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Genetically modifying zebrafish for detection of harmful compounds in drug candidates

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The common zebrafish is a useful proxy for testing whether drug candidates cause organ damage. Now, researchers in Singapore have created two modified types of the fish, one that glows when experiencing toxicity, and another that metabolizes drugs in a similar way to humans. Combined, these may help pharmaceutical companies develop less toxic therapeutics.

"Roche, our partner in the study, want a way to quickly identify which of their drugs may be damaging to the liver," says Tom Carney from the A*STAR Institute of Molecular and Cell Biology.

Zebrafish and humans, despite being very different species, experience toxicity from similar drugs, making them a great model. Carney's team monitored the fish to identify what genes are 'switched on' when they were dosed with a range of drugs known to be damaging to liver cells, or 'hepatotoxic', and identified four common genetic sequences that produced enzymes to neutralize the drugs. "The fish are trying to clear the drugs out, and are doing so by using a detoxification process of which these genes are parts," explains Carney.

With this knowledge, the team produced a breed of modified zebrafish that expressed a fluorescent protein when these genes were switched on, creating fish that glow in response to liver-damaging drugs.

In practice, the fish could offer an easy way for pharmaceutical companies to remove harmful drugs from their pipeline before

superfluous R&D expenditure.

Despite zebrafish and humans sharing similar detoxification pathways, the detoxifying enzymes differ between the species and therefore drugs can be metabolized differently. Addressing this, the scientists produced a second line of zebrafish in which the liver was supplemented with a key human liver enzyme. The result was the first demonstration of a 'humanized' zebrafish model that detoxified drugs in a much more similar way to humans. This is especially important considering that drug metabolites can be more damaging than the originally ingested medication—as is the case with the common painkiller, paracetamol.

These models offer a promising line of inquiry into a drug testing technique that is scalable, affordable, and allows for high-throughput screening. In the future, Carney's team may combine their two models in order to create a line of zebrafish that accurately metabolizes toxic medications and provides an immediate, visible signal for drugs that may harm patients.

More information: Kar Lai Poon et al. Transgenic Zebrafish Reporter Lines as AlternativeIn VivoOrgan Toxicity Models, *Toxicological Sciences* (2016). DOI: 10.1093/toxsci/kfw250

Kar Lai Poon et al. Humanizing the zebrafish liver shifts drug metabolic profiles and improves pharmacokinetics of CYP3A4 substrates, *Archives of Toxicology* (2016). DOI: 10.1007/s00204-016-1789-5

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