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Evaluation of hepatotoxic effects of acetaminophen on HepG2 cells by parallel real-time monitoring in a multi-sensor analysis platform for automated cell-based assays

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Reviewer 1

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*Only major points from review and responses included.

Reviewer 1

The paper presents a new analysis platform which offers the possibility to perform multi-sensory analysis for assessment of drug toxicity on cellular systems.

The paper employs an established cellular model, HEPG2 and a drug known to induce hepatotoxicity to validate the multi-sensor platform analysis.

The results are clear and show the capacity of the system to address questions of cellular toxicity.

The authors could discuss more how this multi-sensor platform compares with other cellular assay platforms that are able to measure various functional and morphological cellular parameters.

Authors

Thank you for your comments, we will gladly try to better clarify this point for the reader. Since the platform in its current technical configuration is very new, there are no official comparative studies with similar products yet. However, we are striving to make comparative measurements in cooperation with Oroboros and the O2k system this year (2022) in order to get a better assessment of our measurement data.

Nevertheless, as a comparison of similar technologies, an indirect comparison with the publication of Sarah Piel "*Cell-permeable succinate prodrugs rescue mitochondrial respiration in cellular models of acute acetaminophen overdose*", which shows dose-

dependent measurements of cellular respiration of primary human hepatocytes and HepG2 under the influence of APAP, is very useful for the discussion of the current manuscript. The measurements in this publication were performed using the Oroboros O2k and Seahorse XF Flux Analyzer systems and determine an IC_{50} value of cellular respiration of 6 mM (APAP on primary hepatocytes) and 6.6 mM (APAP on HepG2), which is in a similar range to our own determination of 7.8 mM. Minor differences in these values are to be expected due to methodological differences, the limited extent of the measurements, and curve fitting within the measurement variants.

Added "Piel et al. 2020" and discussed similar results in systems with comparable measurement methods (Oxygen consumption, Oroboros O2k, Agilent XF Flux Analyzer) in chapter 3.1.

Reviewer 1

The data on acetaminophen toxicity on HEPG2 models could be discussed more including reference to other publications on the subject in addition to Thedinga et al 2007.

Authors

Gladly we do so by listing and comparing further publications with the background liver cell toxicity under APAP. Piel's work is also a good reference for this (like in the last comment), but other measurement methods should also be mentioned here.

Added "Piel et al. 2020; Zhang et al. 2015; Rumack and Matthew 1975" and discussed similar effects of APAP toxicity (EC50, IC50) measured with different methods in chapter 3.1.

Added "Yoon et al. 2016; Ramachandran et al. 2011; Hinson et al. 2010" in chapter 3.1 for more clarification of the harming effect of APAP.