Drug-induced liver injury: prediction using cellular imaging

Purpose

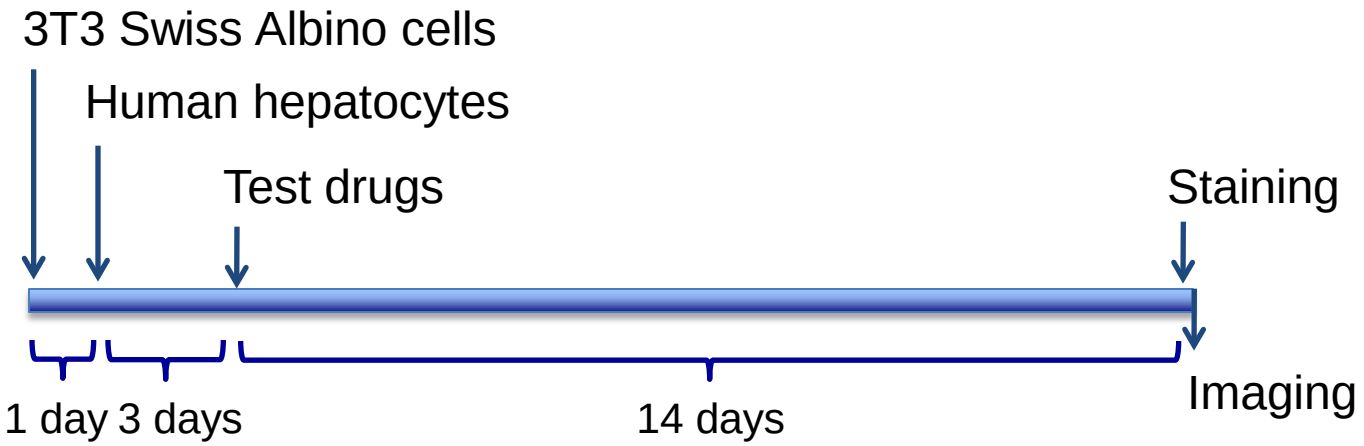
To clarify if long time (14 days) treatment of drugs in a functionally stable human hepatocyte co-culture on Cell-able® increase the predictive performance for clinical drug-induced liver injury (DILI) over that of the short time (24 hours) treatment [a].

[a] Xu, et al., 2008

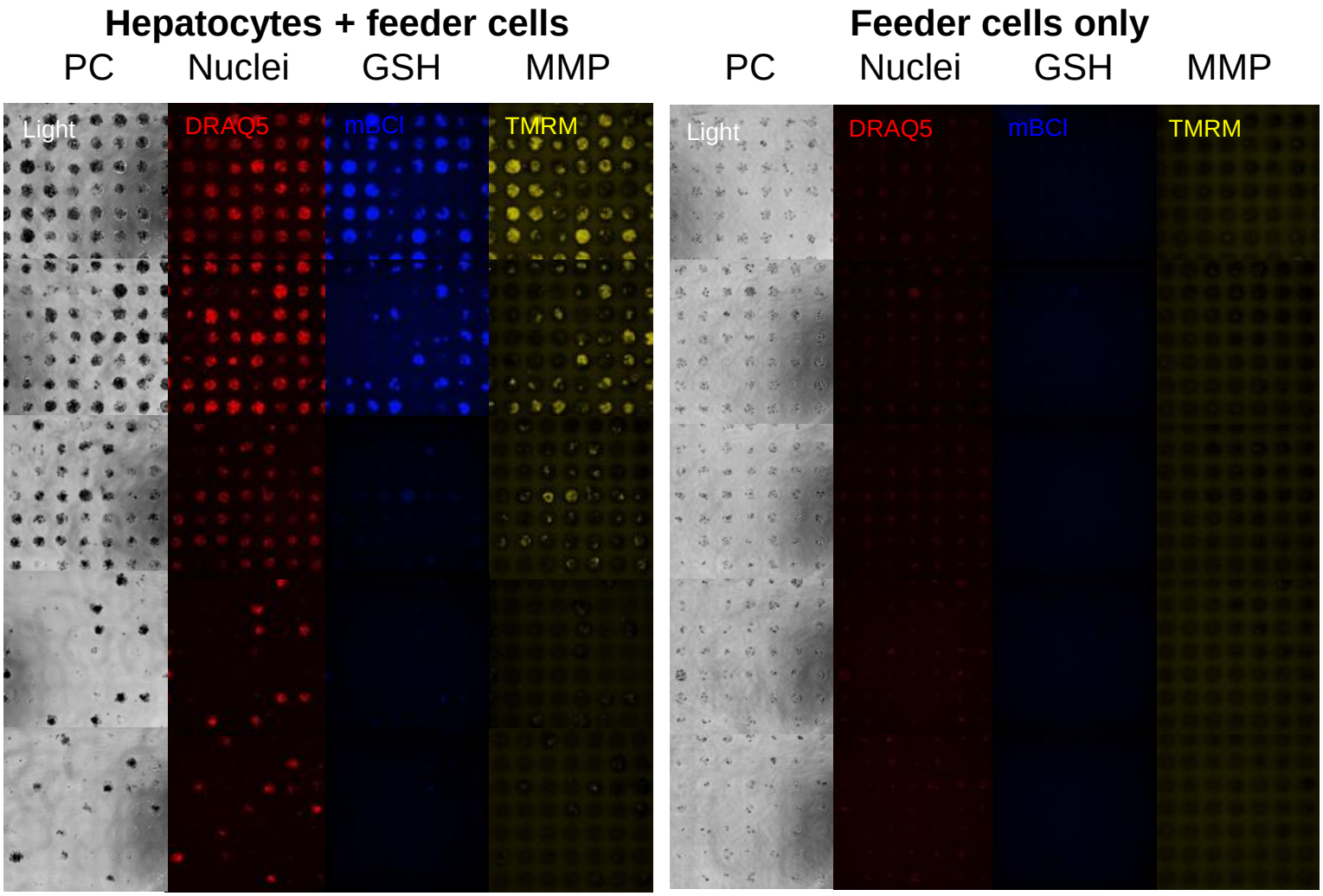
DILI imaging of hepatocytes cultured on Cell-able®

Protocol

1. 3T3 Swiss Albino cells ($8x10^3$ cells/well) were seeded as feeder cells on Cell-able® (96-well plates).
2. The next day, human hepatocytes ($2x10^4$ cells/well) were seeded.
3. Three days later, vehicle or test drugs (1-60*Cmax) were treated.
4. The hepatocytes were maintained for 14 days. The medium was replaced by the new medium containing vehicle or test drugs three times a week.
5. The cells were stained with DRAQ5® for nuclei, monochlorobimane (mBCl) for GSH, tetramethylrhodamine methyl ester (TMRM) for mitochondrial membrane potential (MMP).
6. The cells were taken images by ImageXpress MICRO.



Acetaminophen-induced hepatocyte injury cultured on Cell-able®



The cells were exposed to acetaminophen for 14 days.

Summary of sensitivity and specificity in terms of prediction of clinical DILI

- Human hepatocyte co-culture on Cell-able® maintained the liver functions, such as CYPs activities and albumin secretion for 54 days.
- The imaged GSH and MMP were sensitive parameters for DILI.
- The functionally stable hepatocyte co-culture on Cell-able® enabled the long time (14 days) exposure of drugs to hepatocytes, which conferred high predictive performance for clinical DILI.
- In this study, the sensitivity was about two-times higher than that in the previous report (Xu, 2008) in terms of prediction of clinical DILI.

	TRP, 2013	Xu, 2008
Clinical DILI		
Sensitivity	77% (10/13)	38% (5/13)
Specificity	100% (5/5)	100% (5/5)
Clinical DILI + LTKB		
Sensitivity	90% (9/10)	50% (5/10)
Specificity	88% (7/8)	100% (8/8)

Sensitivity: predicted positive/positive in clinical DILI, specificity: predicted negative/negative in clinical DILI