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# Characterization of human iPS derived cardiomyocytes and application for cardiac toxicity assessment

**Marie-Helene Delmotte, Martin Traebert, Marianne Uteng, Ursula Mueller and Olivier Grenet**
Novartis Institute of Biomedical Research, Switzerland

**Background:** Human cardiomyocytes from induced pluripotent stem cells (iPSCs) are a promising new tool for evaluating cardiotoxicity associated with direct effects on cardiomyocytes. First, genome-wide expression profiling was performed on iPSCs. Then, compound ABC123 showing inhibition of PDE3 and PDE4 and for which major safety findings (Blood pressure drop and Heart Rate increases) were seen in mouse, rat and dog were applied to iPSCs to assess whether this compound has a direct effect on human cardiomyocytes. Cardiac hypertrophy, beating rate and calcium transient were assessed.

**Methods:** For iPSCs characterization, a kinetic assessment of iPS differentiation stages (from 1 to 4 weeks in culture) was performed and RNA and miRNA sequencing profiles were generated. Hypertrophy was assessed looking at ANP and BNP protein and RNA levels. Beating rate (using Xcelligence RTCA cardio Instrument) and $Ca2^{+}$ transient measurement were also assessed.

**Results:** Similar distribution of genes over time and culturing conditions were observed in iPSCs. In comparison to human adult heart tissue, most of the critical ion channels, receptors and second messengers are expressed in the iPSCs. Compound ABC123 induced a 20% increase in beating rate in iPSCs correlating with the *in vivo* findings observed in pre-clinical species (probably through both inhibition of PDE4 and other PDE4 independent mechanisms). ANP increase is observed at high dose (10 μM) indicative of a hypertrophy potential of the test compound. These data suggest that a possible direct effect of ABC123 on human cardiomyocytes cannot be excluded.

**Conclusion:** All together, these data show that iPSCs represent a useful tool for the in vitro assessment of potential drug effects on cardiac toxicity (hypertrophy and beating rate).

## Biography

Marie-Helene Delmotte has completed her PhD from the University of Lille, France. She is an Investigator at Novartis in Preclinical Safety, where she designs mechanistic studies to understand biology and mechanisms of toxicity across species (including human) for optimal drug discovery and development.

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