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# Guest editorial:

# HIGHLIGHT REPORT: CELL TYPE SELECTION FOR TOXICITY TESTING

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An important step in *in vitro* test system development is the choice of an adequate cell line which depends on the intended application of the assay. In a recent study, Tuuli Karhu and colleagues from Helsinki University compared a set of cell lines for their susceptibility towards eight GATA4 targeting compounds (Karhu et al., 2018). GATA4 is a transcription factor involved in cardiac development (Gupta et al., 2013; Kikuchi et al., 2010; Rysä et al., 2010; Pikkarainen et al., 2004). The goal of the study was to identify which cell line allows the most sensitive cytotoxicity screening of these compounds. The tested cell lines included the myoblast cell line H9c2 established from rat myocardium; primary neonatal rat cardiac fibroblasts; mouse embryonic fibroblasts; mouse embryonic stem cells (mECSs), mouse embryonic stem cell derivatives from day 5 embryoid bodies; induced pluripotent human stem cells (hiPSC); and hiPSC-derived cardiomyocytes. The most susceptible cell lines towards the set of test compounds were hiPSC and mESC, while cardiomyocytes, fibroblasts and H9c2 cells were most resistant (Karhu et al., 2018). Of course screening for the most sensitive cell line does not guarantee that the test cells will be most relevant for the human *in vivo* situation. However, if one is interested in a cytotoxicity screening system with the highest sensitivity, the recommendation of the authors to further use hiPSC seems reasonable.

In recent years, the development of stem cell based test systems has been a major focus of research (Leist et al., 2017; Godoy et al., 2013; Krug et al., 2013). The most frequently applied strategy is to expose stem cells to test compounds, when they differentiate to more mature cell types (Shinde et al., 2017; Pallocca et al., 2016).

This approach has been used for developmental neurotoxicity (Waldmann et al., 2014; Meganathan et al., 2015; Weng et al., 2014; Rempel et al., 2015) and for cardiotoxicity (Chaudhari et al., 2016a,b; Sampaio et al., 2016) testing. While tests that analyze the influence of compounds on the differentiation process are already successfully applied, it still remains a challenge to generate mature cell types, e.g. hepatocytes that closely resemble the primary cells in an adult organ (Godoy et al., 2016, 2018). Although much progress has been achieved in stem cell based test system development, systematic analysis of human *in vivo* relevance still remains a major challenge.

## REFERENCES

Chaudhari U, Nemade H, Gaspar JA, Hescheler J, Hengstler JG, Sachinidis A. MicroRNAs as early toxicity signatures of doxorubicin in human-induced pluripotent stem cell-derived cardiomyocytes. Arch Toxicol. 2016a;90:3087-98.

Chaudhari U, Nemade H, Wagh V, Gaspar JA, Ellis JK, Srinivasan SP, et al. Identification of genomic biomarkers for anthracycline-induced cardiotoxicity in human iPSC-derived cardiomyocytes: an in vitro repeated exposure toxicity approach for safety assessment. Arch Toxicol. 2016b;90:2763-77.

Godoy P, Hewitt NJ, Albrecht U, Andersen ME, Ansari N, Bhattacharya S, et al. Recent advances in 2D and 3D in vitro systems using primary hepatocytes, alternative hepatocyte sources and non-parenchymal liver cells and their use in investigating mechanisms of hepatotoxicity, cell signaling and ADME. Arch Toxicol. 2013;87:1315-530.

Godoy P, Widera A, Schmidt-Heck W, Campos G, Meyer C, Cadenas C, et al. Gene network activity in cultivated primary hepatocytes is highly similar to diseased mammalian liver tissue. Arch Toxicol. 2016;90: 2513-29.

Godoy P, Schmidt-Heck W, Hellwig B, Nell P, Feuerborn D, Rahnenführer J, et al. Assessment of stem cell differentiation based on genome-wide expression profiles. Philos Trans R Soc Lond B Biol Sci. 2018;373 (1750).

Gupta V, Gemberling M, Karra R, Rosenfeld GE, Evans T, Poss KD. An injury-responsive gata4 program shapes the zebrafish cardiac ventricle. Curr Biol. 2013; 23:1221-7.

Karhu ST, Välimäki MJ, Jumppanen M, Kinnunen SM, Pohjolainen L, Leigh RS, et al. Stem cells are the most sensitive screening tool to identify toxicity of GATA4-targeted novel small-molecule compounds. Arch Toxicol. 2018 Jul 9. doi: 10.1007/s00204-018-2257-1. [Epub ahead of print].

Kikuchi K, Holdway JE, Werdich AA, Anderson RM, Fang Y, Egnaczyk GF, et al. Primary contribution to zebrafish heart regeneration by gata4(+) cardiomyocytes. Nature. 2010;464(7288):601-5.

Krug AK, Kolde R, Gaspar JA, Rempel E, Balmer NV, Meganathan K, et al. Human embryonic stem cell-derived test systems for developmental neurotoxicity: a transcriptomics approach. Arch Toxicol. 2013;87:123-43.

Leist M, Ghallab A, Graepel R, Marchan R, Hassan R, Bennekou SH, et al. Adverse outcome pathways: opportunities, limitations and open questions. Arch Toxicol. 2017;91:3477-505.

Meganathan K, Jagtap S, Srinivasan SP, Wagh V, Hescheler J, Hengstler J, et al. Neuronal developmental gene and miRNA signatures induced by histone deacetylase inhibitors in human embryonic stem cells. Cell Death Dis. 2015;6:e1756.

Pallocca G, Grinberg M, Henry M, Frickey T, Hengstler JG, Waldmann T, et al. Identification of transcriptome signatures and biomarkers specific for potential developmental toxicants inhibiting human neural crest cell migration. Arch Toxicol. 2016;90:159-80.

Pikkarainen S, Tokola H, Kerkelä R, Ruskoaho H. GATA transcription factors in the developing and adult heart. Cardiovasc Res. 2004;63:196-207.

Rempel E, Hoelting L, Waldmann T, Balmer NV, Schildknecht S, Grinberg M, et al. A transcriptome-based classifier to identify developmental toxicants by stem cell testing: design, validation and optimization for histone deacetylase inhibitors. Arch Toxicol. 2015; 89:1599-618.

Rysä J, Tenhunen O, Serpi R, Soini Y, Nemer M, Leskinen H, et al. GATA-4 is an angiogenic survival factor of the infarcted heart. Circ Heart Fail. 2010;3: 440-50.

Sampaio SF, Branco AF, Wojtala A, Vega-Naredo I, Wieckowski MR, Oliveira PJ. p66Shc signaling is involved in stress responses elicited by anthracycline treatment of rat cardiomyoblasts. Arch Toxicol. 2016; 90:1669-84.

Shinde V, Hoelting L, Srinivasan SP, Meisig J, Meganathan K, Jagtap S, et al. Definition of transcriptome-based indices for quantitative characterization of chemically disturbed stem cell development: introduction of the STOP-Toxukn and STOP-Toxukk tests. Arch Toxicol. 2017;91:839-64.

Waldmann T, Rempel E, Balmer NV, König A, Kolde R, Gaspar JA, et al. Design principles of concentration-dependent transcriptome deviations in drug-exposed differentiating stem cells. Chem Res Toxicol. 2014;27: 408-20.

Weng MK, Natarajan K, Scholz D, Ivanova VN, Sachinidis A, Hengstler JG, et al. Lineage-specific regulation of epigenetic modifier genes in human liver and brain. PLoS One. 2014;9(7):e102035.