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Transgenic Animal Model for Proteinuria and Lysosomal Storage Diseases

The present invention relates to methods for determining the nephrotoxicity or nephron-protective effect of small compounds in a new and innovative transgenic zebrafish model organism. This transgenic zebrafish larvae is the first model organism suitable for high-throughput screening. The methods comprise steps for administration of compounds to larvae expressing a fluorescent fusion protein secreted into the bloodstream, and subsequently detecting the fusion protein in both kidney and/or urine.

Keywords kidney, nephrotoxicity, zebrafish, high throughput screening, model organism, 3R

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Reference **Published Article**: Zhiyong Chen et al., Transgenic zebrafish modeling low-molecular-weight proteinuria and lysosomal storage diseases, kidney international, volume 97, issue 6, P1150-1163, june 01, 2020
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Background The proximal tubule (PT) of the kidney plays a key role in whole body homeostasis, via the reabsorption and processing of a large amount of filtered solutes, including low molecular weight (LMW) proteins, drugs and toxins via apical receptor-mediated endocytosis. This pathway is particularly developed in PT cells, ensuring that the human urine is virtually devoid of plasma proteins under physiological conditions. Detecting the specific loss of LMW proteins in the urine is the most consistent and sensitive indicator of kidney PT dysfunction of genetic and toxic origin. The standard assessment of kidney PT function relies on the visualization of the uptake of injected LMW fluorescent tracers, which is a very labor-intensive method, thus not amenable for high-throughput screens.

Invention This invention consist of the creation of a transgenic zebrafish model organism for LMW proteinuria and lysosomal storage diseases and the description of related analytical methods. In this transgenic reporter line, an LMW fluorescent protein-tagged vitamin D binding protein (for instance, ½vdbp-mCherry) is produced by hepatocytes and released into the bloodstream, filtered through the glomerulus and is entirely reabsorbed by PT cells via megalin-mediated endocytosis. The fluorescence intensity in epithelial cells, or urinary levels of fusion protein are quantified to assess the kidney PT function. This is the first model organism suitable for high-throughput screening.

Fields of Use The zebrafish line and analytic methods are suitable for large-scale screens on the kidney PT function using 96-wells plates, relevant for determining the potential nephrotoxicity of chemicals or nephron-protective effect of a molecule in chemical screening for acute/chronic kidney injury and human rare diseases with kidney involvement.

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