Assessment of drug-induced mitochondrial toxicity on HepaRG®

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Hepatic mitochondria present the particularity to have the respiratory chain complex II more active than the complex IV, as illustrated in the histogram by hepatocytes CII/CIV ratio. The ratio of HepG2 cultured in glucose and galactose is very low while it increases in HepaRG cells. These results indicate that differenciated HepaRG cells present a better mitochondrial hepatic profile than HepG2 cells.
HepaRG: highly functional mitochondria

O₂ consumption (Clark electrode)

HepaRG mitochondria are highly functional as shown by the elevated Respiratory Control Index (RCI: state 3/state 4) after stimulation by ADP and succinate and Clark electrode monitoring. O₂ consumption slope is also sharp with MitoXpress probe (blue curve).
Case study: Amiodarone

45 min-treatment of mitochondria in 96-well plates

On HepaRG mitochondria Amiodarone induced transmembrane potential loss (EC20 = 8.6 µM) and inhibition of respiration driven by complex II (EC20 = 19.2 µM).
HepaRG cells to detect metabolites toxicity

Case study: Acetaminophen

2-days treatment of HepaRG differentiated cells
Comparison with HepG2 cell line

<table>
<thead>
<tr>
<th></th>
<th>Respiration</th>
<th>Potential</th>
<th>Viability</th>
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</thead>
<tbody>
<tr>
<td><strong>HepaRG</strong></td>
<td>64.21 µM</td>
<td>205.12</td>
<td>&gt;200</td>
</tr>
<tr>
<td><strong>HepG2 Glc</strong></td>
<td>&gt;200</td>
<td>&gt;200</td>
<td>&gt;200</td>
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<tr>
<td><strong>HepG2 Gal</strong></td>
<td>&gt;200</td>
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HepaRG cells presented sensitivity to relatively low concentrations of APAP with inhibition of respiration (EC20 = 64 µM) after 2-days of treatment while no effect was observed on HepG2 cells at these concentrations.
HepaRG cells to detect long term mitochondrial effects

Case study: ddC
A Nucleotide Reverse Transcriptase Inhibitor (antiretroviral)

12-days treatment of HepaRG differentiated cells

mtDNA depletion

Decrease of RC activity

After long term treatment of HepaRG differentiated cells ddC induced mtDNA depletion and subsequent inhibition of respiration which remained below 50%.