

CRT Licensing Opportunity



Mouse Model for Drug Metabolism Studies

- Hepatospecific cytochrome b5 knockout mouse model
- Model to examine the role of cytochrome b₅ in drug metabolism and disposition
- Significant reduction of drug metabolism on loss of cytochrome b₅ in the liver
- To study drug efficacy and toxicity in absence of cytochrome b₅ metabolic component

ENABLING TECHNOLOGY

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Inventors

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The Mouse Models

In vivo preclinical studies seek to demonstrate the efficacy of potential drugs and characterise their bioavailability, toxicity and metabolism. One of the key factors in determining the bioavailability and toxicity of a drug is metabolism by the liver associated cytochrome enzymes. As such, models in which specific metabolism associated cytochrome enzymes are selectively deleted provide key tools for preclinical drug development.

Cytochrome b₅ is an electron transfer component in a number of oxidative reactions in biological tissues. These include anabolic metabolism of fats and steroids as well as catabolism of xenobiotics and compounds of endogenous metabolism [1]. Cytochrome b₅ has been shown to be an electron transport hemoprotein for cytochrome P450 and therefore plays an important role in P450 associated drug metabolism [2].

The inventors have developed a mouse model in which cytochrome b₅ has been deleted in the liver (Hepatic cytochrome b₅ Null (HBN) mouse). The loss of hepatic cytochrome b₅ results in a significant reduction of drug metabolism. Metabolism of all cytochrome P450 probe drugs tested (chlorozoxane, metoprolol, midazolam, tolbutamide and phenacetin) was significantly reduced (30-80% reduction) [3]. Circulating levels of the drugs post intravenous delivery

were consistently increased and their clearance was consistently decreased in HBN mice compared to wild-type mice.

Application

Mouse models in which key metabolism enzymes are deleted can provide valuable models for assessing drug metabolism and toxicity at early stage in the drug development process [4]. In addition, valuable information can be obtained on the tested compound relating to its contribution to efficacy and toxicity versus its metabolites.

This mouse model also represents a key tool for studying cytochrome b₅ mediated metabolism in *in vivo* preclinical drug development. Liver cells extracted from the mouse (hepatic microsomes) can also be used to test new drugs *in vitro*.

Intellectual Property

CRT has filed a WO 2009/106882 patent application to protect the mouse model.

Commercial Exploitation

The Hepatic cytochrome b₅ Null mouse and the associated patent application are available for non-exclusive licensing.

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References

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3. Finn R.D., McLaughlin L.A., Ronseaux S., Rosewell I., Henderson C.J. and Wolf C.R.. Unpublished Data (under review)
4. Pass, G.J. *et al.*, Cancer Research 2005 **65**:4211-4217.

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