highlight the use and the study of ovine breeds with different prolificacies that have led to the identification of genes of the Bone Morphogenetic Protein (BMP) system with unexpected role in the control of ovarian follicular growth and ovulation rate.

Identification of the fecundity genes affecting ovulation rate in sheep

BMP-15 and GDF-9

Among the dozen of major genes presently known to affect ovulation rate in sheep [2], Inverdale and Hanna were the first mutations that have been identified [3]. The Inverdale gene (*FecX*) was identified in a flock of Romney sheep in New Zealand. Based on the inheritance pattern, it was predicted the presence of a major gene carried by the X chromosome [4]. One copy of the Inverdale allele ($FecX^I$) increases ovulation rate by 0.8 and enhance both the number and LH sensitivity of antral follicles in ovaries [5]. In contrast, homozygous Inverdale ewes ($FecX^I/FecX^I$) are sterile with small underdeveloped ovaries containing follicles with no more than one layer of granulosa cells [6,7]. The $FecX^I$ allele corresponds to a single T to A transition at nucleotide position 896 in the cDNA coding for the Bone Morphogenetic Protein-15 (BMP-15), also known as Growth and Differentiation Factor-9b (GDF-9b). This mutation causes a non-conservative substitution of valine with aspartic acid at amino acid 299 of the unprocessed peptide (amino acid 31 of the mature protein, V31D, Table 1). Galloway et al. [3] also described the identification of the Hanna mutation ($FecX^H$) showing the same inheritance pattern and phenotype as the Inverdale [8]. Interestingly, the $FecX^H$ allele corresponds also to a single mutation C to T at nucleotide position 871, in the BMP-15 coding sequence. The Hanna mutation introduces a premature stop at the amino acid position 291 of the unprocessed peptide (amino acid 23 in mature protein, Q23stop) leading likely to a loss of bioactivity of the BMP-15 protein produced by the $FecX^H$ allele.

More recently, two new mutations in the BMP-15 gene and one in the closely related GDF-9 gene have been described in Belclare and Cambridge sheep [9]. The additional mutations in BMP-15 named $FecX^G$ (Galway) and $FecX^B$ (Belclare) are a C to T and a G to T transitions at nucleotides 718 and 1100, respectively. $FecX^G$ causes a premature stop codon at amino acid 239 of the unprocessed protein (no mature protein) and $FecX^B$ substitutes a serine with an isoleucine at amino acid position 367 of the unprocessed peptide (amino acid 99 of the mature protein, S99I, Table 1). The ovarian phenotype in animals homozygous for these mutations in BMP-15 is indistinguishable from the Inverdale phenotype [10]. The mutation $FecG^H$ (High fertility) in the GDF-9 gene on chromosome 5 is a C to T transition at position 1184 of the cDNA substituting a serine for a phenylalanine at position 77 of the mature peptide (S77F, [9]). Even if $FecG^H/FecG^H$ ewes are infertile, ovarian follicles develop to an abnormal type 5 early antral stage [10], differing from the phenotype of homozygous *FecX* carriers where follicles are blocked at the primary stage.

Finally, a new autosomal major gene affecting ovulation rate has been evidenced in the French Lacaune breed [11]. The *FecL* locus has been mapped on sheep chromosome 11 [12,13] and the fine mapping is in progress to identify the gene. However, in the Lacaune population, ewes with extremely high ovulation rate have been observed and it has been hypothesized that another mutation is segregating in this population. In fact, a new mutation, named $FecX^L$, was recently identified in the BMP-15 gene. It corresponds to a G to A transition at nucleotide 1196 of the cDNA, replacing a cysteine with a tyrosine at position 53 of the mature protein (C53Y; [13]). $FecX^L/FecX^L$ homozygous ewes present the same "streak" ovaries phenotype than Inverdale homozygous ewes, with follicles blocked at the primary stage (L. Bodin, S. Fabre, P. Monget, unpublished observation).

BMPR-1B

Booroola was the first major gene that has been reported to increase ovulation rate [13,14]. The hyperprolific phenotype of the Booroola ewes appeared in a breeding of

Table 1: Identified major genes affecting ovulation rate in sheep

Name	Gene (Chromosome)	allele	Mutation pro/mature protein	Founder breed	Reference
Inverdale	BMP-15 (X)	$FecX^I$	V299D/V31D	Romney	[3]
Hanna		$FecX^H$	Q291stop/Q23stop	Romney	[3]
Belclare		$FecX^B$	S367I/S99I	Belclare	[9]
Galway		$FecX^G$	T239stop/no	Belclare, Cambridge	[9]
Lacaune X-linked		$FecX^L$	C321Y/C53Y	Lacaune	[13]
High Fertility	GDF-9 (5)	$FecG^H$	S395F/S77F	Belclare, Cambridge	[9]
Booroola	BMPR-1B (6)	$FecB^B$	Q249R	Merino, Garole, Javanese, Hu, Han	[21–25]

GenBank accession numbers: BMP-15 (AH009593); GDF-9 (AF078545); BMPR-1B (AF312016)