

## Genetically Modified Mice and Gonadotrophin Dependent Tumours

I. Huhtaniemi<sup>1,2</sup>, Hellevi Peltoketo<sup>1</sup>, Petteri Ahtiainen<sup>2</sup> and Matti Poutanen<sup>2</sup>

<sup>1</sup>Department of Reproductive Biology, Imperial College London, Hammersmith Campus, Du Cane Road, London W12 0NN, UK, and

<sup>2</sup>Department of Physiology, University of Turku, 20520 Turku, Finland

We have developed several lines of genetically modified mice, which have allowed us to address the role of gonadotrophin action in the formation of a variety of gonadal and non-gonadal tumours. The mouse lines produced include knockouts of *LHR* and *FSHR*, knockins of activating mutations of *FSHR* and transgenic mice expressing *hCG*, *inhibin- $\alpha$*  promoter-driven *SV40 T-antigen* and *aromatase*. High FSH or LH/hCG stimulation results in ovarian granulosa cell tumours and luteomas, respectively. These ovarian tumours trigger a cascade, apparently through to increased oestrogen and progesterone production, with formation of pituitary prolactinomas, followed by mammary gland tumours. An additional phenotype in these mice is LH-dependent adrenal hyperplasia, which appears in the presence of high LH/hCG and/or oestrogen levels. The expression of *SV40 T-antigen* results in malignant granulosa cell tumours that are dependent on LH action. Although gonadotrophin receptors are expressed in numerous extragonadal sites, gonadectomy of the mice abolishes all extragonadal tumours, indicating that modified ovarian endocrine activity, rather than direct gonadotrophin action, is responsible for their formation and maintenance. Another general finding is that male mice are more resistant to the formation of gonadotrophin-dependent tumours. In conclusion, the mouse models created clearly demonstrate the gonadotrophin dependence of numerous gonadal and extragonadal tumours, and gonadotrophin-stimulated ovarian endocrine function seems to be responsible for their formation.

(Supported by grants from The Wellcome Trust and The Academy of Finland)