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Investigating the use of *Xenopus* embryos as a non-mammalian pre-clinical screening tool for the prediction of drug-induced toxicity

Efficient identification of lead compounds that are safe and efficacious is an important aim for the pharmaceutical industry. In order to reduce attrition rates and the associated costs during the clinical phase of drug development, it is increasingly beneficial for pharmaceutical companies to perform drug-safety assessments at the early stages of the drug discovery and development process. *In vitro* pharmacological profiling is used is identify hazards, aid lead compound selection and predict safety margins for preclinical and clinical phases. We hypothesise *Xenopus* embryos can assist *in vitro* drug safety assessment in the early phases of drug development before moving into expensive preclinical trials in mice.

Xenopus are easy to house, the embryos can be obtained in large numbers following hormone stimulation and they are amenable for medium to high throughput small molecule screens. The embryos can develop quickly once collected, depending on the temperature at which they are kept. Drug-induced toxicity can be assessed in larvae prior to coverage by the Animal Scientific Procedures Act, and only a small amount of the compound to be tested would be required.

Drugs that have known organ-specific toxicity phenotypes were tested with *Xenopus laevis* embryos. No obvious morphological change was observed when the embryos were treated with drugs associated with hepatotoxicity, cardiotoxicity and nephrotoxicity phenotypes that have been previously established and observed in humans. However, our results suggest the embryos do share some fundamental metabolic properties with humans for paracetamol-induced liver injury. Paracetamol overdose is associated with acute liver injury largely due to the combination of a reduction of glutathione (GSH) and consequently an increased amount of the reactive metabolite *N*-acetyl-p-benzoquinone imine (NAPQI). When stage 45 *Xenopus laevis* embryos were treated with paracetamol, their GSH content decreased with increasing paracetamol concentration (156.25 μM – 20 mM).

Biomarkers for drug-induced toxicity in humans could be used in *Xenopus laevis*. MicroRNA-122 (miR-122) is a promising biomarker for drug-induced liver injury in humans. MiR-122 is abundant in the human liver and we have used a whole mount in situ hybridisation (WISH) LNA probe for miR-122 to label the hepatocytes in *Xenopus* embryos. For future experiments, we plan to use qPCR to determine if there is a change in the expression of miR-122 in paracetamol-treated *Xenopus* embryos that is similar to the change observed in human paracetamol-induced hepatotoxicity.

In conclusion, we are developing the *Xenopus* embryos as a potential *in vivo* model for preclinical drug safety assessment which could be used along side *in vitro* assays.