

**set**



**Stiftung zur Förderung  
der Erforschung von  
Ersatz- und  
Ergänzungsmethoden  
zur Einschränkung von  
Tierversuchen**

**Stiftung zur Förderung der Erforschung von Ersatz- und  
Ergänzungsmethoden zur Einschränkung von Tierversuchen**

Mainzer Landstraße 55, 60329 Frankfurt am Main

[www.stiftung-set.de](http://www.stiftung-set.de)

## **Completed Project**

**Pharmacological Screening using human embryonic stem cell  
derived cardiomyocytes**

Dr. Michael Reppel, Institut für Neurophysiologie, Universität Köln

June 2006 – May 2008

## ***Pharmacological Screening using human embryonic stem cell derived cardiomyocytes***

### ***Aims:***

Screening of drug safety is typically performed in diverse non-human healthy species with an intact repolarization reserve. Nevertheless, these drugs are later applied in diseased humans with a reduced repolarization reserve. It would be optimal to set up a preclinical screening tool to estimate the proarrhythmic potential of drugs in human cardiac tissue with a reduced repolarization reserve in vitro.

### ***Methods and Results:***

In our study spontaneously beating human embryonic stem cell-derived cardiomyocytes clusters (hESCM) and murine ES cell-derived cardiomyocytes (mESCMs) were plated onto micro-electrode arrays (MEAs, fig. 1) to record the extracellular field potentials (FPs) as well as effects of several antiarrhythmic drugs. In line with clinical observations the class III antiarrhythmic drugs ( $\pm$ )-sotalol, E4031 and class I antiarrhythmic drug quinidine led to a prolongation of the cardiac repolarization phase (FP duration, FP<sub>dur</sub>) and a decrease of the FP frequency. Verapamil (a class IV antiarrhythmic drug) decreased the FP frequency and shortened FP<sub>dur</sub>. Both, quinidine and verapamil, but not ( $\pm$ )-sotalol or E4031 decreased conduction velocities in hESCM clusters.

Moreover, ( $\pm$ )-sotalol exerted stronger effects on FP<sub>dur</sub> in early developmental stages of hESCMs, as proof for a reduced repolarization reserve. The EC<sub>50</sub> of the ( $\pm$ )-sotalol-induced prolongation of the FP<sub>dur</sub> was higher in mESCMs than in hESCMs implying species-dependent differences in cardiac repolarization. Likewise, the incidence of drug-induced early recurrent depolarization (ERDs) was higher in mESCMs than hESCMs. Conclusion: The combined measurement of drug effects on FP parameters in hESCMs and mESCMs serves as a reliable in vitro model for preclinical studies of drug safety.

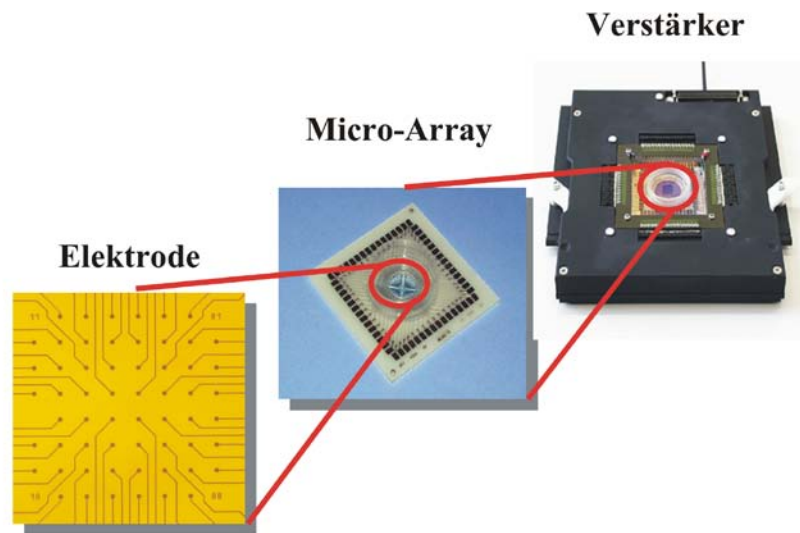


Fig. 1: MEA-Components (Multi Channel Systems, Germany): The standard substrate-integrated MEA culture dish contains 60 Titanium Nitride coated gold electrodes (30  $\mu\text{m}$  diameter) arranged in an 8x8 electrode grid with an interelectrode distance of 200  $\mu\text{m}$ , allowing simultaneous recording of extracellular FPs from all electrodes at a sampling rate of 1 to 25 kHz by the use of the MEA amplifier system.

**Publication:**

Liang H, Matzkies M, Schunkert H, Tang M, Bonnemeier H, Hescheler J, Reppel M. Human and murine embryonic stem cell-derived cardiomyocytes serve together as a valuable model for drug safety screening. *Cell Physiol Biochem.* 2010;25(4-5):459-66. Epub 2010 Mar 23.