

Animal Model

Mice with Kidney-specific Megalin Gene Defect

Reference Number 03-00144

Abstract

Challenge

The Kidney is a vital organ with many multiple functions: besides keeping the homeostasis it is responsible for the generation of essential hormones and vitamins, for some metabolic processes and most importantly for excretion of toxic substances. Unfortunately, following filtration many substances comprised in pharmaceutical compounds accumulate in the kidney leading to nephrotoxicity. To overcome such strong adverse effects of pharmaceutical compounds it is essential to identify the target responsible for their renal uptake and accumulation during filtration. Thus there is a strong demand for animal models enabling detailed studies towards the multiple causes of nephrotoxicity caused by pharmaceutical compounds.

Technology

Recently it has been demonstrated using megalin deficient mouse models, that the endocytic receptor megalin located in proximal tubular cells of the kidney is responsible for renal uptake and accumulation of aminoglycosides, one of the most commonly used antibiotics that cause severe nephrotoxicity: this renal uptake of aminoglycosides can be circumvented by the lack of the megalin receptor offering protection from renal accumulation of these antibiotics. Currently, a new mouse model has been generated with a kidney-specific megalin gene defect using Cre-Lox Technology. This animal model is a powerful tool to study the renal uptake of any pharmaceutical compound via megalin to test whether this pathway is responsible for nephrotoxicity of said compound. Identifying megalin as the relevant renal uptake pathway for a given compound will provide a unique drug target to interfere with renal accumulation and nephrotoxic side effects of such therapeutic drugs. Beside nephrotoxicity also the pathway of megalin's physiological ligands like insulin, transthyretin, carriers for lipophilic vitamins, the vitamin D-binding protein and the retino-binding protein can be investigated with this animal model.

Commercial Opportunity

Breeding pairs available under Tangible Property Licence Agreement. (MDC holds a licence to dispose animal models generated with the Cre-Lox Technology worldwide except the US.)

Further Reading

- Leheste et al., 2003, FASEB, 17, 247-249.
- Schmitz et al., 2002, J. Biol. Chem., 277, 618-622.