Table 4. Targeted transgenes that show an epididymal phenotype

Transgene Characteristics	Phenotype	Reference
Activated *c-neu* oncogene driven by a mouse mammary tumor virus promoter (MMTV)	Epithelial hypertrophy and hyperplasia	Muller et al., 1988; Bouchard et al., 1989, Lucchini et al., 1992
Promoter-enhancer region of MMTV-LTR and constitutively activated allele of human *c-erbB-2* growth factor receptor gene	Epithelial hyperplasia and hypertrophy Infertile males	Guy et al., 1996; Stocklin et al., 1993
Dominant negative mutant of retinoic acid receptor alpha 1 (RARα1) driven by MMTV promoter	Epithelial squamous metaplasia. Infertile or reduced fertility in males	Costa et al., 1997
Human *H-ras* oncogene under the control of L-type pyruvate-kinase gene	Epithelial hyperplasia	Gilbert et al., 1977
N-ras oncogene driven by MMTV-LTR promoter	Abnormal sperm motility, failure of sperm to fertilize eggs in vitro. Male infertility	Mangues et al., 1990
Polyomavirus middle T (PyV-MT) gene. Use of a novel, androgen-inducible expression vector based on rat C3(1) gene	Focal hyperplasia and papillary proliferation of epididymal epithelia, granuloma	Tehranian et al., 1996
Over expression of vascular endothelial growth factor (VEGF) under the mouse MMTV-LTR promoter	Epithelial hyperplasia. Increase epididymal subepithelial capillaries. Male infertility	Korpelainen et al., 1998
Activated *int-3* fused to MMTV-LTR promoter	Epididymal hyperplasia, disorganized pseudo- stratified epithelium. Male infertility	Jhappan et al., 1992
Beta-catenin exon 3 deleted with loxP-mediated recombination utilizing Cre transgene driven by MMTV-LTR	Epididymal hyperplasia and squamous metaplasia	Bierie et al., 2003
5kb GPX5 promoter fused to SV40 small and large T-antigens (GPX5-Tag1 and GPX5-Tag2)	GPX5-Tag1 (higher T-antigen expression) caused severe dysplasia in epididymis and seminal vesicles, adrenal and prostate tumors, spermatogenesis dysfunction. GPX5-Tag2 (lower T-antigen expression) caused slight hyperplastic epithelium of initial segment and seminal vesicles, male infertility	Sipila et al., 2002
MMTV-tTA/tet-op-mEstrogen Receptor alpha	Increased weights of epididymis and vas deferens	Hruska et al., 2002

Table 4. Targeted transgenes that show an epididymal phenotype

References

Muller, W.J., Sinn, E., Pattengale, P.K., Wallace, R., and Leder, P. (1988). Single-step induction of mammary adenocarcinoma in transgenic mice bearing the activated c-neu oncogene. *Cell* **54**, 105-115.

Bouchard, L., Lamarre, L., Tremblay, P.J., and Jolicoeur, P. (1989). Stochastic appearance of mammary tumors in transgenic mice carrying the MMTV/c-neu oncogene. *Cell* **57**, 931-936.

Lucchini, F., Sacco, M.G., Hu, N., Villa, A., Brown, J., Cesano, L., Mangiarini, L., Rindi, G., Kindl, S., Sessa, F. et al. (1992). Early and multifocal tumors in breast, salivary, harderian and epididymal tissues developed in MMTY-Neu transgenic mice. *Cancer Letters* **64**, 203-209.

Guy, C.T., Cardiff, R.C., and Mueller, W.J. (1996). Activated neu induces rapid tumor progression. *J. Biol. Chem.* **27**, 7673-7678.

Stocklin, E., Botteri, F., and Groner, B. (1993). An activated allele of the c-erbB-2 oncogene impairs kidney and lung function and causes early death of transgenic mice. *J. Cell Biol.* **122**, 199-208.

Costa, S.L., Boekelheide, K., Vanderhyden, B.C., Seth, R., and McBurney, M.W. (1997). Male infertility caused by epididymal dysfunction in transgenic mice expressing a dominant negative mutation of retinoic acid receptor alpha. *Biol. Reprod.* **56**, 985-990.

Gilbert, E., Morel, A., Tulliez, M., Maunoury, R., Terzi, F., Miquerol, L., and Kahn, A. (1997). In vivo effects of activated H-ras oncogene expressed in the liver and in the urogenital tissues. *Int. J. Cancer*, **73**, 749-756.

Mangues, R., Seidman, I., Pellicer, A., and Gordon, J.W. (1990). Tumorigenesis and male sterility in transgenic mice expressing a MMTV/N-ras oncogene. *Oncogene* **5**, 1491-1497.

Tehranian, A., Morris, D.W., Min, B.H., Bird, D.J., Cardiff, R.D., and Barry, P.A. (1996). Neoplastic transformation of prostatic and urogenital epithelium by the polyoma virus middle T gene. *Am. J. Path.* **149**, 1177-1191.

Korpelainen, E.I., Karkkainen, M.J., Tenhunen, A., Lasko, M., Rauvala, H., Vierula, M., Parvinen, M., and Alitalo, K., (1998). Overexpression of VEGF in testis and epididymis causes infertility in transgenic mice: evidence for nonendothelial targets for VEGF. *J. Cell Biol.* **143**, 1705-1712.

Jhappan, C., Gallahan, D., Stahle, C., Chu, E., Smith, G.H., Merlino, G., and Callahan, R. (1992). Expression of an activated *Notch*-related *int*-3 transgene interferes with cell differentiation and induces neoplastic transformation in mammary and salivary glands. *Genes Develop.* **6**, 345-355.

Bierie, B., Nozawa, M., Renou, J.P., Shillingford, J.M., Morgan, F., Oka, T., Taketo, M.M., Cardiff, R.D., Miyoshi, K., Wagner, K.U., Robinson, G.W. and Hennighausen. L. (2003). Activation of beta-catenin in prostate epithelium induces hyperplasias and squamous transdifferentiation. *Oncogene*. **22**, 3875-3887.

Sipila, P., Cooper, T.G., Yeung, C.H., Mustonen, M., Penttinen, J., Drevet, J., Huhtaniemi, I. and Poutanen, M. (2002). Epididymal dysfunction initiated by the expression of simian virus 40 T-antigen leads to angulated sperm flagella and infertility in transgenic mice. *Mol. Endocrinol*. **16**, 2603-2617.

Hruska, K.S., Tilli, M.T., Ren, S., Cotarla, I., Kwong, T., Li, M., Fondell, J.D., Hewitt, J.A., Koos, R.D., Furth, P.A. and Flaws, J.A. (2002). Conditional over-expression of estrogen receptor alpha in a transgenic mouse model. *Transgenic Res*. **11**, 361-372.