, Qatar, Israel, India and Japan attended the workshop, which lasted 4 days.

The 2006 workshop was divided into seven symposia, four workshops and seven miniposter sessions. The symposia were grouped according to the topics Mammalian Testis Biology, Endocrine Regulation of Spermatogenesis, Sperm Function, Contraception, Genetics of Germ cells, Germ Cell Potentials and Disturbed Puberty. For the first time in the history of the ETWs, four interactive 2-hour workshops were organized in which experts provided insights into flourishing topics in testis research such as Epigenetics (Sophie Rousseaux), Databases in Reproductive Research (Michael Primig), Germ Cell Transplantation (Joachim Wistuba) and Cellular Imaging in the Testis (Andreas Meinhardt). As a special but traditional feature participants were asked to submit their results in the format of a miniposter before the workshop. These miniposters were compiled in a booklet, which was made available to all participants before the meeting. Overall 123 miniposters were accepted and the corresponding authors were given the opportunity to present and discuss their findings in one of the seven miniposter sessions during the ETW.

In the opening plenary lecture Hans Schöler (Max Planck Institute for Molecular Biomedicine, Münster) delineated the potential of stem cells for curing infertility or treating diseases. He also critically assessed ethical objections with respect to embryo usage and pleaded for the use of adult stem cells as a source of future treatment options. He expressed, in no uncertain terms, a warning to scientists working in the stem cell field not to overemphasize the potential of their work to avoid frustrated and disappointed public expectations. Stem cell research still has a long way to go before meeting clinical and public demands.

In the first symposion on Mammalian Testis Biology Frank Grützner introduced a view from the outside on the evolution of sex chromosomes. He presented fascinating insights into an exclusively Australian animal model, the egg-laying monotreme duck-billed platypus (*Ornithorhynchus anatinus*). Grützner reported that the platypus displays a meiotic chain of 10 unpaired sex-chromosomes sharing genes with the avian Z and the mammalian X chromosomes. Karyotyping and fluorescence in situ hybridization (FISH) exhibited complex organization of the 10 sex chromosomes arranged in a chain that displays different X and Y elements in an alternating manner. During meiosis

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these chromosomes bearing the sex-determining genes in the platypus are distinctly divided in the gametes that only contain X or Y elements, as demonstrated in the FISH analysis of sperm. The findings led to a hypothesis of how mammalian XY and avian ZW sex chromosomes have evolved and diverged from a common early ancestor and are still reflected in the platypus sex chromosome chain.

The second speaker, Marc Luetjens reviewed the use of non-human primate models in research on reproductive biology and medicine. Although the chimpanzee, as the human's closest relative, would be the best model, sharing 99.5% of all genes with the human, its protected status as well as ethical implications forbid its use as a model organism. Therefore species such as Old World and New World monkeys have to be explored for their suitability as non-human primate models. Luetjens reported data on the organization and efficiency of spermatogenesis in primates. Contrary to the assumption generally accepted, it became clear that the meiotic and spermatogenic efficiency of all primate species is independent of the arrangement of spermatogenic stages found in cross-sections of the tubules. Single-stage arrangements (Prosimians and Old World monkeys) as well as multistage arrangements (New World monkeys and Great apes including the human) result in a high testicular efficiency comparable to rodents. The different types of the seminiferous epithelial organization most likely occur because of the various sizes of the germ clones, also leading to the species-specific working load of the Sertoli cells. In addition, the lecture elucidated the differences within the primate order concerning the expression pattern of the boule family members BOULE, CDC 25, DAZ and DAZL, providing insights into the evolutionary development of the function of these genes in male reproduction. Luetjens concluded that Old World monkeys are a valid model in endocrinological studies, while New World monkeys should be preferred in studies addressing organization of the seminiferous epithelium or aiming at mating tests and fertility as an endpoint.

Germ cell–somatic cell interaction was the topic of the final lecture of the first session held by Masaru Okabe. Transgenic mice bearing enhanced green fluorescent protein (eGFP) coupled to X-linked genes served as a tool to produce XX ↔ XY sex-chimeras by aggregating wild type with transgenic embryos. Early male germ cells with a supernumerary X chromosome were isolated from testes and their imprinting was analysed, revealing a paternal imprinting independent of their chromosomal constitution. Normally these XX-"prospermatogonia" disappear from the testis within the first 3 days post partum after having differentiated into the early spermatogonial stages, similar to cells with XXY karyotype. These findings indicate that the supernumerary X chromosome alone causes the loss of these cells and that a Y chromosome does not compensate for the chromosomal imbalance. Few of those XX germ cells survive in the tubules of the chimera and develop into testicular eggs, very likely because of an intermediate imprinting pattern exhibiting more female features. Okabe concluded from the results that, in contrast to what was reported so far, XX germ cells develop as spermatogonia when situated in a testicular environment because of paternal imprinting, some XX germ cells acquiring intermediate imprinting in this environment become testicular eggs.

The second symposion dealt with the Endocrine Regulation of Spermatogenesis. In the first lecture given by Jan Bogerd the ligand-selective determinants of the gonadotropin receptors were delineated. Unlike mammals where there is no heterologous cross activation of the FSHR by LH/CG, in the African catfish (*Clarias gariepinus*), *in vitro* the FSHR is responsive to both, cfFSH and cfLH. Aiming at identifying the amino acid residues which are responsible for the observed ligand specificity in mammals' mutated variants of the human FSHR were constructed by introducing one of the nine LHR leucine reach repeats (LRR). Hormone binding and signal transduction experiments revealed that in LRR1 the amino acid residues; Arg^{52}, Val^{54}, Leu^{55} and in LRR 8 the amino acid residue Val^{221} are essential in the hFSHR for the discrimination between LH and FSH. Similar to these experiments in the human LHR, LRRs were replaced by hFSHR LRRs. After a subsequent alanine-scan, he demonstrated that in LRR3 amino acid residue Asn^{104} and in LRR6 Lys^{179} are crucial for the recognition of LH. Deciphering of ligand selective determinants is important for our understanding of gonadotropin action and is crucial for reproduction in primates where during pregnancy, characterized by high levels of chorionic gonadotropin, a cross reaction with the FSHR would be detrimental for additional follicular recruitment and development. This situation is different from the catfish where LH participates in follicle recruitment.

In the second talk of this symposion Katja Teerds outlined the perspectives of Leydig cell research. She introduced recent findings on Leydig stem cells which will have major implications for understanding steroidogenesis and Leydig cell function. She presented a physiological flowchart of factors involved in the different stages of maturation ranging from Leydig stem cells, precursors of Leydig cells, Leydig cell progenitors, immature to mature Leydig cells. According to him, Leydig stem cell proliferation can be stimulated by various factors such as leucemia inhibiting factor (LIF), stem cell factor (SCF), platelet derived growth factor (PDGF), epidermal growth factor alpha (EGFα) and tumor growth factor alpha (TGFα), whereas the anti Müllerian hormone (AMH) is inhibiting proliferation. Luteinizing hormone (LH) is the most important factor driving the differentiation at each level, stage-dependently supported by insulin-like growth factor 1 (IGF-1), 3,5,3′-triiodinethyronin (T_3), follicle stimulating hormone (FSH), desert hedgehog protein (Dhh), PDGF-A, DHT and testicular macrophages. Thus Leydig cell development resembles a complex and tightly coordinated interaction of a series of paracrine and endocrine factors.

The second symposium was concluded by Charles Tyler presenting clearcut effects of endocrine disruptors on sexual differentiation in fish. He focussed his investigations on the widespread species roach (*Rutilus rutilus*) which comprises about half of the fish mass in UK rivers and studied the effect of contaminating estrogenic compounds present in the water. In 44 of 51 investigated river sites, which were spread over the UK, intersex fish were present at significant percentages. The older the male fish were, the higher was the grade of feminisation and number of intersex individuals. As a consequence, feminisation

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