

What is claimed is:

1. A method for preparing a chimeric non-human animal comprising human hepatocytes, the method comprising:
 - (a) providing a Rag^{-/-} IL-2Rg^{-/-} non-human animal comprising a reduction or deletion of NADPH-P450 oxidoreductase (*Por*) gene resulting in reduced or absent expression of *Por* protein; and
 - (b) transplanting human hepatocytes into the non-human animal.
2. The method of claim 1, wherein the reduced or deleted *Por* gene is a conditional knockdown or knockout of the *Por* gene or is the result of a mutation, a transgene, treatment with an exogenous substance or somatic genome engineering.
3. The method of claim 2, wherein the somatic genome engineering comprises Guide RNA (gRNA) and Cas 9.
4. The method of claim 1 or 2, wherein the non-human animal comprises a floxed allele of the *Por* gene, and wherein the non-human animal is provided with a Cre recombinase sufficient to produce a conditional knockout of the *Por* gene.
5. The method of claim 4, wherein the non-human animal comprising the floxed allele of the *Por* gene is provided with at least a first dose of a virus that encodes Cre recombinase.
6. The method of claim 5, wherein the non-human animal is provided with at least a second dose of a virus that encodes Cre recombinase.
7. The method of any one of claims 1 to 6, comprising:
 - (a) providing a non-human animal comprising a floxed allele of the *Por* gene with a first dose of a virus that encodes Cre recombinase;
 - (b) transplanting human hepatocytes into the non-human animal; and
 - (c) providing the non-human animal with a second dose of a virus that encodes Cre

recombinase.

8. The method of claim 7, wherein steps (a) and (b) occur sequentially or simultaneously.

9. The method of any one of claims 4 to 8, wherein the non-human animal comprising the floxed allele of the *Por* gene is crossed with a transgenic non-human animal strain expressing Cre recombinase.

10. The method of any one of claims 1 to 9, wherein the non-human animal further comprises a reduction or deletion of at least one additional gene encoding an enzyme involved in drug metabolism.

11. The method of claim 10, wherein the at least one additional enzyme is a phase II drug enzyme.

12. The method of any one of claims 1 to 11, wherein the non-human animal further comprises a reduction or deletion of UDP-glucose 6-dehydrogenase (UGDH) gene or Glutathione synthetase (GSS) gene.

13. The method of any one of claims 1 to 12, wherein the non-human animal is selected from the group consisting of (i) a *Fah*^{-/-} non-human animal, (ii) a transgenic urokinase type plasminogen activator (uPA) non-human animal, which overexpress uPA under an inducible promoter, preferably a liver-restricted albumin promoter, (iii) the thymidine kinase-NOD/Shi-*scid*/IL-2R^γ null (TK-NOG) non-human animal, which is a immunodeficient NOG non-human animal with transgenic expression of thymidine kinase under control of liver-restricted promoter, (iv) a non-human animal expressing an inducible Caspase 8 in the liver, and (v) a non-human animal expressing an inducible Caspase 9 in the liver.

14. ~~A chimeric non human animal, or a portion thereof, which has a chimeric liver comprising human hepatocytes, prepared by the method according to any one of claims 1 to 13.~~

~~15. — The method of any one of claims 1 to 13 or the chimeric non-human animal of claim 14, wherein the non-human animal is selected from the group consisting of primate, bird, mouse, rat, fowl, dog, cat, cow, horse, goat, camel, sheep and pig.~~

~~16. — The method of any one of claims 1 to 13 or the chimeric non-human animal of claim 14, wherein the non-human animal is a mouse.~~

~~17. — The chimeric non-human animal of any one of claims 14 to 16, wherein human hepatocytes account for at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95% or at least 99% of all hepatocytes in the chimeric liver.~~

~~18. — The chimeric non-human animal of any one of claims 14 to 17, wherein the chimeric non-human animal is immunodeficient.~~

~~19. — A method for screening for a substance that affects human liver functions, comprising:
—— (a) administering a test substance to the chimeric non-human animal of any one of claims 14 to 18;
—— (b) measuring one or more values in the chimeric non-human animal to which the test substance is administered in (a); and
—— (c) selecting a test substance that causes an increase or decrease in one or more values measured in (b), compared with the one or more values measured in a chimeric non-human animal to which no test substance is administered.~~

~~20. — The method of claim 19, wherein the one or more values is selected from the group consisting of a metabolite of the test substance, human albumin concentration, body weight curve, liver weight to body weight ratio, total albumin level, total protein level, Alanine Aminotransferase (ALT) level, Aspartate Aminotransferase (AST) level, and total bilirubin level, creatinine, Blood Urea Nitrogen (BUN), troponine, blood count, TSH and histological assessment for pathologies in the human and non-human organs.~~

~~21. A method for evaluating the toxicity of a test substance against human hepatocytes and any other non-human organ in the non-human chimeric animal, comprising:~~

~~—— (a) administering a test substance to the chimeric non-human animal of any one of claims 14 to 18;~~

~~—— (b) measuring one or more indicators in the chimeric non-human animal to which the test substance is administered in (a); and~~

~~—— (c) evaluating the effect of the test substance on human hepatocytes using, one or more indicators measured in (b), compared with the one or more indicators measured in a chimeric non-human animal to which no test substance is administered.~~

~~22. The method of claim 21, wherein the one or more indicators is selected from the group consisting of an increase or a decrease in any one or more of a metabolite of the test substance, human albumin concentration, body weight curve, liver weight to body weight ratio, total albumin level, total protein level, ALT level, AST level, and total bilirubin level, creatinine, BUN, troponine, blood count and TSH as well as histological alterations including but not limited to necrosis and apoptosis in the human and non-human organs.~~

~~23~~14. A non-human chimeric animal or a portion thereof, comprising human hepatocytes, wherein the non-human animal is a Rag-/- IL-2Rg-/- non-human animal that has a chimeric liver comprising a reduction or deletion of NADPH-P450 oxidoreductase (*Por*) gene resulting in reduced or absent expression of *Por* protein.

~~24~~15. The non-human chimeric animal or portion thereof, of claim ~~23~~14, wherein the non-human animal is selected from the group consisting of primate, bird, mouse, rat, fowl, dog, cat, cow, horse, goat, camel, sheep and pig.

~~25~~16. The non-human chimeric animal or portion thereof, of claim ~~23~~14, wherein the non-human animal is a mouse.