



Research Interests

- I. The Role of Catecholamines in Cardiac Lineage Commitment
- II. Electrophysiological and pharmacological characterization of ES and iPS cell-derived cardiomyocytes

Martin Lehmann, PhD.
Institute for Neurophysiology
University of Cologne
lehmannm@uni-koeln.de



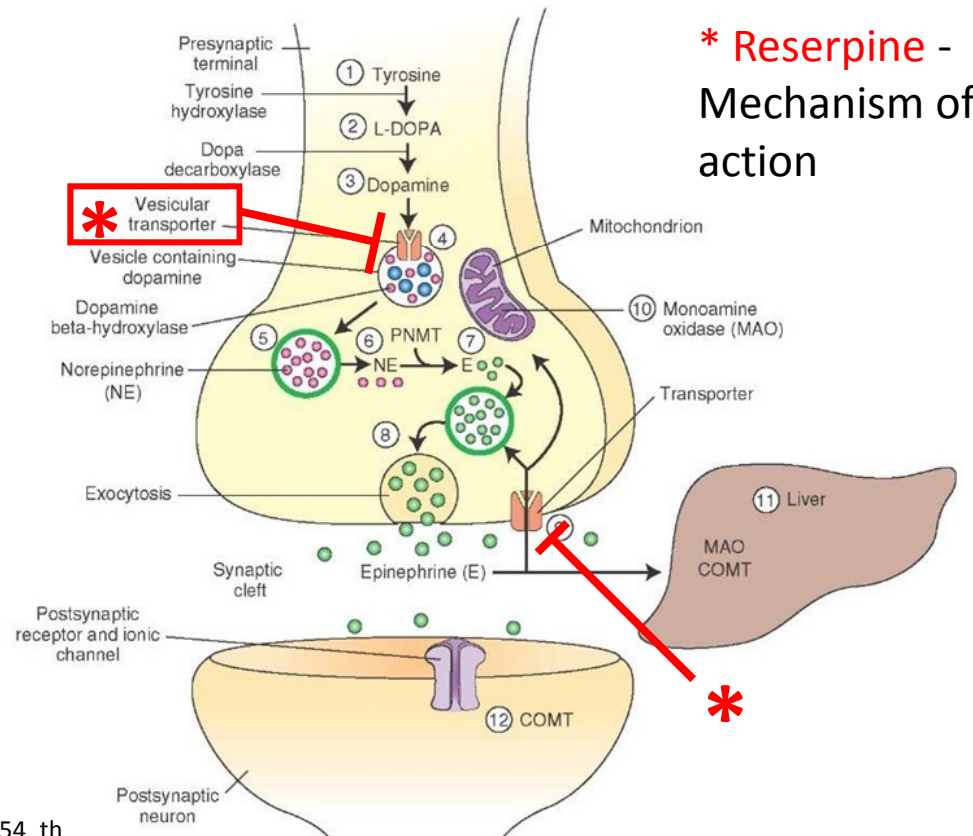
I. The Role of Catecholamines in Cardiac Lineage Commitment

- **Catecholamines play an essential role in heart function of the adult heart**
- Severe developmental effects of Catecholamine Synthesis Gene knockout (TH and DBH) (Kobayashi et al., 1995; Zhou et al., 1995, Thomas et al., 1995)
- **Paracrine action of catecholamines at developmental stage before neuronal innervation was suggested**
- **In Contrast:** *In vivo* Pnmt k.o. (Ebert et al., 2004) did not lead to fetal mortality
- **Noradrenaline is most important amongst the catecholamines in respect to cardiac development**



I. The Role of Catecholamines in Cardiac Lineage Commitment

Intracellular Catecholamine Synthesis



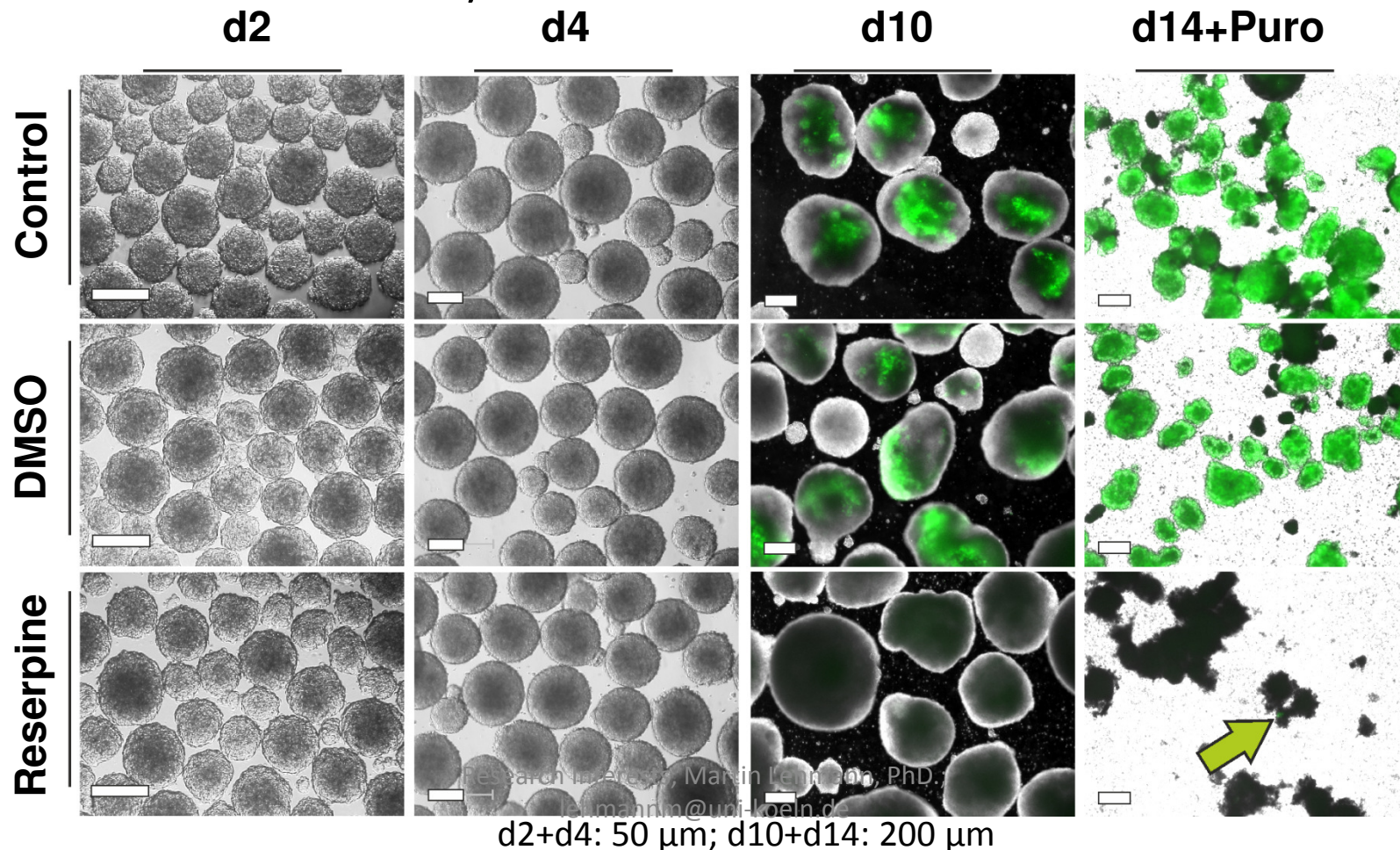
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lehmannm@uni-koeln.de



I. The Role of Catecholamines in Cardiac Lineage Commitment

- Reserpine-induced catecholamine depletion, reduced cardiomyocyte differentiation efficiency

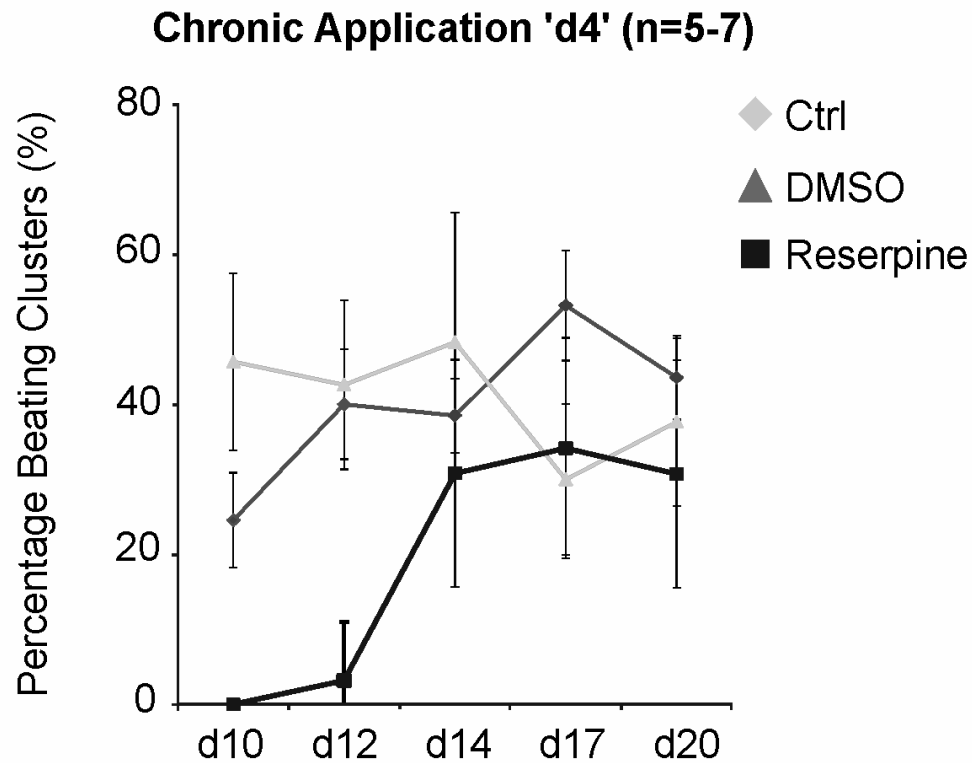


Research in Action, Martin Lemmer, PhD
lemmer@uni-koeln.de



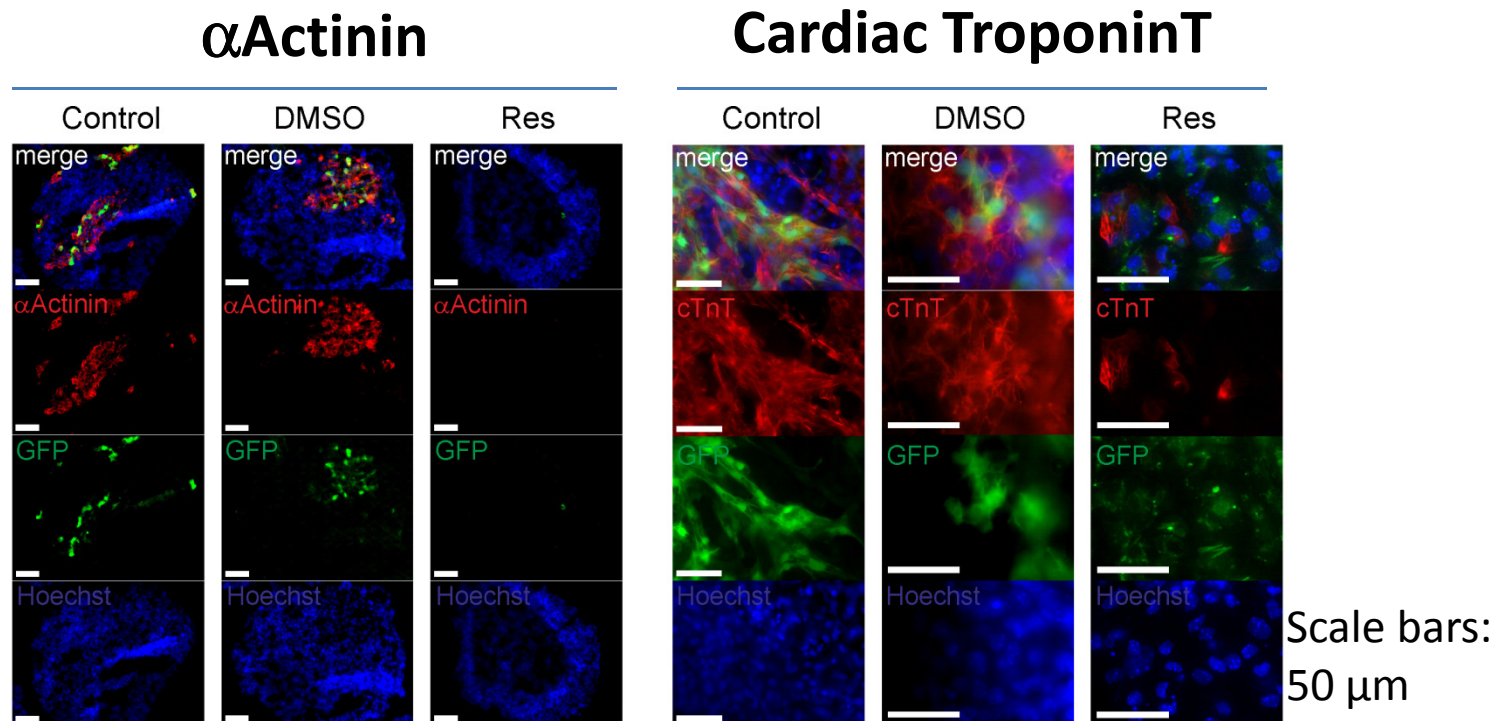
I. The Role of Catecholamines in Cardiac Lineage Commitment

- Reserpine Reduces Numbers of Beating EBs





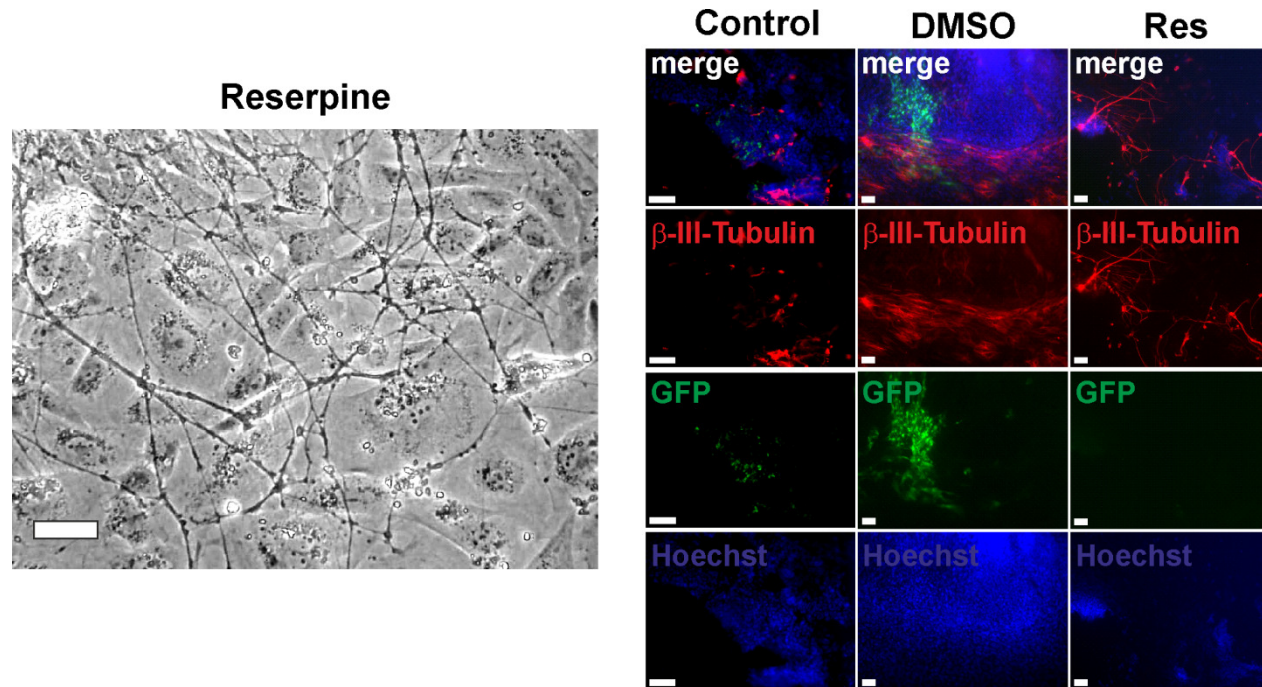
I. The Role of Catecholamines in Cardiac Lineage Commitment



- Expression of cardiac markers is significantly reduced after catecholamine depletion



I. The Role of Catecholamines in Cardiac Lineage Commitment



- Interestingly, catecholamine depletion **promotes neuronal lineage commitment**



I. The Role of Catecholamines in Cardiac Lineage Commitment

- **Catecholamines play a crucial role in cardiac differentiation** exhibiting their action in a paracrine fashion
- The critical period for catecholamine action is **before day 6**
- **α - and β -adrenergic signaling** is critical during cardiac differentiation.

II. Electrophysiological and pharmacological characterization of ES and iPS cell-derived cardiomyocytes





Project Aim

- Drugs can have unexpected cardio-active side effects (e.g. torsade de pointes tachycardia, TdP)
 - Pharmacological Screening Tool to detect possible cardio-active effects before cost-intensive clinical phase

→ **MEA-based human ES or iPS cell-derived Cardiomyocyte (rESCM) screen**

Why Multielectrode Arrays (MEA)?

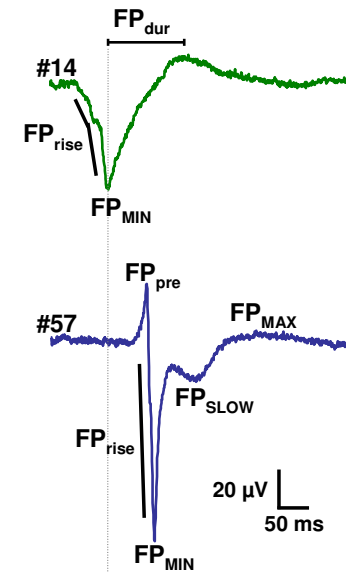
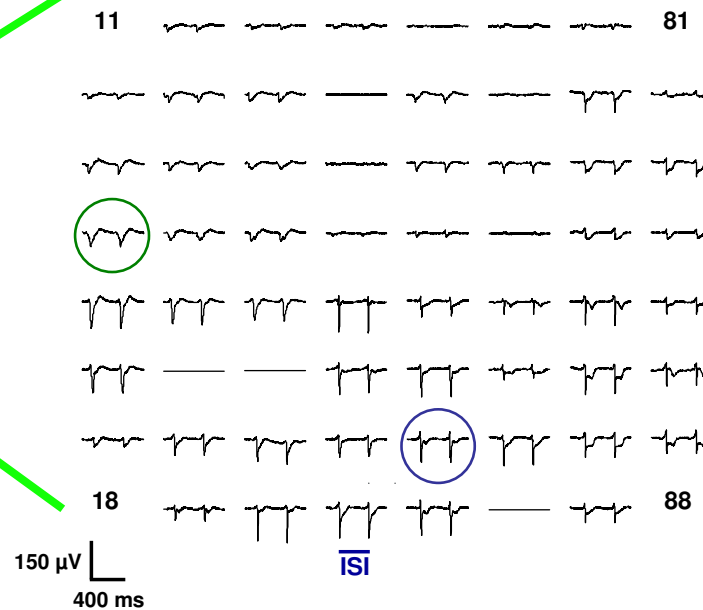
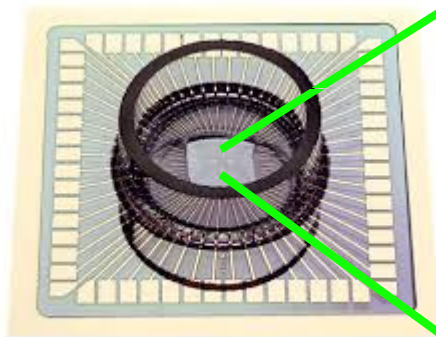
- non-invasive extracellular measurement (of field potentials (FPs))
- long-term recordings
- allows for recording of 2D excitation and conduction (slices, monolayer)





Multielectrode Array (MEA)

The MEA as pharmacological screening set up

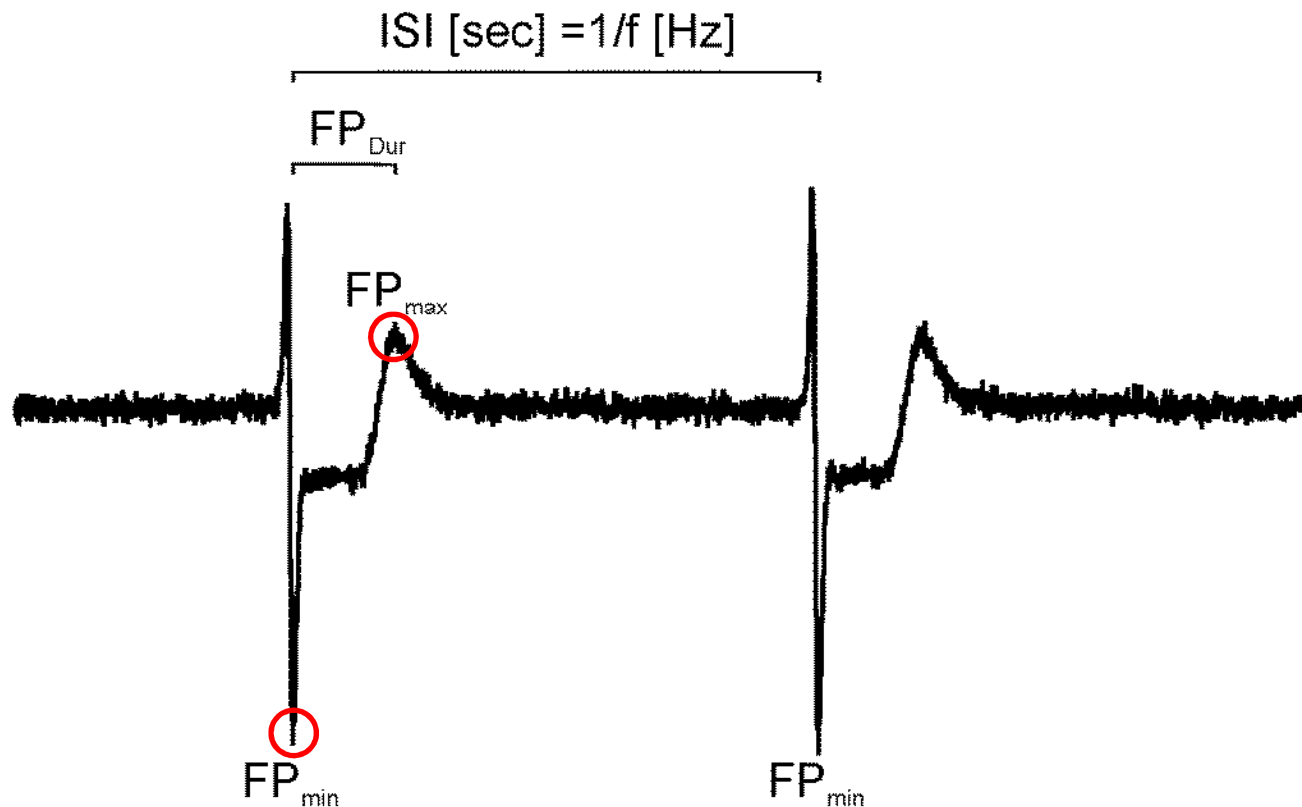


Analysis software is written by U. Egert, Dept. of Neurobiology and Biophysics, Univ. of Freiburg

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lehmannm@uni-koeln.de

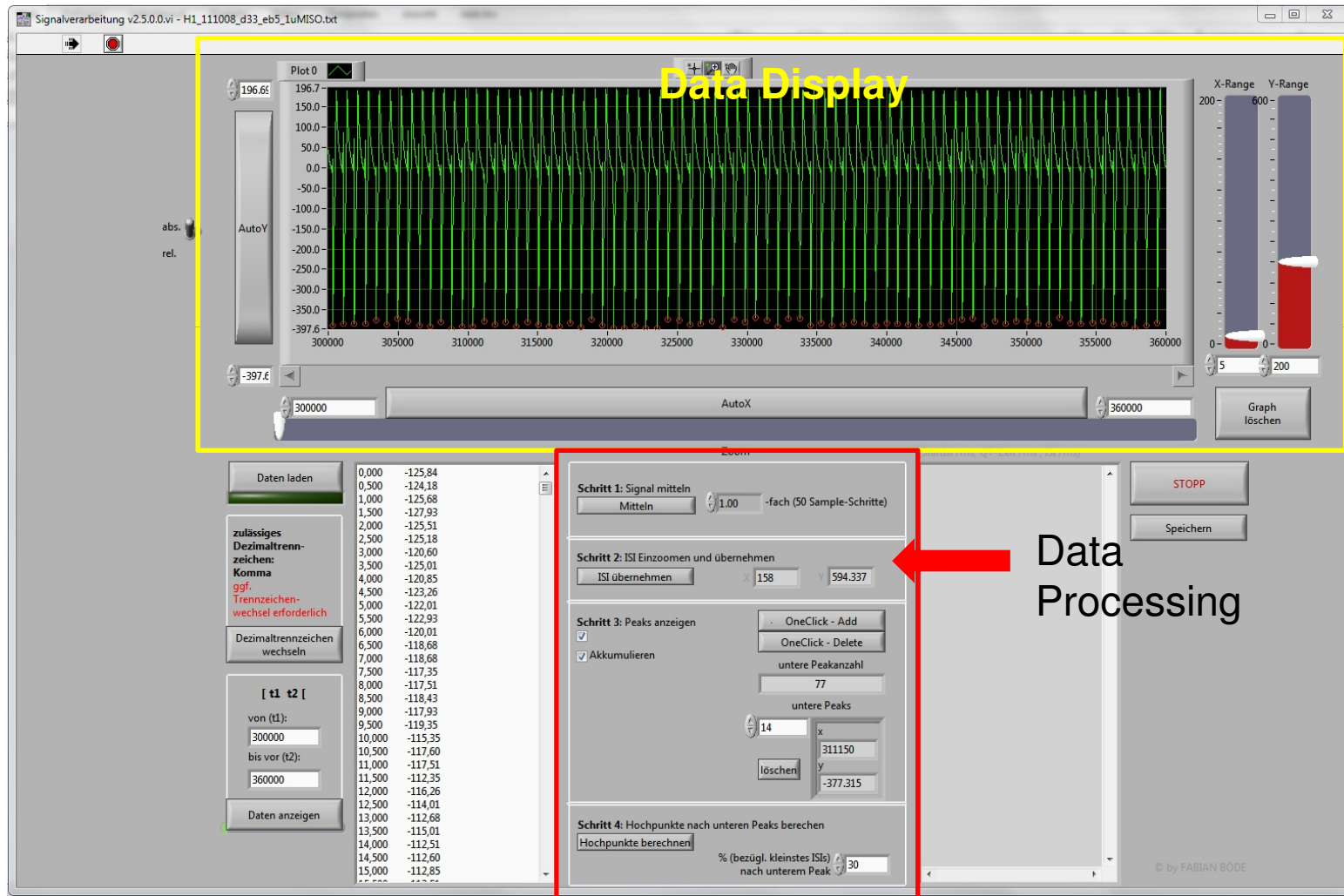


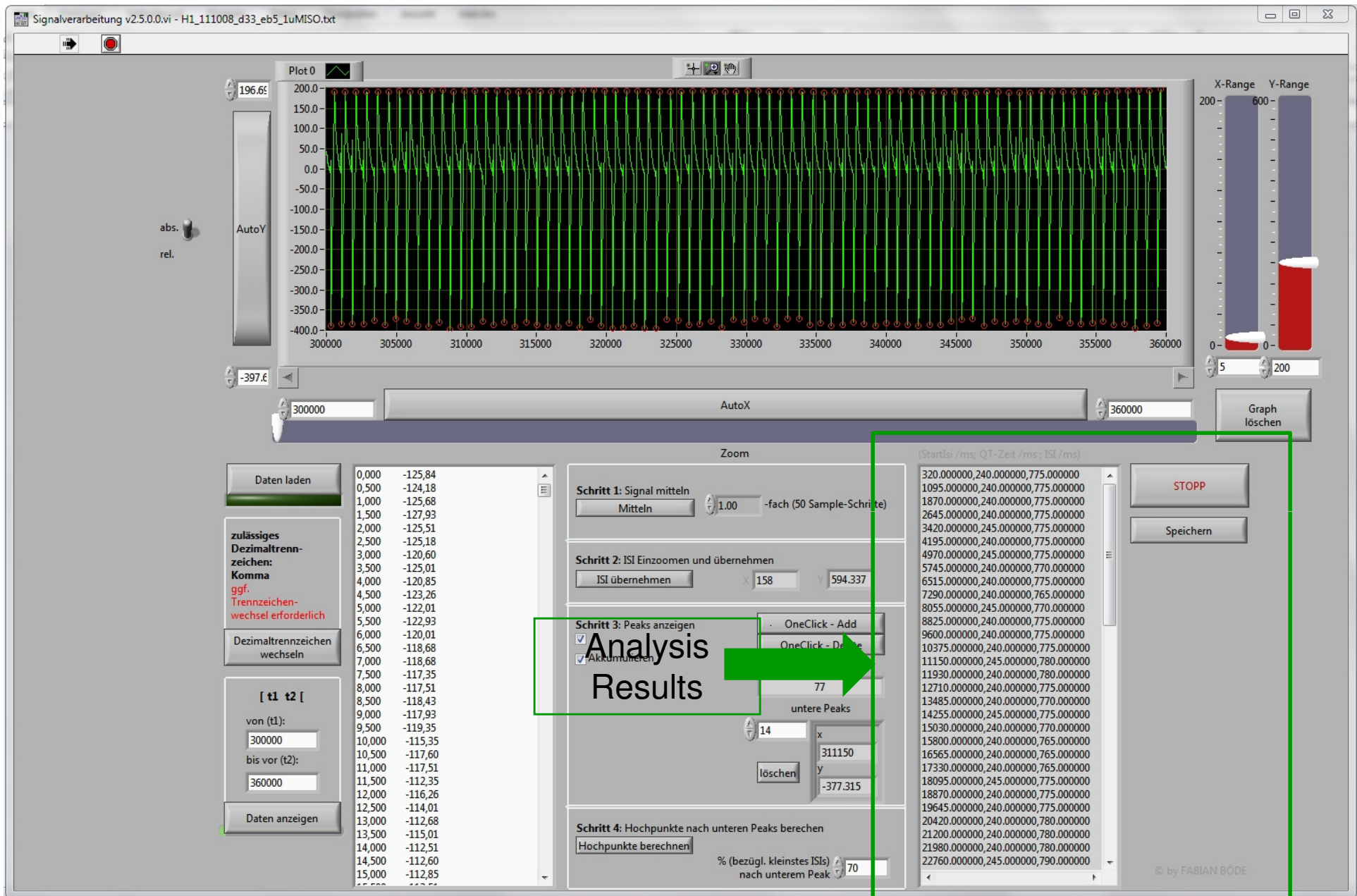
Multielectrode Array (MEA)





LabView-based Analysis Tool



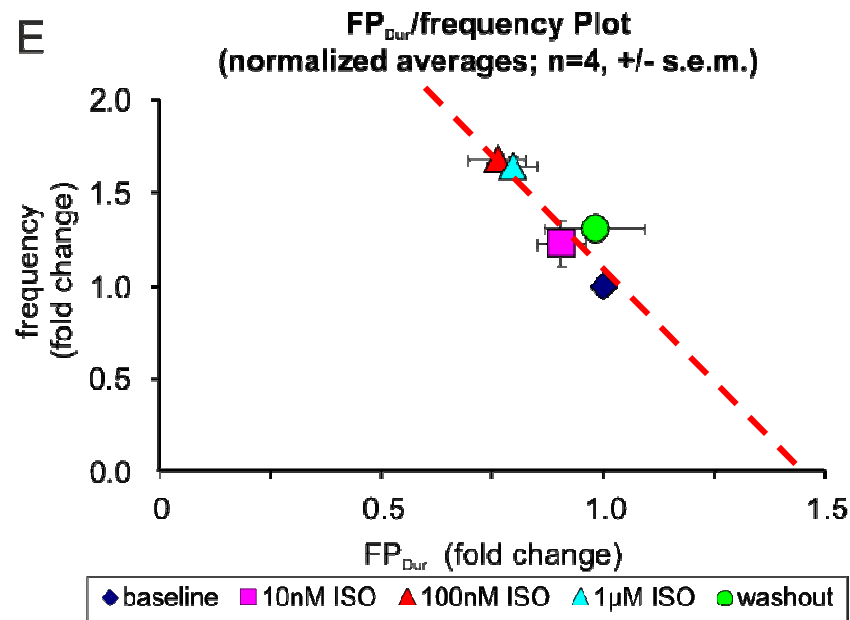


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FP/f Correlations- Physiologic Positive Chronotropic Conditions

Normalized averaged values

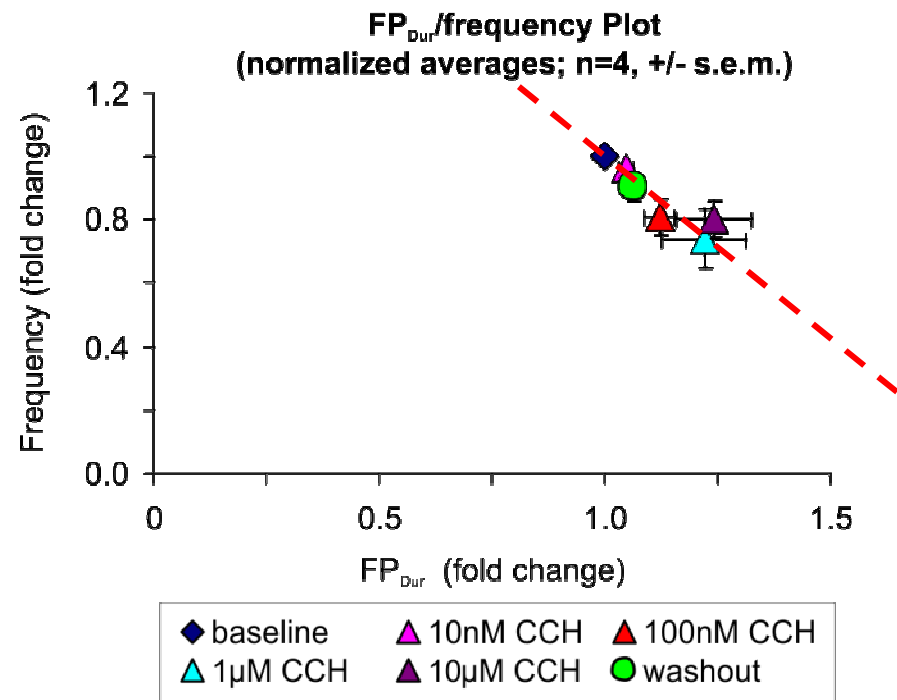


- Negative (linear) FP/f correlation upon physiologic positive chronotropic stimulation
- Normalized and averaged value pairs are representative for a population of EBs



FP/f Correlations- Physiologic Negative Chronotropic Conditions

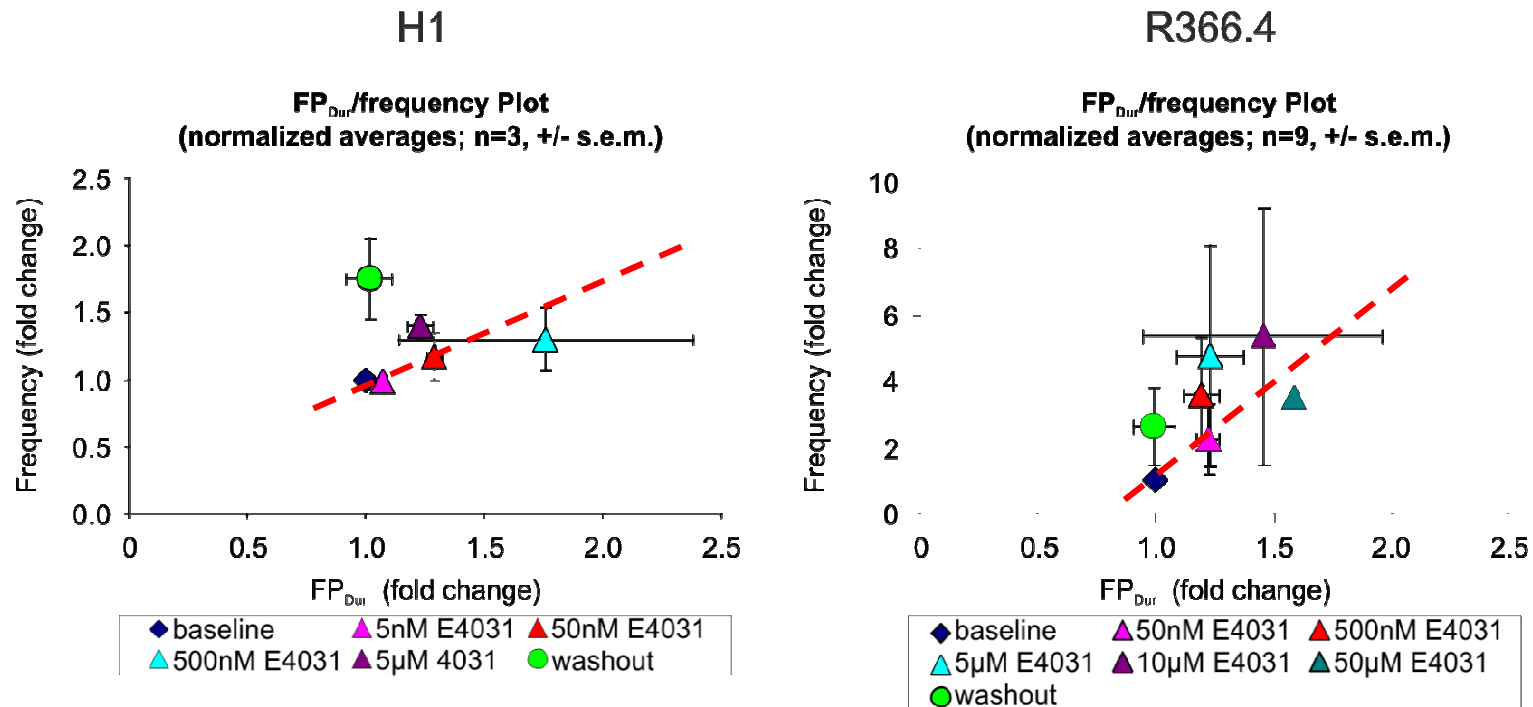
FP/f correlation during negative chronotropic stimulation





FP/f Correlations- QT-prolonging conditions

Hypothetically, **QT-time and repolarization prolonging** drugs should change the FP/f correlation toward **less negative** values, e.g. **E4031**



Antiarrhythmic class III drug (K⁺/HERG-Channel blocker)

→ **positive FP/f correlation**



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Conclusions:

- Drug effects on different EBs/cells is comparable (normalization!!)
- EB-to-EB comparison has to be taken with care (e.g. Long-QT-iPS)
- **A pharmacological screen is feasible with MEA irrespective of cell type (ES or iPS)**