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Mouse Models to Control Gene Expression in the Renal Proximal Tubule

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The aim of this work was to generate and/or characterise transgenic mouse models to conditionally regulate gene expression in the kidney, specifically in renal proximal tubules, and subsequently use these animals to inactivate the *Rb-1* gene in this cell type. In the first part, we tried to generate transgenic mice in which Cre recombinase production was restricted to renal proximal tubules. Using two previously characterised promoters (Sepulveda et al., 1997; Emert et al., 1998) we were, however, unable to drive Cre synthesis specifically in this nephron segment. Indeed, we observed the two most common problems that complicate any transgenic strategy, i.e. mosaic expression of Cre recombinase and its expression in other tissues, both phenomena likely being a function of the site of the integration of the transgene and the susceptibility to position effects of the promoter element (Sauer, 1998; Wilson et al., 1990). It is worth pointing out, however, that for one transgene (*GGT/CreTag*) our characterisation was by no means exhaustive, and the possibility remains that this promoter can still be useful to target Cre recombinase to proximal tubules.

In a parallel line of experiments, we characterised the previously described rTA^{LAP}-1 mouse line, in which the expression of a novel reverse tetracycline-controlled transactivator (rtTA2^{S}-S2; Urlinger et al., 2000; Hasan et al., 2001) is driven by the liver-enriched activator protein (*LAP*) gene promoter. After crossing this line with tet-operator reporter strains, we demonstrated a rapid and tight regulation of gene expression predominantly in cortical proximal tubule cells. We also showed the suitability of this system to control gene expression during gestation. Therefore we took advantage of this transactivator line and of the LC-1 line (Hasan et al., 2001; Schönig et al., 2001) to drive the expression of *Cre* in cortical proximal tubules and inactivate the *Rb-1* gene in this nephron segment. Triple-transgenic mice, in which the *Rb-1* gene can be conditionally inactivated in the proximal tubule, will be used in further studies to investigate the relevance of pRb for the recovery from acute renal failure.