HIGH RESOLUTION MICROSCOPY MEETS HIGH CONTENT SCREENING

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Both technologies, high resolution microscopy and high content screening, underwent a tremendous development within the past decade. To solve upcoming scientific questions it is desirable to combine the high-end microscopic technology with the throughput driven imaging based screening approaches [1]. However, due to it‘s sophisticated technology high resolution microscopy has a limited reliability and often requires time consuming off-line analysis. In contrast screening is mostly performed in multi-well plates lacking numerous requirements for high resolution microscopy.
Here we present technology to combine selected modes of high resolution microscopy and screening excitable cells.

A novel microscopy platform (more™, TILL-Photonics, Gräfelfing, Germany) with the ability to quickly switch between several imaging modes, such as wide-field imaging, TIRF, structured illumination and FRAP is combined with a recently developed 24-well plate/lid-system [2] allowing for well-based electrical field-stimulation, fast solution exchange and high resolution imaging based on oil-immersion high-NA objectives. The latter comprises a foil as a substrate, which meets the optical properties of glass coverslips, an oleophobic coating, which fosters preferential sticking of the immersion oil to the objective. Additionally, an elastic coating facing towards the lumen of the wells proofed to be advantageous for the contraction behaviour of adult cardiac myocytes. The described techniques require communication between the imaging software and the stimulation module which is offered by a real time capable software platform (arivis Grid, arivis, Rostock, Germany). This platform also integrates online communication with image-analysis software (e.g. arivis Browser and MatLab).

Here we provide example applications from the field of cardiac cellular physiology that combine high resolution imaging (spatial and temporal) with automated analysis algorithms. These studies are based on isolated cardiac myocytes from wild-type and genetically manipulated (transgenic) mice. Such an approach allows to probe for cellular responses of primary isolated cells under highly controlled and reproducible conditions.

[1] Lipp, P., and L. Kaestner. 2006. Image based high content screening – A view from basic science. In High-Throughput Screening in Drug Discovery. J. Hüser, editor. Wiley VCH, Weinheim. 129-149.
[2] Müller, O., Q. Tian, R. Zantl, V. Kahl, P. Lipp, and L. Kaestner. 2009. A system for optical high resolution screening of electrical excitable cells. *Cell Calcium*, **e-pub ahead of print**