

Stem cell-based 3D liver models for Biomedical and Toxicological research

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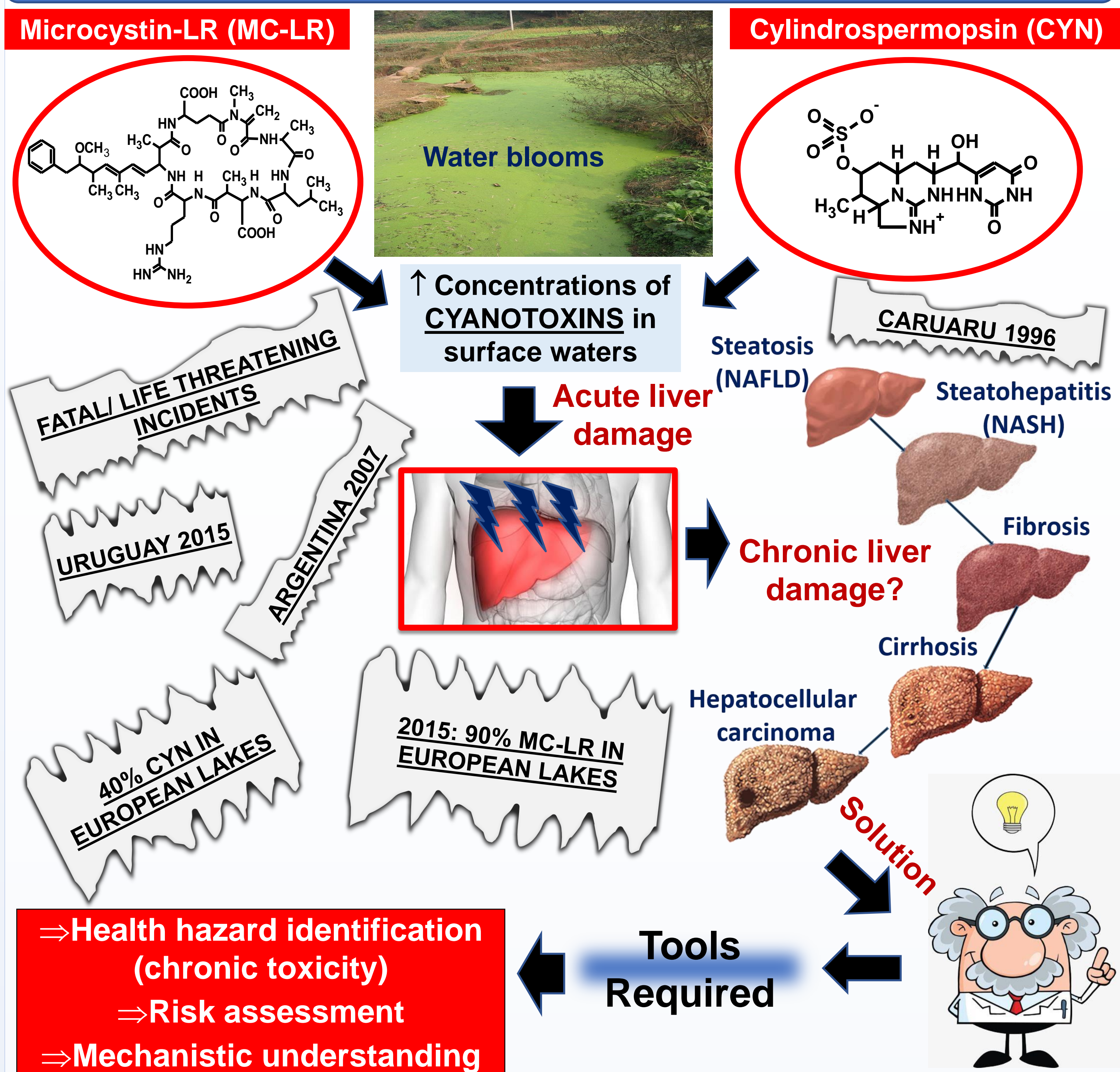
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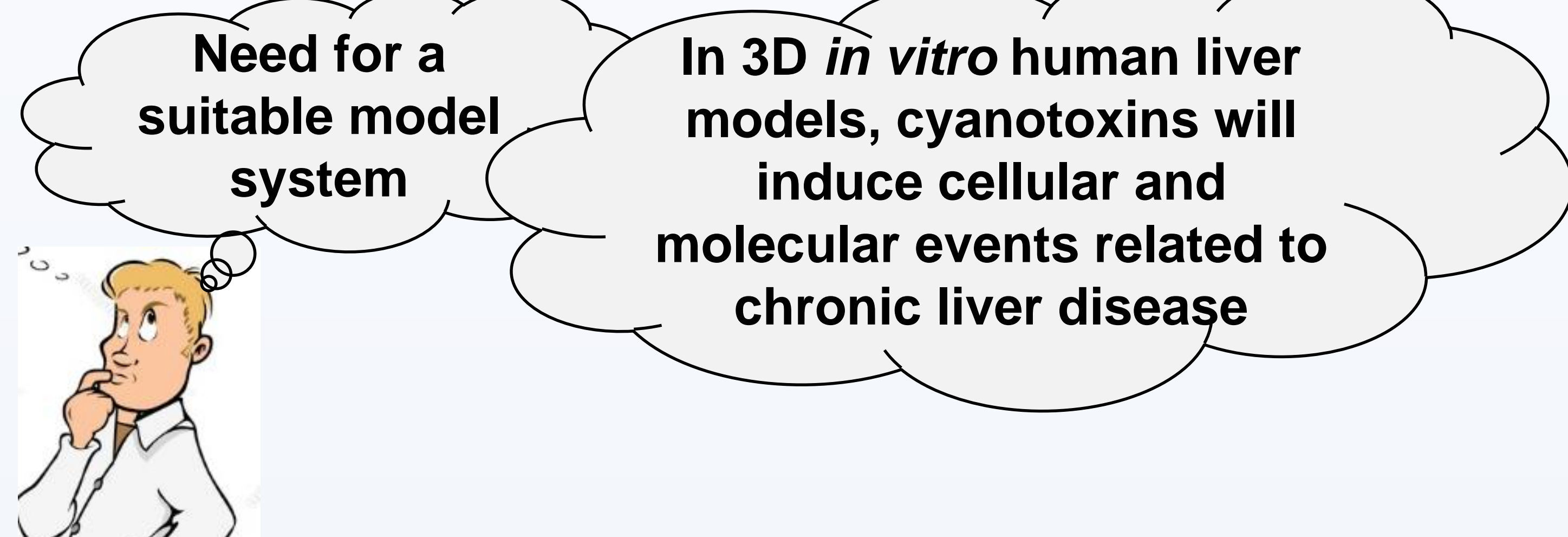
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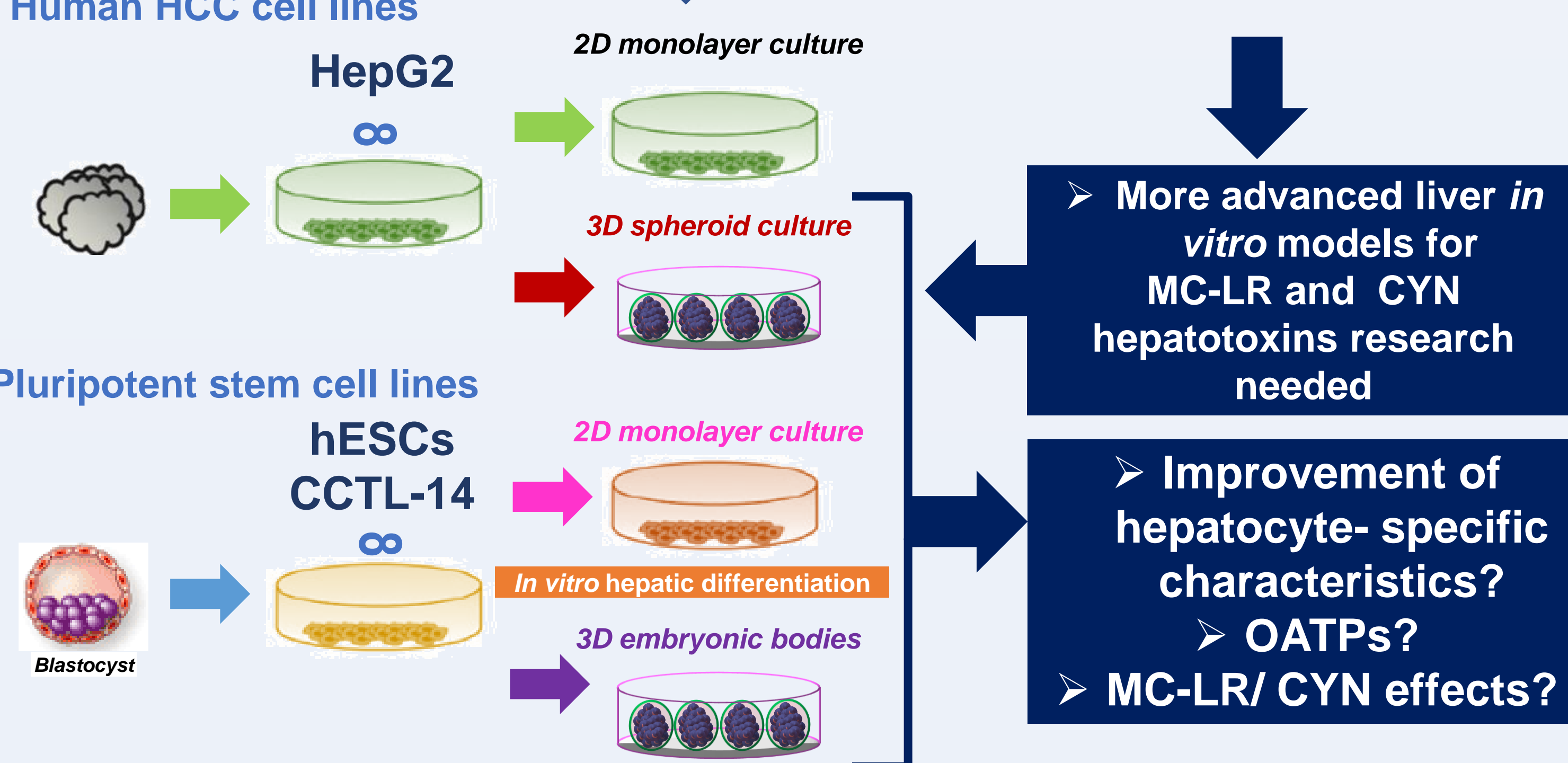
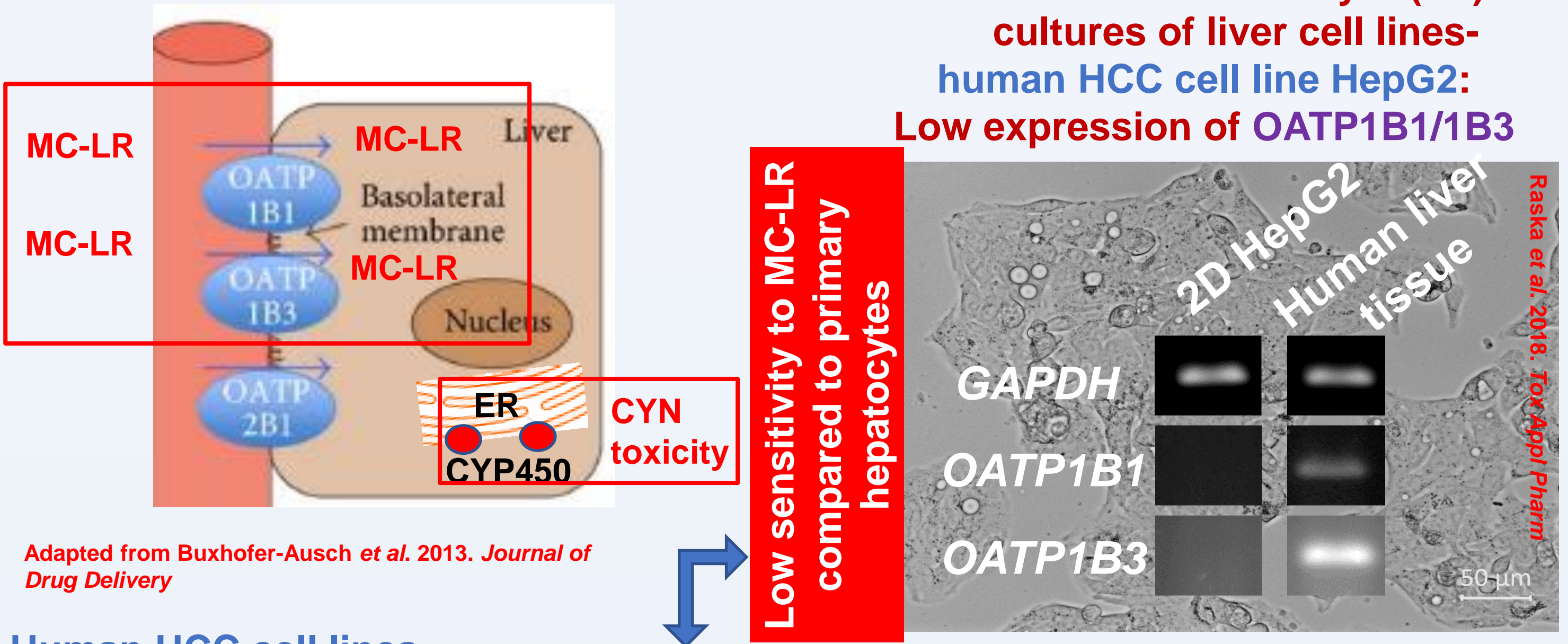
BACKGROUND



HYPOTHESIS AND OBJECTIVES

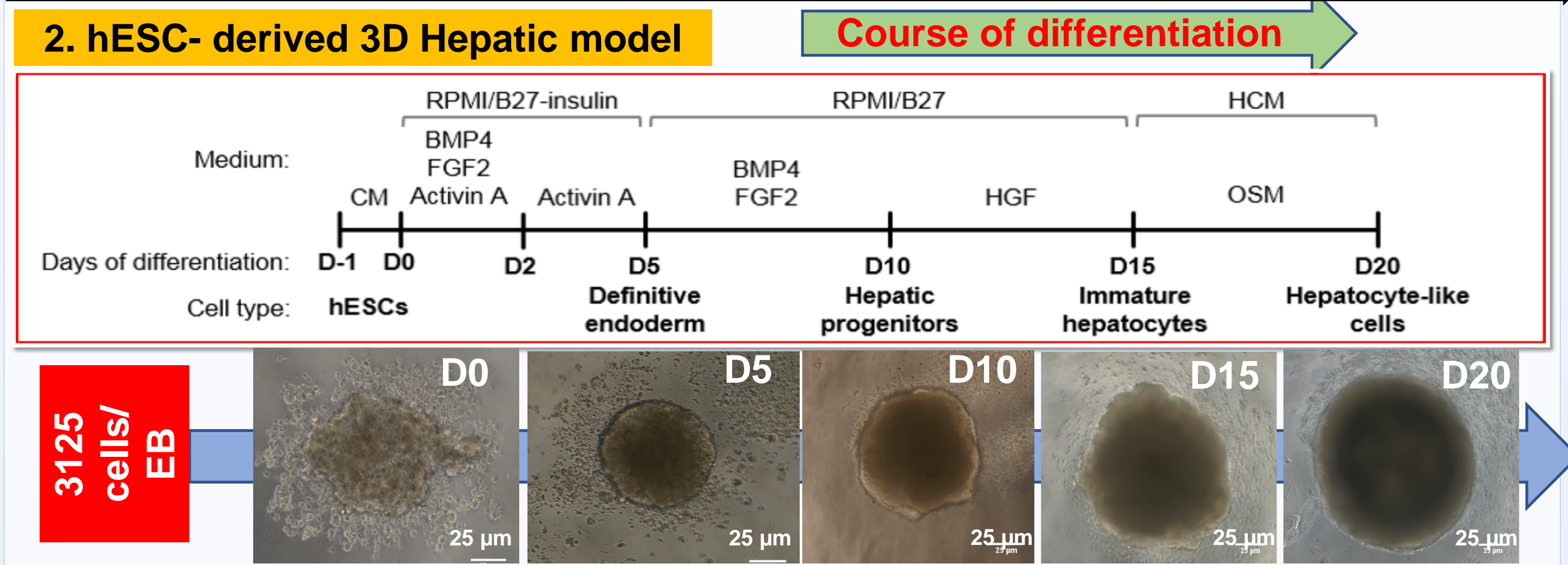
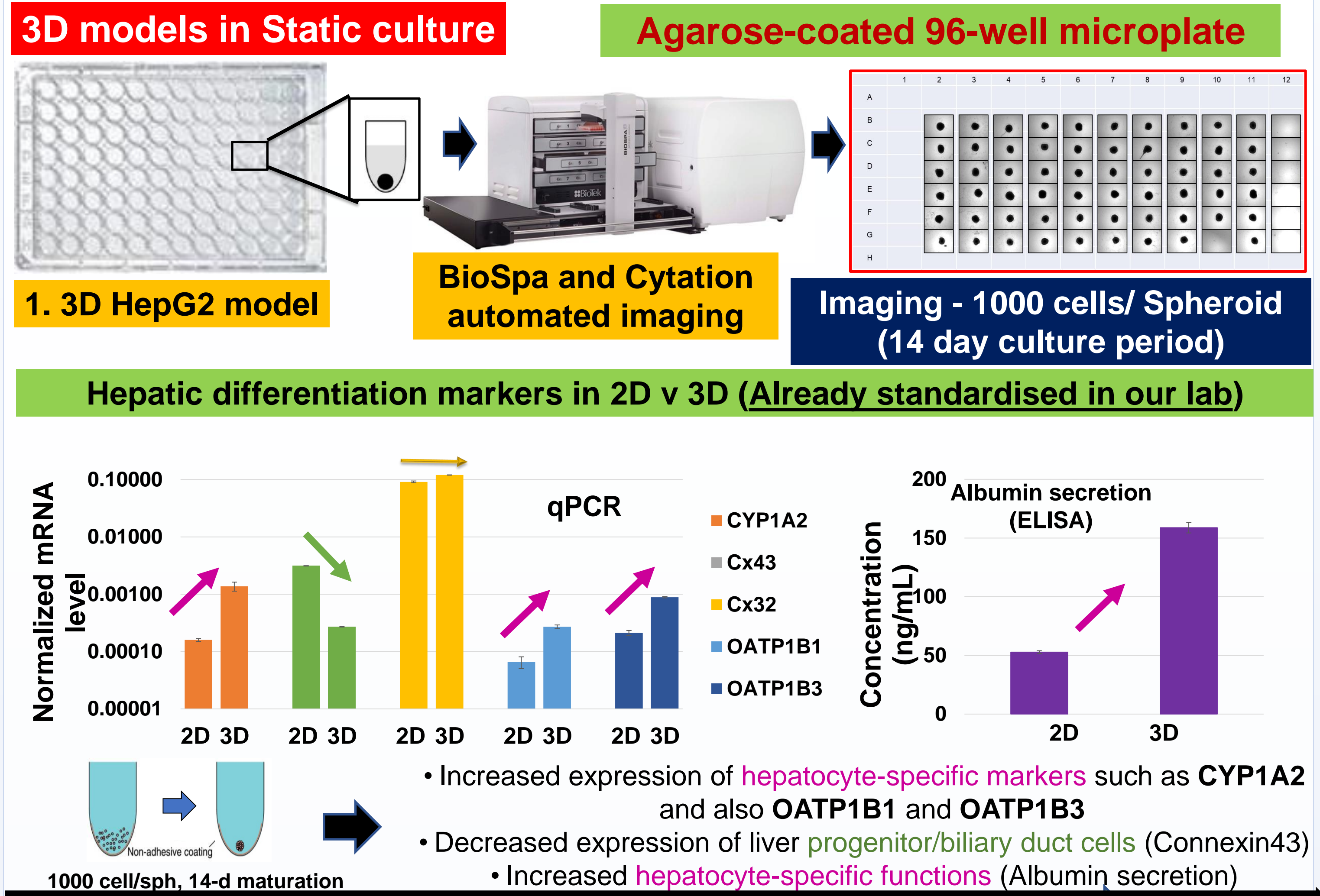


- MC-LR hepatotoxicity depends on cellular uptake by organic anion transporting polypeptides OATP1B1/1B3
- CYN hepatotoxicity depends on Cytochrome P450 (CYP450) induction and bioactivation
- Traditional monolayer (2D) cultures of liver cell lines - human HCC cell line HepG2: Low expression of OATP1B1/1B3

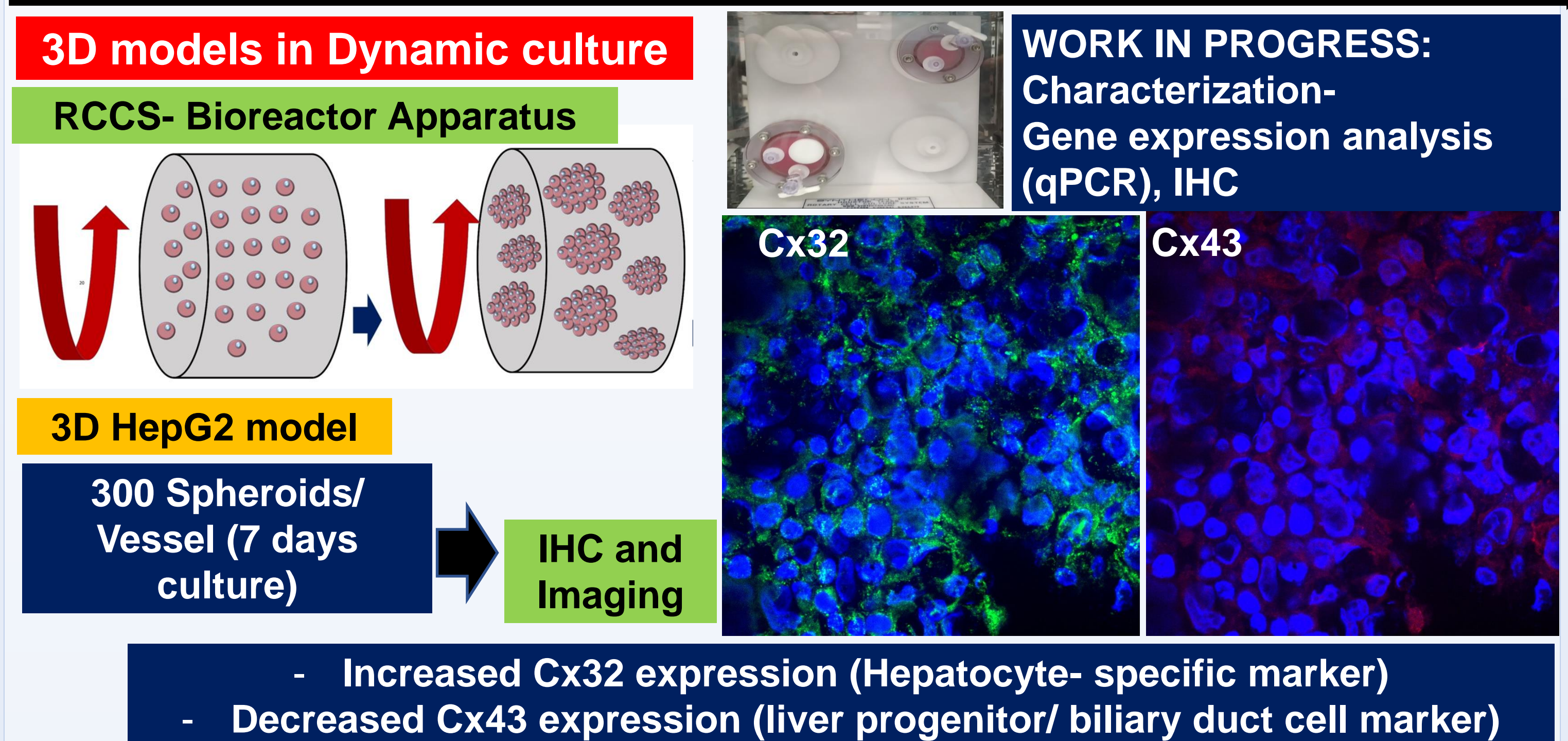


EXPERIMENTAL DESIGN (PLANNED METHODS) W/ RESULTS

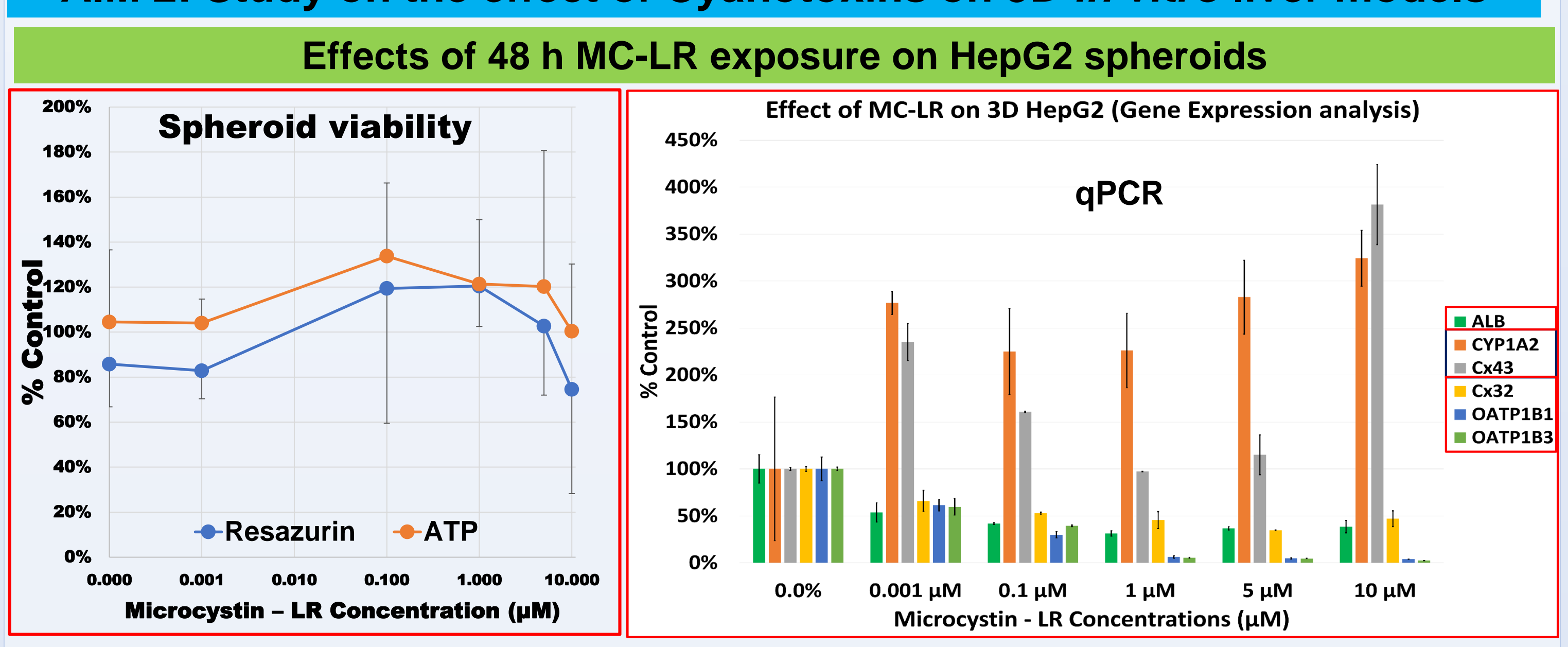
AIM 1: Generation and Characterization of 3D *in vitro* liver models



WORK IN PROGRESS: Characterization- Gene expression analysis (qPCR), IHC, ALB release, LDH release



AIM 2: Study on the effect of Cyanotoxins on 3D *in vitro* liver models



- No strong cytotoxicity up to 10µM (MC-LR ≥1 nM)
 - Decreased expression of Albumin (ALB), ↓ Cx32 and genes involved in MC-LR cellular uptake OATP1B1 and OATP1B3
 - Increased expression of Cx43 and CYP1A2
- Selective elimination of OATP+ cells from the cell population to favour Cx43+ progenitor cells?
- Disruption of liver tissue homeostasis
 - Contribution to the development of chronic liver toxicity and disease?

Differentiation stage-specific toxicity (MC-LR, CYN) and lipid accumulation in hESC-derived 3D Hepatospheroids

MC-LR, CYN toxicity effects in 3D HepG2 (Static and Bioreactor cultures) with different exposure timings

Endpoints to be evaluated:

- Lipid accumulation
- Cell viability assays, ALB & LDH release
- Steatosis gene expression
- Genes for disturbed differentiation-hepatic markers
- Proliferation marker- Ki67
- Steatosis/ Steatohepatitis marker- Ck18

CONCLUSION - 3D advanced models show improved hepatocyte characteristics and specific responses to Cyanotoxins (further evaluated) - linked to development of NAFLD, NASH, HCC

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