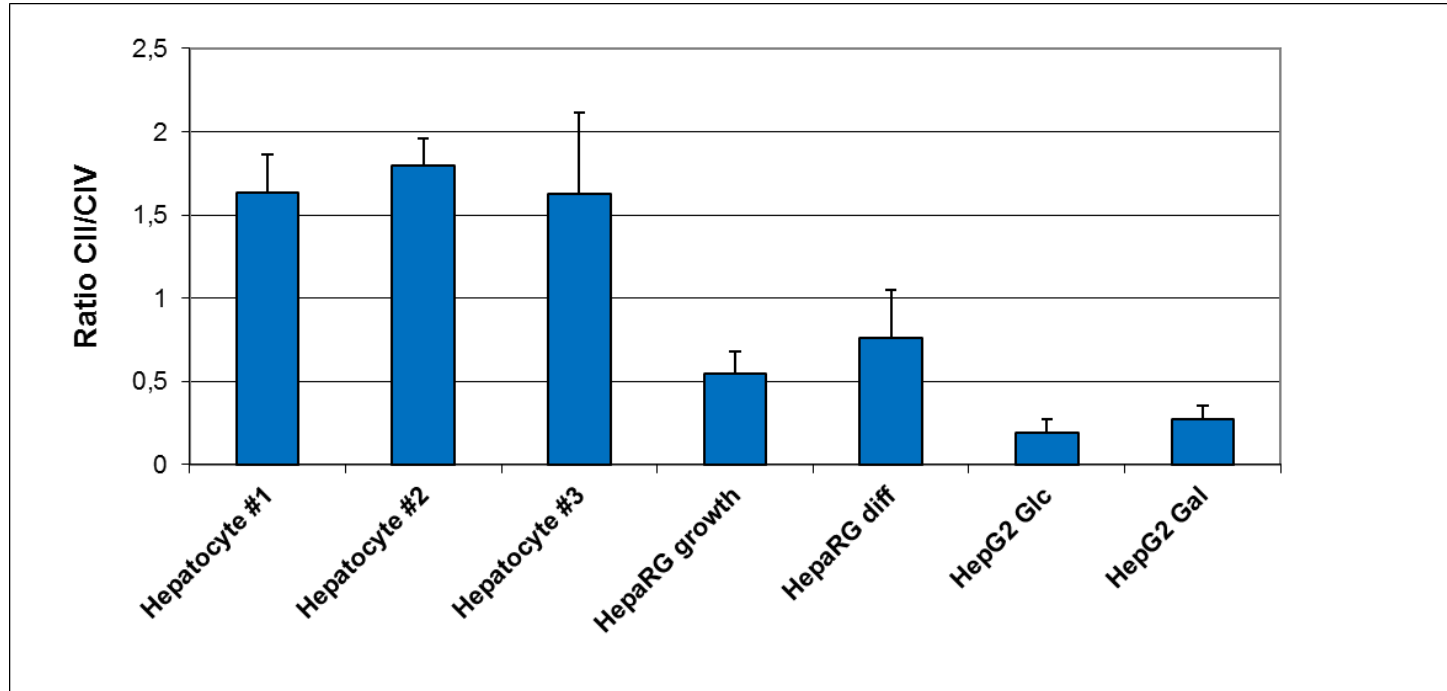


# Assessment of drug-induced mitochondrial toxicity on HepaRG®



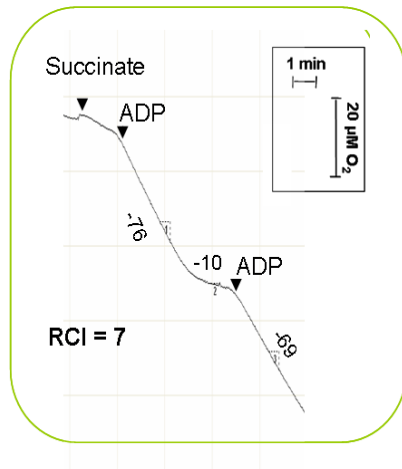
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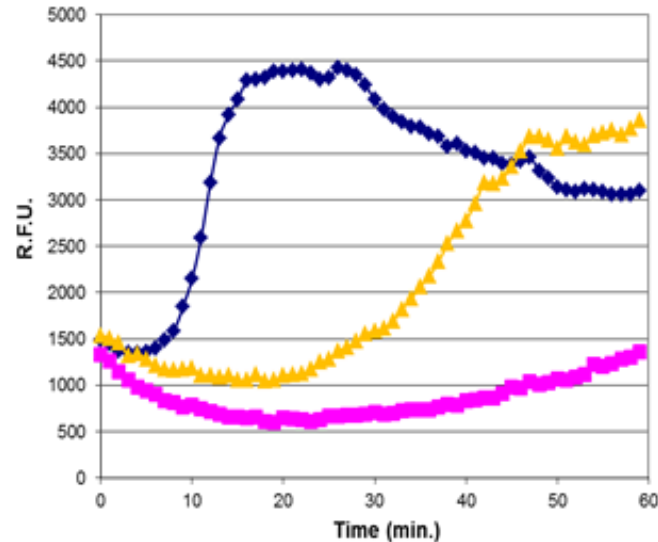
Hepatic mitochondria present the particularity to have the respiratory chain complex II more active than the complex IV, as illustrated in the histogram by hepatocytes CII/CIV ratio. The ratio of HepG2 cultured in glucose and galactose is very low while it increases in HepaRG cells. These results indicate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

## O<sub>2</sub> consumption (Clark electrode)



High respiratory control index

## O<sub>2</sub> consumption (MitoXpress probe)



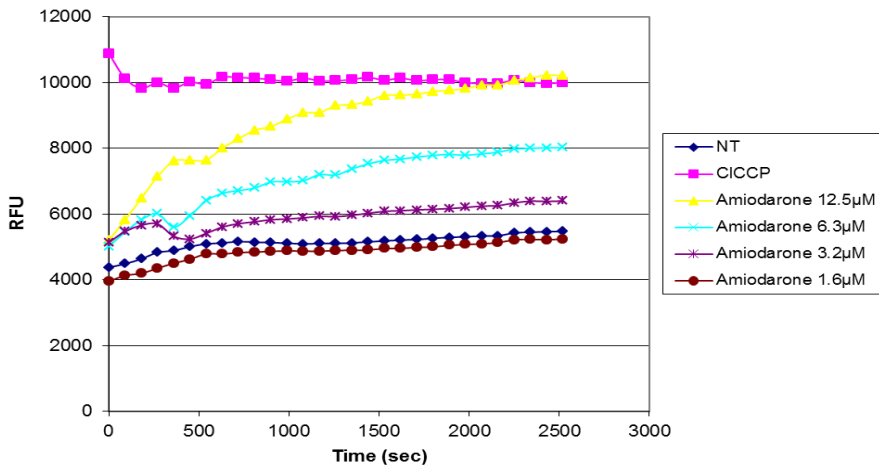
HepaRG mitochondria are highly functional as shown by the elevated Respiratory Control Index (RCI: state 3/state 4) after stimulation by ADP and succinate and Clark electrode monitoring. O<sub>2</sub> consumption slope is also sharp with MitoXpress probe (blue curve).

## Case study: Amiodarone

45 min-treatment of mitochondria in 96-well plates

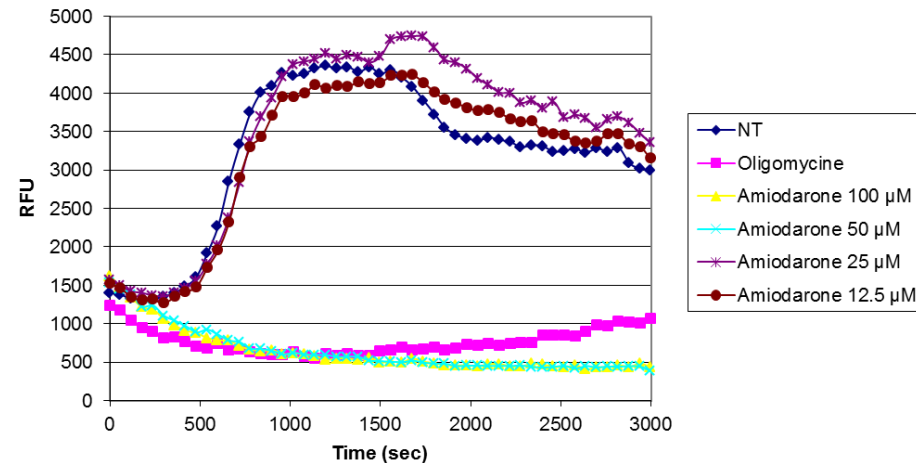
Transmembrane potential loss

Probe: Rh123



Inhibition of respiration (Complex II)

Probe: MitoXpress



On HepaRG mitochondria Amiodarone induced transmembrane potential loss ( $EC_{20} = 8,6 \mu\text{M}$ ) and inhibition of respiration driven by complex II ( $EC_{20} = 19,2 \mu\text{M}$ ).

## Case study: Acetaminophen

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

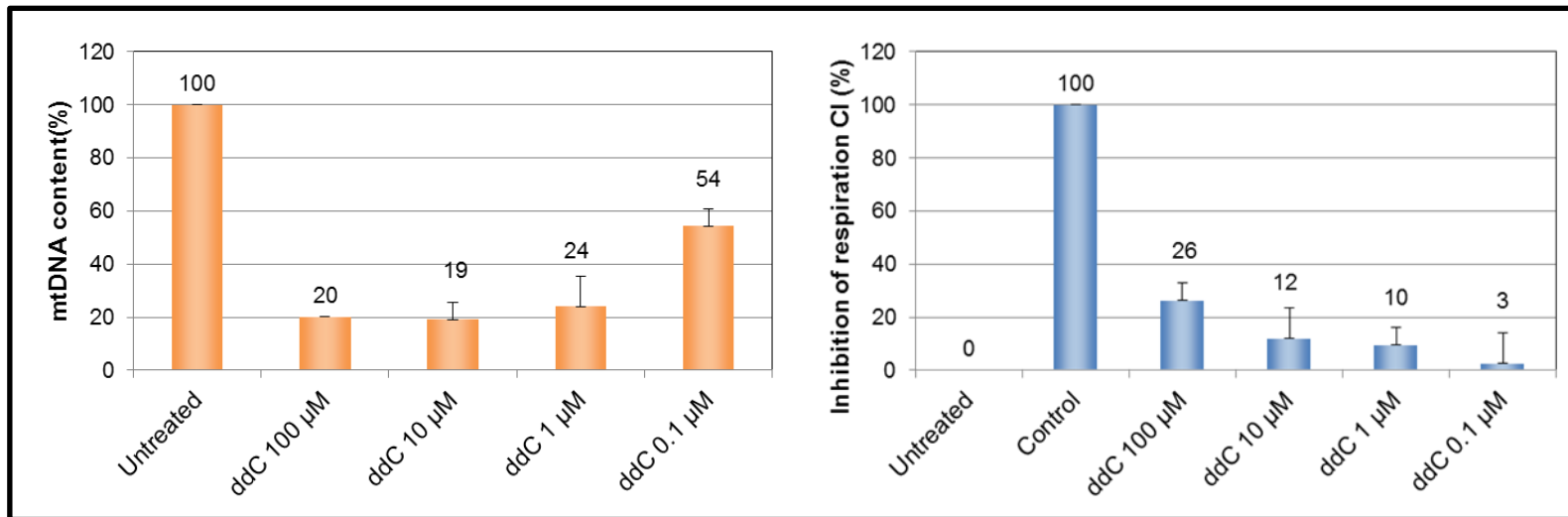
EC20 ( $\mu\text{M}$ )	Respiration	Potential	Viability
<b>HepaRG</b>	64.21	205.12	>200
<b>HepG2 Glc</b>	>200	>200	>200
<b>HepG2 Gal</b>	>200	>200	>200

HepaRG cells presented sensitivity to relatively low concentrations of APAP with inhibition of respiration (EC20 = 64  $\mu\text{M}$ ) after 2-days of treatment while no effect was observed on HepG2 cells at these concentrations.

## 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%.